Design, Development, and Applications of New a-Diazo Carbonyl Compounds as Carbene Surrogates to Access Useful Organic Compounds

A thesis

submitted in partial fulfillment of the requirements
of the degree of

Doctor of Philosophy

By

Debasish Laha

ID: 20173500



Indian Institute of Science Education and Research Pune

2023

"This thesis is dedicated to…
my grandparents, in loving
memory"

भारतीय विज्ञान
INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH FLJNE
IISER PUNE An Autonomous Institution of the Ministry of Education. Govt. of India

Dr. Ramakrishna G. Bhat
Professor
Department of Chemistry
IISER Pune

CERTIFICATE

This is to certify that the research work incorporated in this thesis entitled *"**Design, Development, and Applications of New α-Diazo Carbonyl Compounds as Carbene Surrogates to Access Useful Organic Compounds**"* submitted by **Debasish Laha** and the research was carried out by the candidate at Indian Institute of Science Education and Research (IISER), Pune, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other University or institution.

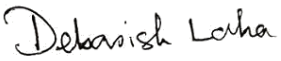
Date: 04/07/2023
Place: Pune (Maharashtra)

Ramakrishna G. Bhat
(Research supervisor)

rgb@iiserpune.ac.in • Ph: +91-20-25908092 • Fax: +91-20-25898022

DECLARATION

I declare that, this written submission represents my ideas in my own words and where others' ideas have been included; I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/ source in my submission. I understand that violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.



Date: 04/07/2023 **Debasish Laha**

Place: Pune (ID: 20173500)

Acknowledgments

I would like to take this opportunity to express my deepest gratitude and appreciation to the numerous individuals and institutions who have contributed to the completion of this research thesis.

First and foremost, I wish to express my sincere gratitude and appreciation to my thesis supervisor, *Prof. **R**amakrishna **G**. **B**hat*, for being a great mentor during my journey as a Ph.D. student in his lab at IISER Pune. I thank him for his invaluable guidance, unwavering support, and encouragement during these years. I highly appreciate his understanding of research and his style of approaching a research problem. His extensive knowledge and experience in my field of study have greatly shaped and refined my research ideas. His insightful comments and suggestions have challenged me to think critically and pushed me to go beyond my limits, resulting in a stronger and more comprehensive thesis. On a personal note, I am grateful to have such a guide who has enlightened this stage of my life to know about the ways of the world. He is an ideal example to me as a friend, philosopher, and guide. Besides, he has been a very approachable person, a very nice human being with a lot of patience, polite nature, and highly encouraging and positive thinking and I take this opportunity to thank him for teaching me.

I thank my RAC members, *Dr. Boopathy Gnanaprakasam* and *Dr. Pradip Maity* for their valuable suggestions and fruitful discussions. I like to extend my sincere gratitude to all faculties of IISER Pune. I thank former Directors of IISER Pune, Prof. K. N. Ganesh, Prof. Jayant B. Udgaonkar, and the current Director Prof. Sunil S. Bhagwat for the facilities provided at IISER Pune.

No words can mention my thanks to my former labmates, Dr. Rajesh, Dr. Tushar, Dr. Trimbak, Dr. Balu, Dr. Nayeem, Dr. Chennakeshawa, Ankit, Dr. Prakash, Dr. Pankaj, Dr. Vikas, Subhayan, Archana, Nitin, Sundaravalli, and my current labmates Javed, Anindita, Abhijeet, Mousumi, Kajal, Onkar, Sidharth with whom I have shared many memories from lab trips, parties to a common lab instrument connecting us all. I thank them for maintaining an enjoyable work atmosphere in the lab, particularly thanks to Kajal and Onkar for the generous helping hand for the synthesis and prolific discussions, debates, entertainment, and encouragement. My sincere heartful thanks goes out to Dr. Balu for the exciting and fruitful discussion as well as for mentoring me at the early stage of my Ph.D. journey in hands-on experiments on the novel reactivity of Diazo-compounds under metal catalysis. It helped me to expand my knowledge beyond my doctoral research topic.

I want to take this opportunity to thank Prof. Debashree Ghosh, IACS, Kolkata, and her student Mr. Supriyo Santra for the excellent collaborative work in helping me with DFT calculations for one of my thesis chapters.

I thank Dr. Rahul Maity for helping me in solving the SCXRD structure. I am indebted to my batchmates and friends Borish, Debashree, Sumanta, Aslam, Tariq, Shabnum, Minhaj, Neetu for making my life at IISER Pune enjoyable. I thank the people who have worked behind the curtains, instrument operators, administrative staff, and other non-teaching staff of IISER Pune.

Words are not enough to convey my deepest gratitude towards the blessings, love, and motivation of my parents (Smt. Dipa Laha and Shri. Ramesh Chandra Laha) and other family members (Late Smt. Satyabhama Laha {Grandmother}, Late Shri. Krishna Chandra Laha {Grandfather}, Mrs. Jayeta {sister}, Mr. Amitava {brother-in-low}). This journey wouldn't have been possible without their unconditional emotional support, encouragement, trust, patience, and sacrifice; they are the main reason and inspiration behind each and every success that I have achieved and will achieve in the future endeavors of my life. I thank all my teachers who taught me from my school days to my Ph.D. cultivating my personality, knowledge and without whom I would not have been in my present position.

Finally, I thank the almighty God for giving me this wonderful life full of opportunities.

Debasish Laha

Contents

Contents……vii

Abbreviations……...xii

Synopsis……..xvi

List of Publications……..xxxiii

Chapter 1: ***Diverse Reactivities of Carbenes and their Applications in Synthetic Strategies***

1.1. Introduction……2

1.2. Classification of organometallic carbenes or Metal Carbenoids……4

1.3. Carbene precursors and generation of carbene……....5

1.3.1.1. α-Elemination……...6

1.3.1.2. Simmon-Smith reaction……6

1.3.2. Fragmentation reactions……...7

1.3.2.1. Diazo decomposition……7

1.3.2.2. Classification of diazo compounds……9

1.3.2.2A. Progress on Metallo-Carbenes……9

1.3.2.2B. Progress on the Photochemical carbene transfer reaction……10

1.3.2.3. General mechanism for photochemical carbene reactivity……...12

1.3.2.4. Diazo compounds and their importance……...13

1.3.2.5. Synthesis of diazo compounds……13

1.3.2.6. Recent advances on catalyst development and utilization diazo compounds under metal catalysis and Photocatalysis……...14

1.4. Aims and rationale of this thesis work ……16

1.5. Conclusions……..20

1.6. Reference……..20

Chapter 2: ***Silver(I)-Catalyzed Diastereoselective Epoxidation of Aldehydes with Vinyl Diazosuccinimides via [2+1]-Cycloaddition Process***

2.1. Introduction……...26

2.2. Results and Discussion……31

2.3. Conclusions……...36

2.4. Experimental section……36

2.4.1. General Details……..36

2.4.2. Preparation of Starting Materials…….. 37

2.4.2.A. General procedure-A for the synthesis of vinylic succinimides……...……37
2.4.2.B. General Procedure-B for the synthesis of vinyl diazosuccinimides……..39
2.4.3. General Procedure-C for the Synthesis of spiro-oxiranes……..….42
2.4.4. Gram Scale Synthesis……..……50
2.4.5. Appendix II…….……51
2.4.6. Appendix IIB……..….59
2.5. References……..……63

Chapter 3: *A One-pot Access to Diastereoselective Benzoxepino[2,3-c]pyrroles via Formal (5+2)-Annulation of Vinyl diazosuccinimide with Ketones Under Silver Catalysis*

3.1. Introduction……...……65
3.2. Results and Discussion…….……72
3.2.1. Investigation for the suitable dipolarophile……..…….74
3.2.2. Optimization of reaction conditions for the formal (5+2)-cycloaddition of donor-/acceptor- type vinyl diazosuccinimide……75
3.2.3. Proposed Mechanism for the transformation…….86
3.3. Conclusion…….……....87
3.4. Experimental Section……88
3.4.1. General Information…….……88
3.4.2. Preparation of Starting Materials……88
3.4.2.1. General procedure-A for the synthesis of vinyl succinimides……..…88
3.4.2.2. General Procedure-B for the synthesis of vinyl diazosuccinimides……..…..94
3.4.3. General Procedure-C for the Synthesis of dihydrobenzo[5,6]oxepino[2,3-*c*]pyrrole-1,3(2*H*)-dione…….…..98
3.4.4. Appendix-II: Applications…….…….106
3.4.4A. Gram Scale synthesis……..…106
3.4.4B. Procedure for reduction of 5aa to access 2-Pyrrolidone-fused dihydrobenzoxepine..107
3.4.5. Procedure for Control Experiments and Stereochemical aspects……..……..107
3.4.6. NMR study of epoxide (3aa) to oxepine (5aa) conversion……..…110
3.4.7. Appendix III……...……112
3.4.8. Molecular Structures of Compounds (1a, 5ga, 3aa, and 5aa) using Single Crystal X-ray Analysis……. 122
3.4.8A. Molecular Structure of 1a……...…112
3.4.8B. Molecular Structure of 5ga……...……..124

3.4.8C. Molecular Structure of 3aa……126
3.4.8D. Molecular Structure of 5aa……128
3.5. References……130

Chapter 4A: *Intramolecular O–H Functionalization under Silver Catalysis: Access to 2H-Chromene*

4A.1. Introduction……134
4A.2. Results and Discussion……136
4A.3. Conclusions……140
4A.4. Experimental Section……140
4A.4.1. General Procedure to synthesized the O–H functionalization product……140
4A.5. Detailed optimization for the intramolecular O–H functionalization……141
4A.5.1. Catalyst optimization[a]……141
4A.5.2. Investigation of suitable solvent[a]……141
4A.5.3. Optimization of reactant concentration[a]……142
4A.5.4. Experimental Section……142
4A.6. References……142

Chapter 4B: *Photochemical Carbene Reactivity of Donor-/Acceptor-type Diazosuccinimide: An Access to 2H-Chromene*

4B.1. Introduction……144
4B.2. Results and Discussion……151
4B.3. Conclusions……163
4B.4. General Information……163
4B.5. Experimental Procedures……165
4B.5.1. Preparation of Starting Materials……165
4B.5.1.1. General procedure-A for the synthesis of vinyl succinimides……165
4B.5.1.2. General procedure-B for the synthesis of vinyl diazosuccinimides……166
4B.5.2. General procedure-C for the photoinduced O–H functionalization……167
4B.6. Optimization details……167
4B.6.1. Model reaction…… 167
4B.6.2. Background reactions……168
4B.6.3. Influence of light intensity……168
4B.6.4. Influence of the light source……169

4B.6.5. Influence of the solvent……169
4B.6.6. Influence of the additives……169
4B.6.7. Influence of the substrate concentration……169
4B.6.8. Influence of reaction time……169
4B.7. Mechanistic studies……170
4B.7.1. UV-Visible studies……170
4B.8. Isotope labeling experiments……171
4B.8.1. Procedure for synthesizing compound 1ac-*d*……175
4B.8.2. Control experiment with aq. NaOH……176
4B.9. Investigation of singlet vs triplet carbene intermediate……177
4B.10. Mechanism for group transfer reaction……178
4B.11. Radical trapping experiments……179
4B.12. EPR studies……182
4B.13. Geometrical arrangement of diazosuccinimide……182
4B.14. Characterization of synthesized compounds……183
4B.15. Crystal Data……214
4B.16. Reference……216

Chapter 5: *Highly Regio- and Chemo-selective Arene Cyclopropanation using Donor-/Acceptor- type Propargyl α-pentafluorophenyl-α-diazoacetate via Scandium Catalysis*

5.1. Introduction……220
5.2. Results and Discussion……225
5.2.1. Our hypothesis to overcome inherent challenges……225
5.2.2. Initial optimization: Survey of arene part of *α*-aryl-*α*-diazoacetate……226
5.2.3. Our postulates……227
5.2.4. Initial optimization – Survey of ester part of *α*-aryl-*α*-diazoacetate……228
5.2.5. Optimization of the reaction condition – for the broader applicability……229
5.2.6. Investigation for feasibility of the protocol – Scope studies……231
5.2.7. Synthetic utility of norcaradiene……233
5.3. Conclusions……234
5.4. Experimental Section……235
5.4.1. General information……235
5.4.2. Experimental Procedure……235
5.4.2.1. Preparation of Starting Materials……235

5.4.2.1.1. General procedure-A for the synthesis of propargyl esters……..….235
5.4.2.1.2. General procedure-B for the synthesis of propargyl diazoacetates……..….236
5.4.2.2. General procedure-C for the optimization of arene part and ester part……..….236
5.4.2.3. General procedure-D for the synthesis of norcaradienes……...…237
5.4.3. Optimization of different parameters of the reaction conditions……..…237
5.4.4. Characterization of synthesized compounds……..…239
5.4.4.1. For ester compounds……..239
5.4.4.2. Data of diazo acetates……240
5.4.4.3. Data of title compounds NCDs and other obtained Final Products……...….241
5.4.5. Application of the Protocol……...250
a) [4+2]-cycloaddition reaction with norcaradiene……...…250
b) Deprotection of Propargyl group: Easy Ester Hydrolysis…….... 251
5.4.6. Appendix-V: ^{1}H, $^{13}C\{^{1}H\}$, and ^{19}F NMR spectral data of representative compounds..252
5.4.7. Crystal Diffraction Data……261
5.5. References……...……265

Summary……...…267

*****

List of Abbreviations

*	Excited state
Å	Angstrom
Ar	Aryl
AR	Analytical Research Grade
BHT	Dibutylhydroxytoluene
Bn	Benzyl
br	Broad
C	carbon
Calcd.	Calculated
°C	Degree Celsius
CCDC	Cambridge Crystallographic Data Centre
CFL	Compact Fluorescent Lamp
CHT	Cycloheptatriene
cm^{-1}	wavenumber(s)
CV C	yclic voltammetry
δ	Chemical shift
d	Doublet
DBU	1,8-Diazabicyclo 5.4.0 undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DFT	Density-functional theory
DIPEA	*N*,*N*-diisopropyl methyl amine
DMF	*N*,*N*-dimethyl formamide
DMSO	Dimethyl sulfoxide
d.r.	Diastereomeric ratio
ee	Enantiomeric excess
EDG	Electron donating group
EnT	Energy transfer
EPR	Electron paramagnetic resonance
equiv.	Equivalent
ESI TOF	Electrospray Ionization Time-of-Flight

Et	Ethyl
EtOAc	Ethyl acetate
EWG	Electron withdrawing group
EY	Eosin Y
g	Gram
GTRC	Group transfer radical cyclisation
h	hour(s)
HAT	Hydrogen atom transfer
HRMS	High-resolution mass spectrometry
hv	Photochemical
Hz	hertz
^{i}Pr	Isopropyl
ISC	Intersystem crossing
J	Coupling constant
K	Kelvin
kcal	kilocalories
λ_{max}	Wavelength
LEDs	Light-emitting diode
m	Multiplate
m-	Meta
M	Molar
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mg	Milli gram
MHz	Mega hertz
min	Minute(s)
mL	Milli litter
mM	Milli molar
mmol	Milli mole
mol%	mole percent
MS	Molecular sieves
m/z	mass-to-charge ratio
NCD	Norcaradiene

nm	Nano meter
NMR	Nuclear magnetic resonance
NR	No reaction
Nu	Nucleophile
o-	Ortho
ORTEP	Oak Ridge Thermal-Ellipsoid Plot Program
OAc	Acetate
OTf	trifluoromethanesulfonate
NTf	trifluoromethylamine
p-	Para
P	phosphorus
PC	Photocatalyst
PCET	Proton couple electron transfer
PET	Photoinduced electron trasnfer
PivOH	Pivalic acid
ppm	parts per million
PPT	Photoinduced proton transfer
Ph	Phenyl
q	Quartet
RB	Round bottom flask
R_f	Retardation Factor
rr	Regioisomeric ratio
rt	Room temperature
s	Singlet
S_1	Singlet ground state
SET	Single-electron trans
t	Triplet
T_1	Triplet ground state
td	triplet of doublet
^{t}Bu	Tertbutyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography

TMS	Trimethylsilyl
μM	Micro molar
UV	Ultraviolet
W	Watt
XRD	X-ray diffraction

SYNOPSIS

The thesis entitled "***Design, Development, and Applications of New a-Diazo Carbonyl Compounds as Carbene Surrogates to Access Useful Organic Compounds***" comprises five main chapters with sub-sections.

Aim of this Thesis

Carbene is the key reactive intermediate that facilitates diverse synthetic transformations ranging from cycloaddition to site-selective functionalization. As they are known as reactive intermediate species with short existence, their application in organic synthesis in a controlled manner is highly challenging owing to their high reactivity nature. Thus, controlling its reactivity is the most crucial so as to achieve selective carbene transfer reactions. Over the years, researchers across the globe have been developing various carbene precursors so as to harness their reactivity for many synthetic applications. The diazo compound is one of the most useful and versatile reagents that are known carbene surrogates for the efficient generation of a carbene intermediate. Over the years traditionally, the reactivity of in situ carbene from the diazo compounds has been often controlled by the use of metal catalysts in the form of metallo-carbenes or metal-carbenoids. For the last few decades, the research area of carbenes has grown rapidly and many state-of-the-art synthetic methods have been developed. These are not only based on the catalyst development but also aimed at tuning the reactivity based on the carbene functionality and modifications of the ligand as well as depending on the reacting partner. Recently, the focus has also been made towards the free-carbene reactivity under visible light energy to trap the excited state reactivity. Despite some of these advances, the ground-state free-triplet carbene generation has seldom been explored. This highly challenging and difficult to generate the ground-state free-triplet carbene and also their application into organic synthesis for the useful transformation is also difficult due to the minimum singlet-triplet gap and their coexisting nature.

We have been working on the diazo compounds and we became more interested to tap their versatile reactivity and explore their broader synthetic challenges. Owing to the importance of these, the thesis has been aimed at the design, and development of newly decorated diazo carbonyl compounds as carbene surrogates to construct useful compounds, biologically active small organic molecules, and natural products and their analogs. The thesis also looked into finding the reactivity profile of different diazo carbonyl compounds to explore a few unprecedented methodologies utilizing newly invented bench-stable diazo compounds in

the presence of metal catalysis as well as under the direct exposure of visible light. Gratifyingly, the thesis also presents the new carbene surrogate that is capable of generating the ground-state triplet spin state and its utility in organic synthesis.

Chapter 1: *Diverse Reactivities of Carbenes and Their Applications in Synthetic Strategies*

This introductory chapter briefly presents the evolutionary development of carbenes and their applications in organic synthesis. Starting from the traditional methods of utilizing the reactive carbene species, the most recent methods for the utility of carbene precursors via transition-metal catalysis via metal-carbenoid reactivity and the most recent exploration of visible-light-induced photochemical free-carbene reactivity have been discussed. A few selected transformations ranging from cycloaddition to site-selective C–H bond functionalization have been outlined.

Diazo carbonyl compounds have been emerging as a revolutionary tool in organic synthesis to accomplish the intriguing reactivity of metal-carbenoids or free-carbene species. This chapter describes diazo compounds, their classifications, preparations, and their utility in organic synthesis. It has also been outlined how the carbene reactivity could be controlled so as to execute selective carbene transfer reactions via metal catalysis as well as photochemical conditions. Further, it gives a brief account on the state-of-the-art synthetic strategies for the carbene transfer reactions (in both spin states) generated from diazo compounds. Also, the chapter presents the unique reactivity nature of vinyl diazo compounds under metal catalysis as well as under photochemical conditions.

Chapter 2. *Silver(I)-Catalyzed Diastereoselective Epoxidation of Aldehydes with Vinyl Diazosuccinimides via (2+1)-Cycloaddition Process*

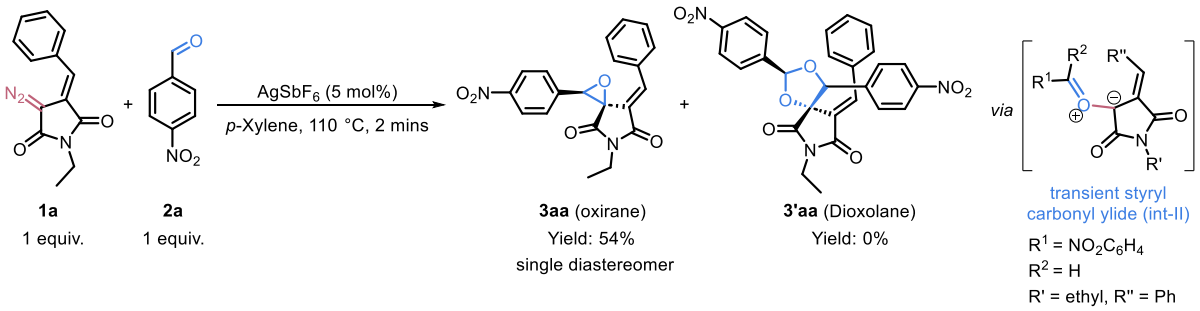
This chapter describes the exploration of silver hexafluoroantimonate as an efficient catalyst for the development of a highly diastereoselective synthesis of oxiranes. The reaction of aldehydes with donor-/acceptor-substituted vinyl diazosuccinimides as metallo-carbene precursors *via* (2+1)-cycloaddition under silver catalysis furnished oxiranes. Earlier, oxiranes have been synthesized using different metal catalysts such as rhodium, copper, etc. However, in a few methods, along with the oxiranes, dioxolanes are also formed as a competitive side product. The natural product TAN-1813 could be achieved starting from the spiro-oxiranes. Owing to the importance, of the spiro-oxiranes, we proposed that the vinyl diazo succinimide and aldehyde could be successfully utilized for constructing the spiro-oxiranes under suitable

conditions. However, the major challenge is to access the desired product exclusively and to avoid side-product formation.

This chapter discloses the design and development of a convenient method for the direct synthesis of oxiranes starting from aldehydes and donor-/acceptor-substituted vinyl diazosuccinimides as metallo-carbene precursors via (2+1)-cycloaddition in presence of catalytic amount of silver hexafluoroantimonate as an efficient catalyst.

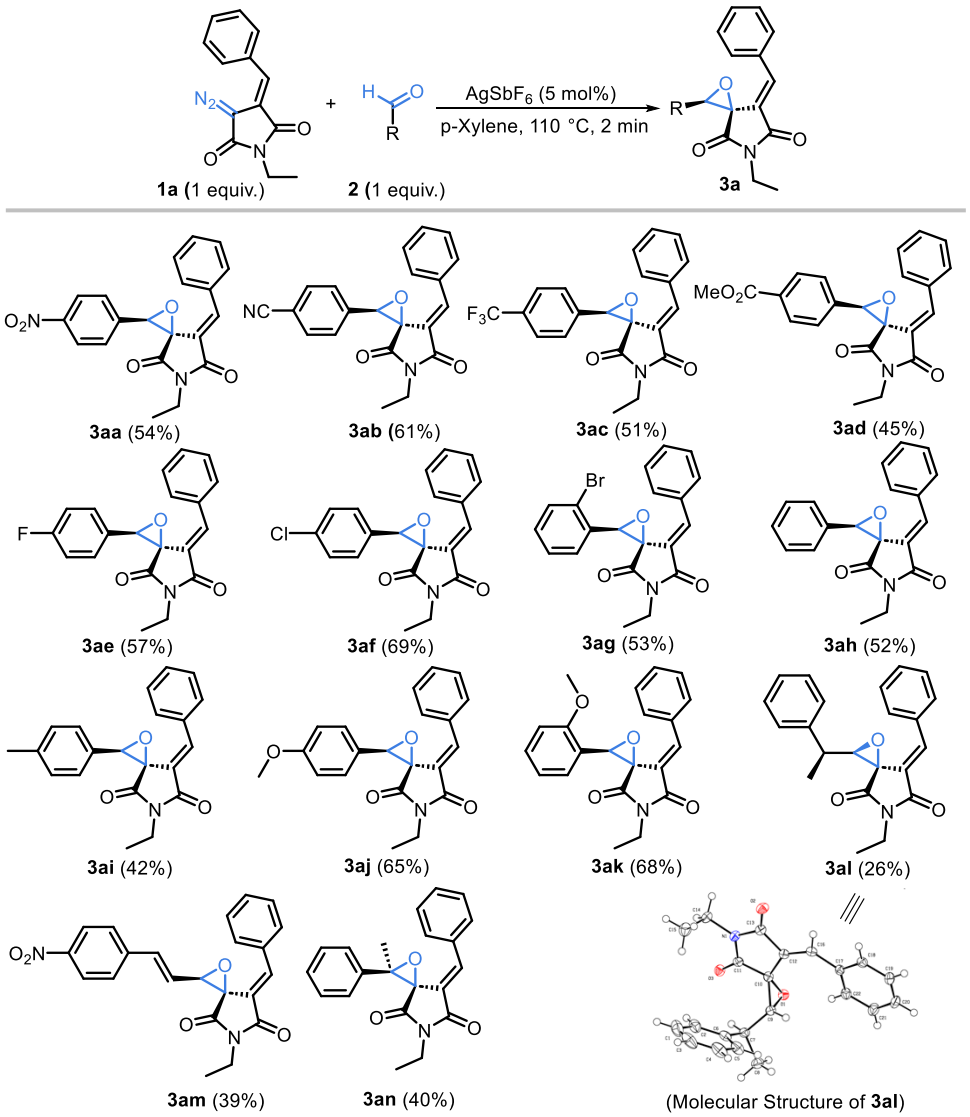
In order to achieve this, the development of a practical and convenient one-step synthesis of the bench-stable diazo succinimide is highly desirable as the available conventional synthetic strategies are long. In this regard, to begin with, we developed a novel protocol for the synthesis of vinyl diazo succinimides starting from biologically active benzylidene succinimides *via* a diazo transfer process.

After the systematic and exhaustive screening, 4-nitrobenzaldehyde **2a** (1 equiv.), *N*-ethyl benzylidene diazo succinimide **1a** (1 equiv.), $AgSbF_6$ (5 mol%) in *p*-xylene at an elevated temperature (110 °C, 2 min) proved to be the optimized reaction condition to access the corresponding spiro-oxirane **3aa** as a single diastereomer without the formation of any dioxolane **3′aa** side product (see Scheme 2.1)



Scheme 2.1. Highly diastereoselective synthesis of spiro-oxiranes under silver(I) catalysis.

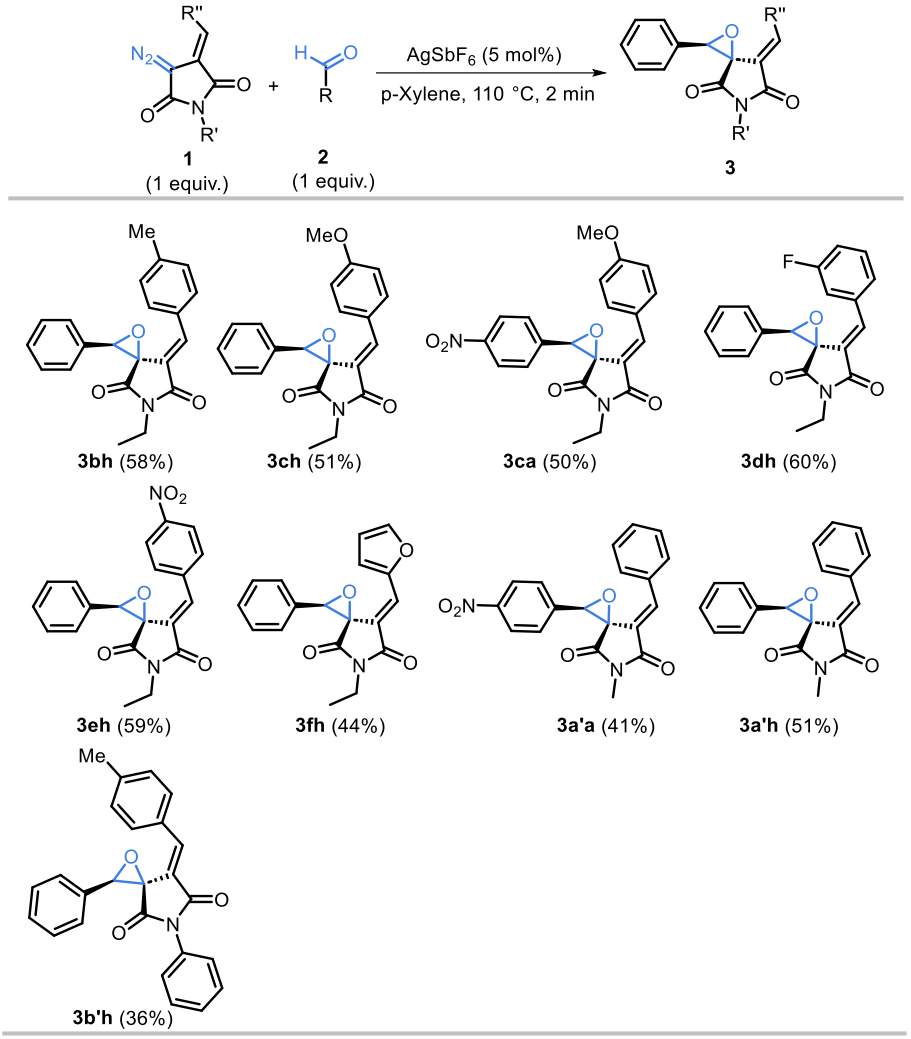
Having obtained the optimized reaction condition, in order to demonstrate the generality of this protocol, to begin with, we treated diazo arylidene succinimide **1a** with various aromatic aldehydes (**2a**-**2n**) containing electron- withdrawing and -donating groups under the optimized reaction conditions. All the aldehydes reacted smoothly with **1a** to afford the desired spiro-oxiranes (**3aa**-**3an**) as a single diastereomer in modest to moderate to good yields with high regio- and chemo-selectivity (up to 69% yield, Table 2.1). It is important to highlight that in all the cases, we did not observe the competitive side product-dioxolane **3′** even in trace (formed by other diazo compounds as mentioned early).



[a]**Reaction conditions**: **1a** (1 equiv.), **2** (1 equiv.), $AgSbF_6$ (5 mol%), *p*-Xylene (3 mL), N_2 atmosphere; [b]Yields of isolated products are obtained by purification using column chromatography and yields are given in the parentheses.

Table 2.1. Substrate scope aldehydes to access spiro-oxiranes via the formal (2+1)-cycloaddition.

We painstakingly isolated two diastereomers of **3al** and their molecular structures and geometric arrangements were unambiguously confirmed using single crystal X-ray diffraction analysis (CCDC – 1971121 and 1972978). Later, we explored the substrate scope of different diazo arylidene succinimides **(1b-1f, 1a′-1b′)** by treating with different aromatic aldehydes under the optimized reaction conditions (Table 2.3). Gratifyingly, all the diazo arylidene succinimides reacted smoothly under the conditions to afford the corresponding spiro-oxiranes (**3bh-3ch, 3ca, 3dh-3fh, 3a′a-3a′h, 3b′h**) in moderate yields with very good diastereoselectivity (up to 60% yield, Table 2.3).



[a]**Reaction conditions**: **1a** (1 equiv.), **2** (1 equiv.), $AgSbF_6$ (5 mol%), *p*-Xylene (3 mL), N_2-atmosphere; [b]Yields are given in parenthesis and are obtained by purification using column chromatography.

Table 2.2. Substrate scope of benzylidene diazo succinimides to access spiro-oxiranes via the formal (2+1)-cycloaddition.

In summary, we have successfully developed a practical and convenient protocol for the synthesis of vinyl diazosuccnimides as well as demonstrated their utility by developing a methodology to directly access spiro-oxiranes starting from different aldehydes under silver(I) catalysis. The protocol proved to be highly efficient to construct the highly diastereoselective spiro-oxiranes exclusively and the highly competitive dioxolanes side-products did not form during the transformation. This is the first method wherein, the silver carbenoids of vinyl succinimides have been explored to access regio-, chemo- and diastereo- selective spiro-oxiranes.

Chapter 3: *A One-pot Access to Diastereoselective Benzoxepino[2,3-c]pyrroles via Formal (5+2)-Annulation of Vinyl diazosuccinimide with Ketones Under Silver Catalysis*

This chapter addresses a challenging strategy for the diastereoselective synthesis of dihydrobenzoxepines **5** *via* formal (5+2)-cycloaddition of vinyl diazosuccinimides **1** as 5-C synthons with different aryl/alkyl methyl ketones **2** under silver catalysis. The chapter gives a brief account on the importance of dihydrobenzoxepines and strategies to access the same along with oxiranes and dihydrofurans via different strategies.

It is known in the literature that in general vinyl diazo compounds **1** react with aldehydes to form a mixture of oxiranes **3** [*via* formal (2+1)-cycloaddition] and dihydrofurans **4** [*via* formal (3+2)- cycloaddition] through styryl carbonyl ylide **int-II** *via* metal-carbene intermediates. However, the direct synthesis of dihydrobenzoxepine derivatives **5** *via* an alternative formal (5+2)-cycloaddition using vinyl diazo compounds as 5-C-synthons is quite challenging and difficult task. The entropic factor and the intrinsic steric hindrance emanating from *Z*-configuration around the C=C bond between benzylidene group of **1** and the 'catalyst wall' makes it highly unfavorable for the desired transformation (see Figure 3.1 A and B).

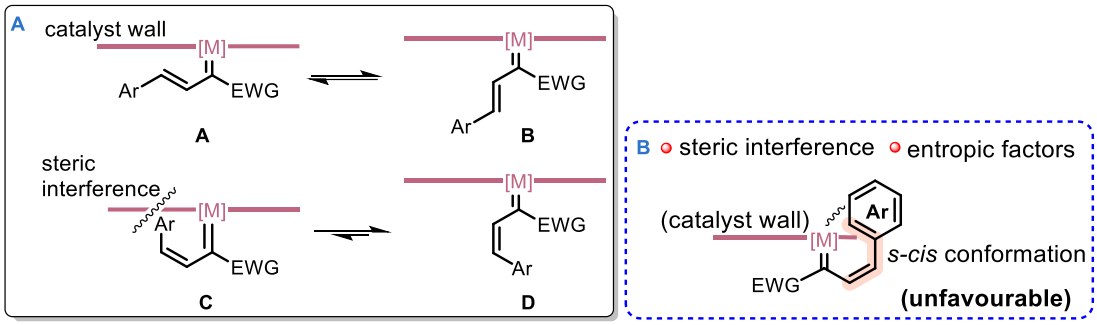


Figure 3.1. A) Conformational changes of acyclic vinyl carbenoid under the influence of catalyst; B) Challenges to access (5+2)-cyclo-annulation of acyclic vinyl diazo compounds.

Due to our continuous research interest in the arylidene diazo succinimides **1** and their utility in different synthetic transformations, we looked into the spacial arrangement of the compound **1a** through its molecular structure (Single crystal X-ray diffraction analysis data). The data revealed that the benzylidene group is oriented at ~34° dihedral angle (θ) [slightly twisted] to that of rest of the molecule across the C=C bond due to its favorable *Z*-configuration (see Figure 3.2). This interesting observation further excited us to envision the possible generation of carbonyl ylide and its further role in driving the 6π-electrocyclization to furnish the dihydrofurans **4** or 8π-electrocyclization followed by rearomatization to afford the dihydrobenzoxepines **5** (see Figure 3.2).

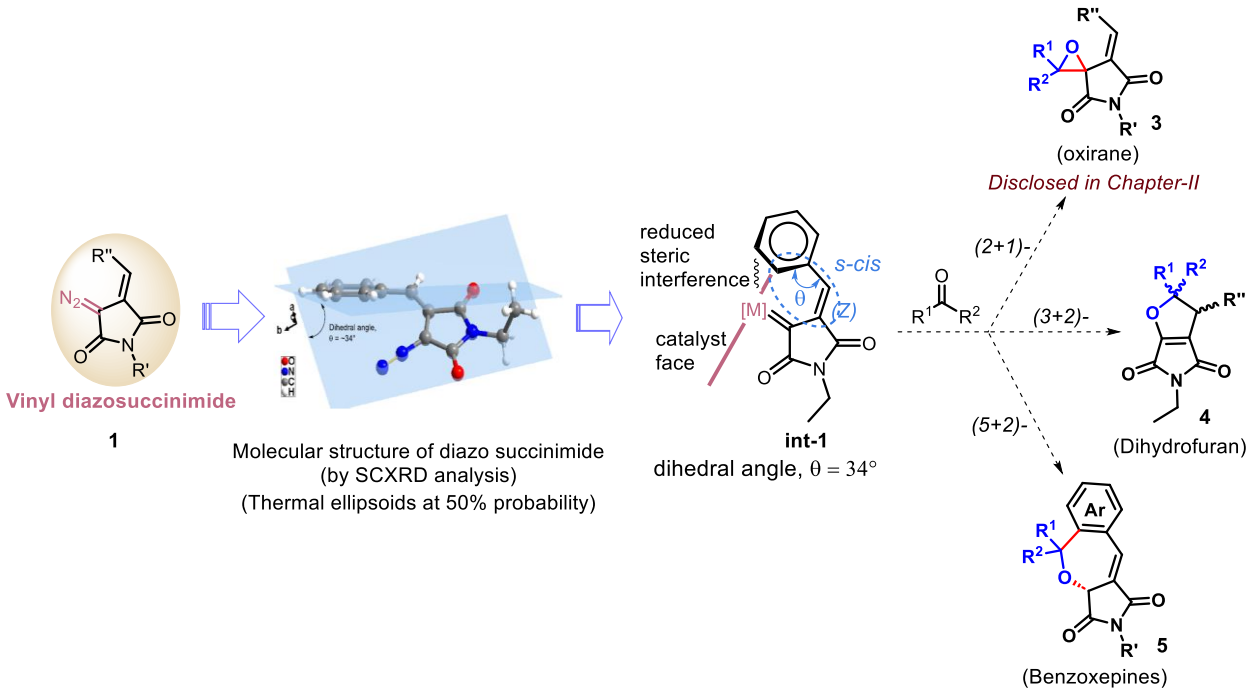
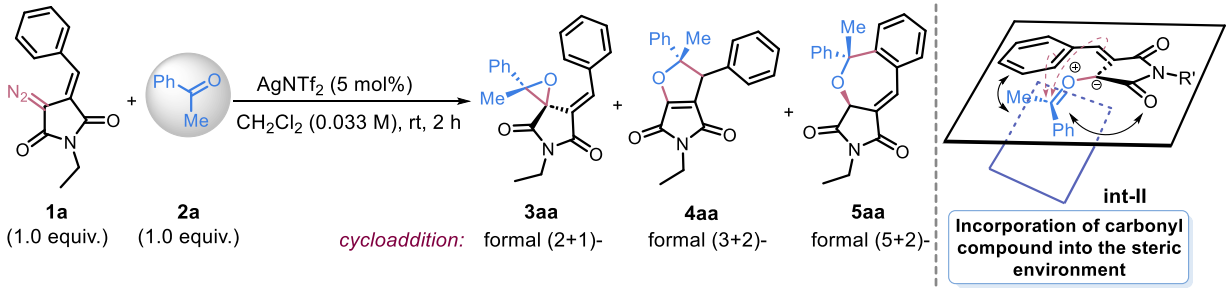


Figure 3.2. Characteristic properties of vinyl diazosuccinimide.

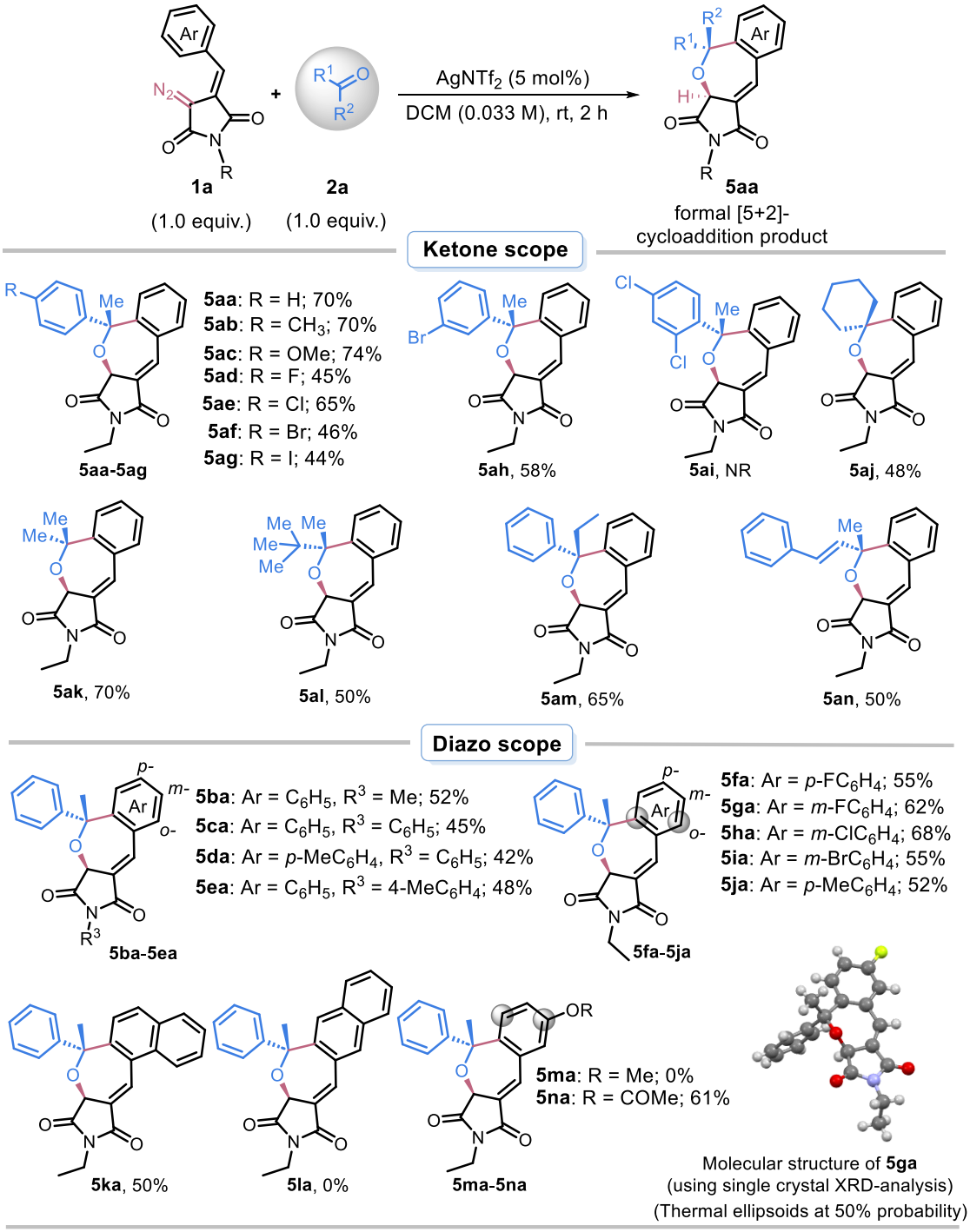
In order to validate the hypothesis, we carried out the systematic screening of various catalysts and other conditions carefully. Based on the screening, vinyl diazo compound **1a** (1 equiv.), acetophenone **2a** (1 equiv.), $AgNTf_2$ (5 mol%) in anhydrous dichloromethane at room temperature at inert atmosphere proved to be optimized reaction conditions to access the desired dihydrobenzoxepine **5aa** *via* formal (5+2) cycloaddition. Notably, we observed that the efficiency of the silver catalyst is also dependent on the non-nucleophilic and low coordinating counteranion (Tf_2N^-).



Scheme 3.1. Optimization of formal (5+2)-cycloaddition of methyl ketones with vinyl diazosuccinimide.

Having optimized the reaction conditions, we further explored the generality of this protocol. Different diazo arylidene succinimide **1a** were treated with various aryl/alkyl methyl ketones (**2a**-**2n**) containing electron-deactivating and -donating groups under the optimized reaction conditions to afford the desired dihydrobenzoxepines (**5aa**-**5an**) as a single

diastereomer with moderate to good yields (up to 74%) with high regio- and chemo-selectivity (Table 3.1). Interestingly, in all the cases we did not observe any competitive dioxolane and dihydrofuran side products even in trace.



[a]**Reaction conditions**: unless otherwise noted, the reactions were carried out with diazo compound **1a-1n** (1.0 equiv., 0.2 mmol), **2a** (1.0 equiv., 0.2 mmol), $AgNTf_2$ (5 mol%) and dry CH_2Cl_2 (0.033M) at room temperature (26° C) under argon atmosphere over 2 h. In all cases single diastereomer was obtained.

Table 3.1. Substrate scope studies with diverse methyl ketones for the formal (5+2)-cycloaddition.

Further, diverse of diazosuccinimides (**1b-1n**) were subjected to the optimized reaction conditions with acetophenone **2a**, and the desired dihydrobenzoxepines **(5ba-5na**) were obtained as a single diastereomer with moderate to good yields (up to 68%) with high regio- and chemo-selectivity (Table 3.1). In all the cases, we did not observe any competitive dioxolane and dihydrofuran side products even in trace.

Later, we carried out a series of control experiments including time-dependent NMR studies to have mechanistic insight into this (5+2)-cycloaddition. The experimental observations clearly revealed the *in-situ* generation of a transient metal-unbound carbonyl ylide that drives the reaction further.

In summary, we have successfully demonstrated an unmet challenge of utilizing the donor-/acceptor-type vinyl diazosuccinimides as 5-C-synthons under silver-catalysis to access very useful dihydrobenzo[5,6]oxepino[2,3-*c*]pyrroles in one pot. The protocol was found to be highly regio-, chemo- and diastereo- selective and worked well with both aliphatic as well as aromatic methyl ketones bearing electron deactivating as well as donating groups. The most plausible mechanism of this transformation has been deciphered by a series of control experiments and time-dependent NMR studies. The protocol also proved to be scalable on the gram quantity.

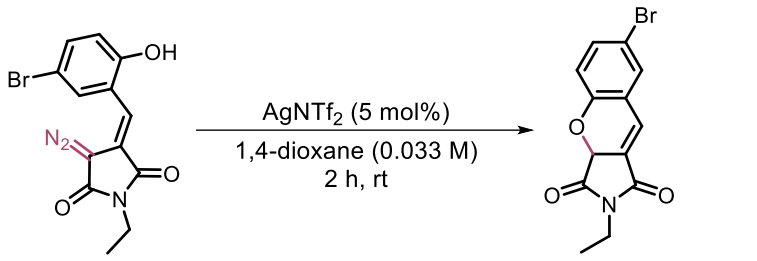
Chapter 4: *Metal-carbenoid vs photoinduced metal-free carbene – Tunable carbene reactivity of vinyl diazosuccinimides*

This chapter greatly describes the design and development of novel synthetic strategies to construct 2H-chromenes via both metal-carbene as well as photoinduced reactions. The use of modified vinyl diazosuccinimides has been effectively explored as carbene surrogates and their reactivity behaviors have been studied in detail under metal as well as visible light conditions (photolysis). Different 2H-chromene derivatives have been synthesized using both protocols by generating different spin-state carbenes. Gratifyingly, control reactions discovered remarkable tunable carbene spin state reactivity under both reaction conditions to furnish the 2*H*-chromenes with high regioselectivity. These two studies have been described in detail under two sections (Chapters 4A and 4B).

Chapter 4 – Section A: *Intramolecular O–H Functionalization under Silver Catalysis: Access to 2H-Chromene*

This Section A discloses the design and development of a novel synthetic protocol for the intramolecular O–H functionalization to access 2*H*-chromenes starting from vinyl

diazosuccinimides as a carbene precursor via metal-carbenoid intermediates. To begin with a brief account on the importance of 2*H*-chromenes and their subfamily dihydrochromeno[2,3-*c*]pyrrol-3(3a*H*)-one has been presented. Also, an overview of the previous synthetic protocols to access 2*H*-chromene subfamily and some of their limitations have been discussed. To overcome some of the challenges, we first envisioned the one-step synthesis of 2*H*-chromene congeners starting from *ortho*-OH substituted arylidene diazosuccinimides *via* intramolecular O–H functionalization (Scheme 4A.1).

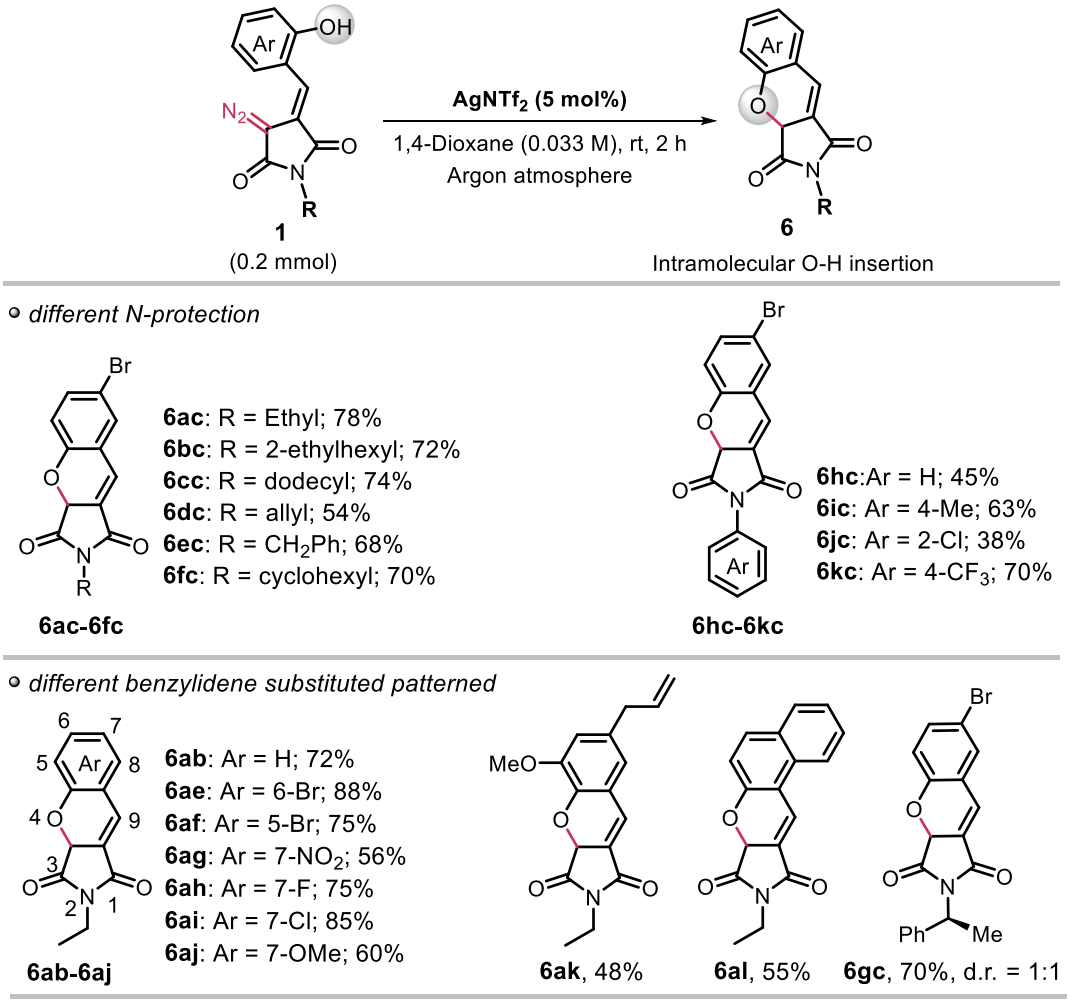


Scheme 4A.1. Regioselective intramolecular O–H functionalization via silver(I) catalysis.

The systematic screening of different reaction parameters such as catalysts, catalyst loading, solvents, temperature range, and reactant concentration has been carried out. Based on the exhaustive screening, 5-bromo-2-hydroxybenylidene diazosuccinimide **1ac** (0.2 mmol, 1.0 equiv.), silver(I) triflimide (5 mol%), in dry 1,4-dioxane at room temperature under inert atmosphere (2 h) proved to be the optimized reaction condition to afford the corresponding O–H functionalization product **6ac** in good yield (78% yield, Scheme 4A.1).

Having optimized the reaction conditions, we further explored the substrate scope of different hydroxy-substituted benzylidene succinimides in order to demonstrate the generality of this protocol. In this regard, a variety of *N*-alkyl/aryl substituted and *ortho*-OH substituted diazo arylidene succinimides (**1ac**-**1al, 1bc**-**1kc**) have been synthesized. These arylidene succinimides (**1ac**-**1al**) under the standard optimized reaction conditions afforded the corresponding dihydrochromeno[2,3-*c*]pyrrol-1,3(2*H*,3a*H*)-dione (**6ac**-**6al**) in moderate to very good yields (up to 88%, Table 4A.1). Among the *N*-substituted benzylidene succinimides, *N*-alkyl substituted benzylidene succinimides furnished the desired products (**6ac**-**6fc**) relatively in highest yields than that derived from *N*-aryl benzylidene succinimides (**6hc**-**6kc**). While the benzylidene succinimides having different substituents at the phenyl ring of benzylidene afforded the desired products in good to very good yields (**6ab**-**6aj**). While the benzylidene succinimides with disubstituted phenyl ring afforded the desired products (**6ak,**

6al) in relatively lower yields (Table 4A.1). Interestingly, *N*-(*S*)-phenyl ethyl benzylidene succinimide furnished the corresponding diastereoselective desired product **3gc** in good yield (70%) with d.r. = 1:1 (Table 4A.1).



[a]**Standard optimized reaction conditions**: **1** (0.2 mmol.) in dry 1,4-Dioxane (3 mL) was added dropwise into a solution of $AgNTf_2$ (5 mol%) in dry 1,4-Dioxane (3 mL) over 2 h, rt, argon atmosphere. [b]Yield of isolated products after column chromatography.

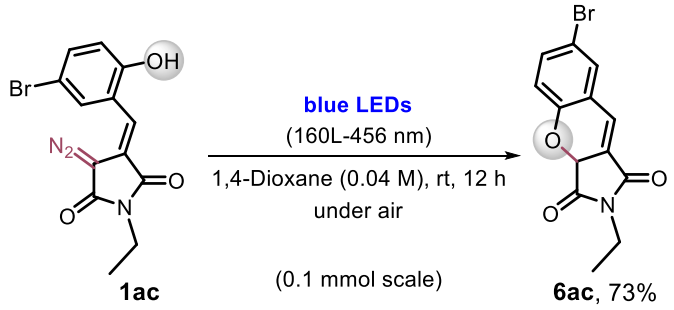
Table 4A.1. Substrate scope of the different hydroxy-substituted benzylidene succinimides

In summary, we have successfully developed the silver-catalyzed one-pot synthesis of regioselective synthesis of chromeno[2,3-*c*]pyrrole-1,3(2*H*,3a*H*)-diones (2*H*-chromenes subfamily). The reaction is believed to proceed through traditional transient silver-carbenoid species through its singlet carbene state to afford the desired products. Diverse *N*-substituted and arylidene-substituted diazosuccinimides tolerated reaction conditions. The protocol proved to be practical and is scalable on gram quantity.

Chapter 4 – Section B: *Photochemical Carbene Reactivity of Donor-/Acceptor-type Diazosuccinimide: An Access to 2H-Chromene*

This section describes the development of a novel strategy to access 2*H*-chromene derivatives from arylidene diazosuccinimides *via* photoinduced intramolecular hydrogen atom transfer (HAT) process. A detailed and systematic screening has been carried out to bring about the visible-light-driven selective and controlled O–H functionalization. The section presents a brief overview of the general photochemical reactivity of diazo compounds and their photolysis to generate carbenes of different spin states. Generation of singlet spin state carbene *via* traditional methods to photoredox chemistry using photocatalyst/photosensitizer to execute the reactions either *via* triplet carbene spin state or *via* radical pathway has been discussed. Some of the earlier pioneering and elegant methods related to this field have also been disclosed. Despite some of the advances, the development of photoinduced sensitizer-free triplet carbene generation is highly challenging and this has seldom been reported in the literature. Moreover, their generation and subsequent application in organic synthesis are even more challenging owing to the rapid singlet vs triplet spin state equilibrium.

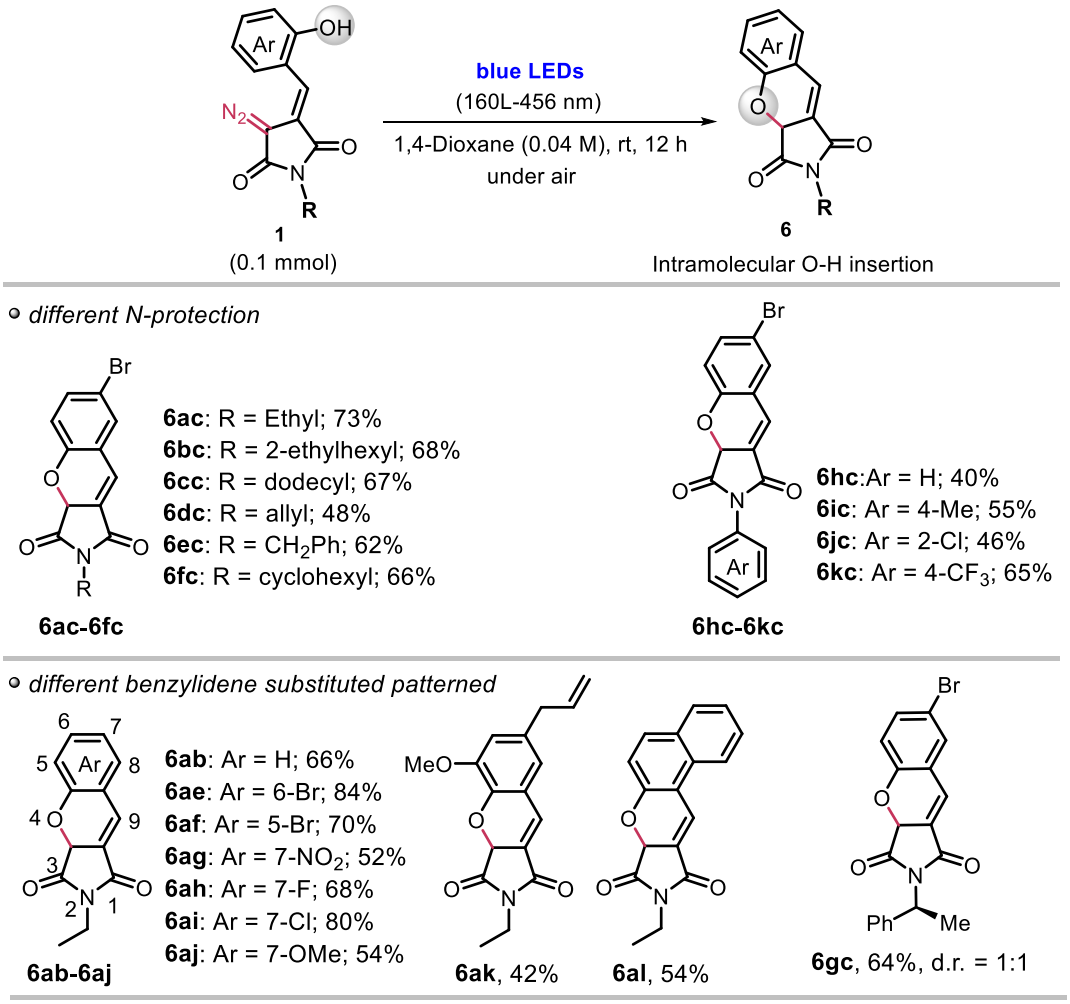
In order to explore this novel study, to begin with, we systematically studied the UV-vis absorbance properties of diazo succinimides. These data encouraged us to further explore their metal free-carbene reactivity under direct visible light irradiation. We looked into different reaction parameters such as light sources (wavelength and intensity), solvent, temperature, reactant concentration, etc. Based on the detailed and careful screening, the arylidene diazo succinimide **1ac** (0.1 mmol) in 1,4-dioxane (c = 0.04 M), Blue LEDs (456 nm) at room temperature under open air, turned out to be optimized reaction condition to afford the desired O–H functionalization product **6ac** in good yield with high regioselectivity (73% yield, Scheme 4B.1).



Scheme 4B.1. Photoinduced intramolecular O–H functionalization: An access to 2*H*-chromenes.

Having optimized the reaction condition, we further explored the substrate of the protocol in order to demonstrate the generality and wider applicability of the protocol. A variety

of arylidene succinimides (**1ac-1al**) under the optimized photoinduced reaction conditions afforded the corresponding dihydrochromeno[2,3-*c*]pyrrol-1,3(2*H*,3a*H*)-diones (**6ac-6al**) in moderate to very good yields (up to 84%, Table 4B.1). Among all the *N*-substituted benzylidene succinimides, *N*-alkyl substituted benzylidene succinimides furnished the desired products (**6ac-6fc**) relatively in highest yields than that derived from *N*-aryl benzylidene succinimides (**6hc-6kc**, Table 4B.1). While the diazo substrates with different substituents at phenyl ring of benzylidene afforded the desired products (**6ab-6aj**) in good to very good yields (up to 80%, Table 4B.1). The benzylidene succinimides having disubstituted phenyl ring furnished the desired products (**6ak, 6al**) in relatively lower yields (Table 4B.1). These observations were similar to that of metal-carbene transfer reactions (Table 4A.1). Interestingly, *N*-(*S*)-phenyl ethyl benzylidene succinimide furnished the corresponding



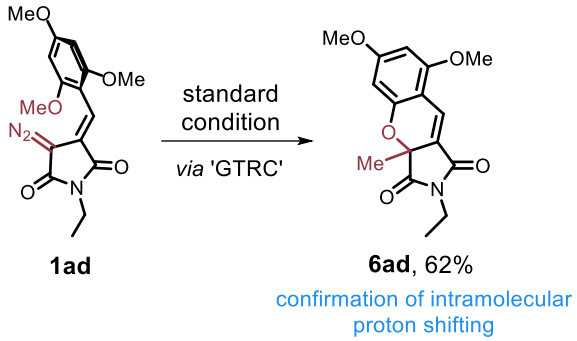
Reaction condition: Diazo succinimide **1** (0.1 mmol), a. r. grade 1,4-Dioxane (c = 0.04 M), blue LEDs (456 nm), under air, 27 °C.

Table 4B.1. Substrate scope studies for the photoinduced intramolecular O–H functionalization.

diastereoselective desired product **6gc** in good yield (64%) with d.r. = 1:1 (Table 4B.1).

We further planned to explore systematic studies to have an insight into the reaction mechanism of this visible light drive protocol. We carried out the labelling experiments as well as radical trapping experiments. The reaction proved to involve a radical intermediate as the reaction of **1ac** in the presence of butylated hydroxytoluene (BHT) did not afford the desired reaction and the corresponding radical trapped intermediate - succinimide-BHT adduct has been detected by HRMS. This result supported that the transformation must be involving the radical pathway. Later, we carried out the low-temperature EPR study by irradiating the carbene surrogate -diazo succinimide **1ab** in frozen matrix of 1,4-dioxane. Interestingly, the observation supported the direct photogeneration of a ground-state triplet carbene.

Later, in order to understand the mechanism in depth, we synthesized a methoxy-substituted diazo succinimide **1ad** and treated it under optimized reaction conditions. We observed an interesting product **6ad** in 62% yield (Scheme 4B.2). This remarkable result unequivocally supported the intramolecular 1,6-methyl group transfer just like the hydrogen of the hydroxyl group. Based on the above experimental observations and we strongly believe that transformation involves a group transfer radical cyclization "GTRC" process.



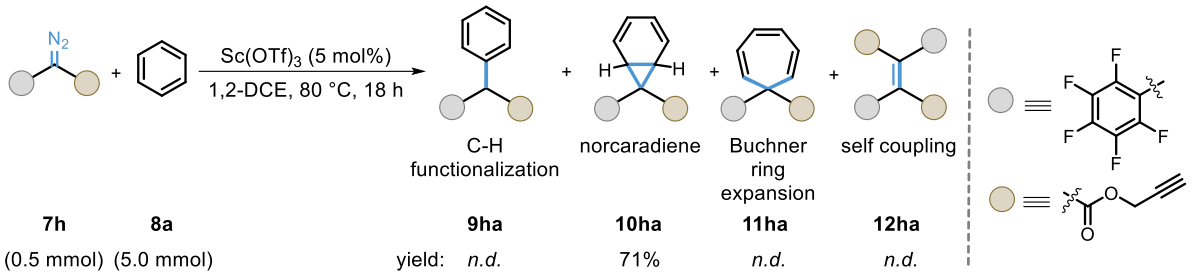
Scheme 4B.2. Control reaction with -OH protection.

In summary, this chapter successfully demonstrated the novel utility of modified diazo succinimides as a new class of reagents that are capable of reacting under the photoinduced reaction conditions. It has been proved that upon exposure to blue LEDs (456 nm), benzylidene diazo succinimides generate ground-state triplet carbene (without intersystem crossing - ISC). This is very important to highlight that this protocol doesn't depend on any photosensitizer. The intramolecular O–H functionalization protocol proved to be practical, and scalable to construct biologically relevant scaffolds 2*H*-chromenes.

Chapter 5: *Highly Regio- and Chemo-selective Arene Cyclopropanation using Donor-/Acceptor- type Propargyl α-pentafluorophenyl-α-diazoacetate via Scandium Catalysis*

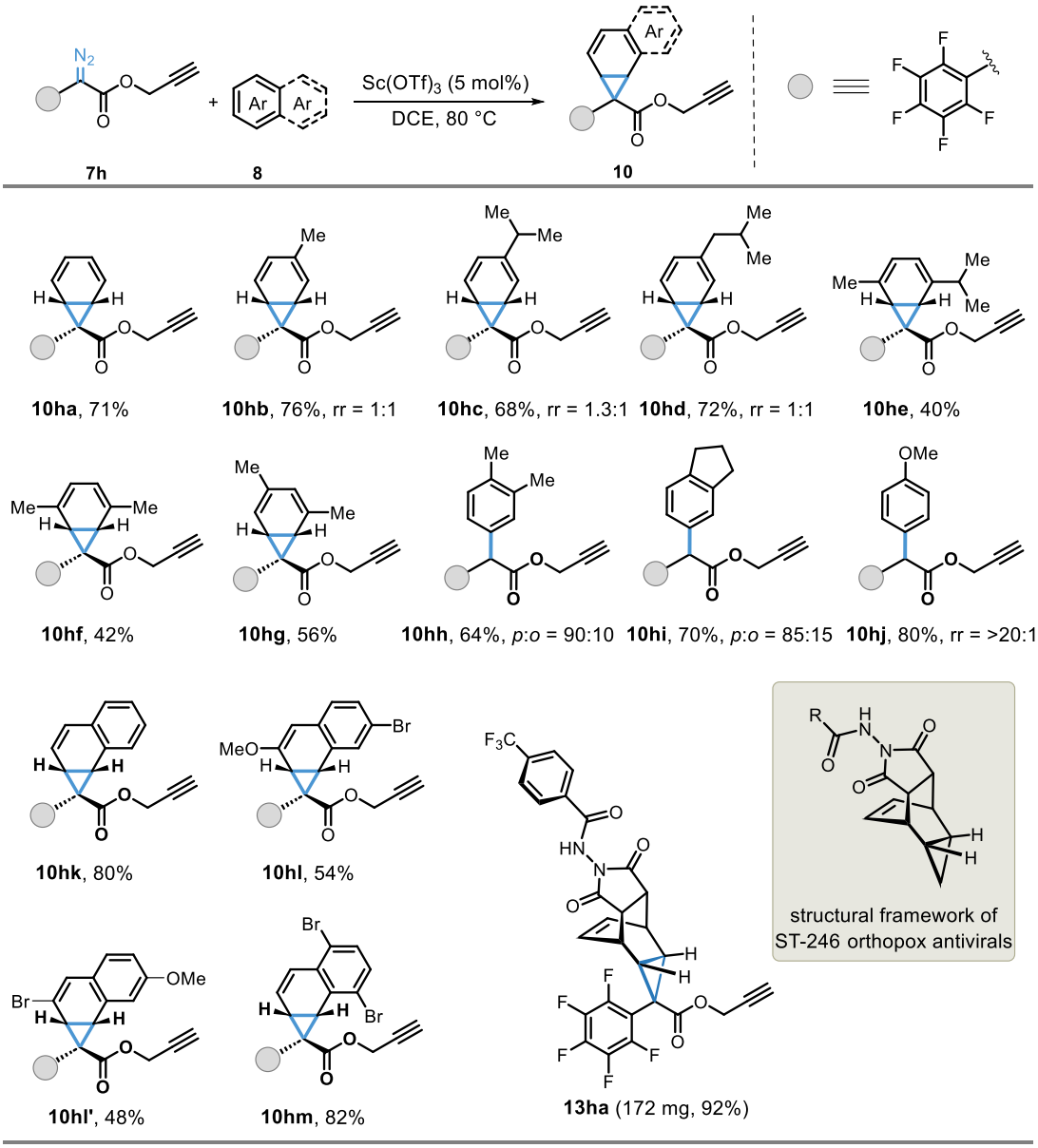
This chapter discloses the very first direct dearomatization of arenes by mobilizing one double bond at the expense of intrinsic aromatic stabilization to access norcaradienes (NCDs) *via* novel scandium catalysis. The design, development of novel donor-/acceptor-type diazoacetates, such as propargyl *α*-pentafluorophenyl-*α*-diazoacetates led to the novel reactivity and synthetic application under commercially viable scandium triflate. It is also important to highlight that protocol afforded the norcaradienes (NCDs) exclusively without any side reactions *viz.* Buchner-type ring expansion product cycloheptatrienes (CHTs) or C–H insertion (functionalization) products. This chapter begins with a brief account on the inherent challenges related to "undirected" strategy to access norcaradienes along with some of the general strategies for dearomatization. Most of the strategies relied on the acceptor-/acceptor-type diazoacetates owing to their strong π-electron acceptance property of the geminal groups which favors the CHTs⇌NCDs equilibrium to shift towards NCDs. The previous attempts and limitations for norcardiene formation utilizing donor-/acceptor-type diazoacetate and the limitation of Lewis acids for accessing norcaradienes have been discussed.

In order to overcome some of the limitations starting from donor-acceptor type diazoacetate for the arene cyclopropanation, we judiciously designed and developed the synthesis a few bench-stable diazoacetates by modifying both the aryl part and ester part. We screened various newly



Scheme 5.1. Highly diastereoselective synthesis of norcaradiene (NCD) via scandium catalysis.

developed bench-stable diazoacetates using different catalysts, solvents, temperature range, and additives. Based on the detailed investigation, propargyl *α*-pentafluorophenyl-*α*-diazoacetate **7h** (0.5 mmol), benzene **8a** (5.0 mmol), $Sc(OTf)_3$ (5 mol%), in 1,2-DCE at an elevated temperature (80 °C) under an inert atmosphere for 18 h proved to be the optimum reaction condition to afford the desired norcaradiene **4ha** in good yield with exclusive diastereoselectivity (71% yield, Scheme 5.1).



[a]Reaction conditions: diazo compound **1h** (0.5 mmol, 1.0 equiv.), arenes **2** (5.0 mmol), and $Sc(OTf)_3$ (5 mol%) was added in 1,2-DCE (2.5 mL) under inert atmosphere and reaction mixture was reflux at 80 °C; reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography.

Table 5.1. Substrate scope studies for the direct dearomatization to access norcaradienes (NCDs).

Having obtained the optimized reaction condition, we further explored the substrate scope in order to examine the generality and advantages of this protocol. In this regard, a variety of alkyl-substituted arenes (**2b-1j**) and polycyclic arenes (**2k-2m**) have been treated with corresponding were investigated utilizing propargyl α-pentafluorophenyl-α-diazoacetate **1h** under the optimized reaction conditions to afford the corresponding desired norcaradienes (**4hb-4hj**, **4hk-4hm)** in moderate to good yields (up to 82%, Table 5.1) with exclusive diastereoselectivity *via* good regio-controlled way. Most importantly we did not observe any

competing side-products emanating from Buchner ring expansion and C–H bond functionalization even in trace.

Later, as an application to the developed protocol, synthesized norcaradiene **4ha** has been further employed for transformation to access the bicyclic carbocycle scaffold which is core to ST-246 orthopox antivirals.

In summary, a robust and synergistic reagent-catalyst system has been developed for the direct efficient dearomatization of the electronically unactivated and activated arenes. After careful analysis, propargyl α-pentafluoro-α-diazoacetate has been designed and developed that is bench stable having the capability to drive the dearomatization when treated with arenes. The protocol proved to work well with various alkyl-substituted arenes as well as polyarenes systems under the optimized condition to furnish the different norcaradienes in moderate to good yield with good regio- and chemo-selectivity without the competitive side products.

*****

(Numbers of substrates and products in the synopsis are different from those in the thesis chapters. Please note that compound numbers have been assigned in the synopsis and subsequent chapters for the flow and convenience of the readers)

List of Publications

Included in the thesis

1. **Debasish Laha** and Ramakrishna G. Bhat* "Silver-Catalyzed Epoxidation of Aldehydes Using Donor-/Acceptor-type Vinyl Diazosuccinimides to Access Spiro-Pyrrolidinedioneoxiranes." *Asian J. Org. Chem.* **2020**, *9*, 918–921. ***#Top Cited Article 2020-2021 recognized by Wiley.***

2. **Debasish Laha,** Kajal B. Meher, Onkar S. Bankar, and Ramakrishna G. Bhat* Silver-Catalyzed One-Pot Access to Diastereoselective Benzo[5,6]oxepino[2,3-*c*]pyrroles *via* Formal (5+2)-Annulation of Donor-/Acceptor-Type Aryl Vinyl Diazosuccinimide with Ketones. *Asian J. Org. Chem*. **2022**, *11*, e202200062.

3. **Debasish Laha**; Onkar S. Bankar, Balu S. Navale, Supriyo Santra, Debashree Ghosh, and Ramakrishna G. Bhat* Intramolecular O–H Functionalization of Donor-/Acceptor-type Vinyldiazosuccinimide *via* Photoinduced Hydrogen Atom Transfer Reactions. *Manuscript is ready to be communicated.*

4. **Debasish Laha**, Onkar S. Bankar, Balu S. Navale, and Ramakrishna G. Bhat* Highly Regio-selective Arene Cyclopropanation using Donor-/Acceptor- type Propargyl *α*-diazoacetate via Scandium Catalysis. *Manuscript under preparation.*

Not included in the thesis

5. Rupesh A. Kunkalkar, **Debasish Laha** and Rodney A. Fernandes* De Novo Protecting-Group-Free Total Synthesis of (+)-Muricadienin, (+)-Ancepsenolide and (+)-3-Hexadesyl-5-methylfuran-2(5*H*)-one. *Org. Biomol. Chem.* **2016**, *14*, 9072–9079.

6. Trimbak. B. Mete, **Debasish Laha** and Ramakrishna G. Bhat* A One Pot Transition-Metal-Free Synthesis of Styrenyl Ethers from 2-Aryloxy/Alkoxy Acetophenones. *ChemistrySelect* **2018**, *3*, 7656–7659.

7. Balu S. Navale, **Debasish Laha** and Ramakrishna G. Bhat* Propargyl *α*-aryl-*α*-diazoacetates as Robust Reagents for the Effective C–H Bond Functionalization of 1,3-diketones via Scandium Catalysis. *Tetrahedron Lett.* **2019**, *60*, 1899–1903.

8. Balu S. Navale, **Debasish Laha**, Subhrashis Banerjee, Kumar Vanka and Ramakrishna G. Bhat* Highly Site-Selective Direct C−H Bond Functionalization of Unactivated

Arenes with Propargyl *α*-Aryl-*α*-diazoacetates via Scandium Catalysis. *J. Org. Chem.* **2022**, *87*, 13583–13597.

9. Balu S. Navale, **Debasish Laha** and Ramakrishna G. Bhat* Chemoselective C(sp^2)–H Bond Functionalization of Arenes Bearing Olefin or Alkyne Functionality with Propargyl *α*-Aryl-*α*-diazoacetates via Scandium Catalysis. *Manuscript under Preparation.*

10. Balu S. Navale, **Debasish Laha** and Ramakrishna G. Bhat* Decarboxylative C(sp^3)–H Bond Functionalization of *ß*-Keto Acids with *α*-Aryl-*α*-diazoacetates via Scandium Catalysis. *Manuscript is ready to be communicated.*

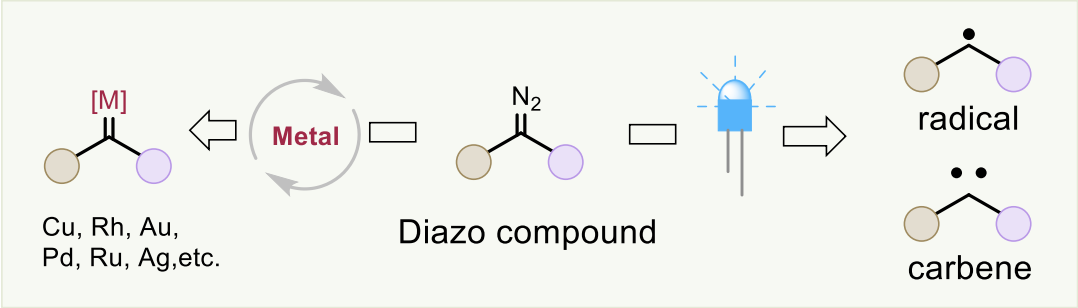
11. Onkar S. Bankar, **Debasish Laha**, Kajal B. Meher and Ramakrishna G. Bhat* Umpolung reactivity of Vinyl Diazosuccinimide. *Manuscript is ready to be communicated.*

Book Chapter

1. Book Name: "Handbook of CH-Functionalization (CHF)". Edited by: Dr. Debabrata Maiti Chapter Title: Site selective C–H bond functionalization with Diazo compounds (Carbenes). Authors: **Debasish Laha**, Javed Y. Shaikh and Ramakrishna G. Bhat*. Publisher: Wiley-VCH. ISBN: 9783527834242; https://doi.org/10.1002/9783527834242.chf0085.

Chapter 1

Diverse Reactivities of Carbenes and their Applications in Synthetic Strategies



Diverse Reactivities of Carbenes and their Applications in Synthetic Strategies

1

This introductory chapter presents a brief overview on the progress carbene chemistry and their great utility in the synthetic organic chemistry. The utility of reactive carbene species in the traditional reactions to various unprecedented transformations in age catalysis have been discussed. The carbene transfer reactions (especially, cycloadditions and functionalization strategies) via transition-metal catalysis (metal-carbenoid reactivity) as well as the novel photoexcited state reactivity of carbenes under visible-light (metal free-carbene reactivity) have been discloses. Controlling the carbene reactivity is the foremost parameter for the selective carbene transfer reactions and it's generally achieved by the combined effect of metal catalyst and ligand to implement successful reactions via singlet carbene intermediate. On the contrary, the application of free-carbene in organic synthesis, particularly, triplet carbene has gained very little attention from researchers across the globe. While the traditional singlet carbene reactivity relied on the use of specific metal complexes over the decades and the reactivity of triplet carbene under visible light in organic synthesis is underdeveloped and it is in the initial phase. Herein, in this chapter, traditional as well as modern strategies of carbene transfer reactions (in both spin states) generated from diazo compounds have been presented.

1.1. Introduction:

Divalent neutral carbon species called carbenes and are termed as reactive intermediates due to their fleeting existence. This coordinately unsaturated reactive species is inherently unstable in its free carbene state as it has incomplete octet. Carbene was first postulated by Eduard Buchner in 1903 during studies on cyclopropanation using ethyl diazoacetate in toluene.[1] Before that, in the early nineteenth century, when the quadrivalency of carbon was not even established, the very first attempt to generate parent carbene (methylene) was made by the dehydration of methanol by employing phosphorus pentoxide.[2] Later, Nef stimulated this field further with his "general methylene theory". [3] In the 1910s, Staudinger's ground-breaking work on the decomposition of diazo compounds and ketenes led to the first recognition of carbene as a *de novo* reactive species and revolutionised the carbene chemistry.[4]

Depending upon the electronic structure, carbene can be classified as singlet and triplet (two distinct spin isomers) carbenes. The two unshared valance electrons in the ground state of carbene can either be in the same orbital with antiparallel spin (i.e., singlet state) or in two distinct orbitals with parallel spins (i.e., triplet state). In the singlet state, the two unshared valance electrons reside on the sp^2-hybridized orbital with spin pairing and the another *p*-orbital is vacant thus making it to exhibit diamagnetic character. While carbene in the triplet state, both the p-orbitals are singly occupied and thus it exhibits paramagnetic character (see Figure 1.1A).

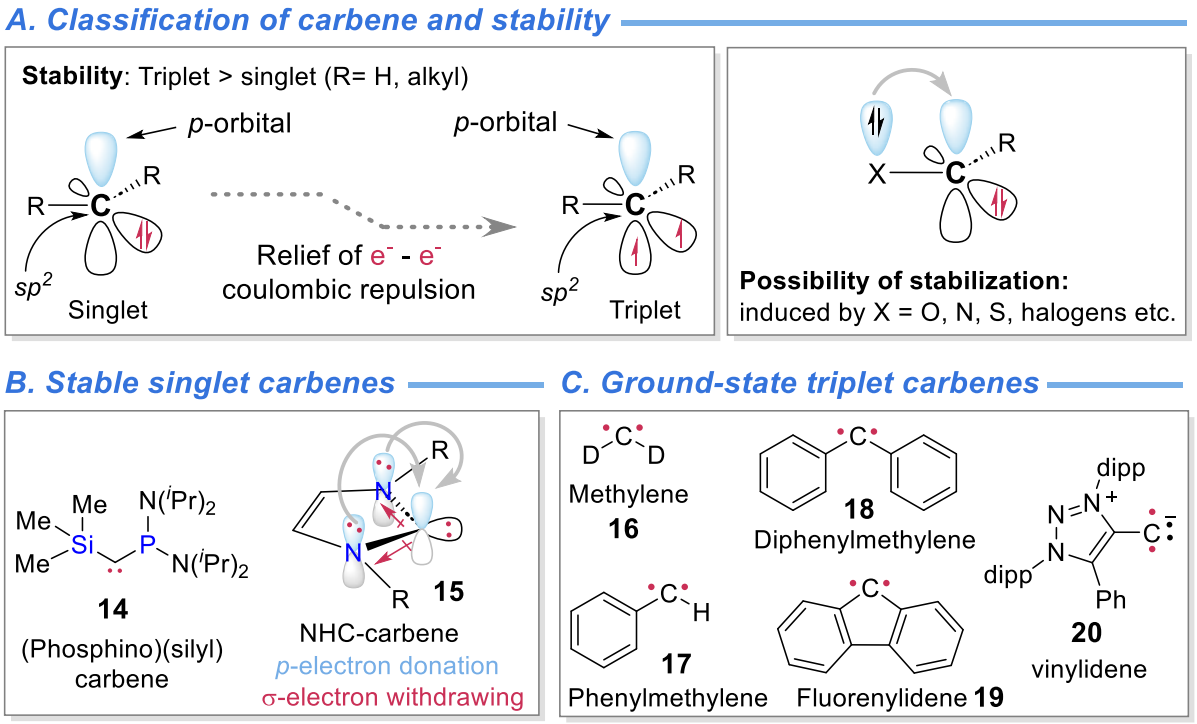


Figure 1.1. Classification of carbene, stability and their examples.

Triplet state carbene is typically more stable than singlet state carbene as it is relieved from the interelectronic ($e^- - e^-$) repulsion in the orbitals as ascribed according to Hund's maximum spin multiplicity rule. Though singlet carbene is energetically higher, it is possible to stabilized, if its energy can be significantly reduced. The carbene species will be stabilized, if any functionalities can donate a pair of its electrons to the carbene carbon center by the delocalization with the empty *p*-orbital (see Figure 1.1A). In the 1950s, Breslow[5a] and Wanzlick[5b] realized that the inclusion of amino substituents on carbene could be substantially enhance its stability and however, they were unable to isolate a "monomeric" carbene (carbene is generally prone to undergo dimerization). In 1988, Bertrand contributed significantly towards the first stable singlet carbene [(phosphino)(silyl)carbene][6a] and this remarkable result

became the turning point for the few stable heterocyclic carbenes[6b] (see Figure 1.1B). Interestingly, in the year 1997 Tomioka discovered the persistent triplet carbene.[7] However, it is quite difficult to stabilize the triplet carbene either by a polar effect internally or externally since it is an electronically neutral species. Triplet carbene can only be stabilized with the aid of a spin-delocalizing substituent. Owing to this, a very few have been reported till date on the of ground state-triplet carbenes (see Figure 1.1C).[8] Moreover, the discovery of persistent triplet carbene is not only of fundamental interest, but also it has numerous and interesting applications due to its paramagnetism properties.[8b,c] Owing to the importance, the generation of persistent triplet carbene is currently a prominent topic of research.[9]

1.2. Classification of organometallic carbenes or Metal Carbenoids:

The concept of double bond between transition metal and carbene carbon led to one of the useful and important organometallic complexes. In 1915, Chugaev and coworkers discovered the first metal-carbene complex *viz.* platinum(II) isocyanide complex (see Figure 1.2A),[10a,b] however due to lack of spectroscopic techniques at that time the structure was not characterized. Nevertheless, about half a century later the structure of the metal-carbene complex was elucidated by NMR and X-ray analysis.[10c]

In 1964, the notion of a metal-carbon double bond was first unambiguously disclosed by Fischer and Maasböl through the synthesis of Tungsten complex $(CO)_5W{=}C(Ph)(OMe)$ (see Figure 1.2B).[11] This metal complex was later named as Fischer-type carbene in which carbene display singlet carbene like character with filled sp^2-hybridized (σ-electrons) orbital and an unoccupied *p*-orbital. The carbene donates its σ-electrons to the vacant *d*-orbital on the metal center, which in turn participates in π-back donation with the vacant *p*-orbital of carbene which is electrophilic in nature (see Figure 1.2C).[11,12] This type of metal-carbene complexes (Fischer carbene) are usually found with middle or late transition metal elements having low oxidation states.

Later in the year 1974, Schrock reported alkyl carbene complexed with tantalum (V), having different character unlike Fischer carbene which later named as Schrock type metal-carbene complex (see Figure 1.2B).[13] In this type complex, the two covalent bonds are formed

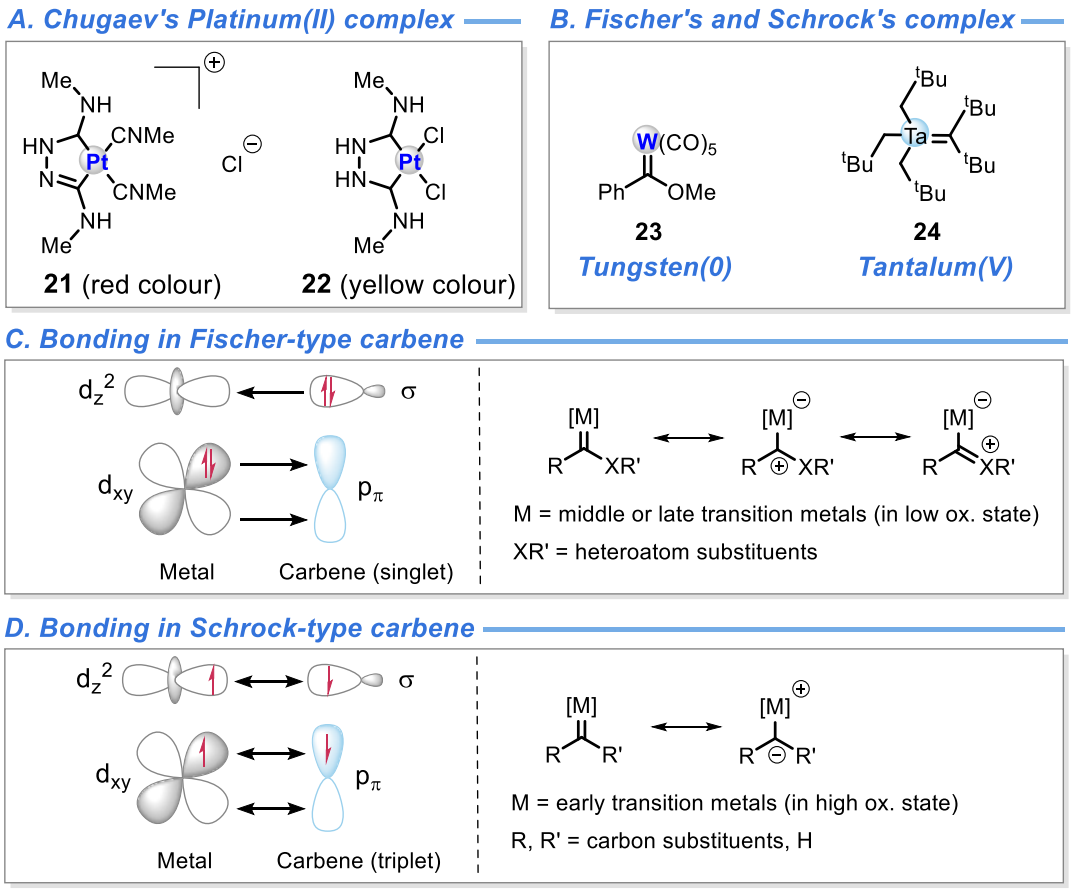


Figure 1.2. Type of organometallic carbenes and their bonding interactions.

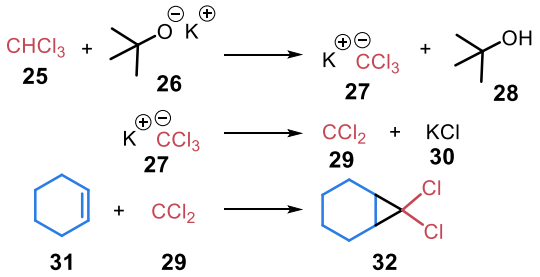
between metal (*d*-orbital) and carbenic carbon. Schrock type of metal-carbenes is generally formed from early transition elements having higher oxidation states and they are nucleophilic in nature (see Figure 1.2D).

1.3. Carbene precursors and generation of carbene:

The synthesis of carbene is generally achieved by two fundamental processes *viz.* a) elimination reaction and b) fragmentation reaction. Carbene is formed as a reactive intermediate in situ when functionalities directly attached to the carbon center surrogate of carbene are broken as a result of photolysis, thermolysis or reacting with metal complexes. Reagents with high entropic or enthalpic driving forces are often required to access this valuable reactive species. Some of the few selected major routes have been highlighted in the next section.

1.3.1.1. *α*-Elemination:

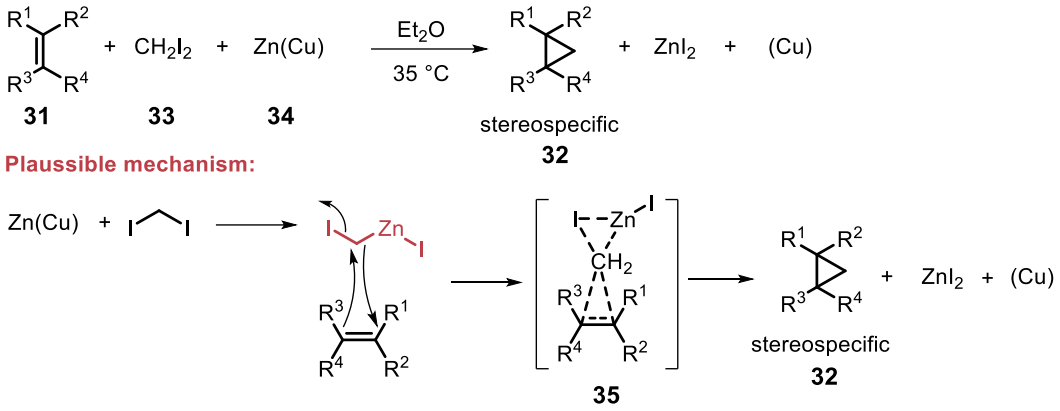
In mid of 19th century, the sensitivity of chloroform towards alkaline medium (aqueous as well as alcoholic) has already been disclosed by Geuther,[14a] Hoffmann[14b] (in the reaction of isonitrile formation) and Reimer and Tiemann[14c] (in the formylation reaction of phenol). However, the formation of "carbon dichloride" as a reactive intermediate in situ was disclosed about a century later by Hine[14d,e] by the kinetic studies of chloroform under alkaline condition. Later, in 1951, Doering[14f] coined the term "dichlorocarbene" for the intermediate :CCl_2 in a quenching experiment with cyclohexene (see Scheme 1.1).



Scheme 1.1. Studies on the existence of dicholoromethene intermediate (:CCl_2).

1.3.1.2. Simmon-Smith reaction:

As an alternative approach, Simmon-Smith reaction[15] enables a versatile stereospecific synthetic strategy towards cyclopropanation by the incorporation of the smallest divalent carbon (:CH_2) in presence of zinc-copper couple system. This was the first protocol for ever to demonstrate the formal addition of unsubstituted methylene group to cyclic alkene. The *gem*-dihalide (diodo methane) first reacts with zinc-copper couple to form an unstable zinc carbenoid intermediate, which is further trapped by alkene in a stereospecific manner to afford the cyclopropanted product (see Scheme 1.2).



Scheme 1.2. Simmon-Smith protocol.

1.3.2. Fragmentation reactions:

1.3.2.1. Diazo decomposition:

In the year 1883, Curtius documented the preparation of the very first diazo compound *viz.* ethyl diazoacetate.[16] Since then, synthesis and utility of diazo compounds have grown significantly and they have been proven as one of the most versatile reagents owing to their diverse applications in organic synthesis (see Figure 1.3). Aliphatic diazo compounds are behaving as surrogates for the reactive carbene intermediates as their decomposition under the influence of thermal, photoinduced, and metal catalysts render the thermodynamically stable dinitrogen extrusion leading to either free carbene entities in their singlet or triplet state or to the metallo-carbene.[17]

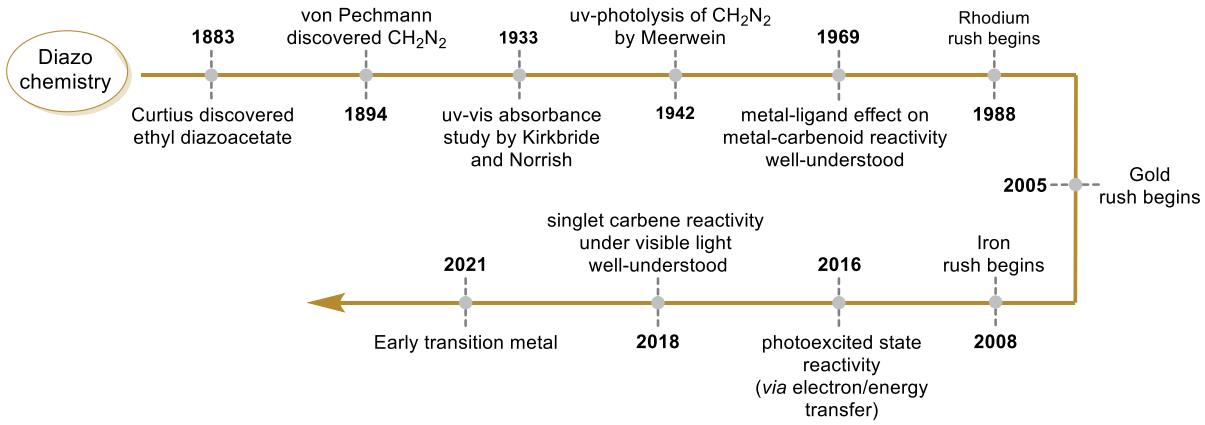
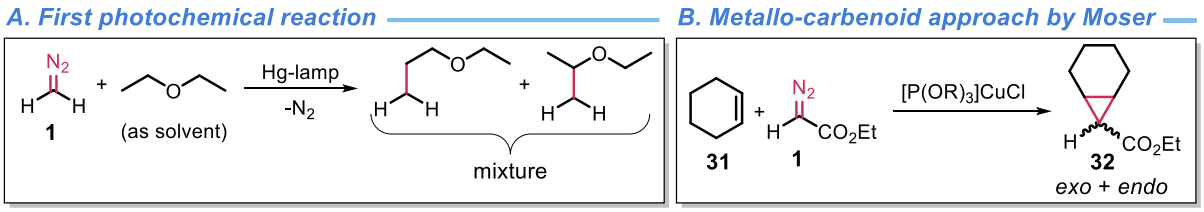


Figure 1.3. Progress in diazo chemistry over a century.

In the year 1894, von Pechmann generated the diazomethane (CH_2N_2) and aptly described it as yellow coloured gas.[18a] Later, in 1933 Kirkbride and Norrish carried out the UV-vis absorption study of gaseous CH_2N_2.[18b] In 1942, Meerwein[18c] for the first time reported the photolysis of diazomethane in diethyl ether solvent under UV light irradiation (see Scheme 1.3A). The methylene gas formed underwent rapid unselective C–H functionalization with diethyl ether. This is the very first example of a carbene transfer reaction ever performed photochemically. Years later, a few carbene transfer reactions under UV-photochemical conditions have been documented.[19] However, low level of selectivity enormously affected this process and did not yield much of success though set a bench mark.

Nevertheless, the transition-metal-catalyzed metallo-carbene transfer reaction turned out to be a promising alternative. Due to their comparative stability, the metallo-carbene transfer reactions turned out to be selective as well. In 1969, Moser[20] reported the copper-

catalyzed decomposition of ethyl diazoacetate that generates carbene in situ that reacts with cyclohexene to furnish the corresponding cyclopropanation product (see Scheme 1.3B). Also, demonstrated the effect of metal-ligand to bring about the successful metal-carbene transfer reaction. This reaction made a paradigm shift as it proved to be considerably better in terms of reactivity, selectivity in comparison to the UV-mediated photolysis approach.



Scheme 1.3. Initial attempts with diazo compounds.

Since this milestone achievement, a vast majority of metallo-carbene transfer reaction has been investigated based on the catalyst-ligand development and selection to render controllable reactivity and selectivity in these reactions. Initial advances were mostly made in the intramolecular processes.[21] However, with the time many state-of-the-art methods on the "undirected" strategy for the unactivated C–H bond functionalization has been developed. Inactivated systems such as alkanes and benzenoid substances have been utilized for the site-selective as well as stereo-selective C–H bond functionalization not only by judicious development of catalysts but also modulating the electronic and steric properties of diazo compounds (see Figure 1.4; see section 1.3.2.2A and 1.3.2.7 for selected examples).[22] Moreover, the bond dissociation energy (BDE) of the C–H bond being functionalized and the steric environment of the substrates are key determining factors for the overall transformation.[23]

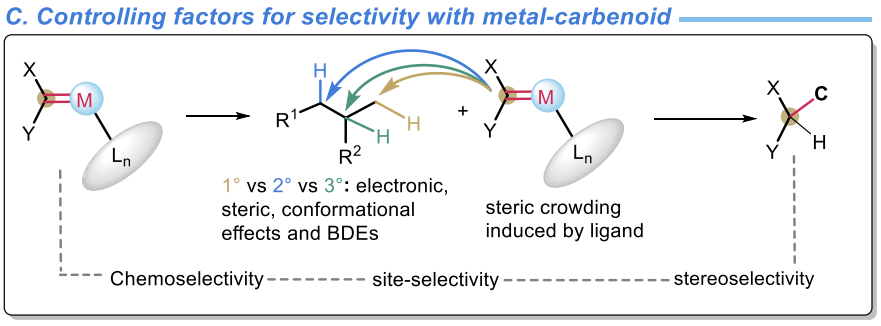
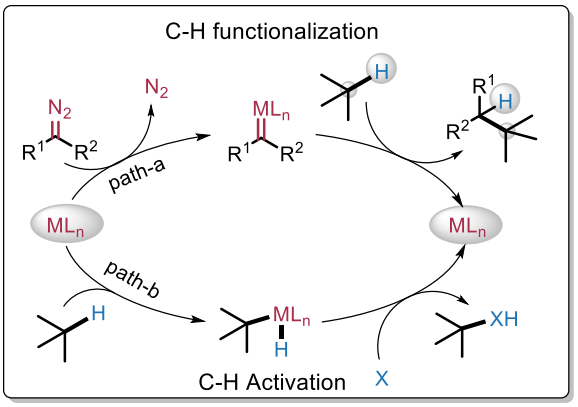


Figure 1.4. Controlling factors for metal-carbenoid reactivity.

Even though the outcome of metallo-carbenoid-induced C–H bond functionalization is similar to that of traditional C–H activation process, yet these are slightly different from the mechanism

point of view (see Scheme 1.4).[24] In the traditional C–H activation reaction metal directly interacts with the alkane C–H bond and activates.[25] While in case of metal-carbenoid-induced reaction, it has been understood that metal atom does not directly interact with the alkane C–H bond, but the metal interacts with reactive carbene (formed from the diazo compound) to form active transient metal-carbenoid which further interacts with the alkane C–H bond to furnish the C–H bond functionalized product.[22,24]



Scheme 1.4. Traditional C–H activation vs metal-carbenoid induced C–H bond functionalization.

1.3.2.2. Classification of diazo compounds:

1.3.2.2A. Progress on Metallo-Carbenes

Recent studies have demonstrated that the reactivity of metallo-carbene intermediates are not only governed by metal/ligand influence but also their reactivity is significantly modulated by the functional groups that are directly attached to the diazo carbon or carbene carbon center (see Figure 1.4).[26] Based on the electronic properties of the functionalities on the diazo compounds, they are typically classified into three major categories *viz.* acceptor-, acceptor-/acceptor- and donor-/acceptor-types (see Figure 1.5).[27] These functionalities on the metal-carbenoids or free-carbene can remarkably tune the reactivity of the same. The presence of 'acceptor' group in the first two types of carbenes (metal-carbenoids) make them highly reactive in nature as the carbene carbon center do not get stabilized by 'acceptor' groups. On the contrary, the resonance effect driven from the donor substituent aids in stabilizing the donor-/acceptor- substituted carbene species quite well.[28] Few representative examples[23] of metal-carbene based reactions from the beginning of this area have been depicted in Scheme 1.5.

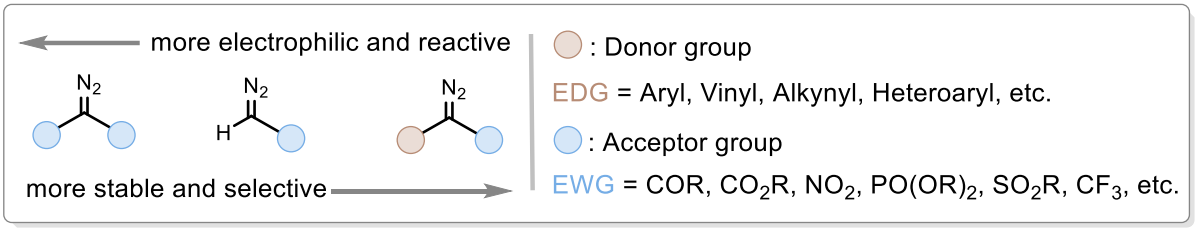
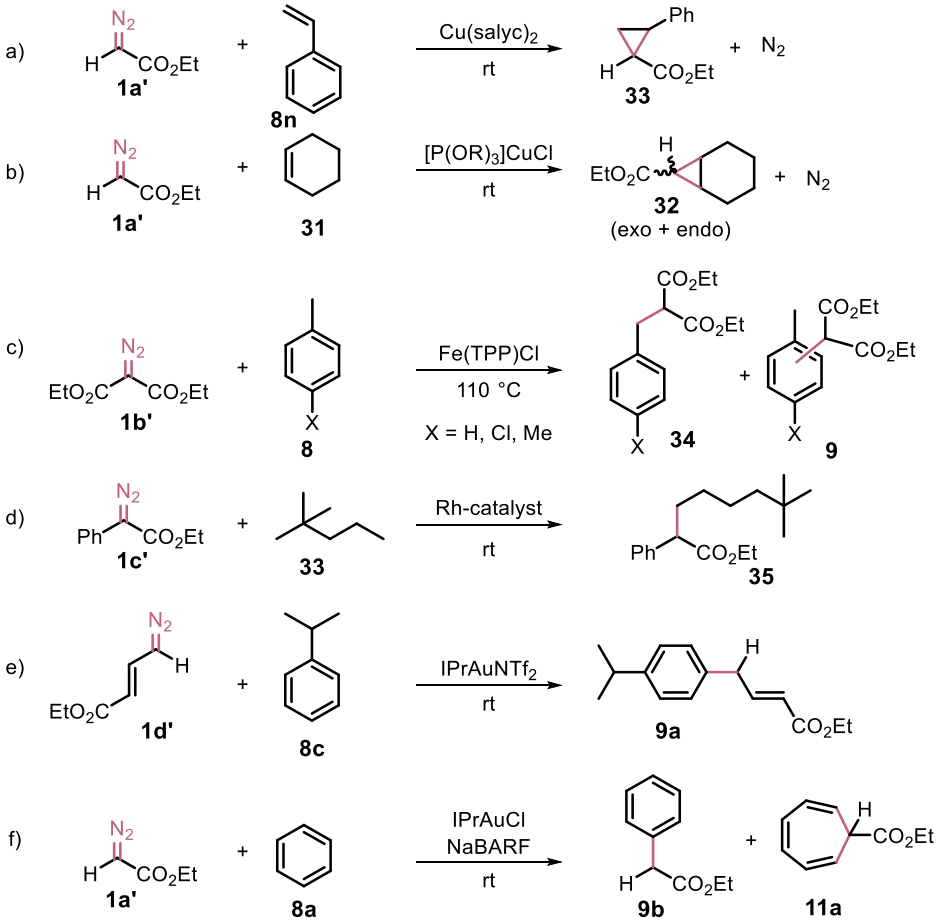


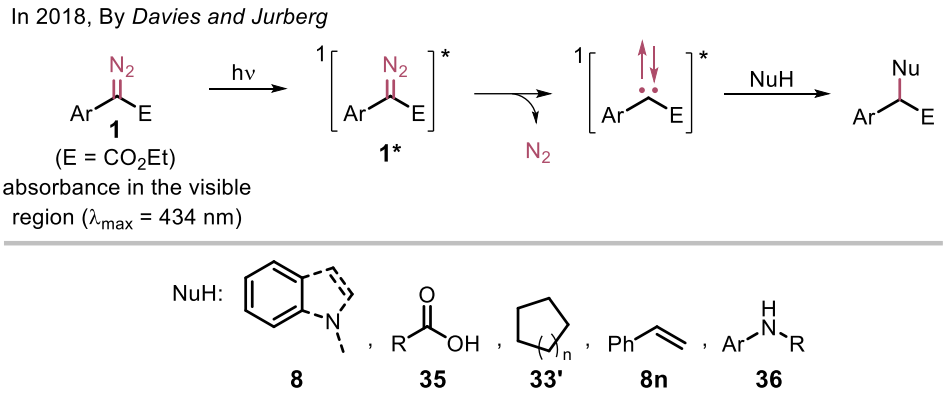
Figure 1.5. Classification of diazo compounds: stability and reactivity trend.



Scheme 1.5. Few representative examples in the progress of metal-carbene based reactions.

1.3.2.2B. Progress on the Photochemical carbene transfer reaction:

The fundamentals on the photolysis of diazo compounds under visible light utilizing matrix isolation and ultra-fast spectroscopic techniques have been well-explored to have an insight into the geometrical as well as electronic properties of carbenes.[29] However, the photolysis of diazo compounds under visible light irradiation to mediate the useful organic transformations has long remained elusive until a very recent remarkable study by Davies and Jurberg (Scheme 1.6).[30]



Scheme 1.6. Photolysis of aryl diazoacetate: singlet carbene reactivity.

This study illustrated the photolysis of aryl diazoacetate that absorbs in the visible region (blue region) and that can further undergo various organic transformations *via* singlet carbene generation. Interestingly, this study further differentiates aryl diazoacetates from the other diazo compounds which mainly require UV light for the direct photoexcitation. Very recently, synthetic applications for the visible light-promoted direct photolysis of a few other diazo compounds have also been reported based on this concept that proceed *via* singlet carbene intermediate (see Figure 1.6).[31]

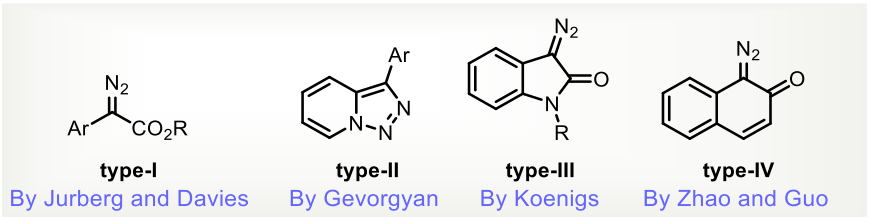
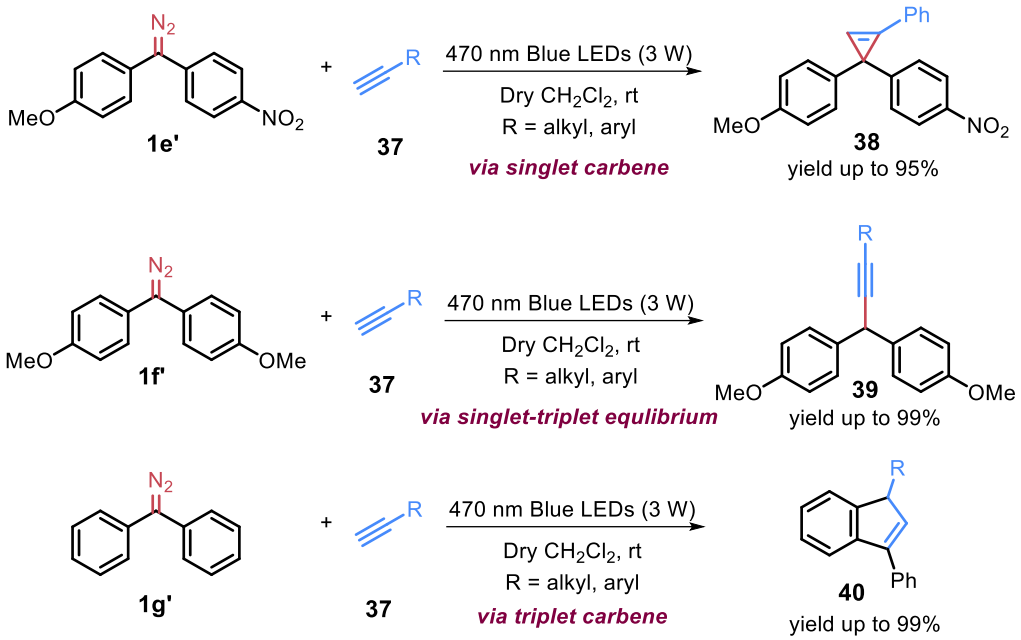


Figure 1.6. Photolysis of diazo compounds explored *via* singlet carbene intermediate.

Very recently Koenigs and coworkers[32] have documented a new type of diazo compounds- diaryl diazoalkanes which display an interesting and unprecedented reactivity when exposed to visible light irradiation. Depending upon the pattern of substituents directly attached to the carbene carbon center, they undergo reactions either via triplet carbene or singlet carbene or through the singlet-triplet carbene equilibrium to afford different products (see Scheme 1.7). These results further supported the photochemical reactivity of free-carbene in the absence of any photocatalyst or sensitizer. This behaviour is greatly influenced not only by the electronic as well as steric properties of its functionalities on diazo compounds, but also it is dependent on the solvent characteristics.[33]

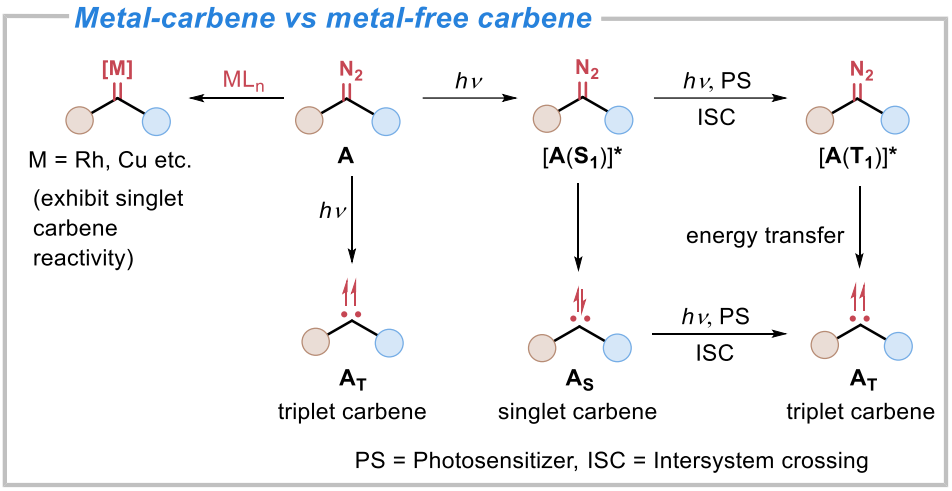


Scheme 1.7. Carbene (in both spin states) reactivity under photochemical conditions.

Notably, in the last few years, a tremendous breakthrough in the photochemical reactivity of diazo compounds has been achieved. A quantum progress has been made from the classical Wolf rearrangement to photochemical singlet as well as triplet carbene reactivity, photoinduced proton transfer reaction (PPT), and eventually the radical chemistry.[34] Some of the related examples are discussed in details later in the Chapter 4B.

1.3.2.3. General mechanism for photochemical carbene reactivity:

The general photochemical pathway[34b] has been depicted below while comparing with the metallo-carbene (see Scheme 1.8). The diazo compound **A** first photochemically gets excited to its singlet excited state [**A**(S_1)]*. This excited state diazo compound [**A**(S_1)]* can have two different fates under photolysis. Either the excited diazo compound [**A**(S_1)]* could undergo photolysis to form singlet carbene $\mathbf{A_S}$ by the extrusion of dinitrogen or it follows two photosensitized pathways such as singlet carbene $\mathbf{A_S}$ undergoes intersystem crossing (ISC) to triplet carbene $\mathbf{A_T}$ or *via* intersystem crossing (ISC) to its triplet excited state [**A**(T_1)]* followed by the nitrogen gas extrusion to triplet carbene $\mathbf{A_T}$. In another alternative pathway, the diazo compound **A** can also undergo direct photoinduced triplet carbene generation without the use of any sensitizer.



Scheme 1.8. Diazo decomposition: possible photochemical pathway to free-carbene.

1.3.2.4. Diazo compounds and their importance:

Diazo moiety is numerously found in few natural products and pharmaceuticals and they exhibit tremendous biological importance.[35] For examples, kanamycin D, isolated from *Streptomyces murayamaensis* in 1970 shows anti-microbial activity against Gram-positive bacteria;[36a] DON and azaserine are natural amino acids containing diazo group.[36b] Both these have been isolated from *Streptomyces* cultures and both display antibiotic and anti-tumor inhibitory activies.[36b-c] Besides, diazo compounds have long been used as chemical reporters[37a] as well as they have been utilized in incorporating into biomolecules as photoaffinity probes (see Figure 1.7).[37b]

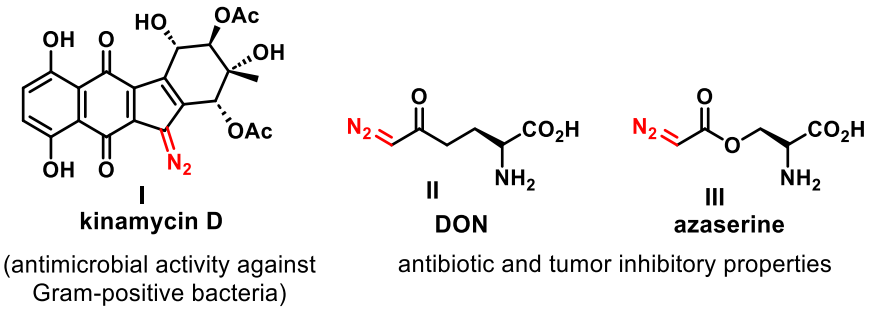


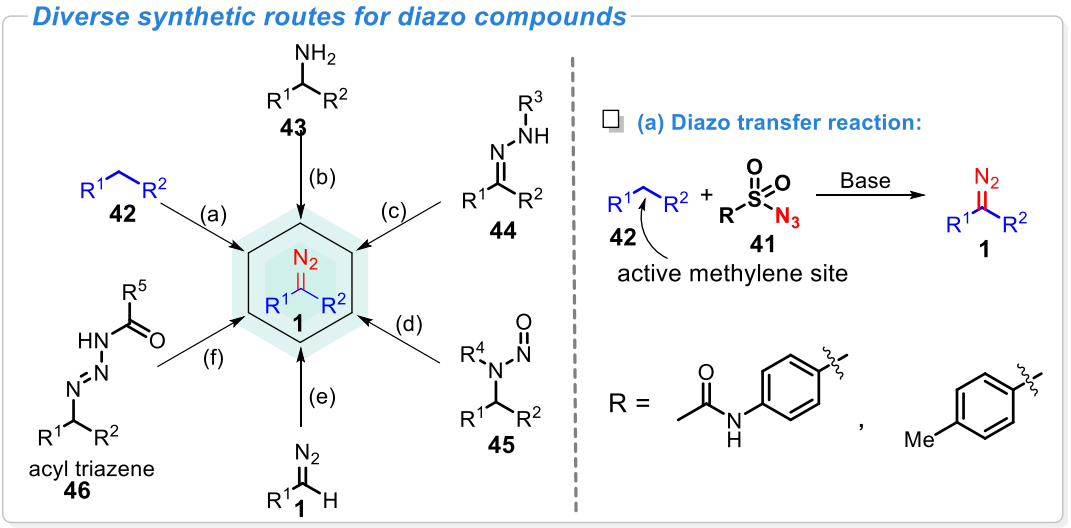
Figure 1.7. Naturally occurring compounds with diazo moiety.

1.3.2.5. Synthesis of diazo compounds:

Owing to the importance of the diazo compounds, many methods have been developed for the effective synthesis of diazo compounds. Some of the selected methods are (a) diazo transfer,[38] (b) diazotization,[16,39] (c) hydrazone decomposition[40a] or hydrazone oxidation,[40b] (d) rearrangement of *N*-alkyl *N*-nitroso compounds,[41] (e) 1,3-disubstituted acyl (or aryl) triazine

fragmentation,[42] and (f) elaboration of other diazo compounds (see Scheme 1.9).[43]

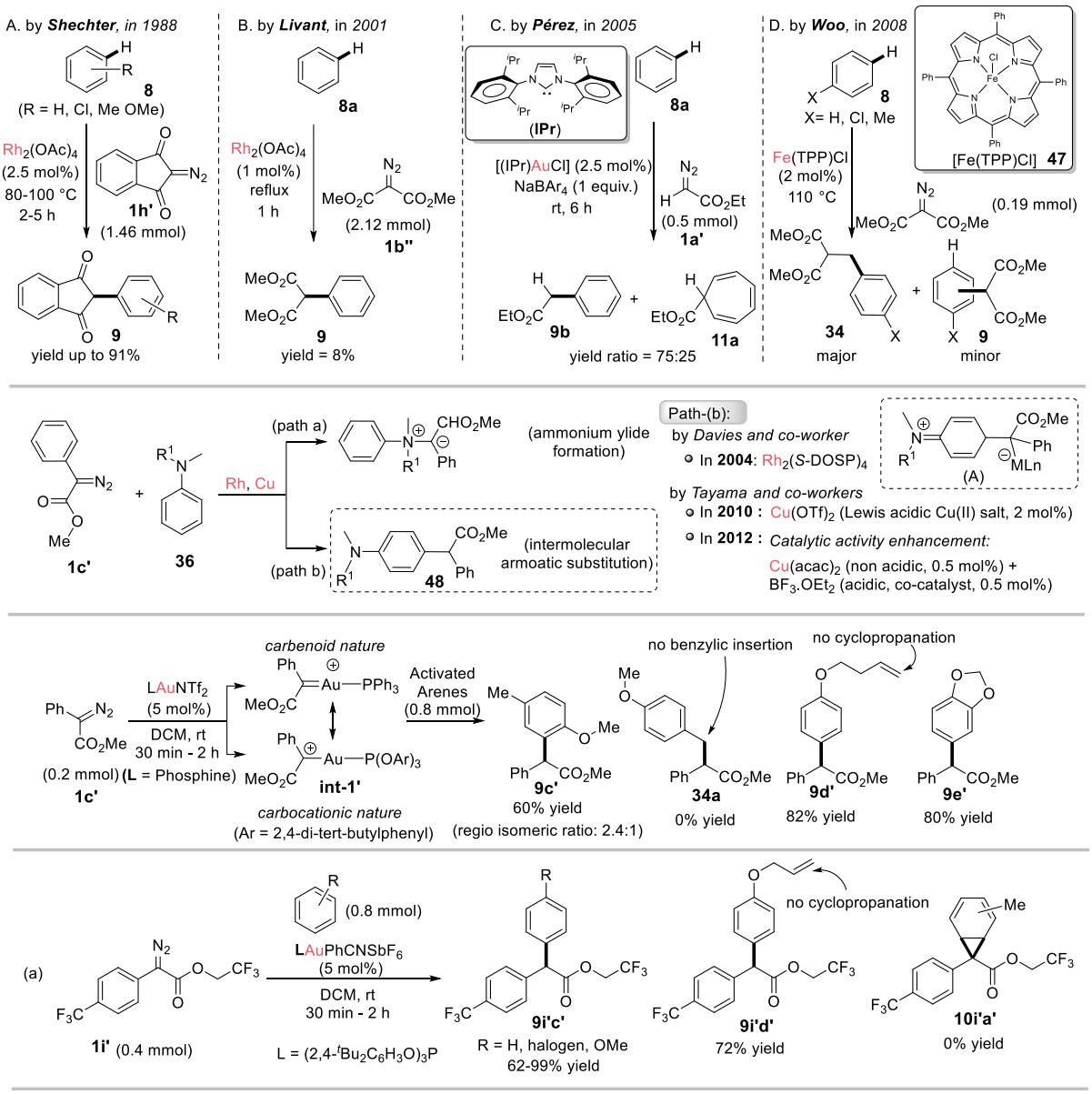
However, the most effective and reliable synthetic method is considered to be the diazo transfer process. Due to the low pK_a of a proton in the acceptor carbon, it can be treated with a mild base which is also necessary for chemical biology aspects. *α*-Methylene carbonyl compounds on treatment with diazo transfer reagent such as *p*-acetamidobenzenesulfonyl azide or tosyl azide in presence base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) furnishes the corresponding diazo compound.[38]



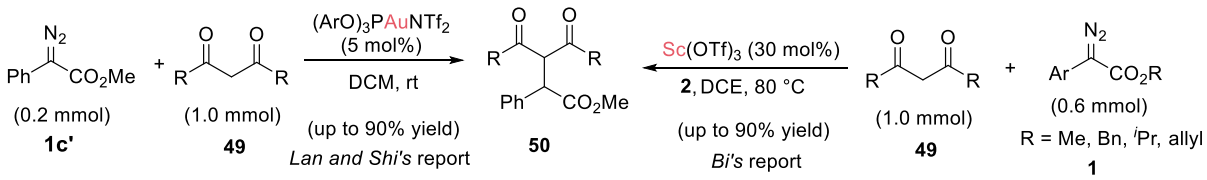
Scheme 1.9. Efficient synthetic routes to diazo compounds.

1.3.2.6. Recent advances on catalyst development and utilization diazo compounds under metal catalysis and Photocatalysis:

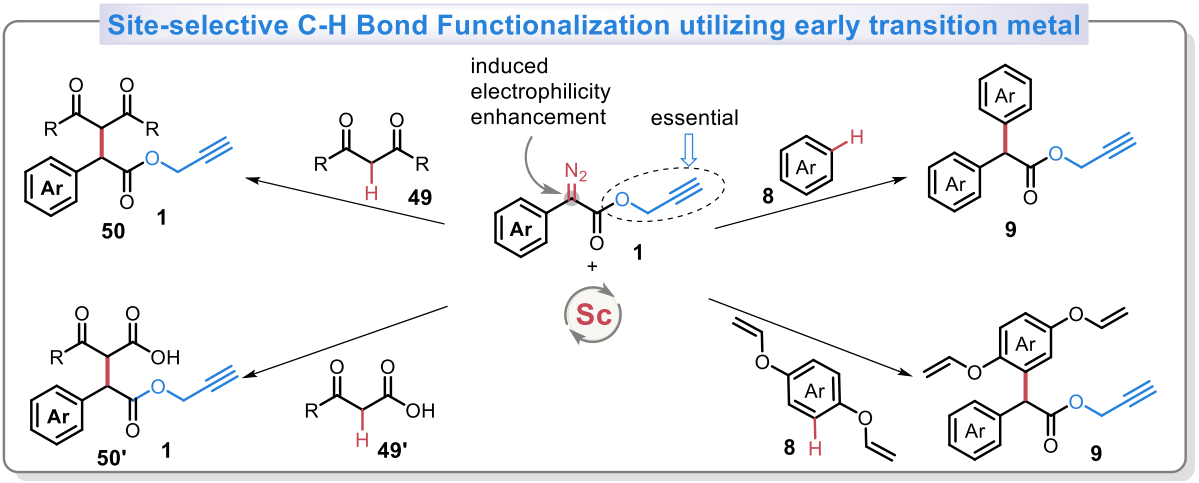
Over the past few decades, metal-carbenoid-induced diazo transfer reactions have been well-established for the effective C–H bond functionalization of unactivated C–H bonds. The site-selective C–H bond functionalizations have been achieved utilizing various metal catalysts such as rhodium,[44] gold,[23,45] iron,[46] copper[47] etc. In this context, very recently, many state-of-the-art methods for the site-selective C–H bond functionalization of benzenoid molecules[44-47] (Scheme 1.10) and 1,3-dicarbonyl compounds[48a] (Scheme 1.11) have been developed modifying catalysts as well as diazo precursors.[48]



Scheme 1.10. Representative examples of recently developed site-selective C–H functionalization of arenes in different metal catalysis.



Scheme 1.11. Representative examples of recently developed site-selective C–H functionalization of 1,3-dicarbonyl compounds.



Scheme 1.12. Site-selective C–H bond functionalization under scandium catalysis.

Very recently, our research group has also developed a robust synergistic catalyst-reagent system for the effective C–H bond functionalization of 1,3-dicarbonyl compounds[49a] and benzenoid substances.[49b] In this aspect, modification of diazo carbonyl reagent with a propargyl group at the ester part was probed for effectively modulating the electronic properties so as to enhance the electrophilicity of the carbene carbon center. In turn this assisted scandium triflate for the effective site-selective C–H bond functionalization synergistically (see Scheme 1.12).[49] This robust reagent-catalyst system (propargyl α-aryl-α-diazoacetate/scandium triflate) has demonstrated effective the site-selective C–H bond functionalization, particularly with benzenoid scaffolds.

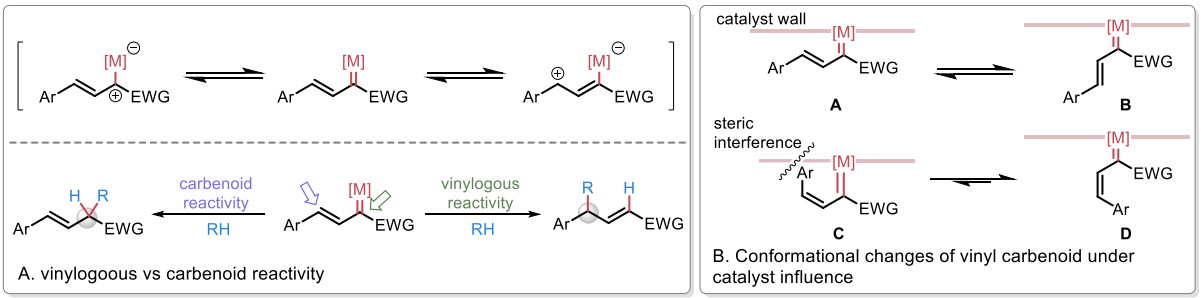
1.4. Aims and rationale of this thesis work

Over the years the diazo compounds have been proved to be very useful in synthetic reagents and have been explored for a wide range of synthetic transformations for the past few decades. Over the years, various diazocarbonyl compounds with different electronic properties have been utilized as useful synthetic precursors for many transition-metal-catalyzed transformations such as insertion reactions, cyclopropanation, and ylide formation, etc.[23,45,47-49] Many protocols have their own advantages such as reactivity, selectivity, etc. and set of limitations such as expensive transition metal catalysts, reagents, reaction conditions, and limited substrate scope etc. In spite of the advancement in the field, there is a great scope to make advancements in the field.

Many aryl diazoacetates have been employed for the highly chemo- and regio-selective C–H bond functionalization of arenes.[45,49b] As mentioned earlier, various transition metals such as rhodium,[44] gold,[23,45] iron,[46] copper[47] have been explored for the effective and selective C–H bond functionalization of substrates that are relatively challenging. Our research group unlike

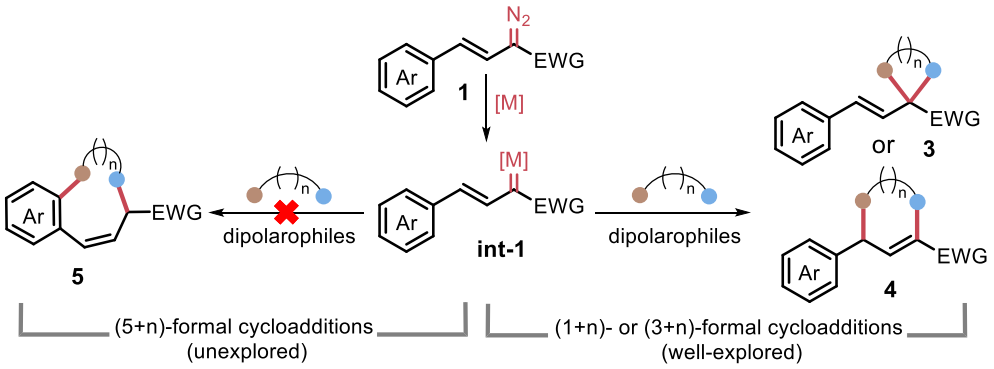
the previous preceding literature, looked into the possibility of early transition metal catalysts for the effective C–H bond functionalization. We have developed the novel and robust diazo carbonyl reagents such propargyl *α*-aryl-*α*-diazoacetates and effectively utilized them for the C–H bond functionalization of 1,3-dicarbonyl compounds[49a] and challenging unactivated arenes via scandium catalysis.[49b] The synergistic combination of propargyl *α*-aryl-*α*-diazoacetates and scandium catalysts has been demonstrated without the assistance of any directing group or ligand.

There is a huge scope to explore diazo carbonyl compounds with different electronic properties for tapping their potential for the synthesis of many interesting scaffolds that are core to a few natural scaffolds. In this regard, we envisaged to explore untapped potential of vinyl diazo carbonyl compounds for the selective C–H bond functionalization. Transition-metal-catalyzed decomposition of vinyl diazo compound enables two distinctive reactive centers (carbenoid center and vinylogous center) to serve as an electrophile (see Scheme 1.13A). Moreover, the addition of nucleophile to its vinylogous terminus is highly challenging due to presence of comparatively more reactive carbenoid site. It has been demonstrated that the intriguing reactivity of metallo-vinylcarbene intermediate is greatly influenced not only by the effect of metal catalyst or ligand[51c-e] but also the geometrical array of the molecule acquired from the changes in *Z*/*E*-configurational across the C=C double bond (because of the steric interference of catalyst surface to that of the vinylogous terminus or with incoming substrate) (see Scheme 1.13B).[51f-h]



Scheme 1.13. Conformational arrangements and distinct reactivity pattern of the vinyl diazo compound.

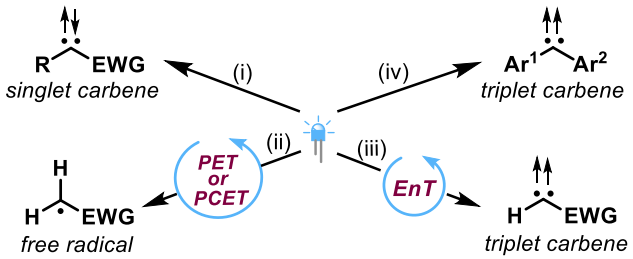
Moreover, vinyl diazo compound has been explored as three carbon synthon in the cycloaddition reactions for the construction of cyclic ring structure (see Scheme 1.14).[52a-b]



Scheme 1.14. Formal cycloaddition approaches with acyclic vinyl diazo compounds.

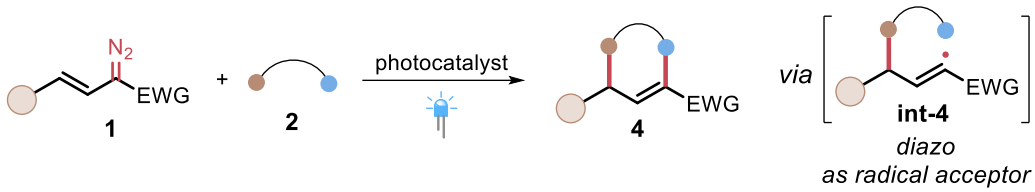
In spite of significant achievements in the synthesis of epoxides starting from cyclic diazo amides, the direct access to oxiranes (epoxides) starting directly from electron-deficient as well as electron-rich aromatic aldehydes and diazo carbonyl compound remains to be an interesting and challenging task. Also, accessing the oxiranes in a chemoselective as well as regioselective manner is highly demanding. The fused polycyclic framework containing 6-7-5 or 5-7 fused ring scaffold such as benzoxepine motif is very useful and it belongs to the oxygenated heterocycle family found in many natural products and pharmaceutical agents with diverse biological activities. The stereoselective synthesis of benzoxepine motif has been pursued many owing to its importance. In this regard, we hypothesized that the metallo-aryl vinyl carbenesuccinimide could be explored for the cycloannulation with suitable carbonyl compounds via (3+2)- and/or (5+2)-cycloaddition reaction to obtain the dihydrofurans and/or dihydrobenzoxepines respectively under suitable reaction conditions. Also, synthesizing the dearomatization product and cyclopropanation *via* carbene intermediate is of great interest. This is quite challenging and difficult as mobilizing one double bond at the expense of intrinsic aromatic stabilization and also this dearomatized product is prone to rearomatize especially under Lewis acid-catalysis.[50] Looking at this daunting task, we envisoned to achieve this dearomatization product in the presence of a Lewis acid, using suitable propargyl α-aryl-α-diazoacetates by modulating their electronic and steric properties.

Also, over the last very few years, the researchers have been exploring the reactivity of diazo compounds under visible light irradiation. Despite the recent advances on the study of different diazo compounds under visible light to achieve photolysis, the singlet or triplet carbene reactivity or even radical reactivity has been rarely explored (see Scheme 1.15).[31,34]



Scheme 1.15. Different diazo surrogates and their photochemical reactivity.

On the contrary, vinyl diazo compound has seldom been studied under photochemical conditions, where vinyl diazo compound has been utilized as a radical acceptor (see Scheme 1.16).[53] However, photoexcited state reactivity of vinyl diazo compound has not been explored till date to the best of our knowledge. It will be interesting to explore the photochemical carbene generation of vinyl diazo compound, as it would open up a more convenient route for organic synthesis.



Scheme 1.16. Vinyl diazo compound under photochemical condition: as radical acceptor.

Looking at these challenges, we planned to explore the reactivity of diazo carbonyl compounds under both transition metal catalysis as well as photolysis. The thesis has been constructed to utilize the interesting vinyl diazocarbonyl compounds as well as novel and modified propargyl α-aryl-α-diazoacetates for constructing very useful scaffolds under different conditions. The thesis discusses in detail regarding the synthesis of spiro-pyrrolidinedioneoxiranes, diastereoselective benzo[5,6]oxepino[2,3-*c*]pyrroles, and dearomatized compounds such as norcaradiene. The thesis also presents the unexplored photochemical reactivity of vinyl diazo compounds based on electronic as well as steric properties paving the way for *de novo* reactivity. Moreover, the thesis also presents the investigation towards its reactivity under metal catalysis to explore its metal-carbenoid reactivity and demonstrated a distinct reactivity pattern that differentiates it from other diazo compounds, especially acyclic vinyl diazo compounds.

1.5. Conclusions:

A brief introduction to the history of carbenes, synthesis, and type of carbenes has been presented. Diazo compounds over the years have turned out to be well-known carbene surrogates and they have been utilized in various synthetic transformations. Diazo carbonyl compounds with different electronic properties have been well explored for effective and selective C–H bond functionalization via transition metal catalysis. Transition metals such as rhodium, gold, copper, iron, and even early transition metal like scandium have been explored for useful C–H bond functionalization. Vinyl diazocarbonyl compound is an interesting scaffold that has been rarely employed for the metal-carbene transfer reaction to access useful framework core to a few natural products and pharmaceuticals. The reactivity of different diazo compounds has been explored under visible light to achieve photolysis. However, the singlet or triplet carbene reactivity or even radical reactivity has been seldom explored to date. Though diazo carbonyl compounds have been utilized for various metal-carbene reactions, still there are many unmet challenges to be explored. In the subsequent chapters, we have explored the reactivity of vinyl diazo carbonyl compounds under transition metal catalysis as well as under visible light irradiation. Also, novel propargyl α-aryl-α-diazoacetates have been designed and developed to explore the dearomatization-ring expansion for accessing norcaradienes. The development of the protocols has been presented in detail.

1.6. Reference:

1. E. Buchner, L. Feldmann, *Berichte der Deutschen Chemischen Gesellschaft*. **1903**, *36*, 3509.
2. a) J. B. Dumas, *Ann. Chim. Phys.* **1835**, *58*, 28; b) See for a brief history of carbenes: Kirmse, W. *Carbene Chemistry*; Academic Press: **1964**; p 5.
3. J. U. Nef, *Ann.* **1897**, *298*, 202.
4. a) H. Staudinger, O. Kupfer, *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2197; b) H. Staudinger, R. Endle, *Ber. Dtsch. Chem. Ges.* **1913**, *46*, 1437; c) H. Staudinger, J. Goldstein, *Ber. Dtsch. Chem. Ges.* **1916**, *49*, 1923; d) H. Staudinger, E. Anthes, F. Pfenninger, *Ber. Dtsch. Chem. Ges.* **1916**, *49*, 1928.
5. a) R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719; b) H.-W. Wanzlick, *Angew. Chem.* **1962**, *74*, 129.

6. a) A. Igau, H. Grutzmacher, A. Baceiredo, G. Bertrand, *J. Am. Chem. Soc.* **1988**, *110*, 6463; b) A. J. Arduengo III, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361–363.
7. H. Tomioka, *Acc. Chem. Res.* **1997**, *30*, 315.
8. a) Kutin, Y.; Reitz, J.; Antoni, P. W.; Savitsky, A.; Pantazis, D. A.; Kasanmascheff, M.; Hansmann, M. M. *J. Am. Chem. Soc.* **2021**, *143*, 21410−21415; b) M. Abe, *Chem. Rev.* **2013**, *113*, 7011−7088; c) D. A. Dougherty, *Acc. Chem. Res.* **1991**, *24*, 88−94; d) W. T., Bordon, Ed.; Diradicals; Wiley-Interscience: New York, **1982**.
9. a) H. Tomioka, E. Iwamoto, H. Itakura, K. Hirai, *Nature* **2001**, *412*, 626–628; b) T. Nakajo, J. Kumagai, S. Kusaka, A. Hori, Y. Hijikata, J. Pirillo, Y. Ma, R. Matsuda, *J. Am. Chem. Soc.* **2021**, *143*, 8129−8136.
10. a) L. Chugaev, M. Skanavy-Grigorizeva, *J. Russ. Chem. Soc.* **1915**, 47, 776; b) L. Chugaev, M. Skanavy-Grigorizeva, A. Posniak, *Z. Anorg. Allg. Chem.* **1925**, *148*, 37; c) W. M. Butler, J. H. Enemark, J. Parks, A. L. Balch, *Inorg. Chem.* **1973**, *12*, 451.
11. E. O. Fischer, A. Maasböl, *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 580− 581.
12. a) T. E. Taylor, M. B. Hall, *J. Am. Chem. Soc.* **1984**, *106*, 1576−1584.
13. a) R. R. Schrock, *Chem. Rev.* **2002**, *102*, 145−179; b) P. de Frémont, N. Marion, S. P. Nolan, *Coord. Chem. Rev.* **2009**, *253*, 862−892.
14. a) A. Geuther, *Ann.* **1862**, *123*, 121; b) A. W. Hofmann, *Ann.* **1867**, *144*, 114; c) K. Reimer, F. Tiemann, *Chem. Ber.* **1876**, *9*, 1268; d) J. Hine, *J. Am. Chem. Soc.* **1950**, *72*, 2438; e) J. Hine, *Divalent Carbon*, Ronald Press, New York, **1964**, pp 36; f) W. v. E. Doering, L. H. Knox, *J. Am. Chem. Soc.* **1956**, *78*, 4947; See selected reviews: M. Mąkoszaa, M. Fedoryński, *Russ. Chem. Bull., Int. Ed.* **2021**, *70*, 2045–2050.
15. H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1958**, *80*, 5323–5324.
16. T. Curtius, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2230.
17. G. Regitz, M. Maas, Diazo Compounds: Properies and Synthesis, Elsevier, **1986**.
18. a) H. V. Pechmann, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 1888–1891; b) F. W. Kirkbride, R. G. W. Norrish, *J. Chem. Soc.* **1933**, 119–126; c) H. Meerwein, H. Rathjen, H. Werner, *Ber. Dtsch. Chem. Ges.* **1942**, *75*, 1610–1622.
19. W. Kirmse, Carbene Chemistry, Academic Press, New York, **1971**, vol. 1, pp. 9–84.
20. a) W. R. Moser, *J. Am. Chem. Soc.* **1969**, *91*, 1135; b) W. R. Moser, *J. Am. Chem. Soc.* **1969**, *91*, 1141.
21. H. M. L. Davies, A. M. Walji, in Modern rhodium-catalyzed organic reactions, ed. P. A. Evans, Wiley-VCH, Weinheim, **2005**, pp. 301–337.

22. a) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704–724; b) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857; c) H. M. L. Davies, K. Liao, *Nat. Rev. Chem.* **2019**, *3*, 347–360; d) D. Laha, J. Y. Shaikh, R. G. Bhat, Handbook of CH-Functionalization. DOI: 10.1002/9783527834242.chf0085.
23. A. Caballero, M. Mar Diaz-Requejo, M. R. Fructos, A. Olmos, J. Urbano, P. J. Perez, *Dalton Trans.* **2015**, *44*, 20295–20307.
24. H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417–424;
25. a) K. M. Waltz, J. F. Hartwig, *Science* 1997, *277*, 211–213; b) R. G. Bergman, *Nature* **2007**, *446*, 391–393.
26. H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861–2904.
27. a) M. P. Doyle, L. J. Westrum, W. N. E. Wolthuis, M. M. See, W. P. Boone, V. Bagheri, M. M. Pearson, *J. Am. Chem. Soc.* **1993**, *115*, 958–964; b) H. M. L. Davies, *J. Mol. Catal. A* **2002**, *189*, 125–135.
28. a) A. Padwa, S. F. Hornbuckle, *Chem. Rev.* **1991**, *91*, 263; b) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861; c) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981.
29. a) W. Sander, G. Bucher, S. Wierlacher, *Chem. Rev.* **1993**, *93*, 1583–1621; b) M. S. Platz, *J. Org. Chem.* **2014**, *79*, 2341–2353.
30. I. D. Jurberg, H. M. L. Davies, *Chem. Sci.* **2018**, *9*, 5112–5118.
31. a) Z. Zhang, D. Yadagiri, V. Gevorgyan, *Chem. Sci.* **2019**, *10*, 8399–8404; b) C. Empel, D. Verspeek, S. Jana, R. M. Koenigs, *Adv. Synth. Catal.* **2020**, *362*, 4716–4722; c) X. Yue, Y. Zhou, Y. Zhang, T. Meng, Y. Zhao, W. Guo, *Chem. Commun.* **2023**, *59*, 6363–6366.
32. S. Jana, C. Pei, C. Empel, R. M. Koenigs, *Angew. Chem. Int. Ed.* **2021**, *60*, 13271–13279.
33. a) N. Candeias, C. Afonso, *Curr. Org. Chem.* **2009**, *13*, 763; b) O. S. Galkina, L. L. Rodina, *Russ. Chem. Rev.* **2016**, *85*, 537.
34. a) Z. Yang, M. L. Stivanin, I. D. Jurberg, R. M. Koenigs, *Chem. Soc. Rev.* **2020**, *49*, 6833–6847; b) J. Durka, J. Turkowska, D. Gryko, *ACS Sustainable Chem. Eng.* **2021**, *9*, 8895–8918; c) C. Empel, C. Pei, R. M. Koenigs, *Chem. Commun.* **2022**, *58*, 2788–2798; d) R. D. C. Gallo, G. Cariello, T. A. C. Goulart, I. D. Jurberg, *Chem. Commun.* **2023**, Advance Article. doi.org/10.1039/D3CC00988B.
35. a) T. Köpke, J. M. Zaleski, *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 292−304; b) K. A. Mix, M. R. Aronoff, R. T. Raines, *ACS Chem. Biol.* **2016**, *11*, 3233−3244.
36. a) S. Ito, T. Matsuya, S. Omura, M. Otani, A. Nakagawa, H. Takeshima, Y. Iwai, M. Ohtani, T. Hata, *J. Antibiot.* **1970**, *23*, 315−317; b) H. W. Dion, S. A. Fusari, Z. L.

Jakubowski, J. G. Zora, Q. R. Bartz, *J. Am. Chem. Soc.* **1956**, *78*, 3075−3077; c) S. A. Fusari, T. H. Haskell, R. P. Frohardt, Q. R. Bartz, *J. Am. Chem. Soc.* **1954**, *76*, 2881−2883.

37. a) K. A. Andersen, M. R. Aronoff, N. A. McGrath, R. T. Raines, *J. Am. Chem. Soc.* **2015**, *137*, 2412−2415; b) H. Bayley, J. R. Knowles, *Methods Enzymol.* **1977**, *46*, 69−114.
38. a) M. Regitz, *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733−749; b) J. S. Baum, D. A. Shook, H. M. L. Davies, H. D. Smith, *Synth. Commun.* **1987**, *17*, 1709−1716.
39. E. B. Womack, A. B. Nelson, *Org. Synth.* **1955**, *24*, 56−57.
40. a) W. R. Bamford, T. S. Stevens, *J. Chem. Soc.* **1952**, *924*, 4735−4740; b) T. L. Holton, H. Schechter, *J. Org. Chem.* **1995**, *60*, 4725−4729.
41. B. Morandi, E. M. Carreira, *Science* **2012**, *335*, 1471−1474.
42. R. J. Baumgarten, *J. Org. Chem.* **1967**, *32*, 484−485.
43. a) J. Fink, M. Regitz, *Synthesis* **1985**, *1985*, 569−585; b) M. E. Meyer, E. M. Ferreira, B. M. Stoltz, *Chem. Commun.* **2006**, 1316−1318; c) Y. Liu, Y. Zhang, N. Jee, M. P. Doyle, *Org. Lett.* **2008**, *10*, 1605−1608.
44. H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857−1869.
45. a) L. Liu, J. Zhang, *Chem. Soc. Rev.* **2016**, *45*, 506–516; b) Y.-Y. Ren, M. Chen, K. Li, S.-F. Zhu, *Chem. Asian J.* **2018**, *13*, 2606–2610; c) B. Ma, L. Liu, J. Zhang, *Asian J. Org. Chem.* **2018**, *7*, 2015−2025.
46. a) C. Empel, S. Jana, R. M. Koenigs, *Molecules* **2020**, *25*, 880; b) Z. Yu, G. Li, J. Zhang, L. Liu, *Org. Chem. Front.* **2021**, *8*, 3770−3775.
47. a) E. Tayama, T. Yanaki, H. Iwamoto, E. Hasegawa, *Eur. J. Org. Chem.* **2010**, 6719−6721. b) B. Ma, Z. Tang, J. Zhang, L. Liu, *Chem. Commun.* **2020**, *56*, 9485−9488.
48. a) Z. Liu, P. Sivaguru, G. Zanoni, E. A. Anderson, X. Bi, *Angew. Chem. Int. Ed.* **2018**, *57*, 8927–8931; b) Z. Yu, Y. Li, P. Zhang, L. Liu, J. Zhang, *Chem. Sci.* **2019**, *10*, 6553−6559; c) J. D. Pizarro, I. L. Schmidtke, A. Nova, M. R. Fructos, P. J. Pérez, *ACS Catal.* **2022**, *12*, 6851−6856.
49. a) B. S. Navale, D. Laha, R. G. Bhat, *Tetrahedron Lett.* **2019**, *60*, 1899−1903; b) B. S. Navale, D. Laha, S. Banerjee, K. Vanka, R. G. Bhat, *J. Org. Chem.* **2022**, *87*, 13583–13597; c) B. S. Navale, **2019**, Novel Strategies for C–H Bond Functionalization of Alkynes, Arenes and Carbonyl Compounds via Copper and Scandium Catalysis, http://dr.iiserpune.ac.in:8080/xmlui/handle/123456789/2588.
50. T. Sugimura, M. Kagawa, N. Ohuchi, K. Hagiya, T. Okuyama, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 671.

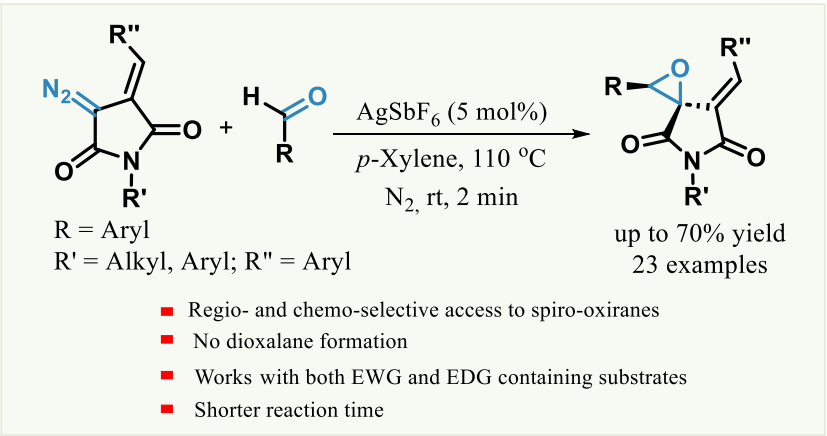
51. a) H. M. L. Davies, E. Saikali, T. J. Clark, E. H. Chee, *Tetrahedron Lett.* **1990**, *31*, 6299–6302. b) H. M. L. Davies, B. Hu, E. Saikali, P. R. Bruzinski, *J. Org. Chem.* **1994**, *59*, 4535–4541; c) H. M. L. Davies, Y. Yokota, *Tetrahedron Lett.* **2000**, *41*, 4851–4854; d) Y. S. Sevryugina, B. Weaver, J. Hansen, J. Thompson, H. M. L. Davies, M. A. Petrukhina, *Organometallics* **2008**, *27*, 1750–1757; e) J. H. Hansen, H. M. L. Davies, *Chem. Sci.* **2011**, *2*, 457–461; f) Y.-J. Lian, H. M. L. Davies, *Org. Lett.* **2010**, *12*, 924–927; g) Y.-J. Lian, H. M. L. Davies, *Org. Lett.* **2012**, *14*, 1934–1937; h) C. Qin, H. M. L. Davies, *Org. Lett.* **2013**, *15*, 6152–6154.

52. a) R. A. Moss, M. P. Doyle, Contemporary Carbene Chemistry; Wiley: New York, **2013**; pp 404− 451; b) Q.-Q. Cheng, Y. D. Deng, M. Lankelma, M. P. Doyle, *Chem. Soc. Rev.* **2017**, *46*, 5425−5443; c) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223−270. d) X. Guo, W. H. Hu, *Acc. Chem. Res.* **2013**, *46*, 2427−2440; e) B. Xu, U. K. Tambar, *J. Am. Chem. Soc.* **2016**, *138*, 12073−12076; f) X. B. Lin, Y. Tang, W. Yang, F. Tan, L. L. Lin, X. H. Liu, X. M. Feng, *J. Am. Chem. Soc.* **2018**, *140*, 3299−3305; g) Y. Xia, D. Qiu, J. B. Wang, *Chem. Rev.* **2017**, *117*, 13810.

53. a) F. J. Sarabia, Q. Li, E. M. Ferreira, *Angew. Chem. Int. Ed.* **2018**, *57*, 11015–11019; b) B. K. Gall, A. K. Smith, E. M. Ferreira, *Angew. Chem. Int. Ed.* **2022**, *61*, e202212187; c) W. Li, X. Zhou, T. Xiao, Z. Ke, L. Zhou, *CCS Chem.* **2021**, *3*, 794−805; d) W. Li, L. Zhou, *Org. Lett.* **2021**, *23*, 4279−4283.

Chapter 2

Silver(I)-Catalyzed Diastereoselective Epoxidation of Aldehydes with Vinyl Diazosuccinimides via [2+1]-Cycloaddition Process



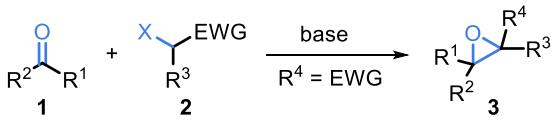
Silver(I)-Catalyzed Diastereoselective Epoxidation of Aldehydes with Vinyl Diazosuccinimides via (2+1)-Cycloaddition Process

2

This chapter describes the development of a method for the synthesis of oxiranes by the reaction of aldehydes with donor-/acceptor-substituted vinyl diazosuccinimides as metallo-carbene precursors via (2+1)-cycloaddition using the catalytic amount of silver hexafluoroantimonate as an efficient catalyst. This novel protocol has been found to be highly regio- as well as chemo-selective that works very well with aromatic aldehydes containing electron- withdrawing and -donating groups. Also, it gives an easy access to spiro-pyrrolidinedioneoxiranes with a broad substrates scope. This chapter also presents a new one-step synthetic strategy for the direct synthesis of vinyl diazosuccinimides from vinyl succinimides using diazo transfer reagent.

2.1 **Introduction:**

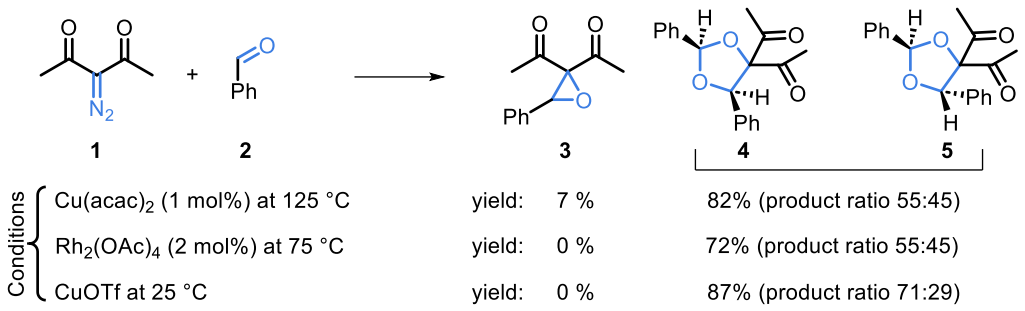
The direct transformation of aldehydes into oxiranes is a very useful method on an account of the fact that a variety of synthetic transformations can further be achieved by manipulating these oxirane-intermediate.[1] Over the years, many synthetic protocols have been explored for the direct synthesis of oxirane derivatives starting from aromatic aldehydes.[2] In 1904, Auguste, Georges and Darzens independently discovered a direct method for the synthesis of epoxides by the reaction of ketones/aldehydes with α-haloester in presence of a base to afford α,β-epoxy ester (also called 'glycidic ester') (Scheme 2.1).[2b-d]



Scheme 2.1. Traditional Darzens glycidic ester condensation reaction.

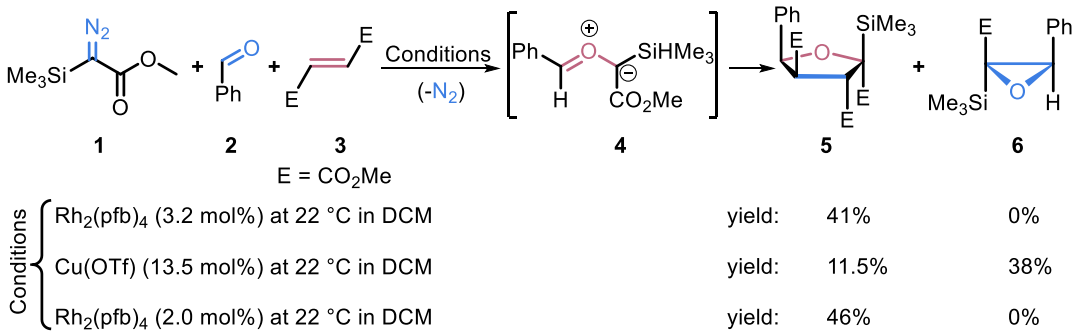
In 1982, originally, Huisgen and co-worker reported the formation of oxirane by the decomposition of dimethyl diazomalonate with benzaldehyde in presence of $Cu(acac)_2$ (1 mol%) as a catalyst at 125 °C (7% yield).[3] Interestingly, the same product was not obtained when the reactions were carried out in presence of $Rh_2(OAc)_4$ (2 mol%) or CuOTf at lower temperatures, instead they obtained dioxolanes (Scheme 2.2).[3]

In 1994, Mass and co-workers reported the selective reactivity of α-diazo(trimethylsilyl)acetates with benzaldehyde and other dipolarophiles under different metal catalysis. It was observed that α-diazo(trimethylsilyl)acetates when treated with a mixture



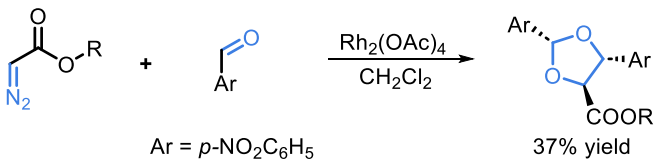
Scheme 2.2. Oxirane and dioxolane formations in different catalytic conditions.

containing benzaldehyde and other dipolarophiles in presence of CuOTf, oxiranes were obtained as major products via carbonyl ylide. However, in contrast the reaction in presence of $Rh_2(pfb)_4$ exclusively furnished the corresponding formal (3+2)-adduct rather than epoxidation product (Scheme 2.3).[4]



Scheme 2.3. Mass and co-workers: Observation of oxirane formation.

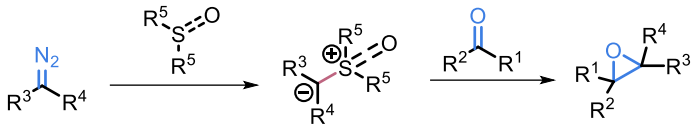
In the year of 1997, Doyle and co-workers have observed that ethyl diazoacetate upon treatment with aryl aldehydes in presence of dirhodium(II) tetraacetate undergoes catalytic decomposition to afford the corresponding 1,3-dioxolanes exclusively though as mixture of diastereomers. They did not observe any trace amount of oxirane during this transformation. Also, it was observed that catalytic dependent diastereocontrol was achieved only with *p*-nitrobenzaldehyde (Scheme 2.4).[5]



Scheme 2.4. Diastereocontrol reaction with ethyl diazoacetate.

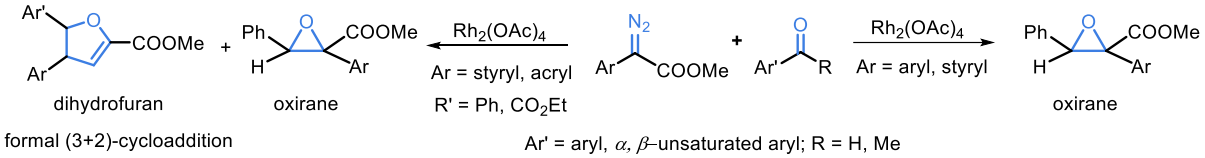
Most of the methods reported were not very selective to access the oxiranes directly from aldehydes. Looking at this limited success, overcome the inherent reactivity issue, and to achieve the direct formation of oxirane from the decomposition of diazo compounds, Aggarwal

and Co-workers developed an unorthodox but elegant strategy. They reported that the alkyl sulfide intercepts with the metal carbenoid to form sulfur ylide that would undergo epoxidation upon reacting with an aldehyde (Scheme 2.5).[6]



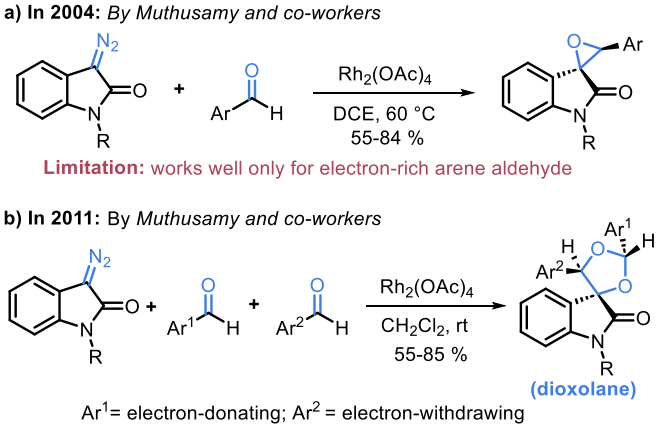
Scheme 2.5. General reaction for oxirane formation via sulfur ylide.

In 2001, Doyle and co-workers[7] disclosed synthetic method to access oxiranes starting from aldehyde and/or ketone and phenyl/styryl diazoacetate in presence of catalytic amount of rhodium(II) acetate in DCM at room temperature. At the same time, Davies group[8] also reported a similar type of reaction with different outcome using styryl/acryl diazoacetate and aryl/*α*, *β*-unsaturated aldehyde as a substrate. Both these transformations afforded *Z*-selective oxiranes product moderate to good yields (Scheme 2.6). However, Davies group reported (3+2)-cycloaaddition product formation dihydrofuran, when the reactions were performed with styryl/acryl diazoacetates.



Scheme 2.6. Regio-and chemoselective epoxidation with phenyl- and styryl/acryl diazoactate.

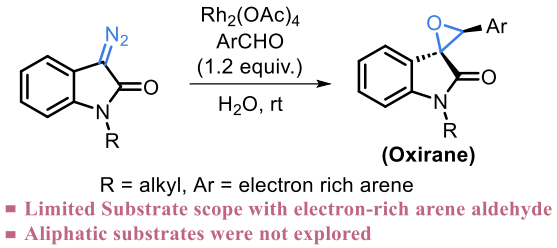
In 2004, Muthusamy and co-workers have reported the $Rh_2(OAc)_4$ catalyzed synthesis of spiro-oxiranes starting from 3-diazooxindolinone and aromatic aldehydes at an helevated temperature (60 °C in DCE). Though this protocol proved to be stereoselective, however it was limited to aromatic aldehydes substituted with electron-donating groups (Scheme 2.7 a).[9]



Scheme 2.7. Stereocontrol products formation from 3-diazooxindolinone; a) spiro-oxirane formation and b) dioxolane formation.

Later the same research group reported the formation of dioxolanes while working with the aromatic aldehydes containing electron-withdrawing substituents (Scheme 2.7b).[10]

In 2015, Muthusamy and co-workers reported the synthesis of oxiranes on water unlike their previous findings in which DCM was used as a solvent. However, this protocol was found to be efficient only with electron rich aromatic aldehydes (scheme 2.8).[11]



Scheme 2.8. On water synthesis of spiro-oxiranes.

In spite of remarkable advances in the synthesis of oxiranes starting from cyclic diazo amides, the direct access to oxiranes starting from both electron-deficient and -rich aromatic aldehydes and diazo compound remains to be a challenging task. More importantly access to oxiranes in a regioselective as well as chemoselective manner is highly demanding.

Maleimide scaffold is a key component and is found in many natural products as well as pharmaceuticals with a remarkable range of biological activities.[12] TAN-1813 is known to have *ras*-farnesyltransferase inhibition activity.[13] We envisioned that TAN-1813 derivatives could be accessed via spiro-oxirane motif **3** at the very early stage of the synthesis (Fig. 2.1). In turn the intermediate **3** could be synthesized starting from donor-/acceptor- substituted type vinyl diazosuccinimides (Fig. 2.1). In order to validate our hypothesis, we mainly turned our attention towards the synthesis of spiro oxiranes derivatives **3** by selecting vinyl diazosuccinimide as a model substrate.

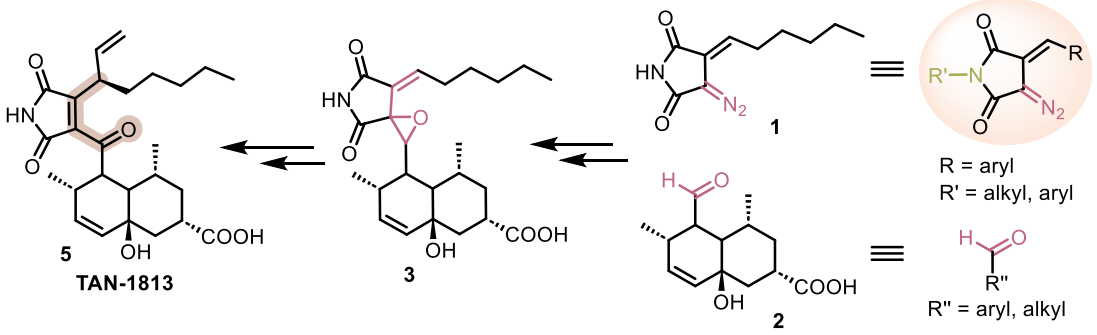
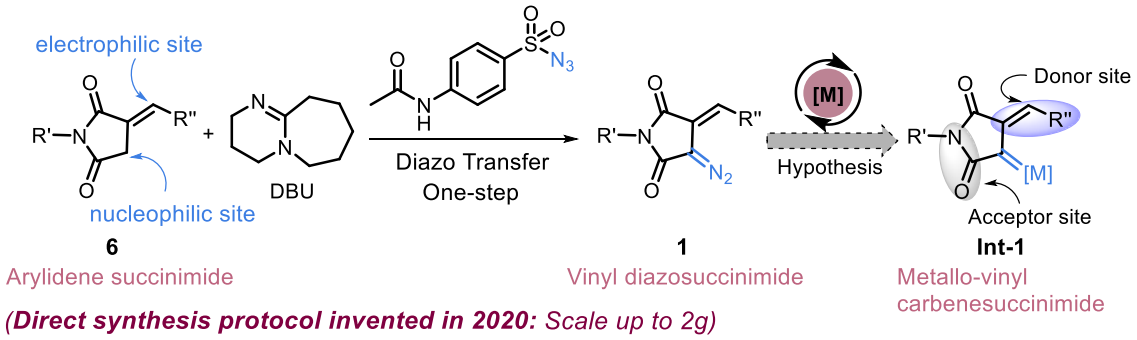


Figure 2.1. Probable synthetic route for TAN-1813.

Though a promising synthetic method for the synthesis of vinyl diazosuccinimide is rare and the reported method involves a multistep synthetic strategy.[14a] In order to overcome this

limitation, to begin with we planned to develop a new one-step synthetic strategy to access vinyl diazosuccinimides starting from the biologically active arylidene succinimides using diazo transfer reagent (*p*-ABSA). The starting material arylidene succinimide **6** is a well-known reagent used in organocatalysis as a Michael acceptor and it exhibits nucleophilic character at the α-carbon to *E*-selective double bond, while the vinylogous carbon acts as an nucleophile acceptor, thereby exhibiting the electrophilic character at that center (See Scheme 2.9).[14b] On contrary, the newly formed arylidene diazosuccinimide **1** exhibits the electrophilic character at the carbon wherein the diazo group is directly attached onto it. Therefore, we hypothesized that arylidene diazosuccinimide as a reagent can exhibit umpolung behavior of reactivity when treated with specific coupling agent under suitable metal catalysis. In order to look into this behaviour, we turned our attention towards ylide based chemistry utilizing this versatile diazo compound under transition metal catalysis.



Scheme 2.9. Synthesis of arylidene diazosuccinimide.

It has been reported that metal-catalyzed intermolecular epoxidation with these donor-/acceptor-substituted type carbenoids is much more diastereoselective and chemoselective than the traditional carbenoids.[8] Interestingly, for some unknown reason vinylcarbenoids have been seldom explored in the literature.[14a,c]

Though a lot has been achieved in carbenoid derived transformation utilizing different rhodium catalysts, simultaneously there have been numerous efforts to utilize alternative transition metal catalysts such as silver catalysts for different transformations in the diazocarbonyl chemistry. It has been shown that silver catalysts are effective in catalyzing the reactions with donor-/acceptor-type carbenoids.[15] Mostly dirhodium catalysts have been explored for the synthesis of oxiranes via formal (2+1)-cycloaddition of the diazo compounds and aromatic aldehydes with limited success.[3,7,8] Interestingly, silver catalysis has proved to be more effective than rhodium in some of the instances.[16] Moreover, some of the silver catalysts are relatively less expensive and easily available. In this regard we planned to explore the silver

catalysis for the proposed synthesis of spiro-oxiranes starting from vinyl diazosuccinimides.

To the best of our knowledge for the first time, herein, in this chapter we have demonstrated the utility of donor-/acceptor-substituted vinyl carbenoids for the direct access of spiro-oxiranes starting from aromatic aldehydes via silver catalysis in regio- and chemoselective manner.

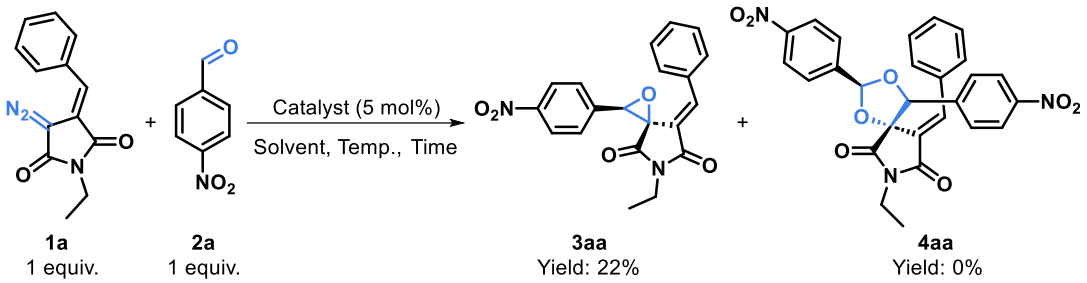
2.2 **Results and Discussion:**

In order to validate our hypothesis, to begin with we planned to screen easily and commercially available silver catalysts and by selecting benzylidene-*N*-ethyldiazosuccinimide **1a** and *p*-nitrobenzaldehyde **2a** as model substrates to evaluate the desired transformation. We commenced with a model reaction by employing catalytic amount of silver triflate in toluene as solvent at room temperature under inert atmosphere (Table 2.1, Entry 1). Interestingly, the reaction furnished the desired oxirane **3aa** albeit in poor yield (22%). We did not observe the anticipated corresponding dioxolane derivative **4aa** even in trace amount (Table 2.1, Entry 1) and a slight excess of **2a** was recovered during the purification. Encouraged by this initial result, we sought to screen various silver(I) salts for a potential catalyst. We further carried out the optimization reaction with different silver catalysts ($AgBF_4$, AgOAc, AgTFA, Ag_2CO_3, $AgNO_3$, $AgNTf_2$, Ag_2O, $AgSbF_6$) and found that among all silver hexafluoroantimonate proved to be most efficient for the effective transformation to afford product **3aa** in 27% yield (Table 2.1, Entries 2-9). The loosely bound non-nucleophilic counterion (SbF_6^-) must have enhanced the efficiency of the catalyst. Later in order to optimize the reaction conditions further, we carried out the reaction of **1a** and **2a** in presence of $AgSbF_6$ in different solvents at room temperature (Table 2.1, Entries 10-14). Among all the solvents, *p*-Xylene proved to be efficient for this transformation by affording the **3aa** in 34% yield at room temperature in 1 h (Table 2.1, Entry 11).

We observed that in all the cases, desired product **3aa** was obtained considerably in low yields with a relatively longer reaction time due to decomposition of the starting vinyl diazo compound. We believed that the silver carbenoid generated in situ might not be efficient and reactive enough to get coupled with the aldehyde at room temperature. In this regard, we planned to carry out the reaction at an elevated temperature.

Later, the reaction of **1a** with **2a** was carried out in *p*-xylene at 60 °C in presence of $AgSbF_6$ to afford the desired product **3aa** in 41% yield (Table 2.1, Entry 15). We observed that at elevated temperature there was an incremental increase in the yield of **3aa** (up to 48%) and

Table 2.1: Optimization of reaction conditions[a]

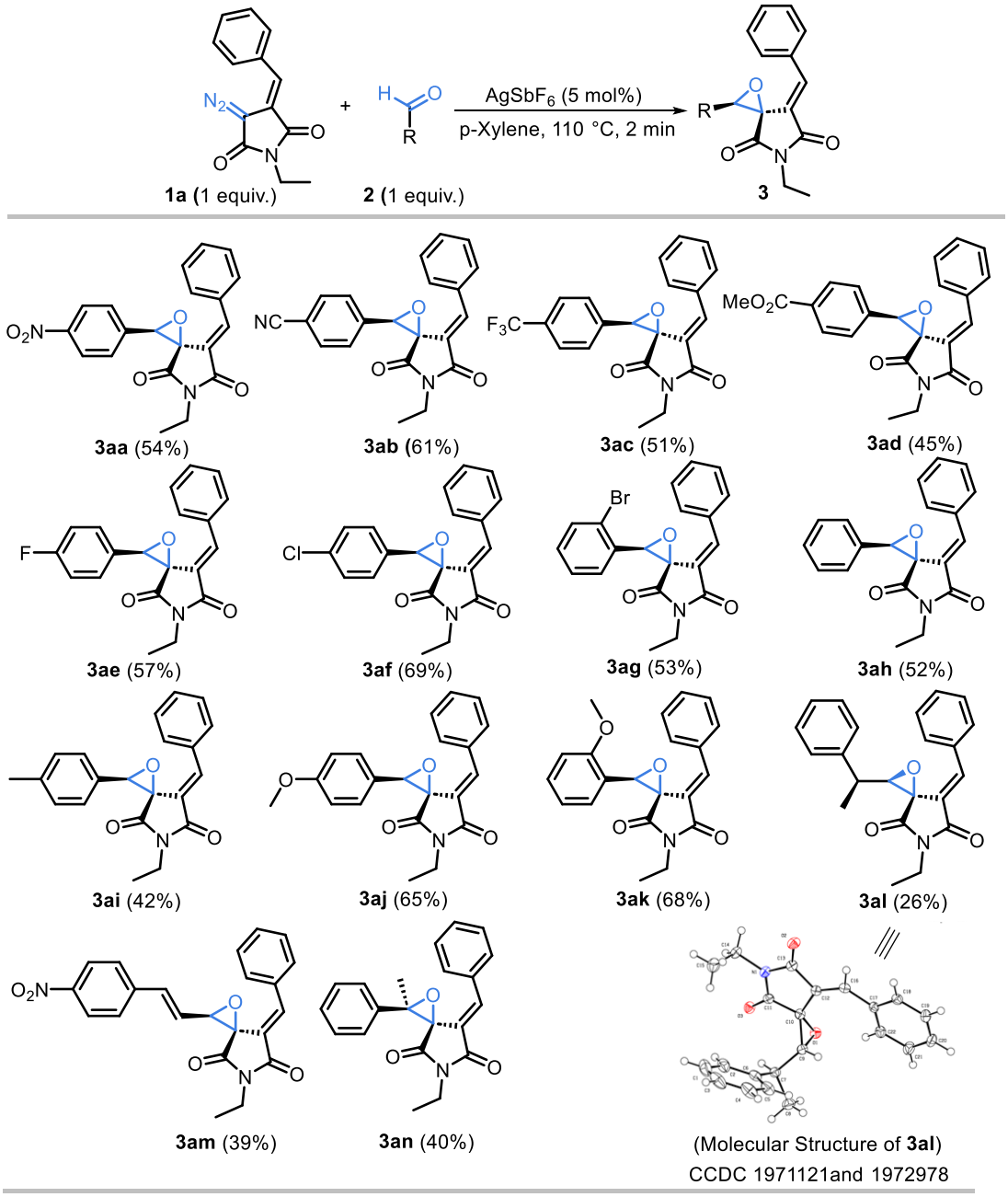


Entry	Catalyst (5 mol%)	Solvent	Temp. (°C)	Time	Yield[b] %
1	AgOTf	Toluene	rt	16 h	22
2	$AgBF_4$	Toluene	rt	16 h	16
3	AgOAc	Toluene	rt	18 h	7
4	AgTFA	Toluene	rt	24 h	<5
5	Ag_2CO_3	Toluene	rt	24 h	<5
6	$AgNO_3$	Toluene	rt	20 h	<5
7	$AgNTf_2$	Toluene	rt	16 h	15
8	Ag_2O	Toluene	rt	24 h	NR
9	$AgSbF_6$	Toluene	rt	12 h	27
10	$AgSbF_6$	CH_2Cl_2	rt	1.5 h	16
11	$AgSbF_6$	*p*-Xylene	rt	1 h	34
12	$AgSbF_6$	DCE	rt	1.5 h	DC
13	$AgSbF_6$	THF	rt	24 h	NR
14	$AgSbF_6$	$CHCl_3$	rt	1.5 h	10
15	$AgSbF_6$	*p*-Xylene	60	10 min	41
16	$AgSbF_6$	*p*-Xylene	80	3 min	44
17	$AgSbF_6$	*p*-Xylene	90	2 min	48
18	$AgSbF_6$	*p*-Xylene	110	2 min	54
19	$AgSbF_6$	*p*-Xylene	125	2 min	DC
20[c]	$AgSbF_6$	*p*-Xylene	110	2 min	DC
21[d]	$AgSbF_6$	*p*-Xylene	110	2 min	50
22[e]	$AgSbF_6$	*p*-Xylene	110	2 min	46
23[f]	$AgSbF_6$	*p*-Xylene	110	2 min	54
24	**No Catalyst**	***p*-Xylene**	**110**	**24 h**	**NR**

[a]**Reaction conditions**: **1a** (1 equiv.), **2a** (1 equiv.), catalyst (5 mol%), solvent (3 mL), N_2 atmosphere. [b]Isolated yield after column chromatography. [c]10 mol% of $AgSbF_6$ was used. [d]1 mol% of $AgSbF_6$ was used. [e]**1a** (1.5 equiv.) and *p*-nitrobenzaldehyde **2a** (1 equiv.) [f]**1a** (1 equiv.) and *p*-nitro benzaldehyde **2a** (1.5 equiv.) NR = No reaction, DC = decomposed.

the starting material was consumed in just 10 min (Table 2.1, Entries 15-17). Gratifyingly, no trace of dioxolane **4aa** was observed during the reaction. Interestingly, further increase in the reaction temperature (110 °C) enhanced the yield up to 54% in just 2 min (Table 2.1, Entry

18). Further increase in temperature (125 °C) as well as catalyst loading (10 mol%) were unsuccessful (Table 2.1, Entries 19-20) and resulted in decomposition of starting diazo compound. While, the decrease in catalyst loading resulted in diminished in yield of **3aa** (Table 2.1, Entry 21). Later, we also observed that increase in the stochiometric amounts of starting materials for different successive reactions proved to be insignificant (Table 2.1, Entries 22-23). However, more importantly we did not observe the formation of dioxolane **4aa** during our

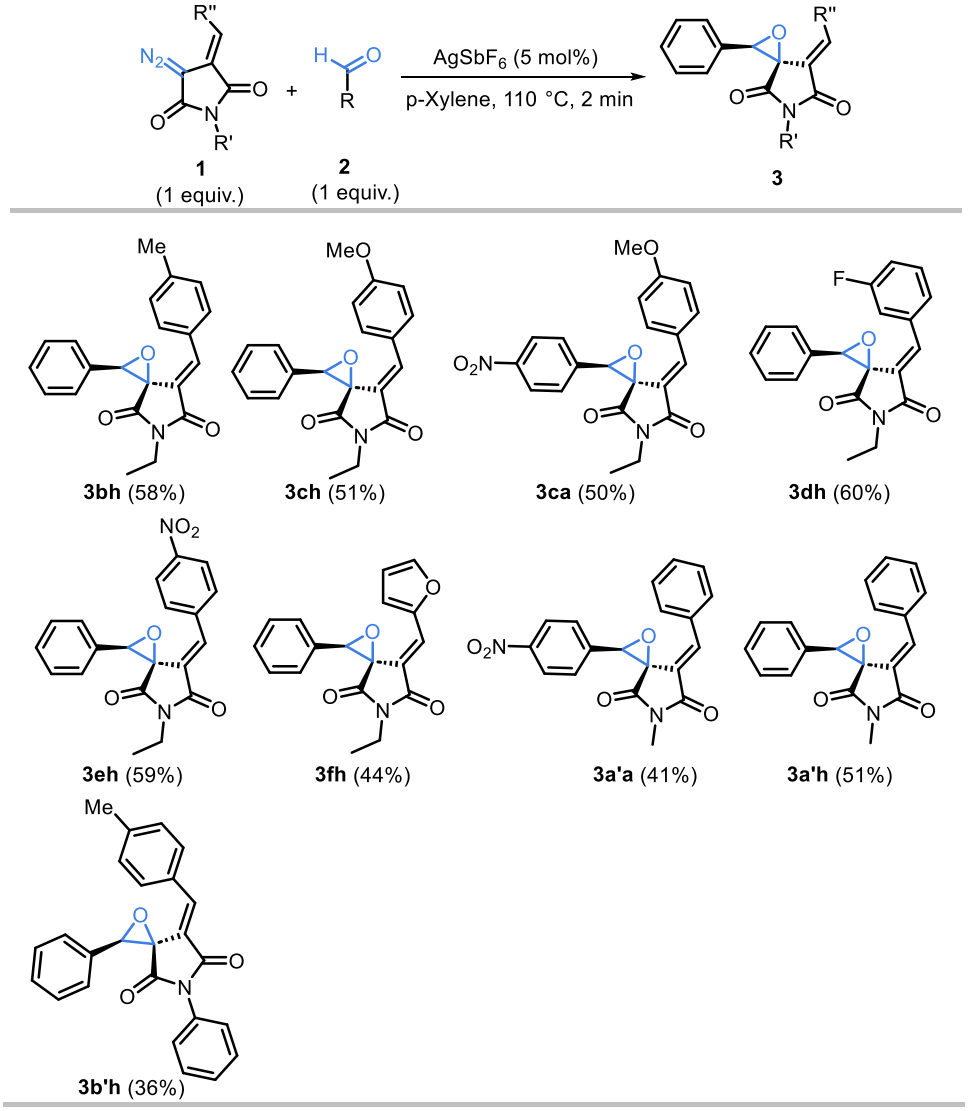


[a]Reaction conditions: **1a** (1 equiv.), **2** (1 equiv.), $AgSbF_6$ (5 mol%), *p*-Xylene (3 mL), N_2-atmosphere; [b]Yields are given in parenthesis and are obtained by purification using column chromatography.

Table 2.2. Substrates scope for diazosuccinimide.

optimization unlike in case of dirhodium acetate catalyzed transformation reported earlier inliterature.[10] The reaction of **1a** and **2a** did not proceed in the absence of any catalyst (Table 2.1, Entry 24). After the exhaustive screening, **1a** (1 equiv.), **2a** (1 equiv.), $AgSbF_6$ catalyst (5 mol%) in *p*-xylene at an elevated temperature (110 °C) under inert atmosphere proved to be the optimum reaction to condition to obtain **3aa**.

Having obtained the optimized reaction conditions, we further examined the substrates scope of the reaction of **1a** with variety of electron-deficient as well as electron-rich aryl aldehydes (Table 2.2). Aromatic aldehydes bearing electron withdrawing as well as electron deactivating substituents reacted smoothly under optimized reaction conditions to afford the corresponding desired products spiro-pyrrolidinedioneoxiranes (**3ab-3ag**) with moderate to

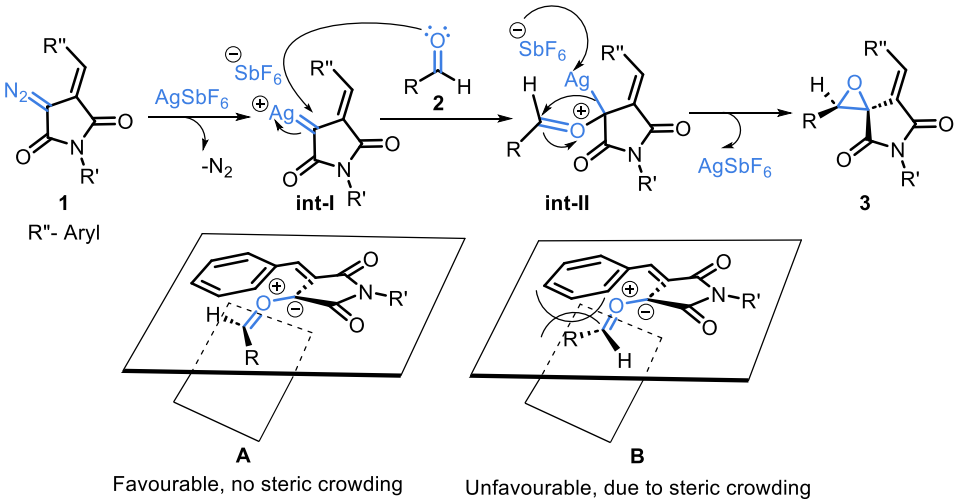


[a]Reaction conditions: **1a** (1 equiv.), **2** (1 equiv.), $AgSbF_6$ (5 mol%), *p*-Xylene (3 mL), N_2-atmosphere; [b]Yields are given in parenthesis and are obtained by purification using column chromatography.

Table 2.3. Scope with different diazosuccinimide derivatives.

good yields (up to 70%). Aromatic aldehydes bearing electron donating substituents also worked well under the optimum reaction conditions to furnish the desired products (**3ah-3ak**) in moderate to good yields (up to 69%). Gratifyingly, 2-phenylpropionaldehyde reacted smoothly with compound **1a** to furnish the desired compound **3al** as *Z*-selective mixture of diastereomers albeit in lower yield (Table 2.2). Later, we painstakingly separated the these two diastereomers and confirmed the molecular structures as well as geometric arrangements of both the isomers of **3al** unambiguously using single crystal X-ray analysis (see **2.4.6. Appendix IIB**). Under the optimized reaction conditions, even the *α, β*-unsaturated aldehyde such as cinnamaldehyde to afford the corresponding product **3am** in 40% yield. Interestingly, the protocol also worked well with the ketone as a suitable reactant for this transformation. The reaction of acetophenone with **1a** furnished the corresponding compound **3an** in moderate yield (Table 2.2). A range of substrates having electron withdrawing as well as donating groups were explored and all of them tolerated the reaction condition well.

Later, we turned our attention to screen different diazosuccinimide substrates to explore the generality and practicality of the protocol (Table 2.3). In this regard, varieties of vinyl diazosuccinamide derivatives (**1b-1f, 1a′, 1b′**) containing electron donating as well as electron withdrawing substituents at the arene ring at the vinylogous position were synthesized. Vinyl diazosuccinamide derivatives on treatment with different aldehydes under the optimum reaction conditions afforded the corresponding products (**3bh, 3ch, 3ca, 3dh, 3eh, 3fh, 3a′a, 3a′h, 3b′h**) in moderate to good yields (up to 60%, Table 2.3). However, *N*-Ph substituted vinyl diazo compound under optimized reaction conditions afforded the corresponding desired product **3b′h** obtained relatively in lower yield (Table 2.3).



Scheme 2.10. Proposed mechanism for the formation of oxirane

A plausible mechanism for the formation of oxirane has been proposed in Scheme 2.10. The treatment of vinyl diazocompound **1** with $AgSbF_6$ under the reaction condition presumably initiated by the loss of dinitrogen to form silver-carbenoid **int-I**. This reactive intermediate **int-I** further reacts with aldehyde **2** to furnish an intermediate **int-II**, which in turn delivers the desired product oxirane **3** with the concomitant regeneration of the active Ag(I) catalyst. We believe that approach of aldehyde is probably more favourable as shown in **A**, as it avoids the steric clash leading to the product with the favourable geometry.

2.3 Conclusions:

In summary, we have demonstrated that silver hexafluoroantimonate as an effective and efficient catalyst for the direct access of spiro-oxirane derivatives starting from donor-/acceptor-substituted vinyl diazosuccinimides. The protocol worked efficiently with aromatic aldehydes/ketone via silver catalysis to afford the desired spiro-oxirane products in very short time. This protocol also proved to be practical and gave a clean access to spiro-pyrrolidinedioneoxiranes in a highly regio- as well as chemo-selective manner without a trace of any dioxolane product.

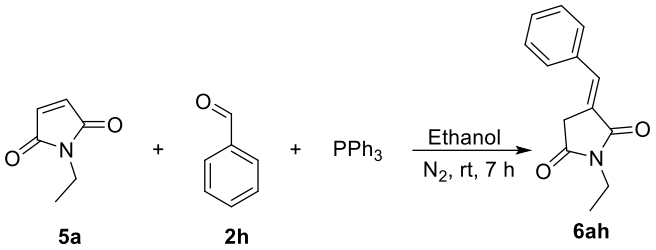
2.4 Experimental section:

2.4.1. General Details:

Unless otherwise noted, all the reactions were carried out with distilled and dried solvents using oven-dried glassware under dry Argon atmosphere. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} precoated aluminum backed plates (2.5 mm) with detection by UV light. The column chromatography was performed using silica gel (200-300 mesh) eluting with petroleum ether and ethyl acetate. The NMR spectra were recorded using tetramethylsilane as the internal standard. ^1H NMR spectra were recorded at 400 MHz, and $^{13}C\{^1H\}$ NMR spectra were recorded at 100/150 MHz (Bruker and Jeol). Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^1H NMR and relative to the central $CDCl_3$ resonance (δ = 77.16 ppm) for ^{13}C NMR spectroscopy. ^{13}C NMR spectra were recorded with complete proton decoupling. ^{19}F NMR spectra were recorded at 377 MHz. Mass samples were analyzed by high resolution mass spectrometry (HRMS) using ESI TOF. Melting points were measured in an open glass capillary and values are uncorrected.

2.4.2. Preparation of Starting Materials

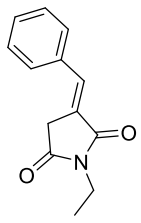
2.4.2.A. General procedure-A for the synthesis of vinylic succinimides:



5a (1 equiv.) **2h** (1.4 equiv.) (1.2 equiv.) **6ah**

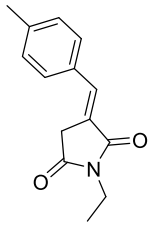
To the stirred solution of *N*-ethyl maleimide **5a** (3 g, 1 equiv., 24 mmol) in ethanol (120 mL) was added triphenylphosphine (7.55 g, 1.2 equiv., 29.0 mmol) in portion at room temperature under N_2 atmosphere. The initial pink coloured reaction mixture slowly turns white suspension over a period of 5-6 min stirring. After which, benzaldehyde (3.5 mL, 1.4 equiv., 34 mmol) was added dropwise into the reaction mixture at rt. During the addition white suspension slowly turns into clear solution. The reaction mixture was allowed to stir for 6 h. The completion of the reaction was monitored by TLC. The white solid formed during the course of the reaction was filtered through sintered glass and was washed with ethanol (10 mL x 2). The crude white solid **6ah** was obtained (3.40 g, 66% yield) and this was used for the next step without further purification.[17]

(E)-3-benzylidene-1-ethylpyrrolidine-2,5-dione ***(6ah):*** Compound **6ah** was synthesized following the general procedure-A. The product was obtained as white solid, 3.40 g (66% yield); R_f =0.30 (petroleum ether/EtOAc 85:15); m.p. 125 – 127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61 (t, *J* = 2.3 Hz, 1H), 7.51 – 7.37 (m, 5H), 3.69 (q, *J* = 7.2 Hz, 2H), 3.55 (d, *J* = 2.3 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 174, 171, 134.3, 134.2, 130.2, 130.2, 129.2, 123.7, 34.2, 34, 13.3. HRMS (ESI TOF): *m/z* calcd for $C_{21}H_{20}NO_3$ $(M + H)^+$: 216.1025, Found: 216.1027.



6ah

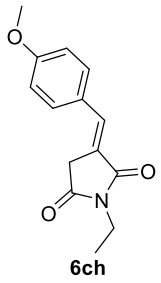
(E)-1-ethyl-3-(4-methylbenzylidene)pyrrolidine-2,5-dione ***(6bh):*** Compound **6bh** was synthesized following the general procedure-A. The product was obtained as white solid, 3.48 g (63% yield); R_f =0.35 (petroleum ether/EtOAc 85:15); m.p. 148 – 150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56 (t, *J* = 2.3 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 3.67 (q, *J* = 7.2 Hz, 2H), 3.51 (d, *J* = 2.3 Hz, 2H), 2.38 (s, 3H), 1.22 (t, *J* = 07.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz,



6bh

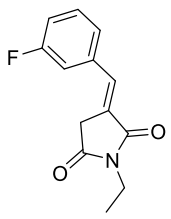
$CDCl_3$): δ (ppm) 174.1, 171.1, 140.7, 134.1, 131.5, 130.3, 130.1, 129.9, 122.6, 34.2, 33.9, 21.6, 13.3. HRMS (ESI TOF): *m/z* calcd for $C_{14}H_{16}NO_2$ $(M + H)^+$: 230.1181, Found: 230.1184.

(E)-1-ethyl-3-(4-methoxybenzylidene)pyrrolidine-2,5-dione ***(6ch)****:* Compound 6ch was synthesized following the general procedure-A. The product was obtained white solid, 4.62 g (79% yield); R_f =0.20 (petroleum ether/EtOAc 85:15); m.p. 142 – 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56 (t, J = 2.2 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.01 – 6.94 (m, 2H), 3.87 (s, 3H), 3.69 (q, J = 7.2 Hz, 2H), 3.52 (d, J = 2.3 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 174.2, 171.2, 161.2, 133.9, 132.1, 127, 120.9, 114.7, 55.5, 34.2, 33.8, 13.3. HRMS (ESI TOF): m/z calcd for $C_{14}H_{16}NO_3$ $(M + H)^+$: 246.1130, Found: 246.1133.



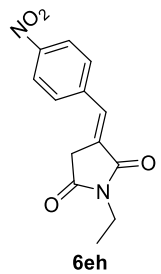
6ch

(E)-1-ethyl-3-(3-fluorobenzylidene)pyrrolidine-2,5-dione ***(6dh)****:* Compound **6dh** was synthesized following the general procedure-A. The product was obtained as white solid, 3.83 g (68% yield); R_f =0.30 (petroleum ether/EtOAc 85:15); m.p. 136 – 138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55 (t, *J* = 2.3 Hz, 1H), 7.42 (td, *J* = 8.0, 5.9 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.19 – 7.07 (m, 2H), 3.69 (q, *J* = 7.2 Hz, 2H), 3.54 (d, *J* = 2.3 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.6, 170.6, 163 (d, *J* = 247.4 Hz), 136.3 (d, *J* = 7.7 Hz), 132.8, 132.8, 130.8 (d, *J* = 8.3 Hz), 126.1, 126.1, 125.2, 117.2 (d, *J* = 21.3 Hz), 116.5 (d, *J* = 22.1 Hz), 34.1, 13.3. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -111.62 (s, 1F). HRMS (ESI TOF): *m/z* calcd for $C_{13}H_{13}FNO_2$ $(M + H)^+$: 234.0930, Found: 234.0931.



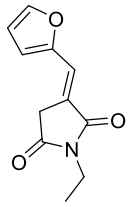
6dh

(E)-1-ethyl-3-(4-nitrobenzylidene)pyrrolidine-2,5-dione ***(6eh)****:* Compound **6eh** was synthesized following the general procedure-A. The product was obtained as white solid, 5 g (80% yield); R_f =0.25 (petroleum ether/EtOAc 85:15); m.p. 195 – 197 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.34 – 8.24 (m, 2H), 7.68 – 7.59 (m, 3H), 3.70 (q, *J* = 7.2 Hz, 2H), 3.59 (d, *J* = 2.3 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.1, 170.1, 148.1, 140.3, 131.3, 130.6, 128, 124.4, 34.2, 34, 13.2. HRMS (ESI TOF): *m/z* calcd for $C_{13}H_{13}N_2O_4$ $(M + H)^+$: 261.0875, Found: 261.0876.



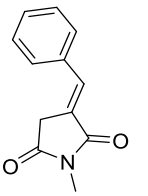
6eh

*(E)-1-ethyl-3-(furan-2-ylmethylene)pyrrolidine-2,5-dione (**6fh**):* Compound **6fh** was synthesized following the general procedure-A. The product was obtained as white solid, 3.10 g (63% yield); R_f =0.30 (petroleum ether/EtOAc 85:15); m.p. 134 – 136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58 (d, *J* = 1.7 Hz, 1H), 7.34 (t, *J* = 2.3 Hz, 1H), 6.68 (d, *J* = 3.5 Hz, 1H), 6.52 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.65 (q, *J* = 7.2 Hz, 2H), 3.58 (d, *J* = 2.3 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 174.4, 170.7, 151.1, 145.8, 121.3, 120.3, 116.7, 112.7, 34.4, 33.8, 13.3. HRMS (ESI TOF): *m/z* calcd for $C_{13}H_{13}N_2O_4$ $(M + H)^+$: 206.0817, Found: 206.0822.



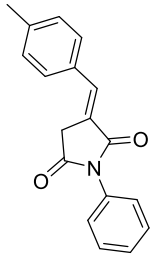
6fh

*(E)-3-benzylidene-1-methylpyrrolidine-2,5-dione (**6a'**):* Compound **6a'** was synthesized following the general procedure-A. The product was obtained as white solid, 4.23 g (78% yield); R_f =0.30 (petroleum ether/EtOAc 85:15); m.p. 169 – 171 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (t, *J* = 2.3 Hz, 1H), 7.50 – 7.38 (m, 5H), 3.55 (d, *J* = 2.3 Hz, 2H), 3.11 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 174.2, 171.2, 134.3, 134.2, 130.2, 129.4, 129.2, 123.6, 34.1, 25. HRMS (ESI TOF): *m/z* calcd for $C_{12}H_{12}NO_2$ $(M + H)^+$: 202.0868, Found: 202.0874.



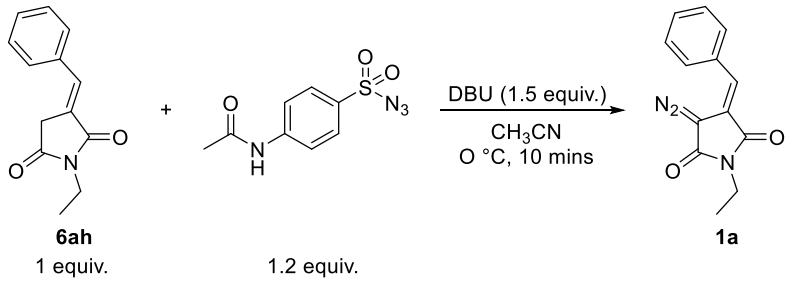
6a'

*(E)-3-(4-methylbenzylidene)-1-phenylpyrrolidine-2,5-dione (**6b'**):* Compound **6b'** was synthesized following the general procedure-A. The product was obtained as white solid, 3.30 g (69% yield); R_f =0.30 (petroleum ether/EtOAc 85:15); m.p. 203 – 205 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72 (t, *J* = 2.3 Hz, 1H), 7.51 (ddd, *J* = 7.8, 6.6, 1.2 Hz, 2H), 7.46 – 7.37 (m, 5H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.76 (d, *J* = 2.3 Hz, 2H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.3, 170.3, 141.1, 135.6, 132.2, 131.5, 130.5, 130.1, 129.3, 128.7, 126.6, 122, 34.5, 21.7. HRMS (ESI TOF): *m/z* calcd for $C_{18}H_{16}NO_2$ $(M + H)^+$: 278.1181, Found: 278.1184.



6b'

2.4.2.B. General Procedure-B for the synthesis of vinyl diazosuccinimides:

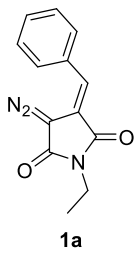


6ah 1 equiv. 1.2 equiv. **1a**

To the stirred solution of *(E)*-3-benzylidene-1-ethylpyrrolidine-2,5-dione **6ah** (2.15 g, 1 equiv., 10 mmol) in 30 mL acetonitrile was added 4-acetamidobenzenesulfonyl azide (2.88

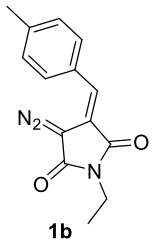
g, 1.2 equiv., 12 mmol) and DBU (2.24 mL, 1.5 equiv., 15 mmol) at 0 °C temperature under inert atmosphere. The reaction mixture was stirred for 10 minutes while maintaining the temperature (0 °C). The reaction mixture was then quenched with saturated solution of NH_4Cl and the product was extracted with diethyl ether (30 mL x 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The extract was filtered and the filtrate was evaporated under reduced pressure. The crude product was purified using column chromatography over silica gel to afford *(E)*-3-benzylidene-4-diazo-1-ethylpyrrolidine-2,5-dione **1a** as orange solid (2.257 g, 94% yield).[18]

*(E)-3-benzylidene-4-diazo-1-ethylpyrrolidine-2,5-dione (**1a**):* Compound **1a** was synthesized following the general procedure-B. The product was obtained as orange solid, 2.257 g, (94% yield); R_f=0.45 (petroleum ether/EtOAc 85:15); m.p.: 94 – 96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (s, 1H), 7.41 (ddd, *J* = 7.6, 6.2, 1.4 Hz, 2H), 7.38 – 7.32 (m, 1H), 7.32 – 7.27 (m, 2H), 3.71 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 167.1, 164.9, 133.5, 129.5, 129, 128.8, 127.5, 117.4, 59.6, 34.5, 13.7. HRMS (ESI TOF): *m/z* calcd for $C_{21}H_{20}NO_3$ $(M + H)^+$: 242.0930, Found: 242.0927.



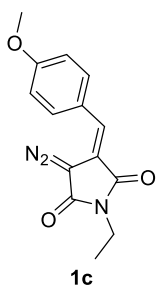
1a

*(E)-3-diazo-1-ethyl-4-(4-methylbenzylidene)pyrrolidine-2,5-dione (**1b**):* Compound **1b** was synthesized from compound **6bh** (0.5 g) following the general procedure-B. The product was obtained as orange red solid (0.475 g, 85% yield): R_f=0.45 petroleum ether/EtOAc (85:15); m.p.: 73 – 75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (s, 1H), 7.24 – 7.16 (m, 4H), 3.70 (q, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 167.2, 164.9, 139.9, 130.7, 129.5, 129.1, 127.7, 116.4, 59.6, 34.4, 21.5, 13.7. HRMS (ESI TOF): *m/z* calcd for $C_{14}H_{14}N_3O_2$ $(M + H)^+$: 256.1086, Found: 256.1086.



1b

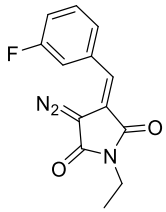
*(E)-3-diazo-1-ethyl-4-(4-methoxybenzylidene)pyrrolidine-2,5-dione (**1c**):* Compound **1c** was synthesized from compound **6ch** (0.5 g) following the general procedure-B. The product was obtained as orange brown solid (0.452 g, 82% yield): R_f =0.30 petroleum ether/EtOAc (85:15); m.p.: 120 – 122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58 (s, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 6.96 – 6.89 (m, 2H), 3.83 (s, 3H), 3.69 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 167.4, 165, 160.7, 130.8, 127.7, 126.1, 115.2, 114.4,



1c

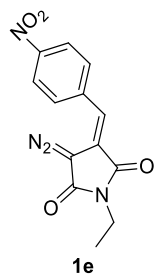
59.5, 55.5, 34.4, 13.7. HRMS (ESI TOF): *m/z* calcd for $C_{14}H_{14}N_3O_3$ $(M + H)^+$: 272.1035, Found: 272.1039.

*(E)-3-diazo-1-ethyl-4-(3-fluorobenzylidene)pyrrolidine-2,5-dione (**1d**):* Compound **1d** was synthesized from compound **6dh** (0.5 g) following the general procedure-B. The product was obtained as orange solid (0.423 g, 76% yield): R_f=0.40 petroleum ether/EtOAc (85:15); m.p.: 65 – 67 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55 (s, 1H), 7.38 (td, *J* = 8.0, 5.9 Hz, 1H), 7.10 – 6.94 (m, 3H), 3.70 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 166.7, 164.6, 162.8 (d, *J* = 248.4 Hz), 135.6 (d, *J* = 7.8 Hz), 130.4 (d, *J* = 8.4 Hz), 125.6, 125.6, 124.6, 124.6, 118.6, 116.4 (d, *J* = 21.2 Hz), 115.7 (d, *J* = 22.1 Hz), 59.7, 34.5, 13.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -111.3 (s, 1F). HRMS (ESI TOF): *m/z* calcd for $C_{13}H_{11}FN_3O_2$ $(M + H)^+$: 260.0835, Found: 260.0838.



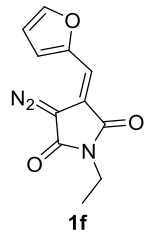
1d

*(E)-3-diazo-1-ethyl-4-(4-nitrobenzylidene)pyrrolidine-2,5-dione (**1e**):* Compound **1e** was synthesized from compound **6eh** (0.5 g) following the general procedure-B. The product was obtained as dark orange solid (0.436 g, 79% yield): R_f=0.30 petroleum ether/EtOAc (85:15); m.p.: 77-79 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.31 – 8.26 (m, 2H), 7.61 (s, 1H), 7.48 – 7.43 (m, 2H), 3.73 (q, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 166.1, 164.3, 147.8, 139.9, 129.7, 124.1, 123.8, 120.6, 60, 34.8, 13.7. HRMS (ESI TOF): *m/z* calcd for $C_{13}H_{11}N_4O_4$ $(M + H)^+$: 287.0780, Found: 287.0778.



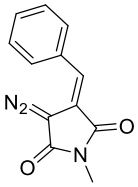
1e

*(E)-3-diazo-1-ethyl-4-(furan-2-ylmethylene)pyrrolidine-2,5-dione (**1f**):* Compound **1f** was synthesized from compound **6fh** (0.5 g) following the general procedure-B. The product was obtained as dark orange solid (0.398 g, 71% yield): R_f=0.35 petroleum ether/EtOAc (85:15); m.p.: 137 – 139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (d, *J* = 1.6 Hz, 1H), 7.24 (s, 1H), 6.69 (d, *J* = 3.5 Hz, 1H), 6.53 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.68 (q, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 167.6, 165.2, 151.3, 145.9, 116.8, 113.4, 113.2, 112.4, 61.3, 34.4, 13.7. HRMS (ESI TOF): *m/z* calcd for $C_{21}H_{20}NO_3$ $(M + H)^+$: 232.0722, Found: 232.0723.



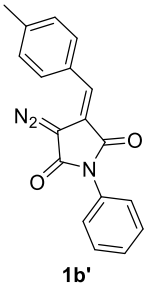
1f

(E)-3-benzylidene-4-diazo-1-methylpyrrolidine-2,5-dione ***(1a'):*** Compound **1a'** was synthesized from compound **6a'** (0.5 g) following the general procedure-B. The product was obtained as orange solid (0.461 g, 82% yield): R_f=0.35 petroleum ether/EtOAc (85:15); m.p.: 100 – 102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (s, 1H), 7.46 – 7.27 (m, 5H), 3.14 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 167.2, 165.1, 133.4, 129.5, 129, 128.8, 127.6, 117.2, 59.7, 25.4. HRMS (ESI TOF): *m/z* calcd for $C_{12}H_{10}N_3O_2$ $(M + H)^+$: 228.0773, Found: 228.0769.



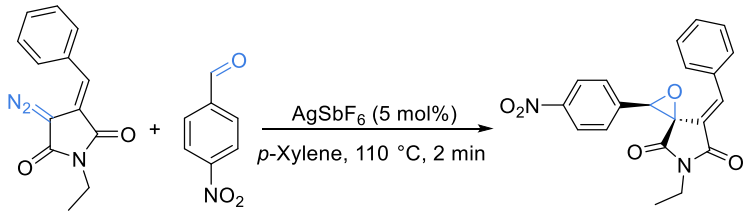
1a'

(E)-3-benzylidene-4-diazo-1-phenylpyrrolidine-2,5-dione ***(1b'):*** Compound **1b'** was synthesized from compound **6b'** (0.5 g) following the general procedure-B. The product was obtained as dark orange solid (0.442 g, 78% yield): R_f=0.40 petroleum ether/EtOAc (85:15); m.p.: 128 – 130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.73 (s, 1H), 7.52 – 7.45 (m, 2H), 7.44 – 7.37 (m, 3H), 7.25 (s, 4H), 2.39 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) 166.5, 164.2, 140.2, 132, 130.7, 129.6, 129.3, 129.2, 128.6, 128.6, 126.6, 115.7, 60.3, 21.6. HRMS (ESI TOF): Calculated for $C_{18}H_{13}N_3O_2$ $(M + H)^+$: 304.1086, Found: 304.1091.



1b'

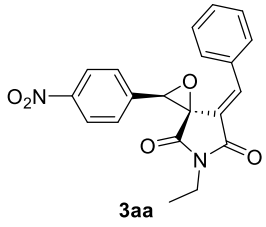
2.4.3. General Procedure-C for the Synthesis of spiro-oxiranes:



1a 2a 3aa

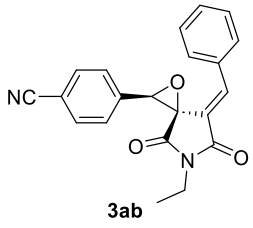
In an oven-dried 25 mL two necked round bottom flask equipped with a magnetic stirrer bar, a mixture of $AgSbF_6$ (7.12 mg, 5 mol%) and *p*-nitrobenzaldehyde **2a** (63 mg, 1 equiv., 0.4 mmol) was stirred in *p*-Xylene (2 mL) at 110 °C under inert atmosphere for a minute. Then vinyl diazosuccinimide **1a** (100 mg, 1 equiv., 0.4 mmol) in *p*-Xylene (1 mL) was added to the reaction mixture dropwise over 2 minutes. As soon as the addition was complete, progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was then purified by column chromatography (petroleum ether/EtOAc 90:10) over silica gel to furnish the desired product **3aa** as white solid (81 mg, 54% yield). The slight amount of *p*-nitrobenzaldehyde **2a** was recovered during the purification.

(2R,3R,E)-7-benzylidene-5-ethyl-2-(4-nitrophenyl)-1-oxa-5-azaspiro[2.4]heptane-4,6-dione



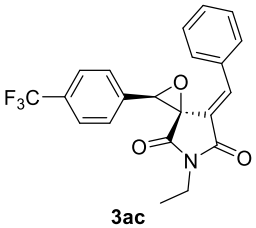
(3aa): Compound **3aa** was synthesized following the general procedure-C. The product was obtained as white solid, 81 mg (54% yield); R_f=0.25 (petroleum ether/EtOAc 85:15); m.p. 176 – 178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.24 – 8.15 (m, 2H), 7.97 (s, 1H), 7.83 – 7.75 (m, 2H), 7.71 – 7.64 (m, 2H), 7.49 – 7.41 (m, 3H), 4.76 (s, 1H), 3.71 – 3.53 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.9, 167.8, 148.2, 140.6, 138.6, 132.4, 131.2, 130.7, 129.3, 128.5, 123.1, 122.2, 61.4, 59.9, 34.5, 13.2. HRMS (ESI TOF): *m/z* calcd for $C_{20}H_{17}N_2O_5$ $(M + H)^+$: 365.1137, Found: 365.1147.

4-((2R,3R,E)-7-benzylidene-5-ethyl-4,6-dioxo-1-oxa-5-azaspiro[2.4]heptan-2-yl)benzonitrile

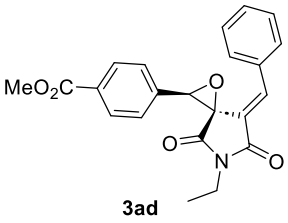


(3ab): Compound **3ab** was synthesized following the general procedure-C. The product was obtained as white solid, 87 mg (61% yield); R_f =0.30 (petroleum ether/EtOAc 85:15); m.p. 169 – 171 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.95 (s, 1H), 7.82 – 7.75 (m, 2H), 7.64 (dd, *J* = 7.7, 5.5 Hz, 4H), 7.44 (dd, *J* = 4.2, 2.4 Hz, 3H), 4.71 (s, 1H), 3.71 – 3.54 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169, 167.8, 140.5, 136.7, 132.4, 131.7, 131.2, 130.7, 129.3, 128.3, 122.4, 118.6, 112.8, 61.4, 60.1, 34.5, 13.2. HRMS (ESI TOF): *m/z* calcd for $C_{21}H_{17}N_2O_3$ $(M + H)^+$: 345.1239, Found: 345.1241.

*(2R,3R,E)-7-benzylidene-5-ethyl-2-(4-(trifluoromethyl)phenyl)-1-oxa-5-azaspiro[2.4]heptane-4,6-dione (**3ac**):* Compound **3ac** was synthesized following the general procedure-C. The product was obtained as white solid, 82 mg (51% yield); R_f =0.40 (petroleum ether/EtOAc 85:15); m.p. 158 – 160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.95 (s, 1H), 7.81 (ddd, *J* = 5.3, 4.4, 2.5 Hz, 2H), 7.61 (s, 4H), 7.47 – 7.41 (m, 3H), 4.73 (s, 1H), 3.73 – 3.54 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.1, 168, 140.2, 135.4, 132.5, 131.2, 131.1, 130.9, 130 (d, *J* = 150.3 Hz), 127.9, 125.4, 125, 124.9, 124.9, 124.9, 122.7, 61.4, 60.5, 34.5, 13.2. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -62.7 (s, 3F). HRMS (ESI TOF): *m/z* calcd for $C_{21}H_{17}F_3NO_3$ $(M + H)^+$: 388.1160, Found: 388.1167.

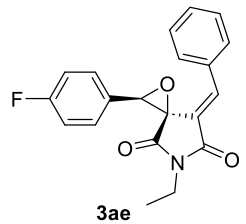


*Methyl 4-((2R,3R,E)-7-benzylidene-5-ethyl-4,6-dioxo-1-oxa-5-azaspiro[2.4]heptan-2-yl)benzoate (**3ad**):* Compound **3ad** was synthesized following the general procedure-C. The product was obtained as white solid, 70 mg (45% yield); R_f =0.35 (petroleum ether/EtOAc 85:15); m.p. 158 – 160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.04 – 8.00 (m, 2H), 7.94 (s, 1H), 7.83 – 7.78 (m, 2H), 7.58 – 7.55 (m, 2H), 7.44 (ddd, *J* = 4.5, 2.8, 1.4 Hz, 3H), 4.74 (s, 1H), 3.90 (s, 3H), 3.71 – 3.54 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ (ppm) 169.1, 168, 166.8, 140.1, 136.4, 132.5, 131, 130.8, 130.6, 129.2, 129.2, 127.5, 122.8, 61.4, 60.7, 52.3, 34.4, 13.2. HRMS (ESI TOF): *m/z* calcd for $C_{22}H_{20}NO_5$ $(M + H)^+$: 378.1341, Found: 378.1340.



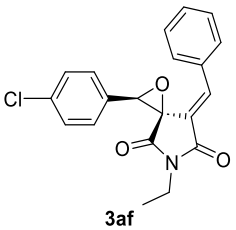
3ad

*(2R,3R,E)-7-benzylidene-5-ethyl-2-(4-fluorophenyl)-1-oxa-5-azaspiro[2.4]heptane-4,6-dione (**3ae**):* Compound **3ae** was synthesized following the general procedure-C. The product was obtained as white solid, 80 mg (57% yield); R_f =0.45 (petroleum ether/EtOAc 85:15); m.p. 145 – 147 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.91 (s, 1H), 7.84 – 7.77 (m, 2H), 7.51 – 7.40 (m, 5H), 7.08 – 7.00 (m, 2H), 4.67 (s, 1H), 3.72 – 3.55 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.3, 168.1, 163.1 (d, *J* = 248.0 Hz), 139.7, 129.4 (d, *J* = 8.4 Hz), 129.2, 127, 126.9, 123, 115 (d, *J* = 21.9 Hz), 61.4, 60.9, 34.4, 13.2. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -112.2 (s, 1F). HRMS (ESI TOF): *m/z* calcd for $C_{20}H_{17}FNO_3$ $(M + H)^+$: 338.1192, Found: 338.1190.



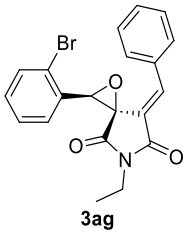
3ae

*(2R,3R,E)-7-benzylidene-2-(4-chlorophenyl)-5-ethyl-1-oxa-5-azaspiro[2.4]heptane-4,6-dione (**3af**):* Compound **3af** was synthesized following the general procedure-C. The product was obtained as white solid, 103 mg (70% yield); R_f =0.45 (petroleum ether/EtOAc 85:15); m.p. 148 – 150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.92 (s, 1H), 7.84 – 7.76 (m, 2H), 7.47 – 7.40 (m, 5H), 7.36 – 7.29 (m, 2H), 4.66 (s, 1H), 3.72 – 3.55 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.2, 168, 139.9, 135, 132.6, 131, 130.8, 129.8, 129.2, 128.9, 128.2, 122.9, 61.4, 60.8, 34.4, 13.2. HRMS (ESI TOF): *m/z* calcd for $C_{20}H_{17}ClNO_3$ $(M + H)^+$: 354.0897, Found: 354.0896.

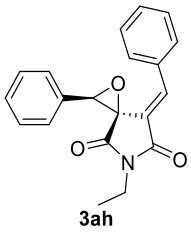


3af

*(2R,3R,E)-7-benzylidene-2-(2-bromophenyl)-5-ethyl-1-oxa-5-azaspiro[2.4]heptane-4,6-dione (**3ag**):* Compound **3ag** was synthesized following the general procedure-C. The product was obtained as white solid, 87 mg (53% yield); R_f =0.45 (petroleum ether/EtOAc 85:15); m.p. 160 – 162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.97 (s, 1H), 7.82 – 7.77 (m, 2H), 7.66 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.48 – 7.36 (m, 5H), 7.24 – 7.18 (m, 1H), 4.67 (s, 1H), 3.73 – 3.58 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.2, 168.2, 140.1, 132.6, 131.8, 130.9, 130.7, 130.2, 129.6, 129.1, 127.2, 122.5, 121.6, 61.2, 61, 34.4, 13.1. HRMS (ESI TOF): *m/z* calcd for $C_{20}H_{17}BrNO_3$ $(M + H)^+$: 398.0392, Found: 398.0397.

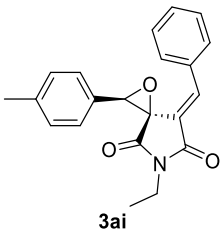


*(2R,3R,E)-7-benzylidene-5-ethyl-2-phenyl-1-oxa-5-azaspiro[2.4]heptane-4,6-dione (**3ah**):*



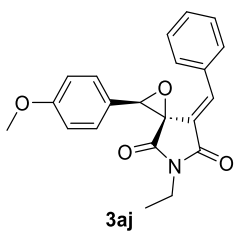
Compound **3ah** was synthesized following the general procedure-C. The product was obtained as white solid, 69 mg (52% yield); R_f =0.50 (petroleum ether/EtOAc 85:15); m.p. 129 – 131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.91 (s, 1H), 7.86 – 7.78 (m, 2H), 7.52 – 7.47 (m, 2H), 7.46 – 7.40 (m, 3H), 7.38 – 7.31 (m, 3H), 4.72 (s, 1H), 3.72 – 3.54 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.3, 168.2, 139.6, 132.6, 131.3, 130.9, 130.8, 129.2, 129, 127.9, 127.4, 123.2, 61.4, 61.4, 34.4, 13.2. HRMS (ESI TOF): *m/z* calcd for $C_{20}H_{18}NO_3$ $(M + H)^+$: 320.1287, Found: 320.1290.

*(2R,3R,E)-7-benzylidene-5-ethyl-2-(p-tolyl)-1-oxa-5-azaspiro[2.4]heptane-4,6-dione (**3ai**):*



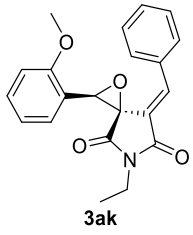
Compound **3ai** was synthesized following the general procedure-C. The product was obtained as white solid, 58 mg (42% yield); R_f =0.45 (petroleum ether/EtOAc 85:15); m.p. 114 – 116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.89 (s, 1H), 7.86 – 7.78 (m, 2H), 7.45 – 7.36 (m, 5H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.69 (s, 1H), 3.72 – 3.54 (m, 2H), 2.34 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.5, 168.2, 139.4, 138.9, 132.7, 130.8, 129.1, 128.7, 128.2, 127.4, 123.3, 61.6, 61.5, 34.3, 21.5, 13.2. HRMS (ESI TOF): *m/z* calcd for $C_{21}H_{20}NO_3$ $(M + H)^+$: 334.1443, Found: 334.1445.

*(2R,3R,E)-7-benzylidene-5-ethyl-2-(4-methoxyphenyl)-1-oxa-5-azaspiro[2.4]heptane-4,6-dione (**3aj**):* Compound **3aj** was synthesized following the general procedure-C. The product was obtained as white solid, 94 mg (65% yield); R_f=0.45 (petroleum ether/EtOAc 85:15); m.p. 134 – 136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.88 (s, 1H), 7.85 – 7.78 (m, 2H), 7.48 –



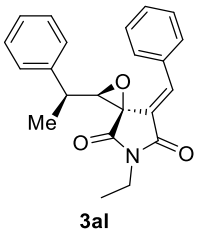
7.38 (m, 5H), 6.91 – 6.83 (m, 2H), 4.66 (s, 1H), 3.80 (s, 3H), 3.72 – 3.55 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 169.4, 168.1, 160, 139.1, 132.6, 130.7, 129, 128.8, 123.2, 122.9, 113.3, 61.6, 61.5, 55.2, 34.2, 13.1. HRMS (ESI TOF): *m/z* calcd for $C_{21}H_{20}NO_4$ $(M + H)^+$: 350.1392, Found: 350.1394.

(2R,3R,E)-7-benzylidene-5-ethyl-2-(2-methoxyphenyl)-1-oxa-5-azaspiro[2.4]heptane-4,6-



*dione (**3ak**):* Compound **3ak** was synthesized following the general procedure-C. The product was obtained as white solid, 100 mg (69% yield); R_f =0.40 (petroleum ether/EtOAc 85:15); m.p. 161 – 163 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.90 (s, 1H), 7.86 – 7.81 (m, 2H), 7.64 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.42 (dd, *J* = 5.1, 1.9 Hz, 3H), 7.34 – 7.27 (m, 1H), 7.06 – 7.01 (m, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 4.77 (s, 1H), 3.72 – 3.56 (m, 5H), 1.18 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 169.5, 168.4, 157.1, 139.1, 132.7, 130.8, 130.6, 129.8, 128.9, 128.6, 123.2, 120.4, 120.1, 109.6, 60.8, 58.4, 55.2, 34.1, 13.1. HRMS (ESI TOF): *m/z* calcd for $C_{21}H_{20}NO_4$ $(M + H)^+$: 350.1392, Found: 350.1393.

(2R,3R,E)-7-benzylidene-5-ethyl-2-((S)-1-phenylethyl)-1-oxa-5-azaspiro[2.4]heptane-4,6-

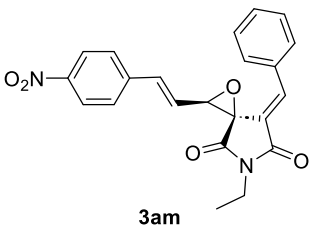


*dione (**3al**):* Compound **3al** was synthesized following the general procedure-C. Two separate diastereomers was obtained.

(A) white solid, 37 mg (26% yield); R_f =0.60 (petroleum ether/EtOAc 85:15); m.p. 110 – 112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.76 – 7.67 (m, 3H), 7.46 – 7.38 (m, 3H), 7.25 – 7.14 (m, 3H), 7.05 – 6.98 (m, 2H), 3.74 – 3.57 (m, 4H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.16 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 171.3, 168.2, 141.6, 139.2, 132.6, 130.9, 130.8, 129, 128.9, 127.2, 127.2, 123.1, 65.9, 60.1, 36.3, 34.3, 18.8, 13.2. HRMS (ESI TOF): *m/z* calcd for $C_{22}H_{22}NO_3$ $(M + H)^+$: 348.1600, Found: 348.1606.

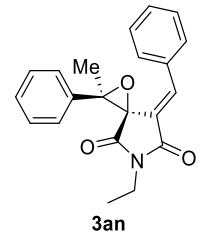
(B) white solid, 35 mg (24% yield); R_f =0.55 (petroleum ether/EtOAc 85:15); m.p. 108 – 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.85 (s, 1H), 7.70 – 7.65 (m, 2H), 7.39 – 7.32 (m, 5H), 7.27 (d, *J* = 7.3 Hz, 3H), 3.85 – 3.77 (m, 3H), 3.68 – 3.59 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.16 (d, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ (ppm) 171.1, 168.4, 142.4, 139.6, 132.5, 130.9, 130.9, 129.1, 128.8, 127.4, 127.1, 123.1, 65.1, 59.6, 36, 34.5, 17.8, 13.4. HRMS (ESI TOF): *m/z* calcd for $C_{22}H_{22}NO_3$ $(M + H)^+$: 348.1600, Found: 348.1606.

*(2R,3R,E)-7-benzylidene-5-ethyl-2-((E)-4-nitrostyryl)-1-oxa-5-azaspiro[2.4]heptane-4,6-dione (**3am**):* Compound **3am** was synthesized following the general procedure-C. The product was obtained as white solid, 65 mg (40% yield); R_f =0.35 (petroleum ether/EtOAc 85:15); m.p. 136 – 138 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 – 8.15 (m, 2H), 7.91 (s, 1H), 7.79 – 7.73 (m, 2H), 7.54 – 7.50 (m, 2H), 7.46 (qd, *J* = 4.0, 2.0 Hz, 3H), 6.90 – 6.79 (m, 2H), 4.28 (dd, *J* = 6.9, 1.0 Hz, 1H), 3.84 – 3.70 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.6, 168.1, 147.7, 141.8, 140.2, 136.3, 132.6, 131.1, 130.8, 129.2, 127.6, 126.1, 124.3, 122.3, 61.5, 60.4, 34.6, 13.3. HRMS (ESI TOF): *m/z* calcd for $C_{22}H_{19}N_2O_5$ $(M + H)^+$: 391.1294, Found: 391.1292.



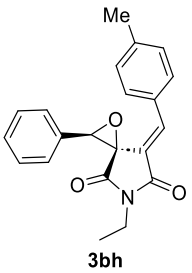
3am

*(2R,3R,E)-7-benzylidene-5-ethyl-2-methyl-2-phenyl-1-oxa-5-azaspiro[2.4]heptane-4,6-dione (**3an**):* Compound **3an** was synthesized following the general procedure-C. The product was obtained as white solid, 55 mg (40% yield); R_f=0.40 (petroleum ether/EtOAc 85:15); m.p. 164 – 166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.92 (s, 1H), 7.85 – 7.79 (m, 2H), 7.46 – 7.29 (m, 8H), 3.66 – 3.51 (m, 2H), 1.43 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.6, 168.5, 139, 137.8, 133.2, 132.3, 130.5, 128.7, 128.3, 128.1, 126.2, 123.2, 72.3, 67.2, 34, 21.5, 13.4. HRMS (ESI TOF): *m/z* calcd for $C_{21}H_{20}NO_3$ $(M + H)^+$: 334.1443, Found: 334.1445.



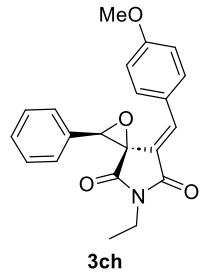
3an

*(2R,3R,E)-5-ethyl-7-(4-methylbenzylidene)-2-phenyl-1-oxa-5-azaspiro[2.4]heptane-4,6-dione (**3bh**):* Compound **3bh** was synthesized following the general procedure-C. The product was obtained as white solid, 76 mg (58% yield); R_f=0.45 (petroleum ether/EtOAc 85:15); m.p. 178 – 180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.88 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.50 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.39 – 7.30 (m, 3H), 7.23 (d, *J* = 8.1 Hz, 2H), 4.77 (s, 1H), 3.71 – 3.53 (m, 2H), 2.39 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.4, 168.4, 141.6, 139.7, 131.4, 131, 130, 129.9, 129, 127.9, 127.4, 122, 61.6, 61.1, 34.3, 21.7, 13.2. HRMS (ESI TOF): *m/z* calcd for $C_{21}H_{20}NO_3$ $(M + H)^+$: 334.1443, Found: 334.1446.



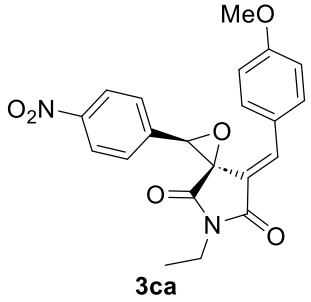
3bh

*(2R,3R,E)-5-ethyl-7-(4-methoxybenzylidene)-2-phenyl-1-oxa-5-azaspiro[2.4]heptane-4,6-dione (**3ch**):* Compound **3ch** was synthesized following the general procedure-C. The product was obtained as white solid, 66 mg (51% yield); R_f =0.35 (petroleum ether/EtOAc 85:15); m.p. 125 – 127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.85 – 7.79 (m, 3H), 7.51 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.39 – 7.30 (m, 3H), 6.96 – 6.91 (m, 2H), 4.83 (s, 1H), 3.85 (s, 3H), 3.70 – 3.53 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.5, 168.6, 162, 139.3, 133.3, 131.4, 129, 127.9, 127.5, 125.4, 120.2, 114.7, 61.8, 60.7, 55.6, 34.3, 13.3. HRMS (ESI TOF): *m/z* calcd for $C_{21}H_{20}NO_4$ $(M + H)^+$: 350.1392, Found: 350.1398.



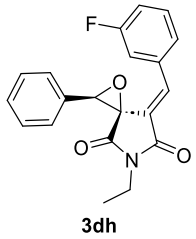
3ch

*(2R,3R,E)-5-ethyl-7-(4-methoxybenzylidene)-2-(4-nitrophenyl)-1-oxa-5-azaspiro[2.4]heptane-4,6-dione (**3ca**):* Compound **3ca** was synthesized following the general procedure-C. The product was obtained as white solid, 72 mg (50% yield); R_f =0.30 (petroleum ether/EtOAc 70:30); m.p. 163 – 165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.24 – 8.18 (m, 2H), 7.88 (s, 1H), 7.81 – 7.76 (m, 2H), 7.74 – 7.65 (m, 2H), 6.99 – 6.93 (m, 2H), 4.87 (s, 1H), 3.86 (s, 3H), 3.70 – 3.52 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.9, 168.1, 162.1, 148, 140.3, 138.7, 133.1, 128.4, 125, 123, 119.1, 114.7, 61.6, 59.2, 55.5, 34.3, 13.1. HRMS (ESI TOF): *m/z* calcd for $C_{21}H_{19}N_2O_6$ $(M + H)^+$: 395.1243, Found: 395.1238.



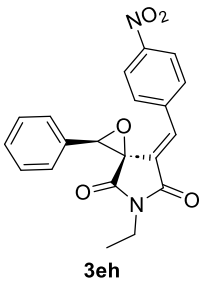
3ca

*(2R,3R,E)-5-ethyl-7-(3-fluorobenzylidene)-2-phenyl-1-oxa-5-azaspiro[2.4]heptane-4,6-dione (**3dh**):* Compound **3dh** was synthesized following the general procedure-C. The product was obtained as white solid, 78 mg (60% yield); R_f=0.45 (petroleum ether/EtOAc 85:15); m.p. 139 – 141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.84 (s, 1H), 7.61 – 7.56 (m, 2H), 7.53 – 7.46 (m, 2H), 7.44 – 7.32 (m, 4H), 7.13 (tdd, *J* = 8.3, 2.5, 0.8 Hz, 1H), 4.67 (s, 1H), 3.72 – 3.54 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169, 167.8, 162.9 (d, *J* = 247.3 Hz), 137.8, 137.8, 134.5 (d, *J* = 8.1 Hz), 131, 130.7 (d, *J* = 8.2 Hz), 129.2, 127.9, 127.5, 126.7, 126.7, 124.6, 117.8 (d, *J* = 21.3 Hz), 117.2 (d, *J* = 22.8 Hz), 61.9, 61.4, 34.5, 13.2. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -111.4 (s, 1F). HRMS (ESI TOF): *m/z* calcd for $C_{20}H_{17}FNO_3$ $(M + H)^+$: 338.1192, Found: 338.1198.



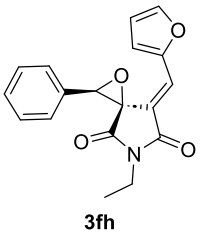
3dh

(2R,3R,E)-5-ethyl-7-(4-nitrobenzylidene)-2-phenyl-1-oxa-5-azaspiro[2.4]heptane-4,6-dione



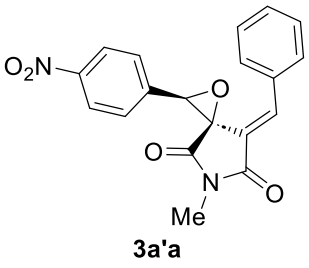
(3eh): Compound **3eh** was synthesized following the general procedure-C. The product was obtained as pale green solid, 75 mg (59% yield); R_f =0.20 (petroleum ether/EtOAc 85:15); m.p. 166 – 168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.31 – 8.23 (m, 2H), 8.00 – 7.94 (m, 2H), 7.90 (s, 1H), 7.47 (dq, *J* = 5.1, 3.0 Hz, 2H), 7.40 – 7.31 (m, 3H), 4.51 (s, 1H), 3.73 – 3.56 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.6, 167.2, 148.6, 138.6, 135.9, 131.3, 130.5, 129.4, 128, 127.4, 127.3, 124.2, 62.9, 61.4, 34.6, 13.2. HRMS (ESI TOF): *m/z* calcd for $C_{20}H_{17}N_2O_5$ $(M + H)^+$: 365.1137, Found: 365.1141.

(2R,3R,E)-5-ethyl-7-(furan-2-ylmethylene)-2-phenyl-1-oxa-5-azaspiro[2.4]heptane-4,6-dione



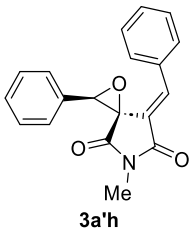
(3fh): Compound **3fh** was synthesized following the general procedure-C. The product was obtained as white solid, 59 mg (44% yield); R_f=0.35 (petroleum ether/EtOAc 85:15); m.p. 140 – 142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.88 (s, 1H), 7.66 (dt, *J* = 3.7, 1.0 Hz, 1H), 7.61 – 7.52 (m, 3H), 7.42 – 7.33 (m, 3H), 7.12 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.11 (s, 1H), 3.70 – 3.52 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.2, 168.2, 135.8, 135.2, 133.4, 131.3, 129.3, 129.1, 128.9, 128, 127.5, 119.6, 62, 61.6, 34.3, 13.3. HRMS (ESI TOF): *m/z* calcd for $C_{18}H_{16}NO_4$ $(M + H)^+$: 310.1079, Found: 310.1083.

(2R,3R,E)-7-benzylidene-5-methyl-2-(4-nitrophenyl)-1-oxa-5-azaspiro[2.4]heptane-4,6-dione



(3a'a): Compound **3a'a** was synthesized following the general procedure-C. The product was obtained as white solid, 63 mg (41% yield); R_f=0.30 (petroleum ether/EtOAc 70:30); m.p. 191 – 193 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.23 – 8.19 (m, 2H), 7.98 (s, 1H), 7.81 – 7.77 (m, 2H), 7.70 – 7.66 (m, 2H), 7.48 – 7.43 (m, 3H), 4.76 (s, 1H), 3.07 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169, 168, 148.1, 140.6, 138.4, 132.2, 131.1, 130.6, 129.2, 128.4, 123, 122, 61.4, 59.8, 25.3. HRMS (ESI TOF): *m/z* calcd for $C_{19}H_{15}N_2O_5$ $(M + H)^+$: 351.0981, Found: 351.0984.

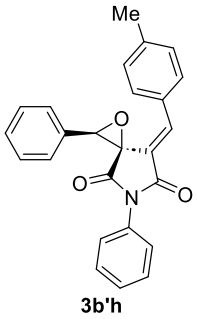
(2R,3R,E)-7-benzylidene-5-methyl-2-phenyl-1-oxa-5-azaspiro[2.4]heptane-4,6-dione ***(3a'h):***



3a'h

Compound **3a'h** was synthesized following the general procedure-D. The product was obtained as white solid, 68 mg (51% yield); R_f=0.45 (petroleum ether/EtOAc 85:15); m.p. 146 – 148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.92 (s, 1H), 7.85 – 7.80 (m, 2H), 7.53 – 7.48 (m, 2H), 7.45 – 7.41 (m, 3H), 7.39 – 7.32 (m, 3H), 4.72 (s, 1H), 3.07 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.6, 168.5, 139.6, 132.6, 131.2, 130.9, 130.8, 129.2, 129.1, 127.9, 127.5, 123.1, 61.6, 61.4, 25.3. HRMS (ESI TOF): *m/z* calcd for $C_{19}H_{16}NO_3$ $(M + H)^+$: 306.1130, Found: 306.1138.

(2R,3R,E)-7-benzylidene-2,5-diphenyl-1-oxa-5-azaspiro[2.4]heptane-4,6-dione ***(3b'h):***



3b'h

Compound **3b'h** was synthesized following the general procedure-D. The product was obtained as white solid, 45 mg (36% yield); R_f=0.50 (petroleum ether/EtOAc 85:15); m.p. 200 – 202 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.01 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.54 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.42 (ddd, *J* = 7.7, 6.5, 1.3 Hz, 2H), 7.37 – 7.30 (m, 6H), 7.27 (s, 1H), 7.25 (s, 1H), 4.86 (s, 1H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.6, 167.6, 141.9, 141, 131.7, 131.2, 131.1, 130, 129.9, 129.1, 129, 128.7, 128, 127.6, 126.4, 121.5, 61.8, 61.7, 21.7. HRMS (ESI TOF): *m/z* calcd for $C_{25}H_{20}NO_3$ $(M + H)^+$: 382.1443, Found: 382.1446.

2.4.4. Gram Scale Synthesis:

In an oven-dried 10 mL two necked round bottom flask equipped with a magnetic stirrer bar, a mixture of $AgSbF_6$ (71.22 mg, 5 mol%) and *p*-nitrobenzaldehyde **2a** (626 mg, 1 equiv., 0.4 mmol) was stirred in *p*-Xylene (20 mL) at 110 °C under inert atmosphere for a minute. Then vinyl diazosuccinimide **1a** (1 g, 1 equiv., 0.4 mmol) in *p*-Xylene (10 mL) was added to the reaction mixture dropwise over 5 minutes. As soon as the addition was complete, progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was then purified by column chromatography (petroleum ether/EtOAc 90:10) over silica gel to furnish the desired product **3aa** as white solid (0.722 g, 48% yield). The slight amount of *p*-nitrobenzaldehyde **2a** was recovered during the purification.

2.4.5. Appendix II: ^{1}H, $^{13}C\{^{1}H\}$, and ^{19}F NMR spectral data of representative compounds

Compound No.	Figure II.X	Data	Page No.
6ah	Figure II.1 and II.2	^{1}H and ^{13}C	52
1a	Figure II.3 and II.4	^{1}H and ^{13}C	53
3aa	Figure II.5 and II.6	^{1}H and ^{13}C	54
3al (A)	Figure II.7A and II.8A	^{1}H and ^{13}C	55
3al (B)	Figure II.9B and II.10B	^{1}H and ^{13}C	56
3am	Figure II.11 and II.12	^{1}H and ^{13}C	57
3bh	Figure II.13 and II.14	^{1}H and ^{13}C	58

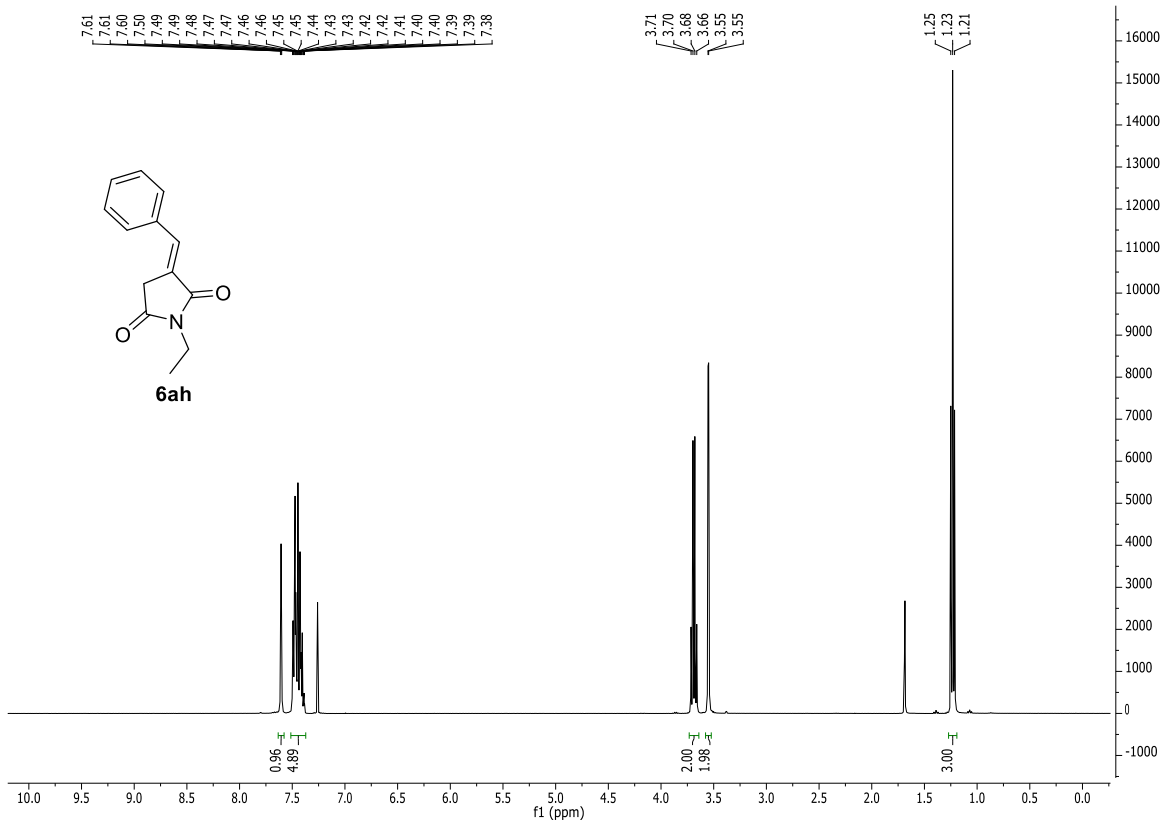


Figure II.1. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **6ah**

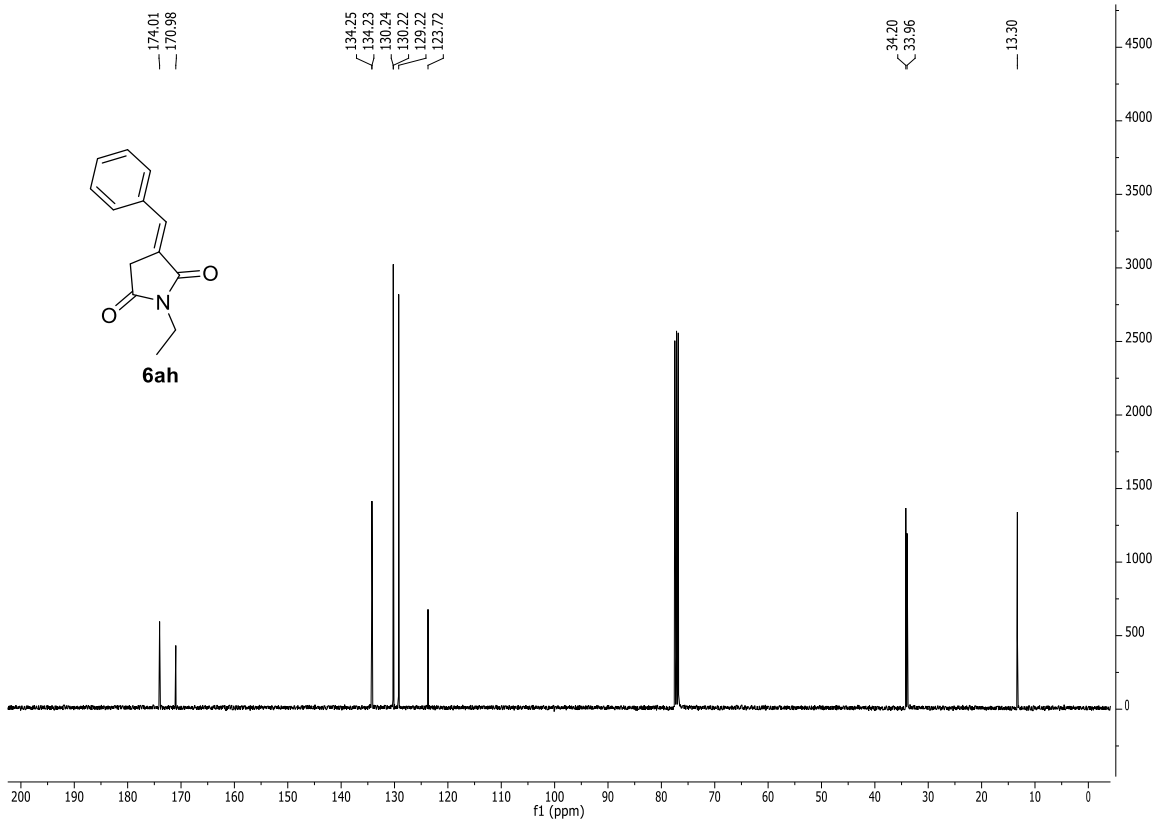


Figure II.2. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **6ah**

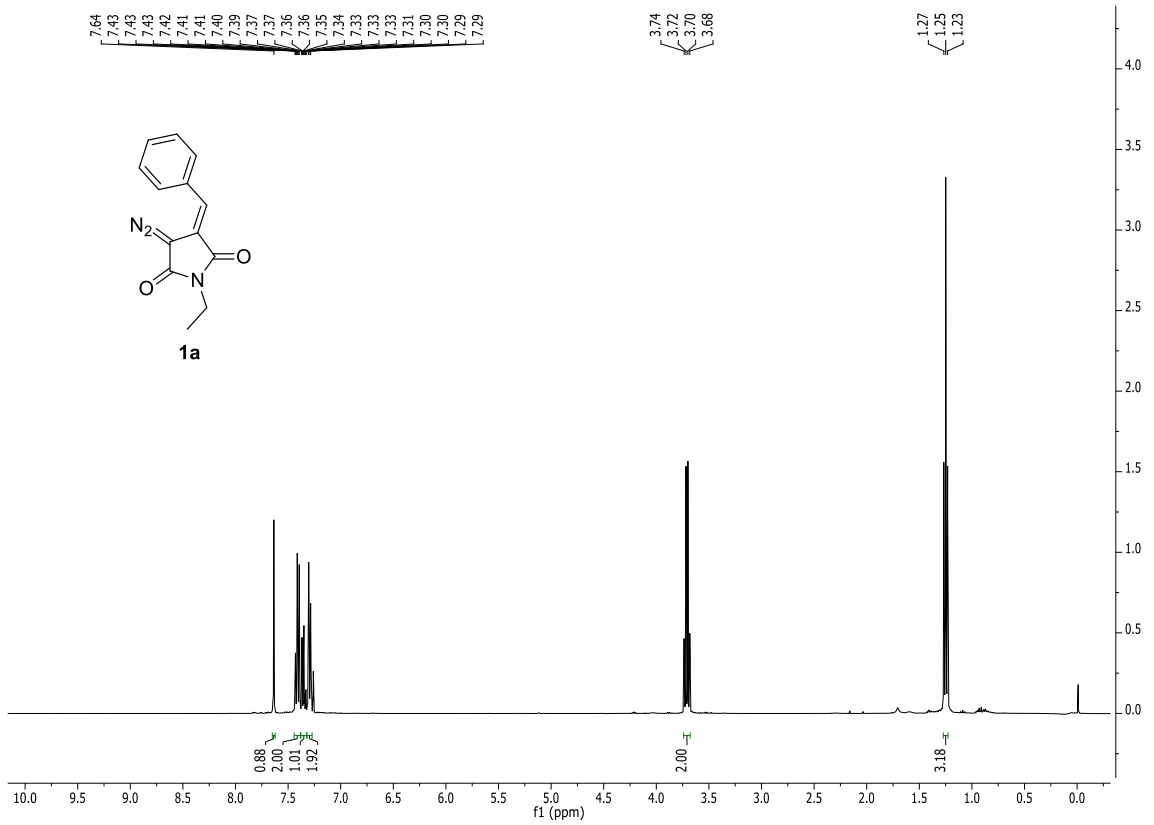


Figure II.3. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **1a**

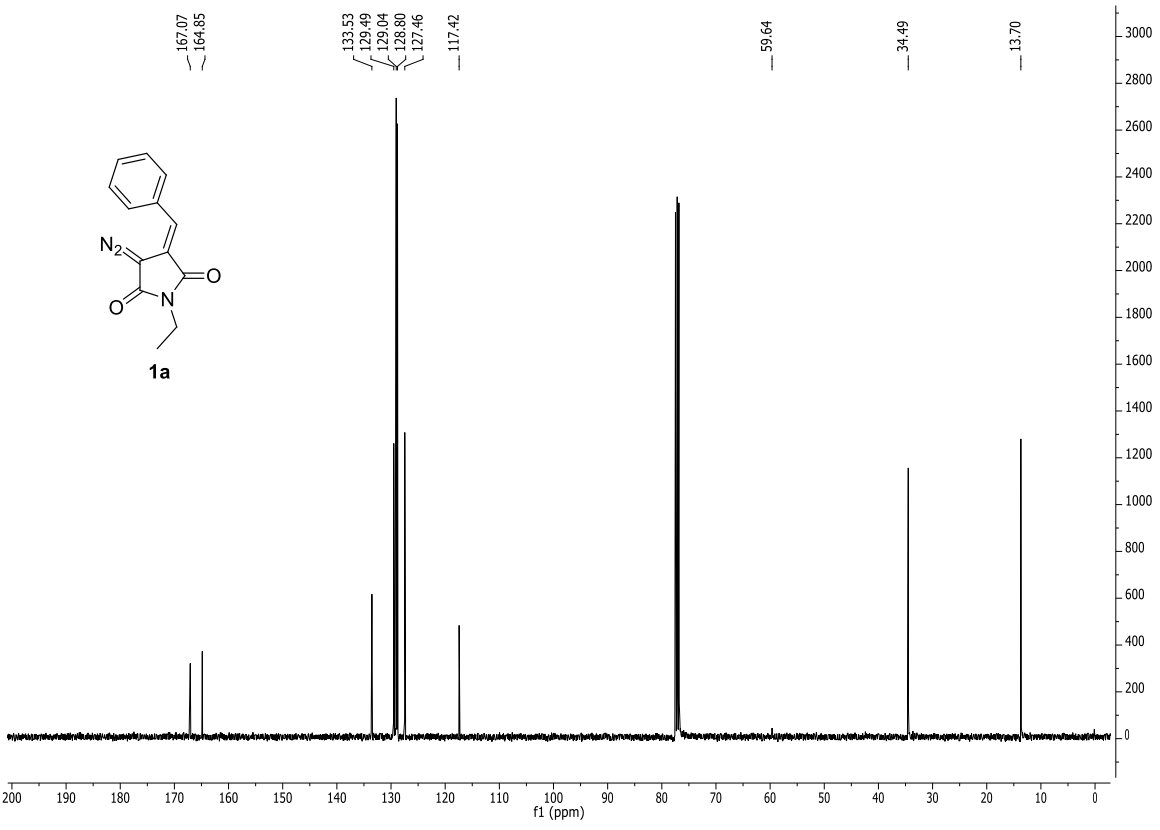


Figure II.4. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **1a**

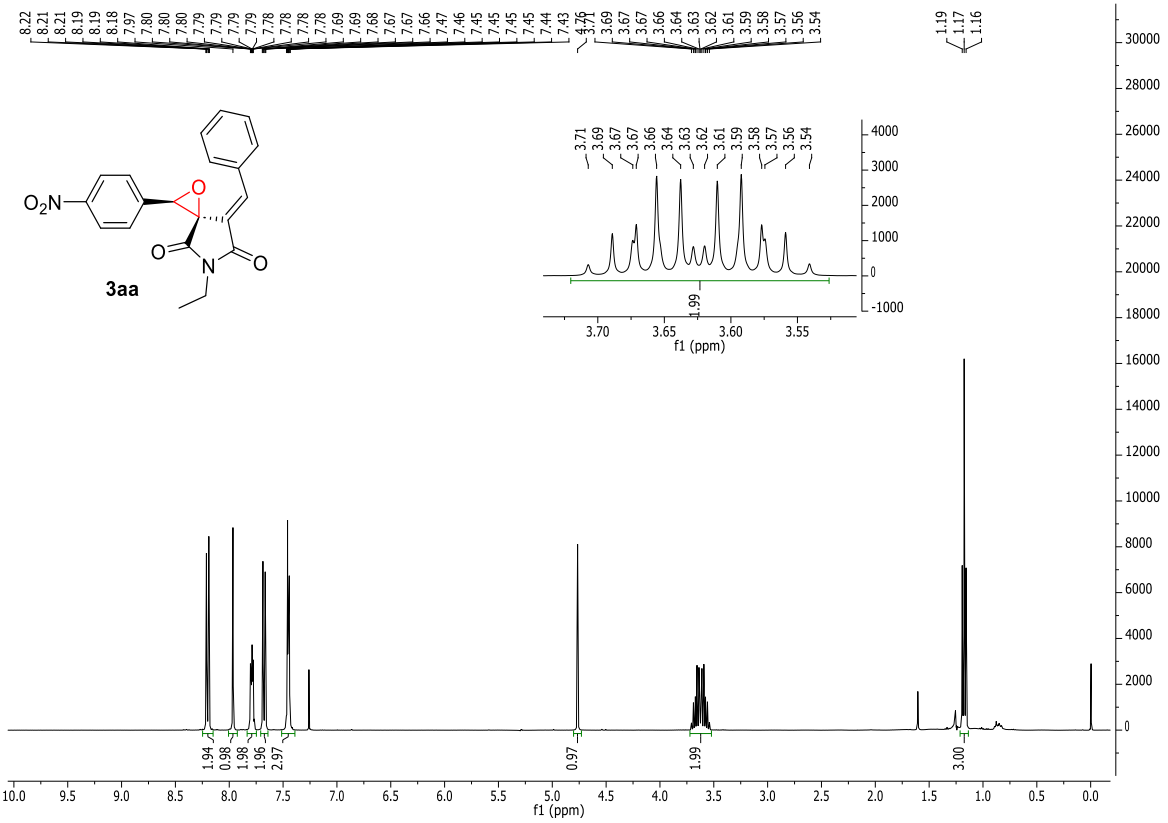


Figure II.5. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3aa**

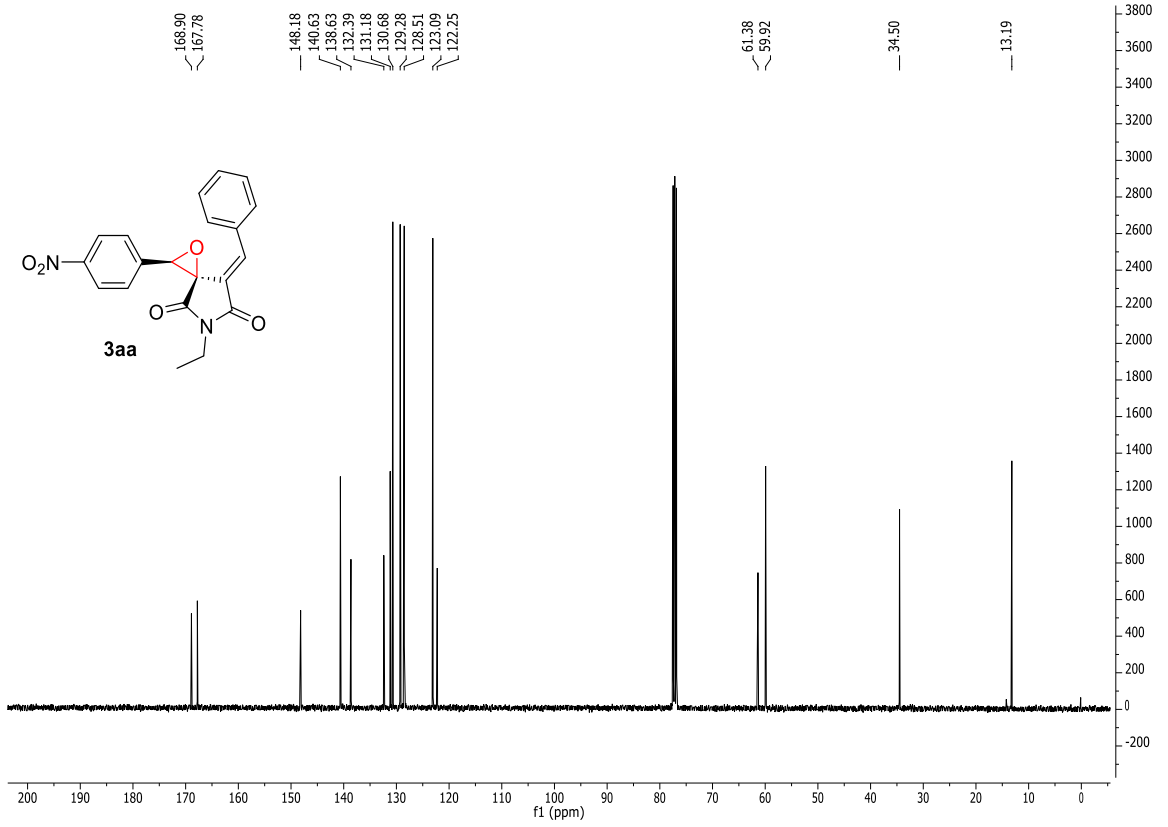


Figure II.6. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3aa**

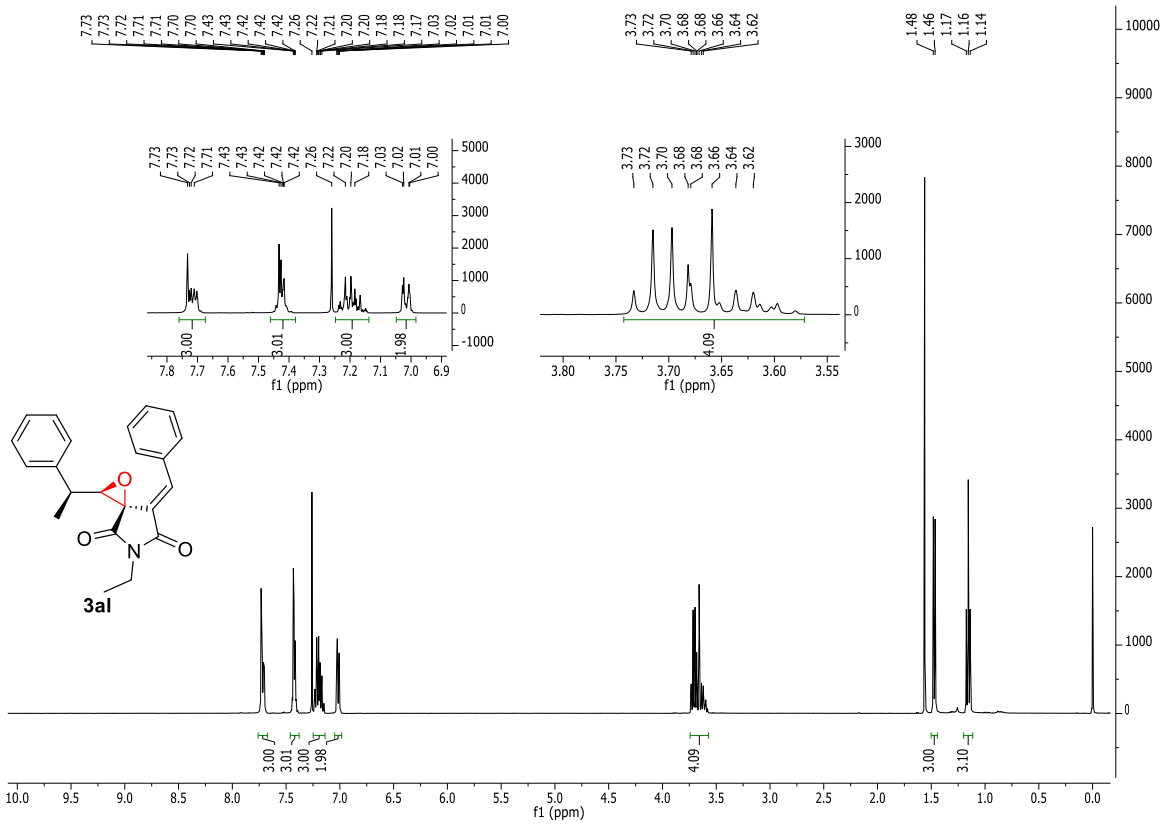


Figure II.7A. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3al**

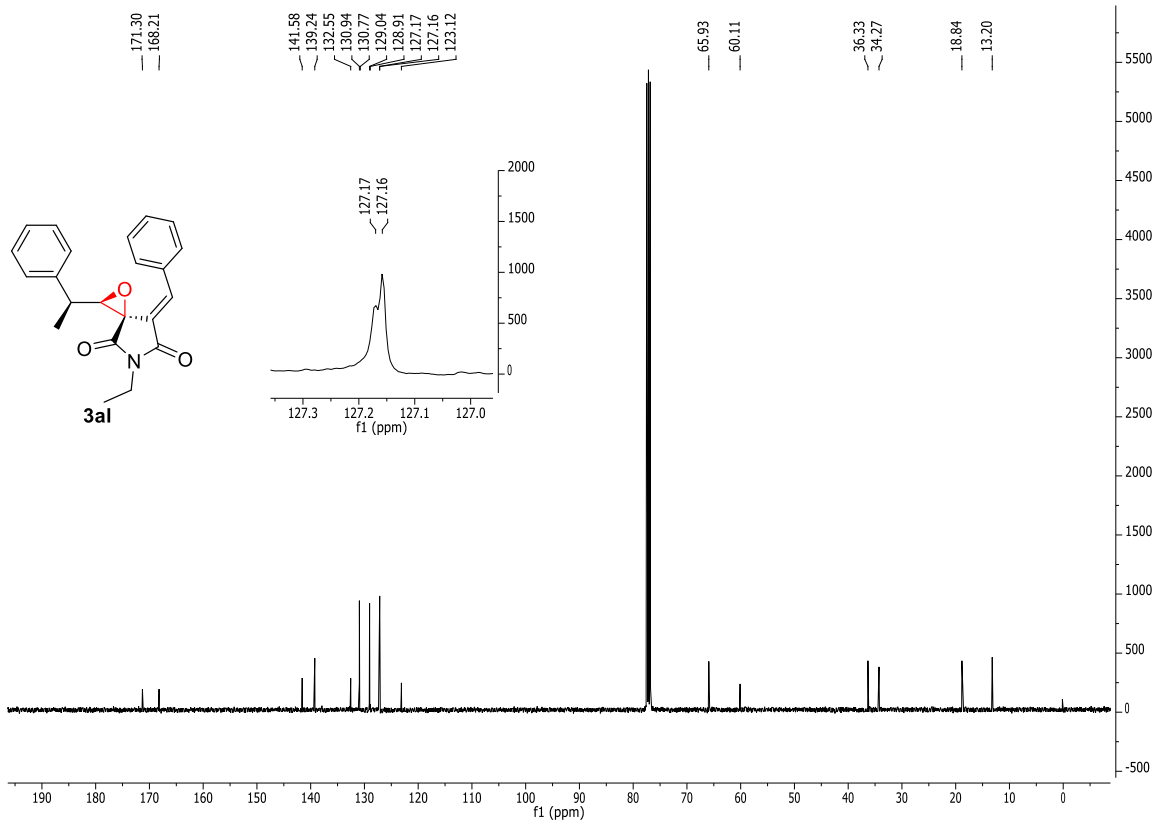


Figure II.8A. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3al**

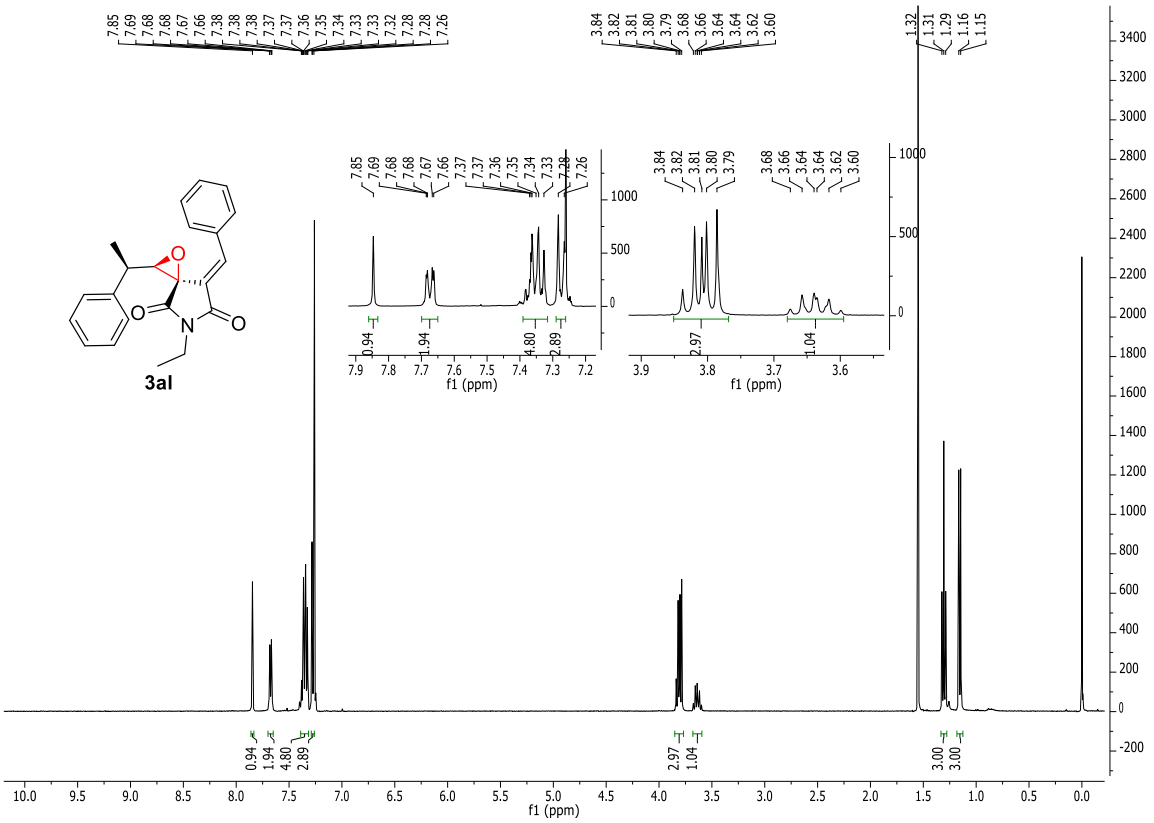


Figure II.9B. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3al**

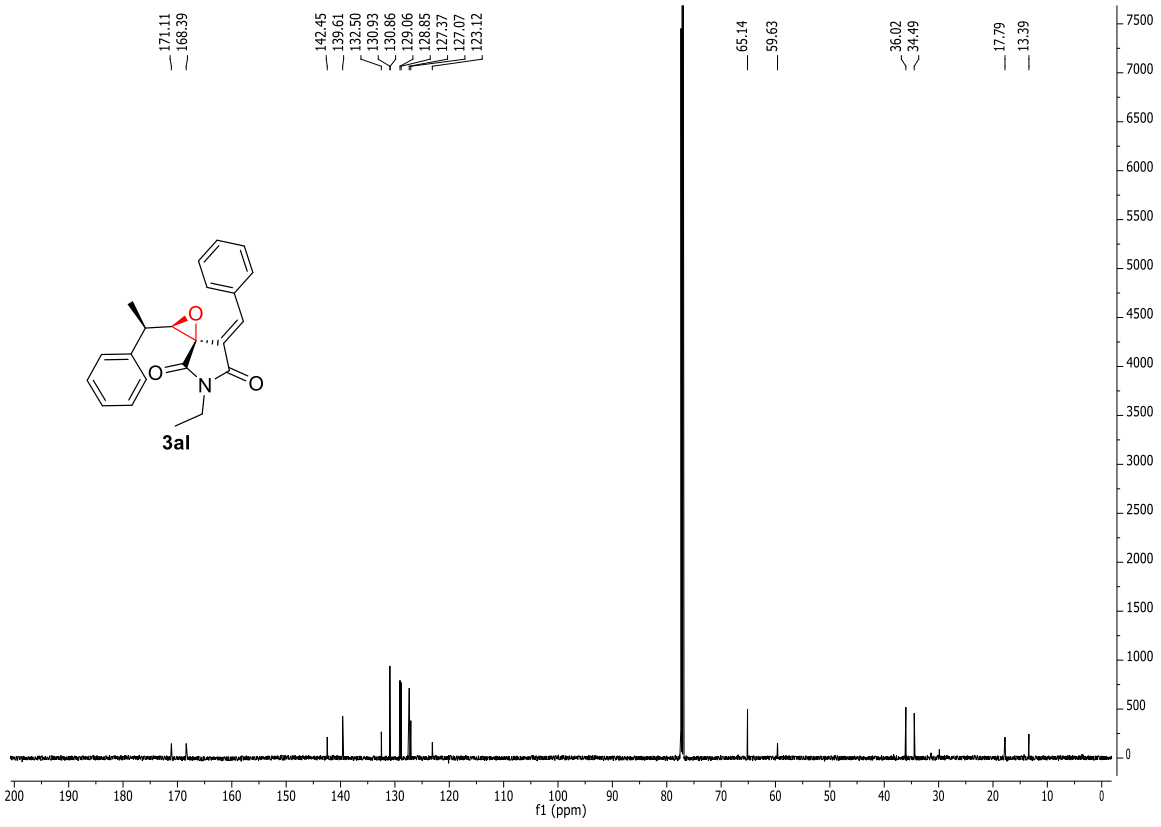


Figure II.10B. $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) spectrum of compound **3al**

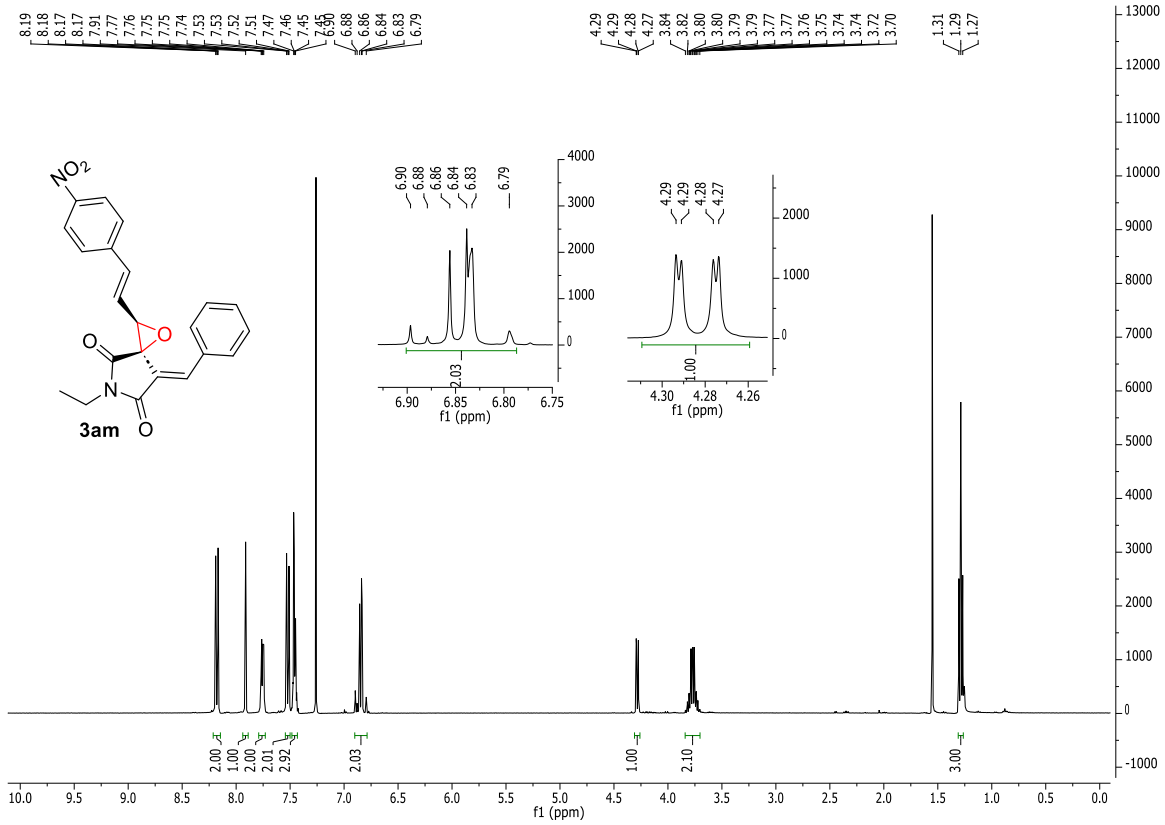


Figure II.11. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3am**

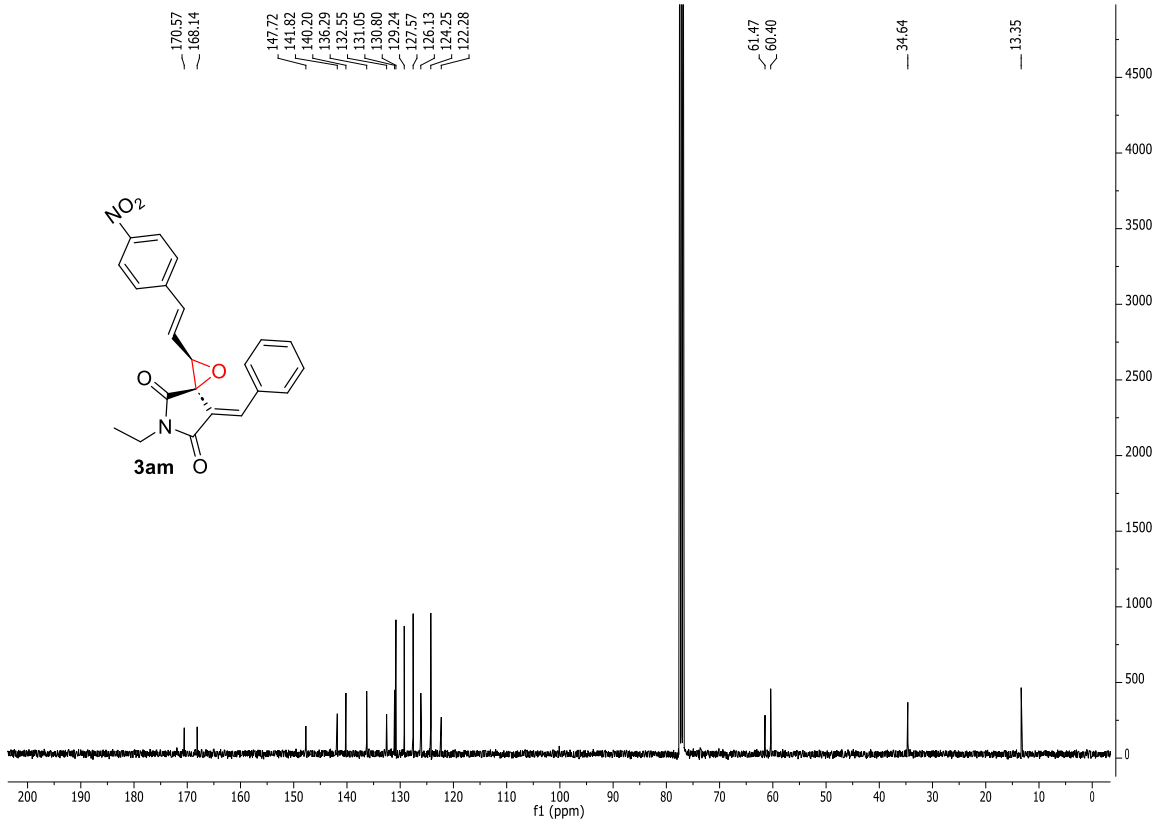


Figure II.12. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3am**

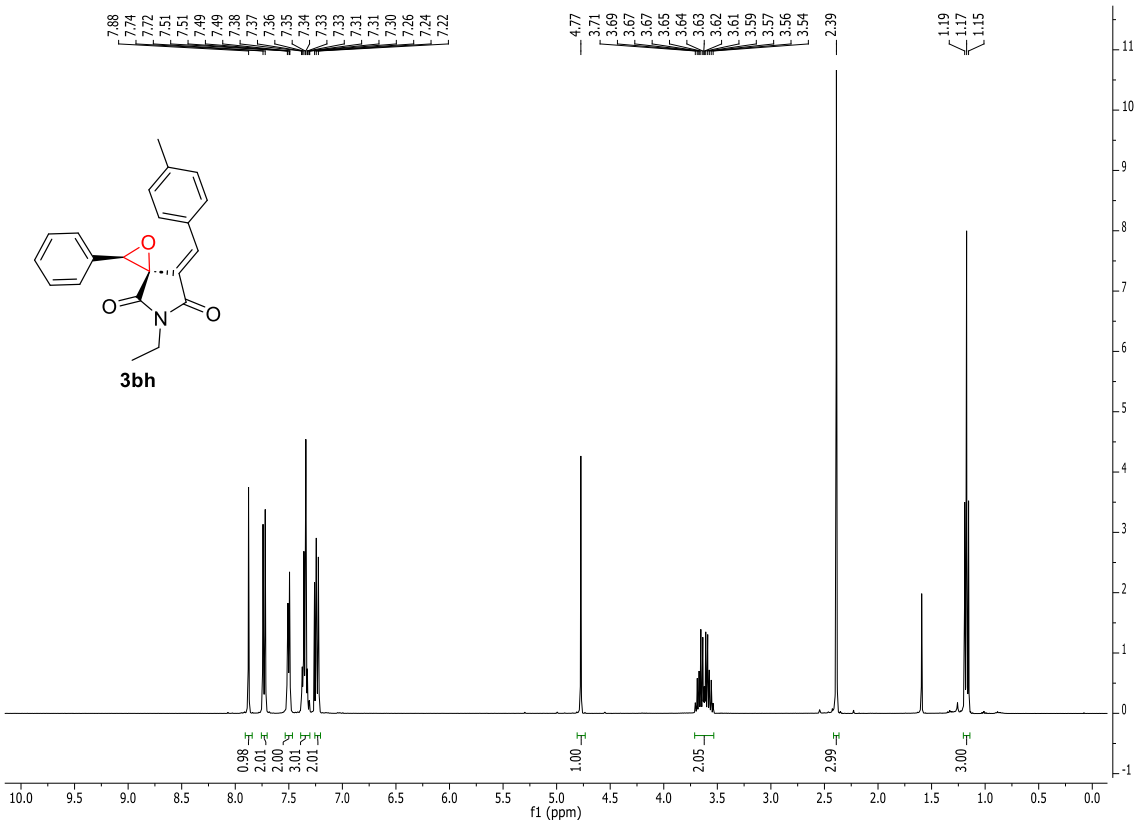


Figure II.13. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3bh**

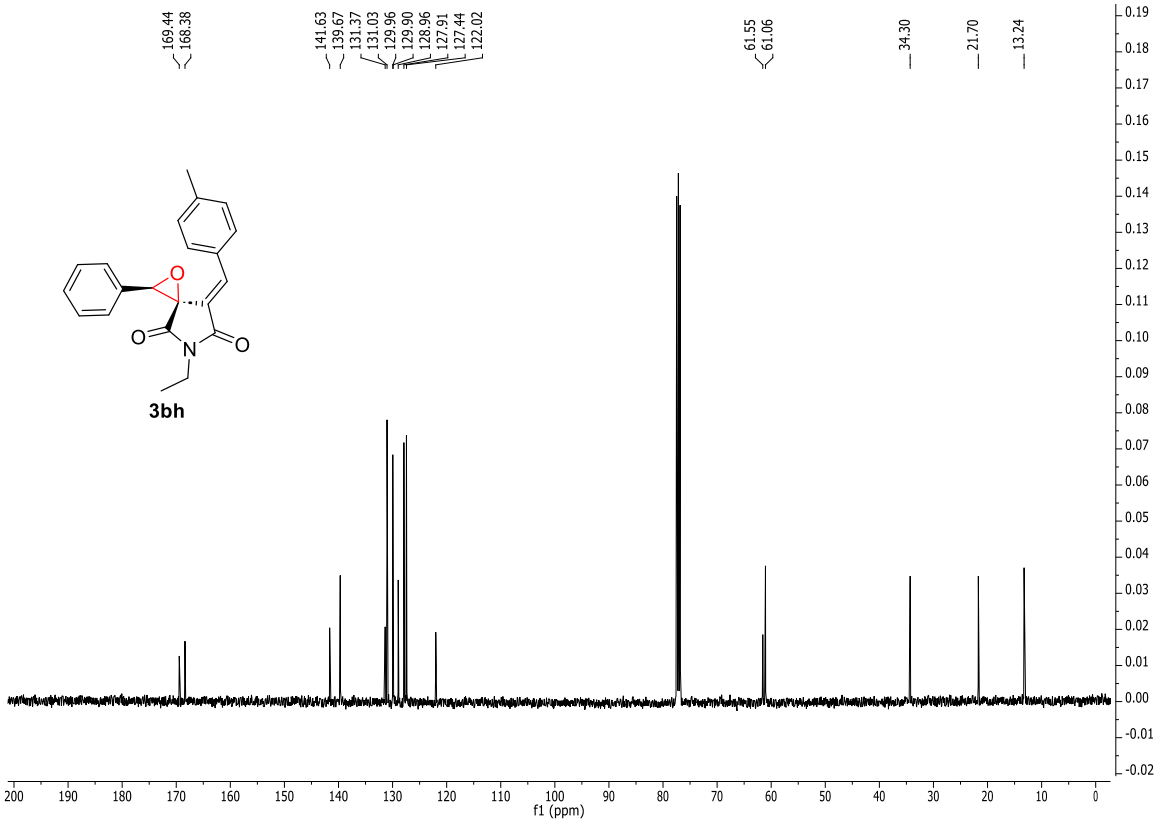


Figure II.14. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3bh**

2.4.6. Appendix IIB: Molecular structures of compound 3al:

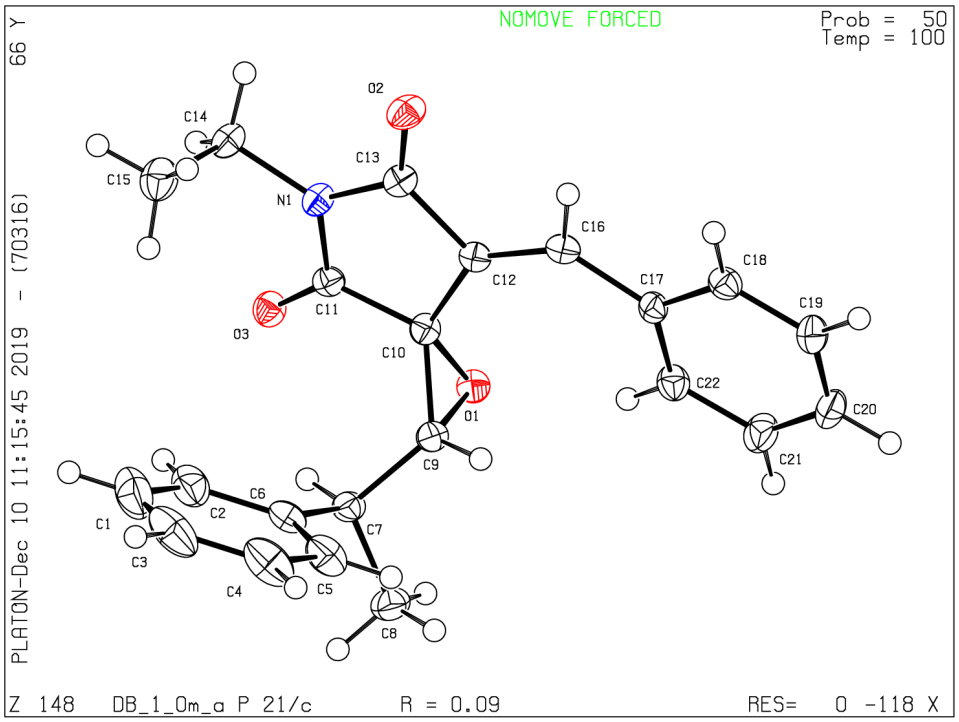
Molecular Structure of compound 3al using Single Crystal X-ray analysis:

[A]

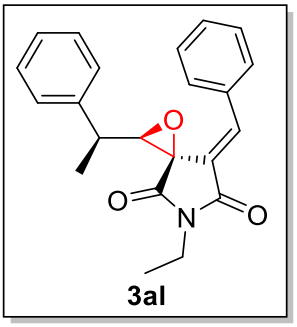
Datablock: DB_1_0m_a

```
Bond precision:  C-C = 0.0049 A          Wavelength=0.71073
Cell:        a=8.739(8) b=32.43(3)     c=6.947(6)
             alpha=90   beta=112.23(2) gamma=90
Temperature: 100 K
                 Calculated                Reported
Volume           1823(3)                   1823(3)
Space group      P 21/c                    P 21/c
Hall group       -P 2ybc                   -P 2ybc
Moiety formula   C22 H21 N O3              C22 H21 N O3
Sum formula      C22 H21 N O3              C22 H21 N O3
Mr               347.40                    347.40
Dx,g cm-3        1.266                     1.266
Z                4                         4
Mu (mm-1)        0.084                     0.084
F000             736.0                     736.0
F000'            736.34
h,k,lmax         11,43,9                   11,43,9
Nref             4580                      4544
Tmin,Tmax        0.941,0.967               0.941,0.967
Tmin'            0.935
Correction method= # Reported T Limits:
Tmin=0.941 Tmax=0.967 AbsCorr = MULTI-SCAN
Data completeness= 0.992  Theta(max)= 28.392
R(reflections)= 0.0858(      wR2(reflections)= 0.2057(
3392)                        4544)
S = 1.176         Npar= 238
```

Molecular Structure of compound 3al using Single Crystal X-ray analysis



ORTEP and thermal ellipsoids at 50% probability



3al

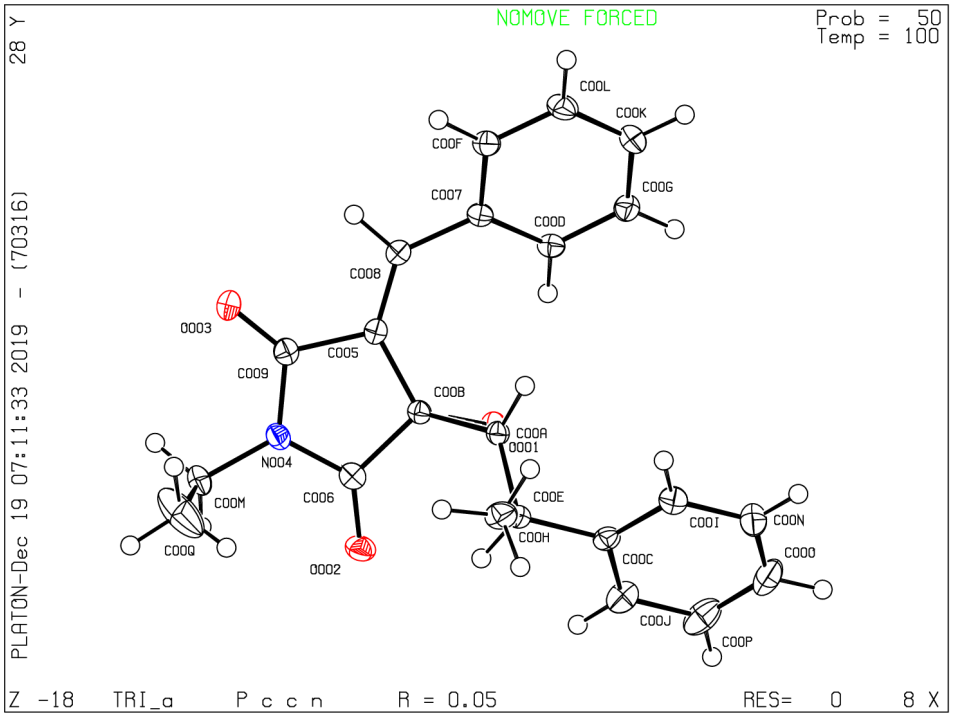
Molecular Structure of compound 3al using Single Crystal X-ray analysis

[B]

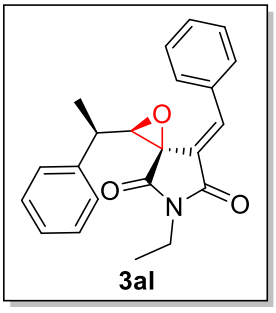
Datablock: TRI_a

```
Bond precision:      C-C = 0.0021 A              Wavelength=0.71073
Cell:        a=19.325(4)    b=21.396(5)    c=8.8602(18)
             alpha=90       beta=90        gamma=90
Temperature:100 K
                    Calculated                    Reported
Volume              3663.5(14)                    3663.4(13)
Space group         P c c n                       P c c n
Hall group          -P 2ab 2ac                    -P 2ab 2ac
Moiety formula      C22 H21 N O3                  ?
Sum formula         C22 H21 N O3                  C22 H21 N O3
Mr                  347.40                        347.40
Dx,g cm-3           1.260                         1.260
Z                   8                             8
Mu (mm-1)           0.084                         0.084
F000                1472.0                        1472.0
F000'               1472.68
h,k,lmax            25,27,11                      25,27,11
Nref                4200                          4197
Tmin,Tmax           0.988,0.992                   0.442,0.746
Tmin'               0.988
Correction method= # Reported T Limits: Tmin=0.442
Tmax=0.746 AbsCorr = MULTI-SCAN
Data completeness= 0.999       Theta(max)= 27.483
R(reflections)= 0.0500( 3473)     wR2(reflections)= 0.1290( 4197)
S = 1.041             Npar= 237
```

Molecular Structure of compound 3al using Single Crystal X-ray analysis



ORTEP and thermal ellipsoids at 50% probability



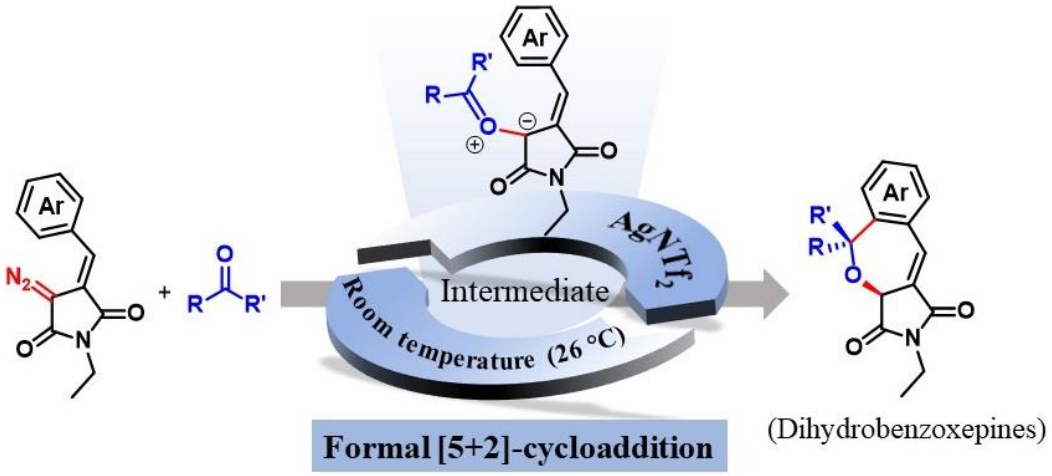
3al

2.5. References:

1. K. Hinterding, E. N. Jacobsen, *J. Org. Chem.* **1999**, *63*, 2164–2165.
2. a) J. M. Concellón, H. Cuervo, R. Fernández-Fano, *Tetrahedron* **2001**, *57*, 8983–8987; b) G. Darzens, *C. R. Hebd. Seances Acad. Sci.* **1904**, *139*, 1214; c) G. Darzens, *C. R. Hebd. Seances Acad. Sci.* **1905**, *141*, 766; d) G. Darzens, *C. R. Hebd. Seances Acad. Sci.* **1906**, *142*, 214.
3. P. de March, R. Huisgen, *J. Am. Chem. Soc.* **1982**, *104*, 4952.
4. M. Alt, G. Maas, *Tetrahedron* **1994**, *50*, 7435.
5. a) M. P. Doyle, D. C. Forbes, M. N. Protopopova, S. A. Stanley, M. M. Vasbinder, K. R. Xavier, *J. Org. Chem*. **1997**, *62*, 7210; b) M. P. Doyle, D. C. Forbes, K. R. Xavier, *Russ. Chem. Bull*. **1998**, *47*, 932.
6. a) A. -H. Li, L. -X. Dai, V. K. Aggarwal, *Chem. Rev.* **1997**, *97*, 2341; b) V. K. Aggarwal, *Synlett* **1998**, 329; c) V. K. Aggarwal, E. Alonso, G. Hynd, K. M. Lydon, M. J. Palmer, M. Porcelloni, J. R. Studley, *Angew. Chem., Int. Ed*. **2001**, *40*, 1430.
7. M. P. Doyle, W. Hu, D. J. Timmons, *Org. Lett*. **2001**, *3*, 933.
8. H. M. L. Davies, J. DeMeese, *Tetrahedron Lett*. **2001**, *42*, 6803–6805.
9. S. Muthusamy, C. Gunanathan, M. Nethaji, *Synlett* **2004**, 639–624.
10. S. Muthusamy, R. Ramkumar, A. K. Mishra, *Tetrahedron Lett*. **2011**, *52*, 148–150.
11. S. Muthusamy, R. Ramkumar, *Tetrahedron* **2015**, *71*, 6219–6226.
12. a) M. Prudhomme, *Eur. J. Med. Chem*. **2003**, *38*, 123; b) G. Zhang, J. Shen, H. Cheng, L. Zhu, L. Fang, S. Luo, M. T. Muller, G. E. Lee, L. Wei, Y. Du, D. Sun, P. Wang, *J. Med. Chem*. **2005**, *48*, 2600.
13. T. Ishii, K. Hayashi, T. Hida, Y. Yamamoto, Y. Nozaki, *J. Antibiot.* **2000**, *53*, 765–778.
14. a) Y. Nakano, M. Hamaguchi, T. Nagai, *J. Org. Chem.* **1989**, *54*, 5912–5919; b) B.-L. Zhaoa, D.-M. Du, *Chem. Commun.* **2016**, *52*, 6162–6165; c) M. Hamaguchi, T. Misumi, T. Oshima, *Tetrahedron Lett.* **1998**, 39, 7113–7116.
15. a) J. Thompson, H. M. L. Davies, *J. Am. Chem. Soc.* **2007**, *129*, 6090; b) J. H. Hansen, H. M. L. Davies, *Chem. Sci.* **2011**, *2*, 457– 461; c) Y. Yue, Y. Wang, W. Hu, *Tetrahedron Lett.* **2007**, *48*, 3975.
16. a) Z. Wang, J. Wen, Q. W. Bi, X. Q. Xu, Z. Q. Shen, X. X. Li, Z. L. Chen, *Tetrahedron Lett*. **2014**, *55*, 2969–2972; b) K. Burgess, H. J. Lim, A. M. Porte, G. A. Sulikowski, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 220–222.
17. K. H. Kim, C. H. Lim, J. W. Lim, J. N. Kim, *Adv. Synth. Catal*. **2014**, *356*, 697–704.
18. S. I. Lee, G.-S. Hwang, D. H. Ryu, *J. Am. Chem. Soc.* **2013**, *135*, 7126.

Chapter 3

A One-pot Access to Diastereoselective Benzoxepino[2,3-*c*]pyrroles via Formal (5+2)-Annulation of Vinyl diazosuccinimide with Ketones Under Silver Catalysis



24 examples, up to 74% yield

- One-pot access to dihydrobenzoxepines
- Regio- & chemo-selective
- Additive and ligand-free synthesis
- Silver catalysis (5 mol%)
- Access to single diastereomer
- Intermediate detection

A One-pot Access to Diastereoselective Benzoxepino[2,3-*c*]pyrroles *via* Formal (5+2)-Annulation of Vinyl diazosuccinimide with Ketones Under Silver Catalysis

3

This chapter addresses a challenging strategy for the diastereoselective synthesis of dihydrobenzoxepines via formal (5+2)-cycloaddition of vinyl diazosuccinimides as 5-C synthons with different aryl/alkyl methyl ketones under silver catalysis. The protocol proved to be highly regio-, chemo-, and diastereoselective, and works well with a diverse set of aryl/alkyl methyl ketones bearing electron-deactivating as well as electron-donating groups. The control experiments and time-dependent ^{1}H-NMR studies have revealed the in-situ formation of transient styryl carbonyl ylide as an intermediate during the course of reaction. The practicality of the protocol has also been demonstrated on the gram-scale synthesis of very useful dihydrobenzoxepine.

3.1 Introduction:

The fused polycyclic architecture containing 6-7-5 or 5-7 fused-ring framework or benzoxepine motifs belong to one of the important classes of oxygenated heterocycles found in pharmaceutical agents[1a] and numerous natural products[1b-d] having a diverse biological activity (Figure 3.1). Some of the illustrative examples include Lincosamide antibiotic that shows potent activity against gram-negative pathogens like *E. coli*, Xylarinol A, is a metabolite that is isolated from the fermentation broth of cultured *Pestalotiopsis virgatula* from *Terminalia chebula* Retz (Combretaceae)[1e] and shows the antibiotic activity.Xylarinol B is known to exhibit antibiotic activity and moderate ABTS radical scavenging activity.[1f]

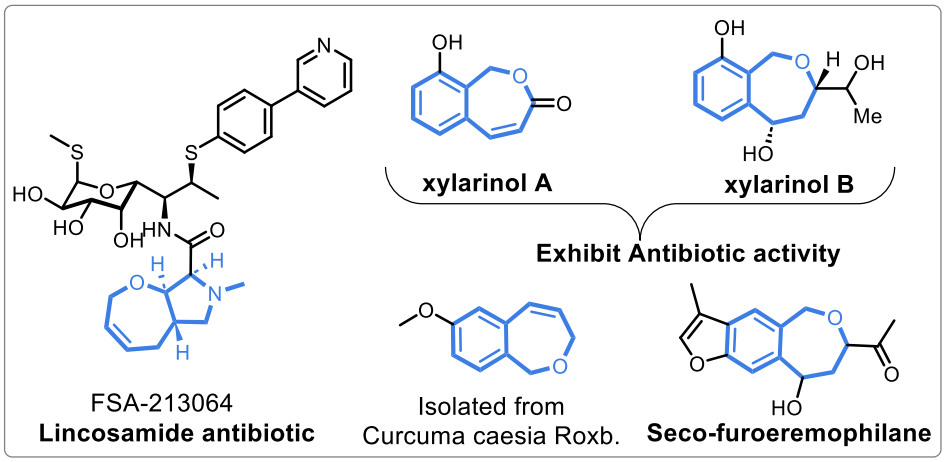
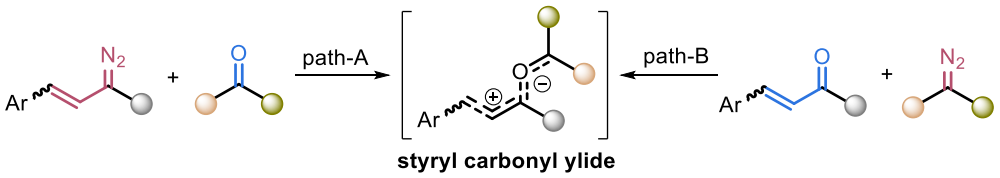


Figure 3.1. Examples of naturally occurring bioactive 1,3-dihydrobenzo[*c*]oxepines and oxepino[2,3-*c*]pyrrole.

Owing to the importance of these compounds, over the years many research groups have contributed to develop synthetic strategies to access the stereoselective highly substituted oxygenated heterocycles[2] and are many researchers are very active and still pursuing the work towards to achieve goal in more attractive manner.[3] Over the last few decades, it has been very well-established that transient carbonyl ylides, generated *in situ via* transition-metal-catalyzed decomposition of diazo compound, can either be paired with suitable trapping agents (or dipolarophiles) or cyclize intramolecularly or intermolecularly to furnish the oxygenated heterocycles.[4-7] Literature reports disclose that the carbonyl ylide can be formed by a coupling of a vinylic metal carbene and a carbonyl group (Scheme 3.1, path-A) and/or through the reaction of a vinyl carbonyl compound with a metal carbene (Scheme 3.1, path-B).

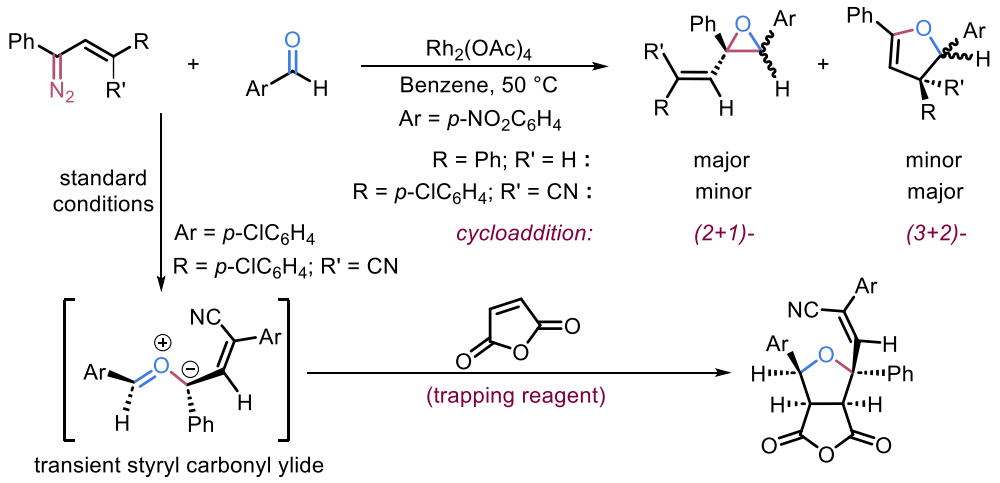


Scheme 3.1. Alternative pathways for the formation of transient styryl carbonyl ylide.

Some of the important examples involving carbonyl ylide as reactive intermediate generated *in situ* from the diazo compound have been discussed here.

❖ ***Examples involving carbonyl ylide via Path-A: By coupling of vinylic metal-carbene and carbonyl group:***

In the year of 2001, for the first time Hamaguchi and co-workers[8a] reported the formation of mixture of diastereomers of dihydrofurans and oxiranes starting from aldehydes

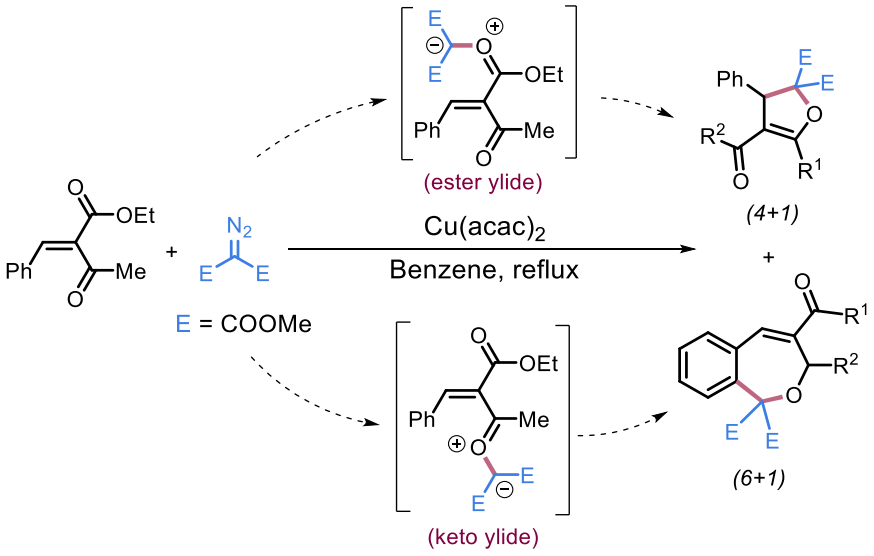


Scheme 3.2. Formal cycloaddition strategy of vinyl diazo compound and aldehydes *via* styryl carbonyl ylide.

and vinyl diazo compounds in presence of dirhodium catalyst in benzene at an elevated temperature (50 °C) under argon atmosphere (Scheme 3.2). However, very importantly electron-deficient aryl aldehydes alone were found to be reactive under the reaction conditions to afford the dihydrofurans. The transformation has been proved to undergo *via* a transient styryl carbonyl ylide intermediate and it has further confirmed by the trapping experiment with maleic anhydride at the optimized condition (Scheme 3.2).

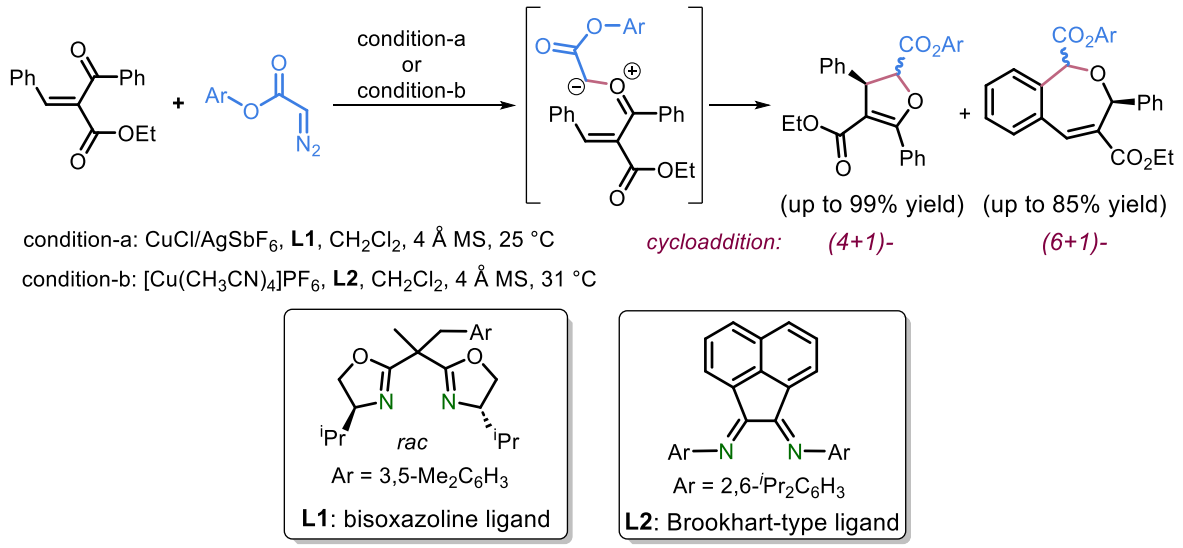
❖ ***Examples involving carbonyl ylide via Path-B: By coupling of vinyl carbonyl compound and metal-carbene:***

In the year of 2008, Anaç *et al.*[7e] have reported the synthesis of dihydrofurans or a mixture (about 1:1) of dihydrofurans and dihydrobenzoxepines starting from *α*-benzylidene-*β, β′*-dicarbonyl compound and dimethyl diazomalonate in presence of copper(II) acetylacetonate (0.7 mol%) in benzene under reflux condition (Scheme 3.3). This study has disclosed a diverse reactivity pattern of *α*-benzylidene-*β, β′*-dicarbonyl compound when reacted with dimethyl diazomalonate. It has been observed that the dihydrofurans mainly formed *via* 'ester ylide' via (4+1) annulation, while the 'keto ylide' preferentially gave an access into the dihydrobenzoxepines via (6+1) annulation (Scheme 3.3).



Scheme 3.3. Formal cycloaddition strategy of vinyl carbonyl compound and diazo compound via styryl carbonyl ylide.

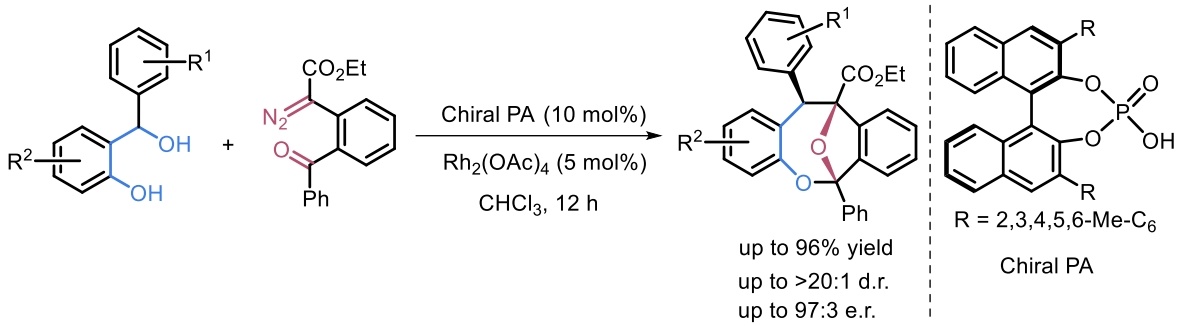
However, the stereoselective synthesis of either of these two scaffolds is quite challenging and it typically needs an elegant ligand-controlled strategy (Scheme 3.4). For example, Tang and co-workers[9] have reported a strategy to control the product distribution of the reaction of *α*-benzylidene-*β, β′*-dicarbonyl compound with diazoacetate (Scheme 3.4). They demonstrated that the selective (diastereoselective) synthesis of either dihydrofurans (*via* (4+1)-annulation) or dihydrobenzoxepines (*via* (6+1)-annulation) by choosing an appropriate ligand in presence of transition-metal catalyst (copper catalysts) in excellent yields and diastereoselectivity (up to >99:1 d.r. for dihydrofurans and up to d.r. 95:5 for dihydrobenzoxepines) (see Scheme 3.4).



Scheme 3.4. Diastereoselective synthesis: cycloaddition strategy of vinyl carbonyl compound and diazo compound *via* styryl carbonyl ylide.

❖ *[4+3]-cycloaddition reaction via carbonyl ylide for the construction of dihydrobenzoxepines:*

Construction of seven-membered-heterocyclic rings *via* carbonyl ylide has recently been demonstrated via the formal (4+3)-cycloaddition reaction. Very recently, Schneider and co-workers[10] have reported a highly stereoselective synthetic protocol for the construction of bicyclic framework. The oxa-bridged dibenzooxacines (5-8 fused rings) have been synthesized *via* the formal (4+3)-cycloaddition involving carbonyl ylide as reactive intermediate by the cooperative rhodium (Rh)/phosphoric acid catalysis at room temperature in excellent yields (up to 96%) with excellent stereoselectivity (up to >20:1 d.r.. and up to 97:3 e.r.) (Scheme 3.5).



Scheme 3.5. (4+3)-Cycloaddition strategy for dihydrobenzoxepines formation *via* carbonyl ylide.

One of the most common reactions of vinyl diazo compound with ketones is the epoxidation, that occurs through formal (2+1)-cycloaddition of carbonyl ylide involving metal carbene intermediates. However, the alternative construction of dihydrofurans *via* formal (3+2)-cycloaddition of ketones and vinyl diazo compounds (3-C synthon) has seldom been explored.[9] It is also important to note that the synthesis of benzoxepine derivatives is quite challenging and moreover, the cyclo-annulation employing vinyl diazo compounds (act as 5-C-synthons) through an alternative formal (5+2)-cycloaddition *via* carbonyl ylide has not been explored till date to the best of our knowledge. The major challenge in this aspect is to explore the vinyl carbenoid as 5-C synthon and this is limited due to the intrinsic steric hindrance emanating from *Z*-configuration around the C=C bond between benzylidene group and the 'catalyst wall' thus making it unfavourable for the desired transformation (see inset, Figure 3.2).[11] Secondly, the construction of the seven-membered heterocyclic scaffold such as oxepine *via* direct cyclization needs high activation energy mainly owing to the combined effect of entropic factors and the non-bonding interactions in the transition state.[12]

Benzylidene succinimide scaffold is a very useful and pre-eminent tool in organic

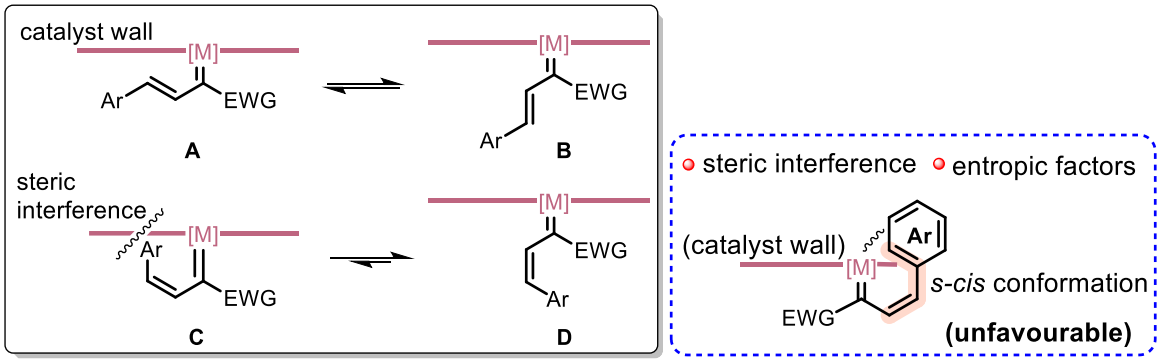


Figure 3.2. a) Conformational changes of acyclic vinyl carbenoid under catalyst influence; b) Challenges to access (5+2)-cyclo-annulation of acyclic vinyl diazo compounds.

synthesis owing to its versatility to serve either as 1-C[13]/2-C[14] synthons or allyl-like 3-C[15] synthons in the tandem annulation reactions. The vinyl diazosuccinimides, a useful carbene precursor that can directly be prepared from benzylidene succinimides following our earlier reported procedure along with the other protocols (Figure 3.3).[16] Credibly, the metallo-vinyl carbenesuccinimides or vinyl carbenesuccinimides are generated catalytically from stable vinylic diazosuccinimides that exhibit electrophilic character at metal carbene carbon and nucleophilic character at vinylogous carbon (see Figure 3.3). These metallo-vinyl carbenesuccinimides have emerged as useful synthons to access metallo-1,1-[16a-16b, 17a-17c] or 1,3-[17c] adducts when paired with suitable dipolarophiles or nucleophiles to construct the cyclic (ring) framework involving π-electrocyclization[16a,17b–f] (Scheme 3.6).

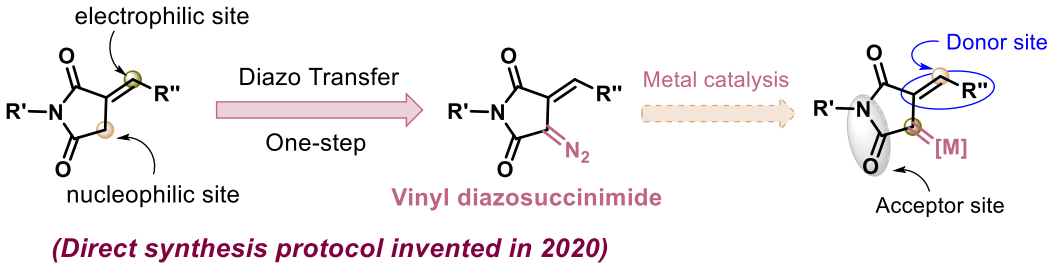
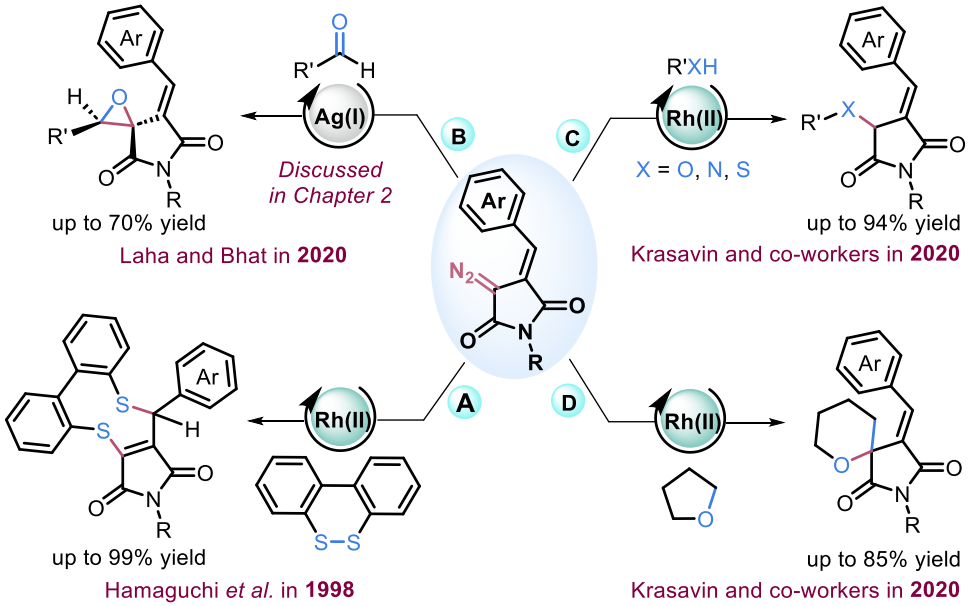


Figure 3.3. General synthetic approach to vinyl diazosuccinimide and its characteristics.

A few important examples involving metallo-vinyl carbenesuccinimides as reactive metallo-1,1- or 1,3- adducts under different metal catalysis have been depicted in Scheme 3.6.



Scheme 3.6. Transformations of vinyl diazosuccinimides under metal catalysis.

In 1998, Hamaguchi *et al.*[17c] have reported dirhodium(II)-catalyzed decomposition of diazosuccinimide in presence of cyclic biphenylene disulfides at room temperature (30 °C) in DCM to afford the 1,3-insertion adducts exclusively in good yields (up to 99%, Route-A, Scheme 3.6). Two decades later to the Hamaguchi's report, our research group has reported the direct one-pot synthesis of spiro-oxiranes starting from the vinyl diazosuccinimides and aldehydes under silver catalysis (Route-B, Scheme 3.6). Silver catalyzed ($AgSbF_6$, 5 mol%) the decomposition of vinyl diazosuccinimides in presence of aryl aldehydes to afford spiro-oxiranes in regio- and chemo-selective manner in *p*-xylene at elevated temperature (110 °C) in 2 min. The desired spiro-oxirane products were obtained as a single diastereomer in moderate to good yields (up to 70%).[16a] Interestingly, no trace of competitive dioxolane formation (as formed by other diazo compounds under dirhodium catalysis as reported[18] early) was observed (Route-B, Scheme 3.6).

Later, Krasavin and co-workers have reported dirhodium(II)-catalyzed heteroatom–H (heteroatoms = O, N, S) insertion reactions[16b] and the construction of spirocyclizations[17b] using tetrahydrofuran that underwent Stevens type rearrangement leading to (n + 1) ring expansion of the tetrahydrofuran moiety at room temperature (Routes C and D, Scheme 3.6). The heteroatom insertion and spirocyclization have been effectively explored in presence of $Rh_2(OAc)_4$ (1 mol%) and $Rh_2(esp)_2$ (0.5 mol%) respectively in good to excellent yields (up to 94% for X–H insertion products and up to 85% for ring expansion products).

Metallo-vinyl carbenesuccinimides have significant difference in their chemical behaviour due to this their metal carbene reactivity can be tuned. They also exhibit versatile regioselectivity due to the presence of benzylidene ring in conjugation with cyclic imide (Figure 3.4).

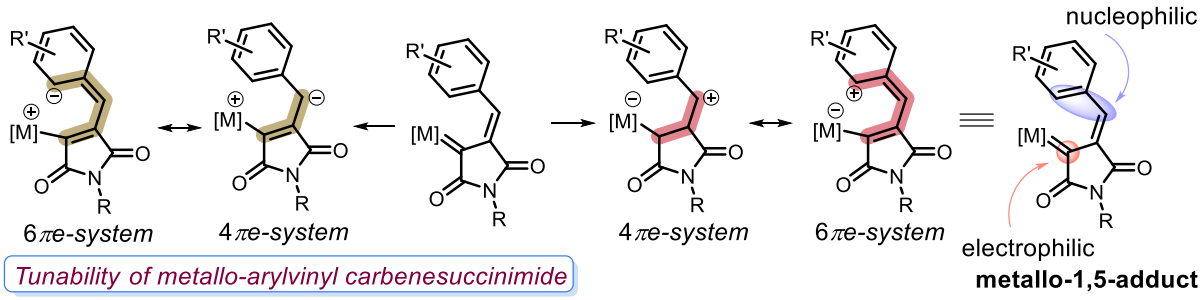


Figure 3.4. Plausible regioselectivity of vinyl diazosuccnimides.

Looking at these important features and owing to the importance of oxaheterocycles, we envisioned that the metallo-arylvinyl carbenesuccinimides could be employed for the effective cycloannulation with carbonyl compounds *via* (3+2)- and/or (5+2)-cycloaddition to enable an access to dihydrofurans and/or dihydrobenzoxepines respectively under suitably optimised reaction conditions.

Herein, in this chapter, for the very first time, we have described the exploration of silver catalyzed direct diastereoselective synthesis of dihydrobenzoxepine derivatives exclusively by tapping the potential of aryl vinyl diazosuccinimides with ketones under ligand-free condition.

3.2 Results and Discussion:

Earlier, in Chapter 2, we have demonstrated the 4π-electrocyclization strategy *via in situ* generation of transient styryl carbonyl ylide from metallo-aryl vinyl diazosuccinimide under silver catalysis ($AgSbF_6$) to access oxiranes at an elevated temperature (110 °C).[16a] It's interesting to observe from the X-ray single crystal analysis about the special nature of the vinyl diazosuccinimide with its spacial arrangement with an unfavourable conformation (*Z*-configuration around the C=C bond between benzylidene group and the 'catalyst wall').[19] This is strikingly almost similar to that the geometry exhibited by acyclic vinyl carbenoids (see Figure 3.2_Conformation C). The details of the X-ray diffraction of the single crystal of phenyl vinyl diazosuccinimide **1a** revealed that the benzylidene group is oriented in *s-cis* conformation with a dihedral angle (θ) ~34° (slightly twisted for the stability, see Figure 3.5, see Experimental section 3.4.8A for more details).

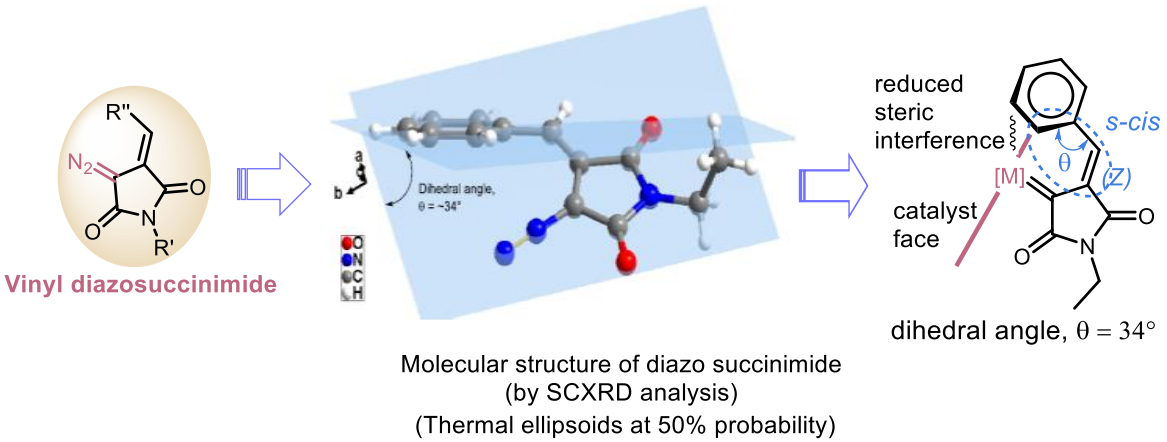
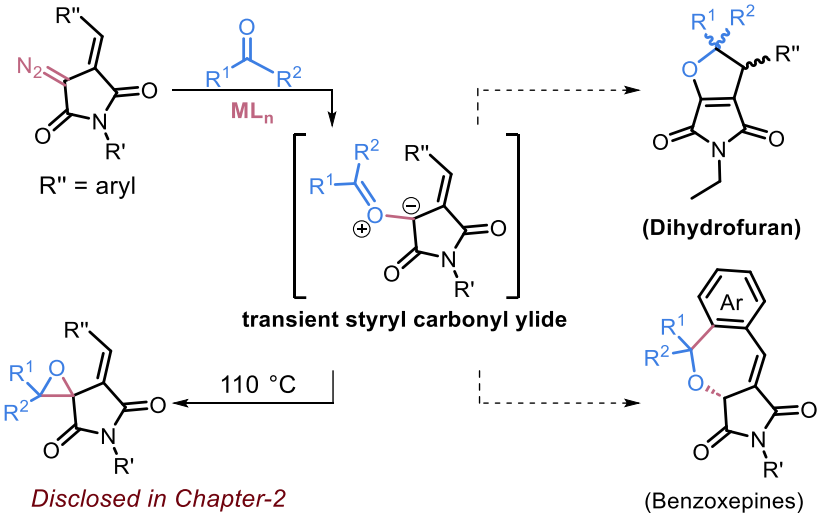


Figure 3.5. Characteristics of vinyl diazosuccinimide

Looking at this unusual and interesting observation, we hypothesized that the *Z*-orientation of the metallo-aryl vinyl diazosuccinimide could be explored for different type of reactivity under suitable conditions even though it's a great a challenge. We surmised due to this unfavourable conformation (*Z*-configuration), aryl group of benzylidene may participate in the reaction as it would be slightly inclined away from the 'catalyst wall' as shown in Figure 3.5. We envisioned that the *in situ* generated styryl carbonyl ylide (from metallo-aryl vinyl diazosuccinimide) may undergo 6π-electrocyclization to form dihydrofuran **4** or 8π-electrocyclization followed by the rearomatization to afford the dihydrobenzoxepines **5** (see Figure 3.4 and Scheme 3.6).

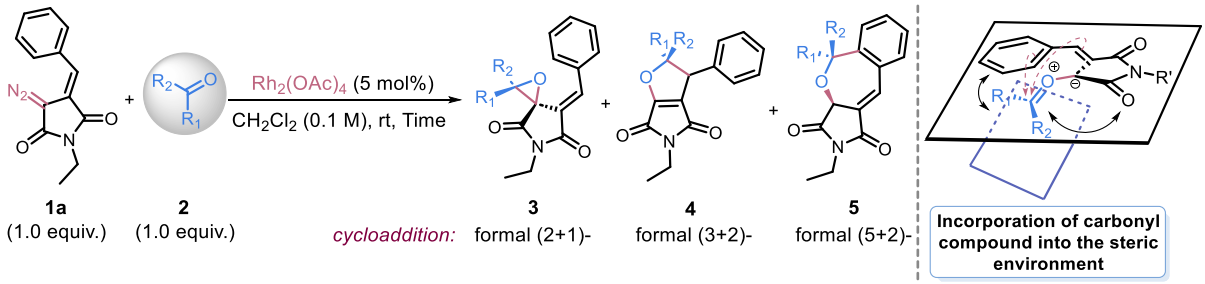


Scheme 3.6. Proposed Strategy: Reaction *via* 1,3- and/or 1,5-adduct formation.

In order to validate this hypothesis, we commenced our investigation with (*E*)-3-benzylidene-4-diazo-1-ethylpyrrolidine-2,5-dione **1a** and benzaldehyde[7] **2a′** as model substrates. The commercially available $Rh_2(OAc)_4$ was initially employed as a catalyst at room temperature. However, we did not observe any 6π- or 8π-cyclized crossed-coupled products but very interestingly the corresponding oxirane product **3aa** was obtained as a single diastereomer in albeit in poor yield (15%, Table 3.1, Entry 1). Later, we explored the reaction with relatively less electrophilic compound such as acetophenone **2a** instead of benzaldehyde **2a′**. Gratifyingly, the 8π-cyclized crossed-product 2-ethyl-5-methyl-5-phenyl-3a,5-dihydro-1*H*-benzo[5,6]oxepino[2,3-*c*]pyrrole-1,3(2*H*)-dione **5aa** was obtained as a single diastereomer albeit in moderate yield (48% yield) along with the corresponding spiro-oxirane **3aa** (as a single diastereomer) in trace amount (6% yield, Table 3.1, Entry 2). Also, we did not observe another anticipated products (5-ethyl-2-methyl-2,3-diphenyl-2*H*-furo[2,3-*c*]pyrrole-4,6(3*H*,5*H*)-dione) **4aa** even in trace amount. Later, the geometry of the product **5aa** was confirmed by ^{1}H NMR and ^{1}H-^{1}H COSY spectra and the geometry was further proved unambiguously

confirmed by the molecular structure using single crystal X-ray diffraction (XRD) analysis (for details, see Experimental section 3.4.8D). Later we planned to explore different substrates for generality. However, benzophenone **2b′** as a coupling partner under initial optimized reaction conditions did not furnish the titled transformation (Table 3.1, Entry 3). While the acetone **2k** under the conditions provided 8π-cyclized crossed-product **5ak** in 50% yield (Table 3.1, Entry 4). Further, we examined the reactivity of phenyl acetate **2d′** as well as *N*, *N*-diethylbenzamide **2e′** under the same reaction condition. However, unfortunately, neither the expected compounds **5ad′** and **5ae′** nor the corresponding **4ad′** and **4ae′** products were formed (Table 3.1, Entries 5, 6). These preliminary results revealed the reactivity of compounds and there by gave an insight for the selection of suitable carbonyl compounds that would be crucial either for generating the necessary steric environment (since benzylidene phenyl ring tilted towards diazo group) or for necessitating the intramolecular cyclization (see Table 3.1 inset).

3.2.1. Table 3.1: Investigation for the suitable dipolarophile[a]:



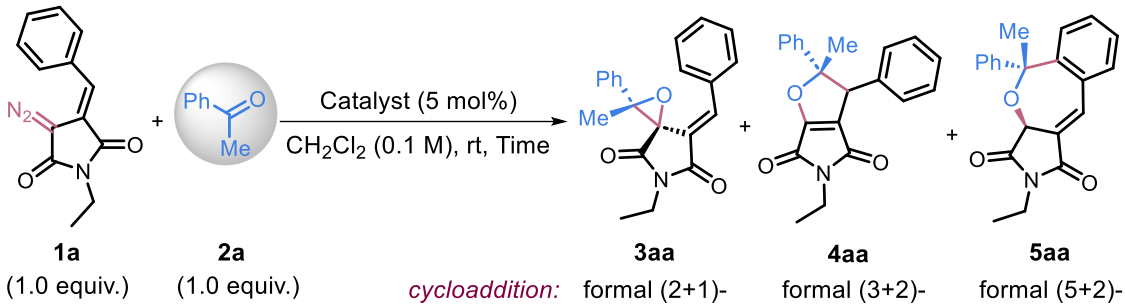
Entry	Substrate	R_1	R_2	Time	Yield[b] (%) of product 3/4/5
1	2a′	Ph	H	2 h	15/0/0
2	**2a**	**Ph**	**Me**	**2 h**	**6/0/48**
3	2b′	Ph	Ph	24 h	0/0/0
4	**2k**	**Me**	**Me**	**2 h**	**5/0/50**
5	2d′	Ph	OEt	24 h	0/0/0
6	2e′	Ph	NEt_2	24 h	0/0/0
7	2f′	Me	OEt	24 h	0/0/0
8	2g′	Ph	CF_3	2 h	0/0/0
9	2h′	Ph	CH_2Br	2 h	0/0/0

[a]**Reaction conditions**: unless otherwise noted, the reactions were carried out with diazo compound **1a** (1.0 equiv., 0.2 mmol), **2a** (1.0 equiv., 0.2 mmol), $AgNTf_2$ (5 mol%) and dry CH_2Cl_2 (0.1 M) at room temperature (26 °C) under argon atmosphere. [b]Isolated yield after column chromatography. In all cases single diastereomer of **5aa** was obtained.

Encouraged by this initial result, we further sought to optimize the reaction conditions to enhance the yield of diastereomer **5aa**. In this regard, we explored the reaction of **1a** and **2a** using rhodium (Table 3.2, Entry 1), silver (Table 3.2, Entries 2–10), copper (Table 3.2, Entries 11–15), iron and gold catalysts in DCM at room temperature (Table 3.2, Entries 16–18). Gratifyingly, among all the catalysts screened, silver triflimide ($AgNTf_2$) with non-coordinating and low nucleophilic (Tf_2N^-) counteranion found to be more efficient for the effective transformation. The reaction of acetophenone **2a** and aryl vinyl diazosuccinimide **1a** in presence of silver triflimide (5 mol%) at room temperature in dry CH_2Cl_2 (0.1 M) afforded the **5aa** (57% yield) along with **3aa** (11% yield) in 2 h (Table 3.2, Entry 6). In all the cases an excess amount of unreacted acetophenone **2a** was recovered. Nickel catalyst as well as some Lewis acid catalysts such as $Sc(OTf)_3$, Tf_2NH and TfOH proved to be not efficient for this transformation (Table 3.2, Entries 19–22). We also observed that the reaction did not work in the absence of any catalyst under prolonged reaction time (Table 3.2, Entry 23).

3.2.2. Optimization of reaction conditions for the formal (5+2)-cycloaddition of donor-/acceptor- type vinyl diazosuccinimide:

Table 3.2: Catalyst investigation for the formal (5+2)-cycloaddition reaction[a]

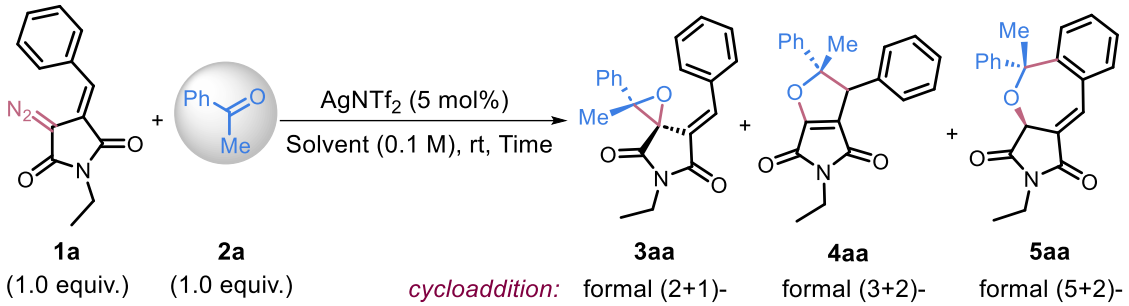


Entry	Catalyst	Solvent	Time	Yield[b] (%) of 3aa	Yield[b] (%) of 4aa	Yield[b] (%) of 5aa
1	$Rh_2(esp)_2$	CH_2Cl_2	2 h	<5	0	31
2	$AgSbF_6$	CH_2Cl_2	2 h	19	0	40
3	AgOTf	CH_2Cl_2	2 h	18	0	38
4	$AgNO_3$	CH_2Cl_2	4 h	<5	0	7
5	$AgBF_4$	CH_2Cl_2	2 h	<5	0	20
6	**$AgNTf_2$**	CH_2Cl_2	**2 h**	**11**	**0**	**57**
7	Ag_2O	CH_2Cl_2	12 h	0	0	5
8	Ag_2CO_3	CH_2Cl_2	24 h	NR	NR	NR
9	AgOAc	CH_2Cl_2	4 h	0	0	14
10	AgTFA	CH_2Cl_2	2 h	<5	0	15

11	$Cu(CH_3CN)_4PF_6$	CH_2Cl_2	2 h	<5	0	17
12	CuCl	CH_2Cl_2	4 h	0	0	21
13	CuBr	CH_2Cl_2	2 h	0	0	8
14	CuI	CH_2Cl_2	2 h	<5	0	28
15	$Cu(OTf)_2$	CH_2Cl_2	5 h	0	0	9
16	$AuCl_3$	CH_2Cl_2	24 h	NR	NR	NR
17	$Au(PPh_3)_3Cl$	CH_2Cl_2	24 h	NR	NR	NR
18	$Fe(OTf)_2$	CH_2Cl_2	24 h	NR	NR	NR
19	$Ni(OTf)_2$	CH_2Cl_2	24 h	NR	NR	NR
20	$Sc(OTf)_3$	CH_2Cl_2	2 h	0	0	0
21	Tf_2NH	CH_2Cl_2	2 h	0	0	0
22	TfOH	CH_2Cl_2	2 h	0	0	0
23	No catalyst	CH_2Cl_2	24 h	NR	NR	NR

[a]**Reaction conditions**: unless otherwise noted, the reactions were carried out with diazo compound **1a** (1.0 equiv., 0.2 mmol), **2a** (1.0 equiv., 0.2 mmol), catalyst (5 mol%) and dry CH_2Cl_2 (0.1 M) at room temperature (26 °C) under argon atmosphere. [b]Isolated yield after column chromatography. In all cases single diastereomer of **5aa** was obtained.

Table 3.3: Investigation of the most suitable solvent for the formal (5+2)-cycloaddition reaction[a]

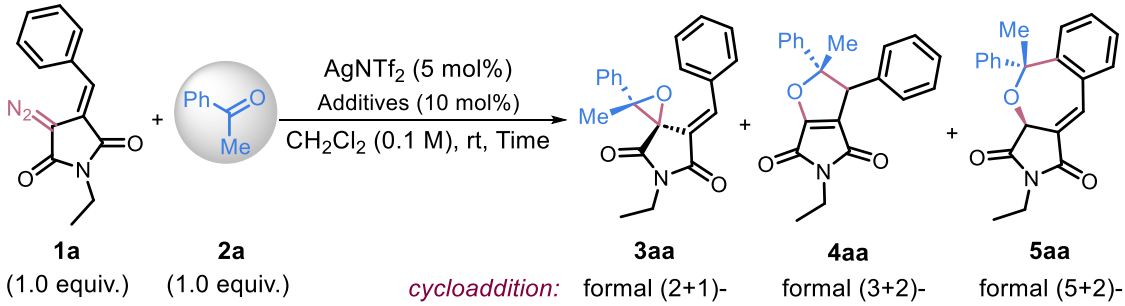


Entry	Solvent	Time	Yield[b] (%) of 3aa	Yield[b] (%) of 4aa	Yield[b] (%) of 5aa
1	Toluene	6 h	20	0	42
2	*p*-Xylene	6 h	<5	0	30
5	CCl_4	4 h	10	0	25
6	EtOAc	2 h	0	0	10
7	DCE	4 h	<5	0	51
8	THF	12 h	<5	0	0
9	CH_3CN	24 h	NR	NR	NR
10	DMSO	12 h	NR	NR	NR

[a]**Reaction conditions**: unless otherwise noted, the reactions were carried out with diazo compound **1a** (1.0 equiv., 0.2 mmol), **2a** (1.0 equiv., 0.2 mmol), $AgNTf_2$ (5 mol%) and dry solvent (0.1 M) at room temperature (26 °C) under argon atmosphere. [b]Isolated yield after column chromatography. NR = No reaction. In all cases single diastereomer of **5aa** was obtained.

Further, in order to improve the yield of the desired product **5aa**, we have systematically screened both non-polar and polar aprotic solvents and they were found to be not useful for the achieving the desired transformation successfully (Table 3.3). Later, different types of additives such as inorganic and organic bases, organic acids and the molecular sieves were screened (see Table 3.4). Interestingly, none of these additives were effective for the desired transformation (Table 3.4, Entries 1–5) and the starting substrate-vinyl diazocarbonyl compound **1a** did not react or even decomposed either. Also, the other additives (Table 3.4, Entries 11-15) were not useful.

Table 3.4: Investigation on the influence of additives on the formal (5+2)-cycloaddition reaction[a]

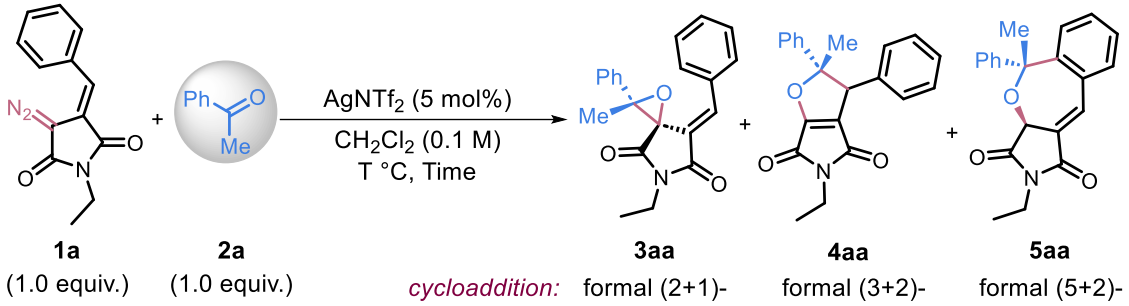


Entry	Additive	Time	Yield[b] (%) of 3aa	Yield[b] (%) of 4aa	Yield[b] (%) of 5aa
1	Cs_2CO_3	24 h	NR	NR	NR
2	K_3PO_4	3 h	0	0	22
3	CsF	24 h	NR	NR	NR
4	Et_3N	24 h	NR	NR	NR
5	$^{i}Pr_2NH$	24 h	NR	NR	NR
6	NaBARF	2 h	0	0	30
7	PhCOOH	1 h	0	0	25
8	$PhCH_2COOH$	30 min	0	0	24
9	$Ph(CH_2)_2COOH$	30 min	0	0	22
10[c]	$Ph(CH_2)_2COOH$	30 min	0	0	14
11	4Å MS (10 mg)	1 h	0	0	<5
12	3Å MS (10 mg)	1 h	0	0	<5
13	H_2O (2 µL)	30 min	0	0	16
14	*n*-Bu_4NPF_6	2 h	<5	0	54
15	CuCl	2 h	0	0	31
16	PPh_3	2 h	0	0	0

[a]**Reaction conditions**: unless otherwise noted, the reactions were carried out with diazo compound **1a** (1.0 equiv., 0.2 mmol), **2a** (1.0 equiv., 0.2 mmol), Additive (10 mol%), $AgNTf_2$ (5 mol%) and dry CH_2Cl_2 (0.1 M) at corresponding temperature under argon atmosphere. [b]Isolated yield after column chromatography. [c]$Ph(CH_2)_2COOH$ 20 mol% was added as additive. In all cases single diastereomer of **5aa** was obtained.

Then the other parameters including reaction temperature, solvent concentration, as well as catalyst loadings were carefully investigated (Table 3.5–3.8). Though the oxirane formation was suppressed on decreasing the reaction temperatures (up to -20 °C), the yield of the desired product **5aa** found to diminish as well with the prolonging reaction time (for the complete consumption of **1a**, Table 3.5, Entries 1–4). While the elevation of the reaction temperature (110 °C) resulted in quick consumption of **1a**, albeit in low yield (24%) of the desired product **5aa** and enhanced the oxirane formation (25% yield) [Table 3.5, Entries 5–9].

Table 3.5: Temperature investigation for the formal (5+2)-cycloaddition reaction[a]

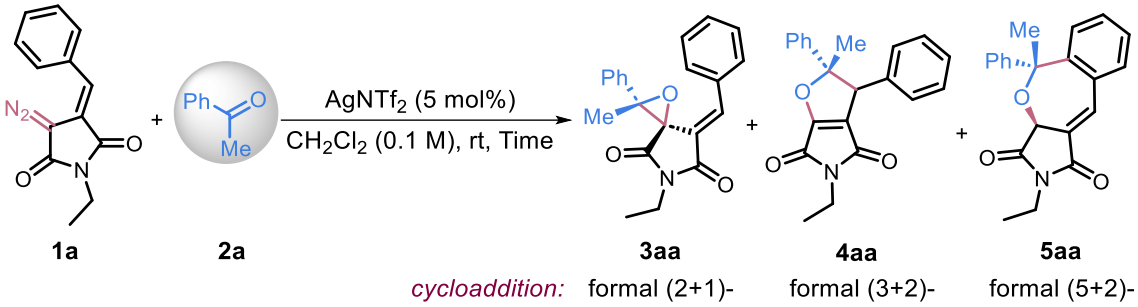


Entry	T (°C)	Time	Yield[b] (%) of 3aa	Yield[b] (%) of 4aa	Yield[b] (%) of 5aa
1	20	2 h	<5	0	54
2	10	2 h	<5	0	42
3	0	4 h	0	0	34
4	-20	10 h	0	0	23
5	35	4 h	<5	0	51
6	40	2 h	6	0	46
7	50	2 h	11	0	37
8	60	2 h	15	0	35
9	110	2 min	25	0	24

[a]**Reaction conditions**: unless otherwise noted, the reactions were carried out with diazo compound **1a** (1.0 equiv., 0.2 mmol), **2a** (1.0 equiv., 0.2 mmol), $AgNTf_2$ (5 mol%) and dry CH_2Cl_2 (0.1 M) at corresponding temperature under argon atmosphere. [b]Isolated yield after column chromatography. In all cases single diastereomer of **5aa** was obtained.

The alteration in the stoichiometric amounts of both of the diazo compound **1a** as well as acetophenone **2a** did not change the yield of the desired product **5aa** significantly (Table 3.6) and also, we did not observe the formation of dihydrofuran under the conditions. The decrease in catalyst loading (up to 1 mol%) resulted in decrease of the yield of the desired product **5aa** (Table 3.7, Entries 2-3) and in some cases we noticed that reaction required longer

Table 3.6: Investigation of the reactant ratio for the formal (5+2)-cycloaddition reaction[a]

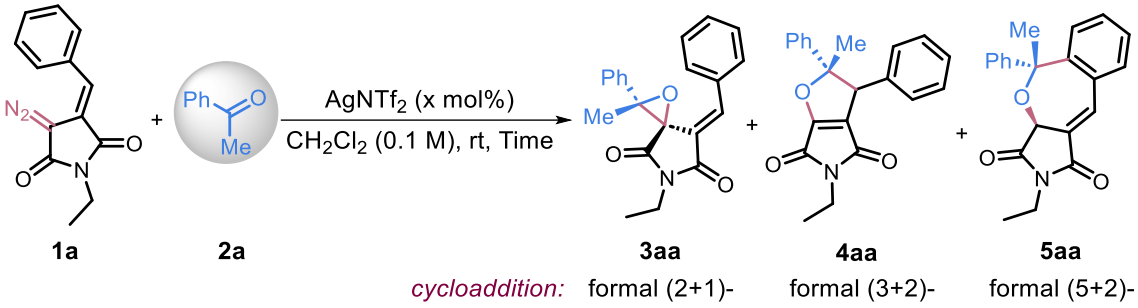


Entry	1a (equiv.)	2a (equiv.)	Time	Yield[b] (%) of 3aa	Yield[b] (%) of 4aa	Yield[b] (%) of 5aa
1	1.5	1.0	4 h	10	0	52
2	1.0	1.5	2 h	11	0	56

[a]**Reaction conditions**: unless otherwise noted, the reactions were carried out with diazo compound **1a**, **2a**, $AgNTf_2$ (5 mol%) and dry CH_2Cl_2 (0.1 M) at room temperature under argon atmosphere. [b]Isolated yield after column chromatography. In all cases single diastereomer of **5aa** was obtained.

reaction times for the complete conversion into desired product (Table 3.7, Entries 3). Unfortunately, increasing the catalyst loading (up to 10 mol%) resulted in the formation of undesired side products thus diminished the yield of **5aa** further (Table 3.7, Entries 4–5).

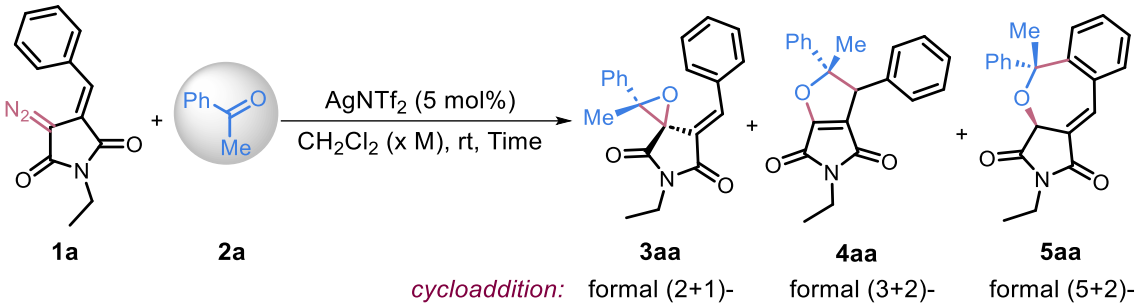
Table 3.7: Catalyst loading investigation for the formal (5+2)-cycloaddition reaction[a]



Entry	1a (equiv.)	2a (equiv.)	*x* mol%	Time	Yield[b] (%) of 3aa	Yield[b] (%) of 4aa	Yield[b] (%) of 5aa
1	1	1	10	2 h	0	0	0
2	1	1	2.5	2 h	<5	0	42
3	1	1	1	6 h	<5	0	31
4	1	1	6	4 h	8	0	34
5	1	1	7	4 h	8	0	23

[a]**Reaction conditions**: unless otherwise noted, the reactions were carried out with diazo compound **1a** (0.2 mmol), **2a** (0.2 mmol), $AgNTf_2$ and dry CH_2Cl_2 (0.1 M) at room temperature under argon atmosphere. [b]Isolated yield after column chromatography. In all cases single diastereomer of **5aa** was obtained.

Table 3.8: Investigation of reactant concentration for the formal (5+2)-cycloaddition reaction[a]



1a **2a** **3aa** **4aa** **5aa**

cycloaddition: formal (2+1)- formal (3+2)- formal (5+2)-

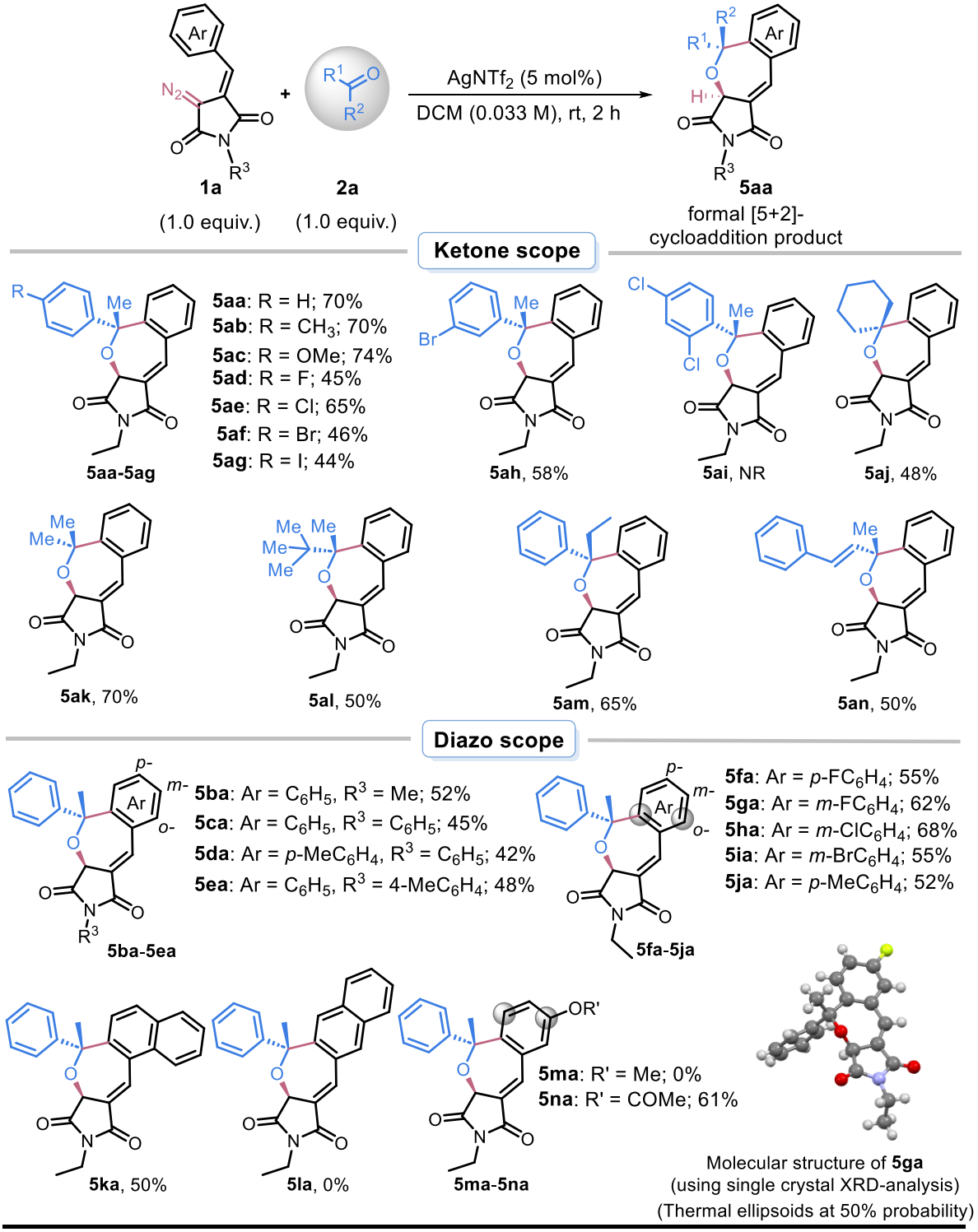
Entry	1a (equiv.)	2a (equiv.)	x M	Time	Yield[b] (%) of 3aa	Yield[b] (%) of 4aa	Yield[b] (%) of 5aa
1	1.0	1.0	0.2	8 h	<5	0	40
2	1.0	1.0	0.02	6 h	8	0	28
3	1.0	1.0	0.033	2 h	5	0	70
4	1.0	1.0	0.066	2 h	12	0	51
5	1.0	1.0	0.08	2 h	<5	0	58
6	1	1	0.05	2 h	9	0	38

[a]**Reaction conditions**: unless otherwise noted, the reactions were carried out with diazo compound **1a** (0.2 mmol), **2a** (0.2 mmol), $AgNTf_2$ (5 mol%) and dry CH_2Cl_2 at room temperature under argon atmosphere. [b]Isolated yield after column chromatography. In all cases single diastereomer of **5aa** was obtained.

Based on the exhaustive screening of different catalysts, additives, solvents, solvent concentration, temperature, and other reaction conditions, vinyl diazo carbonyl compound **1a** (1.0 equiv.), acetophenone **2a** (x equiv.), $AgNTf_2$ (5 mol%) as catalyst in dry CH_2Cl_2 (0.033 M) at 26 °C for 2 h under inert atmosphere proved to optimum reaction conditions to obtain the desired product **5aa** (Table 3.8, Entry 3).

Having optimized the reaction conditions, we further investigated this protocol for the wider substrate scope. Initially we planned to explore the reactivity of phenyl vinyl diazosuccinimide **1a** with different ketones **2**. Different methyl aryl ketones (**2a**–**2l**) reacted smoothly with **1a** in presence of silver triflimide (5 mol%) in dry DCM at room temperature to afford the corresponding 5-aryl-5-methyl substituted dihydrobenzoxepines (**5aa**–**5an**) in moderate to good yields (up to 74%, See Table 3.9). We also observed that aryl methyl ketones bearing electron donating group afforded the corresponding dihydrobenzoxepines (**5aa**–**5ac**) in relatively higher yields than that of aryl methyl ketones having electron-deactivating substituent at *para*- and *meta*- position of phenyl ring (**5ad**–**5ah**). Surprisingly, the reaction of 2,4-dichlorophenyl methyl ketone **2i** and **1a** under the optimized reaction condition did not afford the desired product - dihydrobenzoxepine **5ai**. Further, we explored the reaction of **1a** with electron rich aliphatic methyl ketones including cyclic ketone such as cyclohexanone **2j**

to afford the corresponding dihydrobenzoxepine derivatives (**5aj**–**5al**). Even the enone such as methyl styryl ketone reacted with **1a** to furnish the desired product **5an** in modest yield (50%, Table 3.9).

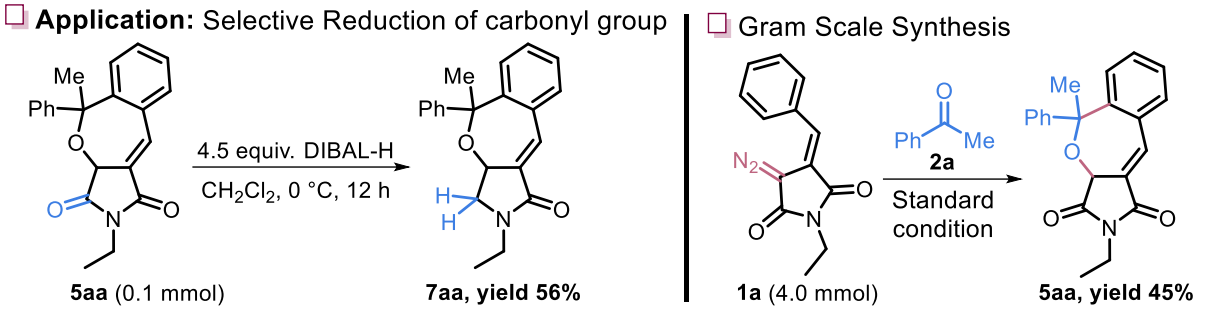


[a]**Reaction conditions**: unless otherwise noted, the reactions were carried out with diazo compound **1a** (1.0 equiv., 0.2 mmol), **2** (1.0 equiv., 0.2 mmol), $AgNTf_2$ (5 mol%) and dry CH_2Cl_2 (0.033M) at room temperature (26°C) under argon atmosphere over 2 h. [b]Isolated yield after column chromatography. In all cases single diastereomer was obtained.

Table 3.9. Substrates Scope for the Formal (5+2)-cycloaddition reaction.[a]

Later, we planned to explore the formal (5+2)-cycloaddition for a range of aryl-substituted as well as *N*-substituted aryl vinyl diazosuccinimides with different ketones. In this regard, we treated different *N*-substituted benzylidene diazo compounds (**1b**–**1e**) with acetophenone **2a** under the optimized reaction condition to afford the corresponding desired products (**5ba**–**5ea**) (see Table 3.9). We observed that among all the *N*-substituted benzylidene diazo compounds screened, *N*-ethyl substituted benzylidene diazo compound **1a** proved to be optimum substrate by affording the desired product **5aa** in relatively higher yield. In view of this, we planned to explore the reactivity of different *N*-ethyl substituted vinyl diazo succinimides (**1f**–**1n**) bearing different substituents with electron-rich and -deficient/-deactivated groups at different positions of the phenyl ring. The reaction of acetophenone **2a** with *N*-ethyl substituted vinyl diazo succinimides (**1f**–**1k**) under the optimized reaction conditions furnished the target products (**5fa**–**5ka**) in moderate to good yields in a very short time (up to 68%, 2 h). It is interesting note that the *N*-ethyl substituted vinyl diazo succinimide derived from *α*-napthal (**1k**) reacted smoothly, while the *β*-napthal derived derivative (**1l**) did not react, probably due to electronic and steric reasons. We observed that the vinyl diazo succinimides bearing electron deactivating groups (F, Cl, Br) at different positions of phenyl ring, afforded the corresponding desired products in relatively higher yields than that of substrates having electron rich system (**1b**–**1d**, **1j**). Unfortunately, the *N*-ethyl substituted vinyl diazo succinimides having methoxy group (**1m**) at *meta*- position found to be not reactive at all. We surmised that probably due to the presence of electron donating group (-OMe), the carbenoid carbon would be relatively less electrophilic for the desirable reaction. In order to validate this reasoning, we replaced the methoxy group with the electron deactivating acetyloxy group at the same position (-*meta*, **1n**) and treated with acetophenone **2a** under the optimized reaction condition. Gratifyingly, we obtained the corresponding desired product **5na** in moderate yield (61%, Table 3.9). This result further supported our assumption. It is interesting to note that relatively sensitive benzylidene scaffold containing *p*-methyl group at phenyl ring (**5da**, **5ja**) tolerated the optimized reaction conditions well. Later, in order to generalize the practicality of the protocol, we explored the reaction of **1a** and **2a** on a gram scale quantity. Also, further as an application, the product **5aa** was utilized to synthesize the corresponding pyrrolidinone derivative **7aa** (see Scheme 3.7).

It's very important to highlight that all the dihydrobenzoxepines **5** were obtained as single diastereomer. We obtained the molecular structure of **5ga** using single crystal X-ray analysis[19] and the structures of all the other compounds were deduced based on analogy.

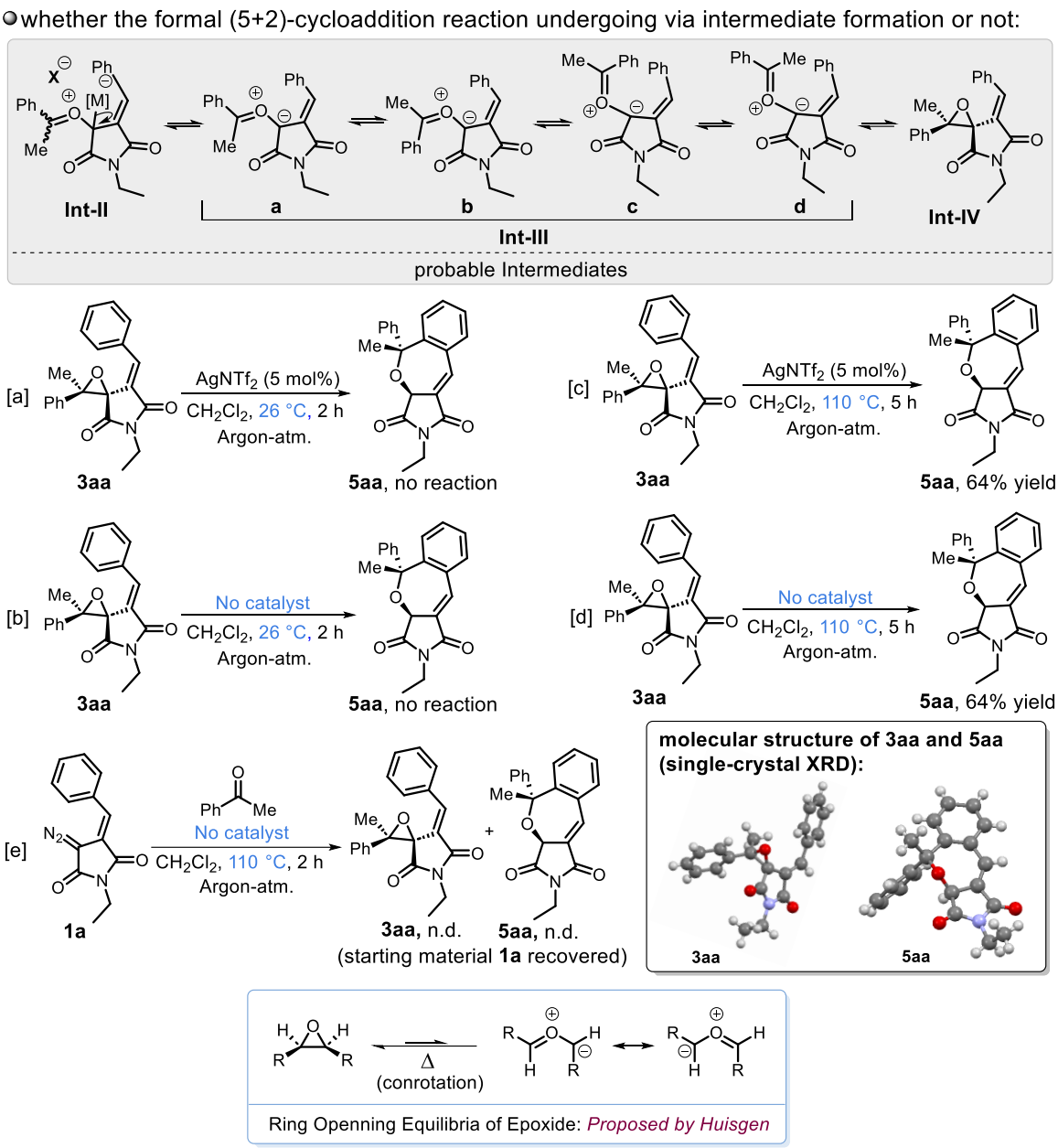


Scheme 3.7. Utility of the protocol.

❖ Investigation of the plausible mechanism of this transformation:

❖ ***Control Experiments:***

In order to have an insight into the reaction mechanism, we performed few control experiments systematically. In order to verify whether or not the reaction undergoes *via* carbonyl ylide intermediate (**int-II** or **III**, Scheme 3.8) or epoxide (**int-IV**, Scheme 3.8), we initially prepared the corresponding epoxide[19] (**int-IV** or **3aa**) using the reported procedure.[16a] This epoxide **3aa** under the optimized reaction conditions did not furnish the desired product **5aa** even in trace and the unreacted epoxide **3aa** was recovered (Scheme 3.8a). Likewise, we observed that reaction did not afford the desired product **5aa** when carried out in absence of catalyst at room temperature (Scheme 3.8b). These results clearly confirm that epoxide **3aa** (**int-IV**) is not the intermediate for the desired transformation at room temperature. The **int-II** (four different conformational forms of metal-bound carbonyl ylides in one inset, see Scheme 3.8) and **int-III** (four different conformational forms of the corresponding metal-unbound carbonyl ylides) might be generating ins situ during the course of the reaction of aryl vinyl diazo succinimide under silver catalysis. It is reported by Huisgen that the epoxide can undergo electrocyclic ring opening reaction upon heating (absence of any catalyst). This report supports the possibility of *in situ* formation of carbonyl ylide at the room temperature reaction condition.[18a,20a] In this regard, in order to verify the possible formation of intermediate (**int-II** or **III**), we further treated compound **3aa** (epoxide) with $AgNTf_2$ (5 mol%) at an elevated temperature (110 °C, Scheme 3.8c). Interestingly we obtained the desired product **5aa** in 64% yield after 5 h (Scheme 3.8c). To understand the possible role of silver catalyst as well as the formation of carbonyl ylide, we performed the reaction in the absence of $AgNTf_2$ at an elevated temperature (110°C, Scheme 3.8d). To our surprise we obtained compound **5aa**[19] in almost similar yield (Scheme 3.8d). Considering the reports of Huisgen[18a,20a] and Eberbach[20b] on the electrocyclic ring opening equilibria of oxirane to carbonyl ylide and different conformational



Scheme 3.8. Control experiments for the detection of an intermediate.

forms of carbonyl ylide, we surmised that at an elevated temperature, epoxide **3aa** would open up to form metal-unbound carbonyl ylide (see **int-IIId**, Scheme 3.8).

This result was further supported by the time-dependent ^{1}H-NMR experiment wherein signals for the epoxide **3aa** were disappearing over a period of time at an elevated temperature to form compound **5aa** (Figure 3.6, for more details, see Experimental section 3.4.6). We also strongly believe that even at room temperature the reaction would undergo *via* the same intermediate (**int-IIId**) to afford **5aa**. However, attempts to trap the carbonyl ylide intermediate (**int-III**) with different dienophiles[7d] were unsuccessful. We observed that none of the dienophiles reacted with the epoxide (**int-IV**) either at 26 °C or at 110 °C (Scheme 3.9).

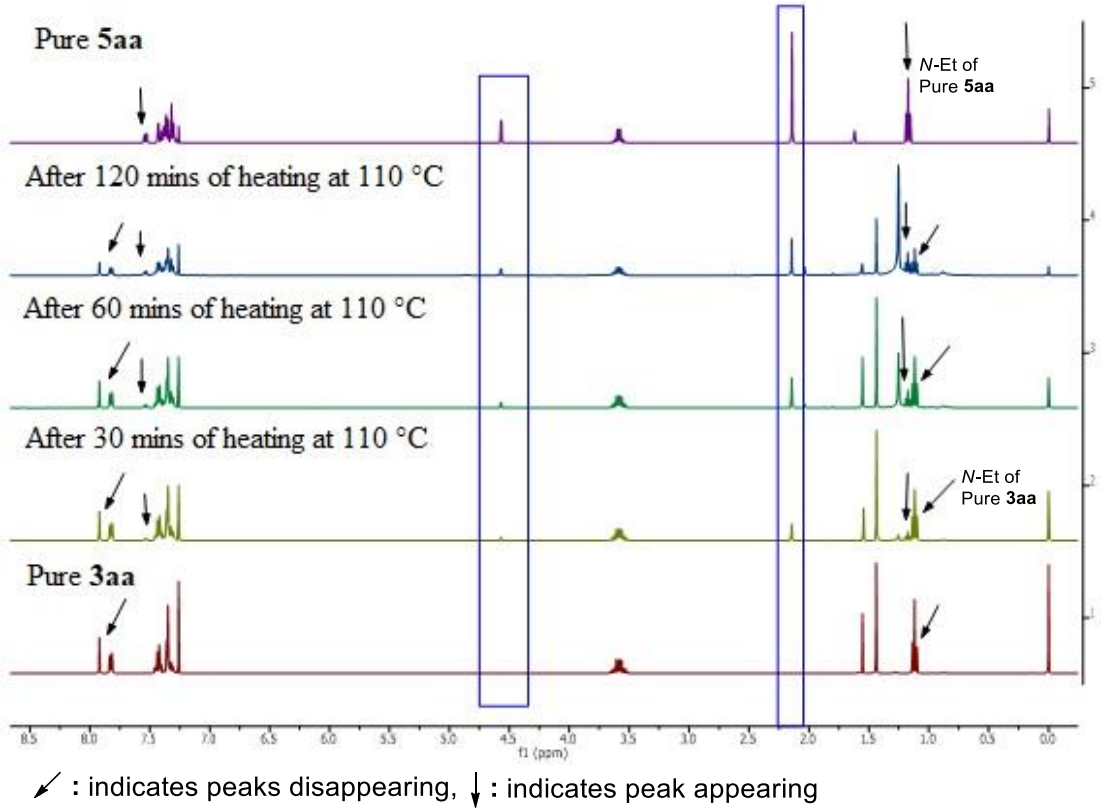
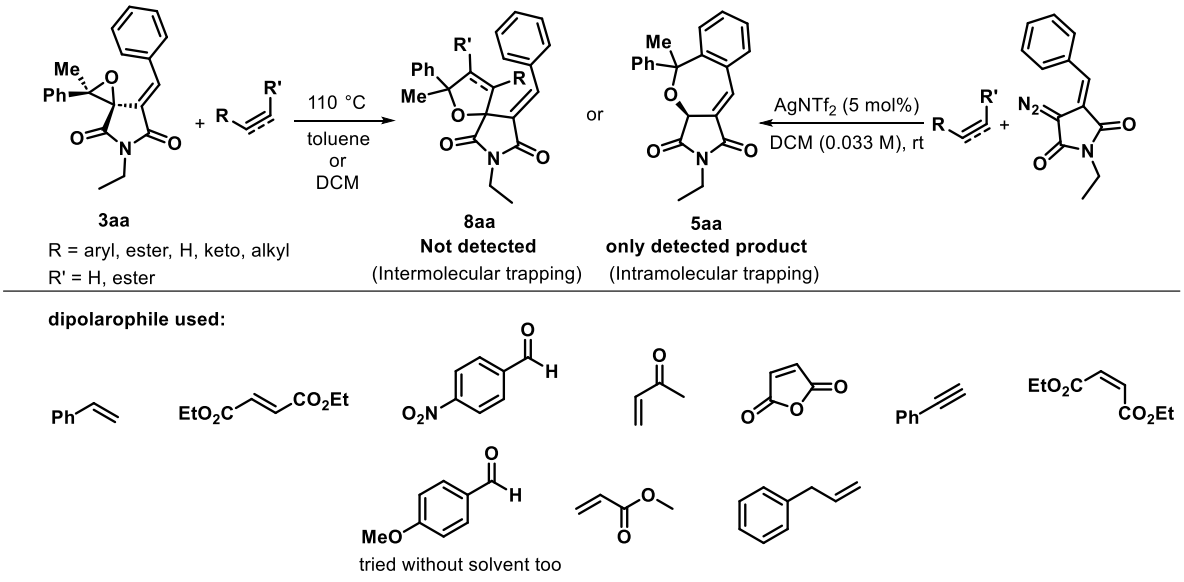


Figure 3.6. Variable time-dependent ^{1}H-NMR experiment for intermediate detection.



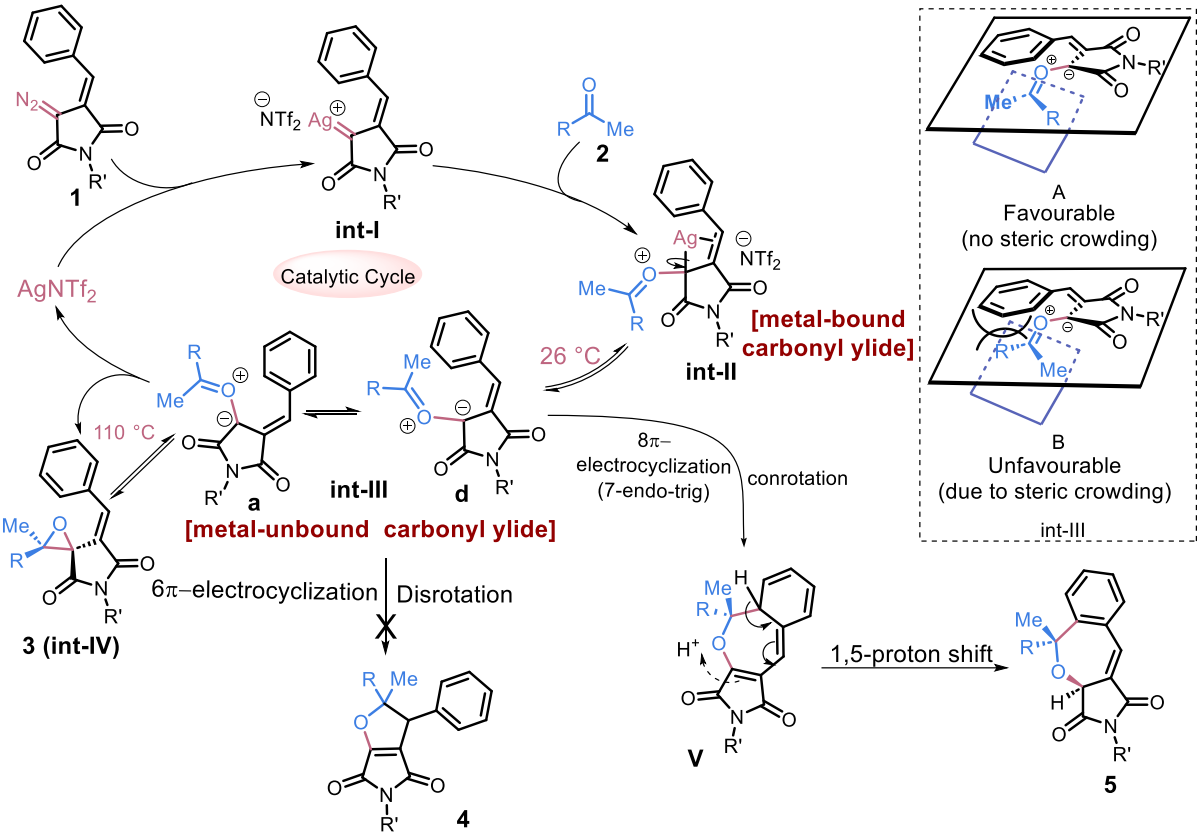
Scheme 3.9. Efforts to trap the intermediate with different dipolarophiles.

In order to understand the role of the catalyst, we carried out the reaction of **1a** and acetophenone **2a** in the absence of catalyst at 110 °C for a prolonged reaction time (Scheme 3.8e). Interestingly, we did not obtain either the desire product **5aa** or the epoxide **3aa** even in trace thus supporting the role of catalyst in the desired transformation (Scheme 3.8e). Earlier

we had observed that the reaction did not work at room temperature and in the absence of catalyst reaction did not procced, and the starting material **1a** was recovered (26 °C, see Table 3.2, Entry 23). These two results indicate that probably a reactive silver carbenoid (**int-I**, see Scheme 3.8) species might be forming *in situ* that eventually may be forming carbonyl ylide (**int-IIId**) *via* the corresponding counteranion stabilized metal-bound carbonyl ylide (**int-II**) both at room temperature as well as at an elevated temperature. These combined results clearly depicted that the epoxide (**int-IV**) may not be the favourable intermediate and probably the desired product **5aa** might be forming *via* carbonyl ylide (**int-IIId**) at room temperature. These control experiments clearly suggest that among the three plausible intermediates, the carbonyl ylide (**int-IIId**) is the most plausible intermediate for the formation of desired dihydrobenzoxepine **5aa**. Moreover, a metal-unbound (free-ylide) carbonyl ylide intermediate, generating *in situ* is proposed to be operative here based on the control experimental observations (see Experimental section 3.4.5 for more details). We believe that a relatively better coordinating and more nucleophilic counteranion Tf_2N^- might be acting as a superior promoter in facilitating the formation of **int-IIId** faster and easily at room temperature than that of SbF_6^- anion. It is also believed that the tight ion pairs that are formed between silver metal and counteranion (Tf_2N^-) as the confined the counteranion (Tf_2N^-) in more close proximity to the metal center than that of SbF_6^- (order of coordinating tendency is SbF_6^- < Tf_2N^-). We also noted that the anticipated product **4aa** (see Scheme 3.10) has not been detected during the course of the reaction. This might be the cause for the steric hindrance exerted by the benzylidene group (phenyl ring tilted towards the carbonyl moiety) on vinyl succinimide, occurring in the transition state or in the carbonyl intermediate (**int-IIId**).

3.2.3. Proposed Mechanism for the transformation:

Based on the experimental observations and preceding literatures survey,[18a,20b,21] the plausible mechanism has been proposed (See Scheme 3.10). The vinyl diazosuccinimide **1** under the optimized reaction condition generates the silver carbenoid (**int-I**) by the extrusion of dinitrogen. This intermediate (**int-I**) further reacts with the ketone **2** (approaches from sterically less hindered site; see Scheme 3.10, inset) to form metal-unbound carbenoid (**int-IIId**) *via* the corresponding counter anion stabilized metal-bound carbonyl ylide (**int-II**). This intermediate would further undergo 8π-electrocyclization (7-*endo*-trig) to form species **V** which after the successive (1,5)-proton abstraction furnishes the corresponding desired oxepine **5**. Also, at higher temperature **int-IV** (**3**) might be in equilibrium with the **int-IIId** to form the corresponding desired product **5** (Scheme 3.10).



Scheme 3.10. Plausible mechanism for the formal (5+2)-annulation.

3.3. Conclusion:

In summary, for the first time we have successfully demonstrated the formal (5+2)-cycloaddition route to access the dihydrobenzoxepines in one-pot using vinyl diazo succinimide as 5-C-synthons and commercially ketones very effectively under silver catalysis. The silver triflimide proved to be an efficient catalyst for this transformation and the protocol found to be highly regio-, chemo- and diastereo-selective. The method proved to be general as it worked well with both aliphatic and aromatic methyl ketones bearing electron deactivating as well as donating groups to afford the corresponding benzo[5,6]oxepino[2,3-*c*]pyrroles as single diastereomer with a broader substrates scope. The control experiments and time-dependent ^{1}H-NMR studies gave an insight into the plausible reaction mechanism of this transformation. To generalize the practically of the protocol, we have also shown the selective reduction of one carbonyl group to access useful compound. The protocol proved to be scalable on gram quantity as well.

3.4. Experimental Section:

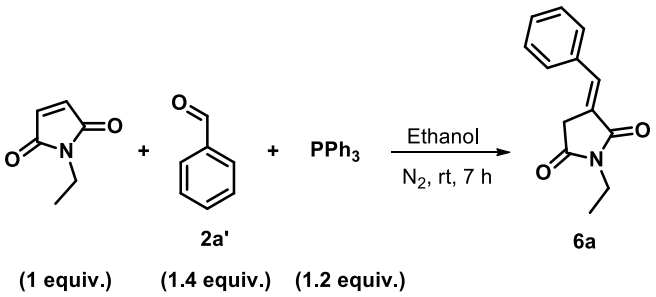
3.4.1. General Information:

❖ **Reagent Information:** All reactions were carried out with distilled and dried solvents using oven-dried glass wares under dry Argon atmosphere, unless otherwise stated. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm) with detection by UV light. Column chromatographic purification of products was carried out using silica gel (60-120 mesh). Petroleum ether and ethyl acetate mixture was used as gradient elution for column chromatography.

❖ **Analytical Information:** All isolated compounds were characterized by ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra. All Nuclear Magnetic Resonance spectra were recorded in $CDCl_3$. The NMR spectra were recorded using tetramethylsilane (TMS) as the internal standard. ^{1}H NMR spectra were recorded at 400 MHz and $^{13}C\{^{1}H\}$ NMR spectra were recorded at 100/150 MHz (Bruker and Jeol), unless otherwise noted. Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) and from DMSO-*d*$_6$ (δ = 2.5 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.16 ppm) and DMSO-*d*$_6$ resonance (δ = 39.52 ppm) for ^{13}C NMR spectroscopy. For ^{1}H NMR, data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*) are given in Hz and integration. $^{13}C\{^{1}H\}$ NMR spectra were recorded with complete proton decoupling. ^{19}F NMR spectra were recorded at 377 MHz. Mass samples were analyzed by high resolution mass spectrometry (HRMS) using ESI TOF. Melting points were measured in an open glass capillary and values are uncorrected.

3.4.2 Preparation of Starting Materials:

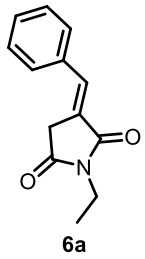
3.4.2.1 General procedure-A for the synthesis of vinyl succinimides:



To the stirred solution of *N*-ethyl maleimide (3 g, 1.0 equiv., 24 mmol) in ethanol (120 mL) was added triphenylphosphine (7.55 g, 1.2 equiv., 29.0 mmol) in portion at room temperature under N_2 atmosphere. The initial pink coloured reaction mixture slowly turned to

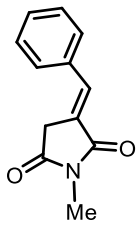
white suspension over a period of 5-6 min of initial stirring. After which, benzaldehyde (3.5 mL, 1.4 equiv., 34 mmol) was added dropwise into the reaction mixture at room temperature. During this addition, the white suspension slowly turned into clear solution. The reaction mixture was allowed to stir for 6 h. Upon completion of the reaction (monitored by TLC), the white solid formed during the course of the reaction was filtered through sintered glass funnel and was washed with ethanol (10 mL x 2). The crude product **6a** was obtained as white solid (3.40 g, 66% yield) and this was used for the next step without further purification.[16a, 22]

*(E)-3-benzylidene-1-ethylpyrrolidine-2,5-dione (**6a**):* Compound **6a** was synthesized following the general procedure-A. The product was obtained as white solid, 3.40 g (66% yield); R_f=0.30 (petroleum ether/EtOAc 85:15); m.p. 125 – 127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61 (t, *J* = 2.3 Hz, 1H), 7.51 – 7.37 (m, 5H), 3.69 (q, *J* = 7.2 Hz, 2H), 3.55 (d, *J* = 2.3 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 174, 171, 134.3, 134.2, 130.2, 130.2, 129.2, 123.7, 34.2, 34, 13.3. HRMS (ESI TOF) *m/z*: calcd for $C_{21}H_{20}NO_3$ $(M + H)^+$ 216.1025; found, 216.1027.



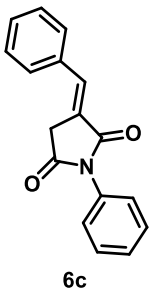
6a

*(E)-3-benzylidene-1-methylpyrrolidine-2,5-dione (**6b**):* Compound **6b** was synthesized following the general procedure-A. The product was obtained as white solid, 4.23 g (78% yield); R_f=0.30 (petroleum ether/EtOAc 85:15); m.p. 169 – 171 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (t, *J* = 2.3 Hz, 1H), 7.50 – 7.38 (m, 5H), 3.55 (d, *J* = 2.3 Hz, 2H), 3.11 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 174.2, 171.2, 134.3, 134.2, 130.2, 129.4, 129.2, 123.6, 34.1, 25. HRMS (ESI TOF) *m/z*: calcd for $C_{12}H_{12}NO_2$ $(M + H)^+$ 202.0868; found, 202.0874.



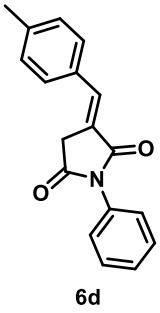
6b

*(E)-3-benzylidene-1-phenylpyrrolidine-2,5-dione (**6c**):* Compound **6c** was synthesized following the general procedure-A. The product was obtained as white solid, 3.20 g (70% yield); R_f=0.20 (petroleum ether/EtOAc 85:15); m.p. 192 – 194 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.76 (t, *J* = 2.4 Hz, 1H), 7.57 – 7.37 (m, 10H), 3.78 (d, *J* = 2.4 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.2, 170.2, 135.5, 134.2, 132.1, 130.5, 130.4, 129.3, 129.3, 128.7, 126.6, 123.2, 34.4. HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{14}NO_2$ $(M + H)^+$ 264.1025; found, 264.1021.



6c

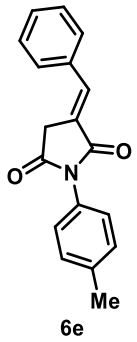
(E)-3-(4-methylbenzylidene)-1-phenylpyrrolidine-2,5-dione ***(6d)***: Compound **6d** was



6d

synthesized following the general procedure-A. The product was obtained as white solid, 3.30 g (69% yield); R_f =0.30 (petroleum ether/EtOAc 85:15); m.p. 203 – 205 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72 (t, *J* = 2.3 Hz, 1H), 7.51 (ddd, *J* = 7.8, 6.6, 1.2 Hz, 2H), 7.46 – 7.37 (m, 5H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.76 (d, *J* = 2.3 Hz, 2H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.3, 170.3, 141.1, 135.6, 132.2, 131.5, 130.5, 130.1, 129.3, 128.7, 126.6, 122, 34.5, 21.7. HRMS (ESI TOF): *m/z* calcd for $C_{18}H_{16}NO_2$ $(M + H)^+$: 278.1181, Found: 278.1184.

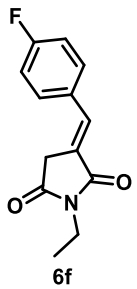
(E)-3-benzylidene-1-(p-tolyl)pyrrolidine-2,5-dione ***(6e)***: Compound **6e** was synthesized



6e

following the general procedure-A. The product was obtained as white solid, 3.28 g (66% yield); R_f =0.25 (petroleum ether/EtOAc 85:15); m.p. 198 – 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.73 (t, *J* = 2.4 Hz, 1H), 7.53 (dt, *J* = 8.3, 2.1 Hz, 2H), 7.50 – 7.41 (m, 3H), 7.32 – 7.23 (m, 4H), 3.74 (d, *J* = 2.4 Hz, 2H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.3, 170.3, 138.8, 135.4, 134.2, 130.4, 130.4, 129.9, 129.4, 129.3, 126.4, 123.3, 77.2, 34.4, 21.4. HRMS (ESI TOF) *m/z*: calcd for $C_{18}H_{16}NO_2$ $(M + H)^+$ 278.1181; found, 278.1185.

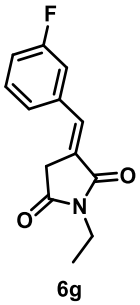
(E)-1-ethyl-3-(4-fluorobenzylidene)pyrrolidine-2,5-dione ***(6f)***: Compound **6f** was synthesized



6f

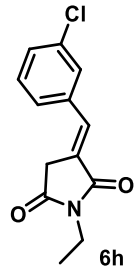
following the general procedure-A. The product was obtained as white solid, 3.69 g (66% yield); R_f =0.20 (petroleum ether/EtOAc 85:15); m.p. 142 – 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.57 (t, *J* = 2.3 Hz, 1H), 7.48 (ddt, *J* = 8.4, 5.2, 2.6 Hz, 2H), 7.18 – 7.11 (m, 2H), 3.69 (q, *J* = 7.2 Hz, 2H), 3.52 (d, *J* = 2.3 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.8, 170.9, 163.6 (d, *J* = 252.7 Hz), 132.9, 132.2, 132.1, 130.57, 130.54, 128.7, 128.5, 123.3 (d, *J* = 2.4 Hz), 116.5 (d, *J* = 21.9 Hz), 34.05, 34.01, 13.3. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -108.83 (s, 1F). HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{13}FNO_2$ $(M + H)^+$ 234.0930; found, 234.0936.

*(E)-1-ethyl-3-(3-fluorobenzylidene)pyrrolidine-2,5-dione (**6g**)*: Compound **6g** was synthesized following the general procedure-A. The product was obtained as white solid, 3.83 g (68% yield); R_f =0.30 (petroleum ether/EtOAc 85:15); m.p. 136 – 138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55 (t, *J* = 2.3 Hz, 1H), 7.42 (td, *J* = 8.0, 5.9 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.19 – 7.07 (m, 2H), 3.69 (q, *J* = 7.2 Hz, 2H), 3.54 (d, *J* = 2.3 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ (ppm) 173.6, 170.6, 163 (d, *J* = 247.4 Hz), 136.3 (d, *J* = 7.7 Hz), 132.8, 132.8, 130.8 (d, *J* = 8.3 Hz), 126.1, 126.1, 125.2, 117.2 (d, *J* = 21.3 Hz), 116.5 (d, *J* = 22.1 Hz), 34.1, 13.3. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -111.62 (s, 1F). HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{13}FNO_2$ $(M + H)^+$ 234.0930; found, 234.0931.



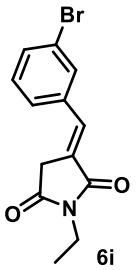
6g

*(E)-3-(3-chlorobenzylidene)-1-ethylpyrrolidine-2,5-dione (**6h**)*: Compound **6h** was synthesized following the general procedure-A. The product was obtained as white solid, 4.8 g (80% yield); R_f =0.25 (petroleum ether/EtOAc 85:15); m.p. 147 – 149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (t, *J* = 2.4 Hz, 1H), 7.45 (s, 1H), 7.38 (qd, *J* = 5.3, 4.8, 2.9 Hz, 3H), 3.70 (q, *J* = 7.2 Hz, 2H), 3.55 (d, *J* = 2.4 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.6, 170.6, 136.0, 135.2, 132.6, 130.5, 130.2, 129.9, 128.3, 125.2, 34.1, 13.3. HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{13}ClNO_2$ $(M + H)^+$ 250.0635; found, 250.0633.



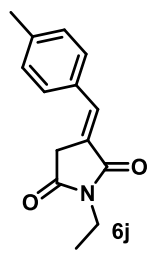
6h

*(E)-3-(3-bromobenzylidene)-1-ethylpyrrolidine-2,5-dione (**6i**)*: Compound **6i** was synthesized following the general procedure-A. The product was obtained as white solid, 5.98 g (85% yield); R_f =0.25 (petroleum ether/EtOAc 85:15); m.p. 137 – 139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61 (t, *J* = 2.3 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 3.69 (q, *J* = 7.2 Hz, 2H), 3.55 (d, *J* = 2.3 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.6, 170.6, 136.3, 133.1, 132.8, 132.6, 130.7, 128.7, 125.3, 123.3, 34.1, 34.1, 13.3. HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{13}BrNO_2$ $(M + H)^+$ 294.0129; found, 294.0133.



6i

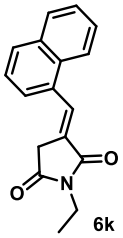
*(E)-1-ethyl-3-(4-methylbenzylidene)pyrrolidine-2,5-dione (**6j**)*: Compound **6j** was synthesized following the general procedure-A. The product was obtained as white solid, 3.48 g (63% yield); R_f =0.35 (petroleum ether/EtOAc 85:15); m.p. 148 – 150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56 (t, *J* = 2.3 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 3.67 (q, *J* = 7.2 Hz, 2H), 3.51 (d, *J* = 2.3 Hz, 2H), 2.38 (s, 3H), 1.22 (t, *J* = 07.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm)



6j

174.1, 171.1, 140.7, 134.1, 131.5, 130.3, 130.1, 129.9, 122.6, 34.2, 33.9, 21.6, 13.3. HRMS (ESI TOF) *m/z*: calcd for $C_{14}H_{16}NO_2$ $(M + H)^+$ 230.1181; found, 230.1184.

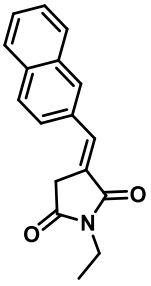
*(E)-1-ethyl-3-(naphthalen-1-ylmethylene)pyrrolidine-2,5-dione (**6k**)*: Compound **6k** was



6k

synthesized following the general procedure-A. The product was obtained as white solid, 3.42 g (54% yield); R_f =0.25 (petroleum ether/EtOAc 85:15); m.p. 148 – 150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.38 (t, *J* = 2.4 Hz, 1H), 8.15 – 8.11 (m, 1H), 7.90 (dt, *J* = 6.8, 2.3 Hz, 2H), 7.62 – 7.50 (m, 4H), 3.73 (q, *J* = 7.2 Hz, 2H), 3.51 (d, *J* = 2.3 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 174.2, 170.6, 133.8, 131.9, 131.6, 131.1, 130.5, 129.0, 127.2, 126.6, 126.5, 126.3, 125.3, 123.8, 34.0, 33.9, 13.4. HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{16}NO_2$ $(M + H)^+$ 266.1181; found, 266.1184.

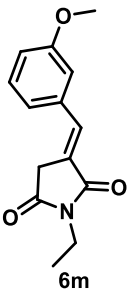
*(E)-1-ethyl-3-(naphthalen-2-ylmethylene)pyrrolidine-2,5-dione (**6l**)*: Compound **6l** was



6l

synthesized following the general procedure-A. The product was obtained as white solid, 4.12 g (65% yield); R_f =0.25 (petroleum ether/EtOAc 85:15); m.p. 190 – 192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.97 (s, 1H), 7.92 – 7.82 (m, 3H), 7.77 (t, *J* = 2.3 Hz, 1H), 7.60 – 7.51 (m, 3H), 3.72 (q, *J* = 7.2 Hz, 2H), 3.66 (d, *J* = 2.3 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 174.1, 171.1, 134.4, 133.8, 133.3, 132.3, 132.2, 131.8, 131.5, 129.0, 128.8, 128.7, 128.6, 127.9, 127.8, 127.1, 126.1, 123.7, 34.4, 34.0, 13.3. HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{16}NO_2$ $(M + H)^+$ 266.1181; found, 266.1181.

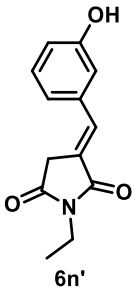
*(E)-1-ethyl-3-(3-methoxybenzylidene)pyrrolidine-2,5-dione (**6m**):* Compound **6m** was



6m

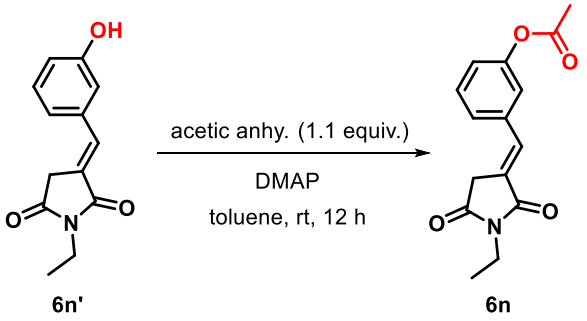
synthesized following the general procedure-A. The product was obtained as white solid, 3.01 g (51% yield); R_f =0.2 (petroleum ether/EtOAc 85:15); m.p. 125 – 127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56 (s, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 7.7 Hz, 1H), 6.99 – 6.93 (m, 2H), 3.83 (s, 3H), 3.68 (q, *J* = 7.2 Hz, 2H), 3.54 (d, *J* = 2.1 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 174.0, 170.9, 160.0, 135.5, 134.1, 130.2, 124.0, 122.6, 115.8, 115.6, 55.4, 34.2, 33.9, 13.3. HRMS (ESI TOF) *m/z*: calcd for $C_{14}H_{16}NO_3$ $(M + H)^+$ 246.1130; found, 246.1134.

(E)-1-ethyl-3-(3-hydroxybenzylidene)pyrrolidine-2,5-dione ***(6n′)***: Compound **6n′** was



synthesized following the general procedure-A. The product was obtained as white solid, 3.71 g (67% yield); R_f=0.30 (petroleum ether/EtOAc 50:50); m.p. 196 – 198 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.64 (s, 1H), 7.36 (t, *J* = 2.3 Hz, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 7.02 – 6.99 (m, 1H), 6.86 – 6.82 (m, 1H), 3.63 (d, *J* = 2.3 Hz, 2H), 3.51 (q, *J* = 7.2 Hz, 2H), 1.11 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 174.0, 170.5, 157.6, 135.3, 132.0, 130.0, 125.1, 121.4, 117.0, 116.5, 33.8, 33.0, 12.9. HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{14}NO_3$ $(M + H)^+$ 232.0973; found, 232.0973.

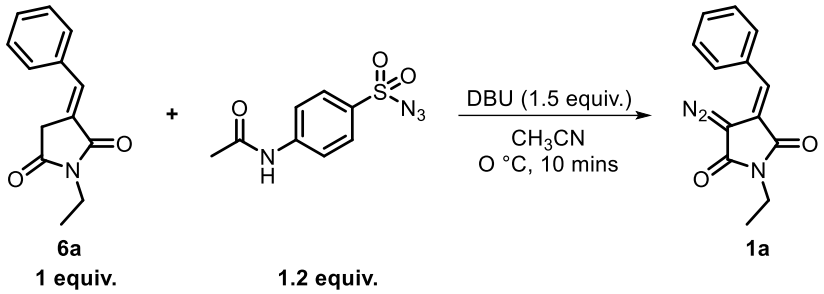
Preparation of (*E*)-3-((1-ethyl-2,5-dioxopyrrolidin-3-ylidene)methyl)phenyl acetate (6n)



To an oven dried 50 mL round bottom flask equipped with a magnetic stirrer bar, were added **6n′** (0.463 g, 1 equiv., 2.0 mmol), acetic anhydride (208 mL, 1.1 equiv., 2.2 mmol) in toluene (6 mL) with dry glass tube containing calcium chloride at the top of the condenser. After that, DMAP (5 mol%, 12.2 mg, 0.1 mmol) was added to the reaction mixture and the reaction mixture was stirred at room temperature for 12 h. After which, obtained white precipitate was filtered off through sintered funnel to afford the corresponding acetylated product **6n**.[23]

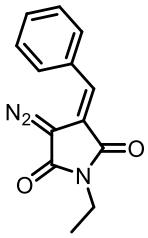
The product **6n** was obtained as white solid, 0.37 g (68% yield); R_f=0.35 (petroleum ether/EtOAc 50:50); m.p. 159 – 161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.57 (t, *J* = 2.3 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 1.9 Hz, 1H), 7.14 (ddd, *J* = 8.1, 2.2, 0.9 Hz, 1H), 3.69 (q, *J* = 7.2 Hz, 2H), 3.54 (d, *J* = 2.3 Hz, 2H), 2.32 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.7, 170.7, 169.3, 151.2, 135.7, 133.1, 130.2, 127.7, 124.8, 123.4, 122.9, 34.1, 34.0, 21.3, 13.3. HRMS (ESI TOF) *m/z*: calcd for $C_{15}H_{16}NO_4$ $(M + H)^+$ 274.1079; found, 274.1079.

3.4.2.2. General Procedure-B for the synthesis of vinyl diazosuccinimides:

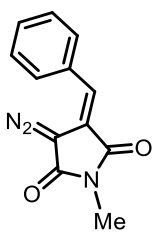


To the stirred solution of (*E*)-3-benzylidene-1-ethylpyrrolidine-2,5-dione **6a** (2.15 g, 1.0 equiv., 10 mmol) in 30 mL acetonitrile, were added 4-acetamidobenzenesulfonyl azide (2.88 g, 1.2 equiv., 12 mmol) and DBU (2.24 mL, 1.5 equiv., 15 mmol) at 0 °C temperature under inert atmosphere. The reaction mixture was stirred for 10 minutes while maintaining the temperature (0 °C). The reaction mixture was then quenched with saturated solution of NH_4Cl and the product was extracted with diethyl ether (30 mL x 3). The combined organic layers were washed with brine solution and dried over anhydrous Na_2SO_4. The extract was filtered and evaporated under reduced pressure. The crude product was purified using column chromatography over silica gel to afford *(E)*-3-benzylidene-4-diazo-1-ethylpyrrolidine-2,5-dione **1a** as orange solid (2.257 g, 94% yield).[16a]

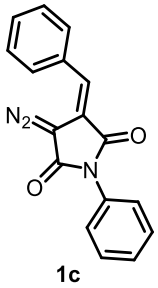
*(E)-3-benzylidene-4-diazo-1-ethylpyrrolidine-2,5-dione (**1a**)*: Compound **1a** was synthesized following the general procedure-B. The product was obtained as orange solid (2.257 g, 94% yield): R_f=0.45 petroleum ether/EtOAc (85:15); m.p. 94 – 96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (s, 1H), 7.41 (ddd, *J* = 7.6, 6.2, 1.4 Hz, 2H), 7.38 – 7.32 (m, 1H), 7.32 – 7.27 (m, 2H), 3.71 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 167.1, 164.9, 133.5, 129.5, 129, 128.8, 127.5, 117.4, 59.6, 34.5, 13.7. HRMS (ESI TOF) *m/z*: calcd for $C_{21}H_{20}NO_3$ $(M + H)^+$ 242.0930; found, 242.0927. Crystallization (30 mg): Haxane:Ethyl acetate = 2:1 (2 mL). CCDC- 2105271.



*(E)-3-benzylidene-4-diazo-1-methylpyrrolidine-2,5-dione (**1b**)*: Compound **1b** was synthesized from compound **6b** (0.5 g) following the general procedure-B. The product was obtained as orange solid (0.461 g, 82% yield): R_f=0.35 petroleum ether/EtOAc (85:15); m.p. 100 – 102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (s, 1H), 7.46 – 7.27 (m, 5H), 3.14 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 167.2, 165.1, 133.4, 129.5, 129, 128.8, 127.6, 117.2, 59.7, 25.4. HRMS (ESI TOF) *m/z*: calcd for $C_{12}H_{10}N_3O_2$ $(M + H)^+$ 228.0773; found, 228.0769.

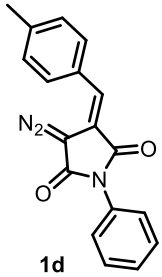


*(E)-3-benzylidene-4-diazo-1-phenylpyrrolidine-2,5-dione (**1c**)*: Compound **1c** was synthesized



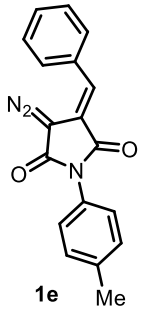
from compound **6c** (0.5 g) following the general procedure-B. The product was obtained as dark orange solid (0.475 g, 85% yield): R_f =0.4 petroleum ether/EtOAc (85:15); m.p. 130 – 132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.76 (s, 1H), 7.53 – 7.34 (m, 10H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 166.3, 164.1, 133.5, 131.9, 129.7, 129.3, 129.1, 128.9, 128.7, 128.3, 126.6, 116.8, 49.1. HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{12}N_3O_2$ $(M + H)^+$ 290.0930; found, 290.0930.

*(E)-3-benzylidene-4-diazo-1-phenylpyrrolidine-2,5-dione (**1d**)*: Compound **1d** was synthesized



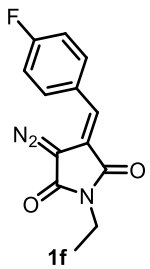
from compound **6d** (0.5 g) following the general procedure-B. The product was obtained as dark orange solid (0.442 g, 78% yield): R_f =0.4 petroleum ether/EtOAc (85:15); m.p. 128 – 130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.73 (s, 1H), 7.52 – 7.45 (m, 2H), 7.44 – 7.37 (m, 3H), 7.25 (s, 4H), 2.39 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ (ppm) 166.5, 164.2, 140.2, 132, 130.7, 129.6, 129.3, 129.2, 128.6, 128.6, 126.6, 115.7, 60.3, 21.6. HRMS (ESI TOF) *m/z*: calcd for $C_{18}H_{13}N_3O_2$ $(M + H)^+$ 304.1086; found, 304.1091.

*(E)-3-benzylidene-4-diazo-1-(p-tolyl)pyrrolidine-2,5-dione (**1e**)*: Compound **1e** was



synthesized from compound **6e** (0.5 g) following the general procedure-B. The product was obtained as orange solid (0.442 g, 78% yield): R_f =0.45 petroleum ether/EtOAc (85:15); m.p. 123 – 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.75 (s, 1H), 7.45 (ddd, *J* = 7.6, 6.3, 1.4 Hz, 2H), 7.42 – 7.33 (m, 3H), 7.29 (s, 4H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 166.4, 164.3, 138.8, 133.5, 130.0, 129.6, 129.3, 129.1, 128.9, 128.2, 126.5, 116.9, 77.2, 21.4. HRMS (ESI TOF) *m/z*: calcd for $C_{18}H_{14}N_3O_2$ $(M + H)^+$ 304.1086; found, 304.1092.

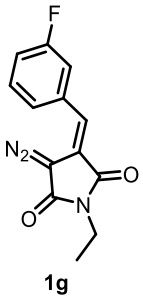
*(E)-3-diazo-1-ethyl-4-(4-fluorobenzylidene)pyrrolidine-2,5-dione (**1f**)*: Compound **1f** was



synthesized from compound **6f** (0.5 g) following the general procedure-B. The product was obtained as orange solid (0.474 g, 85% yield): R_f =0.35 petroleum ether/EtOAc (85:15); m.p. 112 – 114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58 (s, 1H), 7.32 – 7.25 (m, 2H), 7.15 – 7.08 (m, 2H), 3.71 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 166.9, 164.7, 163.2 (d, *J* = 251.6 Hz), 130.9 (d, *J* = 8.5 Hz), 129.7, 129.7, 126.3, 117.4, 116.1 (d, *J* = 22.0 Hz), 59.5, 34.6, 13.7. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -110.1 (s, 1F). HRMS (ESI

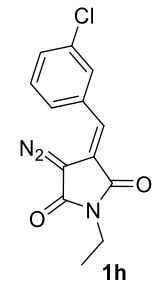
TOF) *m/z*: calcd for $C_{13}H_{11}FN_3O_2$ $(M + H)^+$ 260.0835; found, 260.0855.

*(E)-3-diazo-1-ethyl-4-(3-fluorobenzylidene)pyrrolidine-2,5-dione (**1g**)*: Compound **1g** was synthesized from compound **6g** (0.5 g) following the general procedure-B. The product was obtained as orange solid (0.423 g, 76% yield): R_f =0.4 petroleum ether/EtOAc (85:15); m.p. 65 – 67 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55 (s, 1H), 7.38 (td, *J* = 8.0, 5.9 Hz, 1H), 7.10 – 6.94 (m, 3H), 3.70 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 166.7, 164.6, 162.8 (d, *J* = 248.4 Hz), 135.6 (d, *J* = 7.8 Hz), 130.4 (d, *J* = 8.4 Hz), 125.6, 125.6, 124.6, 124.6, 118.6, 116.4 (d, *J* = 21.2 Hz), 115.7 (d, *J* = 22.1 Hz), 59.7, 34.5, 13.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -111.3 (s, 1F). HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{11}FN_3O_2$ $(M + H)^+$ 260.0835; found, 260.0838.



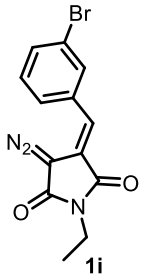
1g

*(E)-3-(3-chlorobenzylidene)-4-diazo-1-ethylpyrrolidine-2,5-dione (**1h**)*: Compound **1h** was synthesized from compound **6h** (0.5 g) following the general procedure-B. The product was obtained as orange solid (0.484 g, 88% yield): R_f =0.4 petroleum ether/EtOAc (85:15); m.p. 57 – 59 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55 (s, 1H), 7.39 – 7.31 (m, 2H), 7.29 – 7.27 (m, 1H), 7.18 (ddt, *J* = 6.4, 1.7, 0.8 Hz, 1H), 3.71 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 166.7, 164.6, 135.3, 135.0, 130.1, 129.5, 128.9, 127.0, 125.4, 118.8, 34.6, 13.7. HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{11}ClN_3O_2$ $(M + H)^+$ 276.0540; found, 276.0538.



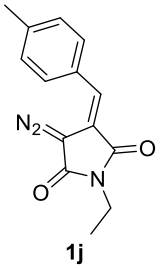
1h

*(E)-3-(3-bromobenzylidene)-4-diazo-1-ethylpyrrolidine-2,5-dione (**1i**)*: Compound **1i** was synthesized from compound **6i** (0.5 g) following the general procedure-B. The product was obtained as yellow solid (0.41 g, 75% yield): R_f =0.4 petroleum ether/EtOAc (85:15); m.p. 74 – 76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (s, 1H), 7.50 – 7.46 (m, 1H), 7.46 – 7.42 (m, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.25 – 7.20 (m, 1H), 3.71 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 166.7, 164.6, 135.5, 132.4, 131.7, 130.3, 127.4, 125.3, 123.0, 118.8, 59.8, 34.6, 13.7. HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{11}BrN_3O_2$ $(M + H)^+$ 320.0034; found, 320.0038.

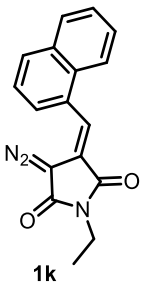


1i

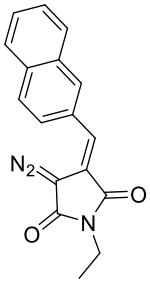
*(E)-3-diazo-1-ethyl-4-(4-methylbenzylidene)pyrrolidine-2,5-dione (**1j**)*: Compound **1j** was synthesized from compound **6j** (0.5 g) following the general procedure-B. The product was obtained as yellow solid (0.475 g, 85% yield): R_f =0.45 petroleum ether/EtOAc (85:15); m.p. 73 – 75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (s, 1H), 7.24 – 7.16 (m, 4H), 3.70 (q, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 167.2, 164.9, 139.9, 130.7, 129.5, 129.1, 127.7, 116.4, 59.6, 34.4, 21.5, 13.7. HRMS (ESI TOF) *m/z*: calcd for $C_{14}H_{14}N_3O_2$ $(M + H)^+$ 256.1086; found, 256.1086.



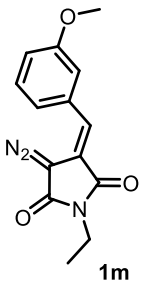
*(E)-3-diazo-1-ethyl-4-(naphthalen-1-ylmethylene)pyrrolidine-2,5-dione (**1k**)*: Compound **1k** was synthesized from compound **6k** (0.5 g) following the general procedure-B. The product was obtained as orange red solid (0.379 g, 69% yield): R_f =0.4 petroleum ether/EtOAc (85:15); m.p. 96 – 98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.17 (s, 1H), 8.03 – 7.99 (m, 1H), 7.92 – 7.86 (m, 2H), 7.61 – 7.54 (m, 2H), 7.53 – 7.48 (m, 1H), 7.38 – 7.34 (m, 1H), 3.75 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 166.8, 164.6, 133.6, 131.5, 130.5, 130.3, 128.9, 127.3, 126.8, 126.6, 125.1, 124.7, 124.6, 119.5, 34.5, 13.8. HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{14}N_3O_2$ $(M + H)^+$ 292.1086; found, 292.1089.



*(E)-3-diazo-1-ethyl-4-(naphthalen-2-ylmethylene)pyrrolidine-2,5-dione (**1l**)*: Compound **1l** was synthesized from compound **6l** (0.5 g) following the general procedure-B. The product was obtained as orange red solid (0.438 g, 80% yield): R_f =0.4 petroleum ether/EtOAc (85:15); m.p. 101 – 103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.88 – 7.78 (m, 4H), 7.77 (s, 1H), 7.52 (dt, *J* = 6.3, 3.5 Hz, 2H), 7.39 (dd, *J* = 8.5, 1.7 Hz, 1H), 3.73 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 167.2, 164.9, 133.5, 132.9, 131.2, 128.9, 128.7, 128.6, 128.0, 127.6, 127.5, 127.2, 126.1, 117.4, 77.5, 77.2, 76.8, 34.5, 13.7. HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{14}N_3O_2$ $(M + H)^+$ 292.1086; found, 292.1116.

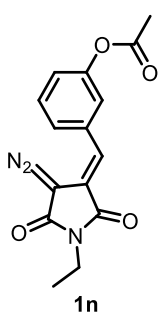


*(E)-3-diazo-1-ethyl-4-(3-methoxybenzylidene)pyrrolidine-2,5-dione (**1m**)*: Compound **1m** was synthesized from compound **6m** (0.5 g) following the general procedure-B. The product was obtained as Brownish red liquid (0.493 g, 89% yield): R_f =0.35 petroleum ether/EtOAc (85:15); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.59 (s, 1H), 7.34 – 7.29 (m, 1H), 6.92 – 6.85 (m, 2H), 6.81 – 6.78 (m, 1H), 3.82 (s, 3H), 3.70 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz,



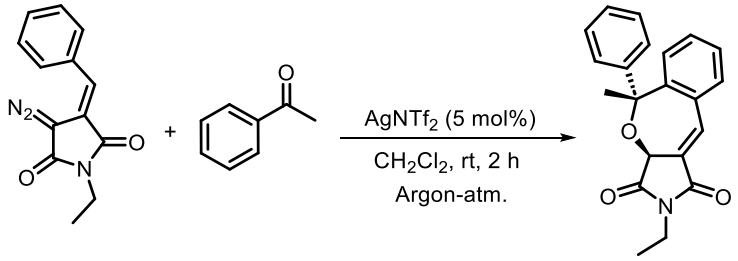
$CDCl_3$): δ (ppm) 167.0, 164.8, 159.8, 134.8, 129.8, 127.4, 121.5, 117.6, 115.4, 114.1, 100.1, 59.7, 55.4, 34.5, 13.7. HRMS (ESI TOF) *m/z*: calcd for $C_{14}H_{14}N_3O_3$ $(M + H)^+$ 272.1035; found, 272.1042.

*(E)-3-((4-diazo-1-ethyl-2,5-dioxopyrrolidin-3-ylidene)methyl)phenyl acetate (**1n**)*: Compound **1n** was synthesized from compound **6n** (0.5 g) following the general procedure-B. The product was obtained as orange solid (0.405 g, 74% yield): R_f =0.45 petroleum ether/EtOAc (50:50); m.p. 105 – 107 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58 (s, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.11 – 7.07 (m, 1H), 7.04 (t, *J* = 1.9 Hz, 1H), 3.71 (q, *J* = 7.2 Hz, 2H), 2.31 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.2, 166.9, 164.7, 151.0, 135.0, 129.9, 126.3, 126.0, 122.8, 122.1, 118.3, 59.7, 34.6, 21.2, 13.7. HRMS (ESI TOF) *m/z*: calcd for $C_{15}H_{11}N_3O_4$ $(M + H)^+$ 300.0984; found, 300.0977.



1n

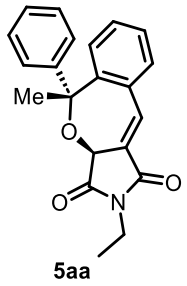
3.4.3. General Procedure-C for the Synthesis of dihydrobenzo[5,6]oxepino[2,3-*c*]pyrrole-1,3(2*H*)-dione:



1a **2a** **5aa**

An oven-dried 25 mL two necked round bottom (RB) flask equipped with a magnetic stirrer bar was charged with $AgNTf_2$ (3.9 mg, 5 mol%) under argon-atmosphere and the RB flask was covered up with aluminium foil. Then dry CH_2Cl_2 (5 mL) and acetophenone **2a** (23.6 μL, 1.0 equiv., 0.2 mmol) was added subsequently and the mixture was stirred at room temperature under for a minute. After that, vinyl diazosuccinimide **1a** (48.3 mg, 1.0 equiv., 0.2 mmol) in CH_2Cl_2 (1 mL) was added to the reaction mixture dropwise over 2 h and the stirring was continued for 10 mins more for full consumption of diazo compound. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography (petroleum ether/EtOAc 92:8) over silica gel to furnish the desired product **5aa** as white solid (47 mg, 70% yield). The slight excess amount of acetophenone **2a** was recovered during the purification.

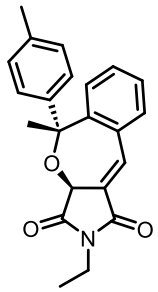
*2-ethyl-5-methyl-5-phenyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5aa**)*: Compound **5aa** was synthesized following the general procedure-C. The product was



5aa

obtained as white solid, 47 mg (70% yield); R_f=0.3 (petroleum ether/EtOAc 85:15); m.p. 167 – 169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (dd, *J* = 6.7, 2.2 Hz, 1H), 7.43 (d, *J* = 2.3 Hz, 1H), 7.42 – 7.28 (m, 8H), 4.57 (d, *J* = 2.3 Hz, 1H), 3.59 (qd, *J* = 7.2, 3.6 Hz, 2H), 2.14 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.9, 167.4, 146.2, 145.2, 136.4, 135.1, 131.8, 131.7, 131.5, 129.2, 128.8, 128.7, 128.5, 127.9, 87.4, 70.7, 33.9, 32.8, 13.2. HRMS (ESI TOF) *m/z*: calcd for $C_{21}H_{20}NO_3$ $(M + H)^+$ 334.1443; found, 334.1447.

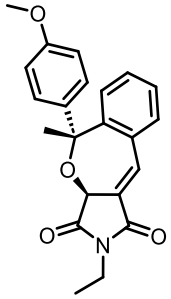
*2-ethyl-5-methyl-5-(p-tolyl)-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5ab**):* Compound **5ab** was synthesized following the general procedure-C. The product



5ab

was obtained as white solid, 49 mg (70% yield); R_f=0.35 (petroleum ether/EtOAc 85:15); m.p. 151 – 153 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55 – 7.50 (m, 1H), 7.42 (d, *J* = 2.2 Hz, 1H), 7.41 – 7.33 (m, 3H), 7.21 – 7.13 (m, 4H), 4.58 (d, *J* = 2.2 Hz, 1H), 3.59 (qd, *J* = 7.0, 3.2 Hz, 2H), 2.33 (s, 3H), 2.13 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.1, 167.4, 146.5, 142.3, 138.4, 136.3, 135.1, 131.9, 131.7, 131.4, 129.5, 129.2, 128.7, 127.9, 87.3, 70.6, 33.9, 32.7, 21.2, 13.2. HRMS (ESI TOF) *m/z*: calcd for $C_{22}H_{22}NO_3$ $(M + H)^+$ 348.1599; found, 348.1608.

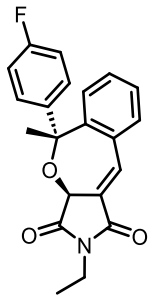
*2-ethyl-5-(4-methoxyphenyl)-5-methyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5ac**):* Compound **5ac** was synthesized following the general procedure-C. The



5ac

product was obtained as white solid, 54 mg (74% yield); R_f=0.25 (petroleum ether/EtOAc 85:15); m.p. 146 – 148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 (dd, *J* = 6.5, 1.8 Hz, 1H), 7.41 (d, *J* = 2.3 Hz, 1H), 7.37 (dddd, *J* = 9.3, 7.4, 5.4, 3.3 Hz, 3H), 7.23 – 7.18 (m, 2H), 6.86 (d, *J* = 9.1 Hz, 2H), 4.57 (d, *J* = 2.3 Hz, 1H), 3.78 (s, 3H), 3.58 (qd, *J* = 7.2, 3.2 Hz, 2H), 2.11 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.0, 167.3, 159.4, 146.5, 137.3, 136.2, 134.9, 131.8, 131.6, 131.2, 130.0, 129.0, 127.7, 113.9, 87.0, 70.3, 55.3, 33.7, 32.5, 13.1. HRMS (ESI TOF) *m/z*: calcd for $C_{22}H_{22}NO_4$ $(M + H)^+$ 364.1549; found, 364.1549.

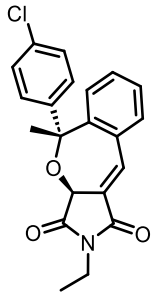
*2-ethyl-5-(4-fluorophenyl)-5-methyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5ad**):* Compound **5ad** was synthesized following the general procedure-C. The



5ad

product was obtained as white solid, 32 mg (45% yield); R_f=0.35 (petroleum ether/EtOAc 85:15); m.p. 174 – 176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.53 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.43 (d, *J* = 2.3 Hz, 1H), 7.42 – 7.28 (m, 5H), 7.08 – 7.01 (m, 2H), 4.53 (d, *J* = 2.3 Hz, 1H), 3.59 (qd, *J* = 7.2, 3.0 Hz, 2H), 2.11 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.9, 167.3, 162.5 (d, *J* = 248.8 Hz), 145.9, 141.2, 141.1, 136.4, 135.1, 131.8, 131.7, 131.4, 130.6 (d, *J* = 8.2 Hz), 129.3, 128.1, 115.7 (d, *J* = 21.3 Hz). ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -113.4 (s, 1F). HRMS (ESI TOF) *m/z*: calcd for $C_{21}H_{19}FNO_3$ $(M + H)^+$ 352.1349; found, 352.1350.

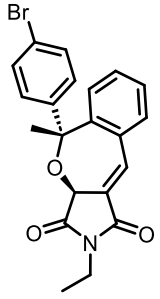
*5-(4-chlorophenyl)-2-ethyl-5-methyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5ae**):* Compound **5ae** was synthesized following the general procedure-C. The



5ae

product was obtained as white solid, 48 mg (65% yield); R_f=0.35 (petroleum ether/EtOAc 85:15); m.p. 160 – 162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (dd, *J* = 7.3, 2.0 Hz, 1H), 7.43 (d, *J* = 2.3 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.36 – 7.30 (m, 3H), 7.27 (d, *J* = 8.2 Hz, 2H), 4.53 (d, *J* = 2.3 Hz, 1H), 3.60 (qd, *J* = 7.2, 2.8 Hz, 2H), 2.11 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.8, 167.3, 145.7, 143.8, 136.5, 135.1, 134.6, 131.8, 131.7, 131.4, 130.1, 129.3, 129.0, 128.2, 87.0, 70.5, 34.0, 32.9, 13.2. HRMS (ESI TOF) *m/z*: calcd for $C_{21}H_{19}ClNO_3$ $(M + H)^+$ 368.1053; found, 368.1050.

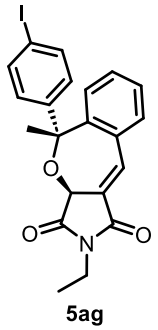
*5-(4-bromophenyl)-2-ethyl-5-methyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5af**):* Compound **5af** was synthesized following the general procedure-C. The



5af

product was obtained as white solid, 38 mg (46% yield); R_f=0.3 (petroleum ether/EtOAc 85:15); m.p. 185 – 187 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.53 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 2.3 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.31 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.24 – 7.18 (m, 2H), 4.53 (d, *J* = 2.3 Hz, 1H), 3.59 (qd, *J* = 7.2, 2.8 Hz, 2H), 2.10 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.7, 167.2, 145.5, 144.3, 136.5, 135.0, 132.0, 131.7, 131.7, 131.4, 130.4, 129.3, 128.2, 122.9, 87.0, 70.6, 33.9, 32.9, 13.2. HRMS (ESI TOF) *m/z*: calcd for $C_{21}H_{19}BrNO_3$ $(M + H)^+$ 412.0548; found, 412.0550.

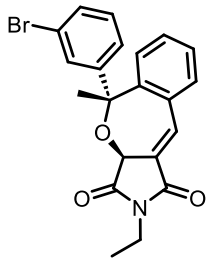
*2-ethyl-5-(4-iodophenyl)-5-methyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5ag**):* Compound **5ag** was synthesized following the general procedure-C. The



5ag

product was obtained as white solid, 40 mg (44% yield); R_f=0.4 (petroleum ether/EtOAc 85:15); m.p. 205 – 207 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72 (d, *J* = 8.7 Hz, 2H), 7.56 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.45 (d, *J* = 2.3 Hz, 1H), 7.41 (ddd, *J* = 14.4, 7.1, 1.7 Hz, 2H), 7.33 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.12 – 7.06 (m, 2H), 4.56 (d, *J* = 2.3 Hz, 1H), 3.62 (qd, *J* = 7.2, 2.7 Hz, 2H), 2.12 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.6, 167.1, 145.4, 144.9, 137.9, 136.4, 134.9, 131.6, 131.3, 130.5, 129.2, 128.0, 94.7, 87.0, 70.5, 33.8, 32.7, 13.1. HRMS (ESI TOF) *m/z*: calcd for $C_{21}H_{19}INO_3$ $(M + H)^+$ 460.0410; found, 460.0413.

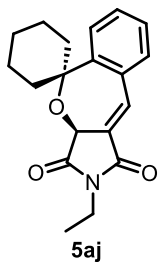
*5-(3-bromophenyl)-2-ethyl-5-methyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5ah**)*: Compound **5ah** was synthesized following the general procedure-C. The



5ah

product was obtained as white solid, 48 mg (58% yield); R_f=0.35 (petroleum ether/EtOAc 85:15); m.p. 173 – 175 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56 – 7.53 (m, 1H), 7.47 – 7.24 (m, 8H), 4.56 (d, *J* = 2.2 Hz, 1H), 3.60 (qd, *J* = 7.2, 3.6 Hz, 2H), 2.10 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.6, 167.2, 147.7, 145.3, 136.5, 135.1, 131.9, 131.7, 131.7, 131.5, 130.5, 129.4, 128.2, 127.1, 123.0, 87.0, 70.6, 34.0, 33.0, 13.2. HRMS (ESI TOF) *m/z*: calcd for $C_{21}H_{19}BrNO_3$ $(M + H)^+$ 412.0548; found, 412.0557.

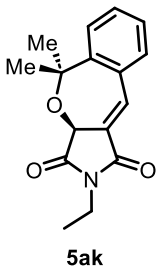
*2-ethylspiro[benzo[5,6]oxepino[2,3-c]pyrrole-5,1'-cyclohexane]-1,3(2H,3aH)-dione (**5aj**)*:



5aj

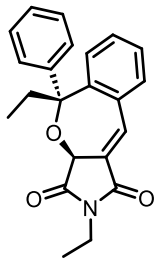
Compound **5aj** was synthesized following the general procedure-C. The product was obtained as white solid, 30 mg (48% yield); R_f=0.4 (petroleum ether/EtOAc 85:15); m.p. 126 – 128 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.46 (d, *J* = 1.9 Hz, 1H), 7.45 – 7.27 (m, 4H), 4.92 (d, *J* = 1.9 Hz, 1H), 3.68 (q, *J* = 7.2 Hz, 2H), 2.38 (d, *J* = 12.9 Hz, 1H), 2.11 – 1.78 (m, 6H), 1.59 (s, 4H), 1.34 (dtt, *J* = 16.7, 8.9, 3.9 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.2, 167.4, 150.3, 135.9, 135.6, 132.0, 131.2, 129.5, 129.2, 127.1, 83.5, 68.3, 40.9, 36.2, 33.8, 25.4, 22.4, 20.0, 13.2. HRMS (ESI TOF) *m/z*: calcd for $C_{19}H_{22}NO_3$ $(M + H)^+$ 312.1599; found, 312.1606.

*2-ethyl-5,5-dimethyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5ak**)*: Compound **5ak** was synthesized following the general procedure-C. The product was obtained as white solid, 38 mg (70% yield); R_f=0.25 (petroleum ether/EtOAc 85:15); m.p. 132 – 134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.48 (d, *J* = 2.2 Hz, 1H), 7.42 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.40 – 7.28 (m, 3H), 5.00 (d, *J* = 2.2 Hz, 1H), 3.68 (qd, *J* = 7.2, 1.2 Hz, 2H), 1.84 (s, 3H), 1.68 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.2, 167.5, 149.7, 135.9, 135.5, 131.9, 130.9, 129.8, 129.2, 127.4, 82.8, 69.6, 34.0, 32.8, 30.4, 13.3, 0.1. HRMS (ESI TOF) *m/z*: calcd for $C_{16}H_{18}NO_3$ $(M + H)^+$ 272.1286; found, 272.1285.



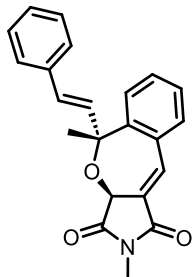
5ak

*2,5-diethyl-5-phenyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5al**)*: Compound **5al** was synthesized following the general procedure-C. The product was obtained as white solid, 45 mg (65% yield); R_f=0.4 (petroleum ether/EtOAc 85:15); m.p. 189 – 191 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (dd, *J* = 5.8, 3.3 Hz, 1H), 7.42 (d, *J* = 2.2 Hz, 1H), 7.41 – 7.27 (m, 8H), 4.58 (d, *J* = 2.2 Hz, 1H), 3.60 (qd, *J* = 7.0, 2.5 Hz, 2H), 2.76 (dq, *J* = 14.2, 7.1 Hz, 1H), 2.25 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.74 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.2, 167.5, 145.9, 144.0, 136.4, 135.1, 133.6, 132.0, 131.8, 129.0, 128.8, 128.7, 128.4, 127.7, 90.7, 70.2, 38.2, 33.9, 13.3, 8.9. HRMS (ESI TOF) *m/z*: calcd for $C_{22}H_{22}NO_3$ $(M + H)^+$ 348.1599; found, 348.1601.



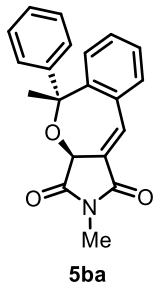
5al

*2-ethyl-5-methyl-5-((E)-styryl)-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5am**)*: Compound **5am** was synthesized following the general procedure-C. The product was obtained as white solid, 36 mg (50% yield); R_f=0.3 (petroleum ether/EtOAc 85:15); m.p. 169 – 171 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 – 7.48 (m, 1H), 7.46 (d, *J* = 2.1 Hz, 1H), 7.39 (td, *J* = 6.5, 6.0, 3.6 Hz, 5H), 7.34 – 7.23 (m, 3H), 6.54 (d, *J* = 16.2 Hz, 1H), 6.23 (d, *J* = 16.2 Hz, 1H), 5.17 (d, *J* = 2.1 Hz, 1H), 3.72 – 3.58 (m, 2H), 1.91 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.3, 167.4, 146.0, 137.0, 136.0, 135.7, 135.4, 135.2, 132.0, 131.9, 131.2, 129.3, 128.8, 128.6, 127.8, 127.0, 85.9, 70.2, 34.0, 32.2, 13.3. HRMS (ESI TOF) *m/z*: calcd for $C_{23}H_{22}NO_3$ $(M + H)^+$ 360.1599; found, 360.1601.



5am

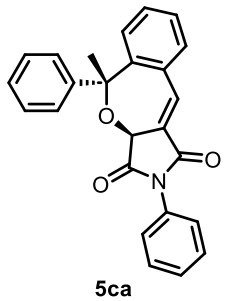
2,5-dimethyl-5-phenyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione ***(5ba)***: Compound **5ba** was synthesized following the general procedure-C. The product was



5ba

obtained as white solid, 33 mg (52% yield); R_f=0.25 (petroleum ether/EtOAc 85:15); m.p. 188 – 190 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56 – 7.52 (m, 1H), 7.44 (d, *J* = 2.3 Hz, 1H), 7.43 – 7.28 (m, 8H), 4.59 (d, *J* = 2.3 Hz, 1H), 3.02 (s, 3H), 2.14 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.2, 167.7, 146.3, 145.1, 136.4, 135.2, 131.7, 131.5, 129.2, 128.8, 128.7, 128.5, 127.9, 87.5, 70.7, 32.7, 24.9. HRMS (ESI TOF) *m/z*: calcd for $C_{20}H_{18}NO_3$ $(M + H)^+$ 320.1286; found, 320.1285.

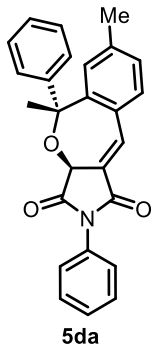
5-methyl-2,5-diphenyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione ***(5ca)***: Compound **5ca** was synthesized following the general procedure-C. The product was



5ca

obtained as white solid, 34 mg (45% yield); R_f=0.3 (petroleum ether/EtOAc 85:15); m.p. 229 – 231 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58 (dd, *J* = 9.8, 2.3 Hz, 2H), 7.47 – 7.31 (m, 13H), 4.77 (d, *J* = 2.3 Hz, 1H), 2.19 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.1, 166.5, 146.4, 145.2, 136.6, 136.4, 131.8, 131.7, 131.5, 131.2, 129.4, 129.2, 129.2, 128.9, 128.7, 128.6, 128.0, 126.3, 87.6, 70.8, 32.8. HRMS (ESI TOF) *m/z*: calcd for $C_{25}H_{20}NO_3$ $(M + H)^+$ 382.1443; found, 382.1441.

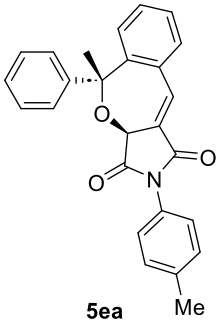
5,7-dimethyl-2,5-diphenyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione ***(5da)***: Compound **5da** was synthesized following the general procedure-C. The product was



5da

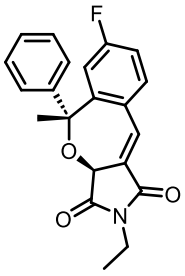
obtained as white solid, 33 mg (42% yield); R_f=0.35 (petroleum ether/EtOAc 85:15); m.p. 230 – 232 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (d, J = 2.3 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.43 – 7.40 (m, 1H), 7.39 – 7.29 (m, 8H), 7.26 – 7.22 (m, 1H), 7.20 (d, J = 1.7 Hz, 1H), 4.75 (d, J = 2.3 Hz, 1H), 2.40 (s, 3H), 2.18 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.2, 166.7, 146.3, 145.2, 140.0, 136.7, 136.5, 132.2, 131.8, 129.9, 129.2, 129.1, 128.9, 128.7, 128.6, 128.6, 126.4, 87.5, 70.8, 32.8, 21.8. HRMS (ESI TOF) *m/z*: calcd for $C_{26}H_{22}NO_3$ $(M + H)^+$ 396.1599; found, 396.1599.

*5-methyl-5-phenyl-2-(p-tolyl)-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5ea**)*: Compound **5ea** was synthesized following the general procedure-C. The product was obtained as white solid, 38 mg (48% yield); R_f=0.3 (petroleum ether/EtOAc 85:15); m.p. 222 – 224 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.59 – 7.55 (m, 2H), 7.46 – 7.31 (m, 8H), 7.26 – 7.22 (m, 2H), 7.21 – 7.17 (m, 2H), 4.76 (d, *J* = 2.3 Hz, 1H), 2.37 (s, 3H), 2.18 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.2, 166.7, 146.4, 145.2, 138.7, 136.6, 136.2, 131.7, 131.5, 131.3, 129.8, 129.4, 129.1, 128.9, 128.7, 128.6, 128.0, 126.1, 87.6, 70.8, 32.8, 21.4. HRMS (ESI TOF) *m/z*: calcd for $C_{26}H_{22}NO_3$ $(M + H)^+$ 396.1600; found, 396.1587.



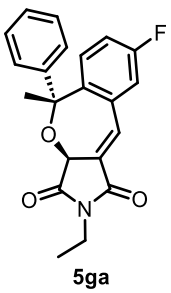
5ea

*2-ethyl-7-fluoro-5-methyl-5-phenyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5fa**)*: Compound **5fa** was synthesized following the general procedure-C. The product was obtained as white solid, 39 mg (55% yield); R_f=0.3 (petroleum ether/EtOAc 85:15); m.p. 189 – 191 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.53 (dd, *J* = 8.7, 6.1 Hz, 1H), 7.41 – 7.36 (m, 3H), 7.35 – 7.27 (m, 3H), 7.15 – 7.05 (m, 2H), 4.56 (d, *J* = 2.2 Hz, 1H), 3.58 (qd, *J* = 7.2, 3.7 Hz, 2H), 2.13 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.7, 167.3, 162.4 (d, *J* = 252.8 Hz), 149.20, 149.13, 144.4, 138.45, 138.37, 133.8, 131.08, 131.05, 129.0, 128.8, 128.5, 128.26, 128.23, 118.6 (d, *J* = 23.3 Hz), 115.4 (d, *J* = 21.3 Hz), 87.1, 70.8, 33.9, 32.7, 13.2. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -109.14. HRMS (ESI TOF) *m/z*: calcd for $C_{21}H_{19}FNO_3$ $(M + H)^+$ 352.1349; found, 352.1359.



5fa

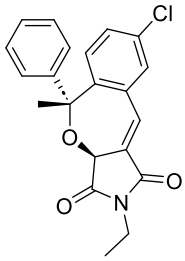
*2-ethyl-8-fluoro-5-methyl-5-phenyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5ga**)*: Compound **5ga** was synthesized following the general procedure-C. The product was obtained as white solid, 44 mg (62% yield); R_f=0.35 (petroleum ether/EtOAc 85:15); m.p. 198 – 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.38 (d, *J* = 6.8 Hz, 1H), 7.37 – 7.26 (m, 6H), 7.23 (dd, *J* = 9.4, 2.7 Hz, 1H), 7.09 (td, *J* = 9.7, 8.6, 2.8 Hz, 1H), 4.56 (d, *J* = 2.1 Hz, 1H), 3.59 (qd, *J* = 7.0, 3.7 Hz, 2H), 2.13 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.6, 167.0, 161.4 (d, *J* = 248.5 Hz), 144.9, 142.0, 142.0, 133.7 (d, *J* = 7.1 Hz), 133.6, 133.6, 133.2, 133.2, 133.2, 128.9, 128.6, 128.5, 121.7 (d, *J* = 21.3 Hz), 116.2 (d, *J* = 20.9 Hz), 87.1, 70.6, 33.9, 32.9, 13.2. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm)



5ga

-114.9. HRMS (ESI TOF) *m/z*: calcd for $C_{21}H_{19}FNO_3$ $(M + H)^+$ 352.1349; found, 352.1348. Crystallization was done in the solvent mixture of Hexane:Chloroform = 2:1. CCDC: 2105766.

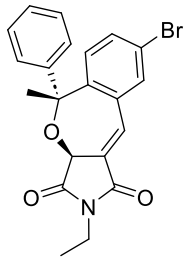
*8-chloro-2-ethyl-5-methyl-5-phenyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5ha**)*: Compound **5ha** was synthesized following the general procedure-C. The



5ha

product was obtained as white solid, 50 mg (68% yield); R_f=0.35 (petroleum ether/EtOAc 85:15); m.p. 219 – 221 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 (d, *J* = 2.3 Hz, 1H), 7.41 – 7.26 (m, 8H), 4.55 (d, *J* = 2.3 Hz, 1H), 3.59 (qd, *J* = 7.2, 3.9 Hz, 2H), 2.12 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.6, 167.0, 144.7, 144.6, 135.3, 133.6, 133.5, 133.5, 133.4, 132.8, 129.0, 128.7,128.6, 124.8, 87.2, 70.6, 34.0, 32.7, 13.2. HRMS (ESI TOF) *m/z*: calcd for $C_{21}H_{19}ClNO_3$ $(M + H)^+$ 368.1053; found, 368.1051.

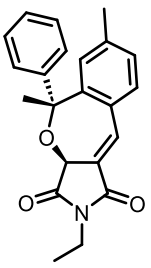
*8-bromo-2-ethyl-5-methyl-5-phenyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5ia**)*: Compound **5ia** was synthesized following the general procedure-C. The



5ia

product was obtained as white solid, 45 mg (55% yield); R_f=0.4 (petroleum ether/EtOAc 85:15); m.p. 223 – 225 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.68 (d, *J* = 2.2 Hz, 1H), 7.48 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.40 – 7.27 (m, 6H), 7.23 (d, *J* = 8.6 Hz, 1H), 4.55 (d, *J* = 2.2 Hz, 1H), 3.59 (qd, *J* = 7.2, 3.8 Hz, 2H), 2.12 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.6, 167.0, 145.1, 144.7, 138.3, 133.8, 133.44, 133.42, 133.0, 131.9, 129.0, 128.7, 128.6, 121.6, 87.3, 70.6, 34.0, 32.7, 13.2. HRMS (ESI TOF) *m/z*: calcd for $C_{21}H_{19}BrNO_3$ $(M + H)^+$ 412.0548; found, 412.0548.

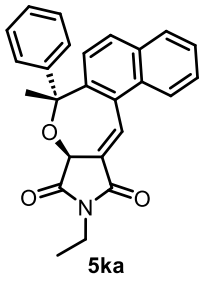
*2-ethyl-5,7-dimethyl-5-phenyl-3a,5-dihydro-1H-benzo[5,6]oxepino[2,3-c]pyrrole-1,3(2H)-dione (**5ja**)*: Compound **5ja** was synthesized following the general procedure-C. The product



5ja

was obtained as white solid, 36 mg (52% yield); R_f=0.35 (petroleum ether/EtOAc 85:15); m.p. 176 – 178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 2.3 Hz, 1H), 7.39 – 7.28 (m, 5H), 7.23 – 7.18 (m, 1H), 7.16 (s, 1H), 4.54 (d, *J* = 2.3 Hz, 1H), 3.58 (qd, *J* = 7.2, 3.6 Hz, 2H), 2.38 (s, 3H), 2.14 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.1, 167.5, 146.1, 145.2, 139.6, 136.5, 135.1, 132.2, 130.6, 129.1, 128.8, 128.8, 128.7, 128.5, 87.3, 70.7, 33.8, 32.8, 21.8, 13.2. HRMS (ESI TOF) *m/z*: calcd for $C_{22}H_{22}NO_3$ $(M + H)^+$ 348.1599; found, 348.1600.

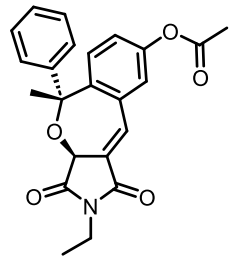
*10-ethyl-7-methyl-7-phenyl-7,8a-dihydro-9H-naphtho[1',2':5,6]oxepino[2,3-c]pyrrole-9,11(10H)-dione (**5ka**)*: Compound **5ka** was synthesized following the general procedure-C.



5ka

The product was obtained as white solid, 38 mg (50% yield); R_f=0.35 (petroleum ether/EtOAc 85:15); m.p. 229 – 231 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.56 (d, *J* = 2.1 Hz, 1H), 8.50 (d, *J* = 8.7 Hz, 1H), 7.90 – 7.86 (m, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.68 (ddd, *J* = 8.6, 6.9, 1.5 Hz, 1H), 7.63 – 7.58 (m, 1H), 7.40 – 7.30 (m, 6H), 4.66 (d, *J* = 2.1 Hz, 1H), 3.64 (qd, *J* = 7.2, 1.8 Hz, 2H), 2.19 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.8, 167.9, 146.1, 145.8, 133.8, 133.2, 132.7, 129.5, 129.1, 129.0, 128.8, 128.7, 128.5, 127.8, 126.8, 126.8, 123.9, 88.0, 69.7, 34.0, 32.1, 13.3. HRMS (ESI TOF) *m/z*: calcd for $C_{25}H_{22}NO_3$ $(M + H)^+$ 384.1599; found, 384.1600.

*2-ethyl-5-methyl-1,3-dioxo-5-phenyl-2,3,3a,5-tetrahydro-1H-benzo[5,6]oxepino[2,3-c]pyrrol-8-yl acetate (**5na**)*: Compound **5na** was synthesized following the general procedure-C.



5na

The product was obtained as white solid, 48 mg (61% yield); R_f=0.15 (petroleum ether/EtOAc 85:15); m.p. 143 – 145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40 – 7.26 (m, 8H), 7.14 (dd, *J* = 8.7, 2.6 Hz, 1H), 4.56 (d, *J* = 2.3 Hz, 1H), 3.58 (qd, *J* = 7.2, 3.8 Hz, 2H), 2.35 (s, 3H), 2.13 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.7, 169.2, 167.1, 149.7, 145.0, 143.6, 134.0, 133.2, 132.9, 132.6, 128.9, 128.6, 128.6, 128.2, 122.3, 87.3, 70.6, 34.0, 32.9, 21.3, 13.2. HRMS (ESI TOF) *m/z*: calcd for $C_{23}H_{22}NO_5$ $(M + H)^+$ 392.1498; found, 392.1498.

3.5.3. **Appendix-II: Applications**

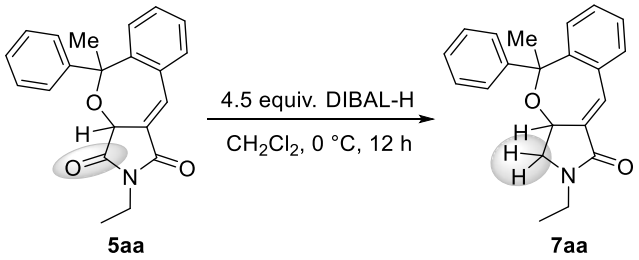
3.4.4A. Gram Scale synthesis:

An oven-dried 25 mL two necked round bottom (RB) flask equipped with a magnetic stirrer bar was charged with $AgNTf_2$ (78 mg, 5 mol%) under argon-atmosphere and the RB flask was covered up with aluminium foil. Then CH_2Cl_2 (100 mL) and acetophenone **2a** (472 µL, 1 equiv., 4.0 mmol) was added subsequently and the mixture was stirred at room temperature for a minute. After that, vinyl diazosuccinimide **1a** (965 mg, 1 equiv., 4.0 mmol) in CH_2Cl_2 (22 mL) was added to the reaction mixture dropwise over 3 h and the stirring was continued for 10 minute for the complete consumption of diazo compound. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed

under reduced pressure. The crude product obtained was then purified by column chromatography (petroleum ether/EtOAc 92:8) over silica gel to furnish the desired product **5aa** as white solid (605 mg, 45% yield). The excess amount of acetophenone **2a** was recovered during the purification.

3.4.4B. Procedure for reduction of 5aa to access 2-Pyrrolidone-fused dihydrobenzoxepine (7aa):

To an oven dried 50 mL RB flask containing the solution of **5aa** (31 mg, 0.1 mmol) in DCM (1 mL), DIBAL-H (1 M solution in cyclohexane, 0.45 mL, 0.45 mmol, 4.5 equiv.) was slowly added at 0 °C and the reaction mixture was stirred for 12 h. After completion of the reaction, the reaction mixture was diluted with ethyl acetate followed by the addition of saturated NH_4Cl aqueous solution. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under the vacuum and purified through column chromatography over silica gel to give the desired product (**7aa**).[24]

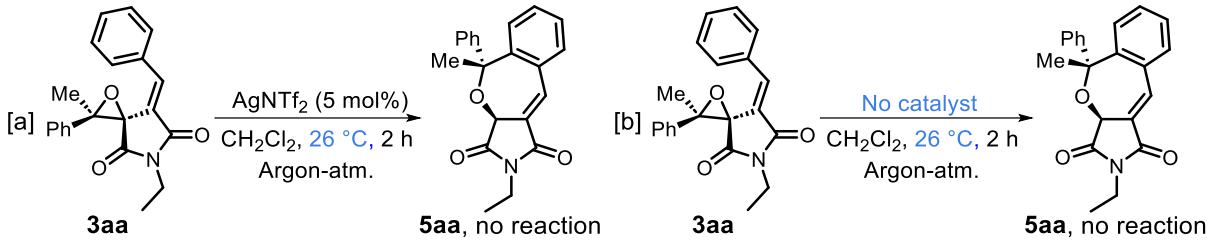


*2-ethyl-5-methyl-5-phenyl-2,3,3a,5-tetrahydro-1H-benzo[5,6]oxepino[2,3-c]pyrrol-1-one (**7aa**)*: The product **7aa** was obtained as white solid, 18 mg (56% yield); R_f =0.4 (petroleum ether/EtOAc 85:15); m.p. 101 – 103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 (d, *J* = 7.4 Hz, 1H), 7.36 – 7.28 (m, 6H), 7.23 (dd, *J* = 6.9, 1.5 Hz, 2H), 7.15 (d, *J* = 2.5 Hz, 1H), 5.04 (d, *J* = 2.8 Hz, 1H), 4.18 (t, *J* = 2.8 Hz, 1H), 3.47 (dq, *J* = 14.5, 7.2 Hz, 1H), 3.15 (dq, *J* = 14.5, 7.2 Hz, 1H), 2.08 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 165.37, 146.11, 145.75, 135.96, 135.48, 132.68, 132.01, 130.95, 128.62, 128.42, 128.17, 128.13, 127.71, 86.11, 85.09, 78.89, 34.43, 32.81, 12.63. HRMS (ESI TOF) *m/z*: calcd for $C_{23}H_{22}NO_5$ $(M + H)^+$ 320.1651; found, 320.1650.

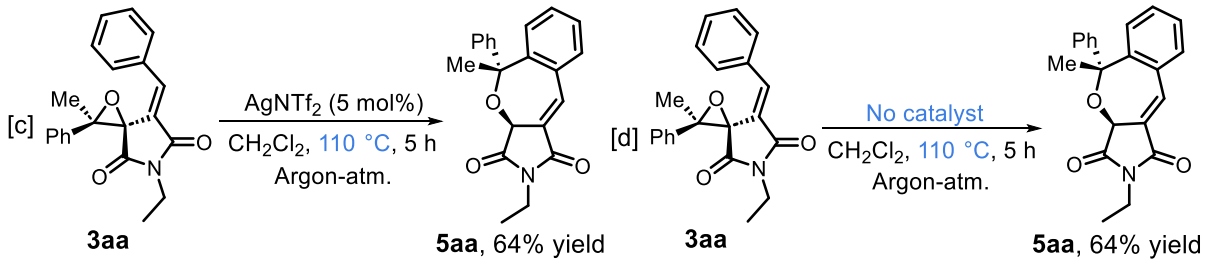
3.4.5. Procedure for Control Experiments and Stereochemical aspects:

Reaction-a and b: To a pressure tube equipped with a magnetic stirrer bar were added pre-prepared oxirane **3aa** (10 mg, 0.03 mmol, 1.0 equiv.) and $AgNTf_2$ (0.58 mg, 0.0015 mmol, 5 mol%; unless otherwise noted). The tube was backfilled with Argon and dry DCM (0.9 mL, 0.033 M) was added via a syringe pump under positive flow of Argon. The tube was then sealed

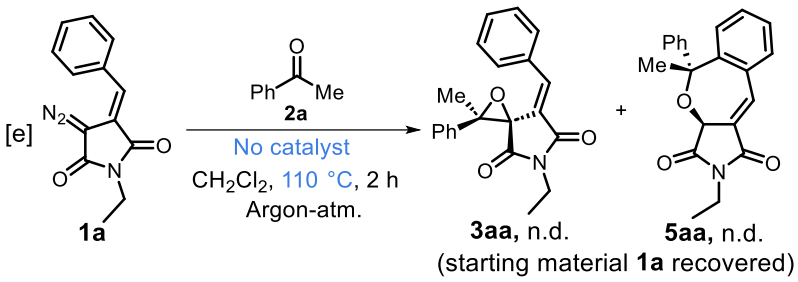
with cap under continuous flow of Argon. After that, the solution mixture was stirred at room temperature (26 °C) about 2 h. The reaction mixture was monitored by ^{1}H NMR spectroscopy periodically and the product **5aa** was not detected.



Reaction-c and d: To a pressure tube equipped with a magnetic stirrer bar were added pre-prepared oxirane **3aa** (10 mg, 0.03 mmol, 1.0 equiv.) and $AgNTf_2$ (0.58 mg, 0.0015 mmol, 5 mol%; unless otherwise noted). The tube was backfilled with Argon and dry DCM (0.9 mL, 0.033 M) was added via a syringe pump under positive flow of Argon. The tube was then sealed with cap under continuous flow of Argon. After that, the solution mixture was stirred at 110 °C about 1 h. The reaction mixture was monitored by taking aliquot for ^{1}H NMR spectroscopy periodically and continued stirring the reaction mixture at 110 °C about 5 h. The isolated yield of product **5aa** was 64%. The obtained product was recrystalized from the solvent mixture DCM: petroleum ether (2:3 ratio). And the single-crystal XRD was taken for the confirmation of molecular geometry (see Figure 3.7). CCDC- 2105272.



Reaction-e: To a schlenk tube equipped with a magnetic stir bar were added acetophenone (24 μL, 0.2 mmol, 1.0 equiv.) in DCM (5 mL). The tube backfilled with Argon, then sealed with rubber septum under continuous flow of Argon was placed in a pre-heated oil bath at 110 °C. The diazo compound **1a** (48.25 mg, 0.2 mmol, 1.0 equiv.) in DCM (1 mL) was added via a syringe pump under constant stirring at 110 °C. After that, the solution mixture was stirred at 110 °C about 1 h. The aliquot of the reaction mixture was submitted for HRMS analysis and then continued stirring the reaction mixture at 110 °C over 24 h. Progress of the reaction was monitored by TLC. The product **5aa** was not detected.



Conclusions: Among the two plausible intermediates, the carbonyl ylide **int-III** is the probable intermediate through the pathway to the product formation of both of the oxirane **3aa** (**int-IV**) and oxepine **5aa**. Further, the stereochemical aspects of the intermediate were confirmed from the geometry (analyzed by the molecular single-crystal XRD data) of the **3aa** and **5aa** (Figure 3.7). The electrocyclic ring-opening and ring-closing equilibria of oxiranes with carbonyl ylides are well-documented by Huisgen (see Scheme 3.9 inset).[20a] Moreover, the **reaction-d, Figure-1** suggested that a metal-unbound (free-ylide) carbonyl ylide intermediate, generating *in situ*, is proposed to be operative here (Figure 3.7).

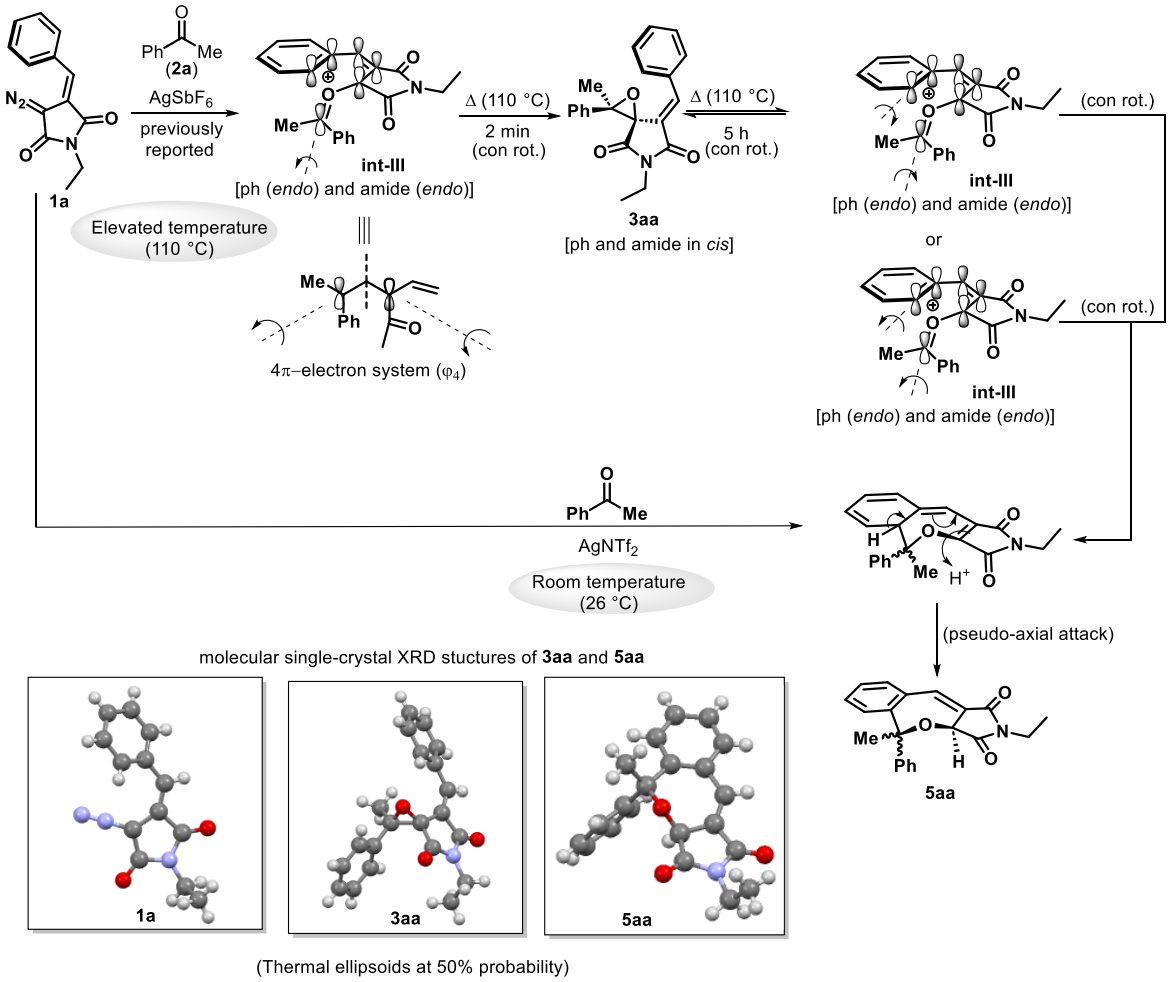
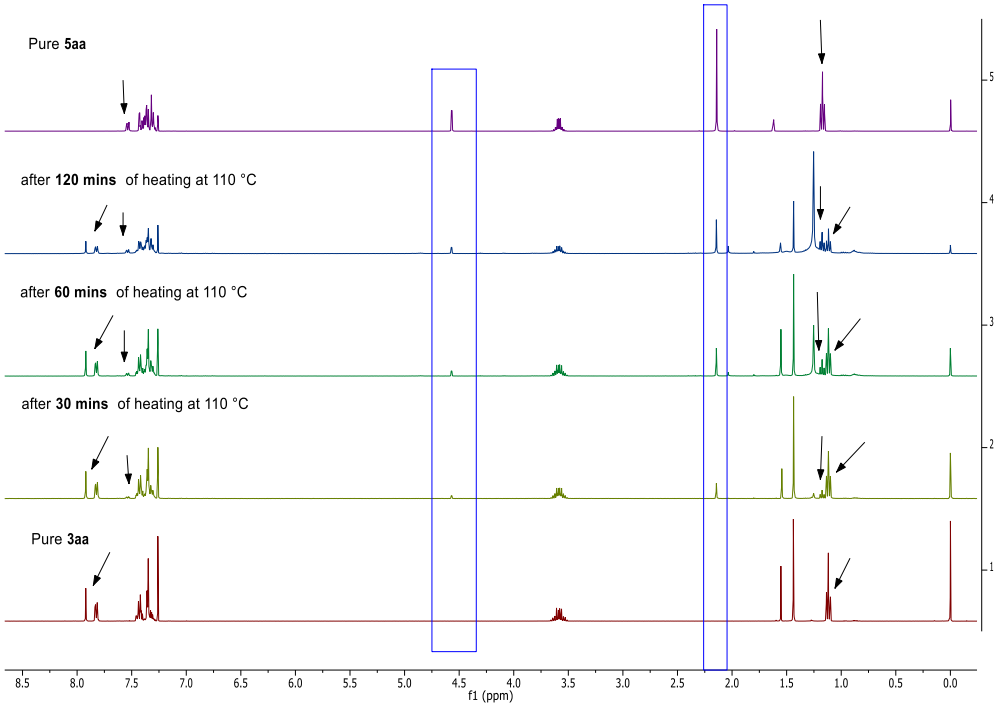


Figure 3.7. Molecular structures of **3aa** and **5aa** (analyzed by Single-Crystal XRD analysis) and proposed stereochemical aspects.

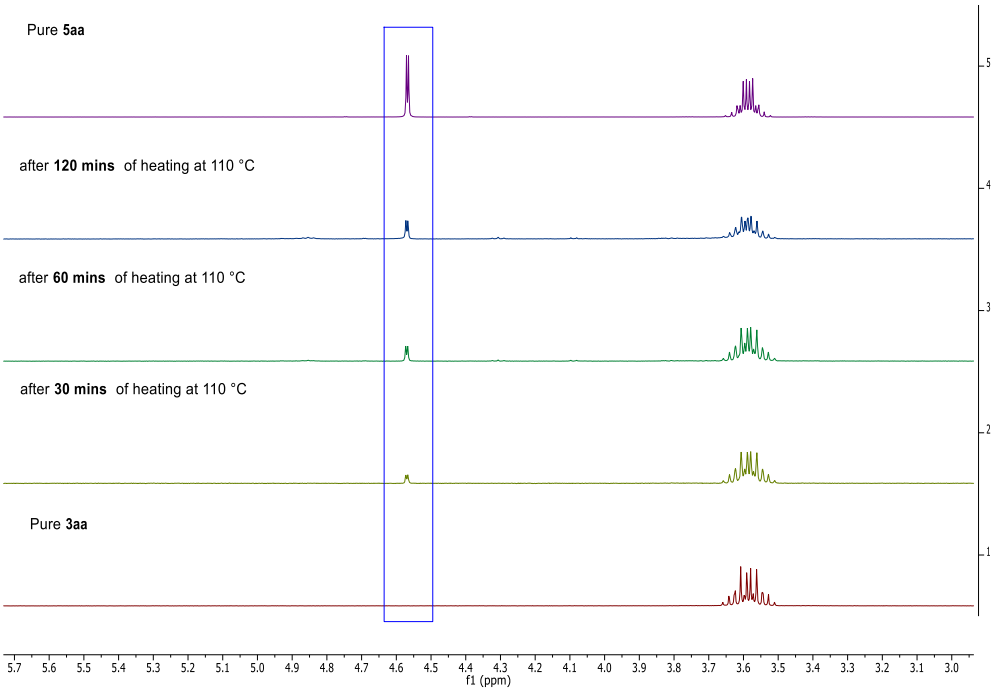
3.4.6. NMR study of epoxide (3aa) to oxepine (5aa) conversion:

To further validate the batch experiment for the detection of the intermediate, we performed time-dependent ^{1}H NMR study in $CDCl_3$ at 110 °C:

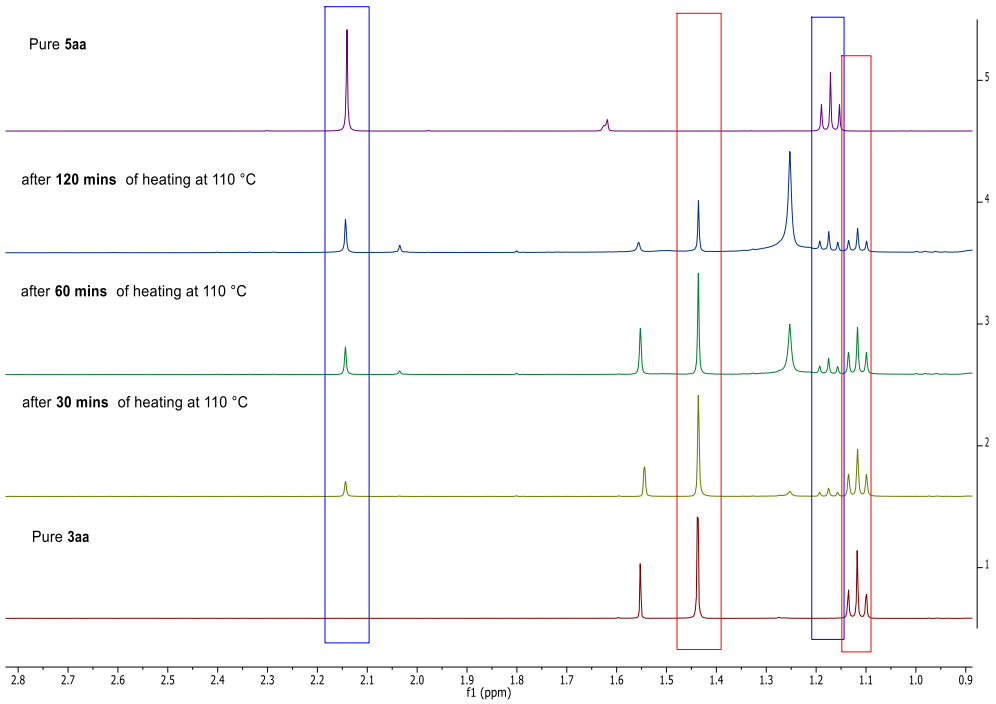
Procedure: In a pressure tube equipped with a magnetic stir bar, recrystallized epoxide **3aa** (30 mg, 0.09 mmol) was added to $CDCl_3$ (3 mL) and a first ^{1}H NMR spectrum was measured as a control. The pressure tube was then heated at 110 °C in an oil-bath by continuous stirring and ^{1}H NMR spectra were recorded after 30 min, 60 min, and 120 min respectively, each time by taking aliquot (at room temperature) from the reaction mixture and measured the spectra at ambient temperature. See the stacked spectra (with zooming at specific region) in the scheme below:



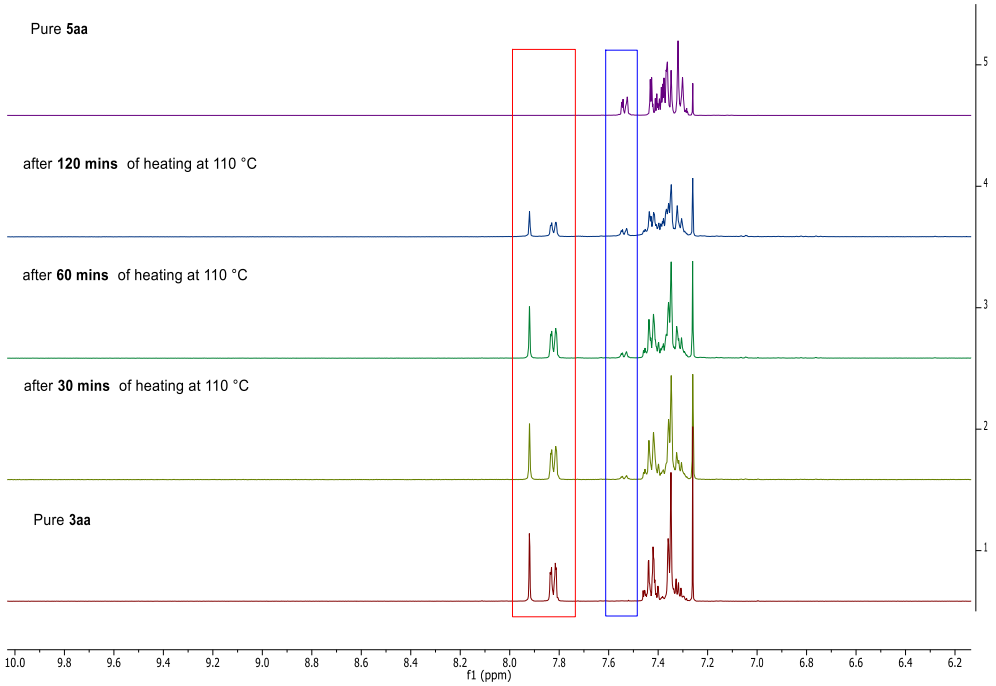
i) **Full stacked spectrum:** the conversion of epoxide to oxepine; blue line: peaks arising; straight arrows are indicating peaks arising and bent arrows indicating peaks getting diminished.



ii) **Zoom-in stacked spectrum:** the conversion of epoxide to oxepine, blue line indicating new peaks arising.



iii) **Zoom-in stacked spectrum:** the conversion of epoxide to oxepine; blue line: peaks arising, red line: peaks diminishing



iv) **Zoom-in stacked spectrum**: the conversion of epoxide to oxepine; blue line indicating new peaks arising, red line indicating peaks getting diminished.

This temperature variant ^{1}H NMR study truly indicated that the carbonyl yield is the logical and most possible intermediate.

3.4.7. Appendix III: ^{1}H, $^{13}C\{^{1}H\}$, and ^{19}F NMR spectral data of representative compounds

Compound No.	Figure III.X	Data	Page No.
5aa	Figure III.1, III2 and III.3	^{1}H, ^{13}C and ^{1}H-^{1}H COSY	113-114
5aj	Figure III.4 and III5	^{1}H and ^{13}C	115
5ak	Figure III.6 and III.7	^{1}H and ^{13}C	116
5am	Figure III.8 and III.9	^{1}H and ^{13}C	117
5ga	Figure III.10, III.11 and III.12	^{1}H, ^{13}C, and ^{19}F	118-119
3aa	Figure III.13 and III.14	^{1}H and ^{13}C	120
7aa	Figure III.15 and III.16	^{1}H and ^{13}C	121

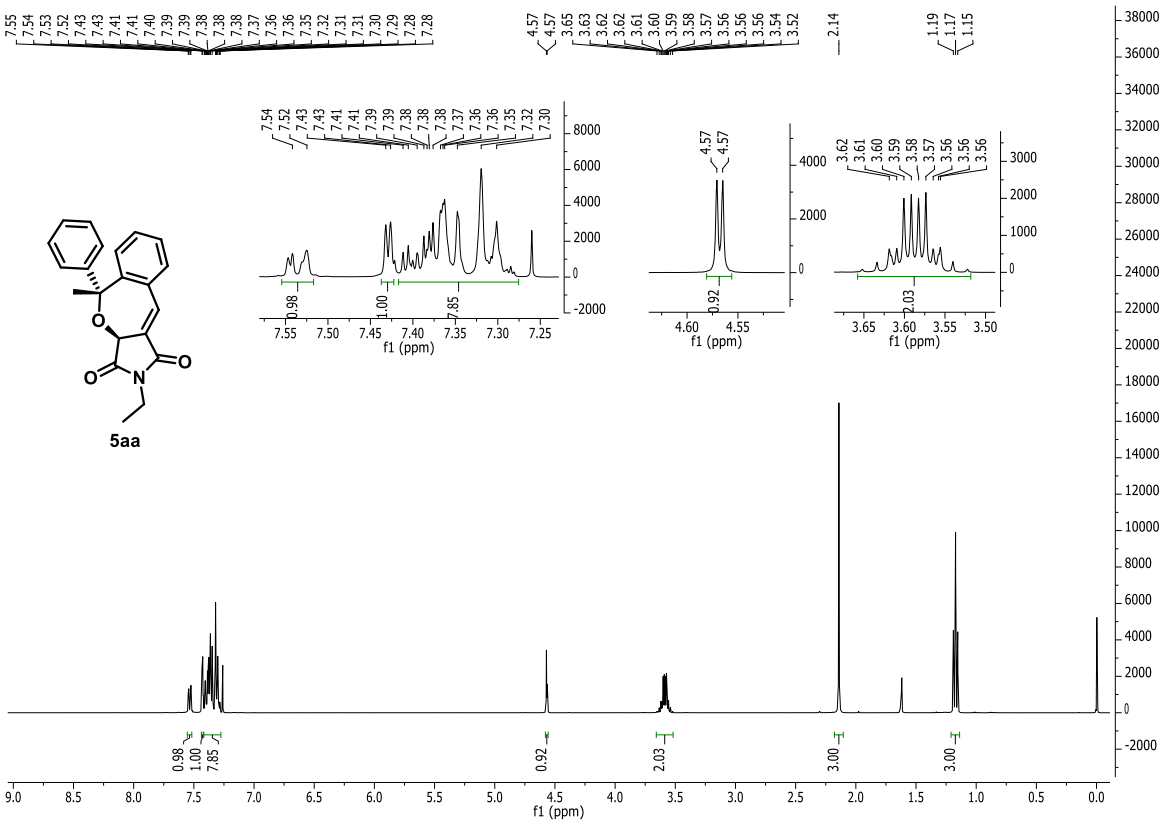


Figure III.1. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5aa**

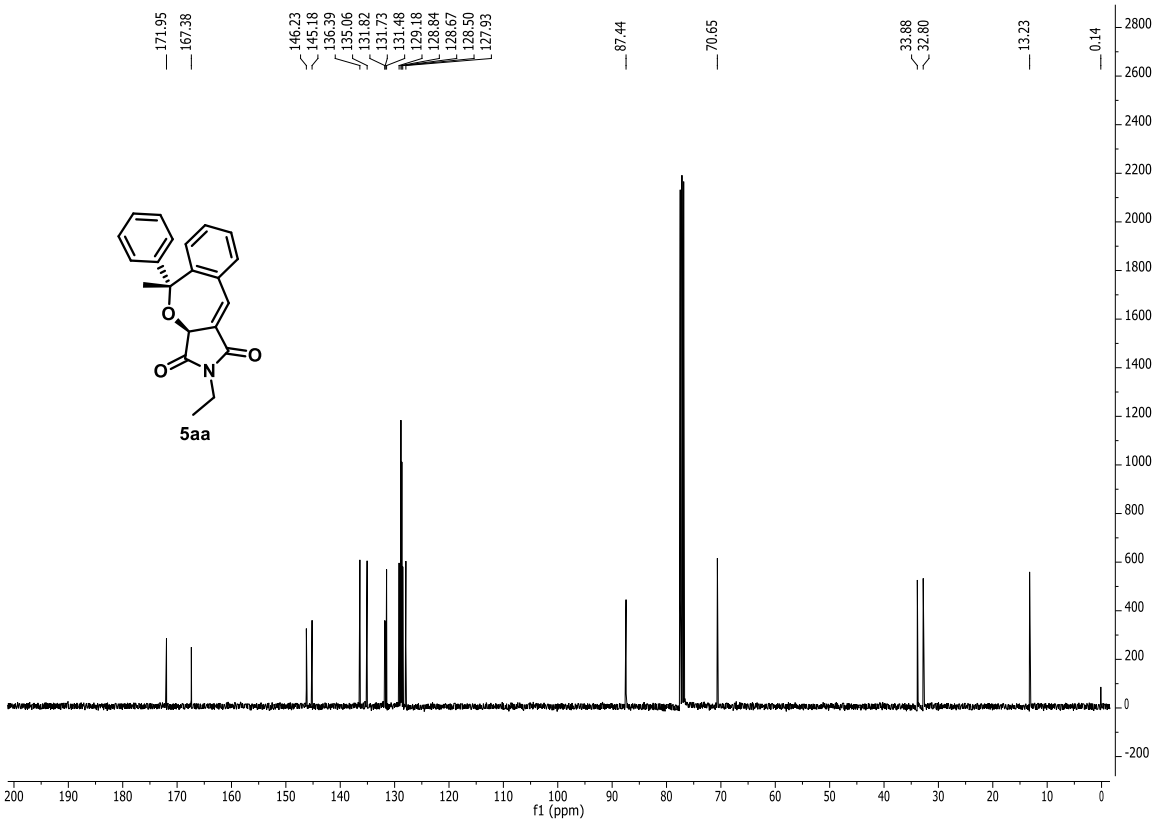


Figure III.1. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **5aa**

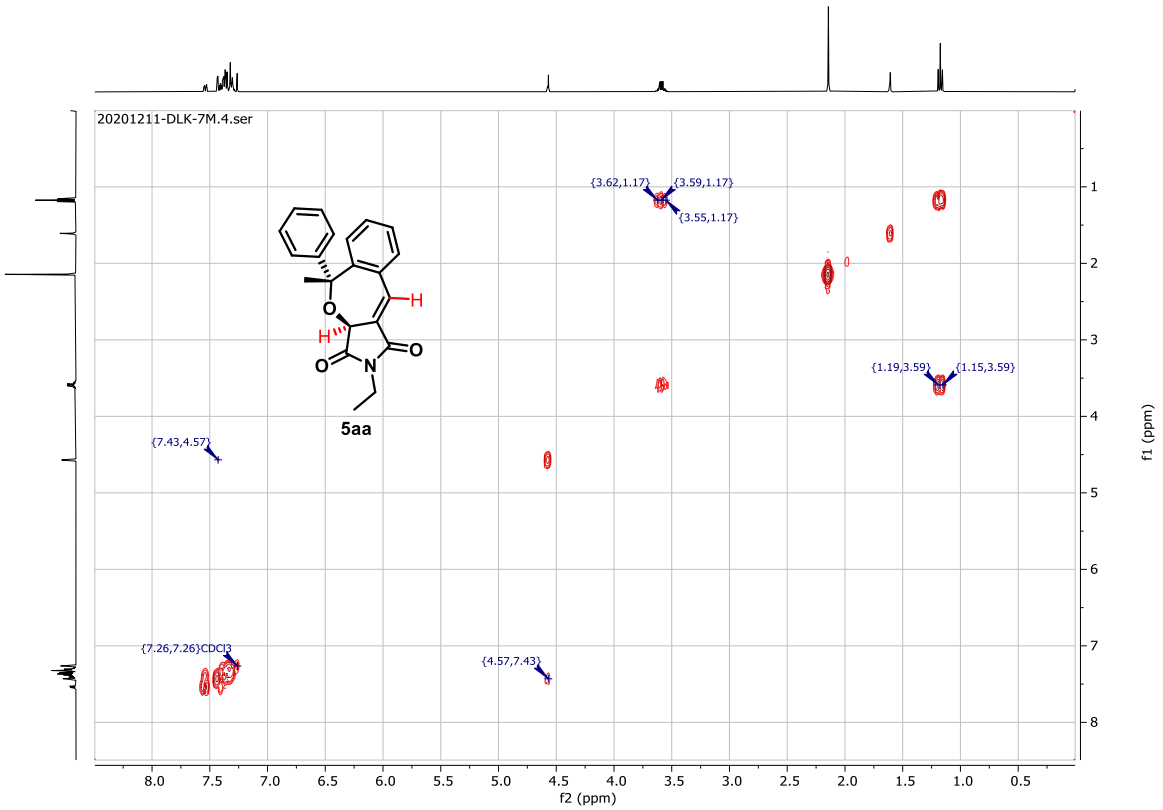


Figure III.3. ^{1}H-^{1}H COSY NMR (400 MHz, $CDCl_3$) spectrum of compound **5aa**

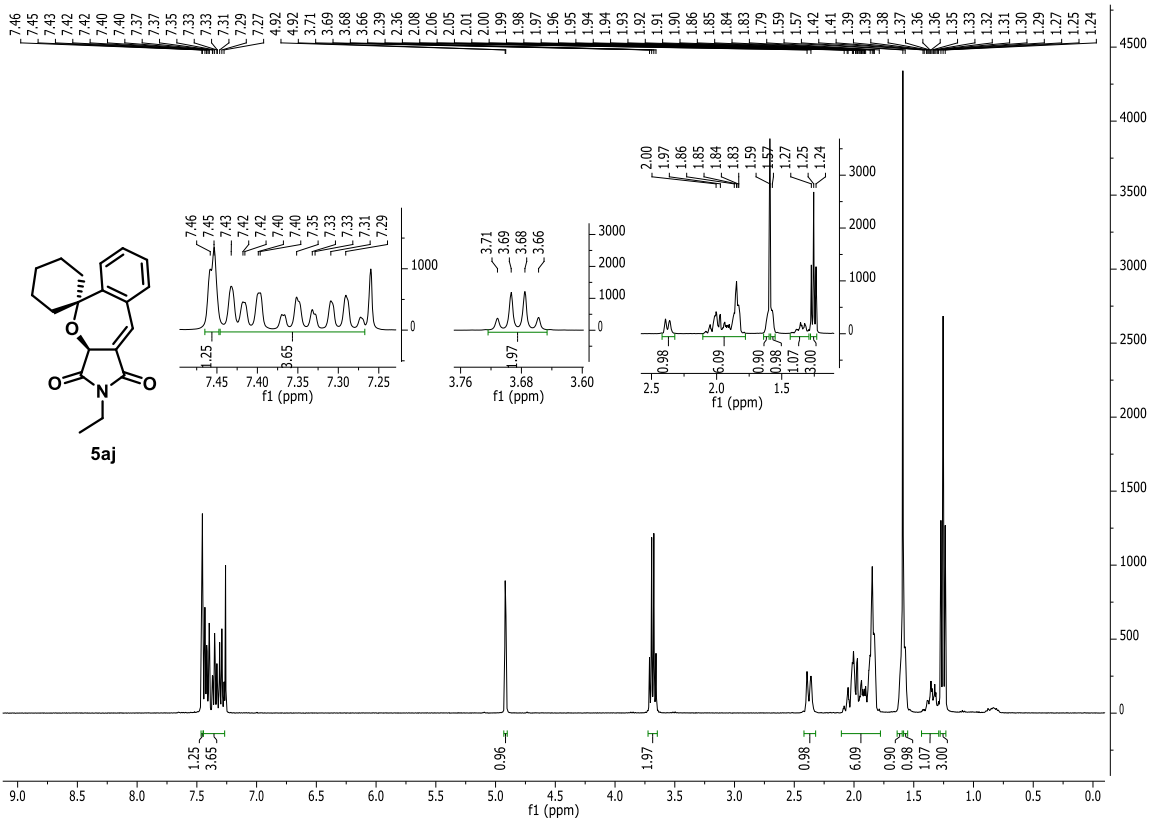


Figure III.4. ^{1}H NMR (100 MHz, $CDCl_3$) spectrum of compound **5aj**

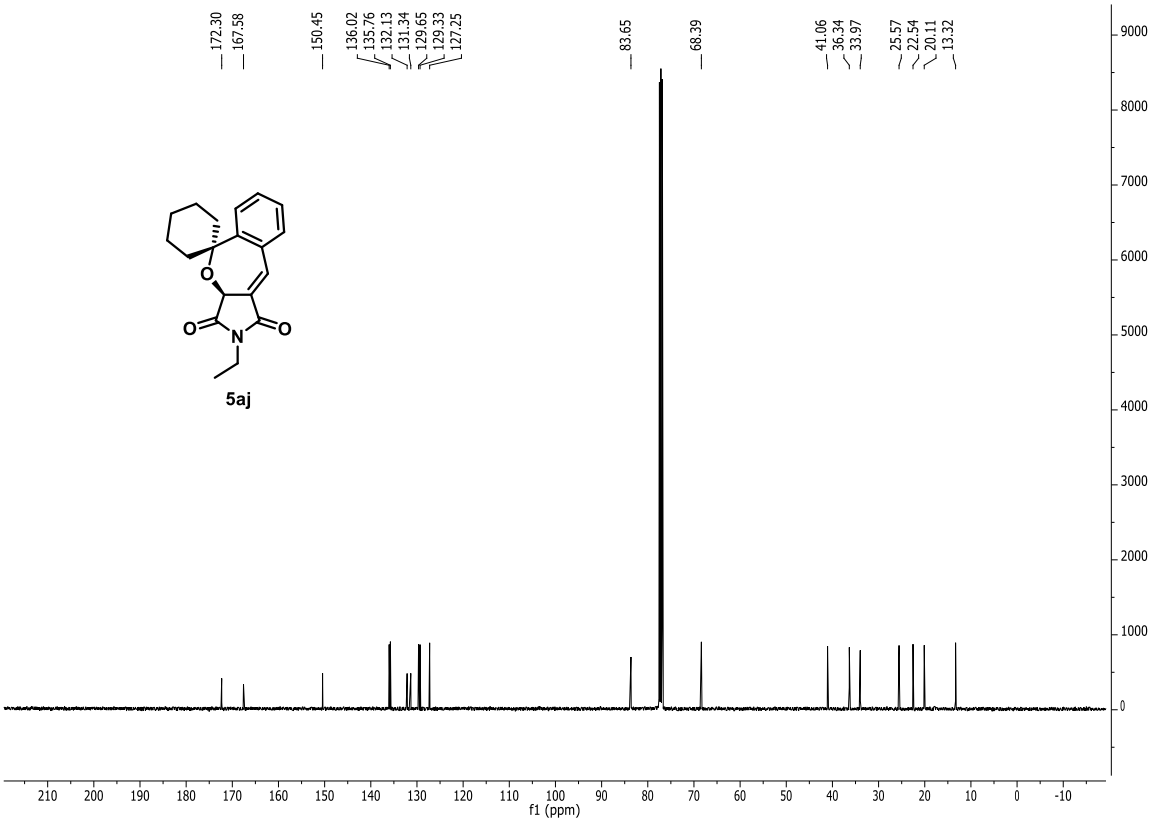


Figure III.5. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **5aj**

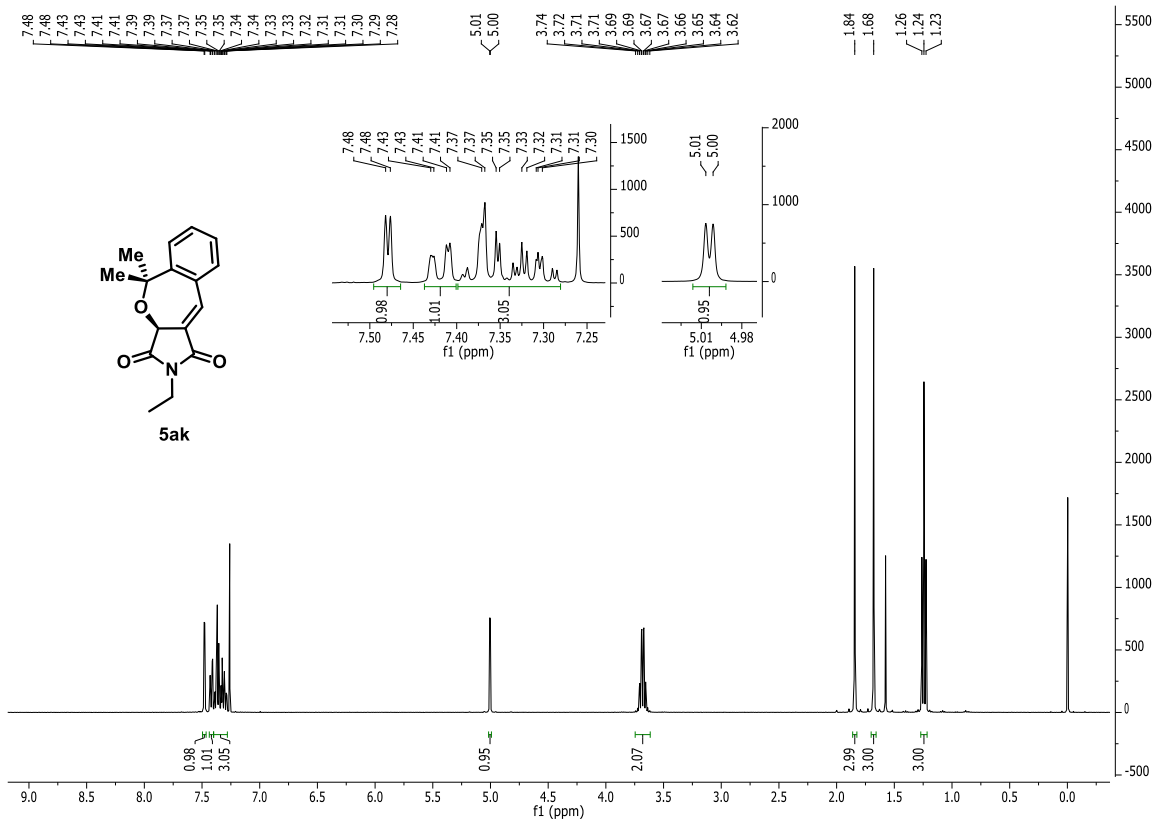


Figure III.6. ^{1}H NMR (100 MHz, $CDCl_3$) spectrum of compound **5ak**

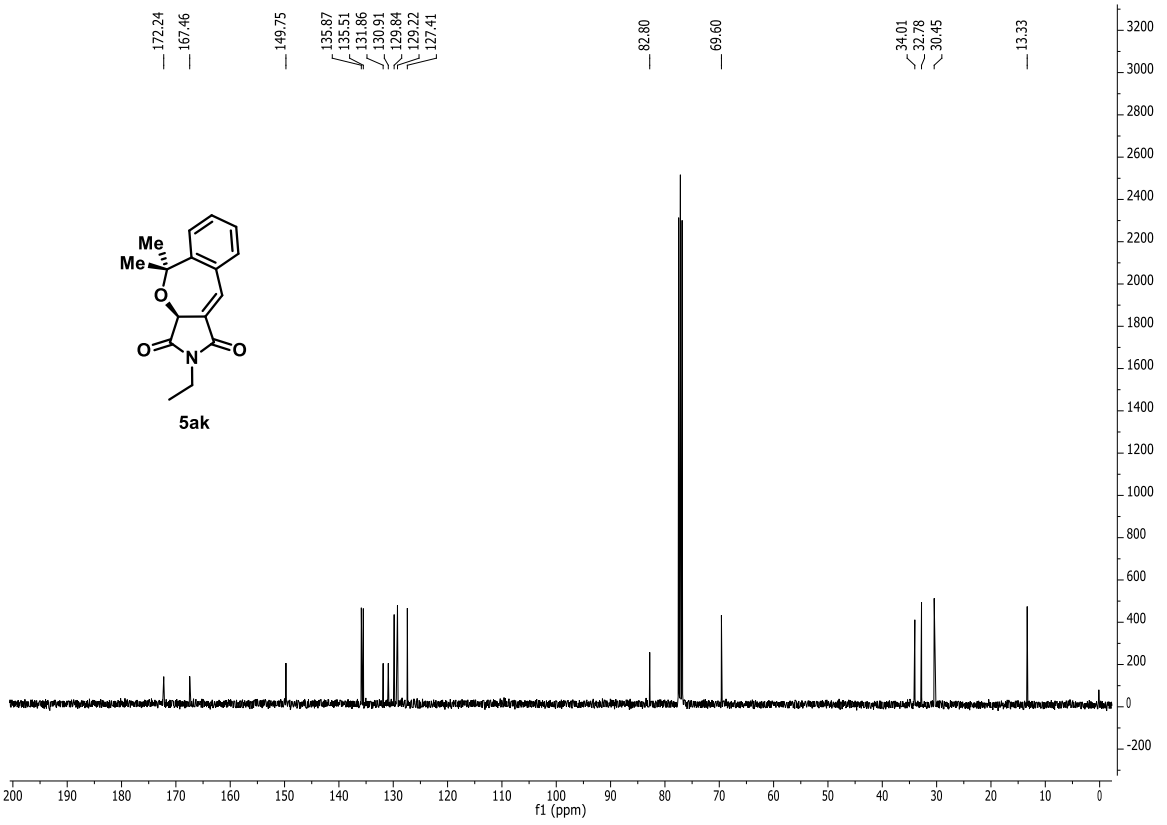


Figure III.7. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **5ak**

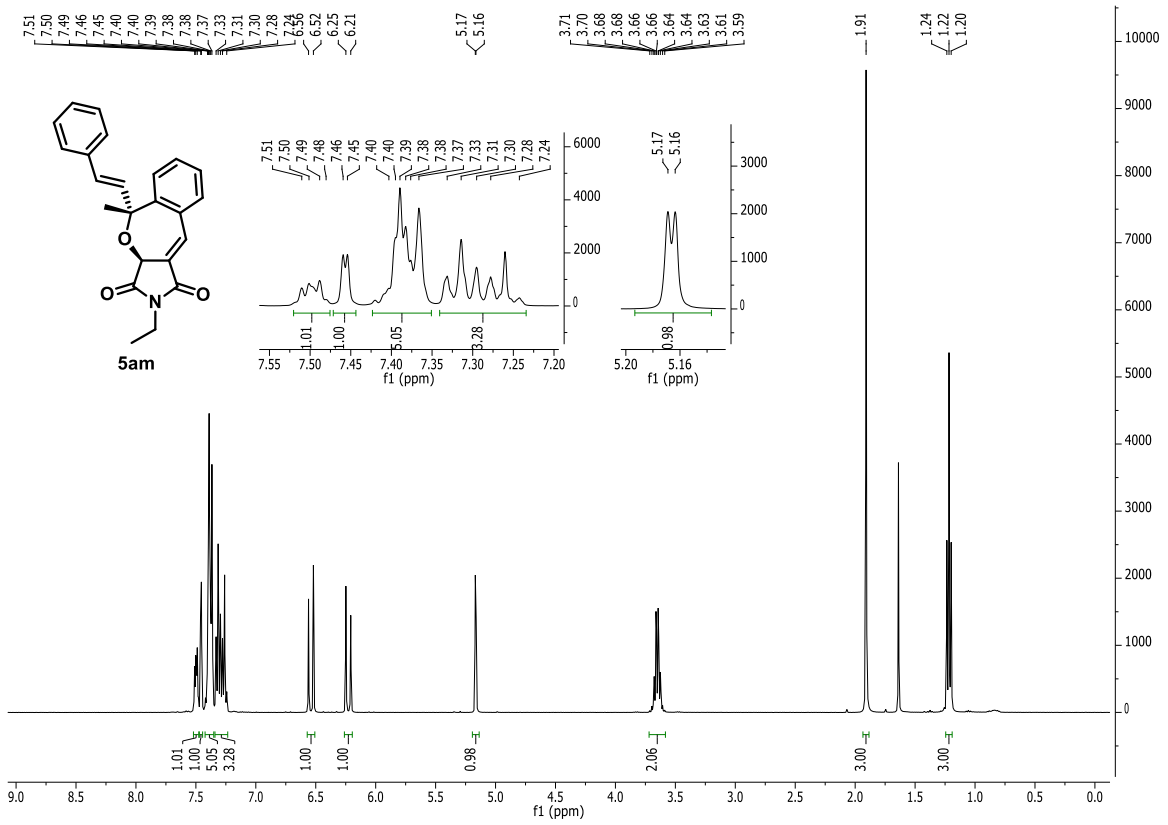


Figure III.8. ^{1}H NMR (100 MHz, $CDCl_3$) spectrum of compound **5am**

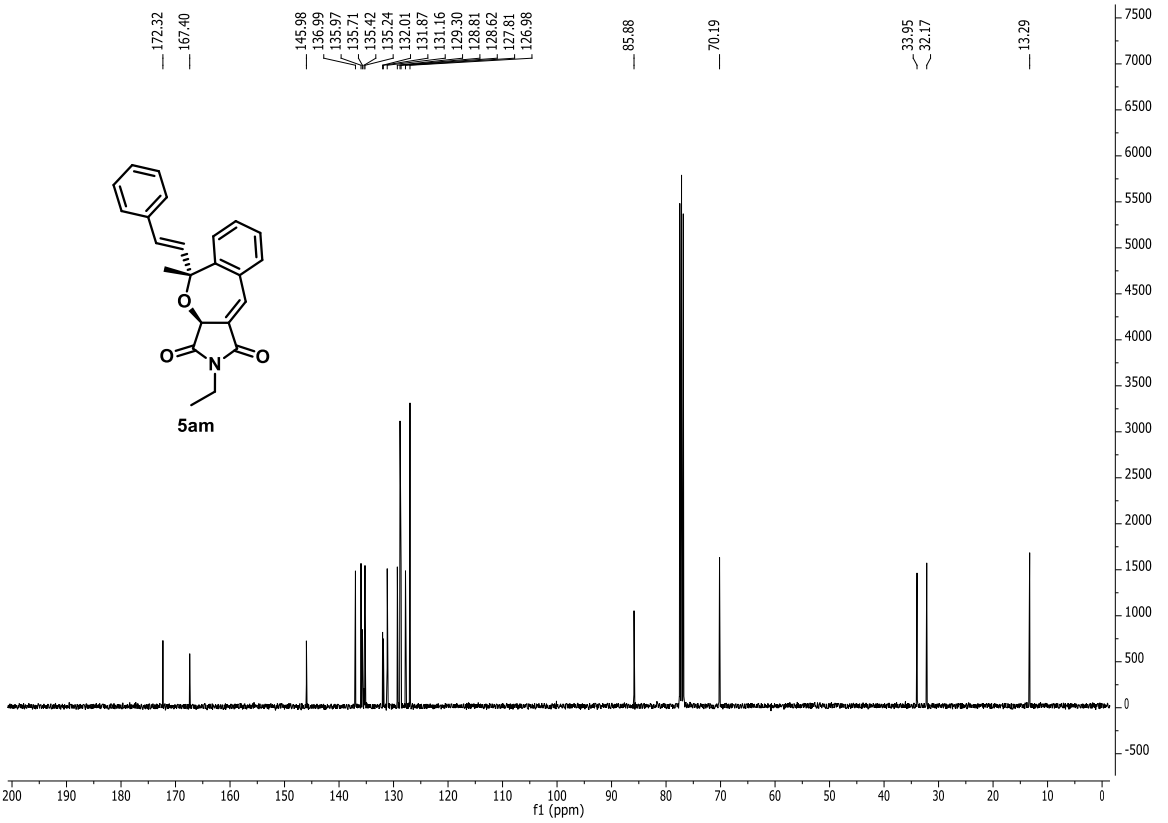


Figure III.9. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **5am**

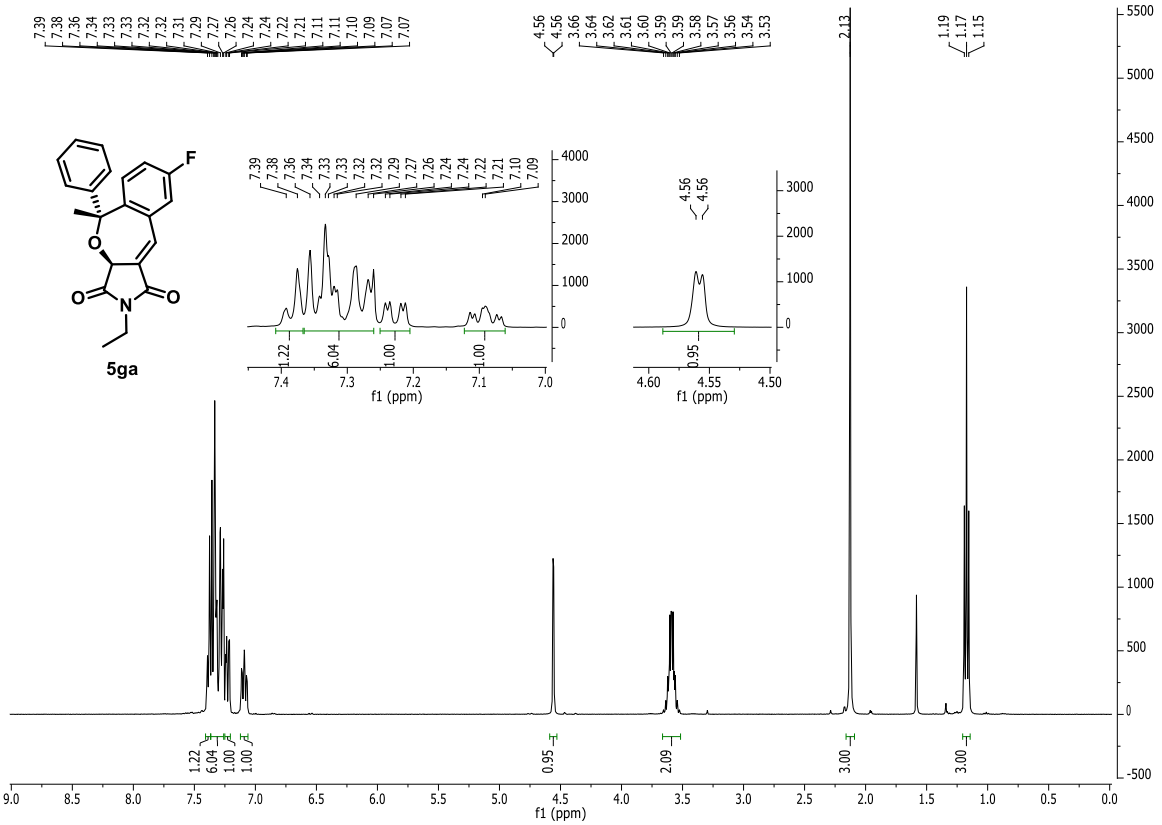


Figure III.10. ^{1}H NMR (100 MHz, $CDCl_3$) spectrum of compound **5ga**

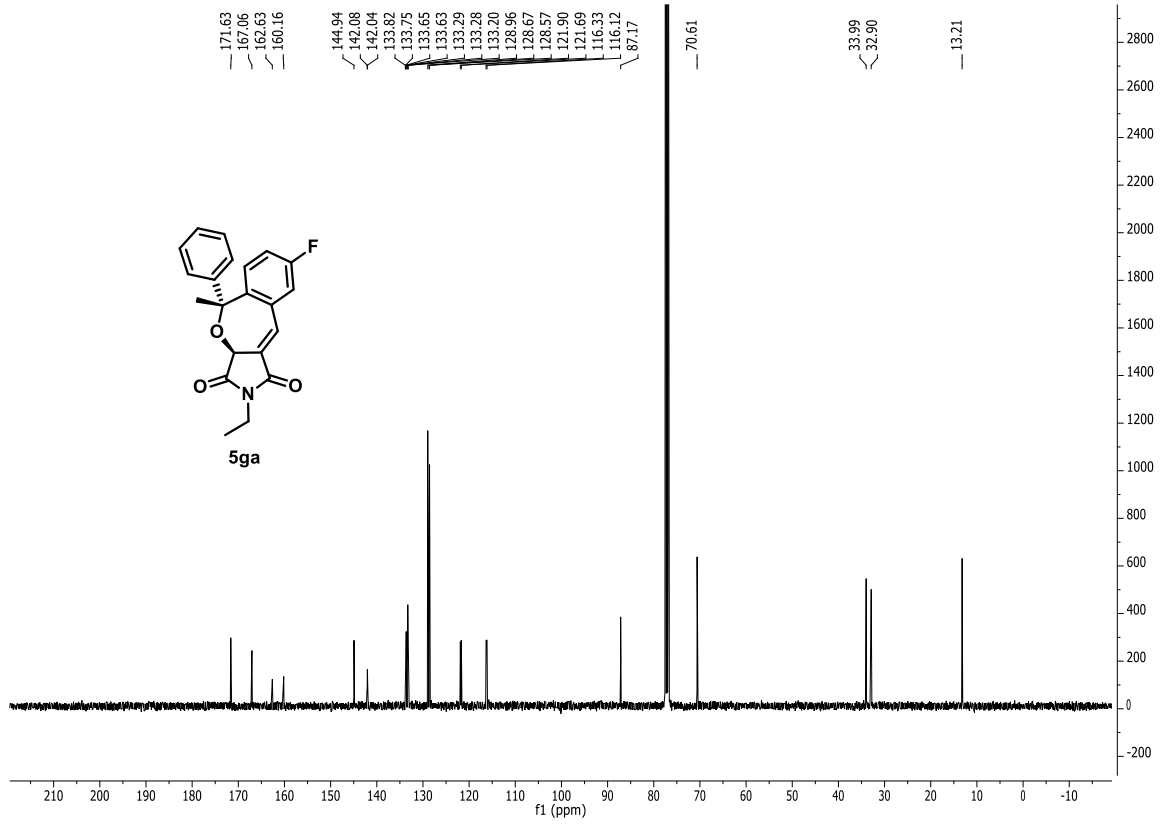


Figure III.11. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **5ga**



Figure III.12. ^{19}F NMR (100 MHz, $CDCl_3$) spectrum of compound **5ga**

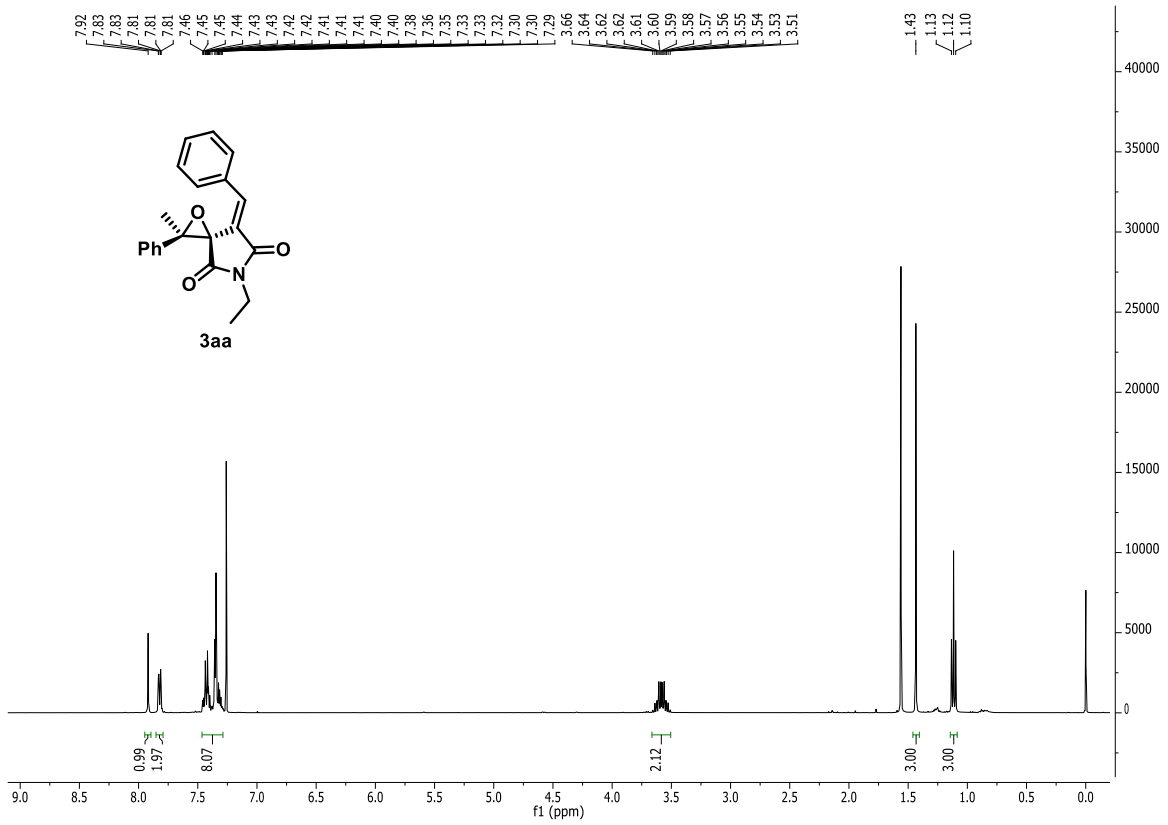


Figure III.13. ^{1}H NMR (100 MHz, $CDCl_3$) spectrum of compound **3aa**

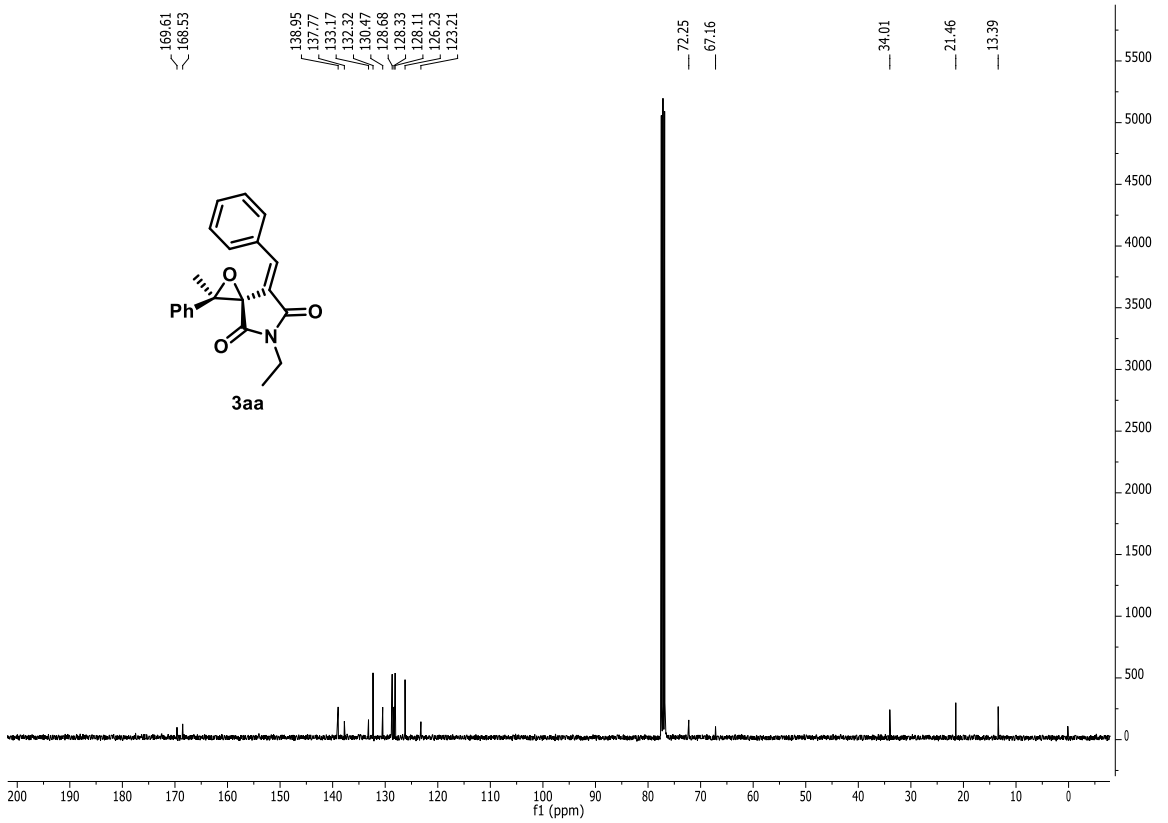


Figure III.14. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3aa**

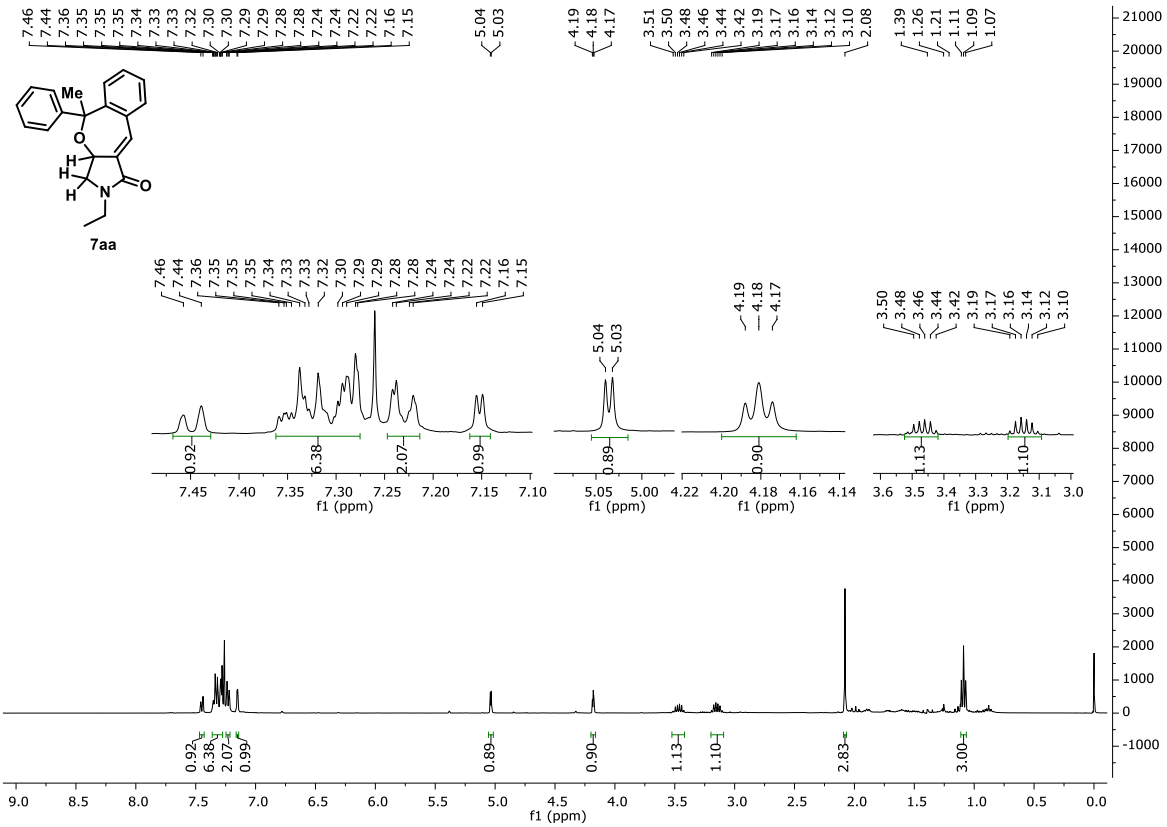


Figure III.15. ^{1}H NMR (100 MHz, $CDCl_3$) spectrum of compound **7aa**

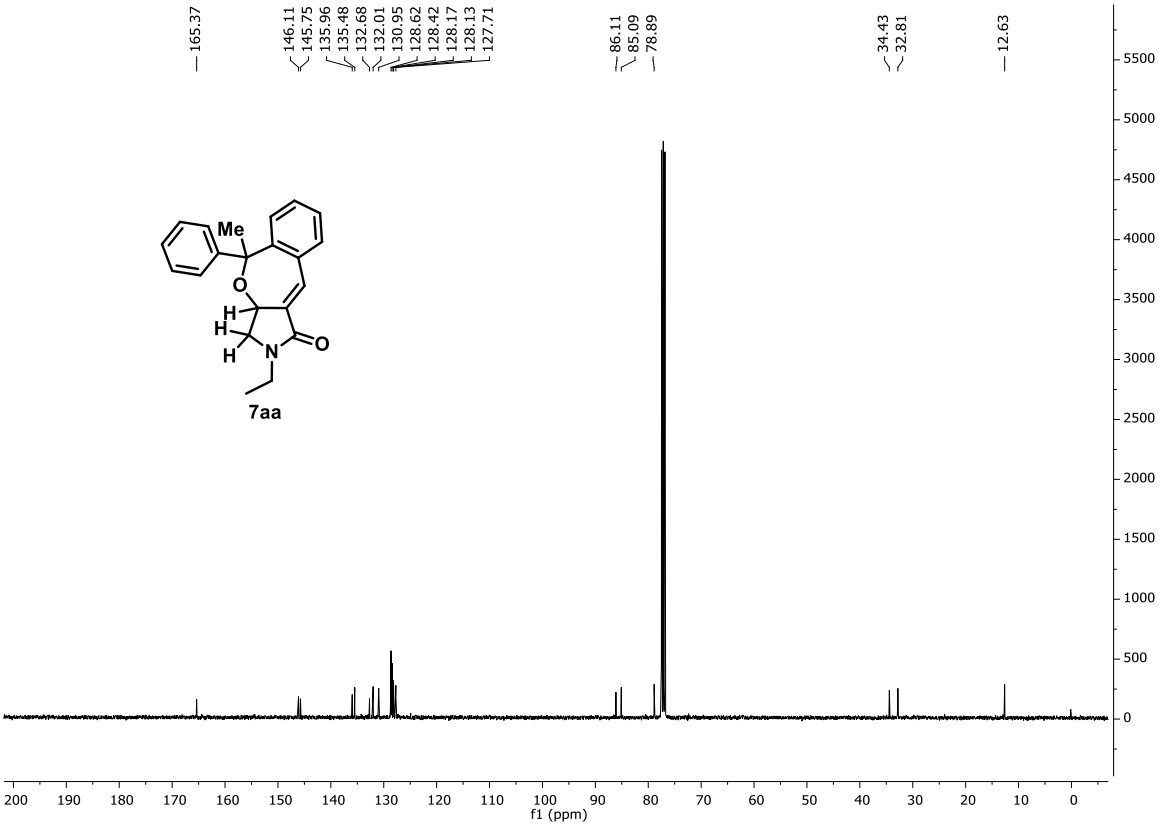


Figure III.13. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **7aa**

3.4.8. Molecular Structures of Compounds (1a, 5ga, 3aa, and 5aa) using Single Crystal X-ray Analysis:

3.4.8A. Molecular Structure of 1a:

Datablock: MONC_a

Bond precision: C-C = 0.0050 A Wavelength=1.54178

Cell: a=8.0151(15) b=19.978(4) c=7.7622(15)
alpha=90 beta=110.135(13)
gamma=90 Temperature: 100 K

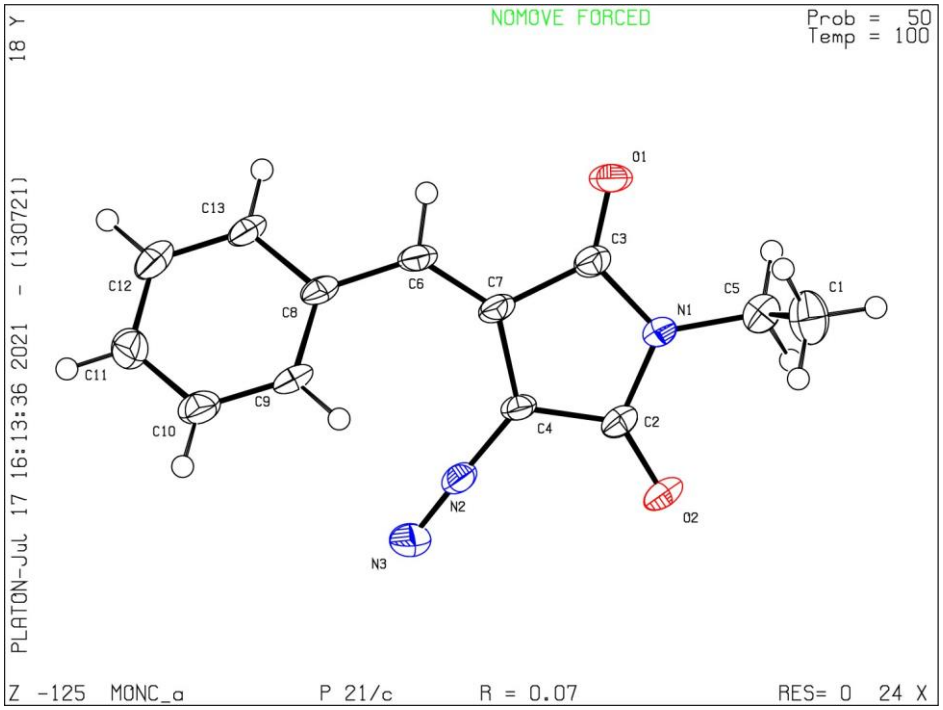
	Calculated	Reported
Volume	1167.0(4)	1167.0(4)
Space group	P 21/c	P 21/c
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C13 H11 N3 O2	C13 H11 N3 O2
Sum formula	C13 H11 N3 O2	C13 H11 N3 O2
Mr	241.25	241.25
Dx,g cm-3	1.373	1.373
Z	4	4
Mu (mm-1)	0.789	0.789
F000	504.0	504.0
F000’	505.60	
h,k,lmax	10,25,9	10,24,9
Nref	2398	2329
Tmin,Tmax	0.654,0.854	0.654,0.854
Tmin’	0.507	

Correction method= # Reported T Limits: Tmin=0.654 Tmax=0.854 AbsCorr = MULTI SCANS

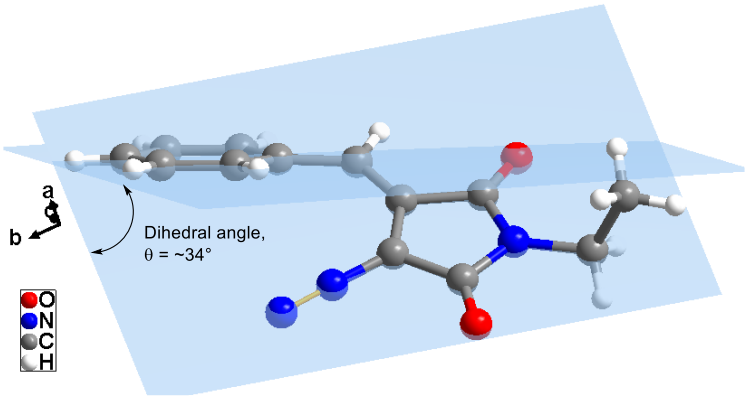
Data completeness= 0.971 Theta(max)= 74.868

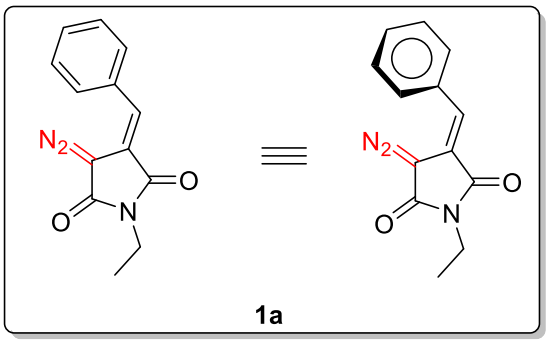
R(reflections)= 0.0696(1415) wR2(reflections)= 0.1580(2329)

S = 1.041 Npar= 165



ORTEP and thermal ellipsoids at 50% probability





1a

3.4.8B. Molecular Structure of 5ga:

Datablock: S1_a

Bond precision: C-C = 0.0042 A Wavelength=0.71073

Cell: a=7.2243(17) b=9.907(3) c=12.468(3)
alpha=76.143(7) beta=73.356(8) gamma=83.506(8)
Temperature: 296 K

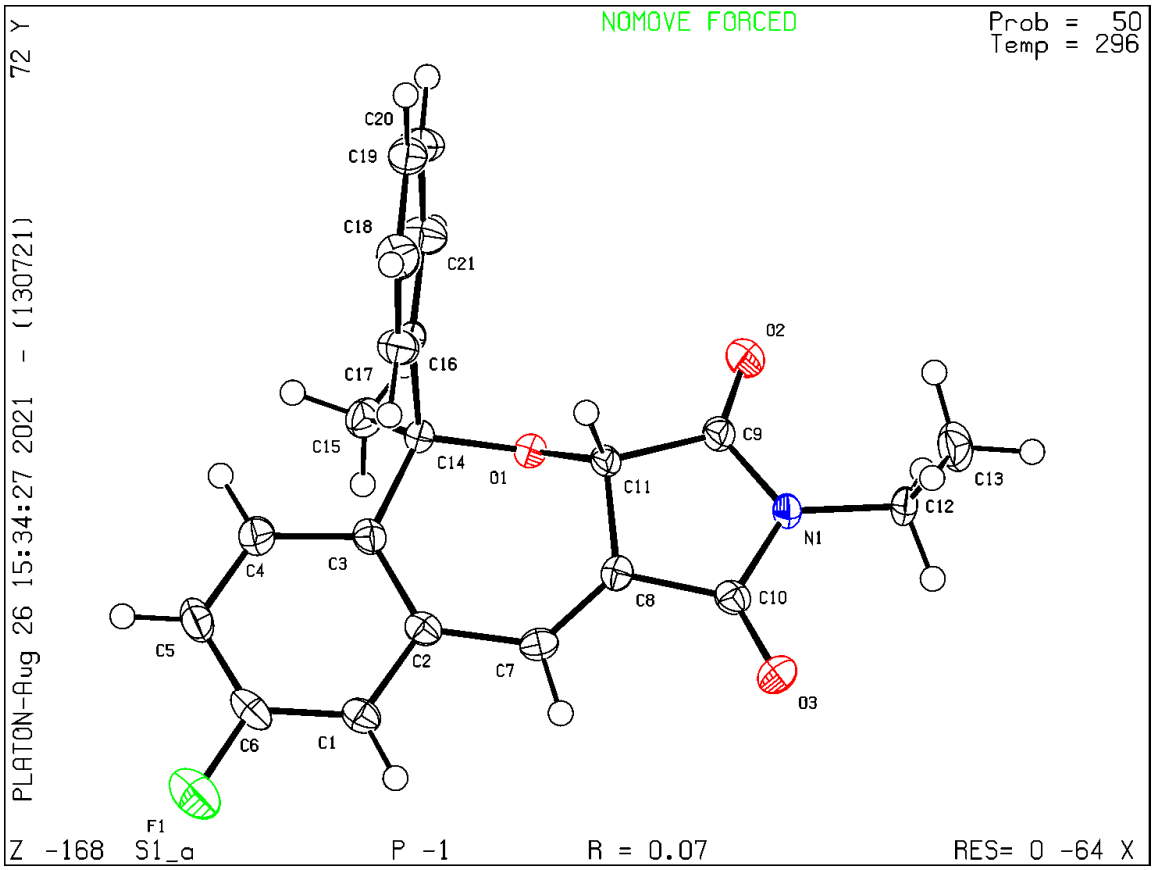
	Calculated	Reported
Volume	829.1(4)	829.2(3)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C21 H18 F N O3	?
Sum formula	C21 H18 F N O3	C21 H18 F N O3
Mr	351.36	351.36
Dx,g cm-3	1.408	1.407
Z	2	2
Mu (mm-1)	0.102	0.102
F000	368.0	368.0
F000'	368.20	
h,k,lmax	9,12,16	9,12,16
Nref	3709	3694
Tmin,Tmax		
Tmin'		

Correction method= Not given

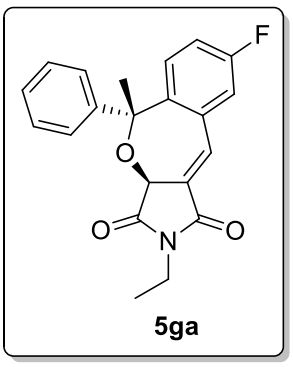
Data completeness= 0.996 Theta(max)= 27.229

R(reflections)= 0.0717(2517) wR2(reflections)= 0.2176(3694)

S = 1.030 Npar= 238



ORTEP and thermal ellipsoids at 50% probability



3.4.8C. Molecular Structure of 3aa:

Datablock: monp_a

Bond precision: C-C = 0.0019 A Wavelength=1.54178

Cell:	a=12.677(2)	b=5.5319(9)	c=24.758(4)
	alpha=90	beta=95.499(7)	gamma=90
Temperature:	100 K		

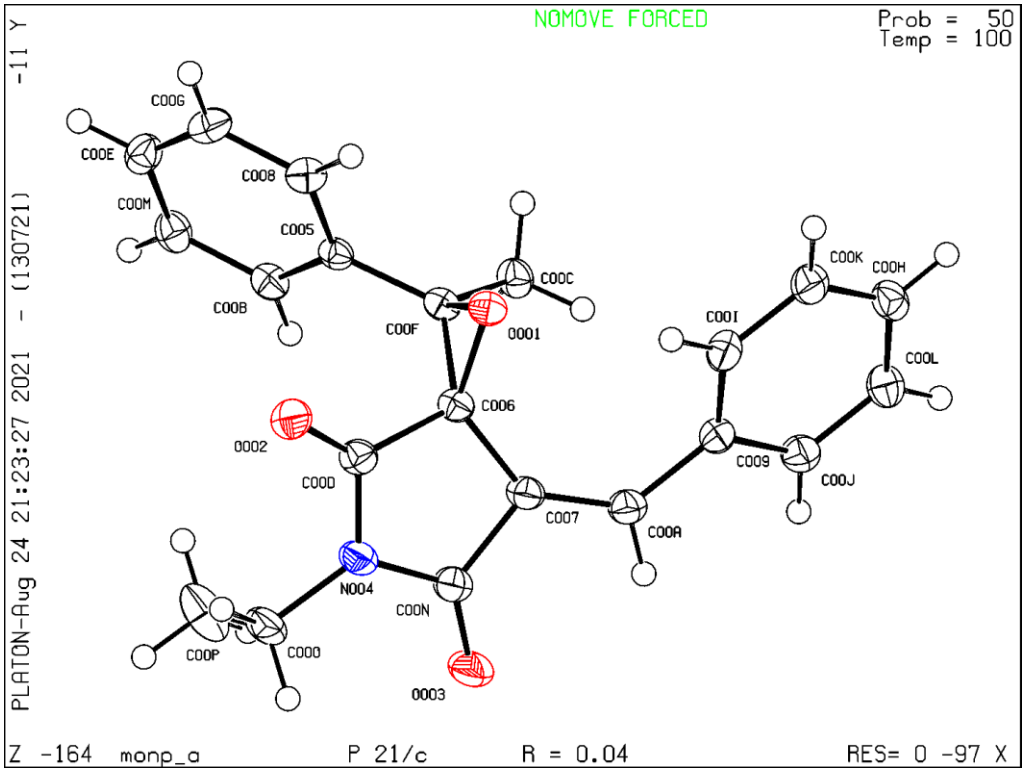
	Calculated	Reported
Volume Space	1728.2(5)	1728.3(5)
group Hall	P 21/c	P 21/c
group	-P 2ybc C21	-P 2ybc
Moiety formula	H19 N O3	?
Sum formula	C21 H19 N O3	C21 H19 N O3
Mr	333.37	333.37
Dx,g cm-3	1.281	1.281
Z	4	4
Mu (mm-1)	0.691	0.691
F000	704.0	704.0
F000'	706.14	
h,k,lmax	15,6,30	15,6,30
Nref	3522	3481
Tmin,Tmax	0.914,0.946	0.626,0.754
Tmin'	0.914	

Correction method= # Reported T Limits: Tmin=0.626 Tmax=0.754 AbsCorr = MULTI SCANS

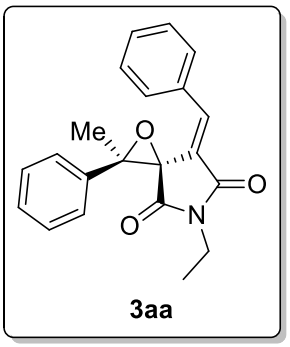
Data completeness= 0.988 Theta(max)= 74.562

R(reflections)= 0.0392(3021) wR2(reflections)= 0.1258(3481)

S = 0.822 Npar= 229



ORTEP and thermal ellipsoids at 50% probability



3aa

3.4.8D. Molecular Structure of 5aa:

Datablock: dlk_a

Bond precision: C-C = 0.0037 A Wavelength=1.54178

Cell: a=18.3257(8) b=7.2282(3) c=12.9858(5)
alpha=90 beta=103.255(2)
gamma=90 Temperature: 100 K

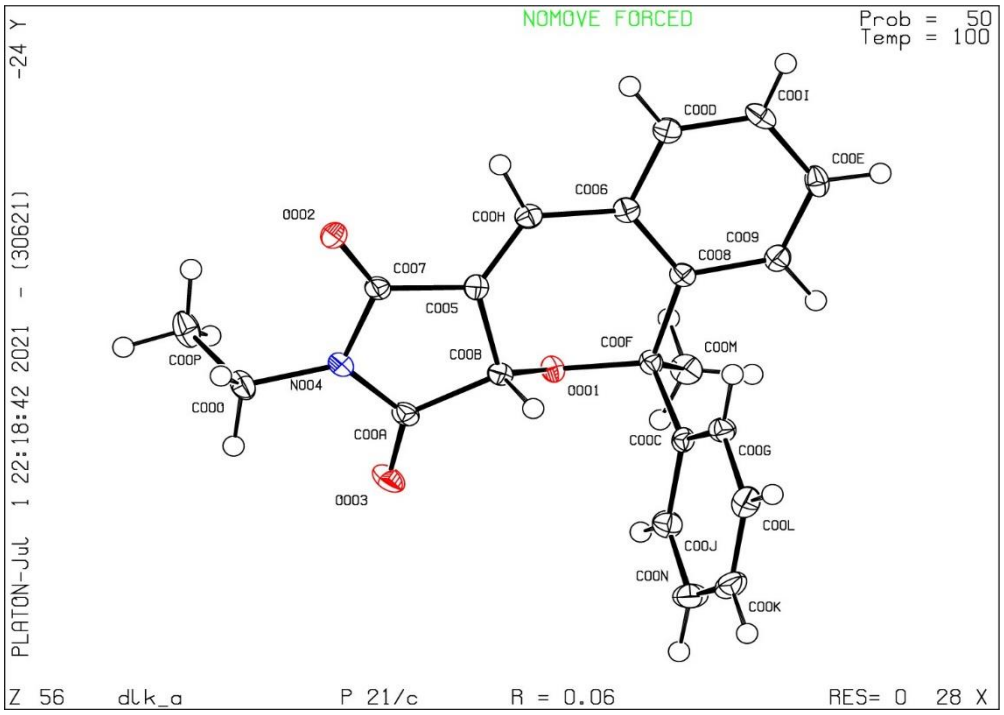
	Calculated	Reported
Volume	1674.30(12)	
	1674.30(12)	
Space group	P 21/c	P 21/c
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C21 H19 N O3	C21 H19 N O3
Sum formula	C21 H19 N O3	C21 H19 N O3
Mr	333.37	333.37
Dx,g cm-3	1.322	1.323
Z	4	4
Mu (mm-1)	0.713	0.713
F000	704.0	704.0
F000'	706.14	
h,k,lmax	22,9,16	22,8,16
Nref	3460	3384
Tmin,Tmax	0.628,0.807	0.628,0.807
Tmin'	0.501	

Correction method= # Reported T Limits: Tmin=0.628
Tmax=0.807 AbsCorr = MULTI-SCAN

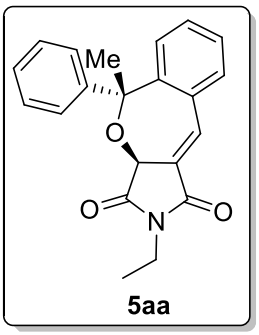
Data completeness= 0.978 Theta(max)= 75.330

R(reflections)= 0.0589(3015) wR2(reflections)= 0.1458(3384)

S = 1.224 Npar= 229



ORTEP and thermal ellipsoids at 50% probability



5aa

3.5. References:

1. a) A. G. Myers, M. J. Mithceltree, K. J. Silvestre, From PCT Int. Appl. (**2009**), WO 2019032936 A1 20190214; b) I. K. Lee, Y. W. Jang, Y. S. Kim, S. H. Yu, K. J. Lee, S. M. Park, B. T. Oh, J. C. Chae, B. S. Yun, *J. Antibiot.* **2009**, *62*, 163–165; c) F. Bohlmann, G. Fritz, *Tetrahedron* **1982**, *38*, 1431; d) A. Ghosh, A. Bandyopadhyay, P. Ghosh, *Padma Chatterjee Journal of Scientific and Innovative Research* **2013**, *2*, 795–801; e) J. R. Kesting, D. Staerk, M. V. Tejesvi, K. R. Kini, H. S. Prakash, J. W. Jaroszewski, *Planta Med.* **2009**, *75*, 1104–1106; f) I. -K. Lee, Y. -W. Jang, Y. -S. Kim, S. H. Yu, K. J. Lee, S. -M. Park, B.-T. Oh, J. -C. Chae, B. -S. Yun, *J. Antibiot.* **2009**, *62*, 163–165.
2. a) S. J. Gharpure, S. R. B. Reddy, *Eur. J. Org. Chem.* **2013**, 2981–2984; b) D. Basavaiah, D. S. Sharada, A. Veerendhar, *Tetrahedron Lett.* **2004**, *45*, 3081–3083; c) B. Das, A. Majhi, J. Banerjee, N. Chowdhury, H. Holla, K. Harakishore, U. S. Murty, *Chem. Pharm. Bull.* **2006**, *54*, 403–405; d) A. A. More, C. V. Ramana, *Chem. Asian. J.* **2014**, *9*, 1557–1562; e) A. G. K. Reddy, J. Krishna, G. Satyanarayana, *Tetrahedron* **2013**, *69*, 10098–10107; f) A. V. Fernndez, C. G. Yebra, J. A. Varela, M. A. Esteruelas, S. Carlos, *Angew. Chem.* **2010**, *122*, 4374–4377; g) H. Bçhme, V. Hitzel, *Liebigs Ann.* **1970**, *734*, 187; h) S. R. Chemler, S. J. Danishefsky, *Org. Lett.* **2000**, *2*, 2695; i) G. Islas- González, J. Benet-Buchholz, M. A. Maestro, A. Riera, M. A. Pericàs, *J. Org. Chem.* **2006**, *71*, 1537; j) J. Francuz, B. Srećo, M. Popsavin, G. Benedeković, V. Divjaković, V. Kojić, G. Bogdanović, A. Kapor, V. Popsavin, *Tetrahedron Lett.* **2012**, *53*, 1819.
3. a) H. Chen, Y. He, L. Zhou, *Org. Chem. Front.* **2018**, *5*, 3240–3244; b) T. Shi, X. Guo, S. Teng, W. Hu, *Chem. Commun.* **2015**, *51*, 15204–15207; c) M.-Y. Chang, Y.-T. Hsiao, K.-H. Lai, *J. Org. Chem.* **2018**, *83*, 14110–14119.
4. a) S. Son, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 1046; b) C. R. Liu, B.-H. Zhu, J.-C. Zheng, X.-L. Sun, Z.-W. Xie, Y. Tang, *Chem. Commun.* **2011**, *47*, 1342.
5. For reviews, see: a) M. P. Doyle in Comprehensive Organometallic Chemistry II, Vol. 12 (Ed.: L. S. Hegedus), Pergamon, New York, **1995**, chap. 5.2; b) A. Padwa, M. D. Weigarten, *Chem. Rev.* **1996**, *96*, 223; c) G. Mehta, S. Muthusamy, *Tetrahedron* **2002**, *58*, 9477; d) M. C. McMills, D. Wright in Synthetic Application of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products (Eds.: A. Padwa, W. H. Pearson), Wiley, New York, **2002**, chap. 4.
6. a) H. Suga, A. Kakehi, S. Ito, K. Inoue, H. Ishida, T. Ibata, *Org. Lett.* **2000**, *2*, 3145; b) H. Suga, A. Kakehi, S. Ito, K. Inoue, H. Ishida, T. Ibata, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1115.

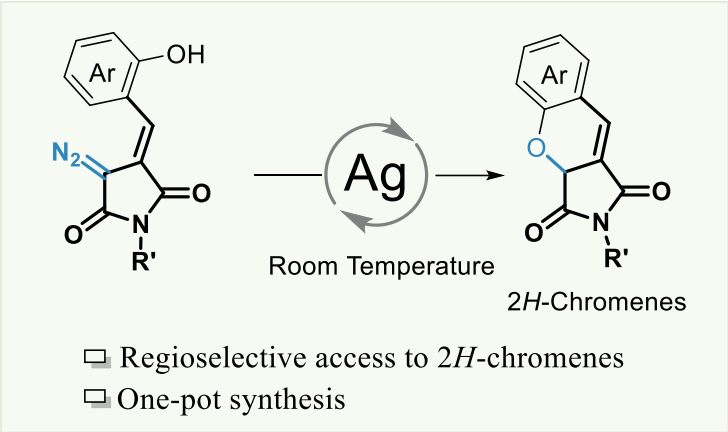
7. For selected examples, see: a) S. Torssell, M. Kienle, P. Somfai, *Angew. Chem.* **2005**, *117*, 3156; *Angew. Chem. Int. Ed.* **2005**, *44*, 3096; b) V. Nair, S. Mathai, S. C. Mathew, N. P. Rath, *Tetrahedron* **2005**, *61*, 2849; c) V. V. Diev, R. R. Kostikov, R. Gleiter, A. P. Molchanov, *J. Org. Chem.* **2006**, *71*, 4066; d) A. DeAngelis, M. T. Taylor, J. M. Fox, *J. Am. Chem. Soc.* **2009**, *131*, 1101–1105; e) O. Anaç, Ö. Sezer, Ö. Candan, F. Ş. Güngör, M. ŞerifCansever, Tetrahedron Lett. 2008, 49, 1062–1065.
8. a) M. Hamaguchi, H. Matsubara, T. Nagai, *J. Org. Chem.* **2001**, *66*, 5395–5404.
9. J.-L. Zhou, Y. Liang, C. Deng, H. Zhou, Z. Wang, X.-L. Sun, J.-C. Zheng, Z.-X. Yu, Y. Tang, *Angew. Chem.* **2011**, *123*, 8020–8024.
10. A. Suneja, H. J. Loui, C. Schneider, *Angew. Chem. Int. Ed.* **2020**, *59*, 5536–5540.
11. Y. Lian, H. M. L. Davies, *Org. Lett.* **2010**, *12*, 924–927.
12. A. Parenty, X. Moreau, J.-M. Campagne, *Chem. Rev.* **2006**, *106*, 911–939.
13. X.-Y. Zhang, Y. You, Z.-H. Wang, J.-Q. Zhao, W.-C. Yuan, *Chem. Commun.* **2020**, *56*, 13449.
14. Z. Gan, M. Zhi, R. Han, E.-Q. Li, Z. Duan, F. Mathey, *Org. Lett.* **2019**, *21*, 2782.
15. B.-L. Zhao, D.-M. Du, *Chem. Commun.* **2016**, *52*, 6162.
16. a) D. Laha, R. G. Bhat, *Asian J. Org. Chem.* **2020**, *9*, 918–921; b) E. Chupakhin, M. Gecht, A. Ivanov, G. Kantin, D. Dar'in, M. Krasavin, *Synthesis* **2021**, *53*, 1292–1300; c) E. G. Chupakhin, G. P. Kantin, D. V. Dar'in, M. Krasavin, *Mendeleev Commun.* **2021**, *31*, 36–38.
17. a) Y. Nakano, M. Hamaguchi, T. Nagai, *J. Org. Chem.* **1989**, *54*, 5912–5919; b) D. Dar'in, G. Kantin, O. Bakulina, A. Inyutina, E. Chupakhin, M. Krasavin, *J. Org. Chem.* **2020**, *85*, 15586–15599; c) M. Hamaguchi, T. Misumi, T. Oshima, *Tetrahedron Lett.* **1998**, *39*, 7113–7116; d) A. Inyutina, D. Dar'in, G. Kantina, M. Krasavin, *Org. Biomol. Chem.* **2021**, *19*, 5068–5071; e) A. Inyutina, G. Kantin, D. Dar'in, M. Krasavin, *J. Org. Chem.* **2021**, *86*, 13673–13683; f) D. Laha, K. B. Meher, O. S. Bankar, R. G. Bhat, DOI: 10.26434/chemrxiv-2021-vv9hv.
18. a) P. de March, R. Huisgen, *J. Am. Chem. Soc.* **1982**, *104*, 4952; b) M. P. Doyle, D. C. Forbes, M. N. Protopopova, S. A. Stanley, M. M. Vasbinder, K. R. Xavier, *J. Org. Chem.* **1997**, *62*, 7210–7215; c) C.-D. Lu, Z.-Y. Chen, H. Liu, W.-H. Hu, A.-Q. Mi, *Org. Lett.* **2004**, *6*, 3071; d) A. D. Angelis, P. Panne, G. P. A. Yap, J. M. Fox, *J. Org. Chem* **2008**, *73*, 1435–1439; e) V. Nair, S. Mathai, S. M. Nair, N. P. Rath, *Tetrahedron Lett.* **2003**, *44*, 8407–8409; f) V. Nair, S. Mathai, S. M. Nair, C. Mathew, N. P. Rath, *Tetrahedron* **2005**,

61, 2849–2856; g) S. Muthusamy, R. Ramkumar, A. K. Mishra, *Tetrahedron Lett.* **2011**, *52*, 148–150.

19. CCDC 2105271 (compound **1a**), 2105766 (compound **5ga**), 2105262 (compound **3aa**), and 2105272 (Compound **5aa**) contain the supplementary crystallographic data. These data can be obtained free of charge by The Cam-bridge Crystallographic Data Centre.
20. a) R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 572–585; b) W. Eberbach, U. Trostrnann, *Chem. Ber.* **1985**, *118*, 4035–4058.
21. G. Zecchi, *Synthesis* **1991**, *3*, 181–188.
22. K. H. Kim, C. H. Lim, J. W. Lim, J. N. Kim, *Adv. Synth. Catal.* **2014**, *356*, 697–704.
23. Z. Liu, Q. Ma, Y. Liu, Q. Wang, *Org. Lett.* **2014**, *16*, 236–239.
24. J. Y. Hwang, A. Y. Ji, S. H. Lee, E. J. Kang**,** *Org. Lett.* **2020**, *22*, 16–21.

Chapter 4A

Intramolecular O–H Functionalization under Silver Catalysis: Access to 2*H*-Chromene



Intramolecular O-H Functionalization under Silver Catalysis: Access to 2*H*-Chromene

4A

This chapter describes the design and development of strategy for the regioselective synthesis of diversely substituted 2H-Chromene derivatives via intramolecular O–H functionalization of the modified diazo succinimides under silver catalysis. A wide range of 2H-Chromenes have been synthesized in good yields. The developed protocol was found to be general and scalable on gram quantity.

4A.1. Introduction

2*H*-Chromene (2*H*-1-benzopyran derivates) framework is usually found in many natural products (e.g., tannins and polyphenols found in fruits, teas, and vegetables) and few pharmaceuticals.[1] This privileged scaffold and its subfamily scaffold are core to many natural products and are known to elicit versatile biological activities, intriguing optical properties that can be used as fluorescence probes and photochromic compounds.[2]

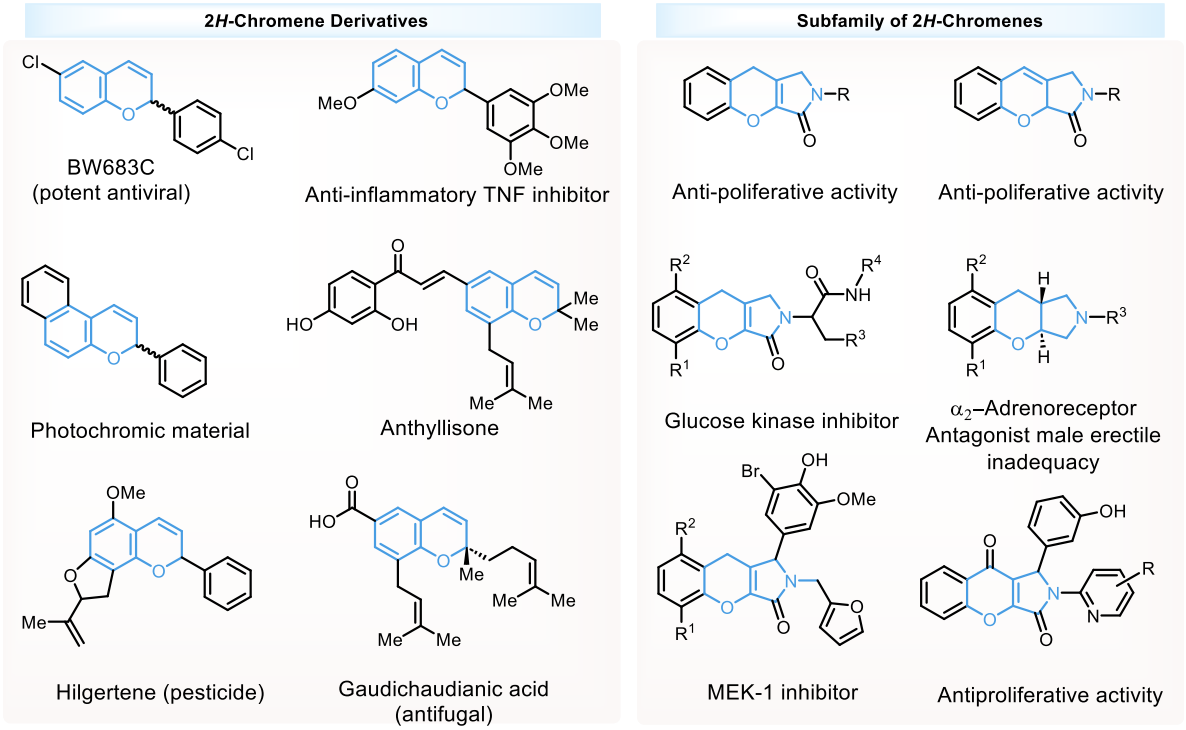
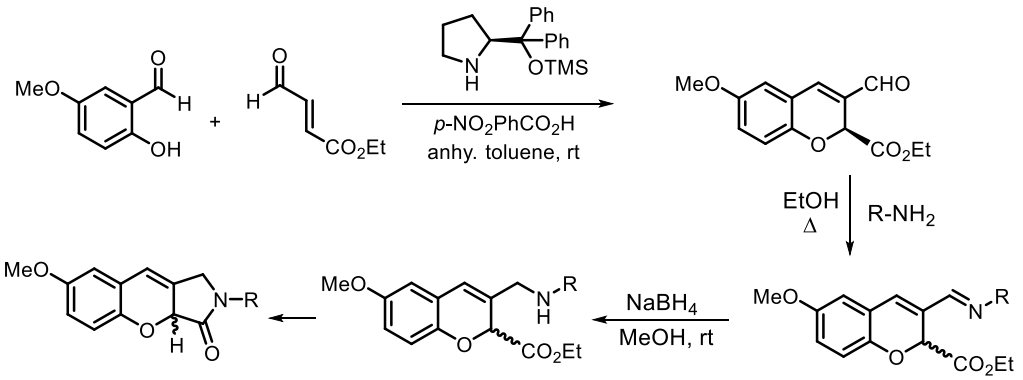


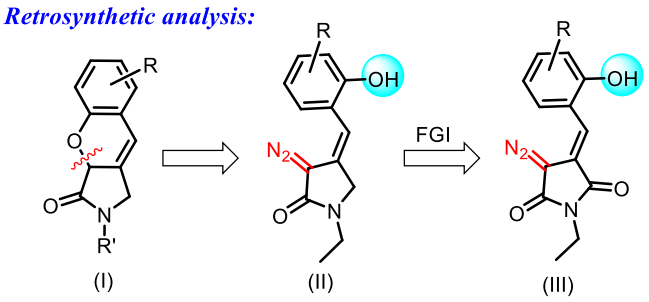
Figure 4A.1. Selected examples of pharmaceutically active and photochromatic compounds having 2*H*-Chromene and its subfamily scaffold.

Dihydrochromeno[2,3-*c*]pyrrol-3(3a*H*)-one is one of the prime subfamily of 2*H*-Chromenes having diverse biological properties such as antiproliferative activity,[3a] antitumor,[3b-c] antiulcer,[3d] antibacterial,[3e] TNF-α-inhibitory activity.[3f] Though considerable efforts have been made towards the synthesis of 2*H*-Chromene derivatives,[4] however, the synthetic route for the skeletal of dihydrochromeno[2,3-*c*]pyrrol-3(3a*H*)-one has rarely been reported.[3a] The cycloaddition and cyclization reactions are two commonly known routes to synthesize this skeletal.[3a] Also, the reported method involves multi-step reaction sequences and requires asymmetric route to synthesize an achiral subunit. This limits its wider applicability to a large extent.



Scheme 4A.1. Previous synthetic route for dihydrochromeno[2,3-*c*]pyrrol-3(3a*H*)-one.

Owing to the importance of this scaffold, some of the limitation of the available protocol, the development of shorter, more efficient and broadly applicable protocol to synthesize this important subclass of 2*H*-Chromene derivatives is highly desirable. We envisioned that this subunit of 2*H*-Chromenes **I** could be synthesized from the *ortho*-OH substituted (*Z*)-3-diazo-(2-hydroxybenzylidene)pyrrolidin-2-ones **II** *via* intramolecular O–H functionalization. This intermediate **II** could be accessed starting from the *ortho*-hydroxy arylidene diazosuccinimides **III** (see Scheme 4A.2).



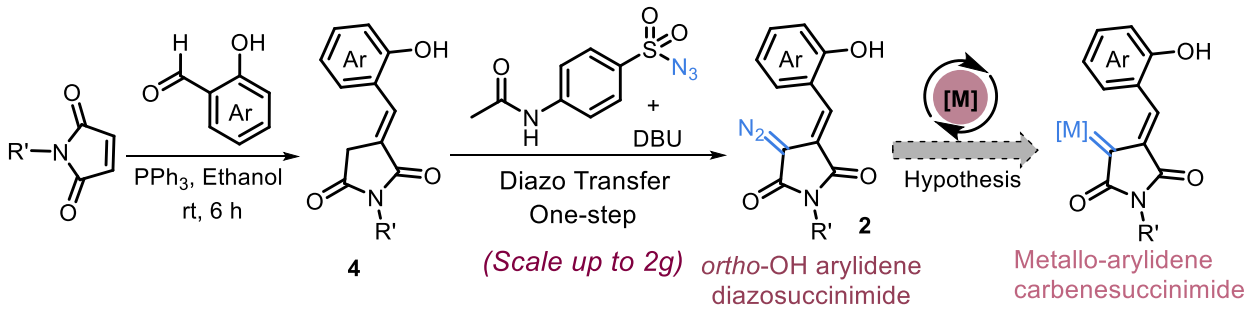
Scheme 4A.2. Retrosynthetic analysis of dihydrochromeno[2,3-*c*]pyrrol-3(3a*H*)-one.

It is also worth mentioning that some substituents including halogens, long-chain alkyl etc. reside at the *para*-position with respect to the oxygen atom in 2*H*-Chromenes are known to enhance the biological activity significantly.[2a] In this regard, we hypothesized that transition metal-catalyzed metallo-carbene promoted strategy via an intramolecular pathway may lead to the desired target scaffold.

Silver salts are relatively non-toxic, less expensive and are also abundant transition metal complexes are available. Also, silver catalysts have a great potential as Lewis acid and the ability to accommodate a variety of ligands.[5] The carbene transfer reactions involving silver carbenoid species have recently emerged as a powerful technique to execute diverse synthetic array of molecules.[6] Herein, in this chapter we present $AgNTf_2$-catalyzed intramolecular O–H functionalization of 2-hydroxy substituted diazosuccinimide to access diverse chromeno[2,3-*c*]pyrrole-1,3(2*H*,3a*H*)-dione derivatives.

4A.2. Results and Discussion:

To begin with, we developed a new synthetic strategy to access *ortho*-OH arylidene diazosuccinimides **2** starting from the biologically active *ortho*-OH arylidene succinimides **4** using diazo transfer reagent (*p*-ABSA) in presence of 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) as a base (Scheme 4A.3). The preparation of this modified diazosuccinimides is prepared according to our previous procedure with few modifications in reaction conditions (discussed later in chapter 4B, Experimental section). The compound **4** has been prepared from the maleimide derivatives. The newly formed bench-stable *ortho*-OH arylidene diazosuccinimide **2** exhibits the electrophilic character at the carbon wherein the diazo group is directly attached onto it (diazo carbon).

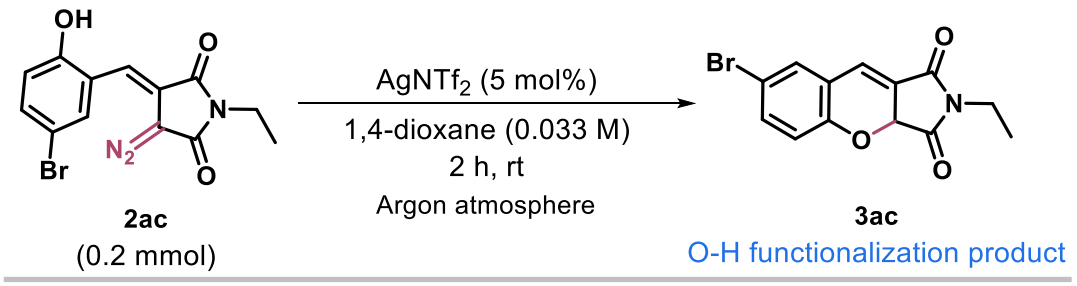


Scheme 4A.3. Synthesis of *ortho*-hydroxy arylidene succinimide.

In order to validate our hypothesis, we embarked to screen easily and commercially available silver catalysts and by selecting 5-bromo-2-hydroxybenzylidene-*N*-ethyl

diazosuccinimide **2ac** as model substrate to evaluate the desired transformation. Initially we screened different catalysts, solvents etc. and among all catalysts screened, silver triflimide and 1,4-dioxane proved to be very efficient catalyst and solvent respectively (Appendix 4A.5). Based on the initial reactions screened, catalytic amount (5 mol%) of silver triflimide in 1,4-dioxane (0.033 M) as solvent at room temperature under inert atmosphere proved to be optimal to obtain the desired O–H functionalization product **3ac** in 78% yield (Table 4A.1, Entry 1). The control reactions revealed that silver triflimide is necessary for the transformation (Table 4A.1, Entry 2). Moreover, replacing $AgNTf_2$ with other metal catalysts such as iron, copper, scandium triflate diminished the yield of the desired product **3ac** (Table 4A.1, Entries 3-5). As mentioned earlier, $AgNTf_2$ proved to be efficient over other silver salts and this may be due to the reason of counter-anion effect that aids the desired transformation (Table 4A.1, Entry 6). Interestingly, the reaction worked well with dirhodium tetraacetate (5 mol%) affording the desired product **3ac** with 73% yield (Table 4A.1, Entry 7). This lowering in the yield of the desired product in the case of dirhodium acetate may be due to the reason of either restricting catalyst proximity over the reactive diazo carbon cavity or steric interference occurring between the catalyst surface to that of benzylidene moiety, resulting in a weaker approach of -OH group to the rhodium carbenoid center.

Table 4A.1. Optimization of the reaction condition for the intramolecular O–H functionalization[a]



2ac (0.2 mmol)

3ac O-H functionalization product

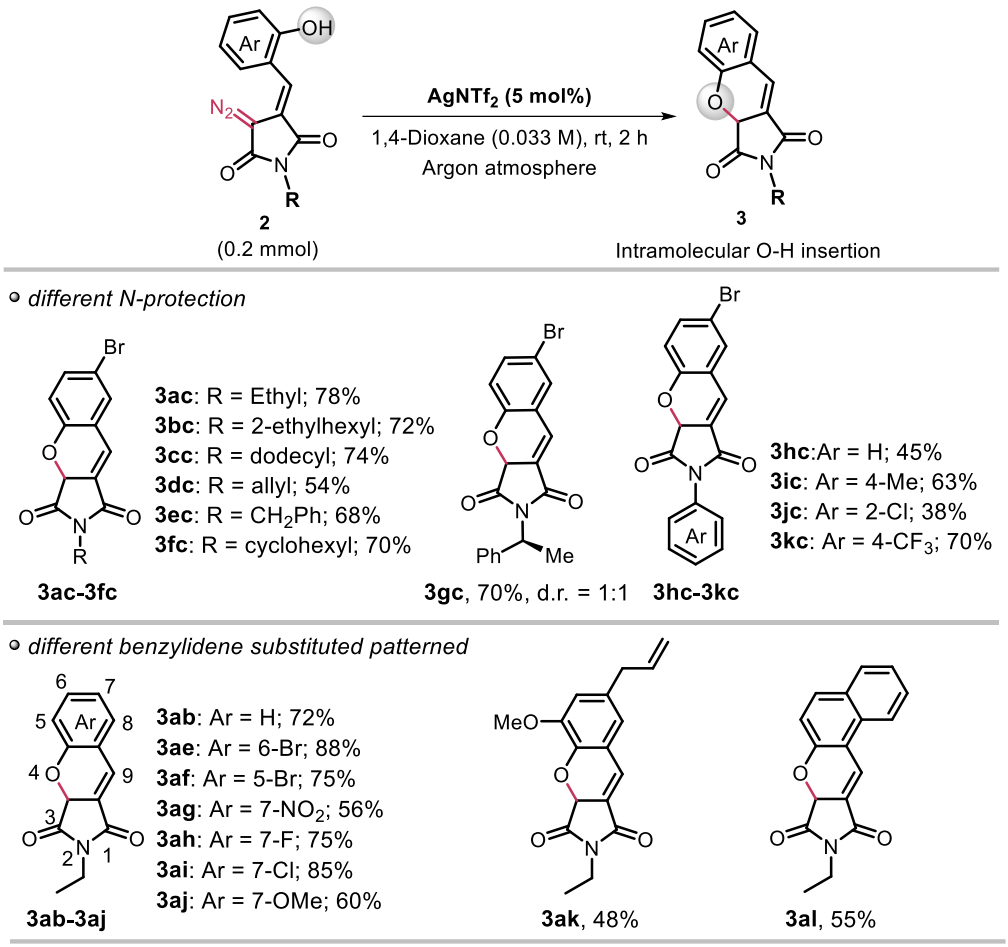
Entry	Variation from the standard reaction conditions[a]	Yield[b] (%) of 3ac
1	**None**	**78**
2	No $AgNTf_2$	N.R.
3	$Sc(OTf)_3$ instead of $AgNTf_2$	50
4	$FeCl_2.4H_2O$ instead of $AgNTf_2$	15
5	$Cu(OTf)_2$ instead of $AgNTf_2$	10
6	AgOTf instead of $AgNTf_2$	56
7	$Rh_2(OAc)_4$ instead of $AgNTf_2$	73
8[c]	$AgNTf_2$, DCM, 40 °C	62

[a]**Standard reaction conditions**: **2ac** (0.2 mmol) in dry 1,4-Dioxane (3 mL) was added dropwise into a solution

of $AgNTf_2$ (5 mol%) in dry 1,4-Dioxane (3 mL) over 2 h, rt, Argon atmosphere. [b]Yield of isolated products after column chromatography. [c]dry DCM was used. N.R. = No reaction.

In order to increase the yield of the desired product **3ac** further we carried out the reaction in presence of $AgNTf_2$ (5 mol%) at 40 °C, however, we observed that yield dropped in comparison to the reaction at rt. (Table 4A.1, Entry 8). Based on the systematic screening, 5-bromo-2-hydroxybenzylidene-*N*-ethyl diazosuccinimide **2ac** (1 equiv.), $AgNTf_2$ (5 mol%) as a catalyst in dry 1,4-dioxane at room temperature to furnish the desired 2*H*-chromene product **3ac** *via* intramolecular OH insertion.

Having obtained the optimized reaction conditions, we further planned evaluate the substrate scope to generalize the developed protocol with different aryl-substituted and *N*-substituted 2-hydroxy arylidene diazosuccinimides **2** on a 0.2 mmol scale (Table 4A.2). In this regard, we treated different *N*-substituted 5-bromo-2-hydroxybenzylidene diazosuccinimides (**2bc**–**2kc**) under optimized reaction condition to afford the corresponding desired products (**3bc**–**3kc**) in modest to good yields (see Table 4A.2). All the *N*-alkyl group substituted diazosuccinimides (**2bc**–**2fc**) under the optimized reaction condition also afforded the corresponding desired products (**3bc**–**3fc**) in moderate to good yields (up to 78%, see Scheme 4A.4). While *N*-aryl substituted diazosuccinimides(**2hc**–**2jc**) having few electron-rich as well as electron deactivating group (chloride) on the *N*-phenyl ring under the reaction condition afforded the desired products (**3hc**–**3jc**) in modest yields (up to 63%). Interestingly, the electronically deactivated -CF_3 group at the *para*-position of *N*-phenyl ring (**2kc**) afforded the desired product **3kc** in good yield (yield 70%). Further, we studied different substituent pattern at the 2-hydroxybenzylidene ring (**2ab**–**2ak**) under the optimized reaction conditions. To our delight, all the substrates well tolerated the optimized reaction conditions to afford the corresponding desired products (**3ab**–**3ak**) in moderate to very good yields (up to 88%). The 2-hydroxynaphthalene substituted diazosuccinimide **2al** also furnished the corresponding desired product **3al** in modest yield.

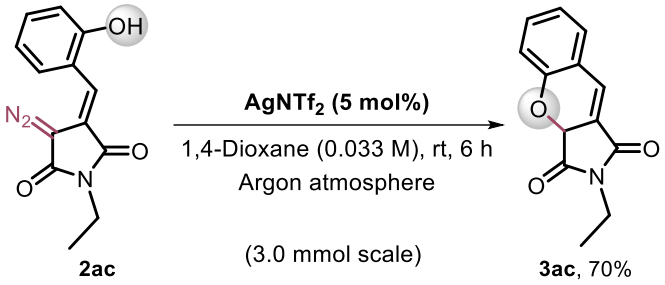


[a]**Reaction conditions**: **2** (0.2 mmol) in dry 1,4-Dioxane (3 mL) was added dropwise into a solution of $AgNTf_2$ (5 mol%) in dry 1,4-Dioxane (3 mL) over 2 h, rt, Argon atmosphere. [b]Yield of isolated products after column chromatography.

Table 4A.2. Studies of intramolecular O–H functionalization with *N*-protection and different substituent pattern at benzylidene ring.[a]

After successfully demonstrating the protocol with many substrates we turned our attention to explore the diastereoselective transformation. In this regard, we prepared the *N*-(*S*)-1-phenylethyl substituted diazosuccinimide **2gc** (chiral auxiliary derived) so as to induce the chirality. However, under the optimized reaction conditions, the desired O–H functionalization product **3gc** was obtained with low diastereoselectivity (d.r. 1:1) in 70% yield (Table 4A.2).

In order to verify the practicability as well generality of this intramolecular O–H functionalization protocol, a gram-scale reaction of 5-bromo-2-hydroxyphenyl vinyl diazosuccinimide **2ac** was conducted under the standard optimized reaction conditions (Scheme (Scheme 4A.4). The reaction proceeded smoothly and the corresponding target product **3ac** was obtained in 70% yield (0.480 g).



Scheme 4A.4. Gram-scale synthesis of Chromenopyrrole-dione.

4A.3. Conclusions:

In summary, we have developed a new one-pot protocol for the regioselective synthesis of 2*H*-chromenes subfamily, chromeno[2,3-*c*]pyrrole-1,3(2*H*,3a*H*)-dione derivatives via silver catalysis. We have successfully employed the vinyl diazosuccinimides for the effective intramolecular O–H insertion reaction using silver triflimide as effective catalyst at room temperature. The protocol is believed to procced via silver carbenoid species. The protocol found to be practical as it worked well with diverse *N*-substituted and arylidene substituted diazosuccinimides and also proved to be scalable on gram quantity.

4A.4. Experimental Section:

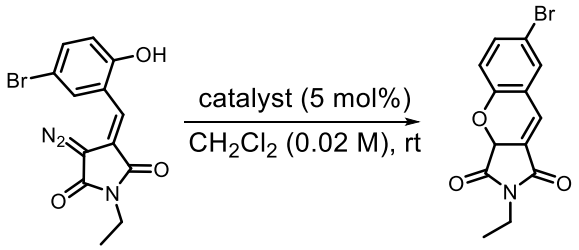
4A.4.1. General Procedure to synthesized the O–H functionalization product:

To oven dried 25 mL two neck round bottom flask equipped with a magnetic stirrer, was added 5 mol% of $AgNTf_2$ in dry 1,4-dioxane (3 mL) under argon atmosphere at room temperature and the reaction flask was wrapped outside with aluminum foil. After that the diazo compound **2** (0.2 mmol) in 1,4-dioxane (3 mL) was added dropwise into the reaction solution by a syringe over 2 h with constant stirring at room temperature while maintaining the inert atmosphere. After the addition, the reaction mixture was stirred for additional 5 min. The completion of the reaction was monitored by TLC. Upon complete consumption of starting material **2**, the reaction mixture was concentrated under vacuo and purified by column chromatography using ethyl acetate and petroleum ether (eluted with 18:82 EtOAc:Hexane) to afford the desired product **3** as white solid (yield up to 88%).

Appendix 4A.5

4A.5. Detailed optimization for the intramolecular O–H functionalization:

4A.5.1. Catalyst optimization[a]:

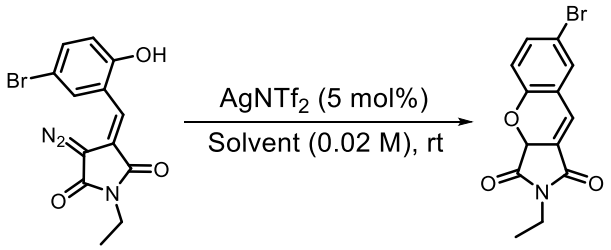


2ac (0.2 mmol) **3ac**

Entry	Catalyst	Time	Yield[b] (%)	Entry	Catalyst	Time	Yield[b] (%)
1	**$AgNTf_2$**	**2 h**	**62**	7	$Sc(OTf)_3$	2 h	50
2	AgOTf	2 h	56	8	$Bi(OTf)_3$	2 h	27
3	$AgBF_4$	2 h	35	9	$FeCl_2.4H_2O$	2 h	15
4	$Cu(OAc)_2$	2 h	20	10	$Rh_2(OAc)_4$	2 h	60
5	$Cu(OTf)_2$	2 h	10	11	$Rh_2(OCOCF_3)_4$	2 h	45
6	$Cu(OAc)_2.H_2O$	2 h	15	12	$Rh_2(esp)_4$	2 h	50

[a]Reaction Conditions: **2ac** (0.2 mmol) in dry DCM (7 mL) was added dropwise into a solution of $AgNTf_2$ (5 mol%) in dry DCM (3 mL) over 2 h, Argon atmosphere, [b]yield of isolated product after column chromatography.

4A.5.2. Investigation of suitable solvent[a]:



2ac (0.2 mmol) **3ac**

Entry	Catalyst	Time	Yield[b] (%)	Entry	Catalyst	Time	Yield[b] (%)
1[c]	DCM	2 h	62	**5**	**1,4-Dioxane**	**2 h**	**68**
2	Toluene	2 h	40	6	DCE	2 h	52
3	Fluorobenzene	2 h	45	7	DMF	2 h	50
4	THF	2 h	64	8	DMSO	2 h	54

[a]**Reaction Conditions**: **2ac** (0.2 mmol) in dry solvent (7 mL) was added dropwise into a solution of $AgNTf_2$ (5 mol%) in dry solvent (3 mL) over 2 h, Argon atmosphere; [b]yield of isolated product after column chromatography; [c]Reaction temperature 40 °C.

4A.5.3. Optimization of reactant concentration[a]:

Entry	x (M)	Time	Yield[b] (%)
1	0.02	2 h	68
2	0.025	2 h	72
3	**0.033**	**2 h**	**78**
4	0.05	2 h	67

[a]Reaction Conditions: **2ac** (0.2 mmol) in dry 1,4-Dioxane was added dropwise into a solution of $AgNTf_2$ (5 mol%) in dry DCM over 2 h, Argon atmosphere. [b]yield of isolated product after column chromatography.

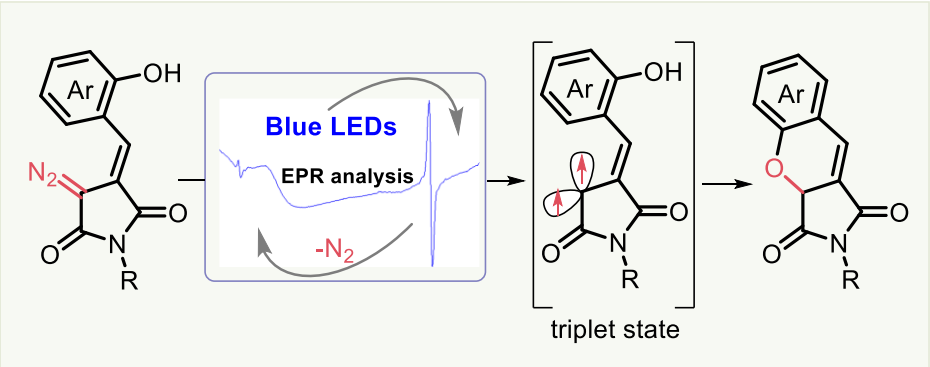
4A.5.4. Experimental Section: Experimental general information, data and spectral copies of the representative compounds are given at the end of Chapter 4B.14.4 Appendix-IV (page no 205).

4A.6. References:

1. a) A. D. Covington, *Chem. Soc. Rev.* **1997**, *26*, 111–126; b) Ellis, G. P., Ed. Chromenes, Chromanones, and Chromones. In The Chemistry of Heterocyclic Compounds; Wiley-Interscience: New York, **1977**; Vol. 31; c) Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds. Comprehensive Heterocyclic Chemistry II; Pergamon: Oxford, **1996**; Vol. 2.
2. a) V. Raj, J. Lee, *Front. Chem.* **2020**, *8*, 623; b) Y. Yue, C. Yin, F. Huo, J. Chao, Y. Zhang, *Sens. Actuators B: Chem.* **2016**, *223*, 496–500.
3. a) L. Tóth, A. Kiss-Szikszai, G. Vasvári, F. Fenyvesi, M. Vecsernyés, P. Mátyus, S. Antus, A. Mándi, T. Kurtán, *Synlett* **2019**, *30*, 799–802; b) Y. Sugita, K. Takao, Y. Uesawa, H. Sakagami, *Anticancer Res*. **2017**, *37*, 5919–5924; c) A. Fouqué, O. Delalande, M. Jean, R. Castellano, E. Josselin, M. Malleter, K. F. Shoji, M. D. Hung, H. Rampanarivo, Y. Collette, P. van de Weghe, P. Legembre, *J. Med. Chem.* **2019**, *62*, 9339–9340; d) Yu. P. Bogza, A. L. Katsiel′, A. N. Sharypova, T. G. Tolstikova & A. S. Fisyuk, *Chem. Heterocycl. Compd.* **2015**, *50*, 1712–1718; e) H. Tanaka, I. Atsumi, O. Shirota, S. Sekita, E. Sakai, M. Sato, J. Murata, H. Murata, D. Darnaedi, I.-S. Chen, *Chem. Biodivers.* **2011**, *8*, 476-482; f) J.-F. Cheng, A. Ishikawa, Y. Ono, T. Arrhenius, A. Nadzan, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3647–3650.
4. a) N. Majumdar, K. A. Korthals, W. D. Wulff, *J. Am. Chem. Soc.* **2012**, *134*, 1357; b) T. J. A. Graham, A. G. Doyle, *Org. Lett.* **2012**, *14*, 1616; c) Q. Wang, M. G. Finn, *Org. Lett.* **2000**, *2*, 4063; d) P. N. Moquist, T. Kodama, S. E. Schaus, *Angew. Chem., Int. Ed.* **2010**, *49*, 7096.
5. P. Sivaguru, S. Cao, K. R. Babu, X. Bi, A*cc. Chem. Res.* **2020**, *53*, 662–675.
6. X. Zhang, Z. Liu, P. Sivaguru, X. Bi, Chem Catalysis **2021**, *1*, 599–630.

Chapter 4B

Photochemical Carbene Reactivity of Donor-/Acceptor-type Diazosuccinimide: An Access to 2*H*-Chromene



Photochemical Carbene Reactivity of Donor-/Acceptor-type Diazosuccinimide: An Access to 2*H*-Chromene

4B

This chapter describes the successful demonstration on the photochemical reaction of vinyl diazosuccinimides under visible light illumination to access the 2H-chromene derivatives. This visible light driven protocol developed proved to practical and did not rely on any transition metal catalysts or additives. Also, more importantly, as an important finding, the transformation is proved to undergo via a triplet carbene intermediate to furnish the desired product unlike the transition metal catalysis where in singlet carbene is known to involve. The triplet carbene has been detected by EPR spectroscopic studies along with various control experiments and DFT photoexcited calculations. Generally, the reactivity of triplet carbene in organic synthesis is underdeveloped as most of the carbene transfer reactions rely on specific metal catalyst. Alternatively, the organic transformations involving a triplet spin state carbene have been explored with a diazo compound under visible light utilizing photosensitizer. Despite this advance, the development of photoinduced sensitizer-free triplet carbene generation is highly challenging and has been seldom reported in the literature owing to the rapid singlet vs triplet spin state equilibrium. Herein, in this chapter, we have successfully demonstrated diazosuccinimide as a new class of diazo compound which upon exposure with blue LEDs (456 nm) generates ground-state triplet carbene (without intersystem crossing - ISC) in the absence of any sensitizer. The protocol has also been utilized for the construction of biologically relevant scaffolds.

4B.1. Introduction

Visible light-induced decomposition of diazo compounds has emerged as a viable as well as an alternative strategy for the generation of free carbene under mild and metal-free conditions.[1] The spin state, the reactivity of carbene and its singlet-triplet splitting are dependent on the nature of the electronic as well as the steric properties of the substituents that are directly attached to the carbene carbon center.[2]

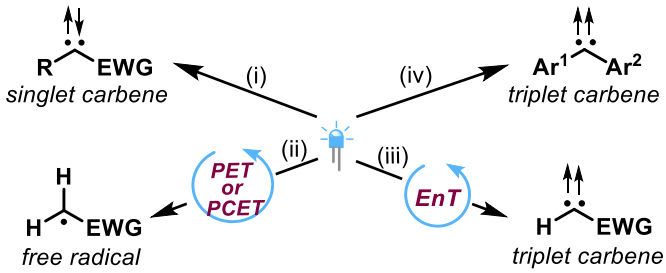
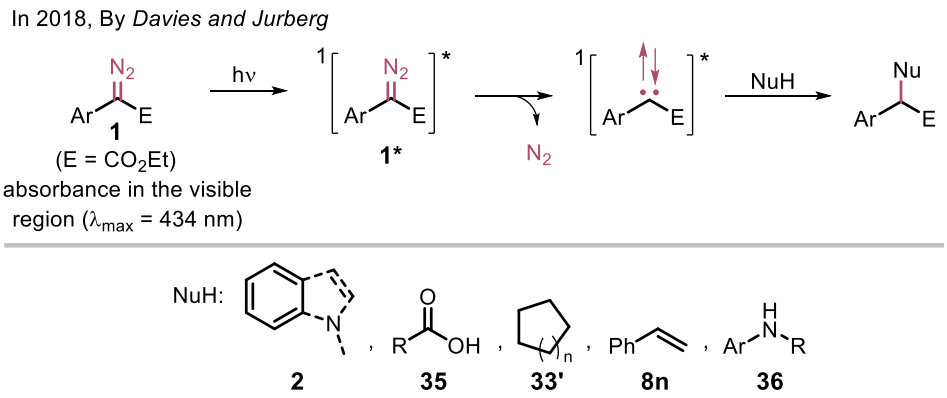


Figure 4B.1. Different diazo compounds as surrogates of carbenes and their photochemical reactivity.

Some of the recent studies have been well demonstrated about the free singlet carbene reactivity that can be selectivity accessed *via* the photolysis of mainly donor-/acceptor-type diazo compounds [Figure 4B.1(i)].[1]

In 2019, Davies and Jurberg have disclosed the generation of singlet carbene under visible light irradiation for the construction of various transformations including functionalization and cyclopropanation. This has been the first documented result that thoroughly studied and provided a detailed information on singlet carbene transfer reactions under visible light. (Scheme 4B.1).[1a] This unprecedented finding attracted the attention as this kind of strategy was previously inaccessible.



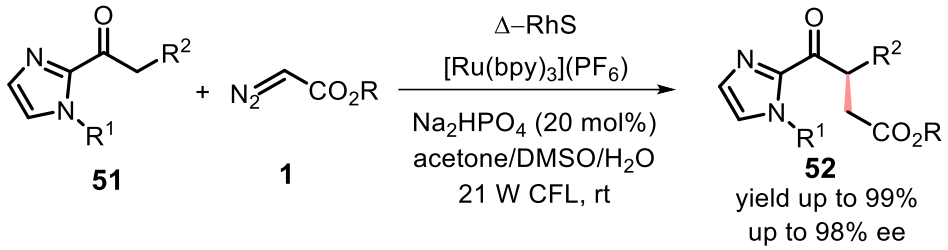
Scheme 4B.1. Singlet carbene transfer reactions under visible light.

On the contrary, very recent a few elegant reports on the free triplet carbene reactivity/radical reactivity have gained a great interest [Figure 4B.1(ii) and (iii)][3] and they are typically based on the use of photosensitizers/energy transfer catalysts over acceptor-type diazoacetates. In this context, Meggers,[3a] Gryko,[3b,e,f] Doyle,[3c] Koenigs,[3e] and their co-workers have reported the an interesting reactivity of diazo compounds that is usually inaccessible in the ground state.[4] These strategies have effectively trapped the photo-excited state reactivity *via* photoinduced electron transfer (PET),[3a,b,e] proton-coupled electron transfer (PCET)[3c,4e]

and/or photoinduced proton transfer (PPT) process.[4a-b,f,5] These approaches have been described in detail below.

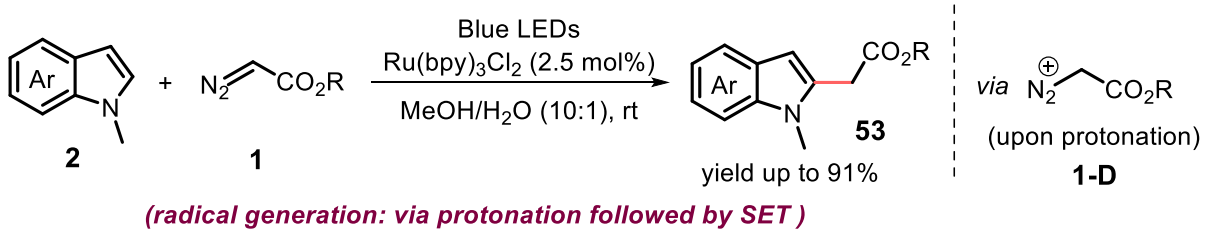
❖ ***Methods of free radical reactivity of diazo compounds:***

In 2016, Meggers research group[3a] has disclosed a proton- and redox-neutral method for the free radical reactivity of ethyl diazoacetates **1** for the α-alkylation of 2-acyl imidazoles **51** using a combination of a chiral rhodium-based Lewis acid catalyst and a photoredox sensitizer/photocatalyst under visible light to access the corresponding enantioselective C-2 alkylated compounds **52** in very good yield and enantioselectivity (Scheme 4B.2).



Scheme 4B.2. Visible-light-promoted *α*-alkylation of 2-acyl imidazoles with ethyl diazoacetate.

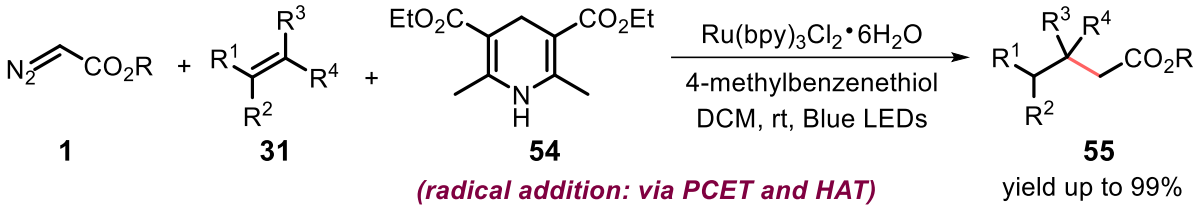
In 2019, Gryko and co-workers[3b] have reported the C2-alkylation of indoles **2** under photocatalytic condition using ethyl diazoacetates via the generation of free radical intermediate. The ethyl diazo acetates **1** first undergo protonation to form a diazonium ion intermediate **1-D** which would subsequently undergo single electron transfer (SET) event in presence of photocatalyst upon the irradiation of blue light to afford the C2-alkylated products **53** in very good yields (Scheme 4B.3).



Scheme 4B.3. C2-alkylation of indoles with ethyl diazoacetates under visible light.

Very recently, Doyle research group[3c] has elegantly reported photocatalytic decomposition of ethyl diazoacetates **1** to generate a free radical which would further undergo an addition reaction with olefins **31** to afford the desired products **55** under visible light. This

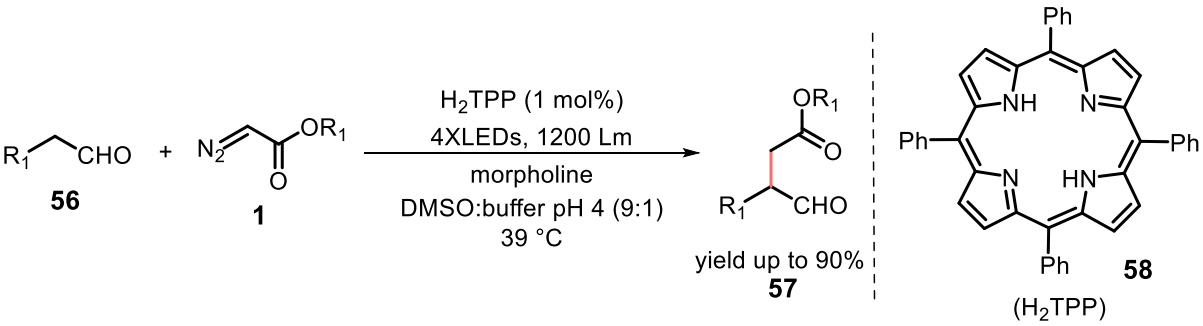
interesting result broaden the concept of SET/protonation events by introducing PCET and HAT process (Scheme 4B.4).



Scheme 4B.4. Visible-light-mediated photocatalytic hydroalkylation with ethyl diazoacetates.

❖ *Methods for the triplet carbene reactivity involving photosensitizer:*

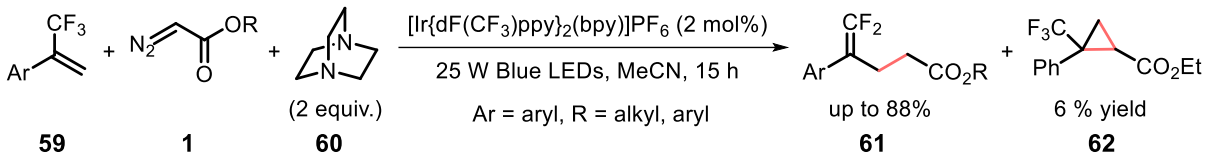
In 2016, Gryko research group has elegantly disclosed a strategy for the *α*-alkylation using a dual catalytic system comprised of a free base - porphyrin as a photosensitizer and morpholine as a secondary amine organocatalyst for the reaction of aldehydes **56** and diazoacetates **1** to furnish *α*-alkylated derivatives **57**. The porphyrin (H_2TPP) enables the two parallel processes such as enabling a reactive triplet carbene intermediate from diazoacetate via energy transfer (EnT) process and PET event in order to form the oxidized enamine intermediate to finally form the desired alkylated aldehydes **57** in good yields (up to 90% Scheme 4B.5).[3d]



Scheme 4B.5. Light-induced α-functionalization of aldehydes using porphyrin as energy transfer catalyst.

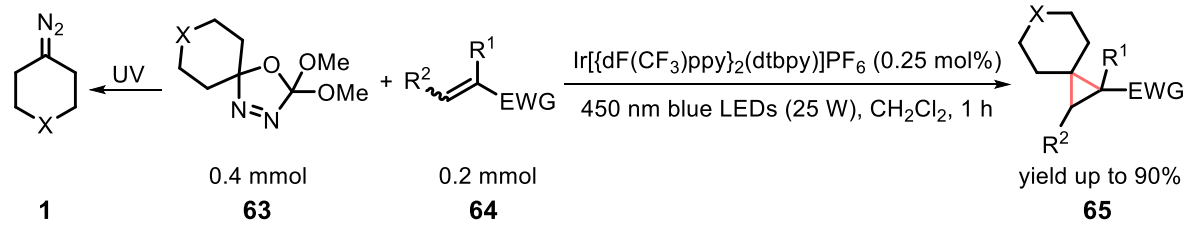
In 2022, the Koenigs research group has demonstrated protocol for the *gem*-difluoroolefination starting from *α*-trifluoromethyl styrenes **59** and diazoesters **1** in presence of dye-photosensitizer under blue light irradiation to afford the desired product **61** in good yields (up to 88%) (Scheme 4B.6). The photocatalytic reaction has been proven to undergo *via* energy transfer process to generate triplet carbene intermediate. It is also important to note that tertiary amine (DABCO) played a key role in unlocking reactivity and interestingly in its absence the

reaction afforded a cyclopropane derivative **62** as a major product (95% yield) though with low diastereoselectivity (Scheme 4B.6).[3e]



Scheme 4B.6. *gem*-Difluoroolefination *via* triplet carbene using dye-photosensitizer.

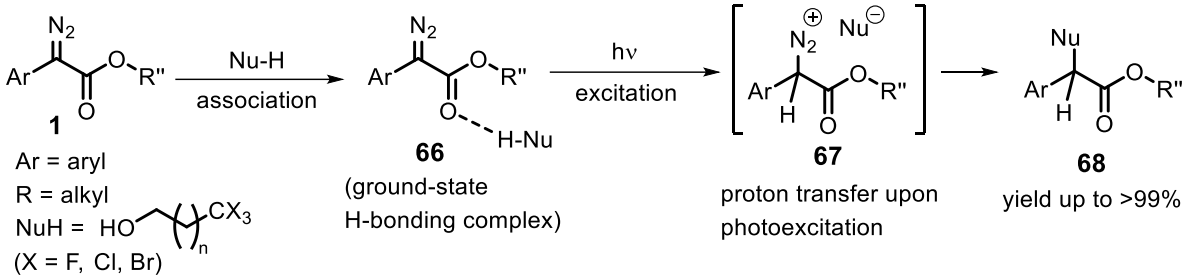
Very recently in 2023, the Gryko research group has disclosed an elegant strategy for the activation of 1,3,4-oxadiazolines using an organic dye-sensitizer under visible light irradiation. The olefin **64** reacts with the triplet carbene generated either *via* the diazo intermediate **1** by energy transfer or directly from 1,3,4-oxadiazolines **63** upon the irradiation of visible light to afford corresponding spirocyclopropanes in excellent yields (up to 90%, Scheme 4B.7). The photoactivation by energy transfer under visible light (450 nm) paved the pathway to explore an alternative reactivity of oxadiazolines which enabled the generation of triplet carbene intermediate, whereas under UV irradiation (<350), 1,3,4-oxadiazolines form the diazo compound **65** (Scheme 4B.7).[3f]



Scheme 4B.7. Photoactivation of 1,3,4-oxadiazolines by triplet energy transfer catalyst.

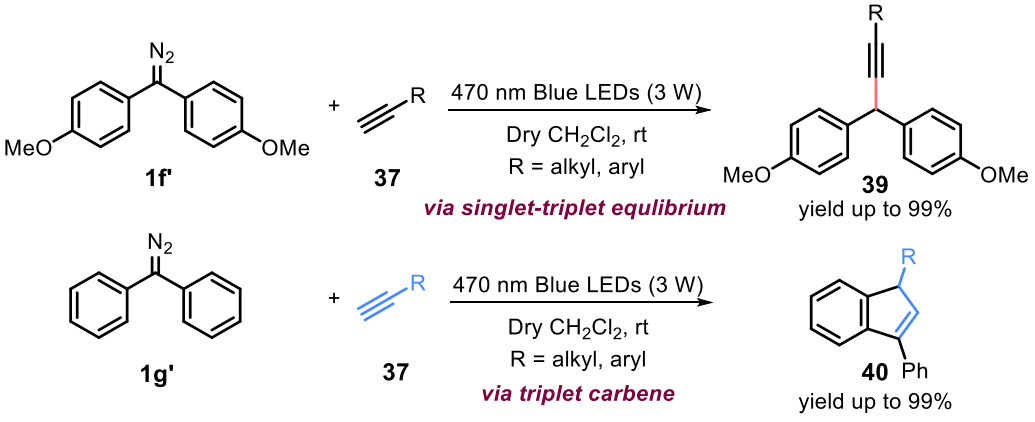
❖ *Methods of photoexcited proton transfer reactivity (PPT reaction):*

Very recently, for the first time Koenigs and co-workers have elegantly explored the photobase-reactivity pattern of unreactive diazoacetates **1** in mild acids for the O–H functionalization exploiting the PPT strategy under low energy visible light irradiation (470 nm) to access the corresponding OH insertion products **68** in good yields (Scheme 4B.8).[5] This strategy is believed to be triggered by the ground state hydrogen-bonded complex under visible light irradiation, unlike the traditional carbene transfer reactions which usually proceed either *via* metallo-carbene O–H insertion pathway[6a-c] or through protonation-substitution reactions with strong acids.[6d]



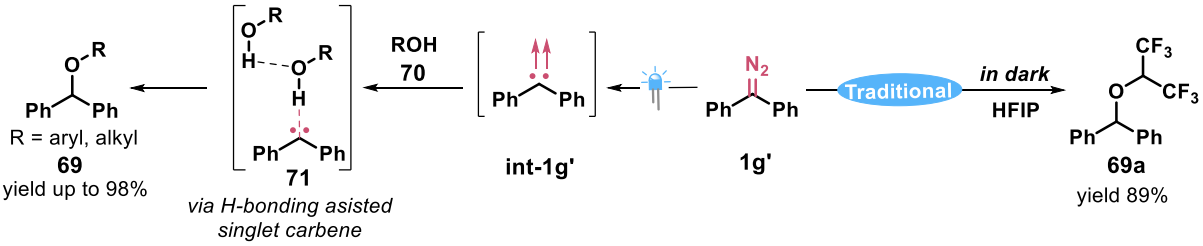
Scheme 4B.8. Photoinduced PPT reaction with mild acids.

Despite such ground-breaking progress on the photoexcited state triplet carbene generation of utilizing photosensitizers and exploring its reactivity, photoinduced photosensitizer-free triplet carbene generation is highly desirable and challenging for the successful organic transformations. Moreover, the direct generation of ground-state triplet carbene[7] and their useful synthetic applications have scarcely been reported.[8] There are numerous applications in material science for their paramagnetism behaviour.[9] Very recently, the Koenigs research group has elegantly demonstrated the protocol for tuning the reactivity of carbene precursors (diazo compounds) selectively to carry out the transformation either *via* singlet carbene or triplet carbene in a controlled manner by varying the electronic properties of the diazo compounds (see Scheme 4B.9).[8a] The different diaryl diazo compounds (**1f′-1g′**) under photolysis conditions undergo carbene transfer reactions with alkynes **37** to afford the C–H bond functionalized products **39** and indene derivatives **40** *via* cascade reaction manner in highly chemoselective manner (up to 99%, Scheme 4B.9). It's important to note that different products were formed based on the carbene involved during the course of the reaction. The reaction via single-triplet carbene equilibrium resulted on the formation of alkyne functionalization product **39**, while the reaction via triplet carbene afforded the corresponding indene derivatives **40** in excellent yields.



Scheme 4B.9. Electronically-controlled carbene transfer reaction of diaryl diazo compounds.

In 2022, the same research group taking further insight from the previous alkylation strategy, successfully demonstrated the O–H functionalization of alcohols **70** (mild acids) with diphenyl diazo alkanes **1g′** under photochemical conditions (*via* triplet carbene to hydrogen-bonding assisted singlet carbene leading to rapid protonation and C–O bond formation).[10] It is important to highlight that as an exceptional case hexafluoro isopropanol (HFIP) underwent O–H insertion reaction in absence of light (dark) to afford the corresponding the product **69a** (Scheme 4B.10).



Scheme 4B.10. O–H functionalization reaction with triplet carbene under photochemical condition.

However, to the best of our knowledge till date there are no reports on the reactivity of diazo compounds to undergo alkylation of the hydroxy group or O–H functionalization *via* photoinduced hydrogen atom transfer (HAT) process. The major challenge or hurdle for this process is that the conducive condition for the diazo compound to form triplet excited state and further react with alcohol. It is important to note that though Koenigs research group demonstrated the reactivity of diphenyl diazoalkane (capable of forming excited state triplet carbene intermediate under visible light irradiation) with alcohols[10] yet is completely different concept that from photoinduced hydrogen atom transfer (HAT) process (Scheme 4B.10). In this context, it is worth mentioning that Koenigs findlings demonstrate a triplet carbene **int-1g′** which undergoes alconhol-assisted ISC leading to a hydrogen-bonding stabilized singlet carbene (**71**) generation followed by rapid protonation and C–O bond formation **69**; whereas in case of photoinduced HAT process, hydrogen atom should be transformed in the triplet state itself to form a radical species.

Vinyl diazosuccinimide scaffold **1** is emerging as a versatile reagent in the recent years for its distinct structural features[11a] and diverse metallo-carbene reactivity. Undoubtedly, vinyl diazosuccinimides have been explored for a variety of transformations ranging from cycloaddition to site-selective C–H bond functionalization.[11] However, surprisingly, its photochemical reactivity has not been investigated in the literature till date. Based on our

continuous interest and experience in dealing with diazo succinimides under metal catalysis, we sought to explore their photochemical reactivity to achieve a convenient and sustainable approach to synthesize the molecules of industrial relevance and potent bioactivity.

In this chapter the exploration of vinyl diazo succinimides for the direct one-pot access to 2*H*-chromenes under visible light irradiation has been disclosed. Also, we have successfully demonstrated the protocol for tuning the reactivity of vinyl diazosuccinimides for generating singlet vs triplet carbene for the first time in the literature. Furthermore, in order to validate the new reactivity pattern involving the HAT process, we have carried out various control experiments such as labelling study, trapping experiments, EPR characterization that greatly supported the triplet carbene generation during the course of the reaction. Further, this has been unambiguously supported by the DFT photoexcited calculations.

4B.2. Results and Discussion

❖ *Initial spectroscopic studies*

In order to gain an insight on the photochemical carbene reactivity of donor-/acceptor-type vinyl diazosuccinimides and also to develop a sustainable synthetic protocol to access useful compounds we planned to carry out the studies in detail. To begin with we carried out the UV-visible absorption studies and analyzed the photochemical properties of diazo succinimides **1aa**-**1ac** and further compared these properties with that of well-established donor-/acceptor-type diazo compound such as phenyldiazoacetate **1** (Figure 4B.2). The phenyl diazoacetate **1** has a distinct absorption spectrum at the visible region (λ_{max} = 432 nm) while the vinyl diazosuccinimide **1aa** exhibits a strong absorption near UV region (335 nm - 380 nm) in DCM. Whereas, the other vinyl diazosuccinimides (**1ab**-**1ac**) display bathochromic shift (342-354 nm) which presumably attributes to the enhancement of electronic delocalization in the system. Though the blue LEDs have a maximum emission at 470 nm, but they can also emit radiation at around 470 nm +/- 50 nm range as well. Based on this we hypothesized that the excitation of carbene surrogates such as vinyl diazo compounds or direct photolysis of vinyl diazo succinimides (**1ab**-**1ac**) are likely to happen under the irradiation of blue light (Blue LEDs). We believed that suitable photochemical reaction conditions may lead to the triplet state carbenes from vinyl diazo succinimides **1** and they can be utilized to construct useful compounds via a novel and practical approach.

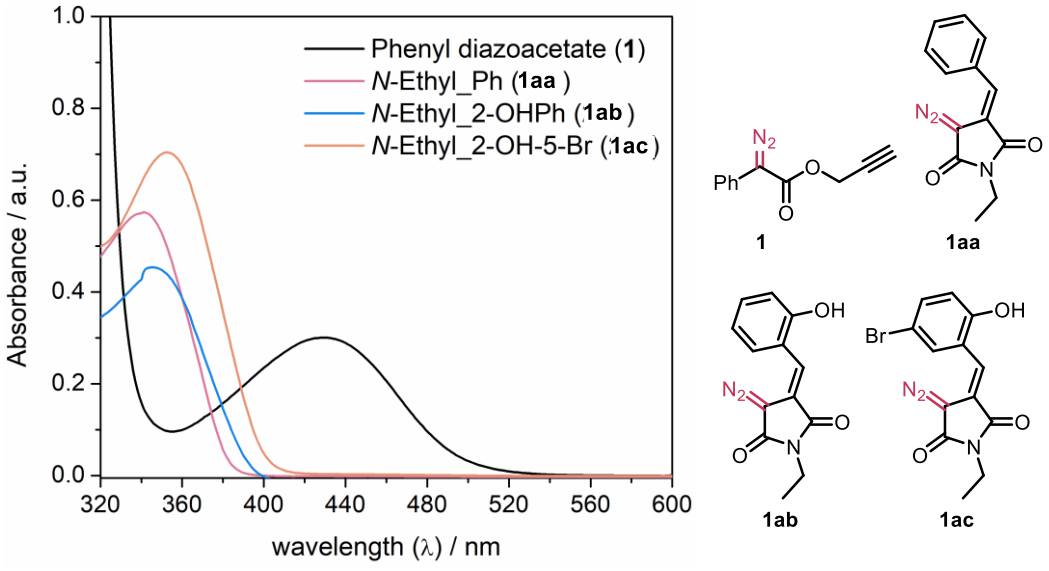


Figure 4B.2. Photochemical properties (UV-visible absorbance spectra) of diazo compounds (**1**-**1ac**) in DCM (c = 0.2 mM).

❖ *Synthetic Applications: Synthesis of chromenopyrroledione under photochemical condition*

2*H*-Chromene is a privileged scaffold and many compounds having this scaffold as core unit are known to elicit versatile biological profiles. Also these 2*H*-chromene derivatives have shown to have interesting optical properties and have been explored as fluorescence probes and photochromic compounds.[15] Chromeno[2,3-*c*]pyrrole-1,3(2*H*,3a*H*)-dione is a prime subfamily of 2*H*-chromenes having diverse biological properties such as antiproliferative activity,[16a] antitumor,[16b-c] antiulcer,[16d] antibacterial,[16e] TNF-α-inhibitory activity.[16f] Thus, the construction of this important subclass of 2*H*-chromene under metal-free conditions is highly desirable.

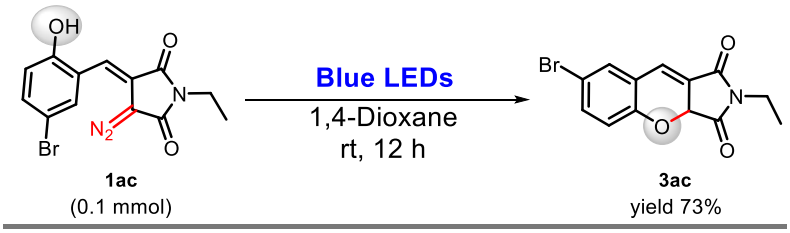
We envisioned that the subclass of 2*H*-chromenes could be directly synthesized starting from the *ortho*-OH modified diazo succinimides **1** in one-step. It is also very important to note that a few substituents such as halogens, long-chain alkyl etc. at the 6-C position of 2*H*-chromenes have significantly increased the biological activities of the 2*H*-chromene derivatives.[17a] Owing to the importance of these compounds and looking at the challenging task to generate triplet state carbene from vinyl diazo compounds we planned study in detail. We hypothesized that the visible light promoted intramolecular O–H insertion through the carbene by the decomposition of vinyl diazo compounds would lead to desired 2*H*-chromene derivatives.

❖ *Optimization studies for the intramolecular O–H functionalization*

In order to validate our hypothesis, we chose 5-bromo-2-hydroxyphenyl vinyl diazo succinimide **1ac** as a model substrate based on the initial UV-vis absorbance spectral studies for the intramolecular O–H functionalization in DCM under visible light (5 W Blue LEDs) at room temperature and under air (Table 4B.1, Entry 1). Gratifyingly, the compound **1ac** reacted and tolerated the initial reaction conditions well to furnish the desired product **3ac** albeit in modest yield (32%, Table 4B.1, Entry 1).

Based on the control experiment it has been proved that light as an energy source is absolutely necessary for the successful transformation as the desired product 3ac did not form in the absence of light (Table 4B.1, Entry 2). Also, the reaction in the absence of light while at an elevated temperature (60 ^{o}C) in acetonitrile did not afford the desired product even in trace thus suggesting that the thermal activation is not a driving force for this process (Table 4B.1, Entry 3). Further optimization studies revealed that the reaction under nitrogen atmosphere afforded the desired product **3ac** and thus indicated that reaction is not sensitive to air and inert atmosphere is not necessary for the smooth transformation (Table 4B.1, Entries 4-5). While the reaction in dry DCM afforded the desired product in relatively lower yield than the AR grade solvent (Table 4B.1, Entry 6).

Table 4B.1. Reaction optimization studies for the visible light-induced intramolecular O–H functionalization[a]



Entry	Deviations from tested conditions[a]	Yield[b] (%) of **3ac**
1	None	32 (28)[c]
2	No light	N.R.
3[d]	No light, CH_3CN, at 60 °C	N.R.
4	under N_2 atmosphere	28
5	under N_2 atmosphere (degassed)	30
6	dry DCM	15
7[e]	456 nm, 1,4-Dioxane, 12 h, 27 °C	65
8[e,f]	**456 nm, 1,4-Dioxane, 12 h, 27 °C**	**73**
9	UV light (370 nm) instead of blue LEDs	0

[a]**Tested reaction conditions**: alkylidene diazo succinimide **1ac** (0.1 mmol), A. R. grade DCM (c = 0.066 M), blue LEDs (5 W), under air, 25 °C, 24 h. [b]Yields of **3ac** were determined by ^{1}H NMR spectroscopic analyses of the reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. [c]Yield of isolated products after column chromatography: given in the parenthesis. [d]A. R. grade CH_3CN was used. [e]A. R. grade 1,4-Dioxane was used. [f]Substrate concentration (c = 0.04 M) was used.

We observed that the reactions take place effectively under both low as well as high intensity of blue light. Later the vinyl diazo succinimide **1ac** reacted smoothly under the irradiation of blue LEDs in 1,4-dioxane at room temperature to afford the desired product **3ac** in moderate yield (65% yield, Table 4B.1, Entry 7). Interestingly, later we have also observed that an intriguing high reaction efficiency in a low concentrated solution (c = 0.04 M in 0.1 mmol scale) in 1,4-dioxane under blue light irradiation (456 nm) for 12 h to afford the desired product **3ac** in 73% yield (Table 4B.1, Entry 8). However, the reaction under the irradiation of UV light (370 nm) did not furnish the desired product **3ac** in even in trace even though the starting material **2ac** was completely consumed (Table 4B.1, Entry 9).

Based on the exhaustive screening the vinyl diazo succinimide **1ac** (1.0 equiv.) in 1,4-dioxane (lower concentration, c = 0.04 M in 0.1 mmol scale) under irradiation of visible light (Blue LEDs, 456 nm) at room temperature in 12 h proved to be optimized reaction conditions to obtain the desired product **3ac** in good yield.

❖ *Substrate Scope studies*

Having obtained the optimization reaction conditions, we further embarked on the synthesis of diverse substrates for the generality and practicality of this transformation. In this regard, we synthesized various aryl-substituted diazosuccinimides **1ac-1aj, 1ak, 1al** as well as different *N*-substituted 2-hydroxyphenyl vinyl diazosuccinimides **1bc-1kc** following the literature procedure[11a-b] (Table 4B.2).

To begin with we treated different *N*-substituted 5-bromo-2-hydroxybenzylidene diazosuccinimides (**1bc**–**1kc**) under optimized reaction conditions to afford the corresponding desired 2H-chromene products (**3bc**–**3kc**) in moderate to good yields (up to 68%, see Table 4B.2). We observed that all the *N*-alkyl substituted diazosuccinimides (**1bc**–**1fc**) under the optimized reaction conditions afforded the corresponding desired products (**3bc**–**3fc**) in moderate to good yields (up to 68%). While the *N*-aryl substituted diazosuccinimides having electron donating, deactivating and withdrawing group as phenyl ring afforded the desired

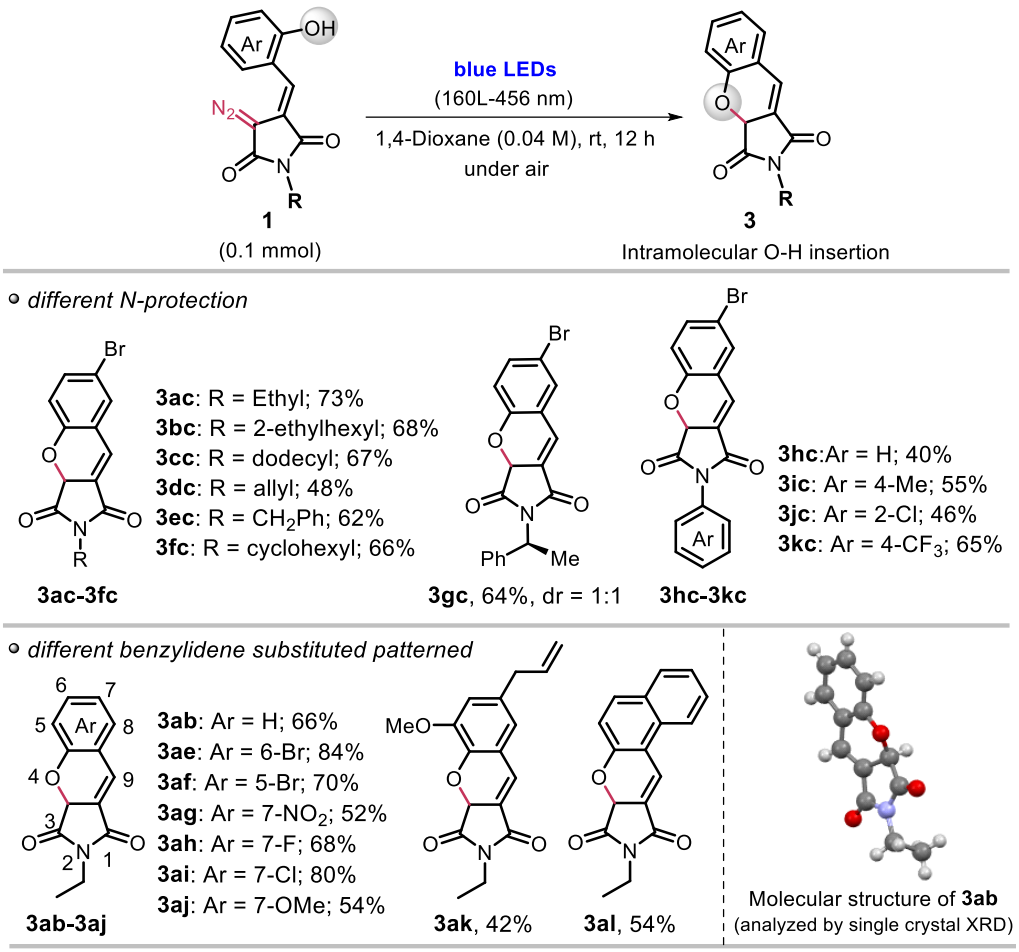


Table 4B.2. Studies on the intramolecular O–H functionalization with *N*-substituted as well different substituents at the phenyl ring (benzylidene) of vinyl diazo succinimides

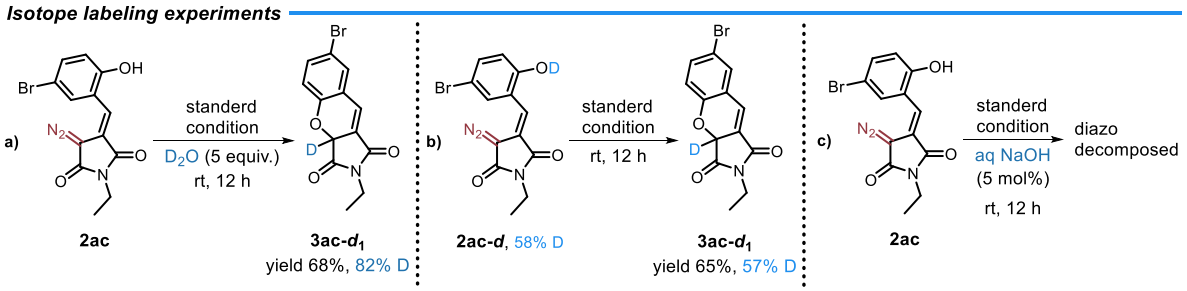
products in relatively modest to moderate yields.

Later, an attempt to synthesize the enantioselective 2*H*-chromene derivative we explored the *N*-(*S*)-1-phenylethyl as protecting group as well as a chiral auxiliary on *N*-protected vinyl diazo succinimides. The reaction of **1gc** under the optimized reaction conditions underwent the desired O–H functionalization to furnish the desired product **3gc** however in low diastereoselectivity (d.r. = 1:1) (64% yield, Table 4B.2). Later, we synthesized a few vinyl (arylidene) diazo succinimides having different substituents on the phenyl group of 2-hydroxybenzylidene ring (**1ab**–**1ak**). Gratifyingly, these vinyl diazo succinimides (**1ab**–**1ak**) under the optimized reaction conditions reacted smoothly to afford the corresponding desired 2H-chromene products (**3ab**–**3ak**) in moderate to good yields (up to 80%, Table 4B.2). The 2-hydroxynaphthalene substituted diazo succinimide **1al** also furnished the corresponding desired product **3al** in moderate yield (in 54% yield). The molecular structure and geometric

arrangements of the 2*H*-Chromene **3ab** obtained was unambiguously determined by the single-crystal X-ray diffraction analysis.[20]

❖ *Mechanistic investigations*

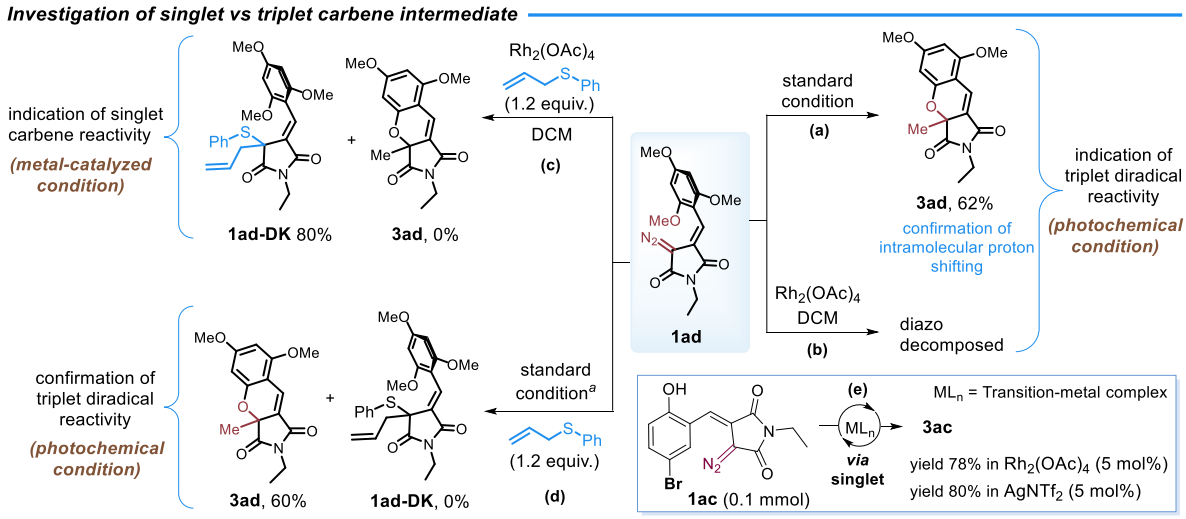
After having demonstrated protocol with generality we switched our attention towards to unravel the mechanistic pathway of this transformation. There could be two plausible pathways for this intramolecular O–H functionalization reaction viz. the photoinduced proton transfer process (PPT) or traditional photolysis of diazo succinimide. In order to validate and prove this, we performed various controlled experiments (Scheme 4B.11). To begin with we studied the labelling experiments to have evidence of the proton source in the reaction. The diazo succinimide **1ec** upon illumination with blue LEDs (456 nm) under standard optimized reaction condition in presence of D_2O (5 equiv.). We observed the potential deuterium incorporation (83%) in the desired deuterated product **3ec-*d*$_1$** [Scheme 4B.11(a)]. This result clearly indicated that the proton source may be either from the moisture present in solvent or from the deuterium exchange with phenolic hydroxy group (-OH) followed by the intramolecular D^+ transfer. In addition, pre-installed deuterated *ortho*-OH substituted diazo succinimide **1ac-*d*$_1$** (58% D incorporated) under blue light irradiation under standard reaction conditions afforded the desired product **3ac-*d*$_1$** with deuterium incorporation exclusively (57% D incorporation) [Scheme 4B.11(b)]. This result clearly further indicated that proton transfer takes placed intramolecularly from the phenolic -OH group of the substrate and the proton shift does not happen from moisture present in the solvent. Moreover, the addition of NaOH (5 mol%) reaction mixture while maintaining other standard optimized reaction conditions completely prevented the product formation and we observed that the vinyl diazo compound decomposed over 12 h [Scheme 4B.11(c)]. We reasoned that this might have happened due to the *in-situ* formation of sodium phenolate (sodium salt of phenoxide ion) and lack of proton. Based on this result we can't rule out the possible photoinduced proton transfer process (PPT) pathway though it is not certain (see Experimental Section 4B.8.2 for details).



Scheme 4B.11. Labeling experiments.

In order to probe the mechanistic insight further, we carried out the transformation using *ortho*-methoxy derivative of arylidene diazo succinimide **1ad (**-OMe instead of free OH group) at the standard optimized reaction condition [Scheme 4B.13(a)]. Surprisingly, we obtained an unanticipated and yet an interesting product **3ad** via an intramolecular 1,6-methyl group shift. This unambiguously confirmed that the hydrogen shift occurs intramolecularly from the *ortho*-OH group of the diazo substrate **1ad** and not from the moisture present in the solvent. It is very interesting as well astonishing that the methylchromeno[2,3-*c*]pyrrole-1,3(2*H*,3a*H*)-dione **3ad** formation through 1,6-methyl-shift indeed ruled out the possibility of PPT pathway during the course of the reaction mechanism. It is important to note that the product **3ad** can be formed via different reactive intermediates. The product **3ad** may form either from the singlet carbene intermediate or *via* the ylide formation or it could also be possible to achieve **3ab** *via* triplet diradical intermediate as well.

In order to have deeper understanding and clear picture on the possible reactive intermediate and type of carbene spin state, we planned to perform few more experiments. To begin with we performed the reaction of **1ad** in presence of dirhodium acetate in DCM [Scheme 4B.12(b)]. The reaction did not work and the diazo succinimide **2ad** was decomposed thus indicating that reaction does not involve any traditional singlet carbene. It is well established in the literature that $Rh_2(OAc)_4$-catalyzed reaction usually undergo *via* a traditional singlet carbene intermediate (through the formation of reactive rhodium carbenoid species).[17] This result in way clearly supported that the title reaction [4B.12(b)] might be undergoing *via* a triplet carbene intermediate.



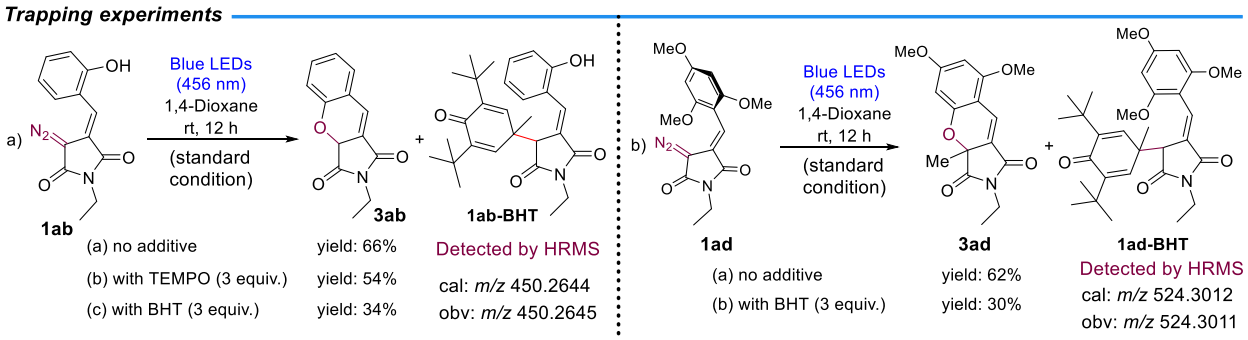
Standard condition: alkylidene diazo succinimide **1ac** (0.1 mmol), A. R. grade 1,4-Dioxane (c = 0.04 M), blue LEDs (456 nm), under air, 25 °C, 12 h.

Scheme 4B.12. Investigation of singlet vs triplet carbene intermediate.

To gain further insight into it, we examined the capability of **1ad** to elicit the singlet carbene reactivity under transition-metal catalysis. In this regard, we performed the reaction of **1ad** in presence of allyl sulfide (a well-known reagent for the Doyle–Kirmse reaction under metal catalysis[18] as well as photochemical condition *via* singlet carbene[19]) and dirhodium acetate as well as under standard optimized reaction conditions under the irradiation of light [Scheme 4B.12 (c), (d)]. The reaction of **1ad** in presence of allyl sulfide and dirhodium acetate led to the formation of Doyle–Kirmse rearrangement product **1ad-DK** in very good yield and the 1,6-methyl shift product: 3a-methylchromeno[2,3-*c*]pyrrole-1,3(2*H*,3a*H*)-dione **3ad** was not detected even in trace [Scheme 4B.13 (c)]. This result clearly proved that the diazo compound **1ad** afforded corresponding **1ad-DK** via singlet carbene intermediate. This distinct reactivity pattern of **1ad** under the photochemical as well and the metal-catalyzed reaction condition further supported and demonstrated that the vinyl diazo succinimides have a tunable carbene reactivity of singlet vs triplet under different reaction conditions. This was further supported by the reaction of **1ad** and allyl sulfide under standard optimized reaction condition under blue light irradiation (photochemical condition instead of dirhoidium catalysis) successfully furnished the desired product: 3a-methylchromeno[2,3-*c*]pyrrole-1,3(2*H*,3a*H*)-dione **3ad** in 60% yield and the Doyle–Kirmse rearrangement product **1ad-DK** was not detected either [Scheme 4B.12(d)]. These results unambiguously proved that under the photochemical condition, the diazo compound **1ad** undergoes carbene transfer reactions *via* triplet carbene spin state, and in turn **1ad** undergoes singlet carbene transfer reaction when reacted with transition-metal catalyst. Based on these systematic and exhaustive control experiments it has been confirmed that the photoinduced intramolecular O–H functionalization reaction undergoes *via* triplet spin state, whereas under transition-metal catalysis singlet carbene pathway favoured [see Scheme 4B.12(d) and (e) for further comparison and similar result].

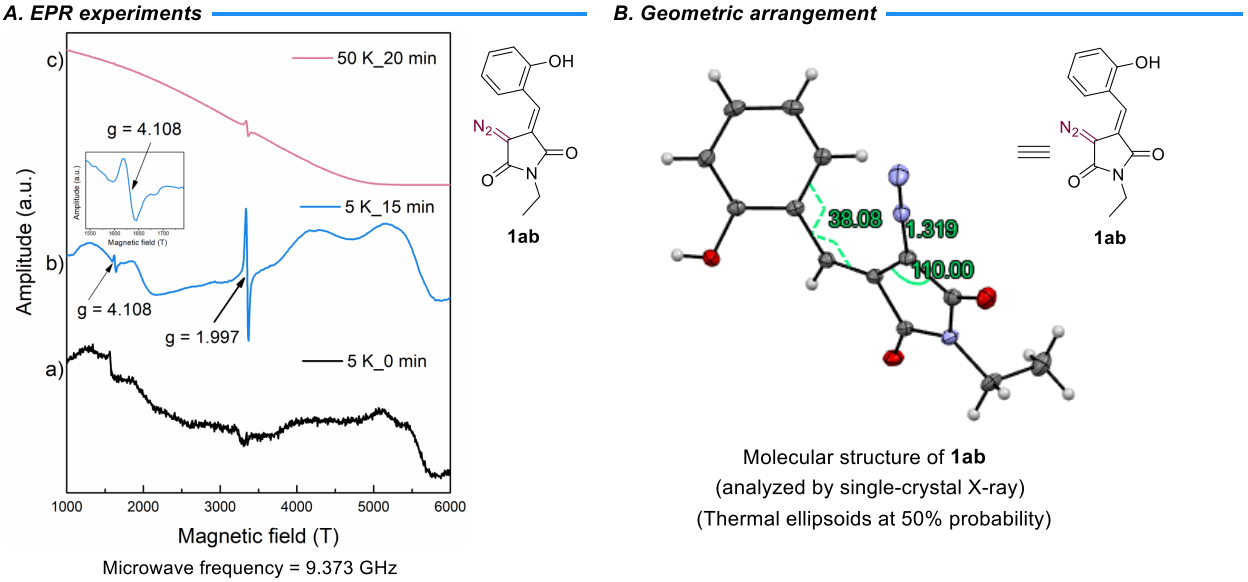
Later, the diradical nature of the mechanism was verified by the control experiments of **1ab** and **1ad** in presence of TEMPO and BHT under blue light irradiation [Scheme 4B.13(a)-(b)] and the corresponding desired products **3ab** and **3ad** respectively were formed in diminished yields. The reactions did not completely stop by the radical quenchers probably due to the reason that intramolecular reaction is relatively faster than the intermolecular one.

Moreover, BHT trapped radical intermediates (**1ab-BHT** and **1ad-BHT** respectively) have been detected using HRMS (ESI TOF). These results clearly supported the formation of a radical species during the course of the reaction.



Scheme 4B.13. Radical trapping experiments.

In order to confirm the ability of diazo succinimide **1ab** to self-generate the triplet carbene (***TC***), we measured the electron paramagnetic resonance (EPR) spectrum of the ***TC*** precursor in a frozen matrix of 1,4-dioxane (1.0 × 10−3 mM) at 5 K (Scheme 4B.15A). After irradiation with blue LEDs (λ = 456 nm) for 15 min, new peaks appeared at 1631 T and 3354 T which is clearly associated with the ***TC***. As the temperature increased to 50 K, the intensities of the EPR peaks gradually decreased after 30 minutes. The molecular structure and geometric arrangements of the diazo succinimide (**1ab**) was unambiguously determined using single-crystal X-ray analysis. The bond angle of ∠C–C(N_2)–C is determined as 110° with a dihedral angle q ~ 38° at the *s-cis* conformation occurring from the orientation of benzylidene ring (Scheme 4B.14B).[20]



Scheme 4B.14. A. EPR experiments [(a) before irradiation of 456 nm; (b) after irradiation with 456 nm diode for 15 minutes in 5 K; (c) gradual increase in temperature from 5 K to 50 K keeping in dark and recorded after 5 minutes] and B. studies of geometrical arrangement of diazo succinimide.

❖ *Computational DFT Caluculations:*

The starting diazo compound was optimized at B3LYP/6-31G(d) level of theory. The excitation energies of the lowest excited states of the azo compound are given in Table 4B.3. It can be noticed that the S2 state is optically bright and there are two triplet states (T3 and T4) that are in the vicinity of the bright state. The spin orbit couplings between S2-T3 and S2-T4 are 8.11 and 11.57 cm^{-1} respectively. This shows that a transition from singlet to triplet state in this situation can be quite favorable.

State	Vertical excitation energy (eV)	Oscillator strength
T1	2.14	-
T2	2.22	-
S1	2.56	0.00
T3	3.04	-
T4	3.22	-
S2	3.35	0.17
S3	3.42	0.03
S4	3.80	0.15

Table 4B.3: TDDFT excitation energies are shown in this table for the diazo compound.

The rest of the calculations are performed on the N_2-abstracted structures to validate the mechanism of rearrangement. Figure 4B.3 shows the potential energy surface along the rearrangement reaction and it can be noticed that the activation energy is extremely low (~ 1 kcal/mol) for the forward reaction. It should be noted that for computational ease we have calculated the rearrangement of the H substituted reaction and we expect qualitatively similar pathways to be feasible for alkyl group substitution.

Further validation for the proposed mechanism and triplet state mediated reaction can be obtained from the relative stability of the final product in its triplet form (see Table 4B.4). The reason for the low activation energy barrier can be attributed to the singly occupied molecular orbitals (SOMOs) of the reactant and TS which are similar in energy and nature (see Figure 4B.5).

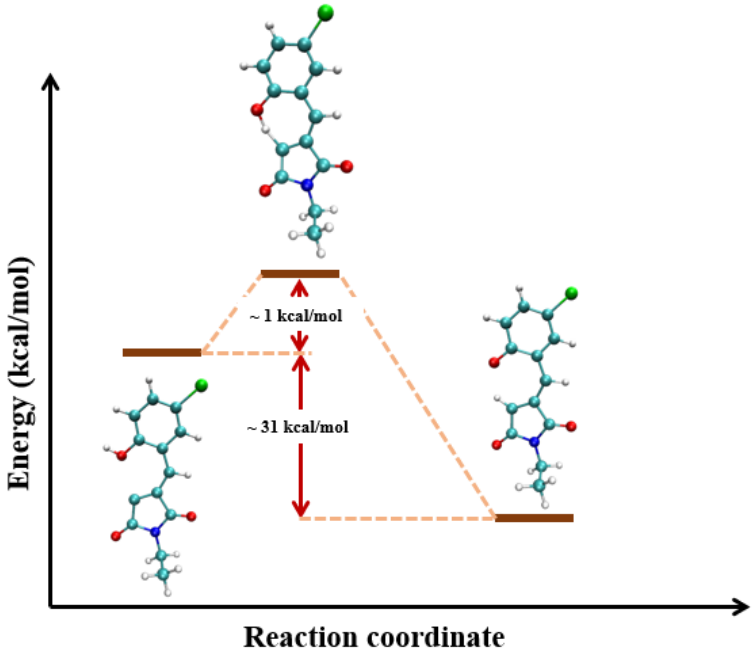


Figure 4B.3: Potential energy surface of the proposed reaction mechanism. It can be seen that there is a minimal barrier for the reactant to cross. The product is also relatively stable. Hence the reaction is very facile on the triplet surface.

Spin state	Energy (in hartree)
Singlet	-3355.5633
Triplet	-3355.6120

Table 4B.4. The energies of the triplet and singlet states of the initial reactant species.

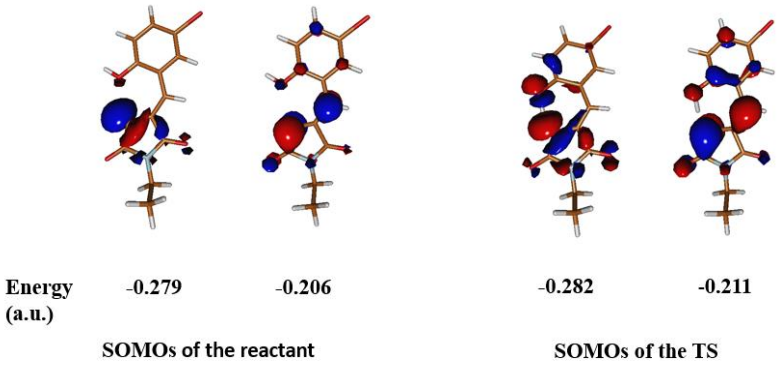
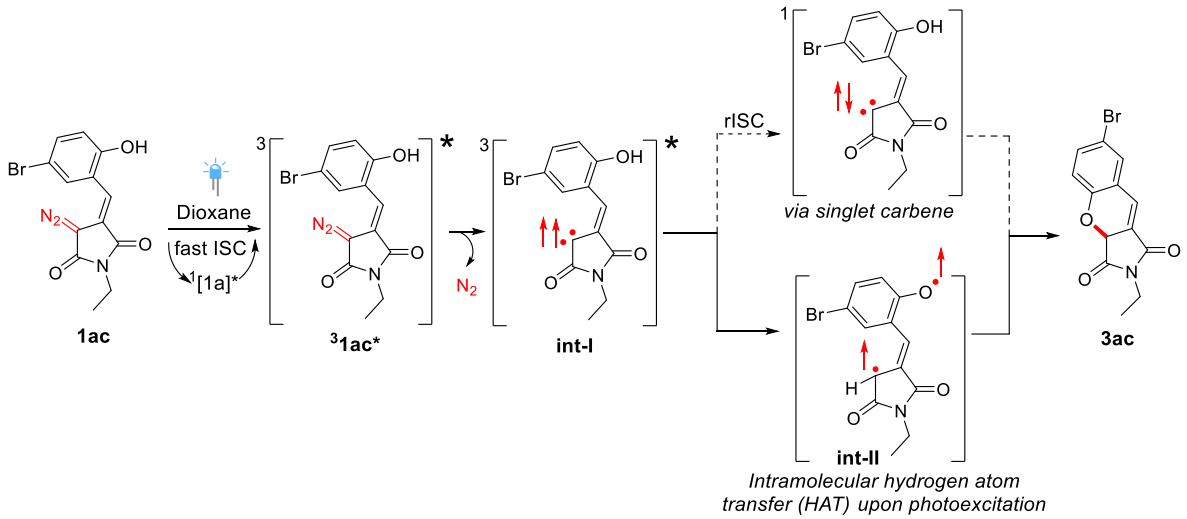


Figure 4B.5. Molecular orbitals of the reactant and the TS along with their energies.

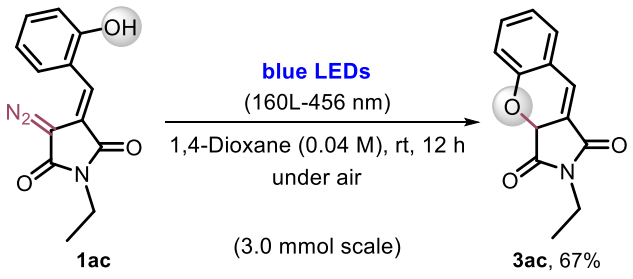
On the basis of a series of control experiments and other experimental findings, a most plausible mechanistic pathway for the intramolecular O–H functionalization has been depicted in Scheme 4B.15.



Scheme 4B.15. Plausible reaction mechanism.

The compound vinyl diazo succinimide **1ac** upon irradiation with blue light directly excited to photoinduced ground-state triplet carbene generation (via faster ISC) ^{3}**1ac*** which eventually leads to the formation of intermediate **int-I** by the exclusion of dinitrogen. This, intermediate int-I further undergoes an intramolecular 1,6-hydrogen atom transfer at the expense of O–H bond breaking and a new C–H bond formation to generate a closed-shell diradical intermediate **int-II**. This intermediate finally furnishes the desired 2H-chromene product **3ac**.

In order to further enhance the usability and practicability of this protocol, a gram-scale reaction of 5-bromo-2-hydroxyphenyl vinyl diazosuccinimide **1ab** was carried out under the standard optimized reaction conditions (Scheme 4B.16). The reaction proceeded smoothly and the corresponding desired product **3ab** was obtained in 67% yield (0.93 g).



Scheme 4B.16. Gram-scale synthesis of chromenopyrroledione.

4B.3. Conclusions

We have successfully demonstrated that vinyl diazo succinimide as a new class of bench-stable diazo compound that is susceptible to undergo direct photo-generation to generate ground-state triplet carbene. We have shown that this class of diazo compounds are capable of generating the ground-state triplet carbene via photolysis without the assistance or any requirement of photosensitizer under visible light irradiation. The distinct electronic structure, as well as geometrical arrangement of diazo succinimide make it a unique scaffold unlike the other diazoalkanes[7a-b] that have been reported to be unstable. This representative diazo compound now enables as the entry point for the further enhancing the fundamental understanding. Though high spin ground state species possess huge applications in magnetic materials,[21] their synthetic applications are rare due to rapid equilibrium between singlet vs triplet prevent their separation.[22] We utilized the new-finding of photogenerated ground-state triplet arylidene succinimide into organic synthesis to achieve direct intramolecular O–H functionalization for the efficient synthesis of biologically important chromeno[2,3-*c*]pyrrole-1,3(2*H*,3a*H*)-dione, a prime subfamily of 2*H*-Chromenes. A series of control experiments and systematic experimental findings have proved that that transformation proceeds via photoinduced hydrogen atom transfer (HAT) pathway and it occurs throughout during the course of the reaction. This result has proved a new concept of group-transfer radical cyclization (GTRC) process.

4B.4. Experimental Section – General Information:

Reagent Information: All reactions were carried out with AR grade, distilled and dried solvents using oven-dried glassware under dry Argon atmosphere, unless otherwise stated. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm) with detection by UV light. The column chromatographic purification of the products was carried out by using silica gel (60-120 mesh). Petroleum ether and ethyl acetate mixture was used as gradient elution for column chromatography.

Analytical Information: All isolated compounds were characterized by ^{1}H NMR and $^{13}C\{H\}$ NMR spectra. Nuclear Magnetic Resonance spectra were recorded in $CDCl_3$ and in DMSO-d_6.

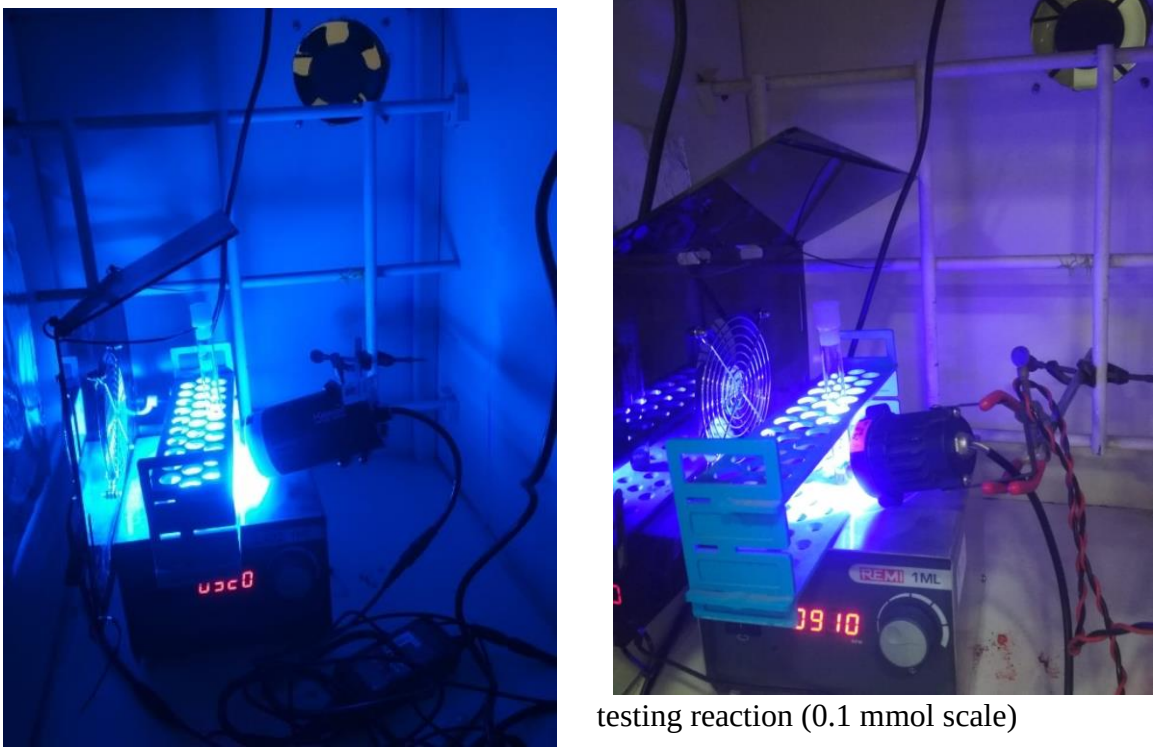
The NMR spectra were recorded using tetramethylsilane (TMS) as the internal standard. ^{1}H NMR spectra were recorded at 400 MHz and $^{13}C\{H\}$ NMR spectra were recorded at 100/150 MHz (Bruker and Jeol), unless otherwise noted. Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) and from DMSO-d_6 (δ = 2.5 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.16 ppm) and DMSO-d_6 resonance (δ = 39.52 ppm) for $^{13}C\{H\}$ NMR spectroscopy. For ^{1}H NMR, data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*) are given in Hz and integration. ^{13}C NMR spectra were recorded with complete proton decoupling. ^{19}F NMR spectra were recorded at 377 MHz. Mass samples were analyzed by high resolution mass spectrometry (HRMS) using ESI TOF. Melting points were measured in an open glass capillary and values are uncorrected. Single-crystal X-ray data were collected on a Bruker SMART APEX four-circle diffractometer equipped with a CMOS photon 100 detector (Bruker Systems Inc.) and Microfocus (IμS) using Mo Kα radiation (0.71073 Å). UV-Vis absorption spectra were recorded on UV-1900 UV-Vis Spectrophotometer.

Computational details: The starting azo compound was optimized at B3LYP/6-31G(d) level of theory using Q-Chem quantum chemistry software. This structure was further used for TDDFT calculations to obtain the singlet and triplet excited states. The N_2-abstracted structure was optimized at the triplet state (based on EPR data). The TS and final rearranged products were also optimized at the same levels of theory using Gaussian09 software to find the reaction barriers. Spin flip TDDFT calculations were also carried out to ascertain the relative stabilities of the singlet and triplet states.

Photoreactor set up:

0.1 mmol scale synthesis of 2*H*-Chromenes **3** were performed on a locally designed and built photoreactor provided with the Kessil blue lamps with an emission maximum at 456 nm (intensity 50%) (Figure 1) from ~ 2 cm distance. The reaction mixture was cooled with two fans, while maintaining temperature 27 °C.

Experiment with irradiation on UV light (370 nm) was carried out with the Kessil light with emission maximum at 370 nm (intensity 50%) (Figure 1) from ~ 2 cm distance. The reaction mixture was cooled with two fans, while maintaining temperature 27 °C.



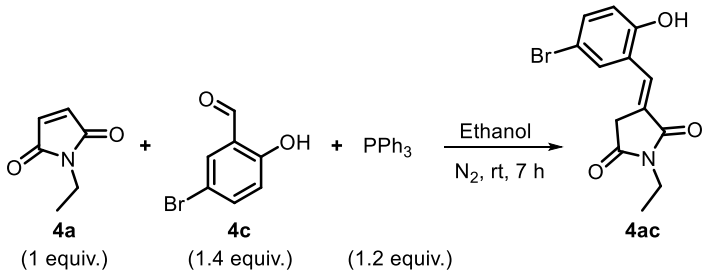
Optimized light source: 0.1 mmol scale testing reaction (0.1 mmol scale)

Figure 4B.3. Locally Designed and built photoreactor with a fan for cooling.

4B.5. Experimental Procedures:

4B.5.1. Preparation of Starting Materials:

4B.5.1.1. General procedure-A for the synthesis of vinyl succinimides:

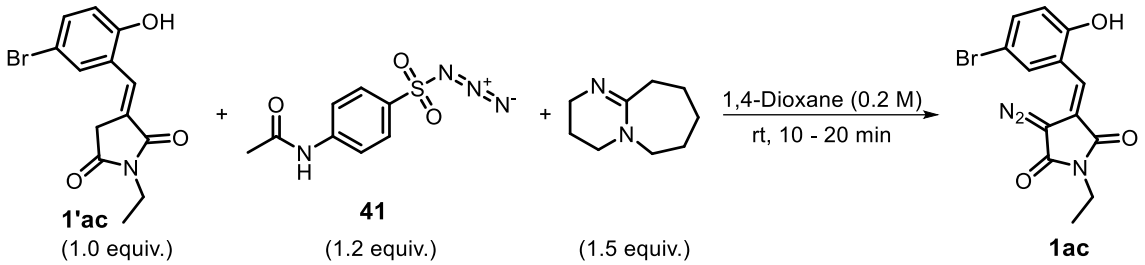


To the stirred solution of *N*-ethyl maleimide (0.5 g, 1.0 equiv., 4.0 mmol) in ethanol (20 mL) was added triphenylphosphine (1.26 g, 1.2 equiv., 4.8 mmol) portion-wise at room temperature under N_2 atmosphere. The initial pink coloured reaction mixture slowly turned to white suspension over a period of 10-15 min of initial stirring. After continuous stirring over 30 min, 5-bromosalicyladehyde (1.12 g, 1.4 equiv., 6.0 mmol) was added in one portion into the reaction mixture at room temperature. During this addition, the white suspension slowly

turned into clear solution. The reaction mixture was allowed to stir for 6 h. Upon completion of the reaction (monitored by TLC), the white solid formed during the course of the reaction was filtered through a sintered glass funnel and was washed with ethanol (6 mL x 2). The crude product **6a** was obtained as white solid (0.990 g, 80% yield) and this was used for the next step without any further purification.[1]

4B.5.1.2. General procedure-B for the synthesis of vinyl diazosuccinimides 1:

❖ **Standard reaction conditions for the synthesis of hydroxy-substituted vinyl diazosuccinimides**[a]



Optimization:

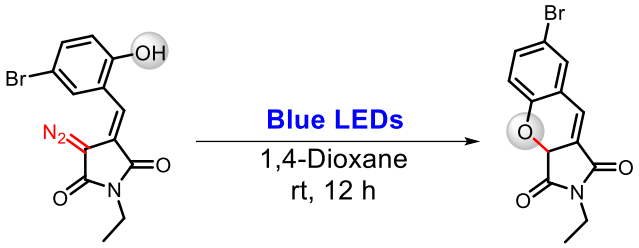
Entry	Variation from the standard reaction conditions	Yield[b] (%)
1	**None**	**91**
2	In CH_3CN (0.1 M)	85
3	In THF	75
4	In DCM (0.1 M)	80
5	In DMF	35
6	In DMSO	30
7	In CH_3CN (0.1 M) at 0 °C	85

[a]**Reaction conditions**: unless otherwise noted, in a solution of **6a** (0.930 g, 1.0 equiv., 3.0 mmol) and 4-acetamidobenzenesulfonyl azide (0.865 g, 1.2 equiv., 3.6 mmol) in 1,4-Dioxane (0.2 M) were added DBU (0.7 mL, 1.5 equiv., 4.5 mmol) at room temperature. [b]yield of isolated product.

To the stirred solution of (*E*)-3-(5-bromo-2-hydroxybenzylidene)-1-ethylpyrrolidine-2,5-dione **4ac** (0.3 g, 1.0 equiv., 0.967 mmol) in 20 mL 1,4-dioxane, were added 4-acetamidobenzenesulfonyl azide (0.279 g, 1.2 equiv., 1.16 mmol) and DBU (0.220 mL, 1.5 equiv., 1.45 mmol) at room temperature under inert atmosphere. The reaction mixture was stirred for 10 - 20 minute and the completion of the reaction was monitored by TLC. The reaction mixture was then quenched with saturated solution of NH_4Cl and the product was extracted with ethyl acetate (20 mL x 2). The combined organic layers were washed with brine solution and dried over anhydrous Na_2SO_4. The extract was filtered and evaporated under

reduced pressure. The crude product was purified using column chromatography over silica gel to afford (*E*)-3-(5-bromo-2-hydroxybenzylidene)-4-diazo-1-ethylpyrrolidine-2,5-dione **2ac** as orange solid (0.297 g, 91% yield).

4B.5.2. General procedure-C for the photoinduced O–H functionalization:



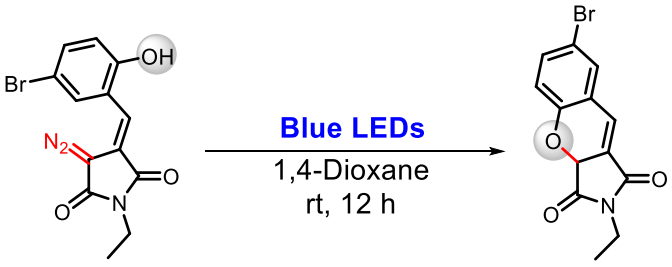
1ac
(0.1 mmol)

3ac
yield 73%

An oven dried test tube equipped with a stirring bar was added diazo succinimide **2ac** (0.1 mmol, 34 mg) in 2.5 mL of 1,4-dioxane (AR grade) and sealed with a rubber septum. The reaction mixture was placed at around ~ 2 cm apart from the Kessil lamps (Blue LEDs, 456 nm) for 12 h at room temperature (27 °C, temperature was monitored by thermometer). After, completion of the reaction (TLC), the crude reaction mixture was concentrated in vacuo and purified by column chromatography to afford 22.6 mg (yield = 73%) of product **3ac** as white solid.

4B.6. Optimization details:

4B.6.1 Model reaction:



1ac
(0.1 mmol)

3ac
yield 73%

Optimal reaction conditions: Diazo succinimide **1ac** (0.1 mmol), 1,4-Dioxane (c = 0.04 M), blue LEDs (456 nm), under air, 27 °C, 12 h.

4B.6.2 Background reactions:

Entry	Deviations from tested conditions[a]	Yield[b] (%) of **2a**
1	**None**	**32 (28)[c]**
2	No light	N.R.
3	under N_2 atmosphere	28
4	under N_2 atmosphere (degassed)	30
5	No light, CH_3CN, at 60 °C	N.R.
6	dry DCM	15
7	UV light (370 nm) instead of blue LEDs	0

Tested reaction conditions: Diazo succinimide **1ac** (0.1 mmol), a. r. grade DCM (c = 0.066 M), blue LEDs (5 W), under air, 25 °C, 24 h. [b]Yields of **3ac** were determined by ^{1}H NMR spectroscopic analyses of the reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. [c]Isolated yield in the parenthesis.

4B.6.3 Influence of light intensity:

Entry	Light power	Time	Yield[b] (%)
1	11 W	12 h	32
2	20 nm	12 h	34
3	40 nm	12 h	34

Reaction conditions: Diazo succinimide **1ac** (0.1 mmol), a.r. grade DCM (c = 0.066 M), blue light power, under air, 27 °C. [b]Yields of **3ac** were determined by ^{1}H NMR spectroscopic analyses of the reaction mixture using 1,3,5-trimethoxybenzene as the internal standard.

4B.6.4. Influence of the light source:

Entry	Light source	Time	Yield[b] (%)	Entry	Light source	Time	Yield[b] (%)
1	370 nm	24 h	0	**4**	**456 nm**	**12 h**	**57**
2	427 nm	24 h	0	5	467 nm	12 h	35
3	440 nm	16 h	50	6	525 nm	12 h	18

Reaction conditions: Diazo succinimide **1ac** (0.1 mmol), a.r. grade DCM (c = 0.066 M), light source, under air, 27 °C. [b]Yields of **3ac** were determined by ^{1}H NMR spectroscopic analyses of the reaction mixture using 1,3,5-trimethoxybenzene as the internal standard.

4B.6.5. Influence of the solvent:

Entry	Light source	Time	Yield[b] (%)	Entry	Light source	Time	Yield[b] (%)
1	$CHCl_3$	24 h	50	**6**	**1,4-Dioxane**	**12 h**	**65**
2	Toluene	24 h	40	7	CH_3CN	12 h	60
3	Fluorobenzene	24 h	42	8	$ClCH_2CH_2Cl$	12 h	35
4	Chlorobenzene	24 h	45	9	DMF	12 h	32
5	THF	16 h	62	10	DMSO	12 h	35

Reaction conditions: Diazo succinimide **1ac** (0.1 mmol), a.r. grade solvent (c = 0.066 M), blue LEDs (456 nm), under air, 27 °C. [b]Yields of **3ac** were determined by ^{1}H NMR spectroscopic analyses of the reaction mixture using 1,3,5-trimethoxybenzene as the internal standard.

4B.6.6. Influence of the additives:

Entry	Additives	Time	Yield[b] (%)	Entry	Additives	Time	Yield[b] (%)
1	K_2CO_3	24 h	<5	4	TfOH	12 h	63
2	Et_3N	24 h	<5	5	TFE	12 h	65
3	AcOH	12 h	55	6	H_2O	12 h	63

Reaction conditions: Diazo succinimide **1ac** (0.1 mmol), additive (5.0 mol%) a. r. grade 1,4-Dioxane (c = 0.066 M), blue LEDs (456 nm), under air, 27 °C. [b]Yields of **2a** were determined by ^{1}H NMR spectroscopic analyses of the reaction mixture using 1,3,5-trimethoxybenzene as the internal standard.

4B.6.7. Influence of the substrate concentration:

Entry	Concentration	Time	Yield[b] (%)	Entry	Concentration	Time	Yield[b] (%)
1	0.1 M	12 h	65	**3**	**0.04 M**	**12 h**	**73**
2	0.05 M	12 h	62	4	0.033 M	12 h	60

Reaction conditions: Diazo succinimide **1ac** (0.1 mmol), a. r. grade 1,4-Dioxane (c = x M), blue LEDs (456 nm), under air, 27 °C. [b]Yields of **3ac** were determined by ^{1}H NMR spectroscopic analyses of the reaction mixture using 1,3,5-trimethoxybenzene as the internal standard.

4B.6.8. Influence of reaction time:

Entry	Time	Yield[b] (%)	Entry	Additives	Yield[b] (%)
1	15 min	<5	4	4 h	42
2	30 min	7	**5**	12 h	72
3	1 h	12	6	24 h	72

Reaction conditions: Diazo succinimide **1ac** (0.1 mmol), a. r. grade 1,4-Dioxane (c = x M), blue LEDs (456 nm), under air, 27 °C, x h. [b]Yields of **3ac** were determined by ^{1}H NMR spectroscopic analyses of the reaction mixture using 1,3,5-trimethoxybenzene as the internal standard.

4B.7. Mechanistic studies:

4B.7.1. UV-Visible studies:

UV-Visible studies were performed at room temperature in 1,4-dioxane.

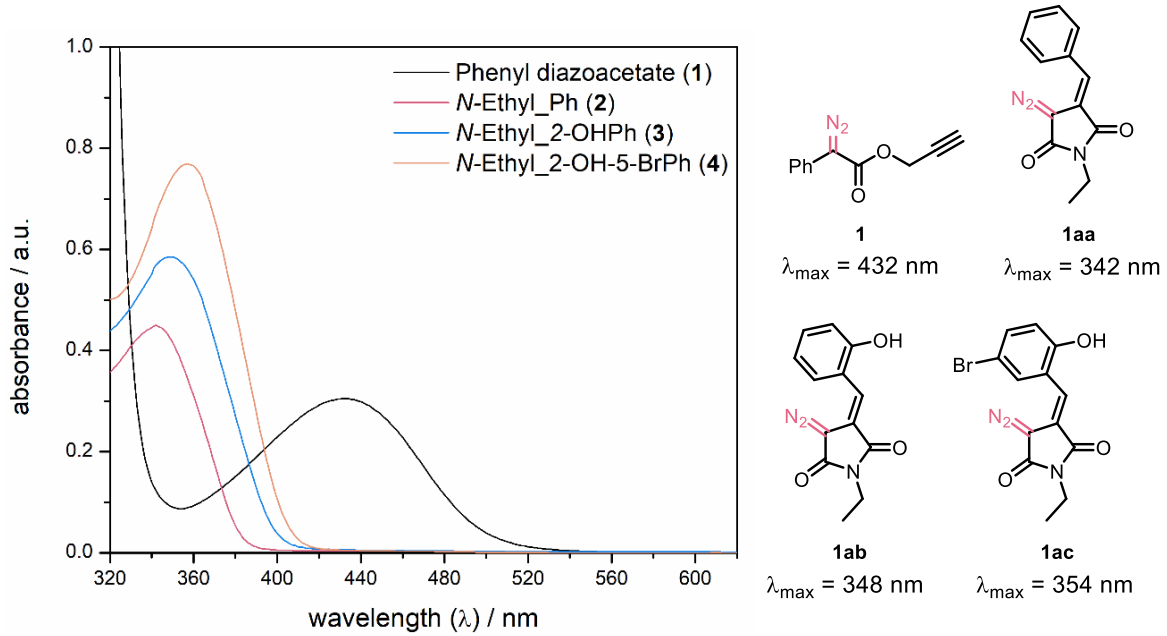


Figure 4B.4.1. UV-Vis absorbance spectra of diazo compounds **1**, **2**, **3**, **4** in 1,4-dioxane (all in c = 0.2 mM).

❖ UV-Vis absorbance spectra of diazo compound **4** in different solvents at room temperature (all in c = 0.2 mM)

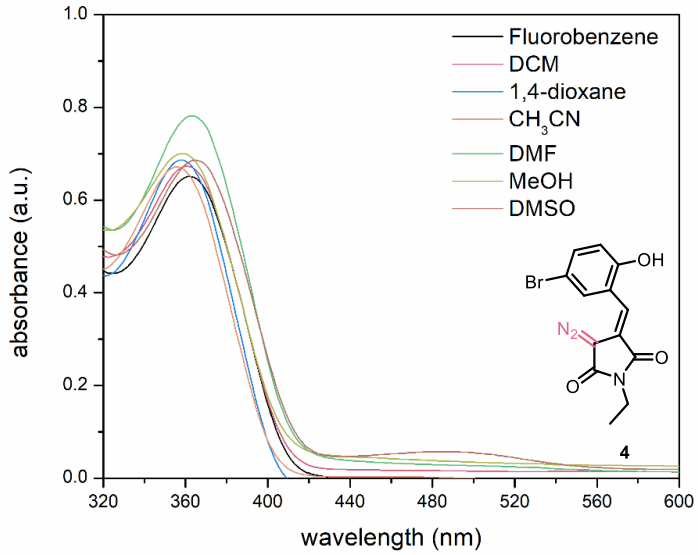


Figure 4B.4.2. UV-Vis absorbance spectra of diazo compounds **4** in different solvents (all in c = 0.2 mM) at room temperature.

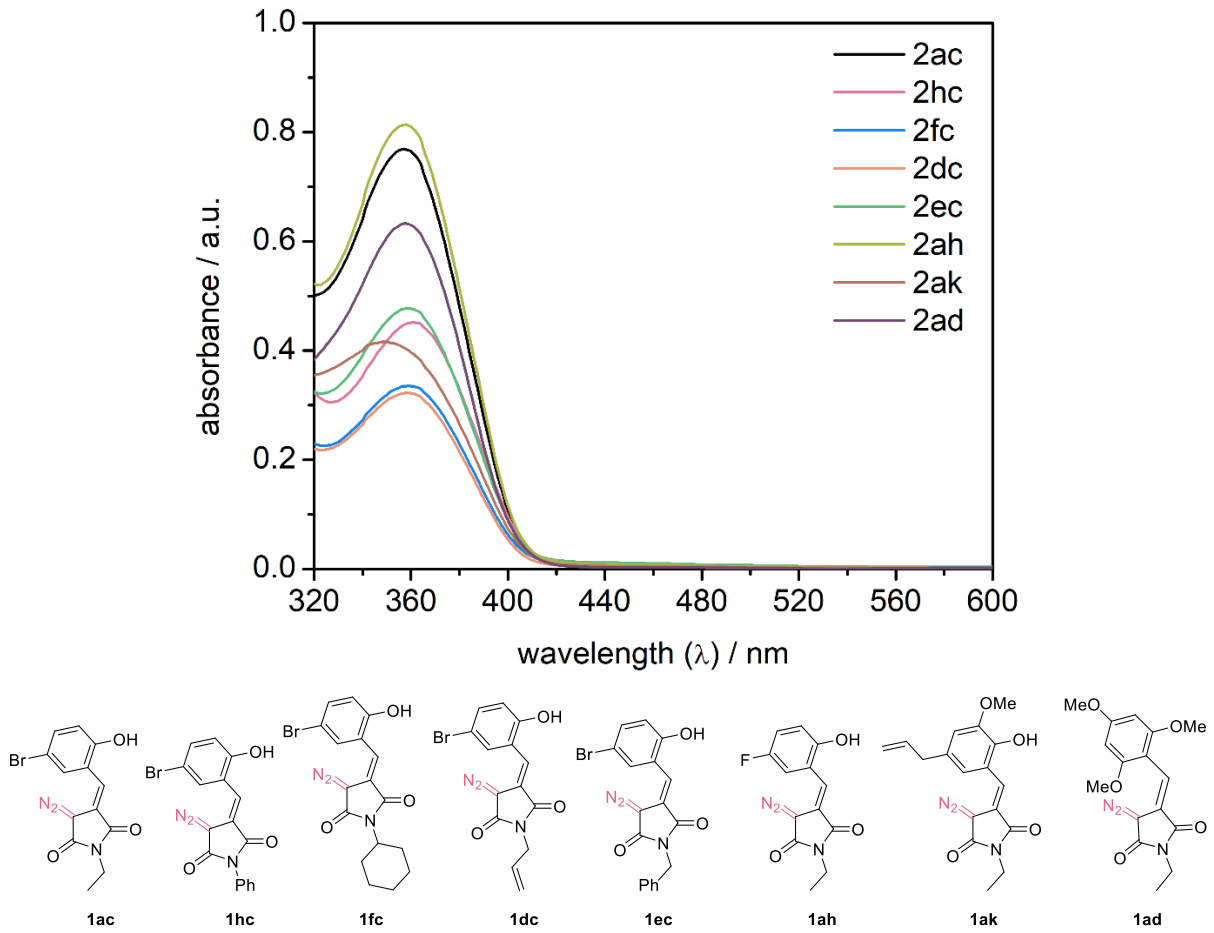
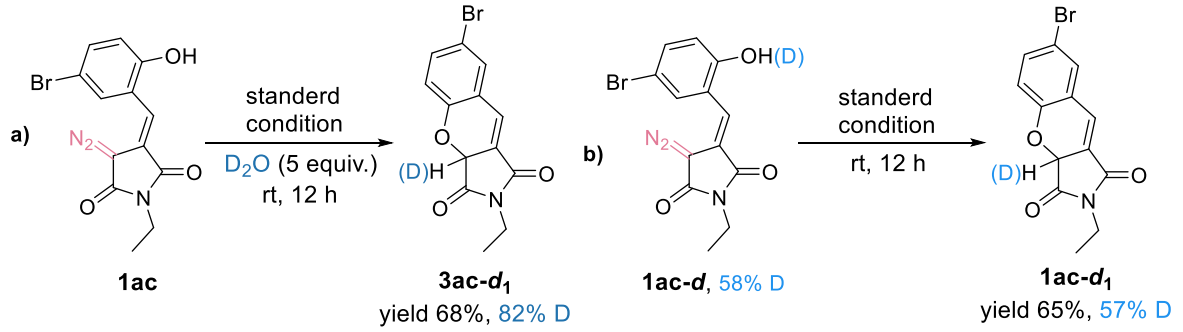


Figure 4B.4.3. UV-Vis absorbance spectra of different diazo compounds (**1ac-1ad)** in 1,4-dioxane (all in 0.2 mM) at room temperature.

Conclusions:

The diazosuccinimides (**1ac-1ad**) absorb light in the near UV to violet range and since, blue LEDs have maximum of emission at 456 nm and they can also emit radiation in 456 nm +/- 50 nm range. Thus, excitation of diazo surrogates or direct photolysis of diazo surrogates (**1ac-1ad**) are likely to happen when applied to 456 nm blue LEDs.

4B.8. Isotope labeling experiments:



Reaction-a: The reaction was set up following the general procedure-C (**4B.11)** for the intramolecular O–H functionalization reaction (Section 3.2) on 0.1 mmol scale of **1ac** with the addition of D_2O (5.0 equiv.). The experiment was conducted for 12 h at room temperature (27 °C). The reaction was monitored by TLC. The reaction solution was purified by column chromatography through silica gel (eluent: hexanes/ethyl acetate = 88:12) to give the corresponding deuterated chromene **3ac-*d*$_1$** (21 mg, 68% yield, 82% D incorporation).

Reaction-b: The reaction was set up following the general procedure-C for the intramolecular O–H functionalization reaction (section 3.2) on 0.1 mmol scale of **1ac-*d*** (58% D incorporated). The experiment was conducted for 12 h at room temperature (27 °C). The reaction was monitored by TLC. The reaction solution was purified by column chromatography through silica gel (eluent: hexanes/ethyl acetate = 88:12) to give the corresponding deuterated chromene **3ac-*d*$_1$** (20 mg, 65% yield, 57% D incorporation).

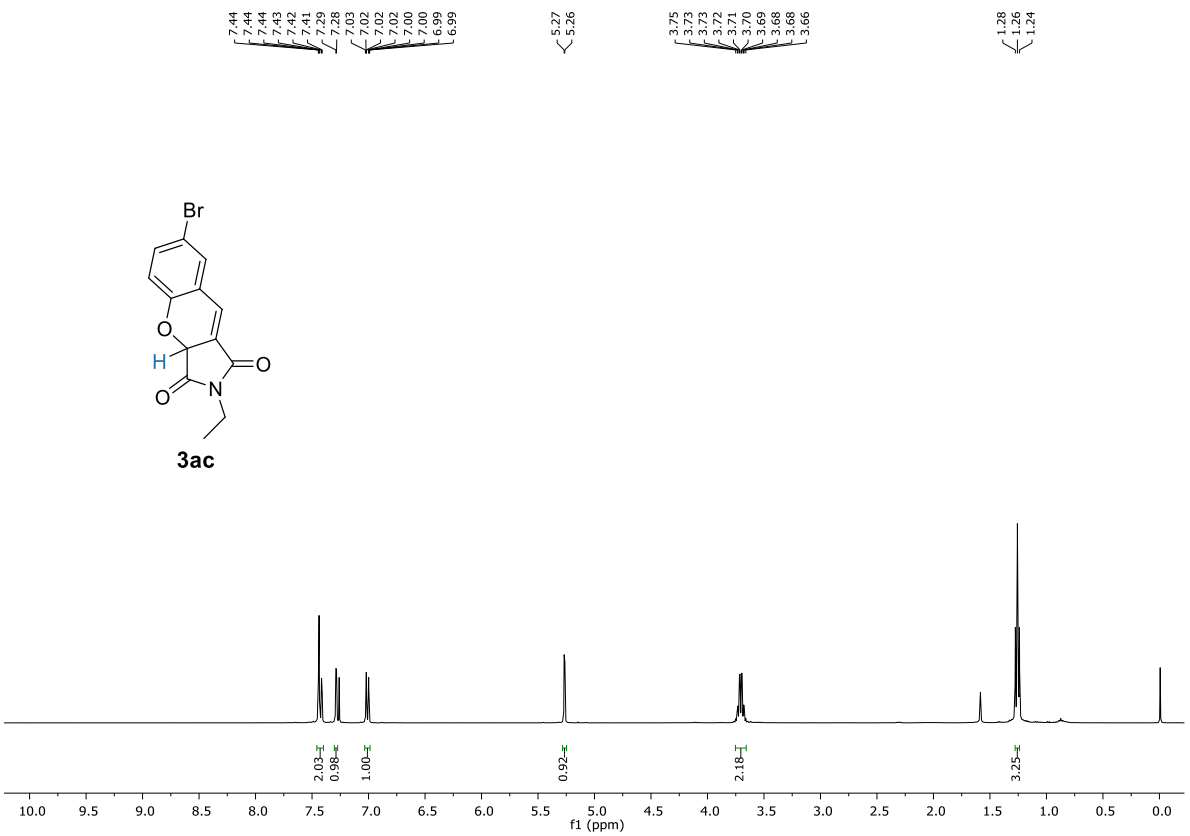


Figure 4B.4.4. ^{1}H NMR (100 MHz, $CDCl_3$) spectrum of compound **3ac**

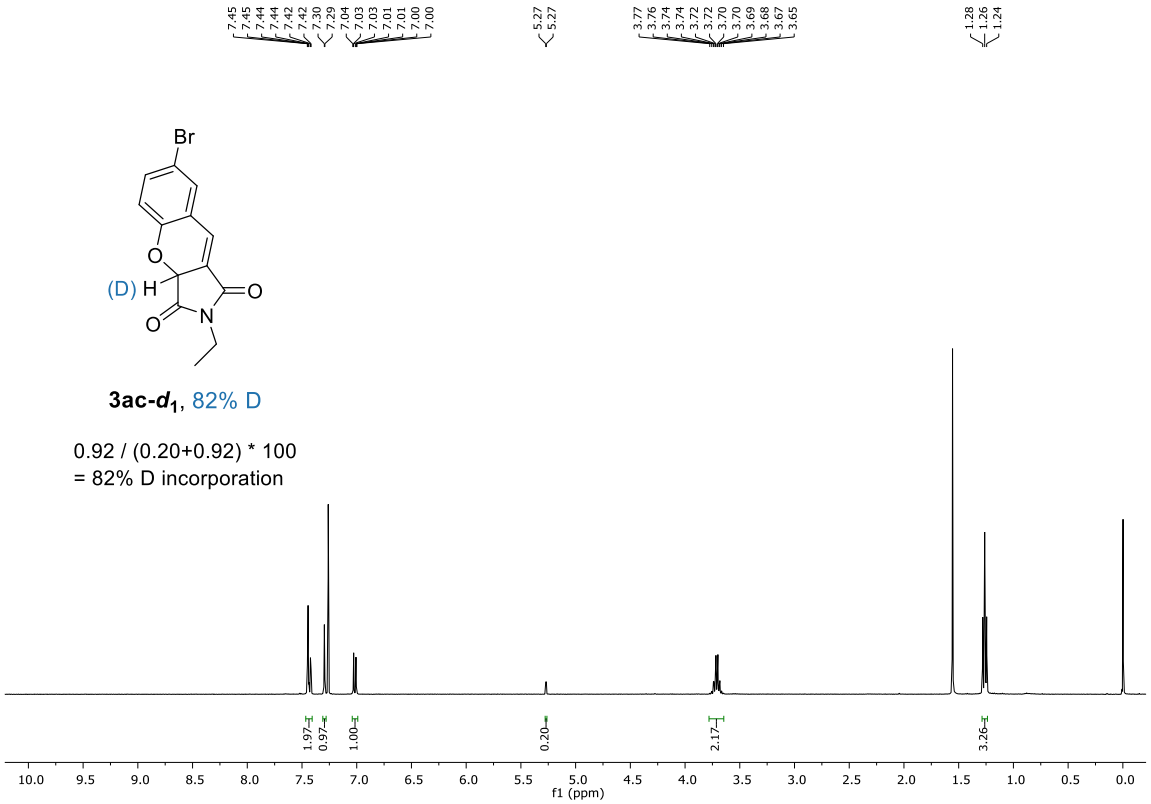


Figure 4B.4.5. ^{1}H NMR (100 MHz, $CDCl_3$) spectrum of compound **3ac-*d*$_1$**

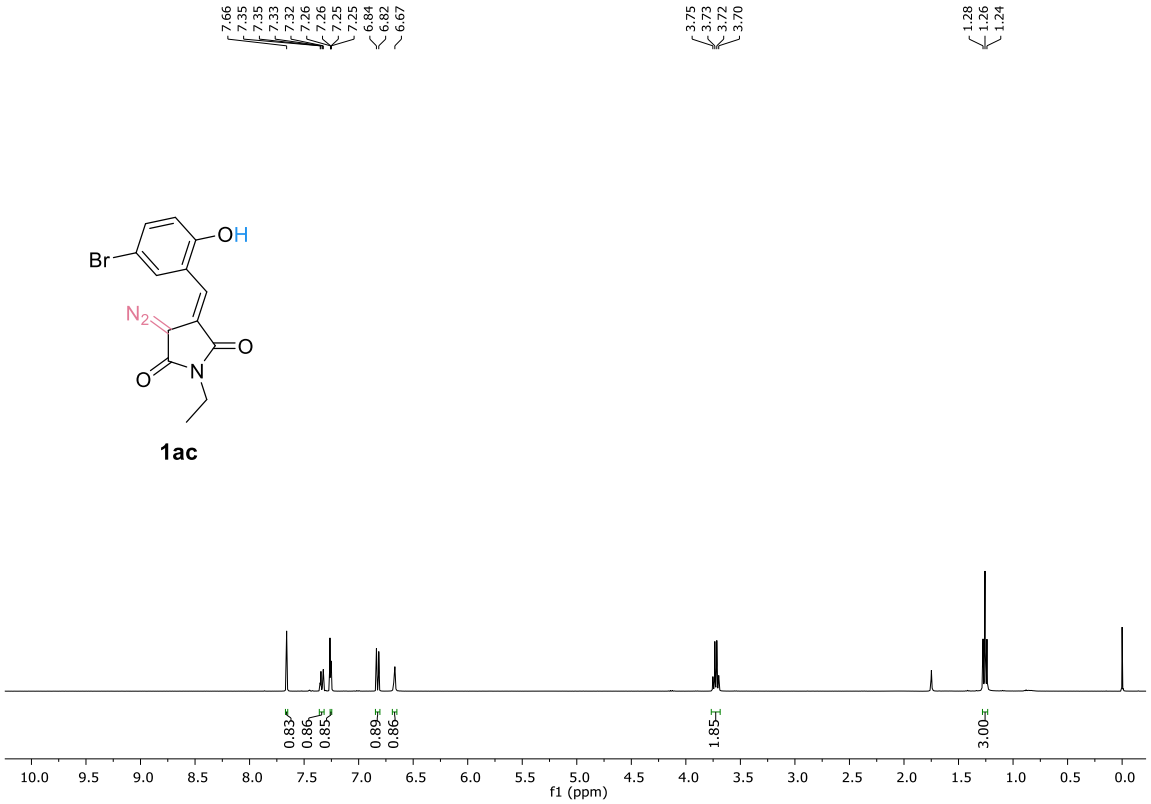


Figure 4B.4.6. ^{1}H NMR (100 MHz, $CDCl_3$) spectrum of compound **1ac**

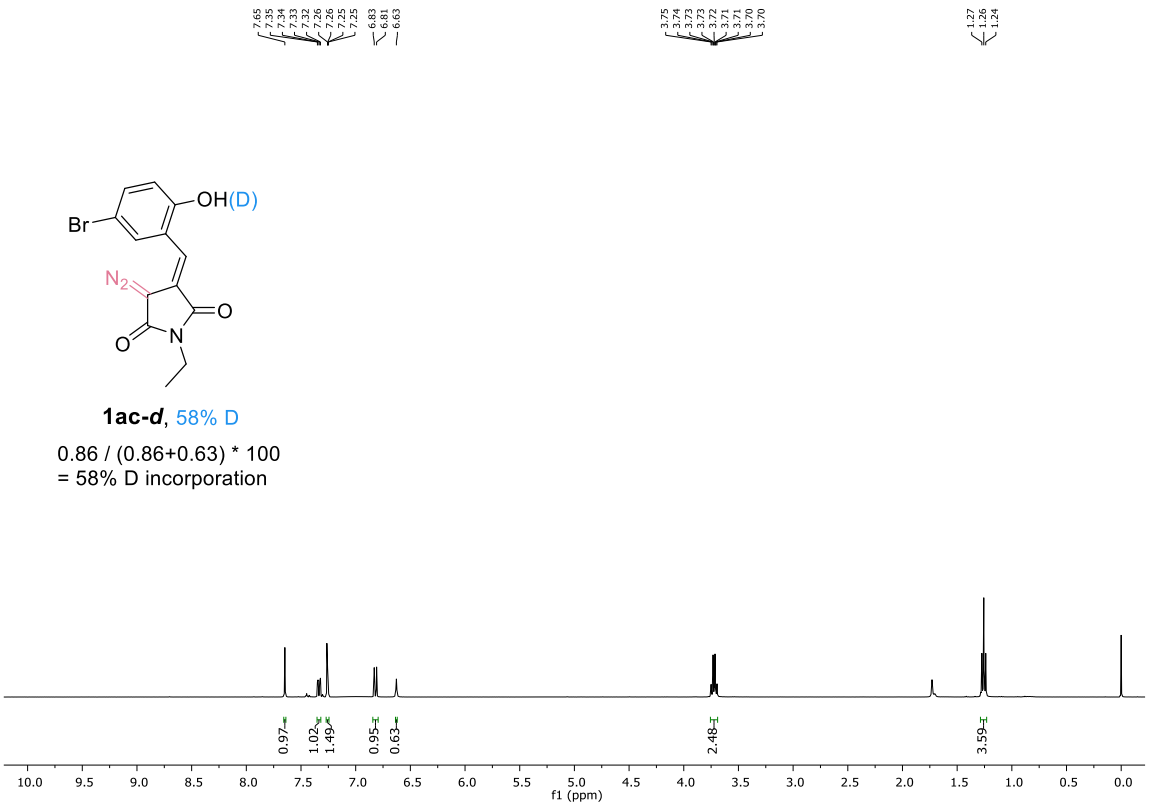


Figure 4B.4.7. ^{1}H NMR (100 MHz, $CDCl_3$) spectrum of compound **1ac-*d***

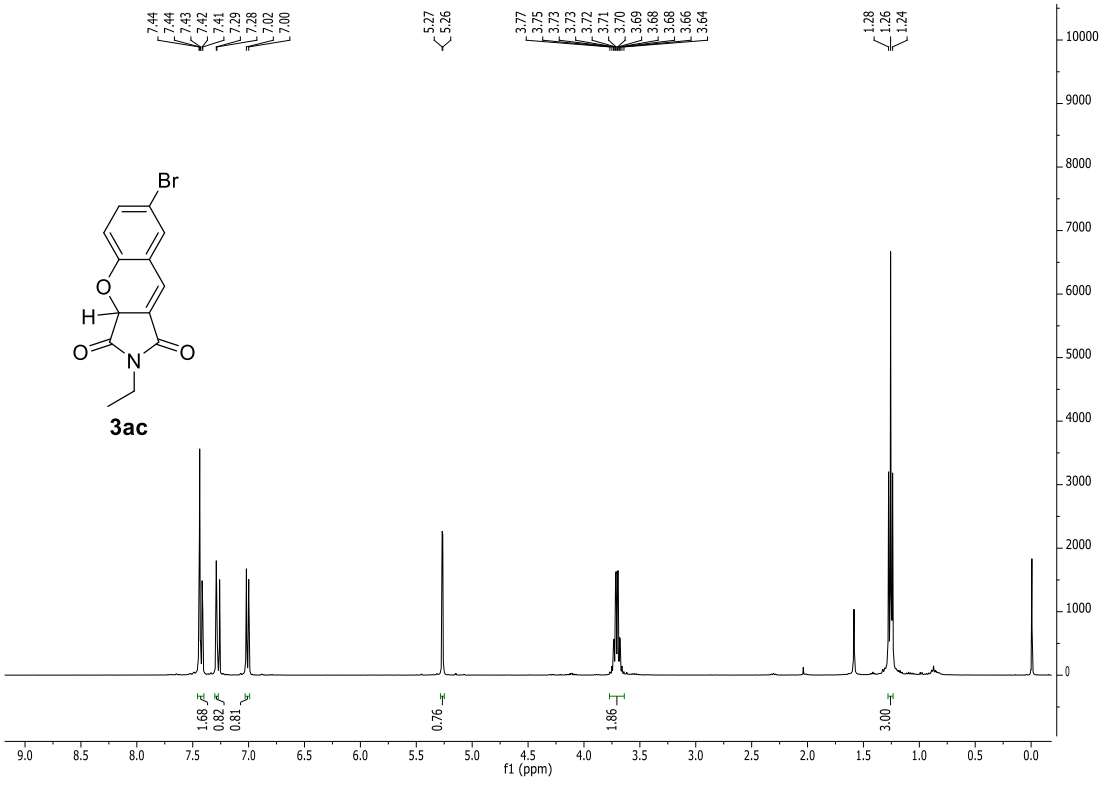


Figure 4B.4.8. ^{1}H NMR (100 MHz, $CDCl_3$) spectrum of compound **3ac**

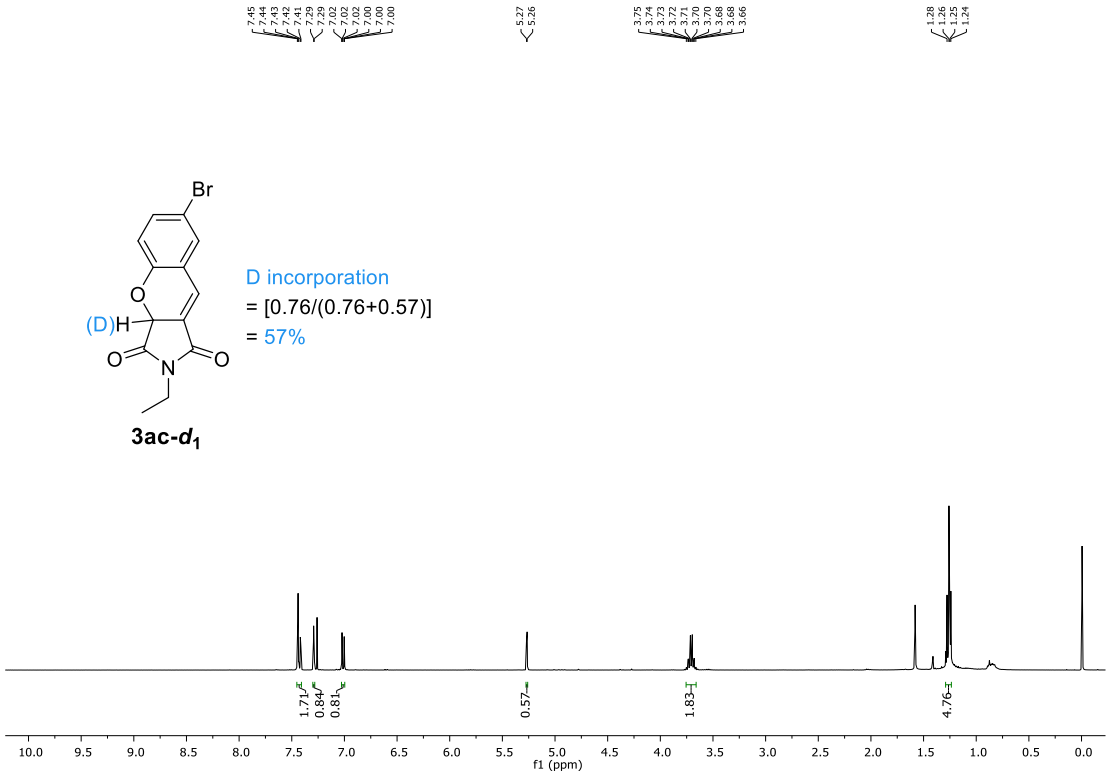
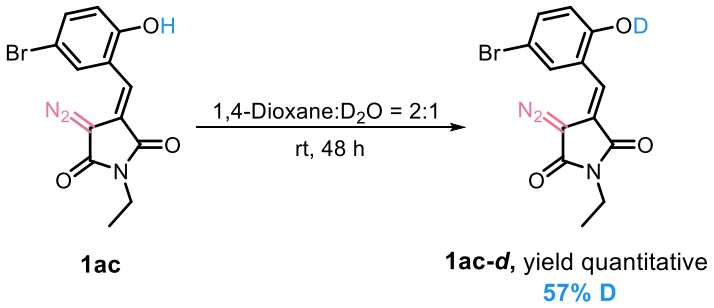


Figure 4B.4.9. ^{1}H NMR (100 MHz, $CDCl_3$) spectrum of compound **3ac-*d*$_1$**

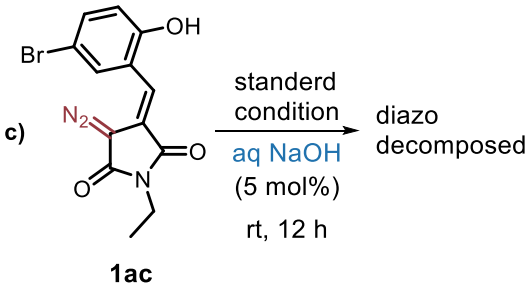
❖ 4B.8.1. Procedure for synthesizing compound 1ac-*d*:



In an over dried round bottom flask equipped with a magnetic stirrer bar, was added diazo succinimide **2ac** (0.5 mmol) in a 2:1 mixture of 1,4-Dioxane:D_2O (6 mL) at room temperature (27 °C) under argon atmosphere under dark (absence of light and covered with aluminum foil). The reaction mixture was stirred for 48 h. After that the solvent was evaporated under reduced pressure (rotary evaporator-bath temperature 45 °C). The compound **1ac-*d*** (quantitative yield, 57% D incorporation) so obtained was used for the next step without further purification.

Conclusion: Though the reaction-a, indicated that the proton at the carbene center of the product **3ac** can either shift from the substrate's -OH group intramolecularly or from the moisture in the solvent, The reaction-b, confirmed that the proton is shifting intramolecularly from the OH group of the substrate **1ac**.

4B.8.2. Control experiment with aq. NaOH:



1ac

Reaction-a: The reaction was set up following the general procedure-C for the intramolecular O–H functionalization reaction (Section 4B.5.2) on 0.1 mmol scale with the addition of aq. NaOH (5 mol%). The experiment was conducted for 12 h at room temperature (27 °C). The reaction was monitored by TLC. The diazo compound was decomposed. No trace of the desired product was observed.

Conclusion:

The *in-situ* formation of sodium phenoxide ion might have hampered the reaction due to lack of hydrogen. The reaction also revealed that a 1,6-hydrogen shifting is occurring in the desired transformation.

To further check whether the phenoxide ion is forming in-situ in this reaction or not, we have checked UV-Vis absorbance spectra of 'diazo compound **1ac**' and '**1ac** + aq. NaOH' in 1,4-Dioxane (c = 0.2 mM).

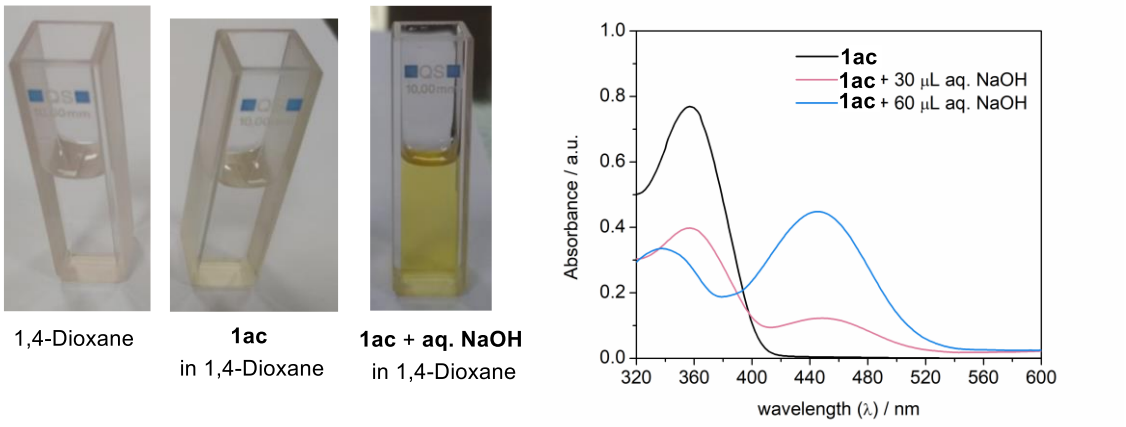


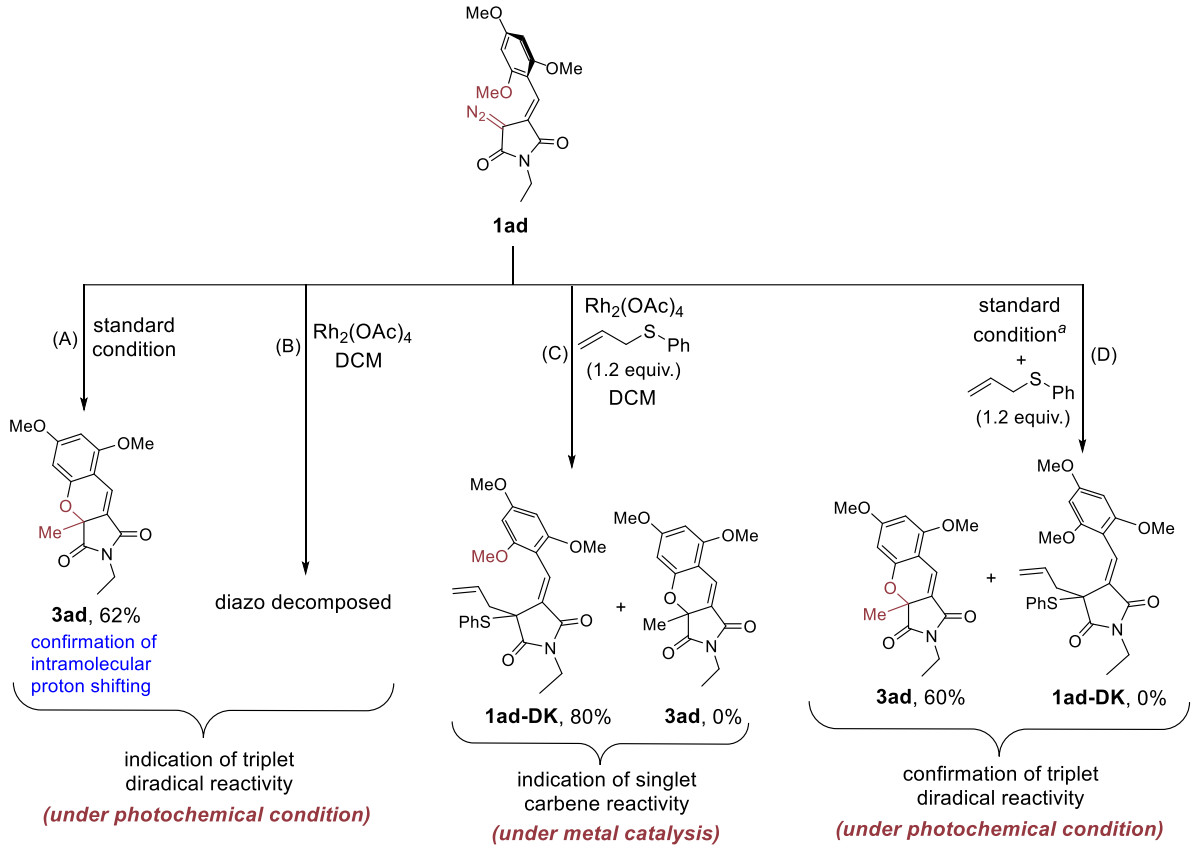
Figure 4B.5. UV-Vis absorbance spectra of diazo compounds **1ac** and '**1ac** + aq. NaOH' in 1,4-Dioxane (c = 0.2 mM) at room temperature.

4B.9. Investigation of singlet vs triplet carbene intermediate:

To further confirm whether the proton shift is occurring intramolecularly or from the moisture in the solvent the following reactions were set up:

Reaction–A: The reaction was set up following the general procedure-C for the intramolecular O–H functionalization reaction (section 3.2, standard reaction condition) on 0.1 mmol scale of (*E*)-3-diazo-1-ethyl-4-(2,4,6-trimethoxybenzylidene)pyrrolidine-2,5-dione **1ad**. The experiment was conducted for 12 h at room temperature (27 °C). The reaction was monitored by TLC. The reaction solution was purified by column chromatography through silica gel to give the corresponding 3a-methylchromeno[2,3-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (19 mg, 62%).

Reaction–B: In an oven dried test tube equipped with a magnetic stirrer was added 3 mol% of $Rh_2(OAc)_4$ in DCM (1 mL). After that 0.1 mmol scale of (*E*)-3-diazo-1-ethyl-4-(2,4,6-trimethoxybenzylidene)pyrrolidine-2,5-dione **1ad** in 1 mL of DCM was added dropwise into the reaction solution over 10 minutes at room temperature (27 °C). The reaction was monitored by TLC. The diazo compound **1ad** was fully consumed, however no trace of the product 3a-methylchromeno[2,3-*c*]pyrrole-1,3(2*H*,3a*H*)-dione was detected.

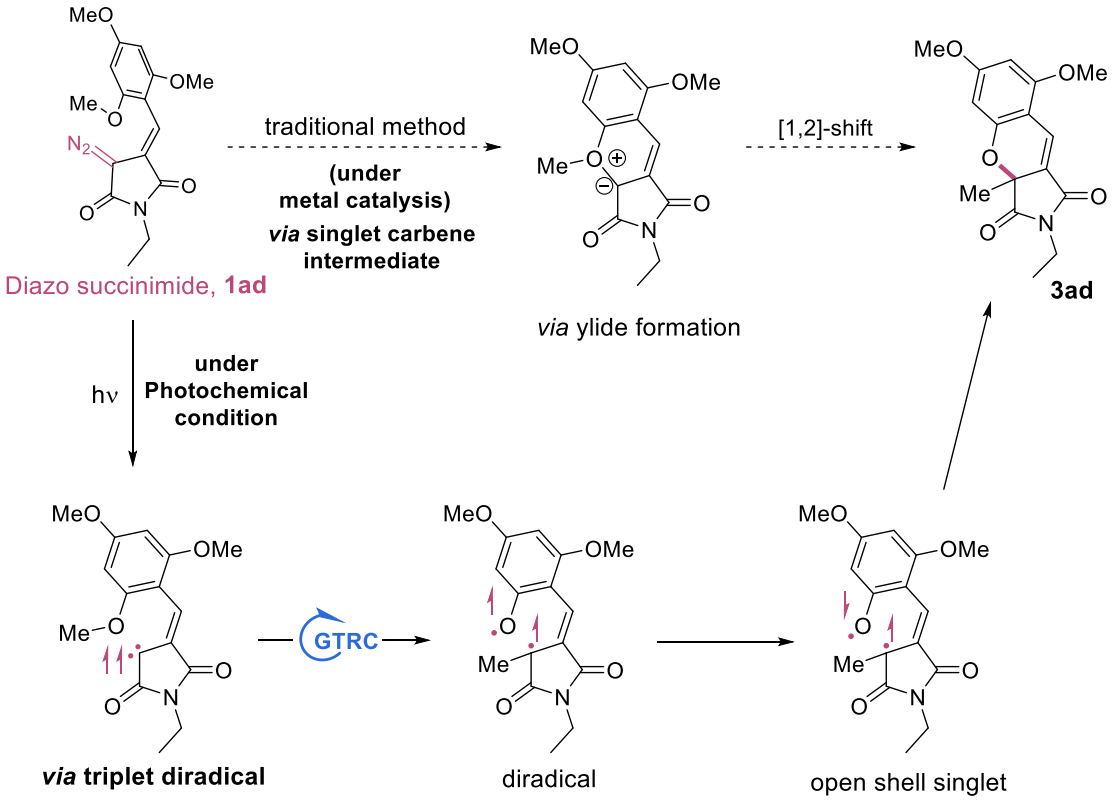


Scheme 4B.18. Control experiments. [a]DCM was used as solvent instead of 1,4-Dioxane.

Reaction–C: In an oven dried test tube equipped with a magnetic stirrer was added allyl sulfide (1.2 equiv.) and 3 mol% of $Rh_2(OAc)_4$ in DCM (1 mL). After that 0.1 mmol scale of (*E*)-3-diazo-1-ethyl-4-(2,4,6-trimethoxybenzylidene)pyrrolidine-2,5-dione **1ad** in 1 mL of DCM was added dropwise into the reaction solution over 10 minutes at room temperature (27 °C). The reaction was monitored by TLC. The diazo compound **1ad** was fully consumed, and the Doyle–Kirmse reaction product **1ad-DK** was formed in excellent yield (36 mg, 80%). But no trace of the product 3a-methylchromeno[2,3-*c*]pyrrole-1,3(2*H*,3a*H*)-dione was detected.

Reaction–D: The reaction was set up following the general procedure-C for the intramolecular O–H functionalization reaction (section 3.2, standard reaction condition) on 0.1 mmol scale of (*E*)-3-diazo-1-ethyl-4-(2,4,6-trimethoxybenzylidene)pyrrolidine-2,5-dione **1ad** with 1.2 equiv. of allyl sulfide in DCM as solvent. The experiment was conducted for 12 h at room temperature (27 °C). The reaction was monitored by TLC. The reaction solution was purified by column chromatography through silica gel to give the corresponding 3a-methylchromeno[2,3-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (18 mg, 60%). But no Doyle–Kirmse reaction product **1ad-DK** was detected.

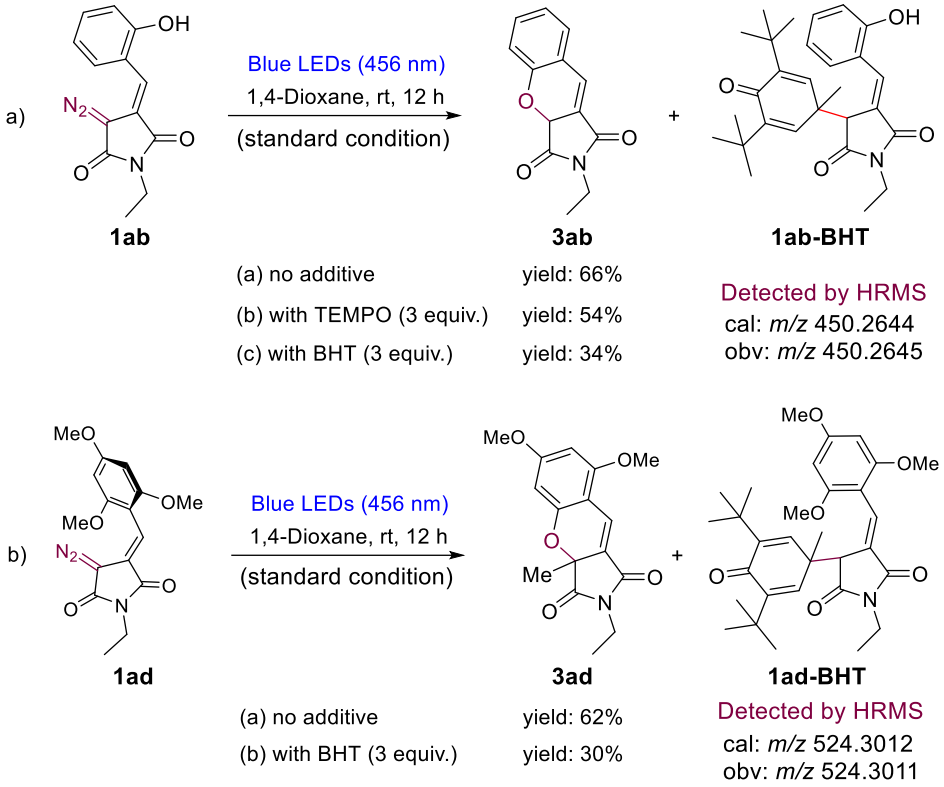
4B.10. Mechanism for group transfer reaction:



Scheme 4B.19. Plausible mechanistic pathway for the group transfer reaction (*via* triplet diradical intermediate).

Conclusion: These reactions collectively proved that the O–H functionalization undergoes *via* triplet carbene intermediate under photochemical conditions, while under metal-based catalysis it follows the traditional singlet carbene pathway.

4B.11. Radical trapping experiments:



Scheme 4B.20. Trapping of radicals by TEMPO and BHT.

Reaction-a: The reaction was set up in separate batches following the general procedure-C for the intramolecular O–H functionalization reaction (section 3.2, standard reaction condition) on 0.1 mmol scale of **1ab** with the addition of TEMPO (0.3 mmol, 3.0 equiv., 47 mg) and BHT (0.3 mmol, 3.0 equiv., 67 mg) before irradiation in 1,4-dioxane solution (c = 0.04 M). The irradiation in both experiments was maintained for 12 h and after that time crude reaction mixtures were analyzed with the use of ESI MS.

HRMS analysis of the crude reaction mixture when BHT was added before irradiation revealed the presence of *m/z* 450.2645 peak, corresponding to substrate-BHT adduct **1ab-BHT**. Whereas addition of TEMPO before irradiation diminishes the yield of the O–H functionalization product. However, no substrate-TEMPO adduct was detected by HRMS analysis of the crude reaction mixture.

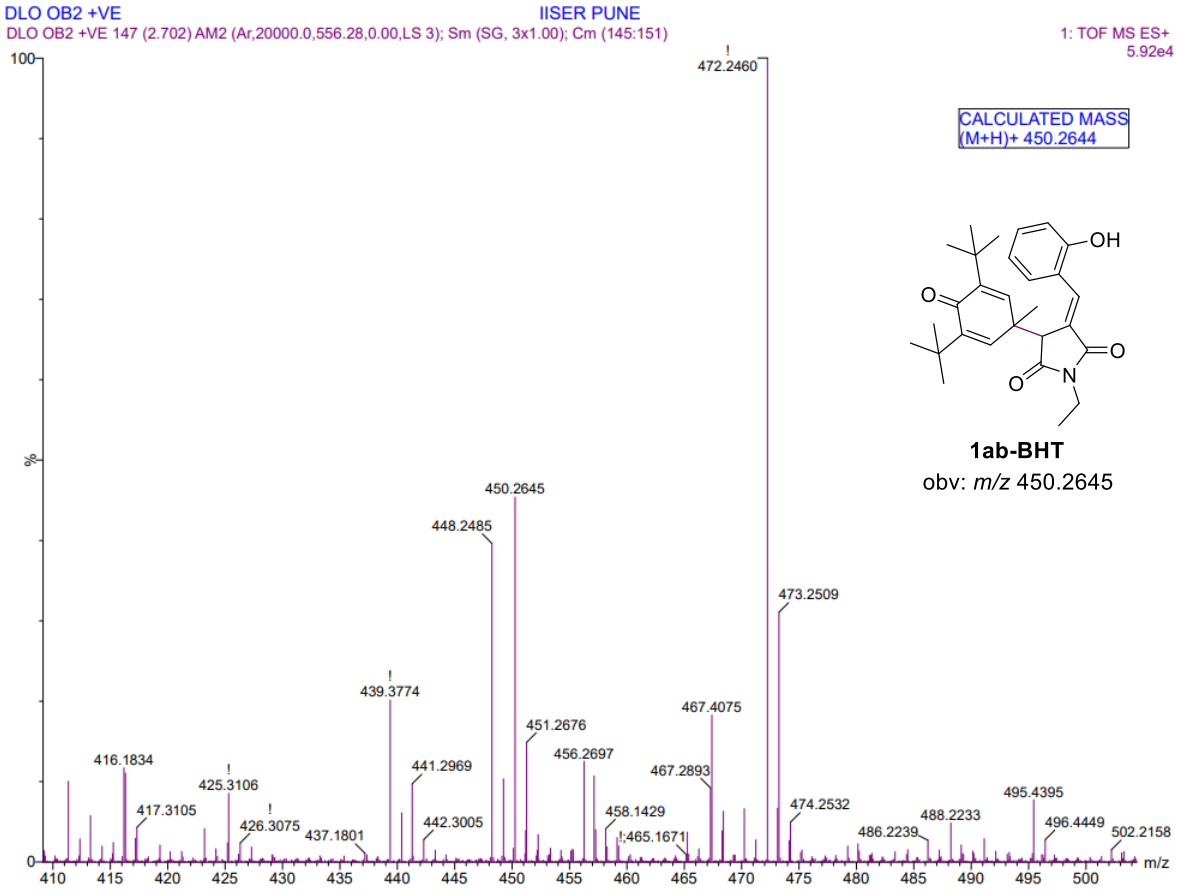


Figure 4B.6.1. HRMS spectrum of the crude reaction mixture with the addition of BHT.

Reaction-b: The reaction was set up following the general procedure-C (section 3.2, standard reaction condition) on 0.1 mmol scale of **1ad** with the addition of BHT (0.3 mmol, 3.0 equiv., 67 mg) before irradiation in 1,4-Dioxane solution (c = 0.04 M). The irradiation in this experiment was maintained for 12 h and after that time crude reaction mixture were analyzed with the use of ESI MS.

HRMS analysis of the crude reaction mixture when BHT was added before irradiation revealed the presence of *m/z* 524.3011 peak, corresponding to substrate-BHT adduct **1ad-BHT**.

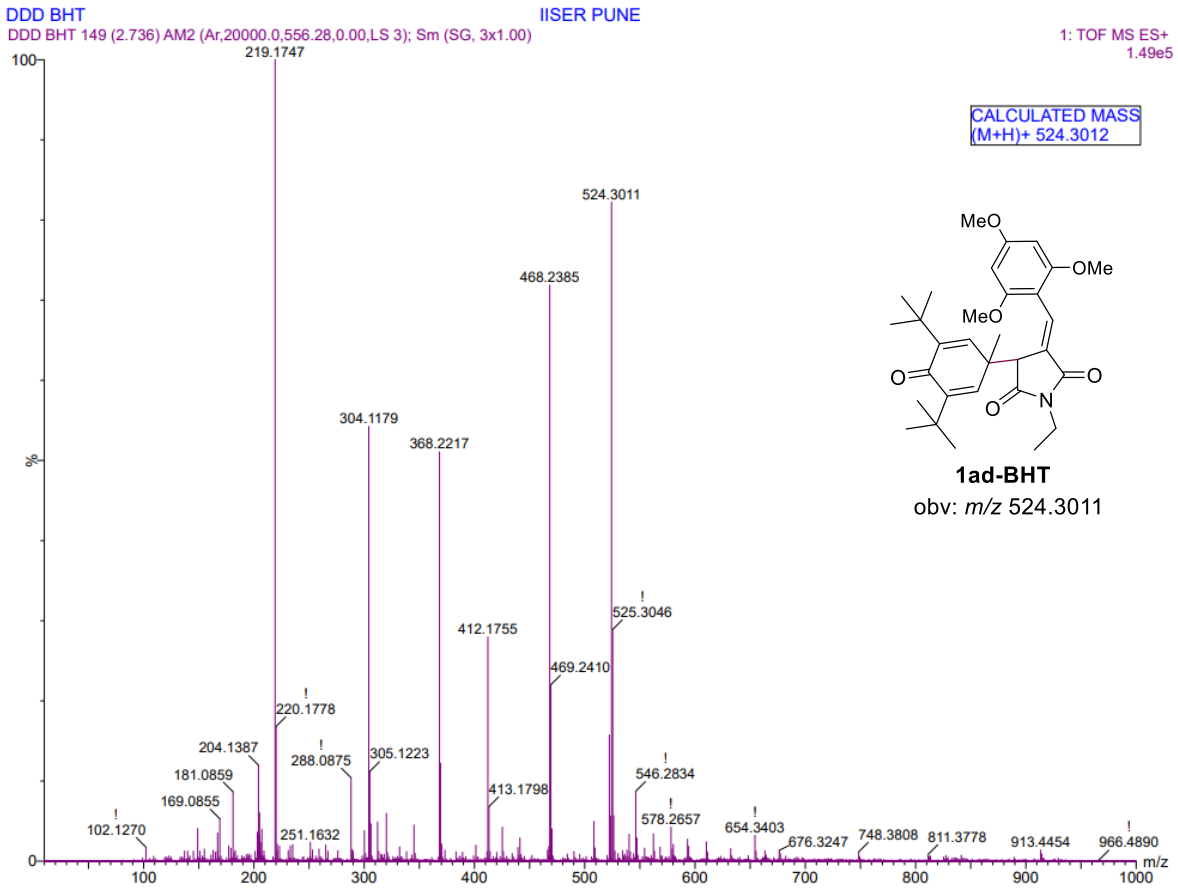


Figure 4B.6.2. HRMS spectrum of the crude reaction mixture with the addition of BHT.

Conclusion:

Diminishing in the yield of product formations, when TEMPO is added prior irradiation, indicates that the reaction may radical in nature. Moreover, diminishing in the yield of product formations, with the addition of BHT prior to irradiation, probes that the reactions are radical in nature. Observation of HRMS peak corresponding to adducts **1ab-BHT** and **1ad-BHT** suggests the formation of a radical species generated throughout the desired product formation.

4B.12. EPR studies:

Measurement conditions:

Microwave frequency: 9.373 GHz

X-Band EPR measurements for the stability study were carried out using a JON Bruker BioSpin connected to Bruker EMX plus spectrometer with a radio wave source (9.373 GHz) in the temperature range 5 – 50 K. The triplet species was generated by irradiating the diazo precursor (40 μM) in frozen 1,4-dioxane solution at 5 K – 50 K using a blue LEDs (λ = 456 nm) inside the resonator for 15 minutes.

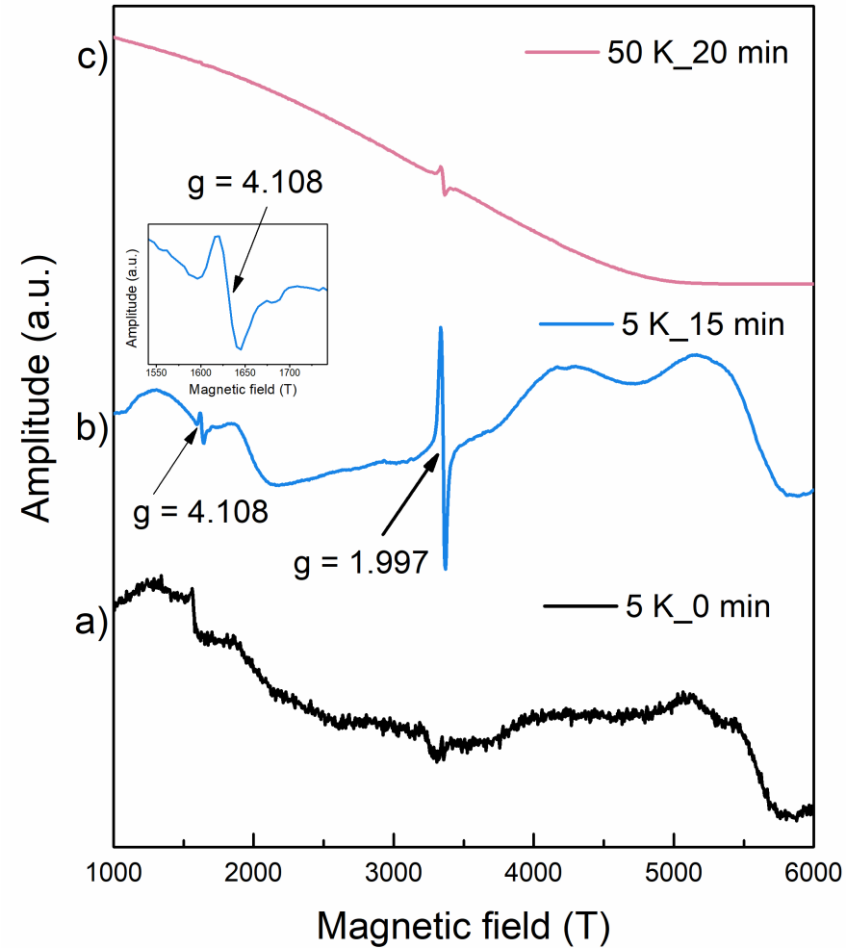
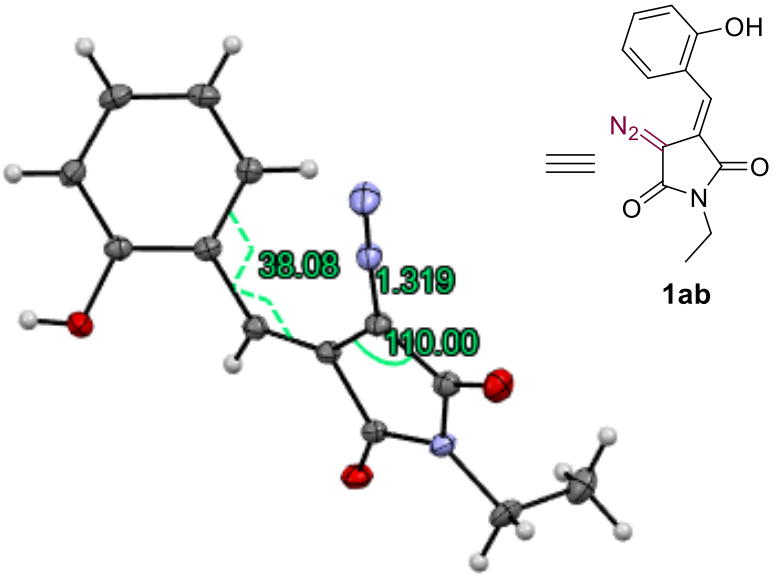


Figure 5.1. X-band EPR spectrum of *ortho*-hydroxy diazosuccinimide.

4B.13. Geometrical arrangement of diazosuccinimide:

The molecular structures and geometric arrangements of the diazosuccinimide (**1ab**) was unambiguously determined using single-crystal X-ray analysis. The bond angle of ∠C–C(N_2)–C is determined as 110° with a dihedral angle θ ~ 38° at the *s-cis* conformation occurring from the orientation of benzylidene ring.



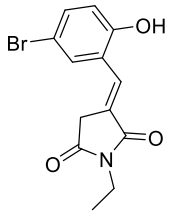
Molecular structure of **2ab**
(analyzed by single-crystal X-ray)
(Thermal ellipsoids at 50% probability)

Figure 4B.7 Crystal data interpretation.

4B.14. Characterization of synthesized compounds:

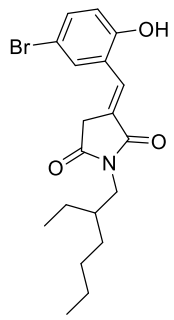
4B.14.1. For vinyl succinimides:

(E)-3-(5-bromo-2-hydroxybenzylidene)-1-ethylpyrrolidine-2,5-dione (1'ac):



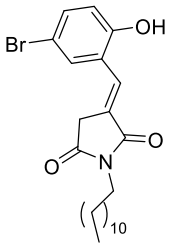
Compound ***1'*ac** was synthesized following the general procedure-A. The product was obtained as white solid, 0.990 g (80% yield); R_f =0.2 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.57 (s, 1H), 7.67 (t, *J* = 2.3 Hz, 1H), 7.55 (d, *J* = 2.4 Hz, 1H), 7.41 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 1H), 3.68 (d, *J* = 2.3 Hz, 2H), 3.51 (q, *J* = 7.1 Hz, 2H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 174.1, 170.5, 156.2, 133.7, 130.9, 125.3, 125.2, 123.3, 118.0, 110.6, 33.3, 33.0, 13.0; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{13}BrNO_3$ $(M + H)^+$ 310.0079; Found, 310.0079.

(E)-3-(5-bromo-2-hydroxybenzylidene)-1-(2-ethylhexyl)pyrrolidine-2,5-dione (1'bc):



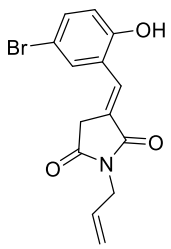
Compound ***1'*bc** was synthesized following the general procedure-A. The product was obtained as white solid, 0.625 g (66% yield); R_f =0.35 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.96 (t, *J* = 2.3 Hz, 1H), 7.48 – 7.37 (m, 2H), 6.81 (d, *J* = 8.6 Hz, 1H), 3.72 (d, *J* = 2.3 Hz, 2H), 3.59 (d, *J* = 7.4 Hz, 2H), 1.79 (hept, *J* = 6.6 Hz, 1H), 1.29 (dp, *J* = 16.2, 6.6, 6.0 Hz, 8H), 0.90 (q, *J* = 6.7, 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$:TFA): δ (ppm) 178.2, 173.8, 154.6, 135.3, 132.1, 131.0, 122.8, 122.7, 118.6, 113.6, 43.9, 37.9, 34.0, 30.6, 28.5, 23.9, 23.1, 14.0, 10.3; HRMS (ESI TOF) *m/z*: calcd for $C_{19}H_{25}BrNO_3$ $(M + H)^+$ 394.1018; Found, 394.1011.

(E)-3-(5-bromo-2-hydroxybenzylidene)-1-dodecylpyrrolidine-2,5-dione (1'cc):



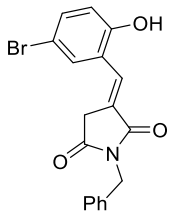
Compound ***1'*cc** was synthesized following the general procedure-A. The product was obtained as white solid, 0.523 g (62% yield); R_f =0.4 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$:TFA): δ (ppm) 7.94 (t, *J* = 2.3 Hz, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 7.40 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 1H), 3.69 – 3.61 (m, 4H), 1.62 (p, *J* = 6.9 Hz, 2H), 1.27 (d, *J* = 22.4 Hz, 18H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6:$CDCl_3$=1:1): δ (ppm) 173.6, 170.2, 156.1, 133.2, 130.6, 125.9, 124.1, 123.0, 117.7, 110.4, 37.9, 33.2, 31.2, 28.95, 28.93, 28.90, 28.8, 28.6, 28.5, 27.2, 26.2, 22.0, 13.7; HRMS (ESI TOF) *m/z*: calcd for $C_{23}H_{33}BrNO_3$ $(M + H)^+$ 450.1644; Found, 450.1641.

(E)-1-allyl-3-(5-bromo-2-hydroxybenzylidene)pyrrolidine-2,5-dione (1'dc):



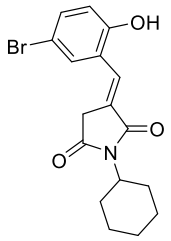
Compound ***1'*dc** was synthesized following the general procedure-A. The product was obtained as white solid, 0.980 g (83% yield); R_f =0.2 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.76 (s, 1H), 7.66 (t, *J* = 2.3 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.39 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 5.78 (ddt, *J* = 17.1, 10.3, 5.1 Hz, 1H), 5.12 – 5.03 (m, 1H), 4.07 (d, *J* = 5.1 Hz, 1H), 3.69 (d, *J* = 2.3 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 174.5, 170.8, 156.6, 134.2, 132.0, 131.3, 126.0, 125.3, 123.6, 118.4, 116.9, 111.1, 40.6, 33.7; HRMS (ESI TOF) *m/z*: calcd for $C_{14}H_{13}BrNO_3$ $(M + H)^+$ 322.0079; Found, 322.0072.

(E)-1-benzyl-3-(5-bromo-2-hydroxybenzylidene)pyrrolidine-2,5-dione (1'ec):



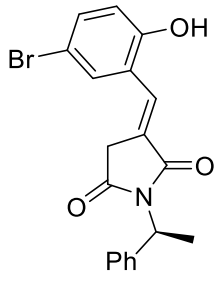
Compound ***1'*ec** was synthesized following the general procedure-A. The product was obtained as white solid, 0.790 g (80% yield); R_f =0.2 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.67 (t, *J* = 2.2 Hz, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.38 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.24 (dt, *J* = 7.0, 2.8 Hz, 3H), 6.87 (d, *J* = 8.7 Hz, 1H), 4.65 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 174.8, 171.1, 156.7, 136.6, 134.4, 131.4, 129.1, 128.0, 127.9, 126.4, 125.3, 123.6, 118.4, 111.2, 42.0, 33.8; HRMS (ESI TOF) *m/z*: calcd for $C_{18}H_{15}BrNO_3$ $(M + H)^+$ 372.0235; Found, 372.0236 (for ^{79}Br), 374.0217 (for ^{81}Br).

(E)-3-(5-bromo-2-hydroxybenzylidene)-1-cyclohexylpyrrolidine-2,5-dione (1'fc):



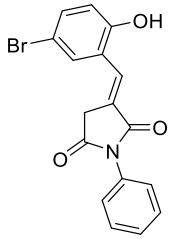
Compound ***1'*fc** was synthesized following the general procedure-A. The product was obtained as white solid, 0.342 g (56% yield); R_f =0.3 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$:TFA): δ (ppm) 7.88 (t, *J* = 2.3 Hz, 1H), 7.70 – 7.51 (m, 1H), 7.46 – 7.38 (m, 2H), 6.80 (d, *J* = 8.5 Hz, 1H), 4.14 (tt, *J* = 12.4, 3.9 Hz, 1H), 3.65 (d, *J* = 2.3 Hz, 2H), 2.16 (qd, *J* = 12.5, 3.6 Hz, 2H), 1.88 (dt, *J* = 13.3, 3.3 Hz, 2H), 1.69 (dt, *J* = 13.0, 6.9 Hz, 3H), 1.43 – 1.17 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 173.6, 170.2, 156.0, 133.2, 130.7, 125.8, 124.1, 123.1, 117.7, 110.4, 50.6, 33.2, 28.4, 25.4, 24.7. HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{19}BrNO_3$ $(M + H)^+$ 364.0548; Found, 364.0552 (for ^{79}Br), 366.0534 (for ^{81}Br).

(S,E)-3-(5-bromo-2-hydroxybenzylidene)-1-(1-phenylethyl)pyrrolidine-2,5-dione (1'gc):



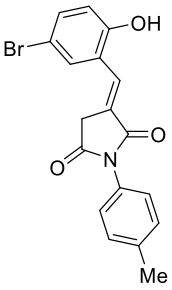
Compound ***1'*gc** was synthesized following the general procedure-A. The product was obtained as white solid, 0.802 g (80% yield); R_f =0.25 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$:TFA): δ (ppm) 7.90 (t, *J* = 2.3 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.37 – 7.27 (m, 4H), 6.74 (d, *J* = 8.7 Hz, 1H), 5.58 (q, *J* = 7.3 Hz, 1H), 3.59 (t, *J* = 2.4 Hz, 2H), 1.88 (d, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$:TFA): δ (ppm) 176.1, 172.4, 154.7, 138.8, 134.8, 131.9, 129.9, 128.8, 128.3, 127.6, 123.3, 123.0, 118.4, 113.1, 51.1, 34.1, 16.6; HRMS (ESI TOF) *m/z*: calcd for $C_{19}H_{17}{}^{79}BrNO_3$ $(M + H)^+$ 386.0392; Found, 386.0389.

***(E)-3-(5-bromo-2-hydroxybenzylidene)-1-phenylpyrrolidine-2,5-dione (1'hc)*:**



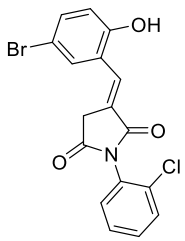
Compound ***1'*hc** was synthesized following the general procedure-A. The product was obtained as white solid, 0.880 g (85% yield); R_f =0.15 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6:$CDCl_3$=1:1): δ (ppm) 10.33 (s, 1H), 7.83 (t, *J* = 2.3 Hz, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.48 – 7.43 (m, 2H), 7.40 – 7.35 (m, 1H), 7.34 – 7.28 (m, 3H), 6.88 (d, *J* = 8.7 Hz, 1H), 3.74 (d, *J* = 2.3 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6:$CDCl_3$=1:1): δ (ppm) 172.7, 169.4, 156.1, 133.4, 132.2, 130.7, 128.4, 127.8, 127.0, 126.5, 123.9, 122.9, 117.7, 110.5, 33.6; HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{13}BrNO_3$ $(M + H)^+$ 358.0079; Found, 358.0074.

(E)-3-(5-bromo-2-hydroxybenzylidene)-1-(p-tolyl)pyrrolidine-2,5-dione (1'ic):



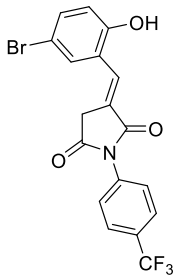
Compound ***1'*ic** was synthesized following the general procedure-A. The product was obtained as white solid, 0.836 g (84% yield); R_f =0.2 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6:$CDCl_3$=1:1): δ (ppm) 10.33 (s, 1H), 7.81 (t, *J* = 2.3 Hz, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.30 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.22 (dd, *J* = 27.4, 8.3 Hz, 4H), 6.87 (d, *J* = 8.7 Hz, 1H), 3.73 (d, *J* = 2.3 Hz, 2H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6:$CDCl_3$=1:1): δ (ppm) 172.8, 169.5, 156.1, 137.5, 133.3, 130.7, 129.6, 128.9, 126.8, 126.3, 124.0, 123.0, 117.7, 110.4, 33.6, 20.6; HRMS (ESI TOF) *m/z*: calcd for $C_{18}H_{15}BrNO_3$ $(M + H)^+$ 372.0235; Found, 372.0228.

(E)-3-(5-bromo-2-hydroxybenzylidene)-1-(2-chlorophenyl)pyrrolidine-2,5-dione (1'jc):



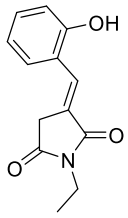
Compound ***1'*jc** was synthesized following the general procedure-A. The product was obtained as white solid, 0.757 g (80% yield); R_f =0.1 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.68 (s, 1H), 7.83 – 7.78 (m, 1H), 7.71 – 7.64 (m, 2H), 7.57 – 7.42 (m, 4H), 6.93 (d, *J* = 8.8 Hz, 1H), 4.10 – 3.84 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 172.9, 169.3, 156.4, 134.1, 131.6, 131.2, 131.1, 130.8, 130.5, 129.9, 128.2, 126.9, 124.8, 123.1, 118.1, 110.8, 33.8; HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{12}BrClNO_3$ $(M + H)^+$ 391.9689; Found, 391.9682.

(*E*)-3-(5-bromo-2-hydroxybenzylidene)-1-(4-(trifluoromethyl)phenyl)pyrrolidine-2,5-dione (*1'*kc):



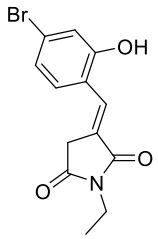
Compound ***1'*kc** was synthesized following the general procedure-A. The product was obtained as white solid, 0.505 g (57% yield); R_f =0.2 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.64 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.81 (t, *J* = 2.4 Hz, 1H), 7.66 – 7.62 (m, 3H), 7.45 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 1H), 3.87 (d, *J* = 2.5 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 173.1, 169.5, 156.4, 136.2, 134.0, 131.0, 128.4 (d, *J* = 32.0 Hz), 127.8, 126.4, 125.9 (d, *J* = 3.1 Hz), 124.9, 124.0 (d, *J* = 271.8 Hz), 123.1, 122.7, 118.9, 118.1, 110.7, 33.8; ^{19}F NMR (377 MHz, DMSO-d_6): δ (ppm) -61.0; HRMS (ESI TOF) *m/z*: calcd for $C_{18}H_{12}BrF_3NO_3$ $(M + H)^+$ 425.9953; Found, 425.9948 (for ^{79}Br), 427.9929 (for ^{81}Br).

(E)-1-ethyl-3-(2-hydroxybenzylidene)pyrrolidine-2,5-dione (1'ab):



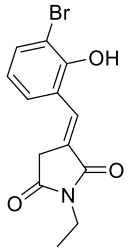
Compound ***1'*ab** was synthesized following the general procedure-A. The product was obtained as white solid, 0.652 g (70% yield); R_f =0.2 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.19 (s, 1H), 7.80 (t, *J* = 2.3 Hz, 1H), 7.48 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.27 – 7.22 (m, 1H), 6.93 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.90 – 6.85 (m, 1H), 3.62 (d, *J* = 2.3 Hz, 2H), 3.51 (q, *J* = 7.2 Hz, 2H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 174.2, 170.7, 157.0, 131.3, 129.1, 126.7, 123.5, 121.0, 119.4, 115.8, 33.6, 32.9, 13.0; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{14}NO_3$ $(M + H)^+$ 232.0973; Found, 232.0982.

(E)-3-(4-bromo-2-hydroxybenzylidene)-1-ethylpyrrolidine-2,5-dione (1'ae):



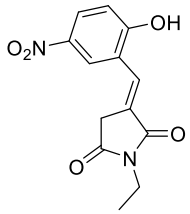
Compound ***1'*ae** was synthesized following the general procedure-A. The product was obtained as white solid, 0.836 g (67% yield); R_f =0.35 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$:DMSO): δ (ppm) 9.81 (s, 1H), 7.87 (t, *J* = 2.4 Hz, 1H), 7.12 – 7.07 (m, 2H), 6.93 (dd, *J* = 8.3, 1.9 Hz, 1H), 3.60 (q, *J* = 7.2 Hz, 2H), 3.40 (d, *J* = 2.4 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$:DMSO): δ (ppm) 174.1, 170.9, 157.9, 130.0, 128.7, 124.8, 122.9, 122.7, 120.6, 119.5, 34.2, 33.6, 13.2; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{13}BrNO_3$ $(M + H)^+$ 310.0079; Found, 310.0080.

(E)-3-(3-bromo-2-hydroxybenzylidene)-1-ethylpyrrolidine-2,5-dione (1'af):



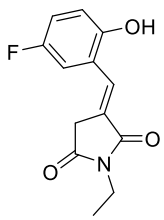
Compound **4af** was synthesized following the general procedure-A. The product was obtained as white solid, 0.680 g (55% yield); R_f =0.3 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.97 (t, *J* = 2.5 Hz, 1H), 7.52 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.32 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.88 (t, *J* = 7.9 Hz, 1H), 6.07 (s, 1H), 3.69 (q, *J* = 7.2 Hz, 2H), 3.50 (d, *J* = 2.5 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 174.0, 170.7, 151.6, 133.6, 128.8, 128.5, 125.2, 122.8, 121.8, 111.7, 34.2, 34.0, 13.3; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{13}BrNO_3$ $(M + H)^+$ 310.0079; Found, 310.0073.

(E)-1-ethyl-3-(2-hydroxy-5-nitrobenzylidene)pyrrolidine-2,5-dione (1'ag):



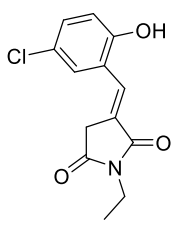
Compound ***1'*ag** was synthesized following the general procedure-A. The product was obtained as white solid, 0.650 g (59% yield); R_f =0.1 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$:TFA): δ (ppm) 8.30 (d, *J* = 2.7 Hz, 1H), 8.22 (dd, *J* = 8.9, 2.7 Hz, 1H), 8.02 (t, *J* = 2.4 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 1H), 3.81 – 3.74 (m, 4H), 1.28 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$:TFA): δ (ppm) 176.7, 172.8, 161.0, 141.4, 132.5, 132.4, 129.5, 127.8, 125.7, 124.9, 121.4, 117.1, 35.0, 34.0, 13.0; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{13}N_2O_5$ $(M + H)^+$ 277.0824; Found, 277.0823.

(E)-1-ethyl-3-(5-fluoro-2-hydroxybenzylidene)pyrrolidine-2,5-dione (1'ah):



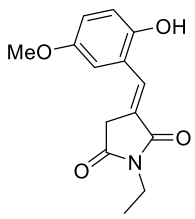
Compound ***1'*ah** was synthesized following the general procedure-A. The product was obtained as white solid, 0.710 g (71% yield); R_f =0.2 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.28 (s, 1H), 7.73 – 7.69 (m, 1H), 7.25 (dd, *J* = 9.8, 3.0 Hz, 1H), 7.10 (td, *J* = 8.6, 3.0 Hz, 1H), 6.91 (dd, *J* = 8.9, 4.9 Hz, 1H), 3.67 (d, *J* = 2.3 Hz, 2H), 3.51 (q, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 174.3, 170.6, 156.6, 154.2, 153.5, 125.8, 125.8, 121.9, 121.8, 118.1, 117.9, 116.94, 116.86, 114.8, 114.6, 33.4, 33.1, 13.0; ^{19}F NMR (377 MHz, DMSO-d_6): δ (ppm) -124.38 (s). HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{13}FNO_3$ $(M + H)^+$ 250.0879; Found, 250.0882.

(E)-3-(5-chloro-2-hydroxybenzylidene)-1-ethylpyrrolidine-2,5-dione (1'ai):



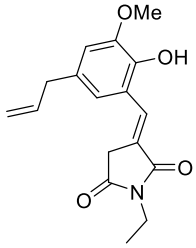
Compound ***1'*ai** was synthesized following the general procedure-A. The product was obtained as white solid, 0.390 g (37% yield); R_f=0.15 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.57 (s, 1H), 7.68 (t, *J* = 1.4 Hz, 1H), 7.44 (d, *J* = 2.3 Hz, 1H), 7.29 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 3.67 (d, *J* = 1.4 Hz, 2H), 3.51 (dd, *J* = 14.5, 7.4 Hz, 2H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 174.2, 170.6, 155.9, 130.9, 128.2, 125.4, 125.3, 123.2, 122.8, 117.6, 33.4, 33.1, 13.0. HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{13}ClNO_3$ $(M + H)^+$ 266.0584; Found, 266.0600.

(E)-1-ethyl-3-(2-hydroxy-5-methoxybenzylidene)pyrrolidine-2,5-dione (1'aj):



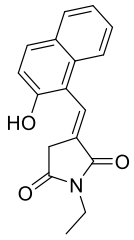
Compound ***1'*aj** was synthesized following the general procedure-A. The product was obtained as white solid, 0.420 g (40% yield); R_f=0.25 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.78 (s, 1H), 7.76 (t, *J* = 2.2 Hz, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.90 – 6.83 (m, 2H), 3.73 (s, 3H), 3.69 (d, *J* = 2.2 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 2H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 174.3, 170.7, 152.1, 151.2, 131.6, 131.5, 128.9, 128.8, 126.8, 123.7, 121.2, 117.9, 116.7, 112.9, 55.5, 33.5, 33.0, 13.0; HRMS (ESI TOF) *m/z*: calcd for $C_{14}H_{16}NO_4$ $(M + H)^+$ 262.1079; Found, 262.1089.

(E)-3-(5-allyl-2-hydroxy-3-methoxybenzylidene)-1-ethylpyrrolidine-2,5-dione (1'ak):



Compound ***1'*ak** was synthesized following the general procedure-A. The product was obtained as white solid, 0.845 g (70% yield); R_f=0.25 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.26 (s, 1H), 7.79 (t, *J* = 2.3 Hz, 1H), 6.90 – 6.83 (m, 2H), 5.97 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.14 – 5.02 (m, 2H), 3.80 (s, 3H), 3.58 (d, *J* = 2.3 Hz, 2H), 3.50 (q, *J* = 7.2 Hz, 2H), 3.31 (d, *J* = 6.7 Hz, 2H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 174.4, 170.8, 147.8, 144.8, 138.0, 130.7, 126.9, 123.7, 121.1, 120.0, 115.8, 113.6, 56.0, 39.2, 33.8, 33.0, 13.1; HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{20}NO_4$ $(M + H)^+$ 302.1392; Found, 302.1393.

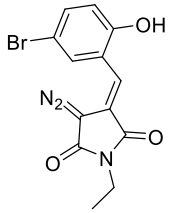
(*E*)-1-ethyl-3-((2-hydroxynaphthalen-1-yl)methylene)pyrrolidine-2,5-dione (*1′*al):



Compound ***1′*al** was synthesized following the general procedure-A. The product was obtained as white solid, 0.465 g (52% yield); R_f=0.2 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.43 (s, 1H), 7.85 (dt, *J* = 5.6, 2.7 Hz, 3H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.50 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.35 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 7.24 (d, *J* = 8.9 Hz, 1H), 3.54 (q, *J* = 7.2 Hz, 2H), 3.22 (d, *J* = 2.4 Hz, 2H), 1.14 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 174.2, 170.0, 153.2, 132.1, 131.0, 128.8, 128.5, 127.8, 127.7, 127.2, 123.4, 123.3, 118.4, 113.1, 34.3, 33.1, 13.1; HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{16}NO_3$ $(M + H)^+$ 282.1130; Found, 282.1131.

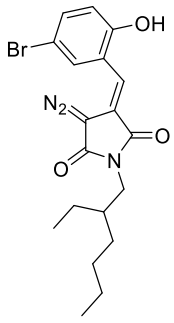
4B.14.2. For vinyl diazosuccinimides:

(E)-3-(5-bromo-2-hydroxybenzylidene)-4-diazo-1-ethylpyrrolidine-2,5-dione (1ac):



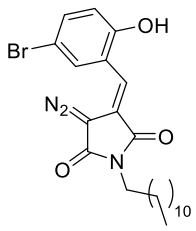
Compound **1ac** was synthesized following the general procedure-B. The product was obtained as orange solid, 0.297 g (91% yield); R_f=0.3 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.54 (s, 1H), 7.46 (s, 1H), 7.40 (d, *J* = 2.5 Hz, 1H), 7.36 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 3.56 (q, *J* = 7.2 Hz, 2H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 166.6, 164.2, 155.3, 133.3, 131.7, 122.5, 121.3, 117.8, 117.8, 109.9, 60.3, 33.7, 13.3; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{11}{}^{79}BrN_3O_3$ $(M + H)^+$ 335.9984; Found, 335.9989.

(E)-3-(5-bromo-2-hydroxybenzylidene)-4-diazo-1-(2-ethylhexyl)pyrrolidine-2,5-dione (1bc):



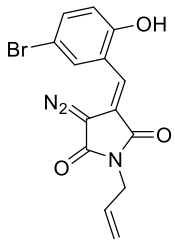
Compound **1bc** was synthesized following the general procedure-B. The product was obtained as orange solid, 0.230 g (72% yield); R_f=0.45 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (s, 1H), 7.33 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.27 (s, 2H), 6.81 (d, *J* = 8.6 Hz, 1H), 6.52 (d, *J* = 2.2 Hz, 1H), 3.59 – 3.52 (m, 2H), 1.81 (hept, *J* = 5.9 Hz, 1H), 1.38 – 1.22 (m, 8H), 0.93 – 0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.4, 165.5, 153.6, 133.8, 132.2, 122.7, 121.6, 118.8, 118.0, 112.6, 43.6, 38.2, 30.6, 28.6, 23.9, 23.1, 14.2, 10.5; HRMS (ESI TOF) *m/z*: calcd for $C_{19}H_{23}{}^{79}BrN_3O_3$ $(M + H)^+$ 420.0923; Found, 420.0924.

(*E*)-3-(5-bromo-2-hydroxybenzylidene)-4-diazo-1-dodecylpyrrolidine-2,5-dione (1cc):



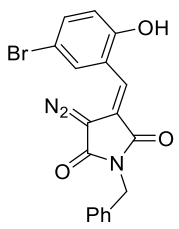
Compound **1cc** was synthesized following the general procedure-B. The product was obtained as yellowish orange solid, 0.260 g (82% yield); R_f=0.5 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.53 (s, 1H), 7.46 (s, 1H), 7.42 – 7.33 (m, 2H), 6.87 (d, *J* = 8.6 Hz, 1H), 3.52 (t, *J* = 6.8 Hz, 2H), 1.58 – 1.49 (m, 2H), 1.23 (s, 18H), 0.84 (t, *J* = 6.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 167.3, 164.9, 155.8, 133.8, 132.2, 123.0, 121.8, 118.3, 118.1, 110.4, 60.8, 39.2, 31.8, 29.54, 29.48, 29.4, 29.2, 29.0, 28.1, 26.6, 22.6, 14.5; HRMS (ESI TOF) *m/z*: calcd for $C_{23}H_{31}BrN_3O_3$ $(M + H)^+$ 476.1549; Found, 476.1544.

(E)-1-allyl-3-(5-bromo-2-hydroxybenzylidene)-4-diazopyrrolidine-2,5-dione (1dc):



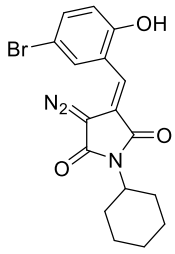
Compound **1dc** was synthesized following the general procedure-B. The product was obtained as yellow solid, 0.163 g (50% yield); R_f =0.3 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.56 (s, 1H), 7.48 (s, 1H), 7.43 (d, *J* = 1.6 Hz, 1H), 7.37 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.88 (dd, *J* = 8.7, 1.4 Hz, 1H), 5.82 (dddd, *J* = 13.5, 10.1, 5.1, 3.5 Hz, 1H), 5.17 – 5.09 (m, 2H), 4.14 (d, *J* = 3.6 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 166.4, 164.0, 155.3, 133.4, 131.8, 122.5, 121.5, 117.8, 117.6, 116.7, 109.9, 60.5, 40.7; HRMS (ESI TOF) *m/z*: calcd for $C_{14}H_{11}{}^{79}BrNO_3$ $(M + H)^+$ 347.9984; Found, 347.9985.

(E)-1-benzyl-3-(5-bromo-2-hydroxybenzylidene)-4-diazopyrrolidine-2,5-dione (1ec):



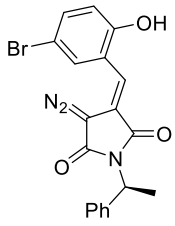
Compound **1ec** was synthesized following the general procedure-B. The product was obtained as orange solid, 0.300 g (93% yield); R_f =0.3 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.56 (s, 1H), 7.49 (s, 1H), 7.45 (d, *J* = 2.5 Hz, 1H), 7.39 – 7.28 (m, 6H), 6.88 (d, *J* = 8.7 Hz, 1H), 4.73 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 166.6, 164.3, 155.3, 136.2, 133.4, 131.8, 128.6, 127.6, 122.5, 121.7, 117.8, 117.6, 109.9, 60.7, 42.0; HRMS (ESI TOF) *m/z*: calcd for $C_{18}H_{13}BrN_3O_3$ $(M + H)^+$ 398.0140; Found, 398.0151 (for ^{79}Br), 400.0108 (for ^{81}Br).

(E)-3-(5-bromo-2-hydroxybenzylidene)-1-cyclohexyl-4-diazopyrrolidine-2,5-dione (1fc):



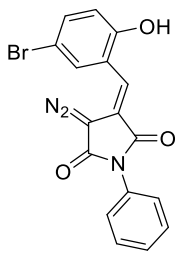
Compound **1fc** was synthesized following the general procedure-B. The product was obtained as yellow solid, 0.178 g (55% yield); R_f=0.4 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.51 (s, 1H), 7.43 (s, 1H), 7.40 (d, *J* = 2.5 Hz, 1H), 7.36 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 3.97 (tt, *J* = 12.2, 3.6 Hz, 1H), 2.05 (qd, *J* = 12.6, 3.2 Hz, 2H), 1.79 (d, *J* = 13.1 Hz, 2H), 1.63 (d, *J* = 12.0 Hz, 3H), 1.36 – 1.24 (m, 2H), 1.20 – 1.10 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 166.7, 164.2, 155.3, 133.2, 131.7, 122.6, 121.1, 117.8, 117.5, 109.9, 60.3, 51.4, 29.0, 25.4, 24.8; HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{17}{}^{81}BrN_3O_3$ $(M + H)^+$ 392.0433; Found, 392.0427.

(S,E)-3-(5-bromo-2-hydroxybenzylidene)-4-diazo-1-(1-phenylethyl)pyrrolidine-2,5-dione (1gc):



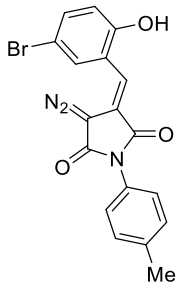
Compound **1gc** was synthesized following the general procedure-B. The product was obtained as orange solid, 0.218 g (68% yield); R_f=0.35 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.53 (s, 1H), 7.46 – 7.43 (m, 2H), 7.40 – 7.33 (m, 5H), 7.31 – 7.26 (m, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 5.45 (q, *J* = 7.2 Hz, 1H), 1.79 (d, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 166.6, 164.1, 155.3, 140.1, 133.3, 131.8, 128.4, 127.4, 126.7, 122.6, 121.4, 117.8, 117.5, 109.9, 60.6, 49.9, 17.1; HRMS (ESI TOF) *m/z*: calcd for $C_{19}H_{15}{}^{81}BrN_3O_3$ $(M + H)^+$ 412.0276; Found, 414.0260.

(E)-3-(5-bromo-2-hydroxybenzylidene)-4-diazo-1-phenylpyrrolidine-2,5-dione (1hc):



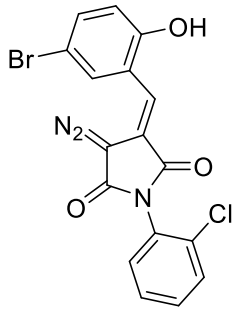
Compound **1hc** was synthesized following the general procedure-B. The product was obtained as yellow solid, 0.175 g (54% yield); R_f=0.25 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.60 (s, 1H), 7.57 – 7.50 (m, 3H), 7.48 – 7.38 (m, 5H), 6.91 (d, *J* = 8.7 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 166.0, 163.7, 155.3, 133.4, 132.0, 131.8, 128.9, 128.4, 127.1, 122.5, 121.8, 117.8, 117.4, 109.9, 61.1. HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{11}BrN_3O_3$ $(M + H)^+$ 383.9984; Found, 383.9984.

(E)-3-(5-bromo-2-hydroxybenzylidene)-4-diazo-1-(p-tolyl)pyrrolidine-2,5-dione (1ic):



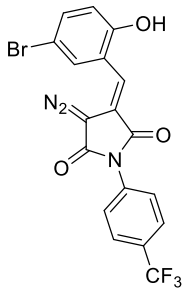
Compound **1ic** was synthesized following the general procedure-B. The product was obtained as brownish yellow solid, 0.180 g (56% yield); R_f =0.3 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.61 (s, 1H), 7.55 (s, 1H), 7.46 (d, *J* = 2.4 Hz, 1H), 7.40 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.29 – 7.25 (m, 2H), 6.90 (d, *J* = 8.7 Hz, 1H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 166.2, 163.8, 155.4, 138.1, 133.5, 131.8, 129.5, 129.4, 127.0, 122.5, 121.8, 117.9, 117.5, 109.9, 61.1, 20.8. HRMS (ESI TOF) *m/z*: calcd for $C_{18}H_{13}BrN_3O_3$ $(M + H)^+$ 398.0140; Found, 398.0146.

(E)-3-(5-bromo-2-hydroxybenzylidene)-1-(2-chlorophenyl)-4-diazopyrrolidine-2,5-dione (1jc):



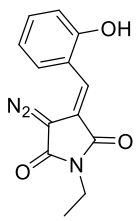
Compound **1jc** was synthesized following the general procedure-B. The product was obtained as orange solid, 0.273 g (85% yield); R_f =0.2 (petroleum ether/EtOAc 75:25); HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{10}BrClN_3O_3$ $(M + H)^+$ 417.9594; Found, 417.9563.

(E)-3-(5-bromo-2-hydroxybenzylidene)-4-diazo-1-(4-(trifluoromethyl)phenyl)pyrrolidine-2,5-dione (1kc):



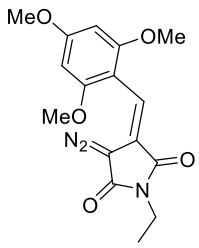
Compound **1kc** was synthesized following the general procedure-B. The product was obtained as yellow solid, 0.140 g (44% yield); R_f =0.3 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.64 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.59 (s, 1H), 7.47 (d, *J* = 2.5 Hz, 1H), 7.41 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 165.7, 163.3, 155.4, 135.6, 133.6, 131.8, 128.5 (q, *J* = 31.3 Hz), 127.7, 126.1 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.3 Hz), 122.4, 122.3, 117.9, 117.2, 110.0, 61.5; ^{19}F NMR (377 MHz, DMSO-d_6): δ (ppm) -61.1; HRMS (ESI TOF) *m/z*: calcd for $C_{18}H_{10}BrF_3N_3O_3$ $(M + H)^+$ 451.9858; Found, 451.9858.

(E)-3-diazo-1-ethyl-4-(2-hydroxybenzylidene)pyrrolidine-2,5-dione (1ab):



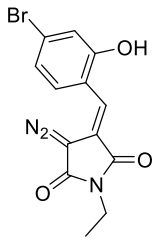
Compound **1ab** was synthesized following the general procedure-B. The product was obtained as yellow solid, 0.213 g (64% yield); R_f=0.3 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.20 (s, 1H), 7.56 (s, 1H), 7.22 (ddd, *J* = 9.4, 7.6, 2.2 Hz, 2H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.88 – 6.82 (m, 1H), 3.56 (q, *J* = 7.2 Hz, 2H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 166.8, 164.3, 156.1, 131.0, 129.8, 123.1, 120.2, 118.7, 116.3, 115.8, 59.9, 33.7, 13.3; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{12}N_3O_3$ $(M + H)^+$ 258.0878; Found, 258.0868.

(E)-3-diazo-1-ethyl-4-(2,4,6-trimethoxybenzylidene)pyrrolidine-2,5-dione (1ad):



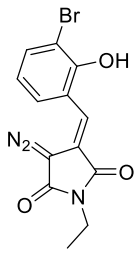
Compound **1ab** was synthesized following the general procedure-B. The product was obtained as yellow solid, 0.280 g (86% yield); R_f=0.2 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.58 (s, 1H), 6.11 (s, 2H), 3.84 (s, 3H), 3.81 (s, 6H), 3.68 (q, *J* = 7.2 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 167.7, 165.3, 163.2, 159.2, 120.4, 116.9, 104.0, 90.3, 62.0, 55.7, 55.6, 34.2, 13.8. HRMS (ESI TOF) *m/z*: calcd for $C_{16}H_{18}N_3O_5$ $(M + H)^+$ 332.1246; Found, 332.1244.

(E)-3-(4-bromo-2-hydroxybenzylidene)-4-diazo-1-ethylpyrrolidine-2,5-dione (1ae):



Compound **1ae** was synthesized following the general procedure-B. The product was obtained as orange solid, 0.217 g (67% yield); R_f =0.4 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (s, 1H), 7.11 (dq, *J* = 4.0, 1.8 Hz, 2H), 7.01 (dd, *J* = 8.6, 0.7 Hz, 1H), 6.71 – 6.67 (m, 1H), 3.73 (q, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 165.2, 155.1, 130.8, 124.5, 124.0, 122.4, 119.9, 119.6, 118.2, 34.6, 13.7; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{11}BrN_3O_3$ $(M + H)^+$ 335.9984; Found, 335.9988.

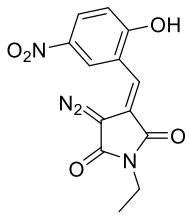
(E)-3-(3-bromo-2-hydroxybenzylidene)-4-diazo-1-ethylpyrrolidine-2,5-dione (1af):



Compound **1af** was synthesized following the general procedure-B. The product was obtained as orange solid, 0.207 g (64% yield); R_f=0.4 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (s, 1H), 7.48 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.11 (dt, *J* = 7.6, 1.1 Hz, 1H), 6.87 (t, *J* = 7.9 Hz, 1H), 5.91 (s, 1H), 3.71 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8,

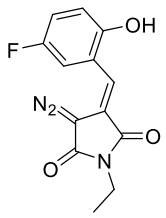
164.6, 150.6, 133.2, 129.3, 122.3, 121.9, 121.4, 118.9, 111.4, 34.5, 13.7; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{11}BrN_3O_3$ $(M + H)^+$ 335.9984; Found, 335.9984.

(E)-3-diazo-1-ethyl-4-(2-hydroxy-5-nitrobenzylidene)pyrrolidine-2,5-dione (1ag):



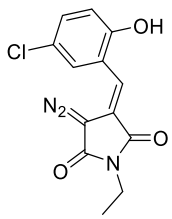
Compound **1ag** was synthesized following the general procedure-B. The product was obtained as yellow solid, 0.165 g (50% yield); R_f =0.15 (petroleum ether/EtOAc 70:30); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (dd, *J* = 8.9, 2.7 Hz, 1H), 8.07 (dd, *J* = 2.7, 0.7 Hz, 1H), 7.68 (d, *J* = 7.0 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 1H), 3.75 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 164.1, 159.1, 143.4, 127.9, 126.4, 125.5, 123.2, 121.8, 118.2, 71.6, 34.2, 13.2; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{11}N_4O_5$ $(M + H)^+$ 303.0729; Found, 303.0721.

(E)-3-diazo-1-ethyl-4-(5-fluoro-2-hydroxybenzylidene)pyrrolidine-2,5-dione (1ah):



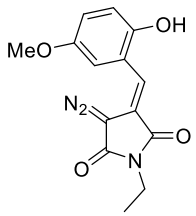
Compound **1ah** was synthesized following the general procedure-B. The product was obtained as orange solid, 0.217 g (67% yield); R_f =0.3 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.66 (s, 1H), 6.96 (ddd, *J* = 8.9, 7.7, 3.0 Hz, 1H), 6.91 – 6.86 (m, 2H), 6.83 (dd, *J* = 8.6, 3.0 Hz, 1H), 3.72 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.3, 165.2, 156.5 (d, *J* = 240.4 Hz), 150.8 (d, *J* = 2.1 Hz), 122.6 (d, *J* = 2.0 Hz), 121.5 (d, *J* = 7.9 Hz), 118.7, 117.9 (d, *J* = 23.2 Hz), 117.3 (d, *J* = 8.1 Hz), 115.8 (d, *J* = 23.6 Hz), 34.6, 13.7; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -122.6; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{11}FN_3O_3$ $(M + H)^+$ 276.0784; Found, 276.0781.

(E)-3-(5-chloro-2-hydroxybenzylidene)-4-diazo-1-phenylpyrrolidine-2,5-dione (1ai):



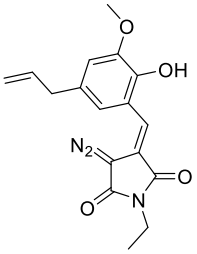
Compound **1ai** was synthesized following the general procedure-B. The product was obtained as white solid, 0.150 g (46% yield); R_f =0.25 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.50 (s, 1H), 7.47 (s, 1H), 7.29 (d, *J* = 2.6 Hz, 1H), 7.25 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 1H), 3.57 (q, *J* = 7.2 Hz, 2H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 166.5, 164.2, 154.8, 130.4, 128.9, 122.5, 121.9, 121.3, 117.8, 117.3, 60.3, 33.7, 13.3; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{11}ClN_3O_3$ $(M + H)^+$ 292.0489; Found, 292.0488.

(E)-3-diazo-1-ethyl-4-(2-hydroxy-5-methoxybenzylidene)pyrrolidine-2,5-dione (1aj):



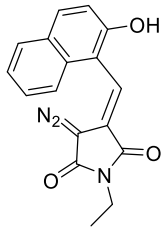
Compound **1aj** was synthesized following the general procedure-B. The product was obtained as white solid, 0.130 g (40% yield); R_f=0.35 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.59 (s, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 6.88 (ddt, *J* = 9.3, 6.8, 0.9 Hz, 2H), 6.80 (t, *J* = 2.1 Hz, 1H), 3.82 (s, 3H), 3.70 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ (ppm) 167.0, 164.8, 159.8, 134.8, 129.8, 127.4, 121.5, 117.6, 115.4, 114.1, 59.7, 55.4, 34.5, 13.7; HRMS (ESI TOF) *m/z*: calcd for $C_{14}H_{14}N_3O_4$ $(M + H)^+$ 288.0984; Found, 288.0989.

(E)-3-(5-allyl-2-hydroxy-3-methoxybenzylidene)-4-diazo-1-ethylpyrrolidine-2,5-dione (1ak):



Compound **1ak** was synthesized following the general procedure-B. The product was obtained as orange red solid, 0.268 g (82% yield); R_f =0.35 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72 (s, 1H), 6.69 (d, *J* = 1.9 Hz, 1H), 6.56 (dt, *J* = 2.0, 0.6 Hz, 1H), 5.98 – 5.86 (m, 2H), 5.15 – 5.06 (m, 2H), 3.90 (s, 3H), 3.70 (q, *J* = 7.2 Hz, 2H), 3.31 (dt, *J* = 6.9, 1.5 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 167.3, 164.9, 146.8, 142.8, 136.9, 131.6, 123.1, 121.1, 119.7, 117.6, 116.6, 112.3, 56.3, 40.1, 34.4, 13.7; HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{18}N_3O_4$ $(M + H)^+$ 328.1292; Found, 328.1281.

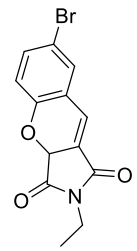
(E)-3-diazo-1-ethyl-4-((2-hydroxynaphthalen-1-yl)methylene)pyrrolidine-2,5-dione (1al):



Compound **1al** was synthesized following the general procedure-B. The product was obtained as orange solid, 0.140 mg (43% yield); R_f =0.3 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (s, 1H), 7.81 (tt, *J* = 9.0, 1.8 Hz, 3H), 7.53 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.41 (ddd, *J* = 7.9, 6.8, 1.2 Hz, 1H), 7.19 (d, *J* = 8.9 Hz, 1H), 6.43 (s, 1H), 3.75 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.8, 165.4, 154.1, 133.7, 131.2, 130.0, 129.0, 128.4, 125.4, 125.3, 122.1, 118.6, 117.8, 116.0, 33.9, 13.3; HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{14}N_3O_3$ $(M + H)^+$ 308.1035; Found, 308.1031.

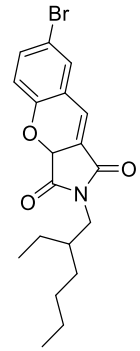
4B.14.3. For O–H functionalization compounds:

7-Bromo-2-ethylchromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3ac):



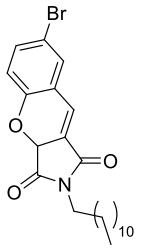
Compound **3ac** was synthesized following the general procedure-C. The product was obtained as white solid, 22.6 mg (73% yield); R_f =0.45 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.46 – 7.40 (m, 2H), 7.29 (d, *J* = 2.3 Hz, 1H), 7.03 – 6.99 (m, 1H), 5.27 (d, *J* = 2.3 Hz, 1H), 3.71 (qd, *J* = 7.2, 1.9 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.1, 164.6, 153.6, 135.3, 132.3, 127.0, 123.5, 122.3, 119.2, 115.6, 71.2, 34.0, 13.3. HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{11}BrNO_3$ $(M + H)^+$: 307.9922, Found:307.9926.

7-Bromo-2-(2-ethylhexyl)chromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3bc):



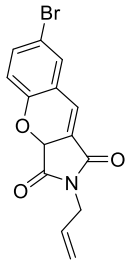
Compound **3bc** was synthesized following the general procedure-C. The product was obtained as white solid, 26.7 mg (68% yield); R_f =0.5 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47 – 7.40 (m, 2H), 7.28 (d, *J* = 2.3 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 5.27 (d, *J* = 2.3 Hz, 1H), 3.60 – 3.49 (m, 2H), 1.81 (dq, *J* = 12.2, 6.0, 5.6 Hz, 1H), 1.36 – 1.20 (m, 8H), 0.90 (dd, *J* = 8.3, 7.2 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.6, 165.1, 165.1, 153.6, 135.3, 132.3, 126.9, 123.6, 122.2, 119.2, 115.6, 71.1, 42.8, 37.8, 30.6, 28.5, 28.5, 24.0, 24.0, 23.1, 23.1, 14.2, 10.5; HRMS (ESI TOF) *m/z*: calcd for $C_{19}H_{23}BrNO_3$ $(M + H)^+$: 392.0861, Found: 392.0851.

7-Bromo-2-dodecylchromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3cc):



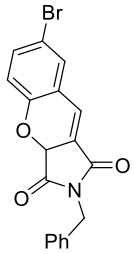
Compound **3cc** was synthesized following the general procedure-C. The product was obtained as white solid, 30.0 mg (67% yield); R_f =0.5 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 – 7.40 (m, 2H), 7.28 (d, *J* = 2.3 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 5.26 (d, *J* = 2.2 Hz, 1H), 3.69 – 3.56 (m, 2H), 1.63 (dd, *J* = 11.4, 5.3 Hz, 3H), 1.27 (d, *J* = 25.0 Hz, 17H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.3, 164.8, 153.6, 135.3, 132.3, 126.9, 123.5, 122.3, 119.2, 115.6, 71.2, 39.1, 32.0, 29.7, 29.7, 29.6, 29.5, 29.2, 27.9, 27.0, 22.8, 14.2; HRMS (ESI TOF) *m/z*: calcd for $C_{23}H_{31}BrNO_3$ $(M + H)^+$: 448.1487, Found: 448.1489.

2-Allyl-7-bromochromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3dc):



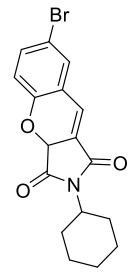
Compound **3dc** was synthesized following the general procedure-C. The product was obtained as white solid, 15.4 mg (48% yield); R_f=0.55 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 – 7.41 (m, 1H), 7.31 (d, *J* = 2.3 Hz, 0H), 7.05 – 6.97 (m, 0H), 5.84 (ddt, *J* = 17.1, 10.1, 6.0 Hz, 1H), 5.34 – 5.20 (m, 1H), 4.24 (dt, *J* = 6.0, 1.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.8, 164.3, 153.6, 135.4, 132.3, 130.2, 127.3, 123.4, 122.0, 119.3, 119.2, 115.7, 71.2, 41.0, 29.8. HRMS (ESI TOF) *m/z*: calcd for $C_{14}H_{11}BrNO_3$ $(M + H)^+$ 319.9922; Found, 319.9922.

2-Benzyl-7-bromochromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3ec):



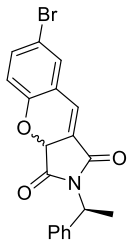
Compound **3ec** was synthesized following the general procedure-C. The product was obtained as white solid, 23 mg (62% yield); R_f=0.55 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.46 – 7.38 (m, 4H), 7.36 – 7.27 (m, 4H), 7.00 (dq, *J* = 9.2, 1.1 Hz, 1H), 5.28 (d, *J* = 2.3 Hz, 1H), 4.79 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.9, 164.5, 153.6, 135.4, 135.2, 132.3, 129.2, 128.9, 128.4, 127.4, 123.4, 121.9, 119.2, 115.6, 71.3, 42.5. HRMS (ESI TOF) *m/z*: calcd for $C_{18}H_{13}BrNO_3$ $(M + H)^+$ 370.0079; Found, 370.0100 (for ^{79}Br), 372.0078 (for ^{81}Br).

7-Bromo-2-cyclohexylchromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3fc):



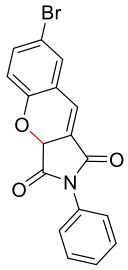
Compound **3fc** was synthesized following the general procedure-C. The product was obtained as white solid, 24 mg (66% yield); R_f=0.65 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 2.3 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 5.21 (d, *J* = 2.3 Hz, 1H), 4.09 (tt, *J* = 12.3, 3.8 Hz, 1H), 2.24 – 2.11 (m, 2H), 1.90 – 1.82 (m, 2H), 1.68 (ddd, *J* = 12.2, 5.6, 2.8 Hz, 3H), 1.41 – 1.22 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.4, 164.8, 153.6, 135.2, 132.2, 126.6, 123.6, 122.4, 119.2, 115.5, 70.9, 52.1, 29.3, 28.9, 25.9, 25.9, 25.1. HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{17}BrNO_3$ $(M + H)^+$ 362.0392; Found, 362.0381 (for ^{79}Br) and 364.0369 (for ^{81}Br).

7-Bromo-2-((S)-1-phenylethyl)chromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3gc):



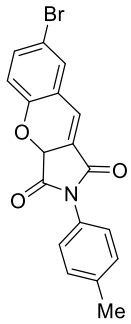
Compound **3gc** was synthesized following the general procedure-C. The product was obtained as white solid, 24.7 mg (64% yield, 1:1 *dr*); R_f =0.65 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 – 7.47 (m, 4H), 7.41 (d, *J* = 7.5 Hz, 4H), 7.32 (dddd, *J* = 13.9, 8.7, 6.7, 1.7 Hz, 6H), 7.26 – 7.23 (m, 2H), 7.01 – 6.96 (m, 2H), 5.53 (qd, *J* = 7.3, 3.1 Hz, 2H), 5.24 (d, *J* = 2.3 Hz, 1H), 5.20 (d, *J* = 2.3 Hz, 1H), 1.89 (dd, *J* = 7.3, 5.8 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.09, 169.99, 164.54, 164.52, 153.60, 139.28, 139.03, 135.28, 132.26, 128.75, 128.72, 128.26, 127.83, 127.81, 127.11, 127.09, 123.50, 122.12, 119.20, 115.57, 71.02, 50.97, 50.71, 16.97, 16.83. HRMS (ESI TOF) *m/z*: calcd for $C_{19}H_{15}BrNO_3$ $(M + H)^+$ 384.0235; Found, 384.0237 (for ^{79}Br) and 386.0213 (for ^{81}Br).

7-Bromo-2-phenylchromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3hc):



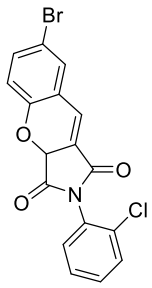
Compound **3hc** was synthesized following the general procedure-C. The product was obtained as white solid, 14.2 mg (40% yield); R_f =0.55 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.79 (d, *J* = 2.5 Hz, 1H), 7.61 (d, *J* = 2.3 Hz, 1H), 7.58 – 7.51 (m, 3H), 7.49 – 7.44 (m, 1H), 7.42 – 7.38 (m, 2H), 7.12 (dd, *J* = 8.7, 0.7 Hz, 1H), 5.75 (d, *J* = 2.3 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 169.6, 164.1, 153.3, 134.8, 132.3, 131.6, 129.1, 128.8, 127.1, 126.5, 124.0, 122.9, 119.0, 114.4, 71.3. HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{11}BrNO_3$ $(M + H)^+$ 355.9922; Found, 355.9927.

7-Bromo-2-(p-tolyl)chromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3ic):



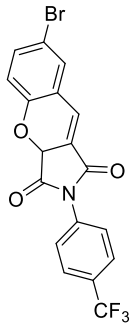
Compound **3ic** was synthesized following the general procedure-C. The product was obtained as white solid, 20.3 mg (55% yield); R_f =0.55 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 – 7.44 (m, 2H), 7.41 (d, *J* = 2.3 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.26 (dd, *J* = 6.2, 2.3 Hz, 2H), 7.05 (d, *J* = 8.5 Hz, 1H), 5.47 (d, *J* = 2.3 Hz, 1H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.5, 164.0, 153.7, 139.4, 135.5, 132.4, 130.1, 128.4, 128.1, 126.2, 123.5, 121.8, 119.3, 115.7, 71.4, 21.4. HRMS (ESI TOF) *m/z*: calcd for $C_{18}H_{13}BrNO_3$ $(M + H)^+$ 370.0079; Found, 370.0042 (for ^{79}Br), 372.0074 (for ^{81}Br).

7-Bromo-2-(2-chlorophenyl)chromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3jc):



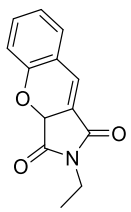
Compound **3jc** was synthesized following the general procedure-C. The product was obtained as white solid, 18 mg (46% yield, 1.6:1 *dr*); R_f =0.55 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.57 (ddd, *J* = 7.1, 3.8, 1.8 Hz, 1H), 7.50 – 7.40 (m, 5H), 7.38 – 7.27 (m, 1H), 7.06 (ddd, *J* = 8.3, 2.3, 1.5 Hz, 1H), 5.57 (d, *J* = 2.3 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.7, 168.6, 163.3, 163.0, 153.6, 135.7, 135.7, 133.0, 132.5, 132.5, 132.1, 131.4, 131.2, 130.8, 130.6, 130.0, 129.8, 129.2, 128.9, 128.8, 128.7, 128.0, 123.4, 123.3, 121.6, 121.4, 119.3, 119.3, 115.8, 115.8, 71.5, 71.4; HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{10}BrClNO_3$ $(M + H)^+$ 389.9533; Found, 389.9527 (for ^{79}Br), 391.9507 (for ^{81}Br).

7-Bromo-2-(4-(trifluoromethyl)phenyl)chromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3kc):



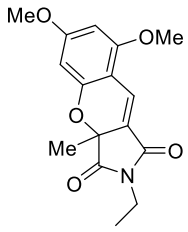
Compound **3kc** was synthesized following the general procedure-C. The product was obtained as white solid, 27.5 mg (65% yield); R_f =0.5 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.79 (d, *J* = 8.4 Hz, 2H), 7.62 – 7.58 (m, 2H), 7.50 (d, *J* = 2.3 Hz, 1H), 7.48 – 7.46 (m, 1H), 7.07 (dt, *J* = 8.3, 0.7 Hz, 1H), 5.51 (d, *J* = 2.3 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.3, 168.9, 156.0, 140.2 (d, *J* = 262.4 Hz), 135.9, 132.6, 131.4, 129.2, 126.6, 126.6, 126.5, 123.3, 120.9 (d, *J* = 21.9 Hz), 119.4, 115.9 (d, *J* = 3.9 Hz), 109.4, 71.3. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -62.8; HRMS (ESI TOF) *m/z*: calcd for $C_{18}H_{10}BrF_3NO_3$ $(M + H)^+$ 425.9776; Found, 425.9789.

2-Ethylchromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3ab):



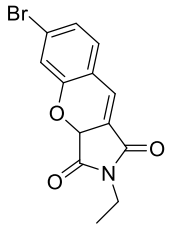
Compound **3ab** was synthesized following the general procedure-C. The product was obtained as white solid, 15.2 mg (66% yield); R_f =0.45 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 (d, *J* = 2.3 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.14 – 7.11 (m, 1H), 7.07 (td, *J* = 7.5, 1.1 Hz, 1H), 5.28 (d, *J* = 2.3 Hz, 1H), 3.71 (qd, *J* = 7.2, 2.0 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.7, 165.1, 154.7, 132.8, 130.1, 128.4, 123.5, 121.8, 121.1, 117.5, 71.2, 33.9, 13.3. HRMS (ESI TOF): *m/z* calcd for $C_{13}H_{12}NO_3$ $(M + H)^+$: 230.0817, Found: 230.0811.

2-Ethyl-6,8-dimethoxy-3a-methylchromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3ad):



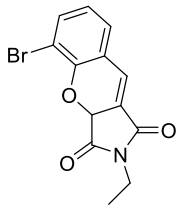
Compound **3ab** was synthesized following the general procedure-C. The product was obtained as yellowish liquid, 19 mg (62% yield); R_f =0.5 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.59 (d, *J* = 0.7 Hz, 1H), 6.28 (dd, *J* = 2.3, 0.7 Hz, 1H), 6.10 (d, *J* = 2.3 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.65 (qd, *J* = 7.2, 1.4 Hz, 2H), 1.52 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 174.3, 165.5, 164.5, 159.2, 155.5, 123.6, 119.6, 104.8, 95.1, 93.2, 75.4, 56.0, 55.7, 33.4, 20.5, 13.3; HRMS (ESI TOF): *m/z* calcd for $C_{16}H_{18}NO_5$ $(M + H)^+$: 304.1185, Found: 304.1185.

6-Bromo-2-ethylchromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3ae):



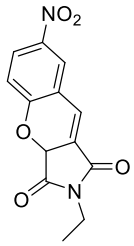
Compound **3ae** was synthesized following the general procedure-C. The product was obtained as white solid, 26 mg (84% yield); R_f =0.5 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31 (dd, *J* = 2.3, 0.8 Hz, 1H), 7.30 (d, *J* = 1.8 Hz, 1H), 7.22 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 5.26 (d, *J* = 2.3 Hz, 1H), 3.70 (qd, *J* = 7.2, 2.0 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.1, 164.8, 155.0, 130.9, 127.5, 126.8, 126.2, 121.3, 121.0, 120.7, 71.3, 34.0, 13.2; HRMS (ESI TOF): *m/z* calcd for $C_{13}H_{12}NO_3$ $(M + H)^+$: 307.9922, Found: 307.9927.

5-Bromo-2-ethylchromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3af):



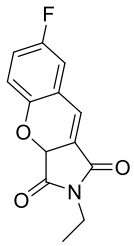
Compound **3af** was synthesized following the general procedure-C. The product was obtained as white solid, 21.5 mg (70% yield); R_f =0.4 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.56 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.33 (d, *J* = 2.3 Hz, 1H), 7.29 – 7.25 (m, 1H), 6.95 (t, *J* = 7.8 Hz, 1H), 5.33 (d, *J* = 2.3 Hz, 1H), 3.71 (qd, *J* = 7.2, 2.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.6, 164.7, 151.5, 136.3, 129.1, 127.7, 124.1, 123.2, 121.9, 111.6, 71.5, 34.0, 13.3; HRMS (ESI TOF): *m/z* calcd for $C_{13}H_{12}NO_3$ $(M + H)^+$: 307.9922, Found: 307.9935.

2-Ethyl-7-nitrochromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3ag):



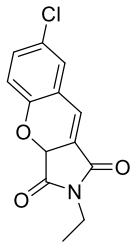
Compound **3ag** was synthesized following the general procedure-C. The product was obtained as white solid, 14.1 mg (52% yield); R_f=0.4 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.27 – 8.21 (m, 2H), 7.40 (d, *J* = 2.3 Hz, 1H), 7.24 (dt, *J* = 8.4, 0.8 Hz, 1H), 5.39 (d, *J* = 2.3 Hz, 1H), 3.73 (qd, *J* = 7.2, 1.8 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.3, 164.1, 159.1, 143.4, 127.9, 126.4, 125.5, 123.2, 121.8, 118.2, 71.6, 34.2, 13.2; HRMS (ESI TOF): *m/z* calcd for $C_{13}H_{11}N_2O_5$ $(M + H)^+$: 275.0668, Found: 275.0671.

2-Ethyl-7-fluorochromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3ah):



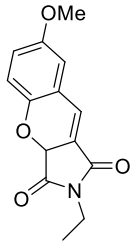
Compound **3ah** was synthesized following the general procedure-C. The product was obtained as white solid, 17.0 mg (68% yield); R_f =0.45 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30 (d, *J* = 2.3 Hz, 1H), 7.12 – 6.98 (m, 3H), 5.26 (d, *J* = 2.3 Hz, 1H), 3.70 (qd, *J* = 7.2, 2.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.3, 164.7, 158.2 (d, *J* = 242.7 Hz), 150.6 (d, *J* = 2.5 Hz), 127.3 (d, *J* = 2.5 Hz), 122.7 (d, *J* = 8.5 Hz), 122.6, 119.2 (d, *J* = 23.6 Hz), 118.7 (d, *J* = 8.1 Hz), 115.8 (d, *J* = 23.9 Hz), 71.3, 34.0, 13.2; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -119.5; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{11}FNO_3$ $(M + H)^+$ 248.0723; Found, 248.0717.

7-Chloro-2-ethylchromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3ai):



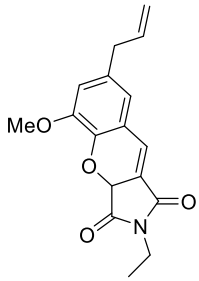
Compound **3ai** was synthesized following the general procedure-C. The product was obtained as white solid, 21.0 mg (80% yield); R_f=0.5 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30 (t, *J* = 2.7 Hz, 1H), 7.28 (d, *J* = 2.5 Hz, 0H), 7.07 (dt, *J* = 8.3, 0.8 Hz, 0H), 5.27 (d, *J* = 2.2 Hz, 0H), 3.71 (qd, *J* = 7.2, 2.0 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.2, 164.7, 153.1, 132.4, 129.4, 128.4, 127.1, 123.0, 122.4, 118.8, 71.3, 34.0, 13.2; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_{11}ClNO_3$ $(M + H)^+$ 264.0427; Found, 264.0422.

2-Ethyl-7-methoxychromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3aj):



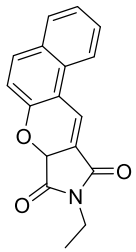
Compound **3aj** was synthesized following the general procedure-C. The product was obtained as white solid, 14.0 mg (54% yield); R_f =0.45 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33 (d, *J* = 2.2 Hz, 1H), 7.06 (dd, *J* = 8.9, 0.7 Hz, 1H), 6.89 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.83 (d, *J* = 3.0 Hz, 1H), 5.22 (d, *J* = 2.2 Hz, 1H), 3.80 (s, 3H), 3.70 (qd, *J* = 7.2, 2.3 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.7, 165.0, 155.4, 148.6, 128.3, 122.3, 121.8, 118.6, 118.2, 114.0, 71.4, 56.0, 33.9, 13.3; HRMS (ESI TOF) *m/z*: calcd for $C_{14}H_{14}NO_4$ $(M + H)^+$: 260.0923, Found:260.0930.

7-Allyl-2-ethyl-5-methoxychromeno[2,3-c]pyrrole-1,3(2H,3aH)-dione (3ak):



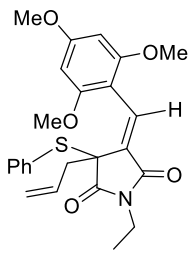
Compound **3ak** was synthesized following the general procedure-C. The product was obtained as white solid, 12.7 mg (42% yield); R_f =0.35 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32 (d, *J* = 2.2 Hz, 1H), 6.77 (dd, *J* = 18.1, 1.9 Hz, 2H), 5.99 – 5.88 (m, 1H), 5.23 (d, *J* = 2.2 Hz, 1H), 5.13 (q, *J* = 1.3 Hz, 1H), 5.09 (dq, *J* = 5.6, 1.6 Hz, 1H), 3.91 – 3.85 (m, 3H), 3.70 (qd, *J* = 7.2, 2.9 Hz, 2H), 3.34 (dt, *J* = 6.6, 1.5 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.2, 165.1, 148.8, 142.3, 136.8, 135.1, 128.5, 122.4, 121.4, 121.2, 116.7, 116.1, 71.3, 56.3, 39.8, 33.8, 13.3; HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{18}NO_4$ $(M + H)^+$ 300.1236; Found, 300.1238.

9-Ethylbenzo[5,6]chromeno[2,3-c]pyrrole-8,10(7aH,9H)-dione (3al):



Compound **3al** was synthesized following the general procedure-C. The product was obtained as white solid, 15.0 mg (54% yield); R_f =0.45 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.03 – 7.97 (m, 2H), 7.85 (d, *J* = 8.9 Hz, 1H), 7.82 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.60 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.46 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.31 (dd, *J* = 8.9, 0.7 Hz, 1H), 5.34 (d, *J* = 2.1 Hz, 1H), 3.74 (qd, *J* = 7.2, 1.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.7, 165.3, 154.0, 133.7, 131.2, 130.0, 129.0, 128.4, 125.4, 125.2, 122.1, 118.6, 117.8, 115.9, 71.3, 33.9, 13.3; HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{14}NO_3$ $(M + H)^+$ 280.0974; Found, 280.0970.

(Z)-3-allyl-1-ethyl-3-(phenylthio)-4-(2,4,6-trimethoxybenzylidene)pyrrolidine-2,5-dione (1ad-DK):



Compound **3al** was synthesized following the procedure in Section 5.5 (Scheme 2C). The product was obtained as yellow liquid, 36.0 mg (80% yield); R_f =0.3 (petroleum ether/EtOAc 75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 – 7.55 (m, 2H), 7.33 – 7.27 (m, 1H), 7.22 (ddt, *J* = 8.3, 6.4, 1.4 Hz, 2H), 7.17 (s, 1H), 6.13 (s, 2H), 5.71 (dddd, *J* = 16.7, 10.1, 8.2, 6.3 Hz, 1H), 5.17 (dq, *J* = 17.1, 1.3 Hz, 1H), 5.07 (dd, *J* = 10.1, 1.9 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 6H), 3.32 (qd, *J* = 7.2, 3.5 Hz, 2H), 2.97 – 2.90 (m, 1H), 2.72 (ddt, *J* = 13.3, 6.3, 1.2 Hz, 1H), 0.78 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 174.7, 166.2, 162.6, 159.3, 137.3, 132.5, 130.9, 129.8, 129.6, 129.5, 128.8, 120.5, 105.9, 90.4, 59.2, 55.6, 55.5, 41.4, 33.2, 13.0; HRMS (ESI TOF) *m/z*: calcd for $C_{25}H_{28}NO_5S$ $(M + H)^+$ 454.1688; Found, 454.1687.

4B.14.4. Appendix-IV: ^{1}H, $^{13}C\{^{1}H\}$, and ^{19}F NMR spectral data of representative compounds

Compounds	Figure IV.X	Data	Page No.
1′ac	Figure IV.1 and IV.2	^{1}H and ^{13}C	206
1′gc	Figure IV.3 and IV.4	^{1}H and ^{13}C	207
1ac	Figure IV.5 and IV.6	^{1}H and ^{13}C	208
1gc	Figure IV.7 and IV.8	^{1}H and ^{13}C	209
3ac	Figure IV.9 and IV.10	^{1}H and ^{13}C	210
3gc	Figure IV.11 and IV.12	^{1}H and ^{13}C	211
3ad	Figure IV.13 and IV.14	^{1}H and ^{13}C	212
1ad-DK	Figure IV.15 and IV.16	^{1}H and ^{13}C	213

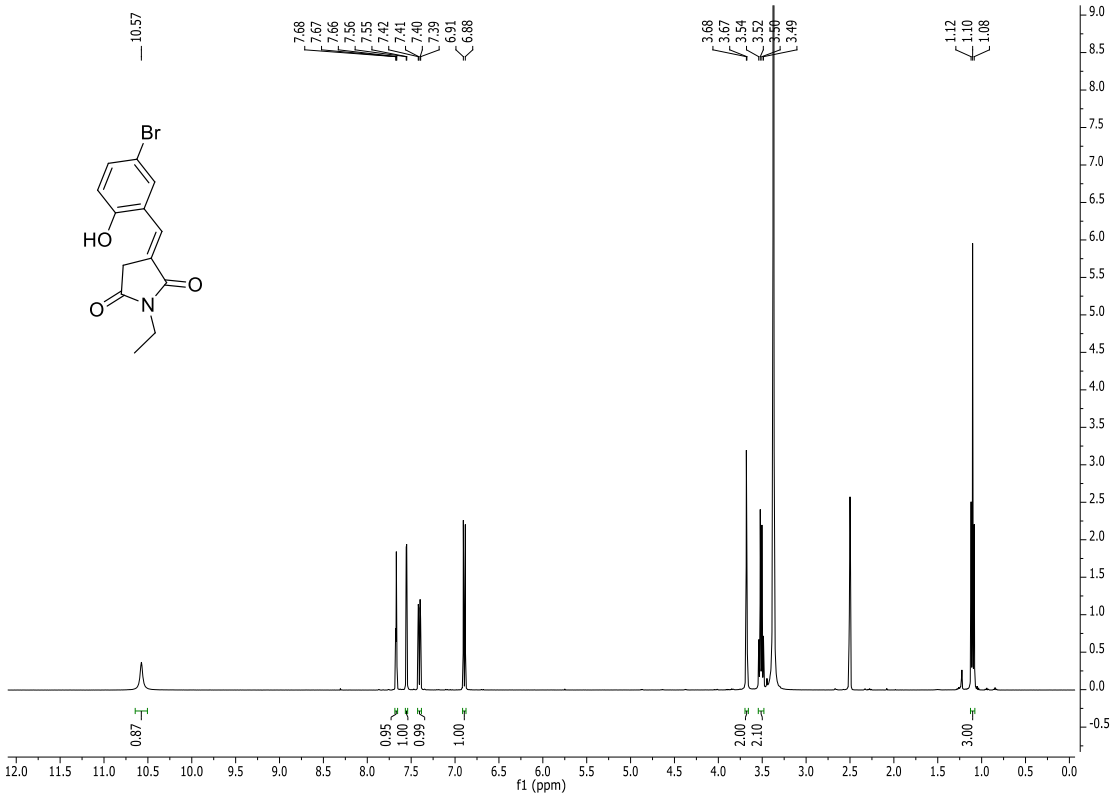


Figure IV.1. ^{1}H NMR (400 MHz, DMSO-d_6) Spectrum of **1′ac**

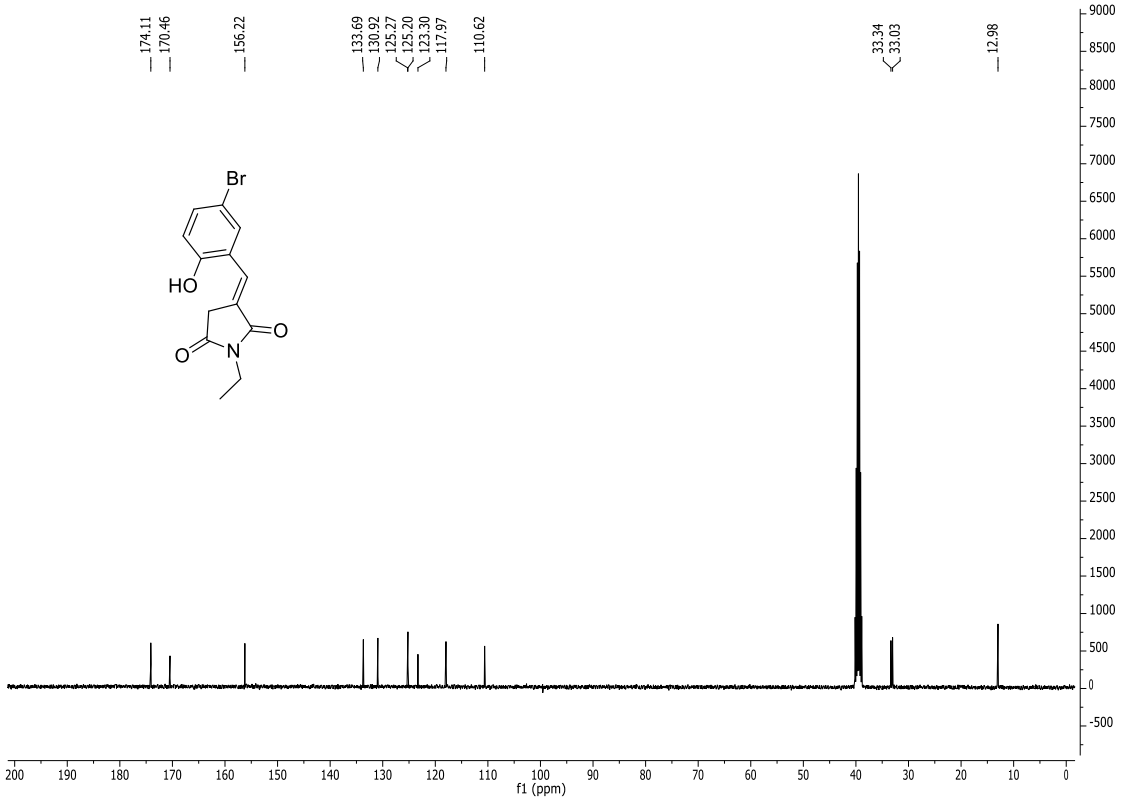


Figure IV.2. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) Spectrum of **1′ac**

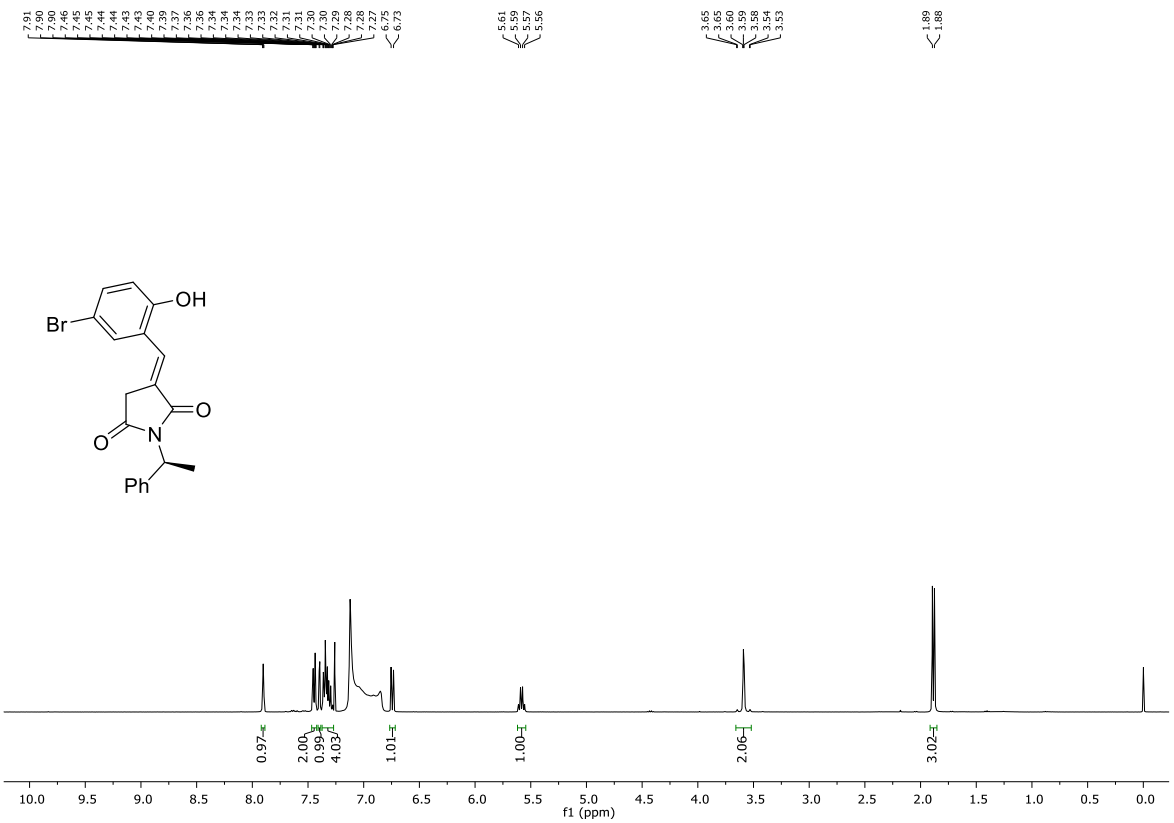


Figure IV.3. ^{1}H NMR (400 MHz, $CDCl_3$:TFA) Spectrum of **1′gc**

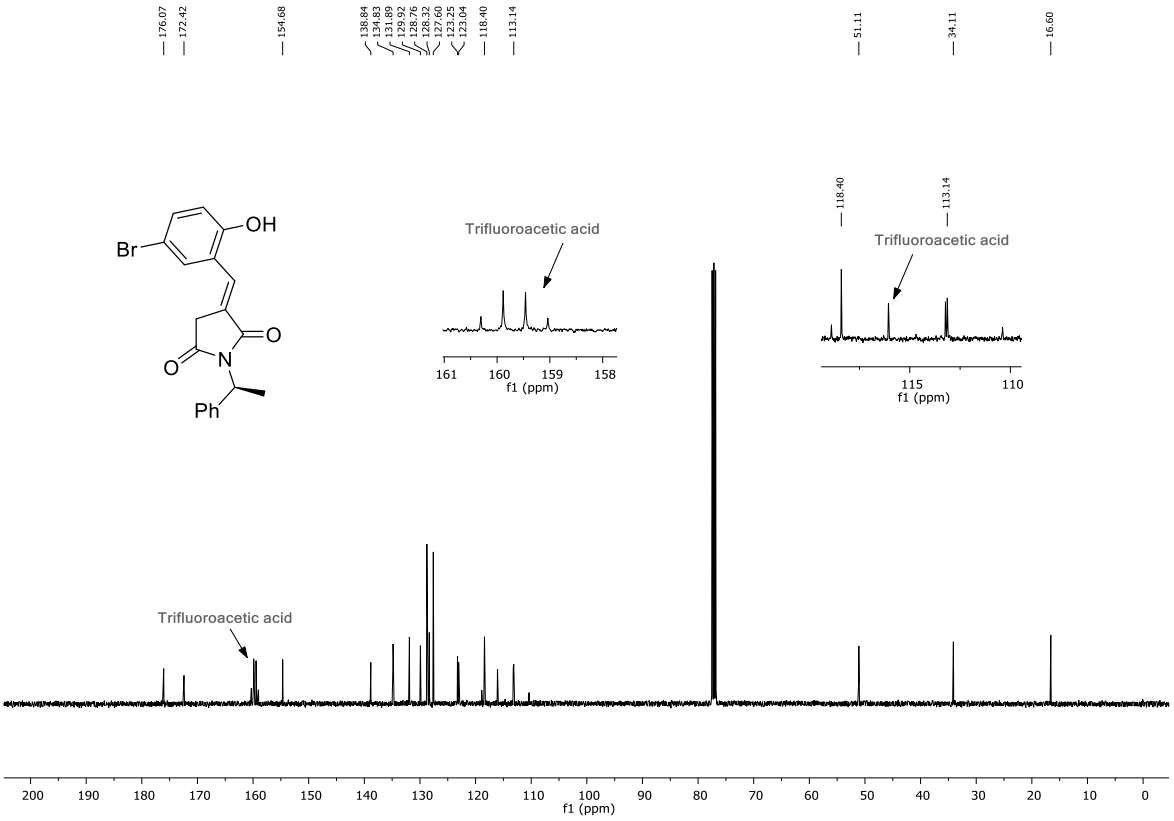


Figure IV.4. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$:TFA) Spectrum of **1′gc**

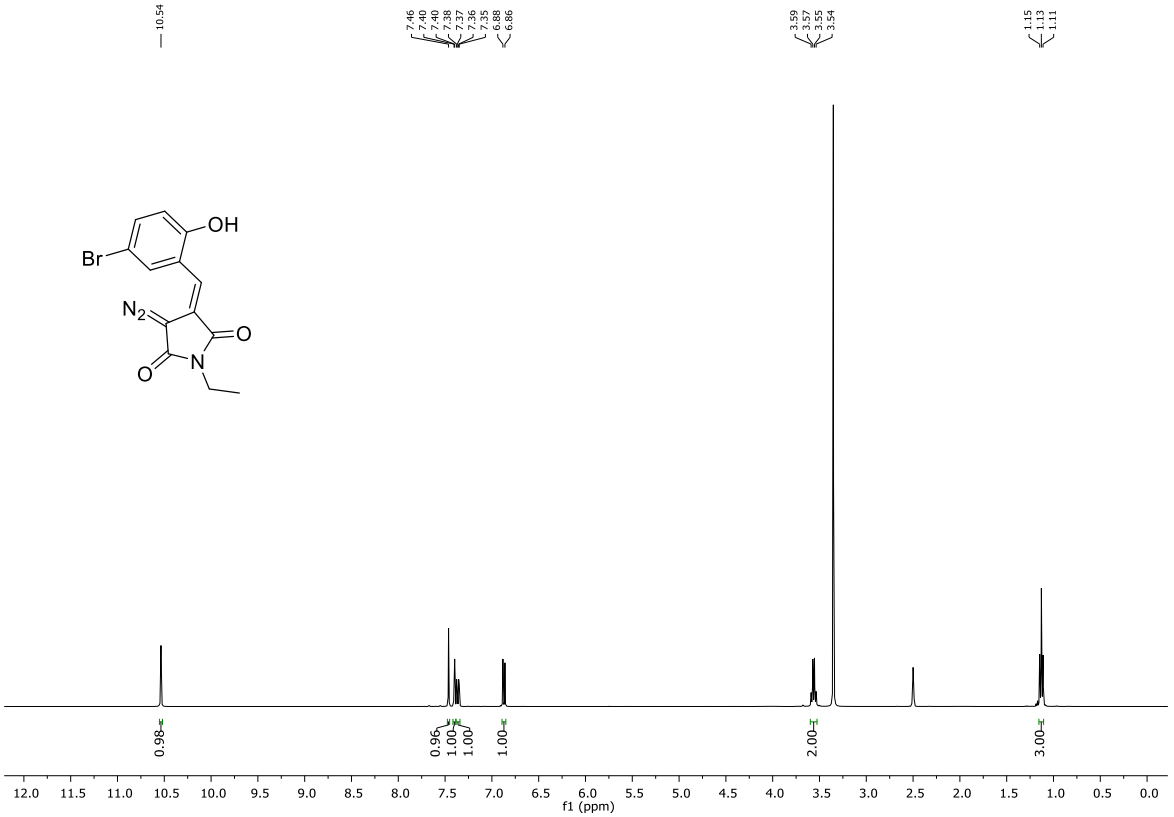


Figure IV.5. ^{1}H NMR (400 MHz, DMSO-d_6) Spectrum of **1ac**

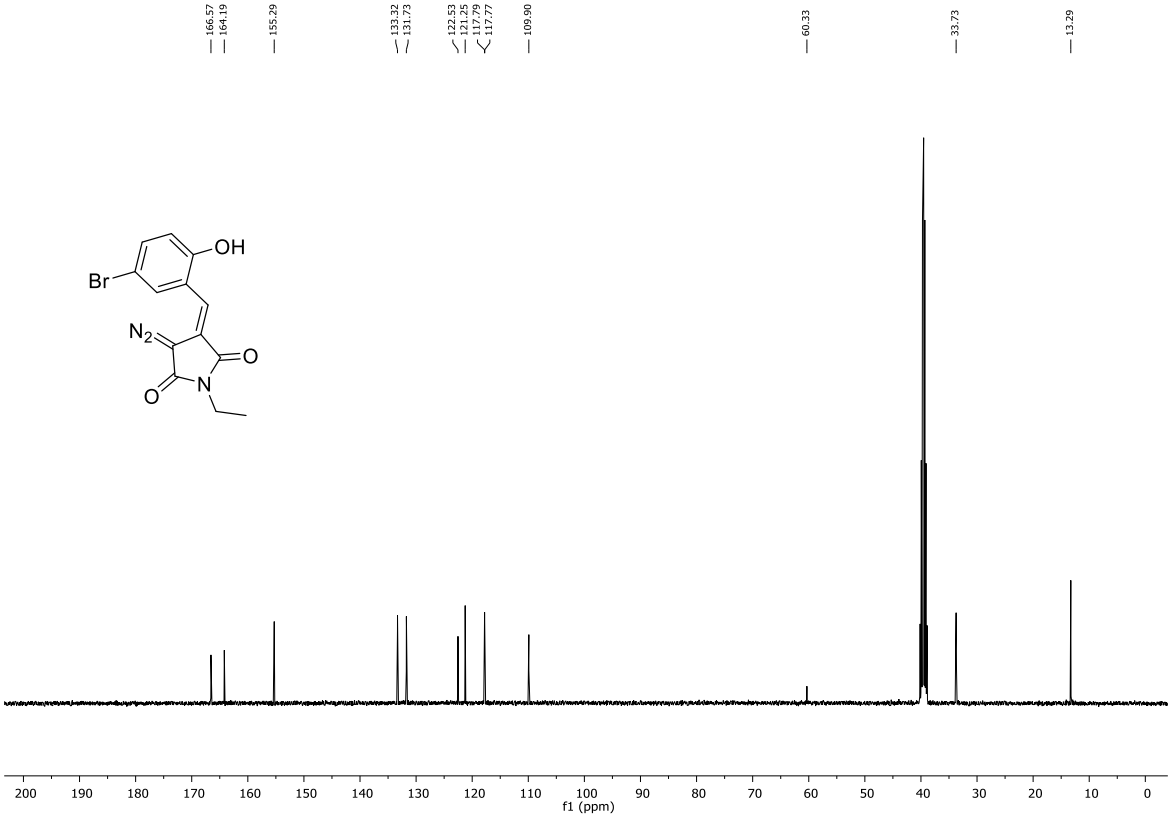


Figure IV.6. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) Spectrum of **1ac**

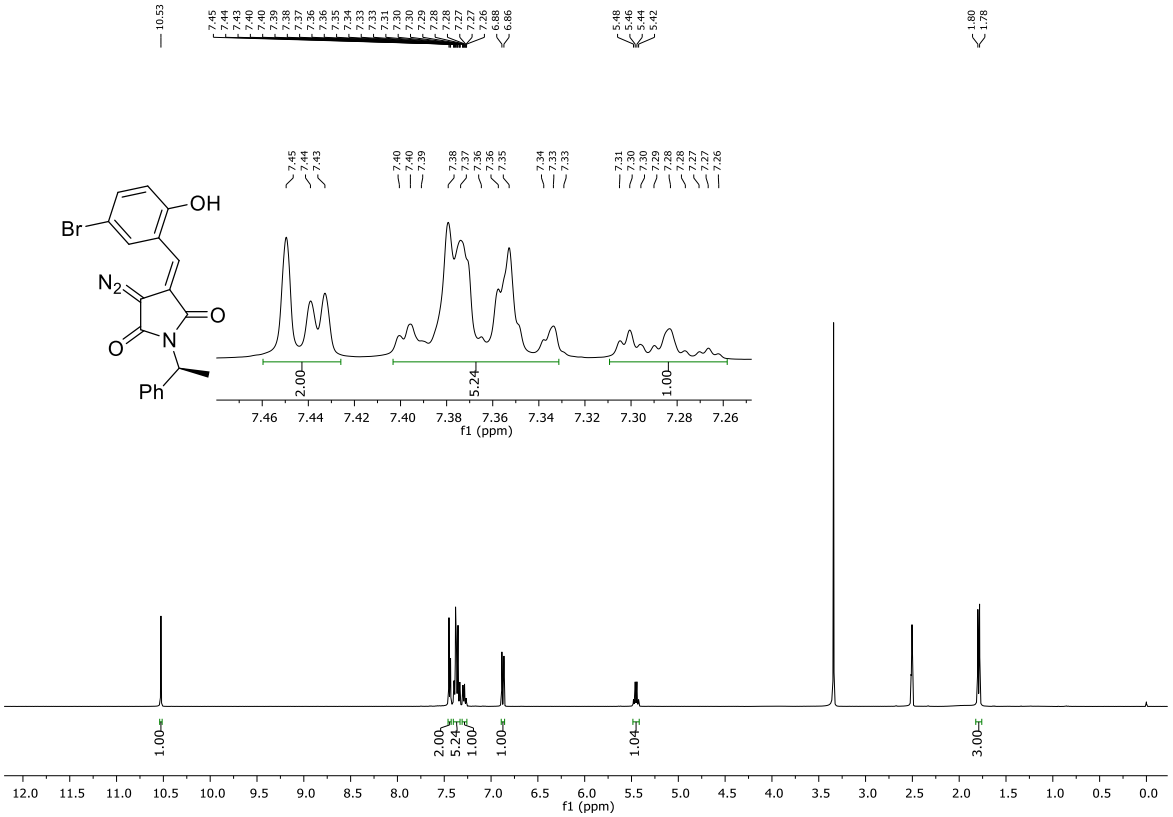


Figure IV.7. ^{1}H NMR (400 MHz, DMSO-d_6) Spectrum of **2gc**

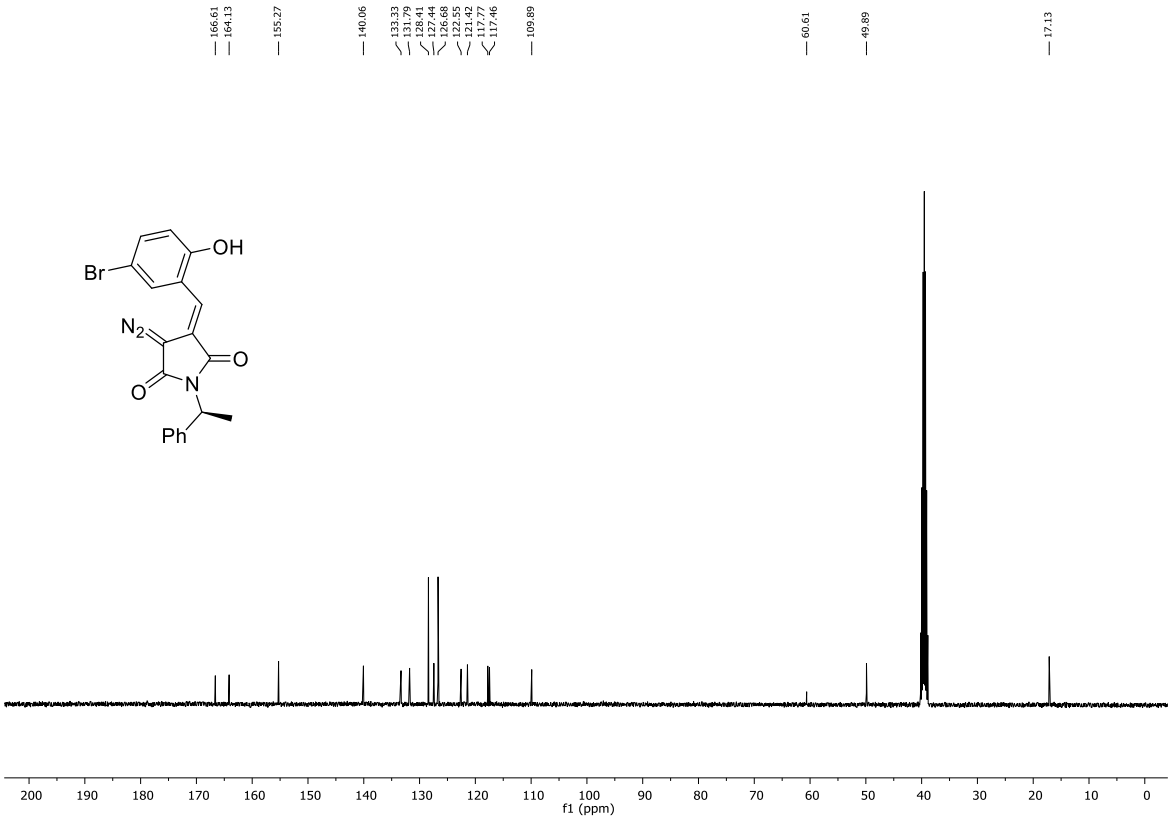


Figure IV.8. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) Spectrum of **2gc**

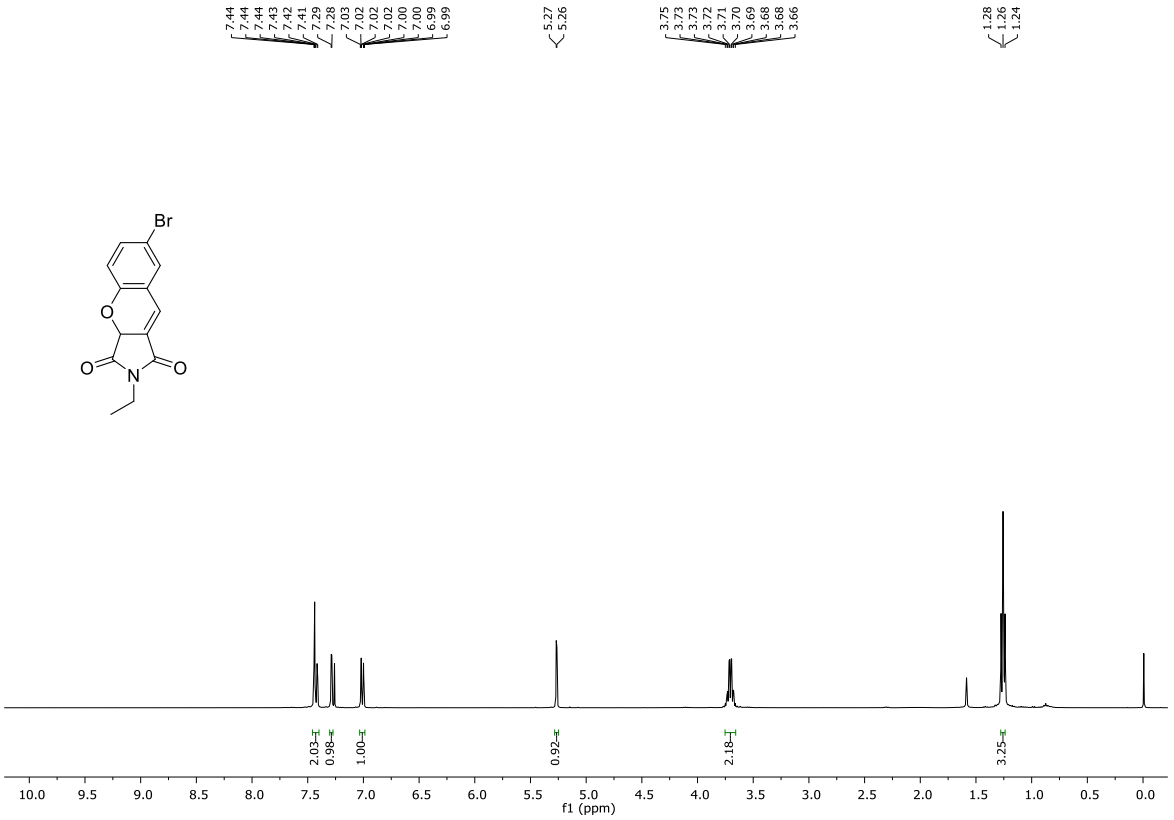


Figure IV.9. ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **3ac**

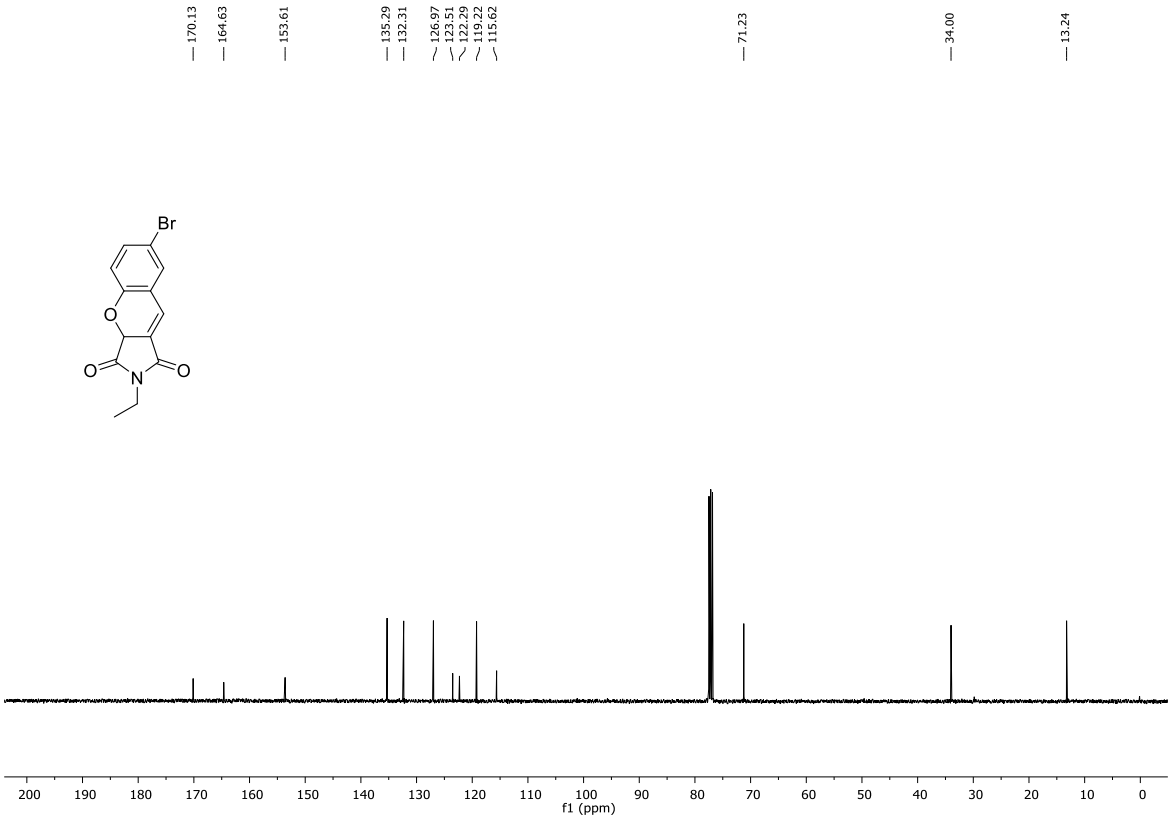


Figure IV.10. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) Spectrum of **3ac**

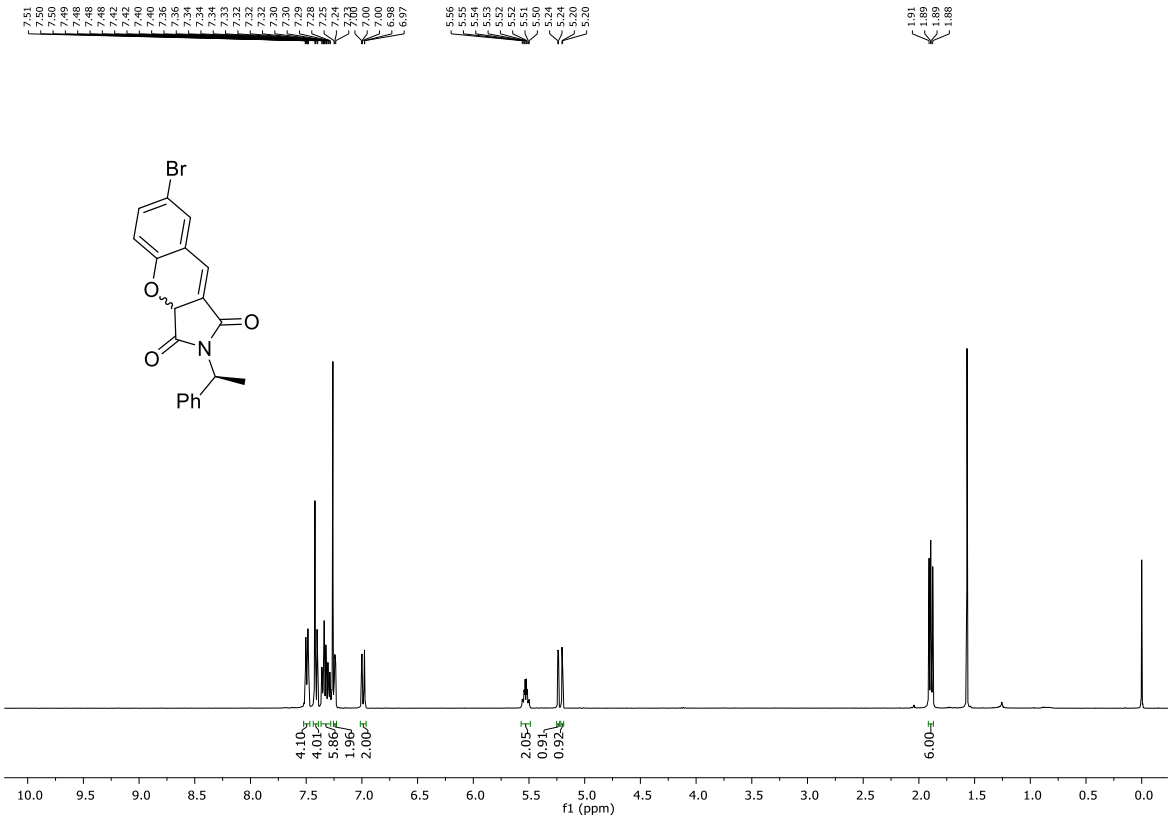


Figure IV.11. ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **3gc**

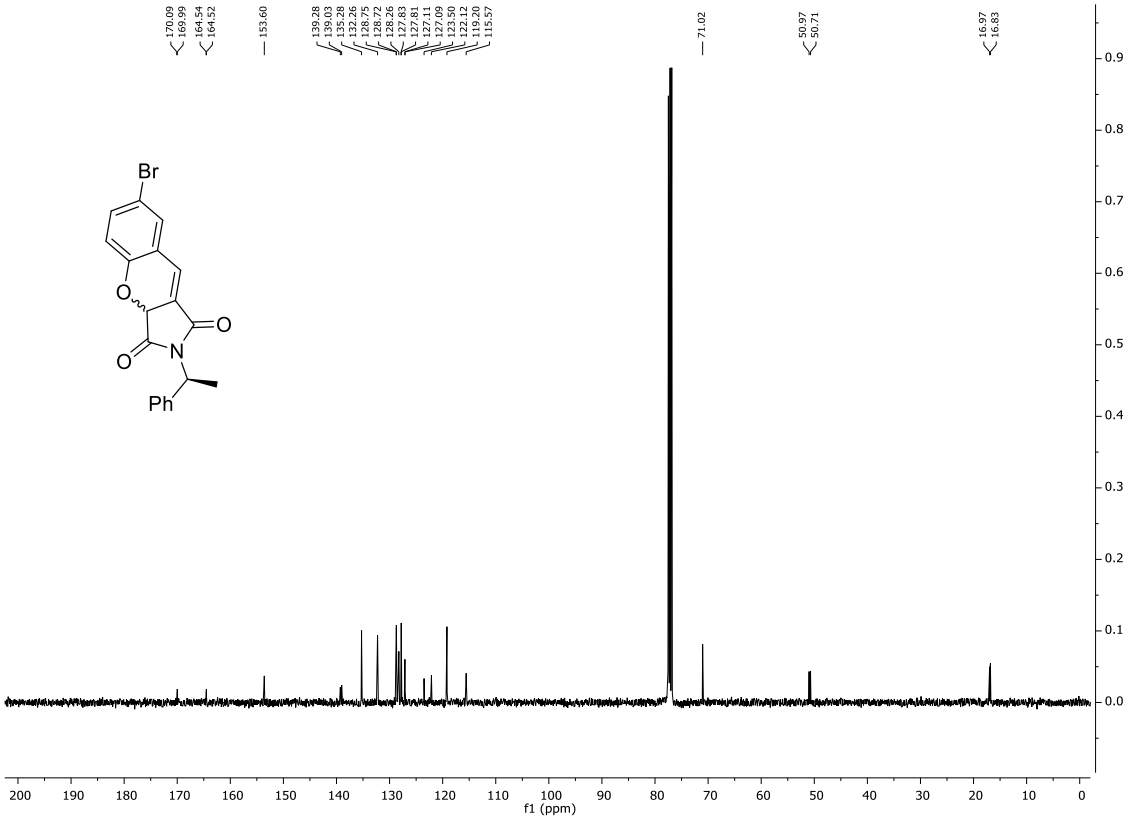


Figure IV.12. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) Spectrum of **3gc**

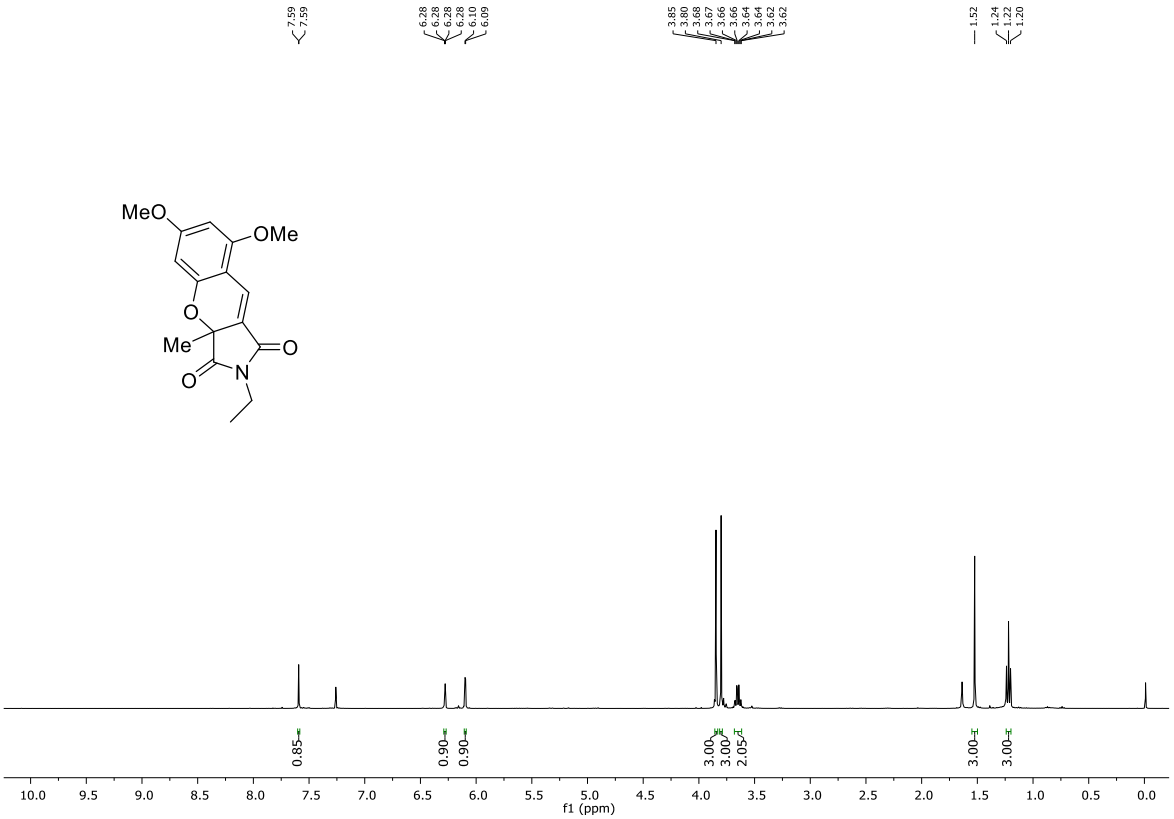


Figure IV.13. ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **3ad**

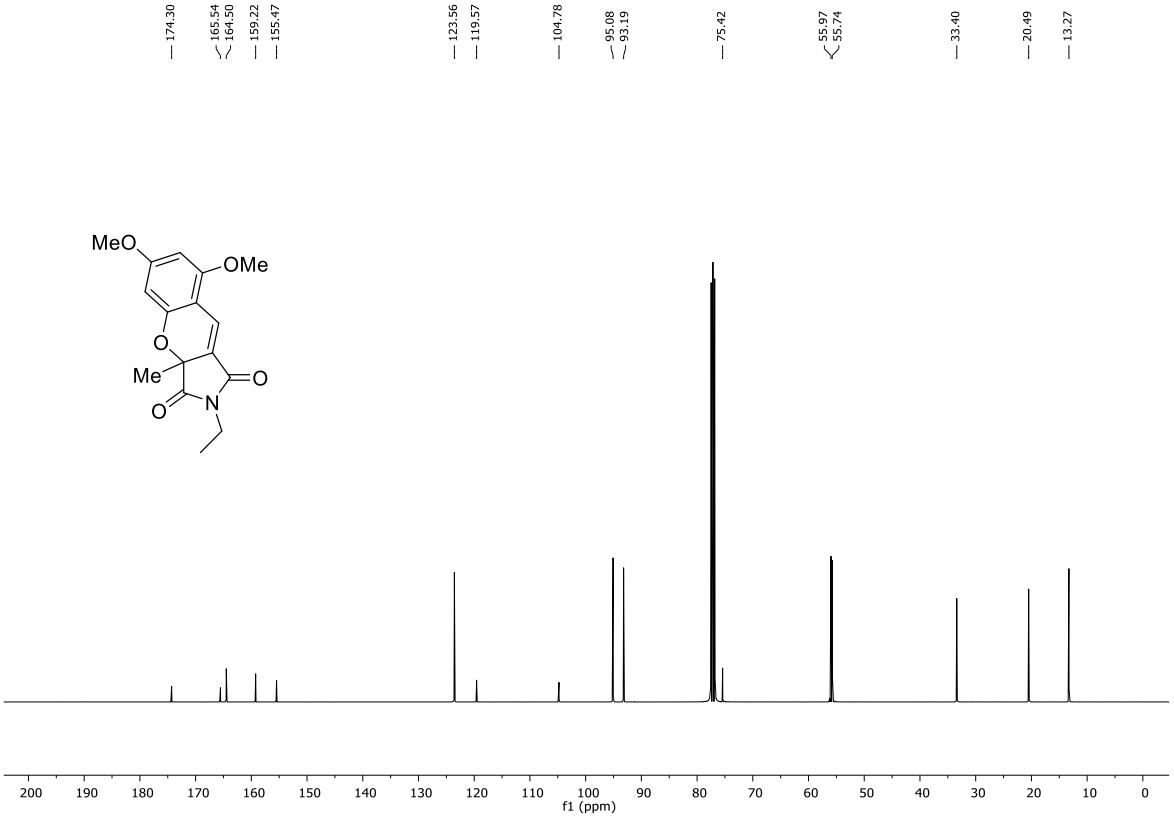


Figure IV.14. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) Spectrum of **3ad**

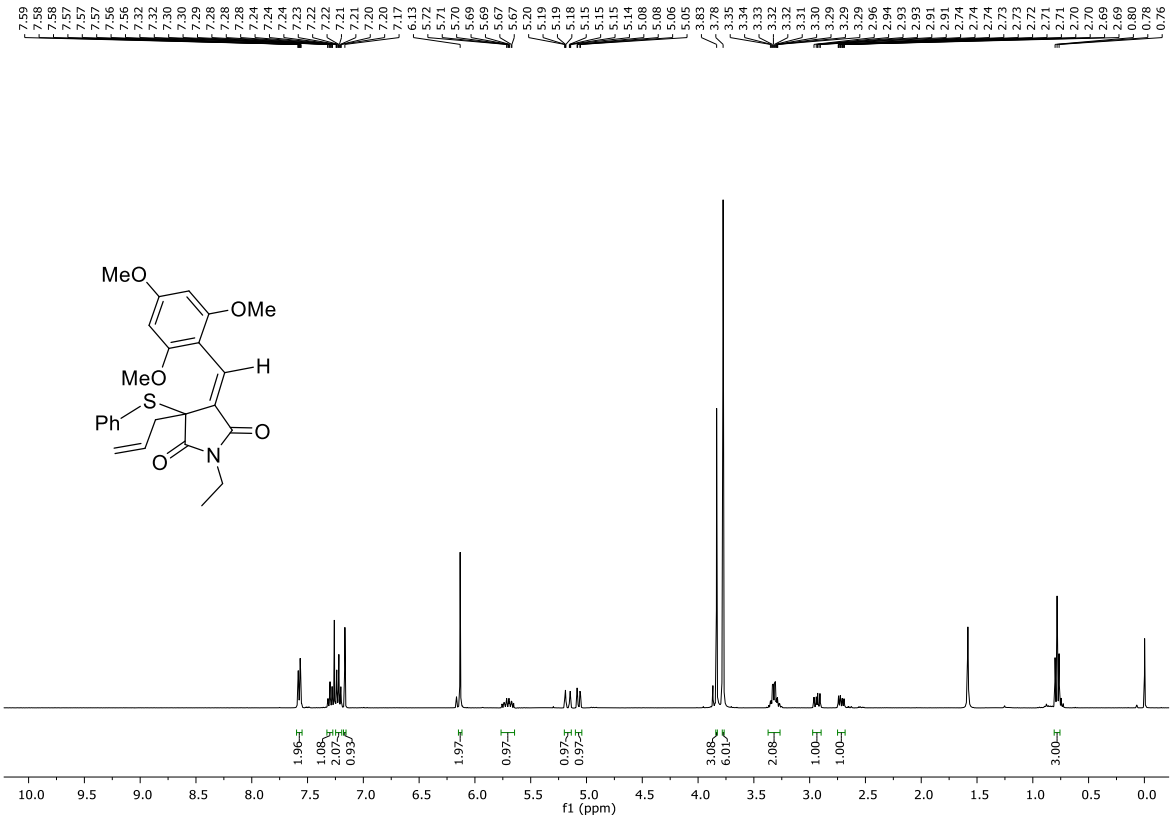


Figure IV.15. ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **1ad-DK**

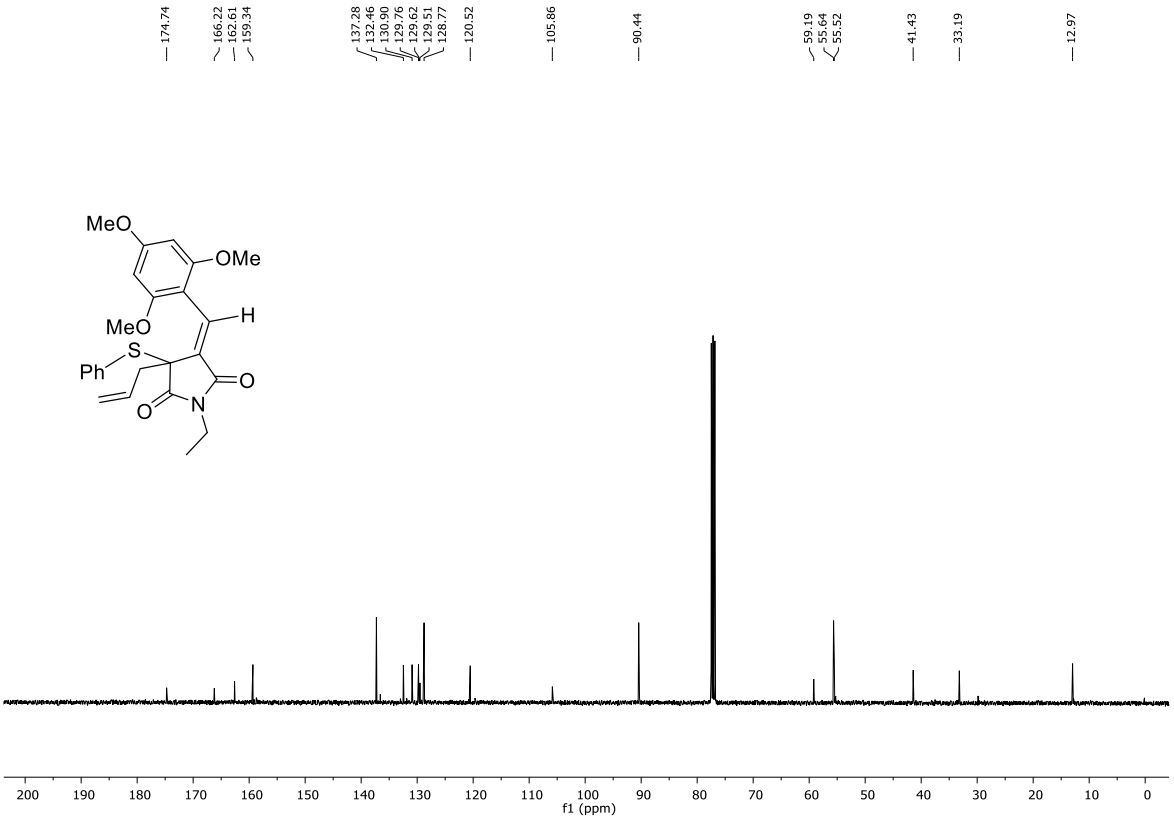


Figure IV.16. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) Spectrum of **1ad-DK**

4B.15. Crystal data:

Datablock: dia_1_a

```
Bond precision:  C-C = 0.0030 A          Wavelength=0.71073
```

Cell:	a=9.835(3)	b=17.357(5)	c=7.511(2)
	alpha=90	beta=110.063(9)	gamma=90
Temperature:	100 K		

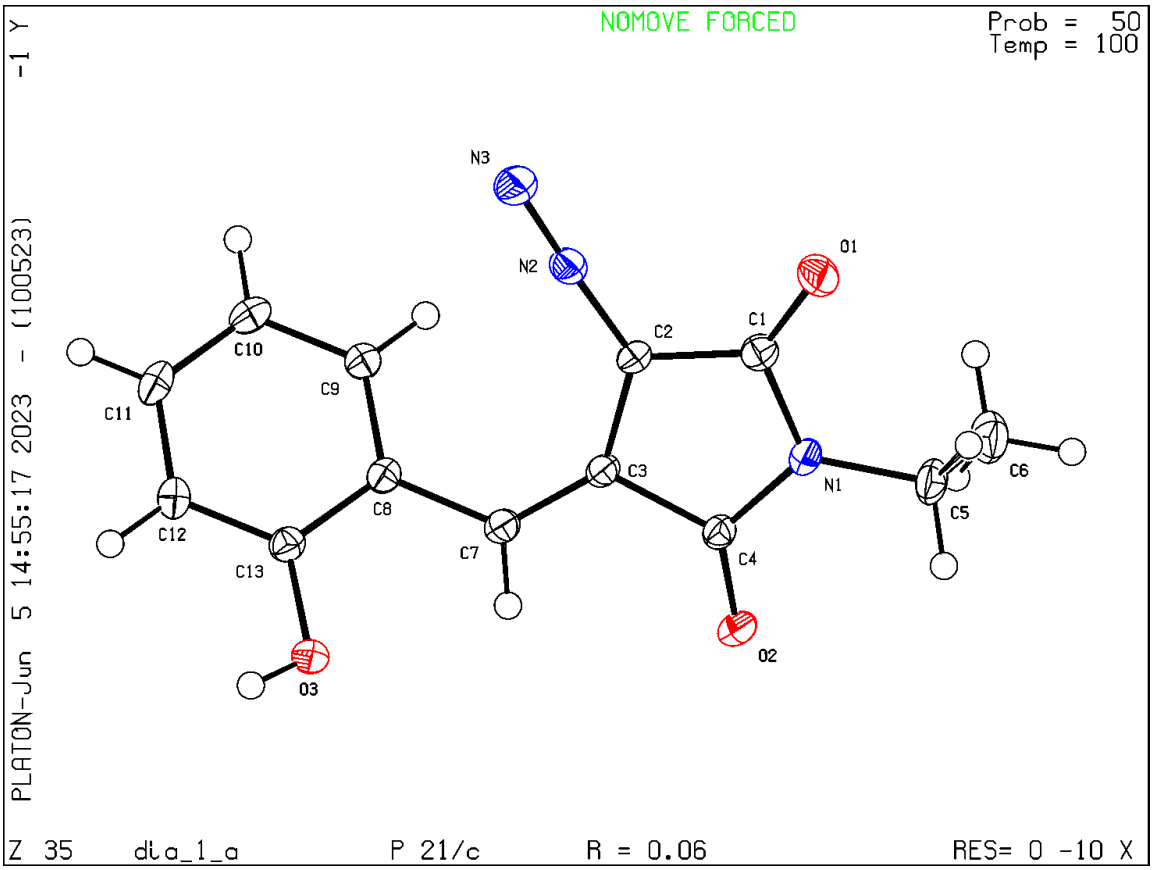
	Calculated		Reported	
Volume Space	1204.4(6)		1204.3(6)	
groupHall	P 21/c		P 21/c	
group	-P 2ybc C13		-P 2ybc C13	
Moiety formula	H11 N3	O3	H11 N3	O3
Sum formula	C13 H11 N3	O3	C13 H11 N3	O3
Mr	257.25		257.25	
Dx,g cm-3	1.419		1.419	
Z	4		4	
Mu (mm-1)	0.104		0.104	
F000	536.0		536.0	
F000’	536.26			
h,k,lmax	12,22,9		12,22,9	
Nref	2812		2741	
Tmin,Tmax				
Tmin’				

```
Correction method= Not given

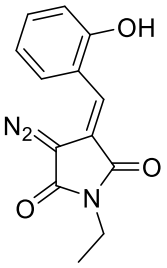
Data completeness= 0.975         Theta(max)= 27.679

R(reflections)= 0.0562( 2332)                    wR2(reflections)=

0.1804( 2741)
S = 1.134               Npar= 174
```



Thermal ellipsoids at 50% probability



2ab

4B.16. Reference

1. a) I. D. Jurberg, H. M. L. Davies, *Chem. Sci.* **2018**, *9*, 5112–5118; b) T. Xiao, M. Mei, Y. He, L. Zhou, *Chem. Commun.* **2018**, *54*, 8865–8868; c) R. Hommelsheim, Y. Guo, Z. Yang, C. Empel, R. M. Koenigs, *Angew. Chem. Int. Ed.* **2019**, *58*, 1203–1207; *Angew. Chem.* **2019**, *131*, 1216–1220; d) Z. Zhang, D. Yadagiri, V. Gevorgyan, *Chem. Sci.* **2019**, *10*, 8399–8404.
2. a) J. L. Wang, I. Likhotvorik, M. S. Platz, *J. Am. Chem. Soc.* **1999**, *121*, 2883–2890; b) Z. Zhu, T. Bally, L. L. Stracener, R. J. McMahon, *J. Am. Chem. Soc.* **1999**, *121*, 2863–2874; c) J. Wang, J. Kubicki, E. F. Hilinski, S. L. Mecklenburg, T. L. Gustafson, M. S. Platz, *J. Am. Chem. Soc.* **2007**, *129*, 13683–13690; d) P. Costa, W. Sander, *Angew. Chem. Int. Ed.*, **2014**, *53*, 5122–5125; *Angew. Chem.* **2014**, *126*, 5222–5225; e) P. Costa, T. Lohmiller, I. Trosien, A. Savitsky, W. Lubitz, M. Fernandez-Oliva, E. Sanchez-Garcia, W. Sander, *J. Am. Chem. Soc.* **2016**, *138*, 1622–1629; f) I. Trosien, E. Mendez-Vega, T. Thomanek, W. Sander, *Angew. Chem. Int. Ed.* **2019**, *58*, 14855–14859; *Angew. Chem.* **2019**, *131*, 14997–15001; g) Hideo Tomioka, E. Iwamoto, H. Itakura, K. Hirai, *Nature* **2001**, *412*, 626–628; h) T. Nakajo, J. Kumagai, S. Kusaka, A. Hori, Y. Hijikata, J. Pirillo, Y. Ma, R. Matsuda, *J. Am. Chem. Soc.* **2021**, *143*, 8129–8136.
3. a) X. Huang, R. D. Webster, K. Harms, E. Meggers, *J. Am. Chem. Soc.* **2016**, *138*, 12636–12642; b) Ciszewski, Ł. W.; Durka, J.; Gryko, D. *Org. Lett.* **2019**, *21*, 7028–7032; c) Y.-L. Su, G.-X. Liu, J.-W. Liu, L. Tram, H. Qiu, M. P. Doyle, *J. Am. Chem. Soc.* **2020**, *142*, 13846–13855; d) K. Rybicka-Jasin´ska, W. Shan, K. Zawada, K. M. Kadish, D. Gryko, *J. Am. Chem. Soc.* **2016**, *138*, 15451–15458; e) F. Li, C. Pei, R. M. Koenigs, *Angew. Chem., Int. Ed.* **2022**, *61*, e202111892; f) Orłowska, K.; Santiago, J. V.; Krajewski, P.; Kisiel, K.; Deperasinska,´ I.; Zawada, K.; Chaładaj, W.; Gryko, D. *ACS Catal.* **2023**, *13*, 1964−1973.
4. a) Z. Yang, M. L. Stivanin, I. D. Jurberg, R. M. Koenigs, *Chem. Soc. Rev.* **2020**, *49*, 6833–6847; b) Durka, J.; Turkowska, J.; Gryko, D. *ACS Sustainable Chem. Eng.* **2021**, *9*, 8895-8918; c) Empel, C.; Pei, C.; Koenigs, R. M. *Chem. Commun.* **2022**, *58*, 2788–2798; d) R. D. C. Gallo, G. Cariello, T. A. C. Goulart, I. D. Jurberg, *Chem. Commun.* **2023**, Advance Article. doi.org/10.1039/D3CC00988B; e) Y.-L. Su, G.-X. Liu, L. De Angelis, R. He, A. Al-Sayyed, K. S. Schanze, W.-H. Hu, H. Qiu, M. P. Doyle, *ACS Catal.* **2022**, *12*, 1357–1363; f) C. Empel, S. Jana, Ł. Ciszewski, K. Zawada, C. Pei, D. Gryko, R. M. Koenigs, *Chem. Eur. J.* **2023**, *29*, e202300214.

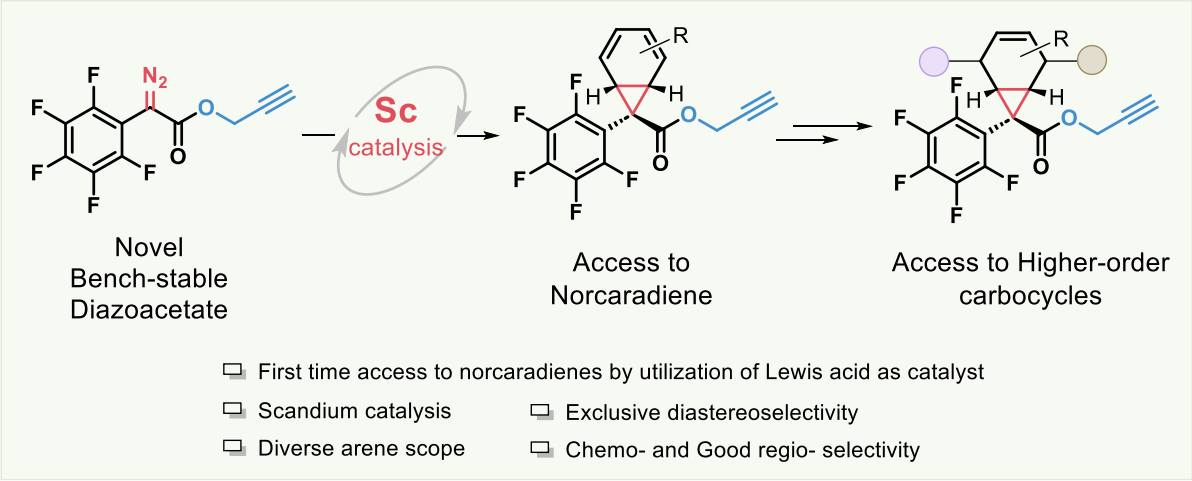
5. a) S. Jana, Z. Yang, F. Li, C. Empel, J. Ho, R. M. Koenigs, *Angew. Chem., Int. Ed.* **2020**, *59*, 5562−5566; (b) C. Empel, S. Jana, C. Pei, T. V. Nguyen, R. M. Koenigs, *Org. Lett.* **2020**, *22*, 7225–7229.
6. (a) A. Padwa, M. M. Sá, *Tetrahedron Lett.* **1997**, *38*, 5087–5090; b) S.-F. Zhu, Y. Cai, H.-X. Mao, J.-H. Xie, Q.-L. Zhou, *Nat. Chem.* **2010**, *2*, 546−551; c) Y. Zhang, Y. Yao, L. He, Y. Liu, L. Shi, *Adv. Synth. Catal.* **2017**, *359*, 2754−2761; (d) E. Kühnel, D. D. P. Laffan, G. C. Lloid-Jones, T. M. del Campo, I. R. Shepperson, J. L. Slaughter, *Angew. Chem., Int. Ed.* **2007**, *46*, 7075.
7. a) R. A. Bernheim, T. Adl, H. W. Bernard, A. Songco, P. S. Wang, R. Wang, L. S. Wood, P. S. Skell, *J. Chem. Phys.* **1976**, *64*, 2747-2755; b) E. Wasserman, A. M. Trozzolo, W. A. Yager, R. W. Murray, *J. Chem. Phys.* **1964**, *40*, 2408–2410; c) R. W. Brandon, G. L. Closs, C. E. Davoust, C. A. Hutchison, B. E. Kohler, R. Silbey, *J. Chem. Phys.* **1965**, *43*, 2006–2016; d) Y. Kutin, J. Reitz, P. W. Antoni, A. Savitsky, D. A. Pantazis, M. Kasanmascheff, M. M. Hansmann, *J. Am. Chem. Soc.* **2021**, *143*, 21410–21415.
8. a) S. Jana, C. Pei, C. Empel, R. M. Koenigs, *Angew. Chem. Int. Ed.* **2021**, *60*, 13271–13279; b) P. W. Antoni, J. Reitz, M. M. Hansmann, *J. Am. Chem. Soc.* **2021**, *143*, 12878–12885.
9. a) D. A. Dougherty, *Acc. Chem. Res.*, 1991, **24**, 88-94; (b) M. Abe, *Chem. Rev.* **2013**, *113*, 7011–7088.
10. C. Empel, C. Pei, F. He, S. Jana, R. M. Koenigs, *Chem. Eur. J.* **2022**, *28*, e202104397.
11. a) D. Laha, K. B. Meher, O. S. Bankar, R. G. Bhat, *Asian J. Org. Chem.* **2022**, *11*, e202200062; b) D. Laha, R. G. Bhat, *Asian J. Org. Chem.* **2020**, *9*, 918–921; c) C.-J. Wallentin, J. D. Nguyen, P. Finkbeiner, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2012**, *134*, 8875–8884; d) Q. H. Nguyen, H. S. Hwang, E. J. Cho, S. Shin, *ACS Catal.* **2022**, *12*, 8833–8840; (e) K. Matsuo, T. Yoshitake, E. Yamaguchi, A. Itoh, *Molecules* **2021**, *26*, 6781.
12. a) M. S. Kharasch, E. V. Jensen, W. H. Urry, *Science* **1945**, *102*, 128; b) M. S. Kharasch, P. S. Skell, P. Fisher, *J. Am. Chem. Soc.* **1948**, *70*, 1055–1059.
13. G. Wu, J. Börger, A. Jacobi von Wangelin, *Angew. Chem., Int. Ed.* **2019**, *58*, 17241–17245.
14. Q. H. Nguyen, H. S. Hwang, E. J. Cho, S. Shin, *ACS Catal.* **2022**, *12*, 8833–8840.
15. (a) V. Raj, J. Lee, *Front. Chem.* **2020**, *8*, 623. (b) Y. Yue, C. Yin, F. Huo, J. Chao, Y. Zhang, *Sens. Actuators B: Chem.* **2016**, *223*, 496–500.
16. a) L. Tóth, A. Kiss-Szikszai, G. Vasvári, F. Fenyvesi, M. Vecsernyés, P. Mátyus, S. Antus, A. Mándi, T. Kurtán, *Synlett* **2019**, *30*, 799–802; b) Y. Sugita, K. Takao, Y. Uesawa, H. Sakagami, *Anticancer Res.* **2017**, *37*, 5919–5924; (c) A. Fouqué, O. Delalande, M. Jean, R. Castellano, E. Josselin, M. Malleter, K. F. Shoji, M. D. Hung, H. Rampanarivo, Y. Collette,

P. van de Weghe, P. Legembre, *J. Med. Chem.* **2019**, *62*, 9339–9340; d) Yu. P. Bogza, A. L. Katsiel, A. N. Sharypova, T. G. Tolstikova, A. S. Fisyuk, *Chem. Heterocycl. Compd.* **2015**, *50*, 1712–1718; e) H. Tanaka, I. Atsumi, O. Shirota, S. Sekita, E. Sakai, M. Sato, J. Murata, H. Murata, D. Darnaedi, I.-S. Chen, *Chem. Biodivers.* **2011**, *8*, 476–482; f) J.-F. Cheng, A. Ishikawa, Y. Ono, T. Arrhenius, A. Nadzan, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3647–3650.

17. a) M. P. Doyle, M. A. McKervey, T. Ye, Modern Catalytic Methods for Organic Synthesis with Diazo Compounds. From Cyclopropanes to Ylides, Wiley-Interscience: New York **1998**; b) G. Mehta, S. Muthusamy, *Tetrahedron* **2002**, *58*, 9477; c) A. Padwa, M. D. Weingarten, *Chem.Rev.* **1996**, *96*, 22; d) M. Lee, Z. Ren, D. G. Musaev, H. M. L. Davies, *ACS Catal.* **2020**, *10*, 6240–6247.
18. a) Y. Zhang, J. Wang, *Coord. Chem. Rev.* **2010**, *254*, 941–953; b) T.H. West, S. Spoehrle, K. Kasten, J.E. Taylor, A.D. Smith, *ACS. Catal.* **2015**, *5*, 7446–7479.
19. a) R. Hommelsheim, Y. Guo, Z. Yang, C. Empel, R. M. Koenigs, *Angew. Chem., Int. Ed.* **2019**, *58*, 1203; b) J. Yang, J. Wang, H. Huang, G. Qin, Y. Jiang, T. Xiao, *Org. Lett.* **2019**, *21*, 2654.
20. CCDC 2267622 (compound **2ab**) contain the supplementary crystallographic data. This data can be obtained free of charge by The Cambridge Crystallographic Data Centre.
21. S. A. Wolf, D. D. Awshalom, R. Buhrman, J. M. Daughton, V. S. Molnar, M. L. Roukes, A. Y. Chtchelkanova, D. M. Treger, *Science* **2001**, *294*, 1488−1495.
22. C. L. Closs, B. E. Rabinow, *J. Am. Chem. Soc.* **1976**, *98*, 8190–8198.

Chapter 5

Highly Regio- and Chemoselective Arene Cyclopropanation using Donor-/Acceptor- type Propargyl α-diazoacetate via Scandium Catalysis



Highly Regio- and Chemo-selective Arene Cyclopropanation using Donor-/Acceptor- type Propargyl α-pentafluorophenyl-α-diazoacetate via Scandium Catalysis

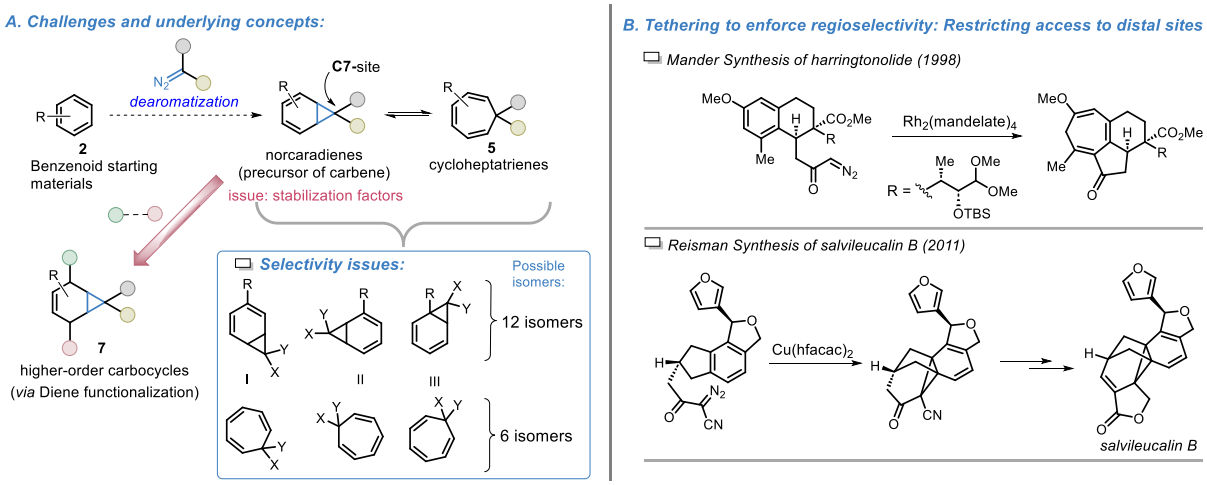
5

This chapter discloses the first ever direct access to norcaradiene by the dearomatization strategy of arenes in presence of a Lewis acid catalyst. The direct dearomatization of benzenoids in presence of a Lewis acid is highly challenging owing to few competitive side reactions. Benzenoid molecules are also important carbogenic feedstock chemicals in organic synthesis. The direct dearomatization of benzenoids holds high synthetic value by mobilizing one double bond of the aromatic ring at the expense of intrinsic aromatic stabilization to form higher-order carbocycles. The inherent challenges such as regiocontrol, stereoselectivity and tautomeric composition for the three non-equivalent sites for dictating site-selectivity limit the "undirected strategy" for the development of intermolecular 1,3-cyclohexadiene motifs or norcaradienes (NCDs). Herein, in this chapter, an undirected strategy for a highly regio- and chemoselective arene cyclopropanation has been described under scandium catalysis via the development of novel propargyl α-pentafluoroaryl-α-diazoacetate to obtain stable NCDs. A variety of unactivated as well as electronically activated arenes have been dearomatized using this protocol. The synergistic combination of scandium triflate as a catalyst and propargyl α-pentafluoroaryl-α-diazoacetate as a novel reagent played a pivotal role for the effective dearomatization of arenes without the assistance of any directing group or ligand. As an application of the strategy, the norcaradienes have been subjected to further transformation to access bicyclic carbocycles of ST-246 orthopox antivirals.

5.1. Introduction

Benzenoid molecules are very important carbogenic feedstock chemicals and have been utilized organic synthesis.[1] The direct dearomatization of benzenoids holds a high synthetic value as it demands the mobilization of one double bond of aromatic ring at the expense of intrinsic aromatic stabilization to form a higher-order carbocyclic product. [2] These higher-order carbocyclic products are very useful as they can further be utilized to construct the complex molecules/building blocks. However, some of the major challenges such as controlling regioselectivity, stereo-selectivity and the tautomeric nature of the three non-equivalent sites limit the "undirected strategy" to develop an intermolecular strategy to access 1,3-

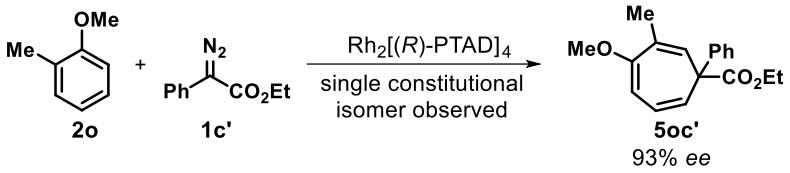
cyclohexadiene motifs or norcaradienes (NCDs) **4** (Scheme 5.1A).[3] Nevertheless, intramolecular strategies have proven to be regioselective by restricting the access to distal sites.[4,5] Numerous studies on the transition-metal-catalyzed arene cyclopropanatio have been developed to access the NCDs. However, the competitive side reaction (Buchner ring expansion product – cycloheptatriene (CHTs **4**) formation) severely hampered NCDs formation.[6] However, this also leads to some of the useful compounds and a couple of examples based on this process have been depicted in Scheme 1B. Nevertheless, stable NCDs formation via "undirected" approach or intermolecularly without any competitive side reactions remain to be challenging especially through metal-catalyzed diazo cycloaddition chemistry.



Scheme 5.1. Previous approaches to NCDs and associated challenges.

Traditionally, extensive metal catalysts and/or ligands have been utilized to carry out the cyclopropanation of arenes via carbene transfer reaction.[3-6] Moreover, unlike the acceptor-only or donor-only diazoalkanes, the donor-/acceptor-type of diazoalkanes are comparatively less reactive as well more stabilized and they found to have relatively limited synthetic applications.[6b,7]

In 2017, Beeler and Fleming[6b] have explored the very first intermolecular strategy using donor-acceptor type diazoacetates such as ethyl phenyl diazoacetate **1c′** and arenes (2-methyl anisole) **8o** in presence of dirhodium catalyst through continuous flow technique. However, Buchner type ring expansion lead to the formation of cycloheptatrienes **5oc′** in good yields (up to 82%) with moderate to high enantioselectivity (up to 96% ee) and regioselectivity (Scheme 5.2).



Scheme 5.2. Continuous Flow technique: Beeler's approach to Buchner ring expansion.

Usually, it is quite intricate to construct the highly substituted cyclopropane motifs exclusively through cycloaddition of disubstituted diazo compounds with arenes as competing and simultaneous C–H insertion process along with Buchner ring expansion reactions thus significantly lowering the yields of the desired cyclopropanation products (Figure 5.1).[8] Thus, continued effort is required in order to get access to fully cyclopropane structural pattern onto the arene, supressing the competitive side reactions.

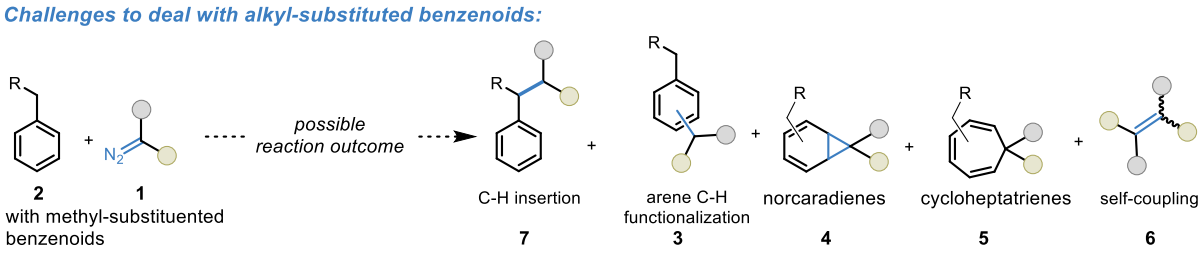
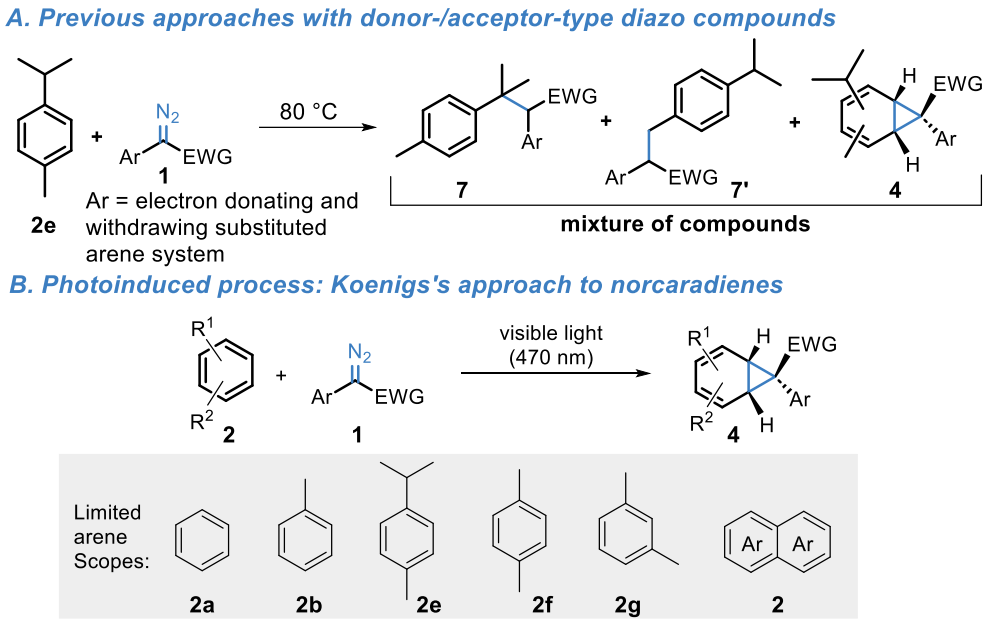


Figure 5.1. Possible reaction outcome of alkyl-substituted arenes and diazo compounds.

Owing to some of these challenges, well explored studies to access norcaradienes directly using donor-/acceptor-type diazo compounds are limited in literature. Nevertheless, few synthetic strategies have been developed at elevated temperature (Scheme 5.3A).[9] Very recently, Koenigs and coworkers[7] have reported the first visible light-induced strategy for the cyclopropanation of arenes **2** using diazo compounds **1** (Scheme 5.3B). However, this protocol utilized a few limited arenes to synthesize norcaradienes **4** selectively. However, the protocol did not explore the arenes having different electronic properties possibly due to the competitive side reactions (Scheme 5.3B).

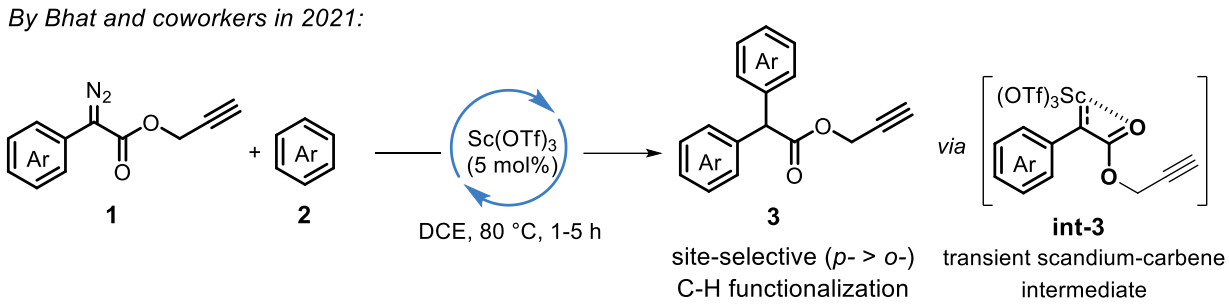
After gleaning through the literature and detailed analysis, we realized that selective formation of norcaradienes with enhanced yields are favoured over intramolecular Buchner-type products depending on the subtle electronic changes in the substrates.[10] Especially, for the intermolecular strategies, CHTs⇌NCDs equilibrium favours NCDs valence tautomers depending on the electronic properties of the geminal substituents at C-7. [11] These substituents



Scheme 5.3. Previous synthetic efforts to access NCDs using donor-acceptor-type diazo compounds.

are strong π-acceptors and are recognized to be strong acceptor-/acceptor-type diazo compounds.[11] Hence, accessing NCDs using donor-/acceptor-type diazo compounds are highly challenging as well as demanding due to electronic stabilization factors and also for the developing alternative wider synthetic applications.

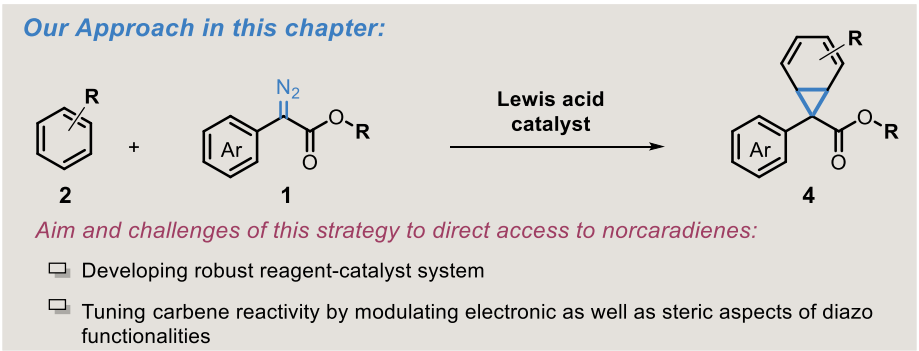
Very recently, our research group[12] for the time successfully demonstrated that Lewis acid catalyst such as scandium triflate is an active, more safer and commercially viable alternative to the many known transition-metal catalysts (Scheme 5.4).[13] It has been proven that "undirect strategy" for the effective C–H bond functionalization of unactivated arenes **2** *via* transient scandium carbene intermediate (Scheme 5.4). It has been shown that synergistic combination of novel propargyl *α*-aryl-*α*-diazoacetates **1** as reagents and scandium triflate as catalyst is necessary for the effective C–H bond functionalization. Interestingly, we did not observe any competitive products emanating from cyclopropanation of arenes **2** as well. This may be due to the Lewis acid effect that favours aromatized products,[14] or the cyclopropanation product might not get stabilized due to C-7 substituents. Consequently, facilitating the cyclopropanation of arenes in presence of a Lewis acid as catalyst is highly challenging and yet unexplored area of arenes *via* dearomatization strategy.



Scheme 5.4. Site-selective C–H functionalization under scandium catalysis.

In order to address some of these inherent challenges, we planned to design and develop newly decorated donor-/acceptor-type diazo compounds. We planned to synthesized new donor-/acceptor-type diazo compounds **1** with tuned electronic properties so that they are potentially capable of overcoming the limitations so as to access the substituted cyclopropane derivatives **4** successfully (Scheme 5.5). In this regard, based on our research experience and understanding we finalized modified the *α*-aryl-*α*-diazoacetates with fluoro-substituents at the phenyl ring and/or propargyl group at the ester part. We strongly believed that these strongly electron deactivating functional moiety (-F) have a great ability to modulate the electronic and steric factors in such a way that the donor-/acceptor-type diazoacetates would behave more like acceptor-/acceptor-type diazoacetates.

Herein, in this chapter, we present the design, development of newer diazoacetates as reagents and successful demonstration of a synthetic protocol for the site-selective carbene addition to the unactivated and electronically deactivated arenes via scandium catalysis.



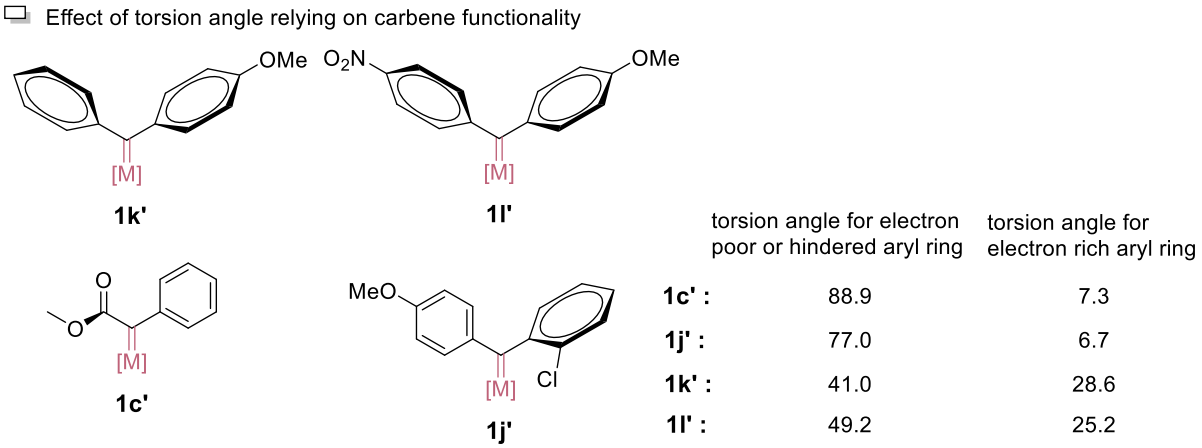
Scheme 5.5. Our synthetic approach to access norcaradiene via the development of novel diazo acetates.

5.2. Results and Discussion

5.2.1. Our hypothesis to overcome inherent challenges:

The reactivity of different metal-carbenoids has been long and well-studied. It has been well understood that not only the manipulation and modulation of the electronic and steric properties of diazo functionalities are important but also the effect of metal/ligand are equally important to bring about the successful synthetic transformations.[8b,15] However, in spite of the research progress, it's still challenging to develop novel reagent and catalysts system looking at intricacies and properties of different substrates and to achieve the desired transformation selectively and exclusively without any side reactions.

Very recently, Davies and coworkers[16] have disclosed that the reactivity profile of the few donor-/donor-type carbenes similar to that of the donor-/acceptor-type carbenes owing to their structural arrangements that are enabled from the electronic as well as steric influences of their carbene functionalities (Scheme 5.6).



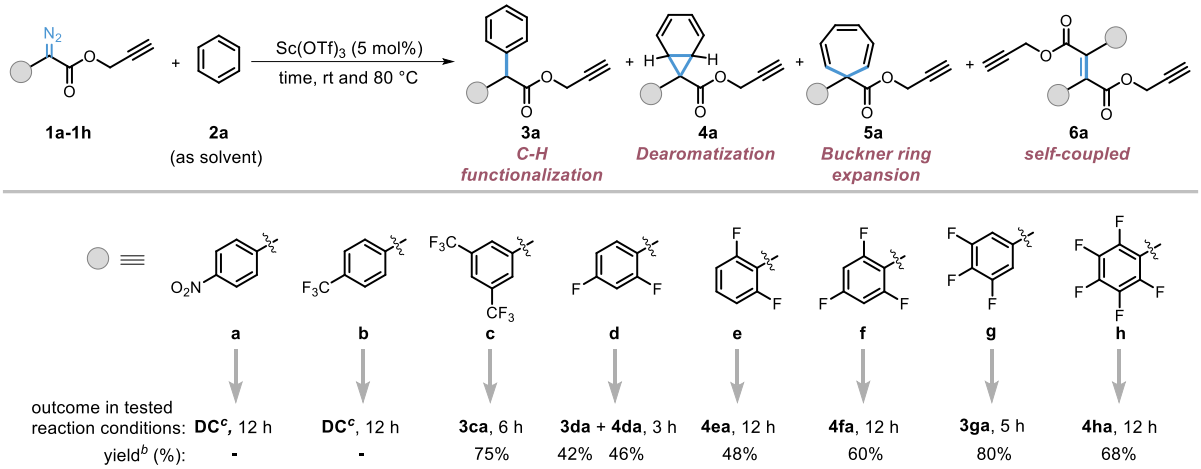
Scheme 5.6. Effect on reactivity profile due to steric and electronic factors.

Influenced by this concept and from the understanding that prime requisite of electronic properties of the substituents that would be facilitate the formation of NCDs with geminal substituents at C-7 positions, we plan to design the diazo acetates accordingly. In view of this, we hypothesized that the strongly electron deactivating/withdrawing groups (strong electron pulling properties) at the ester part as well as the phenyl ring of a donor-/acceptor- type diazoacetate may enhance the electrophilicity so as to react synergistically with Lewis acid catalyst to bring about the dearomatization of arenes. However, optimum balancing of reactivity and stability is the key factor during the development of new reagent-catalysts system for the effective and efficient transformation.

5.2.2. Initial optimization: Survey of arene part of *α*-aryl-*α*-diazoacetate:

In order to validate our hypothesis, we commenced with propargyl *α*-(4-nitrophenyl)-*α*-diazoacetate **1a** as a model reagent in dry benzene as solvent in presence of catalytic amount (5 mol%) of scandium triflate at different temperature ranges in inert atmosphere. However, the *α*-diazoacetate **1a** was decomposed at 80 °C, while at the other temperature range (rt to <75 °C) the *α*-diazoacetate **1a** found to be unreactive (see Experimental Section 5.4.3, Table 5.3). Later, we synthesized the propargyl *α*-(4-trifluoromethylphenyl)-*α*-diazoacetate **1b** and upon treatment of **1b** with benzene **2a** at different temperatures (rt and 80 °C) did furnish the corresponding desired product. However, the propargyl 3,5-(di-trifluoromethylphenyl)-*α*-diazoacetate **1c** furnished the undesired corresponding benzene C–H functionalized product **3ca**. Interestingly, the propargyl *α*-(2,4-difluorophenyl)-*α*-diazoacetate **1d** reacted with benzene **2a** at 80 °C temperature to afford the desired dearomatization product propargyl 7-(2,4-difluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate **4da** in excellent diastereoselectivity (in 6 h) albeit in poor yield (46%) along with the competitive C–H functionalization product propargyl 2-(2,4-difluorophenyl)-2-phenylacetate **3da** (42% yield). However, gratifyingly, we did not detect any Buckner expansion product-cycloheptatriene **5da** even in trace. In order to have deeper understanding on whether or not the electrophilicity profile of the diazo carbon center playing any crucial role to furnish the dearomatized product, we further planned to study the effect of fluorine substituents at different locations. In this regard, we synthesized fluorine substituents at different positions of the phenyl ring of the propargyl *α*-aryl-*α*-diazoacetate (see Scheme 5.6). We explored the reactivity of these different propargyl *α*-(fluorophenyl)-*α*-diazoacetates (**1b**-**1h**) by treating with benzene **2a** at room temperature as well at an elevated temperature (80 °C). Surprising, we observed an intriguing trend of reactivity for the outcome of the desired dearomatization product **4da**, especially when fluorine substituents at the *ortho*-positions of the phenyl ring irrespective the number of fluorine substituents. We observed that in case of *α*-(2,6-difluorophenyl)-*α*-diazoacetate **1e**, (2,4,6-trifluorophenyl)-*α*-diazoacetate **1f** corresponding desired products **4ea** and **4fa** formed exclusively in 48% and 60% yield respectively. Surprisingly, the reaction of (3,4,5-trifluorophenyl)-*α*-diazoacetate **1g** with benzene **2a** afforded the corresponding C–H functionalized product **3ga** in 80% yield (Scheme 5.6). These interesting observations demonstrated that not only the synergistic combination of the reagent-catalyst system, degree of electrophilicity at diazo carbon center are important, but also degree of steric effect driven from the number of *ortho*-substituents is extremely crucial for enabling the formation of desired dearomatization product **4**. Based on these observations, finally we synthesized the propargyl

α-pentafluorophenyl-α-diazoacetate **1h** and subjected the same with benzene **2a** in presence of $Sc(OTf)_3$ (5 mol%) under inert atmosphere at an elevated temperature (80 °C). Interestingly, we obtained the corresponding desired cyclopropanation product in 68% yield with an excellent diastereoselectivity, without any trace of competitive side products (Scheme 5.6).[12]



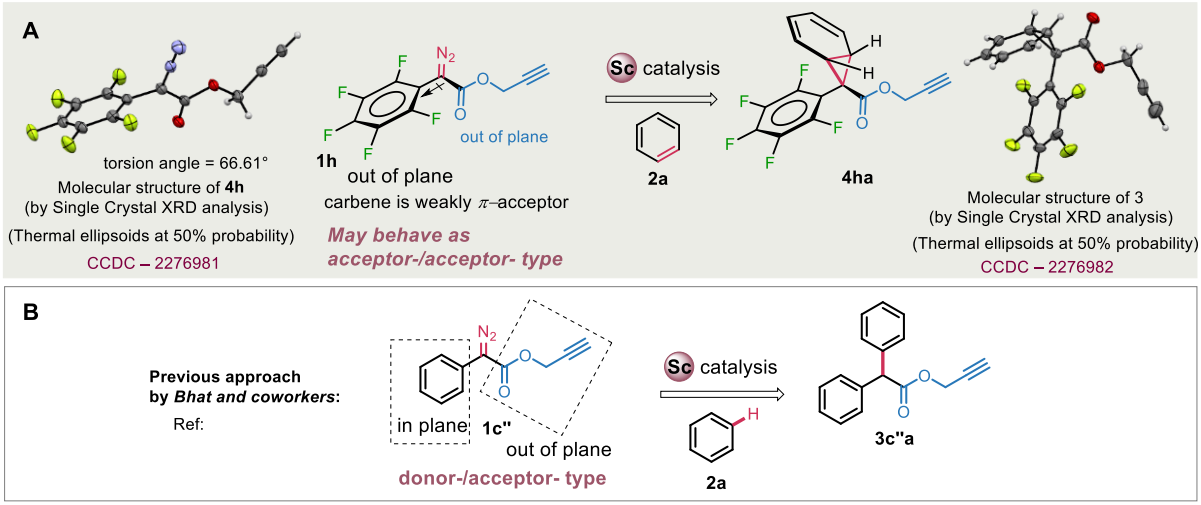
[a]**Tested reaction conditions**: Diazo acetates **1a-1h** (0.5 mmol, 1.0 equiv.) and $Sc(OTf)_3$ (5 mol%) was added in dry Benzene **2a** (2.5 mL) under inert atmosphere, reaction was carried out at both rt and 80 °C. [b]yield of isolated product after purification by column chromatography. [c]DC - Decomposed. All the reactions were remained unaltered at rt (27 °C). In all cases, reactions did not proceed at rt.

Scheme 5.6. Initial optimization: Survey of aryl part in propargyl α-aryl-α-diazoacetate.

5.2.3. Our postulates:

Having obtained certain insights from the exhaustive and systematic screenings, we further observed the torsion angle 66.61° between phenyl group and diazo group in the molecular structure of **1h** (as determined by single crystal X-ray analysis).[16] As per the recent report[17] of Davies, Musaev and coworkers, this steric hindrance is significant enough to twist the group out of the plane. Based on these, we postulated that along with electronic factors, the steric interference may be twisting the phenyl ring to orient out of plane. Hence, as the phenyl group would weakly interact with the empty π-orbital of carbene. Possibly, due to these reasons, the pentafluoro phenyl group in the diazo acetate **1h** is behaving like weak acceptor (see Scheme 5.7A). These factors would enable the reactivity of the α-pentafluorophenyl-α-diazoacetate **1h** with benzene **2a** to obtain the desired product **4ha**. It is very important to note that in our previous report, we had demonstrated that benzene successfully underwent C–H functionalization under the same reaction conditions while using the donor-/acceptor-type propargyl α-phenyl-α-diazoacetate **1c″** (Scheme 5.7B). With the increase in the number of fluorine atoms on the phenyl ring of the diazoacetate clearly enhanced the electrophilicity of

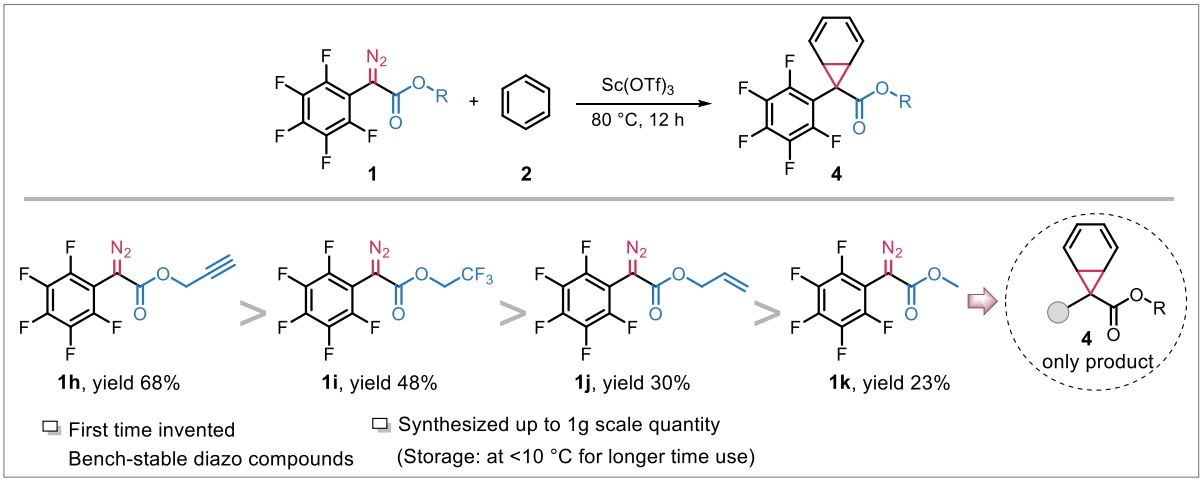
carbene carbon center induced by the electron-pulling effect (by -I effect) of fluorine atoms there by in enhanced the yield of the desired product **4ha** (see Scheme 5.6).



Scheme 5.7. (A) Expected reason for the formation of norcaradiene vs (B) previously reported C–H functionalization.

5.2.4. Initial optimization – Survey of ester part of *α*-aryl-*α*-diazoacetate:

Further, in order to investigate the role and necessity of propargyl group at the ester part of *α*-aryl-*α*-diazoacetate, we prepared few different *α*-pentafluoro-*α*-diazoacetates having different ester moieties (**1i, 1j, 1k)** and were subjected to the reaction in presence of scandium triflate (5 mol%) in benzene **2a** at 80 °C under inert atmosphere (see Scheme 5.8). However, we observed that a gradual and significant decrease in the yields of the dearomatization products **4ia, 4ja, 4ka** moving from 2,2,2-trifluoroethyl group, ally group to methyl group respectively (Scheme 5.8). These results clearly indicated the role of electron withdrawing



Scheme 5.8. Survey of ester part in *α*-pentafluoro-*α*-diazoacetates.

capability there by enhancing the electrophilicity and further demonstrated that crucial role of propargyl group on the overall transformation. In our earlier study,[12] we have clearly disclosed the role and effect of propargyl group in the overall transformation. The propargyl group has been proved to enhance the electrophilicity of carbene center for the better reactivity based on the computational DFT studies, Fukui function calculations of the diazo carbon center and the supporting control experimental results.

5.2.5. Optimization of the reaction condition – for the broader applicability:

Organofluorine compounds, especially polyfluoroarene containing organic compounds have exceptional applications in agrochemicals, pharmaceuticals as well as in the field of material science.[18] For instance, antagonist Atogepant (Qulipta) **IV**, antibiotic Orbifloxcin **V**, Diflunisal **VI** are some of the top-selling pharmaceutics having fluoroarene moiety. While the Fenfluthrin **VIII**, Tefluthrin **IX** are some of the well-known agrochemicals and the useful liquid crystal **VII** contains the polyfluoarene subunit (Figure 5.2).

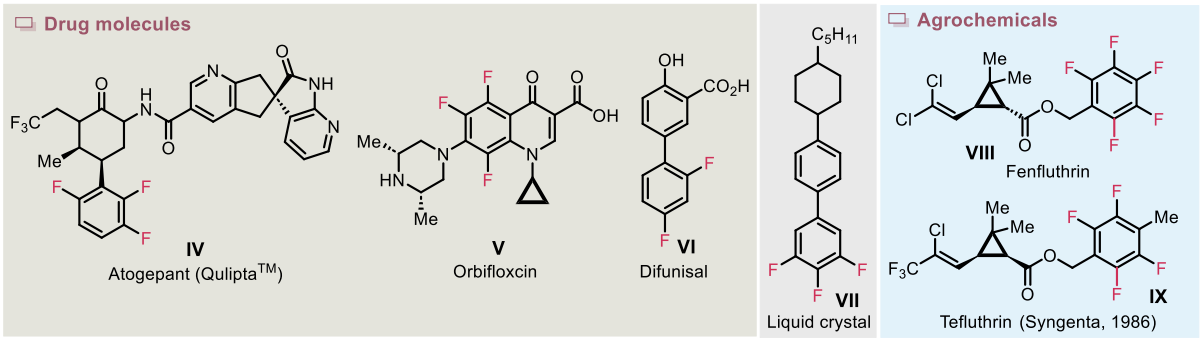
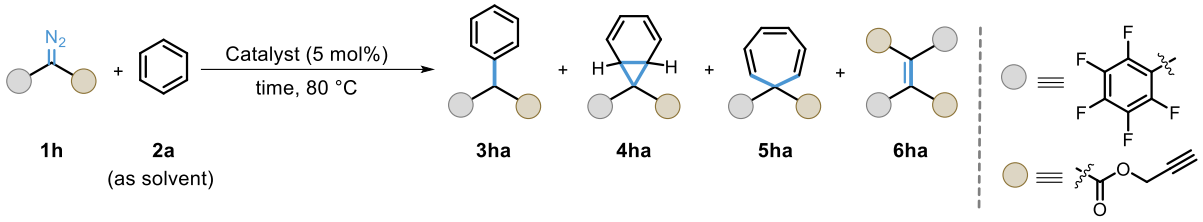


Figure 5.2. Polyfluoroarene and cyclopropane containing Pharmaceuticals, Agrochemicals and Liquid Crystal.

Encouraged by the initial promising results and considering the importance of polyfluoroarene containing organofluorine compounds and their market share, we further planned to optimized the reaction to improvise the yield and broaden the wider substrate scope. In this regard, we planned to screen few different Lewis acid catalysts in dry benzene using initially optimized the model substrate: propargyl α-pentafluoro-α-diazoacetate **1h**. To begin with we screened different triflates of scandium, indium, ytterbium, bismuth, yttrium, and iron as catalysts at an elevated temperature (80 °C, Table 5.1, Entries 1-7). Gratifyingly, among all the catalysts screened, $Sc(OTf)_3$ proved to be more efficient catalyst for the desired transformation to access the desired product **4ha** in higher yield with excellent diastereoselectivity (68%, Table 5.1, Entry 1). Lewis acid such as $FeCl_3.6H_2O$ also found to be

ineffective in catalyzing the reaction as it afforded the desired product 4ha in very poor yield (8%, Table 5.1, Entry 8). Later, we screened silver, rhodium, gold catalysts and they were found to be inefficient for the desired transformation as well (Table 5.1, Entries 8-10). In order to rule out the possibility of formation of triflic acid (TfOH) *in situ* (hydrolysis of scandium triflate due to moisture if any) and possibility of catalyzing the reaction, we screened the reaction of propargyl α-pentafluoro-α-diazoacetate **1h** and benzene **2a** in presence of TfOH (5 mol%) as catalyst at 80 °C (Table 5.1, Entry 11). However, the desired product formed in very poor yield thus ruling out the possibility of TfOH catalyzing the transformation. While the reaction in the absence of $Sc(OTf)_3$ did not proceed even after prolonged reaction time thus confirming the necessity of the scandium triflate for driving the reaction (Table 5.1, Entry 12).

Table 5.1. Optimization of reaction conditions[a]



Entry	Catalyst	Time (h)	Yield[b] (%) of **3ha**/**4ha**/**5ha**/**6ha**
1	$Sc(OTf)_3$	12	*n.d.*/68/*n.d.*/*n.d.*
2	$In(OTf)_3$	12	*n.d.*/60/*n.d.*/*n.d.*
3	$Yb(OTf)_3$	12	*n.d.*/trace/*n.d.*/*n.d.*
4	$Bi(OTf)_3$	12	*n.d.*/10/*n.d.*/*n.d.*
5	$Y(OTf)_3$	12	*n.d.*/18/*n.d.*/*n.d.*
6	$Fe(OTf)_3$	24	*n.d.*/*n.d.*/*n.d.*/*n.d.*
7	$FeCl_3.6H_2O$	12	*n.d.*/8/*n.d.*/*n.d.*
8	$AgSbF_6$	8	*n.d.*/*n.d.*/*n.d.*/<5
9	$Rh_2(OAc)_4$	6	*n.d.*/*n.d.*/*n.d.*/<5
10[c]	**L**AuPhCNSbF_6	30 min	*n.d.*/7/*n.d.*/*n.d.*
11	TfOH	12	*n.d.*/8/*n.d.*/*n.d.*
12	-	24	NR
13[d]	**$Sc(OTf)_3$**	**18**	***n.d.*/71/*n.d.*/*n.d.***
14[d,e]	$Sc(OTf)_3$	18	*n.d.*/38/*n.d.*/*n.d.*
15[d,f]	$Sc(OTf)_3$	24	*n.d.*/40/*n.d.*/*n.d.*

[a]Reaction conditions: diazo compound **1h** (0.5 mmol, 1.0 equiv.) and $Sc(OTf)_3$ (5 mol%) was added in benzene (2.5 mL) under inert atmosphere and reaction mixture was reflux at 80 °C, Note that reaction at room temperature did not work; reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography. [c]**1h** was consumed in 30 min. [d]**1h** (0.5 mmol, 1.0 equiv.), benzene **2a** (5.0 mmol, 10.0 equiv.) and $Sc(OTf)_3$ (5 mol%) in 1,2-DCE (2.5 mL) and reflux the mixture at 80 °C. [e]$AgSbF_6$ (5 mol%) was added. [f] 2.5 mol% of $Sc(OTf)_3$ was used. **L** = $(2,4\text{-}^tBu_2C_6H_3O)_3P$. NR = No reaction. *n.d.* = not detected.

Further, we screened the reaction in different solvents and among all 1,2-dichloroethane (1,2-DCE) was found to be more advantageous for the effective transformation (Table 5.1, Entry 13). After the careful investigations on different parameters, we looked into the effect of any additive on the reaction. The addition of $AgSbF_6$ (5 mol%) as an additive along with $Sc(OTf)_3$ (5 mol%) catalyst reduced the yield of desired product **4ha** significantly (Table 5.1,, Entry 14). Lowering of the catalyst loading further (2.5 mol% of $Sc(OTf)_3$) furnished the desired product **4ha** with diminished yield (40%, Table 5.1, Entry 15).

Based on the detailed and systematic screening, propargyl *α*-pentafluorophenyl-*α*-diazoacetate **1h**, benzene **2a** (10 equiv.) in 1,2-DCE (0.1 M) in presence of $Sc(OTf)_3$ as catalyst (5 mol%) at an elevated temperature (80 °C) for 18 h under inert atmosphere proved to optimum reaction condition to obtain the challenging dearomatized product (NCDs) **4ha** in 71% yield with excellent diastereoselectivity.

5.2.6. Investigation for the feasibility of the protocol – Substrate scope studies:

This robust reagent-catalyst system was found to be applicable to a range of unactivated arenes and the norcaradiene products were obtained with good selectivity. Generally, the alkyl-substituted arenes should have a significant impact on regioselectivity as well as on the NCDs – cycloheptatriene equilibrium.

Having obtained the optimized reaction conditions, we further planned to explore the substrate scope for generality of this dearomatization protocol. To begin with we treated the *α*-pentafluorophenyl-*α*-diazoacetate **1h** with different alkyl-substituted arenes (**2b**-**2d**) under the optimum reaction conditions. Gratifyingly in all the cases, exclusively desired norcaradiene products (**4hb**-**4hd**) were obtained in moderate to good yields (up to 76%) with moderate regio-controlled way without any trace of cycloheptatriene side product (Table 5.2). Moreover, dialkyl substituted substrate such as *p*-cymene **2e** also reacted with **1h** under optimum reaction conditions to furnish the corresponding cyclopropanation product **4he** in modest yield with exclusive diastereo- and regio-selectivity (40% yield, Table 5.2). Notably, the reactions of alkyl-substituted arenes (**2c**-**2e**) also provided an important information of chemoselectivity, as these substrates are also highly suitable for the competitive C–H bond functionalization of arene C–H bond as well as alkyl C–H bond.[8] However, it's very important to highlight that under the reaction conditions the **1h** exclusively afforded the NCDs and we did not detect even trace of C–H functionalized products. Later we treated different xylene derivatives with **1h**

under the optimized reaction conditions and interestingly, we observed a unique reactivity pattern to furnish the norcaradienes (**4hf-4hh)** (Table 5.2). The *p*-xylene **2f** efficiently

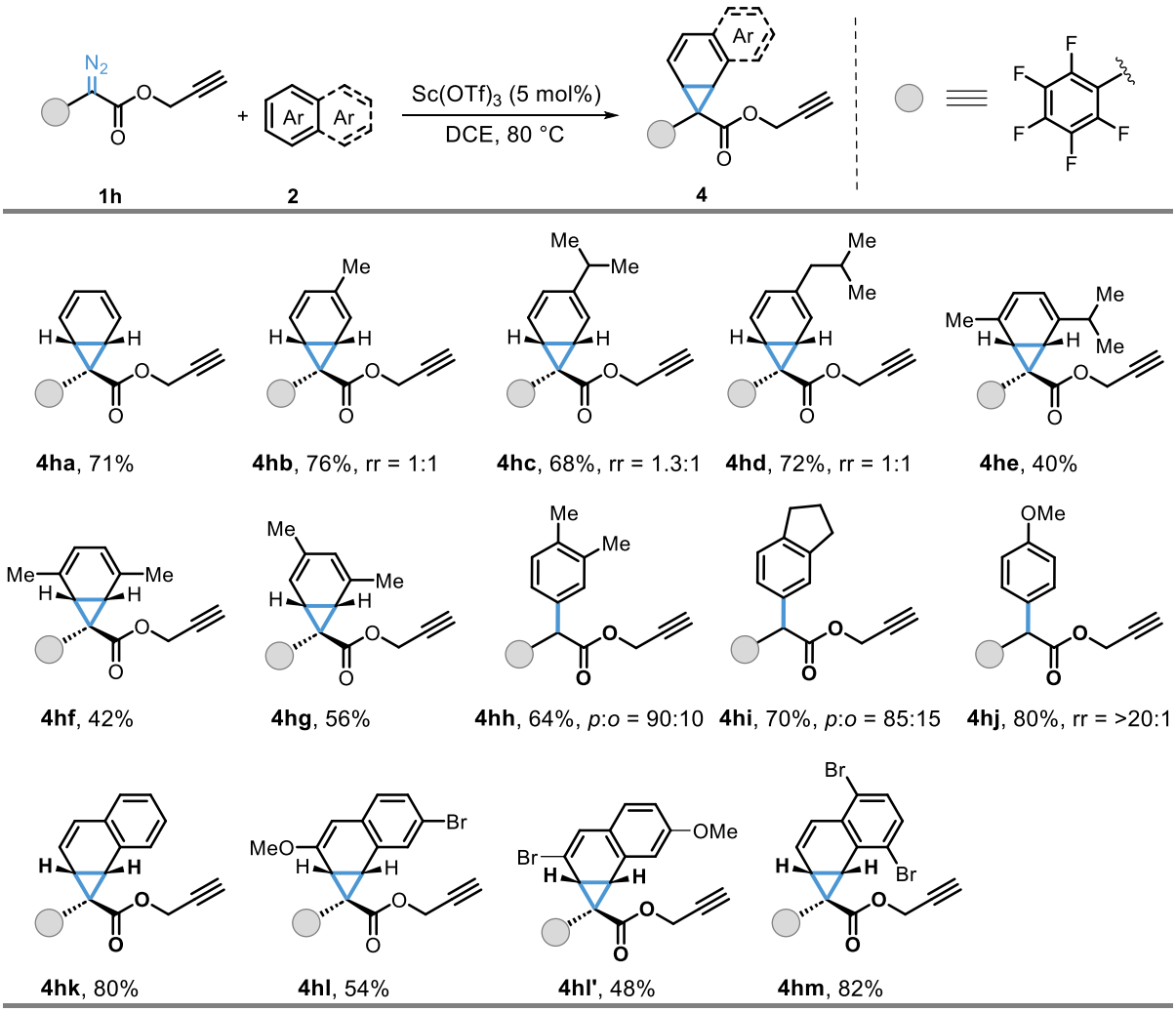


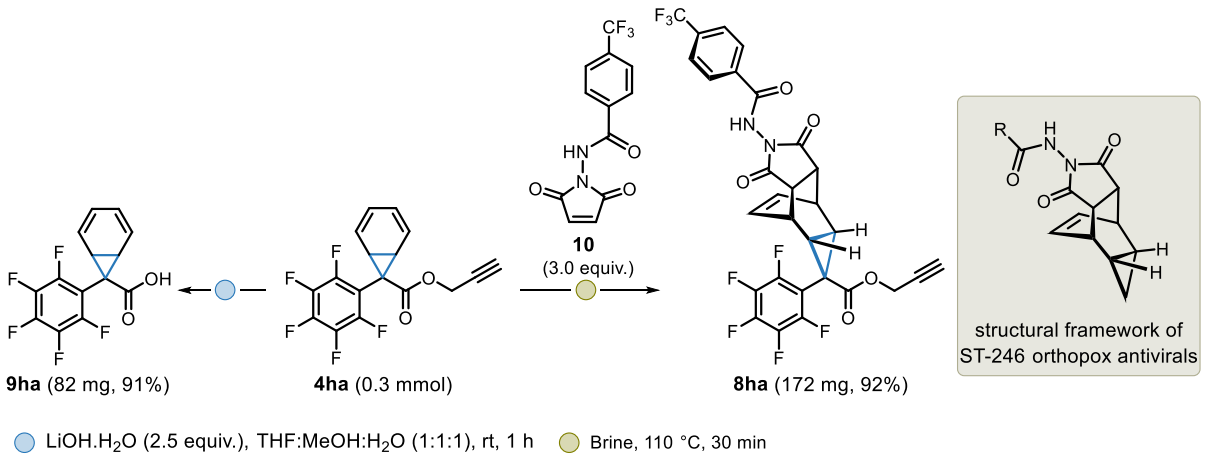
Table 5.2. Survey of substituted arenes and polycyclic arenes in cyclopropanation. Stereochemical structures have been mentioned according to the crystal structure of norcaradiene.

underwent reaction with **1h** to afford the desired norcaradiene **4hf** with excellent selectivity though in modest yield (42% yield). While, the *m*-xylene **2g** afforded the norcaradiene in good yield (56%) with high regio- and diastereo- selectivity. On the contrary, *o*-xylene **2h** furnished the aromatic C–H functionalization product **4hh** in 64% yield of mixture of regioisomers (*p*:*o* - 90:10 regioisomeric ratio). Interestingly, indane **2i** under the optimized condition reacted with **1h** to furnish the corresponding site-selective aromatic C–H functionalization product **4hi** (70% yield). Also, an activated arene such as anisole **2j** on treatment with **1h** afforded the corresponding the C–H functionalization product **4hj** with exclusive regioselectivity (rr >20:1)

and we had not obtained this result in our previous report[12] with propargyl α-phenyl-α-diazoacetate. Further, we explored the reaction with different polycyclic arenes (**2k**-**2m**) in order to understand the practicability of this developed protocol. All of these polycyclic arenes worked reacted smoothly under the optimized reaction condition to afford the corresponding norcaradiene products **4hk**, **4hl**, **4hl'**, **4hm** in good yields with excellent diastereoselectivity and good regioselectivity (up to 82%). Interestingly, 2-bromo-6-methoxynaphthalene **2l** furnished two isolable regioselective norcaradienes (**4hl** and **4hl′**) resulting from reaction at two different sites of two phenyl rings.

5.2.7. Synthetic utility of norcaradiene:

Having developed a robust protocol for accessing the norcaradiene directly and exclusively, we planned to explore the synthetic viability of norcaradiene by further utilizing in transformation to synthesize the molecule of importance. Previously reported methods for the norcaradiene functionalization have been restricted over the use of cycloheptatriene as starting congener and its CHTs⇌NCDs equilibrium.[4b,19] The diene functionalization of the norcaradiene in considered to be challenging as it enables the stereo-defined cyclohexanes. In this regard, we carried out the [4+2]-cycloaddition of **4ha** with a hydrazide-derived maleimide **10**. Gratifyingly, the reaction delivered the desired cycloadduct **8ha** as a single diastereomer in in excellent yield (92%) (Scheme 5.9). This interesting core scaffold is very important and is core to the very useful orthopox antivirals such as ST-246. It is very important to highlight that we have developed a novel pathway to synthesize this bioactive scaffold.



Scheme 5.9. Practical utility of norcaradiene as synthetic application.

Further, in order to show the usability of this protocol, we treated norcaradiene **4ha** with $LiOH.H_2O$ in methanol:THF:H_2O (1:1:1) mixture at room temperature for 1 hour to hydrolyze the ester moiety for further usability. The corresponding 7-(perfluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylic acid **9ha** was obtained in excellent yield (91%, Scheme 5.9).

5.3. Conclusions:

In summary, we have successfully developed a robust reagent-catalyst system for the regio- and chemo-selective dearomatization of the electronically unactivated and activated arenes. We have disclosed a novel direct synthesis of norcardienes (NCDs) starting from newly developed propargyl, *α*-pentafluoro-*α*-diazoacetates and arenes via scandium catalysis. It is very important to highlight that this elegant protocol effectively and selectively gives an access to NCDs without forming the competitive C–H functionalized products and Buckner ring expansion products. We have also demonstrated that modification of diazo functionalities by altering the electronic as well as steric properties may bring out the unusual yet useful synthetic transformations. Intuitively, characteristic changes made on the donor-/acceptor-type diazo compounds prompted them to behave like an acceptor-/acceptor-type carbene precursors. Also, the steric effect stemming from the *ortho*-fluorines at the phenyl ring of the propargyl *α*-pentafluoro-*α*-diazoacetate made it to behave like an acceptor group. Also, the alignment of the subunit of the diazo acetate has been unambiguously proved by the molecular structure of the diazo acetate using the single crystal X-ray analysis. The protocol proved to be efficient, practical and worked well with various alkyl substituted arenes as well as polyarenes system under the optimized condition to furnish the different norcaradienes in moderate to good yields. As an application of this protocol, we have demonstrated the synthesis of a congener of orthopox antiviral such as ST-246. This proved that the core scaffold of this bioactive compound could be accessed easily.

5.4. Experimental Section:

5.4.1. General information:

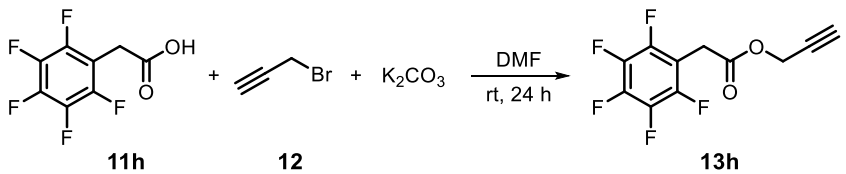
Reagent Information: All reactions were carried out with distilled and dried solvents using oven-dried glassware under dry Argon atmosphere, unless otherwise stated. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm) with detection by UV light. Column chromatographic purification of products was carried out using silica gel (60-120 mesh). Petroleum ether and ethyl acetate mixture was used as gradient elution for column chromatography.

Analytical Information: All isolated compounds were characterized by ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra. Nuclear Magnetic Resonance spectra were recorded in $CDCl_3$ and in Acetonitrile-d_3. The NMR spectra were recorded using tetramethylsilane (TMS) as the internal standard. ^{1}H NMR spectra were recorded at 400/600 MHz and $^{13}C\{^{1}H\}$ NMR spectra were recorded at 100/150 MHz (Bruker and Jeol), unless otherwise noted. Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) and from Acetonitrile-d_3 (δ = 1.94 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.16 ppm) and Acetonitrile-d_3 resonance (δ = 1.32 ppm) for $^{13}C\{^{1}H\}$ NMR spectroscopy. For ^{1}H NMR, data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, dt = doublet triplet, td = triplet doublet, tt = triplet triplet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*) are given in Hz and integration. $^{13}C\{^{1}H\}$ NMR spectra were recorded with complete proton decoupling. ^{19}F NMR spectra were recorded at 377/565 MHz. Mass samples were analyzed using High Resolution Mass Spectrometer (HRMS)-ESI TOF. Single crystal X-ray diffraction data were collected on a Bruker SMART APEX four-circle diffractometer equipped with a CMOS photon 100 detector (Bruker Systems Inc.) and Microfocus (IμS) using Cu Kα radiation (1.54178 Å).

5.4.2. Experimental Procedure:

5.4.2.1. Preparation of Starting Materials:

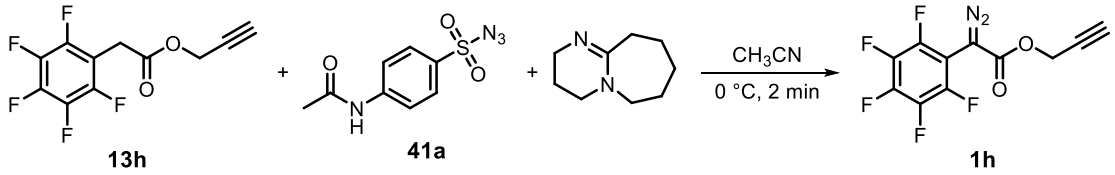
5.4.2.1.1. General procedure-A for the synthesis of propargyl esters:



11h **12** **13h**

The compounds were synthesized following the previously reported procedure.[12,20] To the stirred solution of 2,3,4,5,6-pentafluorophenylacetic acid **11h** (1 g, 4.5 mmol) in DMF (5 mL) were added propargyl bromide **12** solution 80% in toluene (0.803 g, 5.4 mmol) and K_2CO_3 (1.24 g, 9.0 mmol). The reaction mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC. The reaction mixture was filtered through celite, and the filtrate was diluted with ice water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with cold water and brine solution. The extract was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under vacuum and the crude product was purified using column chromatography over silica gel to afford product **11h** as a colourless liquid (1.12 g, 94% yield).

5.4.2.1.2. General procedure-B for the synthesis of propargyl diazoacetates:



*The compounds (**1a-1g**) were synthesized following the previously reported procedure.*[12,20] *The compounds (**1h-1k**) were synthesized following the previously reported procedure with few changes as mentioned below:*

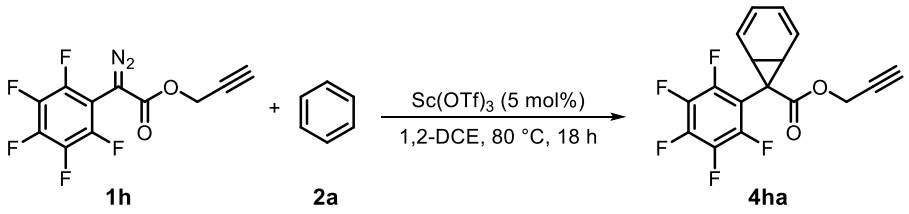
To the stirred solution propargyl 2,3,4,5,6-pentafluorophenylacetate **11h** (1 g, 3.8 mmol) in acetonitrile (8 mL) was added 4-acetamidobenzenesulfonyl azide (1.10 g, 4.56 mmol) and DBU (0.851 mL, 5.7 mmol) at 0 °C under inert atmosphere. The reaction mixture was stirred for 2 min at 0 °C. The reaction was quenched with saturated NH_4Cl and the product was extracted with diethyl ether (30 mL × 3). The combined organic layers were washed with brine solution and dried over anhydrous Na_2SO_4. The extract was filtered and the filtrate was evaporated (bath temperature below 25 °C) under vacuum. The crude product was purified using column chromatography over silica gel to afford *α*-(pentafluorophenyl)-*α*-diazoacetate **1h** as a light green solid (0.898 g, 82% yield).

Crystallization procedure for 1h: 30 mg of propargyl *α*-(pentafluorophenyl)-*α*-diazoacetate **1h** was dissolved in hexane (0.5 mL). Few drops of DCM were added over it and kept at -20 °C for overnight. Crystal shape – cubic, colour – light green. CCDC – 2276981.

5.4.2.2. General procedure-C for the optimization of arene part and ester part:

In an oven dried 25 mL RB flask equipped with a magnetic stirrer bar, alkyl α-aryl-α-diazoacetate (**1a-1h**) (0.5 mmol) and $Sc(OTf)_3$ (5 mol %), dry benzene were added under inert atmosphere. The reactions were carried out both at ambient temperature and then 80 °C in an oil bath for 3 – 24 h independently. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the products **3-6**.

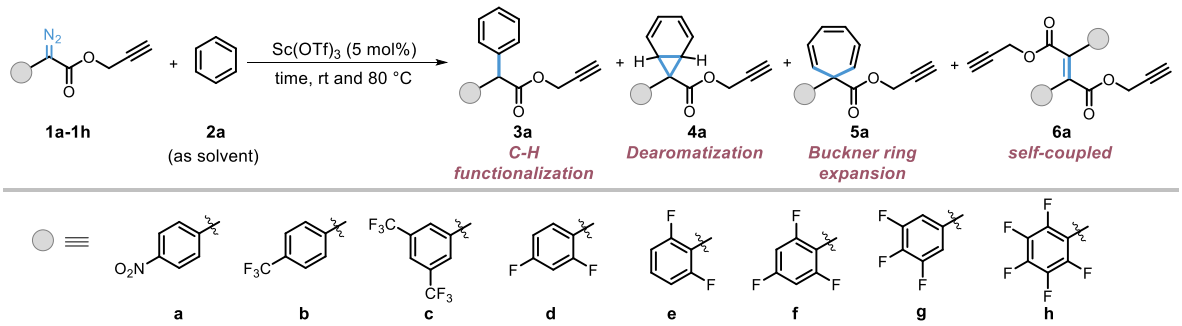
5.4.2.3. General procedure-D for the synthesis of norcaradienes:



In an oven dried 25 mL RB flask equipped with a magnetic stirrer bar, propargyl α-(pentafluorophenyl)-α-diazoacetate **1h** (0.145 g, 0.5 mmol), benzene **2a** (0.45 mL, 5.0 mmol), and $Sc(OTf)_3$ (12.3 mg, 5 mol %) DCE (2.5 mL) were added at room temperature under an inert atmosphere. Then the reaction mixture was refluxed at 80 °C over 18 h in an oil bath. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product **4ha** (0.120 g, 71% yield) as white solid. ***Crystallization procedure for 4ha:*** 30 mg of norcaradiene **4ha** was dissolved in hexane (1 mL). Few drops of DCM were added over it and kept at room temperature for overnight. Crystal shape – Needle, colour – colourless. CCDC – 2276982.

5.4.3. Optimization of different parameters of the reaction conditions:

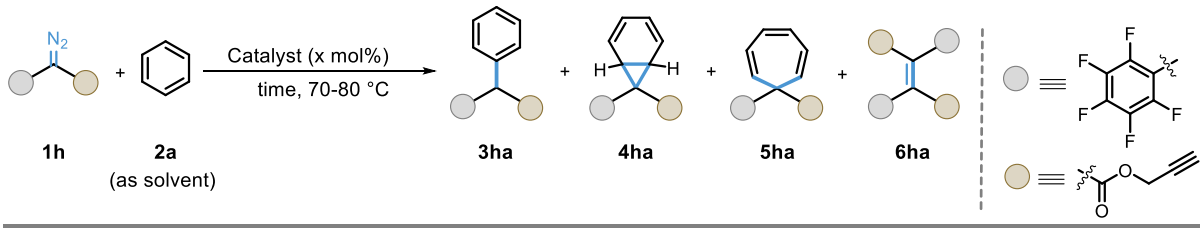
Table 5.3. Initial screening of different temperature range[a]



Entry	Diazo reagent	Temperature	Time (h)	Yield[b] of 3/4/5/6
1	1a	rt	24	NR
2	1a	80	12	DC
3	1b	rt	24	NR
4	1b	80	12	DC
5	1c	rt	24	NR
6	1c	80	6	75/*n.d.*/*n.d.*/*n.d.*
7	1d	rt	24	NR
8	1d	80	3	42/46/*n.d.*/*n.d.*
9	1e	rt	24	NR
10	1e	80	12	*n.d.*/48/*n.d.*/*n.d.*
11	1f	rt	24	NR
12	1f	80	12	*n.d.*/60/*n.d.*/*n.d.*
13	1g	rt	24	NR
14	1g	80	5	80/*n.d.*/*n.d.*/*n.d.*
15	1h	rt	24	NR
16	**1h**	**80**	**12**	***n.d.*/68/*n.d.*/*n.d.***

[a]Tested reaction conditions: Diazo acetates **1a**-**1h** (0.5 mmol, 1.0 equiv.) and $Sc(OTf)_3$ (5 mol%) was added in dry Benzene **2a** (2.5 mL) under inert atmosphere, reaction was carried out at both rt and 80 °C. [b]Yield of isolated product after purification by column chromatography. [c]DC - Decomposed. *n.d.* = not detected. All the reactions were remained unaltered at rt (27 °C).

Table 5.4. Solvent optimization for norcaradiene[a]



Entry	Solvent	$Sc(OTf)_3$ (mol%)	Temperature	Time (h)	Yield[b] of 3ha/4ha/5ha/6ha
1	EtOAc	5	78	10	*n.d.*/40/*n.d.*/*n.d.*
2	DCM	5	70	12	*n.d.*/50/*n.d.*/*n.d.*
3	Nitromethane	5	80	16	*n.d.*/54/*n.d.*/*n.d.*
4	**1,2-DCE**	**5**	**80**	**18**	***n.d.*/71/*n.d.*/*n.d.***
5	DMF	5	80	10	NR
6	Acetonitrile	5	80	10	NR
7	1,2-DCE	2.5	80	18	*n.d.*/37/*n.d.*/*n.d.*
8	1,2-DCE	10	80	16	*n.d.*/58/*n.d.*/*n.d.*
9[c]	1,2-DCE	5	80	18	*n.d.*/16/*n.d.*/*n.d.*

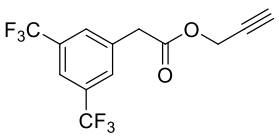
[a]Reaction conditions: diazo compound **1h** (0.5 mmol, 1.0 equiv.), benzene 2a (5.0 mmol, 10.0 equiv.), and

$Sc(OTf)_3$ (5 mol%) was added in solvent (2.5 mL) under inert atmosphere and reaction mixture was reflux at specified temperatures; reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography. [c]$AgSbF_6$ (5 mol%) was added. NR = No reaction. n.d. = not detected.

5.4.4. Characterization of synthesized compounds:

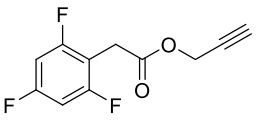
5.4.4.1. For ester compounds*:*

*Prop-2-yn-1-yl 2-(3,5-bis(trifluoromethyl)phenyl)acetate (**11c**):* Compound **11c** was



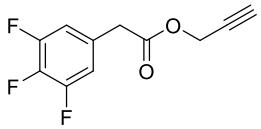
synthesized following the general procedure-A. The product was obtained as colourless liquid, 1.20 g (86% yield); *Rf* =0.30 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.80 (d, *J* = 8.7 Hz, 1H), 7.77 (s, 2H), 4.74 (d, *J* = 2.5 Hz, 2H), 3.82 (s, 2H), 2.50 (t, *J* = 2.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.4, 135.8, 132.1 (q, *J* = 33.4 Hz), 129.9 – 129.8 (m), 123.3 (d, *J* = 272.8 Hz), 121.6 (dt, *J* = 7.7, 3.8 Hz), 77.1, 75.6, 53.0, 40.4; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -62.9; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_9F_6O_2$ $(M + H)^+$ 311.0507; Found, 311.0510.

*Prop-2-yn-1-yl 2-(2,4,6-trifluorophenyl)acetate (**11f**):* Compound **11f** was synthesized



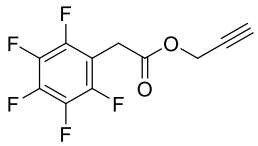
following the general procedure-A. The product was obtained as colourless liquid, 0.923 g (90% yield); *Rf* =0.35 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 – 6.64 (m, 2H), 4.72 (d, *J* = 2.5 Hz, 2H), 3.71 (s, 2H), 2.49 (t, *J* = 2.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.9, 162.3 (dt, *J* = 249.2, 15.5 Hz), 161.7 (ddd, *J* = 249.5, 15.0, 10.7 Hz), 106.4 (td, *J* = 20.4, 4.7 Hz), 100.6 – 99.9 (m), 77.3, 75.4, 52.9, 27.5 (t, *J* = 2.9 Hz); ^{19}F NMR (377 MHz, $CDCl_3$): δ -108.6 (t, *J* = 6.1 Hz), -111.4 (d, *J* = 6.1 Hz); HRMS (ESI TOF) *m/z*: calcd for $C_{11}H_8F_3O_2$ $(M + H)^+$ 229.0476; Found, 229.0477.

Prop-2-yn-1-yl 2-(3,4,5-trifluorophenyl)acetate (11g): Compound **11g** was synthesized



following the general procedure-A. The product was obtained as colourless liquid, 0.848 g (82% yield); *Rf* =0.35 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.97 – 6.89 (m, 2H), 4.71 (d, *J* = 2.4 Hz, 2H), 3.62 – 3.59 (m, 2H), 2.50 (t, *J* = 2.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.6, 151.3 (ddd, *J* = 250.1, 10.0, 4.2 Hz), 139.3 (dt, *J* = 251.5, 15.2 Hz), 129.5 (td, *J* = 8.1, 5.0 Hz), 114.0 – 113.3 (m), 77.2, 75.5, 52.9, 40.1; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -134.2, -162.2; HRMS (ESI TOF) *m/z*: calcd for $C_{11}H_8F_3O_2$ $(M + H)^+$ 229.0476; Found, 229.0481.

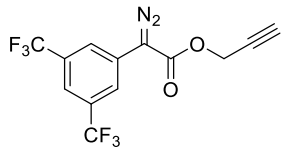
Prop-2-yn-1-yl 2-(perfluorophenyl)acetate (11h): Compound **11h** was synthesized following



the general procedure-A. The product was obtained as colourless liquid, 1.12 g (94% yield); *Rf* =0.35 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.74 (d, *J* = 2.5 Hz, 2H), 3.78 (td, *J* = 1.7, 0.6 Hz, 2H), 2.51 (t, *J* = 2.5 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 167.7, 145.5 (dddt, *J* = 247.9, 11.5, 7.9, 4.1 Hz, C^2), 141.0 (d, *J* = 253.9 Hz, C^1), 137.7 (d, *J* = 252.2 Hz, C^3), 107.7 (td, *J* = 18.4, 3.9 Hz, C^4), 76.9, 75.7, 53.3, 27.7 (d, *J* = 2.1 Hz); ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -142.1 (d, *J* = 13.6 Hz, F^3), -154.8 (t, *J* = 20.8 Hz, F^1), -162.1 (dd, *J* = 20.9, 13.7 Hz, F^2); HRMS (ESI TOF) *m/z*: calcd for $C_{11}H_6F_5O_2$ $(M + H)^+$ 265.0288; Found, 265.0285.

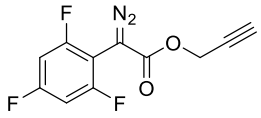
5.4.4.2. Data of diazo acetates:

Prop-2-yn-1-yl 2-(3,5-bis(trifluoromethyl)phenyl)-2-diazoacetate (1c): Compound **1c** was



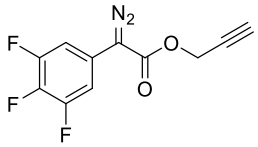
synthesized following the general procedure-B. The product was obtained as yellow oil, 0.978 g (77% yield); *Rf* =0.40 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.94 (m, 2H), 7.68 (s, 1H), 4.91 (d, *J* = 2.5 Hz, 2H), 2.55 (t, *J* = 2.5 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 163.1, 132.4 (q, *J* = 33.6 Hz), 128.7, 123.4 – 122.8 (m), 123.1 (d, *J* = 272.8 Hz), 119.4 (dt, *J* = 7.7, 3.7 Hz), 77.0, 75.7, 52.8; ^{19}F NMR (377 MHz, $CDCl_3$): δ -63.1; HRMS (ESI TOF) *m/z*: calcd for $C_{13}H_7F_6N_2O_2$ $(M + H)^+$ 337.0412; Found, 337.0420.

Prop-2-yn-1-yl 2-diazo-2-(2,4,6-trifluorophenyl)acetate (1f): Compound **1f** was synthesized



following the general procedure-B. The product was obtained as yellow oil, 0.750 g (78% yield); *Rf* =0.45 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 – 6.73 (m, 2H), 4.83 (d, *J* = 2.5 Hz, 2H), 2.50 (t, *J* = 2.5 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 179.6, 163.8 (d, *J* = 252.5 Hz), 161.0 (d, *J* = 252.8 Hz), 101.5 – 100.8 (m), 99.8 (d, *J* = 5.0 Hz), 77.4, 75.4, 52.9; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -104.9 (t, *J* = 7.5 Hz), -105.5 (d, *J* = 7.5 Hz); HRMS (ESI TOF) *m/z*: calcd for $C_{11}H_6F_3N_2O_2$ $(M + H)^+$ 255.0381; Found, 255.0381.

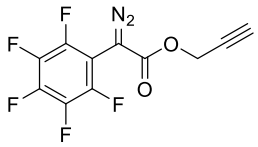
Prop-2-yn-1-yl 2-diazo-2-(3,4,5-trifluorophenyl)acetate (1g): Compound **1g** was synthesized



following the general procedure-B. The product was obtained as yellow oil, 0.722 g (75% yield); *Rf* =0.4 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 – 7.11 (m, 2H), 4.87 (d, *J* = 2.5 Hz, 2H), 2.53

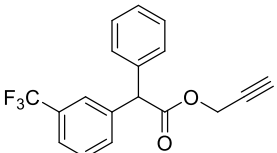
(t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 151.8 (ddd, *J* = 249.3, 10.2, 4.7 Hz), 137.6 (ddd, J = 249.3, 15.3), 122.1 (d, *J* = 4.7 Hz), 108.1 – 107. 8 (m), 77.3, 75.7, 52.8; ^{19}F NMR (377 MHz, $CDCl_3$): δ -132.8 (d, *J* = 21.0 Hz), -162.8 (t, *J* = 20.8 Hz); HRMS (ESI TOF) *m/z*: calcd for $C_{11}H_6F_3N_2O_2$ $(M + H)^+$ 255.0381; Found, 255.0380.

Prop-2-yn-1-yl 2-diazo-2-(perfluorophenyl)acetate (1h): Compound **1h** was synthesized following the general procedure-B. The product was obtained as light green solid, 0.898 g (82% yield); *Rf* =0.45 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.85 (d, *J* = 2.5 Hz, 2H), 2.52 (t, *J* = 2.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 162.7, 144.8 (d, *J* = 251.5 Hz, C^2), 142.1 (d, *J* = 252.0 Hz, C^1), 138.1 (d, *J* = 250.7 Hz, C^3), 101.3 (td, *J* = 17.1, 4.3 Hz, C^4), 77.1, 75.7, 53.2; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -136.3 (dd, *J* = 14.9, 2.6 Hz, F^3), -151.5 (tt, *J* = 21.1, 2.5 Hz, F^1), -160.8 (dd, *J* = 20.9, 14.9 Hz, F^2); HRMS (ESI TOF) *m/z*: calcd for $C_{11}H_4F_5N_2O_2$ $(M + H)^+$ 291.0193; Found, 291.0197.

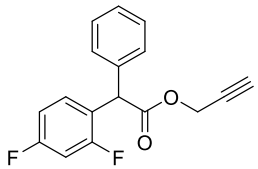


5.4.4.3. Data of title compounds NCDs and other obtained Final Products:

Prop-2-yn-1-yl 2-(3,5-bis(trifluoromethyl)phenyl)-2-phenylacetate (3ca): Compound **3ac** was synthesized following the general procedure-C. The product was obtained as colourless liquid, 0.145 g (75% yield); *Rf* =0.3 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.79 (s, 3H), 7.41 – 7.27 (m, 5H), 5.16 (s, 1H), 4.84 – 4.71 (m, 2H), 2.50 (t, *J* = 2.4 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 170.6, 140.8, 136.6, 132.1 (q, *J* = 33.4 Hz), 129.4, 129.1 (d, *J* = 3.9 Hz), 128.5, 128.4, 123.3 (d, *J* = 272.8 Hz), 121.7 (p, *J* = 3.7 Hz), 76.9, 75.8, 56.3, 53.2; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -62.8; HRMS (ESI TOF) *m/z*: calcd for $C_{19}H_{13}F_6O_2$ $(M + H)^+$ 387.0820; Found, 387.0820.

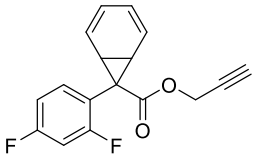


Prop-2-yn-1-yl 2-(2,4-difluorophenyl)-2-phenylacetate (3da): Compound **3dc** was synthesized following the general procedure-C. The product was obtained as colourless liquid, 0.060 g (42% yield); *Rf* =0.4 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40 – 7.28 (m, 5H), 7.21 (td, *J* = 8.4, 6.3 Hz, 1H), 6.86 – 6.79 (m, 2H), 5.29 (s, 1H), 4.80 – 4.70 (m, 2H), 2.47 (t, *J* = 2.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.0, 162.4 (dd, *J* = 249.0, 12.1 Hz), 160.5 (dd, *J* = 249.3, 11.8 Hz), 136.5, 130.9 (dd, *J* = 9.6, 4.9 Hz), 129.0, 128.8, 127.9, 121.9 (dd, *J* = 14.7, 3.9 Hz), 111.5 (dd, *J* = 21.2, 3.7 Hz), 104.0 (t, *J* = 25.7 Hz),



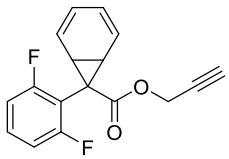
77.3, 75.4, 53.0, 49.2 (d, *J* = 2.9 Hz); ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -111.0 (d, *J* = 8.0 Hz), -112.4 (d, *J* = 7.5 Hz); HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{13}F_2O_2$ $(M + H)^+$ 287.0883; Found, 287.0885.

Prop-2-yn-1-yl 7-(2,4-difluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (4da):



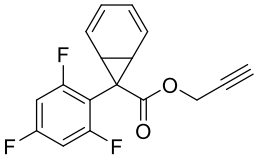
Compound **4da** was synthesized following the general procedure-C. The product was obtained as white solid, 0.066 g (46% yield); *Rf* =0.45 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.93 (tdd, *J* = 8.4, 6.4, 1.8 Hz, 1H), 6.73 – 6.62 (m, 2H), 6.22 – 6.14 (m, 2H), 5.82 – 5.76 (m, 2H), 4.66 (d, *J* = 2.4 Hz, 2H), 3.24 – 3.18 (m, 2H), 2.42 (t, *J* = 2.4 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 175.1, 162.6 (dd, *J* = 251.1, 12.2 Hz), 162.4 (dd, *J* = 248.3, 12.0 Hz), 136.1 (dd, *J* = 9.7, 5.2 Hz), 125.6, 124.2, 115.2 (dd, *J* = 14.2, 3.8 Hz), 109.9 (dd, *J* = 21.2, 3.5 Hz), 104.0 (t, *J* = 25.5 Hz), 77.7, 74.9, 53.2, 38.5, 31.7; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -108.9 (d, *J* = 8.8 Hz), -110.6 (d, *J* = 8.9 Hz). HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{13}F_2O_2$ $(M + H)^+$ 287.0883; Found, 287.0880.

Prop-2-yn-1-yl 7-(2,6-difluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (4ea):



Compound **4ea** was synthesized following the general procedure-C. The product was obtained as white solid, 0.068 g (48% yield); *Rf* =0.45 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.17 (tt, *J* = 8.4, 6.3 Hz, 1H), 6.79 – 6.71 (m, 2H), 6.22 – 6.13 (m, 2H), 5.79 – 5.74 (m, 2H), 4.67 (d, *J* = 2.5 Hz, 2H), 3.23 (dd, *J* = 3.7, 2.5 Hz, 2H), 2.41 (t, *J* = 2.4 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 174.89, 162.80 (dd, *J* = 250.5, 8.0 Hz), 129.50 (t, *J* = 10.7 Hz), 124.37 (t, *J* = 1.9 Hz), 124.28, 111.41 (dd, *J* = 21.3, 4.5 Hz), 108.99 (t, *J* = 17.9 Hz), 77.73, 74.89, 53.24, 36.84, 15.73; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -112.67; HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{13}F_2O_2$ $(M + H)^+$ 287.0883; Found, 287.0883.

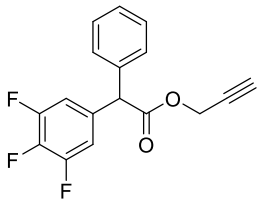
Prop-2-yn-1-yl 7-(2,4,6-trifluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (4fa):



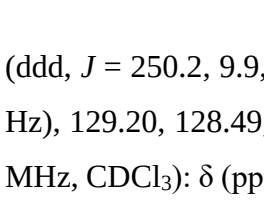
Compound **4fa** was synthesized following the general procedure-C. The product was obtained as white solid, 0.091 g (60% yield); *Rf* =0.45 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.56 – 6.48 (m, 2H), 6.16 (ddt, *J* = 8.1, 4.6, 2.3 Hz, 2H), 5.83 – 5.77 (m, 2H), 4.68 (d, *J* = 2.4 Hz, 2H), 3.23 (dd, *J* = 3.7, 2.5 Hz, 2H), 2.43 (t, *J* = 2.5 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 174.6, 163.1 (d, *J* = 251.6 Hz), 162.4 (d, *J* = 249.0 Hz), 124.5, 124.3, 105.4 (d, *J* = 5.1 Hz), 100.7 – 100.1 (m), 77.6, 75.0, 53.3, 36.8, 15.3; ^{19}F NMR (565 MHz, $CDCl_3$):

δ (ppm) -109.4 (t, *J* = 7.3 Hz), -110.7 (d, *J* = 7.3 Hz); HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{12}F_3O_2$ $(M + H)^+$ 305.0789; Found, 305.0789.

Prop-2-yn-1-yl 2-phenyl-2-(3,4,5-trifluorophenyl)acetate (3ga): Compound **3ga** was synthesized following the general procedure-C. The product was obtained as white semi-solid, 0.122 g (80% yield); *Rf* =0.45 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.25 (m, 5H), 7.00 – 6.91 (m, 2H), 4.97 (s, 1H), 4.81 – 4.69 (m, 2H), 2.50 (t, *J* = 2.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.74, 151.24 (ddd, *J* = 250.2, 9.9, 4.0 Hz), 139.26 (dt, *J* = 251.9, 15.3 Hz), 136.81, 134.52 (td, *J* = 7.4, 4.6 Hz), 129.20, 128.49, 128.23, 113.29 – 112.89 (m), 77.05, 75.70, 55.71, 53.11; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -133.8 (d, *J* = 20.6 Hz), -161.8 (t, *J* = 20.7 Hz); HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{12}F_3O_2$ $(M + H)^+$ 305.0789; Found, 305.0785.



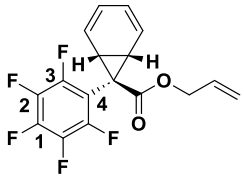
Prop-2-yn-1-yl 7-(perfluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (4ha): Compound **4ha** was synthesized following the general procedure-D. The product was obtained as white solid, 0.120 g (71% yield); *Rf* =0.45 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.22 – 6.16 (m, 2H), 5.88 – 5.83 (m, 2H), 4.69 (d, *J* = 2.5 Hz, 2H), 3.28 (dd, *J* = 3.8, 2.5 Hz, 2H), 2.45 (t, *J* = 2.5 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.5, 146.7 (d, *J* = 249.6 Hz, C^2), 141.0 (d, *J* = 253.7 Hz, C^1), 137.6 (d, *J* = 251.4 Hz, C^3), 124.8, 124.1 (t, *J* = 1.8 Hz), 106.8 (d, *J* = 4.2 Hz, C^4), 77.3, 75.4, 53.6, 36.8, 15.4. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -140.6 (td, *J* = 15.0, 2.8 Hz, F^3), -154.5 (tt, *J* = 21.0, 2.8 Hz, F^1), -162.8 (dt, *J* = 21.0, 15.0 Hz, F^2); HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{10}F_5O_2$ $(M + H)^+$ 341.0601; Found, 341.0600.



2,2,2-trifluoroethyl 7-(perfluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (4ia): Compound **4ia** was synthesized following the general procedure-C. The product was obtained as white solid, 0.092 g (48% yield); *Rf* =0.4 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.24 – 6.17 (m, 2H), 5.92 – 5.86 (m, 2H), 4.49 (q, *J* = 8.3 Hz, 2H), 3.32 (dd, *J* = 3.8, 2.5 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.9, 146.7 (d, *J* = 252.8 Hz, C^2), 141.2 (d, *J* = 254.1 Hz, C^1), 137.6 (d, *J* = 251.8 Hz, C^3), 125.1, 124.0 (t, *J* = 2.0 Hz), 122.7 (q, *J* = 277.4 Hz), 106.4 (td, *J* = 16.5, 4.1 Hz, C^4), 61.6 (q, *J* = 36.9 Hz), 37.3, 27.5; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -140.9 (dd, *J* = 14.8, 2.5 Hz, F^3), -154.0 (tt, *J* = 20.9, 2.6

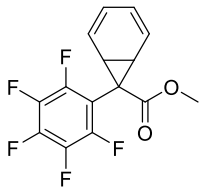
Hz, F^1), -162.7 (dd, J = 20.9, 14.8 Hz, F^2); HRMS (ESI TOF) *m/z*: calcd for $C_{16}H_9F_8O_2$ $(M + H)^+$ 385.0475; Found, 385.0480.

Allyl 7-(perfluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (4ja): Compound **4ja**



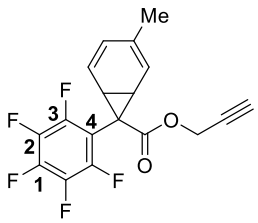
was synthesized following the general procedure-C. The product was obtained as white solid, 0.050 g (30% yield); *Rf* =0.45 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.22 – 6.14 (m, 2H), 5.87 – 5.76 (m, 3H), 5.19 (dq, J = 3.1, 1.5 Hz, 1H), 5.15 (dq, J = 11.0, 1.5 Hz, 1H), 4.61 (dt, J = 5.4, 1.5 Hz, 2H), 3.25 (dd, J = 3.8, 2.4 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.7, 146.6 (d, J = 249.5 Hz, C^2), 140.9 (d, J = 253.4 Hz, C^1), 137.5 (d, J = 247.0 Hz, C^3), 131.8, 124.6, 124.2 (t, J = 1.6 Hz), 118.0, 107.3 (m, C^4), 66.6, 66.4, 36.6, 15.4. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -140.8 (td, J = 15.0, 2.7 Hz, F^3), -154.8 (tt, J = 21.0, 2.5 Hz, F^1), -163.0 (dt, J = 21.0, 15.0 Hz, F^2); HRMS (ESI TOF) *m/z*: calcd for $C_{17}H_{12}F_5O_2$ $(M + H)^+$ 343.0757; Found, 343.0757.

Methyl 7-(perfluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (4ka): Compound



4ka was synthesized following the general procedure-C. The product was obtained as white solid, 0.036 g (23% yield); *Rf* =0.45 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.21 – 6.14 (m, 2H), 5.87 – 5.80 (m, 2H), 3.70 (s, 3H), 3.23 (dd, J = 3.8, 2.5 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 174.6, 146.7 (d, J = 245.2 Hz, C^2), 140.9 (d, J = 253.3 Hz, C^1), 137.6 (d, J = 251.4 Hz, C^3), 124.6, 124.2 (t, J = 1.9 Hz), 107.3 (d, J = 4.0 Hz, C^4), 53.5, 36.5, 15.3; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -140.75 (d, J = 15.0, 2.5 Hz), -154.94 (tt, J = 20.8, 2.4 Hz), -163.03 (dd, J = 20.9, 15.2 Hz); HRMS (ESI TOF) *m/z*: calcd for $C_{15}H_{10}F_5O_2$ $(M + H)^+$ 317.0601; Found, 317.0600.

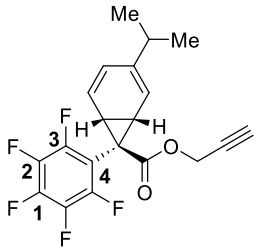
Prop-2-yn-1-yl 3-methyl-7-(perfluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate



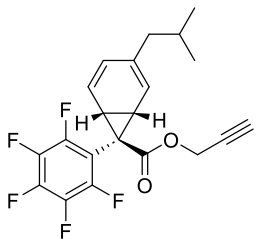
(4hb): Compound **4hb** was synthesized following the general procedure-D. The product was obtained as colourless viscous liquid, 0.135 g (76% yield); *Rf* =0.45 (petroleum ether/EtOAc 95:5); rr = 1:1, rr ratio determined by ^{1}H NMR; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.16 (ddd, J = 9.7, 4.4, 2.2 Hz, 1H), 6.04 (ddt, J = 8.6, 5.6, 2.5 Hz, 1H), 5.88 (dq, J = 3.4, 1.8 Hz, 1H), 5.80 (dd, J = 9.4, 6.2 Hz, 1H), 5.71 (dd, J = 9.5, 1.3 Hz, 1H), 5.66 (dt, J = 6.0, 1.7 Hz, 1H), 4.68 (dd, J = 7.1, 2.4 Hz, 4H), 3.29 (dd, J = 8.9, 5.4 Hz, 1H), 3.25 – 3.19 (m, 2H), 3.16 (d, J = 8.9 Hz, 1H), 2.45 (dt, J = 4.1, 2.5 Hz, 2H), 2.08 (s, 3H), 1.61 (s, 3H); ^{13}C{^{1}H}

NMR (100 MHz, $CDCl_3$): δ (ppm) 173.5, 173.4, 146.8 (d, *J* = 254.4 Hz, C^2), 140.9 (d, *J* = 252.0 Hz, C^1), 137.5 (d, *J* = 251.1 Hz, C^3), 133.9, 133.1, 128.7, 125.9, 124.5 – 124.2 (m), 121.1 (d, *J* = 1.7 Hz), 121.0, 119.0 (t, *J* = 1.9 Hz), 107.0 (dt, *J* = 17.2, 4.0 Hz, C^4), 77.6, 77.3, 75.4, 75.3, 53.6, 53.5, 40.8, 37.8, 36.9, 35.6, 23.5 (t, *J* = 3.6 Hz), 21.3, 16.2, 16.1; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -140.6 – -140.8 (m, F^3), -154.6 – -154.8 (m, F^1), -162.8 – -163.0 (m, F^2). HRMS (ESI TOF) *m/z*: calcd for $C_{18}H_{12}F_5O_2$ $(M + H)^+$ 355.0757; Found, 355.0759.

Prop-2-yn-1-yl 3-isopropyl-7-(perfluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (4hc): Compound **4hc** was synthesized following the general procedure-D. The product was obtained as colourless viscous liquid, 0.130 g (68% yield); *Rf* =0.45 (petroleum ether/EtOAc 95:5); rr = 1.3:1, determined by ^1H NMR; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.22 – 6.14 (m, 1H), 6.07 – 6.00 (m, 1H), 5.89 (s, 1H), 5.84 (dd, *J* = 9.3, 6.4 Hz, 1H), 5.79 (dd, *J* = 9.6, 1.4 Hz, 1H), 5.66 (d, *J* = 6.4 Hz, 1H), 4.69 (dd, *J* = 4.6, 2.5 Hz, 4H), 3.34 – 3.21 (m, 2H), 2.76 (hept, *J* = 6.9 Hz, 1H), 2.45 (q, *J* = 2.4 Hz, 1H), 2.17 (hept, *J* = 7.1 Hz, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.73 (d, *J* = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 173.7, 173.4, 146.9 (d, *J* = 246.4 Hz, C^2), 143.9, 143.4, 126.8, 126.1, 124.6, 121.5, 116.8, 116.5, 107.1 (d, *J* = 3.2 Hz, C^4), 77.4, 77.3, 75.3, 75.3, 53.6, 53.5, 40.4, 38.0, 36.7, 36.2, 34.0, 34.0, 34.0, 33.4, 22.3, 21.9, 21.1, 21.1, 20.2, 16.3, 16.3 (C^1 and C^3 not observed); ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -140.2 (4F, F^3), -154.7 (tt, *J* = 21.1, 2.0 Hz, 1F, F^1), -155.1 (tt, *J* = 21.0, 2.0 Hz, 1F, F^1), -163.3 (4F, F^2); HRMS (ESI TOF) *m/z*: calcd for $C_{20}H_{16}F_5O_2$ $(M + H)^+$ 383.1070; Found, 383.1075.

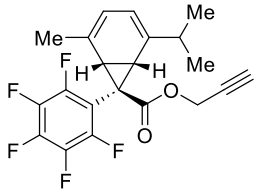


Prop-2-yn-1-yl 3-isobutyl-7-(perfluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (4hd): Compound **4hd** was synthesized following the general procedure-D. The product was obtained as colorless oil, 0.142 g (72% yield); *Rf* =0.4 (petroleum ether/EtOAc 95:5); rr = 1:1, rr ratio determined by ^1H NMR; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.16 (ddd, *J* = 9.2, 4.3, 2.1 Hz, 1H), 5.88 – 5.78 (m, 1H), 5.75 (dd, *J* = 9.6, 1.3 Hz, 1H), 4.68 (dd, *J* = 6.2, 2.5 Hz, 2H), 3.32 – 3.16 (m, 2H), 2.50 – 2.42 (m, 1H), 2.03 (dd, *J* = 14.0, 9.4 Hz, 1H), 1.93 – 1.84 (m, 1H), 1.73 (dd, *J* = 13.4, 7.8 Hz, 1H), 1.41 – 1.30 (m, 1H), 0.98 (d, *J* = 6.5 Hz, 1H), 0.83 (d, *J* = 6.5 Hz, 1H), 0.62 (dd, *J* = 18.8, 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 173.7, 173.4, 146.8 (d, *J* = 248.6 Hz, C^2), 140.9 (d, *J* = 248.0 Hz, C^1), 137.4 (d, *J* = 247.3 Hz, C^3), 136.2, 128.6, 128.0, 125.8, 124.2, 124.1, 124.1, 121.4, 121.4, 121.4,

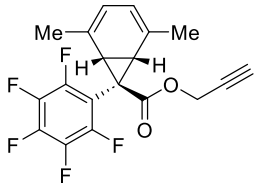


121.2, 119.9, 119.9, 119.8, 106.9 (d, *J* = 3.7 Hz, *C*^{4}), 77.3, 77.3, 75.3, 75.3, 53.6, 53.5, 46.1, 46.0, 46.0, 45.1, 40.4, 37.9, 37.0, 35.7, 28.5, 26.8, 23.4, 22.3, 21.9, 21.8; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -140.5 (dd, *J* = 15.0, 2.3 Hz, *F*^{3}), -154.7 (tt, *J* = 21.2, 2.3 Hz, *F*^{1}), -155.1 (tt, *J* = 20.9, 2.6 Hz, *F*^{1}), -163.1 (d, *J* = 15.9 Hz, *F*^{2}); HRMS (ESI TOF) *m/z*: calcd for $C_{21}H_{18}F_5O_2$ $(M + H)^+$ 397.1227; Found, 397.1225.

Prop-2-yn-1-yl (1R,6S,7S)-2-isopropyl-5-methyl-7-(perfluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (4he): Compound **4he** was synthesized following the general procedure-D. The product was obtained as white solid, 0.080 g (40% yield); *Rf* =0.45 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.64 (dt, *J* = 6.7, 1.3 Hz, 1H), 5.60 (d, *J* = 6.7 Hz, 1H), 4.70 (d, *J* = 2.5 Hz, 2H), 3.30 – 3.27 (m, 1H), 3.20 – 3.17 (m, 1H), 2.80 – 2.72 (m, 1H), 2.46 (t, *J* = 2.5 Hz, 1H), 2.05 (s, 3H), 1.08 (dd, *J* = 8.9, 6.8 Hz, 6H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 173.5, 145.6 (d, *J* = 245.9 Hz), 141.0, 140.6 (d, *J* = 252.0 Hz), 137.3 (d, *J* = 251.0 Hz), 131.1, 122.1, 117.5, 106.8 (td, *J* = 17.1, 3.4 Hz), 77.3, 75.4, 53.5, 41.7, 41.1, 33.5, 22.6, 20.3, 16.8. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -138.8, -139.6, -154.9 (tt, *J* = 21.1, 2.3 Hz), -163.2, -163.6; HRMS (ESI TOF) *m/z*: calcd for $C_{21}H_{18}F_5O_2$ $(M + H)^+$ 397.1227; Found, 397.1227.



Prop-2-yn-1-yl (1R,6S,7s)-2,5-dimethyl-7-(perfluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (4hf): Compound **4hf** was synthesized following the general procedure-D. The product was obtained as white solid, 0.077 g (42% yield); *Rf* =0.45 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.61 (s, 2H), 4.70 (d, *J* = 2.4 Hz, 2H), 3.17 (s, 2H), 2.46 (t, *J* = 2.5 Hz, 1H), 2.06 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.6, 147.5 (d, *J* = 248.7 Hz, *C*^{2}), 130.7, 122.1, 106.7 (d, *J* = 4.8 Hz, *C*^{4}), 77.3, 75.4, 53.6, 41.9, 23.1 – 22.8 (m), 16.8 (*C*^{1} and *C*^{3} not observed); ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -138.7 (dd, *J* = 15.3, 2.3 Hz), -154.8 (tt, *J* = 21.1, 2.3 Hz), -163.1 (dd, *J* = 21.1, 15.3 Hz); HRMS (ESI TOF) *m/z*: calcd for $C_{19}H_{14}F_5O_2$ $(M + H)^+$ 369.0914; Found, 369.0925.



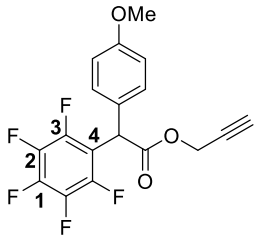
Prop-2-yn-1-yl (1R,6R,7S)-2,4-dimethyl-7-(perfluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (4hg): Compound **4hg** was synthesized following the general procedure-D. The product was obtained as colorless viscous liquid, 0.104 g (56% yield); *Rf* =0.4 (petroleum ether/EtOAc 95:5); rr = 1.5:1, rr ratio determined by ^{1}H NMR; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.00 (dt, *J* = 9.5, 4.7 Hz, 2H), 5.91 (s, 1H), 5.69 (d, *J* = 9.4 Hz, 1H), 4.68 (dd, *J* = 6.6, 2.3 Hz, 4H), 3.28 – 3.23 (m, 2H), 3.20 (dd, *J* = 3.9, 2.3 Hz, 1H), 3.16 (d, *J* = 9.0 Hz, 1H), 2.44 (h, *J* = 2.1 Hz, 2H), 2.02 (s, 4H), 1.63 – 1.57 (m, 8H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.6, 173.5, 146.8 (d, *J* = 254.9 Hz), 140.8 (d, *J* = 253.4 Hz), 137.4 (d, *J* = 251.1 Hz), 134.9, 130.7, 129.6, 127.2, 126.8, 126.1, 121.1, 120.5, 107.2 (d, *J* = 18.0, 4.3 Hz), 77.4, 75.3, 75.2, 53.4, 53.3, 42.2, 37.3, 36.6, 32.1, 19.9, 19.8, 19.4, 18.4, 16.5, 16.1; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -139.0 – -139.3 (m), -140.4 – -140.6 (m), -140.7 (dd, *J* = 15.0, 2.0 Hz), -154.8 (tt, *J* = 21.3, 3.1 Hz); -162.9 (td, *J* = 23.6, 6.9 Hz), -163.3 (td, *J* = 21.3, 15.1 Hz), -163.6 (td, *J* = 23.2, 6.6 Hz); HRMS (ESI TOF) *m/z*: calcd for $C_{19}H_{14}F_5O_2$ $(M + H)^+$ 369.0914; Found, 369.0920.

Prop-2-yn-1-yl 2-(3,4-dimethylphenyl)-2-(perfluorophenyl)acetate (4hh): Compound **4hh** was synthesized following the general procedure-D. The product was obtained as colorless viscous liquid, 0.118 g (64% yield); *Rf* =0.4 (petroleum ether/EtOAc 95:5); major product *para*-isomer (*p*:*o* = 90:10), *p*:*o* ratio determined by ^{1}HNMR; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.16 – 6.99 (m, 3H), 5.45 (s, 1H), 4.83 – 4.73 (m, 2H), 2.49 (t, *J* = 2.5 Hz, 1H), 2.30 (d, *J* = 2.7 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.4, 145.3 (d, *J* = 248.6 Hz), 140.9 (d, *J* = 253.9 Hz), 138.2, 137.8 (d, *J* = 252.3 Hz), 136.4, 131.8, 130.3, 129.5, 128.5 (t, *J* = 3.1 Hz), 127.3, 76.9, 75.6, 53.4, 43.0, 21.1, 19.6; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -139.9 (td, *J* = 14.7, 4.2 Hz, F^3), -154.6 (t, *J* = 21.0 Hz, F^1), -161.5 (dt, *J* = 20.9, 14.7 Hz, F^2); HRMS (ESI TOF) *m/z*: calcd for $C_{19}H_{14}F_5O_2$ $(M + H)^+$ 369.0914; Found, 369.0925.

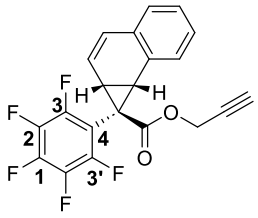
Prop-2-yn-1-yl 2-(2,3-dihydro-1H-inden-5-yl)-2-(perfluorophenyl)acetate (4hi): Compound **4hi** was synthesized following the general procedure-D. The product was obtained as colorless oil, 0.132 g (70% yield); *Rf* =0.35 (petroleum ether/EtOAc 95:5); major product *para*-isomer (*p*:*o* = 85:15), *p*:*o* ratio determined by ^{1}HNMR; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.22 –

7.12 (m, 2H), 7.07 (d, *J* = 7.7 Hz, 1H), 5.29 (s, 1H), 4.85 – 4.72 (m, 2H), 2.98 – 2.72 (m, 4H), 2.49 (t, *J* = 2.5 Hz, 1H), 2.06 (p, *J* = 7.5 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 169.3, 147.3 (d, *J* = 254.0 Hz, C^2), 145.3, 144.6, 142.4 (d, *J* = 249.6 Hz, C^1), 137.8 (d, *J* = 253.3 Hz, C^3), 133.0, 126.7 (d, *J* = 1.4 Hz), 124.9, 124.8 (d, *J* = 1.8 Hz), 113.9 (d, *J* = 3.4 Hz, C^4), 77.0, 75.6, 53.4, 46.0, 33.0, 32.7, 25.5; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -140.7 (td, *J* = 14.6, 3.4 Hz, F^3), -155.1 (t, *J* = 20.9 Hz, F^1), -161.48 (dt, *J* = 21.0, 14.6 Hz, F^2); HRMS (ESI TOF) *m/z*: calcd for $C_{20}H_{14}F_5NaO_2$ $(M + Na)^+$ 403.0733; Found, 403.0732.

Prop-2-yn-1-yl 2-(4-methoxyphenyl)-2-(perfluorophenyl)acetate (4hj): Compound **4hj** was synthesized following the general procedure-D. The product was obtained as colorless oil, 0.148 g (80% yield); *Rf* =0.25 (petroleum ether/EtOAc 95:5); rr >20:1, rr ratio determined by ^{1}HNMR; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.24 (d, *J* = 8.5 Hz, 2H), 6.90 – 6.85 (m, 2H), 5.27 (s, 1H), 4.85 – 4.74 (m, 2H), 3.79 (s, 3H), 2.50 (t, *J* = 2.5 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 169.2, 159.5, 144.8 (d, *J* = 247.6 Hz, C^2), 140.8 (d, *J* = 254.2 Hz, C^1), 137.8 (d, *J* = 253.3 Hz, C^3), 130.0 (t, *J* = 1.8 Hz), 127.2, 114.4, 113.8 (td, *J* = 17.2, 4.0 Hz, C^4), 76.9, 75.6, 55.4, 53.4, 45.3. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -141.1 (dt, *J* = 14.6, 2.9 Hz, F^3), -155.0 (td, *J* = 21.2, 2.8 Hz, F^1), -161.4 (td, *J* = 21.4, 14.4 Hz, F^2); HRMS (ESI TOF) *m/z*: calcd for $C_{18}H_{12}F_5O_3$ $(M + H)^+$ 371.0707; Found, 371.0710.



Prop-2-yn-1-yl 1-(perfluorophenyl)-1a,7b-dihydro-1H-cyclopropa[a]naphthalene-1-carboxylate (4hk): Compound **4hk** was synthesized following the general procedure-D. The product was obtained as white solid, 0.155 g (80% yield); *Rf* =0.35 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (dt, *J* = 7.6, 1.9 Hz, 1H), 7.27 (td, *J* = 7.5, 1.4 Hz, 1H), 7.18 (td, *J* = 7.5, 1.3 Hz, 1H), 6.90 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.34 – 6.23 (m, 2H), 4.73 (d, *J* = 2.4 Hz, 2H), 3.78 (d, *J* = 8.9 Hz, 1H), 3.34 (dd, *J* = 8.9, 5.2 Hz, 1H), 2.47 (t, *J* = 2.5 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 172.7, 146.8 (d, *J* = 247.1 Hz, C^2), 141.0 (d, *J* = 253.9 Hz, C^1), 137.4 (d, *J* = 249.3 Hz, C^3), 131.3, 131.0 (d, *J* = 3.7 Hz, C^4), 128.9 (d, *J* = 1.8 Hz), 128.4 (d, *J* = 2.2 Hz), 128.1, 127.9, 127.4, 122.7 (d, *J* = 3.2 Hz), 106.8 (d, *J* = 4.0 Hz), 77.2, 75.5, 53.6, 37.0, 33.8, 19.4. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -137.5 (td, *J* = 15.2, 2.5 Hz, 1F, F^3), -138.0 (td, *J* = 15.3, 2.6 Hz, 1F, $F^{3'}$), -154.0 (tt, *J* = 21.1, 2.7 Hz, 1F, F^1), -162.7 (dt, *J* = 21.1, 15.2 Hz, 2F, F^2); HRMS (ESI TOF) *m/z*: calcd for



$C_{21}H_{12}F_5O_2$ $(M + H)^+$ 391.0757; Found, 391.0730.

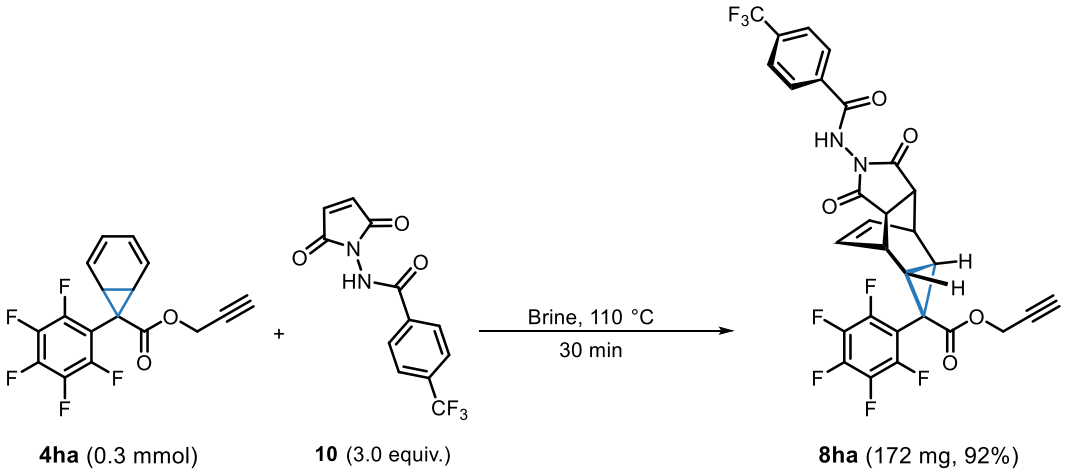
Prop-2-yn-1-yl 6-bromo-2-methoxy-1-(perfluorophenyl)-1a,7b-dihydro-1H-cyclopropa[a]naphthalene-1-carboxylate (4hl): Compound **4hl** was synthesized following the general procedure-D. The product was obtained as white solid, 0.134 g (54% yield); *Rf* =0.25 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.63 (t, *J* = 2.5 Hz, 1H), 7.23 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 5.39 – 5.37 (m, 1H), 4.77 – 4.67 (m, 2H), 3.77 (d, *J* = 9.5 Hz, 1H), 3.73 (s, 3H), 3.35 (dd, *J* = 9.5, 1.5 Hz, 1H), 2.48 (t, *J* = 2.4 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 171.71, 154.76, 146.82 (dd, *J* = 250.8, 74.1 Hz), 141.10 (d, *J* = 254.1 Hz), 137.17 (d, *J* = 251.1 Hz), 133.06 (d, *J* = 3.7 Hz), 132.65, 131.02, 127.12, 118.19, 106.16 (td, *J* = 17.4, 4.1 Hz), 96.95, 76.98, 75.71, 55.83, 53.87, 37.13, 34.56, 29.85. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -136.9 (td, *J* = 15.2, 2.6 Hz, 1F, F^3), -139.9 (td, *J* = 14.9, 2.2 Hz, 1F, $F^{3'}$), -153.4 (tt, *J* = 21.1, 2.4 Hz, 1F, F^1), -162.1 (dt, *J* = 20.7, 14.9 Hz, 2F, F^2), -162.6 (dt, *J* = 20.4, 15.5 Hz, 2F, $F^{2'}$); HRMS (ESI TOF) *m/z*: calcd for $C_{22}H_{13}BrF_5O_3$ $(M + H)^+$ 498.9968; Found, 498.9975.

Prop-2-yn-1-yl 2-bromo-6-methoxy-1-(perfluorophenyl)-1a,7b-dihydro-1H-cyclopropa[a]naphthalene-1-carboxylate (4hl'): Compound **4hl′** was synthesized following the general procedure-D. The product was obtained as white solid, 0.120 g (48% yield); *Rf* =0.2 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.09 (t, *J* = 2.7 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 6.75 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.63 (t, *J* = 0.9 Hz, 1H), 4.80 – 4.69 (m, 2H), 3.84 (s, 3H), 3.79 (d, *J* = 9.4 Hz, 1H), 3.58 (dd, *J* = 9.4, 1.2 Hz, 1H), 2.49 (t, *J* = 2.5 Hz, 1H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 171.8, 159.7, 146.9 (dd, *J* = 254.0, 82.4 Hz), 141.2 (d, *J* = 254.3 Hz), 137.2 (d, *J* = 258.3 Hz), 129.4, 129.1, 128.2, 125.3, 115.5 (d, *J* = 4.2 Hz), 114.7, 114.4, 105.8 (d, *J* = 3.7 Hz), 77.0, 75.8, 55.6, 54.0, 40.3, 39.4, 29.8. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -134.3 (td, *J* = 15.5, 2.2 Hz, 1F, F^3), -135.9 (td, *J* = 15.3, 2.4 Hz, 1F, $F^{3'}$), -153.1 (tt, *J* = 21.0, 2.6 Hz, 1F, F^1), -161.9 (dt, *J* = 20.9, 15.7 Hz, 2F, F^2), -162.6 (dt, *J* = 20.9, 15.4 Hz, 2F, $F^{2'}$); HRMS (ESI TOF) *m/z*: calcd for $C_{22}H_{13}BrF_5O_3$ $(M + H)^+$ 498.9968; Found, 498.9968.

Prop-2-yn-1-yl 4,7-dibromo-1-(perfluorophenyl)-1a,7b-dihydro-1H-cyclopropa[a]naphthalene-1-carboxylate (4hm): Compound **4hm** was synthesized following the general procedure-D. The product was obtained as white solid, 0.224 g (82% yield); *Rf* =0.25 (petroleum ether/EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40 (d, *J* = 8.6 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 6.73 (dd, *J* = 9.8, 0.8 Hz, 1H), 6.38 (dt, *J* = 9.4, 5.5 Hz, 1H), 4.81 – 4.68 (m, 2H), 4.11 (d, *J* = 9.0 Hz, 1H), 3.36 (dd, *J* = 9.1, 5.4 Hz, 1H), 2.48 (t, *J* = 2.5 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.9, 132.9, 132.8, 132.2, 130.9, 126.7 (d, *J* = 2.1 Hz), 126.4 (d, *J* = 3.2 Hz), 125.9 (d, *J* = 3.4 Hz), 121.8, 106.0 (d, *J* = 4.3 Hz, *C*^{4}), 77.0, 75.7, 54.0, 37.3, 34.0, 18.8, (*C*^{1} to *C*^{3} not observed). ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -137.7 (td, *J* = 15.0, 2.6 Hz, 1F, *F*^{3}), -138.7 (td, *J* = 15.3, 2.8 Hz, 1F, *F*$^{3'}$), -152.7 (tt, *J* = 21.0, 2.7 Hz, 1F, *F*^{1}), -161.8 (dt, *J* = 21.2, 14.9 Hz, 2F, *F*^{2}); HRMS (ESI TOF) *m/z*: calcd for $C_{21}H_{10}Br_2F_5O_2$ $(M + H)^+$ 546.8968; Found, 546.8975.

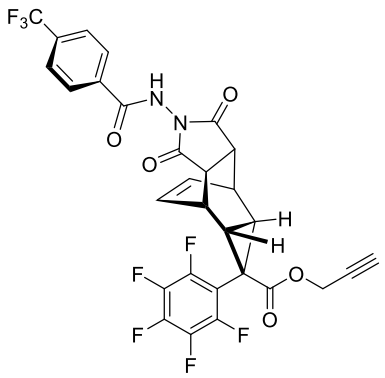
5.4.5. Application of the Protocol:

a) [4+2]-cycloaddition reaction with norcaradiene:



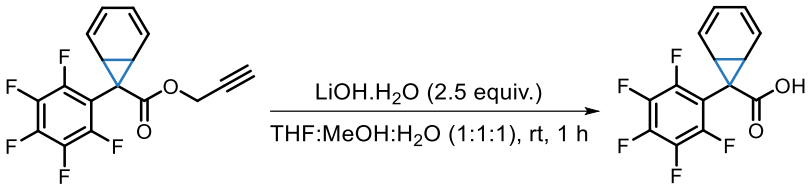
To a RB flask (25 mL) quipped with a magnetic stirrer was charged with norcaradiene **4ha** (102 mg, 0.3 mmol) and *N*-(2,5-dioxo-2,5- dihydro-1*H*-pyrrol-1-yl)-4-(trifluoromethyl)benzamide (256 mg, 0.9 mmol, 3.0 equiv.) and the reaction mixture was purged with argon. Then the brine (3 mL) solution was added and the suspension was subjected to oil bath for heating at 110 °C for 30 min. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate (3 X 10) and the combined organic layer was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product **7ha** (172 mg, 92% yield) as white solid.

Prop-2-yn-1-yl 4R,4aS,5aR,6S)-1,3-dioxo-5-(perfluorophenyl)-2-((4-(trifluoromethyl)phenyl)amino)-1,2,3,3a,4,4a,5,5a,6,6a-decahydro-4,6-ethenocyclopropa[f]isoindole-5-carboxylate (8ha):



The product **8ha** was obtained as white solid, 172 mg (92% yield); *Rf* =0.35 (petroleum ether/EtOAc 50:50); ^{1}H NMR (400 MHz, Acetonitrile-d_3): δ (ppm) 9.17 (s, 1H), 7.95 (d, *J* = 8.2 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 2H), 5.53 (p, *J* = 4.4 Hz, 2H), 4.61 (d, *J* = 2.5 Hz, 2H), 3.71 (s, 2H), 3.35 (s, 2H), 2.77 (t, *J* = 2.5 Hz, 1H), 2.49 (t, *J* = 2.4 Hz, 2H); ^{13}C{^{1}H} NMR (150 MHz, Acetonitrile-d_3): δ (ppm) 174.6, 170.4, 164.9, 146.3 (d, *J* = 245.8 Hz), 141.8 (d, *J* = 255.4 Hz), 138.6 (d, *J* = 249.8 Hz), 135.6, 134.3 (q, *J* = 32.9 Hz), 131.2, 129.4, 126.8 (q, *J* = 4.0 Hz), 124.9 (q, *J* = 271.8 Hz), 112.9 (td, *J* = 17.5, 3.6 Hz), 78.3, 76.6, 54.3, 44.1, 34.0, 29.7, 26.2; ^{19}F NMR (377 MHz, Acetonitrile-d_3): δ (ppm) -63.7, -143.0, -158.0 (t, *J* = 20.1 Hz), -165.3 (dt, *J* = 20.0, 9.8 Hz); HRMS (ESI TOF) *m/z*: calcd for $C_{29}H_{15}F_8N_2O_5$ $(M + H)^+$ 623.0853; Found, 623.0850.

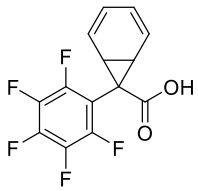
b) Deprotection of Propargyl group: Easy Ester Hydrolysis



4ha (0.3 mmol) **9ha** (82 mg, 91%)

A mixture of norcaradiene **4ha** (102 mg, 0.3 mmol, 1.0 equiv.) and LiOH·H_2O (32 mg, 0.75 mmol 2.5 equiv.) was taken RB flask (25 mL). Further 3 mL of solvent mixture (THF:MeOH:H2O = 1:1:1) was added into the mixture under an open atmosphere. The reaction mixture was stirred at room temperature over 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was acidified by using 3 N HCl and adjusted to pH 2−3. The white suspension was filtered through a sintered funnel with celite and the white residue was washed with water to furnish the product **9ha** as a white solid (82 mg, 91% yield).

7-(Perfluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylic acid (9ha): The compound



9ha was obtained as white solid, 82 mg (91% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.20 (ddq, *J* = 8.4, 4.3, 2.2 Hz, 2H), 5.91 – 5.83 (m, 2H), 3.31 (dd, *J* = 3.7, 2.5 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 180.7, 146.7 (d, *J* = 250.2 Hz, *C*^{2}), 141.1 (d, *J* = 253.7 Hz, *C*^{1}), 137.6 (d, *J* = 252.5 Hz, *C*^{3}), 125.0, 124.2 (t, *J* = 1.8 Hz), 106.7 (d, *J* = 4.2 Hz, *C*^{4}), 49.9, 37.2; ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -140.7 (td, *J* = 15.1, 2.3 Hz, *F*^{3}), -154.4 (tt, *J* = 21.2, 2.6 Hz, *F*^{1}), -162. 8 (dt, *J* = 21.3, 15.0 Hz, *F*^{2}); HRMS (ESI TOF) *m/z*: calcd for $C_{14}H_6F_5O_2$ $(M + H)^+$ 301.0288; Found, 301.0281.

5.4.6. Appendix-V: ^{1}H, ^{13}C{^{1}H}, and ^{19}F NMR spectral data of representative compounds

Compound No.	Figure V.X	Data	Page No.
1h	Figure V.1, V.2 and V.3	^{1}H, ^{13}C, and ^{19}F	253-254
4ha	Figure V.4, V.5 and V.6	^{1}H, ^{13}C, and ^{19}F	254-255
4hb	Figure V.7, V.8 and V.9	^{1}H, ^{13}C, and ^{19}F	256-257
4hk	Figure V.10, V.11 and V.12	^{1}H, ^{13}C, and ^{19}F	257-258
8ha	Figure V.13, V.14 and V.15	^{1}H, ^{13}C, and ^{19}F	259-260

5.4.6. Copies of ^{1}H, $^{13}C\{^{1}H\}$, and ^{19}F NMR Spectra of representative compounds:

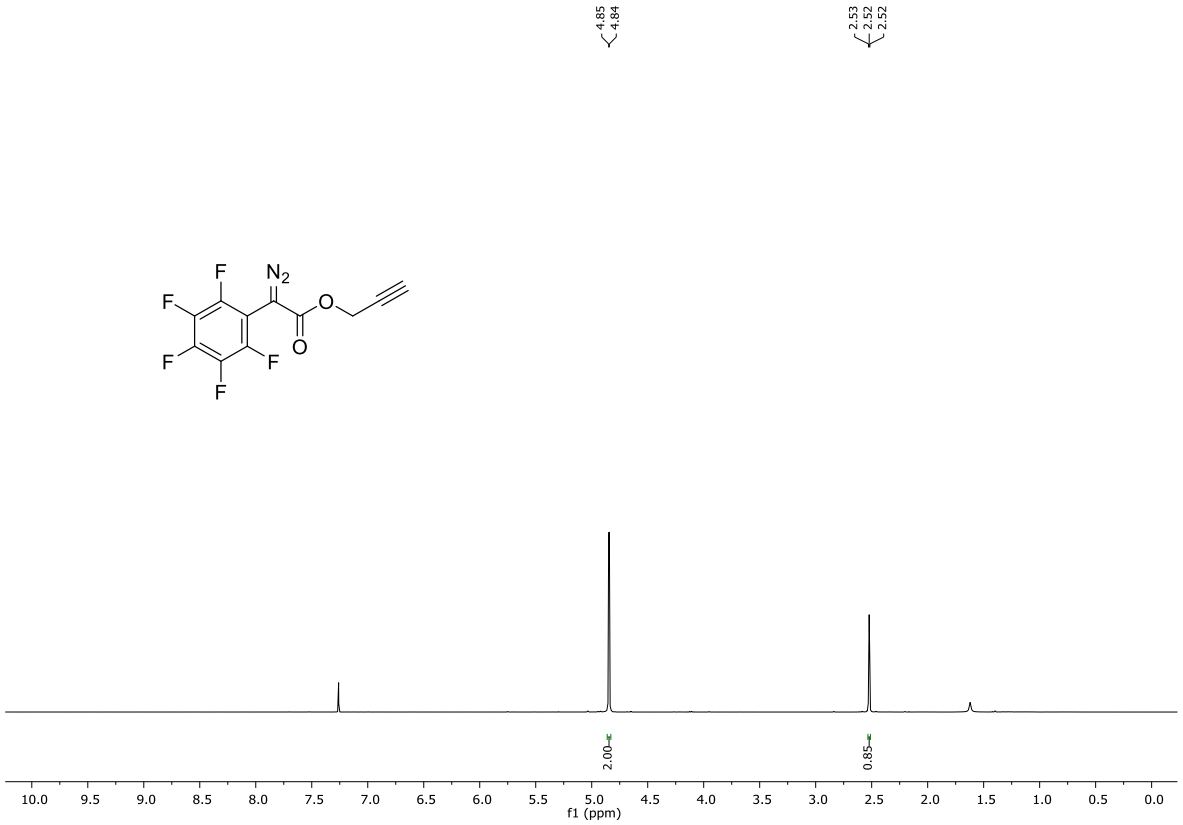


Figure V.1. ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **1h**

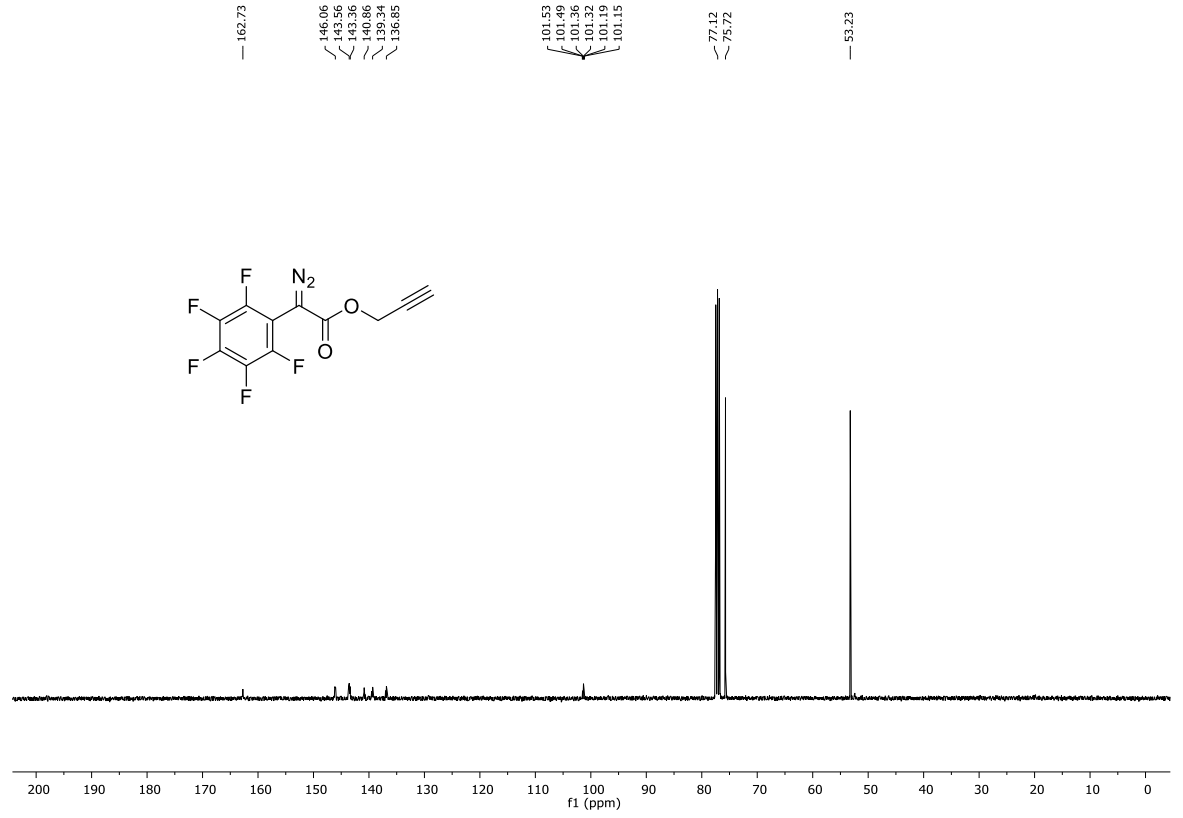


Figure V.2. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) Spectrum of **1h**

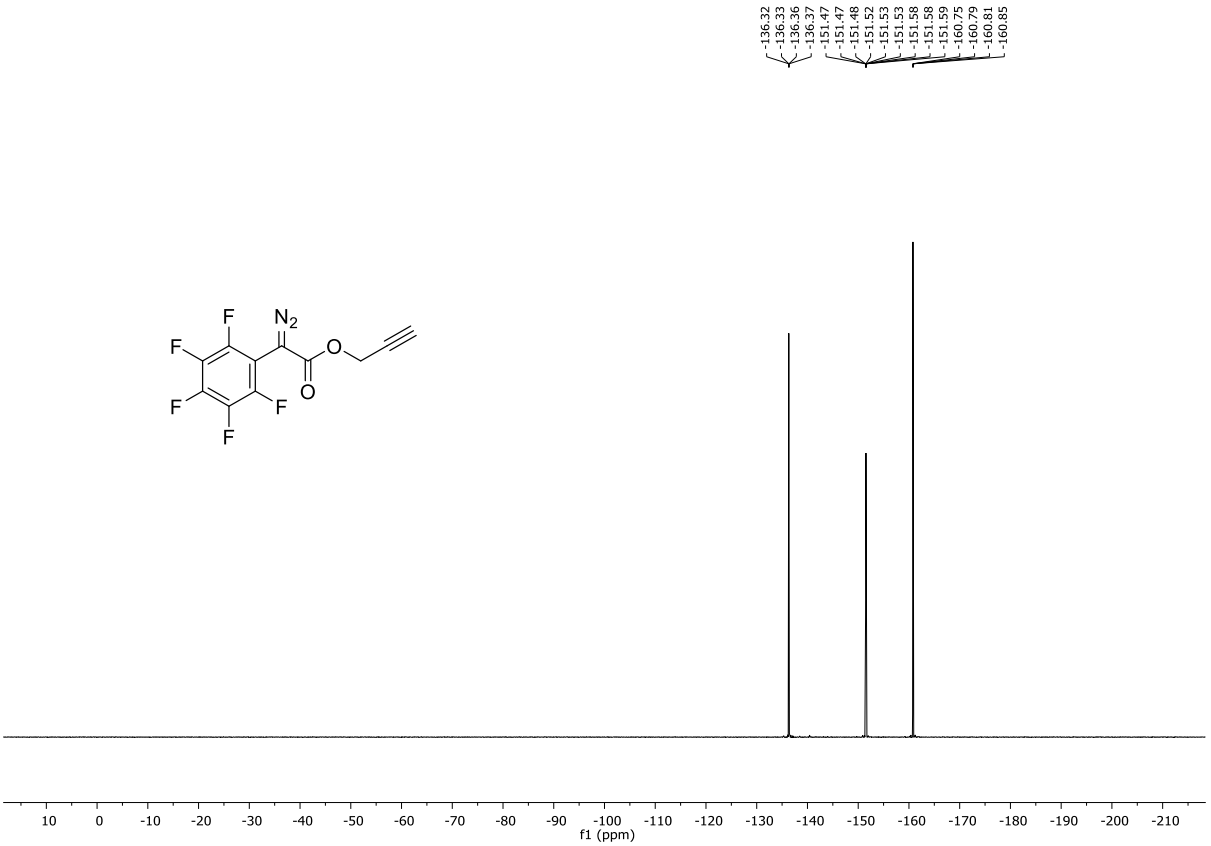


Figure V.3. ^{19}F NMR (377 MHz, $CDCl_3$) Spectrum of **1h**

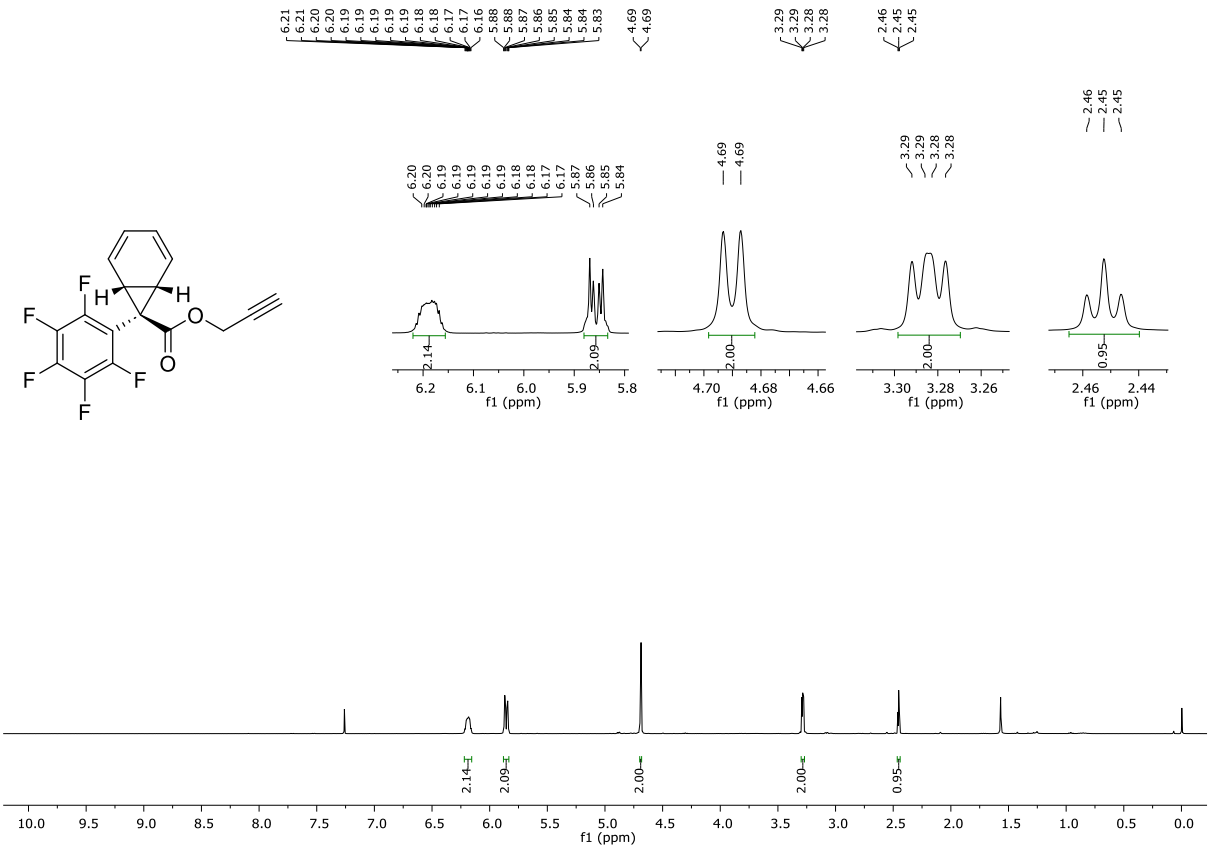


Figure V.4. ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **4ha**

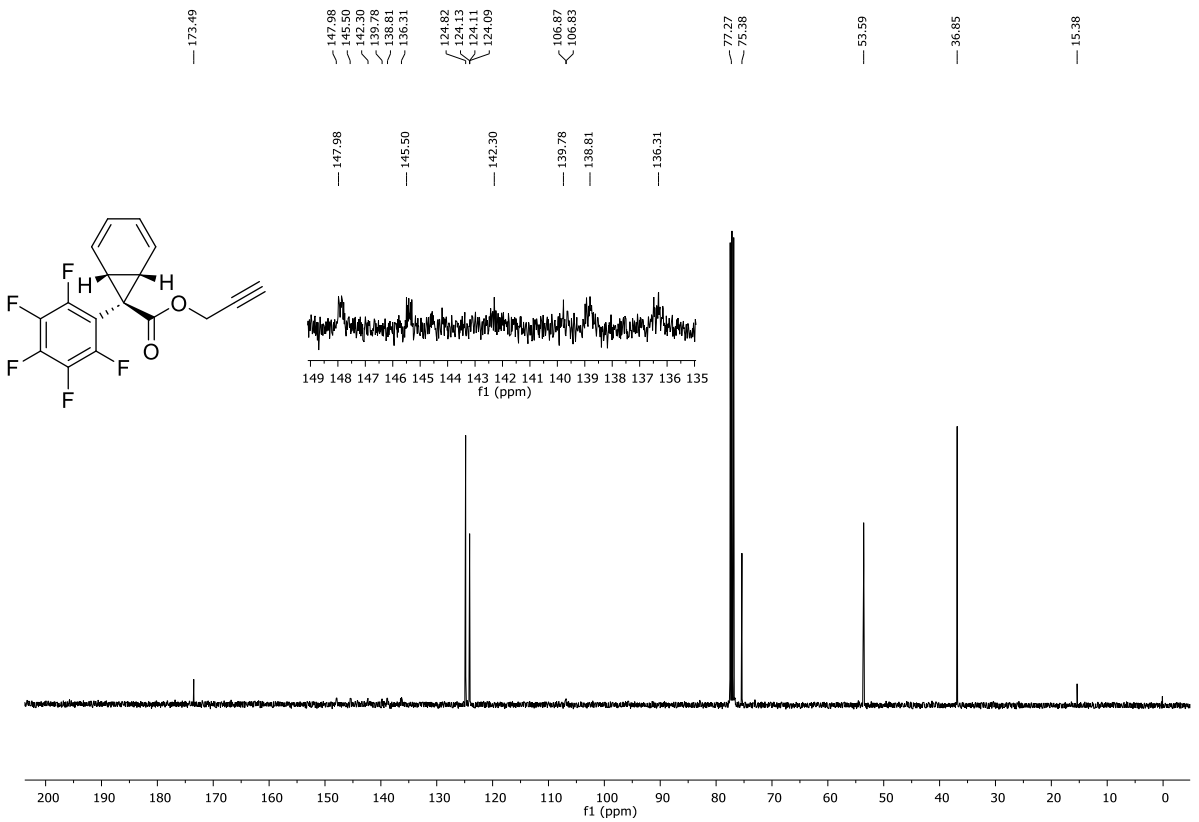


Figure V.5. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) Spectrum of **4ha**

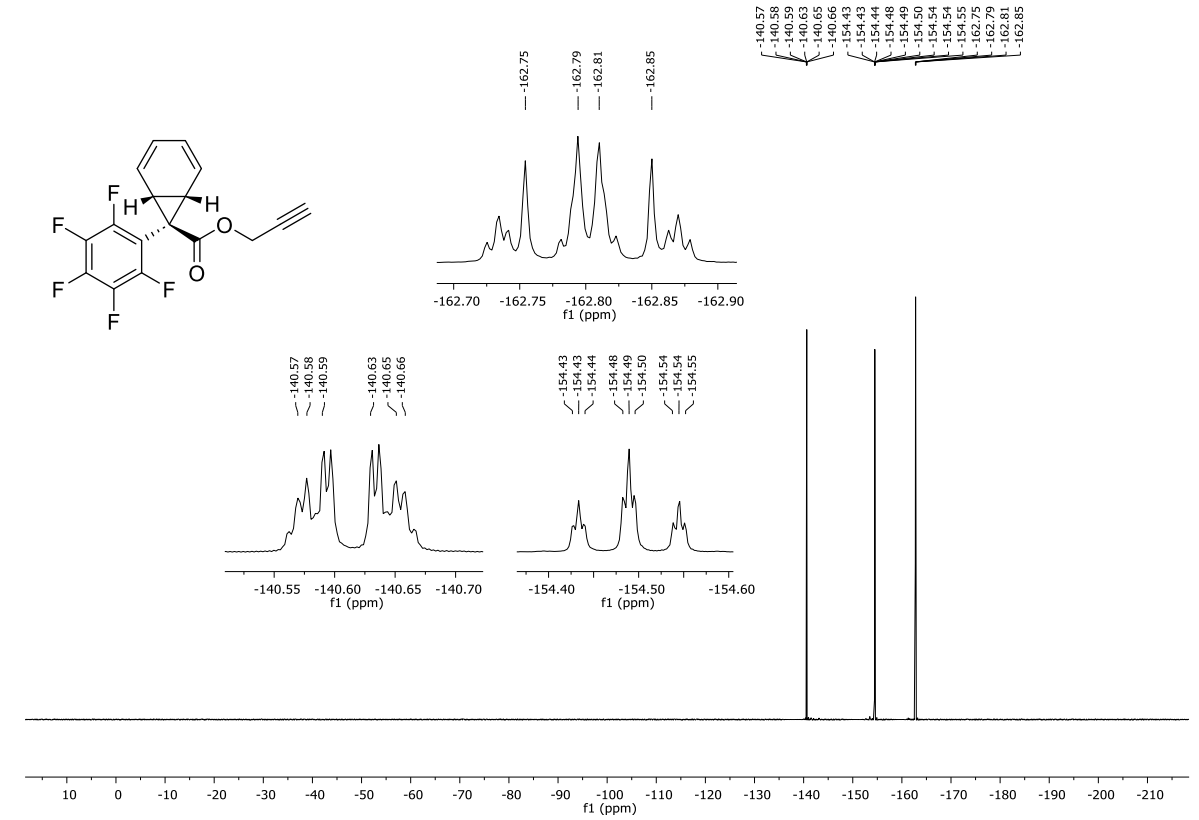


Figure V.6. ^{19}F NMR (377 MHz, $CDCl_3$) Spectrum of **4ha**

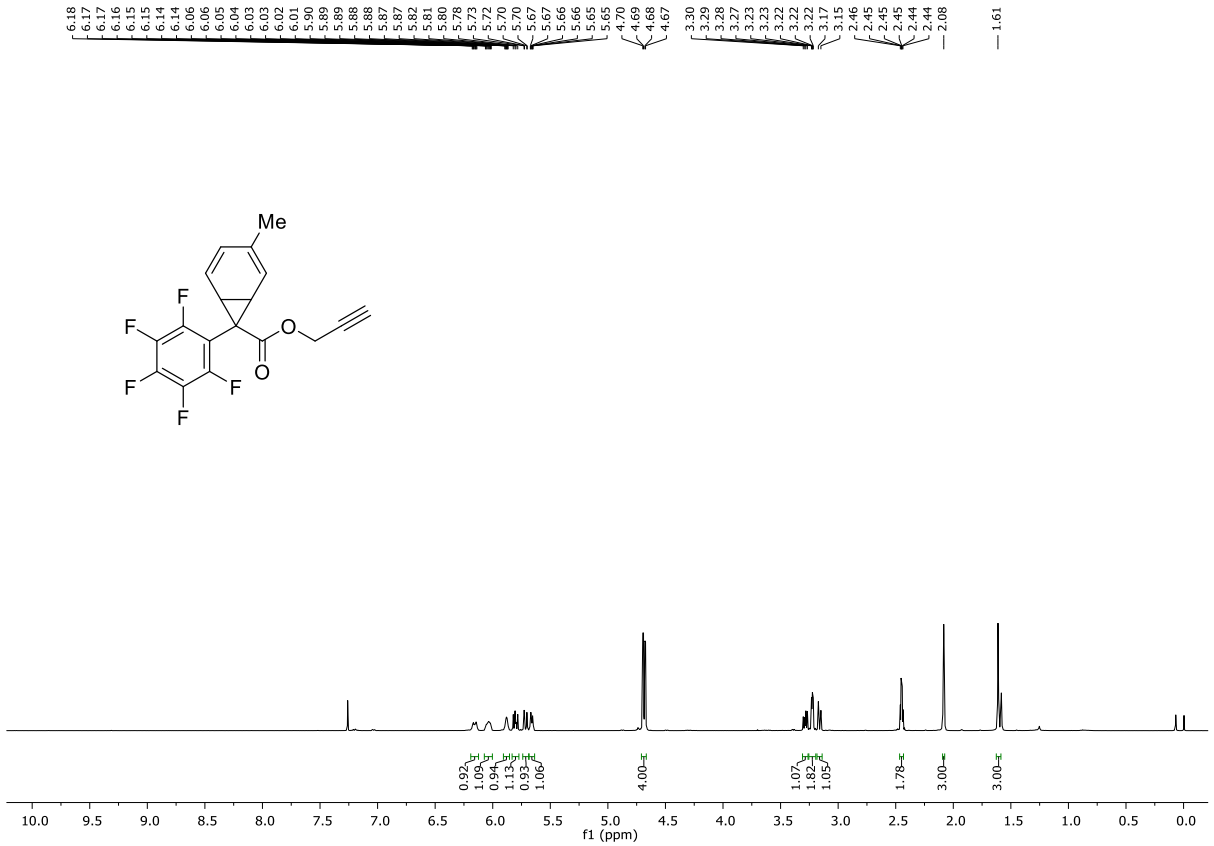


Figure V.7. ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **4hb**

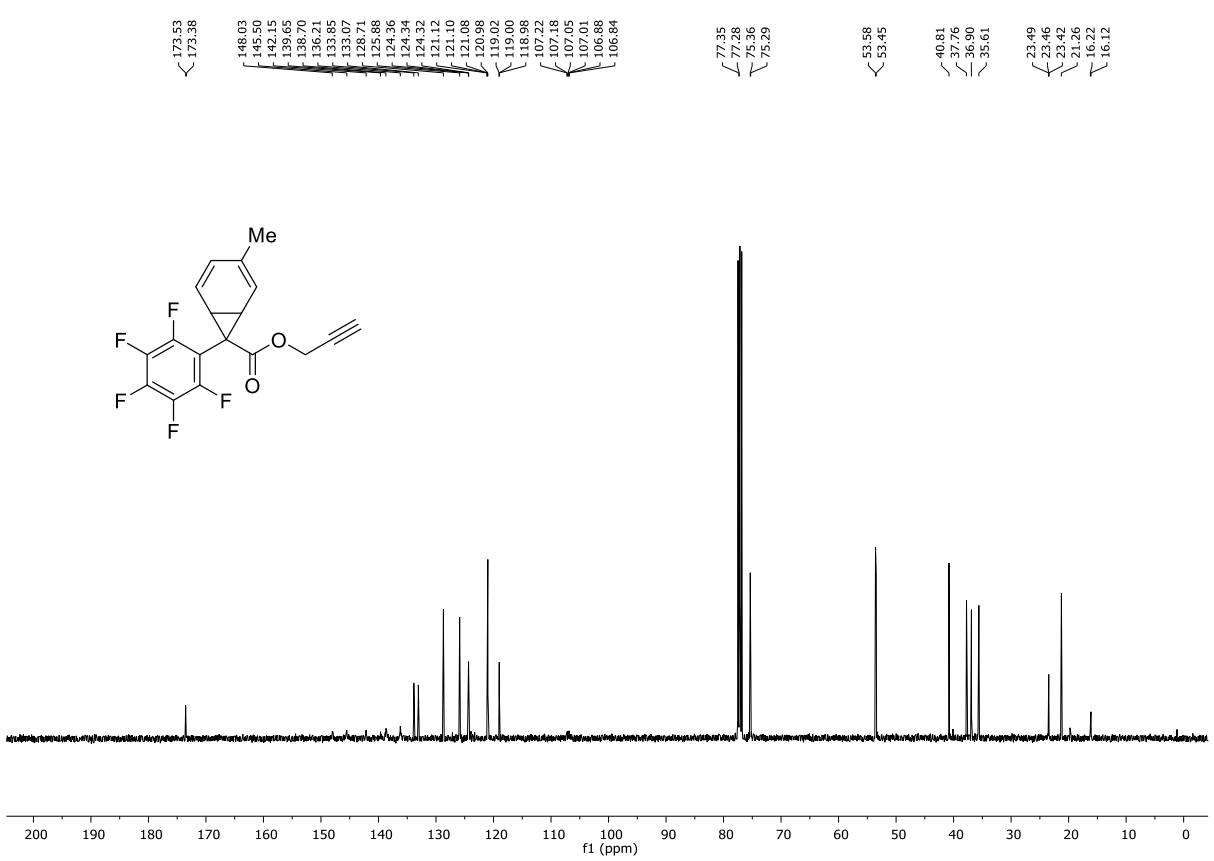


Figure V.8. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) Spectrum of **4hb**

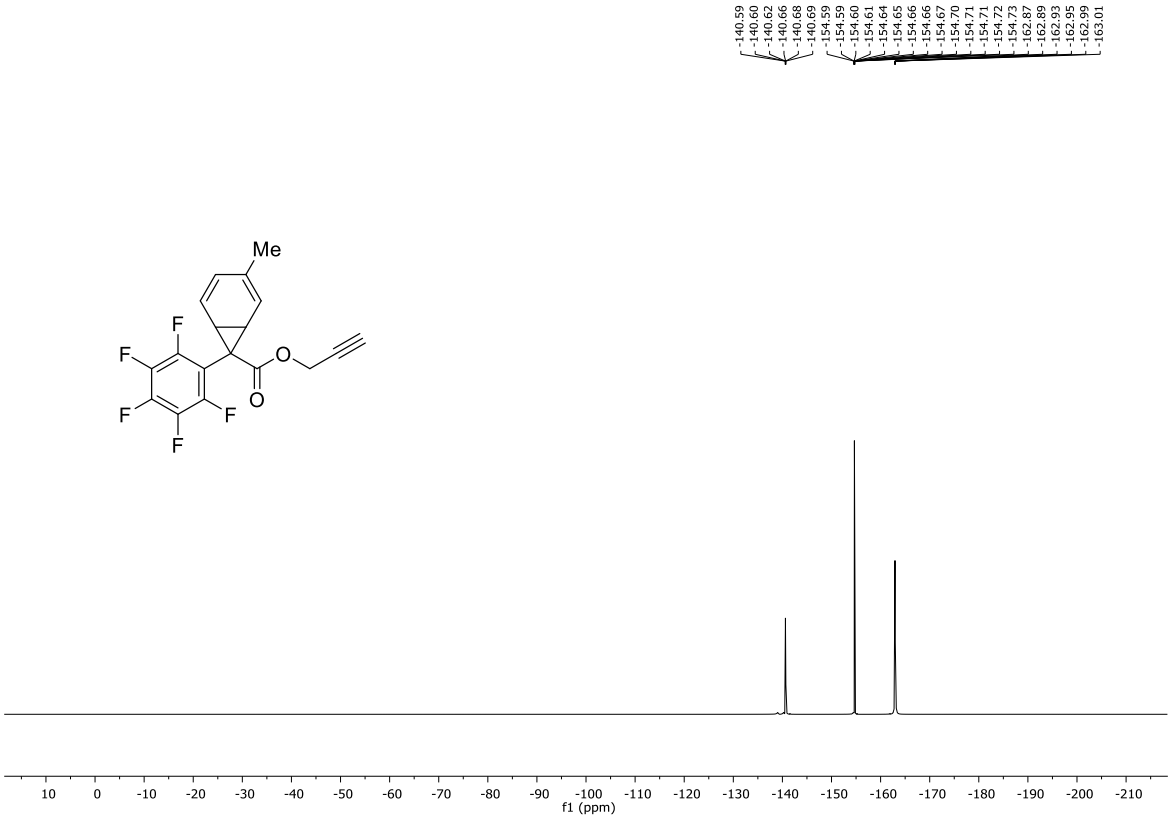


Figure V.9. ^{19}F NMR (377 MHz, $CDCl_3$) Spectrum of **4ha**

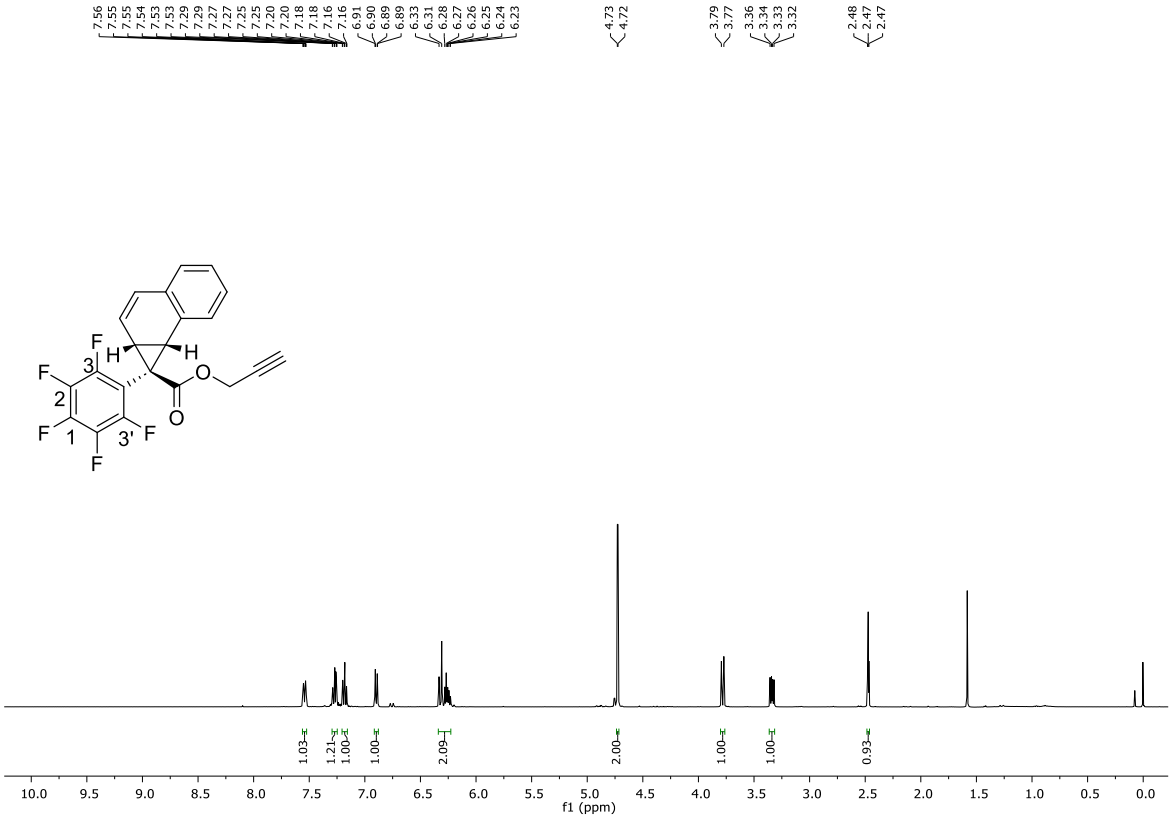


Figure V.10. ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **4hk**

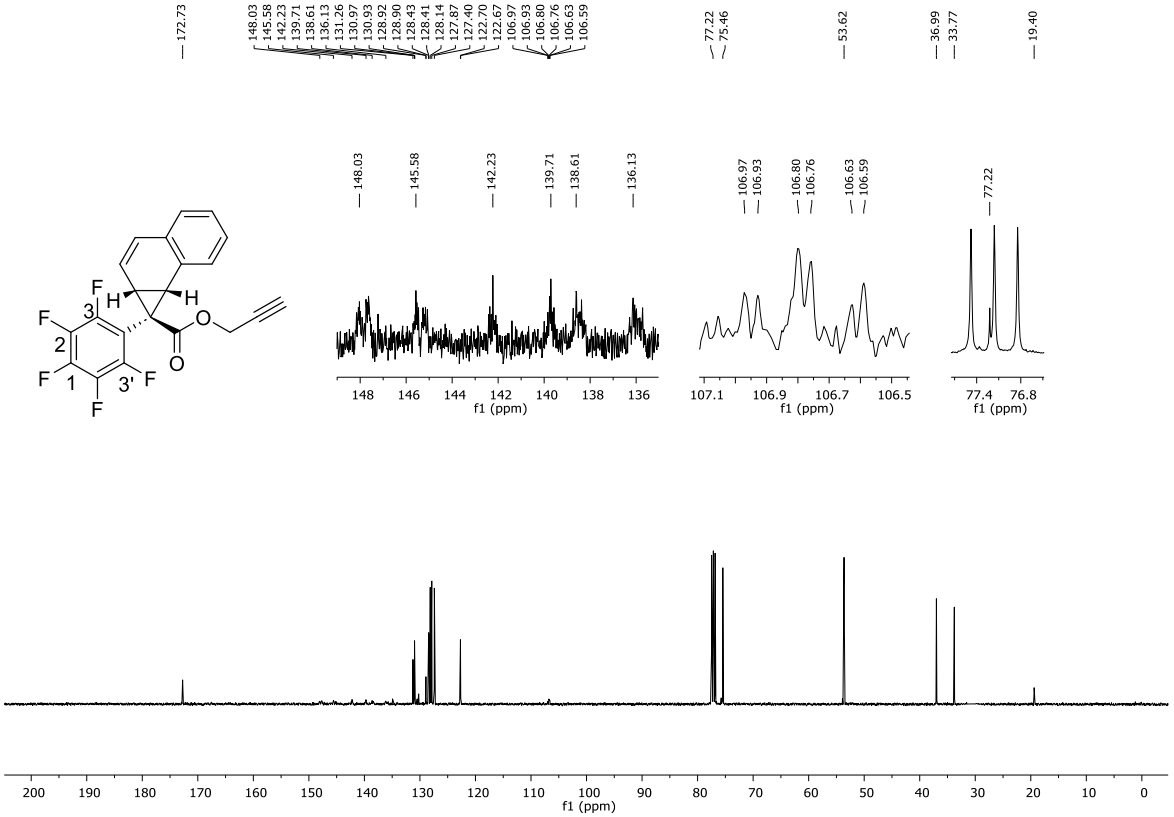


Figure V.11. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) Spectrum of **4hk**

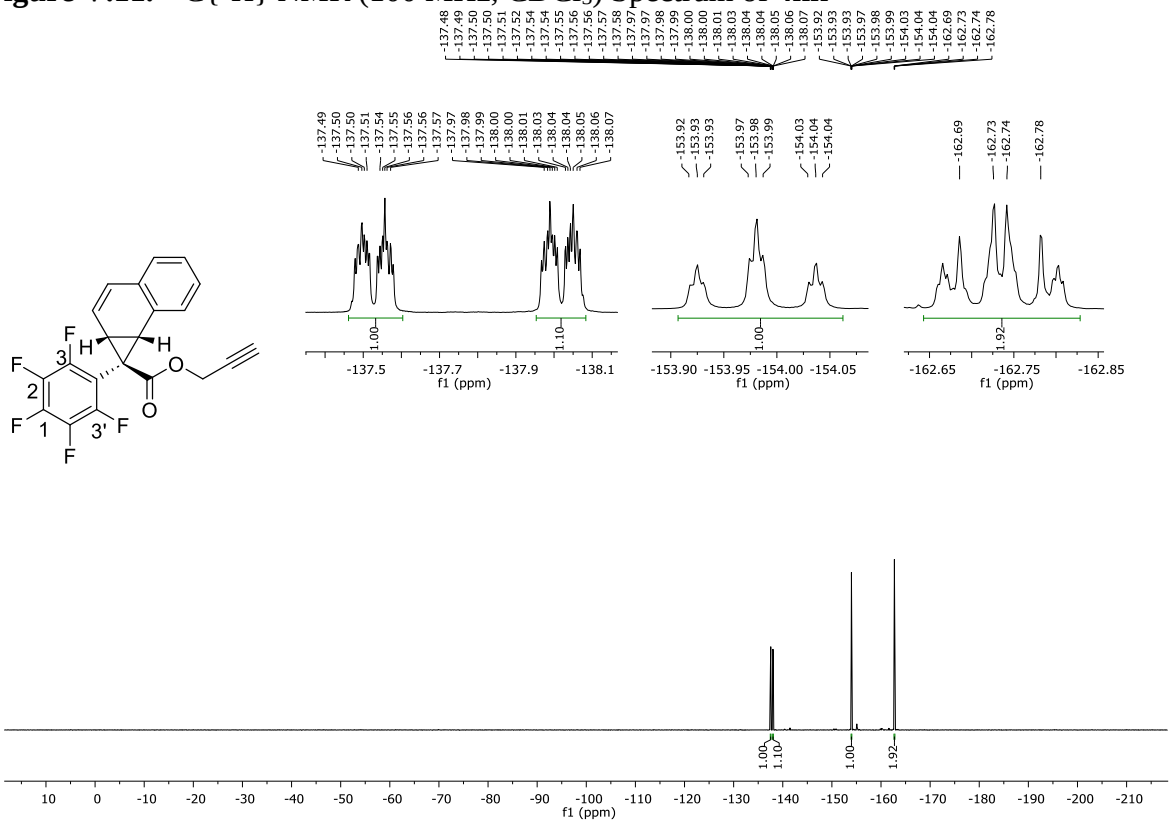


Figure V.12. ^{19}F NMR (377 MHz, $CDCl_3$) Spectrum of **4ha**

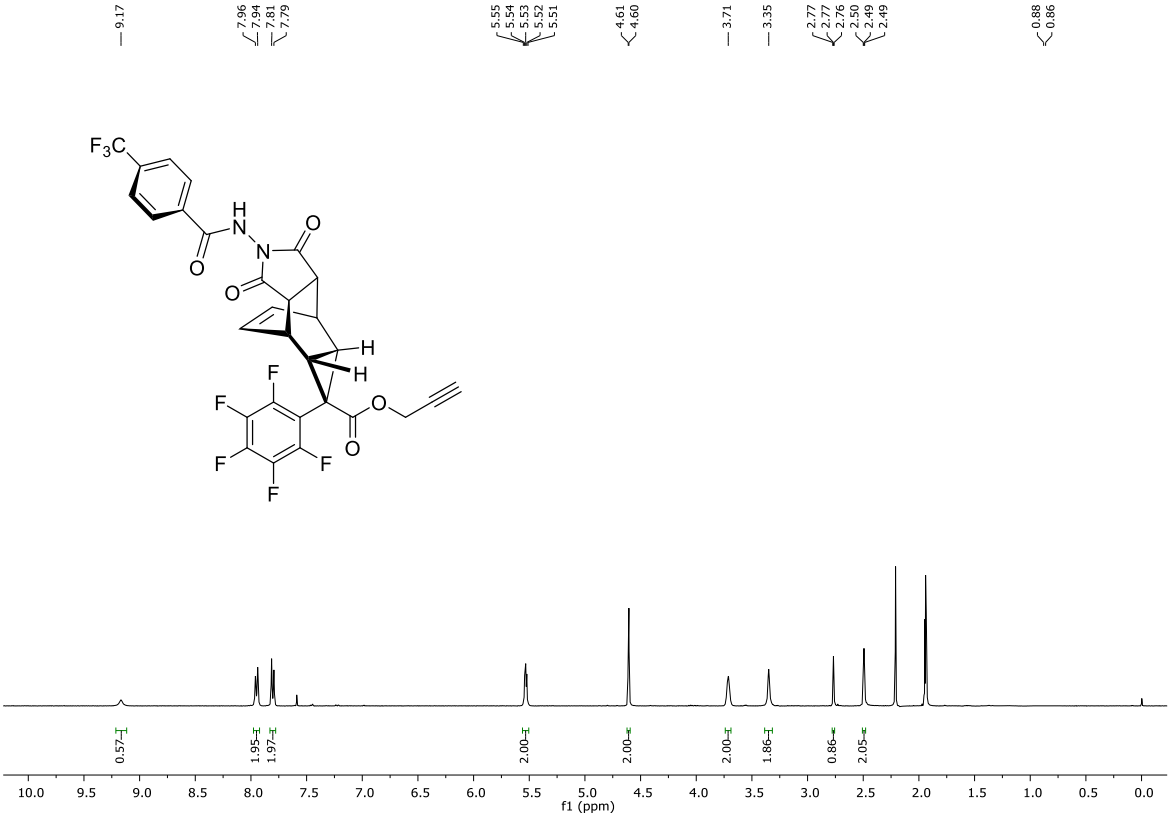


Figure V.13. ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **8ha**

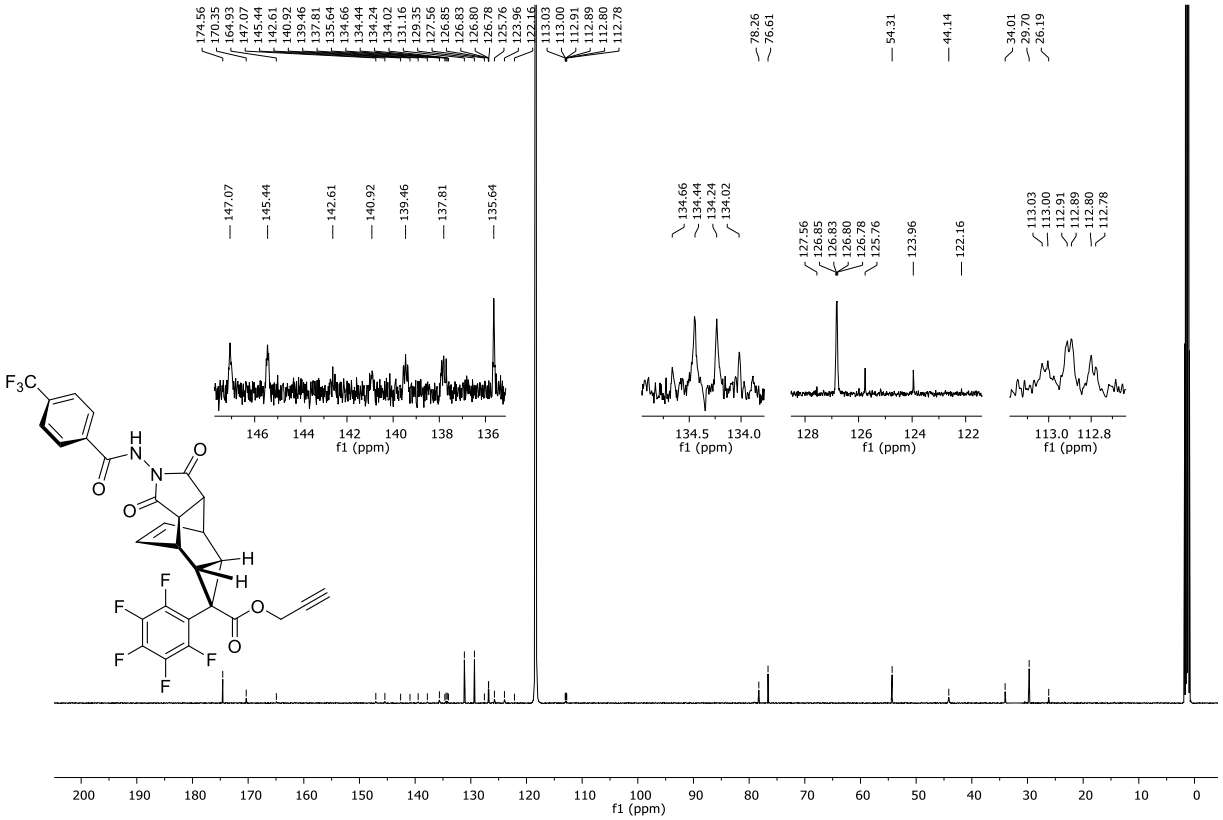


Figure V.14. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) Spectrum of **8ha**

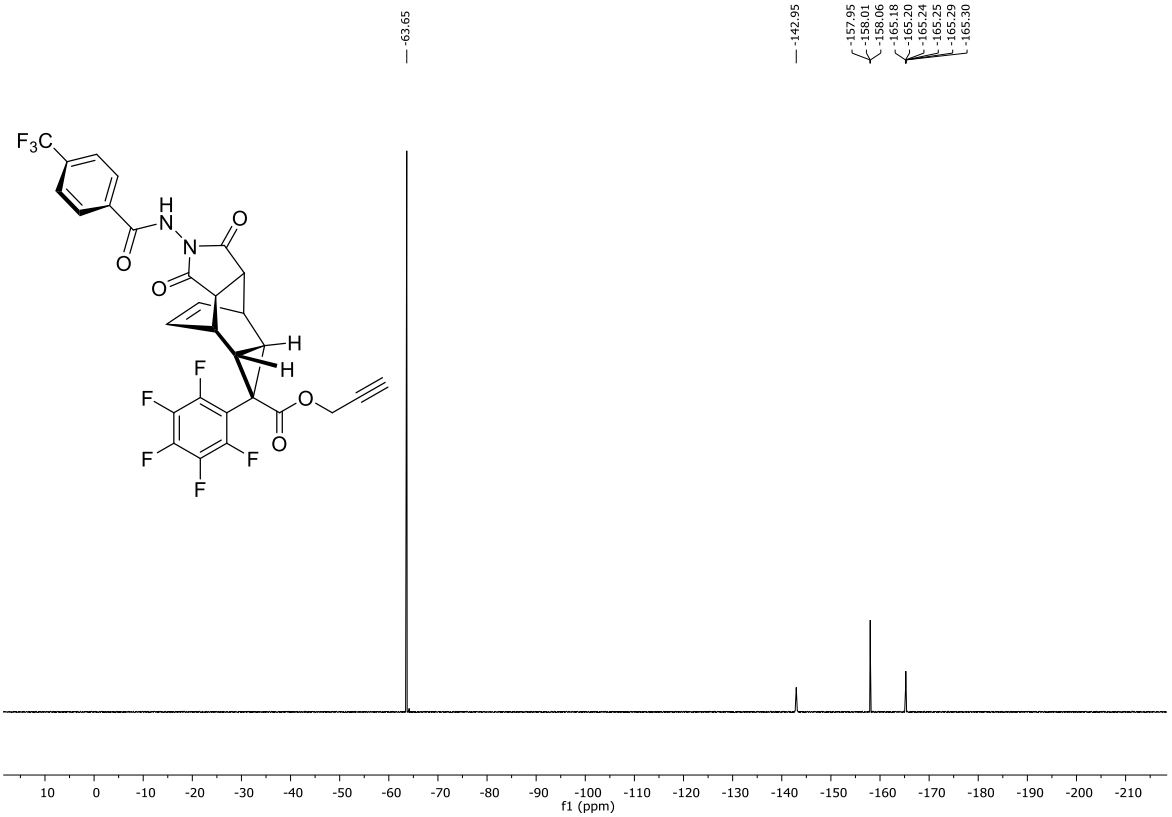


Figure V.15. ^{19}F NMR (377 MHz, $CDCl_3$) Spectrum of **8ha**

5.4.7. Crystal Diffraction Data:

a) Prop-2-yn-1-yl 2-diazo-2-(perfluorophenyl)acetate:

Datablock: D1_a

Bond precision: C-C = 0.0019 A Wavelength=1.54178

Cell:	a=6.4451(11)	b=10.6433(18)	c=16.340(3)
	alpha=90	beta=98.062(6)	gamma=90
Temperature:	100 K		

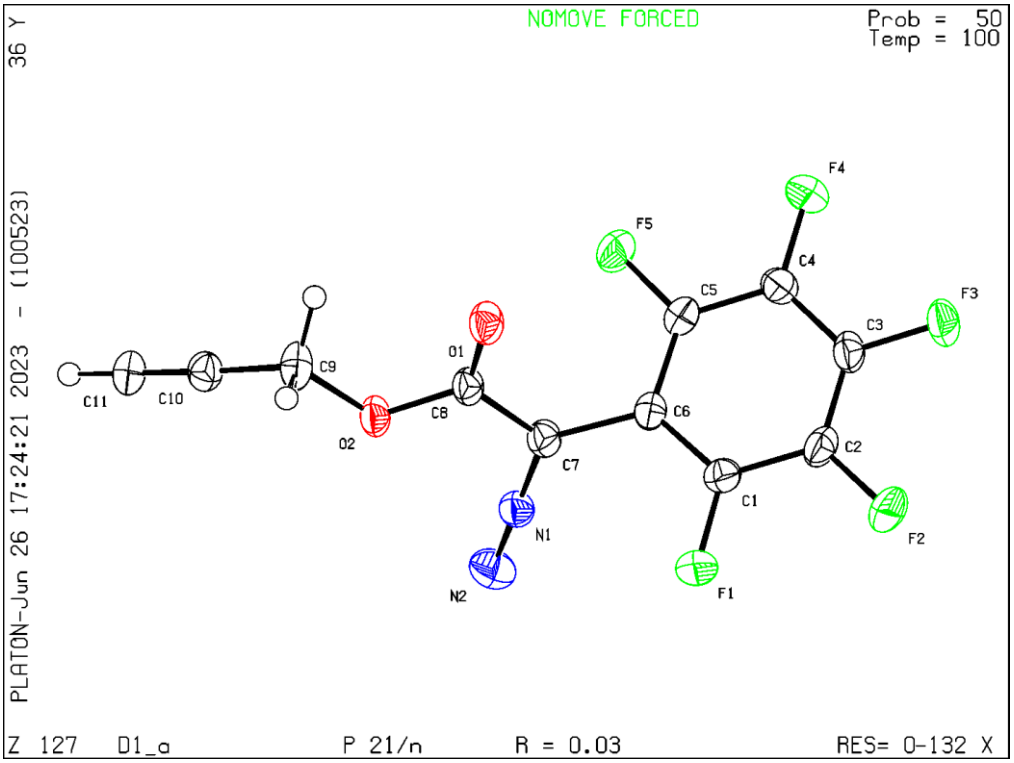
	Calculated	Reported
Volume	1109.8(3)	1109.8(3)
Space group	P 21/n	P 21/n
Hall group	-P 2yn	-P 2yn
Moiety formula	C11 H3 F5 N2 O2	C11H3F5N2O2
Sum formula	C11 H3 F5 N2 O2	C11H3F5N2O2
Mr	290.15	290.15
Dx,g cm-3	1.737	1.737
Z	4	4
Mu (mm-1)	1.598	1.598
F000	576.0	576.0
F000′	578.80	
h,k,lmax	7,13,20	7,13,20
Nref	2199	2194
Tmi		
n,T		
max		
Tmi		
n′		

Correction method= Not given

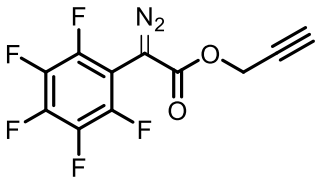
Data completeness= 0.998 Theta(max)= 72.580

R(reflections)= 0.0327(1901) wR2(reflections)= 0.0767(2194)

S = 1.094 Npar= 182



ORTEP and thermal ellipsoids at 50% probability



1h

b) prop-2-yn-1-yl 7-(perfluorophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate: 4ah

Datablock: do_3_a

Bond precision: C-C = 0.0028 A Wavelength=1.54178

Cell:	a=29.816(3)	b=12.4367(12)	c=7.8860(7)
	alpha=90	beta=90	gamma=90
Temperature:	100 K		

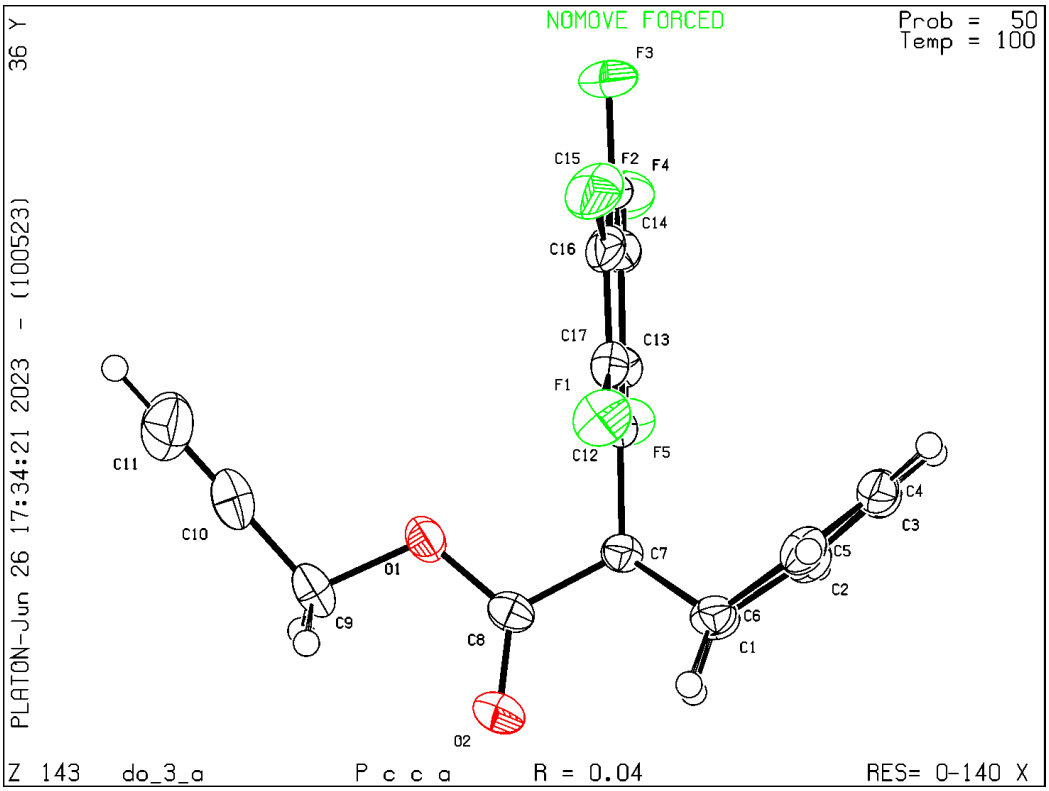
	Calculated	Reported
Volume	2924.2(5)	2924.2(5)
Space group	P c c a	P c c a
Hall group	-P 2a 2ac	-P 2a 2ac
Moiety formula	C17 H9 F5 O2	C17 H9 F5 O2
Sum formula	C17 H9 F5 O2	C17 H9 F5 O2
Mr	340.24	340.24
Dx,g cm-3	1.546	1.546
Z	8	8
Mu (mm-1)	1.267	1.267
F000	1376.0	1376.0
F000'	1382.01	
h,k,lmax	37,15,9	37,15,9
Nref	3032	3010
Tmi		
n,T		
max		
Tmi		
n'		

Correction method= Not given

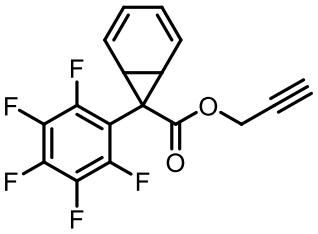
Data completeness= 0.993 Theta(max)= 75.425

R(reflections)= 0.0410(2189) wR2(reflections)= 0.0966(3010)

S = 1.039 Npar= 218



ORTEP and thermal ellipsoids at 50% probability



4ah

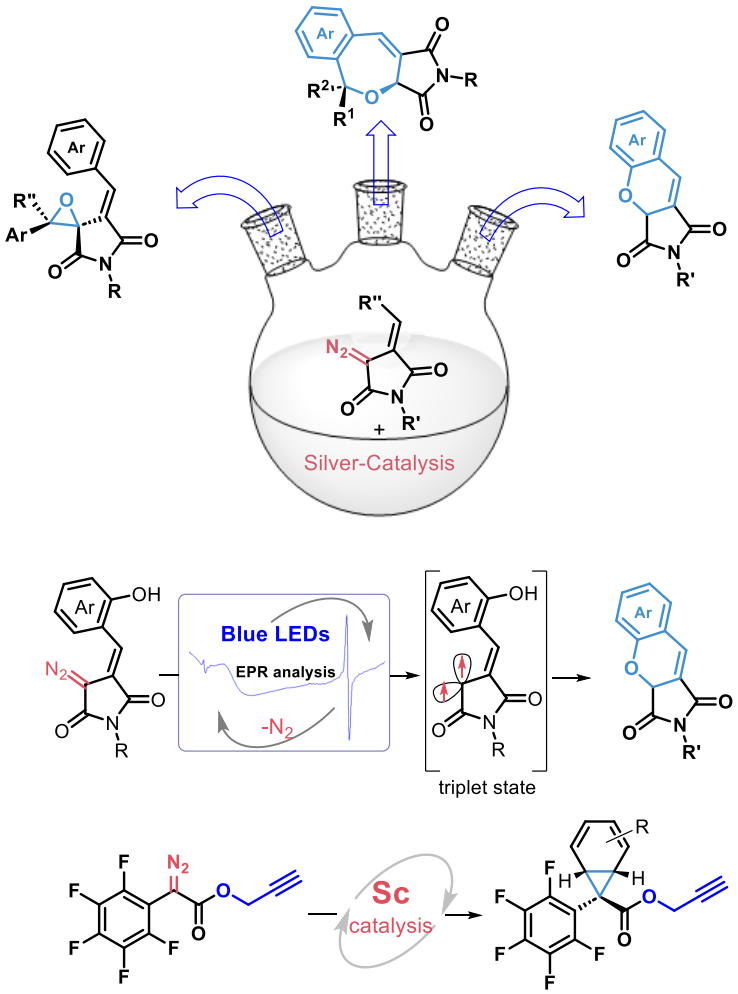
5.5. References:

1. a) S. Matar, L. F. Hatch, Chemicals Based on Benzene, Toluene, and Xylenes. Chemistry of Petrochemical Processes, 2nd ed.; Gulf Professional Publishing: Houston, TX, **2001**; pp 262−300; b) T. Pfennig, A. Chemburkar, S. Cakolli, M. Neurock, B. H. Shanks, *ACS Sustainable Chem. Eng.* **2018**, *6*, 12855; c) K. Cheng, W. Zhou, J. Kang, S. He, S. Shi, Q. Zhang, Y. Pan, W. Wen, Y. Wang, *Chem.* **2017**, *3*, 334.
2. a) W. Wertjes, E. Southgate, D. Sarlah, *Chem. Soc. Rev.* **2018**, *47*, 7996; for oxidative strategies, see: b) K. B. Wilson, J. A. Smith, H. S. Nedzbala, E. K. Pert, S. J. Dakermanji, D. A. Dickie, W. D. Harman, *J. Org. Chem.* **2019**, *84*, 6094; c) E. H. Southgate, J. Pospech, J. Fu, D. R. Holycross, D. Sarlah, *Nat. Chem.* **2016**, *8*, 922; for reductive strategy, see: d) H. E. Zimmerman, *Acc. Chem. Res.* **2012**, *45*, 164; for stoichiometric metal complexation strategies, see: e) A. R. Pape, K. P. Kaliappan, E. P. Kündig, *Chem. Rev.* **2000**, *100*, 2917; f) M. D. Chordia, W. D. Harman, *J. Am. Chem. Soc.* **2000**, *122*, 2725; for enzymatic reactions, see: g) T. Hudlicky, J. W. Reed, *Synlett* **2009**, 685.
3. A. J. Anciaux, A. Demonceau, A. F. Noels, A. J. Hubert, R. Warin, P. Teyssie, *J. Org. Chem.* **1981**, *46*, 873.
4. For intramolecular tethering methods, see: a) M. Kennedy, M. A. McKervey, A. R. Maguire, G. H. P. Roos, *J. Chem. Soc., Chem. Commun.* **1990**, 361; b) R. R. Nani, S. E. Reisman, *J. Am. Chem. Soc.* **2013**, *135*, 7304; c) S. O′Neill, S. O′Keeffe, F. Harrington, A. R. Maguire, *Synlett* **2009**, *2009*, 2312; d) X. Xu, X. Wang, P. Y. Zavalij, M. P. Doyle, *Org. Lett.* **2015**, *17*, 790; e) A. K. Clarke, W. P. Unsworth, R. J. Taylor, *Tetrahedron* **2018**, *74*, 5374; f) H. Wang, C.-Y. Zhou, C.-M. Che, *Adv. Synth. Catal.* **2017**, *359*, 2253; g) N. P. T. Thanh, M. Tone, H. Inoue, I. Fujisawa, S. Iwasa, *Chem. Commun.* **2019**, *55*, 13398.
5. a) S. Levin, R. R. Nani, S. E. Reisman, *J. Am. Chem. Soc.* **2011**, *133*, 774; b) B. Frey, A. P. Wells, D. H. Rogers, L. N. Mander, *J. Am. Chem. Soc.* **1998**, *120*, 1914.
6. a) W. D. Mackay, J. S. Johnson, *Org. Lett.* **2016**, *18*, 536; b) G. S. Fleming, A. B. Beeler, *Org. Lett.* **2017**, *19*, 5268.
7. Y. Guo, T. V. Nguyen, R. M. Koenigs, *Org. Lett.* **2019**, *21*, 8814.
8. a) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861; b) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704; (c) A. Archambeau, F. Miege, C. Meyer, J. Cossy, *Acc. Chem. Res.* **2015**, *48*, 1021.

9. a) T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091; b) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem., Int. Ed.* **2014**, *53*, 5504; c) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981.
10. a) O. A. McNamara, A. R. Maguire, *Tetrahedron* **2011**, *67*, 9; b) L. M. Bateman, O. A. McNamara, N. R. Buckley, P. O'Leary, F. Harrington, N. Kelly, S. O'Keeffe, A. Stack, S. O'Neill, D. G. McCarthy, A. R. Maguire, *Org. Biomol. Chem.* **2015**, *13*, 11026.
11. a) V. N. Lindsay, D. Fiset, P. J. Gritsch, S. Azzi, A. B. Charette, *J. Am. Chem. Soc.* 2013, 135, 1463; b) H. Hui, H. Shechter, *Tetrahedron Lett.* **1982**, *23*, 5115; c) M. Matsumoto, T. Shiono, H. Mutoh, M. Amano, S. Arimitsu, *J. Chem. Soc., Chem. Commun.* **1995**, 24, 101.
12. B. S. Navale, D. Laha, S. Banerjee, K. Vanka, R.G. Bhat, *J. Org. Chem.* 2022, 87, 21, 13583–13597.
13. a) L. Liu, J. Zhang, *Chem. Soc. Rev.* **2016**, *45*, 506–516; b) Y.-Y. Ren, M. Chen, K. Li, S.-F. Zhu, *Chem. Asian J.* **2018**, *13*, 2606–2610; c) B. Ma, L. Liu, J. Zhang, *Asian J. Org. Chem.* **2018**, *7*, 2015−2025.
14. T. Sugimura, M. Kagawa, N. Ohuchi, K. Hagiya, T. Okuyama, *Bull. Chem. Soc. Jpn.* **2005**, 78, 671.
15. a) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857; b) H. M. L. Davies, K. Liao, *Nat. Rev. Chem.* **2019**, *3*, 347–360; c) D. Laha, J. Y. Shaikh, R. G. Bhat, Handbook of CH-Functionalization. DOI: 10.1002/9783527834242.chf0085.
16. CCDC number of compounds **1h** and **4ha** are 2276981 and 2276982 respectively. The number contains all crystallographic details of this publication and is available free of charge at https://www.ccdc.cam.ac.uk/structures/.
17. M. Lee, Z. Ren, D. G. Musaev, H. M. L. Davies, *ACS Catal.* **2020**, *10*, 6240−6247.
18. a) T. Hiyama, Organofluorine Compounds, Chemistry and Applications; Springer, Berlin, **2000**; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320−330; c) A. R. Murphy, J. M. J. Fréchet, *Chem. Rev.* **2007**, *107*, 1066−1096; d) J. He, Z. Li, G. Dhawan, W. Zhang, A. E. Sorochinsky, G. Butler, V. A. Soloshonok, J. Han, *Chin. Chem. Lett.* **2023**, *34*, 107578; e) J. R. Lucas, Y. Shono, T. Iwasaki, T. Ishiwatari, N. Spero, G. Benzon, *J. Am. Mosq. Control Assoc.* **2007**, *23*, 47-54; f) Y. Shono, K. Ujihara, T. Iwasaki, M.; Mori, T. Sugano, T. Matsunaga, N. Matsuo, in Pesticide Chemistry (Eds.: H. Ohkawa, H. Miyagawa, P. W. Lee), Wiley-VCH, Weinheim, Germany, **2007**; p 149.
19. W. D. Mackay, J. S. Johnson, *Org. Lett.* **2016**, *18*, 536.
20. B. S. Navale, D. Laha, R. G. Bhat, *Tetrahedron Lett.* **2019**, *60*, 1899−1903.

Summary

Carbene is the key reactive intermediate that has been utilized widely in varieties of synthetic transformations ranging from cycloaddition to site-selective functionalizations. Controlling the reactivity of carbenes is the most crucial and foremost parameter for achieving the selective carbene transfer reactions. The combined effect of metal catalysts, reagents and ligands plays a major role for exploring the reactions via singlet carbene intermediate. Contrarily, triplet carbene has gained very little attention from the researchers as its reactivity relied on the use of specific metal complexes, and as such dealing with the reactivity of triplet carbene in organic synthesis is underdeveloped.



To implement the tuneable and unmet reactivity of carbenes for the different cycloaddition reactions *via* carbene for the construction of small organic molecules, we designed and developed different novel donor-/acceptor-type diazo compounds as carbene precursors or surrogates. We have disclosed the unique reactivity pattern of diazosuccinimide at both of its carbene spin states under different reaction conditions. We have also demonstrated

that the synergistic combination of catalyst (early transition-metal based) and reagent (diazoacetate) play a crucial role over benzenoid substrates for the controlled regio- and chemo-selective dearomatization of benzenoids by mobilizing one double bond at the expense of intrinsic aromatic stabilization. We have explored the reactivity of these carbene surrogates under traditional metal as well as photochemical condition. We have successfully utilized these novel carbenes precursor for the synthesis of various useful compounds and bioactive compounds.

ACES Asian Chemical Editorial Society

DOI: 10.1002/ajoc.202000123

ASIAN JOURNAL OF ORGANIC CHEMISTRY Communication

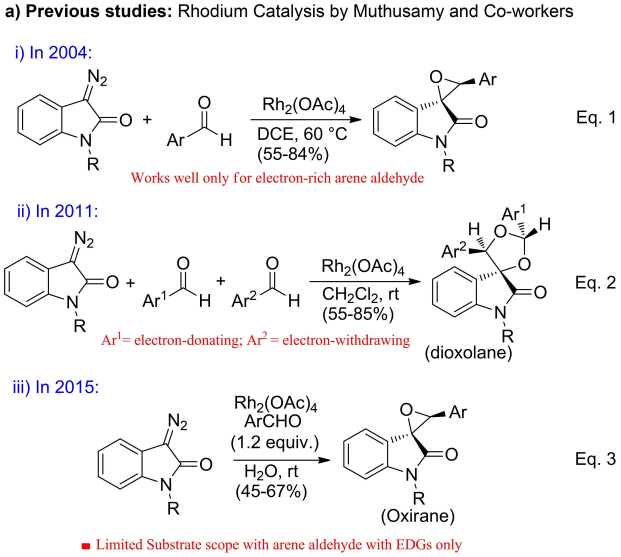
Silver-Catalyzed Epoxidation of Aldehydes Using Donor-/Acceptor-type Vinyl Diazosuccinimides to Access Spiro-Pyrrolidinedioneoxiranes

Debasish Laha and Ramakrishna G. Bhat*[a]

Abstract: A silver(I)-catalyzed method to access spiro-pyrrolidinedioneoxiranes has been developed. Silver hexafluoroantimonate was found to be an efficient catalyst for the epoxidation of aldehydes using donor-/acceptor-substituted vinyl diazosuccinimides as carbenoid precursors. The protocol has been found to be highly regio- and chemoselective, and works well with aromatic aldehydes containing electron-withdrawing and -donating groups to afford spiro-pyrrolidinedioneoxiranes with a broad substrate scope.

Introduction

The class of diazo compounds is useful for a wide range of synthetic transformations for the past few decades. The diazocarbonyl compounds have been explored as useful precursors in various transition metal catalyzed transformations viz. cyclopropanation, insertion reaction and ylide formation.[1] The transient ylides such as 1,3-dipolar species are usually formed either intramolecularly or intermolecularly via metal carbenoid intermediate. The in situ formed ylide can undergo various transformations such as cycloaddition in presence of suitable dipolarophiles, rearrangement reactions or cyclization to afford oxiranes or aziridines.[2,3] Over the years, many protocols have been explored for the direct synthesis of oxirane derivatives starting from aromatic aldehydes.[4] Transition metals such as copper, rhodium have been commonly explored along with the carbonyl ylides derived from a variety of diazo compounds as coupling partners albeit with limited success.[5–7] Aggarwal and Co-workers elegantly developed an unorthodox strategy wherein alkyl sulfide intercepts with the metal carbenoid to form sulfur ylide that undergo epoxidation on reacting with an aldehyde.[8] Likewise, Doyle and co-workers[9] and Davies and co-worker[10] reported direct method to synthesize oxiranes via rhodium(II) acetate catalyzed decomposition of donor-/acceptor- substituted diazocarbonyl compound in a highly regio- as well as chemo-selective manner. Muthusamy and co-workers subsequently reported the $Rh_2(OAc)_4$ catalyzed synthesis of spiro-oxiranes starting from 3-diazooxindolinone and aromatic aldehydes (Scheme 1a, Eq. 1).[11] Though this protocol is



Scheme 1. Spiro-oxirane and spiro-dioxolane formation.

stereoselective, it is just limited to aromatic aldehydes substituted with electron-donating groups.

Later the same research group observed the formation of dioxolanes while working with the aromatic aldehydes containing electron-withdrawing substituents (Scheme 1a, Eq. 2).[12] In the year 2015, they reported the synthesis of oxiranes on water unlike their previous findings in which DCM was used as a solvent (Scheme 1a, Eq. 3).[13] However, this protocol was found to be efficient only to electron rich aromatic aldehydes.

In spite of remarkable advances in the synthesis of oxiranes starting from cyclic diazo amides, the direct access to oxiranes starting from both electron-deficient and -rich aromatic aldehydes and diazo compound remains to be a challenging task. More importantly access to oxiranes in a regioselective as well as chemoselective manner is highly demanding.

Maleimide scaffold is a key component found in many natural products as well as pharmaceuticals with remarkable range of

[a] D. Laha, Prof. Dr. R. G. Bhat
Department of Chemistry
Indian Institute of Science Education and Research (IISER) Pune
Dr. Homi Bhabha Road, Pashan, Pune, 411008 Maharashtra (India)
E-mail: rgb@iiserpune.ac.in

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ajoc.202000123

© 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

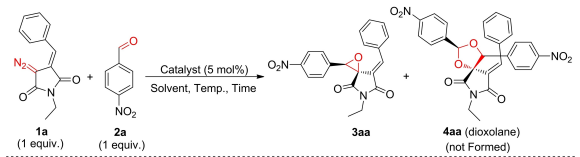
biological activities.[14] TAN-1813 is known to have ras-farnesyl-transferase inhibition activity.[15] We envisioned that TAN-1813 derivatives could be accessed via spiro-oxirane motif **3** at the very early stage of the synthesis (Scheme 2). In turn the intermediate **3** can be synthesized starting from donor-/acceptor-substituted type vinyl diazosuccinimides (Scheme 2). It has been reported that metal-catalyzed intermolecular epoxidation with these donor-/acceptor-substituted type carbenoids is much more diastereoselective and chemoselective than traditional carbenoids.[10] Interestingly, vinylcarbenoids have been explored seldom in the literature.[16] Also there have been numerous efforts to utilize alternative transition metals such as silver for different transformations in the diazocarbonyl chemistry. It has been shown that silver catalysts are effective in catalyzing the reactions with donor-/acceptor-type carbenoids.[17] Mostly dirhodium catalysts have been explored for the synthesis of oxiranes via [2+1] cycloaddition of the diazo compounds and aromatic aldehydes with limited success.[5,9,10] Interestingly, silver catalysis has proved to be more effective than rhodium in some of the instances.[18] Moreover, some of the silver catalysts are relatively less expensive and easily available. In this regard we planned to explore silver catalysis for the possible synthesis of spiro-oxiranes starting from vinyl diazosuccinimides.

Herein, we wish to report silver hexafluoroantimonate ($AgSbF_6$)-catalyzed reactions of donor-/acceptor-substituted vinyl carbenoids for the direct access of spiro-oxiranes in regioselective and chemoselective manner. To the best of our knowledge for the first time we have demonstrated the utility of vinyl diazosuccinimides to synthesize useful spiro-oxiranes starting from aromatic aldehydes via silver catalysis.

To begin with we planned to screen easily and commercially available silver catalysts for the desired transformation. In this regard, benzylidene-*N*-ethyldiazosuccinimide **1a** was easily prepared in two steps from commercially available *N*-ethylmaleimide by well-known Wittig reaction with benzaldehyde **2h** and diazo transfer reagent (see ESI, Ref no. [1], [2]). We commenced with the model reaction by treating benzylidene-*N*-ethyldiazosuccinimide **1a** with *p*-nitrobenzaldehyde **2a** in presence of catalytic amount of silver triflate in toluene at room temperature under inert atmosphere (Table 1, Entry 1). The reaction afforded the desired compound **3aa** albeit in poor yield (22%) and we did not observe the formation of the corresponding dioxolane derivative **4aa** (Table 1, Entry 1). A slight excess of **2a** was recovered during the purification. Encouraged by this initial result, we sought to screen various silver(I) salts as catalyst. Further we screened different silver catalysts ($AgBF_4$, AgOAc, AgTFA, Ag_2CO_3, $AgNO_3$, $AgNTf_2$, Ag_2O) and they proved to be not efficient for the desired reaction (Table 1, Entries 2–8). Later, the reaction of **1a** with **2a** in presence of $AgSbF_6$ (5 mol%) in toluene afforded the desired product **3aa** in 27% yield at room temperature in 1.5 h (Table 1, Entry 9). Silver hexafluoroantimonate proved to be promising catalyst and we observed that the catalytic efficiency of other silver(I) based catalysts found to be low under the same reaction conditions at room temperature (Table 1, Entries 1–9). We observed that the efficiency of the catalysts was largely dependent on the counterions of the corresponding silver(I) salts. The catalysts with tightly bound counterions afforded relatively lower percentage of yields. Later in order to optimize the reaction condition, we further carried out the reaction of **1a** and **2a** in presence of $AgSbF_6$ in different solvents at room temperature (Table 1, Entries 10–14). Among all the solvents, *p*-xylene proved to be efficient for this transformation by affording the **3aa** in 34% yield at room temperature in 1 h (Table 1, Entry 11).

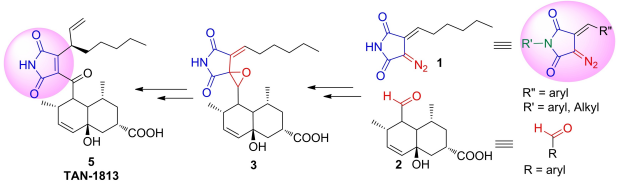
We believed that the silver carbenoid generated in situ might not be efficient and reactive enough to get coupled with the aldehyde at room temperature. We observed that in all the cases, considerably low yields of the desired product were obtained with a relatively longer reaction time because of the decomposition of the starting vinyl diazo compound. In this regard, we planned to carry out the reaction at elevated temperature.

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst [5 mol%]	Solvent	Temp. [°C]	Time	Yield [%][b]
1	AgOTf	Toluene	rt	16 h	22
2	$AgBF_4$	Toluene	rt	16 h	16
3	AgOAc	Toluene	rt	18 h	7
4	AgTFA	Toluene	rt	24 h	<5
5	Ag_2CO_3	Toluene	rt	24 h	<5
6	$AgNO_3$	Toluene	rt	20 h	<5
7	$AgNTf_2$	Toluene	rt	16 h	15
8	Ag_2O	Toluene	rt	24 h	NR
9	$AgSbF_6$	Toluene	rt	12 h	27
10	$AgSbF_6$	CH_2Cl_2	rt	1.5 h	16
11	$AgSbF_6$	*p*-Xylene	rt	1 h	34
12	$AgSbF_6$	DCE	rt	1.5 h	DC
13	$AgSbF_6$	THF	rt	24 h	NR
14	$AgSbF_6$	$CHCl_3$	rt	1.5 h	10
15	$AgSbF_6$	*p*-Xylene	60	10 min	41
16	$AgSbF_6$	*p*-Xylene	80	3 min	44
17	$AgSbF_6$	*p*-Xylene	90	2 min	48
18	$AgSbF_6$	*p*-Xylene	110	2 min	54
19	$AgSbF_6$	*p*-Xylene	125	2 min	DC
20[c]	$AgSbF_6$	*p*-Xylene	110	2 min	DC
21[d]	$AgSbF_6$	*p*-Xylene	110	2 min	50
22[e]	$AgSbF_6$	*p*-Xylene	110	2 min	52
23[f]	$AgSbF_6$	*p*-Xylene	110	2 min	54
24	No Catalyst	*p*-Xylene	110	24 h	NR

[a] Reaction conditions: **1a** (1 equiv.), **2a** (1 equiv.), catalyst (5 mol%), solvent (3 mL), N_2 atmosphere. [b] Isolated yield after column chromatography. [c] 10 mol% of $AgSbF_6$ was used. [d] 1 mol% of $AgSbF_6$ was used. [e] **1a** (1.5 equiv.) and *p*-nitrobenzaldehyde **2a** (1 equiv.) [f] **1a** (1 equiv.) and *p*-nitro benzaldehyde **2a** (1.5 equiv.) NR = No reaction, DC = decomposed.



Scheme 2. Possible synthetic route for TAN-1813.

© 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

21935815, 2020, 6, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajoc.202000123 by Indian Institute Of Science Education And Research Pune, Wiley Online Library on [03/07/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Later, the reaction of **1a** with **2a** was carried out in *p*-xylene at 60 °C in presence of $AgSbF_6$ to afford the desired product **3aa** in 41% yield (Table 1, Entry 15). We observed that at elevated temperature there was an incremental increase in the yield of **3aa** (up to 48%) and the starting material was consumed in 10 min (Table 1, Entries 15–17). Gratifyingly, we did not observe the formation of dioxolane **4aa** during the reaction. Interestingly, further increase in the reaction temperature (110 °C) enhanced the yield of the desired product **3aa** up to 54% in 2 min (Table 1, Entry 18). Further increase in reaction temperature (125 °C) led to the decomposition of vinyl diazosuccinimide (Table 1, Entry 19). Further increment in catalyst loading (10 mol%) also resulted in the decomposition of diazo compound (Table 1, Entry 20). Furthermore, decrease in catalyst loading resulted in diminished yield of the desired product (Table 1, Entry 21). Later we increased the stochiometric amount of diazo compound. However, we observed that there was no significant increase in the desired product (52%) (Table 1, Entry 22). Alternatively, increasing the stoichiometric amount of aldehyde did not improve the yield and also we did not observe formation of any dioxolanes as reported previously with dirhodium acetate[12] (Table 1, Entry 23). We also observed that reaction did not work in the absence of any catalyst.

After the exhaustive screening of different silver catalysts, solvents, temperature and other reaction conditions, vinyl diazo succinimide **1a** (1 equiv.), *p*-nitrobenzaldehyde **2a** (1 equiv.) and $AgSbF_6$ (5 mol%) in *p*-xylene at 110 °C under inert atmosphere proved to be the optimum reaction condition.

Having obtained the optimized reaction conditions in hand, further we investigated the substrate scope of the reaction of **1a** with variety of electron-deficient as well as electron-rich aryl aldehydes (Table 2). Aromatic aldehydes bearing electron-withdrawing as well as deactivating substituents reacted smoothly under optimized reaction conditions to furnish the corresponding desired products spiro-pyrrolidinedioneoxiranes (**3ab**–**3ag**) with moderate to good yields (up to 70%). Aromatic aldehydes containing electron donating substituents also worked well under the optimum reaction conditions to afford the desired products (**3ah**–**3ak**) in moderate to good yield (up to 69%). Gratifyingly, 2-phenylpropionaldehyde reacted smoothly with **1a** to afford the desired compound **3al** *Z*-selective mixture of diastereomers though in low yield (Table 2). We painstakingly separated the two diastereomers and confirmed the molecular structures and geometric arrangements of both the isomers unambiguously using single-crystal X-ray analysis (See ESI). Further, we treated $\alpha,\ \beta$-unsaturated aldehyde such as cinnamaldehyde under the optimum reaction conditions to afford the corresponding product **3am** in 40% yield. Interestingly, protocol also worked well with ketone. The reaction of acetophenone with **1a** furnished the corresponding compound **3an** in moderate yield. A range of substrates with both electron withdrawing and donating groups were explored and all of them tolerated the reaction condition well.

Further we turned our attention to screen various diazosuccinimide substrates to generalize the protocol (Table 3).

We synthesized different vinyl diazosuccinamide derivatives (**1b**–**1f**, **1a′**, **1b′**) containing electron donating as well as

Table 2. Substrate scope for vinyl diazosuccinimide (Reaction condition: **1a** (1 equiv.), **2** (1 equiv.), $AgSbF_6$ (5 mol%), *p*-Xylene (3 mL), N_2-atmosphere; Yields are given in parenthesis and are obtained by purification using column chromatography).

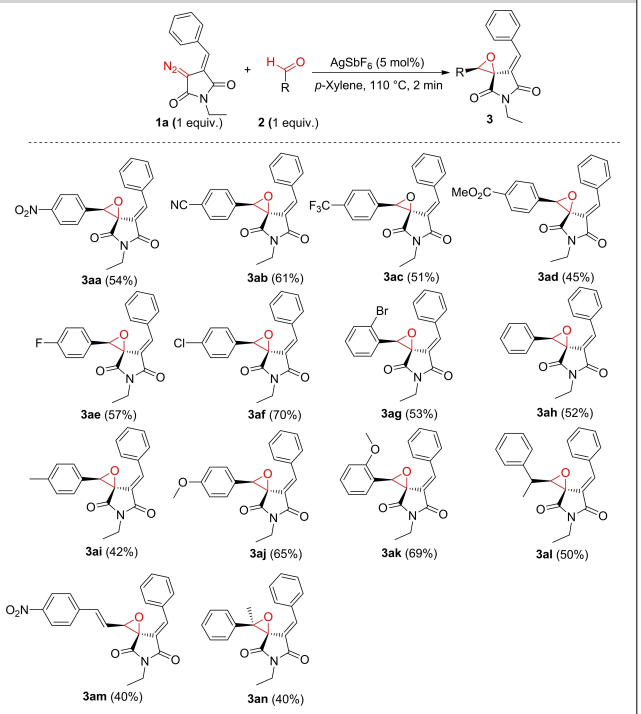
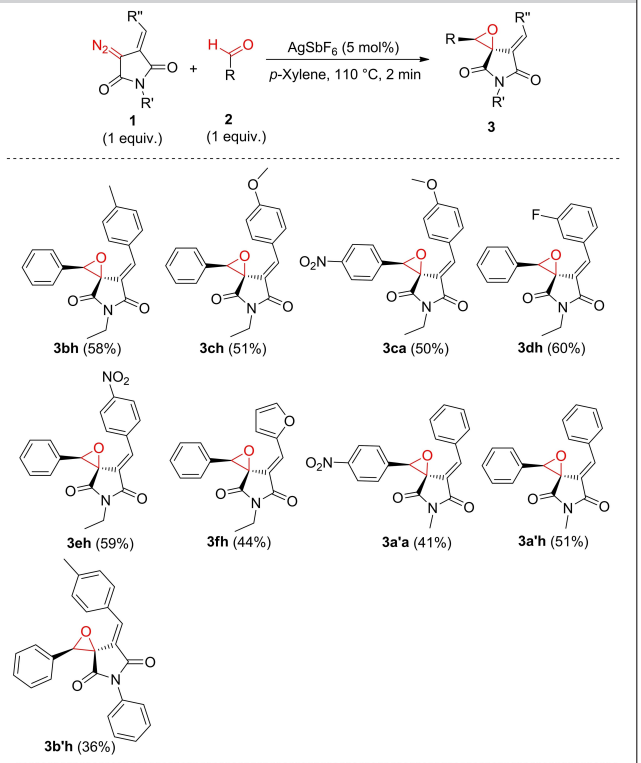
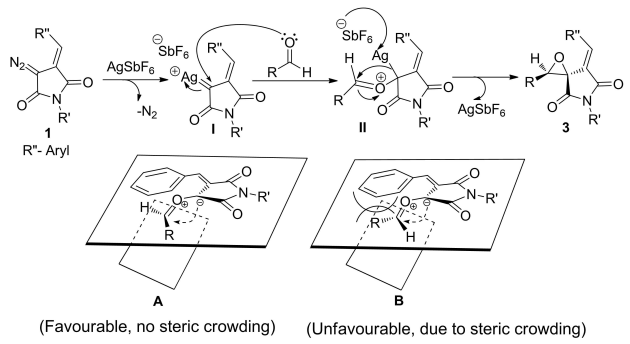


Table 3. Scope with different diazosuccinimide derivatives (Reaction condition: **1** (1 equiv.), **2** (1 equiv.), $AgSbF_6$ (5 mol%), *p*-Xylene (3 mL), N_2-atmosphere; Yields are given in parenthesis and are obtained by purification using column chromatography).



© 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

21935815, 2020, 6, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajoc.202000123 by Indian Institute Of Science Education And Research Pune, Wiley Online Library on [03/07/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



Scheme 3. Proposed mechanism for the oxirane formation.

electron withdrawing substituents at the arene ring at the vinylogous position. Vinyl diazosuccinamide derivatives on treatment with different aldehydes under the optimum reaction condition afforded the corresponding products (**3 bh**, **3 ch**, **3 ca**, **3 dh**, **3 eh**, **3 fh**, **3 a′a**, **3 a′h**, **3 b′h**) in moderate to good yields (up to 60%, Table 3). We observed that *N*-Ph substituted vinyl diazo compound provided relatively lower yield of the desired product. A plausible mechanism for the formation of oxirane is proposed in Scheme 3.

The treatment of diazocompound **1** with $AgSbF_6$ under the reaction condition presumably initiated by the loss of nitrogen gas to form silver-carbenoid **I**. This reactive intermediate **I** further reacts with aldehyde to produce intermediate **II**. This intermediate finally delivers the desired product oxirane **3** with the concomitant regeneration of the active Ag(I) catalyst. We surmise that approach of aldehyde is probably more favourable as shown in A, as it avoids the steric clash leading to the product with the favourable geometry.

In summary, we have demonstrated that silver hexafluoroantimonate is an effective catalyst that provides direct access to spiro-oxirane derivatives using donor-/acceptor-substituted vinyl diazosuccinimides. This protocol gives clean access to spiro-pyrrolidinedioneoxiranes without the formation of dioxolanes. The protocol proved to be general and worked with aromatic aldehydes/ketones to afford the desired products in very short time.

Experimental Section

General Procedure for the Synthesis of Spiro-pyrrolidinedioneoxiranes

In an oven-dried 25 mL two necked round bottom flask equipped with a magnetic stirrer bar, a mixture of $AgSbF_6$ (5 mol%) and aldehyde **2** (1 equiv., 0.4 mmol) was stirred in *p*-xylene (2 mL) at 110 °C under inert atmosphere for a minute. Then vinyl diazosuccinimide **1** (1 equiv., 0.4 mmol) in *p*-xylene (1 mL) was added to the reaction mixture dropwise over 2 minutes. As soon as the addition was complete, progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was then purified by column chromatography (petroleum ether/EtOAc 90:10) over silica gel to furnish the desired product **3** as a white solid. The slight amount of aldehyde **2** was recovered during the purification.

Acknowledgements

R. G. B. thanks DST-SERB (CRG/2019/005753), Govt. of India for the generous research grant. D. L. thank UGC, New Delhi for the fellowship. Authors also thank IISER Pune for the financial assistance.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: spiro-oxiranes · diazo compounds · silver · carbenoids · synthetic methods

[1] M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds. From Cyclopropanes to Ylides*, Wiley-Interscience: New York **1998**.
[2] For reviews see: a) G. Mehta, S. Muthusamy, *Tetrahedron* **2002**, *58*, 9477; b) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223; c) D. M. Hodgson, F. Y. T. M. Pierard, P. A. Stupple, *Chem. Soc. Rev.* **2001**, *30*, 50.
[3] A. Padwa, S. F. Hornbuckle, *Chem. Rev.* **1991**, *91*, 263.
[4] a) J. M. Concellón, H. Cuervo, R. Fernández-Fano, *Tetrahedron* **2001**, *57*, 8983–8987; b) G. Darzens, *C. R. Hebd. Seances Acad. Sci.* **1904**, *139*, 1214; c) G. Darzens, *C. R. Hebd. Seances Acad. Sci.* **1905**, *141*, 766; d) G. Darzens, *C. R. Hebd. Seances Acad. Sci.* **1906**, *142*, 214.
[5] P. de March, R. Huisgen, *J. Am. Chem. Soc.* **1982**, *104*, 4952.
[6] M. Alt, G. Maas, *Tetrahedron* **1994**, *50*, 7435.
[7] a) M. P. Doyle, D. C. Forbes, M. N. Protopopova, S. A. Stanley, M. M. Vasbinder, K. R. Xavier, *J. Org. Chem.* **1997**, *62*, 7210; b) M. P. Doyle, D. C. Forbes, K. R. Xavier, *Russ. Chem. Bull.* **1998**, *47*, 932.
[8] a) A. -H. Li, L. -X. Dai, V. K. Aggarwal, *Chem. Rev.* **1997**, *97*, 2341; b) V. K. Aggarwal, *Synlett* **1998**, *329*; c) V. K. Aggarwal, E. Alonso, G. Hynd, K. M. Lydon, M. J. Palmer, M. Porcelloni, J. R. Studley, *Angew. Chem. Int. Ed.* **2001**, *40*, 1430.
[9] M. P. Doyle, W. Hu, D. J. Timmons, *Org. Lett.* **2001**, *3*, 933.
[10] H. M. L. Davies, J. DeMeese, *Tetrahedron Lett.* **2001**, *42*, 6803–6805.
[11] S. Muthusamy, C. Gunanathan, M. Nethaji, *Synlett* **2004**, 639–624.
[12] S. Muthusamy, R. Ramkumar, A. K. Mishra, *Tetrahedron Lett.* **2011**, *52*, 148–150.
[13] S. Muthusamy, R. Ramkumar, *Tetrahedron* **2015**, *71*, 6219–6226.
[14] a) M. Prudhomme, *Eur. J. Med. Chem.* **2003**, *38*, 123; b) G. Zhang, J. Shen, H. Cheng, L. Zhu, L. Fang, S. Luo, M. T. Muller, G. E. Lee, L. Wei, Y. Du, D. Sun, P. Wang, *J. Med. Chem.* **2005**, *48*, 2600.
[15] T. Ishii, K. Hayashi, T. Hida, Y. Yamamoto, Y. Nozaki, *J. Antibiot.* **2000**, *53*, 765–778.
[16] a) Y. Nakano, M. Hamaguchi, T. Nagai, *J. Org. Chem.* **1989**, *54*, 5912–5919; b) M. Hamaguchi, T. Misumi, T. Oshima, *Tetrahedron Lett.* **1998**, 39, 7113–7116.
[17] a) J. Thompson, H. M. L. Davies, *J. Am. Chem. Soc.* **2007**, *129*, 6090; b) J. H. Hansen, H. M. L. Davies, *Chem. Sci.* **2011**, *2*, 457–461; c) Y. Yue, Y. Wang, W. Hu, *Tetrahedron Lett.* **2007**, *48*, 3975.
[18] a) Z. Wang, J. Wen, Q. W. Bi, X. Q. Xu, Z. Q. Shen, X. X. Li, Z. L. Chen, *Tetrahedron Lett.* **2014**, *55*, 2969–2972; b) K. Burgess, H. J. Lim, A. M. Porte, G. A. Sulikowski, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 220–222.
[19] CCDC 1971121 and 1972978 (Compound **3 al**-diastereomers) contain the supplementary crystallographic data. These data can be obtained free of charge by The Cambridge Crystallographic Data Centre.

Manuscript received: March 4, 2020
Accepted manuscript online: March 5, 2020
Version of record online: April 7, 2020

© 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

21935815, 2020, 6, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajoc.202000123 by Indian Institute Of Science Education And Research Pune, Wiley Online Library on [03/07/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

ACES Asian Chemical Editorial Society

doi.org/10.1002/ajoc.202200062

ASIAN JOURNAL OF ORGANIC CHEMISTRY
Research Article

www.asianjoc.org

Silver-Catalyzed One-Pot Access to Diastereoselective Benzo[5,6]oxepino[2,3-*c*]pyrroles *via* Formal (5+2)-Annulation of Donor-/Acceptor-Type Aryl Vinyl Diazosuccinimide with Ketones

Debasish Laha, Kajal B. Meher, Onkar S. Bankar, and Ramakrishna G. Bhat*[a]

Abstract: A silver triflimide catalyzed one-pot protocol for the diastereoselective synthesis of dihydrobenzoxepines has been developed. Silver triflimide was found to be an efficient catalyst for the formal (5+2)-cycloaddition to access dihydrobenzoxepines as a single diastereomer using vinyl diazosuccinimides as 5-C-synthons and ketones. An unmet challenge of utilizing the donor-/acceptor-type vinyl diazosuccinimides as 5-C-synthons under silver-catalysis is presented. This protocol was found to be highly regio-, chemo- and diastereoselective, and works well with aliphatic as well as aromatic methyl ketones bearing electron deactivating as well as donating groups to afford dihydrobenzo[5,6]oxepino[2,3-*c*]pyrroles. The control experiments and time-dependent NMR studies revealed the plausible mechanism of this transformation. The protocol also proved to be scalable on the gram-scale synthesis.

Introduction

The fused polycyclic architecture containing 6-7-5 or 5-7 fused ring framework such as benzoxepine motif belongs to one of the important classes of oxygenated heterocycles found in pharmaceutical agents[1a] and numerous natural products[1b–d] having diverse biological activities (Figure 1). The stereoselective syntheses of these highly substituted oxygenated heterocycles have immensely been pursued by the scientific community.[2] Directly accessing this scaffold is highly challenging and few approaches have been explored in this regard.[3] It is well known that the transient carbonyl ylide, generated *in situ via* transition-metal-catalyzed decomposition of diazo compounds can either be paired with suitable trapping agents (or dipolarophiles) or it can be utilized in cyclization (intramolecularly or intermolecularly) to access oxygenated heterocycles.[4–6] A few methods involving vinyl carbonyl compound have been revealed the preferential formation of dihydrofurans [*via* (4+1)-annulation] or a mixture of dihydrofurans and dihydrobenzoxepines [*via* (6+1)-annulation] from specific ylide starting from ester and ketone moiety respectively (Scheme 1A).[6e] However, the stereoselective synthesis of either of these scaffolds is quite challenging and it typically needs an elegant ligand-controlled strategy (Scheme 1B).[7] Very recently, Schneider and co-workers[8a] reported a protocol for the construction of bicyclic framework: oxa-bridged dibenzooxacines (5-8 fused rings) *via* formal (4+3)-cycloaddition[8b–e] involving carbonyl ylide as reactive intermediate. Besides, the reaction of vinyl diazo compounds with aldehydes usually known to form a mixture of oxiranes [*via* (2+1)-cycloaddition] and dihydrofurans [*via*

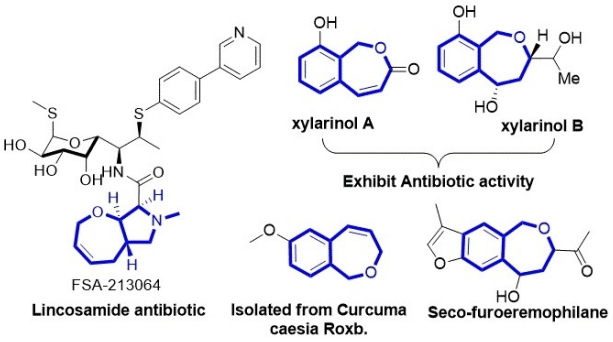
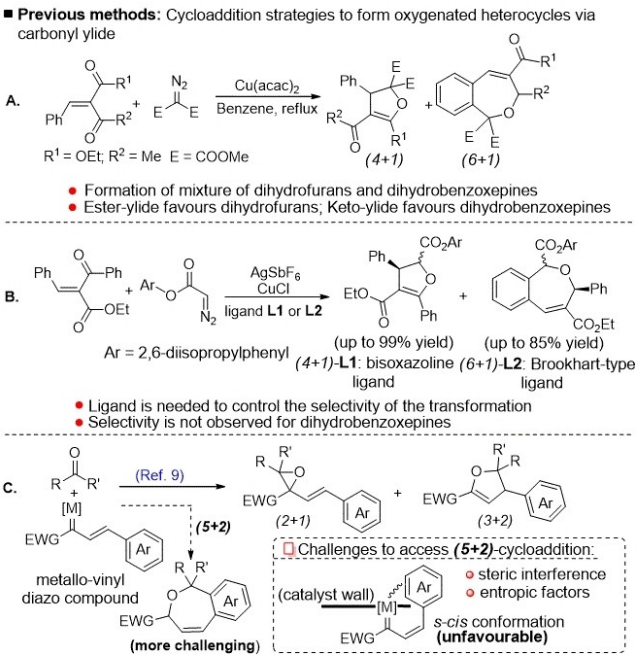


Figure 1. Examples of natural bioactive 1,3-dihydrobenzo[*c*]oxepines and oxepino[2,3-*c*]pyrrole.



Scheme 1. Access to oxygenated heterocycles via carbonyl ylides.

[a] *D. Laha, K. B. Meher, O. S. Bankar, Prof. Dr. R. G. Bhat*
Department of Chemistry
Indian Institute of Science Education and Research (IISER)-Pune
Dr. Homi Bhabha Road, Pahsan, Pune, Maharashtra, 411008 (India)
E-mail: rgb@iiserpune.ac.in

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ajoc.202200062

© 2022 Wiley-VCH GmbH

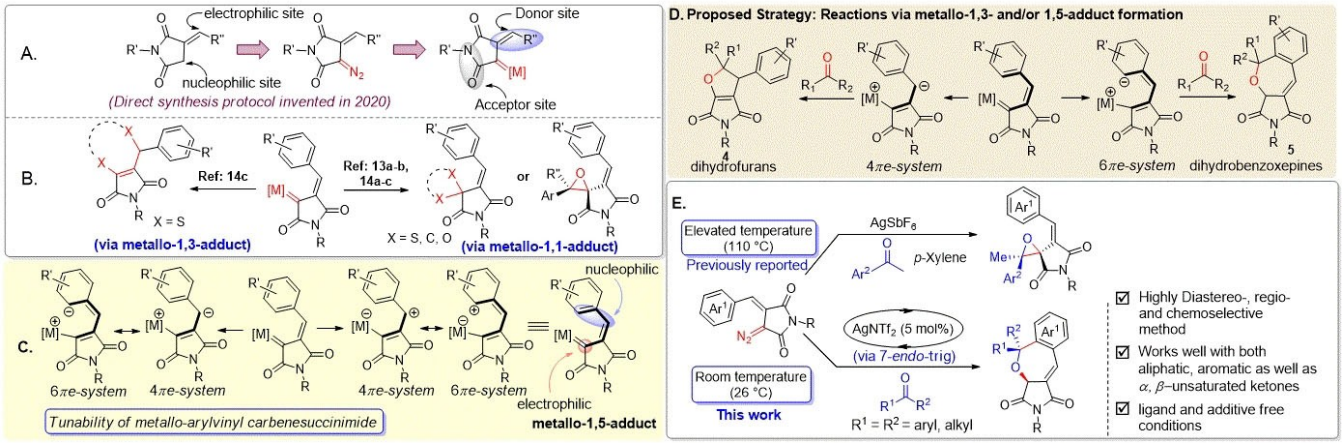
formal (3 + 2)-cycloaddition] through carbonyl ylide involving metal carbene intermediates (Scheme 1C).[9] It is important to note that the synthesis of benzoxepine derivatives is quite challenging and moreover cycloannulation *via* alternative formal (5 + 2)-cycloaddition *via* carbonyl ylide has not been explored till date to the best of our knowledge; wherein vinyl diazo compounds act as 5-C-synthons. The major challenge in this aspect to explore the vinyl carbenoid as 5-C synthon is limited due to the intrinsic steric hindrance emanating from *Z*-configuration around the C=C bond between benzylidene group and the 'catalyst wall' thus making it unfavorable for the desired transformation (See Scheme 1C inset).[10] Secondly, construction of the seven-membered heterocyclic scaffold such as oxepine via the direct cyclization needs high activation energy mainly owing to the combined effect of entropic factors and the non-bonding interactions in the transition state.[11]

The vinyl diazosuccinimide, a useful carbene precursor for the tandem annulation reaction and this can be directly prepared from benzylidene succinimides[12] following our earlier reported procedure and other protocols (Scheme 2A).[13] The metallo-carbenoid of vinyl carbenesuccinimides or vinyl carbenesuccinimides are generated catalytically from stable vinylic diazosuccinimides (*Z*-geometry across C=C bond) that exhibit electrophilic character at metal carbene carbon and nucleophilic character at vinylogous carbon (Scheme 2A). These metallo-vinyl carbenesuccinimides have emerged as useful synthons to access metallo-1,1-[13a–b,14a–c] or 1,3-[14c] adducts when paired with suitable dipolarophiles or nucleophiles to construct cyclic ring structures involving π-electrocyclization[13a,14b–f] (Scheme 2B and 2C). Looking at these important features and owing to the importance of oxaheterocycles, we envisioned that the metallo-aryl vinyl carbenesuccinimide could be employed for the cycloannulation with carbonyl compounds via (3 + 2)- and/or (5 + 2)-cycloaddition to access to dihydrofurans and/or dihydrobenzoxepines respectively under suitably optimized reaction conditions (Scheme 2D).[14f] Herein, for the first time, we report the silver catalyzed direct diastereoselective synthesis of dihydrobenzoxepine derivatives exclusively by exploring the potential of aryl vinyl diazosuccinimide with ketones under ligand-free condition.

Results and Discussion

Our previous report had demonstrated the 4π-electrocyclization strategy *via in situ* generation of transient carbonyl ylide from metallo-aryl vinyl diazosuccinimide under silver catalysis ($AgSbF_6$) to access oxiranes at elevated temperature (see Scheme 2E).[13a] The single crystal X-ray analysis[15] of the phenyl vinyl diazosuccinimide **1a** revealed that the benzylidene group is oriented in *s-cis* conformation with a dihedral angle (*θ*) ~34° (slightly twisted, see SI, page no. S73–S74). Looking at this observation we surmised that even though it is a great challenge, metallo-aryl vinyl diazosuccinimide could be explored for different type of reactivity under suitable conditions wherein aryl group may participate in the reaction as it would be slightly inclined away from the 'catalyst wall' as shown in Table 1. We envisioned that the *in situ* generated carbonyl ylide (from metallo-aryl vinyl diazosuccinimide) may undergo 6π-electrocyclization to form dihydrofuran **4** or 8π-electrocyclization followed by rearomatization to afford the dihydrobenzoxepines **5** (see Scheme 2C and D).

In order to validate our hypothesis, initially we treated (*E*)-3-benzylidene-4-diazo-1-ethylpyrrolidine-2,5-dione **1a** with few ketones, aldehydes, amides and esters. Among all the substrates that were screened for the optimization, compound **1a** reacted with either acetophenone **2a** or acetone **2k** to afford the desired dihydrobenzoxepines **5aa** or **5ak** as single diastereomer in modest yields respectively (up to 50%, see Appendix-I, SI for details). No trace of product **4** was observed in all of these cases. Encouraged by the initial results, we further sought to optimize the reaction conditions to enhance the yield of diastereomer **5aa**. In this regard, we explored the reaction of **1a** and **2a** using rhodium (Table 1, Entry 1), silver (Table 1, Entries 2–5), copper, iron and gold catalysts in DCM at room temperature (See SI, *Table-S1* Entries 11–19). Gratifyingly, among all, the reaction of acetophenone **2a** with aryl vinyl

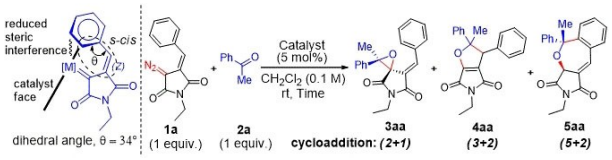


Scheme 2. General characteristics of metallo-aryl vinyl carbenesuccinimide and the current challenges.

© 2022 Wiley-VCH GmbH

21935815, 2022, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajoc.202200062 by Indian Institute Of Science Education And Research Pune, Wiley Online Library on [03/07/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1. Selected Optimization Results[a]



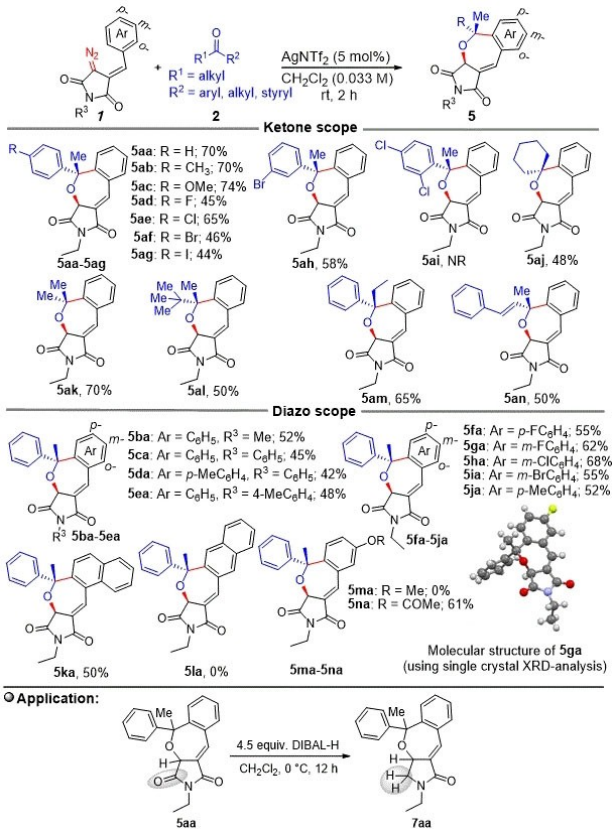
Entry	Catalyst [5 mol%]	Solvent	Time [h]	Yield[b] [%] of **3aa/4aa/5aa**
1	$Rh_2(esp)_2$	CH_2Cl_2	2	<5/0/31
2	$AgSbF_6$	CH_2Cl_2	2	19/0/40
3	AgOTf	CH_2Cl_2	2	18/0/38
4	$AgBF_4$	CH_2Cl_2	2	<5/0/20
5	$AgNTf_2$	CH_2Cl_2	2	11/0/57
6	–	CH_2Cl_2	24	NR
7[c]	$AgNTf_2$	CH_2Cl_2	4	0/0/34
8[d]	$AgNTf_2$	CH_2Cl_2	10	0/0/23
9[e]	$AgNTf_2$	CH_2Cl_2	2	15/0/35
10[f]	$AgNTf_2$	CH_2Cl_2	2 min	25/0/24
11[f]	$AgSbF_6$	CH_2Cl_2	2 min	27/0/23
12[g]	$AgNTf_2$	CH_2Cl_2	2	5/0/70

[a] Reaction conditions: unless otherwise noted, the reactions were carried out with diazo compound **1a** (1.0 equiv., 0.2 mmol), **2a** (1.0 equiv., 0.2 mmol), $AgNTf_2$ (5 mol%) and dry CH_2Cl_2 (0.1 M) at room temperature (26 °C) under argon atmosphere. [b] Isolated yields. [c] 0 °C; [d] −20 °C. [e] 60 °C. [f] Diazo compound **1a** was completely consumed in 2 min at 110 °C. [g] dry CH_2Cl_2 (0.033 M) was used. NR- No reaction. In all cases single diastereomer of **5aa** was obtained.

diazosuccinimide **1a** in presence of silver triflimide ($AgNTf_2$, 5 mol%) in dry CH_2Cl_2 afforded the corresponding dihydrobenzoxepine **5aa** at room temperature (57% yield, Table 1, Entry 5) along with **3aa** as a minor product. The catalytic activity of different silver catalysts was seemed to be dependent on the counter anions. The non-coordinating and low nucleophilic (Tf_2N^-) counter anion was found to more prominent over others to effect the transformation. We also observed that the reaction did not work in the absence of catalyst for the prolonged reaction time (Table 1, Entry 6). In order to improvise the yield of **5aa** and to optimize the reaction conditions further, different solvents, additives, stoichiometric ratio of the substrates, catalyst loading (see SI, Table S2, S4–6) were screened. Later we carefully investigated the other parameters such as temperature (Table 1, Entries 7–11, see SI Table S2 for details) and reactant concentration (Table 1, Entry 10, see SI Table S7). We also observed that in all the cases no trace of compound **4aa** was detected during the course of the reaction. Based on the exhaustive screening, we observed that **1a** (1 equiv.) and **2a** (1 equiv.) in presence of $AgNTf_2$ (5 mol%) as catalyst in dry CH_2Cl_2 (0.033 M) at 26 °C for 2 h under inert atmosphere proved to be the optimum reaction condition (Table 1, Entry 12).

Having obtained the optimized reaction condition, we planned to extend this protocol for the wider substrate scope. Initially we planned to explore the reactivity of phenyl vinyl diazosuccinimide **1a** with different ketones. Different methyl aryl ketones (**2a**–**2l**) reacted with **1a** in presence of silver triflimide (5 mol%), in dry DCM at room temperature to afford the corresponding 5-aryl-5-methyl substituted dihydrobenzoxepines (**5aa**–**5an**) in moderate to good yields (up to 74%, See Table 2). We observed that aryl methyl ketones bearing electron donating groups afforded the corresponding dihydrobenzoxepines (**5aa**–**5ac**) in relatively higher yields than that of aryl

Table 2. Substrates Scope for the Formal (5 + 2)-cycloaddition reaction[a]



[a] Reaction conditions: unless otherwise noted, the reactions were carried out with diazo compound **1a** (1.0 equiv., 0.2 mmol), **2** (1.0 equiv., 0.2 mmol), $AgNTf_2$ (5 mol%) and dry CH_2Cl_2 (0.033 M) at room temperature (26 °C) under argon atmosphere over 2 h. In all cases single diastereomer was obtained.

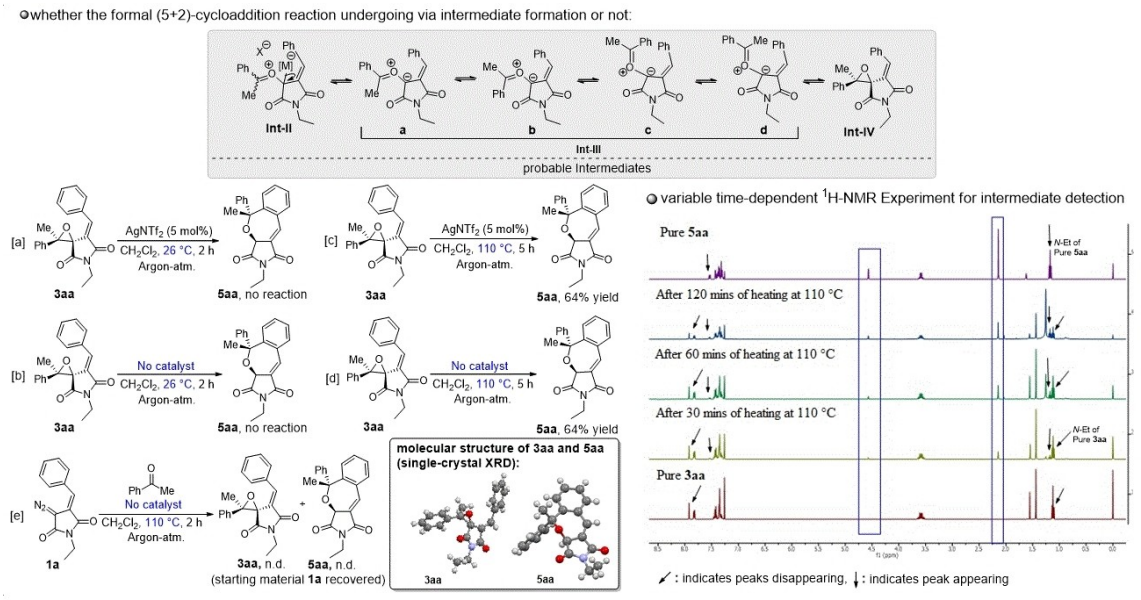
© 2022 Wiley-VCH GmbH

21935815, 2022, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajoc.202200062 by Indian Institute Of Science Education And Research Pune, Wiley Online Library on [03/07/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

methyl ketones having electron-deactivating substituents at *para*- and *meta*-position of phenyl ring (**5 ad**–**5 ah**). Surprisingly, the desired dihydrobenzoxepine **5 ai** was not formed as 2,4-dichlorophenyl methyl ketone **2 i** did not react with **1 a** under the optimized reaction condition. Further, we explored the reaction of **1 a** with electron rich aliphatic methyl ketones including cyclic ketone such as cyclohexanone **2 j** to afford the corresponding dihydrobenzoxepine derivatives (**5 aj**–**5 al**). Even the enone such as methyl styryl ketone reacted with **1 a** to give the desired product **5 an** in modest yield (50%, Table 2).

Later, we planned to explore formal (5 + 2)-cycloaddition for a range of aryl-substituted and *N*-substituted aryl vinyl diazosuccinimides with different ketones. In this regard, we treated different *N*-substituted benzylidene diazo compounds (**1 b**–**1 e**) with acetophenone **2 a** under optimized reaction condition to afford the corresponding desired products (**5 ba**–**5 ea**) (see Table 2). We observed that among all the *N*-substituted benzylidene diazo compounds screened, *N*-ethyl substituted benzylidene diazo compound **1 a** proved to be optimum substrate by affording the desired product **5 aa** in relatively higher yield. In view of this, we planned to explore the reactivity of different *N*-ethyl substituted vinyl diazo compounds (**1 f**–**1 n**) bearing different substituents with electron-rich and -deficient/-deactivated groups at different positions of phenyl ring of the vinyl diazo succinimide. The reaction of acetophenone **2 a** with *N*-ethyl substituted vinyl diazo compounds (**1 f**–**1 k**) under the optimized reaction conditions afforded the target products (**5 fa**–**5 ka)** in moderate to good yields at room temperature in a very short time (up to 68%, 2 h). It is Interestingly, we obtained the desired product **5 aa** in 64% yield after 5 h (Scheme 3c). interesting that the *N*-ethyl substituted vinyl diazo compound derived from α-napthal (**1 k**) reacted smoothly, while β-napthal derived derivative (**1 l**) did not react probably due to electronic and steric reasons. We observed that the vinyl diazo compounds bearing electron deactivating groups (–F, –Cl, –Br) at different positions of phenyl ring, afforded the target products in relatively higher yields than that of electron rich system (**1 b**–**1 d**, **1 j**). Unfortunately, the *N*-ethyl substituted vinyl diazo compounds having methoxy group (**1 m)** at *meta* position found to be not reactive. We reasoned that probably due to the presence of electron donating group (–OMe), the carbenoid carbon would be relatively less electrophilic for desirable reaction. In order to validate this, we replaced the methoxy group with the electron deactivating acetyloxy group at the same position (*meta*, **1 n**) and treated with acetophenone **2 a** under the optimized reaction condition. Gratifyingly, we obtained the corresponding desired product **5 na** in moderate yield (61%, Table 2). It is interesting to note that relatively sensitive benzylidene scaffold containing *p*-methyl group at phenyl ring (**5 da**, **5 ja**) tolerated the optimized reaction conditions. Later, in order to generalize the practicality of the protocol, we explored the reaction of **1 a** and **2 a** on gram scale quantity and further as an application, the transformation of **5 aa** was carried to obtain the pyrrolidinone derivative **7 aa** (see Table 2 or Appendix-II, SI). All the dihydrobenzoxepines were obtained as single diastereomer. We obtained the molecular structure of **5 ga** using single crystal X-ray analysis[15] and the structures of all the other compounds were deduced based on analogy.

In order to have an insight into the reaction mechanism, we performed few control experiments systematically. To verify whether or not the reaction undergoes *via* carbonyl ylide (**int-II** or **III**, Scheme 3) or epoxide (**int-IV**, Scheme 3), we initially prepared the corresponding epoxide[15] (**int-IV** or **3 aa**) using the reported procedure.[13a] This epoxide **3 aa** under the optimized reaction conditions did not afford the desired product **5 aa** even in trace and the unreacted epoxide **3 aa** was recovered (Scheme 3a). Likewise, we observed that reaction did not afford

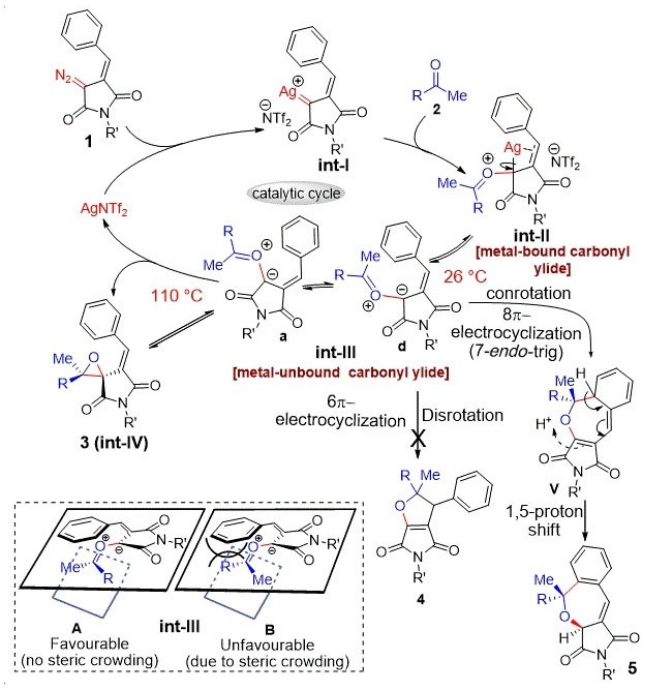


Scheme 3. Control Experiments for Intermediate Detection.

© 2022 Wiley-VCH GmbH

21935815, 2022, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajoc.202200062 by Indian Institute Of Science Education And Research Pune, Wiley Online Library on [03/07/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

the desired product **5 aa** when carried out in absence of catalyst at room temperature (Scheme 3b). These results confirm that epoxide **3 aa** (**int-IV**) is not the intermediate for the desired transformation at room temperature. The **int-II** (four different conformational forms of metal-bound carbonyl ylides in one inset, see Scheme 3) and **int-III** (four different conformational forms of the corresponding metal-unbound carbonyl ylides) might be generating from the reaction of aryl vinyl diazosuccinimide under silver catalysis, presented here. It is reported by Huisgen that the epoxide can undergo electrocyclic ring opening reaction upon heating (absence of any catalyst). This report confirms about the *in situ* formation of carbonyl ylide at the room temperature reaction condition.[16a–b] In this regard, in order to verify the possible formation of intermediate (**int-II** or **III**), we further treated compound **3 aa** (epoxide) with $AgNTf_2$ (5 mol%) at an elevated temperature (110 °C, Scheme 3c). Interestingly we obtained the desired product **5 aa** in 64% yield after 5 h (Scheme 3c). To understand the possible role of silver catalyst as well as carbonyl ylide, we performed the reaction in the absence of $AgNTf_2$ at elevated temperature (110 °C, Scheme 3d). To our surprise we obtained compound **5 aa**[15] in almost similar yield (Scheme 3d, for more details, see SI]. Considering Huisgen's[16a–b] and Eberbach's reports[16c] on the electrocyclic ring-opening equilibria of oxirane to carbonyl ylide and different conformational forms of carbonyl ylide, we surmise that at an elevated temperature, epoxide **3 aa** would open up to form metal-unbound carbonyl ylide (see **int-IIId**, Scheme 3). This result was further supported by the time-dependent ^{1}H-NMR experiment wherein signals for the epoxide **3 aa** were disappearing over a period of time at an elevated temperature to form **5 aa** (Scheme 3, for more details, see SI page no. S34–35). We also strongly believe that even at room temperature the reaction would undergo via the same intermediate (**int-IIId**) to afford **5 aa**. Apart from that an attempt to trap the carbonyl ylide intermediate (**int-III**) with different dienophiles[6d] were unsuccessful. We observed that none of dienophiles reacted with the epoxide (**int-IV**) either at 26 °C or at 110 °C. In order to understand the role of catalyst, we carried out the reaction of **1 a** and acetophenone **2 a** in the absence of catalyst at 110 °C for prolonged reaction time (Scheme 3e). Interestingly, we did not obtain either the desire product **5 aa** or the epoxide **3 aa** even in trace thus supporting the role of catalyst in the desired transformation (Scheme 3e). Earlier also we had observed that the reaction at room temperature did not work in the absence of catalyst and the starting material **1 a** was recovered (26 °C, see Table 1, Entry 6). These two results indicate that probably a reactive silver carbenoid (**int-I**, see Scheme 4) species might be forming *in situ* that eventually may be forming carbonyl ylide (**int-IIId**) *via* the corresponding counter anion stabilized metal-bound carbonyl ylide (**int-II**) both at room temperature as well as at elevated temperature. These combined results clearly depicted that the epoxide (**int-IV**) may not be the favourable intermediate and probably the desired product **5 aa** might be forming *via* carbonyl ylide (**int-IIId**) at room temperature. These control experiments suggest that among the three plausible intermediates, the carbonyl ylide (**int-IIId**) is the plausible intermediate for the formation of



Scheme 4. Plausible Mechanism for the (5 + 2)-Annulation.

dihydrobenzoxepine **5 aa** products. Moreover, a metal-unbound (free-ylide) carbonyl ylide intermediate, generating *in situ*, is proposed to be operative here based on the control experimental observations (for details, see SI page no. S33–35). We surmise that relatively better coordinating and more nucleophilic counter anion Tf_2N^- might be acting as a superior promoter in facilitating the formation of **int-IIId** faster and easily at room temperature than that of SbF_6^- anion.[17] We also noted that the anticipated product **4 aa** (see Table 1) has not been detected during the transformation. This might be the cause of steric hindrance exerted by the benzylidene group (phenyl ring tilted towards the carbonyl moiety) on vinyl succinimide, occurring in the transition state or in the carbonyl intermediate (**int-IIId**).

Based on the experimental observations and preceding literature,[16b–c,18] the plausible mechanism has been proposed (See Scheme 4). The vinyl diazosuccinimide **1** under the reaction conditions generates the silver carbenoid (**int-I**) by the extrusion of dinitrogen. This intermediate (**int-I**) further reacts with the ketone **2** (approaches from sterically less hindered site; see Scheme 4, inset) to form metal unbound carbenoid (**int-IIId**) *via* the corresponding counter anion stabilized metal bound carbonyl ylide (**int-II**). This intermediate would further undergo 8π-electrocyclization (7-*endo*-trig) to form species **V** which after the successive (1,5)-proton abstraction affords the corresponding desired oxepine **5**. Also, at higher temperature **int-IV (3)** might be in equilibrium with the **int-IIId** to form the desired product **5** as well (Scheme 4).

© 2022 Wiley-VCH GmbH

21935815, 2022, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajoc.202200062 by Indian Institute Of Science Education And Research Pune, Wiley Online Library on [03/07/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Conclusion

In summary, we have demonstrated the formal (5 + 2)-cycloaddition route to access the dihydrobenzoxepines in one-pot using vinyl diazosuccinimide as 5-C-synthons and ketones very effectively for the first time. The silver triflimide proved to be an efficient catalyst for this transformation and the protocol found to be highly regio-, chemo- and diastereo-selective. The method proved to be general as it worked well with aliphatic and aromatic methyl ketones bearing electron deactivating as well as donating groups to afford the corresponding benzo[5,6]oxepino[2,3-*c*]pyrroles as single diastereomer with a broad substrates scope. The control experiments and time-dependent NMR studies gave an insight into the plausible reaction mechanism of this transformation. The protocol proved to be scalable on gram quantity as well.

Experimental Section

General procedure for the synthesis of vinyl succinimides (6 a–6 n): The compounds were prepared according to a previously reported method[13a]

To the stirred solution of *N*-ethyl maleimide (3 g, 1.0 equiv., 24 mmol) in ethanol (120 mL) was added triphenylphosphine (7.55 g, 1.2 equiv., 29.0 mmol) in portion at room temperature under N_2 atmosphere. The initial pink coloured reaction mixture slowly turned to white suspension over a period of 5–6 min of initial stirring. After which, benzaldehyde (3.5 mL, 1.4 equiv., 34 mmol) was added dropwise into the reaction mixture at room temperature. During this addition, the white suspension slowly turned into clear solution. The reaction mixture was allowed to stir for 6 h. Upon completion of the reaction (monitored by TLC), the white solid formed during the course of the reaction was filtered through sintered glass funnel and was washed with ethanol (10 mL × 2). The crude product 6a was obtained as white solid (3.40 g, 66% yield) and this was used for the next step without further purification.

General Procedure for the synthesis of vinyl diazosuccinimides (1 a–1 n): The compounds were prepared according to a previously reported method[13a]

To the stirred solution of (*E*)-3-benzylidene-1-ethylpyrrolidine-2,5-dione **6 a** (2.15 g, 1.0 equiv., 10 mmol) in 30 mL acetonitrile, were added 4-acetamidobenzenesulfonyl azide (2.88 g, 1.2 equiv., 12 mmol) and DBU (2.24 mL, 1.5 equiv., 15 mmol) at 0 °C temperature under inert atmosphere. The reaction mixture was stirred for 10 minutes while maintaining the temperature (0 °C). The reaction mixture was then quenched with saturated solution of NH_4Cl and the product was extracted with diethyl ether (30 mL × 3). The combined organic layers were washed with brine solution and dried over anhydrous Na_2SO_4. The extract was filtered and evaporated under reduced pressure. The crude product was purified using column chromatography over silica gel to afford *(E)*-3-benzylidene-4-diazo-1-ethylpyrrolidine-2,5-dione **1 a** as orange solid (2.257 g, 94% yield).

General procedure for the synthesis of dihydrobenzo[5,6]oxepino[2,3-*c*]pyrrole-1,3(2*H*)-dione (5): An oven-dried 25 mL two necked round bottom (RB) flask equipped with a magnetic stirrer bar was charged with $AgNTf_2$ (3.9 mg, 5 mol%) under argon-atmosphere and the RB flask was covered up with aluminium foil. Then dry CH_2Cl_2 (5 mL) and acetophenone **2 a** (23.6 μL, 1.0 equiv., 0.2 mmol) were added subsequently and the mixture was stirred at room temperature under for a minute. After that, vinyl diazosuccinimide **1 a** (48.3 mg, 1.0 equiv., 0.2 mmol) in CH_2Cl_2 (1 mL) was added to the reaction mixture dropwise over 2 h and the stirring was continued for 10 min more for full consumption of diazo compound. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography (petroleum ether/EtOAc 92 : 8) over silica gel to furnish the desired product **5 aa** as white solid (47 mg, 70% yield). The slight excess amount of acetophenone **2 a** was recovered during the purification.

Acknowledgements

R. G. B. thanks the Science and Engineering Research Board, Department of Science and Technology (SERB-DST), New Delhi, Government of India (File no: CRG/2019/005753) for the generous research grant. D. L., K. B. M. and O. S. B. thank the UGC, New Delhi, Government of India for providing fellowship. The authors thank IISER Pune for the financial assistance. We acknowledge Dr. Rahul Maity and Prakash K. Warghude of IISER Pune for helping in for obtaining the crystal data.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Annulation · Diastereoselective · Dihydrobenzoxepines · Silver catalysis · Vinyl diazosuccinimide

[1] a) A. G. Myers, M. J. Mithceltree, K. J. Silvestre, *From PCT Int. Appl.* (**2009**), WO 2019032936 A1 20190214; b) I. K. Lee, Y. W. Jang, Y. S. Kim, S. H. Yu, K. J. Lee, S. M. Park, B. T. Oh, J. C. Chae, B. S. Yun, *J. Antibiot.* **2009**, *62*, 163–165; c) F. Bohlmann, G. Fritz, *Tetrahedron* **1982**, *38*, 1431; d) A. Ghosh, A. Bandyopadhyay, P. Ghosh, *J. Sci. Innov. Res.* **2013**, *2*, 795–801.
[2] a) D. Basavaiah, D. S. Sharada, A. Veerendhar, *Tetrahedron Lett.* **2004**, *45*, 3081–3083; b) B. Das, A. Majhi, J. Banerjee, N. Chowdhury, H. Holla, K. Harakishore, U. S. Murty, *Chem. Pharm. Bull.* **2006**, *54*, 403–405; c) G. Islas-González, J. Benet-Buchholz, M. A. Maestro, A. Riera, M. A. Pericàs, *J. Org. Chem.* **2006**, *71*, 1537–1544; d) A. V. Fernndez, C. G. Yebra, J. A. Varela, M. A. Esteruelas, S. Carlos, *Angew. Chem.* **2010**, *122*, 4374–4377; *Angew. Chem. Int. Ed.* **2010**, *49*, 4278–4281; e) J. Francuz, B. Srećo, M. Popsavin, G. Bene-deković, V. Divjaković, V. Kojić, G. Bogdanović, A. Kapor, V. Popsavin, *Tetrahedron Lett.* **2012**, *53*, 1819; f) S. J. Gharpure, S. R. B. Reddy, *Eur. J. Org. Chem.* **2013**, 2981–2984; g) A. G. K. Reddy, J. Krishna, G. Satyanarayana, *Tetrahedron* **2013**, *69*, 10098–10107; h) A. A. More, C. V. Ramana, *Chem. Asian J.* **2014**, *9*, 1557–1562.
[3] a) H. Chen, Y. He, L. Zhou, *Org. Chem. Front.* **2018**, *5*, 3240–3244; b) M.-Y. Chang, Y.-T. Hsiao, K.-H. Lai, *J. Org. Chem.* **2018**, *83*, 14110–14119.
[4] For reviews, see: a) M. P. Doyle in *Comprehensive Organometallic Chemistry II*, Vol. 12 (Ed.: L. S. Hegedus), Pergamon, New York, **1995**, chap. 5.2; b) A. Padwa, M. D. Weigarten, *Chem. Rev.* **1996**, *96*, 223; c) G.

© 2022 Wiley-VCH GmbH

21935815, 2022, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajoc.202200062 by Indian Institute Of Science Education And Research Pune, Wiley Online Library on [03/07/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Mehta, S. Muthusamy, *Tetrahedron* **2002**, *58*, 9477; d) M. C. McMills, D. Wright in *Synthetic Application of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), Wiley, New York, **2002**, chap. 4.

[5] a) H. Suga, A. Kakehi, S. Ito, K. Inoue, H. Ishida, T. Ibata, *Org. Lett.* **2000**, *2*, 3145; b) H. Suga, A. Kakehi, S. Ito, K. Inoue, H. Ishida, T. Ibata, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1115.

[6] For selected examples, see: a) S. Torssell, M. Kienle, P. Somfai, *Angew. Chem.* **2005**, *117*, 3156; *Angew. Chem. Int. Ed.* **2005**, *44*, 3096; b) V. Nair, S. Mathai, S. C. Mathew, N. P. Rath, *Tetrahedron* **2005**, *61*, 2849; c) V. V. Diev, R. R. Kostikov, R. Gleiter, A. P. Molchanov, *J. Org. Chem.* **2006**, *71*, 4066; d) A. DeAngelis, M. T. Taylor, J. M. Fox, *J. Am. Chem. Soc.* **2009**, *131*, 1101; e) O. Anaç, Ö. Sezer, Ö. Candan, F. Ş. Güngör, M. ŞerifCansever, *Tetrahedron Lett.* **2008**, *49*, 1062–1065.

[7] J.-L. Zhou, Y. Liang, C. Deng, H. Zhou, Z. Wang, X.-L. Sun, J.-C. Zheng, Z.-X. Yu, Y. Tang, *Angew. Chem.* **2011**, *123*, 8020–8024; *Angew. Chem. Int. Ed.* **2011**, *50*, 7874–7878.

[8] a) A. Suneja, H. J. Loui, C. Schneider, *Angew. Chem. Int. Ed.* **2020**, *59*, 5536–5540; *Angew. Chem.* **2020**, *132*, 5580–5585; See recent reviews on [4+3] cycloadditions: b) Q.-Q. Cheng, Y. Deng, M. Lankelma, M. P. Doyle, *Chem. Soc. Rev.* **2017**, *46*, 5425–5443; c) Z. Yin, Y. He, P. Chiu, *Chem. Soc. Rev.* **2018**, *47*, 8881–8924; d) J. L. Mascareñas, I. Varela, F. López, *Acc. Chem. Res.* **2019**, *52*, 465–479; e) K. Selvaraj, S. Chauhan, K. Sandeep, K. C. Kumara Swamy, *Chem. Asian J.* **2020**,*15*, 2380–2402.

[9] a) M. Hamaguchi, H. Matsubara, T. Nagai, *J. Org. Chem.* **2001**, *66*, 5395–5404; b) H. M. L. Davies, J. DeMeese, *Tetrahedron Lett.* **2001**, *42*, 6803–6805.

[10] Y. Lian, H. M. L. Davies, *Org. Lett.* **2010**, *12*, 924–927.

[11] a) A. Parenty, X. Moreau, J.-M. Campagne, *Chem. Rev.* **2006**, *106*, 911–939.

[12] a) X.-Y. Zhang, Y. You, Z.-H. Wang, J.-Q. Zhao, W.-C. Yuan, *Chem. Commun.* **2020**, *56*, 13449; b) Z. Gan, M. Zhi, R. Han, E.-Q. Li, Z. Duan, F. Mathey, *Org. Lett.* **2019**, *21*, 2782; c) B.-L. Zhao, D.-M. Du, *Chem. Commun.* **2016**, *52*, 6162.

[13] a) D. Laha, R. G. Bhat, *Asian J. Org. Chem.* **2020**, *9*, 918–921; b) E. Chupakhin, M. Gecht, A. Ivanov, G. Kantin, D. Dar'in, M. Krasavin, *Synthesis* **2021**, *53*, 1292–1300; c) E. G. Chupakhin, G. P. Kantin, D. V. Dar'in, M. Krasavin, *Mendeleev Commun.* **2021**, *31*, 36–38.

[14] a) Y. Nakano, M. Hamaguchi, T. Nagai, *J. Org. Chem.* **1989**, *54*, 5912–5919; b) D. Dar'in, G. Kantin, O. Bakulina, A. Inyutina, E. Chupakhin, M. Krasavin, *J. Org. Chem.* **2020**, *85*, 15586–15599; c) M. Hamaguchi, T. Misumi, T. Oshima, *Tetrahedron Lett.* **1998**, *39*, 7113–7116; d) A. Inyutina, D. Dar'in, G. Kantina, M. Krasavin, *Org. Biomol. Chem.* **2021**, *19*, 5068–5071; e) A. Inyutina, G. Kantin, D. Dar'in, M. Krasavin, *J. Org. Chem.* **2021**, *86*, 13673–13683; f) D. Laha, K. B. Meher, O. S. Bankar, R. G. Bhat, *DOI: 10.26434/chemrxiv-2021-vv9hv*.

[15] CCDC 2105271 (compound **1a**), 2105766 (compound **5ga**), 2105262 (compound **3aa**), and 2105272 (Compound **5aa**) contain the supplementary crystallographic data. These data can be obtained free of charge by The Cam-bridge Crystallographic Data Centre.

[16] a) R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 572–585; b) P. de March, R. Huisgen, *J. Am. Chem. Soc.* **1982**, *104*, 4952; c) W. Eberbach, U. Trostrnann, *Chem. Ber.* **1985**, *118*, 4035–4058.

[17] It is believed that the tight ion pairs that are formed between silver metal and counteranion (Tf_2N^-), confine the counteranion (Tf_2N^-) in more close proximity to the metal center than that of SbF_6^-; since the order of coordinating tendency of these two anions is $SbF_6^- < Tf_2N^-$].

[18] G. Zecchi, *Synthesis* **1991**, *3*, 181–188.

Manuscript received: February 7, 2022
Revised manuscript received: March 4, 2022
Accepted manuscript online: March 10, 2022
Version of record online: March 30, 2022

© 2022 Wiley-VCH GmbH

21935815, 2022, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ajoc.202200062 by Indian Institute Of Science Education And Research Pune, Wiley Online Library on [03/07/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

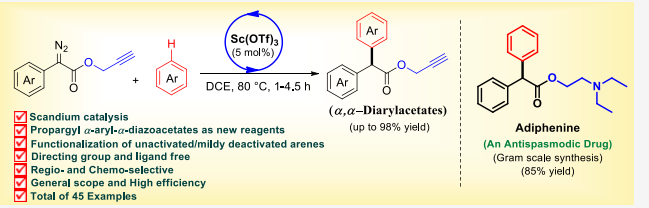
Highly Site-Selective Direct C−H Bond Functionalization of Unactivated Arenes with Propargyl α-Aryl-α-diazoacetates via Scandium Catalysis

Balu S. Navale, Debasish Laha, Subhrashis Banerjee, Kumar Vanka, and Ramakrishna G. Bhat*

Cite This: J. Org. Chem. 2022, 87, 13583−13597 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Highly chemo- and regio-selective C−H bond functionalization of unactivated arenes with propargyl α-aryl-α-diazoacetates has been developed using scandium catalysis. A variety of unactivated, mildly deactivated, and electronically activated arenes have been functionalized using this protocol. The synergistic combination of scandium triflate as a catalyst and propargyl α-aryl-α-diazoacetate as a reagent played a pivotal role in the effective C−H bond functionalization of arenes without the assistance of any directing group or ligand. The practicality of the protocol has been demonstrated by the gram-scale synthesis of very useful α,α-diarylacetates including antispasmodic drug-adiphenine. Based on the experimental observations, labeling experiment, and density functional theory calculations, a plausible reaction mechanism has been outlined.



INTRODUCTION

Catalytic C−H bond functionalization is one of the most important and viable methods for the synthesis of complex organic molecules.[1] Developing catalytic methods for the chemo- and regio-selective C−H bond functionalization is highly desirable but a challenging task for the synthetic community. Substituted arenes are widespread and present in various biologically active compounds and drug molecules.[2] Owing to the importance, the chemo- and regio-selective C−H bond functionalization of arenes is highly desirable in order to access different bioactive compounds in a minimum number of steps. Aromatic C−H bond functionalization using α-diazocarbonyl compounds is one of the important approaches to access substituted arenes.[3] As the α-diazocarbonyl compounds can be easily prepared from readily available starting materials, the utility of α-diazocarbonyl compounds in aromatic C−H bond functionalization has grown over the years.[3,4,5] Efforts have been made to increase the practicality of these protocols for the aromatic C−H bond functionalization by modifying catalysts and/or α-diazocarbonyl reagents for the aromatic C−H bond functionalization. The transition metal complexes of rhodium,[4] gold,[6] copper,[7] and iron[8] have been widely used for the aromatic C−H bond functionalization reactions with α-diazocarbonyl compounds. Recently, Pérez and co-workers have utilized the manganese catalyst for the aromatic C−H bond functionalization using α-diazocarbonyl compounds.[9] Likewise, transition metal-free C−H bond functionalization reactions of electron-rich arenes have been also explored.[5] Recently, Zhang, Liu and co-workers have reported a highly chemoselective C−H bond functionalization of phenols with α-aryl-α-diazoacetates by exploring the gold catalysis.[6d] Interestingly, under the reaction conditions, C−H insertion occurred exclusively, and the O−H insertion product was not obtained. This was the first elegant protocol wherein the unprotected phenols were effectively functionalized using α-aryl-α-diazoacetates and gold catalyst. This transformation proved to be highly *para*-selective. In 2014, Shi and co-workers have reported the ligand-controlled gold-catalyzed C−H bond functionalization of substituted arenes (Figure 1A).[6e] Various electronically rich arenes underwent the C−H bond functionalization reaction with α-aryl-α-diazoacetates in the presence of a gold catalyst to afford the corresponding desired α,α-diarylacetates. However, this method had a limited substrate scope as the protocol worked only with the electronically activated arenes. In 2017, Zhang, Liu and co-workers have reported the *para*-selective C−H alkylation of arenes with 2,2,2-trifluoroethyl α-aryl-α-diazoesters via gold catalysis (Figure 1B).[6f] However, the C−H bond functionalization of benzene and unactivated arenes worked only with 2,2,2-trifluoroethyl α-(4-trifluormethyl)-phenyl-α-diazoacetate. The presence of an electron-withdrawing group such as trifluoromethyl on the aryl group of diazoester (*p*-position) and 2,2,2-trifluoroethyl group at ester was found to be essential for this transformation.

Received: May 20, 2022
Published: October 1, 2022



Downloaded via IISER PUNE on July 3, 2023 at 18:44:26 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

ACS Publications © 2022 American Chemical Society

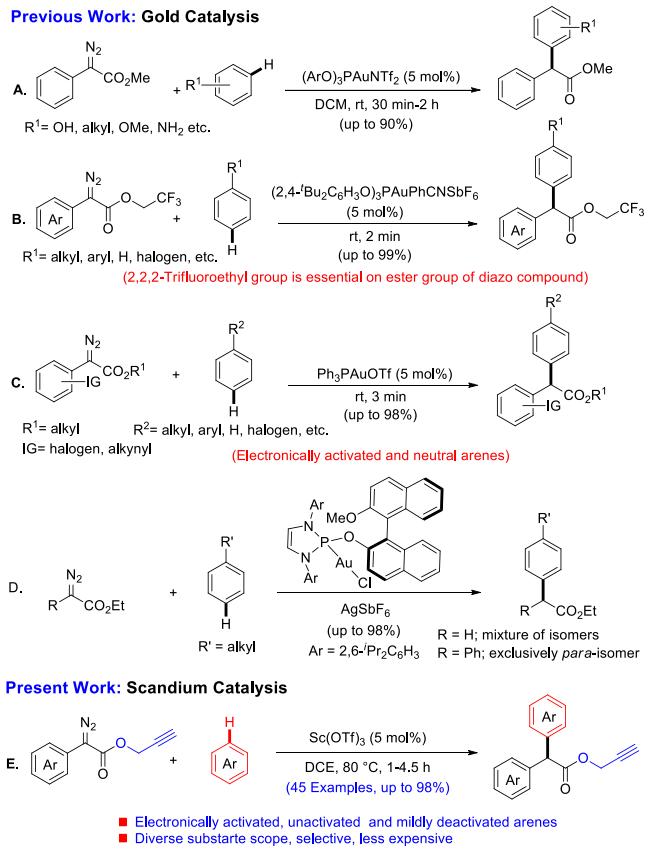


Figure 1. C−H bond functionalization of arenes with α-aryl-α-diazoacetates.

To overcome this limitation, the same research group has very recently developed another method for the C−H bond functionalization of arenes with alkyl α-aryl-α-diazoacetates in the presence of gold catalyst-triphenylphosphine gold(I) trifluoromethanesulfonate (Figure 1C).[6g] It is important to note that in order to address the inherent low reactivity of the normal alkyl α-aryl-α-diazoacetates, this method relied only on aryl diazoacetates containing electron-deactivating substituents such as halogens on the phenyl ring for the desired transformation. Very recently, Pérez, Fructos, Nova, and co-workers have reported an elegant strategy for the selective functionalization of monoalkylated benzenes utilizing the novel gold complex bearing an alkoxydiaminophosphine ligand. The method relied on nonelaborated ethyl α-phenyl-α-diazoacetates for achieving the *para*-selective C−H bond functionalization of arenes exclusively (Figure 1D).[6i]

Although gold catalysts have been well explored for the synthesis of α,α-diarylacetates, however, usually they are expensive and not all of these gold catalysts are commercially available as well.[6] The synthesis of α,α-diarylacetates using unactivated arenes and electronically deactivated arenes by modifying the catalyst and modulating the diazoacetate reagent system electronically remains an interesting and challenging task for the synthetic chemists.[6f,g,i] Also, it would be highly interesting and demanding to explore the C−H bond functionalization of unactivated arenes with α-phenyl-α-diazoacetates or aryl diazoesters containing an unsubstituted phenyl group.[10]

It is very common that the late transition metals are being explored for the C−H bond functionalization for their efficiency; however, interestingly, to the best of our knowledge, early transition elements (rare earth) have been seldom explored in the literature.[11] It would also be interesting to tap the potential of the unexplored early transition metal (rare earth)-based catalysts for the site-selective C−H bond functionalization of unactivated arenes. However, the synergistic combination of reagents and catalysts is very crucial for the effective C−H bond functionalization. As part of our ongoing efforts to explore the diazocarbonyl compounds for the effective C−H bond functionalization using early transition elements,[12a,b] and also based on some of the preceding reports on Lewis acid catalysts,[12c−e] we planned to explore the suitable combination of the catalyst and the modified diazocarbonyl reagent. We believed that the reagents with suitable electronic properties may be necessary for the effective C−H bond functionalization using early transition metal (rare earth) catalysts.

Herein, we report the novel scandium-catalyzed C−H bond functionalization of unactivated arenes and mildly deactivated arenes with propargyl α-aryl-α-diazoacetates as new robust reagents to synthesize useful and biologically important α,α-diarylacetates in good to excellent yields (Figure 1E).

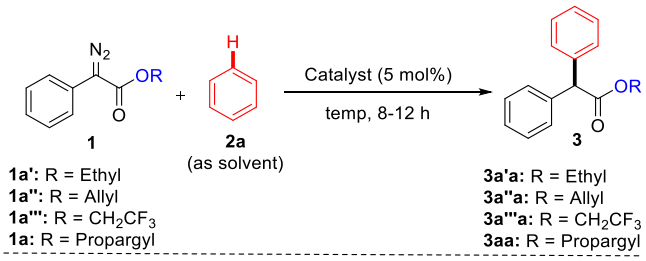
RESULTS AND DISCUSSION

To explore the feasibility of the proposed strategy, we commenced our study using ethyl α-phenyl-α-diazoacetate **1a′** and benzene **2a** as model substrates. Considering the importance of electronic properties of donor-/acceptor-type diazo compounds, we planned to modulate the reactivity of α-aryl-α-diazoacetates having different ester groups for the C−H bond functionalization. In this regard, we also planned to screen various catalysts including Lewis acids to tap the reactivity of different α-aryl-α-diazoacetates for the C−H bond functionalization. Initially, we commenced with the reaction of ethyl α-phenyl-α-diazoacetate **1a′** and benzene **2a** using well-established metal catalysts that have long been explored for the C−H bond functionalization of aromatic compounds with α-aryl-α-diazoacetates in dry benzene (Table 1, entries 1−7). Rhodium,[4] copper,[7] and gold[6] catalysts were found to be ineffective for the C−H bond functionalization of benzene at room temperature as well as under refluxing conditions (Table 1, entries 1−7). We observed that in all the cases (rhodium, copper, and gold catalysis), reactions led to very fast decomposition of diazo acetate **1a′** to afford a complex inseparable reaction mixture (dark brown color).

Later we turned our attention to screen few Lewis acids for the C−H bond functionalization based on previous literature studies.[12a−e] In this regard, we explored the reaction of ethyl α-phenyl-α-diazoacetate **1a′** using $Sc(OTf)_3$ (5 mol %) at room temperature (12 h, Table 1, entry 8). However, the starting material **1a′** remained intact even after prolonged reaction time. Interestingly, the reaction of ethyl α-phenyl-α-diazoacetate **1a′** and benzene **2a** in the presence of a catalytic amount of $Sc(OTf)_3$ (5 mol %) at an elevated temperature (80 °C) afforded the desired C−H bond functionalization product ethyl 2,2-diphenylacetate **3a′a** in 21% yield (Table 1, entry 9). Encouraged by this preliminary result, we synthesized allyl α-phenyl-α-diazoacetate **1a″**. The treatment of **1a″** with benzene **2a** in the presence of catalytic amount of $Sc(OTf)_3$ (5 mol %) in dry benzene at 80 °C afforded the desired product allyl 2,2-diphenylacetate **3a″a** in slightly improved yield in comparison to the ethyl α-phenyl-α-diazoacetate **1a′** (33%, Table 1, entry 10). Furthermore, we planned to explore the reactivity of 2,2,2-

https://doi.org/10.1021/acs.joc.2c01185
J. Org. Chem. 2022, 87, 13583−13597

Table 1. Optimization of the Reaction Conditions[abcd]



entry	catalyst	R	time [h]	temp [°C]	yield[bcd] [%]
1	$Rh_2(OAc)_4$	ethyl	12	rt	DC
2	$Rh_2(OAc)_4$	ethyl	4	80	DC
3	$Cu(OTf)_2$	ethyl	12	rt	DC
4	$Cu(OTf)_2$	ethyl	4	80	trace
5	$(ArO)_3PAuNTf_2$	ethyl	12	rt	DC
6	**L**$AuPhCNSbF_6$	ethyl	12	rt	NR
7	**L**$AuPhCNSbF_6$	ethyl	12	80	trace
8	$Sc(OTf)_3$	ethyl	12	rt	NR[d]
9	$Sc(OTf)_3$	ethyl	12	80	21
10	$Sc(OTf)_3$	allyl	12	80	33
11	$Sc(OTf)_3$	CH_2CF_3	8	80	52
12*	**L**$AuPhCNSbF_6$	CH_2CF_3	20*	rt	8
13	$Sc(OTf)_3$	propargyl	12	rt	NR
14	$Sc(OTf)_3$	propargyl	8	80	70
15	$Cu(OTf)_2$	propargyl	12	80	trace
16	$(ArO)_3PAuNTf_2$	propargyl	12	rt	DC
17	$(ArO)_3PAuNTf_2$	propargyl	4	80	DC
18	$Rh_2(OAc)_4$	propargyl	12	rt	DC
19	$[RuCl_2(p\text{-cymene})]_2$	propargyl	12	rt	DC
20	$In(OTf)_3$	propargyl	12	rt	NR
21	$In(OTf)_3$	propargyl	12	80	47%
22	$Bi(OTf)_3$	propargyl	12	rt	NR
23	$Bi(OTf)_3$	propargyl	12	rt	10
24	$Y(OTf)_3$	propargyl	12	80	20
25	$Yb(OTf)_3$	propargyl	12	80	trace
26	$FeCl_3{\cdot}6H_2O$	propargyl	12	rt	NR
27	$FeCl_3{\cdot}6H_2O$	propargyl	12	80	19
28	Triflic acid	propargyl	12	80	23
29	$AgSbF_6$	propargyl	4 h	rt	DC
30	no catalyst	propargyl	24 h	80	NR

[a]Reaction conditions: a solution of α-aryl-α-diazoacetate **1** (0.5 mmol, 1 equiv) in 1 mL benzene was added to a solution of catalyst (5 mol %) and benzene **2a** (1.5 mL) under an inert atmosphere; the reaction was monitored by thin-layer chromatography (TLC). [b]Isolated yield after purification by column chromatography. [c]DC-decomposed. [d]NR-no reaction, ***L** = $(2,4\text{-}^tBu_2C_6H_3O)_3P$. ***1a'''** was completely consumed in 20 min.

trifluoroethyl α-phenyl-α-diazoacetate **1a'''** under scandium catalysis. Gratifyingly, the reaction of **1a'''** and **2a** in the presence of $Sc(OTf)_3$ (5 mol %) at 80 °C afforded the desired product **3a'''a** in 52% yield (Table 1, entry 11). However, surprisingly, the reaction of 2,2,2-trifluoroethyl α-phenyl-α-diazoacetate **1a'''** and benzene under the reported gold catalysis furnished the desired product in poor yield (Table 1, entry 12).[13]

The initial results of the scandium-catalyzed C−H bond functionalization proved to be encouraging. However, based on our initial observations, we hypothesized that ethyl/allyl/2,2,2-trifluoroethyl α-phenyl-α-diazoacetate reagents **1** (**1a'**, **1a''**, **and 1a'''**) may be relatively less reactive (donor-/acceptor-type α-diazoacetates) to afford the desired products α,α-diarylacetates **3** in higher yields. Also, the limited catalytic activity of scandium triflate and low reactivity (nucleophilicity) of unactivated arenes such as benzene **2a** toward C−H bond functionalization may be the other prime cause for lower yields of **3a'a** and **3a''a**. It is known in the literature that the propargyl group is weakly electron-withdrawing[14] and in this regard, we planned to explore the effect of the propargyl group on C−H bond functionalization of unactivated arenes. To explore the feasibility and to enhance the reactivity of α-aryl-α-diazoacetate toward the C−H bond functionalization, we synthesized the propargyl α-phenyl-α-diazoacetate **1a** containing an electron-withdrawing propargyl group on the ester part that can also be removed after the functionalization easily.

To validate our hypothesis, we planned to explore the reactivity of propargyl α-phenyl-α-diazoacetate **1a**. The reaction of **1a** and benzene **2a** in the presence of $Sc(OTf)_3$ at room temperature did not afford the desired product **3aa** (Table 1, entry 13). Gratifyingly, the reaction of propargyl α-phenyl-α-diazoacetate **1a** and benzene **2a** afforded the desired C−H bond functionalization product propargyl 2,2-diphenylacetate **3aa** in 70% yield in the presence of $Sc(OTf)_3$ (5 mol %) at 80 °C in 8 h (Table 1, entry 14). Furthermore, we planned to explore the reactivity of **1a** in the presence of different metal catalysts at room temperature to an elevated temperature in dry benzene **2a** (Table 1, entries 15−27). It is interesting to note that copper and gold catalysts were found to be unsuccessful in affording the desired product **3aa** (Table 1, entries 15−17). Rhodium and ruthenium catalysts were also found to be ineffective for the desired direct C−H bond functionalization of benzene **2a** (Table 1, entries 18 and 19). The reaction of benzene **2a** with propargyl α-phenyl-α-diazoacetate **1a** in presence of other metal catalysts afforded the direct C−H bond functionalization product **3aa** either in low or moderate yields; in some cases starting materials remained intact (Table 1, entries 20−27). We observed that the most of the catalysts were found to be ineffective in catalyzing the desired transformation. In few cases, the reactions led to the decomposition of the reagent. Also, varying the reaction temperatures from rt to 80 °C did not influence the outcome of the reaction in most of the cases. To confirm the role of $Sc(OTf)_3$ as a catalyst and to rule out the possible formation of a trace amount of triflic acid in situ by the hydrolysis of $Sc(OTf)_3$ if any due to the moisture[15] and its subsequent catalysis, we carried out the reaction of **1a** and **2a** in the presence of a catalytic amount of triflic acid (Table 1, entry 28). However, the desired product **3aa** was formed in poor yield, while the reaction in the presence of a catalytic amount of $AgSbF_6$ (5 mol %) led to the decomposition of diazoacetate **1a** (Table 1, entry 29). It is very important to note that the C−H bond functionalization did not work in the absence of $Sc(OTf)_3$ thus indicating the necessity of this catalyst for the desired transformation (Table 1, entry 30).

Encouraged by the initial success, we screened the reaction in diverse solvents at different temperatures and varied the catalyst loadings of $Sc(OTf)_3$ to optimize the synthesis of desired product **3aa** (Appendix-I, ESI). Among all, dichloroethane proved to be the optimum solvent by affording the desired product **3aa** in 72% yield at 80 °C in 4 h (Appendix-I, entry 4, ESI). However, the polar solvents such as DMF and acetonitrile were found to be disadvantageous (Appendix-I, entries 5 and 6, ESI). Solvents such as ethyl acetate, nitromethane, and dichloromethane afforded the desired

https://doi.org/10.1021/acs.joc.2c01185
J. Org. Chem. 2022, 87, 13583−13597

product **3aa** in low to moderate yields (Appendix-I, entries 1−3, ESI). We also observed that the lower catalyst loading of $Sc(OTf)_3$ (2.5 mol %) afforded the desired product **3aa** in moderate yield in 8 h (Appendix-I, entry 7, ESI).

We further looked into the possible effect of a cocatalyst on this transformation. We screened two different silver cocatalysts along with the $Sc(OTf)_3$ to optimize the reaction (Appendix-II, ESI). Interestingly, both $AgSbF_6$ and AgOTf were found to be ineffective and led to the formation of the desired product **3aa** in lower yields (Appendix-II, entries 1−5, ESI). However, the reaction worked smoothly in the absence of a cocatalyst to afford the desired product **3aa** in good yield (72% yield, Appendix-II entry 6, ESI). It is very important to note that C−H bond functionalization of benzene and unactivated arenes is quite challenging, and many efforts have been made earlier by different strategies. Furthermore, the molecular structure of the compound **3aa** was unambiguously confirmed by single crystal X-ray analysis.[16] To generalize the reaction conditions further, we treated different alkyl α-(4-bromophenyl)-α-diazoacetates **1b′**, **1b″**, **1b‴**, and **1b** (ethyl, allyl, 2,2,2-trifluoroethyl and propargyl) with benzene under the initially optimized reaction conditions to obtain the corresponding **3b′a**, **3b″a**, **3b‴a**, and **3ba**, respectively (see Appendix-III, ESI). We noticed a similar trend of results as observed in the case of α-phenyl-α-diazoacetates **1a-a‴** (entries 9−11, 14, Table 1). Based on exhaustive screening, propargyl α-phenyl-α-diazoacetate **1a** (1 equiv), benzene **2a** (10 equiv), and $Sc(OTf)_3$ (5 mol %) in DCE at 80 °C under an inert atmosphere proved to be the optimum reaction condition.

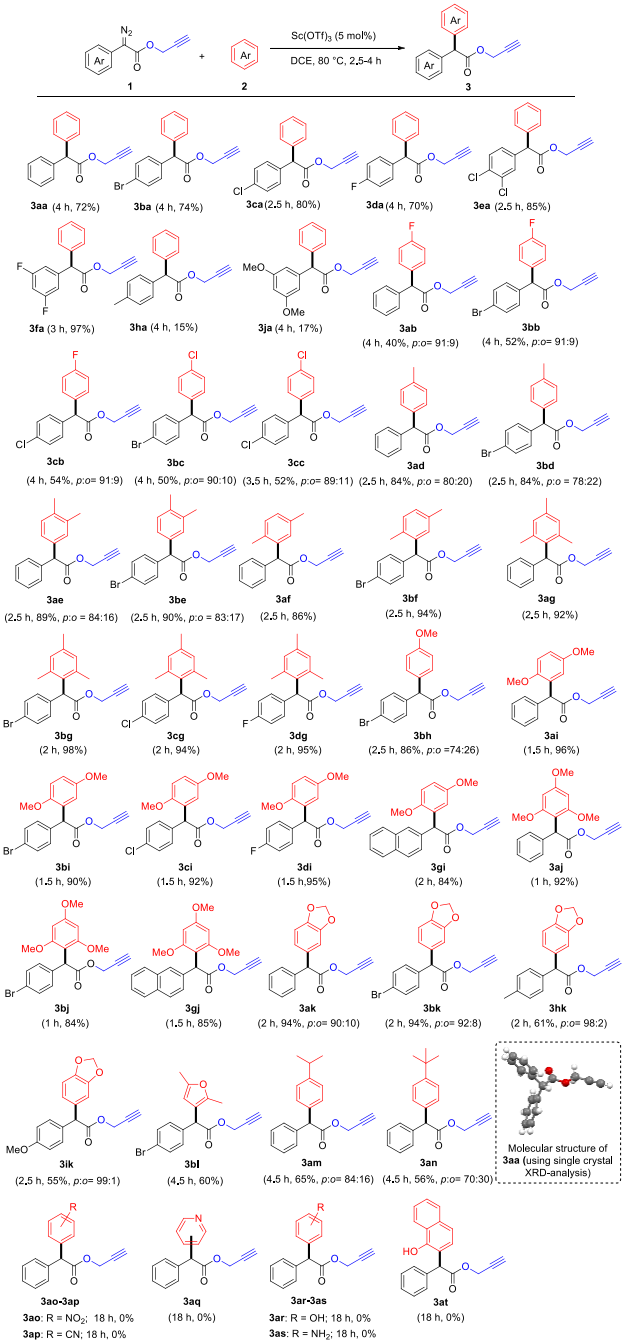
Having optimized the reaction conditions, we then focused our attention to explore the reagent scope of this C−H bond functionalization protocol using unactivated arenes such as benzene **2a** with different propargyl α-aryl-α-diazoacetates **1**. Benzene **2a** reacted with propargyl α-aryl-α-diazoacetates (**1a**−**1f**, **1h**, **1j**) smoothly to afford the desired products (**3aa**−**3fa**, **3ha**, **3ja**) in excellent yields (up to 97% yield, Scheme 1). Propargyl α-aryl-α-diazoacetates (**1b**−**1f**) with weak electron-withdrawing substituents on the phenyl ring proved to be very good reagents for the C−H bond functionalization of benzene **2a** to afford the desired products (**3ba**−**3fa**) in good to excellent yields (up to 97% yield, Scheme 1).

However, the α-aryl-α-diazoacetates (**1h**, **1j**) with electron-donating substituents on the phenyl ring greatly reduced the reactivity of propargyl α-aryl-α-diazoacetates toward the C−H bond functionalization under the optimum reaction conditions to afford the desired products (**3ha**, **3ja**) in lower yields (Scheme 1). These observations indicated that electron-withdrawing substituents on the phenyl ring of propargyl α-aryl-α-diazoacetates play a major role in tuning the reactivity of the reagent.

After the initial success on the C−H bond functionalization of an unactivated arene such as benzene, we turned our attention to explore the relatively more challenging mildly deactivated arenes. Gratifyingly, the reactions of fluorobenzene **2b** with different propargyl α-aryl-α-diazoacetates (**1a**, **1b**, and **1c**) under the optimal reaction conditions afforded the corresponding desired products (**3ab**, **3bb**, **3cb**) in moderate yields with good regioselectivity (up to 54% yield, up to 91:9 *p*:*o* ratio, Scheme 1). Likewise, the chlorobenzene **2c** reacted smoothly with propargyl α-aryl-α-diazoacetates (**1b**, **1c**) under the optimum reaction conditions to furnish the corresponding desired products (**3bc**, **3cc**) in moderate yields with very good regioselectivity (up to 52% yield, up to 90:10 *p*:*o* ratio, Scheme 1).

Later, we planned to explore the reactivity of electron-rich arenes. Mildly activated arenes such as toluene **2d** reacted with propargyl α-aryl-α-diazoacetates (**1a** and **1b**) under the optimum reaction conditions to afford the corresponding desired products (**3ad**−**3bd**) in good yields with good regioselectivity (up to 84% yield, up to 80:20 *p*:*o* ratio,

Scheme 1. Scope of Diazoacetates and Arenes[a]



[a]Reaction conditions: Propargyl α-aryl-α-diazoacetates **1** (0.5 mmol, 1 equiv), arene **2** (10 equiv) and $Sc(OTf)_3$ (5 mol %) was added in DCE (2.5 mL) under an inert atmosphere, and the reaction mixture was refluxed at 80 °C; the reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography (time and yields are given in parenthesis).

https://doi.org/10.1021/acs.joc.2c01185
J. Org. Chem. 2022, 87, 13583−13597

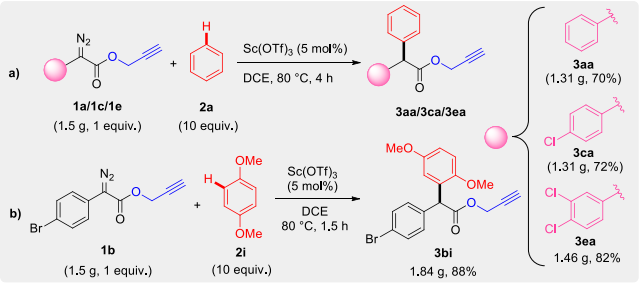
Scheme 1). *o*-Xylene **2e** and *p*-xylene **2f** reacted smoothly with propargyl α-aryl-α-diazoacetates (**1a** and **1b**) under the optimum reaction conditions to afford the corresponding desired products (**3ae** and **3be**, **3af** and **3bf**) in good to excellent yields (up to 94% yield, Scheme 1).

Mesitylene (**2g**), when treated with propargyl α-aryl-α-diazoacetates (**1a**−**1d**) under optimum reaction conditions, furnished the corresponding products (**3ag**−**3dg**) in excellent yields (up to 98% yield, Scheme 1). Under the reaction conditions, the activated arene such as anisole **2h** reacted smoothly with the propargyl α-aryl-α-diazoacetate **1b** to afford the corresponding desired product **3bh** in very good yield. Activated arenes such as 1,4-dimethoxybenzene **2i** reacted with different propargyl α-aryl-α-diazoacetates (**1a**−**1d**, **1g**) to afford the corresponding desired products (**3ai**−**3di**, **3gi**) in excellent yields (up to 96%, Scheme 1). Highly activated arenes such as 1,3,5-trimethoxybenzene **2j** reacted smoothly with propargyl α-aryl-α-diazoacetates (**1a**, **1b**, **1g**) to furnish the corresponding C−H bond functionalization products (**3aj**, **3bj**, **3gj**) in very good to excellent yields (up to 92%, Scheme 1). 1,3-Benzodioxole **2k** also reacted smoothly with various propargyl α-aryl-α-diazoacetates (**1a**, **1b**, **1h**, **1i**) under the optimized reaction conditions to afford the corresponding desired C−H functionalized products (**3ak**, **3bk**, **3hk**, **3ik**) in moderate to excellent yields with excellent regioselectivity (up to 94% yield, up to 99:1 *p*:*o* ratio, Scheme 1).

It is significant to note that C−H bond functionalization of 1,3-benzodioxole **2k** worked smoothly with α-(4-methoxyphenyl)-α-diazoacetate **1i**, unlike the previous procedure wherein dimerized product formation was reported.[6f] Even the heteroaromatic arene such as 2,5-dimethylfuran **2l** when treated with propargyl α-(4-bromophenyl)-α-diazoacetate **1b** under the optimum reaction conditions afforded the C−H functionalization product **3bl** in 60% yield (see Scheme 1). We demonstrated the robustness of this protocol using different arenes such as unactivated benzene, fluorobenzene, and 1,3-benzodioxole without having any electron-withdrawing substituents on the phenyl group of propargyl α-phenyl-α-diazoacetate. It is also very significant to note that substrates containing C(sp^3)−H bonds (benzylic C−H) also underwent chemo-selective arene C−H bond functionalization exclusively.[6g,17] It is also remarkable that arenes [C(sp^2)−H] were chemo- and site-selectively functionalized and the side products emanating from some of the most common reactions such as cyclopropanation and Buchner reaction were not observed during the transformation. Later, we explored the arenes with bulky alkyl substituents such as isopropyl/^{t}butyl benzenes under optimized reaction conditions. Gratifyingly, the desired products **3am** and **3an** were obtained in good yields with moderate to good regioselectivity, while the highly unactivated arenes such as nitrobenzene, cyanobenzene and the heteroarene such as pyridine did not afford the respective desired products (**3ao**, **3ap**, **3aq**, Scheme 1) even after prolonged reaction times. Even the substrates such as phenol, aniline, and α-naphthol did not react with **1a** under the optimized reaction conditions, and the desired products (**3ar**, **3as**, **3at**, Scheme 1) were not obtained.

To demonstrate the practicality and the generality of the protocol, we further explored this protocol for the gram-scale synthesis of few α,α-diarylacetates. Reactions of propargyl α-aryl-α-diazoacetates (**1a**, **1c**, **1e**, and **1b**) and arenes (**2a** and **2i**) on a gram scale afforded the corresponding α,α-diarylacetates (**3aa**, **3ca**, **3ea**, **3bi**) in very good yields under the optimum reaction conditions (up to 88% yield, Scheme 2). The protocol proved to be very effective on a gram scale and

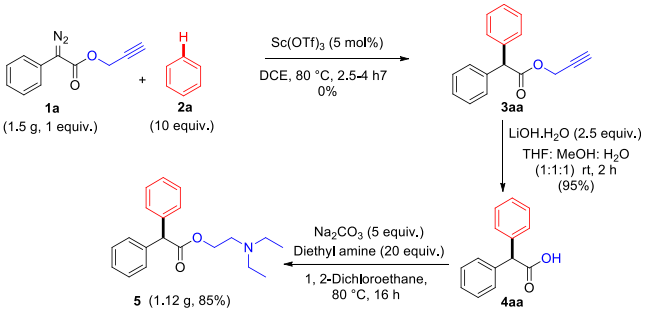
Scheme 2. Gram-Scale Synthesis of α,α-Diarylacetates



was also found to be reproducible. Later, the hydrolysis of propargyl α-diarylacetates (**3aa**, **3ca**, **3ea**) was carried out using LiOH.H_2O (2.5 equiv) in ethanol-tetrahydrofuran-water (1:1:1) mixture at room temperature in 1 h to furnish the corresponding α,α-diaryl carboxylic acids (**4aa**, **4ca**, and **4ea**) in excellent yields (up to 96% yield, see ESI, page no *S4*). The easy removal of the propargyl group under mild conditions proved to be very useful for the further synthetic transformations.

Furthermore, in order to demonstrate the applicability of this protocol, we explored the synthesis of biologically active adiphenine **5** on a gram scale (Scheme 3).

Scheme 3. Gram-Scale Synthesis of Adiphenine—An Antispasmodic Drug



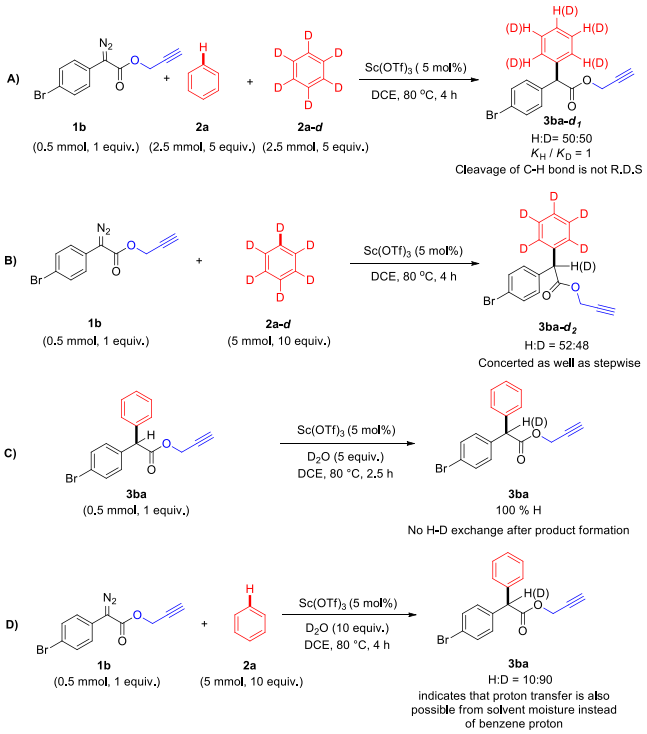
Adiphenine is a nicotinic receptor inhibitor, used as an antispasmodic drug.[18] The C−H bond functionalization of benzene **2a** with propargyl α-phenyl-α-diazoacetate **1a** in the presence of a catalytic amount of Sc$(OTf)_3$ (5 mol %) afforded the corresponding product **3aa**. This was further utilized for the synthesis of adiphenine **5** (via diphenylacetic acid **4aa**) in two steps in good yield (85%, Scheme 3).

After successfully demonstrating the practicability of the protocol, we further planned to understand the plausible reaction pathway.

To understand whether or not the C−H bond cleavage of benzene is a rate-determining step in this reaction, we carried out kinetic isotope effect studies. The studies indicated that cleavage of the C−H bond of benzene was not a rate-determining step (K_H/K_D = 1, see Scheme 4A). Furthermore, to confirm whether or not the direct [1,2]-H shift from benzene takes place in this transformation, we carried out another controlled experiment (see Scheme 4B). This result indicated that 48% of direct [1,2]-D shift from the deuterated

https://doi.org/10.1021/acs.joc.2c01185
J. Org. Chem. 2022, 87, 13583−13597

Scheme 4. Studies of the Kinetic Isotopic Effect



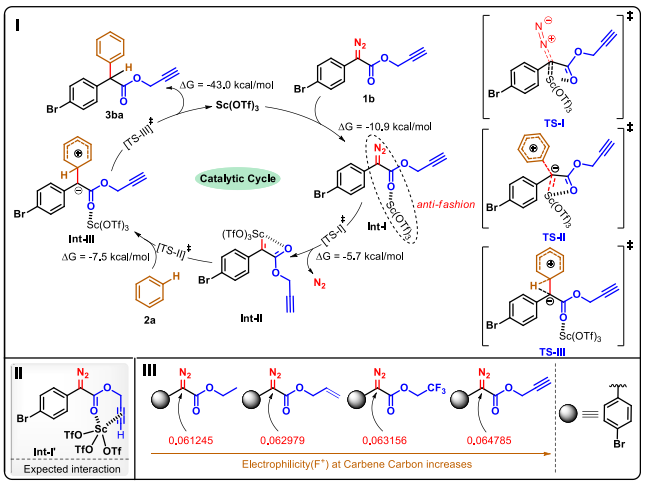


Figure 2. (I) Possible mechanism for the C−H bond functionalization of benzene under scandium catalysis; (II) expected alkyne—scandium interaction; (III) electrophilicity measurement employing Fukui function indices.

benzene occurred in this transformation. Later the controlled experiment in D_2O (5 equiv) indicated that there was no direct proton exchange of **3ba** with D_2O under the optimized reaction conditions (see Scheme 4C). Interestingly, we observed the 90% deuterium incorporation in product **3ba,** when the reaction of **1a** and **2a** was carried out in presence of excess D_2O (10 equiv) in DCE (see Scheme 4D). This result strongly indicated that moisture in the solvent can also be the possible source of proton in desired transformation.

To gain further insight into the mechanism, computational calculations have been performed in detail using density functional theory (DFT) at the PBE/TZVP level of theory. We also calculated the Fukui function indices to investigate the electrophilicity of the carbon wherein the diazo moiety (carbene precursor) is attached. The turnover frequency (TOF) has also been calculated to compare the activity for different groups associated with the ester carbon of α-aryl-α-diazoacetates. Based on the experimental results, quantum chemical calculations, and previous literature reports,[19] the plausible catalytic cycle has been depicted in Figure 2.

At first, the Hirshfeld population of carbene carbon of different alkyl α-(4-bromophenyl)-α-diazoacetates has been calculated to get an insight into the electrophilicity of diazoacetates. Based on the Fukui function indices, the diazo carbon of propargyl α-(4-bromophenyl)-α-diazoacetate was found to be the most electrophilic (F^+ = 0.064785, see Figure 2III). As this preliminary result supported our hypothesis of electron-withdrawing nature of the propargyl group, we further sought to optimize the interaction of propargyl α-(4-bromophenyl)-α-diazoacetate **1b** with $Sc(OTf)_3$ to investigate the most stable conformation. We optimized different interactions of $Sc(OTf)_3$ with ester oxygen(s) of propargyl α-(4-bromophenyl)-α-diazoacetate as the scandium ion is highly oxophilic (see ESI, Appendix-IV, Figure 1). We have also looked into all possible modes of interactions of $Sc(OTf)_3$ with the propargyl ester moiety.[20] It is proposed that propargyl α-(4-bromophenyl)-α-diazoacetate **1b** interacts with scandium triflate to form an intermediate **Int-I** (scandium triflate-coordinated complex) in an energetically favorable antifashion (ΔG = −10.9 kcal/mol) as shown in Figure 2(I,IV). Furthermore, the intermediate **Int-I** forms the intermediate **Int-II** (scandium-carbene complex) via the transition state **TS-I** wherein the $Sc(OTf)_3$ catalyst approaches and interacts with the diazo carbon of the propargyl α-(4-bromophenyl)-α-diazoacetate, and simultaneously bond formation by $Sc(OTf)_3$ and bond breaking of the diazo group take place (as dinitrogen moiety) with a free energy (**TS-I**) of 18.5 kcal/mol. This intermediate **Int-II** further reacts with benzene at an elevated temperature (80 °C) to furnish an energetically feasible (ΔG = −7.5 kcal/mol) zwitterionic intermediate **Int-III** via considerably low-barrier transition state **TS-II** (ΔG = 2.5 kcal/mol). The intermediate **Int-III** finally affords the highly stable product **3ba** (ΔG = −43.0 kcal/mol) via the transition state **TS-III** (ΔG = 18.0 kcal/mol) by the abstraction of protons and regenerating the catalyst. Alternatively, we also looked into the possibility of direct interaction of benzene with the **Int-I** (scandium triflate coordinated complex) to form the desired product **3ba** without the involvement of any scandium-carbene complex intermediate. Based on the calculations, it was found to be less feasible, and the pathway seems to be unfavorable as the energy barrier was relatively very high (ΔG = 33.4 kcal/mol, see ESI, Appendix-IV).

To correlate the experimental observations, we further explored the thermodynamics and kinetics calculations for the α-diazoacetates containing different ester moieties (see ESI, Appendix-IV). These computational results are in accordance with the experimental results wherein we observed that propargyl α-(4-bromophenyl)-α-diazoacetate **1b** reacted smoothly by affording the desired product **3ba** in higher yield than that of 2,2,2-trifluorethyl α-(4-bromophenyl)-α-diazoacetate as well as other α-diazoacetates containing an ethyl or allyl moiety as a part of ester group (see Table 1, entries 9−11, 14, Appendix-III and computational data for the comparison, ESI, Appendix-IV). The TOF has also been calculated and compared for all the energy profiles associated with the different groups (see ESI, Appendix-IV). All these

https://doi.org/10.1021/acs.joc.2c01185
J. Org. Chem. 2022, 87, 13583−13597

results are in accordance with the experimental observations. The TOF calculations suggest that the reaction of propargyl α-aryl-α-diazoacetates with $Sc(OTf)_3$ would give the product with highest efficiency. This indicated that the propargyl group plays a significant role in α-diazoacetate for the effective C−H functionalization of arenes.

CONCLUSIONS

In conclusion, we have developed novel scandium-catalyzed highly chemo- and regio-selective C−H bond functionalization of unactivated arenes and mildly deactivated arenes with propargyl α-aryl-α-diazoacetates as new reagents. Relatively low reactive benzene and mildly deactivated arenes reacted smoothly with propargyl α-aryl-α-diazoacetates containing electron-donating and mildly deactivating groups. The combination of catalyst-$Sc(OTf)_3$ and reagent-propargyl α-aryl-α-diazoacetate worked synergistically, and this was further evident from the computational studies. The practicability of this protocol has been demonstrated on a gram scale for the reproducibility. This methodology has been successfully applied for the gram-scale synthesis of biologically active adiphenine, an antispasmodic drug.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reactions were carried out with distilled and dried solvents using oven-dried glassware. All the reagents were purchased from commercial sources and used as received unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} precoated aluminum-backed plates (2.5 mm) with detection by UV light. ^1H NMR and $^{13}C\{^1H\}$ NMR spectra were recorded in $CDCl_3$ and DMSO-d_6. Chemical shifts in ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard or from the residual solvent peak as the internal standard, and *J* values are given in Hz. $^{13}C\{H\}$ NMR spectra are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-d and DMSO-d_6. $^{13}C\{^1H\}$ NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by high-resolution mass spectrometry (HRMS) using ESI TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as neat and reported in cm^{-1}. Melting points were measured in an open glass capillary, and values are uncorrected. Single-crystal X-ray data were collected on a Bruker SMART APEX four-circle diffractometer equipped with a CMOS photon 100 detector (Bruker Systems Inc.) and Microfocus (IμS) using Mo Kα radiation (0.71073 Å).

General Procedure for the Synthesis of Propargyl Esters (6a−6j). The compounds were synthesized following the previously reported procedure.[12a] To the stirred solution of 2-phenylacetic acid **4a** (2.72 g, 20 mmol) in DMF (15 mL) were added propargyl bromide solution 80% in toluene (3.57 g, 24 mmol) and K_2CO_3 (5.53 g, 40 mmol). The reaction mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC. The reaction mixture was filtered through celite, and the filtrate was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with cold water and brine solution. The extract was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under vacuum, and the crude product was purified using column chromatography over silica gel to afford product **6a** as a colorless liquid (3.34 g, 96% yield).

*Prop-2-yn-1-yl 2-Phenylacetate (**6a**).* Pale yellow liquid (3.34 g, 96% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3288, 2946, 2128, 1737, 1605, 1496, 1446, 1333, 1239, 1136, 999, 938, 760, 697; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42−7.19 (m, 5H), 4.69 (d, *J* = 2.5 Hz, 2H), 3.68 (s, 2H), 2.47 (t, *J* = 2.5 Hz, 1H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 170.9, 133.5, 129.4, 128.8, 127.4, 77.6, 75.2, 52.5, 41.1; HRMS (ESI TOF): calculated for $C_{11}H_{10}NaO_2$ $(M + Na)^+$: 197.0578, found: 197.0576.

*Prop-2-yn-1-yl 2-(4-Bromophenyl)acetate (**6b**).* White solid (4.657 g, 92% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); m.p.: 41−43 °C; IR (neat) cm^{-1}: 3288, 3032, 2946, 2128, 1737, 1605, 1239, 1136, 831, 760, 697, 639; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 4.70 (d, *J* = 2.5 Hz, 2H), 3.63 (s, 2H), 2.48 (t, *J* = 2.5 Hz, 1H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 170.4, 131.9, 131.2, 129.7, 121.5, 77.4, 75.3, 52.6, 40.4; HRMS (ESI TOF): Calculated for $C_{11}H_{10}BrO_2$ $(M + H)^{+:}$ 252.9864, found: 252.9871.

*Prop-2-yn-1-yl 2-(4-Chlorophenyl)acetate (**6c**).* Viscous liquid (3.964 g, 95% yield): R_f = 0.3 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3293, 2948, 2129, 1738, 1597, 1492, 1371, 1143, 1091, 938, 807, 758, 676, 641; ^1H NMR (400 MHz, DMSO-d_6): δ 7.41−7.36 (m, 2H), 7.33−7.27 (m, 2H), 4.72 (d, *J* = 2.5 Hz, 2H), 3.75 (s, 2H), 3.55 (t, *J* = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 170.1, 133.0, 131.6, 131.2, 128.2, 78.2, 77.7, 52.1, 39.0; HRMS (ESI TOF): calculated for $C_{11}H_{10}ClO_2$ $(M + H)^+$: 209.0369, found: 209.0365.

*Prop-2-yn-1-yl 2-(4-Fluorophenyl)acetate (**6d**).* Colorless liquid (3.611 g, 94% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3295, 2948, 2129, 1739, 1606, 1510, 1222, 1140, 937, 826, 785, 681, 643; ^1H NMR (400 MHz, DMSO-d_6): δ 7.38−7.28 (m, 2H), 7.20−7.11 (m, 2H), 4.71 (d, *J* = 2.5 Hz, 2H), 3.73 (s, 2H), 3.54 (t, *J* = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 170.3, 161.2 (d, *J* = 242.8 Hz), 131.3 (d, *J* = 8.1 Hz), 130.1 (d, *J* = 3.1 Hz), 115.0 (d, *J* = 21.3 Hz), 78.3, 77.7, 52.0, 38.8; HRMS (ESI TOF): calculated for $C_{11}H_9FNaO_2$ $(M + Na)^+$: 215.0484, found: 215.0490.

*Prop-2-yn-1-yl 2-(3,4-Dichlorophenyl)acetate (**6e**).* Colorless liquid (4.473 g, 92% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3295, 2948, 2130, 1738, 1133, 1026, 998, 877, 820, 781, 743, 637; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44−7.35 (m, 2H), 7.13 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.71 (d, *J* = 2.5 Hz, 2H), 3.63 (s, 2H), 2.50 (t, *J* = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.6, 133.5, 130.9, 129.8, 125.7, 125.4, 122.8, 77.4, 75.6, 52.6; HRMS (ESI TOF): calculated for $C_{11}H_9Cl_2O_2$ $(M + H)^+$: 242.9979, found: 242.9984.

*Prop-2-yn-1-yl 2-(3,5-Difluorophenyl)acetate (**6f**).* Colorless liquid (3.909 g, 93% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3299, 3094, 2951, 2130, 1741, 1626, 1306, 1120, 994, 936, 850, 787, 667, 642; ^1H NMR (400 MHz, $CDCl_3$): δ 6.91−6.79 (m, 2H), 6.75 (m, 1H), 4.72 (d, *J* = 2.5 Hz, 2H), 3.65 (s, 2H), 2.50 (t, *J* = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.7, 163.1 (dd, *J* = 248.7, 12.9 Hz), 136.9 (t, *J* = 9.8 Hz), 113.5−111.6 (m), 103.1 (t, *J* = 25.2 Hz), 77.3, 75.4, 52.8, 40.6 (t, *J* = 2.0 Hz); HRMS (ESI TOF): calculated for $C_{11}H_9FNaO_2$ $(M + Na)^+$: 233.0389, found: 233.0392.

*Prop-2-yn-1-yl 2-(Naphthalen-2-yl)acetate (**6g**).* White solid (4.261 g, 95% yield): R_f = 0.3 petroleum ether/EtOAc (95:5); m.p.: 50−51 °C; IR (neat) cm^{-1}: 3288, 3055, 2311, 2129, 1736, 1509, 1325, 1135, 946, 900, 857, 748, 679, 636; ^1H NMR (400 MHz, $CDCl_3$): δ 7.82−7.78 (m, 3H), 7.74 (s, 1H), 7.54−7.29 (m, 3H), 4.71 (d, *J* = 2.5 Hz, 2H), 3.83 (s, 2H), 2.47 (t, *J* = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.8, 133.6, 132.7, 131.0, 128.5, 128.2, 127.83, 127.80, 127.4, 126.3, 126.0, 77.7, 75.2, 52.5, 41.3; HRMS (ESI TOF): calculated for $C_{13}H_{13}O_2$ $(M + H)^+$: 225.0915, found: 225.0908.

*Prop-2-yn-1-yl 2-(p-Tolyl)acetate (**6h**).* Pale yellow liquid (3.539 g, 94% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3288, 2945, 2129, 1740, 1515, 1241, 1141, 1005, 938, 808, 774, 682, 644; ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 4.68 (d, *J* = 2.5 Hz, 2H), 3.63 (s, 2H), 2.47 (t, *J* = 2.5 Hz, 1H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.0, 137.0, 130.5, 129.4, 129.3, 77.7, 75.1, 52.4, 40.7, 21.2; HRMS (ESI TOF): calculated for $C_{12}H_{13}O_2$ $(M + H)^+$: 189.0915, found: 189.0912.

*Prop-2-yn-1-yl 2-(4-Methoxyphenyl)acetate (**6i**).* Colorless liquid (3.88 g, 95% yield): R_f = 0.5 petroleum ether/EtOAc (80:20); IR

https://doi.org/10.1021/acs.joc.2c01185
J. Org. Chem. 2022, 87, 13583−13597

(neat) cm^{-1}: 3285, 2948, 2128, 1736, 1511, 1242, 1138, 1025, 938, 819, 780, 682, 643; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23−7.17 (m, 2H), 6.89−6.83 (m, 2H), 4.68 (d, J = 2.5 Hz, 2H), 3.79 (s, 3H), 3.61 (s, 2H), 2.47 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.1, 159.0, 130.4, 125.6, 114.2, 77.7, 75.1, 55.4, 52.4, 40.2; HRMS (ESI TOF): calculated for $C_{12}H_{12}NaO_3$ $(M + Na)^+$: 227.0683, found: 227.0685.

*Prop-2-yn-1-yl 2-(3,5-Dimethoxyphenyl)acetate (**6j**).* Colorless liquid (4.263 g, 91% yield): R_f = 0.25 petroleum ether/EtOAc (90:10); IR (neat) cm^{-1}: 3282, 2946, 2127, 1739, 1597, 1201, 1142, 1061, 941, 835, 782, 683, 651; ^1H NMR (400 MHz, $CDCl_3$): δ 6.44 (d, J = 2.2 Hz, 2H), 6.37 (t, J = 2.2 Hz, 1H), 4.69 (d, J = 2.5 Hz, 2H), 3.77 (s, 6H), 3.60 (s, 2H), 2.48 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.6, 161.0, 135.5, 107.4, 99.5, 77.6, 75.1, 55.4, 52.4, 41.3; HRMS (ESI TOF): calculated for $C_{13}H_{15}O_4$ $(M + H)^+$: 235.0970, found: 235.0971.

General Procedure for the Synthesis of α-Aryl-α-diazoacetates (1a−1j). The compounds were synthesized following the previously reported procedure.[12a] To the stirred solution propargyl 2-phenylacetate **6a** (1.74 g, 10 mmol) in 15 mL, acetonitrile was added to 4-acetamidobenzenesulfonyl azide (2.88 g, 12 mmol) and DBU (2.24 mL, 15 mmol) at ambient temperature under an inert atmosphere. The reaction mixture was stirred for 16 h at room temperature. The reaction was quenched with saturated NH_4Cl, and the product was extracted with diethyl ether (30 mL × 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The extract was filtered, and the filtrate was evaporated under vacuum. The crude product was purified using column chromatography over silica gel to afford α-aryl-α-diazoacetates **1a** as an orange solid (1.934 g, 84% yield).

*Prop-2-yn-1-yl 2-Diazo-2-phenylacetate (**1a**).* Orange solid (1.521 g, 76% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); m.p.: 41−43 °C; IR (neat) cm^{-1}: 3295, 3062, 2948, 2085, 1696, 1597, 1497, 1240, 1143, 1017, 950, 752, 682, 637; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50−7.46 (m, 2H), 7.44−7.36 (m, 2H), 7.24−7.15 (m, 1H), 4.88 (d, J = 2.5 Hz, 2H), 2.52 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 129.1, 126.2, 125.1, 124.1, 77.7, 75.3, 52.3; HRMS (ESI TOF): calculated for $C_{11}H_8N_2NaO_2$ $(M + Na)^+$: 223.0483, found: 223.0478.

*Ethyl 2-Diazo-2-phenylacetate (**1a′**).* Orange liquid (1.522 g, 80% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 2984, 2081, 1696, 1597, 1496, 1387, 1286, 1156, 1094, 979, 823, 688; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51−7.45 (m, 2H), 7.41−7.35 (m, 2H), 7.20−7.15 (m, 1H), 4.33 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.4, 129.0, 125.9, 125.8, 124.1, 61.1, 14.6; HRMS (ESI TOF): calculated for $C_{10}H_{10}N_2NaO_2$ $(M + Na)^+$: 213.0639, found: 213.0631.

*Allyl 2-Diazo-2-phenylacetate (**1a″**).* Orange liquid (1.516 g, 75% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3028, 2952, 2085, 1700, 1598, 1497, 1242, 1151, 1043, 1012, 929, 753, 694; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50−7.47 (m, 2H), 7.41−7.34 (m, 2H), 7.21−7.15 (m, 1H), 5.98 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 5.36 (dq, J = 17.2, 1.5 Hz, 1H), 5.27 (ddd, J = 10.4, 2.6, 1.3 Hz, 1H), 4.84−4.70 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.9, 132.3, 129.1, 126.0, 125.6, 124.2, 118.5, 65.6; HRMS (ESI TOF): calculated for $C_{11}H_{10}N_2O_2$ $(M)^+$: 202.0742, found: 202.0760.

*2,2,2-Trifluoroethyl 2-Diazo-2-phenylacetate (**1a‴**).* Orange solid (1.48 g, 76% yield): R_f = 0.55 petroleum ether/EtOAc (95:5); m.p.: 55−57 °C; IR (neat) cm^{-1}: 3067, 2985, 2099, 1719, 1502, 1413, 1355, 1288, 1245, 1170, 1078, 972, 758, 692, 570; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.50−7.39 (m, 4H), 7.26−7.21 (m, 1H), 4.66 (q, J = 8.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 163.3, 129.2, 126.5, 124.6, 124.2, 123.1 (q, J = 277.5 Hz), 63.6, 60.4 (q, J = 36.9 Hz). ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) −73.9. HRMS (ESI TOF): calculated for $C_{10}H_7F_3N_2NaO_2$ $(M + Na)^+$: 267.0357, found: 267.0362.

*Prop-2-yn-1-yl 2-(4-Bromophenyl)-2-diazoacetate (**1b**).* Orange solid (2.261 g, 81% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); m.p.: 57−59 °C; IR (neat) cm^{-1}: 3294, 2948, 2085, 1695, 1488, 1336, 1236, 1144, 1030, 999, 948, 813, 678, 632; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54−7.47 (m, 2H), 7.38−7.33 (m, 2H), 4.87 (d, J = 2.3 Hz, 2H), 2.52 (t, J = 2.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.0, 132.2, 125.5, 124.4, 119.7, 77.6, 75.5, 52.5; HRMS (ESI TOF): calculated for $C_{11}H_7BrN_2NaO_2$ $(M + Na)^+$: 300.9584, found: 300.9574.

*Prop-2-yn-1-yl 2-(4-Chlorophenyl)-2-diazoacetate (**1c**).* Orange solid (1.736 g, 74% yield). R_f = 0.35 petroleum ether/EtOAc (95:5); m.p.: 61−63 °C; IR (neat) cm^{-1}: 3295, 2949, 2086, 1697, 1492, 1336, 1276, 1237, 1146, 1093, 1005, 820, 734, 680, 637; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45−7.39 (m, 2H), 7.38−7.33 (m, 2H), 4.87 (d, J = 2.5 Hz, 2H), 2.52 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.1, 131.9, 129.3, 125.3, 123.8, 77.6, 75.4, 52.5; HRMS (ESI TOF): calculated for $C_{11}H_7ClN_2NaO_2$ $(M + Na)^+$: 257.0097, found: 257.0098.

*Prop-2-yn-1-yl 2-Diazo-2-(4-fluorophenyl)acetate (**1d**).* Yellow solid (1.833 g, 84% yield). R_f = 0.3 petroleum ether/EtOAc (95:5); m.p.: 62−64 °C; IR (neat) cm^{-1}: 3298, 2950, 2086, 1696, 1508, 1339, 1286, 1233, 1145, 1033, 829, 683, 642; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51−7.38 (m, 2H), 7.17−7.02 (m, 2H), 4.87 (d, J = 2.5 Hz, 2H), 2.52 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.4, 161.3 (d, J = 246.7 Hz), 126.1 (d, J = 8.0 Hz), 120.9 (d, J = 3.2 Hz), 116.2 (d, J = 22.0 Hz), 77.7, 75.4, 52.4; HRMS (ESI TOF): calculated for $C_{11}H_7FN_2NaO_2$ $(M + Na)^+$: 241.0389, found: 241.0384.

*Prop-2-yn-1-yl 2-Diazo-2-(3,4-dichlorophenyl)acetate (**1e**).* Orange solid (2.206 g, 82% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); m.p.: 52−54 °C; IR (neat) cm^{-1}: 3297, 2950, 2090, 1698, 1589,1475, 1274, 1149, 1039, 956, 884, 815, 736, 680, 640; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 2.3 Hz, 1H), 7.44 (d, J = 8.6 Hz, 1H), 7.28 (dd, J = 8.6, 2.4 Hz, 1H), 4.87 (d, J = 2.6 Hz, 2H), 2.53 (t, J = 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.6, 133.5, 130.9, 129.8, 125.7, 125.4, 122.8, 77.4, 75.6, 52.6; HRMS (ESI TOF): calculated for $C_{11}H_6Cl_2N_2NaO_2$ $(M + Na)^+$: 290.9703, found: 290.9701.

*Prop-2-yn-1-yl 2-Diazo-2-(3,5-difluorophenyl)acetate (**1f**).* Orange solid (1.842 g, 78% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); m.p.: 36−38 °C; IR (neat) cm^{-1}: 3301, 3099, 2953, 2094, 1704, 1623, 1589, 1479, 1445, 1269, 1124, 1067, 987, 926, 839, 741, 669, 641; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26−6.82 (m, 2H), 6.65−6.59 (m, 1H), 4.88 (d, J = 2.5 Hz, 2H), 2.54 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.5 (dd, J = 247.8, 13.7 Hz), 163.3, 129.2 (t, J = 11.5 Hz), 106.7−106.2 (m), 101.2 (t, J = 25.5 Hz), 77.3, 75.6, 52.6; HRMS (ESI TOF): calculated for $C_{11}H_6F_2N_2NaO_2$ $(M + Na)^+$: 259.0290, found: 259.0281.

*Prop-2-yn-1-yl 2-Diazo-2-(naphthalen-2-yl)acetate (**1g**).* Pale orange solid (1.927 g, 77% yield). R_f = 0.35 petroleum ether/EtOAc (95:5); m.p.: 82−84 °C; IR (neat) cm^{-1}: 3291, 3057, 2947, 2083, 1698, 1323, 1248, 1147, 1121, 1038, 895, 852, 812, 736, 680, 639; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 1.7 Hz, 1H), 7.92−7.69 (m, 3H), 7.58−7.37 (m, 3H), 4.91 (d, J = 2.5 Hz, 2H), 2.53 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.5, 133.7, 131.7, 128.9, 127.8, 127.8, 126.8, 126.0, 122.8, 122.3, 121.9, 77.7, 75.4, 52.4; HRMS (ESI TOF): calculated for $C_{15}H_{10}N_2NaO_2$ $(M + Na)^+$: 273.0639, found: 273.0642.

*Prop-2-yn-1-yl 2-Diazo-2-(p-tolyl)acetate (**1h**).* Orange solid (1.392 g, 65% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); m.p.: 52−54 °C; IR (neat) cm^{-1}: 3293, 2947, 2084, 1699, 1567, 1514, 1242, 1154, 1037, 949, 811, 771, 735, 680, 640; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 4.86 (d, J = 2.5 Hz, 2H), 2.51 (t, J = 2.5 Hz, 1H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.7, 136.1, 129.9, 124.3, 121.8, 77.8, 75.2, 52.3, 21.1; HRMS (ESI TOF): calculated for $C_{12}H_{10}N_2NaO_2$ $(M + Na)^+$: 237.0639, found: 237.0635.

*Prop-2-yn-1-yl 2-Diazo-2-(4-methoxyphenyl)acetate (**1i**).* Dark orange solid (1.934 g, 84% yield): R_f = 0.3 petroleum ether/EtOAc (95:5); m.p.: 68−69 °C; IR (neat) cm^{-1}: 3289, 2949, 2837, 2081, 1694, 1609, 1573, 1510, 1240, 1142, 1022, 949, 825, 735, 680, 640; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48−7.30 (m, 2H), 7.09−6.81 (m, 2H), 4.86 (d, J = 2.4 Hz, 2H), 3.81 (s, 3H), 2.51 (t, J = 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.0, 158.3, 126.2, 116.5,

https://doi.org/10.1021/acs.joc.2c01185
J. Org. Chem. 2022, 87, 13583−13597

114.8, 77.8, 75.2, 55.5, 52.3; HRMS (ESI TOF): calculated for $C_{12}H_{10}N_2NaO_3$ $(M + Na)^+$: 253.0588, found: 253.0584.

*Prop-2-yn-1-yl 2-Diazo-2-(3,5-dimethoxyphenyl)acetate (**1j**).* Yellow solid (1.822 g, 70% yield): R_f = 0.25 petroleum ether/EtOAc (95:5); m.p.: 91−93 °C; IR (neat) cm^{-1}: 3254, 2946, 2839, 2075, 1703, 1594, 1454, 1383, 1324, 1272, 1154, 1035, 954, 926, 830, 736, 672; ^1H NMR (400 MHz, $CDCl_3$): δ 6.67 (d, J = 2.2 Hz, 2H), 6.30 (t, J = 2.2 Hz, 1H), 4.86 (d, J = 2.5 Hz, 2H), 3.80 (s, 6H), 2.52 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.2, 161.3, 127.3, 102.1, 98.4, 77.7, 75.3, 55.5, 52.3; HRMS (ESI TOF): calculated for $C_{13}H_{13}N_2O_4$ $(M + H)^+$: 261.0875, found: 261.0868.

General Procedure for Optimization of Reaction Conditions. A mixture of 5 mol % of catalyst and 1.5 mL of benzene **2a** was stirred at room temperature in a dried 25 mL two-necked RB flask under an inert atmosphere for 5 min. Then α-aryl-α-diazoacetate **1** (0.5 mmol) in 1 mL of benzene was added to the above reaction mixture dropwise over 5 min, and then the reaction mixture was stirred at room temperature or refluxed at 80 °C over 4−12 h in an oil bath. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the product **3**.

General Procedure for Screening of Solvents. In a dried 25 mL RB flask, $Sc(OTf)_3$ (2.5−5 mol %), propargyl α-phenyl-α-diazoacetate **1a** (0.1 g, 0.5 mmol), and benzene **2a** (0.45 mL, 5 mmol) were added into 2.5 mL of solvent at room temperature under an inert atmosphere. Then the reaction mixture was refluxed at 72−80 °C over 4−12 h in an oil bath. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product **3aa** (see ESI, Appendix-I).

General Procedure for Screening of the Cocatalyst. In a dried 25 mL RB flask, $Sc(OTf)_3$ (2.5−5 mol %), cocatalyst (0−5 mol %), propargyl α-phenyl-α-diazoacetate **1a** (0.1 g, 0.5 mmol), and benzene **2a** (0.45 mL, 5 mmol) were added into 2.5 mL of DCE at room temperature under an inert atmosphere. Then the reaction mixture was refluxed at 80 °C over 2−12 h in an oil bath. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product **3aa** (see ESI, Appendix-II).

General Procedure for the Synthesis of α-Diarylacetates (3). In a dried 25 mL RB flask, $Sc(OTf)_3$ (12.3 mg, 5 mol %), propargyl α-phenyl-α-diazoacetate **1a** (0.1 g, 0.5 mmol), and benzene **2a** (0.45 mL, 5 mmol) were added into 2.5 mL of DCE at room temperature under an inert atmosphere. Then the reaction mixture was refluxed at 80 °C over 4 h in an oil bath. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product **3aa** (0.09 g, 72% yield).

*Prop-2-yn-1-yl 2,2-Diphenylacetate (**3aa**).* White solid (0.09 g, 72% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); m.p.: 46−48 °C; crystal growth process: In a 10 mL round bottom flask, 30 mg of compound was dissolved in 1 mL of chloroform, and the mixture was diluted with 2 mL of hexane. Then the mixture was kept open for 24 h without further disturbance. IR (neat) cm^{-1}: 3289, 3031, 2941, 2126, 1739, 1598, 1494, 1448, 1370, 1220, 1181, 1080, 997, 739, 694, 638, 564; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49−7.12 (m, 10H), 5.07 (s, 1H), 4.74 (d, J = 2.5 Hz, 2H), 2.46 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.8, 138.3, 128.8, 128.7, 127.5, 77.4, 75.3, 56.8, 52.7; HRMS (ESI TOF): calculated for $C_{17}H_{14}NaO_2$ $(M + Na)^+$: 273.0891, found: 273.0899.

*Ethyl 2,2-Diphenylacetate (**3a′a**).* Colorless liquid (0.037 g, 31% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3029, 2984, 1730, 1598, 1493, 1452, 1148, 1093, 1025, 961, 697, 633, 561; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.29 (m, 8H), 7.28−7.22 (m, 2H), 5.01 (s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.6, 138.9, 128.7, 128.7, 127.3, 61.3, 57.3, 14.3; HRMS (ESI TOF): calculated for $C_{16}H_{16}NaO_2$ $(M + Na)^+$: 263.1043, found: 263.1042.

*Allyl 2,2-Diphenylacetate (**3a″a**).* Colorless liquid (0.042 g, 33% yield): R_f = 0.6 petroleum ether/EtOAc (95:5); IR(neat) cm^{-1}: 3029, 2942, 2109, 1734, 1648, 1494, 1450, 1184, 1145, 1083, 989, 931, 740, 700, 624, 559; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.17 (m, 10H), 5.89 (ddt, J = 15.4, 10.4, 5.7 Hz, 1H), 5.22 (ddq, J = 15.4, 10.4, 1.4 Hz, 1H), 5.05 (s, 1H), 4.65 (dt, J = 5.7, 1.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.3, 138.8, 132.0, 128.8, 128.7, 127.4, 118.6, 65.9, 57.2; HRMS (ESI TOF): calculated for $C_{17}H_{16}NaO_2$ $(M + Na)^+$: 275.1047, found: 275.1044.

*2,2,2-Trifluoroethyl 2,2-Diphenylacetate (**3a‴a**).* Colorless liquid (0.076 g, 52% yield): R_f = 0.6 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3032, 2945, 1758, 1497, 1451, 1408, 1282, 1170, 1137, 1047, 976, 845, 741, 702, 646, 561. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36−7.24 (m, 10H), 5.12 (s, 1H), 4.51 (q, J = 8.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 171.2, 137.8, 128.9, 128.6, 127.7, 122.9 (q, J = 277.4 Hz), 60.8 (q, J = 36.7 Hz), 56.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) −73.6. HRMS (ESI TOF): calculated for $C_{16}H_{14}F_3O_2$ $(M + H)^+$: 295.0946, found: 295.0941.

*Prop-2-yn-1-yl 2-(4-Bromophenyl)-2-phenylacetate (**3ba**).* White solid (0.122 g, 74% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); m.p.: 104−106 °C; IR (neat) cm^{-1}: 3292, 3032, 2940, 2126, 1739, 1597, 1488, 1271, 1368, 1139, 1002, 810, 746, 694, 639, 579; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48−7.43 (m, 2H), 7.36−7.25 (m, 5H), 7.22−7.17 (m, 2H), 5.02 (s, 1H), 4.85−4.62 (m, 2H), 2.48 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.4, 137.8, 137.3, 131.9, 130.5, 128.9, 128.6, 127.8, 121.7, 77.3, 75.5, 56.2, 52.9; HRMS (ESI TOF): calculated for $C_{17}H_{14}$ $^{81}BrO_2$ $(M + H)^+$: 331.0151, found: 331.0144.

*Ethyl 2-(4-Bromophenyl)-2-phenylacetate (**3b′a**).* White solid (0.051 g, 32% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); m.p.: 63−65 °C; IR (neat) cm^{-1}: 3029, 2979, 1738, 1601, 1492, 1445, 1162, 1097, 1020, 964, 697, 637, 569; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46−7.42 (m, 2H), 7.35−7.26 (m, 5H), 7.22−7.17 (m, 2H), 4.95 (s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.2, 138.4, 137.9, 131.8, 130.5, 128.8, 128.6, 127.6, 121.5, 61.5, 56.6, 14.3. HRMS (ESI TOF): calculated for $C_{16}H_{16}$ $^{81}BrO_2$ $(M + H)^+$: 321.0313, found: 321.0299.

*Allyl 2-(4-Bromophenyl)-2-phenylacetate (**3b″a**).* Colorless liquid (0.060 g, 36% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3029, 2949, 2129, 1738, 1644, 1489, 1448, 1184, 1144, 1083, 984, 936, 744, 702, 629, 550; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47−7.42 (m, 2H), 7.36−7.25 (m, 6H), 7.22−7.18 (m, 2H), 5.94−5.83 (m, 1H), 5.28−5.19 (m, 2H), 5.00 (s, 1H), 4.65 (dt, J = 5.8, 1.3 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.9, 138.2, 137.8, 131.8, 130.5, 128.9, 128.6, 127.7, 121.5, 118.9, 66.1, 56.6. HRMS (ESI TOF): calculated for $C_{17}H_{16}$ $^{79}BrO_2$ $(M + H)^+$: 331.0334, found: 331.0327.

*2,2,2-Trifluoroethyl 2-(4-Bromophenyl)-2-phenylacetate (**3b‴a**).* Colorless liquid (0.098 g, 53% yield): R_f = 0.55 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3032, 2949, 1760, 1498, 1454, 1402, 1279, 1164, 1132, 1048, 972, 847, 742, 700, 649, 559; ^1H NMR (400 MHz, $CDCl_3$):δ 7.49−7.44 (m, 2H), 7.38−7.26 (m, 5H), 7.21−7.16 (m, 2H), 5.07 (s, 1H), 4.53 (qd, J = 8.4, 2.5 Hz, 2H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.8, 137.2, 136.8, 132.0, 130.4, 129.0, 128.5, 128.0, 122.9 (d, J = 277.4 Hz), 121.9, 60.9 (q, J = 36.8 Hz), 56.0. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) −73.6. HRMS (ESI TOF): calculated for $C_{16}H_{13}$ $^{79}BrF_3O_2$ $(M + H)^+$: 373.0051, found: 373.0063.

*Prop-2-yn-1-yl 2-(4-Chlorophenyl)-2-phenylacetate (**3ca**).* White solid (0.114 g, 80% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); m.p.: 83−85 °C; IR (neat) cm^{-1}: 3293, 3033, 2127, 1739, 1598, 1490, 1272, 1222, 1138, 1001, 813, 751, 691, 636, 550; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.24 (m, 9H), 5.03 (s, 1H), 4.79−4.69 (m, 2H), 2.47 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 171.0, 138.4, 137.7, 132.0, 130.4, 128.7, 128.5, 128.3, 127.3, 78.1 (for 2-C), 54.5, 52.6; HRMS (ESI TOF): calculated for $C_{17}H_{13}ClNaO_2$ $(M + Na)^+$: 307.0501, found: 307.0505.

https://doi.org/10.1021/acs.joc.2c01185
J. Org. Chem. 2022, 87, 13583−13597

*Prop-2-yn-1-yl 2-(4-Fluorophenyl)-2-phenylacetate (**3da**).* White solid (0.094 g, 70% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); m.p.: 65−67 °C; IR (neat) cm^{-1}: 3293, 3064, 2130, 1739, 1604, 1506, 1448, 1370, 1276, 1182, 1137, 996, 809, 732, 692, 636; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.25 (m, 7H), 7.09−6.92 (m, 2H), 5.05 (s, 1H), 4.78−4.67 (m, 2H), 2.47 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.7, 162.2 (d, J = 246.3 Hz), 138.2, 134.1(d, J = 3.3 Hz), 130.4 (d, J = 8.1 Hz), 128.9, 128.6, 127.7, 115.6 (d, J = 21.5 Hz), 77.4, 75.4, 56.0, 52.8; HRMS (ESI TOF): calculated for $C_{17}H_{14}FO_2$ $(M + H)^+$: 269.0978, found: 269.0980.

*Prop-2-yn-1-yl 2-(3,4-Dichlorophenyl)-2-phenylacetate (**3ea**).* Colorless liquid (0.136 g, 85% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3295, 3071, 2948, 2124, 1743, 1596, 1470, 1269, 1145, 1028, 907, 772, 702; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 2.2 Hz, 1H), 7.41−7.26 (m, 6H), 7.16 (dd, J = 8.3, 2.2 Hz, 1H), 5.00 (s, 1H), 4.80−4.69 (m, 2H), 2.49 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.0, 138.4, 137.2, 132.8, 131.8, 130.7, 130.6, 129.1, 128.5, 128.2, 128.0, 75.6(for 2-C), 55.8, 53.0; HRMS (ESI TOF): calculated for $C_{17}H_{12}Cl_2NaO_2$ $(M + Na)^+$: 341.0107, found: 341.0099.

*Prop-2-yn-1-yl 2-(3,5-Difluorophenyl)-2-phenylacetate (**3fa**).* Colorless liquid (0.139 g, 97% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3297, 3091, 2130, 1742, 1623, 1597, 1495, 1450, 1302, 1219, 1146, 1119, 1026, 987, 848, 770, 697; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49−7.27 (m, 5H), 6.98−6.79 (m, 2H), 6.71 (tt, J = 8.8, 2.3 Hz, 1H), 5.01 (s, 1H), 4.92−4.48 (m, 2H), 2.49 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.8, 163.1 (dd, J = 248.8, 12.8 Hz), 142.0 (t, J = 9.2 Hz), 137.0, 129.1, 128.6, 128.1, 112.11−111.55 (m), 103.1 (t, J = 25.3 Hz), 77.4, 75.6, 56.2 (t, J = 1.9 Hz), 53.0; HRMS (ESI TOF): calculated for $C_{17}H_{13}F_2O_2$ $(M + H)^+$: 287.0883, found: 287.0888.

*Prop-2-yn-1-yl 2-Phenyl-2-(p-tolyl)acetate (**3ha**).* White solid (0.02 g, 15% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); m.p.: 88−90 °C; IR (neat) cm^{-1}: 3290, 3028, 2927, 2128, 1742, 1509, 1448, 1370, 1221, 1182, 1141, 999, 731, 695; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.24 (m, 5H), 7.20 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 5.03 (s, 1H), 4.73 (d, J = 2.5 Hz, 2H), 2.45 (t, J = 2.5 Hz, 1H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.0, 138.5, 137.2, 135.4, 129.5, 128.7, 128.66, 128.6, 127.4, 77.5, 75.3, 56.4, 52.7, 21.2; HRMS (ESI TOF): calculated for $C_{18}H_{16}NaO_2$ $(M + Na)^+$: 287.1047, found: 287.1040.

*Prop-2-yn-1-yl 2-(3,5-Dimethoxyphenyl)-2-phenylacetate (**3ja**).* Colorless liquid (0.026 g, 17% yield): R_f = 0.5 petroleum ether/EtOAc (80:20); IR (neat) cm^{-1}: 3284, 2936, 2841, 2128, 1740, 1595, 1460, 1298, 1201, 1143, 1062, 999, 938, 834, 761; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.22 (m, 5H), 6.48 (d, J = 2.2 Hz, 2H), 6.37 (t, J = 2.2 Hz, 1H), 4.99 (s, 1H), 4.74 (d, J = 2.5 Hz, 2H), 3.75 (s, 6H), 2.46 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.6, 161.0, 140.3, 138.0, 128.7, 128.7, 127.6, 107.0, 99.4, 77.5, 75.3, 56.9, 55.4, 52.7; HRMS (ESI TOF): calculated for $C_{19}H_{19}O_4$ $(M + H)^+$: 311.1283, found: 311.1287.

*Prop-2-yn-1-yl 2-(4-Fluorophenyl)-2-phenylacetate (**3ab**).* Major product *para*-isomer (*p*:*o* = 91:9), *p*:*o* ratio determined by ^1H NMR. The product was obtained as a viscous colorless liquid (0.054 g, 40% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3294, 3071, 2945, 2125, 1742, 1604, 1506, 1447, 1370, 1279, 1227, 1144, 1001, 816, 733, 695, 641, 560; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51−7.18 (m, 7H), 7.13−6.85 (m, 2H), 5.05 (s, 1H), 4.73 (dd, J = 2.4, 1.0 Hz, 2H), 2.46 (t, J = 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.7, 162.2 (d, J = 246.3 Hz), 138.1, 134.1 (d, J = 2.9 Hz), 130.4 (d, J = 8.0 Hz), 128.9, 128.5, 127.7, 115.6 (d, J = 21.3 Hz), 77.3, 75.4, 55.9, 52.8; HRMS (ESI TOF): calculated for $C_{17}H_{14}FO_2$ $(M + H)^+$: 269.0978, found: 269.0988.

*Prop-2-yn-1-yl 2-(4-Bromophenyl)-2-(4-fluorophenyl)acetate (**3bb**).* Major product *para*-isomer (*p*:*o* = 91:9), *p*:*o* ratio determined by ^1H NMR. The product was obtained as a semisolid (0.090 g, 52% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3295, 3060, 2130, 1741, 1603, 1504, 1438, 1369, 1273, 1227, 1144, 950, 822, 760, 683, 641; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50−7.41 (m, 2H), 7.30−7.22 (m, 2H), 7.21−7.13 (m, 2H), 7.07−6.94 (m, 2H), 4.99 (s, 1H), 4.74 (dd, J = 3.8, 2.5 Hz, 2H), 2.48 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.3, 162.3 (d, J = 246.9 Hz), 137.2, 133.6 (d, J = 3.3 Hz), 132.0, 130.3, 130.2, 121.8, 115.8 (d, J = 21.6 Hz), 77.2, 75.5, 55.4, 53.0; HRMS (ESI TOF): calculated for $C_{17}H_{13}BrFO_2$ $(M + H)^+$: 347.0083, found: 347.0092.

*Prop-2-yn-1-yl 2-(4-Chlorophenyl)-2-(4-fluorophenyl)acetate (**3cb**).* Major product *para*-isomer (*p*:*o* = 91:9), *p*:*o* ratio determined by ^1H NMR. The product was obtained as a colorless liquid (0.082 g, 54% yield). R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3297, 2947, 2130, 1741, 1602, 1439, 1270, 1227, 1143, 1093, 1005, 823, 762, 683, 641; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.16 (m, 6H), 7.15−6.90 (m, 2H), 5.01 (s, 1H), 4.73 (d, J = 2.5 Hz, 2H), 2.48 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.3, 163.0 (d, J = 246.8 Hz), 136.6, 133.7, 133.6 (d, J = 3.3 Hz), 130.3 (d, J = 8.1 Hz), 129.9, 129.0, 115.8 (d, J = 21.6 Hz), 77.2, 75.5, 55.3, 52.9; HRMS (ESI TOF): calculated for $C_{17}H_{13}ClFO_2$ $(M + H)^+$: 303.0588, found: 303.0595.

*Prop-2-yn-1-yl 2-(4-Bromophenyl)-2-(4-chlorophenyl)acetate (**3bc**).* Major product *para*-isomer (*p*:*o* = 90:10), *p*:*o* ratio determined by ^1H NMR. The product was obtained as a viscous colorless liquid (0.091 g, 50% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3294, 2946, 2130, 1740, 1591, 1488, 1369, 1301, 1183, 1142, 1088, 1006, 954, 807, 761, 681, 638; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50−7.43 (m, 2H), 7.34−7.14 (m, 6H), 4.98 (s, 1H), 4.74 (d, J = 2.5 Hz, 2H), 2.49 (t, J = 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.0, 136.8, 136.2, 133.8, 132.0, 130.3, 130.0, 129.1, 121.9, 77.4, 75.6, 55.5, 53.0; HRMS (ESI TOF): calculated for $C_{17}H_{13}BrClO_2$ $(M + H)^+$: 362.9787, found: 362.9785.

*Prop-2-yn-1-yl 2,2-Bis(4-chlorophenyl)acetate (**3cc**).* Major product *para*-isomer (*p*:*o* = 89:11), *p*:*o* ratio determined by ^1H NMR. The product was obtained as a colorless liquid (0.083 g, 52% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3295, 2947, 2130, 1740, 1594, 1489, 1369, 1268, 1141, 1090, 1003, 954, 905, 808, 762, 681, 637; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42−7.28 (m, 4H), 7.25−7.18 (m, 4H), 5.00 (s, 1H), 4.74 (d, J = 2.5 Hz, 2H), 2.48 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.1, 136.3, 133.8, 130.0, 129.1, 77.2, 75.6, 55.4, 53.0; HRMS (ESI TOF): calculated for $C_{17}H_{13}Cl_2O_2$ $(M + H)^+$: 319.0292, found: 319.0305.

*Prop-2-yn-1-yl (S)-2-Phenyl-2-(p-tolyl)acetate (**3ad**).* Major product *para*-isomer (*p*:*o* = 80:20), *p*:*o* ratio determined by ^1H NMR. The product was obtained as a viscous colorless liquid (0.111 g, 84% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3290, 2925, 2124, 1743, 1603, 1501, 1449, 1371, 1306, 1275, 1219, 1142, 999, 806, 732, 696, 640; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45−6.99 (m, 9H), 5.03 (s, 1H), 4.73 (d, J = 2.4 Hz, 2H), 2.46 (t, J = 2.4 Hz, 1H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.0, 138.5, 137.2, 135.3, 129.5, 128.7, 128.7, 128.6, 127.5, 77.4, 75.3, 56.4, 52.7, 21.2; HRMS (ESI TOF): calculated for $C_{18}H_{16}NaO_2$ $(M + Na)^+$: 287.1047, found: 287.1054.

*Prop-2-yn-1-yl 2-(4-Bromophenyl)-2-(p-tolyl)acetate (**3bd**).* Major product *para*-isomer (*p*:*o* = 78:22), *p*:*o* ratio determined by ^1H NMR. The product was obtained as a colorless liquid (0.144 g, 84% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3291, 3025, 2945, 2130, 1739, 1592, 1487, 1441, 1369, 1270, 1219, 1073, 1002, 951, 809, 754, 680, 638; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51−7.37 (m, 2H), 7.28−7.03 (m, 6H), 4.98 (s, 1H), 4.82−4.65 (m, 2H), 2.46 (t, J = 2.5 Hz, 1H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.5, 137.6137.5, 134.8, 131.8, 130.4, 129.6, 128.4, 121.6, 77.4, 75.4, 55.8, 52.8, 21.2; HRMS (ESI TOF): calculated for $C_{18}H_{16}BrO_2$ $(M + H)^+$: 343.0333, found: 343.0330.

*Prop-2-yn-1-yl 2-(3,4-Dimethylphenyl)-2-phenylacetate (**3ae**).* Major product *para*-isomer (*p*:*o* = 84:16), *p*:*o* ratio determined by ^1H NMR. The product was obtained as a white solid (0.124 g, 89% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); m.p.: 88−90 °C; IR (neat) cm^{-1}: 3287, 3027, 2934, 2126, 1740, 1601, 1497, 1448, 1371, 1207, 1137, 1079, 997, 815, 695, 637, 573; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33−7.21 (m, 5H), 7.11−7.02 (m, 3H), 5.01 (s, 1H), 4.79−4.68 (m, 2H), 2.46 (t, J = 2.5 Hz, 1H), 2.30−2.15 (m, 6H) (for 2-CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.0, 138.6, 137.0, 135.9, 135.7, 130.0, 129.9, 128.7, 128.7, 127.4, 126.0, 77.6, 75.2, 56.4,

https://doi.org/10.1021/acs.joc.2c01185
J. Org. Chem. 2022, 87, 13583−13597

52.7, 20.0, 19.5; HRMS (ESI TOF): calculated for $C_{19}H_{19}O_2$ $(M + H)^+$: 279.1385, found: 279.1387.

*Prop-2-yn-1-yl 2-(4-Bromophenyl)-2-(3,4-dimethylphenyl)-acetate (**3be**).* Major product *para*-isomer (*p*:*o* = 83:17), *p*:*o* ratio determined by ^1H NMR. The product was obtained as a colorless liquid (0.161 g, 90% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3293, 2939, 2123, 1744, 1590, 1490, 1446, 1371, 1272, 1145, 1073, 1007, 949, 818, 762, 681, 641, 568; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48−7.39 (m, 2H), 7.21−6.99 (m, 5H), 4.95 (s, 1H), 4.79−4.66 (m, 2H), 2.52−2.41 (m, 1H), 2.29−2.12 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.6, 137.6, 137.2, 136.2, 135.2, 131.8, 130.4, 130.1, 129.7, 125.9, 121.5, 77.4, 75.4, 55.8, 52.8, 20.0, 19.5; HRMS (ESI TOF): calculated for $C_{19}H_{18}BrO_2$ $(M + H)^+$: 357.0490, found: 357.0487.

*Prop-2-yn-1-yl 2-(2,5-Dimethylphenyl)-2-phenylacetate (**3af**).* White solid (0.12 g, 86% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); m.p.: 79−81 °C; IR (neat) cm^{-1}: 3289, 2929, 2126, 1740, 1606, 1498, 1447, 1370, 1273, 1213, 1141, 996, 946, 812, 736, 692, 637, 578; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51−7.14 (m, 5H), 7.09−6.95 (m, 3H), 5.22 (s, 1H), 4.74 (d, J = 2.5 Hz, 2H), 2.46 (t, J = 2.5 Hz, 1H), 2.28 (s, 3H), 2.23 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.2, 137.6, 136.3, 135.8, 133.4, 130.7, 129.1, 128.8, 128.7, 128.3, 127.4, 77.6, 75.2, 53.5, 52.7, 21.3, 19.5; HRMS (ESI TOF): calculated for $C_{19}H_{18}NaO_2$ $(M + Na)^+$: 301.1204, found: 301.1209.

*Prop-2-yn-1-yl 2-(4-Bromophenyl)-2-(2,5-dimethylphenyl)-acetate (**3bf**).* White solid (0.168 g, 94% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); m.p.: 115−117 °C; IR (neat) cm^{-1}: 3292, 2930, 2123, 1743, 1613, 1491, 1445, 1370, 1315, 1213, 1149, 1074, 1007, 813, 761, 679, 641; ^1H NMR (400 MHz, $CDCl_3$): δ 7.61−7.33 (m, 2H), 7.19−6.94 (m, 5H), 5.16 (s, 1H), 4.90−4.64 (m, 2H), 2.48 (t, J = 2.5 Hz, 1H), 2.30 (s, 3H), 2.21 (s, 3H); $^{13}C\{^1H\}$ NMR ((100 MHz, $CDCl_3$): δ 171.8, 136.7, 136.1, 135.8, 133.3, 131.8, 130.9, 130.8, 128.59, 128.58, 121.5, 77.4, 75.3, 53.0, 52.8, 21.2, 19.4; HRMS (ESI TOF): calculated for $C_{19}H_{17}BrNaO_2$ $(M + Na)^+$: 379.0304, found: 379.0305.

*Prop-2-yn-1-yl 2-Mesityl-2-phenylacetate (**3ag**).* Colorless liquid (0.135 g, 92% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3286, 2922, 2125, 1742, 1608, 1489, 1448, 1371, 1271, 1154, 1000, 943, 853, 734, 693, 569; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33−7.20 (m, 3H), 7.15−7.08 (m, 2H), 6.90 (s, 2H), 5.42 (s, 1H), 4.79−4.68 (m, 2H), 2.43 (t, J = 2.5 Hz, 1H), 2.29 (s, 3H), 2.18 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.6, 137.6, 137.1, 136.5, 131.9, 130.1, 128.8, 128.3, 127.0, 77.8, 75.0, 52.5, 50.8, 21.0 (for two type of carbons); HRMS (ESI TOF): calculated for $C_{20}H_{20}NaO_2$ $(M + Na)^+$: 315.1361, found: 315.1365.

*Prop-2-yn-1-yl 2-(4-Bromophenyl)-2-mesitylacetate (**3bg**).* Colorless liquid (0.182 g, 98% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3292, 2949, 2120, 1743, 1611, 1486, 1447, 1159, 1075, 1005, 946, 878, 778, 679, 634; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45−7.35 (m, 2H), 7.06−6.97 (m, 2H), 6.91 (s, 2H), 5.33 (s, 1H), 4.89−4.57 (m, 2H), 2.44 (t, J = 2.4 Hz, 1H), 2.30 (s, 3H), 2.16 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.2, 137.5, 137.4, 135.5, 131.4, 131.4, 130.6, 130.1, 121.1, 77.6, 75.2, 52.6, 50.1, 21.0, 20.9; HRMS (ESI TOF): calculated for $C_{20}H_{20}BrO_2$ $(M + H)^+$: 371.0646, found: 371.0674.

*Prop-2-yn-1-yl 2-(4-Chlorophenyl)-2-mesitylacetate (**3cg**).* Colorless liquid (0.154 g, 94% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3293, 2923, 2123, 1742, 1610, 1489, 1448, 1268, 1159, 1093, 1008, 848, 775, 681, 635; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29−7.21 (m, 2H), 7.10−7.03 (m, 2H), 6.91 (s, 2H), 5.35 (s, 1H), 4.78−4.68(m, 2H), 2.43 (t, J = 2.5 Hz, 1H), 2.30 (s, 3H), 2.16 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.2, 137.5, 137.3, 135.0, 132.9, 131.5, 130.2, 130.1, 128.5, 77.6, 75.1, 52.6, 50.1, 21.0, 20.9; HRMS (ESI TOF): calculated for $C_{20}H_{19}ClNaO_2$ $(M + Na)^+$: 349.0966, found: 349.0966.

*Prop-2-yn-1-yl 2-(4-Fluorophenyl)-2-mesitylacetate (**3dg**).* Colorless liquid (0.148 g, 95% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3293, 2924, 2122, 1743, 1606, 1509, 1452, 1372, 1273, 1227, 1158,1004, 847, 799, 681, 639; ^1H NMR (400 MHz, $CDCl_3$): δ 7.14−7.07 (m, 2H), 7.02−6.94 (m, 2H), 6.92 (s, 2H), 5.36 (s, 1H), 4.83−4.64 (m, 2H), 2.44 (t, J = 2.5 Hz, 1H), 2.31 (s, 3H), 2.18 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.5, 161.9 (d, J = 245.6 Hz), 137.5, 137.3, 132.1 (d, J = 3.2 Hz), 131.8, 130.4 (d, J = 7.9 Hz), 130.1, 115.1 (d, J = 21.4 Hz), 77.7, 75.1, 52.6, 50.0, 21.0, 20.9; HRMS (ESI TOF): calculated for $C_{18}H_{19}FNaO_2$ $(M + Na)^+$: 333.1266, found: 333.1268.

*Prop-2-yn-1-yl 2-(4-Bromophenyl)-2-(4-methoxyphenyl)acetate (**3bh**).* Major product *para*-isomer (*p*:*o* = 74:26), *p*:*o* ratio determined by ^1H NMR. The product was obtained as colorless oil (0.169 g, 94% yield). R_f = 0.3 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3290, 2946, 2838, 2309, 2126, 1899, 1739, 1504, 1368, 1297, 1147, 1007, 815, 681; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51−7.38 (m, 2H), 7.31−7.12 (m, 4H), 6.94−6.80 (m, 2H), 4.96 (s, 1H), 4.78−4.65 (m, 2H), 3.78 (s, 3H), 2.46 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.6, 159.1, 137.7, 131.8, 131.0, 130.3, 129.7, 121.6, 114.3, 77.4, 75.4, 55.4, 55.3, 52.8; HRMS (ESI TOF): calculated for $C_{18}H_{16}BrO_3$ $(M + H)^+$: 359.0283, found: 359.0275.

*Prop-2-yn-1-yl 2-(2,5-Dimethoxyphenyl)-2-phenylacetate (**3ai**).* White solid (0.149 g, 96% yield): R_f = 0.4 petroleum ether/EtOAc (80:20); m.p.: 74−76 °C; IR (neat) cm^{-1}: 3286, 2945, 2836, 2126, 1741, 1595, 1496, 1455, 1369, 1277, 1219, 1145, 1026, 947, 807, 699, 640; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37−7.24 (m, 5H), 6.82−6.74 (m, 2H), 6.61 (d, J = 2.9 Hz, 1H), 5.30 (s, 1H), 4.79−4.66 (m, 2H), 3.78 (s, 3H), 3.68 (s, 3H), 2.44 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.1, 153.6, 151.3, 137.0, 129.2, 128.8, 128.6, 127.6, 116.2, 112.5, 111.4, 77.9, 74.9, 56.2, 55.7, 52.5, 51.0; HRMS (ESI TOF): calculated for $C_{19}H_{19}O_4$ $(M + H)^+$: 311.1283, found: 311.1277.

*Prop-2-yn-1-yl 2-(4-Bromophenyl)-2-(2,5-dimethoxyphenyl)-acetate (**3bi**).* White solid (0.175 g, 90% yield): R_f = 0.45 petroleum ether/EtOAc (80:20); m.p.: 97−99 °C; IR (neat) cm^{-1}: 3289, 2944, 2837, 2126, 1741, 1593, 1494, 1222, 1148, 1010, 945, 806, 712, 641, 537; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49−7.42 (m, 2H), 7.23−7.17 (m, 2H), 6.86−6.73 (m, 2H), 6.62 (d, J = 2.8 Hz, 1H), 5.25 (s, 1H), 4.78−4.67 (m, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 2.45 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.7, 153.6, 151.1, 136.3, 131.9, 130.9, 128.0, 121.6, 115.9, 112.7, 111.5, 77.7, 75.1, 56.2, 55.8, 52.6, 50.4; HRMS (ESI TOF): calculated for $C_{19}H_{17}BrO_4$ $(M)^+$: 388.0310, found: 388.0305.

*Prop-2-yn-1-yl 2-(4-Chlorophenyl)-2-(2,5-dimethoxyphenyl)-acetate (**3ci**).* White solid (0.159 g, 92% yield): R_f = 0.45 petroleum ether/EtOAc (80:20); m.p.: 98−99 °C; IR (neat) cm^{-1}: 3290, 2947, 2836, 2125, 1741, 1595, 1494, 1278, 1222, 1174, 1095, 1014, 806, 755, 709, 639, 539; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33−7.28 (m, 2H), 7.27−7.22 (m, 2H), 6.85−6.74 (m, 2H), 6.62 (d, J = 2.8 Hz, 1H), 5.27 (s, 1H), 4.78−4.67 (m, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 2.45 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.8, 153.7, 151.2, 135.8, 133.5, 130.6, 128.9, 128.1, 115.9, 112.8, 111.6, 77.7, 75.0, 56.2, 55.8, 52.6, 50.3; HRMS (ESI TOF): calculated for $C_{19}H_{17}ClNaO_4$ $(M + Na)^+$: 367.0712, found: 367.0710.

*Prop-2-yn-1-yl 2-(2,5-Dimethoxyphenyl)-2-(4-fluorophenyl)-acetate (**3di**).* Colorless liquid (0.156 g, 95% yield): R_f = 0.35 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 3291, 2948, 2838, 2122, 1744, 1603, 1503, 1457, 1369, 1280, 1226, 1153, 1040, 844, 808, 712, 642; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.25 (m, 2H), 7.07−6.96 (m, 2H), 6.78 (dt, J = 8.8, 5.8 Hz, 2H), 6.61 (d, J = 2.8 Hz, 1H), 5.27 (s, 1H), 4.78−4.66 (m, 2H), 3.77 (s, 3H), 3.69 (s, 3H), 2.45 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.0, 162.2 (d, J = 245.8 Hz), 153.6, 151.1, 132.9 (d, J = 3.2 Hz), 130.8 (d, J = 8.2 Hz), 128.4, 115.8 (d, J = 18.1 Hz), 115.5, 112.6, 111.5, 77.7, 75.0, 56.1, 55.7, 52.5, 50.2; HRMS (ESI TOF): calculated for $C_{19}H_{17}FNaO_4$ $(M + Na)^+$: 351.1003, found: , found: 351.1000.

*Prop-2-yn-1-yl 2-(2,5-Dimethoxyphenyl)-2-(naphthalen-2-yl)-acetate (**3gi**).* White solid (0.151 g, 84% yield): R_f = 0.45 petroleum ether/EtOAc (80:20); m.p.: 91−93 °C; IR (neat) cm^{-1}: 3287, 2945, 2837, 2125, 1740, 1597, 1497, 1455, 1369, 1222, 1148, 1032, 863, 808, 750, 709, 644; ^1H NMR (400 MHz, $CDCl_3$): δ 7.87−7.73 (m, 4H), 7.52−7.40 (m, 3H), 6.84−6.75 (m, 2H), 6.63 (d, J = 3.0 Hz, 1H), 5.47 (s, 1H), 4.82−4.69 (m, 2H), 3.80 (s, 3H), 3.65 (s, 3H),

https://doi.org/10.1021/acs.joc.2c01185
J. Org. Chem. 2022, 87, 13583−13597

2.45 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.1, 153.6, 151.3, 134.5, 133.6, 132.8, 128.6, 128.5, 128.1, 128.0, 127.7, 127.3, 126.3, 126.1, 116.3, 112.6, 111.4, 77.9, 75.0, 56.2, 55.8, 52.6, 51.1; HRMS (ESI TOF): calculated for $C_{23}H_{20}NaO_4$ $(M + Na)^+$: 383.1259, found: 383.1262.

Prop-2-yn-1-yl 2-Phenyl-2-(2,4,6-trimethoxyphenyl)acetate (**3aj**). White solid (0.157 g, 92% yield): R_f = 0.35 petroleum ether/EtOAc (80:20); m.p.: 121−123 °C; IR (neat) cm^{-1}: 3281, 2937, 2842, 2127, 1741, 1597, 1496, 1420, 1337, 1195, 1114, 1002, 949, 864, 814, 746, 696, 664; ^1H NMR ((400 MHz, $CDCl_3$)): δ 7.34−7.30 (m, 2H), 7.28−7.23 (m, 2H), 7.22−7.16 (m, 1H), 6.14 (s, 2H), 5.33 (s, 1H), 4.77−4.64 (m, 2H), 3.80 (s, 3H), 3.78 (s, 6H), 2.38 (t, J = 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.1, 160.7, 158.2, 138.7, 129.4, 128.1, 126.8, 109.2, 90.9, 78.5, 74.2, 55.9, 55.4, 52.0, 45.8; HRMS (ESI TOF): calculated for $C_{20}H_{21}O_5$ $(M + H)^+$: 341.1389, found: 341.1398.

Prop-2-yn-1-yl 2-(4-Bromophenyl)-2-(2,4,6-trimethoxyphenyl)-acetate (**3bj**). Colorless liquid (0.176 g, 84% yield): R_f = 0.3 petroleum ether/EtOAc (80:20); IR(neat) cm^{-1}: 3287, 2943, 2841, 2121, 1743, 1600, 1460, 1420, 1195, 1157, 1061, 1009, 950, 814, 759, 668, 634; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41−7.33 (m, 2H), 7.26−7.17 (m, 2H), 6.13 (s, 2H), 5.27 (s, 1H), 4.75−4.64 (m, 2H), 3.79 (s, 3H), 3.77 (s, 6H), 2.39 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.6, 160.8, 158.1, 137.8, 131.2, 131.1, 120.7, 108.6, 90.9, 78.3, 74.4, 55.8, 55.4, 52.1, 45.2; HRMS (ESI TOF): calculated for $C_{20}H_{20}BrO_5$ $(M + H)^+$: 419.0494, found: 419.0494.

Prop-2-yn-1-yl 2-(Naphthalen-2-yl)-2-(2,4,6-trimethoxyphenyl)-acetate (**3gj**). White solid (0.166 g, 85% yield): R_f = 0.25 petroleum ether/EtOAc (80:20); m.p.: 99−101 °C; IR (neat) cm^{-1}: 3285, 2941, 2842, 2122, 1741, 1598, 1499, 1458, 1422, 1154, 1115, 1026, 950, 857, 812, 751, 662; ^1H NMR (400 MHz, $CDCl_3$): δ 7.80−7.72 (m, 3H), 7.67 (s, 1H), 7.55 (dd, J = 8.5, 1.8 Hz, 1H), 7.42−7.36 (m, 2H), 6.16 (s, 2H), 5.50 (s, 1H), 4.82−4.66 (m, 2H), 3.81 (s, 3H), 3.80 (s, 6H), 2.40 (t, J = 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.1, 160.8, 158.3, 136.3, 133.4, 132.6, 128.1, 128.0, 127.9, 127.6, 125.6, 125.5, 109.0, 91.0, 78.5, 77.4, 74.3, 55.9, 55.5, 52.1, 46.0; HRMS (ESI TOF): calculated for $C_{24}H_{23}O_5$ $(M + H)^+$: 391.1545, found: 391.1546.

Prop-2-yn-1-yl 2-(Benzo[d][1,3]dioxol-5-yl)-2-phenylacetate (**3ak**). Major product *para*-isomer (p:o = 90:10), p:o ratio determined by ^1H NMR. The product was obtained as a colorless liquid (0.138 g, 94% yield): R_f = 0.55 petroleum ether/EtOAc (80:20); IR(neat) cm^{-1}: 3288, 3027, 2895, 2126, 1739, 1490, 1444, 1367, 1239, 1138, 1032, 997, 930, 807, 735, 694, 643; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.25 (m, 5H), 6.85−6.71 (m, 3H), 5.93 (d, J = 3.9 Hz, 2H), 4.98 (s, 1H), 4.73 (d, J = 2.6 Hz, 2H), 2.50−2.43 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.8, 148.0, 147.1, 138.4, 132.1, 128.8, 128.5, 127.6, 122.1, 109.3, 108.4, 101.3, 77.4, 75.4, 56.3, 52.8; HRMS (ESI TOF): calculated for $C_{18}H_{14}NaO_4$ $(M + Na)^+$: 317.0784, found: 317.0778.

Prop-2-yn-1-yl 2-(Benzo[d][1,3]dioxol-5-yl)-2-(4-bromophenyl)-acetate (**3bk**). Major product *para*-isomer (p:o = 92:8), p:o ratio determined by ^1H NMR. The product was obtained as a colorless liquid (0.175 g, 94% yield): R_f = 0.6 petroleum ether/EtOAc (80:20); IR (neat) cm^{-1}: 3290, 2896, 2126, 1738, 1606, 1487, 1442, 1301, 1238, 1140, 1031, 1002, 931, 800, 760, 676, 640; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51−7.39 (m, 2H), 7.24−7.13 (m, 2H), 6.82−6.69 (m, 3H), 5.94 (s, 2H), 4.92 (s, 1H), 4.78−4.68 (m, 2H), 2.48 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.4, 148.1, 147.2, 137.4, 131.9, 131.5, 130.3, 122.0, 121.7, 109.1, 108.5, 101.4, 77.3, 75.5, 55.7, 52.9; HRMS (ESI TOF): calculated for $C_{18}H_{13}BrNaO_4$ $(M + Na)^+$: 394.9889, found: 394.9894.

Prop-2-yn-1-yl 2-(Benzo[d][1,3]dioxol-5-yl)-2-(p-tolyl)acetate (**3hk**). Major product *para*-isomer (p:o = 98:2), p:o ratio determined by ^1H NMR. The product was obtained as a white solid (0.094 g, 61% yield): R_f = 0.6 petroleum ether/EtOAc (80:20); m.p.: 59−61 °C; IR (neat) cm^{-1}: 3288, 2894, 2779, 2129, 1739, 1611, 1489, 1441, 1306, 1241, 1185, 1140, 1034, 997, 932, 808, 755, 681; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23−7.16 (m, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.86−6.78 (m, 1H), 6.78−6.69 (m, 2H), 5.92 (s, 2H), 4.94 (s, 1H), 4.72 (d, J = 2.5 Hz, 2H), 2.46 (t, J = 2.5 Hz, 1H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.0, 148.0, 147.0, 137.3, 135.4, 132.3, 129.5, 128.4, 122.0, 109.2, 108.3, 101.2, 77.5, 75.3, 56.0, 52.7, 21.2; HRMS (ESI TOF): calculated for $C_{19}H_{17}O_4$ $(M + H)^+$: 309.1127, found: 309.1127.

Prop-2-yn-1-yl 2-(Benzo[d][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)acetate (**3ik**). Major product *para*-isomer (p:o = 99:1), p:o ratio determined by ^1H NMR. The product was obtained as a colorless liquid (0.089 g, 55% yield): R_f = 0.5 petroleum ether/EtOAc (80:20); IR (neat) cm^{-1}: 3287, 2904, 2124, 1740, 1610, 1501, 1443, 1367, 1246, 1143, 1034, 933, 807, 760, 683, 637; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24−7.19 (m, 2H), 6.88−6.82 (m, 2H), 6.80 (s, 1H), 6.77−6.70 (m, 2H), 5.91 (s, 2H), 4.93 (s, 1H), 4.72 (d, J = 2.5 Hz, 2H), 3.77 (s, 3H), 2.47 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.1, 159.0, 148.0, 147.0, 132.5, 130.5, 129.6, 121.9, 114.2, 109.2, 108.3, 101.2, 77.5, 75.3, 55.5, 55.4, 52.7; HRMS (ESI TOF): calculated for $C_{19}H_{17}O_5$ $(M + H)^+$: 325.1076, found: 325.1092.

Prop-2-yn-1-yl 2-(4-Bromophenyl)-2-(2,5-dimethylfuran-3-yl)-acetate (**3bl**). Colorless liquid (0.104 g, 60% yield): R_f = 0.5 petroleum ether/EtOAc (80:20); IR (neat) cm^{-1}: 3296, 2924, 2126, 1742, 1583, 1487, 1222, 1146, 1079, 1003, 935, 805, 762, 677, 640; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 5.98 (s, 1H), 4.75 (s, 1H), 4.71 (dd, J = 2.5, 1.9 Hz, 2H), 2.47 (t, J = 2.5 Hz, 1H), 2.21 (s, 3H), 2.17 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.4, 150.1, 146.9, 137.3, 131.8, 129.9, 121.5, 116.4, 106.8, 77.3, 75.4, 52.8, 47.3, 13.6, 11.8; HRMS (ESI TOF): calculated for $C_{17}H_{16}BrO_3$ $(M + H)^+$: 347.0283, found: 347.0290.

Prop-2-yn-1-yl 2-(4-Isopropylphenyl)-2-phenylacetate (**3am**). Major product *para*-isomer (p:o = 84:16), p:o ratio determined by ^1H NMR. The product was obtained as a colorless viscous liquid (0.095 g, 65% yield). R_f = 0.25 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3290, 2957, 1742, 1598, 1140, 1006, 703; ^1H NMR (400 MHz, CDCl3): δ 7.39−7.00 (m, 9H), 5.04 (s, 1H), 4.73 (m, 2H), 2.87 (hept, J = 6.9 Hz, 1H), 2.45 (t, J = 2.5 Hz, 1H), 1.22 (d, J = 6.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.0, 148.1, 138.5, 135.6, 128.8, 128.7, 128.6, 127.5, 126.9, 78.0, 75.3, 56.5, 52.7, 33.8, 24.1; HRMS (ESI TOF): calculated for $C_{20}H_{21}O_2$ $(M + H)^+$: 293.1541, found: 293.1537.

Prop-2-yn-1-yl 2-(4-(tert-Butyl)phenyl)-2-phenylacetate (**3an**). Major product *para*-isomer (p:o = 70:30), p:o ratio determined by ^1H NMR. The product was obtained as a colorless viscous liquid (0.086 g, 56% yield). R_f = 0.3 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3291, 2958, 1743, 1139, 1006, 700; ^1H NMR (400 MHz, CDCl3): δ 7.44−7.16 (m, 9H), 5.04 (s, 1H), 4.73 (m, 2H), 2.46 (t, J = 2.3 Hz, 1H), 1.29 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 172.0, 150.4, 138.5, 135.3, 128.7, 128.74, 128.72, 128.3, 127.5, 77.6, 75.3, 56.4, 52.7, 34.6, 31.4; HRMS (ESI TOF): calculated for $C_{21}H_{23}O_2$ $(M + H)^+$: 307.1698, found: 307.1691.

General Procedure for Gram-Scale Synthesis of α-Diarylacetates. In a dried 100 mL RB flask, $Sc(OTf)_3$ (0.184 g, 5 mol %), propargyl α-phenyl-α-diazoacetate **1a** (1.5 g, 1 equiv), and benzene **2a** (6.7 mL, 10 equiv) were added into 25 mL of DCE at room temperature under an inert atmosphere. Then the reaction mixture was refluxed at 80 °C over 4 h in an oil bath. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product **3aa** as a white solid (1.31 g, 70% yield).

Prop-2-yn-1-yl 2,2-Diphenylacetate (**3aa**). White solid (1.31 g, 70% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); m.p.: 46−48 °C; IR (neat) cm^{-1}: 3289, 3031, 2941, 2126, 1739, 1598, 1494, 1448, 1370, 1220, 1181, 1080, 997, 739, 694, 638, 564; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49−7.12 (m, 10H), 5.07 (s, 1H), 4.74 (d, J = 2.5 Hz, 2H), 2.46 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.8, 138.3, 128.8, 128.7, 127.5, 77.4, 75.3, 56.8, 52.7; HRMS (ESI TOF): calculated for $C_{17}H_{14}NaO_2$ $(M + Na)^+$: 273.0891, found: 273.0899.

https://doi.org/10.1021/acs.joc.2c01185
J. Org. Chem. 2022, 87, 13583−13597

*Prop-2-yn-1-yl 2-(4-Chlorophenyl)-2-phenylacetate (**3ca**).* White solid (1.31 g, 72% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); m.p.: 83−85 °C; IR (neat) cm^{-1}: 3293, 3033, 2127, 1739, 1598, 1490, 1272, 1222, 1138, 1001, 813, 751, 691, 636, 550; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35−7.24 (m, 9H), 5.03 (s, 1H), 4.79−4.69 (m, 2H), 2.47 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ 171.0, 138.4, 137.7, 132.0, 130.4, 128.7, 128.5, 128.3, 127.3, 78.1 (for 2-C), 54.5, 52.6; HRMS (ESI TOF): calculated for $C_{17}H_{13}ClNaO_2$ $(M + Na)^+$: 307.0501, found: 307.0505.

*Prop-2-yn-1-yl 2-(3,4-Dichlorophenyl)-2-phenylacetate (**3ea**).* Colorless liquid (1.46 g, 82% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3295, 3071, 2948, 2124, 1743, 1596, 1470, 1269, 1145, 1028, 907, 772, 702; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 2.2 Hz, 1H), 7.41−7.26 (m, 6H), 7.16 (dd, J = 8.3, 2.2 Hz, 1H), 5.00 (s, 1H), 4.80−4.69 (m, 2H), 2.49 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.0, 138.4, 137.2, 132.8, 131.8, 130.7, 130.6, 129.1, 128.5, 128.2, 128.0, 75.6(for 2-C), 55.8, 53.0; HRMS (ESI TOF): calculated for $C_{17}H_{12}Cl_2NaO_2$ $(M + Na)^+$: 341.0107, found: 341.0099.

*Prop-2-yn-1-yl 2-(4-Bromophenyl)-2-(2,5-dimethoxyphenyl)-acetate (**3bi**).* White solid (1.84 g, 88% yield): R_f = 0.45 petroleum ether/EtOAc (80:20); m.p.: 97−99 °C; IR (neat) cm^{-1}: 3289, 2944, 2837, 2126, 1741, 1593, 1494, 1222, 1148, 1010, 945, 806, 712, 641, 537; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49−7.42 (m, 2H), 7.23−7.17 (m, 2H), 6.86−6.73 (m, 2H), 6.62 (d, J = 2.8 Hz, 1H), 5.25 (s, 1H), 4.78−4.67 (m, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 2.45 (t, J = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.7, 153.6, 151.1, 136.3, 131.9, 130.9, 128.0, 121.6, 115.9, 112.7, 111.5, 77.7, 75.1, 56.2, 55.8, 52.6, 50.4; HRMS (ESI TOF): calculated for $C_{19}H_{17}BrO_4$ $(M)^+$: 388.0310, found: 388.0305.

General Procedure for the Deprotection of the Propargyl Group. A mixture of diarylacetate **3aa** (1.25 g, 1 equiv) and LiOH·H_2O (0.524 g, 2.5 equiv) was taken in a 100 mL RB flask, and 30 mL solvent (THF:MeOH:H_2O = 1:1:1) was added into the above mixture under an open atmosphere. The reaction mixture was stirred at room temperature over 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was acidified by using 3 N HCl and adjusted to pH 2−3. The crude product was extracted by using ethyl acetate. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography over silica gel (100−200 mesh size) to furnish the product **4aa** as a white solid (1.01 g, 95% yield).

*2,2-Diphenylacetic Acid (**4aa**).* White solid (1.01 g, 95% yield). R_f = 0.5 petroleum ether/EtOAc (70:30); m.p.: 147−149 °C; IR (neat) cm^{-1}: 3027, 2910, 1699, 1494, 1451, 1411, 1306, 1218, 1031, 934, 737, 698, 635; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45−7.16 (m, 10H), 5.04 (s, 1H); $^{13}C\{^1H\}$ (100 MHz, $CDCl_3$): δ 178.9, 138.0, 128.8 (for two carbon), 127.6, 57.1; HRMS (ESI TOF): calculated for $C_{14}H_{13}O_2$ $(M + H)^+$: 213.0915, found: 213.0917.

*2-(4-Chlorophenyl)-2-phenylacetic Acid (**4ca**).* White solid (1.02 g, 94% yield). R_f = 0.25 petroleum ether/EtOAc (80:20); m.p.: 117−119 °C; IR (neat) cm^{-1}: 3029, 2695, 1704, 1599, 1491, 1452, 1408, 1280, 1213, 1091, 1015, 930, 812, 749, 700, 663; ^1H NMR ((400 MHz, $CDCl_3$): δ 7.39−7.20 (m, 9H), 5.01 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 178.6, 137.5, 136.4, 133.7, 130.2, 129.0 (for two carbons), 128.7, 127.9, 56.4; HRMS (ESI TOF): calculated for $C_{14}H_{11}ClNaO_2$ $(M + Na)^+$: 269.0345, found: 269.0342.

*2-(3,4-Dichlorophenyl)-2-phenylacetic Acid (**4ea**).* White solid (1.06 g, 96% yield). R_f = 0.30 petroleum ether/EtOAc (75:25); m.p.: 118−121 °C; IR (neat) cm^{-1}: 3028, 1706, 1596, 1560, 1469, 1404, 1274, 1214, 1136, 1032, 917, 816, 755, 705; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45−7.29 (m, 7H), 7.18 (dd, J = 8.4, 2.1 Hz, 1H), 5.00 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 178.0, 138.0, 136.9, 132.9, 132.0, 130.8, 130.7, 129.1, 128.6, 128.2, 128.2, 56.1. HRMS (ESI TOF): calculated for $C_{14}H_9Cl_2O_2$ $(M - H)^+$: 278.9980, found: 278.9971.

Procedure for Gram-Scale Synthesis of Adiphenine (5). *Antispasmodic Drug.* A mixture of 2,2-diphenylacetic acid **4aa** (0.9 g, 1 equiv), sodium carbonate (2.25 g, 5 equiv), and diethyl amine (8.8 mL, 20 equiv) was stirred in 30 mL of DCE at room temperature in a 100 mL RB flask under an inert atmosphere for 5 min. The reaction mixture was refluxed at 80 °C over 16 h in an oil bath. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The residue was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with cold water and brine and dried over Na_2SO_4, and filtered, and the filtrate was evaporated under vacuum. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product 5 obtained as a colorless liquid (1.12 g, 85% yield).

2-(Diethylamino)ethyl 2,2-Diphenylacetate (5). Colorless liquid (1.12 g, 85% yield). R_f = 0.30 petroleum ether/EtOAc (75:25); IR (neat) cm^{-1}: 2969, 2805, 1735, 1597, 1496 1447, 1304, 1189, 1149, 1079, 1020, 741, 697. ^1H NMR (400 MHz, $CDCl_3$): δ 7.38−7.20 (m, 10H), 5.03 (s, 1H), 4.22 (t, J = 6.2 Hz, 2H), 2.68 (t, J = 6.2 Hz, 2H), 2.50 (q, J = 7.2 Hz, 4H), 0.97 (t, J = 7.2 Hz, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 172.6, 138.8, 128.8, 128.7, 127.3, 63.6, 57.3, 51.1, 47.7, 12.0; HRMS (ESI TOF): calculated for $C_{20}H_{26}NO_2$ $(M + H)^+$: 312.1963, found: 312.1969.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01185.

Reaction optimization tables; comparison of reactivity; general procedure for the deprotection of ester; gram-scale synthesis of adiphenine: antispasmodic drug; DFT calculations; copies of ^1H, ^{13}C, and ^{19}F NMR spectra for all compounds; and single crystal X-ray crystallography data for **3aa** (CCDC 1848210) (PDF)

Copies of HRMS spectra of compounds (PDF)

Accession Codes

CCDC 1848210 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Ramakrishna G. Bhat − *Department of Chemistry, Indian Institute of Science Education and Research (IISER)-Pune, Pune, Maharashtra 411008, India;* orcid.org/0000-0002-7739-9553; Email: rgb@iiserpune.ac.in

Authors

Balu S. Navale − *Department of Chemistry, Indian Institute of Science Education and Research (IISER)-Pune, Pune, Maharashtra 411008, India;* Present Address: Department of Chemistry, Institute of Science, Nagpur, Maharashtra 440001, India (B.S.N.)

Debasish Laha − *Department of Chemistry, Indian Institute of Science Education and Research (IISER)-Pune, Pune, Maharashtra 411008, India;* orcid.org/0000-0002-2479-6467

Subhrashis Banerjee − *Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory, Pune, Maharashtra 411008, India; Academy of Scientific and Innovative Research (AcSIR), New Delhi 110001, India*

Kumar Vanka − *Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory, Pune, Maharashtra 411008, India; Academy of Scientific and Innovative*

Research (AcSIR), New Delhi 110001, India; orcid.org/0000-0001-7301-7573

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.2c01185

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

R.G.B. thanks Science and Engineering Research Board (SERB)-DST (CRG/2019/005753) and (EMR/2015/000909), New Delhi, Govt. of India for the generous research grant. R.G.B., B.S.N., and D.L. also thank IISER Pune for the financial assistance. B.S.N. and S.B. thank CSIR, and D.L. thanks UGC, New Delhi, Government of India for providing fellowship. S.B. and K.V. acknowledge the Multi-Scale simulation and Modeling project−MSM and PARAM Brahma for the computational facilities. K.V. thanks DST-SERB (EMR/2014/000013) for providing financial assistance.

■ REFERENCES

(1) (a) Ribas, X.; Ma, D.; Spivey, J. J.; Casitas, A.; Fairlamb, I. J. S.; Vedernikov, A. N.; Mirica, L. *C−H and C-X Bond Functionalization: Transition Metal Mediation*; Royal Society of Chemistry: Cambridge, U.K., 2013. (b) Li, C. J. *From C−H to C−C bonds: Cross-Dehydrogenative-Coupling*; Royal Society of Chemistry: Cambridge, U.K., 2015. (c) Li, B.-J.; Shi, Z.-J. *Homogeneous Catalysis for Unreactive Bond Activation*; Shi, Z.-J., Ed.; John Wiley & Sons: NJ, 2015; pp 498−521. (d) Li, J. J. *C−H Bond Activation in Organic Synthesis*; CRC Press: Boca Raton, FL, 2015.

(2) (a) Lednicer, D. *Strategies for Organic Drug Synthesis and Design*; Wiley: Hoboken, 2008; pp 43−88. (b) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in drugs. *J. Med. Chem.* **2014**, *57*, 5845−5859.

(3) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998. (b) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981−10080. (c) Liu, L.; Zhang, J. Gold-Catalyzed Transformations of α-Diazocarbonyl Compounds: Selectivity and Diversity. *Chem. Soc. Rev.* **2016**, *45*, 506−516. (d) Zhang, Z.-H.; Wang, J.-B. Recent studies on the reactions of α-diazocarbonyl compounds. *Tetrahedron* **2008**, *64*, 6577−6605. (e) Ma, B.; Liu, L.; Zhang, J. Gold-Catalyzed Site-Selective C−H Bond Functionalization with Diazo Compounds. *Asian J. Org. Chem.* **2018**, *7*, 2015−2025. (f) Zhang, W.; Xu, G.; Qiu, L.; Sun, J. Gold catalyzed C5-alkylation of indolines and sequential oxidative aromatization: access to C5-functionalized indoles. *Org. Biomol. Chem.* **2018**, *16*, 3889−3892.

(4) (a) Park, C. P.; Nagle, A.; Yoon, C. H.; Chen, C.; Jung, K. W. Formal Aromatic C−H Insertion for Stereoselective Isoquinolinone Synthesis and Studies on Mechanistic Insights into the C−C Bond Formation. *J. Org. Chem.* **2009**, *74*, 6231−6236. for an instructive review, see: (b) Davies, H. M. L.; Morton, D. Guiding Principles for Site Selective and Stereoselective Intermolecular C−H Functionalization by Donor/Acceptor Rhodium Carbenes. *Chem. Soc. Rev.* **2011**, *40*, 1857−1869. (c) Chen, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W. Y. Rh-Catalyzed Intermolecular Carbenoid Functionalization of Aromatic C−H Bonds by α-Diazomalonates. *J. Am. Chem. Soc.* **2012**, *134*, 13565−13568. (d) Best, D.; Burns, D. J.; Lam, H. W. Direct Synthesis of 5-Aryl Barbituric Acids by Rhodium(II)-Catalyzed Reactions of Arenes with Diazo Compounds. *Angew. Chem., Int. Ed.* **2015**, *54*, 7410−7413. (e) Best, D.; Jean, M.; van de Weghe, P. Modular Synthesis of Arylacetic Acid Esters, Thioesters, and Amides from Aryl Ethers via Rh(II)-Catalyzed Diazo Arylation. *J. Org. Chem.* **2016**, *81*, 7760−7770. (f) Xu, B.; Li, M.-L.; Zuo, X.-D.; Zhu, S.-F.; Zhou, Q.-L. Catalytic asymmetric arylation of α-aryl-α-diazoacetates with aniline derivatives. *J. Am. Chem. Soc.* **2015**, *137*, 8700−8703.

(5) (a) Auvil, T. J.; So, S. S.; Mattson, A. E. Double Arylation of Nitro Diazoesters via a Transient N−H Insertion Organocascade. *Angew. Chem., Int. Ed.* **2013**, *52*, 11317−11320. (b) Zhai, C.; Xing, D.; Jun Zhou, C. J.; Wang, C.; Wang, D.; Hu, W. Facile Synthesis of 3-Aryloxindoles via Brønsted acid Catalyzed Friedel-Crafts Alkylation of Electron-Rich Arenes with 3-Diazooxindoles. *Org. Lett.* **2014**, *16*, 2934−2937. (c) Yu, Z.; Li, Y.; Shi, J.; Ma, B.; Liu, L.; Zhang, J. $(C_6F_5)_3B$ Catalyzed Chemoselective and ortho-Selective Substitution of Phenols with α-Aryl α-Diazoesters. *Angew. Chem., Int. Ed.* **2016**, *55*, 14807−14811. (d) Gallo, R. D. C.; Momo, P. B.; Day, D. P.; Burtoloso, A. C. B. Catalytic Friedel-Crafts Alkylation of Electron Rich Aromatic Derivatives with alpha-Aryl Diazoacetates Mediated by Bronsted Acids. *Org. Lett.* **2020**, *22*, 2339−2343.

(6) (a) Fructos, M. R.; Belderrain, T. R.; Frémont, P.; Scott, N. M.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. A Gold Catalyst for Carbene-Transfer Reactions from Ethyl Diazoacetate. *Angew. Chem., Int. Ed.* **2005**, *44*, 5284−5288. (b) Rivilla, I.; Gómez-Emeterio, B. P.; Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J. Exclusive Aromatic vs Aliphatic C−H Bond Functionalization by Carbene Insertion with Gold-Based Catalysts. *Organometallics* **2011**, *30*, 2855−2860. (c) Pérez, P. J.; Díaz-Requejo, M. M.; Rivilla, I. Gold-catalyzed Naphthalene Functionalization. *Beilstein J. Org. Chem.* **2011**, *7*, 653−657. (d) Yu, Z.; Ma, B.; Chen, M.; Wu, H.-H.; Liu, L.; Zhang, J. Highly Site-Selective Direct C−H Bond Functionalization of Phenols with α-Aryl-α-diazoacetates and Diazooxindoles via Gold Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 6904−6907. (e) Xi, Y.; Su, Y.; Yu, Z.; Dong, B.; McClain, E. J.; Lan, Y.; Shi, X. Chemoselective Carbophilic Addition of α -Diazoesters through Ligand-Controlled Gold Catalysis. *Angew. Chem., Int. Ed.* **2014**, *53*, 9817−9821. (f) Ma, B.; Chu, Z.; Huang, B.; Liu, Z.; Liu, L.; Zhang, J. Highly *para*-Selective C-H Alkylation of Benzene Derivatives with 2,2,2-Trifluoroethyl α-Aryl-α-Diazoesters. *Angew. Chem., Int. Ed.* **2017**, *56*, 2749−2753. (g) Ma, B.; Wu, J.; Liu, L.; Zhang, J. Gold-Catalyzed para-selective C−H Bond Alkylation of Benzene Derivatives with Donor−/Acceptor-Substituted Diazo Compounds. *Chem. Commun.* **2017**, *53*, 10164−10167. (h) Yu, Z.; Li, Y.; Zhang, P.; Liu, L.; Zhang, J. Ligand and Counteranion Enabled Regiodivergent C−H Bond Functionalization of Naphthols with α-Aryl-α-Diazoesters. *Chem. Sci.* **2019**, *10*, 6553−6559. (i) Pizarro, J. D.; Schmidtke, I. L.; Nova, A.; Fructos, M. R.; Pérez, P. J. Selective Functionalization of Arene $C(sp^2)$−H Bonds by Gold Catalysis: The Role of Carbene Substituents. *ACS Catal.* **2022**, *12*, 6851−6856.

(7) (a) Tayama, E.; Yanaki, T.; Iwamoto, H.; Hasegawa, E. Copper (II) Triflate Catalyzed Intermolecular Aromatic Substitution of N, NDisubstituted Anilines with Diazo Esters. *Eur. J. Org. Chem.* **2010**, 6719−6721. (b) Ma, B.; Tang, Z.; Zhang, J.; Liu, L. Copper-Catalysed ortho-selective C−H Bond Functionalization of Phenols and Naphthols with α-Aryl-α-Diazoesters. *Chem. Commun.* **2020**, *56*, 9485−9488.

(8) (a) Mbuvi, H. M.; Woo, L. K. Catalytic C−H Insertions Using Iron(III)-Porphyrin Complexes. *Organometallics* **2008**, *27*, 637−645. (b) Yang, J. M.; Cai, Y.; Zhu, S. F.; Zhou, Q. L. Iron-Catalyzed Arylation of α-Aryl-α-Diazoesters. *Org. Biomol. Chem.* **2016**, *14*, 5516−5519. (c) Yu, Z.; Li, G.; Zhang, J.; Liu, L. Iron-Catalysed Chemo- and ortho-Selective C−H bond Functionalization of Phenols with α-Aryl α-Diazoacetates. *Org. Chem. Front.* **2021**, *8*, 3770−3775.

(9) Conde, A.; Sabenya, G.; Rodríguez, M.; Postils, V.; Luis, J. M.; Díaz-Requejo, M. M.; Costas, M.; Pérez, P. J. Iron and Manganese Catalysts for the Selective Functionalization of Arene $C(sp^2)$−H Bonds by Carbene Insertion. *Angew. Chem., Int. Ed.* **2016**, *55*, 6530−6534.

(10) All the available methods (refs 6g, h) in the literature relied on the use of α-aryl-α-diazoacetates containing either electron withdrawing or deactivating group on phenyl group or ester with EWG group for the functionalization of benzene or halobenzenes. For the α-(2-chlorophenyl)-α-diazoacetate, chloro group was essential for the functionalization of benzene. Till date α-phenyl-α-diazoacetates (no substituent on phenyl group) are not capable of functionalizing electron deficient arenes or even benzene due to their low reactivity.

Also, relatively electron rich α-phenyl-α-diazoacetates (containing EDG substituted phenyl group) have not been shown to react with arenes such as benzene and arenes with deactivating groups.

(11) The application of early transition metal (rare-earth metal) catalysts in C−H bond functionalization is still rare due to the high energy of the C−H bonds and low reactivity of the rare earth metal catalysts in comparision to versatile late transition metal catalysts. See few selected references-(a) Huang, W.; Diaconescu, P. L. C-H Bond Activation of Hydrocarbons Mediated by Rare-Earth Metals and Actinides: Beyond σ-Bond Metathesis and 1,2-Addition. In *Adv. Organomet. Chem.*; Pérez, P. J., Ed.; Academic Press, 2015; vol *64*, Chapter 2, pp 41−75. (b) Liu, Z.; Sivaguru, P.; Zanoni, G.; Anderson, E. A.; Bi, X. Catalyst-Dependent Chemoselective Formal Insertion of Diazo Compounds into C−C or C−H Bonds of 1, 3-Cicarbonyl Compounds. *Angew. Chem., Int. Ed.* **2018**, *57*, 8927−8931. (c) Li, W.; Wang, J.; Hu, X. L.; Shen, K.; Wang, W. T.; Chu, Y. Y.; Lin, L. L.; Liu, X. H.; Feng, X. M. Catalytic Asymmetric Roskamp reaction of α-Alkyl-α-Diazoesters with Aromatic Aldehydes: Highly Enantioselective Synthesis of α-Alkyl-β-Keto Esters. *J. Am. Chem. Soc.* **2010**, *132*, 8532−8533. (d) Hao, X.; Lin, L.; Tan, F.; Ge, S.; Liu, X.; Feng, X. Asymmetric Synthesis of Chromans via the Friedel−Crafts Alkylation−Hemiketalization Catalysed by an *N,N′*- Dioxide Scandium(iii) Complex. *Org. Chem. Front.* **2017**, *4*, 1647−1650. (e) Carvalho, R. L.; de Miranda, A. S.; Nunes, M. P.; Gomes, R. S.; Jardim, G. A. M.; da Silva Júnior, E. N. On the application of 3d metals for C−H activation toward bioactive compounds: The key step for the synthesis of silver bullets. *Beilstein J. Org. Chem.* **2021**, *17*, 1849−1938.

(12) (a) Navale, B. S.; Laha, D.; Bhat, R. G. Propargyl α-aryl-α-Diazoacetates as Robust Reagents for the Effective C−H Bond Functionalization of 1,3-Diketones via Scandium Catalysis. *Tetrahedron Lett.* **2019**, *60*, 1899−1903. (b) Laha, D.; Bhat, R. G. Silver-Catalyzed Epoxidation of Aldehydes Using Donor-/Acceptor-type Vinyl Diazosuccinimides to Access Spiro-Pyrrolidinedioneoxiranes. *Asian J. Org. Chem.* **2020**, *9*, 918−921. (c) Liu, Z.; Sivaguru, P.; Zanoni, G.; Anderson, E. A.; Bi, X. Catalyst-Dependent Chemoselective Formal Insertion of Diazo Compounds into C−C or C−H Bonds of 1,3-Dicarbonyl Compounds. *Angew. Chem., Int. Ed.* **2018**, *57*, 8927−8931. (d) Muthusamy, S.; Babu, S. A.; Gunanathan, C. Indium triflate: A Mild and Efficient Lewis Acid Catalyst for O−H Insertion Reactions of α-Diazo Ketones. *Tetrahedron Lett.* **2002**, *43*, 3133−3136. (e) Zhao, D.; Luo, J.; Liu, L.; Liu, Y. Regiospecific and Site-Selective C−H Allylation of Phenols with Vinyldiazo Compounds Catalyzed by In(III). *Org. Chem. Front.* **2021**, *8*, 6252−6258.

(13) We followed the reported procedure by Zhang, Liu and coworkers (see ref 6g) for the C−H bond functionalization of benzene with 2,2,2-trifluoroethyl α-phenyl-α-diazoactate without much success. It is important to note as per the literature (ref 5g) that the C−H bond functionalization of benzene worked only with 2,2,2-trifluoroethyl α-(4-trifluormethyl)-phenyl-α-diazoactate. The presence of electron withdrawing group such as trifluoromethyl moiety on the phenyl group of diazoester (*p*-position) was necessary for the desired transformation.

(14) Vong, K. K. H.; Maeda, S.; Tanaka, K. Propargyl-Assisted Selective Amidation Applied in C-terminal Glycine Peptide Conjugation. *Chem. − Eur. J.* **2016**, *22*, 18865−18872. (It is speculated that in addition to being weakly electron-withdrawing, the propargyl moiety may also play a previously undescribed role).

(15) In comparison to the traditional Lewis acids, the rare-earth metal triflates are relatively quite stable. In presence of water rare earth triflates are usually neither gets deactivated nor decomposed. Yu, Y-H.; Zhang, L-Y.; Wang, N-X.; Xing, Y. Recent Advances in the Rare-EarthMetal Triflates-Catalyzed Organic Reactions. *Catal. Rev.: Sci. Eng.* **2020**, 1−37.

(16) CCDC number of compound **3aa** is 1848210. The number contains all crystallographic details of this publication and is available free of charge at https://www.ccdc.cam.ac.uk/structures/.

(17) Compounds containing C(sp^3)−H bonds (benzylic C−H) are known to undergo or participate in benzylic C−H bond functionalization or give mixture of products: (a) Davies, H. M. L.; Jin, Q.; Ren, P.; Kovalevsky, A. Y. Catalytic Asymmetric Benzylic C-H Activation by Means of Carbenoid-Induced C-H Insertions. *J. Org. Chem.* **2002**, *67*, 4165−4169. (b) Davies, H. M. L.; Jin, Q. Intermolecular C−H Activation at Benzylic Positions: Synthesis of (+)-Imperanene and (−)-α-Conidendrin. *Tetrahedron: Asymmetry* **2003**, *14*, 941−949. (c) Guptill, D. M.; Davies, H. M. L. 2,2,2-Trichloroethyl Aryldiazoacetates as Robust Reagents for the Enantioselective C-H Functionalization of Methyl Ethers. *J. Am. Chem. Soc.* **2014**, *136*, 17718−17721.

(18) Spitzmaul, G.; Gumilar, F.; Dilger, J. P.; Bouzat, C. The Local Anaestheticsproadifen and Adiphenine Inhibit Nicotinic Receptors by Different Molecular Mechanisms. *Br. J. Pharmacol.* **2009**, *157*, 804−817.

(19) (a) Li, W.; Liu, X.; Hao, X.; Hu, X.; Chu, Y.; Cao, W.; Qin, S.; Hu, C.; Lin, L.; Feng, X. New Electrophilic Addition of α-Diazoesters with Ketones for Enantioselective C-N Bond Formation. *J. Am. Chem. Soc.* **2011**, *133*, 15268−15271. (b) Liu, F.; Zhu, L.; Zhang, T.; Zhong, K.; Xiong, Q.; Shen, B.; Liu, S.; Lan, Y.; Bai, R. Nucleophilicity versus Brønsted Basicity Controlled Chemoselectivity: Mechanistic Insight into Silver- or Scandium-Catalyzed Diazo Functionalization. *ACS Catal.* **2020**, *10*, 1256−1263. (c) Shanshan, C.; Zhaohong, L.; Haiyan, Y.; Liu, Y.; Jingping, Z.; Xihe, B. Computational Studies on Reaction Mechanism of the Catalyst-Controlled Selective Insertion of Metal Carbenoids into C−C and C−H bonds of 1,3-dicarbonyl compounds. *Chin. J. Org. Chem.* **2020**, *40*, 2468−2475. (d) Liu, Y.; Yu, Z.; Zhang, J. Z.; Liu, L.; Xia, F.; Zhang, J. Origins of Unique Gold-Catalysed Chemo- and Site-Selective C−H Functionalization of Phenols with Diazo compounds. *Chem. Sci.* **2016**, *7*, 1988−1995. (e) Liu, Y.; Yu, Z.; Luo, Z.; Zhang, J. Z.; Liu, L.; Xia, F. Mechanistic Investigation of Aromatic C(sp^2)−H and Alkyl C(sp^3)−H Bond Insertion by Gold Carbenes. *J. Phys. Chem. A* **2016**, *120*, 1925−1932. (f) Babaahmadi, R.; Dasgupta, A.; Hyland, C. J. T.; Yates, B. F.; Melen, R. L.; Ariafard, A. Understanding the Influence of Donor-Acceptor Diazo Compounds on the Catalyst Efficiency of $B(C_6F_5)_3$ Towards Carbene Formation. *Chem. − Eur. J.* **2022**, *28*, No. e2021043.

(20) We have also looked into different orientations of propargyl group with respect to scandium to observe any strong and reliable interactions that may stabilize the acetylene-scandium complex (see ESI, Appendix-IV, Figure 9). Based on the calculations (nearest to farthest scandium-acetylene interactions-difference in energy is 0.3 kcal/mol), we surmised that acetylenic moiety of propargyl group probably does not have any direct strong interaction with scandium to stabilize the complex.

https://doi.org/10.1021/acs.joc.2c01185
J. Org. Chem. 2022, 87, 13583−13597

Tetrahedron Letters 60 (2019) 1899–1903

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Propargyl α-aryl-α-diazoacetates as robust reagents for the effective C—H bond functionalization of 1,3-diketones via scandium catalysis

Balu S. Navale, Debasish Laha, Ramakrishna G. Bhat *

Department of Chemistry, Main Building, Indian Institute of Science Education and Research (IISER)-Pune, Dr. Homi Bhabha Road, Pashan, Pune 411008, Maharashtra, India

ARTICLE INFO

Article history:
Received 18 March 2019
Revised 12 June 2019
Accepted 15 June 2019
Available online 15 June 2019

Keywords:
C—H bond functionalization
1,3-Diketones
Propargyl α-aryl-α-diazoacetate
Scandium triflate

ABSTRACT

Propargyl α-aryl-α-diazoacetate a new class of reagent is developed for the effective C—H bond functionalization of 1,3-diketones at room temperature. The combination of scandium triflate and propargyl α-aryl-α-diazoacetate proved to be efficient catalyst-reagent system for the controlled C—H bond functionalization to afford 1,3-dicarbonyl alkylation. The protocol uses inexpensive $Sc(OTf)_3$ (5 mol%) and the reaction did not require the use of expensive catalysts or ligands and worked efficiently at room temperature. The practicality of the protocol has been demonstrated by the gram scale synthesis.
© 2019 Elsevier Ltd. All rights reserved.

Introduction

Selective C—H bond functionalization for the construction of new C—C bonds presents an alternative and powerful strategy to the traditional methods in organic synthesis. The direct C—H bond functionalization has several advantages and has attracted a great attention from the synthetic community [1,2]. The direct C—H bond functionalization reduces the number of synthetic steps and the pre-activation of starting materials could be avoided to increase the overall atom-efficiency. It has rapidly become one of the powerful tools for the synthesis and modification of complex molecules [3]. A great progress has been made in this field using different transition metal catalysts [4]. However, identifying and developing a suitable combination of catalyst and reagent system for the selective C—H bond functionalization is always a challenging task. The diazo compounds have been established as versatile reagents for various metal-catalyzed reactions [5]. Davies is one of the pioneers who embarked on comprehensive investigations of the scope of intermolecular C—H bond functionalization using diazo compounds [6]. The C—H bond functionalization using α-diazo esters normally proceeds via transient metal-carbenoid species, which are usually formed by the reaction with transition-metal complexes [7]. The transition metals such as rhodium [8], copper [9], silver [10] and recently gold [11] have been successfully explored for the decomposition of α-diazo esters to achieve the C—H bond functionalization. Different carbon nucleophiles have been explored for the intermolecular C—H bond functionalization with donor/acceptor type α-diazo esters [11g,12].

Reactive 1,3-dicarbonyl compounds are very useful scaffolds and they have been utilized for the transition-metal catalyzed oxidative C—H bond functionalization to access useful compounds [13]. However, these useful protocols need oxidants, excess substrates and high temperature for the effective transformation. In the year 2014, Lan and Shi, and co-workers elegantly presented the first gold-catalyzed C—H bond functionalization of 1,3-dicarbonyl compounds with α-aryl-α-diazoacetate (see Fig. 1A) [14].

It was demonstrated that the reaction followed the gold catalyzed decomposition of α-aryl-α-diazoacetate via the formation of a carbophilic carbocation. However, there is a great challenge to develop novel catalyst and reagent systems that are easily available and less expensive. A lot more efforts is needed to avoid the use of any expensive catalysts and ligands to make the protocol simple and practical which work at room temperature under mild conditions. Although, coinage metals and few of the heavy transitional-metals have been successfully explored for the C—H bond functionalization of α-diazo esters, alternative yet useful catalyst systems are desirable. Group 3 transition metals, e.g., scandium and lanthanides, have been used as environmentally friendly Lewis acid catalysts or promoters for a variety of chemical transformations [15].

Scandium catalysis has been promising and scandium triflate has been explored for the reactions of diazo compounds to achieve the successful C—H bond functionalization [16]. It would be very interesting to study the efficiency of scandium catalyst on the C—H bond functionalization of 1,3-dicarbonyl compounds with

* Corresponding author.
E-mail address: rgb@iiserpune.ac.in (R.G. Bhat).

https://doi.org/10.1016/j.tetlet.2019.06.026
0040-4039/© 2019 Elsevier Ltd. All rights reserved.

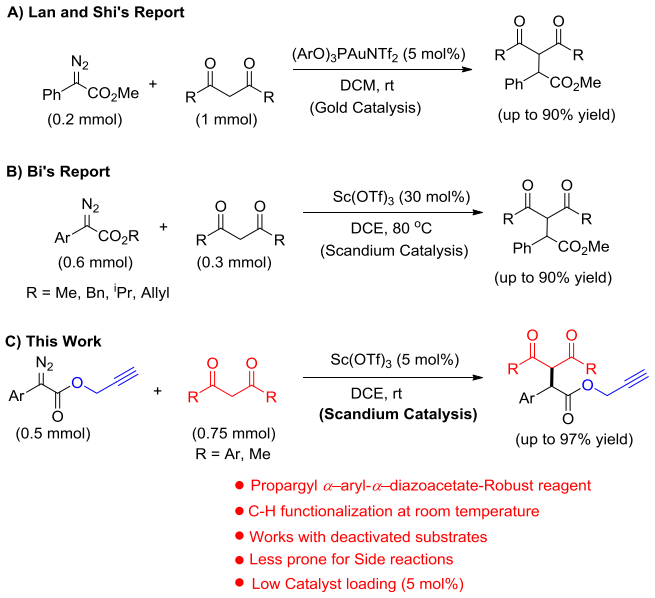


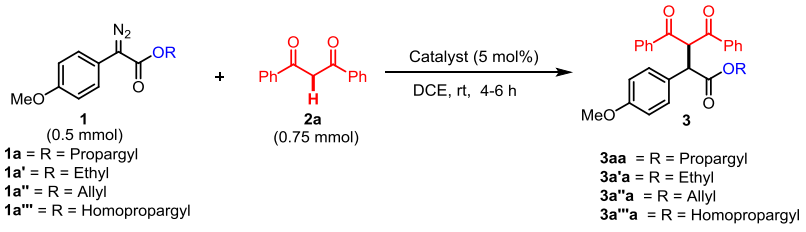
Fig. 1. C—H bond functionalization of 1, 3-dicarbonyl compounds with α-aryl-α-diazoacetates-Influence of ester groups.

α-aryl-α-diazo esters. The main challenges of this type of reaction are to avoid the side reactions such as dimerization of α-diazo esters, formation of α-oxoesters and to minimize the catalytic amount of the metal catalyst. It would also be a challenging task to have a catalyst control over insertion processes such as C—H insertion over O—H insertion. While this manuscript was under preparation, Bi and Co-workers disclosed the C—H bond functionalization of 1,3-dicarbonyl compounds with α-aryl-α-diazoacetates via scandium catalysis using higher catalyst loading and excess of α-aryl-α-diazoacetates at elevated temperature (see Fig. 1B) [10e]. Our group has been independently pursuing the development of catalyst-reagent system to expand the scope of C—H bond functionalization of α-diazo esters using early transition elements and lanthanides [17]. Despite many advances, still there are numerous limitations such as high reaction temperature, high substrate-reagent ratio, use of excess catalytic amount and expensive catalysts etc. Some of these limitations need to be overcome to make the protocols more practical and affordable. Herein, we report the discovery of propargyl α-aryl-α-diazoacetates as robust and useful new class of reagents for the C—H bond functionalization.

Results and discussion

At the outset, we began our investigation by choosing ethyl α-(4-methoxyphenyl)-α-diazoacetate **1a′** and 1,3-diketone **2a** (1,3-diphenyl-1,3-propanedione) as model substrates. The reaction of ethyl α-(4-methoxyphenyl)-α-diazoacetate **1a′** and 1,3-diketone **2a** in presence of $Cu(OTf)_2$ (5 mol%) in DCE at room temperature afforded the corresponding desired C—H functionalized product **3a′a** in 52% yield in 6 h (Entry 1, Table 1). While, the reaction in presence of gold catalyst [$(ArO)_3PAuNTf_2$ (5 mol%)] afforded the **3a′a** in moderate yield (36%, Entry 2, Table 1). Interestingly, Sc $(OTf)_3$ (5 mol%) catalyzed the reaction of ethyl α-(4-methoxyphenyl)-α-diazoacetate **1a′** (0.5 mmol) and 1,3-diketone 2a (0.75 mmol) to afford the desired product **3a′a** in 51% yield in 6 h at room temperature (See Entry 3, Table 1). A slight excess of unreacted **2a** was recovered during the purification. It was very encouraging that desired reaction worked at room temperature under scandium catalysis. Likewise, allyl α-(4-methoxyphenyl)-α-diazoacetate **1a″** (0.5 mmol) and 1,3-diketone **2a** (0.75 mmol) reacted in presence of $Sc(OTf)_3$ (5 mol%) to afford the desired product **3a″a** in 53% yield in 6 h at room temperature (See, Entry 4,

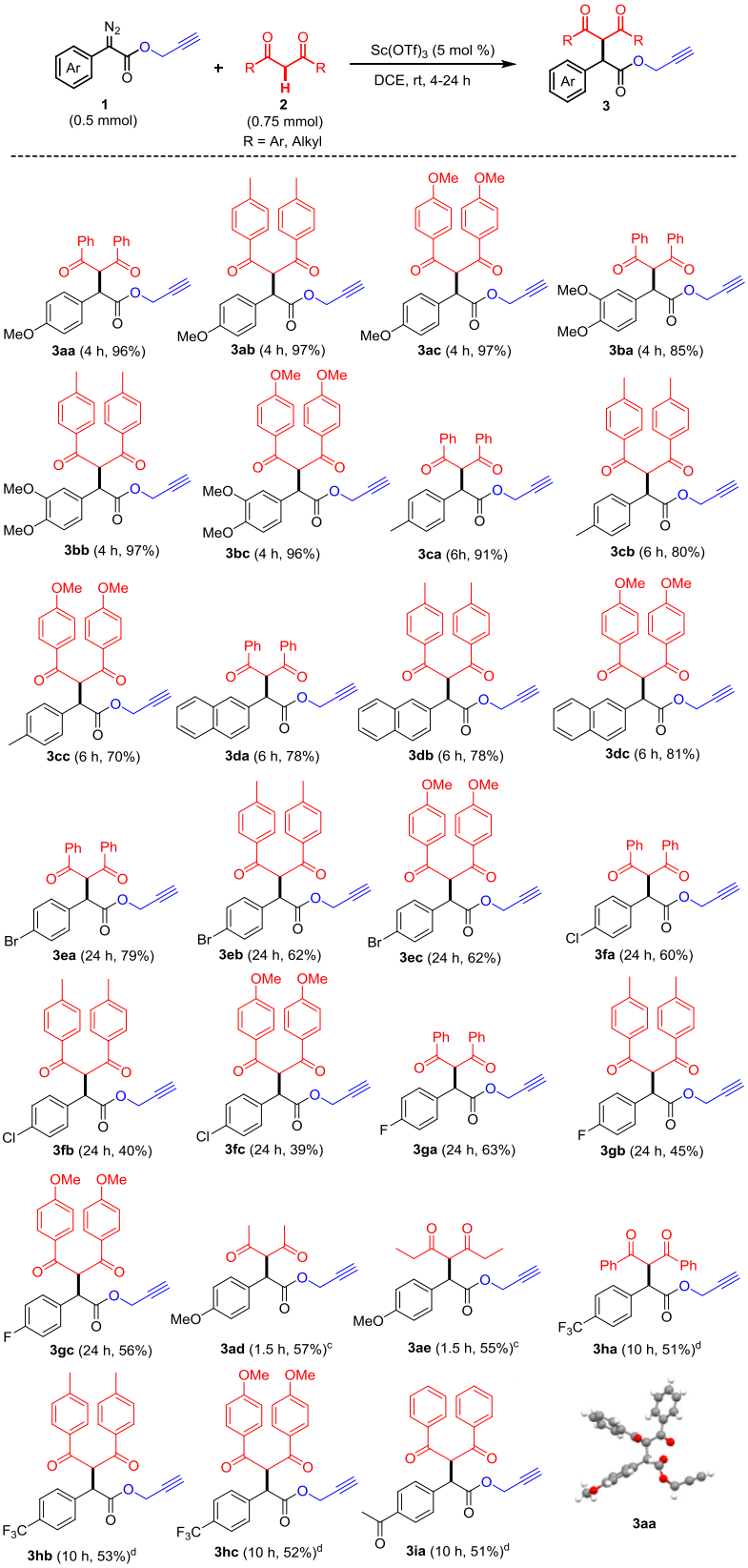
Table 1
Optimization of the reaction conditions for C—H functionalization.[a–d]



Entry	Catalyst	Substrate (1) R	Time (h)	Yield[b] (%)
1	$Cu(OTf)_2$	Ethyl	6	52
2	$(ArO)_3PAuNTf_2$	Ethyl	4	36
3	$Sc(OTf)_3$	Ethyl	6	51
4	$Sc(OTf)_3$	Allyl	6	53
5	$(ArO)_3PAuNTf_2$	Allyl	6	39
6	$(ArO)_3PAuNTf_2$	Propargyl	4	37
7	**$Sc(OTf)_3$**	**Propargyl**	**4**	**96**
8	$Bi(OTf)_3$	Propargyl	6	trace
9	$Cu(OTf)_2$	Propargyl	6	71
10	Dichloro(*p*-cymene)ruthenium(II) dimer	Propargyl	6	DC[c]
11	$Y(OTf)_3$	Propargyl	6	18
12	$In(OTf)_3$	Propargyl	6	68
13	$Rh_2(OAc)_4$	Propargyl	4	DC [c]
14	$Yb(OTf)_3$	Propargyl	6	Trace
15	Triflic acid	Propargyl	6	DC[c]
16	$Sc(OTf)_3$	Homopropargyl	6	73
17	No Catalyst	Propargyl	6	NR[d]

[a]Reaction conditions: α-Aryl-α-diazoacetate **1** (1 equiv., 0.5 mmol), 1,3-diketone **2a** (1.5 equiv., 0.75 mmol), DCE (3 mL) at room temperature, [b]Isolated yield after purification by column chromatography. [c]DC-Decomposed, [d]NR-no reaction.

Table 2
Scope of propargyl α-aryl-α-diazoacetates for the effective C—H bond functionalization of 1,3-diketones.[a–d]



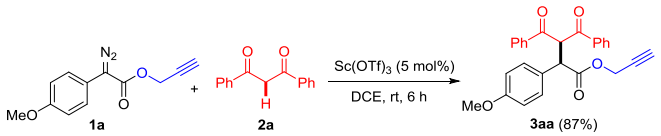
[a]Reaction conditions: α-aryl-α-diazoacetate **1** (1 equiv., 0.5 mmol), 1,3-diketone **2** (1.5 equiv., 0.75 mmol), $Sc(OTf)_3$ (5 mol%) in DCE (3 mL) at room temperature under inert atmosphere, [b]Isolated yield after purification by column chromatography (Time and Yield are given in parenthesis), [c]reaction was carried out at 50 °C, [d]$Sc(OTf)_3$ (10 mol%) in DCE at 70 °C under inert atmosphere.

Table 1). The reactions in presence of gold catalyst [$(ArO)_3PAuNTf_2$ (5 mol%)] afforded the desired products in modest yields (see Entries, 5, 6 Table 1). It is known in the literature that propargyl moiety is a weakly electron withdrawing group [18] and in this regard we planned to explore the effect of propargyl group in C—H bond functionalization of 1,3-dicarbonyl compounds. Propargyl α-(4-methoxyphenyl)-α-diazoacetate **1a** upon treatment with **2a** in presence of $Sc(OTf)_3$ (5 mol%) in DCE at room temperature afforded the corresponding **3aa** in relatively shorter reaction time with an excellent yield (96%, Entry 7, Table 1). Later, we screened various catalysts to explore the reactivity of propargyl α-(4-methoxyphenyl)-α-diazoacetate **1a** (see Entries 8–14). Cu $(OTf)_2$ catalyzed the desired reaction affording **3aa** in 71% yield in 6 h, where as other catalysts found to be not useful. In order to confirm the catalytic efficiency of $Sc(OTf)_3$, and to rule out the possibility of the formation of trace amount of triflic acid in situ by the hydrolysis of $Sc(OTf)_3$ if any due to the moisture and its subsequent catalysis, we carried out the reaction of **1a** and **2a** in presence of catalytic amount triflic acid (Entry 15, Table 1).

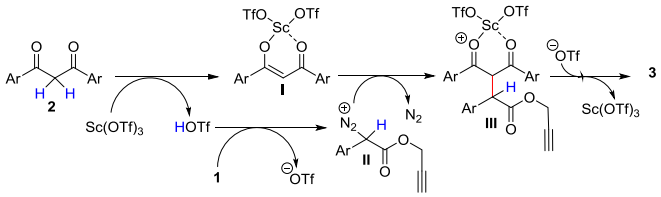
Interestingly, the reaction led to the decomposition of propargyl α-(4-methoxyphenyl)-α-diazoacetate **1a** in presence of triflic acid. The reaction of homopropargyl α-(4-methoxyphenyl)-α-diazoacetate **1a‴** (0.5 mmol) and 1,3-diketone **2a** (0.75 mmol) in presence of $Sc(OTf)_3$ (5 mol%) afforded the corresponding product **3a‴a** in 73% yield in 6 h at room temperature (See, Entry 16, Table 1). The reaction did not work in absence of any catalyst (Entry 17, Table 1).

Later, in order to optimize the reaction condition further, we carried out the reaction of **1a** and **2a** in presence of $Sc(OTf)_3$ in different solvents and among all the solvents, DCE proved to be the optimal solvent (See Appendix 1, ESI). The combination of propargyl α-aryl-α-diazoacetate **1** and scandium triflate as reagent-catalyst system proved to be efficient for the effective C—H bond functionalization of 1,3-diketones.

We observed that propargyl α-aryl-α-diazoesters and scandium catalyst worked synergistically to bring about desired C—H bond functionalization very efficiently at room temperature. Based on the exhaustive screening, propargyl α-aryl-α-diazoacetate **1** (0.5 mmol), 1,3-diketone **2** (0.75 mmol), $Sc(OTf)_3$ (5 mol%) in DCE at room temperature proved to be the optimum reaction condition. Encouraged by the initial success, we planned to explore the reactivity and scope of different propargyl α-aryl-α-diazoacetates for the effective C—H bond functionalization of 1,3-diketones. In order to study the protocol in more detail we synthesized various propargyl α-aryl-α-diazoacetates (**1a–1g**). Relatively, electron rich propargyl α-aryl-α-diazoacetates (**1a–1d**) reacted smoothly with different 1,3-diketones under the optimum reaction conditions to afford the corresponding desired products (**3aa–3dc**) in good to excellent yields (Table 2). Mildly electron deactivated substrates such as bromo-, chloro-, fluoro-propargyl α-aryl-α-diazoacetates (**1e–1g**) reacted smoothly with nucleophilic acyclic 1,3-diketones (**2a–2c**) successfully to afford the corresponding tricarbonyl compounds (**3ea–3ec, 3fa–3fc, 3ga–3gc**) in moderate to good yields (Table 2). It is very important to note that mildly electron deactivated substrates such as chloro-, fluoro-propargyl α-aryl-α-diazoacetates reacted under the reaction conditions at room temperature. Further, the treatment of propargyl α-(4-methoxyphenyl)-α-diazoacetate **1a** with aliphatic 1,3-diketones (**2d, 2e)** afforded the corresponding desired products (**3ad, 3ae)** at slightly elevated temperature in moderate yields (Table 2). While, the reactions of few propargyl α-aryl α-diazoacetates (**1h, 1i**) containing electron withdrawing groups (CF_3, Ac) with different 1,3-diketones in presence of $Sc(OTf)_3$ (10 mol%) afforded the corresponding desired products (**3ha–3hc, 3ia**) in moderate yields at elevated temperature (70 °C). Surprisingly, the reactions of propargyl α-(4-methoxyphenyl)-α-diazoacetate **1a** with cyclic 1,3-diketones



Scheme 1. Gram scale synthesis.



Scheme 2. Plausible reaction pathway for the scandium catalyzed C—H insertion.

(1,3-cyclohexanedione and 1,3-cyclopentanedione) under the optimum reaction conditions exclusively furnished the corresponding O—H insertion products. Based on the earlier findings [10e], it is believed that the formation of *cis* enol is crucial for the formation of bidentate complex with the metal for facilitating the C—H insertion reaction of acyclic 1,3-diketones. While the cyclic ketone such as 1,3-cyclohexanedione may not be able to form the effective bidentate complex as it is known to form *trans* enol [19] thus leading to O—H insertion product.

We observed that relatively electron rich propargyl α-aryl-α-diazoacetates (**1a–1d**) showed better reactivity in terms of yields under standard conditions. Both electron-rich and electron-deactivated/withdrawing propargyl α-aryl-α-diazoacetates tolerated the reaction conditions. We did not observe any side products such as carbene dimerization, α-oxoesters and azines during the C—H bond functionalization of 1,3-diketones under the optimal reaction conditions.

In order to extend the scope the methodology we carried out the reaction of propargyl α-(4-methoxyphenyl)-α-diazoacetate **1a** and 1,3-diketone **2a** on a gram scale under optimum reaction conditions. The protocol proved to be scalable and worked smoothly to afford the corresponding desired product **3aa** in 87% yield (Scheme 1).

Further, the structure of the compound **3aa** was unambiguously confirmed by single crystal X-ray analysis [20]. Based on the earlier literature report [10e], we proposed the plausible reaction pathway [21]. The 1,3-diketone **2** interacts with the $Sc(OTf)_3$ to form the scandium enolate **I** and triflic acid as by-product. This eventually acts as a proton source to protonate the propargyl α-aryl-α-diazoacetate **1** to generate the intermediate diazonium ion **II**, which undergoes a facile nucleophilic attack by the scandium enolate **I** to afford the complex **III** (Scheme 2).

Eventually the reaction of triflate anion with complex **III** furnishes the desired product **3** by regenerating the catalyst (Scheme 2). We presume that unlike electron donating power of ethyl/methyl group in ester, relatively weak electron deactivating propargyl moiety played a significant role in enhancing the electrophilicity of the diazonium ion which eventually leads to the reactive carbocation towards the facile C—H insertion at room temperature.

Conclusions

In conclusion, we have developed the new reagent-catalyst controlled effective C—H bond functionalization to afford 1,3-dicarbonyl alkylation via scandium catalysis. We have developed a new series of α-aryl-α-diazoacetates with propargyl ester as the

robust acceptor group and employed them as reagents for the effective C—H bond functionalization at room temperature. The protocol avoids the use of excess, expensive catalysts and ligands under practical conditions at room temperature. Practicality of the protocol has been demonstrated by the gram scale synthesis.

Acknowledgements

R. G. B. thanks DST-SERB (EMR/2015/000909), Govt. of India for the generous research grant. Authors also thank Indian Institute of Science Education and Research (IISER), Pune for the financial support. B. S. N. thanks CSIR, New Delhi, India and D. L. thanks UGC, New Delhi, India for the fellowship. Authors also thank Mr. Sandeep Kanade for optimizing the protocol for recording mass spectra of diazoesters.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.06.026.

References

[1] (a) C.-J. Li, Chem. Rev. 105 (2005) 3095;
(b) C.S. Yeung, V.M. Dong, Chem. Rev. 111 (2011) 1215.
[2] (a) R.G. Bergman, Nature 446 (2007) 391;
(b) J. Wencel-Delord, F. Glorius, Nat. Chem. 5 (2013) 369;
(c) A. McNally, B. Haffemayer, B.S.L. Collins, M.J. Gaunt, Nature 510 (2014) 129;
(d) R.-Y. Tang, G. Li, J.-Q. Yu, Nature 507 (2014) 215.
[3] (a) K. Godula, D. Sames, Science 312 (2006) 67;
(b) W.R. Gutekunst, P.S. Baran, Chem. Soc. Rev. 40 (2011) 1976;
(c) L. McMurray, F. O'Hara, M.J. Gaunt, Chem. Soc. Rev. 40 (2011) 1885;
(d) J. Egger, E.M. Carreira, Nat. Prod. Rep. 31 (2014) 449.
[4] (a) Z. Li, C.-J. Li, J. Am. Chem. Soc. 126 (2004) 11810;
(b) C. Guo, J. Song, S.-W. Luo, L.-Z. Gong, Angew. Chem. Int. Ed. 49 (2010) 5558;
(c) J.E.M.N. Klein, A. Perry, D.S. Pugh, R.J.K. Taylor, Org. Lett. 12 (2010) 3446;
(d) G. Zhang, J. Miao, Y. Zhao, H. Ge, Angew. Chem. Int. Ed. 51 (2012) 8318;
(e) K.L. Hull, M.S. Sanford, J. Am. Chem. Soc. 129 (2007) 11904;
(f) S.H. Cho, S.J. Hwang, S. Chang, J. Am. Chem. Soc. 130 (2008) 9254;
(g) K.M. Engle, D.-H. Wang, J.-Q. Yu, Angew. Chem. Int. Ed. 49 (2010) 6169;
(h) R. Zhu, S.L. Buchwald, Angew. Chem. Int. Ed. 51 (2012) 1926;
(i) Y. Horino, T. Yamamoto, K. Ueda, S. Kuroda, F.D. Toste, J. Am. Chem. Soc. 131 (2009) 2809;
(j) J. Canivet, J. Yamaguchi, I. Ban, K. Itami, Org. Lett. 11 (2009) 1733;
(k) H. Hachiya, K. Hirano, T. Satoh, M. Miura, Org. Lett. 11 (2009) 1737;
(l) T. Sugiishi, H. Nakamura, J. Am. Chem. Soc. 134 (2012) 2504.
[5] (a) M.P. Doyle, M.A. McKervey, T. Ye, Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides Vol (1998) 652;
(b) A.G.H. Wee, Curr. Org. Synth. 3 (2006) 499;
(c) Y. Zhang, J. Wang, Eur. J. Org. Chem. 2011 (2011) 1015;
(d) X. Zhao, Y. Zhang, J. Wang, Chem. Commun. 48 (2012) 10162.
[6] M.P. Doyle, Chem. Rev. 86 (1986) 919.
[7] (a) H.M.L. Davies, J.R. Manning, Nature 451 (2008) 417;
(b) Z. Zhang, J. Wang, Tetrahedron 64 (2008) 6577;
(c) M.P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, Chem. Rev. 110 (2010) 704;
(d) A. Ford, H. Miel, A. Ring, C.N. Slattery, A.R. Maguire, M.A. McKervey, Chem. Rev. 115 (2015) 9981;
(e) Y. Xia, D. Qiu, J. Wang, Chem. Rev. 117 (2017) 13810.
[8] H.M.L. Davies, D. Morton, Chem. Soc. Rev. 40 (2011) 1857.
[9] S.-F. Zhu, Q.-L. Zhou, ACC Chem. Res. 45 (2012) 1365.
[10] (a) J.L. Thompson, H.M.L. Davies, J. Am. Chem. Soc. 129 (2007) 6090;
(b) H. Luo, G. Wu, Y. Zhang, J. Wang, Angew. Chem. Int. Ed. 54 (2015) 14503;
(c) Z. Liu, Q. Li, P. Liao, X. Bi, Chem. Eur. J. 23 (2017) 4756;
(d) H. Nakayama, S. Harada, M. Kono, T. Nemoto, J. Am. Chem. Soc. 139 (2017) 10188;
(e) Z. Liu, P. Sivaguru, G. Zanoni, E.A. Anderson, X. Bi, Angew. Chem. Int. Ed. 57 (2018) 8927.
[11] (a) M.R. Fructos, T.R. Belderrain, P. de Frémont, N.M. Scott, S.P. Nolan, M.M. Díaz-Requejo, P.J. Pérez, Angew. Chem. Int. Ed. 117 (2005) 5418;
(b) M.R. Fructos, P. de Frémont, S.P. Nolan, M.M. Díaz-Requejo, P.J. Pérez, Organometallics 25 (2006) 2237;
(c) M.R. Fructos, M.M. Díaz-Requejo, P.J. Pérez, Chem. Commun. (2009) 5153;
(d) V.V. Pagar, A.M. Jadhav, R.-S. Liu, J. Am. Chem. Soc. 133 (2011) 20728;
(e) J.F. Briones, H.M.L. Davies, J. Am. Chem. Soc. 134 (2012) 11916;
(f) A.M. Jadhav, V.V. Pagar, R.-S. Liu, Angew. Chem. Int. Ed. 51 (2012) 11809;
(g) J.F. Briones, H.M.L. Davies, J. Am. Chem. Soc. 135 (2013) 13314;
(h) S.K. Pawar, C.-D. Wang, S. Bhunia, A.M. Jadhav, R.-S. Liu, Angew. Chem. 125 (2013) 7707.
[12] (a) M.J. Rosenfeld, B.K.R. Shankar, H. Shechter, J. Org. Chem. 53 (1988) 2699;
(b) M. Yang, T.R. Webb, P. Livant, J. Org. Chem. 66 (2001) 4945;
(c) M.R. Fructos, T.R. Belderrain, P. de Frémont, N.M. Scott, S.P. Nolan, M.M. Díaz-Requejo, P.J. Pérez, Angew. Chem. Int. Ed. 44 (2005) 5284;
(d) W.-J. Zhao, M. Yan, D. Huang, S.-J. Ji, Tetrahedron 61 (2005) 5585.
[13] (a) Z. Li, L. Cao, C.-J. Li, Angew. Chem. Int. Ed. 46 (2007) 6505;
(b) C. He, S. Guo, J. Ke, J. Hao, H. Xu, H. Chen, A. Lei, J. Am. Chem. Soc. 134 (2012) 5766;
(c) S. Pan, J. Liu, Y. Li, Z. Li, Chin. Sci. Bull. 57 (2012) 2382;
(d) K. Yang, Q. Song, Org. Lett. 17 (2015) 548;
(e) C. Wang, Y. Li, M. Gong, Q. Wu, J. Zhang, J.K. Kim, M. Huang, Y. Wu, Org. Lett. 18 (2016) 4151.
[14] Y. Xi, Y. Su, Z. Yu, B. Dong, E.J. McClain, Y. Lan, X. Shi, Angew. Chem. Int. Ed. 53 (2014) 9817.
[15] H. Yamamoto, K. Ishihara, Acid catalysis in modern organic synthesis (Shibasaki, M.; Matsunaga, S.; Kumagai, N. Lanthanide Lewis acid), Vol. 1, Wiley-VCH, Weinheim, 2008.
[16] (a) D.C. Moebius, J.S. Kingsbury, J. Am. Chem. Soc. 131 (2009) 878;
(b) W. Li, J. Wang, X. Hu, K. Shen, W. Wang, Y. Chu, L. Lin, X. Liu, X. Feng, J. Am. Chem. Soc. 132 (2010) 8532.
[17] We have been pursuing scandium triflate catalyzed C-H bond functionalizations under the sanctioned research project-Site-selective direct C-H bond functionalization by early transition metal-carbenoid insertion and its applications-EMR/2015/000909, SERB-DST Govt. of India.
[18] K.K.H. Vong, S. Maeda, K. Tanaka, Chem. Eur. J. 22 (2016) 18865.
[19] (a) A. Yigev, Y. Mazur, J. Org. Chem. 32 (1967) 2162;
(b) M. Curini, F. Epifano, S. Genovese, Tetrahdron Lett. 47 (2006) 4697.
[20] CCDC number of **3aa** is 1848209. This number contains all crystallographic details of this publication and is available free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html.
[21] It is believed that the formation of *cis* enol is crucial for the formation of bidentate complex with the metal for facilitating the C-H insertion reaction of acyclic 1,3-diketones (See ref 10e).

ChemPubSoc Europe

DOI: 10.1002/slct.201801522

Chemistry SELECT Communications

Organic & Supramolecular Chemistry

A One Pot Transition-Metal-Free Synthesis of Styrenyl Ethers from 2-Aryloxy/Alkoxy Acetophenones

Trimbak B. Mete, Debasish Laha, and Ramakrishna G. Bhat*[a]

A one-pot transition-metal-free synthesis of styrenyl ethers starting from 2-aryloxy/alkoxy acetophenones is described. The protocol explores the use of tosyl hydrazide and potassium carbonate as a mild base via Bamford-Stevens reaction to synthesize the styrenyl ethers. The protocol is very simple, practical and uses mild reaction conditions with simple reaction set-up. This practical protocol proved to be scalable on gram quantity.

The vinyl functionality is very important and useful in organic synthesis as well as in polymer and pharma industries. Aryl vinyl/styrenyl ethers have been explored as nucleophiles in cycloaddition reactions,[1] ene and aldol-type additions,[2] cyclopropanations[3] and metathesis reactions[4] and are commonly used as acyl anion equivalents.[5] They have been effectively explored in the synthesis of polymers as well.[6] Vinyl group is also a very useful protecting group for the phenol derivatives.[7] Considering the importance of this scaffold and its applications, many research groups have developed transition-metal catalyzed cross coupling reactions as well as traditional multi-step strategies for the synthesis of aryl vinyl ethers.[8] Mostly, transition metal catalyzed cross-coupling of vinyl halides and phenols has been explored for the synthesis of vinyl/styrenyl ethers (Figure 1 A).[9] Likewise, it has been demonstrated that rhodium can effectively catalyze the Bamford-Stevens reaction to access vinyl ethers starting from Eschenmoser hydrazone (Figure 1 B).[10] However, most of the methods rely on the use of expensive palladium and rhodium catalysts which is not cost effective for the large scale industrial applications.[9a–b,10] On the other hand less expensive metals such as copper, nickel require supporting ligands for the transformation.[9c–h] Most of the transition metals are toxic to different extents, and it is very expensive and challenging to remove the trace amounts of transition metal residues from desired products.[11] Also some of the transition metals are sensitive to oxygen and some require the assistance of co-catalysts or additives.[12] Traditional methods for the synthesis of vinyl/styrenyl ethers rely on double bond isomerization or carbonyl olefination like Wittig reaction and strong base mediated elimination of halides as well as alcohols.[8a,d] Transition-metal-free protocols are gaining a great importance for the last few years. It would be really useful to develop a protocol that does not rely on transition metals, ligands and strong bases for the large scale practical applications. Sulfonylhydrazones have been proved to be excellent and versatile synthetic intermediates for the in situ generation of diazo compounds in organic synthesis.[13] The role of sulfonylhydrazones to access olefins via Bamford-Stevens reaction is well established.[14] However, surprisingly, the synthesis of functionalized olefin derivatives has not been explored till date via Bamford-Stevens reaction under transition-metal-free conditions. Hence alternative transition-metal-free pathways to synthesize styrenyl ethers are highly appealing and demanding. Herein, for the first time we describe transition-metal-free application of sulfonyl hydrazones to access styrenyl ethers via Bamford-Stevens reaction. Aryl vinyl ethers have been synthesized starting from 2-aryloxy and alkoxy acetophenones and tosyl hydrazide using K_2CO_3 as a base under mild reaction conditions.

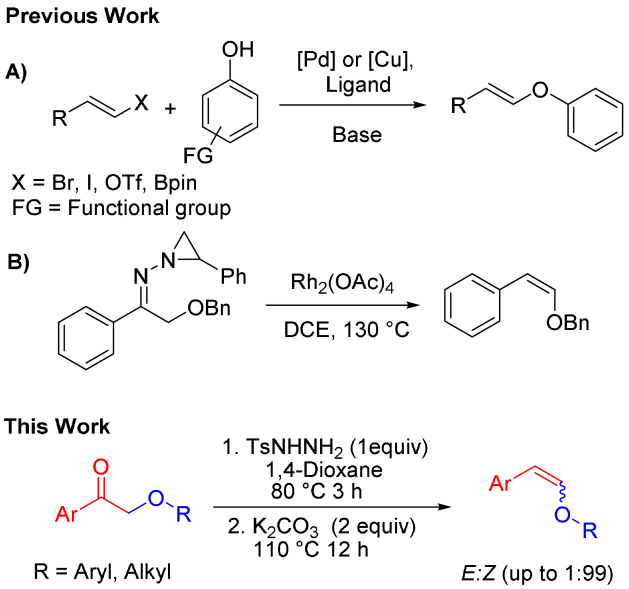


Figure 1. (A) Metal catalyzed cross coupling reactions. (B) Rhodium catalyzed Bamford-Stevens reaction

Initially, a model one pot reaction was carried out by heating phenyloxy acetophenone (2-phenoxy-1-phenylethan-1-one) **1a** and tosylhydrazide **2** in DCE at 80 °C for 3 h followed

[a] *Dr. T. B. Mete, D. Laha, Prof. R. G. Bhat*
Department of Chemistry, Indian Institute of Science Education and Research (IISER)-Pune, Main Building, Dr. Homi Bhabha Road, Pashan, Pune, 411008, Maharashtra, India
E-mail: rgb@iiserpune.ac.in

Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.201801522

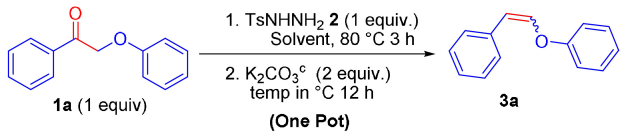
© 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

by the addition of K_2CO_3 (2 equiv.). The reaction was continued for 12 h while maintaining the temperature. Gratifyingly, we observed that the desired product (2-phenoxyvinyl)benzene **3a** was obtained in 40% yield (entry 1, Table 1). Encouraged by the initial result, we screened several solvents and varied the reaction temperature for achieving the optimum yield of **3a**. Using THF as a solvent, we observed the formation of the desired product **3a** in modest yield (entry 2, Table 1). Among all the solvents screened, 1,4-dioxane was found to be optimum solvent at 80 °C thus affording the desired product **3a** in moderate yield (entry 3, Table 1). Further increase in the reaction temperature (110 °C) afforded the corresponding product **3a** in 84% yield (entry 10, Table 1). Thereafter increase in reaction temperature (130 °C) did not have any significant effect on the yield of the product **3a** (entry 11, Table 1). After screening several solvents at different temperatures, we found that heating substrate **1** and tosyl hydrazide **2** (1 equiv.) in 1,4-dioxane at 80 °C for 3 h followed by the addition of K_2CO_3 (2 equiv.) at 110 °C for 12 h was found to be the optimum reaction condition (entry 10, Table 1).

With this initial success and having an optimized reaction condition in hand, we planned to explore the wider substrate scope for the generality of the method. In this regard various aryloxy acetophenones (**1a-1w**) were synthesized starting from different phenacyl bromide and phenol derivatives. Similarly alkoxy acetophenones (**1aa-1gg**) were synthesized starting from different α-diazoacetophenone derivatives and alcohols (see ESI for details). Various aromatic substrates containing phenyl, methyl, methoxy, bromo, chloro, fluoro substituents worked smoothly under the optimized reaction conditions to afford the corresponding desired products (**3a-3q**) in moderate to very good yields (see Table 2, up to 84% yield). Likewise, ketoethers bearing naphthyl functionality adjacent to oxygen also worked smoothly affording the desired products (**3r-3w**) in moderate to very good yields (67-83%). Further we turned our attention towards the synthesis of aliphatic keto ether substrates. Gratifyingly variety of substrates (**1aa-1gg**) worked nicely under optimized reaction conditions to afford the corresponding products **3aa-3gg** (see Table 2).

Benzyl ketoethers under the optimized reaction condition afforded the corresponding products (**3aa, 3bb**) in good yields. The branched as well as long chain ketoethers also reacted smoothly to afford the corresponding styrenyl ethers (**3cc, 3ff** and **3gg**) in moderate to good yields (up to 80%). Chiral ketoether derived from (+)-menthol worked efficiently to give the corresponding product **3ee** in moderate yield 67%. A variety of electron-donating and mildly deactivating substitu-

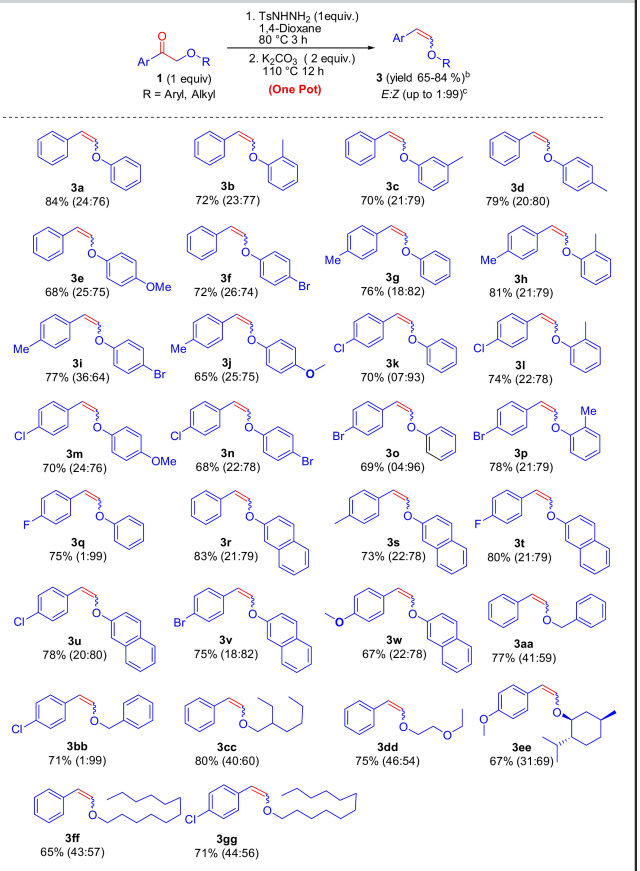
Table 1. Optimization of the reaction conditions[a]



Entry	Solvent	Temp Step-1 (°C)	Temp Step-2 (°C)	Time (h)	Yield (%)[b]	*E:Z* ratio
1	DCE	80	80	12	34	30:70
2	THF	80	80	12	39	31:69
3	1,4-dioxane	80	80	12	52	23:77
4	DMF	80	80	12	45	45:55
5	DMSO	80	80	12	41	33:67
6	DCE	80	90	12	37	28:72
7	1,4-dioxane	80	100	12	73	25:75
8	DMF	80	100	12	61	42:58
9	DMSO	80	100	12	57	31:69
10	**1,4-dioxane**	**80**	**110**	**12**	**84**	**24:76**
11	1,4-dioxane	80	130	12	80	23:77

[a]Reaction conditions: Step-1: 2-phenoxy-1-phenylethan-1-one **1a** (1 equiv.), 4-methylbenzenesulfonohydrazide **2** (1 equiv.), solvent (2 mL) in pressure tube at 80 °C for 3 h, Step-2: potassium carbonate (2 equiv.), heated for 12 h, [b]Isolated yield after purification by column chromatography. [c]Reactions with bases such as LiO^{t}Bu, Cs_2CO_3 afforded the desired product in lower yield and selectivity.

Table 2. Aryl/alkyl styrenyl ethers formation[a]



[a]Reaction conditions: Step-1: 2-aryloxy/alkoxy acetophenone derivative **1** (1 equiv.), 4-methylbenzenesulfonohydrazide **2** (1 equiv.), 1,4-dioxane (2 mL) in pressure tube at 80 °C for 3 h, Step-2 potassium carbonate (2 equiv.), heated for 12 h, [b]Isolated yield after purification by column chromatography. [c]diastereomeric ratio was determined by ^{1}H NMR and the *E:Z* ratio has been given in parenthesis.

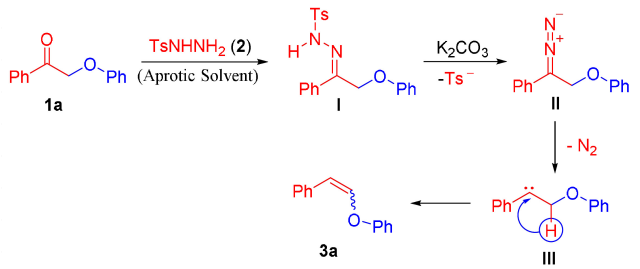
© 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

ents (F, Cl, Br) on either phenyl rings tolerated the reaction conditions to afford the desired products and the results are summarized in Table 2. However, these functional groups did not have any significant effect on the reaction rate and yields.

We observed that styrenyl ethers derived from aryloxy acetophenones were highly *Z*-selective (up to *E*:*Z* = 1:99)[15] while the products derived from alkoxy acetopheonones (**3aa**, **3cc**-**3gg**) were found to be relatively less selective (up to *E*:*Z* = 31:69).The styrenyl ether **3bb** derived from benzyloxy acetopheonone **1bb** was found to be highly *Z*-selective (*E*:*Z* = 01:99). It is very interesting to note that unlike the previous report[10] we did not observe any side products or multiple decomposition products during the reaction of any substrates. Likewise, the reaction worked smoothly without the assistance of any metal.

In order to make this approach more practical and for the wider applicability, we demonstrated the synthesis of **3 a** on a gram scale starting from the corresponding 2-phenoxy-1-phenylethan-1-one **1 a** under optimum reaction conditions (86% yield).

Based on our investigations and previous literature[14,16,17] we propose that tosyl hydrazide **2** reacts with 2-phenoxy-1-phenylethan-1-one **1 a** to form tosyl hydrazone **I**, which then reacts with base K_2CO_3 to form diazo intermediate **II**. This further undergoes thermal decomposition to form carbene intermediate **III** that subsequently leads to 1, 2-hydride shift followed by the formation of double bond (Scheme 1).



Scheme 1. Plausible Mechanism

In conclusion, a novel transition-metal-free one-pot two step method has been developed for the synthesis of styrenyl ethers starting from 2-aryloxy/alkoxy acetophenones. The method works smoothly on both aromatic and aliphatic substrates. The protocol employs mild, commercially available and less expensive K_2CO_3 as a mild base and the desired products were obtained in good to excellent yields. Moreover, a wide range of functional groups was well tolerated. The Bamford-Stevens reaction has been explored for the synthesis of functionalized olefins under transition-metal-free conditions. Experimental conditions are simple and the method proved to be scalable for wider application.

Supporting Information Summary

Supporting information includes **the experimental procedure, characterization data, and the copies of ^{1}H and ^{13}C NMR spectra.**

Acknowledgements

R. G. B. thanks DST-SERB (EMR/2015/000909), Govt. of India for the generous research grant. Authors also thank Indian Institute of Science Education and Research (IISER), Pune for the financial support. T. B. M. thanks CSIR, New Delhi, India and D. L. thanks UGC. New Delhi, India for the fellowship.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Aryloxy/Alkoxy acetophenone · Bamford-Stevens reaction · Styrenyl ether · Transition-Metal-Free

[1] a) H. A. A. El-Nabi, *Tetrahedron* **1997**, *53*, 1813–1822; b) J. Firl, S. Sommer, *Tetrahedron Lett.* **1970**, 1929–1932; c) D. A. Boger, K. D. Robarge, *J. Org. Chem.* **1988**, *53*, 3373–3377.

[2] E. Kitazawa, T. Imamura, K. Saigo, T. Mukaiyama, *Chem. Lett.* **1975**, 569–571.

[3] P. E. Maligres, M. M. Waters, J. Lee, R. A. Reamer, D. Askin, *J. Org. Chem.* **2002**, *67*, 1093–1101.

[4] O. Fujimura, G. C. Fu, R. H. Grubbs, *J. Org. Chem.* **1994**, *59*, 4029–4031.

[5] J. E. Baldwin, G. A. Höfle, Jr. O. W. Lever, *J. Org. Chem.* **1974**, *96*, 7125–7127.

[6] a) A. Ouali, R. Laurent, A.-M. Caminade, J.-P. Majoral, M. Taillefer, *J. Am.Chem. Soc.* **2006**, *128*, 15990–15991; b) M. Taillefer, A. Ouali, B. Renard, J.-F. Spindler, *Chem. Eur. J.* **2006**, *12*, 5301–5313; c) W. Bao, Y. L. Xin Lv, *Synthesis* **2008**, *12*, 1911–1917; d) H. Kaddouri, V. Vicente, A. Ouali, F. Ouazzani, M. Taillefer, *Angew. Chem*, **2009**, *121*, 339–342; *Angew. Chem., Int. Ed.* **2009**, *48*, 333–336.

[7] a) T. W. Green, P. G. M. Wuts, Protecting groups, 3rd ed.; Wiley: New York, **1991**; p 619; b) Y. L. Chen, K. G. Hedberg, K. J. Guarino, *Tetrahedron Lett.* **1989**, *30*, 1067–1068.

[8] a) J. Ying, N. L. Bauld, *J. Org. Chem.* **1999**, *64*, 9251–9253; b) Y. Okimoto, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc.* **2002**, *124*, 1590–1591; c) S. Suprenant, W. Y. Chan, C. Berthelette, *Org. Lett.* **2003**, *5*, 4851–4854; d) D. J. Winternheimer, R. E. Shade, C. A. Merlic, *Synthesis* **2010**, *42*, 2497–2511; e) C. Cao, L. Zhang, G. Zhou, W. Dan, X. Wang, X. Zhao. *ChemistrySelect* **2017**, *2*, 2985–2988.

[9] a) R. Rossi, F. Bellina, L. Mannina, *Tetrahedron* **1997**, *53*, 1025–1044; b) M. C. Willis, D. Taylor, A. T. Gillmore, *Chem. Commun.* **2003**, 2222–2223; c) Z. Wan, C. D. Jones, T. M. Koenig, Y. J. Pu, D. Mitchell, *Tetrahedron Lett.* **2003**, *44*, 8257–8259; d) D. Kundu, P. Maity, B. C. Ranu, *Org. Lett.* **2014**, *16*, 1040–1043; e) M. Taillefer, A. Ouali, B. Renard, J. -F. Spindler, *Chem. Eur. J.* **2006**, *12*, 5301–5313; f) M. S. Kabir, M. Lorenz, O. A. Namjoshi, J. M. Cook, *Org. Lett.* **2010**, *12*, 464–467; g) J. Limberger, B. C. Leal, D. F. Back, J. Dupont, A. L. Monterio, *Adv. Synth. Catal.* **2012**, *354*, 1429–1436; h) K. Jouvin, A. Bayle, F. Legrand, G. Evano, *Org. Lett.* **2012**, *14*, 1652–1655; i) R. E. Shade, A. M. Hyde, J–C. Olsen, C. A. Merlic, *J. Am. Chem. Soc.* **2010**, *132*, 1202–1203.

[10] J. A. May, B. M. Stoltz, *J. Am. Chem. Soc.* **2002**, *124*, 12426–12427.

[11] a) D. Nair, J. Scarpello, L. White, L. Freista dos Santos, I. Vankelecom, A. Livingston, *Tetrahedron Lett.* **2001**, *42*, 8219–8222; b) C. Garett, K. Prasad, *Adv. Synth. Catal.* **2004**, *346*, 889–900; c) J. Rivera-Utrilla, I. Bautista-Toledo, M. Ferro-Garcia, C. Moreno-Catilla, *J. Hazard. Mater.* **2003**, *41*, 323–330.

[12] a) A. Gansauer, H. Bluhm, *Chem. Rev.* **2000**, *100*, 2771–2788; b) M. Shibasaki, Y. Yamamoto, Weinheim, *Multimetallic Catalysts in Organic*

© 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Synthesis Eds, Wiley-VCH, **2004**; c) C. Wang, Z. Xi, *Chem. Soc. Rev.* **2007**, *36*, 1395–1406; d) J. Oxgaard, W. J. III Tenn, R. J. Nielsen, R. A. Periana, W. A., III. Goddard, *Organometallics* **2007**, *26*, 1565–1567; e) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; f) Y. Boutadla, D. L. Davies, S. A. Macgregor, A. I. Poblador-Bahamonde, *Dalton Trans.* **2009**, 5820–5831; g) D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118–1126.

[13] a) V. K. Aggarwal, J. de Vicente, R. V. Bonnert, *Org. Lett.* **2001**, *3*, 2785–2788; b) V. K. Aggarwal, E. Alonso, G. Fang, M. Ferrara, G. Hynd, M. Porcelloni, *Angew. Chem.* **2001**, *113*, 1482–1485; *Angew. Chem. Int. Ed.* **2001**, *40*, 1433–1436; c) J. R. Fulton, V. K. Aggarwal, J. de Vicente, *Eur. J. Org. Chem.* **2005**, 1479–1492; d) V. K. Aggarwal, E. Alonso, G. Hynd, K. M. Lydon, M. J. Palmer, M. Porcelloni, J. R. Studley, *Angew. Chem.* **2001**, *113*, 1479–1482; *Angew.Chem. Int. Ed.* **2001**, *40*, 1430–1433; e) W.-H. Cheung, S.-L. Zheng, W.-Y. Yu, G.-C. Guo-Chuan Zhou, C.-M. Che, *Org. Lett.* **2003**, *5*, 2535–2538.

[14] W. R. Bamford, T. S. Stevens, *J. Chem. Soc.* **1952**, 4735–4740.

[15] Time dependent ^{1}HNMR study revealed that chemoselectivity did not change with the reaction time (see ESI)

[16] D. F. Taber, R. J. Herr, S. K. Pack, J. M. Geremia, *J. Org. Chem.* **1996**, *61*, 2908–29010.

[17] It is known in the literature that use of aprotic solvents for Bamford-Stevens reaction favors the *Z*-selectivity via carbene intermediate followed *syn*-1, 2-hydride shift. Whereas, protic solvents leads to the mixture of *E* and *Z* olefins via ionic intermediate.

Submitted: May 22, 2018
Accepted: June 29, 2018

© 2018 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Handbook of CH-Functionalization

Site-Selective C—H Functionalization with Diazo Compounds (Carbenes)

Diverse Strategies

Debasish Laha, Javed Y. Shaikh, Ramakrishna G. Bhat

First published: 29 November 2022
https://doi.org/10.1002/9783527834242.chf0085

Abstract

The realization of the direct C—H bond functionalization has really brought the radical change in planning the organic synthetic strategies via traditional logics. The C—H bond functionalization is an art of selective functionalization even in presence of more reactive functional groups. In this article, we have highlighted more challenging intermolecular site-selective C—H bond functionalization of unactivated C—H bonds of small organic scaffolds using different diazo carbonyl reagents, substrates, and catalysts-controlled processes. This article has covered the selective and undirected C—H functionalization of alkanes, arenes, *N*-substituted and free aromatic amines, phenols, naphthols, 1,3-dicarbonyl compounds, and benzofurans with different diazo carbonyl compounds under metal catalysis. This article has been written to serve as a guide for understanding the principle and for accessing newer approaches to achieve the selective C—H bond functionalization.

References

1 Doyle, M.P., Duffy, R., Ratnikov, M., and Zhou, L. (2010). *Chem. Rev.* **110**: 704– 724.
View | CAS | PubMed | Web of Science® | Google Scholar

2 Zalatan, D.N. and Du Bois, J. (2010). In: *C–H Activation*, vol. **292** (ed. J.-Q. Yu and Z. Shi), 347– 379. Heidelberg: Wiley-VCH Verlag.
Google Scholar

3 (a) Davies, H.M.L. and Manning, J.R. (2008). *Nature* **451**: 417– 424.
View | CAS | PubMed | Web of Science® | Google Scholar
(b) Giri, R., Shi, B.-F., Engle, K.M. et al. (2009). *Chem. Soc. Rev.* **38**: 3242– 3272.
View | CAS | PubMed | Web of Science® | Google Scholar

(b) Yu, Z., Li, Y., Shi, J. et al. (2016). *Angew. Chem. Int. Ed.* **55**: 14807– 14811.

(c) Gallo, R.D.C., Momo, P.B., Day, D.P., and Burtoloso, A.C.B. (2020). *Org. Lett.* **22**: 2339– 2343.

92 Zhang, Q., Zhang, X.-F., Li, M. et al. (2019). *J. Org. Chem.* **84**: 14508– 14519.

About Wiley Online Library

Privacy Policy
Terms of Use
About Cookies
Manage Cookies
Accessibility
Wiley Research DE&I Statement and Publishing Policies
Developing World Access

Help & Support

Contact Us
Training and Support
DMCA & Reporting Piracy

Opportunities

Subscription Agents
Advertisers & Corporate Partners

Connect with Wiley

The Wiley Network
Wiley Press Room

Copyright © 1999-2023 John Wiley & Sons, Inc. All rights reserved