Meldrum's Acid: A Useful Platform for Tandem Organocatalytic Synthesis of Pyroglutamic Acids, δ-Ketoesters, γ-Butyrolactones and α,β-Unsaturated Carbonyl Compounds

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By

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This thesis is dedicated to...

My parents

And

My beloved family

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "***Meldrum's Acid: A Useful Platform for Tandem Organocatalytic Synthesis of Pyroglutamic Acids, δ-Ketoesters, γ-Butyrolactones and α,β-Unsaturated Carbonyl Compounds"*** submitted by **Mr. Tushar Manik Khopade** was carried out by the candidate, 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.

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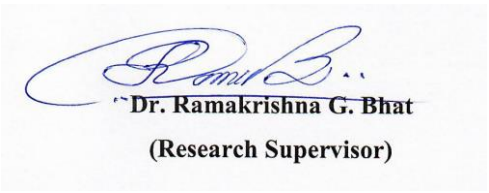

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DECLARATION

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Mr. Tushar Manik Khopade

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Tushar Manik Khopade

CONTENTS

ABBREVIATIONS

Å	Angstrom
ACN	Acetonitrile
Ar	Aryl
Au	*Aurum* (Gold)
ATH	Asymmetric Transfer Hydrogenation
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
^{t}Boc	*tert*-butoxycarbonyl
BOX	Bisoxazoline
bs	broad singlet
C	Carbon
^{o}C	degree Celsius
Calcd.	Calculated
Cat.	Catalytic
Cbz	benzyloxycarbonyl
Cr	Cromium
Cu	Copper
d	doublet
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
D-Asp	D-Aspartic acid
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
D-Glu	D-Glutamic acid
DFT	Density functional theory
DMAP	*N,N'*-dimethylaminopyridine
DMEDA	*N,N'*-dimethylethylenediamine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid

D-Pip	D-Pipecolic acid
D-Phg	D-Phenyl glycine
D-Pro	D-Proline
ee	enantiomeric excess
E	Electrophile
equiv.	Equivalent
ENM	Enamine
ESI	electrospray ionisation
EtOAc	ethyl acetate
g	gram
FTIR	Fourier Transform InfraRed
Fmoc	Fluorenylmethyloxycarbonyl
H	Hydrogen
h	hour
HOMO	Highest energy occupied molecular orbital
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IBX	2-Iodoxybenzoic acid
iGluRs	ionotropic glutamate receptors
Int	Intermediate
Ir	Iridium
J	Spin coupling constant
KMHL	Knoevenagel-Michael-Hydrolysis-Lactamization
KMHLD	Knoevenagel-Michael-Hydrolysis-Lactamization-decarboxylation
m	multiplet
LUMO	Lowest energy occupied molecular orbital
m/z	mass/charge
Me	methyl
mg	milligram
min	minute
mL	millilitres
mmL	microlitre
mmol	millimole

mol	mole
m.p.	melting point
MTBE	Methyl tert-butyl ether
MCR	Multicomponent reaction
N	Nitrogen
NHC	*N*-Heterocyclic Carbenes
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
O	Oxygen
OMCR	Organocatalytic Multicomponent reaction
P	Phosphorus
PCC	Pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
PTC	Phase Transfer Catalyst
p-TSA	*p*-Toluenesulfonic acid
q	quartet
R_f	Retention factor
rt	room temperature
Ru	Ruthenium
S	Sulphur
s	singlet
t	triplet
TADDOL	*α,α,α,α*-tetraaryl-1,3-dioxolane-4,5-dimethanols
TBDMS	*tert*-Butyldimethylsilyl
td	triplet of doublet
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TS	Transition state
Ts	Tosyl
UV	Ultra violet
XRD	X-ray diffraction

SYNOPSIS

The thesis entitled "***Meldrum's Acid: A Useful Platform for Tandem Organocatalytic Synthesis of Pyroglutamic Acids, δ-Ketoesters, γ-Butyrolactones and α,β-Unsaturated Carbonyl Compounds***" comprises of five main chapters.

Chapter 1: ***A Brief Overview on Asymmetric Organocatalysis and Meldrum's Acid as a Useful Substrate in Stereoselective Transformations***

This chapter presents a brief introduction about organocatalysis and recent organocatalytic transformations of Meldrum's acid **1a** and alkylidene Meldrum's acid **3**. The chapter is divided into two sections. Section 1 gives a brief introduction on organocatalysis and section 2 updates on the recent organocatalytic transformations of Meldrum's acid and alkylidene Meldrum's acid.

Over the past decade, the field of organocatalysis has grown at a faster phase and the term organocatalysis refers to a form of catalysis whereby, the rate of reaction is increased substantially by the addition of catalytic amount of small organic molecules termed as organocatalysts which consist of elements such as C, H, O, N, S, P, etc. essentially. Most of the organocatalysts are non-toxic to the living organisms, and often found to be environmentally benign. They are usually robust for handling and are inert toward moisture and oxygen at many instances. Depending upon their interactions and mode of activation organocatalysis are broadly classified into covalent organocatalysis and non-covalent organocatalysis.

Covalent interactions between catalyst and substrate lead to covalent organocatalysis. Amine catalysts (primary, secondary and tertiary amines), phosphines, *N*-heterocyclic carbenes (NHC) are some of the examples of its kind. Enamine and iminium catalysis are some of the most studied and frequently explored organocatalysis for many synthetic transformations.

On the other hand, non-covalent organocatalysis depends on ionic or hydrogen bonding interactions for the activation of substrates. Chiral thiourea/urea, phase transfer catalysts and Brønsted acids are the most frequently used catalysts of its kind.

Section 2 describes the recent development of organocatalytic transformations involving Meldrum's acid **1a**. 2,2-dimethyl-1,3-dioxan-4,6-dione, known as Meldrum's acid **1a** was first synthesized by Andrew Norman Meldrum in 1908 and is an unusual cyclic organic compound which has surprisingly high acidity (pKa = 4.97 in water, 7.3 in DMSO) than that of its acyclic analogues such 1,3-dicarbonyl compounds. Owing to their peculiar properties and reactivity, Meldrum's acids **1** have turned out to be very useful substrates for the synthesis of many useful compounds such as alkylidene Meldrum's acid **3** via Knoevenagel condensation with aldehyde **2**, Michael addition products **4** and **5** via Michael addition with *α,β*-unsaturated ketones **9** and *α,β*-unsaturated nitro compounds **10**, cycloaddition products **6** and **7** via cycloaddition reaction with phenols **11** and nitrones **12**, acyl/aroyl Meldrum's acid **8** via reaction with acyl/aroyl chlorides **13** etc (Figure 1.1).

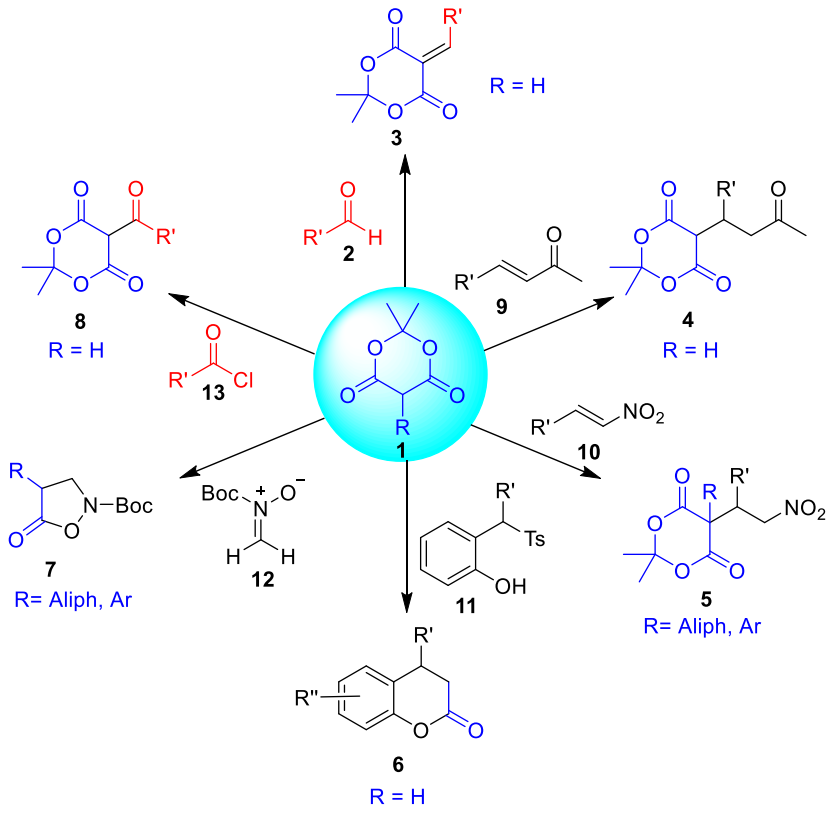
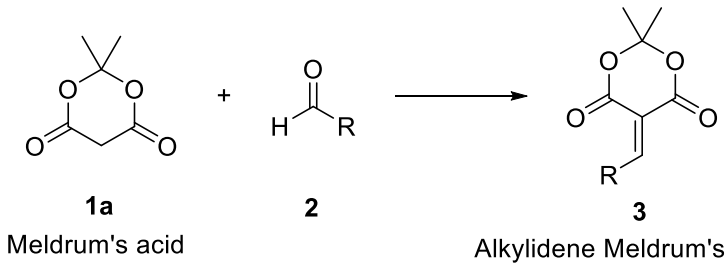


Figure 1.1: Meldrum's acids in useful organocatalytic transformations

Meldrum's acid **1a** readily reacts with aldehyde **2** to form highly electrophilic and reactive alkylidene Meldrum's acid **3** via Knoevenagel condensation (Scheme 1.1).



Scheme 1.1: Synthesis of alkylidene Meldrum's acid via Knoevenagel condensation

Due to its high electrophilicity alkylidene Meldrum's acid **3** has been explored in various synthetically useful organocatalytic transformations such as [4+2] cycloaddition reaction with *α,β*-unsaturated ketones **9** to afford spiro compounds **14**, Michael addition reaction with ketones **17**, nitromethane **18** and terminal alkynes **19** to afford corresponding valuable compounds (**4**, **5**, **15**) and [3+2] cycloaddition reactions with compounds **20** and **21** to afford useful heterocycles **7** and **16** respectively (Figure 1.2).

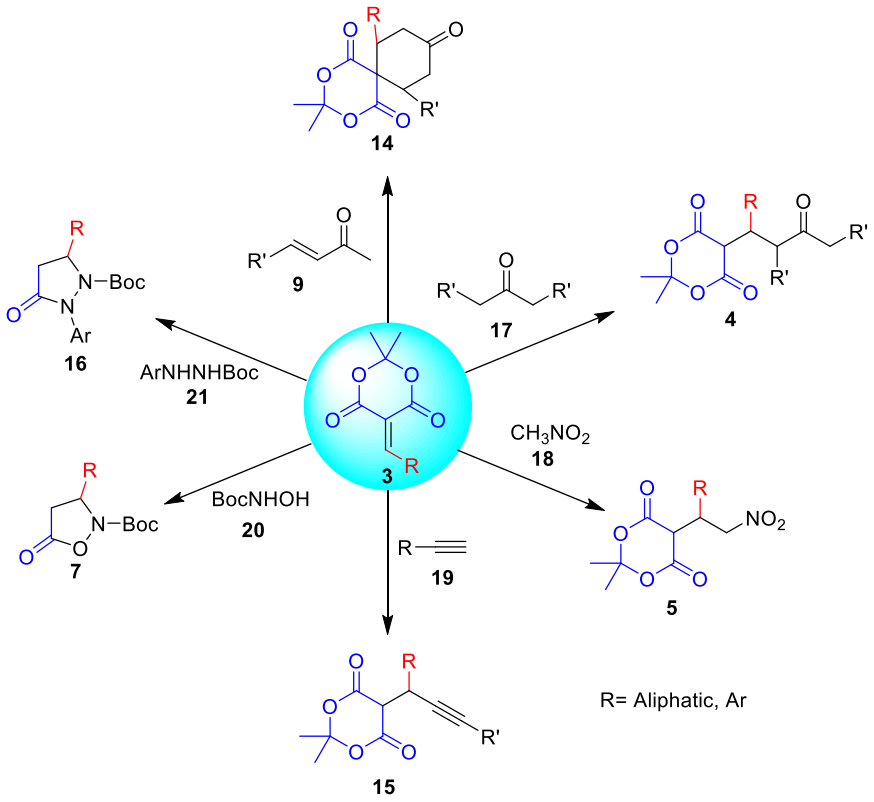


Figure 1.2: Alkylidene Meldrum's acid in organocatalytic transformations

Though Meldrum's acid **1a** has been explored in various enantioselective organocatalytic transformations, yet some of the methodologies involving Meldrum's acid still need to meet very high enantioselectivity. Strategies involving novel and practical uses

of Meldrum's acid and its derivatives in organocatalytic transformations is very demanding and desirable for accessing useful synthetic intermediates with very high enantioselectivity.

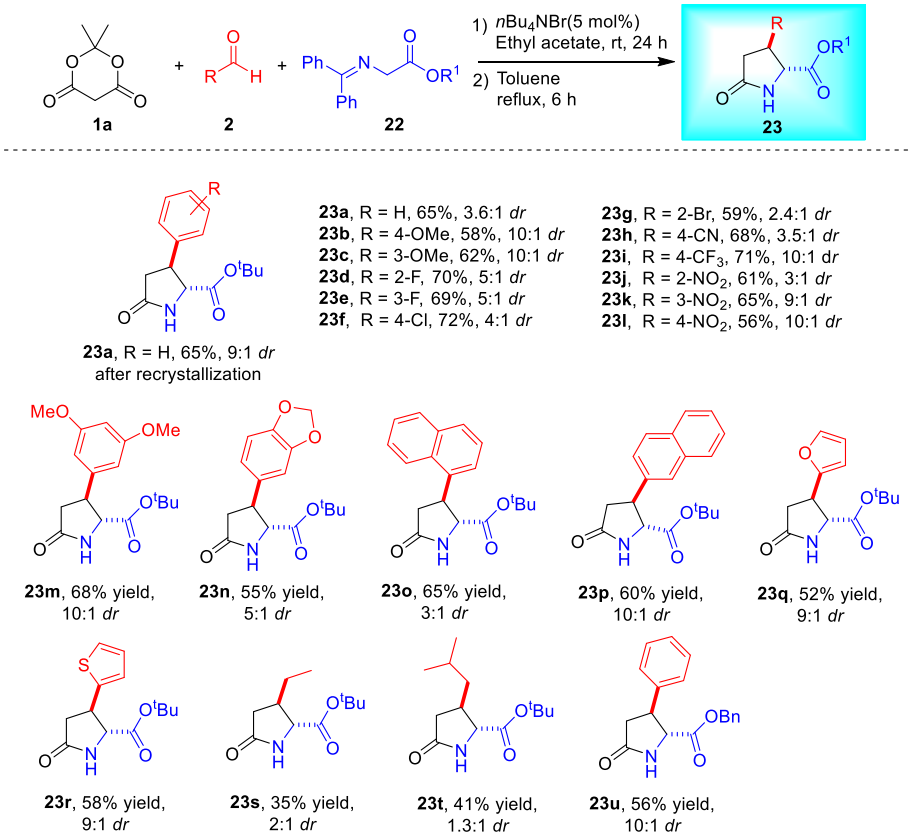
Chapter 2: ***Multicomponent Synthesis of Pyroglutamic Acid Derivatives Under Mild Conditions via Knoevenagel-Michael-Hydrolysis-Lactamization-Decarboxylation (KMHLD) Sequence***

This chapter describes the development of a novel protocol for the synthesis of pyroglutamic acid derivatives **23** using multicomponent reaction of Meldrum's acid **1a**, aldehyde **2** and Schiff's base **22** (glycine imine ester) via an unprecedented chemoselective Knoevenagel-Michael-hydrolysis-lactamization-decarboxylation (KMHLD) sequence. The chapter begins with a brief account on the importance of pyroglutamic acid derivatives and some of the selected methods for their synthesis.

Pyroglutamic acid scaffold is ubiquitously found in various natural products and pharmaceuticals. Owing to its importance many multicomponent synthetic strategies have been developed to access pyroglutamic acid and complex heterocycles containing pyroglutamic acid scaffold. However, some of the shortcomings of these methods are limited substrate scope and limited substituents on lactam ring. In this regard, the development of a facile, general and more practical protocol with a broader substrate scope is still of a great importance. Taking these into consideration, we hypothesized a novel tandem multicomponent reaction of Meldrum's acid **1a**, aldehyde **2** and Schiff's base **22** (*N*-(diphenylmethylene) glycine ester) for the synthesis of pyroglutamic ester derivatives **23**. To validate our hypothesis, various catalysts such as Lewis base and phase transfer catalyst were screened in different solvents and reaction conditions. After exhaustive screening Meldrum's acid **1a** (1 equiv.), aldehyde **2** (1.05 equiv.) and Schiff's base **22** (1.5 equiv.), nBu$_4$NBr as a catalyst (5 mol%) in ethyl acetate was emerged as optimum reaction condition (then base/acid workup followed by refluxing in toluene for 6 hours) to afford pyroglutamic acid derivatives **23** (See, Table 2.1).

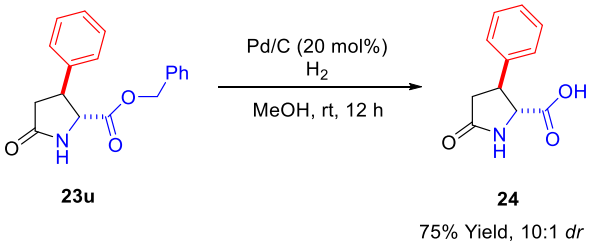
Having obtained the optimized reaction conditions in hand, the scope of KMHLD three component reaction was investigated by using various aldehydes **2a-u,** Meldrum's acid **1a** and Schiff's base **22** (*N*-(diphenylmethylene) glycine *tert*-butyl ester **22a** and *N*-(diphenylmethylene) glycine benzyl ester **22b**) to afford various pyroglutamic acid derivatives **23a-23u** (Table 2.1).

Table 2.1: Substrate scope of KMHLD reaction to access Pyroglutamic acid derivatives[a-c]



[a]Reaction conditions: Meldrum's acid **1a** (1 equiv.), aldehyde **2** (1.05 equiv.), Schiff's base **22** (1.5 equiv.) nBu$_4$NBr (5 mol%), in EtOAc at rt, 24 h then then base/acid workup followed by reflux for 6 h in toluene for the decarboxylation; [b]isolated yield after purification by column chromatography, [c]*dr* was calculated by ^{1}H NMR.

Aliphatic aldehydes, aromatic aldehydes containing electron donating as well as electron withdrawing functional groups and heterocyclic aldehydes afforded the corresponding desired pyroglutamic esters **23a-23u** in moderate to good yields (up to 72% yield) with moderate to excellent diastereoselectivity (up to 10:1 *dr*) (See Table 2.1). Further, pyroglutamic acid derivative **24** was prepared starting from **23u** under hydrogenolytic conditions (Scheme 2.1).

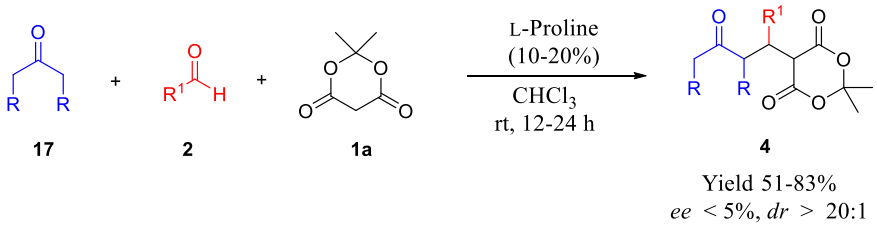


Scheme 2.1: Pyroglutamic acid derivative via the deprotection of ester **23u**

We have developed an easy, practical and mild protocol to access pyroglutamic acid derivatives via an unprecedented Knoevenagel-Michael-hydrolysis-lactamization-decarboxylation (KMHLD) chemoselective sequence. The generality and practicality of the protocol have been demonstrated by synthesizing a total of 21 examples. This novel domino protocol tolerated a wide variety of aldehydes including enolizable aliphatic aldehydes under mild reaction conditions.

Chapter 3: ***An Adverse Effect of Higher Catalyst Loading and Longer Reaction Time on Enantioselectivity in Organocatalytic Multicomponent Reaction***

This chapter presents a highly enantioselective organocatalytic multicomponent reaction to access δ-keto esters and an adverse effect of higher catalyst loading and longer reaction time on enantioselectivity in organocatalytic multicomponent reaction. Earlier, List and co-workers had reported an efficient proline-catalyzed three component Knoevenagel-Michael addition reaction of Meldrum's acid **1a**, aldehyde **2** and ketone **17** for the synthesis of δ-keto Meldrum's acid **4** (Scheme 3.1). Although this elegant C-C bond forming reaction was highly diastereoselective, however, it lacked enantioselectivity.

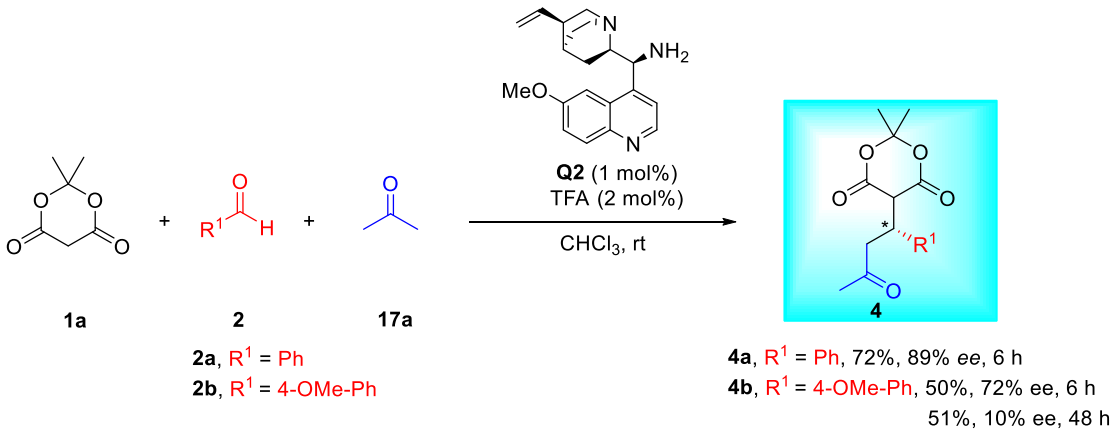


Scheme 3.1: Multicomponent reaction of ketones, aldehydes, and Meldrum's Acid

Later, Barbas and co-workers revisited the same reaction by using pyrrolidine as a catalyst. However, the reaction furnished four different products and proved to be not practical. To our surprise, this highly efficient C-C bond forming three-component reaction still remained an unmet challenge for achieving enantioselectivity.

We believe that the modularly designed organocatalyst assembly or cinchona based primary amines may promote effective stereoinduction in the very same reaction. In order to investigate the possibility, initially, we screened various modularly designed organocatalytic assemblies comprising of amino acids such as D-proline, D-phenylglycine, D-aspartic acid, D-glutamic acid and cinchona based thiourea catalyst. However, all the catalysts proved to be unsatisfactory for achieving excellent enantioselectivity. After exhaustive screening of

catalysts, solvents and temperature conditions, quinine based bi-functional primary amine catalyst **Q2** (10 mol%) in $CHCl_3$ at room temperature proved to be the optimum catalytic conditions to afford the desired product **4a** in 72% yield with an excellent enantioselectivity (89% *ee*) in 12 h (Scheme 3.2).

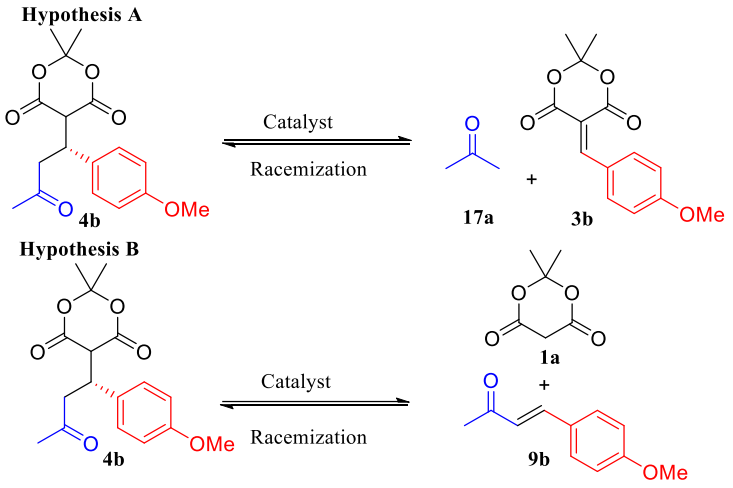


Scheme 3.2: Bifunctional amine catalyzed reaction of Meldrum's acid, aldehyde and acetone

Having optimized reaction conditions in hand, we planned to extend the scope of the reaction using various aldehydes and ketones for the generality of the protocol. Initially, the reaction of Meldrum's acid **1a**, 4-methoxybenzaldehyde **2b** and acetone **17a** under optimized reaction conditions afforded the corresponding product **4b** in 50% yield with 72% *ee* after 6 h. However, when we tried to increase the yield by stirring the reaction for an extended period of time, to our surprise the enantioselectivity was drastically lowered from 72% *ee* at 6 h to 10% *ee* at 48 h (Scheme 3.2). To confirm the negative influence of longer reaction time on the enantioselectivity we repeated the same reaction and recorded enantiomeric ratio of the product **4b** at different time interval. We found that enantioselectivity eroded continuously over a period of time and virtually became racemic after 72 h. We carried out systematic study to understand and investigate the root cause of racemization over a period of time. The time dependent NMR experiments and cross over chemical experiments proved that the Knoevenagel reaction of Meldrum's acid **1a** and aldehyde **2b** followed by Michael addition of acetone **17a** is the most probable pathway for this transformation.

We proposed two probable hypotheses for the root cause of erosion of enantioselectivity over a period of time (Scheme 3.3). In the hypothesis A, equilibrating retro-Michael-Michael addition regenerates acetone **17a** and Knoevenagel product alkylidene

Meldrum's acid **3b**. On the other hand, in hypothesis B equilibrating retro-Michael-Michael addition leads to the formation of Meldrum's acid **1a** and 4-methoxy benzylidene acetone **9b**. To validate these two hypotheses we carried out a cross-over experiment of enantiopure product **4b** and benzylidene acetone in presence of 10 mol% of catalyst **Q2** in chloroform. The formation of 4-methoxybenzylidene acetone **9b** and product **4a** unambiguously supported the hypothesis B which is causing the erosion of enantioselectivity through non-stereoselective equilibrating retro-Michael-Michael addition.



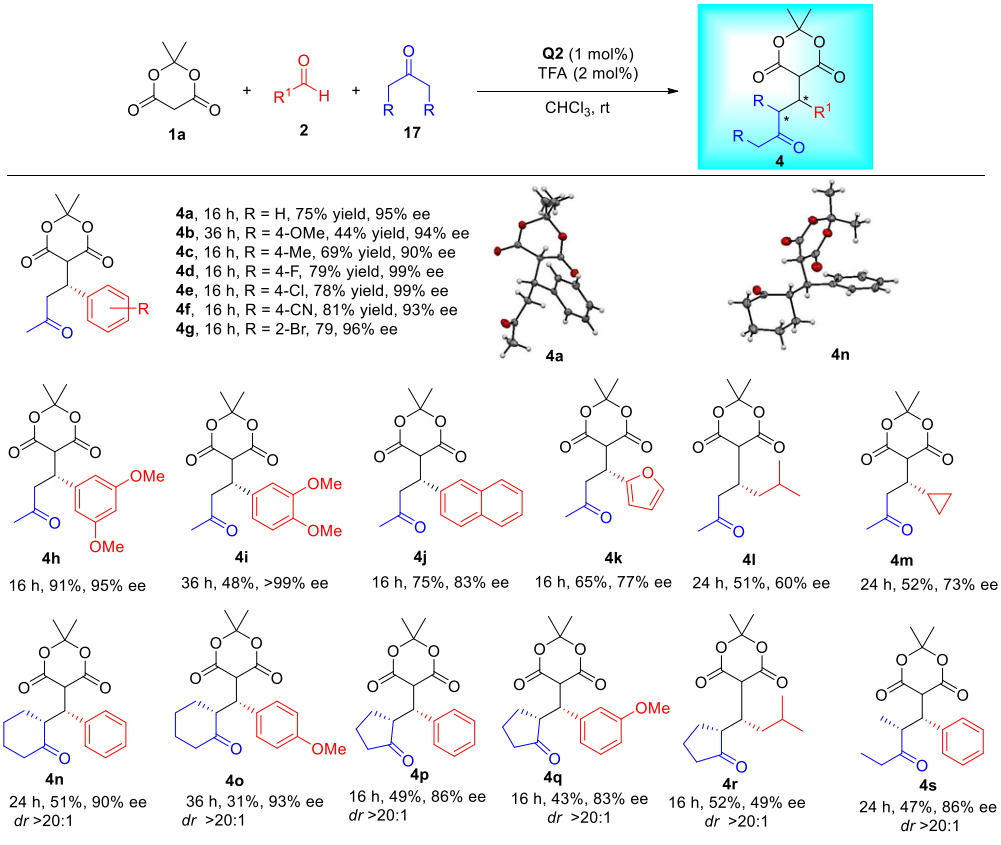
Scheme 3.3: Possible pathways for the racemization

This led us to believe that possibly the higher concentration of the catalyst **Q2** may be the key factor (acting like base) for the erosion of enantiopurity. We surmised that either the addition of acidic additive such as trifluoroacetic acid (20 mol% TFA, pKa 0.23) along with the catalysts may reduce undesirable base effect of the catalyst or lowering the catalyst loading may sustain the enantioselectivity over period of time. Finally, 1 mol% of catalyst **Q2** and 2 mol% of TFA as an additive found to be highly effective and the enantiopurity of **4b** remained almost unchanged even after prolonged reaction time 72 h. After re-establishing the optimum catalytic loading (**Q2** 1 mol% and 2 mol% TFA) the generality of the reaction was explored by using various aromatic as well as aliphatic aldehydes and ketones to afford the desired products **4a-4m** in good to excellent yields with excellent enantioselectivity (up to 91% yield and 99% *ee*, Table 3.1)**.** Both electron-rich and -deficient aromatic aldehydes and aliphatic aldehydes were found to be compatible under optimized reaction conditions. Similarly, substituted Michael donors such as cyclohexanone, cyclopentanone and 3-pentanone reacted smoothly to give the corresponding products (**4n**-**4s**) with moderate to excellent enantioselectivity (up to 94% *ee*) and with single diastereomers (Table 3.1). The

stereochemistry of products **4a/4n** were proved unambiguously by single crystal X-ray diffraction analysis (see Table 3.2)

In order to demonstrate the practicality of the protocol, the product **4a** was converted to important precursors of many useful molecules such as carboxylic acid, esters and amide. In order to understand the mechanism we carried out DFT calculations of the proposed reaction mechanism.

Table 3.1: Substrate scope[a-d]



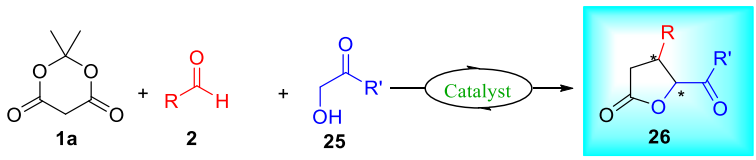
[a]Reaction conditions: Meldrum's acid **1a** (1 equiv.), aldehyde **2** (1.05 equiv.), ketone **17** (5 equiv.) catalyst **Q2** (1 mol%), TFA as an additive (2 mol%), in chloroform at rt, [b]isolated yield after purification by column chromatography, [c]*dr* was calculated based ^{1}H NMR, [d]*ee* was determined by HPLC using chiral column.

We demonstrated a highly enantioselective organocatalytic multicomponent reaction of aldehyde, ketone and Meldrum's acid for the first time since its discovery. We carried out a systematic study on the adverse effect of higher catalytic loading and longer reaction time on the outcome of enantioselectivity. The protocol worked efficiently under very low catalyst loading (1 mol%) and proved to be scalable on a gram scale.

Chapter 4: ***Direct Organocatalytic Multicomponent Synthesis of Enantiopure γ-Butyrolactones via Domino Knoevenagel-Michael-Lactonization Sequence***

This chapter describes an expedient and straightforward protocol for the synthesis of highly enantiopure synthesis of *γ*-butyrolactones via domino Knoevenagel-Michael-lactonization sequence. The chapter begins with a brief introduction on the importance of *γ*-butyrolactones derivatives and some of the selected methods for their synthesis.

γ-Butyrolactone core abundantly found in a wide range natural products and many of these possess a broad range of biological activities. Considering the inevitable importance, numbers of metal catalyzed and organocatalyzed approaches are known in the literature for the synthesis of *γ*-butyrolactone scaffolds. However, some of the major limitations of these methodologies are the use of heavy and expensive transitional metal catalysts (Ir, Ru, Au, Cr etc), very expensive ligands and commercially unavailable pre-functionalized starting materials. Only few organocatalyzed protocols are limited to either highly reactive fluorinated ketones or aromatic *α*-hydroxy ketones and aromatic Michael acceptors as substrates. These synthetic challenges encouraged us to design one-pot multicomponent organocatalytic approach to obtain the enantiopure *γ*-butyrolactones in a cost effective and efficient manner. We hypothesized a novel three component chemoselective domino Knoevenagel-Michael-lactonization reaction of Meldrum's acid **1a**, aldehyde **2** and *α*-hydroxy ketone **25** as shown in scheme 4.1.

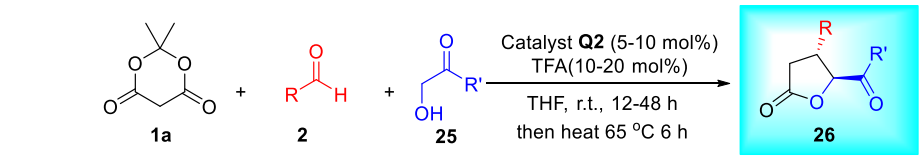


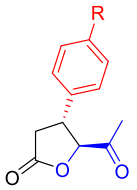
Scheme 4.1: Domino Knoevenagel-Michael-lactonization reaction

Initially, a model reaction was performed by using Meldrum's acid **1a**, benzaldehyde **2a** and hydroxyacetone **25a** in presence of catalytic amount of D-proline (20 mol%) in chloroform. Gratifyingly, the desired lactone **26a** was obtained but as two separable diastereomers (1:2.1 *dr*), albeit in poor enantioselectivity (26% *ee*) at room temperature. Later we screened various catalysts including modularly designed catalytic assemblies. After screening various catalysts, cinchona based chiral diamine **Q2** found to be the best catalyst for the desired transformation. After screening various solvents and varying the catalyst loading the optimum reaction condition was emerged as 5 mol% **Q2**, 10 mol% TFA in THF

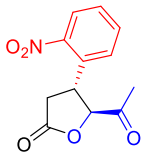
at room temperature for 24 h followed heating at 65 ^{o}C for 6 h in one pot to afford the desired enantioselective lactone **26a**. Having obtained the optimized reaction conditions in hand, further the scope of Knoevenagel-Michael-lactonization was investigated using various aldehydes and α-hydroxy ketones (Table 4.1).

Table 4.1: Substrate scope[a-e]

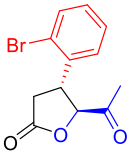




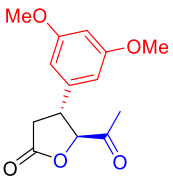
26a, R = H, 78% yield, 94% *ee* (58%), *dr* 2.5:1
26b, R = OMe, 76% yield, 91% *ee* (87%), *dr* 1.5:1
26c, R = Me, 65% yield, >99% *ee* (91%),*dr* 1.8:1
26d, R = F, 82% yield, >99% *ee* (98%), *dr* 1.7:1
26e, R = Cl, 61% yield, 91% *ee* (87%), *dr* 1.6:1
26f, R = CN, 86% yield, 97% *ee* (87%), *dr* > 20:1
26g, R = CF_3, 55% yield, >99% *ee* (96%), *dr* 3.5:1



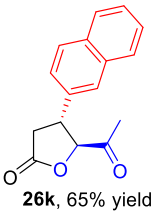
26h, 51% yield, 86% *ee* *dr* >20:1



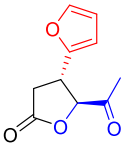
26i, 65% yield, 91% *ee* *dr* >20:1



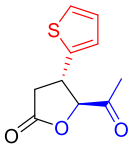
26j, 81% yield, 94% *ee* (91%) *dr* 2.4:1



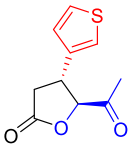
26k, 65% yield, 94% *ee* (93%) *dr* 1.5:1



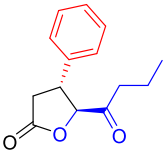
26l, 59% yield, 87% *ee* (67%) *dr* 3.5:1



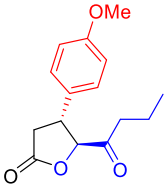
26m, 64% yield, 90% *ee* (94%) *dr* 1.1:1



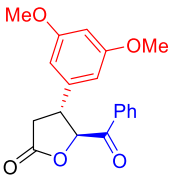
26n, 59% yield, 94% *ee* (95%) *dr* 1.2:1



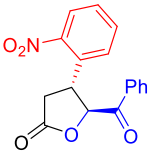
26o, 64% yield,[b] 91% *ee*(83%) *dr* 6:1



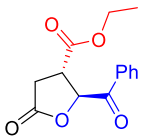
26p, 58% yield,[b] >99% *ee*(94%) *dr* 5:1



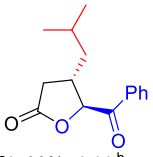
26q, 69% yield,[b] 80% *ee* *dr* >20:1



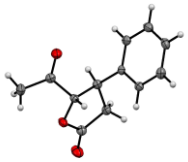
26r, 59% yield,[b] 61% *ee*(4%) *dr* 3:1



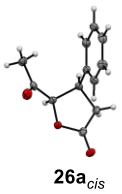
26s, 64% yield,[b] 67% *ee*(75%) *dr* >10:1



26t, 62% yield,[b] 70% *ee* *dr* >20:1



26a$_{trans}$



26a$_{cis}$

[a]Reaction conditions: Meldrum's acid **1a** (1 equiv.), aldehyde **2** (1.05 equiv.), α-hydroxyl ketone **25** (3 equiv.), **Q2** (5 mol%), TFA as additive (10 mol%), in THF at rt, 24 h then heat at 65 ^{o}C in one pot; [b]10 mol% of catalyst **Q2** and TFA (20 mol%) were used for the complete conversion, [c]isolated yield after purification by column chromatography, [d]*dr* was calculated based on isolated yields, [e]*ee* was determined by HPLC; *ee* of *cis*-isomer is given in parenthesis.

Various aromatic as well as aliphatic aldehydes and different *α*-hydroxy ketones (aliphatic and aromatic) reacted smoothly under the optimized reaction conditions to afford the corresponding lactones (**26a-26t,** Table 4.1) in moderate to good yields with high to excellent enantioselectivity (up to 99% *ee*). We have also demonstrated the gram scale synthesis of product **26a**. Further, the absolute and relative configurations of lactone **26a** were unambiguously determined by single crystal X-ray diffraction analysis (Table 4.1). The DFT calculations were performed to understand the mechanistic insights of the reaction and enantioselectivity.

We have developed a novel, robust and a straightforward protocol for the highly enantiopure synthesis of *γ*-butyrolactones via one-pot organocatalytic multicomponent reaction (OMCR) strategy. The protocol avoids the use of pre-functionalized substrates, additional base and, expensive transition metals. Reaction proved to be highly enantioselective and reproducible on a gram scale and is proved to be practical to access synthetically useful enantiopure lactones.

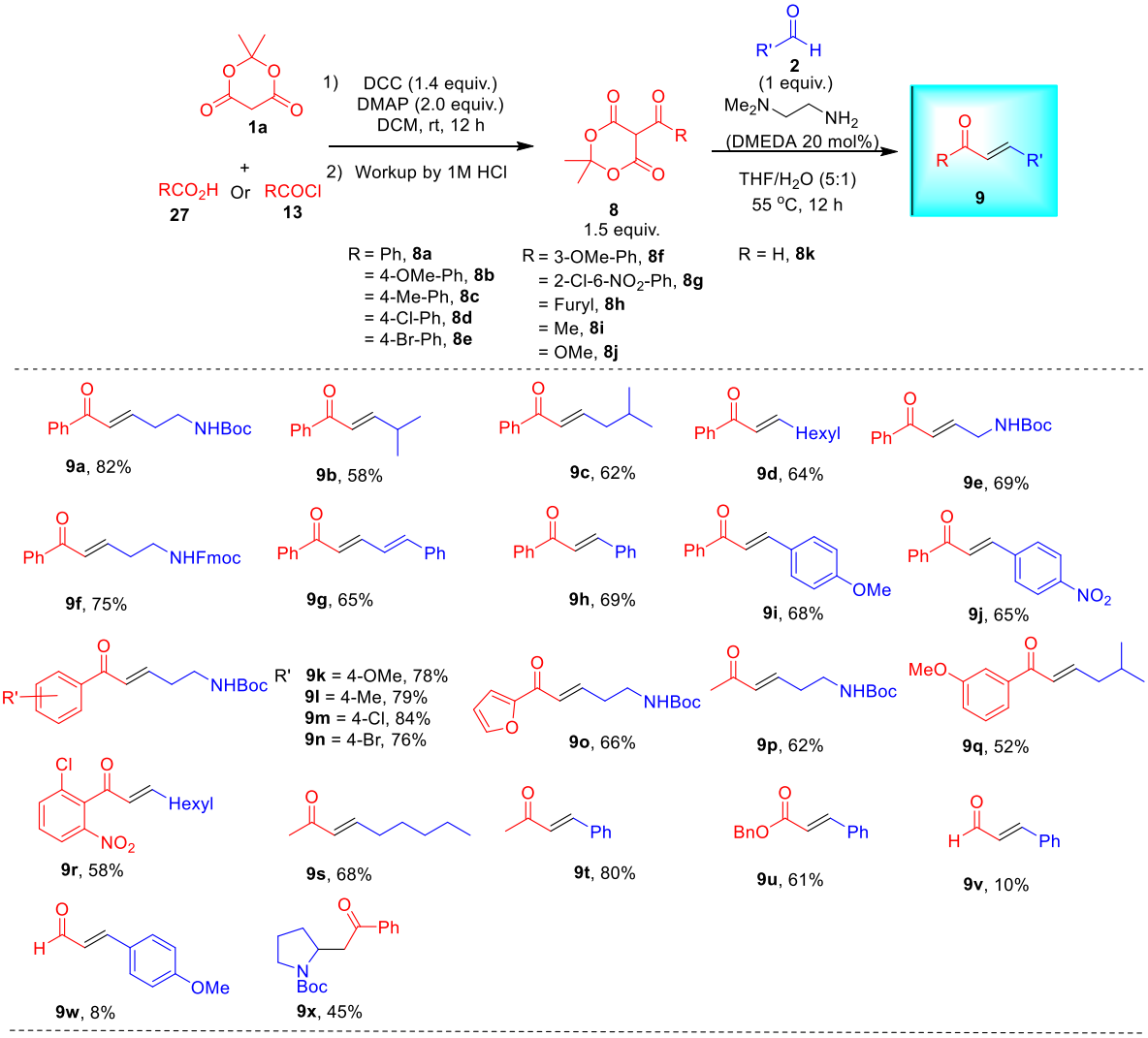
Chapter 5: ***Direct Organocatalytic Synthesis of α,β-Unsaturated Carbonyl Compounds***

This chapter presents a facile and straightforward protocol for the synthesis of *α,β*-unsaturated carbonyl compounds using a novel strategy. The chapter begins with a brief account on the previous synthetic approaches for the synthesis of *α,β*-unsaturated carbonyl compounds.

α,β-unsaturated carbonyl compounds are frequently used as starting materials in various transformations such as 1,4-Michael addition, aldol reaction, Diels-Alder reaction, hetero-Diels-Alder reaction, cascade reactions to name few. Evidently, plenty of methods are available in the literature for the synthesis of *α,β*-unsaturated carbonyl compounds. Most frequently used methods include Wittig reaction and Horner–Wadsworth–Emmons reaction and other organocatalytic approaches like Doebner-Knoevenagel type reactions. Although, various methods are available, some of these methods suffer due to limited substrate scope, generation of stoichiometric amount of by-product, and use of a stoichiometric amount of base. Taking these into account, we designed an operationally simple strategy that utilizes rather more simple substrates and employs mild reaction conditions. We surmised that aroyl/acyl Meldrum's acid **8** could effectively be used as an enolate surrogate as it slowly undergoes decarboxylation to produce active methylene species. To test our hypothesis we performed reaction between benzoyl Meldrum's acid **8a** and Boc-*β*-alaninal **2a'** in presence

of various catalysts and reaction conditions. After screening various catalysts and solvents, *N*,*N*′-dimethylethylenediamine (DMEDA, 20 mol%) as a catalyst in THF/H_2O solvent system at 55 ^oC for 12 h was established as optimized reaction conditions to afford the desired products **9**. Both aliphatic as well as aromatic aldehydes reacted smoothly with benzoyl Meldrum's acid **8a** under optimum reaction conditions to afford the corresponding *α,β*-unsaturated ketones **9a-9j** in good yields with excellent *E*-selectivity (up to 82% yield, *E/Z* >99:1 for all compounds, Table 5.1)

Table 5.1: Substrate scope[a-e]



Reaction conditions: Unless otherwise noted, [a]acyl/aroyl Meldrum's acid (**8a-8i**) were freshly prepared by coupling of Meldrum's acid **1a** (1 equiv.) with corresponding carboxylic acids **3**, DCC (1.4 equiv.) as coupling reagent, DMAP (2 equiv.) as a base in DCM at rt followed by workup with 1 M HCl; [b]ester analogue **8j** prepared by treatment of benzyl chloroformate with Meldrum's acid **1a** in DCM at rt, [c]aldehyde analogue **8k** was prepared by the reaction of triethyl formate and Meldrum's acid **1a** followed by treatment with 1 M HCl. Then aldehyde **2** (1 equiv.), **8** (1.5 equiv.), DMEDA (20 mol%) in THF/H_2O (5:1) at 55 ^oC for 12 h, [d]isolated yield after purification by column chromatography, [e]*E/Z* ratio are >99:1 in all the cases.

Likewise, in order to have a wider applicability of the protocol acyl and aroyl Meldrum's acid **8b**-**8i** were synthesized and treated with various aldehydes to afford corresponding the *α,β*-unsaturated ketones **9k**-**9t** in good yields with excellent *E*-selectivity (up to 84% yield, *E/Z* >99:1 for all compounds, Table 5.1). In order to have enhanced substrate scope and generality, the protocol was explored further for the synthesis of *α,β*-unsaturated ester **9u** and aldehydes (**9v** and **9w)** in modest to good yields with excellent *E*-selectivity (8-61% yield, *E/Z* >99:1 for all compounds, Table 5.1). The method also proved to be very useful for the synthesis of heterocyclic compound **9x** in modest yield (45%, Table 5.1).

We have developed a facile, practical and mild protocol for the synthesis of *α,β*-unsaturated carbonyl compounds. The process utilizes simple starting materials accessed through one step from easily available carboxylic acid, acyl/aroyl chlorides and Meldrum's acid. This catalytic protocol explored the novel use of acyl/aroyl Meldrum's acid as enolate equivalent or surrogate for the construction of *α,β*-unsaturated carbonyl scaffold. This straightforward protocol tolerates a wide variety of aldehydes and various acyl/aroyl Meldrum's acid derivatives. Similarly, mild reaction conditions tolerated acid and base sensitive protecting groups.

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(*Numbers of substrates and products in the synopsis are different from those in thesis. Please note that compound numbers have been assigned for the convenience in every chapter and number of few compounds may vary from chapter to chapter*)

List of Publications

1. Trimbak B. Mete, **Tushar M. Khopade** and Ramakrishna G Bhat* "Transition-Metal-Free Regioselective Thiocyanation of Phenols, Anilines and Heterocycles". *Tetrahedron Lett.* **2017**, 58, 415.

2. Trimbak B. Mete, **Tushar M. Khopade** and Ramakrishna G Bhat* "Oxidative Decarboxylation of Arylacetic Acids in Water: One-Pot Transition-Metal-Free Synthesis of Aldehydes and Ketones". *Tetrahedron Lett.* **2017**, 58, 2822.

3. **Tushar M. Khopade**, Amol D. Sonawane, Jyotsna S. Arora and Ramakrishna G. Bhat* "Direct Organocatalytic Multicomponent Synthesis of Enantiopure γ-Butyrolactones via Tandem Knoevenagel-Michael-Lactonization Sequence". *Adv. Synth. Catal.* **2017,** *359,* 3905**.**

4. **Tushar M. Khopade**, Trimbak B. Mete and Ramakrishna G Bhat* "An Adverse Effect of Higher Catalyst Loading and Longer Reaction Time on Enantioselectivity in Organocatalytic Multicomponent Reaction". **Just accepted Manuscript (*Chem. Eur. J.* doi:10.1002/chem.201800278)**

5. **Tushar M. Khopade**, Amol D. Sonawane, Prakash K. Warghude and Ramakrishna G. Bhat* "Multicomponent Synthesis of Pyroglutamic Acid Derivatives under Mild Conditions via Knoevenagel-Michael-Hydrolysis-Lactamization-Decarboxylation (KMHLD) Sequence". **Manuscript under review.**

6. **Tushar M. Khopade**, Prakash K. Warghude, Trimbak B. Mete and Ramakrishna G. Bhat* "Direct Organocatalytic Synthesis of α,β-Unsaturated Carbonyl Compounds" **Manuscript under preparation**

7. **Tushar M. Khopade**, Rameshwar Shinde and Ramakrishna G Bhat* An Organocatalytic Approach for the Synthesis of Piperidynyl Aziridines /Oxiranes: Diastereoselective Synthesis of Piperidine Derivatives" **Manuscript under preparation.**

8. **Tushar M. Khopade**, Lakshmi V.R. Babu Syamala and Ramakrishna G. Bhat* "Meldrum's Acid Catalyzed Direct One Pot Organocatalytic Synthesis of α,β-Unsaturated Ketones" **Manuscript under preparation.**

Chapter 1

A Brief Overview on Asymmetric Organocatalysis and Meldrum's Acid as a Useful Substrate in Stereoselective Transformations

Organocatalysis  Meldrum's Acid

1 *A Brief Overview on Asymmetric Organocatalysis and Meldrum's Acid as a Useful Substrate in Stereoselective Transformations*

Organocatalysis is one of the essential pillars in the field of catalysis and is often explored in several synthetic transformations. At the dawn of asymmetric organocatalysis, various research groups independently discovered that organocatalysts possess an unprecedented strength of catalyzing a number of diverse reactions very efficiently and selectively to generate a broad array of optically active compounds. At many instances, the substrate-organocatalysts interactions are more selective that allow one to design a target oriented synthesis. These interactions help to design various new methods useful not only in academia but in large scale industries, for instance, pharmaceutical, polymer, food etc. Meldrum's acid is one of the efficient substrates that have been explored in the fields of organic synthesis and it has been utilized as a useful platform in numerous organocatalytic approaches. Organocatalytic processes that explore the use of Meldrum's acid have gained a gradual attention in the last decade. In this chapter the use of Meldrum's acid in various efficient organocatalytic transformations is discussed.

Section 1

1.1 Introduction to Organocatalysis

The term organocatalysis refers to a form of catalysis, wherein the rate of the chemical reaction is enhanced by simple organic molecule as a catalyst. Organocatalysis is one of the essential pillars in the field of catalysis. Usually, they are small molecules and as the name indicates they consist of non-metal elements such as C, H, O, N, S, P, etc. essentially. Though it is known for a century that these small molecules catalyze reactions, it only took last two decades to expand the field of organocatalysis exponentially. Historic elucidation of the organocatalysis dates back to 1928 by German chemist Wolfgang Langenbeck.[1] The same author named these small organic molecules as 'organic catalyst.' Later it became the subject of many articles and books. Conceptualized at the end of 20th century by MacMillan,[2] it has helped to overcome many synthetic hurdles suffered by chemists. Apart from that, they have

changed a long-standing notion that only metal and enzyme catalysis are better options for providing optically active organic compounds.

In general, organocatalysts are naturally occurring amino acids and alkaloids or modified forms of such compounds or purely synthetic organic compounds such as C2 symmetric binaphthyl derivatives.[3] Evidently, most of them are non-toxic to the living organisms, and often found to be environmentally benign. They are usually robust for handling and inert towards moisture and air at many instances, which make them an attractive tool for many synthetic strategies that use water or water miscible solvents. Organocatalysis with these practical advantages and above all their strength in facilitating efficient catalysis in the absence of transition metals place them in the category of green and sustainable chemistry.[3c]

The efficiency of organocatalyst has been tested so far in different chemical transformations including aldol reaction, Mannich reaction, Michael addition, α-functionalization (alkylation, amination, oxyamination, halogenation, etc.), cycloaddition, Diels-Alder reaction, cascade reaction to name a few. Recently, the most striking capability of organocatalyst has been demonstrated in the C-H functionalization strategies.[3d] The multiple experimental and computational studies have been carried out to understand their interactions with substrates.[3e] Depending upon their interactions and mode of activation organocatalysis are broadly classified into two major categories namely covalent organocatalysis and non-covalent organocatalysis (Figure 1.1).[3a]

Covalent interactions between catalyst and substrate lead to covalent organocatalysis. Iminium/enamine catalyzed aldol reaction is one of the best examples of its kind. On the other hand, in the non-covalent organocatalysis catalyst forms ionic or hydrogen bonding interactions with the substrates. Thiourea or phase transfer catalyzed reactions are considered in non-covalent organocatalysis. The types of organocatalyst are schematically represented in the Figure 1.1.

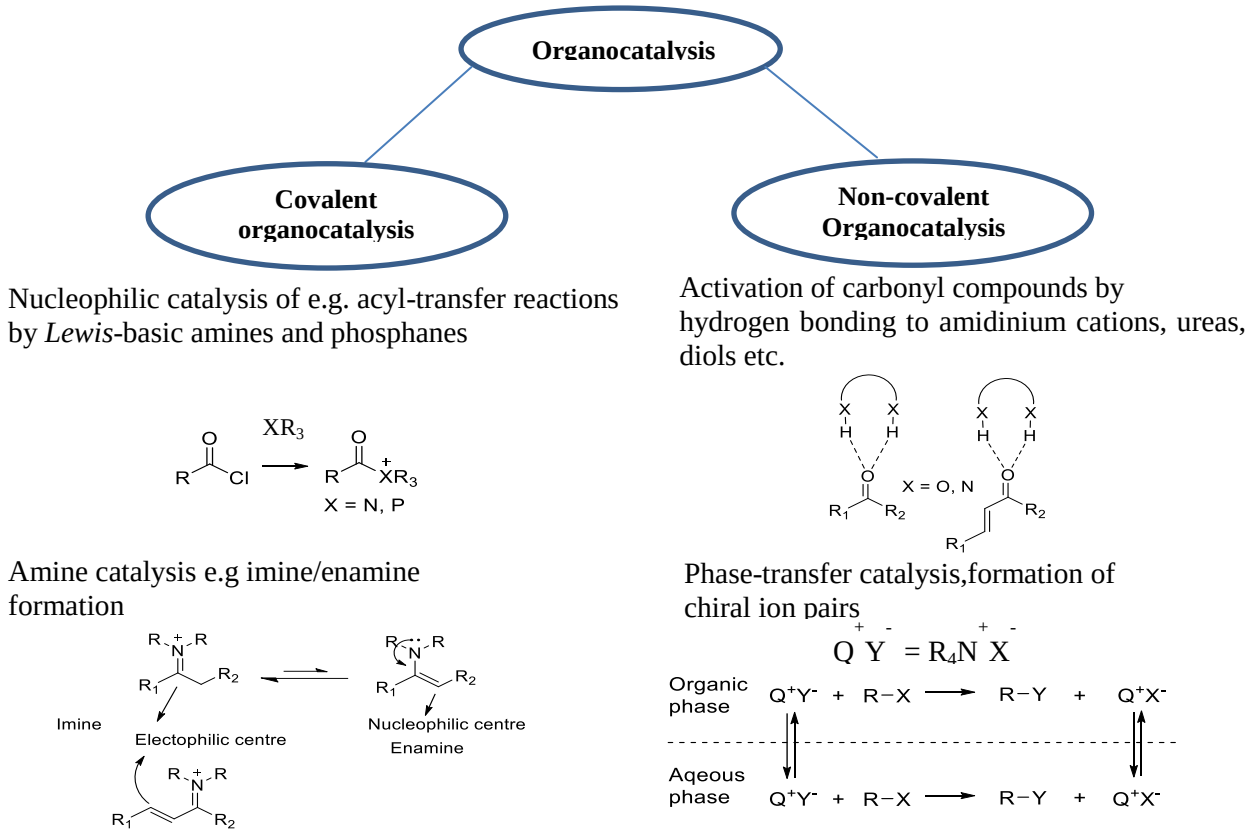
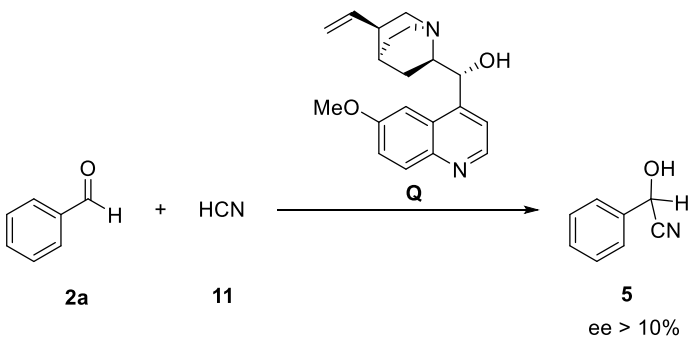


Figure 1.1: Types of Organocatalysts

A very first example of an organocatalysis traced back to as early as 1913 by the German chemists Bredig and Fiske (Scheme 1.1).[4] They reported quinine **Q** catalyzed enantioselective synthesis of cyanohydrin **5** by the addition of HCN **11** to benzaldehyde **2a**. Though the enantioselectivity obtained was much lower (*ee* = >10%), however, it had broken new ground in the field of catalysis. Later pioneering work by various chemists had proved the strength of organocatalysis at number of occasions.

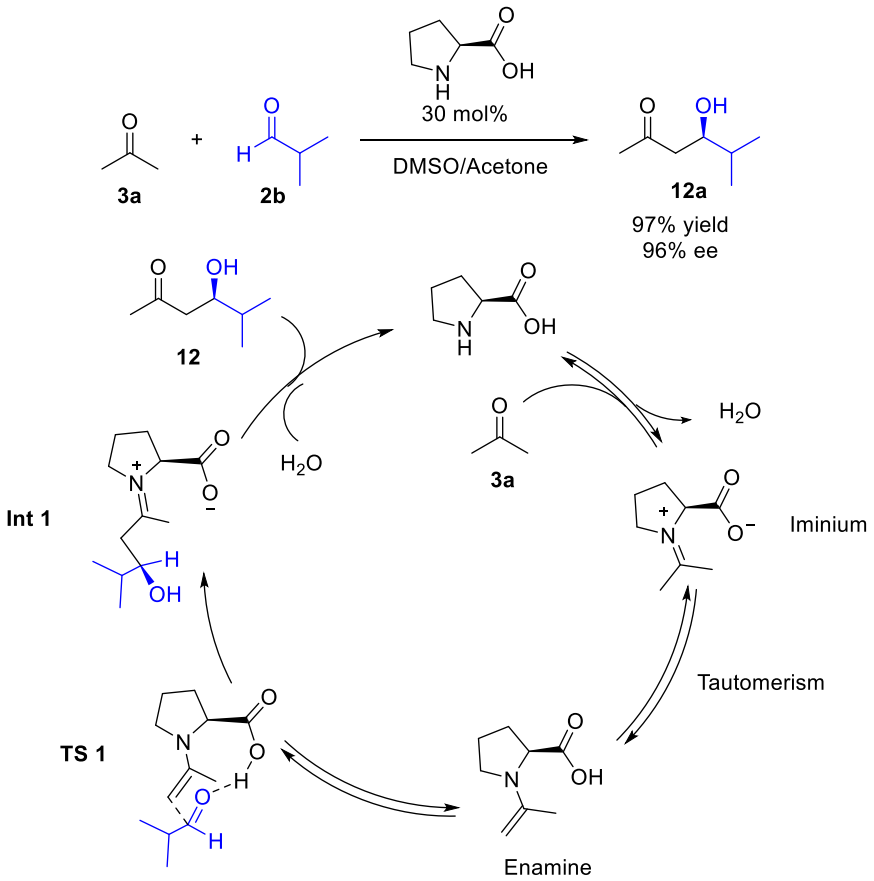


Scheme 1.1: Quinine catalyzed nucleophilic addition of HCN to benzaldehyde

1.2 Covalent organocatalysis

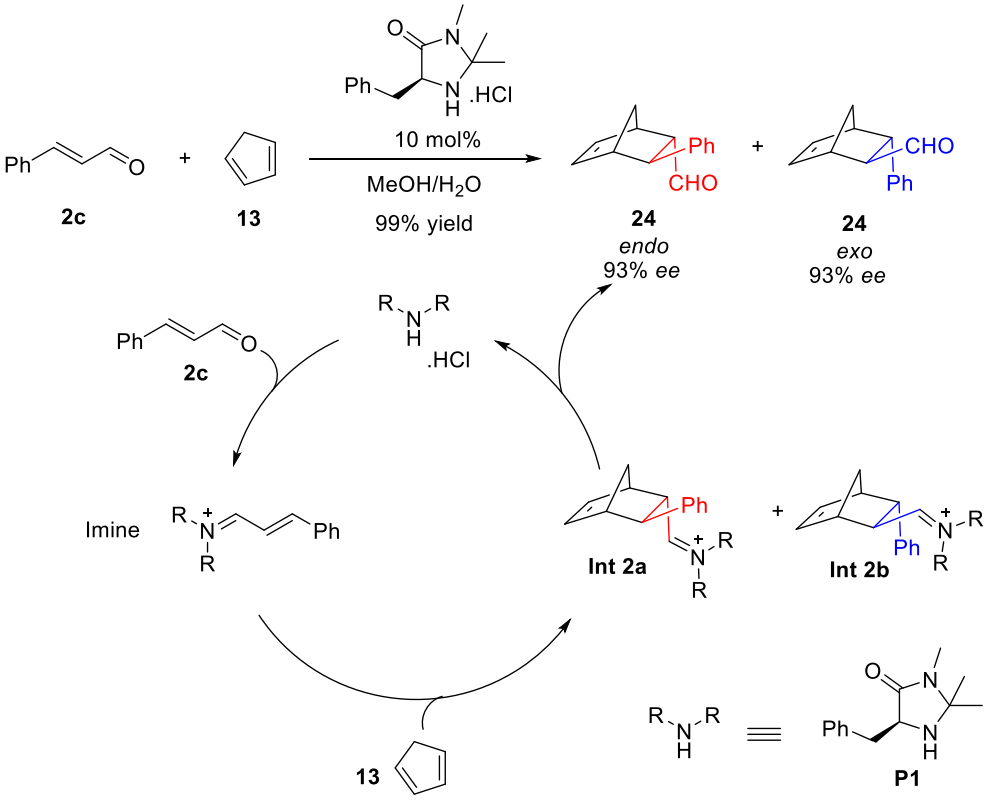
1.2.1 Iminium/Enamine catalysis

It was the end of the 20th century; chemists started paying attention to these highly efficient small molecules when List[5] and MacMillan[2] published a seminal work on organocatalyzed aldol (Scheme 1.2) and Diels-Alder reaction (Scheme 1.3). In 2000 List, Lerner, and Barbas reported a proline catalyzed aldol reaction between aldehyde **2** and acetone **3a**. The reaction proceeded via enamine formation between proline and acetone **3a**. As shown in scheme 1.2, the proline acts as a bifunctional catalyst, at one side it activates nucleophile via enamine formation; on the other side acidic proton provides a stereocontrol in the transition state **TS1**. This benchmark enantioselective aldol reaction further provided a solid platform for various proline catalyzed α-functionalization reactions like alkylation, amination, oxyamination, halogenation, etc.[6]



Scheme 1.2: Proline catalyzed enantioselective aldol reaction

In the same year, MacMillan and co-workers[2] reported chiral imidazolium **P1** salt-catalyzed Diels-Alder reaction between *α,β*-unsaturated aldehyde **2c** and cyclopentadiene **13** (Scheme 1.3). The iminium ion intermediate **Int 2a** acts as dienophile which further undergoes cycloaddition reaction with diene **13** by giving two diastereomers (**24** *exo* and **24** *endo* in Scheme 1.3). The bulky benzyl group in **P1** provides sufficient enantioface discrimination by blocking one face of the dienophile.



Scheme 1.3: Chiral imidazolium salt-catalyzed Diels-Alder reaction

Later various research groups have shown the catalytic efficiency of amine catalyst in asymmetric syntheses including aldol reaction, Mannich reaction, Michael addition, epoxidation, aziridination, *α*-amination and *α*-oxyamination, *α*-halogenation and various other cascade and tandem transformations to afford valuable compounds (**14**, **16**, **18**, **19**, **20**, **21**, **23**) respectively (Figure 1.2).

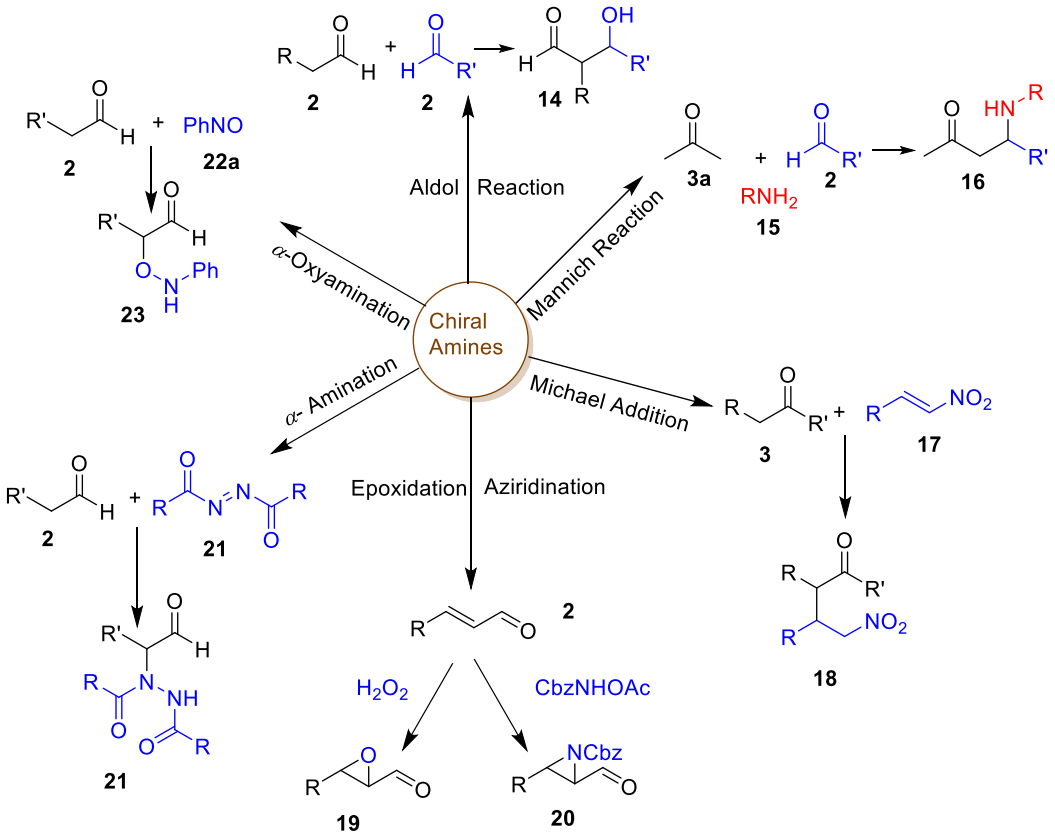


Figure 1.2: Reactions catalyzed by chiral amines

Apart from the above mentioned examples, amine catalysis also found to be a useful tool in tandem, cascade, and synergistic (along with metal catalyst) catalysis.

1.2.2 *N*-heterocyclic carbenes (NHC) catalysis

Another well studied organocatalysis is the catalysis by *N*-heterocyclic carbenes (NHC) or persistent carbene denoted by the general formula $(R_2N)_2C$**:**, where the 'R's are typically derived from the heterocycles such as triazolium, imidazole, imidazoline, thiazole or triazole.[7] Some of the frequently used carbenes in organocatalysis are shown in Figure 1.3.

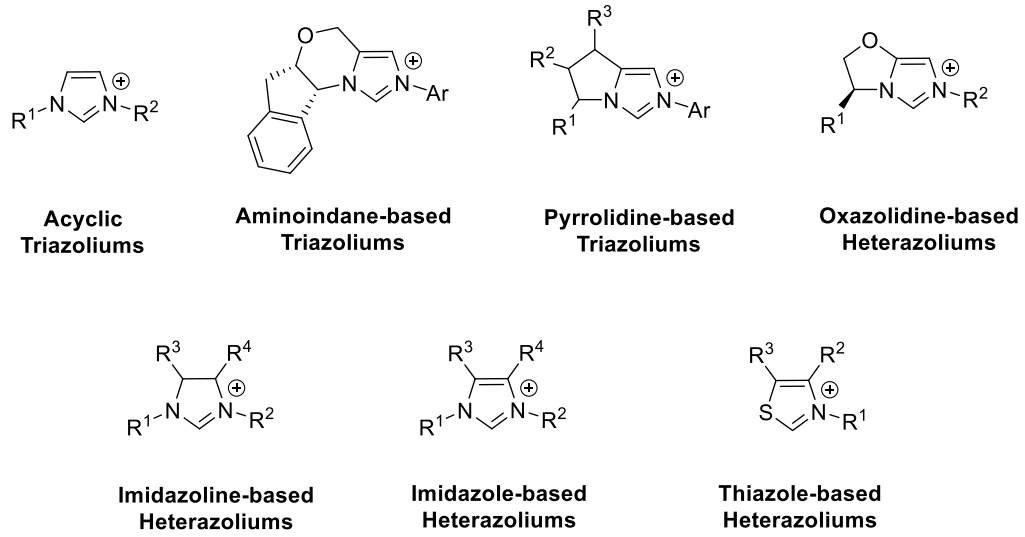
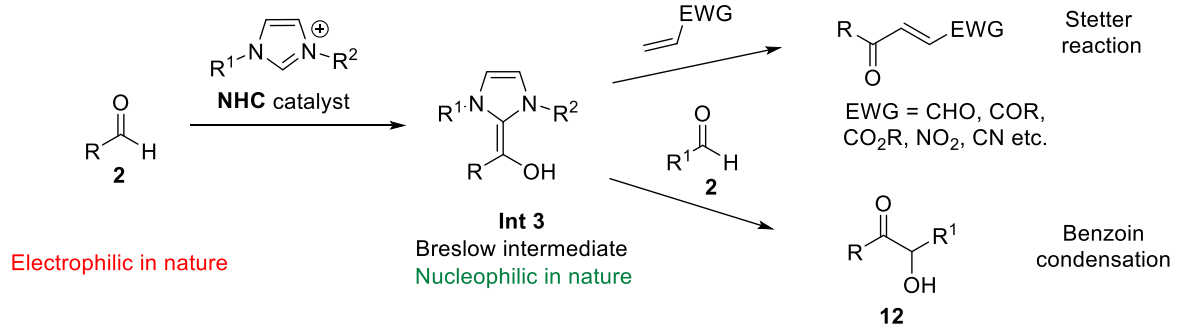


Figure 1.3: Representative examples of *N*-heterocyclic carbenes

Mostly, organocatalysis using stable carbenes are dominated by triazolylidene carbenes. Unlike traditional carbenes, NHCs are stable and electron rich in nature. They show high affinity towards carbonyl carbon. The reversal in polarity known as umpolung via formation of the Breslow intermediate **Int 3** is the most salient feature of NHC catalysis and this has popularized NHC catalysis within a short period of time (Scheme 1.4). Intermediate **Int 3** further can undergo conjugate addition and benzoin condensation to afford corresponding alcohol **12** (see, Scheme 1.4).



Scheme 1.4: Formation of Breslow intermediate and its reactions

1.3 Non-covalent organocatalysis

1.3.1 Activation of carbonyl compounds by H-bonding

Hydrogen bonding (H-bonding) catalysis is the classic example of non-covalent organocatalysis. In Nature, hydrogen bonding plays a crucial role in enzyme catalysis, 2D and 3D structures of proteins and double helical structure of DNA.[8] In enzyme catalysis it

plays an important role by substrate recognition, substrate activation, and stereocontrol of organic transformations,[9] on the other hand in proteins and DNA, it causes them to fold into specific shapes. Although H-bonding interaction is well known for a century,[10] it was not acknowledged until Kelly, Schreiner, Jorgensen, Etter, Curran, Hine, Göbel, and De Mendoza introduced the urea and thiourea catalysis in organic synthesis.[11] It was found that H-bonding catalyst acting as weak Lewis acid interacts with carbonyl oxygen and greatly accelerates the reaction rate in Diels-Alder reaction. Systematic studies on these interactions have shown that H-bonding reduces the HOMO-LUMO energy gap by decreasing the LUMO energy of dienophile (Figure 1.4). Alternately, H-bonding can also be used to stabilize anion in the transition state.

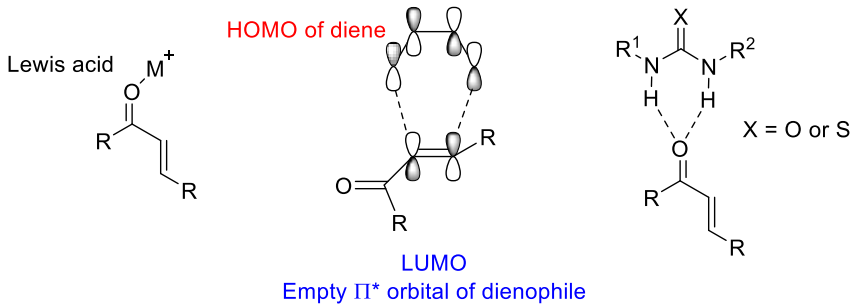
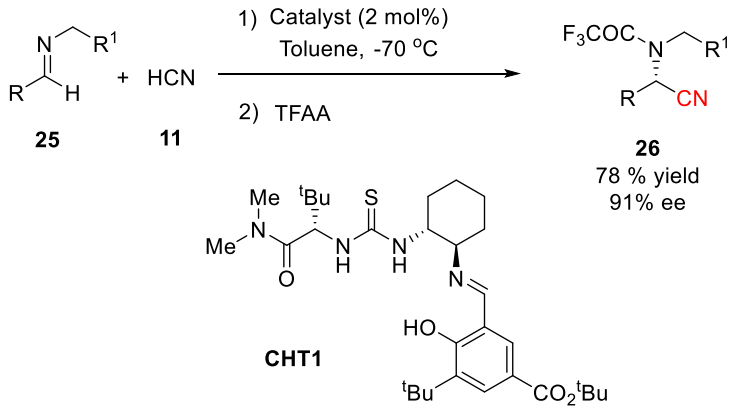


Figure 1.4: Decreasing the LUMO energy of dienophile

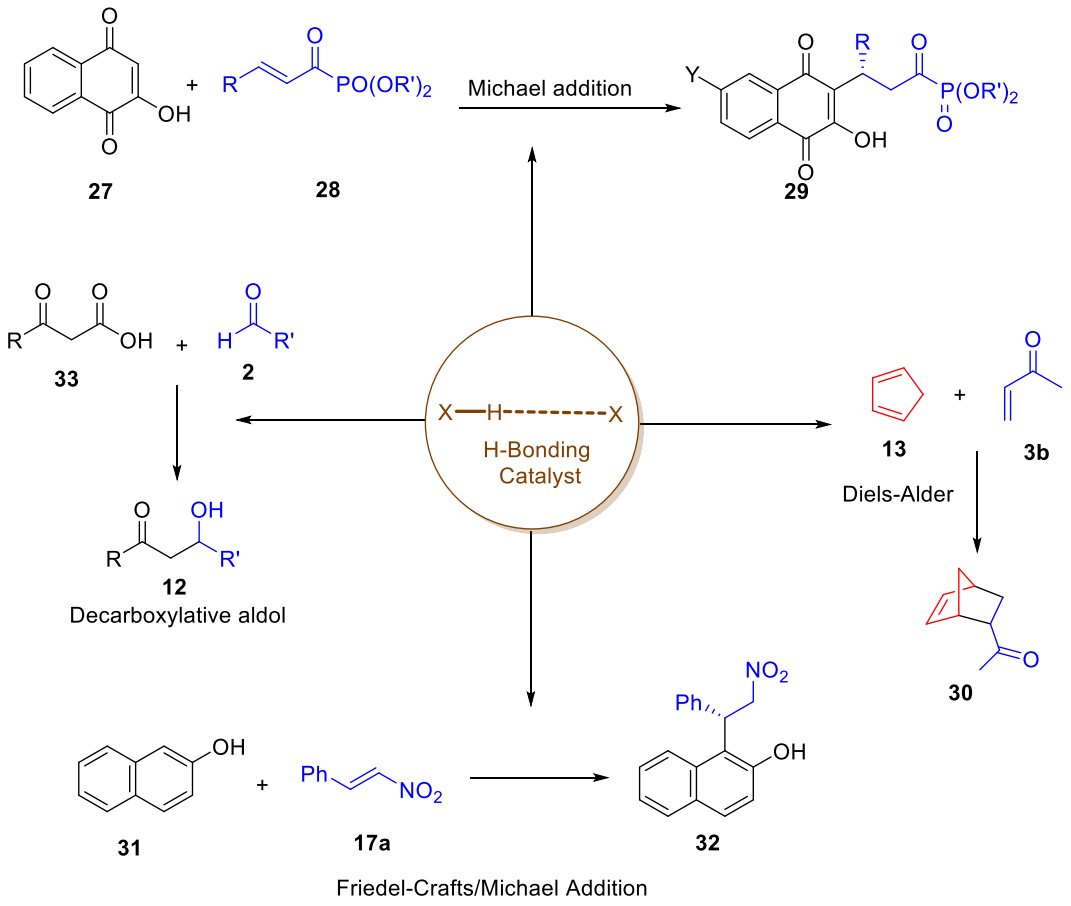
H-bonding organocatalysts are mostly robust, mild, bench stable and at many instances can easily be tuned. In asymmetric enantioselective organocatalysis H-bonding moiety can be coupled with various active variables such as primary or secondary amine, Brønsted base and quaternary amines. These exquisite multifunctional combinations are far superior in catalyzing the reaction as active variable by directly interacting with the substrate and H-bonding further orients the substrate molecule in order to minimize the energy barriers in the transition state.

The simultaneous double H-bonding strategy found to be far more efficient for the activation of an electrophile, both in enzymes and in synthetic catalyst systems. Jacobsen and co-workers harnessed the power of double H-bonding catalysis in asymmetric version of Strecker reaction by using imine thiourea catalyst **CHT**.[12] HCN **11** undergoes nucleophilic addition to the imine **25** to afford the corresponding amine product **26** in the presence of catalyst **CHT** (Scheme 1.5). Further, advances in the H-bonding catalysis led to more sophisticated versions of catalysts such as urea, thiourea, squaramide, supramolecular, guanidinium, amidinium, phosphoric acid, bisphenol, BINOL, TADDOL to name a few.[13]



Scheme 1.5: Thiourea catalyzed enantioselective Strecker reactions by Jacobsen and co-workers.

Hydrogen bonding catalysts are known for their versatile catalytic activities. They can catalyze various reactions including decarboxylative addition, Michael addition, Diels-Alder reaction, Friedel-Craft reaction, to afford the various valuable products (**12**, **29**, **30**, **32**) respectively (Scheme 1.6).



Scheme 1.6: Representative examples of H-bonding catalysis

1.3.2 Phase transfer catalysis

Phase-transfer catalysis (PTC) has long been recognised as an essential chemical strategy that allows the transport of reactant from one phase to other phase, most commonly between organic and aqueous phase (Figure 1.5).[14] The addition of PTC makes sure that one reactive ionic component of ionic reagent to distribute between aqueous/organic phases thereby accelerate the rate of the reaction.[15] By allowing the use of water, it also helps to reduce excess use of organic solvents which in turn is very useful in large scale industrial synthesis and in green chemistry applications.

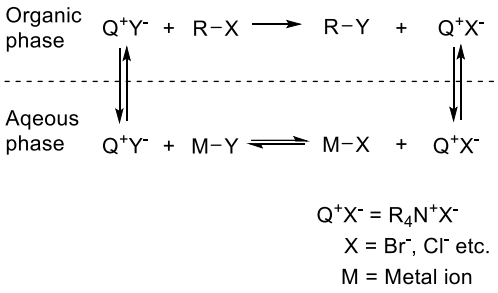
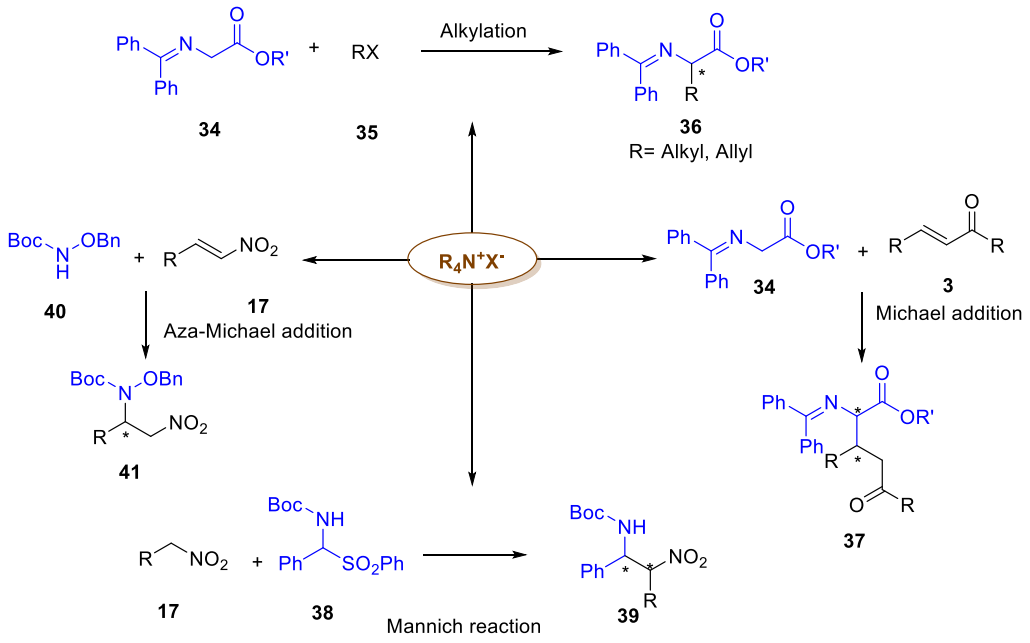


Figure 1.5: Mode of action of PTC

Quaternary ammonium salts of halides are the most commonly used as PTCs.[16] Phase transfer catalysts have been proved to be very useful in many synthetic transformations including alkylation, Michael addition, Mannich reaction, aza-Michael addition to afford the corresponding products respectively (**36**, **37**, **39**, **41**) (Scheme 1.7).



Scheme 1.7: Representative examples of PTC catalysis

1.3.3 Brønsted acid catalysis

Another important type of non-covalent organocatalyst is the catalysis by Brønsted acid. Unlike weak Lewis acid catalyst such as thiourea that activates a substrate by H-bonding, these strong acid (Brønsted acid) catalysts activate the substrate by protonation of certain functional groups like amine, imine, carbonyl oxygen etc.[17] Most frequently used Brønsted acid catalysts are chiral phosphoric acid catalysts derived from BINOL (Figure 1.6).[17b]

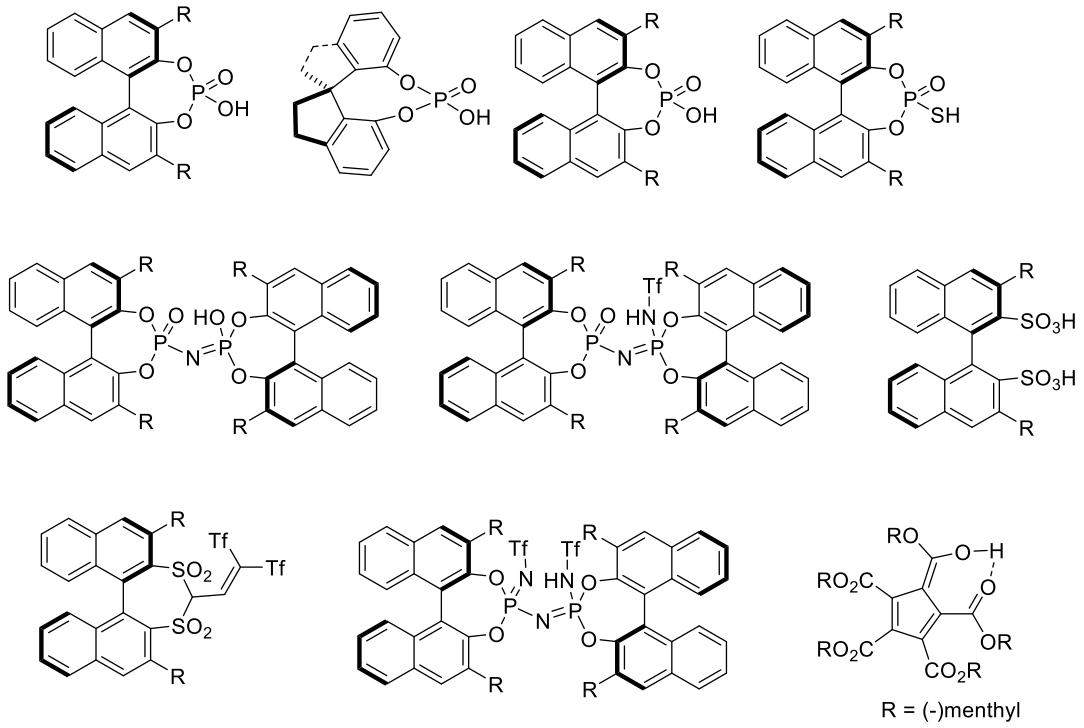
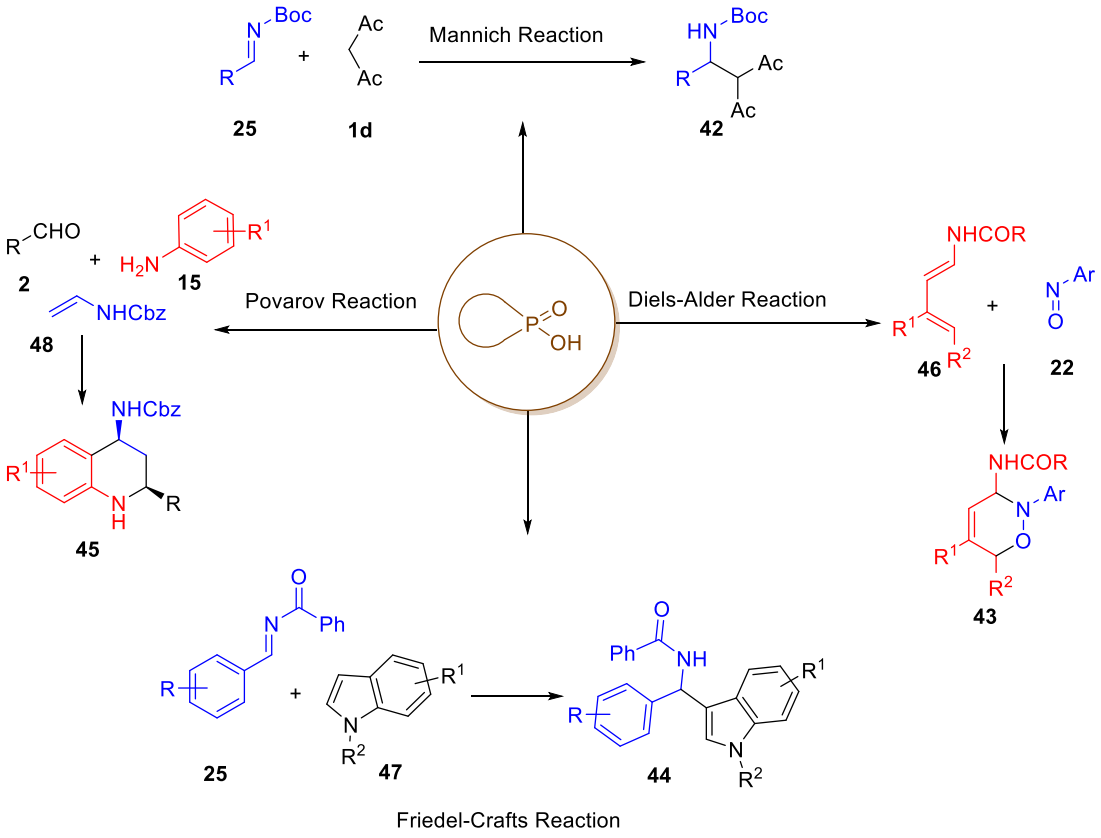


Figure 1.6: Representative examples of chiral Brønsted acids

Brønsted acids have been recognised as highly efficient and versatile catalysts for numerous synthetic transformations. Brønsted acid catalysts are capable of lowering the LUMO of an electrophile via protonation and activate the substrate toward nucleophiles. They have gained considerable attention due to their versatility by catalysing numerous enantioselective chemical transformations such as Mannich reaction, Michael addition, Diels-Alder reaction, cycloaddition reactions, Povarov reaction, tandem and cascade reactions to afford value added compounds respectively (**42**-**45** see Scheme 1.7).



Scheme 1.7: Representative examples of chiral Brønsted acid catalysis

Section 2

1.4 Meldrum's acid in organocatalysis

At many instances, the substrate-organocatalysts interactions are more selective that allow one to design a target oriented synthesis. These interactions help to design various new methods useful not only in academia but in large scale industries, for instance, pharmaceutical, polymer, food based companies.

Meldrum's acid **1a**, namely 2,2-dimethyl-1,3-dioxan-4,6-dione first synthesized by Andrew Norman Meldrum[18] in 1908 and is a peculiar cyclic organic compound which has surprisingly high acidity (pKa = 4.97 in water, 7.3 in DMSO) than its *β*-dicarbonyl counterparts (Figure 1.7). At the same time this small architectural scaffold shows lower nucleophilicity than other dicarbonyl compounds.[19] Consequently, being highly acidic in nature proton of Meldrum's acid **1a** can easily be removed by even weakly basic organocatalysts.

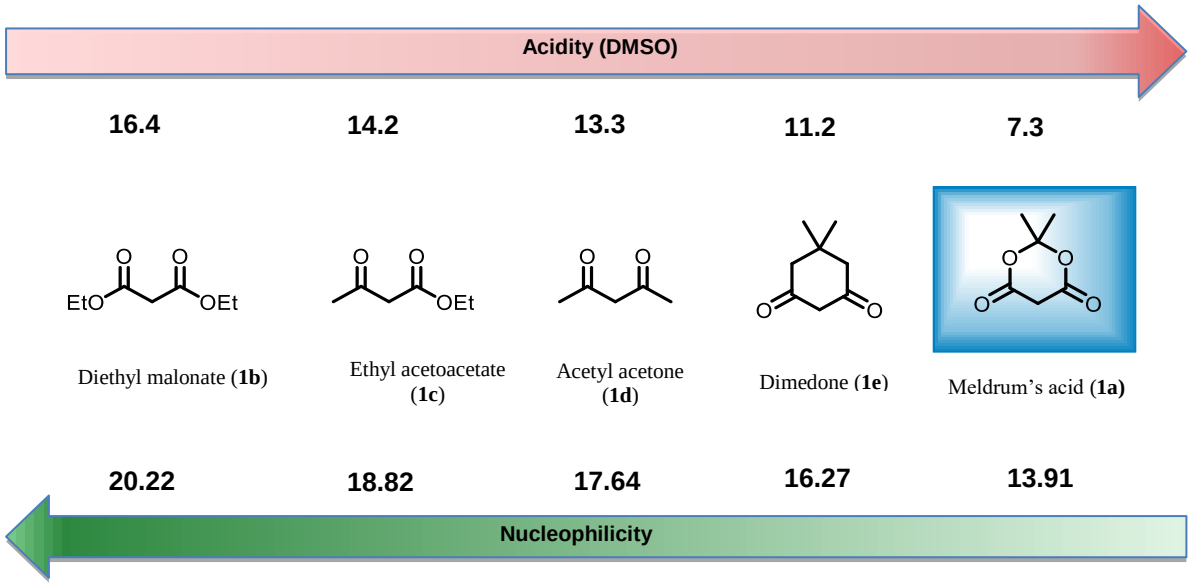
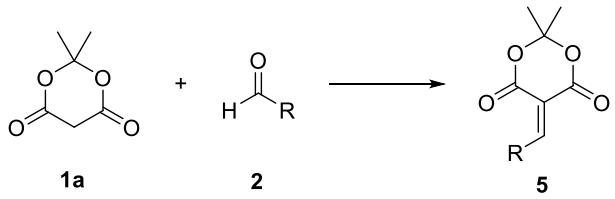


Figure 1.7: Acidity and nucleophilicity of Meldrum's acid and *β*-dicarbonyl compounds

Although known for its weak nucleophilicity, Meldrum's acid **1a** readily reacts with aldehyde **2** via Knoevenagel condensation to form alkylidene Meldrum's acid **5** (Scheme 1.9). This *α,β*-unstaurated carbonyl compound displays a marked higher electrophilicity even greater than that of *β*-nitrostyrenes **17**, with regards to electrophilicity parameters developed by Mayr and colleagues.[19]



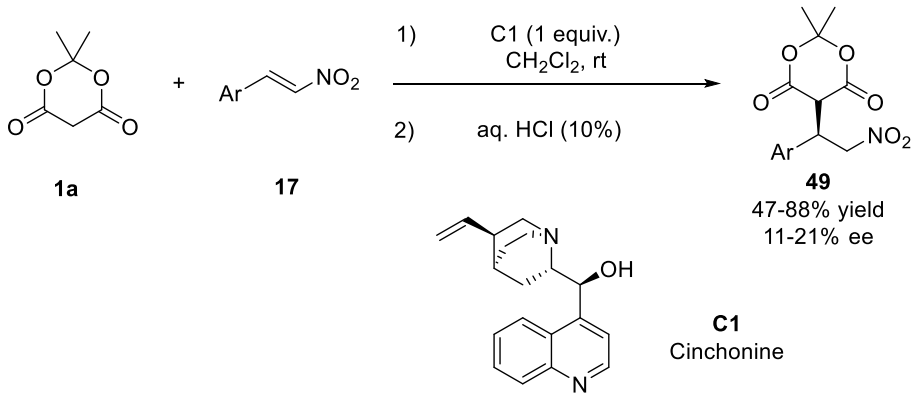
Scheme 1.9: Formation of alkylidene Meldrum's acid

Usefulness of Meldrum's acid **1a** has been testified in several synthetic applications.[20] In this regard, numerous organocatalytic approaches have been designed based on the platform of Meldrum's acid **1a** and alkylidene Meldrum's acid **5** and these transformations have gained a gradual attention in the last decade.[20h] Some of the recent development of organocatalytic transformations based on cyclic 1,3-dicarbonyl compounds, either utilized Meldrum's acid **1a** and its derivatives **1** or alkylidene Meldrum's acid **5** for the useful transformations. Hence, in this regard, the important methodologies have been further classified into two main categories, namely, a) the reactions of Meldrum's acid as a nucleophile and b) reactions of alkylidene Meldrum's acid as electrophile. These reactions have been discussed in brief in the next sub section.

1.4.1 Meldrum's acid as a nucleophile

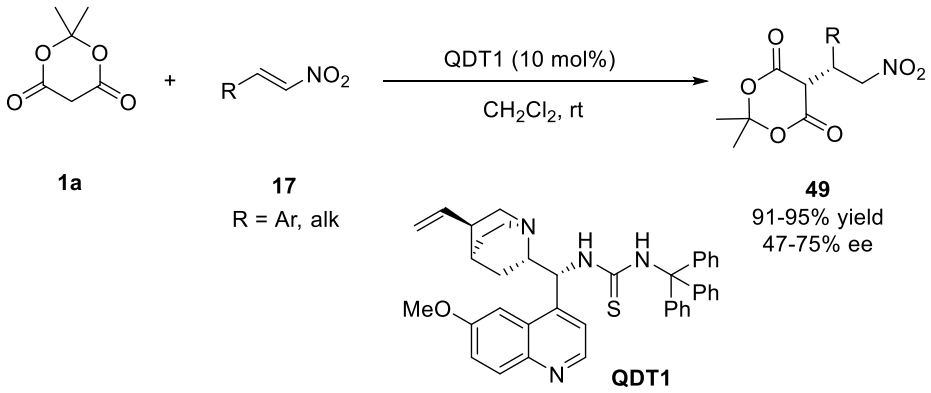
Meldrum's acid **1a** acts as an excellent malonate surrogate which makes it an attractive alternative in the synthesis that is targeted towards carboxylic acids and esters. Similarly, due to its thermal instability, carbonyl/cyclic ester backbone in Meldrum's acid **1a** is prone to be attacked by hard nucleophiles that make Meldrum's acid **1a** as an attractive tool in domino/cascade methodologies.

First enantioselective synthesis was attempted by Sas and co-workers[21] in 2007 (Scheme 1.10). They reported the Michael addition between Meldrum's acid **1a** and nitroalkenes **17** using stoichiometric amount of cinchonine **C1** to afford the corresponding products **49** in very good yields with modest to poor enantioselectivity. It was proposed that basic cinchonine **C1** deprotonates Meldrum's acid **1a** which further undergoes Michael addition with nitroalkene **17**. The initially obtained product-a salt of cinchonine was further treated with 10% HCl to obtain the final product **49**.



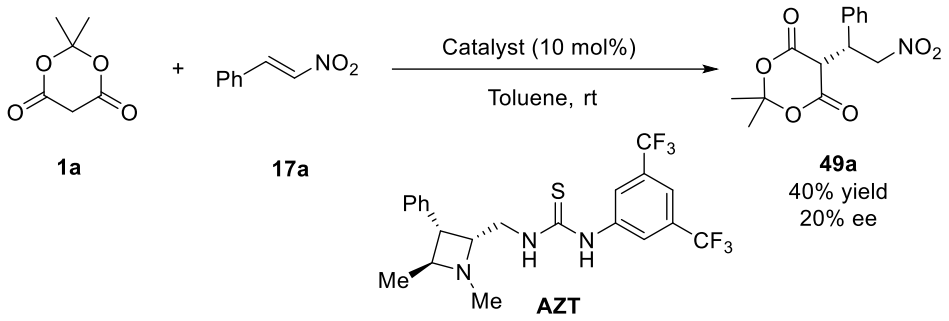
Scheme 1.10: First enantioselective Michael addition of Meldrum's acid by Sas and co-workers

In 2009, Koskinen and co-workers[22] succeeded in improving the enantioselectivity of Michael addition by using bifunctional cinchona based thiourea catalyst **QDT1** (Scheme 1.11). Both aliphatic and aromatic derivatives of nitroalkenes **17** reacted smoothly to give the corresponding products **49** with very good yield with significantly improved enantiomeric excess (up to 75% *ee*). Probably, H-bonding is the key factor for this enantiomeric transformation. This was further proved by the reaction of *N*-methylated analogue of thiourea catalyst **QDT1** which furnished only modest enantioselectivity (13% *ee*).



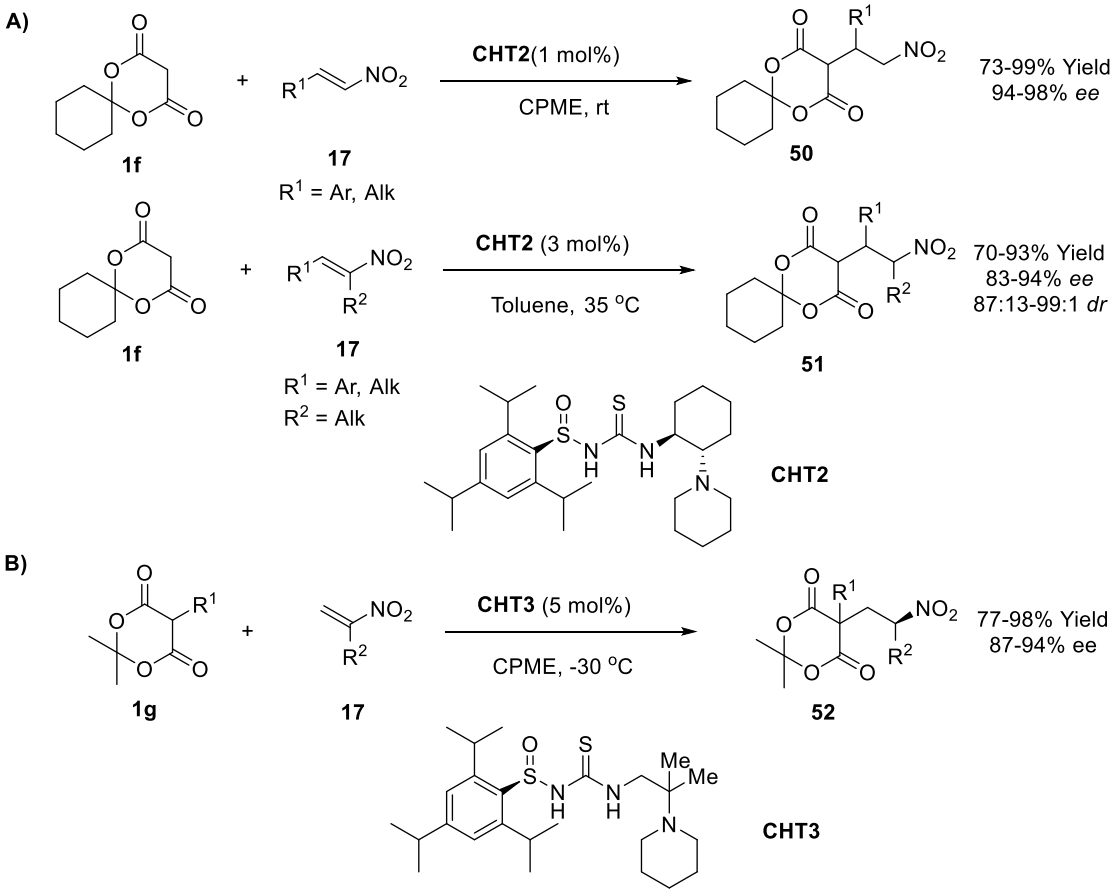
Scheme 1.11: Enantioselective reaction by Koskinen and co-workers

In 2010, Couty and co-workers[23] tested the efficiency of azetidines derived thiourea catalyst **AZT** towards the Michael addition of Meldrum's acid **1a** to *β*-nitrostyrene **17a** (Scheme 1.12). However, the reaction furnished product **49a** in 40% yield with modest enantioselectivity (20% *ee*).



Scheme 1.12: Enantioselective reaction by Couty and co-workers

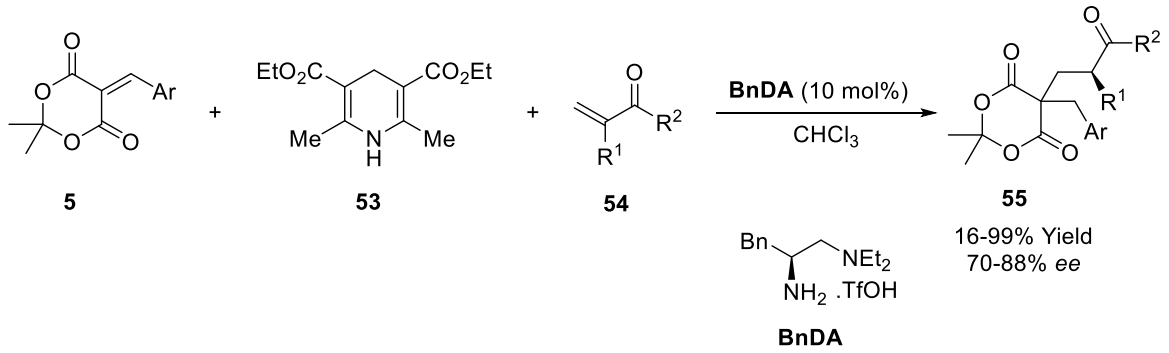
In 2012, Ellman and co-workers[24] sought a chiral sulfinamide based thiourea catalysts **CHT2** for the efficient Michael addition reaction between cyclohexyl Meldrum's acid **1f** and *α,β*-unsaturated nitro compounds **17** (Scheme 1.13 A). The reaction afforded the corresponding protonated nitro adducts **50** and **51** in excellent enantioselectivity and good to excellent *dr* ratio under 1 mol% of catalyst loading.



Scheme 1.13: Organocatalytic Michael addition/protonation reaction by Ellman and co-workers

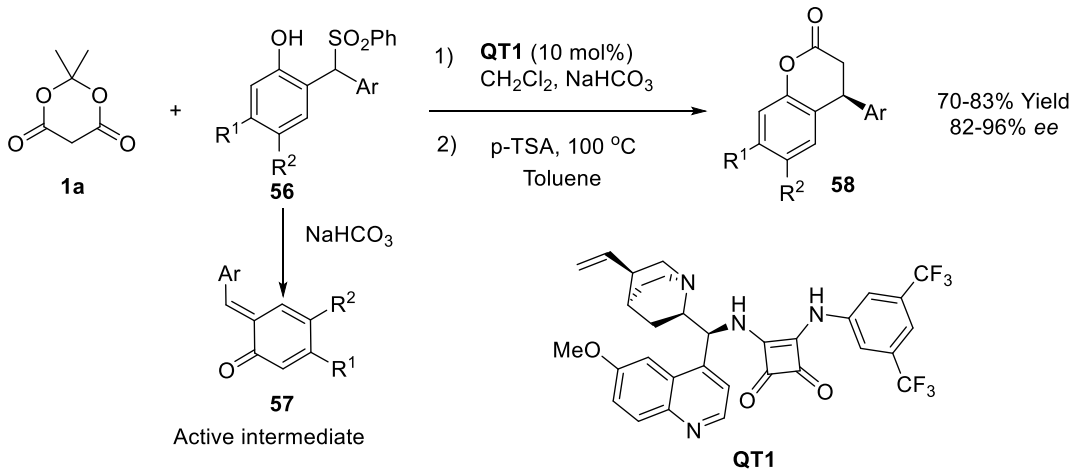
Further, in continuation of their work, quaternary-substituted Meldrum's acid architectures **52** were synthesized through Michael addition of mono-substituted Meldrum's acid **1g** on *α,β*-disubstituted nitro compounds **17** (Scheme 1.13 B). It has been observed that even simple chiral sulfinamide backbone of catalyst **CHT3** could effectively induce better stereocontrol for the outcome of the reaction.[24b]

In 2015, Luo and co-workers demonstrated the utility of alkylidene Meldrum's acid **5** in domino 1,4-addition/protonation reaction (Scheme 1.14).[25] Initially, reduced alkylidene Meldrum's acids **5** by Hantzsch ester **53**, further provides an enolate intermediate *in situ* (alkylated Meldrum's acid) that undergoes smooth Michael addition/protonation to *α*-substituted vinyl ketones **54** to afford the corresponding disubstituted Meldrum's acid derivatives **55** in excellent yields with very good enantioselectivity.



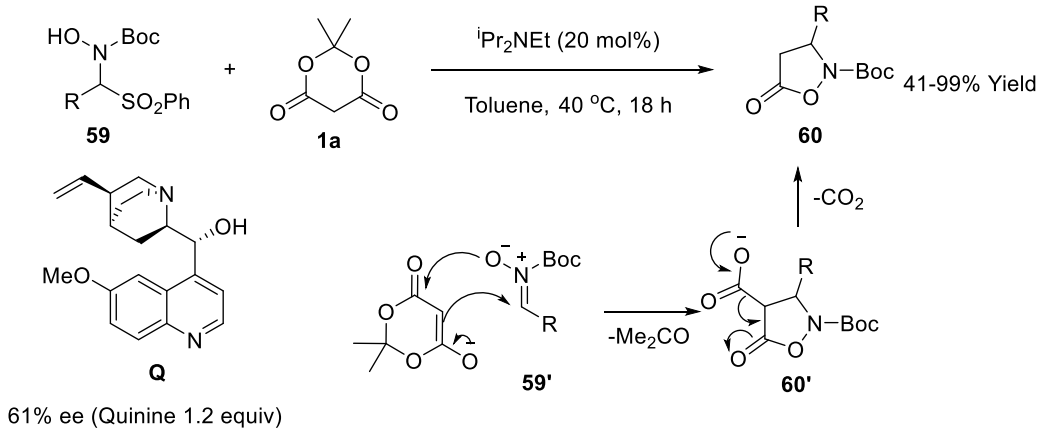
Scheme 1.14: Organocatalytic domino 1,4-addition/protonation reaction by Luo and co-workers

In 2015, Bernardi and co-workers[26] employed the organocatalytic approach by using Meldrum's acid **1a** as substrate for the enantioselective synthesis of 3,4-dihydrocoumarins **58** (Scheme 1.15). The reaction was assumed to proceed via the formation of highly reactive and unstable *ortho*-quinone methide **57** from phenol **56**. The deprotonated Meldrum's acid **1a** accompanied by cinchona based squaramide organocatalyst **QT1** attacks *ortho*-quinone methide **57** followed by lactonization process to afford 3,4-dihydrocoumarin **58**.



Scheme 1.15: Enantioselective synthesis of 3,4-dihydrocoumarins by Bernardi and co-workers

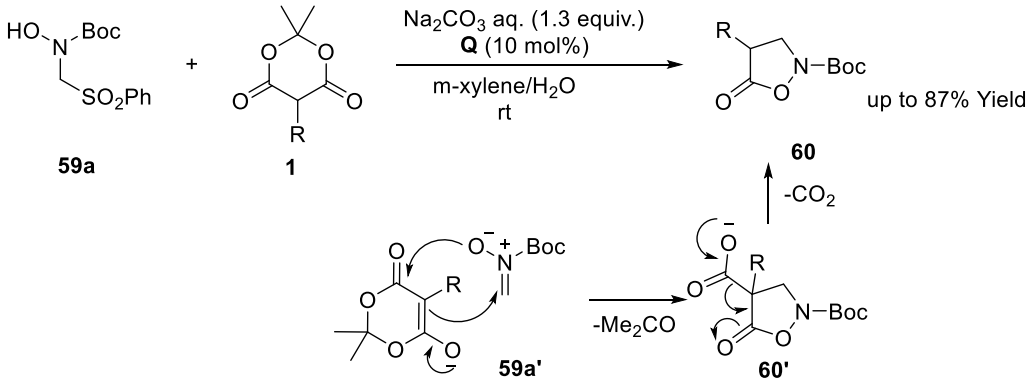
In 2013, Brière and co-workers[27] reported formal [3+2] cycloaddition/fragmentation/decarboxylation/protonation strategy for the synthesis of *β*-substituted isoxazolidin-5-ones **60** starting from Meldrum's acid **1a** and nitrone precursor **59** (Scheme 1.16). In *situ* formed nitrone **59'** generated by the treatment of nitrone precursor **59** with K_2CO_3 underwent formal [3+2] cycloaddition/decarboxylation/protonation. The stoichiometric amount of Brønsted base like quinine **Q** afforded the product with moderate to good enantioselectivity (up to 61% *ee*)



Scheme 1.16: Synthesis of isoxazolidin-5-one by Brière and co-workers

In the same year, Brière group[28] successfully developed organocatalytic enantioselective version of formal [3+2] cycloaddition between Meldrum's acid **1a** and nitrone **59'** (Scheme 1.17). Mono-substituted Meldrum's acid **1** was employed instead of simple Meldrum's acid **1a** to address the key issue regarding enantioselective protonation of

the intermediate 60'to afford α-substituted isoxazolidin-5-one **60** (up to 87% yield,88% *ee*). These two approaches (Scheme 1.16 and Scheme 1.17) can be utilized for the direct synthesis of β-amino acids.



Scheme 1.17: Enantioselective synthesis of isoxazolidin-5-one by Brière and co-workers

1.4.2 Alkylidene Meldrum's acid as a Michael acceptor

Alkylidene Meldrum's acid **5** is one of the excellent Michael acceptors and these have been widely explored in plenty of synthetic processes. Some of the properties such as high electrophilicity, ability to form in *situ*, and labile ring opening make Alkylidene Meldrum's acid **5** an attractive substrate for many multicomponent domino reactions.[19] Most interesting feature of alkylidene Meldrum's acid chemistry is that ability of the nucleophilic attack strongly depends upon the nature and type of incoming nucleophile (Figure 1.8). This intrinsic feature has led to the development of various heterocycles and synthetically important and useful products.

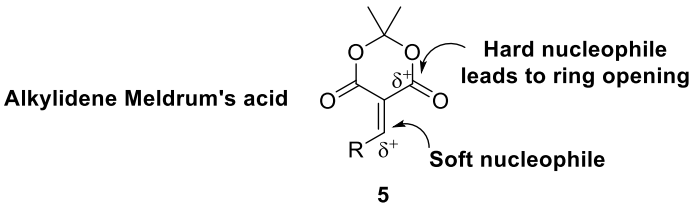
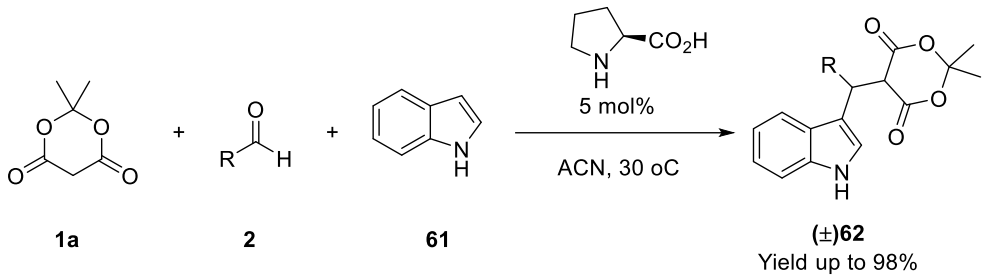


Figure 1.8: Alkylidene Meldrum's acid

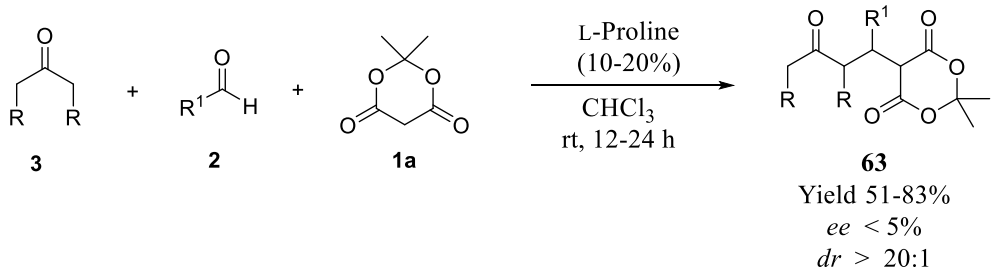
The direct implications of in *situ* generated alkylidene Meldrum's acid **5** have been demonstrated at many instances. In 1978 Yonemitsu and co-workers reported proline catalyzed three component reaction between Meldrum's acid **1a**, aldehyde **2** and indole **61** to give substituted Meldrum's acid derivatives **62** in excellent yield (Scheme 1.18).[29]

Presumably, the reaction proceeded via formation of alkylidene Meldrum's **5** acid followed by Michael addition of indole **61**.



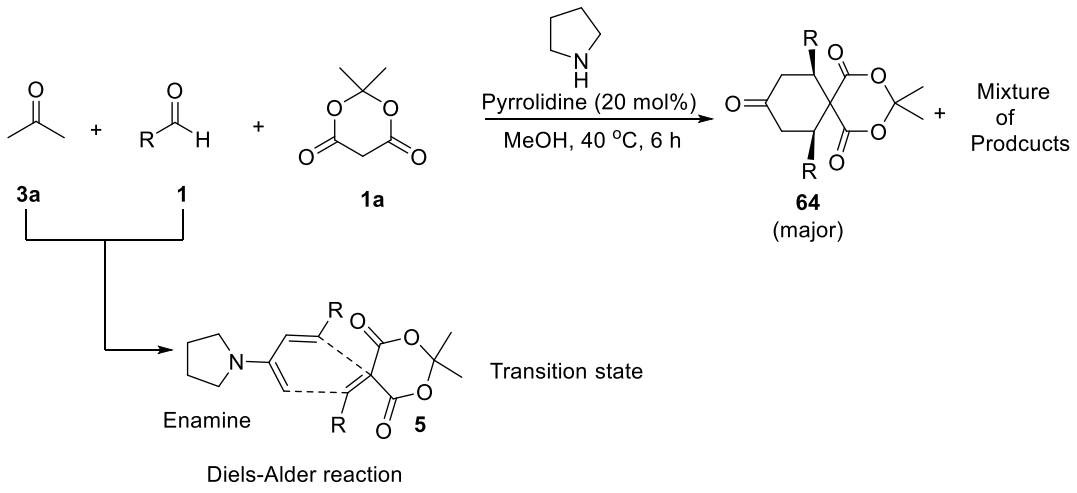
Scheme 1.18: Proline catalyzed multicomponent reaction by Yonemitsu and co-workers

In 2001, List and Castello[30] reported proline catalyzed three component reaction between Meldrum's acid **1a**, aldehyde **2** and enolizable ketone **3** (Scheme 1.19). Proline played a dual role by catalyzing the Knoevenagel condensation via imine catalysis followed by promoting the Michael addition through enamine intermediate. Though reaction proceeded with poor enantioselectivity, however, the reaction was highlighted due to very good diastereomeric ratio.



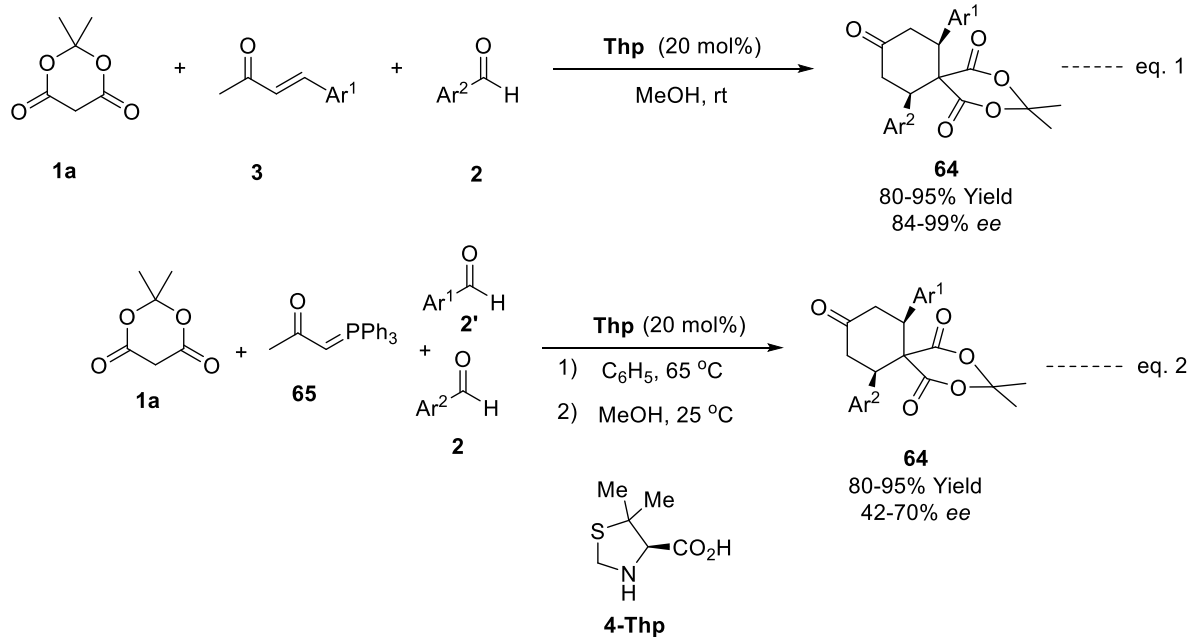
Scheme 1.19: Multicomponent reaction of Meldrum's acid, aldehydes, and ketones by List and co-workers

Two years later, Barbas and co-workers[31] revisited the same reaction, however by using cyclic secondary amine such as pyrrolidine as a catalyst (Scheme 1.20). Interestingly, reaction turns out to be not practical and furnished spiro-cycloaddition product **64** along with three other minor side-products.



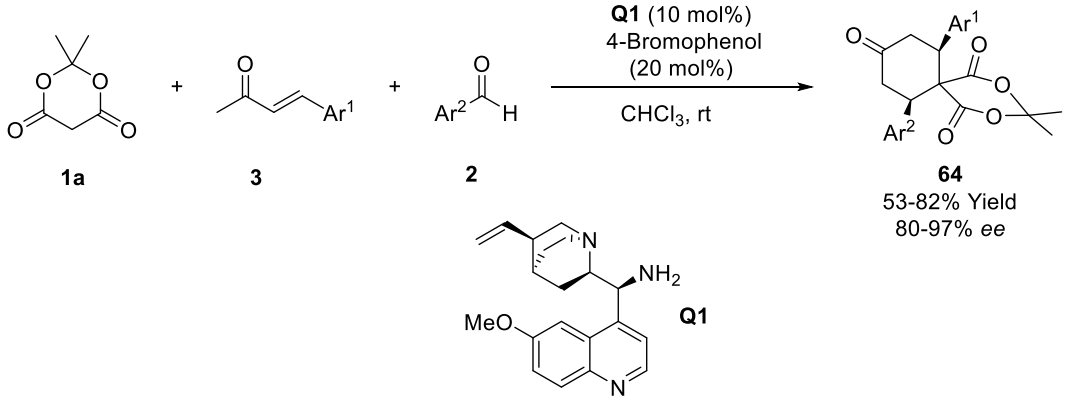
Scheme 1.20: Pyrrolidine catalyzed multicomponent reaction by Barbas and co-workers

For the enantioselective transformation, the reactions were further explored using enones **3** instead of ketones (Scheme 1.21 eq. 1). 4-Thiaproline **Thp** catalyzed multicomponent reaction proceeded via enamine-iminium tandem catalysis.[32] Chiral diene species reactwith alkylidene Meldrum's acid **5** via Diels-Alder reaction to afford optically active spiro products **64** (88-99% *ee*). One year later, the same group adopted sequential Wittig/Diels-Alder reaction approach for the enantioselective synthesis of product **64** (See eq 2, Scheme 1.21).



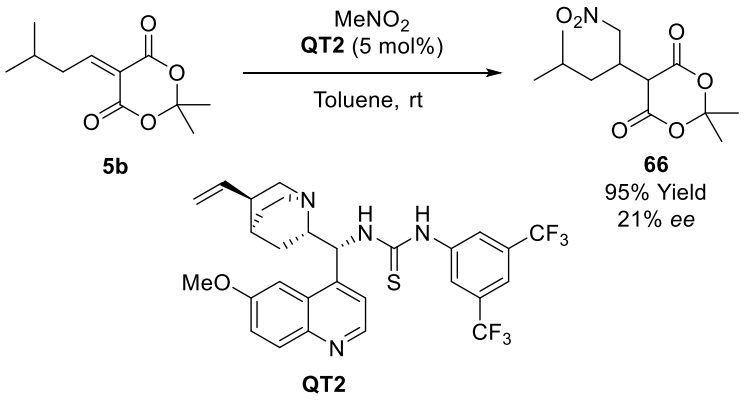
Scheme 1.21: Enantioselective multicomponent domino reaction by Barbas and co-workers

Again in 2011, Feng and co-workers[33] revisited the reaction by using cinchona based primary amine catalyst **Q1** (Scheme 1.22). The catalyst worked efficiently by providing very high enantiomeric excess of the product **64** (up to 97% *ee*).



Scheme 1.22: Primary amine catalyzed enantioselective multicomponent domino reaction by Feng and co-workers

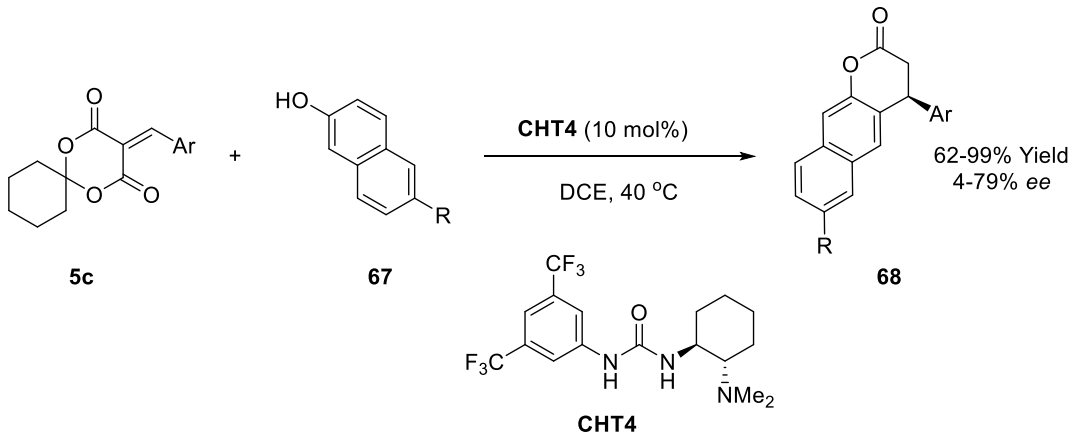
In search for facile route for the synthesis of Pregabalin, Koskinen and co-workers[34] performed the Michael addition of nitromethane on alkylidene Meldrum's acid **5b** by using cinchona based thiourea catalyst **QT2** (Scheme 1.23). Unfortunately, the reaction furnished the product **66** with modest enantioselectivity (21% *ee*).



Scheme 1.23: Michael addition of nitromethane by Koskinen and co-workers

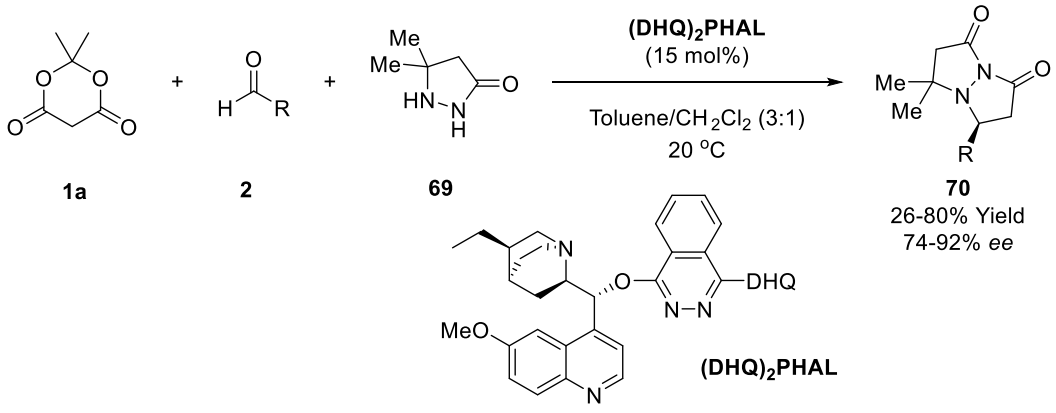
In 2012, Zhang and co-workers[35] reported an elegant bifunctional thiourea (**CHT4)** catalyzed enantioselective domino Friedel–Craft/cyclocondensation reaction between cyclohexanone derived alkylidene Meldrum's acid **5c** and 2-naphthols **67** (Scheme 1.24). It is interesting to note that Michael addition of 2-naphthol-lactonization-decarboxylation

occurred in one pot at 40 ^{o}C to afford the the product **68** in excellent yields (99%) with good enantioselectivity (up to 79% *ee*).



Scheme 1.24: Enantioselective Friedel–Craft type reaction by Zhang and co-workers

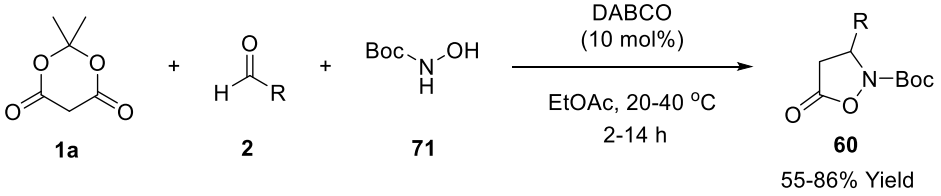
In 2014, Brière and co-workers[36] reported enantioselective multicomponent Knoevenagel/aza-Michael/cyclocondensation reaction (Scheme 1.25). The method utilized the cinchona based $(DHQ)_2PHAL$ catalyst for the three component reaction between Meldrum's acid **1a**, aldehyde **2** and pyrazolidinone **69**. The reaction proceeded via chemoselective hetero-Michael addition of pyrazolidinone to in *situ* generated alkylidene Meldrum's acid **5.** The method gave access to a straightforward synthesis of 1,5-diazabicyclo[3.3.0]octane-2,6-diones **70 (**up to 92% *ee*).



Scheme 1.25: Enantioselective Knoevenagel/aza-Michael/cyclocondensation reaction

In 2015, same group[37] extrapolated Knoevenagel/hetero-Michael/cyclocondensation sequence to the novel synthesis of isoxazolidin-5-ones **60** (Scheme 1.26). Unlike their previous work (based on [3+2] cycloaddition between nitrone **59'** on Meldrum's acid **1a**), the

newer method demonstrated a facile and direct multicomponent synthesis of isoxazolidin-5-ones **60**.



Scheme 1.26: Multicomponent Knoevenagel/hetero-Michael/cyclocondensation reaction by Brière and co-workers

1.5 Conclusions

In conclusions, Meldrum's acid and its derivatives have been proved to be very useful substrates and they have provided an access to various valuable synthetic products. Its versatility has been efficiently demonstrated in the complex multicomponent processes. Since last two decades the use of Meldrum's acid has been explored in various enantioselective organocatalytic transformations. Though Meldrum's acid has been explored in the various enantioselective organocatalytic transformations, yet some of the methodologies involving Meldrum's acid still need to meet very high enantioselectivity. Similarly, novel and practical uses of Meldrum's acid and its derivatives are highly demanding and challenging to pursue.

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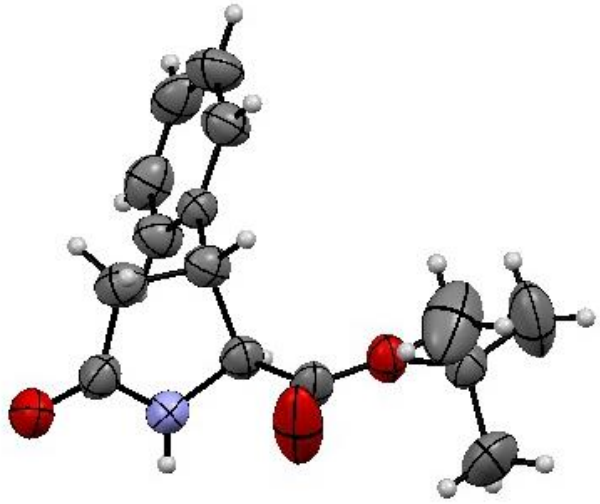
Chapter 2

Multicomponent Synthesis of Pyroglutamic Acid Derivatives Under Mild Conditions via Knoevenagel-Michael-Hydrolysis-Lactamization-Decarboxylation Sequence



3-Phenyl pyroglutamic ester

(X-ray Crystal structure)

2 Multicomponent Synthesis of Pyroglutamic Acid Derivatives Under Mild Conditions via Knoevenagel-Michael-Hydrolysis-Lactamization-Decarboxylation Sequence

Novel and practical protocol is developed for the multicomponent synthesis of pyroglutamic acid derivatives starting from easily available Meldrum's acid, aldehyde and glycine imine ester. This facile approach tolerates a wide variety of aliphatic and aromatic aldehydes and glycine imine esters. Pyroglutamic ester further can easily be converted into functionalized pyroglutamic acids, piperidines and pyrrolidinones.

2.1 Introduction

Pyroglutamic acid is analogous to glutamic acid in which free amine group of glutamic acid or glutamine cyclizes to afford cyclic amide, *i.e.*, lactam ring. Although pyroglutamic acid is ubiquitously found in nature, interestingly it is seldom or little-studied amino acid in the literature. Pyroglutamic acid has been recognized as one of the metabolites of very important glutathione cycle that is converted to glutamate by pyroglutamate hydrolase (5-oxoprolinase). Pyroglutamic acid derivatives and its substituent variants are found in a number of natural products and pharmaceuticals (Figure 2.1).[1] For example derivative of pyroglutamic acid:(-)-dysibetaine, a natural product extracted from the marine sponge *Dysidea herbacea* acts as an ionotropic glutamate receptors (iGluRs) in the mammalian central nervous system.[2a] Likewise, (-)-salinosporamide A marine natural product obtained from obligate marine bacteria *Salinispora tropica* and *Salinispora arenicola* acts as a proteasome inhibitor and being studied as anti-cancer agent.[2b] Salinosporamide A is derived from pyroglutamic acid or it has pyroglutamic acid as a major covalent bonding of piece. Similarly, kainic acid isolated from some seaweed acts as a potent neuroexcitatory amino acid agonist works by activating excitatory neurotransmitter receptors in the central nervous system.[2c] Kainic acid also can be constructed starting from pyroglutamic acid. Apart from that, they are often elaborated as starting materials in the synthesis of very important biologically active compounds and natural products. Its core structure can be easily

transformed into functionalized piperidines and pyrrolidinones which find extensive applications in peptidomimetics[3] and neuroexcitatory chemistry.[4]

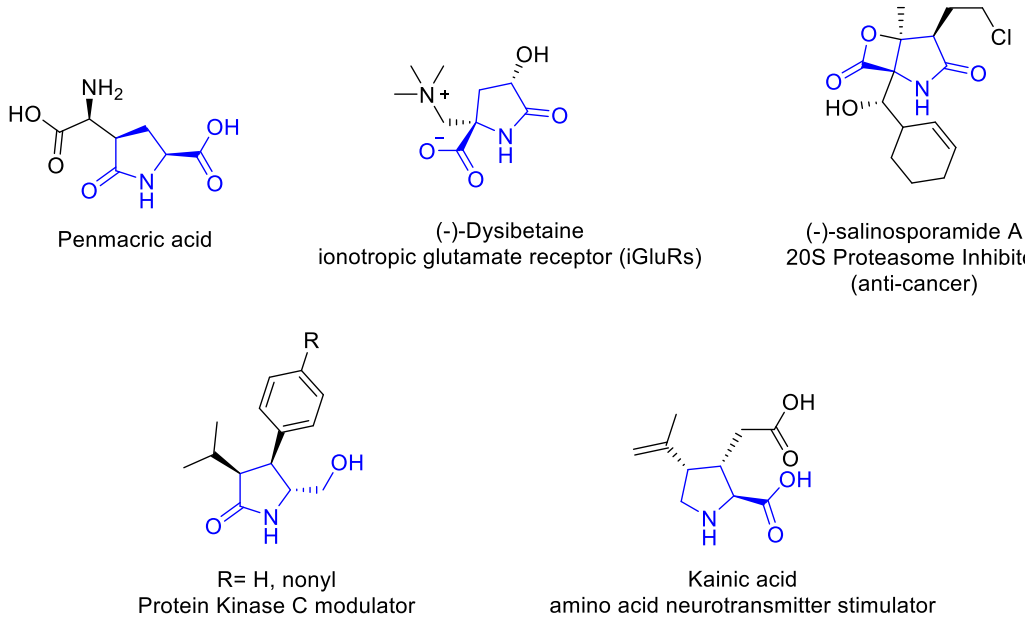
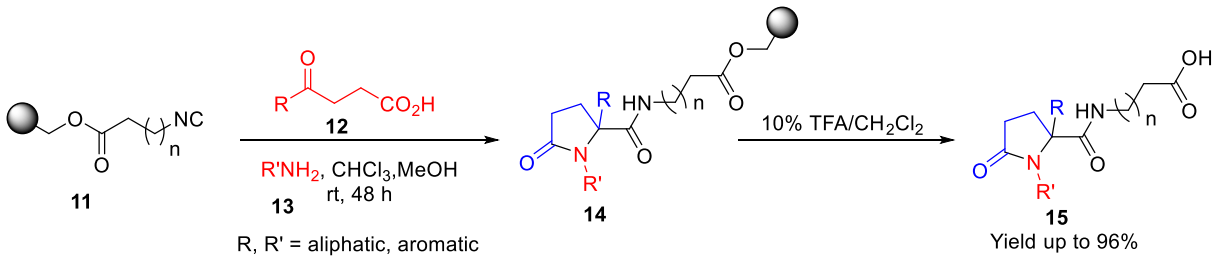


Figure 2.1: Pyroglutamic acid derivatives and pyrrolidinones in natural products

2.2 Previous approaches for the synthesis of pyroglutamic acid derivatives

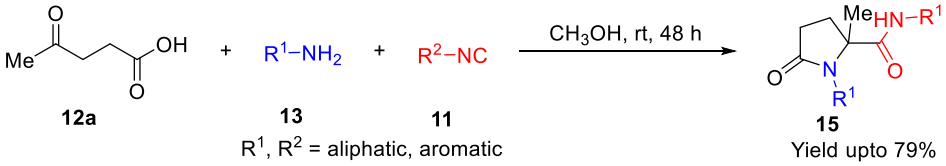
Owing to the importance of pyroglutamic acid and its applications, numerous synthetic approaches have been developed for the synthesis of pyroglutamic acid and its derivatives. Likewise, catalytic multicomponent and multistep approaches have been developed for the construction of substituted pyroglutamic acid scaffolds. The multicomponent reaction strategies have been found to be a fruitful synthetic tool for the construction of these complex heterocycles.[5] Some of the selected multicomponent approaches for the synthesis of pyroglutamic acid have been described.

In 1997 Mjalli and co-workers explored a solid-phase combinatorial approach for the synthesis of pyroglutamyl amide **15** and six-membered lactams (Scheme 2.1).[5a] In order to avoid tedious chromatographic purifications, isocyanide bound Wang resin **11** was utilized as immobilized solid support for the three component reaction. The three component reaction between different isocyanides **11**, keto-acids **12** and amines **13** afforded relatively pure pyroglutamyl amides **15** in good to excellent yields (up to 96%).



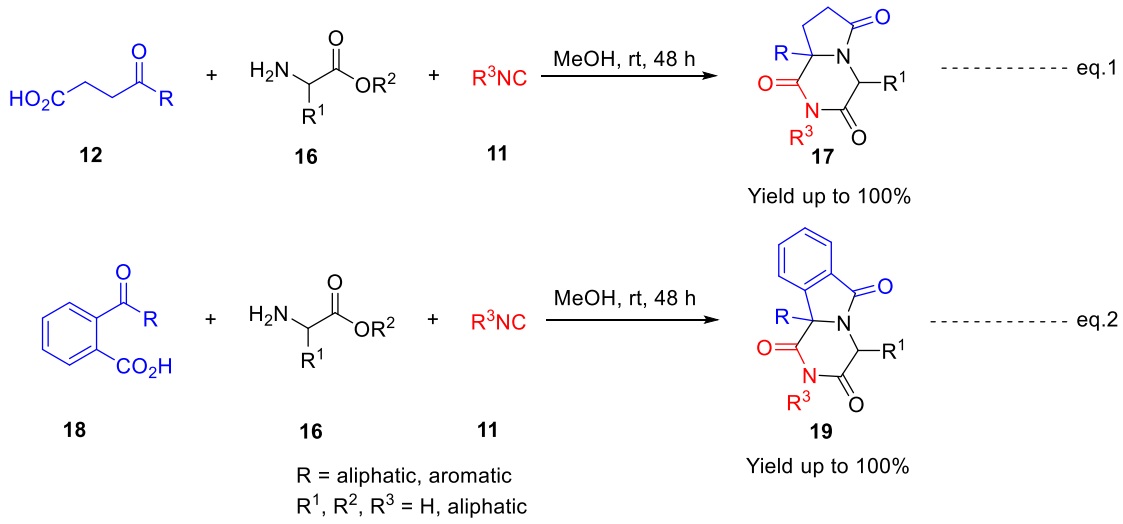
Scheme 2.1: Synthesis by Mjalli and co-workers.

Harriman reported a three component Ugi reaction utilizing *γ*-keto acid **12a** for the synthesis of lactams **15** (Scheme 2.2).[5a] *γ*-Keto acid **12a**, amine **13** and isocyanide **11** were effectively utilized for the construction of the pyroglutamyl amide framework **15** (up to 79% of yield). The 1,4-functionality of keto-acid **12a** is the key factor for the lactamization.



Scheme 2.2: Harriman's synthesis via Ugi reaction

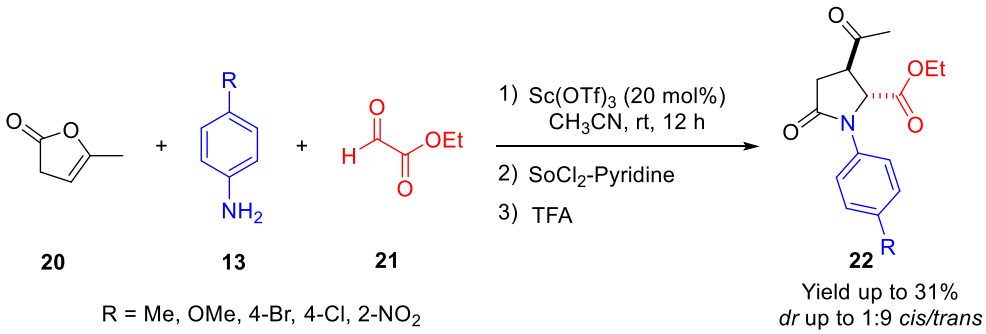
Ugi and Hanusch-Kompa[5c] demonstrated the generality of intramolecular Ugi reaction for the construction of lactam scaffold (Scheme 2.3). The method utilized *γ*-keto acid (aliphatic **12,** eq 1 and aromatic **18**, eq 2, Scheme 2.3) and amino acid ester **16** for the synthesis of fused lactams **17** and **19** respectively.



Scheme 2.3: Synthesis by Ugi and Hanusch-Kompa

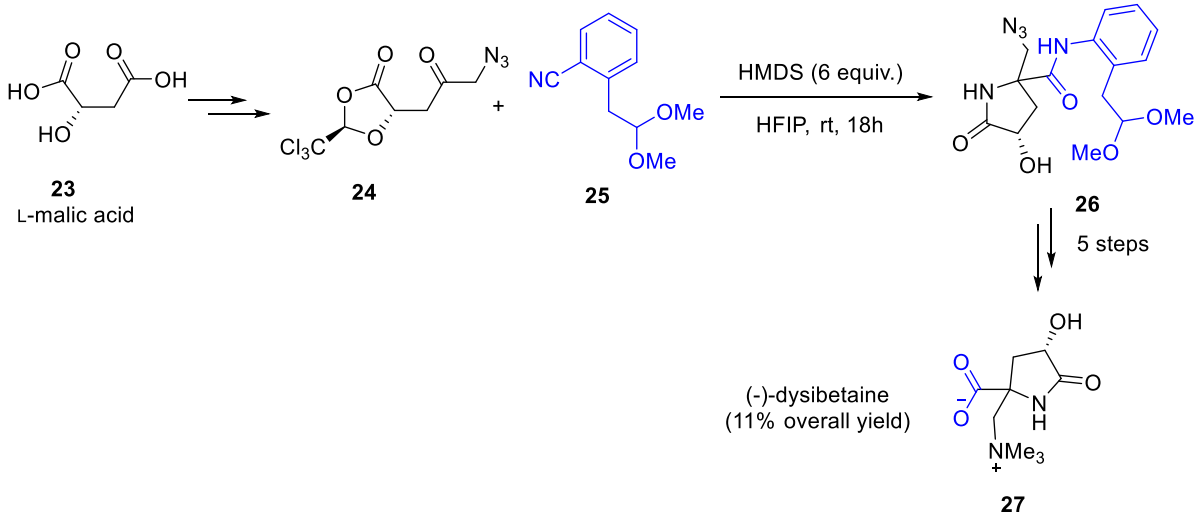
The protocol tolerated a wide variety of amino esters derived from amino acids and γ-keto-acids furnishing the desired products in quantitative yields.

In 2007 Lavilla and co-workers[5f] reported a multicomponent reaction of α-angelica lactone **20**, amine **13** and ethyl glyoxylate **21** for the synthesis of disubstituted lactams **22** (Scheme 2.4). Scandium triflate (20 mol%) was found to be the best catalyst for this transformation. The protocol gave access to *trans*-pyroglutamic esters **22** by the epimerization of the initially formed mixture containing predominantly *cis*-isomer in modest yield (up to 31%) with good diastereoselectivity (up to 1:9 *dr*). The reaction pathway is believed to undergo via Mannich reaction followed by the rearrangement to afford the corresponding lactam derivatives.



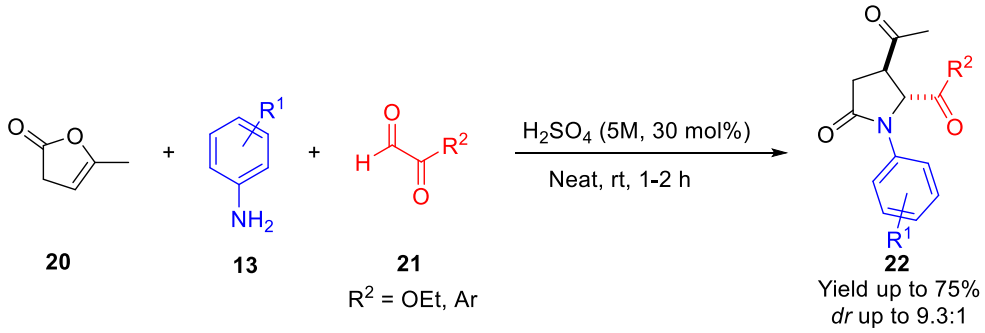
Scheme 2.4: Synthesis by Lavilla and co-workers

In 2009 Kobayashi and co-workers[5g] employed an intramolecular Ugi reaction approach for the total synthesis of a natural product (-)-dysibetaine **27**. Naturally occurring L-malic acid **23** was initially converted into α-azido ketone **24** which further upon treatment with specially tailored aromatic isocyanide **25** afforded the corresponding pyroglutamic acid derivative **26** (Scheme 2.5). The aromatic isocyanide **25** was designed in such a way that it would readily convert into corresponding pyroglutamyl amide **26**, which further under mild hydrolytic conditions afforded pyroglutamic acid derivative (-)-dysibetaine **27** (11% overall yield).



Scheme 2.5: Synthesis (-)-dysibetaine via Ugi reaction by Kobayashi and co-workers

In 2015 Yuan and co-workers[5h] developed a solvent-free green approach for the three-component synthesis of lactams **22** starting from easily available aniline derivatives **13**, *α*-oxoaldehydes **21**, and *α*-angelica lactone **20** by using dilute sulfuric acid (5 M) as the catalyst (Scheme 2.6). This approach afforded *γ*-lactams derivatives **22** in good to excellent yields (up to 75%) with satisfactory diastereoselectivity (up to 9.3:1 *dr*) at room temperature.

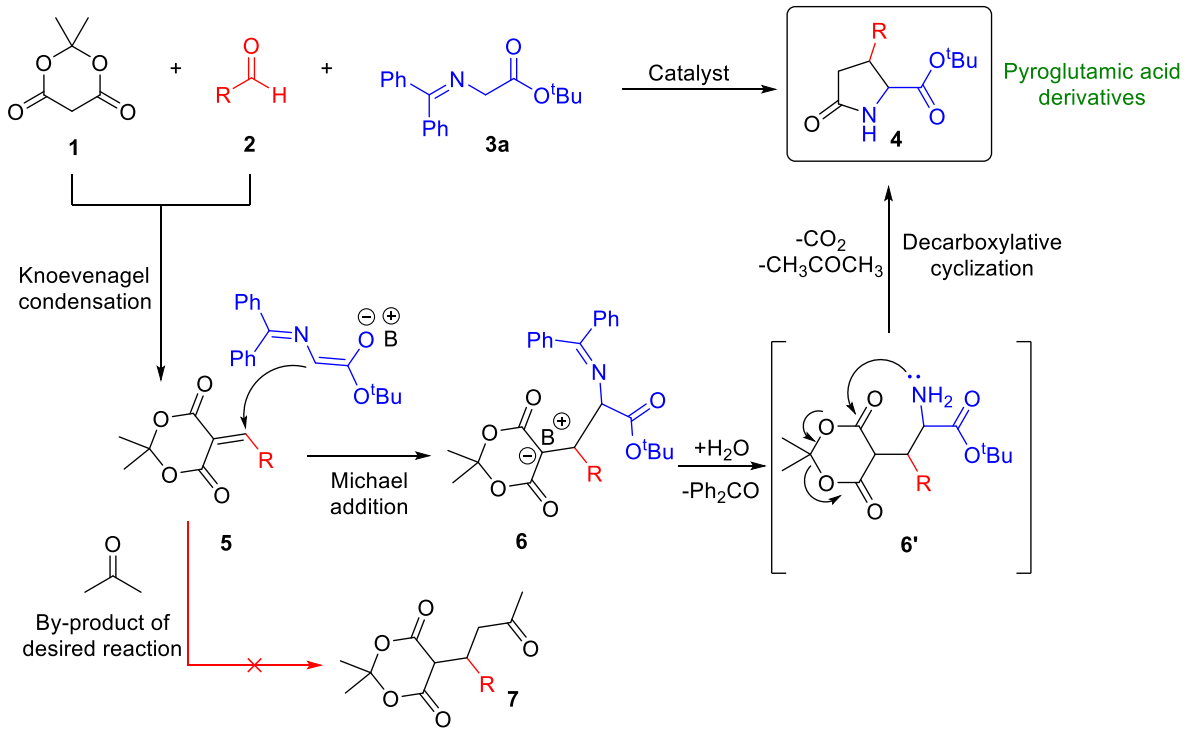


Scheme 2.6: Synthesis by Yuan and co-workers

The major shortcomings of most of these methods are limited substrate scope and limited substituents on lactam ring. Therefore, the development of a facile, general and more practical protocol to address these shortcomings is still of great importance. Keeping these considerations in mind, we ventured into a novel, multicomponent and more practical strategy to synthesize pyroglutamic acid derivatives. Herein, we have developed a novel and expedient multicomponent synthesis of pyroglutamic esters allowing new entries to the family of substituted variants of pyroglutamic acid.

2.3 Our synthetic plan

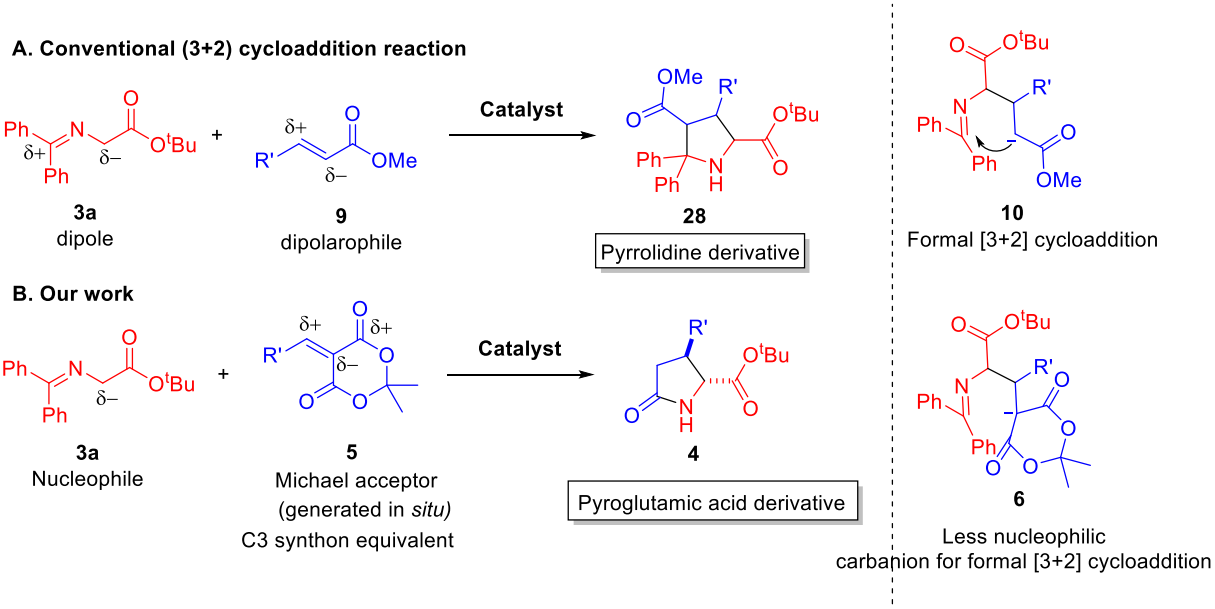
Recently our group has developed strategies for the synthesis of *α,β*-unsaturated acids, esters and thioesters through catalytic decarboxylation of alkylidene Meldrum's acids.[6] Alkylidene Meldrum's acid **5** being an excellent Michael acceptor, it has been utilized in various C-C and C-N bond forming Michael addition reactions to afford a range of chiral Meldrum's acid derivatives and biologically active chiral heterocycles.[7] Alkylidene Meldrum's acid **5** also acts as an excellent C3 synthon for several synthetic applications. Despite much progress, novel use and practical exploration of alkylidene Meldrum's acid **5** in organic synthesis is highly appreciable. By taking these into consideration, we hypothesized a novel multicomponent route for the synthesis of pyroglutamic ester **4** (Scheme 2.7).



Scheme 2.7: Proposed synthesis of pyroglutamic ester via KMHLD sequence

Our synthetic route has to follow an unprecedentedly daunting Knoevenagel-Michael-hydrolysis-lactamization-decarboxylation (KMHLD) chemoselective sequence as shown in scheme 2.7. Kobayashi[8a] and several other groups[8] reported elegant [3+2] cycloaddition reactions of Schiff's base **3a** and *α,β*-unsaturated ester **9** for the synthesis of highly substituted pyrrolidine derivatives **28** (Scheme 2.8 A). In view of this, the possible competitive or dominant [3+2] cycloaddition reaction between Schiff's base **3a** and

alkylidene Meldrum's acid **5** may prove to be the major hurdle to our proposed chemoselective reaction sequence as shown 2.7. However, we naively assumed that Schiff's base **3a** may undergo Michael addition with *α,β*-unsaturated alkylidene Meldrum's acid **5** followed by lactamization to give the corresponding pyroglutamic ester **4** owing to the weak nucleophilicity of Meldrum's acid intermediate **6** and its steric factor (Scheme 2.8 B).



Scheme 2.8: (3+2) cycloaddition vs KMHLD

The next important challenge is to suppress the favorable Michael addition of acetone (a by-product of the desired reaction) to alkylidene Meldrum's acid **5** to afford compound **7** (Scheme 2.7).[9] In order to validate our hypothesis and to execute the desired transformation, Lewis bases such as tertiary amine organocatalysts or phase transfer catalysts (PTC) could effectively be utilized. On the other hand, we decided to avoid the use of primary and secondary amines as they can catalyze undesired Michael addition of by-product acetone and alkylidene Meldrum's acid **5** (Scheme 2.7).

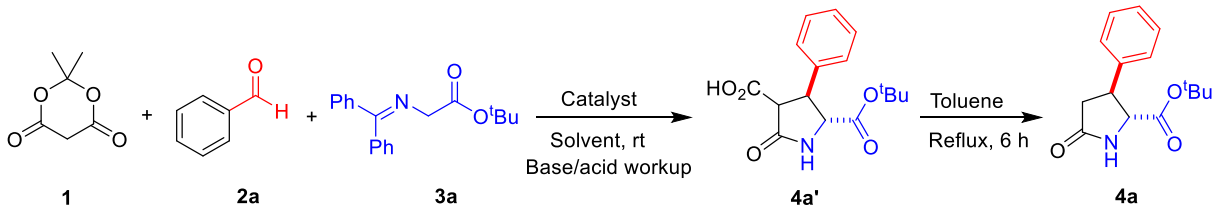
2.4 Results and discussion

To validate the feasibility of our designed strategy, we carried out a model reaction between Meldrum's acid **1**, benzaldehyde **2a** and Schiff's base **3a** (*N*-(diphenylmethylene) glycine *tert*-butyl ester) in presence of 20 mol% of Et_3N as a catalyst in chloroform at room temperature (Table 2.1, entry 1). We observed that though the reaction was sluggish, the initially formed benzylidene Meldrum's acid **5a,** further underwent reaction with Schiff's base **3a** to afford the undecarboxylated acid intermediate **4a'** in 72% yield after 24 hours (See

Table 2.1). It is interesting to note that the formal [3+2] cycloaddition product did not form even after prolonged reaction time. The absence of cycloaddition product may be rationalized by the low nucleophilicity of Meldrum's acid intermediate **6**.[10] Attempt to decarboxylate **4a'** in one pot by heating the reaction mixture afforded the desired product **4a** (2-phenyl *tert*-butyl pyroglutamate) along with the inseparable trace amount of impurities. Alternatively, upon base/acid work-up of undecarboxylated product **4a'** followed by reflux in toluene for 6 hours afforded the desired product **4a** in 65% yield with good diastereoselectivity (3.6:1 *dr*) without the formation of any side products. The product **4a** was confirmed by NMR spectroscopy and relative stereochemistry was assigned by single crystal XRD analysis.[11] Gratifyingly, the proposed Knoevenagel-Michael-hydrolysis-lactamization (KMHL) domino process took place in one pot albeit with a trace amount of Michael addition by-product **7a** (see Scheme 2.7). In order to achieve the decarboxylation in one pot and to suppress the formation of by-product **7a**, we planned to screen a series of Lewis bases in catalytic amounts for the desired transformation. In the beginning, strong basic organocatalysts such as DBU, Hünig's base, DMAP and DABCO were screened. Though all these catalysts afforded the corresponding **4a'** to our dismay, they failed to decarboxylate intermediate **4a'** at room temperature under various solvents conditions under prolonged reaction time (Table 2.1, entries 2-13).

These results prompted us to explore the use of phase transfer catalyst condition wherein the Brønsted base could be used for the decarboxylation of the intermediate acid **4a'**.[12] Surprisingly, the treatment of **1**, **2a** and **3a** in the presence of phase transfer catalyst *n*Bu_4NBr (5 mol%) and stoichiometric amount of base (NaOH, 1 equiv.) in water-rich biphasic solvent system did not afford the desired acid intermediate **4a'** (Table 2.1, entry 14). It is very interesting to note that the acid intermediate **4a'** was isolated in 66% yield when the neutral phase transfer catalyst condition was employed without the use of any additional base (Table 2.1, entry 15).[13] The isolated intermediate acid **4a'** was then heated in toluene to furnish the desired product **4a** in 55% yield and good diastereoselectivity (3.6:1). This observation showed that Brønsted bases may be disadvantageous as they react with Meldrum's acid **1** to form undesired salt thus inhibiting the formation of Knoevenagel intermediate **5a**.[14] Further additional solvent screening revealed that neutral phase transfer catalyst works very well in various solvents such as toluene, chloroform, ethyl acetate, acetonitrile and MTBE (Table 2.1, entries 16-20).

Table 2.1: Screening of catalysts and solvents[a]



Entry	Catalyst (mol%)	Solvent	Yield[b] (%) **4a**	*dr*[c] (trans/cis)
1	Et_3N(20 mol%)	$CHCl_3$	65	3.6:1
2	DBU(20 mol%)	$CHCl_3$	62	3.0:1
3	DMAP(20 mol%)	$CHCl_3$	59	3.5:1
4	DABCO(20 mol%)	$CHCl_3$	61	3.5:1
5	*i*PrNEt_2(20 mol%)	$CHCl_3$	68	3.6:1
6	*i*PrNEt_2(20 mol%)	ACN	52	3.7:1
7	*i*PrNEt_2(20 mol%)	THF	50	3.6:1
8	*i*PrNEt_2(20 mol%)	MTBE	51	3.1:1
9	*i*PrNEt_2(20 mol%)	Toluene	66	3.3:1
10	*i*PrNEt_2(20 mol%)	EtOAc	62	3.6:1
11	*i*PrNEt_2(20 mol%)	DMSO	-	-
12	*i*PrNEt_2(20 mol%)	DMF	-	-
13	*i*PrNEt_2(20 mol%)	Water	-	-
14[d]	*n*Bu_4NBr(5 mol%)	H_2O/toluene(5/1)	-	-
15	*n*Bu_4NBr(5 mol%)	H_2O/toluene(5/1)	55	3.6:1
16	*n*Bu_4NBr(5 mol%)	Toluene	58	3.6:1
17	*n*Bu_4NBr(5 mol%)	$CHCl_3$	66	3.6:1
18	*n*Bu_4NBr(5 mol%)	EtOAc	65	3.6:1
19	*n*Bu_4NBr(5 mol%)	ACN	56	3.5:1
20	*n*Bu_4NBr(5 mol%)	MTBE	54	3.5:1

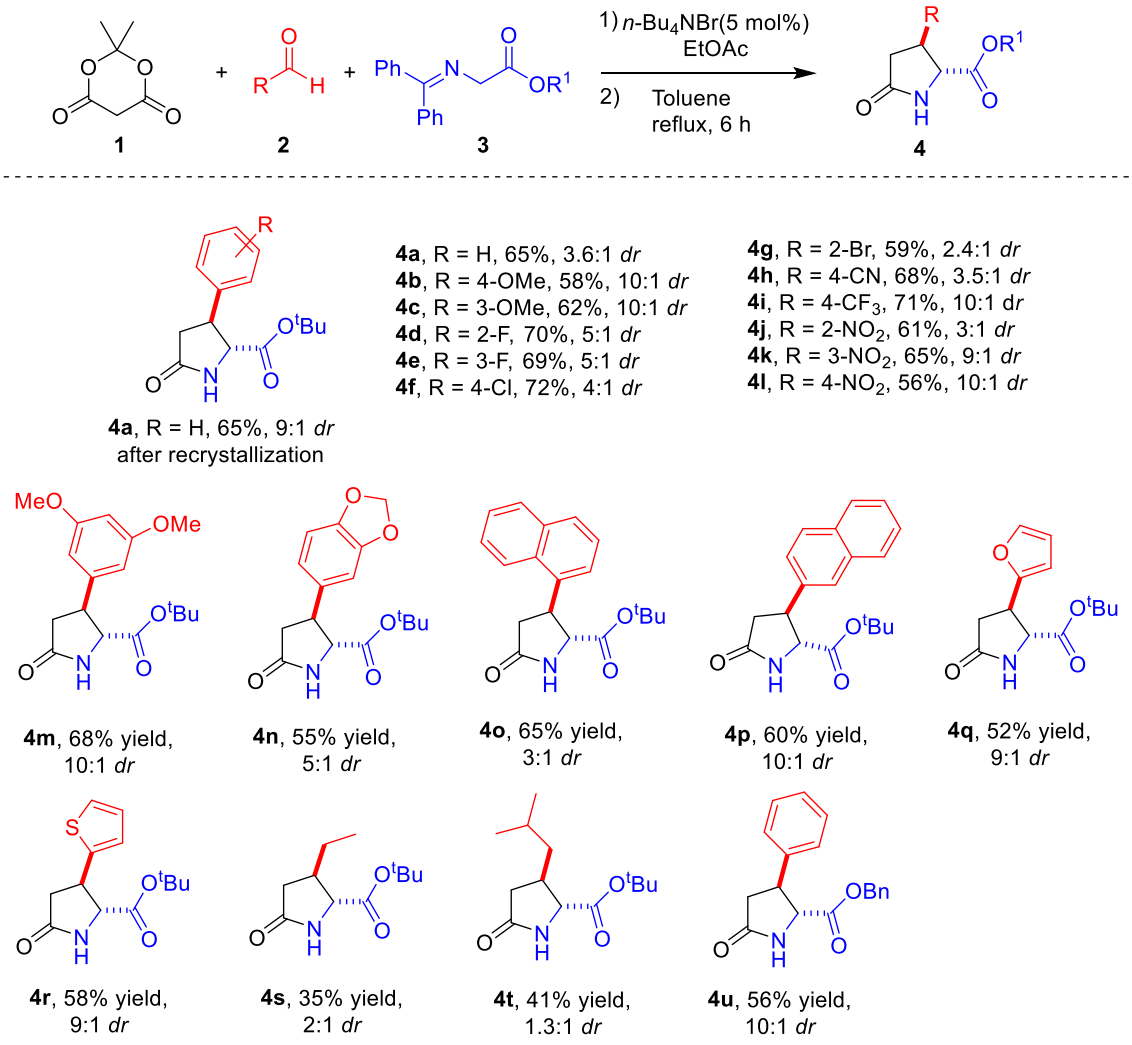
[a]Reaction Conditions: Meldrum's acid **1** (1 equiv.), benzaldehyde **2a** (1.05 equiv.), Schiff's base (glycine imine ester) **3a** (1.5 equiv.) catalyst (5-10 mol%), in solvent at rt for 24 h then base/acid workup followed by reflux for 6 h in toluene for the decarboxylation, [b]isolated yield after purification by column chromatography, [c]*dr* was calculated by ^{1}H NMR, [d]1 equiv. of NaOH used.

After the exhaustive screening, *n*Bu_4NBr as a catalyst (5 mol%) and ethyl acetate as a solvent (then base/acid workup followed by heating in toluene for 6 hours) were

proved to be optimum for the reaction conditions to obtain the desired product **4a** (Table 2.1 entry 20). These initial results encouraged us to explore the scope and generality of the protocol.

Having optimized reaction conditions in hand, the scope of KMHLD tandem three component reaction was investigated by using various aldehydes (**2a-2t**) and Schiff's bases (**3a-3b**) (Table 2.2).

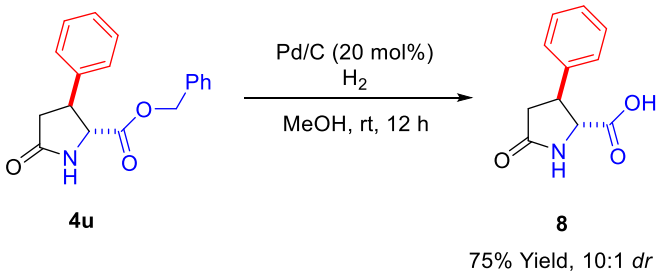
Table 2.2: Substrate scope of tandem KMHLD reaction[a,-c]



[a]Reaction conditions: Meldrum's acid **1** (1 equiv.), aldehyde **2** (1.05 equiv.), Schiff's base **3** (1.5 equiv.) nBu$_4$NBr (5 mol%), in EtOAc at rt, 24 h then then base/acid workup followed by reflux for 6 h in toluene for the decarboxylation; [b]isolated yield after purification by column chromatography, [c]*dr* was calculated by ^{1}H NMR.

Different aromatic aldehydes (**2a-2n**) containing electron donating as well as electron withdrawing functional groups furnished the corresponding desired pyroglutamic esters (**4b-4n**) in moderate to good yields (up to 72% yield) with moderate to excellent diastereoselectivity (up to 10:1 *dr*). Similarly, bicyclic aromatic aldehydes such as 1/2-naphthaldehyde (**2o** and **2p**) and heteroaromatic aldehydes such as 2-furfural (**2q**) and 2-thiophenecarboxaldehyde (**2r**) reacted smoothly to afford **4o** and **4r** in good yields with good diastereoselectivity (up to 65% yield, up to 10:1 *dr*). In order to have a wider scope of the method, the reaction was explored on aliphatic aldehydes. Notably, even enolizable aliphatic aldehydes such as propanal **2s** and isovaleraldehyde **2t** were utilized to synthesize the corresponding pyroglutamic esters (**4s** and **4t**) in moderate yield and diastereoselectivity (up to 41% yield, up to 2:1 *dr*). Alternatively, Schiff's base **3b** (glycine imine benzyl ester) also proved to be an efficient nucleophile providing the product **4u** in moderate yield (56%) with good diastereoselectivity (10:1).

Further, substituted pyroglutamic acid **4u** under hydrogenolytic conditions afforded the corresponding pyroglutamic acid derivative **8** (Scheme 2.9).[15] The protocol tolerated a wide variety of aromatic as well as aliphatic aldehydes and Schiff's base esters. The strength of this KMHLD protocol is that it provides practical and easy access to diastereoselective 3-substituted pyroglutamic esters and acids in good yields.



4u **8**

75% Yield, 10:1 *dr*

Scheme 2.9: Deprotection of ester to access pyroglutamic acid

2.5 Conclusions

In conclusions, we developed an easy, practical and mild protocol to access pyroglutamic acid derivatives. This domino protocol tolerated a wide variety of aldehydes including enolizable aliphatic aldehydes under mild reaction conditions. The exact role of catalyst and the effect of Meldrum's acid on the hydrolysis of Schiff's base and the outcome of the final product need to be studied further in detail. The enantioselective version of this reaction is under progress by our research group.

2.6 Experimental Section

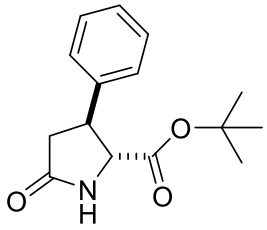
General Methods

Unless otherwise stated, all reagents were purchased from commercial suppliers and used further without purification. Meldrum's acid was purchased from Spectrochem. Aldehydes and ketones were purchased from Aldrich, Spectrochem and Alfa-aeser. Compounds **3a** and **3b** prepared according to the reported procedure.[1] All reactions were carried out in oven dried glassware. Thin-layer chromatography (TLC) was performed using silica gel 60 GF254 pre-coated aluminum backed plates (2.5 mm). Visualization was accomplished by irradiation with UV light at 254 nm and/or ninhydrin stain. Column chromatography was performed using silica gel (200-300 mesh) eluting with petroleum ether and ethyl acetate. NMR spectra were recorded with tetramethylsilane as the internal standard. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz (Bruker and Jeol). Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) and CD_3OD (δ = 4.87 and 3.31 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.16 ppm) and CD_3OD (δ = 49.00) for ^{13}C NMR spectroscopy. Coupling constants (*J*) are given in Hz. IR spectra were obtained using a FT-IR spectrophotometer as neat and are reported in cm^{-1}. Mass samples were analyzed by High-resolution mass spectrometry using ESI TOF.

General procedure for the synthesis of pyroglutamic acid derivative 4:

In an oven dried 10 mL round bottomed flask with a teflon-coated stir bar, *n*Bu_4NBr (0.07 mmol, 22.4 mg, 5 mol%) was dissolved in 2 mL of EtOAc. Then Meldrum's acid **1** (200 mg, 1.39 mmol, 1 equiv.), benzaldehyde **2a** (150 mmL, 1.47 mmol, 1.06 equiv.) and Schiff's base **3a** (614.8 mg, 2.05 mmol, 1.5 equiv.) were added subsequently and the reaction mixture was stirred for 24 h at room temperature. Upon completion of the reaction (confirmed by TLC), the reaction mixture was directly transferred into separating funnel. Then saturated aq. $NaHCO_3$ solution (25 mL) and EtOAc (20 mL) were added to the separating funnel and extracted. The aqueous layer containing pyroglutamic acid derivative **4a'** was separated and the extraction procedure repeated twice. The combined aqueous layers were acidified with 1 N aq. HCl solution till it becomes a turbid solution (~ pH 2). After which, the pyroglutamic acid derivative **4a'** was extracted with EtOAc (3 X 20 mL) and the combined organic layers was washed with brine solution and dried over anhydrous Na_2SO_4. The organic extract was evaporated under *vacuuo* to afford **4a'**. Then crude pyroglutamic acid derivative **4a'** was dissolved in 2 mL toluene and refluxed for 6 hours in order to have a complete decarboxylation. After complete decarboxylation (monitored by TLC) the toluene was evaporated and the crude product **4a** was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as an eluent. Compound **4a** was obtained as a white solid in 65% yield.

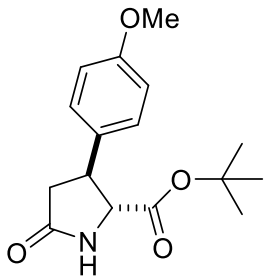
***trans-tert*-butyl 5-oxo-3-phenylpyrrolidine-2-carboxylate (4a)**



Compound **4a** was synthesized following the general procedure. Compound **4a** was obtained as white solid in 65% (235 mg, *trans*/*cis*; 3.6:1, 9: 1 after recrystallization).

m.p. 108-112 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 2H), 7.30 – 7.26 (m, 3H), 6.31 (s, 1H), 4.15 (d, *J* = 6.0 Hz, 1H), 3.68 – 3.63 (m, 1H), 2.85 (dd, *J* = 17.3, 9.5 Hz, 1H), 2.54 (dd, *J* = 17.3, 7.4 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 170.3, 141.9, 129.1, 127.6, 127.2, 82.8, 63.6, 44.4, 38.4, 28.1; HRMS (ESI TOF) *m/z* calcd. For $C_{15}H_{19}NO_3$ + H^+ $[M + H]^+$ 262.1443, found 262.1450. FTIR cm^{-1} (neat) 3233.35, 2977.92, 2927.14, 1702.61, 1452.82, 1370.49, 1236.68, 1154.51, 845.00, 761.44, 699.42.

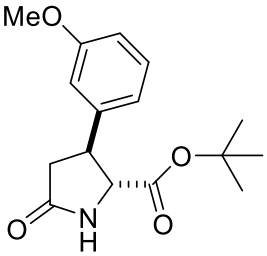
***trans-tert*-butyl 3-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate (4b)**



Compound **4b** was synthesized following the general procedure. Compound **4b** was obtained as colourless oil in 58% (235 mg, *trans*/*cis*; 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.18 (s, 1H), 4.09 (d, *J* = 6.0 Hz, 1H), 3.80 (s, 3H), 3.60 (ddd, *J* = 9.4, 7.5, 6.2 Hz, 1H), 2.81 (dd, *J* = 17.2, 9.4 Hz, 1H), 2.50 (dd, *J* = 17.2, 7.5 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 170.4, 159.0, 133.9, 128.3, 114.4, 82.8, 63.8, 55.5, 43.8, 38.5, 28.1; HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{21}NO_4$ + H^+ $[M + H]^+$ 292.1549, found 292.1554. FTIR cm^{-1} (neat) 3233.98, 2976.09, 2925.69, 1698.72, 1613.88, 1513.47, 1455.87, 1369.17, 1294.73, 1243.57, 1153.22, 1032.92, 833.59, 784.03, 736.17, 688.43.

***trans-tert*-butyl 3-(3-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate (4c)**

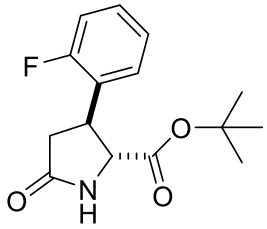


Compound **4c** was synthesized following the general procedure. Compound **4c** was obtained as colourless oil in 62% (251 mg, *trans*/*cis*; 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dt, *J* = 7.6, 4.3 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.84 – 6.78 (m, 2H), 6.11 (s, 1H), 4.13 (d, *J* = 5.8 Hz, 1H), 3.81 (s, 3H), 3.68 – 3.58 (m, 1H), 2.83 (dd, *J* = 17.3, 9.5 Hz, 1H), 2.53 (dd, *J* = 17.3, 7.3 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3,

170.3, 160.1, 143.6, 130.1, 119.4, 113.3, 112.6, 82.9, 63.4, 55.4, 44.3, 38.3, 28.1; HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{21}NO_4 + H^+$ $[M + H]^+$ 292.1549, found 292.1548. FTIR cm^{-1} (neat) 3232.83, 2924.64, 2853.19, 1704.56, 1601.57, 1489.51, 1457.04, 1369.86, 1245.05, 1156.99, 1046.21, 846.51, 782.92, 700.09.

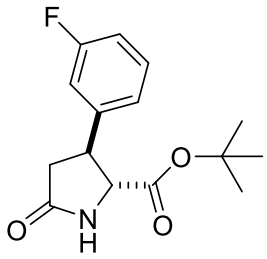
***trans-tert*-butyl 3-(2-fluorophenyl)-5-oxopyrrolidine-2-carboxylate (4d)**



Compound **4d** was synthesized following the general procedure. Compound **4d** was obtained as colourless oil in 70% (270 mg, *trans*/*cis*; 5:1).

^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 2H), 7.19 – 7.03 (m, 2H), 6.52 (s, 1H), 4.24 (dd, *J* = 16.8, 7.7 Hz, 1H), 3.86 (td, *J* = 8.7, 7.0 Hz, 1H), 2.80 (ddd, *J* = 17.1, 9.5, 0.9 Hz, 1H), 2.60 (dd, *J* = 17.1, 8.4 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 176.1, 170.1, 169.1, 161.2 (d, *J* = 247.0 Hz), 160.8 (d, *J* = 246.4 Hz), 129.4 (d, *J* = 8.4 Hz), 129.2 (d, *J* = 8.4 Hz), 128.9 (d, *J* = 4.2 Hz), 128.4 – 128.1 (m), 124.6 (d, *J* = 3.6 Hz), 124.6 (d, *J* = 3.5 Hz), 116.0 (d, *J* = 22.0 Hz), 115.3 (d, *J* = 22.3 Hz), 82.8, 82.4, 62.1, 60.2, 38.5, 37.4, 36.1, 34.9, 27.9, 27.5; HRMS (ESI TOF) *m/z* calcd. For $C_{15}H_{18}FNO_3 + H^+$ $[M + H]^+$ 280.1349, found 280.1355. FTIR cm^{-1} (neat) 3231.25, 2979.51, 2929.68, 1700.35, 1492.67, 1455.12, 1369.80, 1230.36, 1152.95, 844.61, 758.10, 693.60.

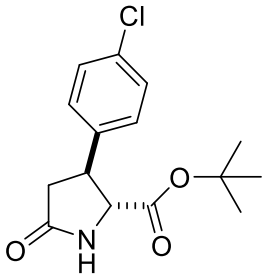
***trans-tert*-butyl 3-(3-fluorophenyl)-5-oxopyrrolidine-2-carboxylate (4e)**



Compound **4e** was synthesized following the general procedure. Compound **4e** was obtained as colourless oil in 69% (267 mg, *trans*/*cis*; 5:1).

^1H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.25 (m, 1H), 7.13 – 7.03 (m, 1H), 7.03 – 6.84 (m, 2H), 6.48 (s, 1H), 4.12 (d, *J* = 6.0 Hz, 1H), 3.73 – 3.57 (m, 1H), 2.93 – 2.76 (m, 1H), 2.51 (dd, *J* = 17.3, 7.4 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 176.1, 170.1, 168.7, 163.1 (d, *J* = 246.8 Hz), 144.4 (d, *J* = 7.1 Hz), 141.7 (d, *J* = 7.2 Hz), 130.6 (d, *J* = 8.4 Hz), 130.3 (d, *J* = 8.1 Hz), 123.5 (d, *J* = 3.0 Hz), 122.8 (d, *J* = 2.9 Hz), 115.2 (d, *J* = 21.8 Hz), 114.7 (d, *J* = 21.0 Hz), 114.5 (d, *J* = 19.4 Hz), 114.3 (d, *J* = 20.2 Hz), 83.0, 82.6, 63.3, 61.2, 44.1, 42.9, 38.3, 36.9, 28.1, 27.6; HRMS (ESI TOF) *m/z* calcd. For $C_{15}H_{18}FNO_3 + H^+$ $[M + H]^+$ 280.1349, found 280.1357. FTIR cm^{-1} (neat) 3232.99, 2978.43, 2919.69, 1704.98, 1621.79, 1592.21, 1489.32, 1452.04, 1371.55, 1241.21, 1156.47, 786.09, 696.98.

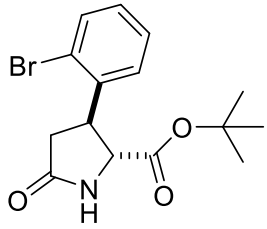
***trans-tert*-butyl 3-(4-chlorophenyl)-5-oxopyrrolidine-2-carboxylate (4f)**



Compound **4f** was synthesized following the general procedure. Compound **4f** was obtained as colourless oil in 72% (295 mg, *trans*/*cis*; 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.25 – 7.19 (m, 2H), 6.39 (s, 1H), 4.09 (d, *J* = 6.0 Hz, 1H), 3.68 – 3.58 (m, 1H), 2.83 (dd, *J* = 17.3, 9.4 Hz, 1H), 2.48 (dd, *J* = 17.3, 7.5 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 176.1, 170.1, 168.7, 140.4, 137.8, 133.6, 133.4, 129.3, 129.2, 128.8, 128.6, 83.1, 82.7, 63.4, 61.2, 43.8, 42.6, 38.3, 37.1, 28.1, 27.6; HRMS (ESI TOF) *m/z* calcd. For $C_{15}H_{18}ClNO_3 + H^+$ $[M + H]^+$ 296.1053, found 296.1058. FTIR cm^{-1} (neat) 3228.95, 2978.05, 2926.94, 1700.40, 1492.10, 1369.67, 1235.50, 1154.34, 1093.59, 1014.80, 832.79, 730.89, 661.20.

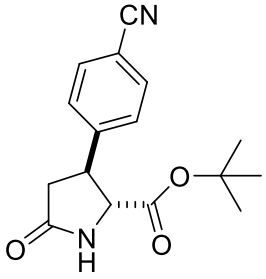
***trans-tert*-butyl 3-(2-bromophenyl)-5-oxopyrrolidine-2-carboxylate (4g)**



Compound **4g** was synthesized following the general procedure. Compound **4g** was obtained as colourless oil in 59% (235 mg, *trans*/*cis*; 2.4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.46 (m, 1H), 7.35 – 7.28 (m, 2H), 7.20 – 7.08 (m, 1H), 6.31 (s, 1H), 4.27 – 4.06 (m, 1H), 2.88 (ddd, *J* = 10.8, 9.5, 6.2 Hz, 1H), 2.72 (qd, *J* = 16.7, 8.3 Hz, 1H), 2.53 – 2.38 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 176.3, 170.2, 169.1, 140.9, 138.0, 133.4, 133.1, 129.3, 129.0, 128.3, 128.2, 128.1, 128.0, 125.8, 124.2, 82.9, 82.5, 62.3, 59.5, 43.1, 42.3, 37.6, 35.6, 28.0, 27.6; HRMS (ESI TOF) *m/z* calcd. For $C_{15}H_{18}BrNO_3 + H^+$ $[M + H]^+$ 340.0548, found 340.0538. FTIR cm^{-1} (neat) 3232.88, 2977.80, 2927.92, 1699.64, 1471.19, 1437.38, 1369.35, 1233.62, 1153.56, 1024.72, 845.09, 754.74, 663.51.

***trans-tert*-butyl 3-(4-cyanophenyl)-5-oxopyrrolidine-2-carboxylate (4h)**

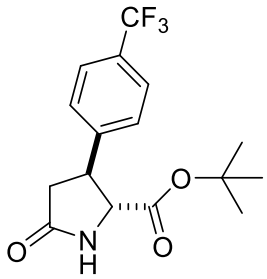


Compound **4h** was synthesized following the general procedure. Compound **4h** was obtained as colourless oil in 68% (270 mg, *trans*/*cis*; 3.5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 2H), 7.43 – 7.39 (m, 2H), 6.97 (s, 1H), 4.13 (d, *J* = 6.0 Hz, 1H), 3.80 – 3.57 (m, 1H), 3.00 – 2.73 (m, 1H), 2.60 – 2.38 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 175.8, 169.7, 168.3, 147.1, 144.9, 132.9, 132.5, 128.8, 128.2, 118.6,

114.2, 111.7, 111.6, 83.4, 82.9, 63.0, 60.9, 44.2, 43.0, 38.1, 37.1, 29.8, 28.1; HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{18}N_2O_3 + H^+$ $[M + H]^+$ 287.1395, found 287.1402. FTIR cm^{-1} (neat) 3233.26, 2924.11, 2855.75, 2229.29, 1697.52, 1611.34, 1457.37, 1421.57, 1370.49, 1237.38, 1153.19, 972.10, 839.89, 784.59, 734.67, 697.68.

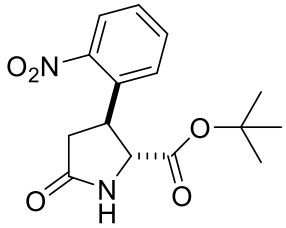
***trans-tert*-butyl 5-oxo-3-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (4i)**



Compound **4i** was synthesized following the general procedure. Compound **4i** was obtained as colourless oil in 71% (324 mg, *trans*/*cis*; 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 6.10 (s, 1H), 4.14 (d, *J* = 6.0 Hz, 1H), 3.87 – 3.59 (m, 1H), 2.87 (dd, *J* = 17.3, 9.5 Hz, 1H), 2.53 (dd, *J* = 17.3, 7.4 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 169.7, 145.7, 129.9 (q, *J* = 37 Hz), 127.5, 126.7(q, *J* = 267 Hz), 125.96 (q, *J* = 3.7 Hz), 83.1, 62.9, 43.9, 38.0, 27.9; HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{18}F_3NO_3 + H^+$ $[M + H]^+$ 330.1317, found 330.1328. FTIR cm^{-1} (neat) 3232.22, 2979.63, 2925.79, 1706.74, 1623.07, 1424.21, 1371.13, 1327.17, 1240.46, 1160.52, 1122.64, 1069.69, 842.84.

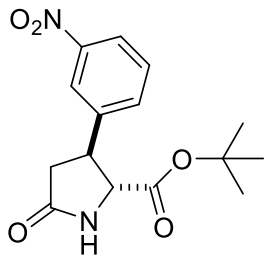
***trans-tert*-butyl 3-(2-nitrophenyl)-5-oxopyrrolidine-2-carboxylate (4j)**



Compound **4j** was synthesized following the general procedure. Compound **4j** was obtained as colourless oil in 61% (259 mg, *trans*/*cis*; 3:1).

^{1}H NMR (400 MHz, CDCL3) δ 7.87 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.55 – 7.51 (m, 1H), 7.47 – 7.42 (m, 1H), 6.64 (s, 1H), 4.22 (m, 2H), 3.01 (dt, *J* = 18.0, 8.9 Hz, 1H), 2.56 – 2.39 (m, 1H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 176.2, 169.8, 168.9, 150.1, 149.6, 136.7, 133.6, 133.6, 130.2, 128.7, 128.6, 128.4, 128.3, 124.9, 124.8, 83.3, 82.9, 62.9, 60.0, 38.5, 38.2, 37.8, 36.4, 27.9, 27.5; HRMS (ESI TOF) m/z calcd. For $C_{15}H_{18}N_2O_5 + H^+$ $[M + H]^+$ 307.1294, found 307.1300. FTIR cm^{-1} (neat) 3232.19, 2923.82, 2854.66, 1697.58, 1453.84, 1369.47, 1234.82, 1151.81, 1044.44, 967.45, 843.97, 728.86.

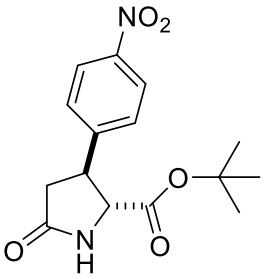
***trans-tert*-butyl 3-(3-nitrophenyl)-5-oxopyrrolidine-2-carboxylate (4k)**



Compound **4k** was synthesized following the general procedure. Compound **4k** was obtained as colourless oil in 65% (276 mg, *trans*/*cis*; 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.07 (m, 2H), 7.68 – 7.62 (m, 1H), 7.59 – 7.50 (m, 1H), 6.57 (s, 1H), 4.18 (d, *J* = 6.4 Hz, 1H), 3.79 (ddd, *J* = 9.4, 7.9, 6.4 Hz, 1H), 2.90 (dd, *J* = 17.3, 9.5 Hz, 1H), 2.56 (dd, *J* = 17.3, 7.9 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 169.6, 148.6, 143.7, 133.4, 130.2, 122.7, 122.6, 83.5, 63.1, 43.9, 38.2, 28.0; HRMS (ESI TOF) *m/z* calcd. For $C_{15}H_{18}N_2O_5$ + H^+ $[M + H]^+$ 307.1294, found 307.1298. FTIR cm^{-1} (neat) 3233.67, 2977.07, 2924.99, 1702.07, 1529.21, 1451.39, 1348.41, 1236.77, 1154.23, 812.45, 736.94, 688.20.

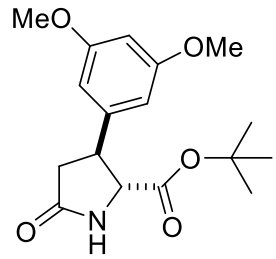
***trans-tert*-butyl 3-(4-nitrophenyl)-5-oxopyrrolidine-2-carboxylate (4l)**



Compound **4l** was synthesized following the general procedure. Compound **4l** was obtained as colourless oil in 56% (238 mg, *trans*/*cis*; 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 6.55 (s, 1H), 4.15 (d, *J* = 6.1 Hz, 1H), 3.94 – 3.60 (m, 1H), 2.89 (dd, *J* = 17.3, 9.5 Hz, 1H), 2.53 (dd, *J* = 17.3, 7.5 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 169.6, 149.1, 147.4, 128.3, 124.4, 83.5, 62.9, 44.0, 38.2, 28.1; HRMS (ESI TOF) m/z calcd. For $C_{15}H_{18}N_2O_5$ + H^+ $[M + H]^+$ 307.1294, found 307.1300. FTIR cm^{-1} (neat) 3234.12, 2978.86, 2925.62, 1702.24, 1602.78, 1520.12, 1454.88, 1346.85, 1238.07, 1154.93, 1113.43, 852.16, 754.14, 700.07.

***trans-tert*-butyl 3-(3,5-dimethoxyphenyl)-5-oxopyrrolidine-2-carboxylate (4m)**

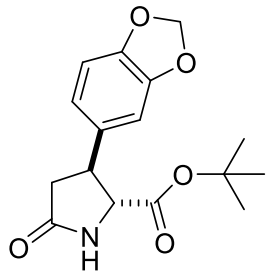


Compound **4m** was synthesized following the general procedure. Compound **4m** was obtained as colourless oil in 68% (303 mg, *trans*/*cis*; 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, *J* = 2.2 Hz, 2H), 6.38 – 6.36 (m, 1H), 6.32 (s, 1H), 4.13 (d, *J* = 5.7 Hz, 1H), 3.79 (s, 6H), 3.65 – 3.51 (m, 1H), 2.82 (dd, *J* = 17.4, 9.6 Hz, 1H), 2.51 (dd, *J* = 17.4, 7.1 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 170.3, 161.3, 144.5, 105.3, 99.1, 82.8, 63.4, 55.5, 44.4, 38.2, 28.1; HRMS (ESI TOF) *m/z* calcd. For $C_{17}H_{23}NO_5$ + H^+ $[M + H]^+$

322.1654, found 322.1657. FTIR cm^{-1} (neat) 3227.64, 2925.71, 2851.19, 1701.02, 1598.73, 1462.16, 1365.52, 1295.81, 1237.64, 1202.87, 1150.98, 1063.99, 968.82, 926.67, 840.46, 734.52, 696.02.

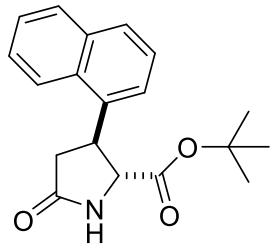
***trans-tert*-butyl 3-(benzo[d][1,3]dioxol-5-yl)-5-oxopyrrolidine-2-carboxylate (4n)**



Compound **4n** was synthesized following the general procedure. Compound **4n** was obtained as colourless oil in 55% (233 mg, *trans*/*cis*; 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 – 6.75 (m, 2H), 6.74 – 6.69 (m, 1H), 6.22 (s, 1H), 5.96 (s, 2H), 4.07 (d, *J* = 6.0 Hz, 1H), 3.57 (ddd, *J* = 9.4, 7.4, 6.0 Hz, 1H), 2.89 – 2.73 (m, 1H), 2.47 (dd, *J* = 17.3, 7.4 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 170.3, 148.2, 147.0, 135.7, 120.6, 108.6, 107.3, 101.3, 82.9, 63.7, 44.2, 38.5, 28.1; HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{19}NO_5$ + H^+ $[M + H]^+$ 306.1341, found 306.1348. FTIR cm^{-1} (neat) 3232.85, 2976.60, 2924.63, 1696.98, 1492.91, 1445.30, 1369.83, 1237.57, 1152.55, 1036.11, 931.78, 846.98, 812.18, 732.43, 698.30, 643.80.

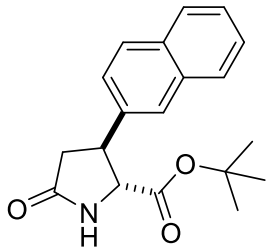
***trans-tert*-butyl 3-(naphthalen-1-yl)-5-oxopyrrolidine-2-carboxylate (4o)**



Compound **4o** was synthesized following the general procedure. Compound **4o** was obtained as colourless oil in 65% (281 mg, *trans*/*cis*; 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.3 Hz, 1H), 7.90 (dd, *J* = 6.6, 5.4 Hz, 1H), 7.84 – 7.76 (m, 1H), 7.65 – 7.38 (m, 4H), 6.80 (s, 1H), 4.56 – 4.41 (m, 1H), 4.26 (d, *J* = 3.8 Hz, 1H), 3.06 – 2.94 (m, 1H), 2.73 – 2.61 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 177.5, 170.8, 169.2, 137.8, 137.7, 134.2, 133.8, 132.5, 132.3, 131.0, 130.2, 129.4, 129.0, 128.4, 128.2, 126.6, 126.5, 126.0, 125.9, 125.6, 125.6, 123.4, 122.9, 82.9, 81.7, 63.1, 60.7, 39.5, 38.8, 37.2, 35.3, 28.0, 27.1; HRMS (ESI TOF) *m/z* calcd. For $C_{19}H_{21}NO_3$ + H^+ $[M + H]^+$ 312.1599, found 312.1608. FTIR cm^{-1} (neat) 3223.76, 2976.34, 2926.35, 1700.48, 1425.38, 1369.36, 1237.54, 1151.73, 967.24, 845.79, 779.99, 733.22, 698.12.

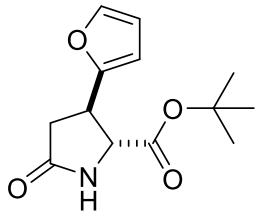
***trans-tert*-butyl 3-(naphthalen-2-yl)-5-oxopyrrolidine-2-carboxylate (4p)**



Compound **4p** was synthesized following the general procedure. Compound **4p** was obtained as colourless oil in 60% (259 mg, *trans*/*cis*; 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.07 (d, *J* = 8.2 Hz, 2H), 7.53 (m, 4H), 6.42 (s, 1H), 5.29 (ddd, *J* = 11.4, 9.0, 7.5 Hz, 1H), 4.81 (d, *J* = 7.3 Hz, 1H), 3.16 (dd, *J* = 18.0, 9.1 Hz, 1H), 3.04 (dd, *J* = 18.0, 11.4 Hz, 1H), 1.20 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 171.0, 147.2, 132.2, 131.9, 128.4, 126.6, 125.0, 123.6, 82.9, 62.2, 38.2, 36.4, 27.8; HRMS (ESI TOF) *m/z* calcd. For $C_{19}H_{21}NO_3$ + H^+ $[M + H]^+$ 312.1599, found 312.1608. FTIR cm^{-1} (neat) 3209.70, 2975.08, 2924.41, 2855.79, 1695.93, 1452.86, 1369.35, 1238.81, 1153.71, 887.91, 842.34, 733.35, 696.72.

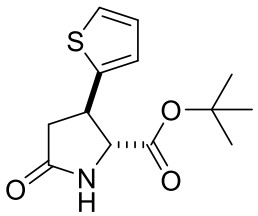
***trans-tert*-butyl 3-(furan-2-yl)-5-oxopyrrolidine-2-carboxylate (4q)**



Compound **4q** was synthesized following the general procedure. Compound **4q** was obtained as colourless oil in 52% (181 mg, *trans*/*cis*; 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.33 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 5.93 (s, 1H), 4.23 (d, *J* = 6.4 Hz, 1H), 3.86 – 3.71 (m, 1H), 2.74 (dd, *J* = 17.0, 9.2 Hz, 1H), 2.64 (dd, *J* = 17.0, 7.9 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 169.9, 153.4, 142.3, 110.5, 106.6, 83.1, 60.7, 37.9, 35.4, 28.1; HRMS (ESI TOF) *m/z* calcd. For $C_{13}H_{17}NO_4$ + Na^+ $[M + Na]^+$ 274.1055, found 274.1057. FTIR cm^{-1} (neat) 3295.15, 2975.95, 2927.41, 1694.89, 1370.84, 1241.71, 1153.91, 1017.51, 971.53, 840.57, 736.63.

***trans-tert*-butyl 5-oxo-3-(thiophen-2-yl)pyrrolidine-2-carboxylate (4r)**

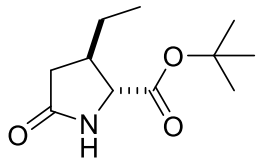


Compound **4r** was synthesized following the general procedure. Compound **4r** was obtained as colourless oil in 58% (215 mg, *trans*/*cis*; 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.22 (dd, *J* = 3.8, 2.5 Hz, 1H), 6.98 – 6.95 (m, 2H), 6.06 (s, 1H), 4.17 (d, *J* = 6.1 Hz, 1H), 3.98 (ddd, *J* = 9.1, 7.8, 6.2 Hz, 1H), 2.89 (dd, *J* = 17.1, 9.2 Hz, 1H), 2.60 (dd, *J* = 17.1, 7.7 Hz, 1H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 169.8, 144.7, 127.1, 124.9, 124.5,

83.2, 63.8, 39.7, 39.1, 28.1; HRMS (ESI TOF) *m/z* calcd. For $C_{13}H_{17}NO_3S + Na^+$ $[M + Na]^+$ 290.0826, found 290.0831. FTIR cm^{-1} (neat) 3227.88, 2924.06, 2856.48, 1704.35, 1453.59, 1369.75, 1240.13, 1154.90, 844.02, 780.57, 699.56.

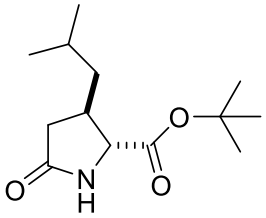
***trans-tert*-butyl 3-ethyl-5-oxopyrrolidine-2-carboxylate (4s)**



Compound **4s** was synthesized following the general procedure. Compound **4s** was obtained as colourless oil in 35% (104 mg, *trans*/*cis*; 2:1).

^1H NMR (400 MHz, $CDCl_3$) δ 6.05 (s, 1H), 4.09 (d, *J* = 8.2 Hz, 1H), 2.59 – 2.47 (m, 1H), 2.42 – 2.33 (m, 1H), 2.21 – 2.11 (m, 1H), 1.63 – 1.52 (m, 1H), 1.46 (s, 9H), 1.33 (m, 1H), 0.95 (t, *J* = 7.4, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 177.3, 171.2, 170.4, 82.7, 82.5, 61.4, 60.2, 40.7, 40.6, 35.8, 35.0, 29.8, 28.2, 28.1, 23.4, 12.4, 11.7; HRMS (ESI TOF) *m/z* calcd. For $C_{11}H_{19}NO_3 + Na^+$ $[M + Na]^+$ 236.1262, found 236.1264. FTIR cm^{-1} (neat) 3236.52, 2967.39, 2926.73, 1698.84, 1457.75, 1422.31, 1369.94, 1227.33, 1154.94, 844.37, 769.42.

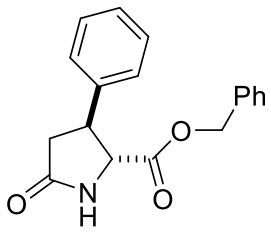
***trans-tert*-butyl 3-isobutyl-5-oxopyrrolidine-2-carboxylate (4t)**



Compound **4t** was synthesized following the general procedure. Compound **4t** was obtained as colourless oil in 41% (137 mg, *trans*/*cis*; 1.3:1).

^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 4.01 (d, *J* = 7.9 Hz, 1H), 2.55 – 2.39 (m, 1H), 2.34 – 2.22 (m, 1H), 2.19 – 2.05 (m, 1H), 1.65 – 1.49 (m, 1H), 1.46 – 1.36 (m, 9H), 1.33 – 1.15 (m, 2H), 0.92 – 0.77 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 177.6, 171.1, 170.5, 82.4, 82.2, 61.9, 60.4, 44.5, 39.3, 37.1, 36.6, 35.4, 28.1, 28.0, 26.0, 23.3, 23.0, 22.0, 21.8; HRMS (ESI TOF) *m/z* calcd. For $C_{13}H_{23}NO_3 + H^+$ $[M + H]^+$ 242.1756, found 242.1763. FTIR cm^{-1} (neat) 3233.07, 2958.57, 1698.93, 1460.12, 1423.31, 1368.90, 1292.80, 1225.29, 1152.17, 844.81, 773.89.

***trans*-benzyl-5-oxo-3-phenylpyrrolidine-2-carboxylate (4u)**



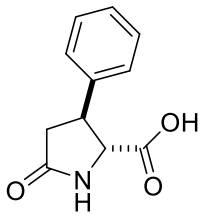
Compound **4u** was synthesized following the general procedure using **3b** as Schiff's base. Compound **4u** was obtained as colourless oil in 56% (229 mg, *trans*/*cis*; 10:1).

^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 10H), 6.78 (s, 1H), 5.23 (d, *J* = 12.2 Hz, 1H), 5.13 (d, *J* = 12.2 Hz, 1H), 4.29 (d, *J* = 5.5

Hz, 1H), 3.67 (ddd, *J* = 9.5, 6.8, 5.6 Hz, 1H), 2.85 (dd, *J* = 17.4, 9.5 Hz, 1H), 2.53 (dd, *J* = 17.4, 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 171.1, 141.6, 135.1, 129.2, 128.8, 128.7, 128.5, 127.7, 127.1, 67.5, 63.1, 44.1, 38.1; HRMS (ESI TOF) *m/z* calcd. For $C_{18}H_{17}NO_3 + H^+$ $[M + H]^+$ 296.1281, found 296.1287.

Application of the protocol

***trans*-5-oxo-3-phenylpyrrolidine-2-carboxylic acid**



To the stirred solution of product **4u** (200 mg) in methanol, 10% Pd/C was added at room temperature. The resulting mixture was stirred for 12 hours under H_2 (1 atm, balloon) and then filtered through celite bed and concentrated under reduced pressure on rotatory evaporator. Further, the crude product **8** was purified by column chromatography on silica gel using dichloromethane/methanol as an eluent. The acid **8** obtained as a white solid in 75% (139 mg) yield with 10:1 *dr* ratio.

m.p. 141-143 ^{o}C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.38 – 7.24 (m, 5H), 4.22 (d, *J* = 4.9 Hz, 1H), 3.73 – 3.66 (m, 1H), 2.85 (dd, *J* = 17.2, 9.4 Hz, 1H), 2.43 (dd, *J* = 17.2, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 179.7, 175.0, 143.9, 123.0, 128.4, 127.9, 64.6, 45.5, 39.2; HRMS (ESI TOF) *m/z* calcd. For $C_{13}H_{23}NO_3 + H^+$ $[M + H]^+$ 206.0812, found 206.0808.

2.7 Appendix II: ^{1}H, ^{13}C spectral data of representative compounds

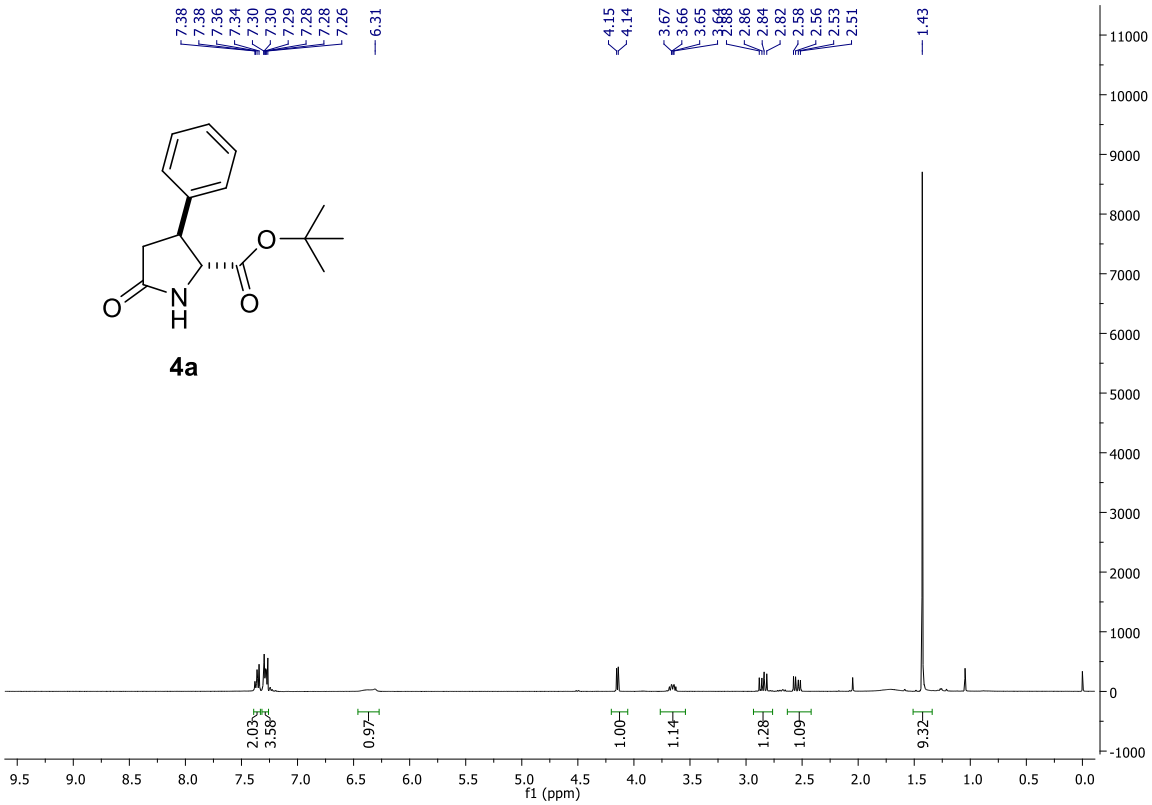


Figure AII.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4a**

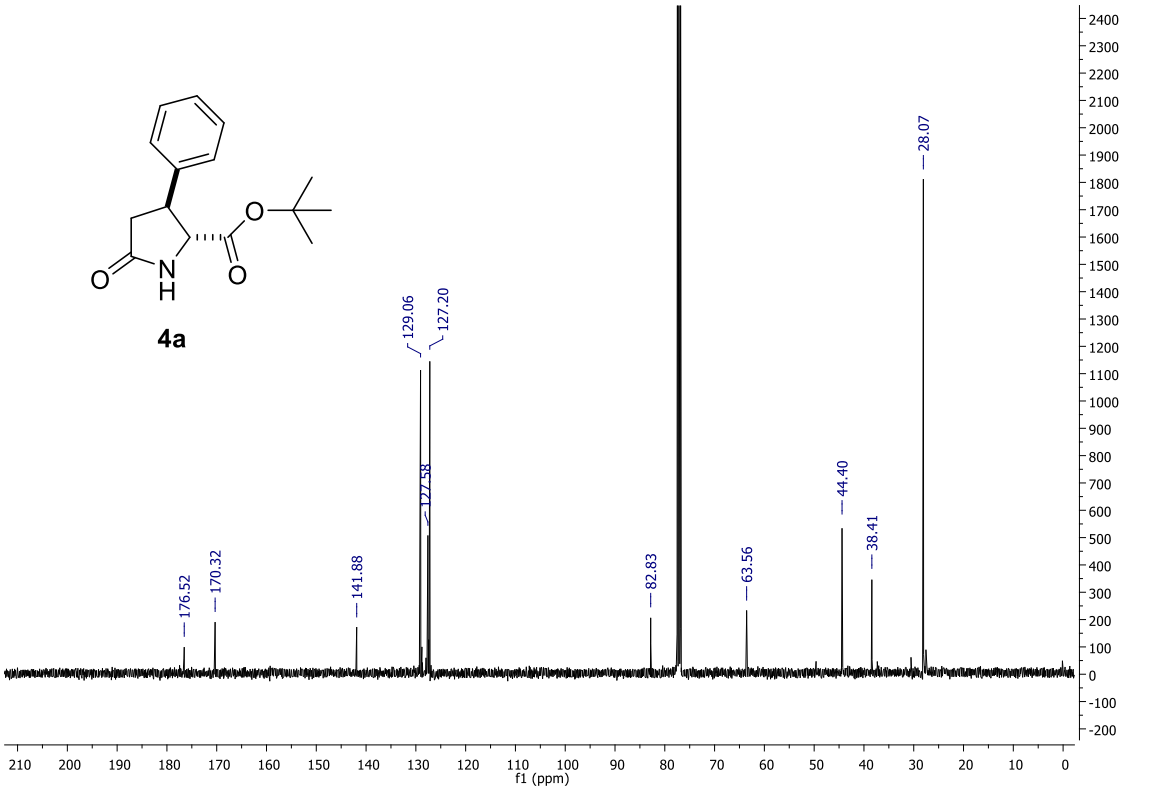


Figure AII.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **4a**

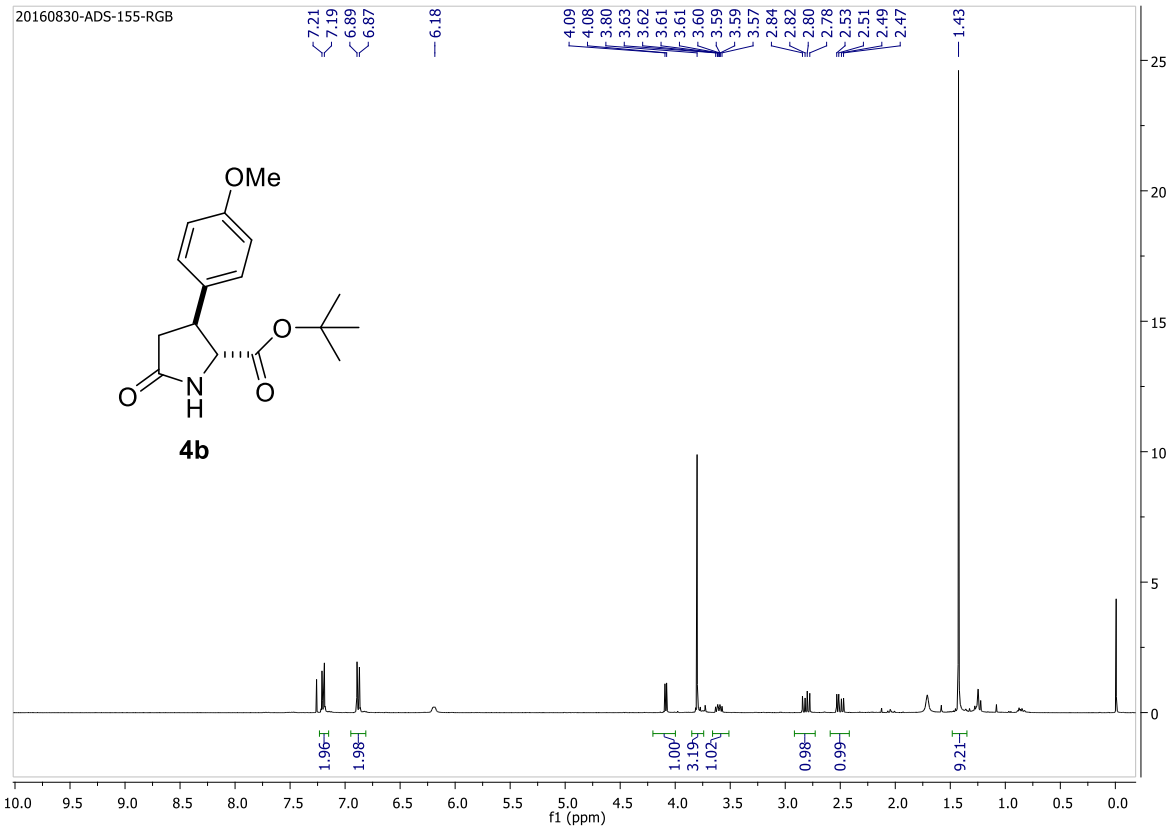


Figure AII.3: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4b**

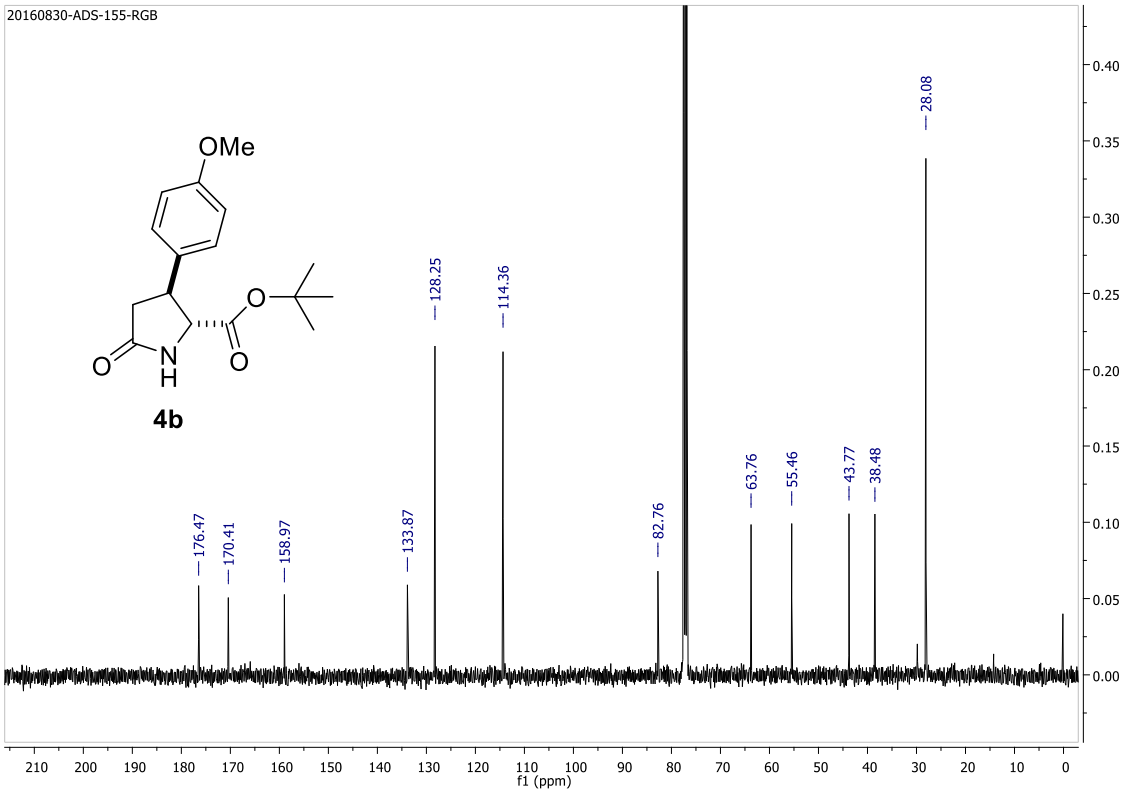


Figure AII.4: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **4b**

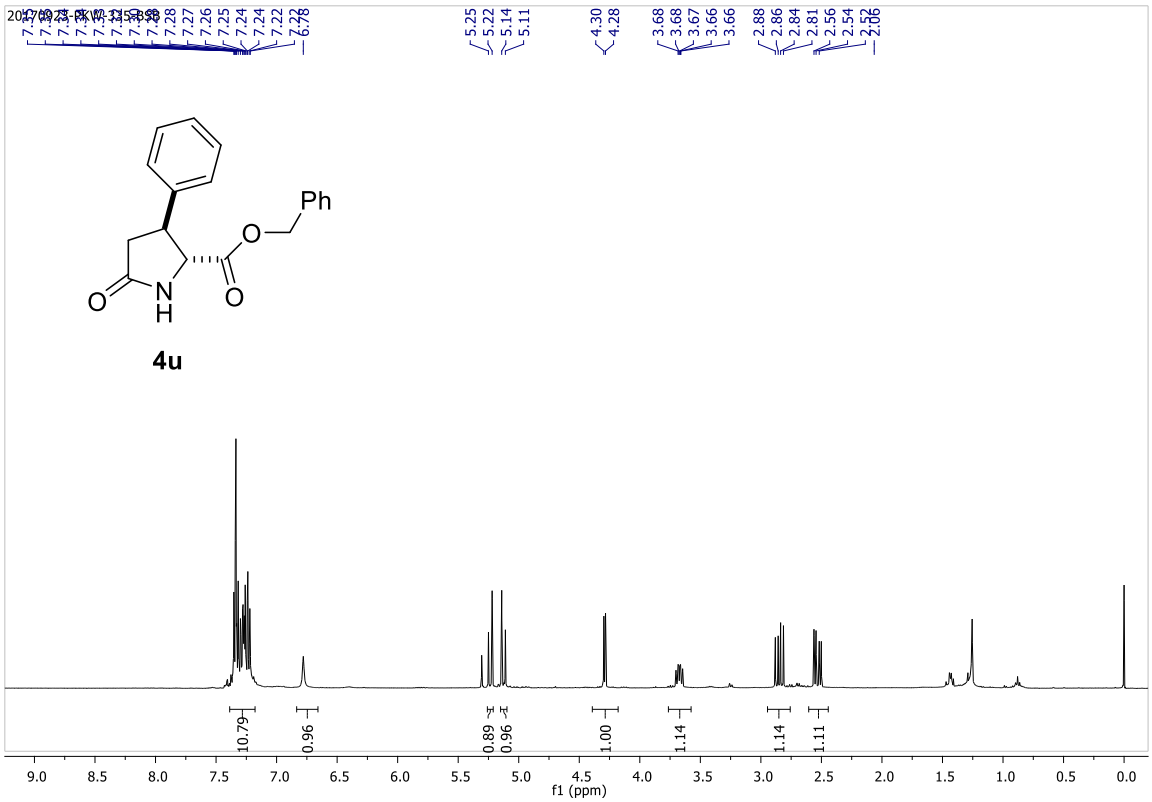


Figure AII.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4u**

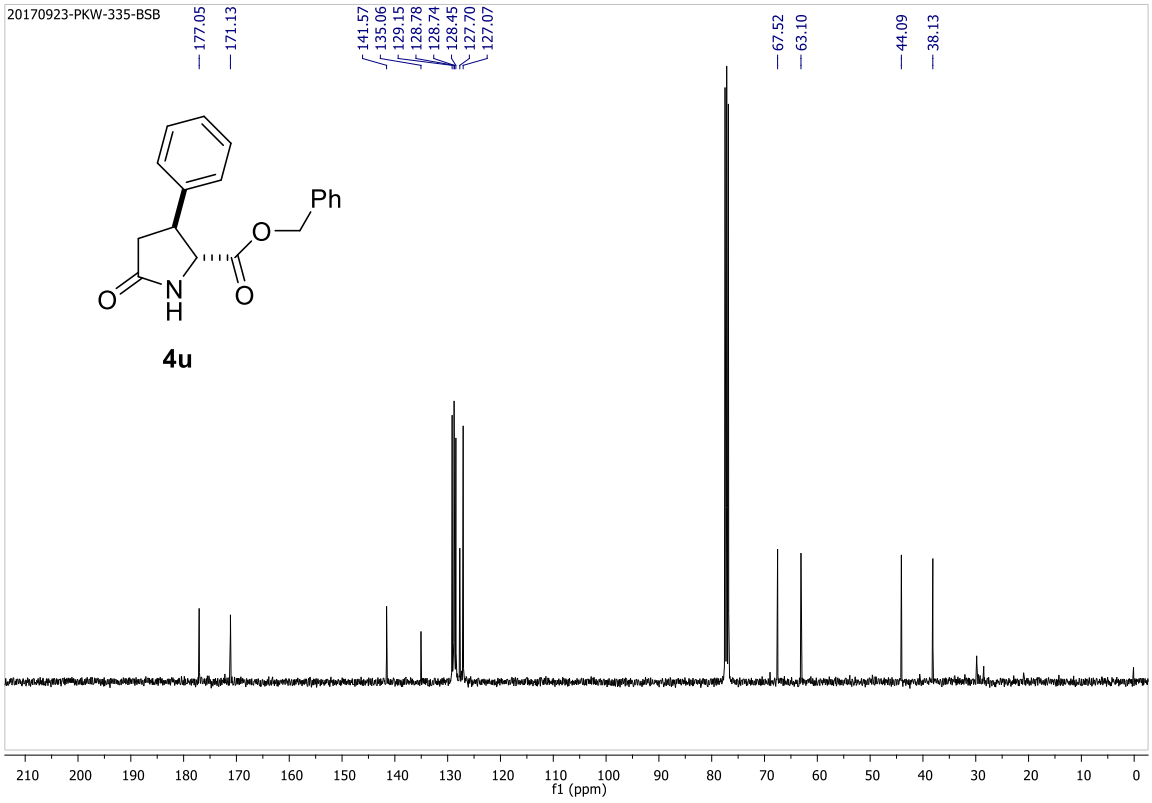


Figure AII.6: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **4u**

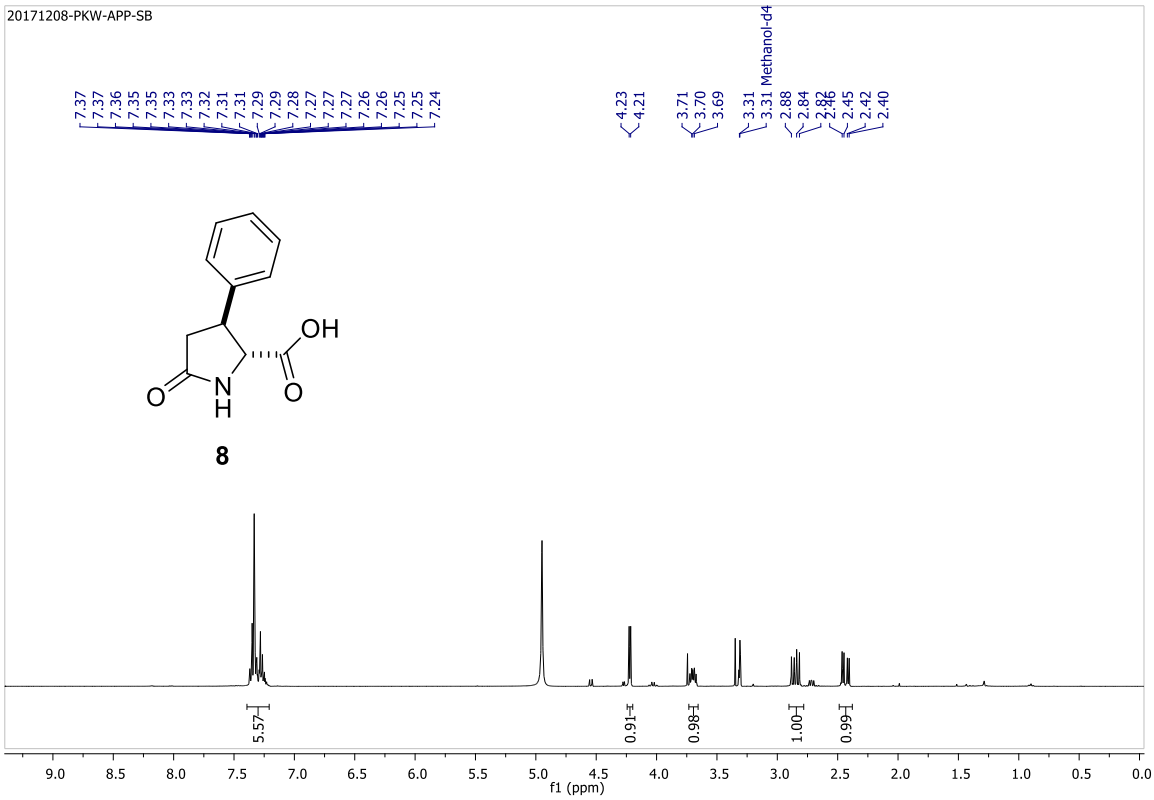


Figure AII.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8**

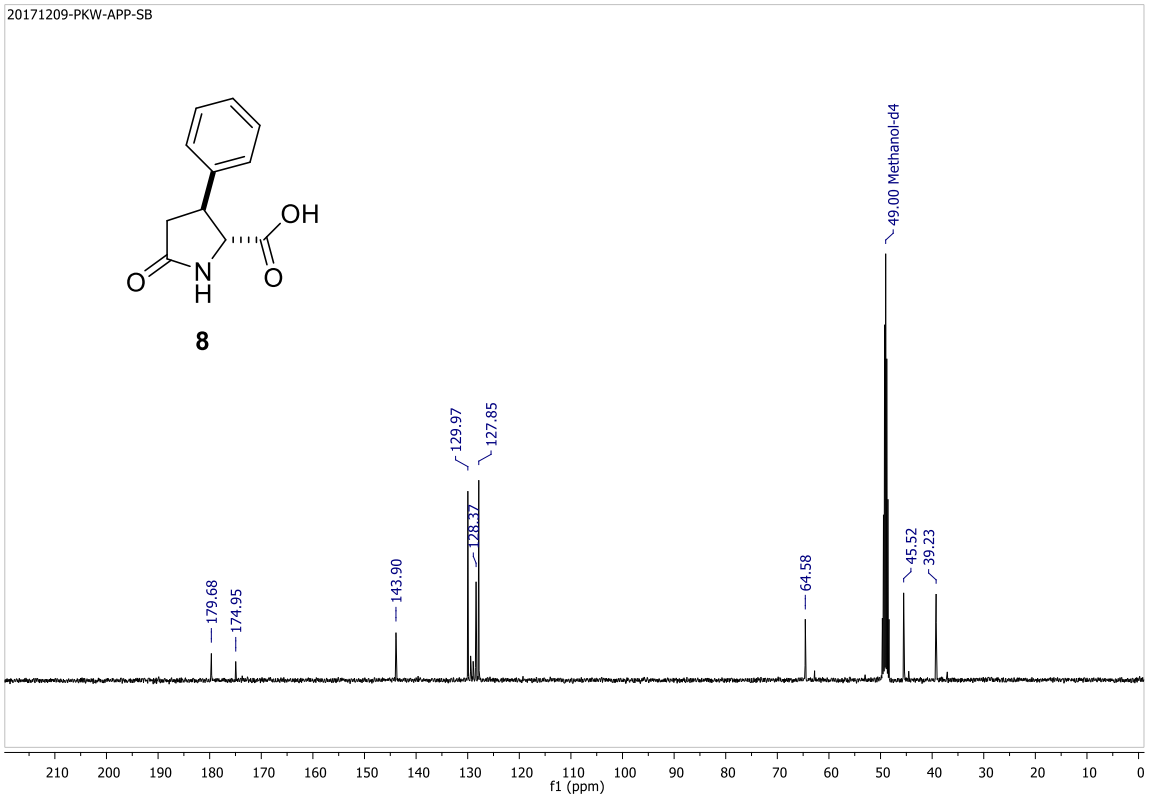


Figure AII.8: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **8**

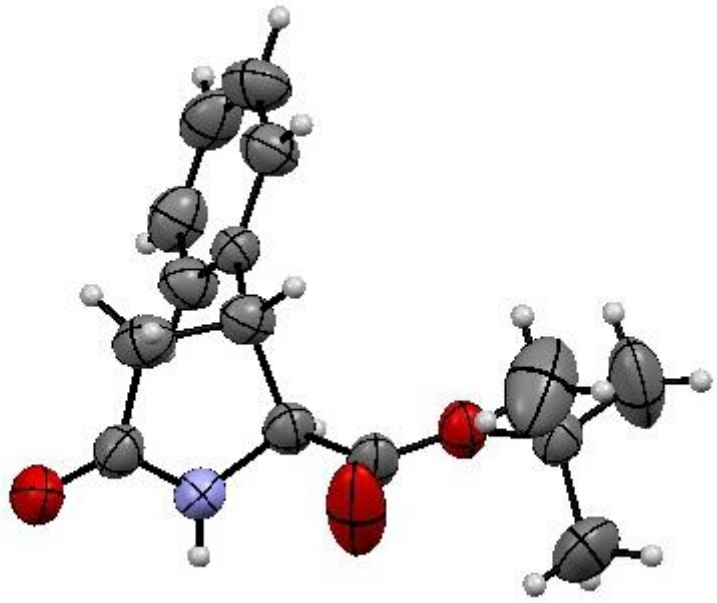


Figure AII.9: X-ray single crystal structures of compouns **4a**$_{trans}$

2.8 References

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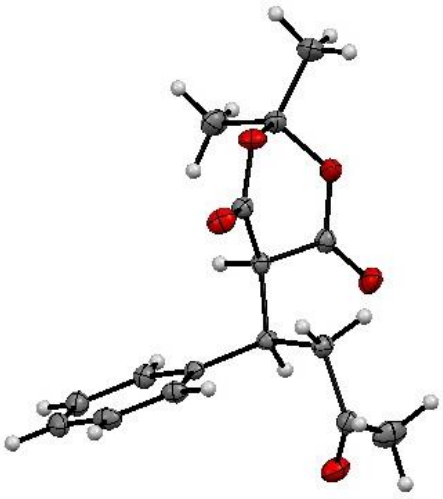
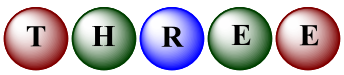
Chapter 3

An Adverse Effect of Higher Catalyst Loading and Longer Reaction Time on Enantioselectivity in Organocatalytic Multicomponent Reaction



δ-Keto Meldrum's acid

(X-ray Crystal structure)



3 An Adverse Effect of Higher Catalyst Loading and Longer Reaction Time on Enantioselectivity in Organocatalytic Multicomponent Reaction

Enantioselective organocatalytic multicomponent reaction of aldehyde, ketone and Meldrum's acid is developed for the first time since its discovery. Cinchona based primary amine (1 mol%) catalyzes the multicomponent reaction via the formation of Knoevenagel product and chiral enamine to form enantiopure δ-keto Meldrum's acids in a tandem catalytic pathway. An adverse effect of higher catalyst loading and longer reaction time on enantioselectivity is studied. This mild protocol provides an easy access to enantiopure carboxylic acids, esters and amides and the method proved to be scalable on a gram scale. The DFT calculations were carried out and they were in close agreement with the experimental results.

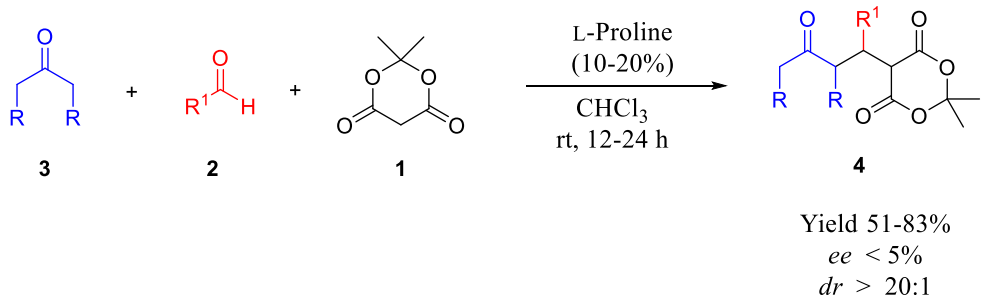
3.1 Introduction

In multicomponent reactions, three or more components react in one pot to form a product in single operation. The newly formed product essentially consists of most of the atoms of starting reactants. In this context, the catalytic multicomponent approach provides a simple and feasible way to synthesize complex value-added building blocks.[1] Organocatalysis has been proved to be an effective tool in organic synthesis as it is found to be a good alternative for the metal and enzyme catalysis.[2] Organocatalysts are non-toxic, simple, environmentally benign and more feasible and practical to use, thereby they satisfy most of the principles of green chemistry. At the beginning of asymmetric organocatalysis era, various research groups around the world have shown the unprecedented strength of organocatalysts.[3] It was found that these organocatalysts can catalyze a number of diverse multicomponent reactions very efficiently and selectively to generate a broad range of diverse and complex building blocks.[4] Nonetheless, the enantioselective multicomponent domino processes remained as challenging task for synthetic chemists especially for the stereoselective construction of complex chiral molecular architectures starting from simply accessible starting materials. While gleaning through the literature, we came across some of

the reactions wherein, the corresponding organocatalysts found to be inefficient in terms of inducing stereoselectivity.

3.2 Multicomponent reaction reported by List and co-workers

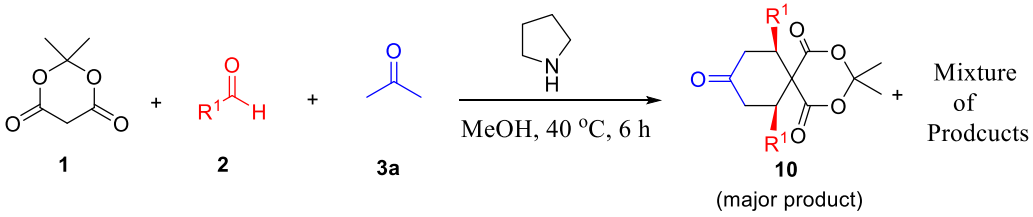
Earlier, List and co-workers[5] had reported an efficient L-proline-catalyzed three component Knoevenagel-Michael addition reaction of Meldrum's acid **1**, aldehyde **2** and ketone **3** (Scheme 3.1). Although this elegant C-C bond forming reaction proved to be highly diastereoselective, yet it lacked the enantioselectivity.



Scheme 3.1: Multicomponent reaction of ketones, aldehydes, and Meldrum's acid

3.3 Multicomponent reaction reported by Barbas and co-workers

Furthermore, in addition to the desired reaction, numerous pathways are possible which can compete with each other and can lead to undesired products. For example, Barbas and co-workers[6] reported the pyrrolidine catalyzed reaction between Meldrum's acid **1**, aldehyde **2** and acetone **3a** that furnished four different products (Scheme 3.2).



Scheme 3.2: Multicomponent reaction of Meldrum's acid, aldehydes and acetone

The negligible enantioselectivity of this iminium/enamine catalyzed reaction may be explained by either inadequate steric bulk of proline or less efficient steric interactions, or due to some undesirable mechanistic pathways. To our surprise, this highly efficient C-C bond forming three component process remained as an unmet challenge till date, consequently this encouraged us to investigate an appropriate catalyst system.

We believe that the modularly designed organocatalyst assembly developed by Zhao group[7] or cinchona based primary amine bifunctional catalysts[3c] could overcome the inherent difficulties suffered by proline in promoting effective enantiodiscrimination (Figure 3.1).

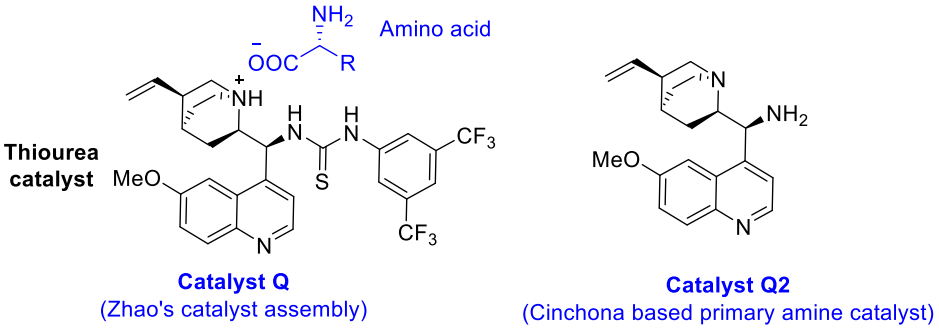


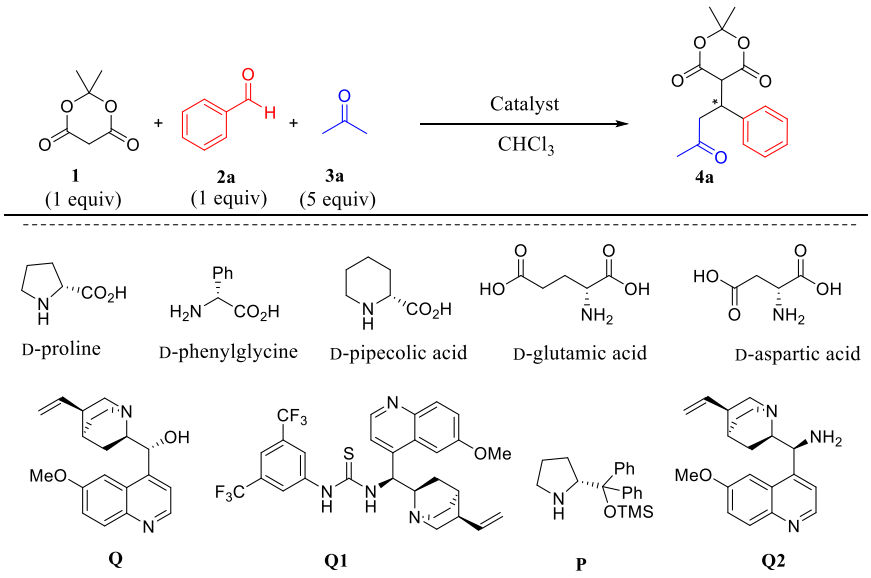
Figure 3.1: Modularly designed organocatalysts and primary amine bifunctional catalyst

Similarly, it is always important to identify a suitable catalyst and a set of conditions for the success of enantioselective multicomponent reactions. In general, it is often assumed that reactions work smoothly when aminocatalysts are employed in the range of 10-30 mol%. However, their counterproductive effects on the chemoselectivity and stereoselectivity are rarely observed and studied.[8] To the best of our knowledge, the counterproductive effects of high-catalyst loading of aminocatalyst and longer reaction time in the multicomponent reactions are not observed till date. Hence, we focussed our studies mainly on the development of enantioselective version of the reaction (Scheme 3.1) and to investigate the adverse effect of high catalyst loading on the enantioselectivity if any.

3.4 Results and discussion

At the outset, we began our investigation by using D-proline (D-Pro)-Thiourea (**Q1**) as a catalyst module and Meldrum's acid **1**, benzaldehyde **2a** and acetone **3a** as model substrates. However, the reaction was extremely sluggish under low catalytic loading[7] (D-Pro and **Q1** 5 mol% each) even after prolonged reaction time (Table 3.1, entry 1). When the catalytic loading of both the catalysts was increased to 20 mol%, the desired product **4a** was isolated in 55% yield after stirring the reaction mixture for 2 days at room temperature. However, to our dismay, we observed virtually racemic product (±)-**4a** in the presence of D-proline and D-phenyl glycine (Table 3.1, entry 2 and 3).

Table 3.1: Catalyst screening and optimization of reaction[a]



Entry	Catalyst (mol%)	Additive (mol%)	Time (in hours)	Yield[b] (%)	ee[c] (%)
1	D-Pro(5)	Q1(5)	120	10	-
2	D-Pro(20)	Q1(20)	48	55	5
3	D-Phg(20)	Q1(20)	72	40	8
4	D-Pro(20)[d]	Q1(20)	48	-	-
5	D-Pip(20)	Q1(20)	72	32	-
6	D-Glu(20)	Q1(20)	72	50	65
7	D-Asp(20)	Q1(20)	72	55	90
8	D-Asp(20)	Q(20)	120	30	-
9	P(20)	-	48	trace	-
10	Q2(10)	-	6	72	89
11	Q2(10)[d]	-	48	trace	-
12	Q2(10)	TFA(20)	24	83	91
13	Q2(1)	TFA(2)	16	74	95
14	Q2(0.1)	TFA(0.2)	120	32	95

[a]Reaction conditions: Meldrum's acid **1** (1 equiv.), benzaldehyde **2a** (1.05 equiv.), acetone **3a** (5 equiv.) catalyst (0.1-20 mol%), additive (0.2-40 mol%), in $CHCl_3$ at rt, 6-120 h; [b]isolated yield after purification by column chromatography, [c]*ee* was determined by HPLC using chiral column; [d]reaction at 0 ^oC.

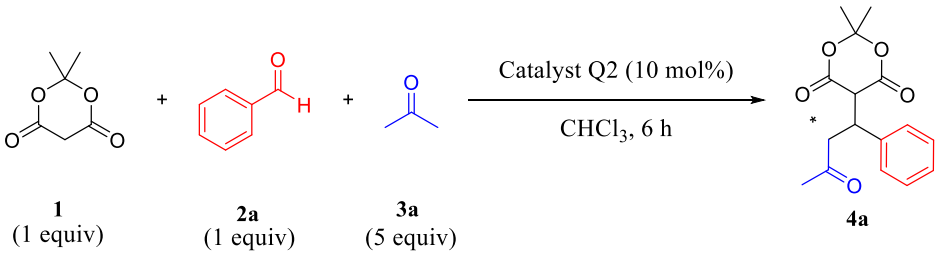
Subsequently, at 0℃ neither the intermediate nor the product was observed even after prolonged reaction time (Table 3.1, entry 4). Further, D-pipecolic acid exhibited very poor reactivity (Table 3.1, entry 5). We surmised that the unanticipated but probably favourable acid-base interaction between more acidic Meldrum's acid **1** (pKa 4.9) and thiourea catalyst (**Q1**) might have dominantly suppressed the formation of proline-thiourea catalyst self-assembly. This in turn might have compelled solely proline to catalyze the reaction resulting in negligible enantiomeric excess. This consideration led us to explore the use of more acidic amino acids which have lower pKa (pI) than Meldrum's acid **1** may enable to reduce the undesired Meldrum's acid **1**-thiourea **Q1** interaction. To test our hypothesis, D-glutamic acid and D-aspartic acid were employed along with thiourea **Q1** for the catalytic assembly for the desired transformation. To our delight, we observed that desired product **4a** was formed in 65% *ee* when D-glutamic was used as a catalyst and 90% *ee* observed in case of D-aspartic acid, however with unsatisfactory yields (Table 3.1, entry 6, 7). Later, when thiourea was replaced by quinine **Q**, a very poor conversion was observed (Table 3.1, entry 8). After exhaustive screening, we turned our attention towards much more bulky secondary amine catalyst and cinchona based primary amine bi-functional catalysts. In the beginning, mono-functional secondary amine **P** was investigated. However, secondary amine catalyst **P** afforded the product **4a** in extremely poor yield (Table 3.1, entry 9). Gratifyingly, quinine based bi-functional primary amine catalyst **Q2** (10 mol%) furnished the desired product **4a** in 72% yield with very good enantioselectivity (89% *ee*) in considerably a shorter reaction time (6 h) at room temperature (Table 3.1, entry 10).

In contrast reaction at 0℃ was extremely sluggish as Knoevenagel condensation is known to be highly unfavourable at low temperature (Table 3.1, entry 11). We observed that formation of the corresponding intermediate-alkylidene Meldrum's acid **5a** was accelerated rapidly in presence of bi-functional primary amine catalyst **Q2** whereas, it was slower in presence of modularly designed organocatalysts and secondary amine-Jørgenson catalyst **P**. Moreover, bifunctional cinchona based primary amine catalyst (**Q2**) proved to be superior catalyst, with respect to reactivity and enantioselectivity.

After establishing the suitable catalyst system, further, the effect of solvents on enantioselectivity was examined (Table 3.2). Screening of various solvents revealed that chloroform is the best solvent for the desired transformation. Other solvents such as toluene, dichloromethane, acetonitrile, EtOAc and MTBE turned out to be unsatisfactory in terms of enantioselectivity. While the polar solvents such as DMF, DMSO, methanol, ethanol and

water had a detrimental effect on the reactivity. The use of primary amine catalyst (**Q2**, 10 mol%) in chloroform at room temperature (6 h) was established as optimized reaction condition.

Table 3.2: Solvents screening



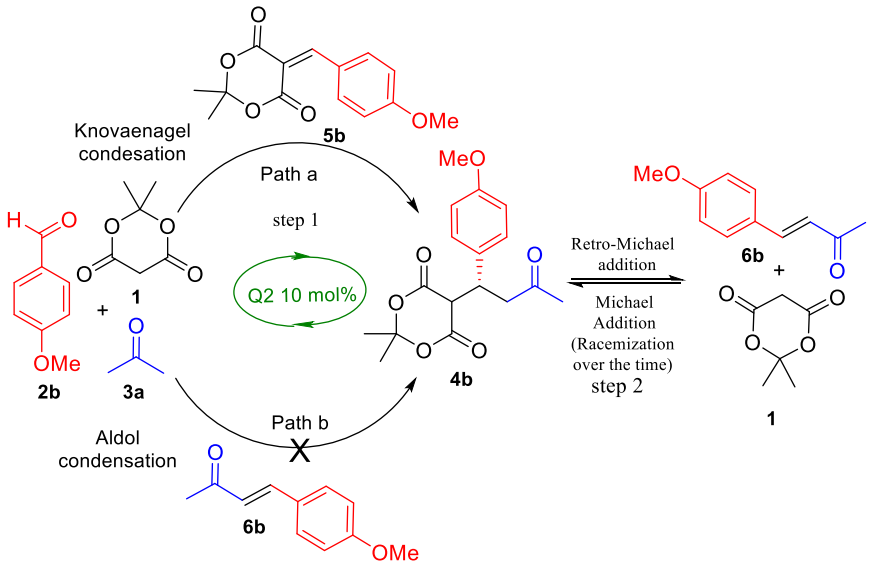
Sr. No.	Solvent	Yield(%)[a]	*ee*(%)[b]
1	$CHCl_3$	83	89
2	EtOAc	70	68
3	Toluene	68	85
4	THF	75	89
5	ACN	70	84
6	DMF	-	-
7	DMSO	-	-
8	Water	Trace	-
9	CH_2Cl_2	78	87
10	MTBE	69	87

[a]Isolated yield after column chromatography, [b]*ee* determined by chiral HPLC

Having optimized the reaction conditions in hand, we planned to extend the scope of the reaction using various aldehydes **2** and ketones **3** for the generality of the protocol. Initially, the reaction of Meldrum's acid **1**, 4-methoxybenzaldehyde **2b** and acetone **3a** under optimized reaction conditions afforded the corresponding product **4b** in 50% yield with 72% *ee* after 6 h. However, when we tried to increase the yield by stirring the reaction for an extended period of time, to our surprise the enantioselectivity was drastically lowered from 72% *ee* at 6 h to 10% *ee* at 48 h. This unanticipated observation indicated the probable

negative influence of longer reaction time on the enantioselectivity. In order to validate this finding, further we repeated the same reaction and recorded enantiomeric ratio of the product **4b** at different time interval as summarized in figure 3.3 (Black line, see page 67). Surprisingly, we observed that the initial very good enantioselectivity (86% *ee* at 1.5 h) was found to be eroding continuously over a period of time and afforded virtually racemic product **4b** after 72 h (Fig. 3.3, see black line 10 mol% **Q2**, page 67).

Prior to unravel the root cause of racemization over a period of time, it was important to understand the possible pathways of this transformation. We firmly believed that three component reaction of **1**, **2b** and **3a** can proceed via either Knoevenagel-Michael reaction pathway (path a) or Aldol-Michael reaction pathway (path b) as shown in scheme 3.3.



Scheme 3.3: Possible pathways for the product **4b**

In order to investigate the most plausible pathway, we carried out the time dependent ^{1}H NMR experiments of the reaction mixture (Figure 3.2).

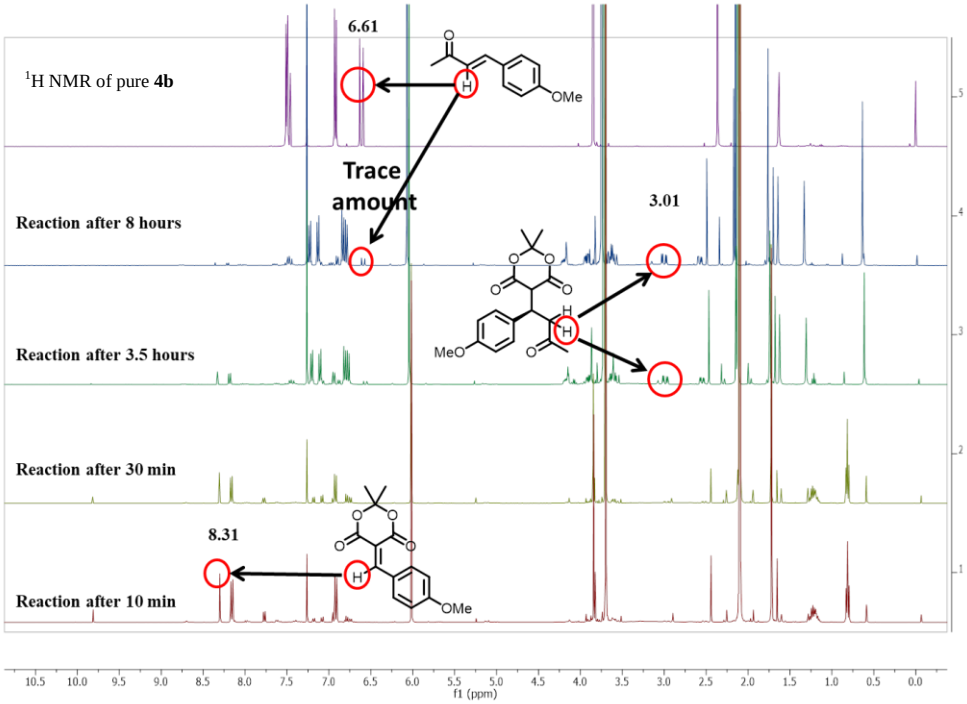
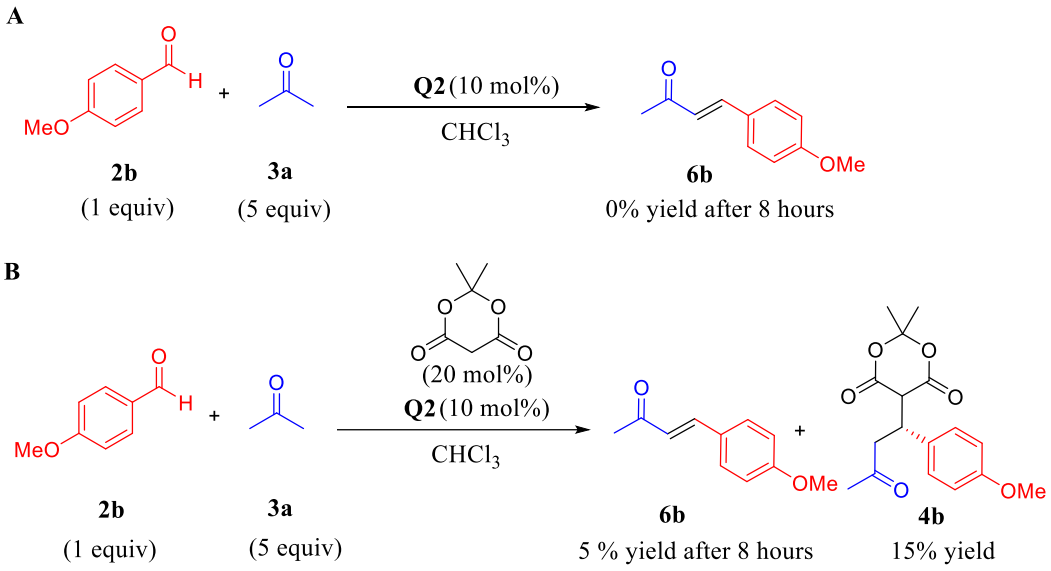


Figure 3.2: ^{1}H NMR experiment to find possible pathway of reaction

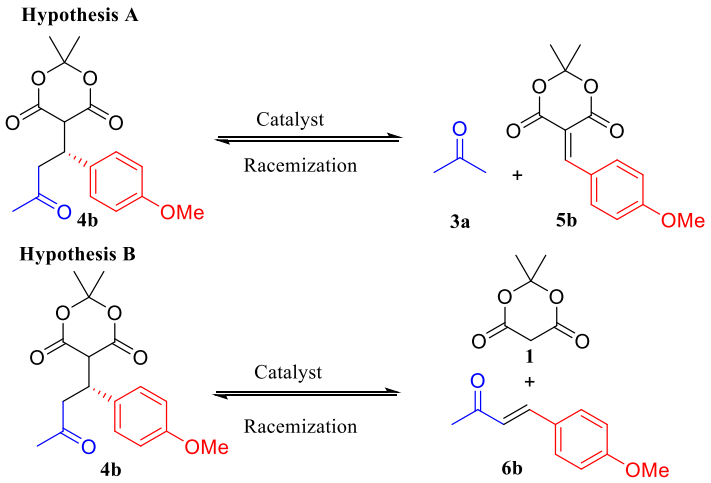
It was very interesting to observe that an intense peak (s, 8.31 ppm) corresponding to alkylidene Meldrum's acid **5b** appeared immediately within 10 minutes. This peak disappeared over a period of time, while the characteristic peak (dd, 3.01 ppm) corresponding to the product **4b** intensified gradually over a period of time (10 min-8 h). Likewise, the time dependent ^{1}H NMR experiments of the reaction mixture of **4a** gave a similar pattern of results. However, interestingly we also noticed that initially absent or insignificant characteristic peaks corresponding to benzylidene acetone **6a** (d, 6.72 ppm) and 4-methoxybenzylidene acetone **6b** (d, 6.61 ppm, Figure 3.2) slowly appeared along with the product peak. Based on this interesting observation we surmised that either the initially formed products **4a**/**4b** (via Knoevenagel-Michael pathway, path a) slowly underwent elimination of Meldrum's acid **1** thus leading to **6a**/**6b** or aldol condensation competed meekly with the path a.

In order to validate further we carried out the reaction of 4-methoxybenzaldehyde **2b** and acetone **3a** in the presence of catalyst **Q2** (10 mol%) (Scheme 3.4 A). Interestingly, the anticipated aldol condensation product **6b** (*p*-methoxybenzylidene acetone) was not obtained. Surprisingly, 20 mol% of Meldrum's acid **1** along with **Q2** (10 mol%) catalyzed the formation of **6b** in trace amount (Scheme 3.4 B). These findings unambiguously infer that the reaction is proceeding via Knoevenagel-Michael reaction pathway (path a).



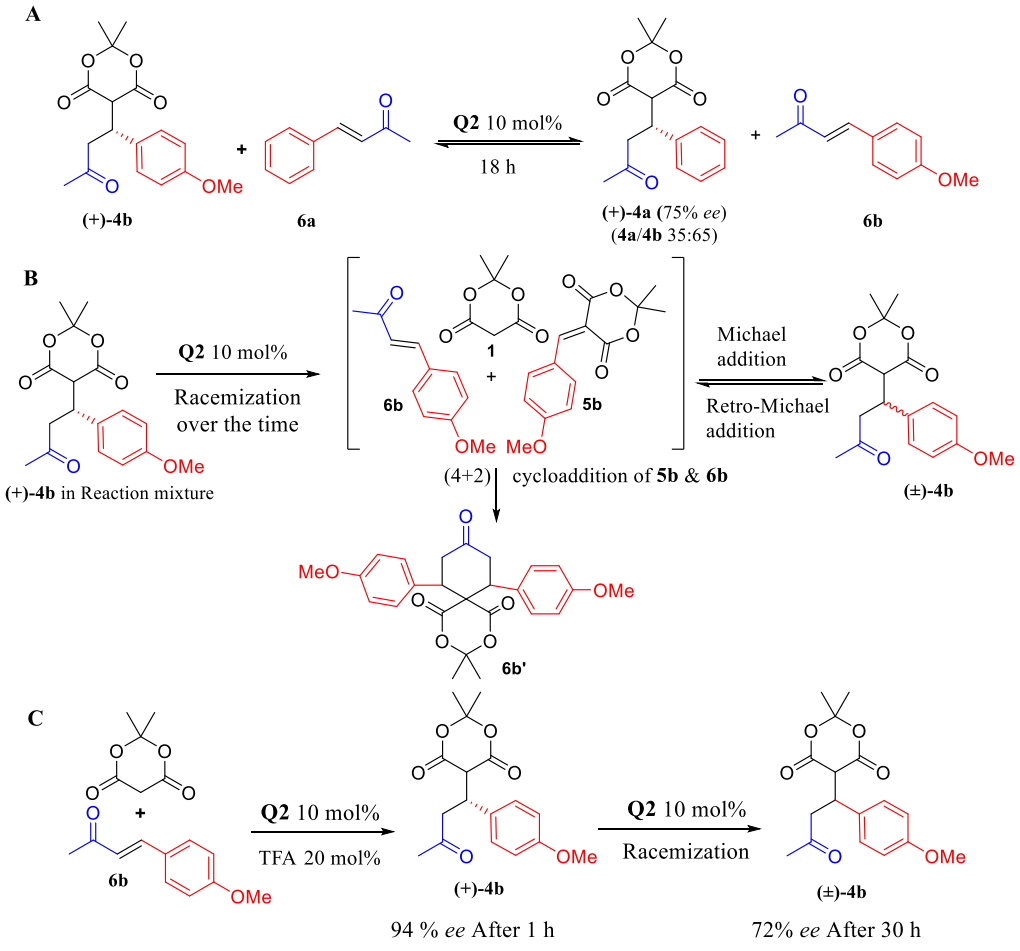
Scheme 3.4: Attempted aldol reaction with and without Meldrum's acid

Further, in quest for finding the reason for the erosion in enantioselectivity over a period of time we conceived two probable hypotheses A and B (Scheme 3.5). In both the hypotheses enantiopure compound **4b** may be undergoing racemizing equilibrating retro-Michael-Michael addition. However, based on the earlier NMR experiments, hypothesis A seems to be unlikely as 4-methoxybenzylidene Meldrum's acid **5b** disappeared over a period of time. Instead, 4-methoxybenzlylidene acetone **6b** formed over a period of time via the racemizing equilibriating retro-Michael-Michael addition starting from enantiopure **4b**.



Scheme 3.5: Possible routes for the racemization

Further, in order to validate the possible reversible retro-Michael/Michael addition reaction (Hypothesis B), we carried out a cross-over experiment of enantiopure product **4b** and benzylidene acetone **6a** in the presence of 10 mol% of catalyst **Q2** in chloroform (18 h, Scheme 3.6A). The formation of 4-methoxybenzylidene acetone **6b** and product **4a** (75% ee) unambiguously supported the hypothesis B for the reversible retro-Michael/Michael addition pathway. This clearly gives an insight that compound **4b** undergoes an elimination process to afford Meldrum's acid **1** and 4-methoxybenzylidene acetone **6b** over a period of time. Interestingly, longer reaction time also resulted in spiro compound **6b'** (4+2 cycloaddition of **5b** and **6b**, 40% yield)[6] along with racemic product **4b** (see Scheme 3.6 B) and this finding further supported the hypothesis B.[10]



Scheme 3.6: Crossover experiment to validate hypothesis B

This unexpected finding led us to believe that possibly the higher concentration of the catalyst **Q2** may be the key factor (acting like base) for the reversible retro-Michael/Michael addition thus causing erosion of enantiopurity. In order to overcome this problem, we

planned to add acidic additive such as trifluoroacetic acid (20 mol% TFA, pKa 0.23) along with the catalysts to reduce any undesirable base effect of the catalyst (Table 3.1, entry 12). However, interestingly we observed that the initial excellent enantioselectivity eroded slowly over a period of time (Fig 3.3, see red line). Nevertheless, erosion of enantioselectivity was found to be relatively slower than in the presence of sole catalyst **Q2** (Fig 3.3, see black line). This led us to believe that reducing the catalyst loading instead of compromising the reaction time would be more beneficial. It was gratifying to note that the reaction of Meldrum's acid **1**, **2b** and **3a** in presence of 1 mol% of **Q2** in chloroform (24 h) afforded the corresponding product **4b** in excellent enantioselectivity (93% *ee*). However, over a period of time very slow erosion of enantioselectivity was inevitable (Fig. 3.3, see green line). Gratifyingly, the addition of 2 mol% of TFA along with **Q2** (1 mol%) found to be highly effective and the enantiopurity of **4b** remained almost unchanged even after prolonged reaction time 72 h (Table 3.1, entry 13, Fig. 3.3, see blue line,).

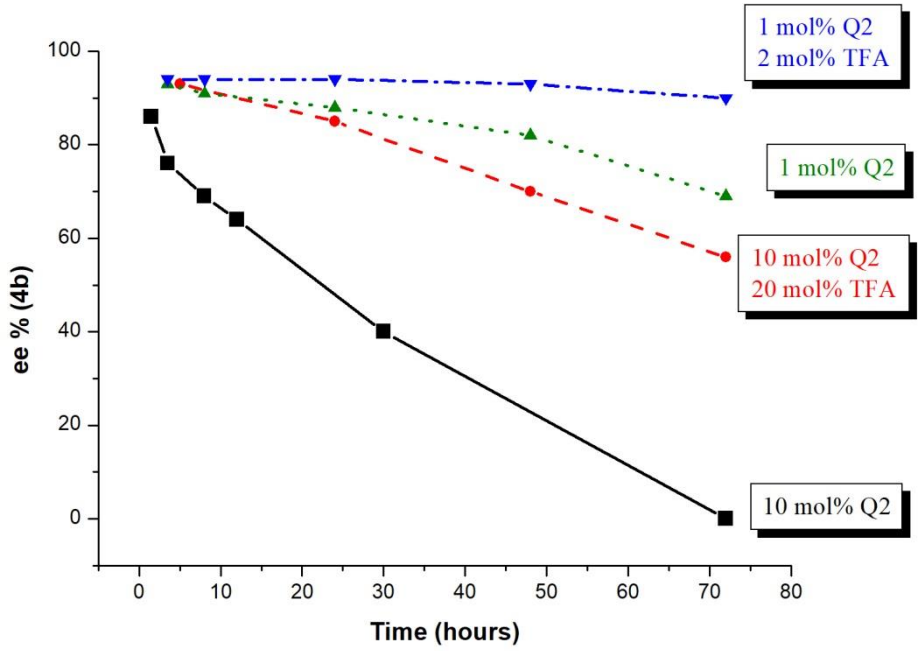


Figure 3.3: Effect of catalyst loading, additive and time on enantioselectivity of **4b**

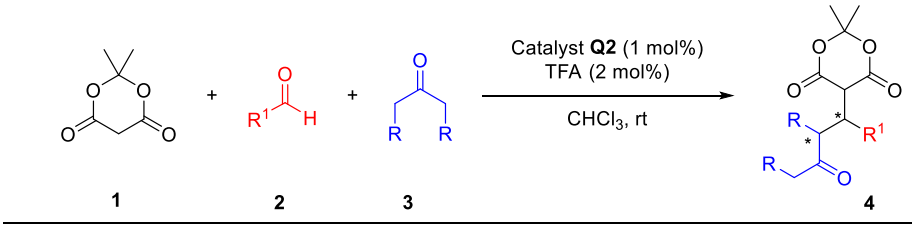
This interesting but unusual phenomenon may be explained by considering the kinetic vs thermodynamic control. Under higher catalytic loading the initial kinetically controlled reaction that leads to enantiopure product **4b**, slowly undergoes retro Michael-Michael addition under thermodynamic equilibrium (Scheme 3.3, step 2). The more favorable increase in entropy could be the driving force for the irreversible racemization and would reach the

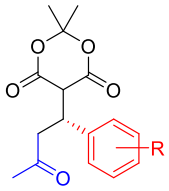
completion when thermodynamic equilibrium is achieved (*ee* = 0%).[11] This assumption was further revalidated by the reaction of Meldrum's acid **1** and 4-methoxy benzylidene acetone **6b** in the presence of 10 mol% of **Q2** and 20 mol% TFA (Scheme 3.6 C).[12] It is interesting to note that initially formed enantiomerically pure product (+)-**4b** (94% *ee*) was susceptible to the erosion of enantiopurity over a period of time (30 h, 72% ee). On the other hand, under the lower catalytic loading (1 mol% and 2 mol% TFA) due to the slower reaction rate Michael addition favors over racemizing retro-Michael/Michael pathway (Scheme 3.3, step 2) resulting in the enantiomerically pure product (+)-**4b**.

After re-establishing the optimum catalytic loading (**Q2** 1 mol% and 2 mol% TFA), we explored the generality of the reaction by using various aldehydes **2** and ketones **3**. The aromatic aldehydes, both electron-rich and -deficient were found to be compatible under optimized reaction conditions by affording the corresponding products (**4a-4j**, Table 3.3) in good yields with excellent enantioselectivity (up to 99% *ee*). However, we observed that aromatic aldehydes such as 4-methoxy benzaldehyde **2b** and 3, 4-dimethoxy benzaldehyde **2h** reacted relatively slow (36 h) affording **4b** and **4i**.[12] Heteroaromatic aldehyde such as furfural **2k**, worked well under the reaction conditions and afforded the corresponding **4k** in good yields with relatively lower enantioselectivity (77% *ee*). In order to have a wider scope, further, we examined the feasibility of reaction on the aliphatic aldehydes. It was found that even the enolizable aldehydes (**2l** and **2m**) were well tolerated in the presence of primary amine catalyst **Q2**, affording the products (**4l** and **4m**) in good yield with good enantioselectivity (60-73% *ee*). The scope of the reaction was extended further towards substituted Michael donors such as cyclohexanone **3b**, cyclopentanone **3c** and 3-pentanone **3c** with various aldehydes. In all the cases corresponding products (**4n-4s**) were obtained as single diastereomers with moderate to excellent enantioselectivity (up to 94% *ee*).

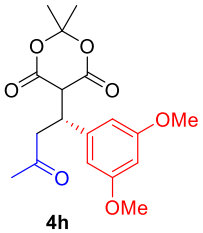
Notably, this protocol tolerated a wide variety of aldehydes under very mild reaction conditions. The strength and practicality of this protocol was also demonstrated on a gram scale by the synthesis of product **4a** (74% yield) without the loss of enantioselectivity (94% *ee*) under optimized reaction conditions. Attempts to lower the catalytic loading (0.1 mol%) on a gram scale resulted in a modest yield of **4a** (32%), however with excellent enantioselectivity (Table 3.1, entry 14).

Table 3.3: Substrate Scope[a-d]

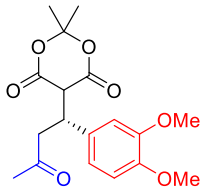




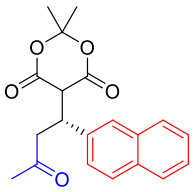
4a, 16 h, R = H, 75% yield, 95% ee
4b, 36 h, R = 4-OMe, 44% yield, 94% ee
4c, 16 h, R = 4-Me, 69% yield, 90% ee
4d, 16 h, R = 4-F, 79% yield, 99% ee
4e, 16 h, R = 4-Cl, 78% yield, 99% ee
4f, 16 h, R = 4-CN, 81% yield, 93% ee
4g, 16 h, R = 2-Br, 79, 96% ee



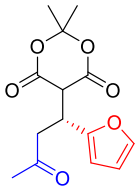
4h
16 h, 91%, 95% ee



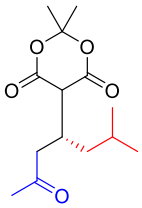
4i
36 h, 48%, >99% ee



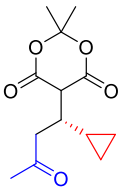
4j
16 h, 75%, 83% ee



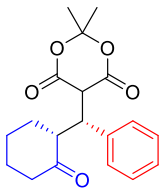
4k
16 h, 65%, 77% ee



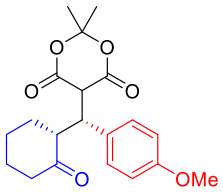
4l
24 h, 51%, 60% ee



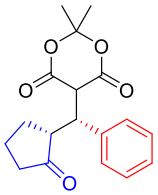
4m
24 h, 52%, 73% ee



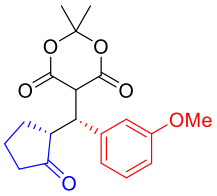
4n
24 h, 51%, 90% ee
dr >20:1



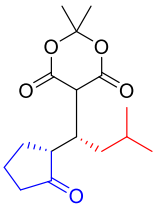
4o
36 h, 31%, 93% ee
dr >20:1



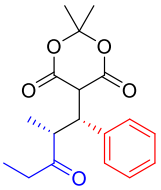
4p
16 h, 49%, 86% ee
dr >20:1



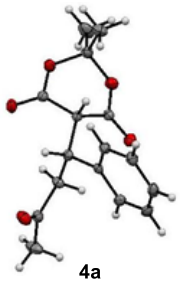
4q
16 h, 43%, 83% ee
dr >20:1



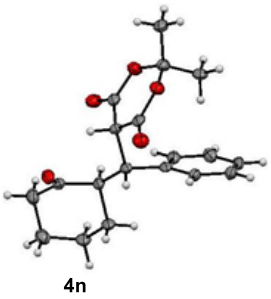
4r
16 h, 52%, 49% ee
dr >20:1



4s
24 h, 47%, 86% ee
dr >20:1



4a

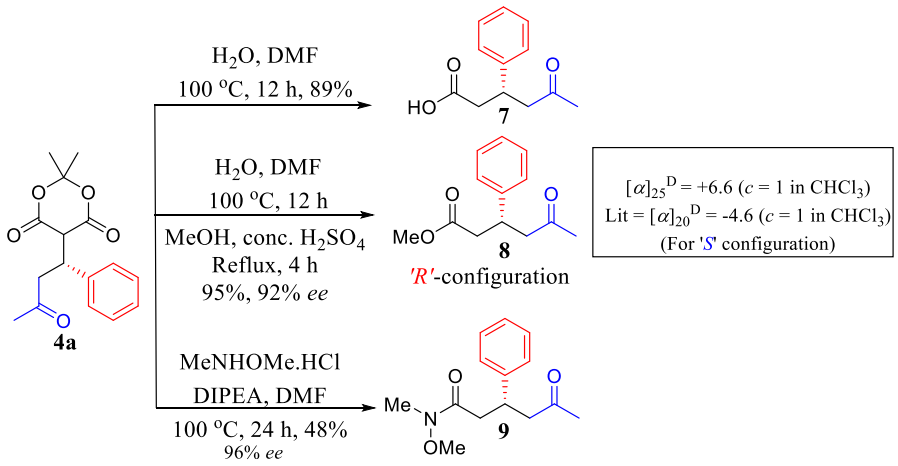


4n

[a]Reaction conditions: Meldrum's acid **1** (1 equiv.), aldehyde **2** (1.05 equiv.), ketone **3** (5 equiv.) catalyst **Q2** (1 mol%), TFA as an additive (2 mol%), in chloroform at rt, [b]isolated yield after purification by column chromatography, [c]*dr* was calculated based ^{1}H NMR; [d]*ee* was determined by HPLC using chiral column.

In order to show the wider applicability of this protocol we demonstrated enantiopure synthesis of some of the important precursors of many useful molecules such as carboxylic acid **7**, ester **8** and amide **9** starting from **4a** (Scheme 3.7). The synthesis of compound **8** also

helped to identify the absolute configuration of **4a.** The specific rotation of methyl ester **8** was in a close agreement with the literature value (see scheme 3.7).[13]



Scheme 3.7: Quick access to carboxylic acid, ester and amide

Based on these findings the absolute configuration of **4a** was assigned as '*R*'. The molecular structures of compounds **4a** and **4n** were unambiguously established using single crystal X-ray diffraction analysis (Figure 3.4).[14]

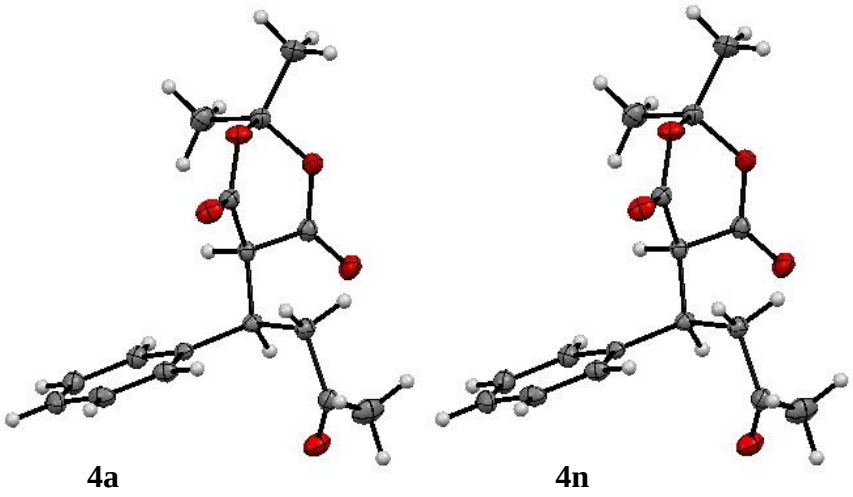
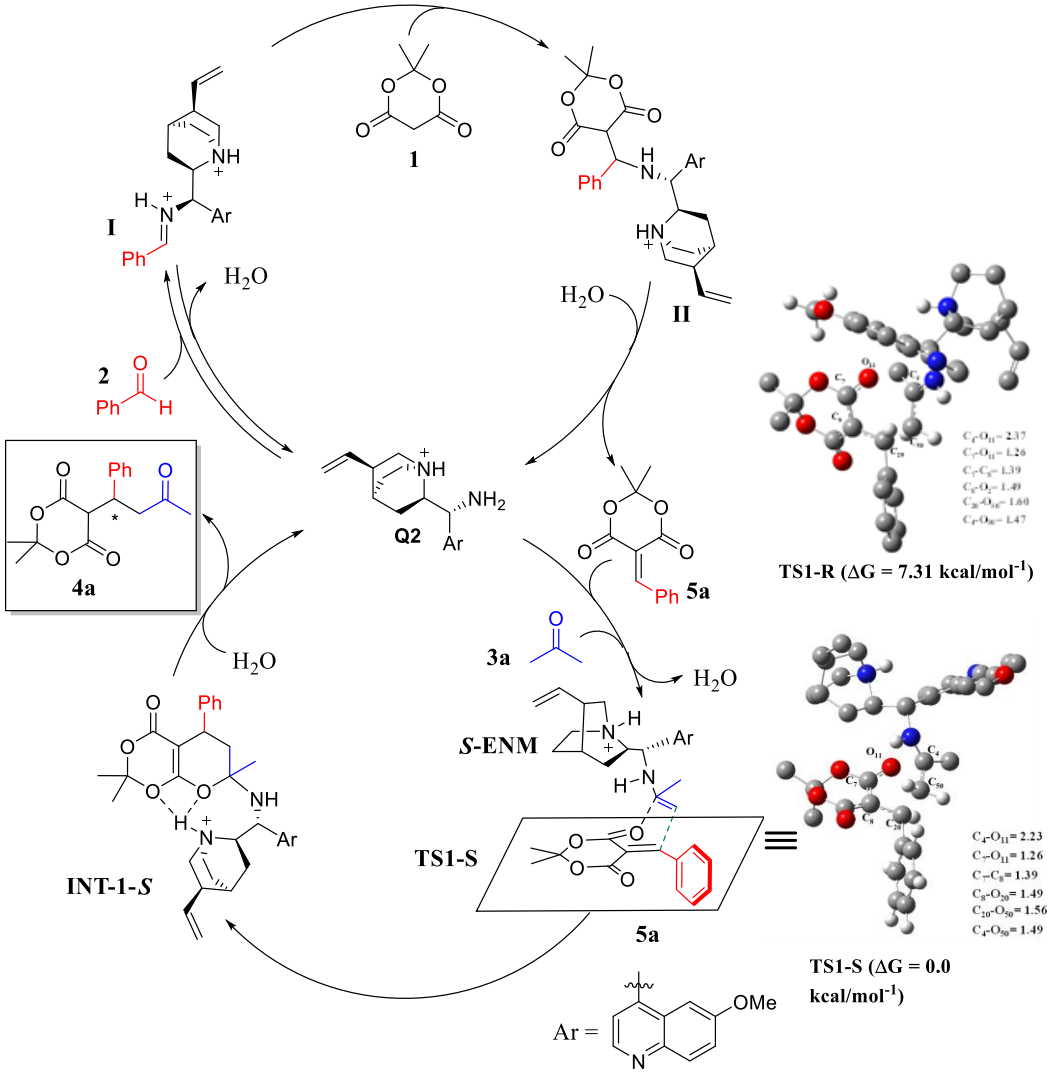


Figure 3.4: X-ray single crystal structures of compounds **4a** and **4n**

The proposed mechanism was computationally studied using the density functional theoretical (DFT) calculations (Scheme 3.8, see pages 98-100). Initially protonated primary amine **Q2** catalyzes Knoevenagel condensation via iminium ion intermediate (**I**) and intermediate (**II**) to generate heterodiene **5a**. In the second step catalyst **Q2** forms chiral enamine (***S*-ENM**) with acetone **3a** that further reacts with heterodiene **5a** via [4+2]-hetero-Diels-Alder cycloaddition pathway (Scheme 3.8).[15] The transition states (TS's) for the [4+2]

cycloaddition step could follow the enamine/**5a** *si* facial attack or enamine/**5a** *re* facial attack, thus resulting in **TS1-*S*** and **TS1-*R*** TS's, respectively. Of these two TS's formed, **TS1-*S*** is 7.31 kcal/mol more stable than the **TS1-*R*** resulting in product **4a** (***R***-configuration, see page 98) with high stereoselectivity (Theoretical *ee* = 99% is in very good agreement with the experimental *ee* = 95%).



Schme 3.8: Proposed Mechanism[a,b]

[a]Transition state structures for the addition of enamine ***S*-ENM** to **5a** (both *si* and *re* face). [b]Selected bond distances are in Å. Relative free energies are given in parenthesis (kcal·mol^{-1}); M06-2X/6-311++G(d,p)/SMD//M06-2X/6-31G(d). Most of the H-atoms have been omitted for the sake of clarity.

3.5 Conclusions

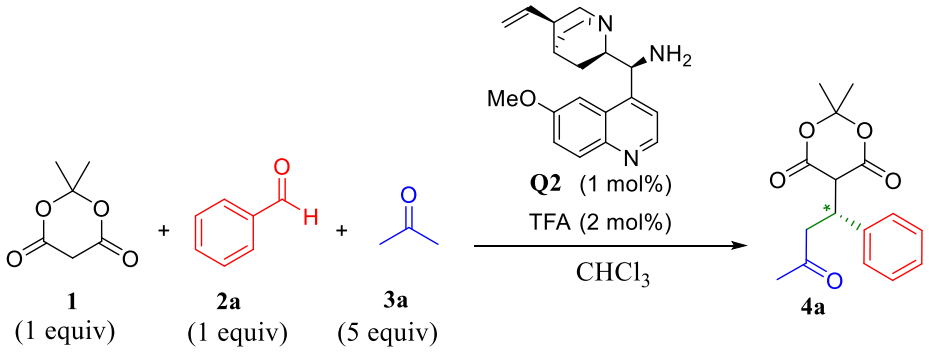
In conclusion, we demonstrated a highly enantioselective organocatalytic multicomponent reaction of aldehyde, ketone and Meldrum's acid for the first time since its discovery. We carried out a systematic study on the adverse effect of higher catalytic loading and longer reaction time on outcome of enantioselectivity. In order to understand the mechanism of racemization in depth further detailed investigation is needed. The protocol worked efficiently under very low catalyst loading (1 mol%) and proved to be scalable. Protocol is practical as it gives a quick access to very useful precursors and intermediates such as enantiopure δ-keto esters, carboxylic acids and amides. This mild and useful reaction may find a wider application in future**.**

3.6 Experimental section

General methods

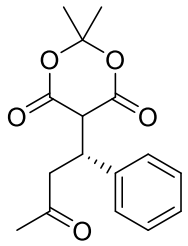
Unless otherwise stated, all reagents were purchased from commercial suppliers and used without purification. Meldrum's acid was purchased from Spectrochem. Aldehydes and ketones were purchased from Aldrich, Spectrochem and Alfa-aeser. HPLC grade solvents were purchased from RANKEM. Catalyst was prepared and characterized by using reported procedure.[16] All the reactions were carried out in oven dried glassware. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm). Visualization was accomplished by irradiation with UV light at 254 nm and/or ninhydrin stain. Column chromatography was performed using silica gel (200-300 mesh) eluting with petroleum ether and ethyl acetate. NMR spectra were recorded with tetramethylsilane as the internal standard. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz (Bruker and Jeol). Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.16 ppm) for ^{13}C NMR spectroscopy. Coupling constants (*J*) are given in Hz. IR spectra were obtained using FT-IR spectrophotometer as neat and are reported in cm^{-1}. Mass samples were analyzed by High-resolution mass spectrometer (HRMS) using ESI TOF. Optical rotations were measured at 589 nm at 25 °C. HPLC analysis was performed using an Agilent 1200 infinity series HPLC System with a diode array detector. Enantiomeric excess was determined by HPLC analysis on Chiralpak IC and Chiralpak IE columns by using *n*-hexane, *n*-heptane and isopropanol as eluents. Data were analyzed by using Agilent EZChrom Elite and Agilent OpenLAB software.

General Procedure for the enantioselective three-component reaction



In a vial equipped with a teflon-coated stir bar, 9-amino(9-deoxy)*epi*quinine **Q2** (10.41µmol, 3.37 mg, 1 mol%) was dissolved in 2 mL of chloroform. After addition of trifluoroacetic acid (20.82 µmol, 1.6 µL, 2 mol%), the reaction mixture was stirred for 15 minutes. Then Meldrum's acid **1** (1.04 mmol, 150 mg, 1equiv.), aldehyde **2** (1.14 mmol, 1.05 equiv.) and ketone (5.2 mmol, 5 equiv.) were added subsequently and the reaction mixture was stirred for the indicated time (12-24 h). Upon completion of the reaction (Confirmed by TLC), it was purified by column chromatography (as slurry) without work up. The product was purified on silica gel using petroleum ether/ethyl acetate (70:30).

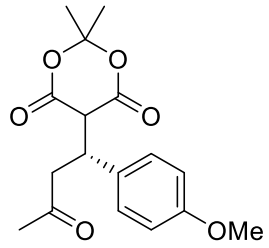
(*R*)-2,2-dimethyl-5-(3-oxo-1-phenylbutyl)-1,3-dioxane-4,6-dione (4a)



4a

Compound **4a** prepared following the General procedure. Obtained as white solid in 75% yield (227 mg); m.p. 104-108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 5H), 4.28 (ddd, *J* = 10.2, 5.1, 3.5 Hz, 1H), 4.22 (d, *J* = 3.4 Hz, 1H), 3.72 (dd, *J* = 18.6, 10.3 Hz, 1H), 3.06 (dd, *J* = 18.6, 5.2 Hz, 1H), 2.21 (s, 3H), 1.68 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 165.6, 165.3, 139.9, 128.9, 128.9, 127.9, 105.4, 49.2, 45.6, 39.9, 30.5, 28.3, 28.1; HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{18}O_5$ + Na $[M + Na]^+$ 313.1051, found 313.1063. FT IR cm^{-1} (neat) 3001.65, 2927.32, 1724.19, 1495.05, 1297.55, 1202.70, 1091.41, 1016.01, 898.45, 762.46, 702.28, 633.10. The enantiomeric excess was determined by HPLC analysis using Chiralpak IE, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL /min, λ = 254 nm, t_R = 29.4 min (minor) and t_R= 30.0 min (major). *ee* = 95%. Specific rotation $[\alpha]_D^{25}$ = + 30.0 (c = 1.0, $CHCl_3$).

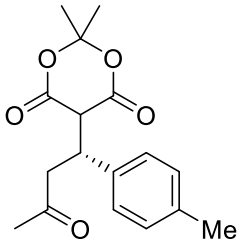
(*R*)-5-(1-(4-methoxyphenyl)-3-oxobutyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4b)



4b

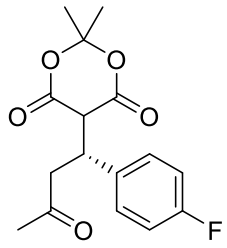
Compound **4b** prepared following the General procedure. Obtained as white solid in 44% yield (147 mg); m.p. 110-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 4.25 – 4.20 (m, 1H), 4.18 (m, 1H), 3.76 (s, 3H), 3.68 (dd, J = 18.6, 10.1 Hz, 1H), 3.01 (dd, J = 18.6, 5.0 Hz, 1H), 2.19 (s, 3H), 1.66 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 165.6, 165.4, 159.2, 131.8, 130.1, 114.2, 105.4, 55.4, 49.3, 45.9, 39.1, 30.5, 28.3, 28.0; HRMS (ESI TOF) *m/z* calcd. For $C_{17}H_{20}O_6$ + H $[M + H]^+$ 321.1338, found 321.1335. FT IR cm^{-1} (neat) 2924.91, 2855.48, 1736.70, 1610.75, 1512.89, 1457.18, 1378.77, 1295.10, 1247.21, 1178.33, 1108.88, 1025.15, 903.12, 829.88, 735.27, 700.17, 636.46. The enantiomeric excess was determined by HPLC analysis using ChiralCel OX-H, *n*-hexane/*i*-PrOH = 80:20, flow rate = 0.5 mL /min, λ = 230 nm, t_R= 16.9 min (minor) and t_R= 22.3 min (major). *ee* = 94%. Specific rotation $[\alpha]_D^{25}$ = +28.2 (c = 1.0, $CHCl_3$).

(*R*)-2,2-dimethyl-5-(3-oxo-1-(p-tolyl)butyl)-1,3-dioxane-4,6-dione (4c)



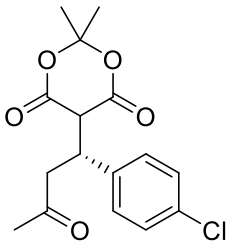
Compound **4c** prepared following the General procedure. Obtained as colorless viscous oil in 69% yield (219 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 4.46 – 4.02 (m, 2H), 3.67 (dd, *J* = 18.6, 10.1 Hz, 1H), 3.01 (dd, *J* = 18.6, 5.1 Hz, 1H), 2.29 (s, 3H), 2.18 (s, 3H), 1.66 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 165.6, 165.3, 137.6, 136.8, 129.6, 128.8, 105.3, 49.2, 45.7, 39.4, 30.5, 28.2, 28.0, 21.1; FT IR cm^{-1} (neat) 2925.01, 2857.61, 1724.07, 1514.46, 1366.05, 1297.96, 1205.42, 1099.78, 1018.73, 811.52, 734.42, 701.09; HRMS (ESI TOF) *m/z* calcd. For $C_{17}H_{20}O_5$-H $[M - H]^-$ 303.1233, found 303.1235. The enantiomeric excess was determined by HPLC analysis using Chiralpak IC, *n*-heptane /*i*-PrOH = 85:15, flow rate = 0.6 mL /min, λ = 254 nm, t_R = 31.6 min (minor) and t_R= 45.5 min (major). *ee* = 90%. Specific rotation $[\alpha]_D^{25}$ = +30.2 (c = 1.0, $CHCl_3$).

(*R*)-5-(1-(4-fluorophenyl)-3-oxobutyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4d)



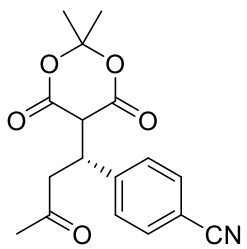
Compound **4d** prepared following the General procedure. Obtained as colorless viscous oil in 79% yield (253 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.01 – 6.90 (m, 2H), 4.28 – 4.19 (m, 2H), 3.67 (dd, *J* = 18.7, 10.1 Hz, 1H), 3.02 (dd, *J* = 18.7, 5.2 Hz, 1H), 2.18 (s, 3H), 1.68 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 165.4, 165.1, 162.3(d, *J* = 246.7 Hz), 135.5 (d, *J* = 3.3 Hz), 130.8(d, *J* = 8.0 Hz), 115.7(d, *J* = 21.2 Hz), 105.4, 49.2, 45.7, 38.8, 30.5, 28.2, 27.8; FT IR cm^{-1} (neat) 1738.77, 1605.52, 1510.81, 1382.83, 1298.79, 1220.66, 1165.29, 1095.72, 1058.69, 1012.34, 903.27, 830.79, 737.08, 634.04; HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{17}FO_5$-H [M - H]$^-$ 307.0992, found 307.0985. The enantiomeric excess was determined by HPLC analysis using Chiralpak IC, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL /min, λ = 254 nm, t_R = 20.9 min (minor) and t_R= 29.1 min (major). *ee* = 99%. Specific rotation $[\alpha]_D^{25}$ = +37.5 (c = 2.0, $CHCl_3$).

(*R*)-5-(1-(4-chlorophenyl)-3-oxobutyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4e)



Compound **4e** prepared following the General procedure. Obtained as colorless viscous oil in 78% yield (264 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.29 – 7.26 (m, 2H), 4.29 – 4.24 (m, 2H), 3.67 (dd, *J* = 18.7, 10.0 Hz, 1H), 3.07 – 2.85 (m, 1H), 2.12 (s, 3H), 1.71 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 165.3, 165.0, 138.3, 133.8, 130.5, 129.0, 105.4, 49.1, 45.5, 38.9, 30.5, 28.3, 27.8; FT IR cm^{-1} (neat) 2924.55, 1705.79, 1491.83, 1414.43, 1363.97, 1246.07, 1164.48, 1093.52, 1014.27, 825.59, 730.64; HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{17}ClO_5$-H [M - H]$^-$ 323.0687, found 323.0671. The enantiomeric excess was determined by HPLC analysis using Chiralpak IC, *n*-hexane /*i*-PrOH = 90:10, flow rate = 0.5 mL /min, λ = 210 nm, t_R = 23.9 min (minor) and t_R= 26.9 min (major). *ee* = 99%. Specific rotation $[\alpha]_D^{25}$ = +29.0 (c = 2.0, $CHCl_3$).

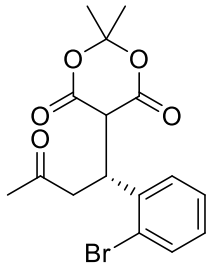
(*R*)-4-(1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-oxobutyl)benzonitrile (4f)



Compound **4f** prepared following the General procedure. Obtained as white solid in 81% yield (266 mg); m.p. 102-109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.55 (m, 2H), 7.52 – 7.48 (m, 2H), 4.34 – 4.29 (m, 2H), 3.65 (dd, *J* = 18.7, 9.7 Hz, 1H), 3.10 – 3.03 (m, 1H), 2.20 (s, 3H), 1.72 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 165.0, 164.6, 145.2, 132.5, 130.1, 118.6, 111.8, 105.5, 48.9, 45.1, 39.0, 30.4, 28.3, 27.5; FT

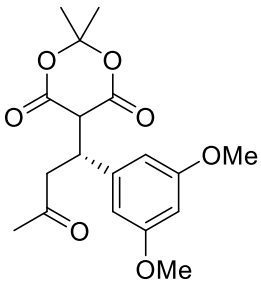
IR cm^{-1} (neat) 3515.94, 3058.64, 2232.30, 1712.45, 1612.94, 1416.92, 1365.07, 1244.75, 1164.59, 836.83; HRMS (ESI TOF) *m/z* calcd. For $C_{17}H_{17}NO_5$-H $[M - H]^-$ 314.1029, found 314.1024. The enantiomeric excess was determined by HPLC analysis using ChiralCel OX-H, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL /min, λ = 210 nm, t_R= 24.6 min (minor) and t_R= 34.3 min (major). *ee* = 93%. Specific rotation $[\alpha]_D^{25}$ = +29.2 (c = 2.0, $CHCl_3$).

(*R*)-5-(1-(2-bromophenyl)-3-oxobutyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4g)



Compound **4g** prepared following the General procedure. Obtained as colorless viscous oil in 79% yield (304 mg). ^{1}H NMR (400 MHz, CDCl3) δ 7.58 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.47 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.29 (td, *J* = 7.7, 1.4 Hz, 1H), 7.12 (td, *J* = 7.7, 1.7 Hz, 1H), 4.70 (dt, *J* = 7.8, 3.9 Hz, 1H), 4.16 (d, *J* = 3.3 Hz, 1H), 3.25 – 3.11 (m, 2H), 2.17 (s, 3H), 1.77 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 165.0, 164.1, 139.8, 133.4, 129.3, 129.0, 128.0, 124.8, 105.3, 48.7, 43.3, 37.5, 30.3, 28.6, 27.1; FT IR cm^{-1} (neat) 2925.77, 2857.46, 1710.27, 1421.29, 1364.37, 1264.11, 1167.01, 1023.67, 733.76, 701.60; HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{17}BrO_5$-H $[M - H]^-$ 367.0181, found 367.0179. The enantiomeric excess was determined by HPLC analysis using Chiralpak IC, *n*-heptane /*i*-PrOH = 85:15, flow rate = 0.5 mL /min, λ = 254 nm, t_R = 25.3 min (minor) and t_R= 29.5 min (major). *ee* = 96%. Specific rotation $[\alpha]_D^{25}$ = +10.5 (c = 2.0, $CHCl_3$).

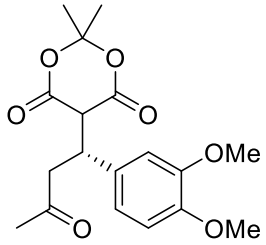
(*R*)-5-(1-(3,5-dimethoxyphenyl)-3-oxobutyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4h)



Compound **4h** prepared following the General procedure. Obtained as white solid in 91% yield (332 mg); m.p. 121-125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (d, *J* = 2.2 Hz, 2H), 6.33 (t, *J* = 2.2 Hz, 1H), 4.18 (ddd, *J* = 10.2, 5.1, 3.4 Hz, 1H), 4.13 (d, *J* = 3.4 Hz, 1H), 3.74 (s, 6H), 3.64 (dd, *J* = 18.6, 10.3 Hz, 1H), 3.02 (dd, *J* = 18.6, 5.2 Hz, 1H), 2.18 (s, 3H), 1.66 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1 , 165.6, 165.3, 161.1, 142.3, 106.9, 105.4, 100.0, 55.5, 49.0, 45.6, 40.0, 30.4, 28.3, 28.0; FT IR cm^{-1} (neat) 2930.54, 2846.95, 1739.87, 1599.17, 1463.50, 1432.86, 1352.94. 1293.76, 1203.53, 1156.47, 1060.02, 993.45, 932.30, 894.50, 840.75, 733.03, 699.11; HRMS (ESI TOF) *m/z* calcd. For $C_{18}H_{22}O_7$+Na $[M + Na]^+$ 373.1263, found 373.1264. The enantiomeric excess was determined by HPLC analysis using ChiralCel OX-

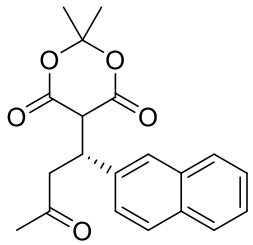
H, *n*-heptane /*i*-PrOH = 80:20, flow rate = 0.5 mL /min, λ = 254 nm, t_R = 21.2 min (minor) and t_R= 22.6 min (major). *ee* = 95%. Specific rotation $[\alpha]_D^{25}$ = +33.4 (c = 1.0, $CHCl_3$).

(*R*)-5-(1-(3,4-dimethoxyphenyl)-3-oxobutyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4i)



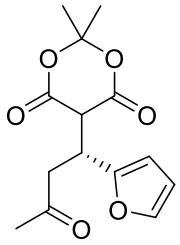
Compound **4i** prepared following the General procedure. Obtained as white solid in 48 % yield (175 mg); m.p. 121-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 – 6.79 (m, 2H), 6.73 (d, *J* = 8.8 Hz, 1H), 4.39 – 4.06 (m, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.64 (dd, *J* = 18.6, 9.9 Hz, 1H), 3.02 (dd, *J* = 18.7, 9.4 Hz, 1H), 2.16 (s, 3H), 1.63 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 165.6, 165.3, 148.9, 148.5, 132.1, 120.9, 112.1, 111.2, 105.2, 55.9, 55.8, 49.2, 45.7, 39.4, 30.3, 28.1, 27.9; FT IR cm^{-1} (neat) 2925.54, 2853.85, 1723.96, 1595.47, 1515.17, 1458.01, 1372.86, 1251.32, 1146.78, 1069.36, 1023.33, 870.69, 812.16, 734.83, 698.71, 633.94; HRMS (ESI TOF) *m/z* calcd. For $C_{18}H_{22}O_7$+Na [M + Na]$^+$ 373.1263, found 373.1268. The enantiomeric excess was determined by HPLC analysis using Chiralpak IC, *n*-hexane /*i*-PrOH = 70:30, flow rate = 0.9 mL /min, λ = 254 nm, t_R= 50.1 min (major). *ee* = >99%. Specific rotation $[\alpha]_D^{25}$ = +35.8 (c = 1.0, $CHCl_3$).

(*R*)-2,2-dimethyl-5-(1-(naphthalen-2-yl)-3-oxobutyl)-1,3-dioxane-4,6-dione (4j)



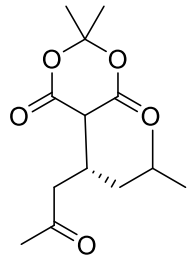
Compound **4j** prepared following the General procedure. Obtained as white solid in 75% yield (266 mg); m.p. 104-109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.72 (m, 4H), 7.52 – 7.43 (m, 3H), 4.44 (ddd, *J* = 10.3, 5.1, 3.5 Hz, 1H), 4.29 (d, *J* = 3.4 Hz, 1H), 3.82 (dd, *J* = 18.6, 10.4 Hz, 1H), 3.13 (dd, *J* = 18.6, 5.2 Hz, 1H), 2.22 (s, 3H), 1.67 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 165.6, 165.2, 137.3, 133.4, 132.8, 128.6, 128.1, 128.0, 127.6, 126.8, 126.3, 126.2, 105.3, 49.1, 45.6, 39.6, 30.5, 28.2, 27.9; FT IR cm^{-1} (neat) 2924.05, 2857.17, 1716.17, 1363.61, 1296.17, 1202.46, 1163.75, 818.81, 745.53; HRMS (ESI TOF) *m/z* calcd. For $C_{20}H20O_5$+Na [M + Na]$^+$ 363.1208, found 363.1216. The enantiomeric excess was determined by HPLC analysis using Chiralpak IC, *n*-hexane /*i*-PrOH = 85:15, flow rate = 1.0 mL /min, λ = 254 nm, t_R = 22.5 min (minor) and t_R= 27.8 min (major). *ee* = 83%. Specific rotation $[\alpha]_D^{25}$ = +40.2 (c = 1.0, $CHCl_3$).

(*R*)-5-(1-(furan-2-yl)-3-oxobutyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4k)



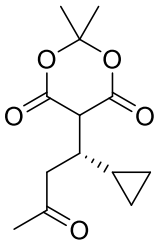
Compound **4k** prepared following the General procedure. Obtained as white solid in 65% yield (189 mg); m.p. 103-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.28 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.11 (dt, *J* = 3.3, 0.8 Hz, 1H), 4.39 (ddd, *J* = 5.3, 4.6, 3.2 Hz, 1H), 4.27 (d, *J* = 3.2 Hz, 1H), 3.52 (dd, *J* = 18.7, 9.8 Hz, 1H), 3.14 (dd, *J* = 18.7, 5.4 Hz, 1H), 2.22 (s, 3H), 1.74 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 164.9, 164.9, 153.1, 141.8, 110.7, 107.1, 105.3, 47.2, 43.8, 33.4, 30.4, 28.3, 27.6; FT IR cm-1 (neat) 3002.91, 2885.76, 1780.39, 1744.37, 1715.10, 1505.31, 1387.87, 1297.20, 1203.40, 1066.17, 1012.92, 930.26, 897.92, 814.54, 742.60, 633.06; HRMS (ESI TOF) *m/z* calcd. For $C_{14}H_{16}O_6$-H [M - H]$^-$ 279.0869, found 279.0883. The enantiomeric excess was determined by HPLC analysis using Chiralpak IC, *n*-hexane /*i*-PrOH = 85:15, flow rate = 0.5 mL /min, λ = 210 nm, t_R = 38.4 min (minor) and t_R= 66.6 min (major). *ee* = 77%. Specific rotation $[\alpha]_D^{25}$ = -3.4 (c = 1.0, $CHCl_3$).

(*R*)-2,2-dimethyl-5-(2-methyl-6-oxoheptan-4-yl)-1,3-dioxane-4,6-dione (4l)



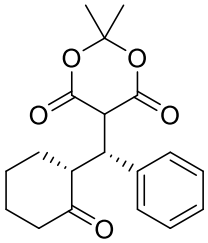
Compound **4l** prepared following the General procedure. Obtained as colorless viscous oil in 51% yield (143 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (d, *J* = 2.6 Hz, 1H), 3.10 – 2.98 (m, 2H), 2.72 (dd, *J* = 17.6, 3.6 Hz, 1H), 2.16 (s, 3H), 1.75 (d, *J* = 1.7 Hz, 6H), 1.63 – 1.51 (m, 1H), 1.51 – 1.39 (m, 1H), 1.11 (ddd, *J* = 13.3, 9.1, 4.0 Hz, 1H), 0.91 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 165.5, 165.3, 104.9, 48.0, 44.1, 40.7, 31.1, 30.6, 28.4, 27.1, 25.6, 23.6, 21.6; FT IR cm-1 (neat) 2957.14, 2875.07, 1737.89, 1462.64, 1382.03, 1297.45, 1203.67, 1070.14, 993.79, 940.23, 886.51, 735.79, 694.06, 635.32; HRMS (ESI TOF) *m/z* calcd. For $C_{14}H_{22}O_5$+Na [M + Na]$^+$ 293.1364, found 293.1368. The enantiomeric excess was determined by HPLC analysis using Chiralpak IC, *n*-hexane/*i*-PrOH = 85:20, flow rate = 0.5 mL /min, λ = 210 nm, t_R = 13.4 min (minor) and t_R= 18.5 min (major). *ee* = 60%. Specific rotation $[\alpha]_D^{25}$ = -10.5 (c = 1.0, $CHCl_3$).

(*S*)-5-(1-cyclopropyl-3-oxobutyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4m)



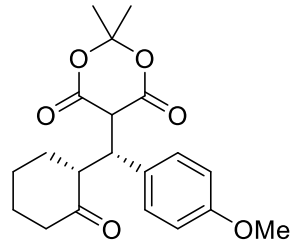
Compound **4m** prepared following the General procedure. Obtained as white solid in 55% yield (146 mg); m.p. 60-62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (t, *J* = 2.1 Hz, 1H), 3.16 – 3.08 (m, 1H), 2.87 (ddd, *J* = 17.9, 4.9, 1.2 Hz, 1H), 2.25 – 2.17 (m, 1H), 2.16 (d, *J* = 2.1 Hz, 3H), 1.77 (s, 3H), 1.75 (s, 3H), 1.15 – 0.95 (m, 1H), 0.56 – 0.48 (m, 1H), 0.47 – 0.40 (m, 1H), 0.39 – 0.29 (m, 1H), 0.27 – 0.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9, 165.7, 165.6, 105.0, 48.4, 45.3, 39.2, 30.6, 28.3, 27.6, 14.4, 5.0, 4.6; FT IR cm-1 (neat) 2925.10, 2859.96, 1741.96, 1459.54, 1384.86, 1301.19, 1205.69, 1068.51, 1019.79; HRMS (ESI TOF) *m/z* calcd. For $C_{13}H_{18}O_5$-H [M - H]$^-$ 253.1076, found 253.1073. The enantiomeric excess was determined by HPLC analysis using ChiralCel OX-H, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL /min, λ = 210 nm, t_R = 40.4 min (minor) and t_R= 44.9 min (major). *ee* = 73%. Specific rotation $[\alpha]_D^{25}$ = -10.2 (c = 1.0, $CHCl_3$).

2,2-dimethyl-5-((*R*)-((*R*)-2-oxocyclohexyl)(phenyl)methyl)-1,3-dioxane-4,6-dione (4n)



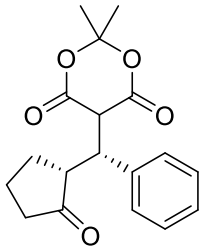
Compound **4n** prepared following the General procedure. Obtained as white solid in 51% yield (175 mg); m.p. 100-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.13 (m, 5H), 4.61 (d, *J* = 2.3 Hz, 1H), 3.87 (dd, *J* = 11.1, 3.1 Hz, 1H), 3.69 (td, *J* = 11.9, 4.9 Hz, 1H), 2.60 – 2.35 (m, 2H), 2.16 – 2.07 (m, 1H), 1.86 – 1.76 (m, 2H), 1.76 – 1.68 (m, 1H), 1.65 (s, 3H), 1.63 – 1.55 (m, 1H), 1.38 (s, 3H), 1.25 – 1.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.9, 166.2, 165.7, 139.8, 129.4, 129.0, 127.8, 105.1, 51.2, 49.1, 45.4, 42.9, 34.2, 28.9, 28.2, 28.0, 25.5; FT IR cm-1 (neat) 2926.24, 2859.02, 1709.74, 1452.04, 1385.03, 1286.14, 1204.96, 1026.05, 971.27, 934.88, 758.75, 702.90; HRMS (ESI TOF) *m/z* calcd. For $C_{19}H_{12}O_5$-H [M - H]$^-$ 329.1389, found 329.1392. The enantiomeric excess was determined by HPLC analysis using Chiralpak IE, *n*-hexane /*i*-PrOH = 85:15, flow rate = 1.0 mL /min, λ = 210 nm, t_R = 18.5 min (major) and t_R= 23.3 min (minor). *ee* = 90%. Specific rotation $[\alpha]_D^{25}$ = +13.5 (c = 0.5, $CHCl_3$).

5-((*R*)-(4-methoxyphenyl)((*R*)-2-oxocyclohexyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4o)



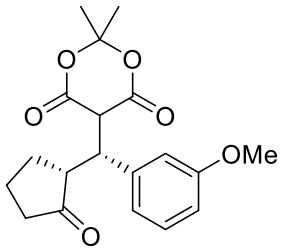
Compound **4o** prepared following the General procedure. Obtained as colorless viscous oil in 31% yield (116 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 12.2 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.65 (d, *J* = 3.1 Hz, 1H), 3.84 – 3.78 (m, 1H), 3.77 (s, 3H), 3.75 – 3.56 (m, 2H), 2.58 – 2.31 (m, 3H), 2.16 – 2.07 (m, 1H), 1.90 – 1.70 (m, 2H), 1.65 (s, 3H), 1.39 (s, 3H), 1.17 (dt, *J* = 12.7, 10.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.0, 166.3, 165.8, 159.1, 131.5, 130.6, 114.3, 105.1, 55.4, 51.4, 49.2, 44.7, 43.0, 34.2, 29.0, 28.3, 28.0, 25.6; FT IR cm-1 (neat) 2939.98, 2862.25, 1737.87, 1703.27, 1612.73, 1512.06, 1451.04, 1386.82, 1295.43, 1246.85, 1208.08, 1183.11, 1125.80, 1075.89, 1030.46, 894.37, 832.44, 733.38; HRMS (ESI TOF) *m/z* calcd. For $C_{20}H_{24}O_6$-H [M -H]$^-$ 359.1495, found 359.1498. The enantiomeric excess was determined by HPLC analysis using ChiralCel OX-H, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL /min, λ = 254 nm, t_R = 34.9 min (major) and t_R= 38.2 min (minor). *ee* = 93%. Specific rotation $[\alpha]_D^{25}$ =+7.8(c=1.0, $CHCl_3$)

2,2-dimethyl-5-((*R*)-((*R*)-2-oxocyclopentyl)(phenyl)methyl)-1,3-dioxane-4,6-dione (4p)



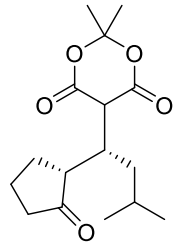
Compound **4p** prepared following the General procedure. Obtained as white solid in 49% yield (161 mg); m.p. 96-100 °C; ^{1}H NMR (400 MHz, CDCl3) δ 7.47 – 7.37 (m, 2H), 7.36 – 7.21 (m, 3H), 4.62 (s, 1H), 3.85 (dd, *J* = 11.6, 2.3 Hz, 1H), 3.46 (tdd, *J* = 11.7, 7.8, 1.4 Hz, 1H), 2.52 – 2.33 (m, 1H), 2.25 (ddd, *J* = 19.2, 11.0, 8.6 Hz, 1H), 2.03 – 1.87 (m, 2H), 1.82 – 1.72 (m, 1H), 1.72 (s, 3H), 1.53 (s, 3H), 1.50 – 1.34 (m, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 221.6, 165.7, 165.3, 140.4, 129.4, 128.9, 127.8, 105.2, 49.2, 47.5, 45.1, 39.3, 30.7, 28.4, 27.6, 20.1; FT IR cm^{-1} (neat) 2924.76, 2857.50, 1725.68, 1454.70, 1387.76, 1307.95, 1205.15, 1165.22, 1081.22, 736.95, 702.89; HRMS (ESI TOF) *m/z* calcd. For $C_{18}H_{20}O_5$-H [M - H]$^-$ 315.1233, found 315.1219. The enantiomeric excess was determined by HPLC analysis using Chiralpak IC, *n*-heptane /*i*-PrOH = 85:15, flow rate = 0.5 mL /min, λ = 254 nm, t_R = 21.3 min (major) and t_R= 40.1 min (minor). *ee* = 86%. Specific rotation $[\alpha]_D^{25}$ = +83.7 (c = 2.0, $CHCl_3$).

5-((*R*)-(3-methoxyphenyl)((*R*)-2-oxocyclopentyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4q)



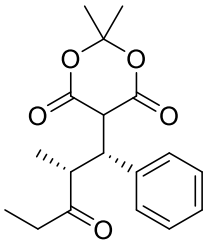
Compound **4q** prepared following the General procedure. Obtained as white solid in 43% yield(155 mg); m.p. 137-143 °C; ^{1}H NMR (400 MHz, CDCl3) δ 7.22 (t, *J* = 7.9 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 2H), 6.88 – 6.67 (m, 1H), 4.54 (s, 1H), 3.87 – 3.78 (m, 1H), 3.79 (s, 3H), 3.43 (td, *J* = 11.6, 7.9 Hz, 1H), 2.40 (dd, *J* = 19.1, 8.4 Hz, 1H), 2.33 – 2.10 (m, 1H), 2.06 – 1.88 (m, 2H), 1.82 – 1.74 (m, 1H), 1.72 (s, 3H), 1.57 (s, 3H), 1.45 (qd, *J* = 11.7, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.4, 165.7, 165.2, 159.9, 142.1, 129.8, 121.6, 114.9, 113.2, 105.1, 55.3, 49.2, 47.5, 45.0, 39.2, 30.7, 28.4, 27.5, 20.1; FT IR cm^{-1} (neat) 2927.65, 1776.84, 1737.11, 1600.19, 1489.75, 1456.47, 1388.06, 1304.65, 1207.51, 1159.77, 1049.65, 1009.48, 763.32; HRMS (ESI TOF) *m/z* calcd. For $C_{19}H_{22}O_6$-H [M - H]$^-$ 345.1338, found 345.1334. The enantiomeric excess was determined by HPLC analysis using Chiralpak IC, *n*-heptane /*i*-PrOH = 90:10, flow rate = 1.0 mL /min, λ = 254 nm, t_R = 21.6 min (major) and t_R= 45.1 min (minor). *ee* = 83%. Specific rotation $[\alpha]_D^{25}$ = +82.5 (c = 2.0, $CHCl_3$).

2,2-dimethyl-5-((*R*)-3-methyl-1-((*R*)-2-oxocyclopentyl)butyl)-1,3-dioxane-4,6-dione (4r)



Compound **4r** prepared following the General procedure. Obtained as white solid in 52% yield (160 mg); m.p. 109-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (d, *J* = 1.6 Hz, 1H), 2.66 (tdd, *J* = 10.1, 4.0, 1.7 Hz, 1H), 2.52 (dddd, *J* = 10.8, 9.7, 7.9, 1.4 Hz, 1H), 2.37 (dddt, *J* = 12.0, 8.1, 6.0, 1.8 Hz, 1H), 2.32 – 2.21 (m, 1H), 2.15 (ddd, *J* = 18.7, 10.7, 8.6 Hz, 1H), 2.08 – 1.98 (m, 1H), 1.83 (s, 3H), 1.78 (s, 3H), 1.77 – 1.66 (m, 2H), 1.65 – 1.60 (m, 1H), 1.60 – 1.53 (m, 1H), 1.35 (ddd, *J* = 13.8, 9.7, 4.0 Hz, 1H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.8, 166.3, 165.0, 105.0, 48.4, 45.7, 42.3, 39.4, 36.7, 30.7, 28.5, 27.3, 25.5, 23.7, 21.8, 20.6; FT IR cm^{-1} (neat) 2956.94, 2870.27, 1776.75, 1736.97, 1462.30, 1385.67, 1311.05, 1207.78, 1161.57, 1071.16, 1013.46, 884.94; HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{24}O_5$-H [M - H]$^-$ 295.1546, found 295.1541. The enantiomeric excess was determined by HPLC analysis using Chiralcel OX-H, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL /min, λ = 254 nm, t_R = 16.7 min (major) and t_R= 23.4 min (minor). *ee* = 49%%. Specific rotation $[\alpha]_D^{25}$ = +19.6 (c = 2.0, $CHCl_3$).

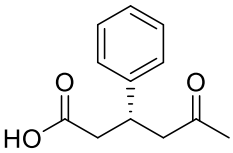
2,2-dimethyl-5-((1*R*,2*R*)-2-methyl-3-oxo-1-phenylpentyl)-1,3-dioxane-4,6-dione (4s)



Compound **4s** prepared following the General procedure. Obtained as colorless viscous oil in 47% yield (156 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.13 (m, 5H), 4.09 (d, *J* = 3.7 Hz, 1H), 3.93 – 3.72 (m, 2H), 2.89 – 2.56 (m, 2H), 1.58 (s, 3H), 1.16 (s, 3H), 1.08 (t, *J* = 7.3 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.9, 166.0, 165.5, 138.4, 129.4, 129.0, 128.0, 105.5, 48.1, 47.6, 47.3, 34.8, 28.4, 28.1, 17.3, 7.8; FT IR cm^{-1} (neat) 2923.37, 2855.65, 1703.03, 1455.15, 1412.66, 1382.16, 1316.67, 1283.97, 1207.78, 934.97, 759.35, 705.41; HRMS (ESI TOF) *m/z* calcd. For $C_{18}H_{22}O_5$-H [M - H]$^-$ 317.1389, found 317.1383. The enantiomeric excess was determined by HPLC analysis using ChiralCel OX-H, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL /min, λ = 254 nm, t_R = 25.4 min (minor) and t_R=28.6 min (major). *ee* = 86%. Specific rotation $[\alpha]_D^{25}$ = +13.2 (c = 0.5, $CHCl_3$).

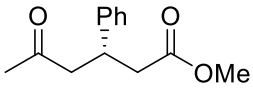
Application of the Protocol: Synthesis of *δ*-keto acid, ester and amide

(*R*)-5-oxo-3-phenylhexanoic acid (7)



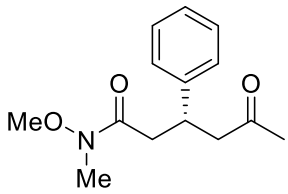
To a solution of **4a** (100 mg, 0.34 mmol) in DMF (20 mL), H_2O (2.5 mL) was added and the reaction mixture was stirred at 100°C for 12 h. Then DMF was evaporated on rotary evaporator at 60 ^{o}C. Further the crude product was extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (30% EtOAc in pet ether) to afford compound **7** as a white solid with 85% yield (60 mg); m.p. 87 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dt, *J* = 7.9, 2.6 Hz, 2H), 7.23 – 7.14 (m, 3H), 3.64 (p, *J* = 7.2 Hz, 1H), 2.82 – 2.74 (m, 2H), 2.66 (m, 7.4 Hz, 2H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 177.8, 142.9, 128.8, 127.4, 127.1, 49.4, 40.4, 37.0, 30.5. FTIR cm^{-1} (neat) 3029.02, 2924.99, 1706.55, 1494.80, 1411.67, 1362.86, 1266.94, 1228.92, 1157.05, 1082.24, 1021.31, 913.74, 844.33, 761.38, 700.90; HRMS (ESI TOF) *m/z* calcd. For $C_{12}H_{14}O_3$ + Na [M + Na]$^+$ 229.0835, found 229.0833. Specific rotation $[\alpha]_D^{25}$ = +1.0 (c = 0.5, $CHCl_3$).

Methyl (*S*)-5-oxo-3-phenylhexanoate (8)



To a solution of **7** (100 mg, 0.49 mmol) in Methanol (50 mL), conc. H_2SO_4 (2 drops) was added and the reaction mixture was stirred at 100°C for 1 h. Then after completion of the reaction, methanol was evaporated on rotary evaporator. Further the crude product was dissolved in 50 ml EtOAc and washed with water. The organic layer was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (15% EtOAc in pet ether) to afford compound **8d** as viscous oil in 95 % yield (101 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 7.23 – 7.17 (m, 3H), 3.68 (p, *J* = 7.3 Hz, 1H), 3.58 (s, 3H), 2.84 – 2.80 (m, 2H), 2.64 (qd, *J* = 15.3, 7.4 Hz, 2H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.9, 172.3, 143.1, 128.7, 127.3, 126.9, 51.7, 49.4, 40.7, 37.4, 30.5; HRMS (ESI TOF) *m/z* calcd. For $C_{13}H_{16}O_3$ + Na $[M + Na]^+$ 243.0992, found 243.0989. The enantiomeric excess was determined by HPLC analysis using Chiralpak IC, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL /min, λ = 254 nm, t_R = 27.2 min (major) and t_R= 32.5 min (minor). *ee* = 92%. Specific rotation $[\alpha]_D^{25}$ = +6.6 (c = 1.0, $CHCl_3$).

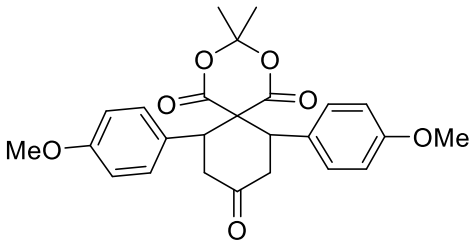
(*R*)-*N*-methoxy-*N*-methyl-5-oxo-3-phenylhexanamide (10)



To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride salt (100.8 mg, 1.03 mmol, 3 equiv.) in a dry sealed tube, compound **4a** (100 mg, 0.34 mmol, 1equiv.) dissolved in DMF (10 mL) was added followed by Hünig's base (360 µL, 2.04 mmol, 6 equiv.). The reaction mixture was heated to 110 ^{o}C for 16 h. After completion of reaction, the reaction mixture was cooled to room temperature and transferred to round bottom flask. Then DMF was evaporated on rotary evaporator at 60 ^{o}C under reduced pressure. The reaction mixture was dissolved in 20 mL EtOAc and washed with 1M HCl (20 mL) followed by brine solution (20 X 3). The organic layer was dried over Na_2SO_4. The product was purified by column chromatography (EtOAc in pet ether 45:55) to afford compound **10** colorless viscous liquid with 45% yield (39 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.27 – 7.23 (m, 2H), 7.23 – 7.17 (m, 1H), 3.76 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.59 (s, 3H), 3.12 (s, 3H), 2.94 (dd, *J* = 16.4, 6.6 Hz, 1H), 2.85 – 2.66 (m, 3H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5, 172.6, 143.9, 128.7, 127.5, 126.8, 61.3, 49.6, 38.6, 37.1, 32.2, 30.4; FTIR cm^{-1} 2929.82, 2312.38, 1712.41, , 651.53, 1543.92, 1451.79, 1420.95, 1380.91, 1284.54, 1190.83,

997.76, 935.00, 759.14, 701.56; HRMS (ESI TOF) *m/z* calcd. For $C_{14}H_{19}NO_3$ + Na [M + Na]$^+$ 272.1262, found 272.1263. The enantiomeric excess was determined by HPLC analysis using Chiralpak IC, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL /min, λ = 210 nm, t_R = 37.8 min (major) and t_R= 44.8 min (minor). *ee* = 95%. Specific rotation $[\alpha]_D^{25}$ = +6.5 (c = 0.5, $CHCl_3$).

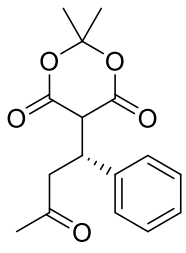
7,11-bis(4-methoxyphenyl)-3,3-dimethyl-2,4-dioxaspiro[5.5]undecane-1,5,9-trione (6b')



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.8 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 1H), 3.94 (dd, *J* = 14.4, 4.3 Hz, 1H), 3.76 (s, 2H), 3.65 (t, *J* = 14.7 Hz, 1H), 2.59 (dd, *J* = 14.9, 4.3 Hz, 1H), 0.64 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1 , 168.6, 165.6, 159.8, 129.7, 129.4, 114.6, 106.5, 61.1, 55.5, 49.4, 43.3, 28.7. HRMS (ESI TOF) *m/z* calcd. For $C_{25}H_{26}O_7$ + Na [M + Na]$^+$ 461.1571, found 461.1575.

This side cycloaddition product **6b'**was obtained during the prolonged reaction of Meldrum's acid **1**, 4-methoxybenzaldehyde **2b** and acetone **3a**.

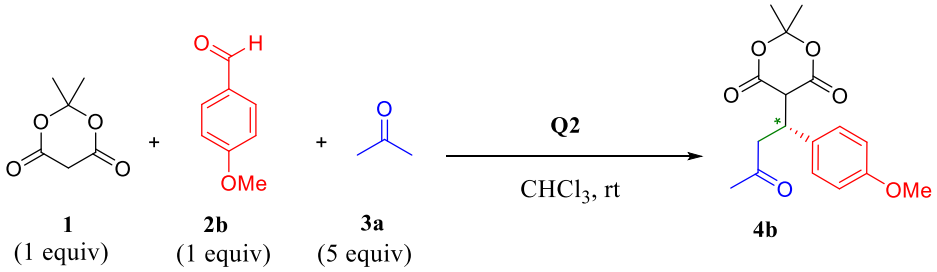
Gram Scale Synthesis of (*R*)-2,2-dimethyl-5-(3-oxo-1-phenylbutyl)-1,3-dioxane-4,6-dione (4a)



4a

For the gram scale synthesis general procedure described on page S3 was followed on a higher scale. Meldrum's acid (2.1 gm, 14.6 mmol, 1 equiv.), benzaldehyde (1.64 mL, 16.0 mmol, 1.1 equiv.), acetone (5.35 mL, 72.9 mmol, 5 equiv.), **Q2** (47.27 gm, 0.15 mmol, 1 mol%), TFA (22.3 µL, 0.29 mmol, 2 mol%). After completion of the reaction (Confirmed by TLC), product was purified by column chromatography (as slurry) without work up. The product was purified on silica gel using petroleum ether/ethyl acetate (70:30). Compound **4a** was obtained as a white solid in 74% yield (3.13 gm) without loss of enantioselectivity (95% *ee*).

HPLC chromatograms of product 4b at different time interval



1 (1 equiv) **2b** (1 equiv) **3a** (5 equiv) **4b**

In a vial equipped with a teflon-coated stir bar, 9-amino(9-deoxy)*epi*quinine **Q2** was dissolved in 2 mL of chloroform. After two fold addition of trifluoroacetic acid the reaction mixture was stirred for 15 minutes. Then Meldrum's acid **1** (1equiv.), 4-methoxy benzaldehyde **2b** (1.05 equiv.) and acetone **3a** (5 equiv.) were added subsequently and the reaction mixture was stirred. Then 200 mL of reaction mixture was taken out and directly loaded to the column chromatography at different time interval. The purified product **4b** was immediately submitted for the HPLC for determination of enantiomeric excess (page no. 88-91).

3.7 Appendix III: ^{1}H, ^{13}C and HPLC spectral data of representative compounds

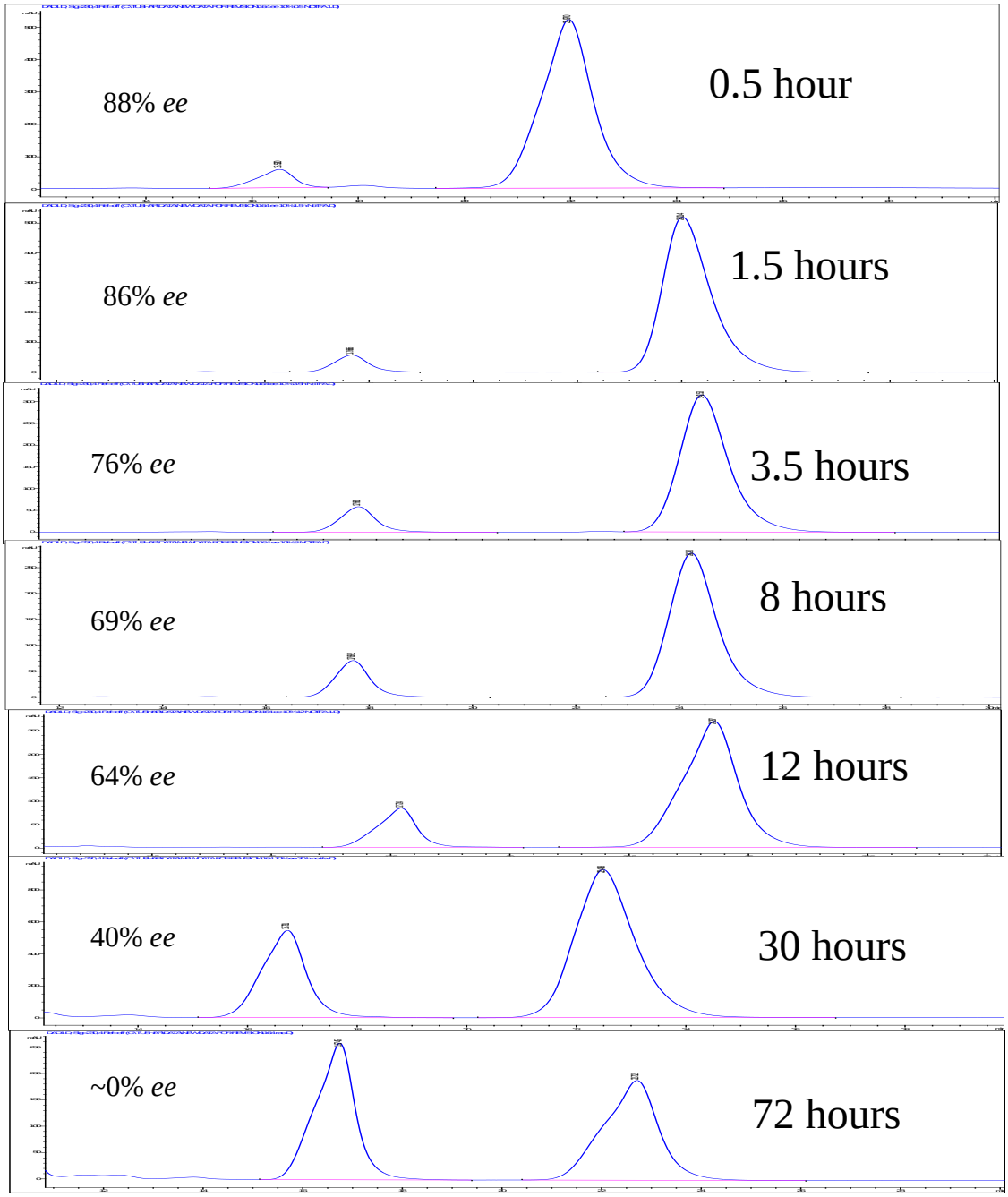


Figure AIII.1: HPLC chromatograms of product **4b** at different time interval (10 mol% **Q2**)

*Reaction performed using 10 mol% of primary amine catalyst **Q2,** Meldrum's acid **1** (1 equiv.), 4-methoxybenzaldehyde **2b** (1.05 equiv.) and acetone **3a** (5 equiv.) in chloroform (0.5M) at room temperature. The enantiomeric excess was determined by HPLC analysis using Chiralcel OX-H, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL /min, λ = 254 nm.

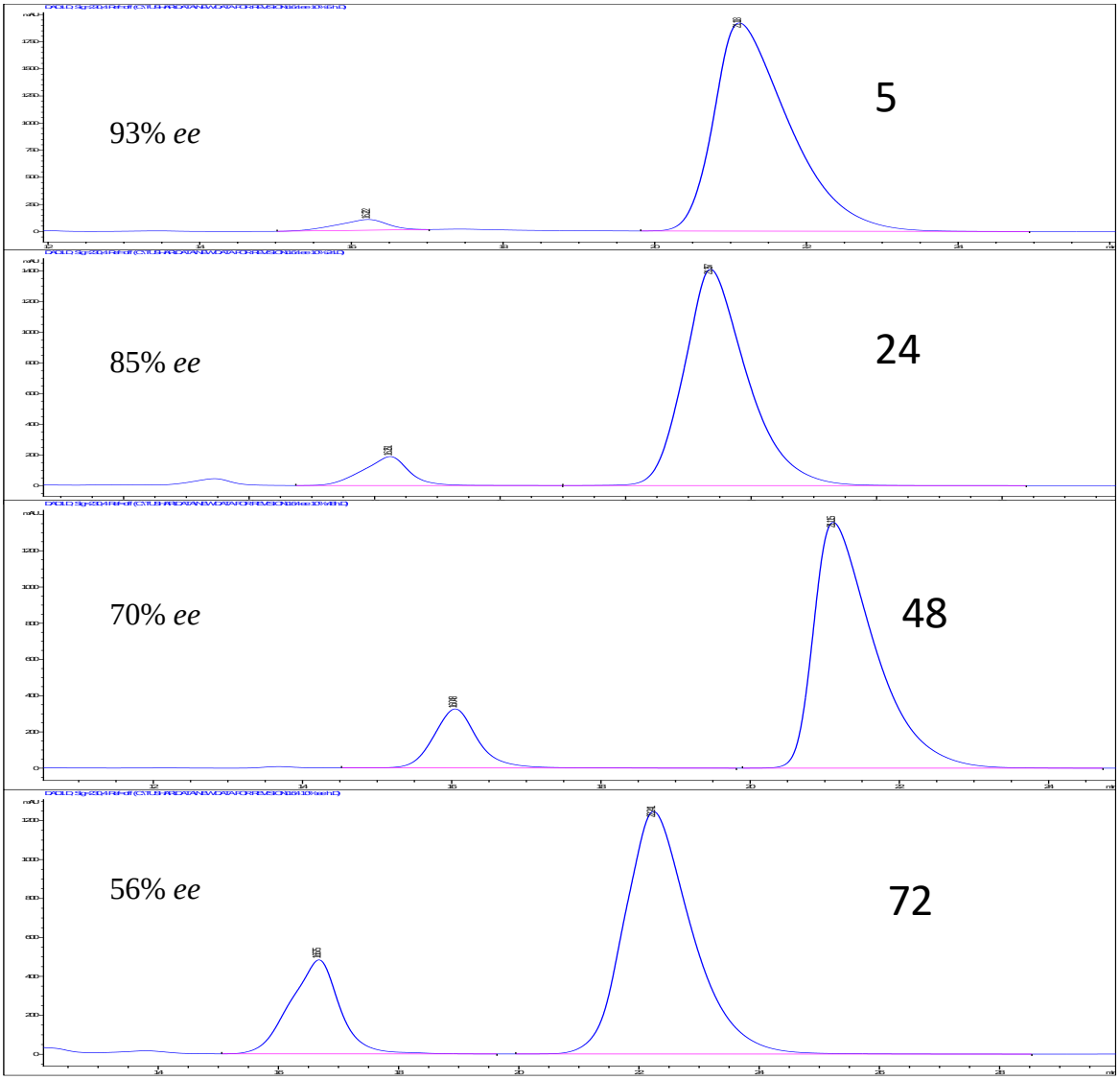


Figure AIII.2: HPLC chromatograms of product **4b** at different time interval (10 mol% **Q2** and 20 mol% TFA)

*Reaction performed using 10 mol% of primary amine catalyst **Q2**, 20 mol% TFA as additive, Meldrum's acid **1** (1 equiv.), benzaldehyde **2a** (1.05 equiv.) and acetone **3a** (5 equiv.) in chloroform(0.5 M) at room temperature. The enantiomeric excess was determined by HPLC analysis using Chiralcel OX-H, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL /min, $\lambda = 254$ nm.

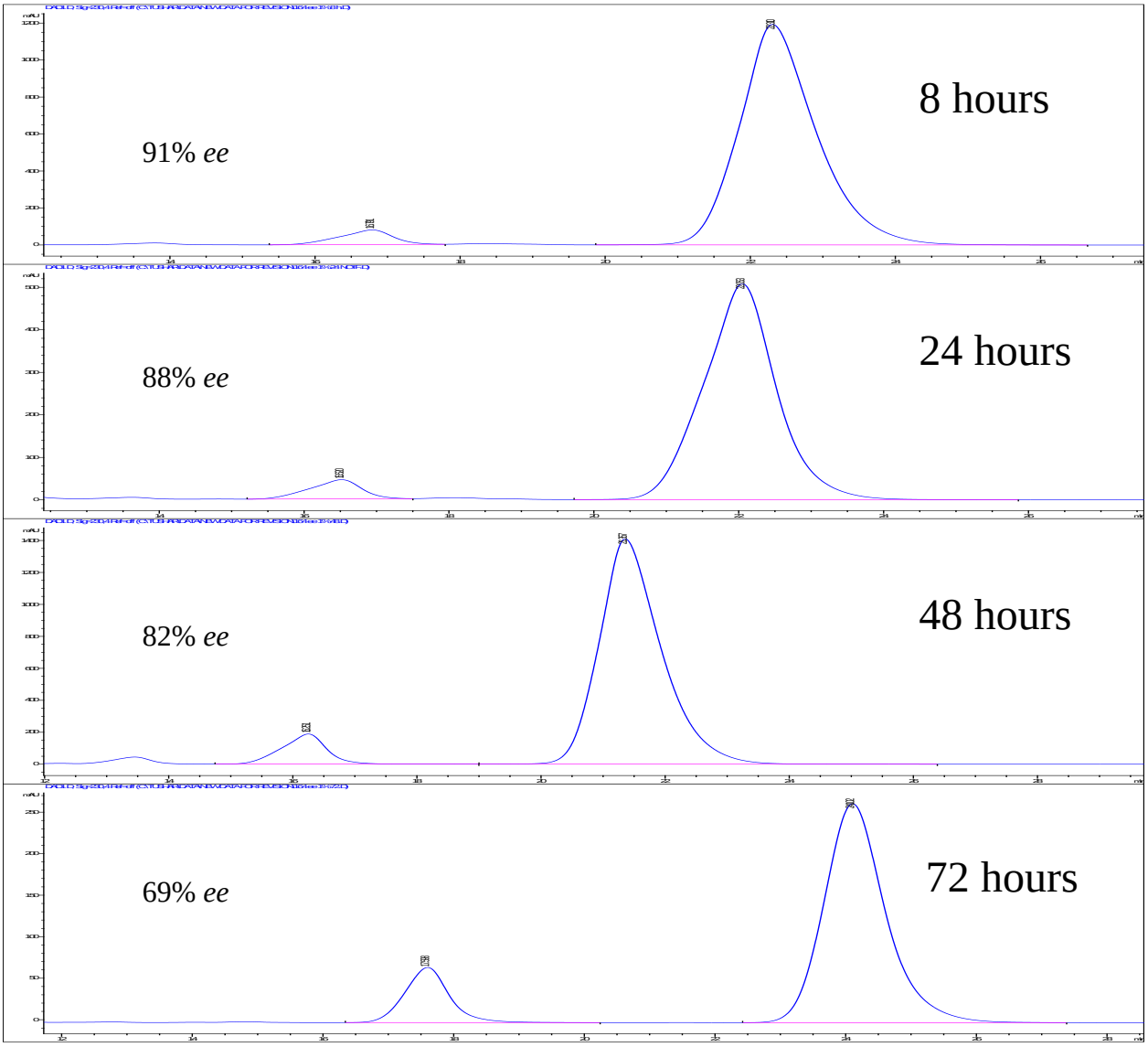


Figure AIII.3: HPLC chromatograms of product **4b** at different time interval (1 mol% **Q2**)

*Reaction performed using 1 mol% of primary amine catalyst **Q2,** Meldrum's acid **1** (1 equiv.), benzaldehyde **2a** (1.05 equiv.) and acetone **3a** (5 equiv.) in chloroform (0.5 M) at room temperature. The enantiomeric excess was determined by HPLC analysis using Chiralcel OX-H, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL /min, λ = 254 nm.

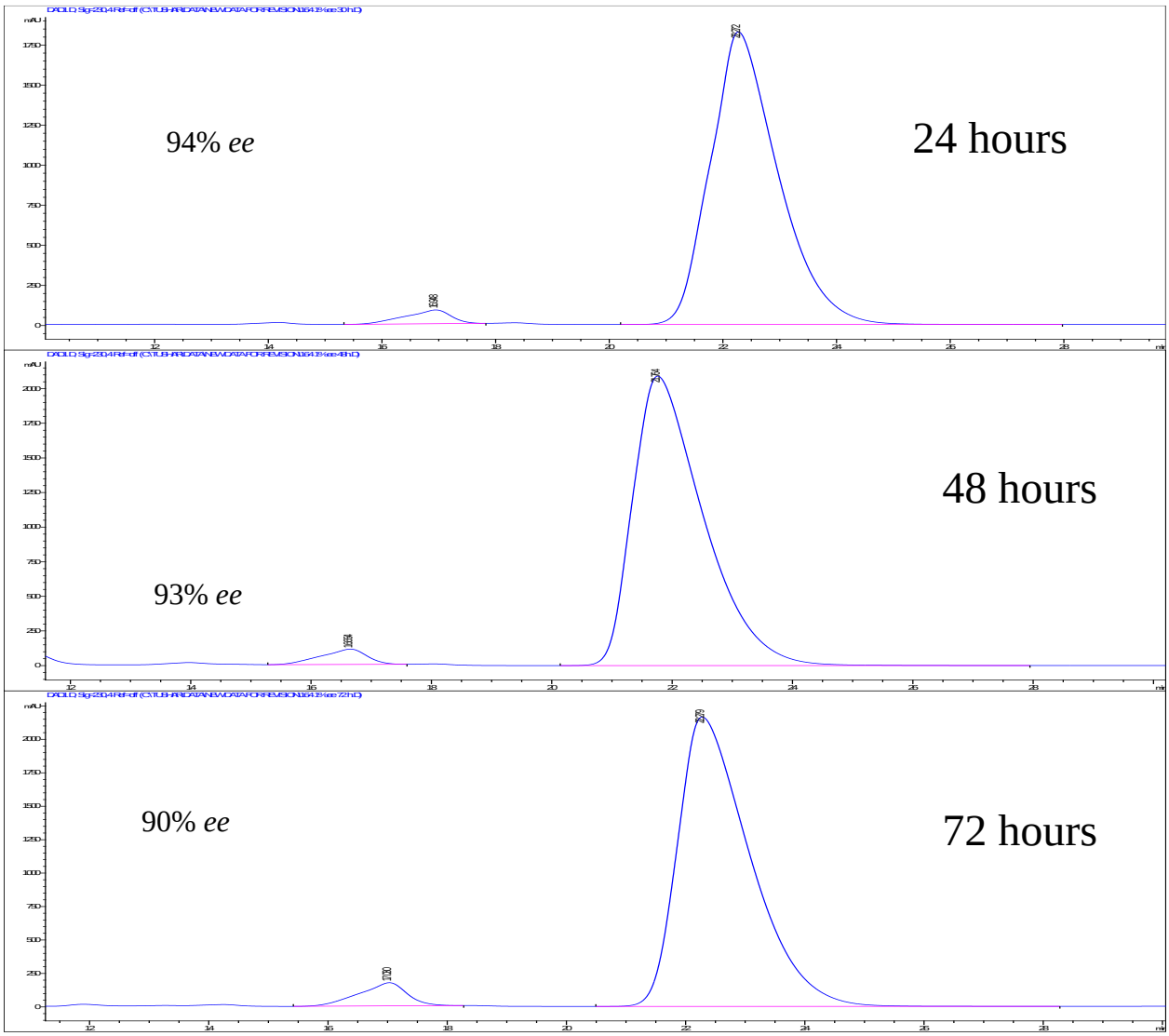


Figure AIII.4: HPLC chromatograms of product **4b** at different time interval (1 mol% **Q2** and 2 mol% TFA)

*Reaction performed using 1 mol% of primary amine catalyst **Q2**, 2 mol% TFA as additive, **Meldrum's** acid **1** (1 equiv.), benzaldehyde **2a** (1.05 equiv.) and acetone **3a** (5 equiv.) in chloroform (0.5 M) at room temperature. The enantiomeric excess was determined by HPLC analysis using Chiralcel OX-H, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL /min, λ = 254 nm.

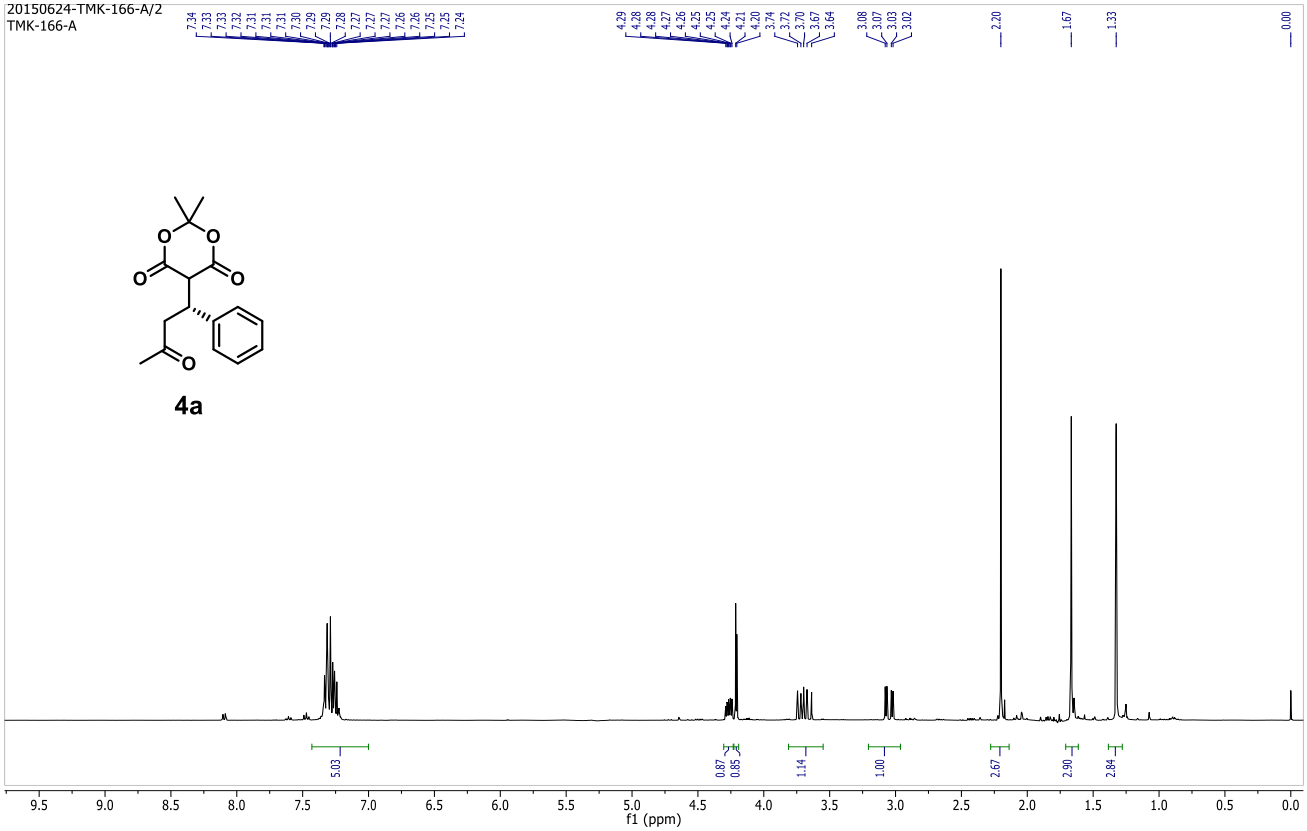


Figure AIII.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4a**

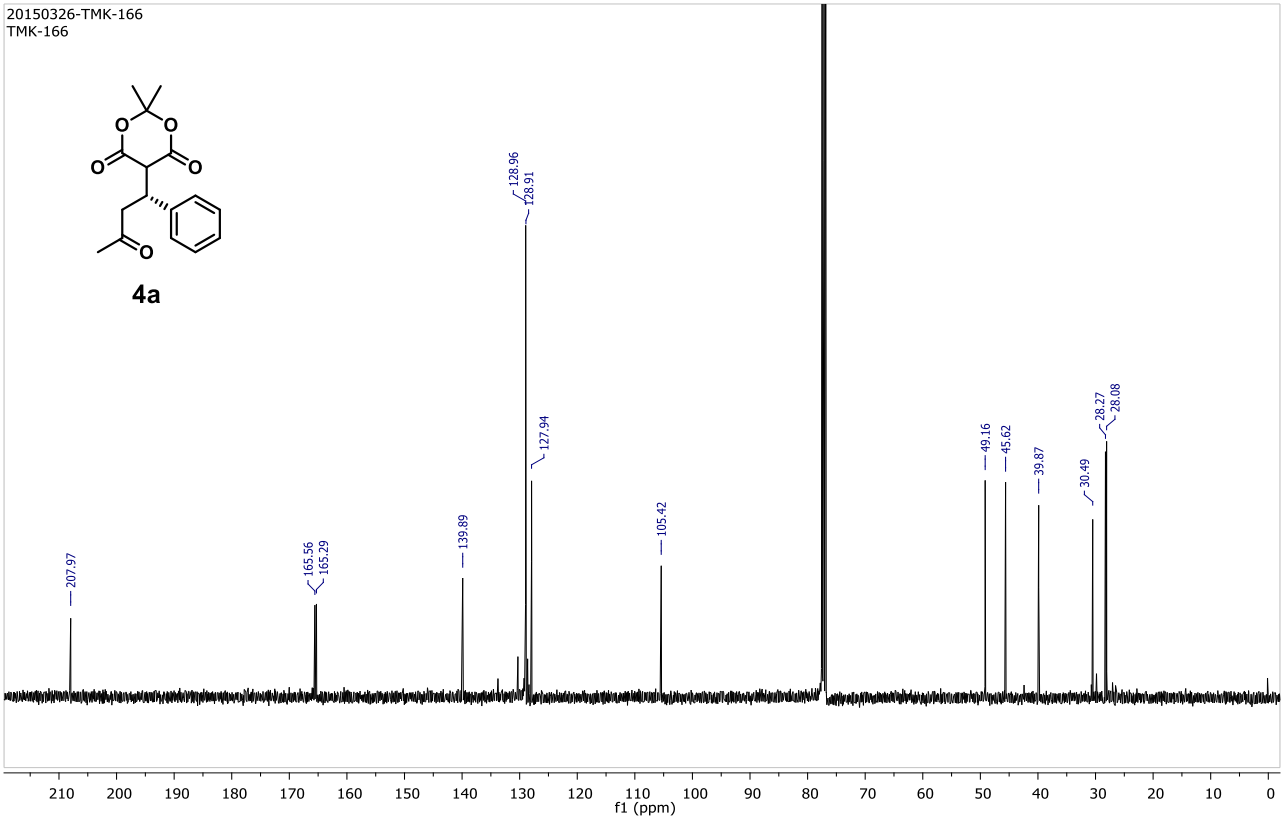
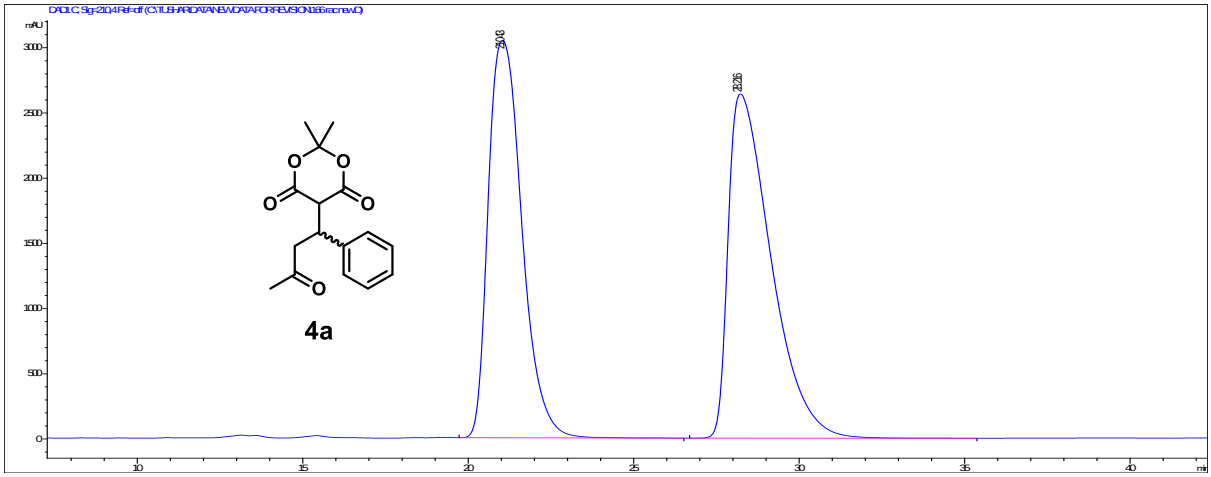
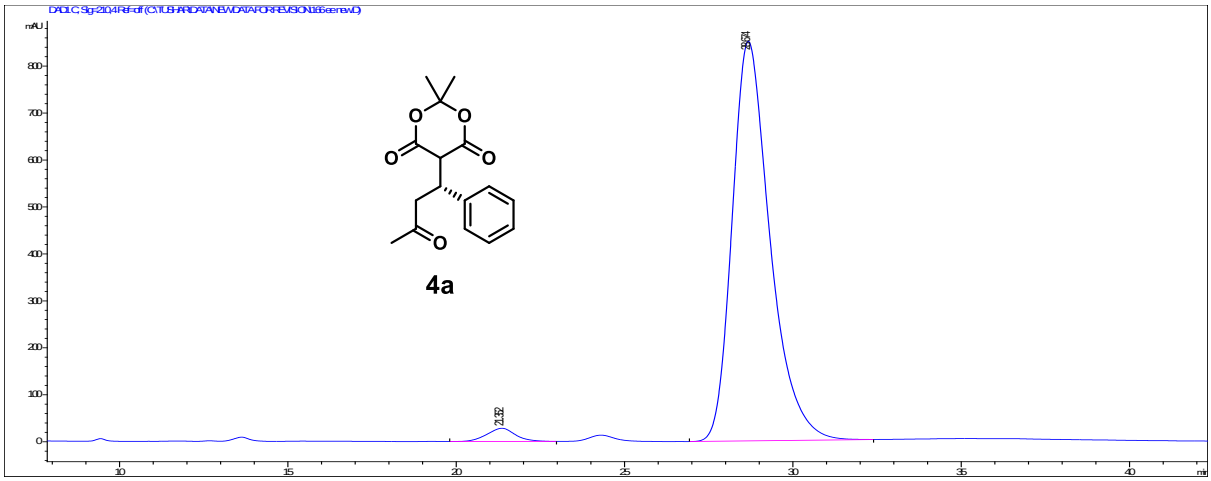


Figure AIII.6: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **4a**



Signal 1: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.335	MF	0.9632	1.06385e4	184.08440	50.9917
2	30.341	FM	1.6834	1.02247e4	101.23034	49.0083
Totals :				2.08632e4	285.31474	



Signal 1: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.441	MF	0.3307	859.55933	43.31715	2.5741
2	29.992	FM	1.4159	3.25337e4	382.95163	97.4259
Totals :				3.33933e4	426.26878	

Figure AIII.7: HPLC profile of compound **4a**

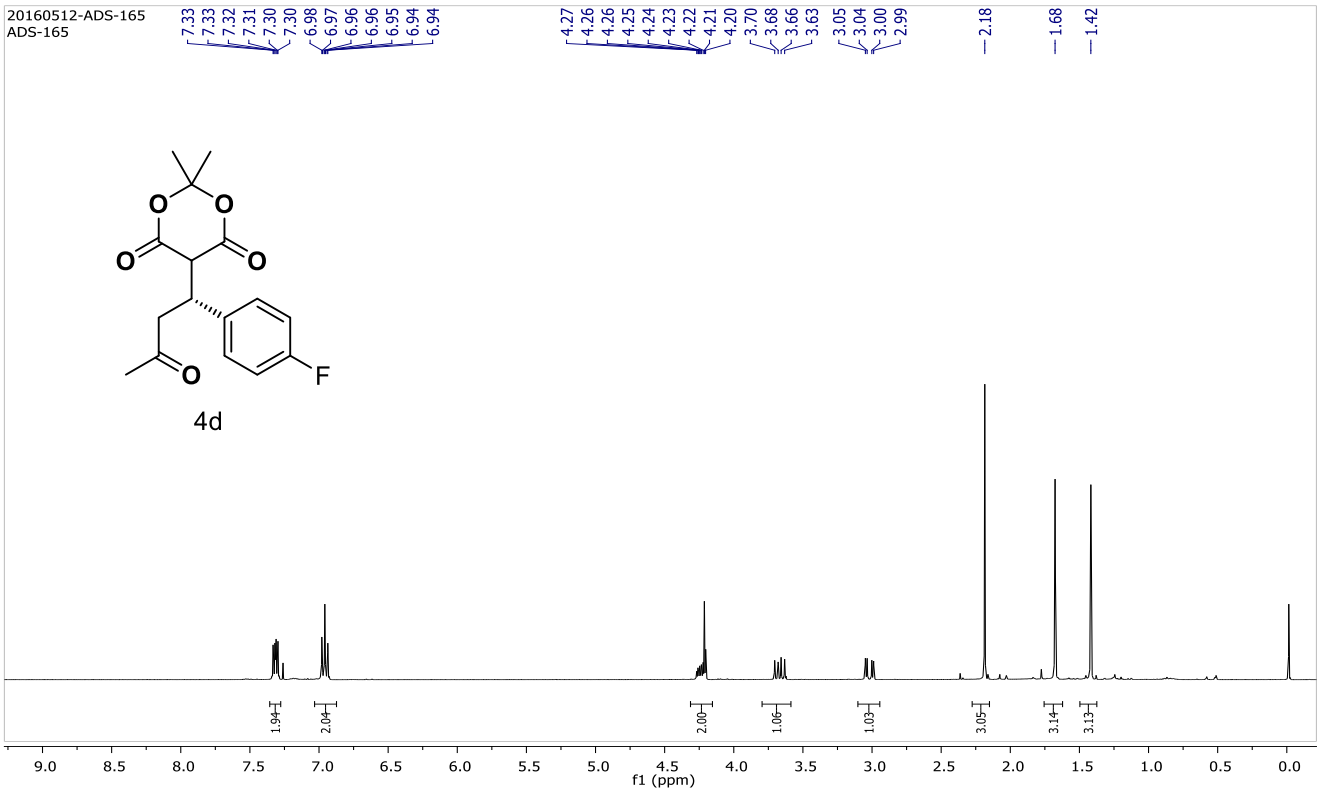


Figure AIII.8: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4d**

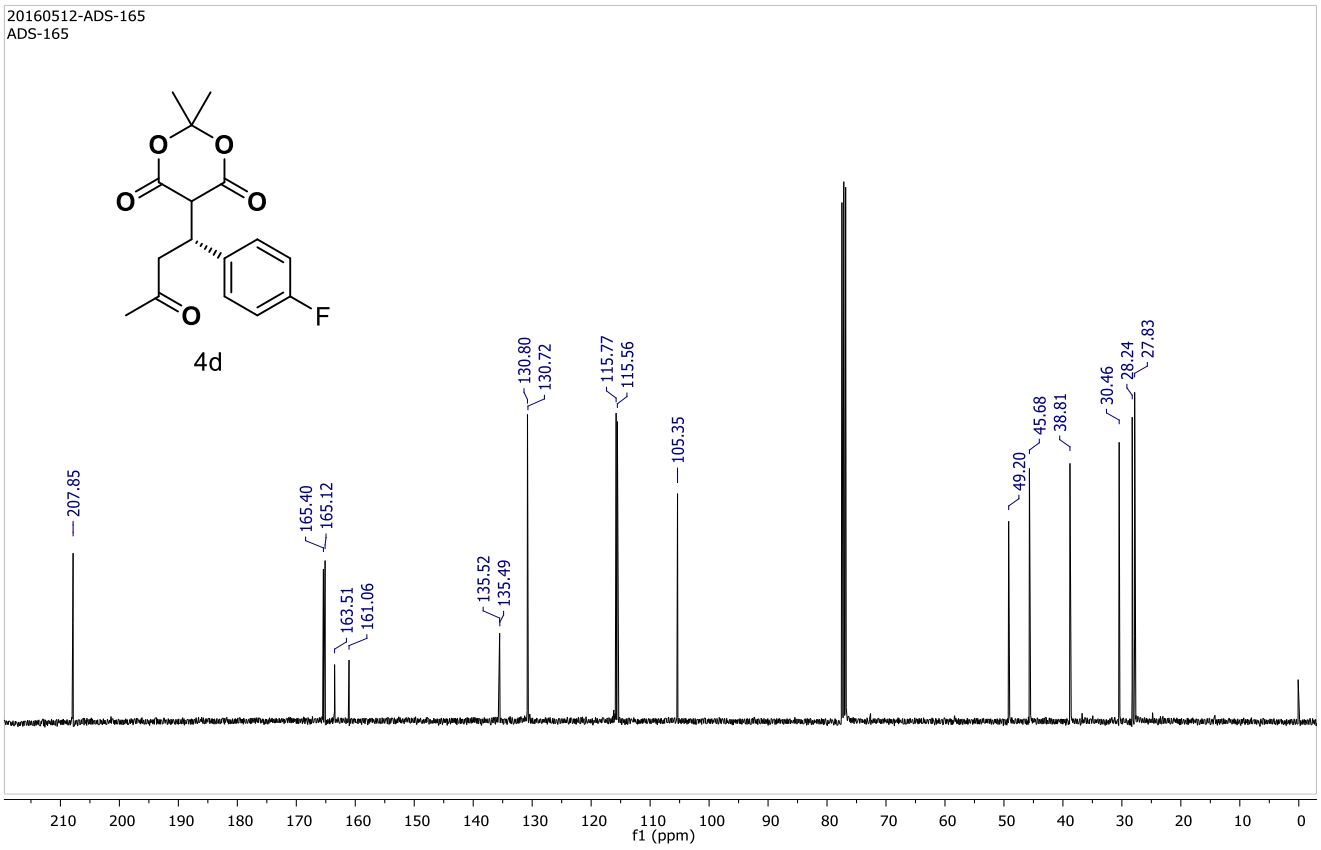
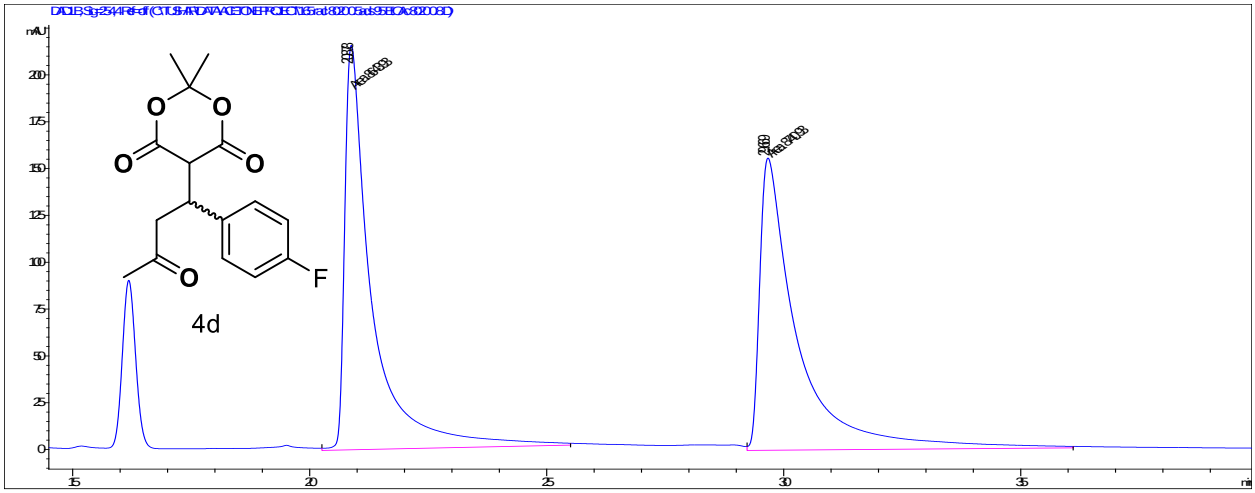
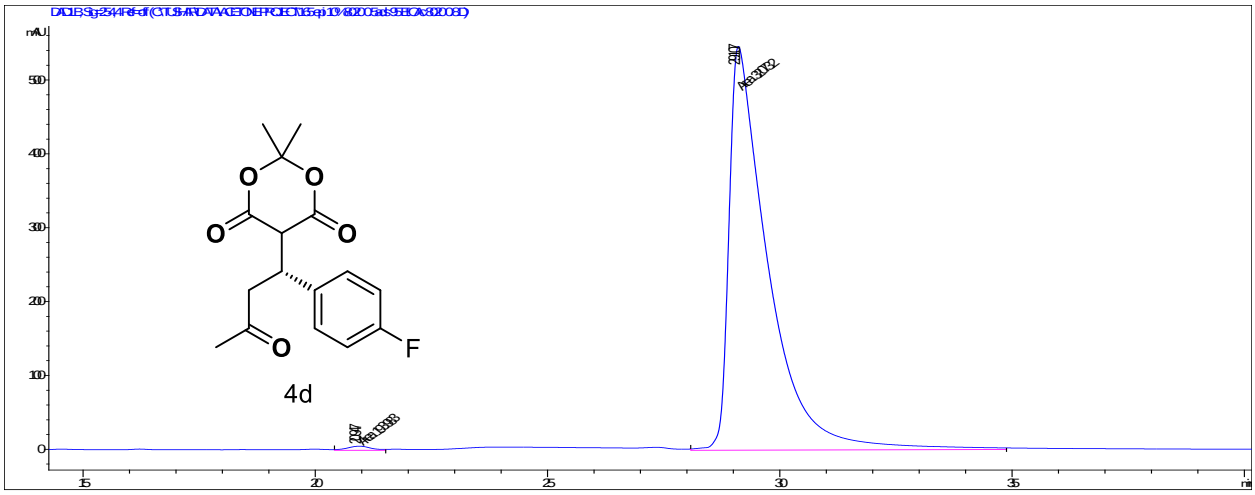


Figure AIII.9: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **4d**



Signal 1: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.878	MM	0.6668	8643.92871	216.04831	49.7210
2	29.669	MM	0.9336	8740.93359	156.05087	50.2790
Totals :				1.73849e4	372.09918	



Signal 1: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.947	MM	0.5878	193.98329	5.49984	0.6012
2	29.107	MM	0.9778	3.20732e4	546.68146	99.3988
Totals :				3.22672e4	552.18129	

Figure AIII.10: HPLC profile of compound **4d**

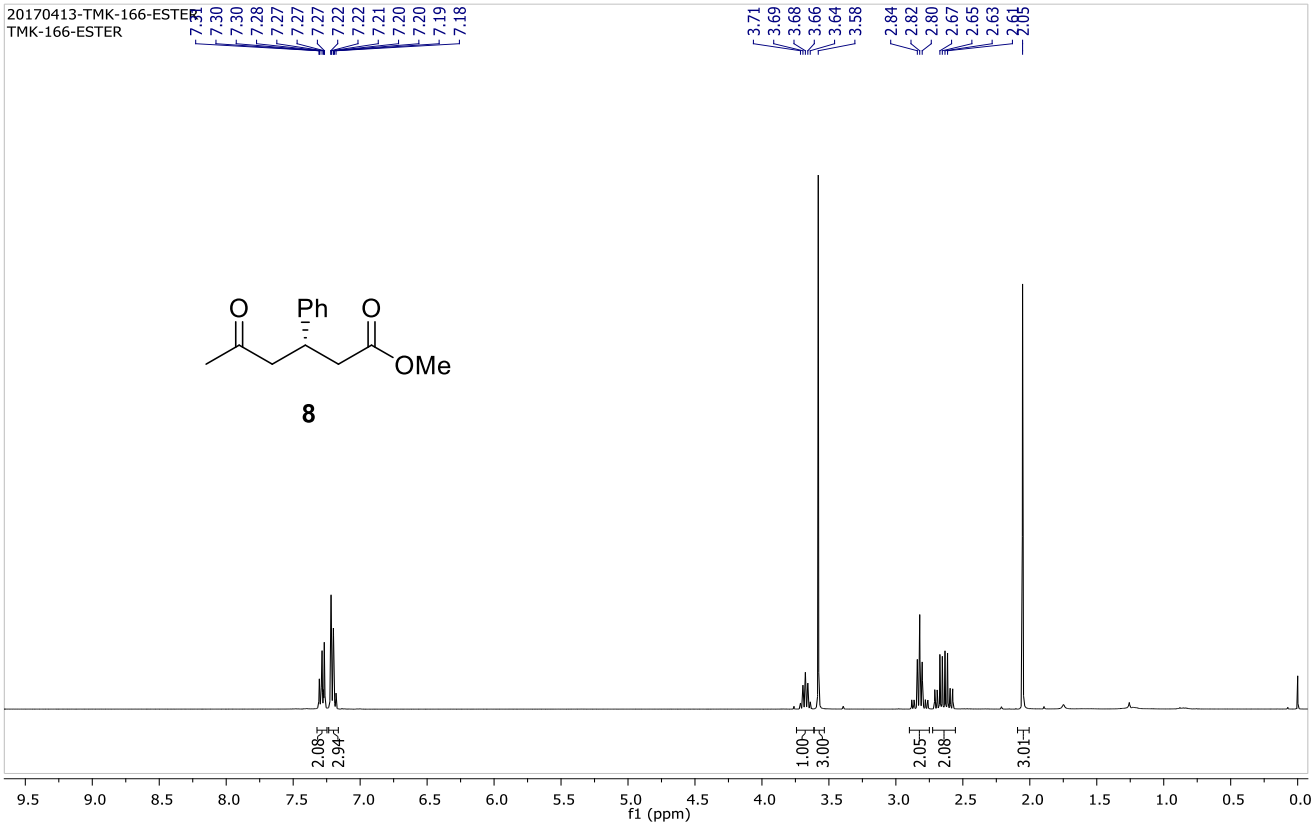


Figure AIII.11: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8**

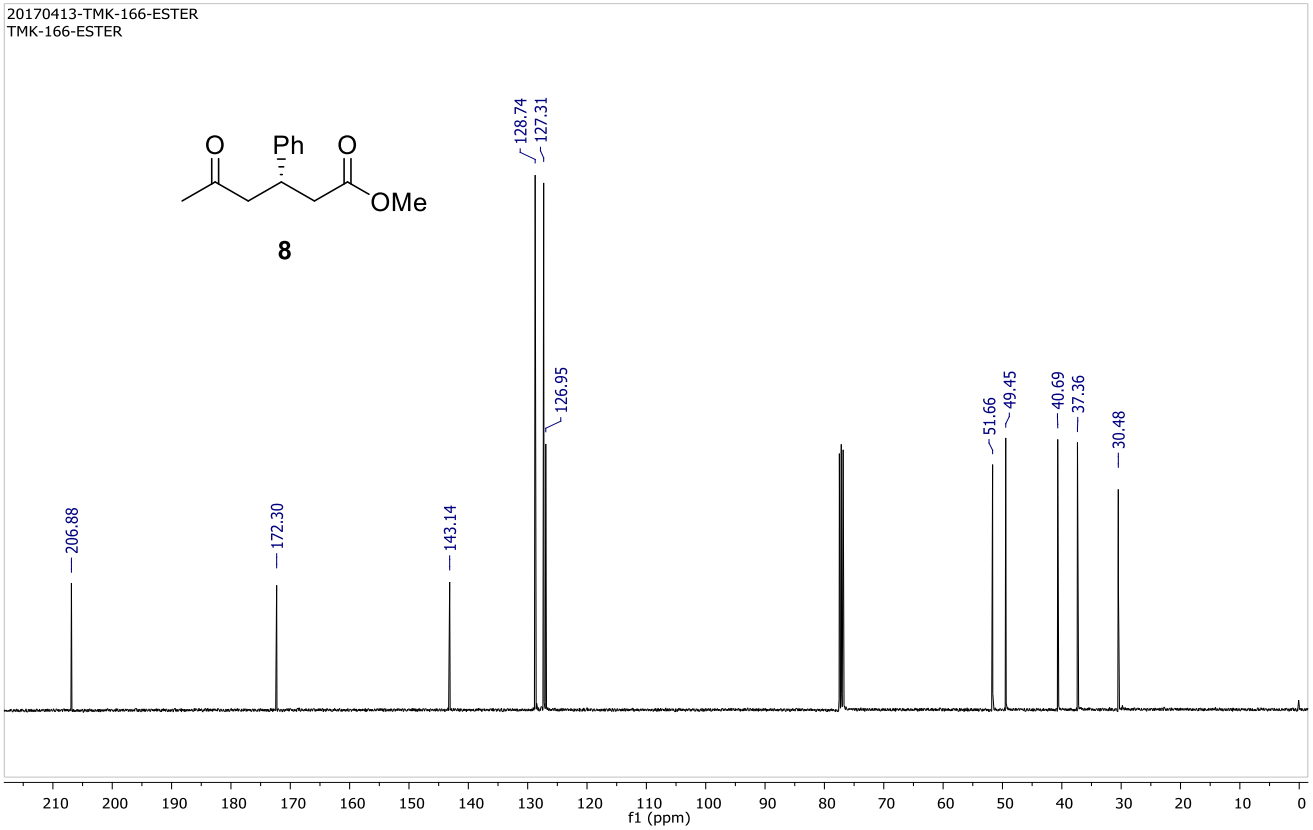
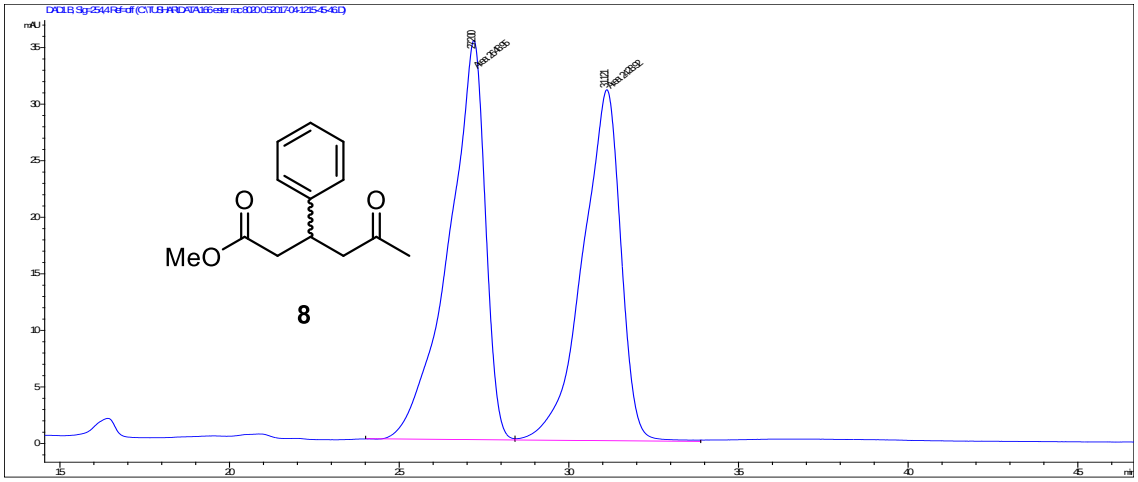
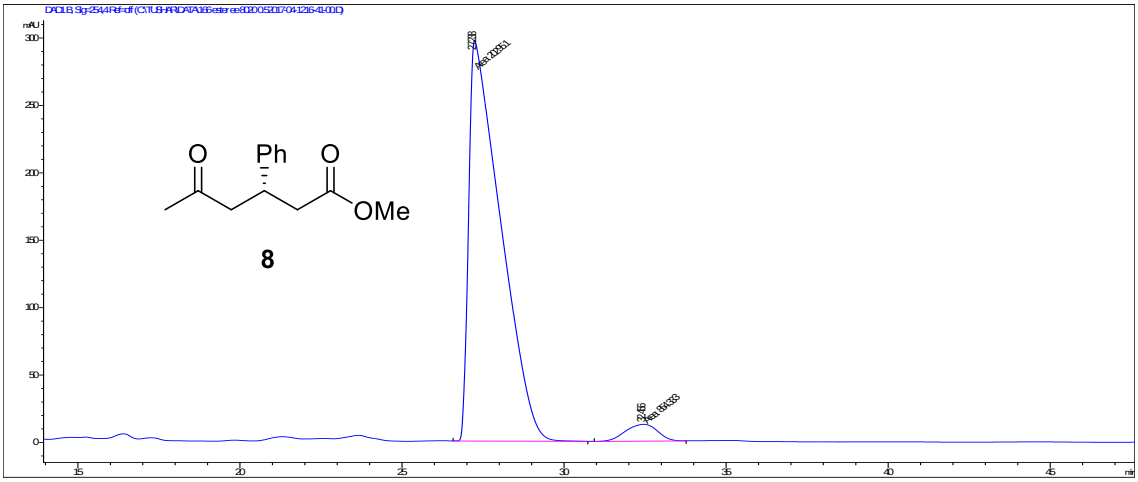


Figure AIII.12: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **8**



Signal 1: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.200	MF	1.2509	2648.95117	35.29356	52.1665
2	31.121	FM	1.3046	2428.92407	31.02913	47.8335
Totals :				5077.87524	66.32269	



Signal 1: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.238	MM	1.1389	2.02951e4	296.98654	95.9605
2	32.456	MM	1.1437	854.33252	12.45024	4.0395
Totals :				2.11494e4	309.43678	

Figure AIII.13: HPLC profile of compound **8**

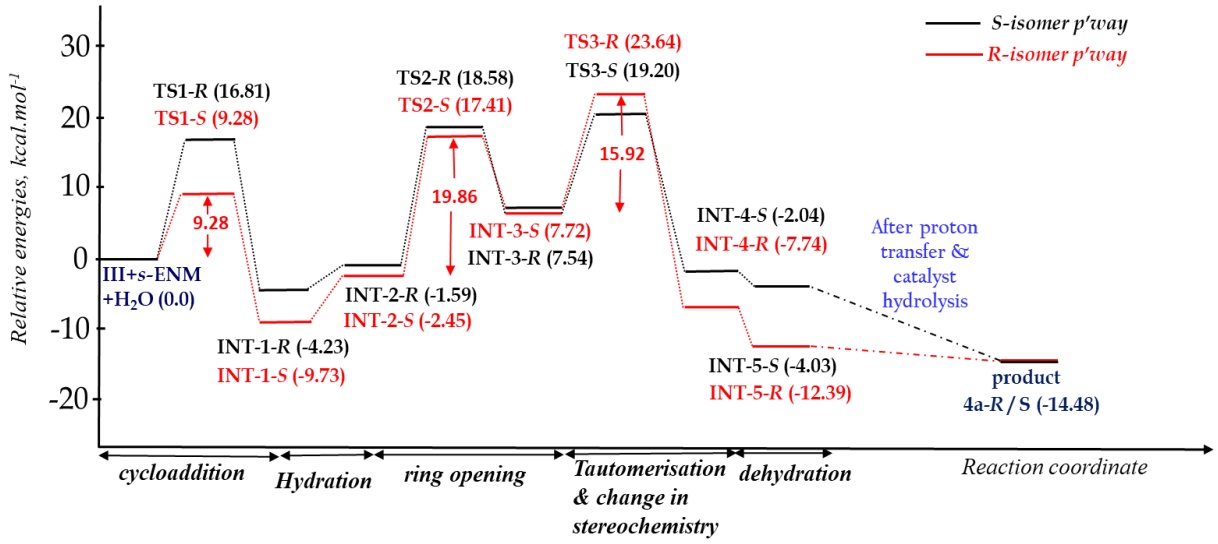
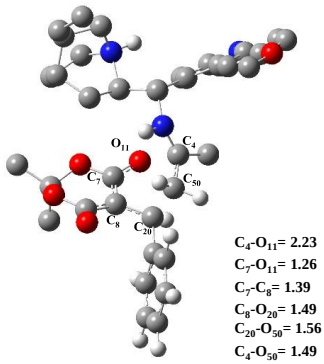
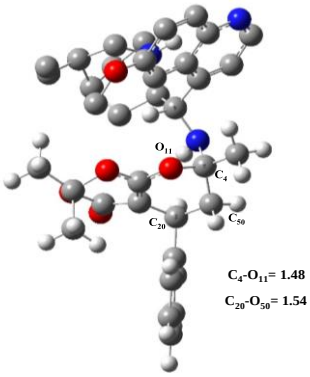


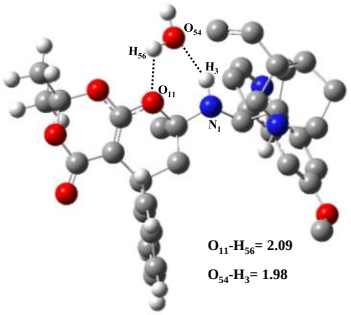
Figure AIII14: Relative energy profiles for the cycloaddition reaction between III and *s*-ENM for hydroxyester formation (values of ΔG are given in parentheses). *R*-product is generated along the red pathway. *S*-product is generated along the black pathway.



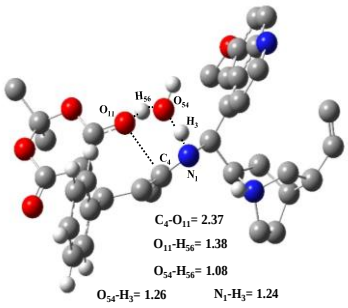
TS1-*S*



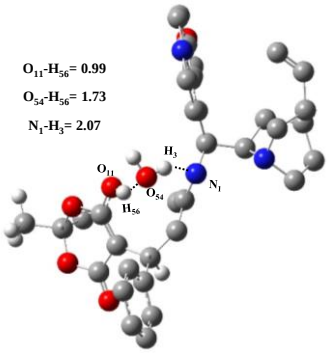
INT-1-*S*



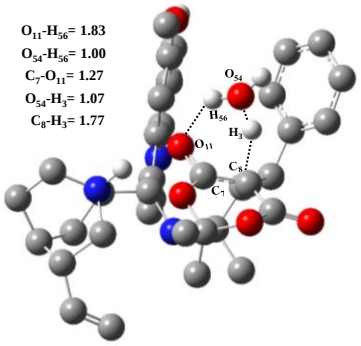
INT-2-*S*



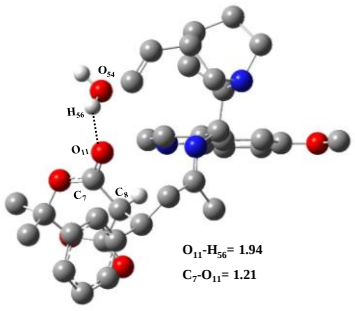
TS2-*S*



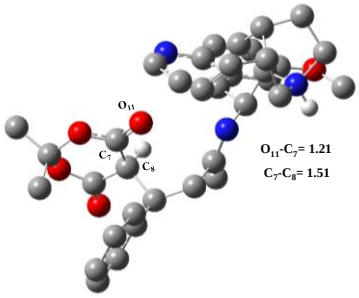
INT-3-*S*



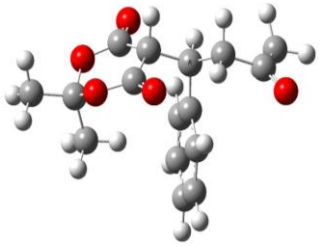
TS3-*R*



INT-4-*R*

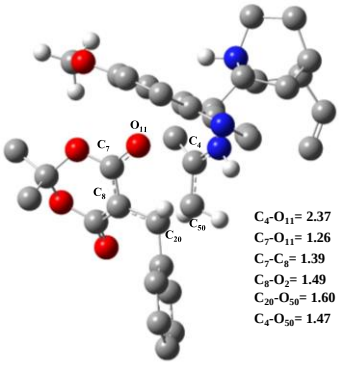


INT-5-*R*

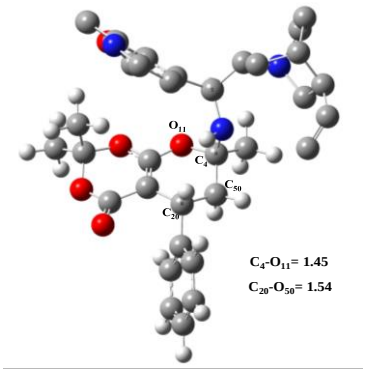


4a-*R*

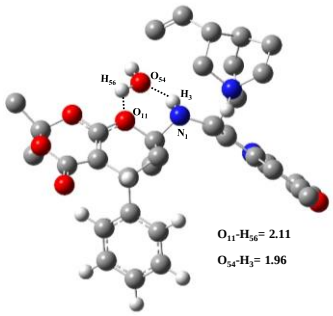
Figure AIII15: Optimized geometries and selected geometric parameters for the formation of hydroxyester (*R* conformer). Some hydrogen atoms not involved in reaction sites are omitted. Distances are in Å.



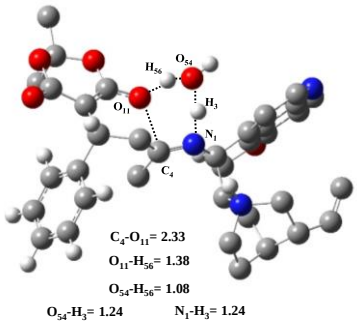
TS1-*R*



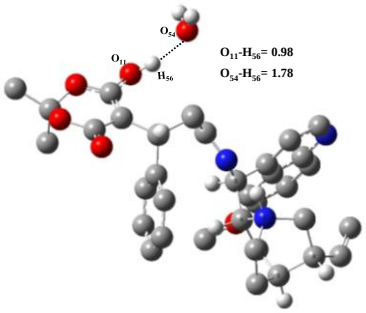
INT-1-*R*



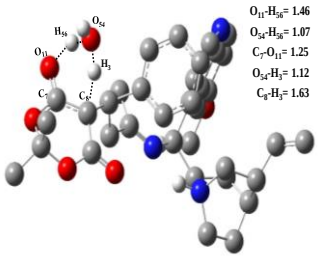
INT-2-*R*



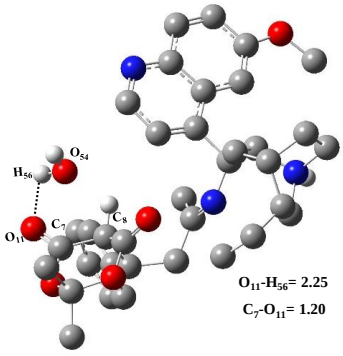
TS2-*R*



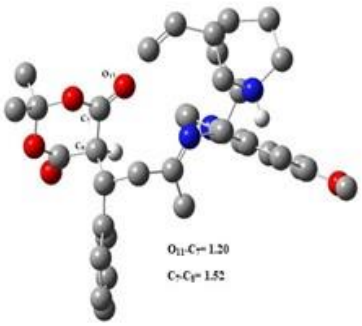
INT-3-*R*



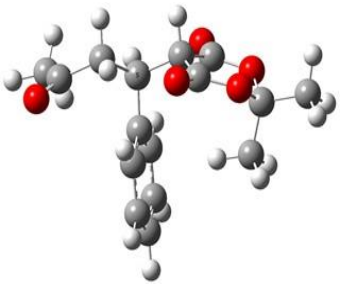
TS3-*S*



INT-4-*S*



INT-5-*S*



4a-*S*

Figure AIII16: Optimized geometries and selected geometric parameters for the formation of hydroxyester (*S* conformer). Some hydrogen atoms not involved in reaction sites are omitted. Distances are in Å.

3.8 References

(1) Herrera RP, Marques-Lopez E. Multicomponent reactions: concepts and applications for design and synthesis. Hoboken (NJ):Wiley; 2015.

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(5) List, B.; Castello, C. *Synlett* **2001**, *11*, 1687.

(6) Ramachary, D. B.; Barbas, C. F., III *Chem. - Eur. J.* **2004**, *10*, 5323

(7) Mandal, T.; Zhao, C.-G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7714. (5 mol% catalyst module was used as per the literature report)

(8) Ruli, G.; Duangdee, N.; Baer, K.; Hummel, W.; Berkessel, A.; Gröger, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 7944.

(9) Likewise, the reaction in presence of D-proline as a sole catalyst we observed that racemic product **4b** was being formed in just one hour (1-12 h) unlike the catalyst **Q2** which afforded enantiopure product **4b** which racemized over a period of time.

(10) We observed that reactions were neat and afforded compounds **4a, 4c-4h, 4j-4s** with a negligible amount of corresponding spiro compounds. However, 4-methoxy

benzaldehyde and 3,4-dimethoxy benzaldehyde afforded corresponding compounds **4b, 4i** along with modest amount (30-35%) of corresponding spiro compounds.

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(14) CCDC numbers of **4a** and **4n** are 1531221 and 1531211 respectively. These numbers contain all crystallographic details of this publication and is available free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html

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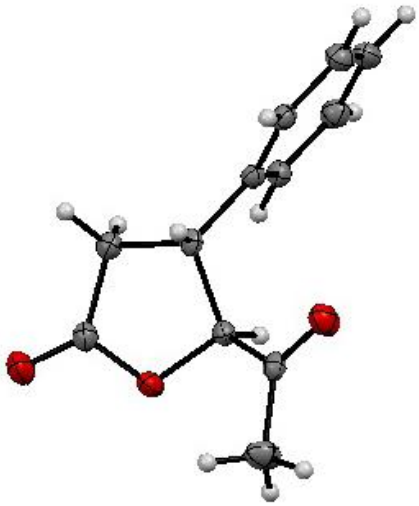
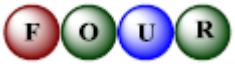
Chapter 4

Direct Organocatalytic Multicomponent Synthesis of Enantiopure γ-Butyrolactones via Domino Knoevenagel-Michael-Lactonization Sequence



γ-Butyrolactone

(X-ray Crystal structure)



4 Direct Organocatalytic Multicomponent Synthesis of Enantiopure γ-Butyrolactones via Domino Knoevenagel-Michael-Lactonization Sequence

An expedient and straightforward protocol is developed for the synthesis of highly enantiopure γ-butyrolactones. For the first time one pot enantioselective organocatalytic multicomponent reaction (OMCR) is explored to construct functionalized γ-butyrolactones without the use of pre-functionalized substrates and expensive transition metals. The protocol is proved to be reproducible on a gram scale. The density functional theory (DFT) calculations strongly support the proposed mechanism and were in close agreement with the observed high stereoselectivity.

4.1 Introduction

γ-Butyrolactone core abundantly found in a wide range of biologically active natural products (Figure 4.1).[1] In fact, the γ-butyrolactone core constitutes about 10% of naturally occurring compounds[2] and many of these possess a broad range of biological activities and are known as potent anticancer, antibacterial and antifungal agents.[3] For example, hydrochloric salt of naturally occurring sesquiterpene lactone, arglabin has been used as a promising drug against breast, lung, and liver cancer.[3e] Similarly other sesquiterpene lactones constunolide[3f] and parthenolide[3a] show anticancer activity (Figure 4.1). Alantolactone[3g] which is found in the roots of *Inula helenium* and other *Inula* species shows antimicrobial activity. Norrisolide[3h] which is obtained from marine diterpenes bind to a receptor on the Golgi membranes and irreversibly disrupts the Golgi apparatus. Phenatic acid B extracted from the culture s*treptomyces* sp. K03-1032 shows antifungal activity.[3i]

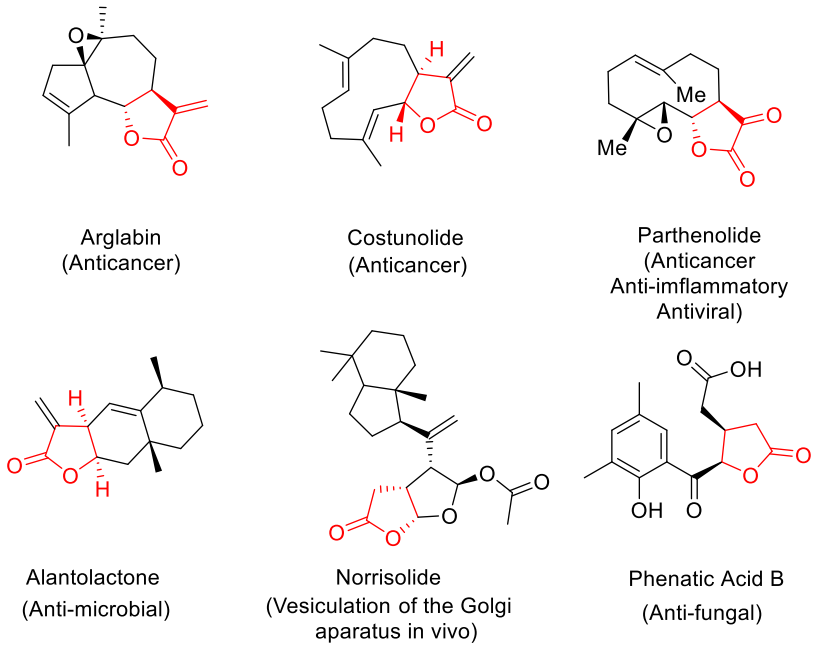
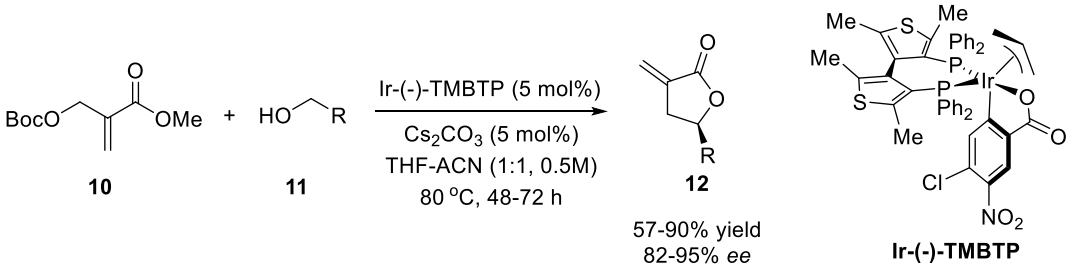


Figure 4.1: Natural products containing *γ*-butyrolactone core

4.2 Selected methods for the synthesis of *γ*-butyrolactone

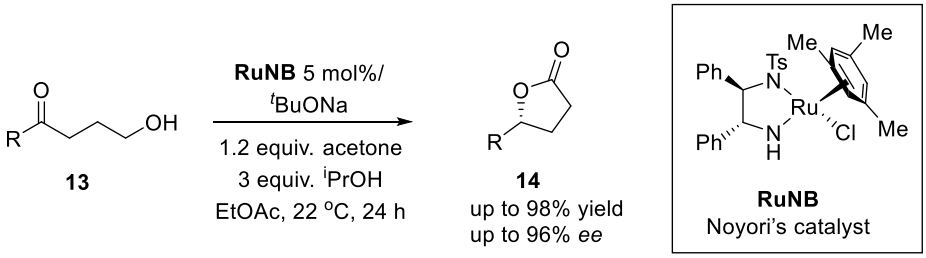
Considering the inevitable importance of *γ*-lactone scaffold, a number of methods have been developed for the synthesis of optically active *γ*-butyrolactone core.[4,5] Some of the selected enantioselective methodologies have been described.

In 2012 Krische and co-workers[5a] reported the iridium-catalyzed (**Ir-(-)-TMBTP**) enantioselective carbonyl 2-(alkoxycarbonyl) allylation through transfer hydrogenative C−C coupling between protected Morita–Baylis–Hillman adduct **10** and primary aliphatic alcohol **11** (Scheme 4.1). This method gives an access to *α*-exo-methylene *γ*-butyrolactones **12** which are usually found in a wide family of natural products. The *α*-exo-methylene *γ*-butyrolactones **12** were synthesized in good to excellent yields with very good enantioselectivity (up to 90% yield, 95% *ee*).



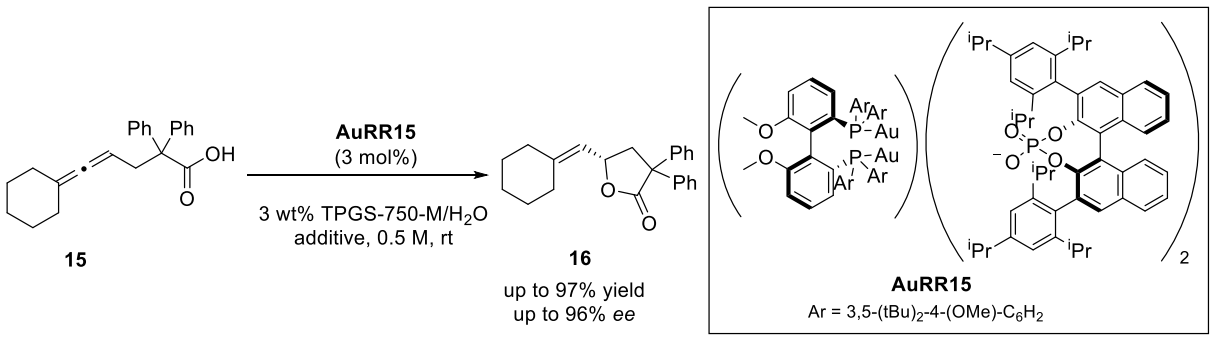
Scheme 4.1: Asymmetric transfer hydrogenation by Krische and co-workers.

Similarly, in 2013 Dong and co-workers[5b] reported a novel enantioselective intramolecular ketone hydroacylation catalyzed by Noyori's transfer hydrogenation catalyst (Scheme 4.2). This strategy enabled the transformation of 4- or 5-hydroxy ketones **13** into the corresponding optically active *γ*- and *δ*-lactones **14**. The protocol utilized the asymmetric transfer hydrogenation (ATH) strategy using chiral catalyst **RuNB** (chiral mono-N-tosylated 1,2-diphenylethylenediamine-ruthenium complex). The ATH catalyst initially catalyzes the reduction of the ketone to diol followed by the selective oxidation of terminal primary alcohol via transfer hydrogenation. Finally, the oxidation of cyclic hemiacetal leads to the desired chiral lactone **14** in good to excellent yields with very high enantioselectivity (up to 98% yield, 95% *ee*).



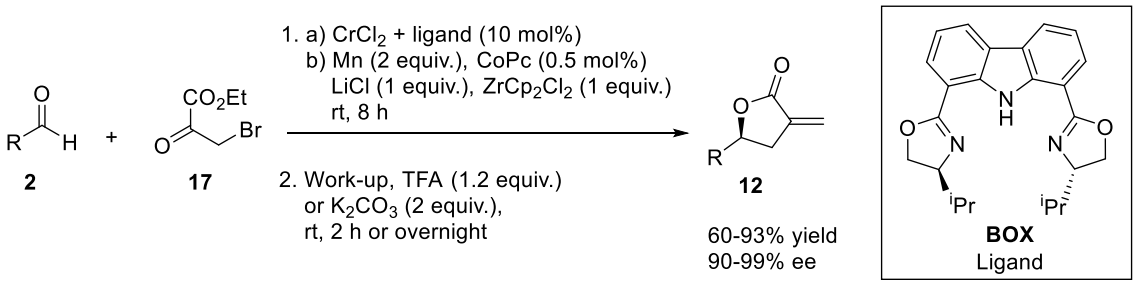
Scheme 4.2: Lactonization via asymmetric transfer hydrogenation by Dong and co-workers.

Lipshutz and co-workers[5d] synthesized *γ*-butyrolactones **16** via the asymmetric gold-catalyzed (**AuRR15**) intramolecular hydrocarboxylation of allene **15** in water (Scheme 4.3). *In situ* formed aqueous nanomicellar chiral pockets lead to an improved enantiocontrol than conventional organic solvents. A suitable combination of axially chiral ligand-gold complex and the counter anion of the axially chiral phosphoric acid catalyzes enantioselective intramolecular lactonization via synergistic interactions (Scheme 4.3).



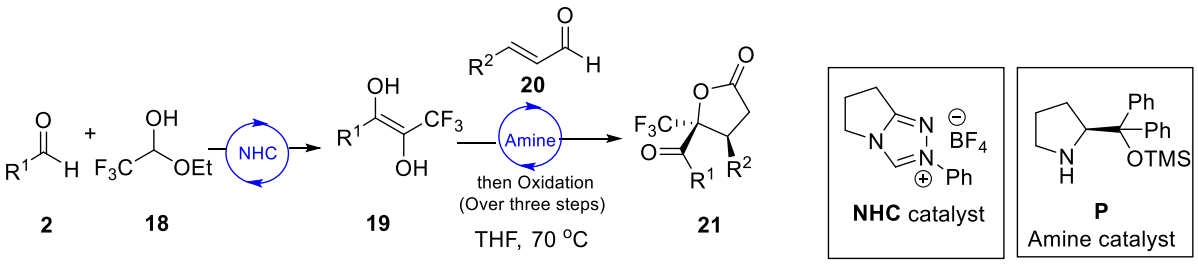
Scheme 4.3: Gold-catalyzed lactonization starting from allenes by Lipshutz and co-workers.

Zhang and co-workers[5e] used chromium catalyzed multi-step approach to synthesize chiral *α*-exo-methylene *γ*-butyrolactones **12** (Scheme 4.4). The C2 symmetric bisoxazoline (**BOX**) based chiral ligand is believed to form a complex with chromium to generate a chiral chromium catalyst which catalyzes the allylation of aldehyde **2** through an allyl chromium intermediate generated from allyl radical. Finally a series of operations led to the enantioselective *α-exo*-methylene *γ*-butyrolactones **12** (up to 99% *ee*). However, this multistep methodology is dependent on the use of four different transition metals (Cr, Mn, Co and Zr).



Scheme 4.4: *α-exo*-Methylene *γ*-butyrolactones via chromium catalysis by Zhang and co-workers

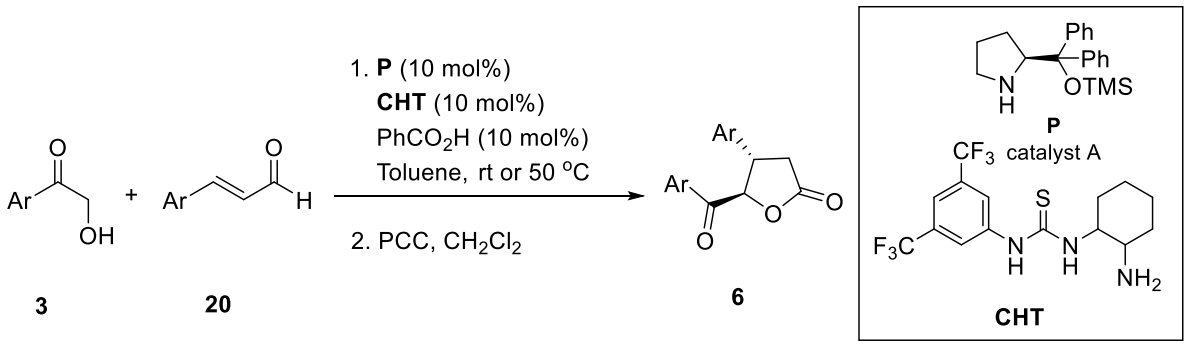
Han and coworkers[5f] developed NHC-amine (**P**) catalyzed sequential aldol/Michael addition followed by an oxidation strategy to synthesize CF_3-substituted chiral *γ*-butyrolactone derivatives **21** with vicinal quaternary and tertiary stereocenters (Scheme 4.5). However, this methodology was dependent on a highly reactive key intermediate fluoroketones **19**, which was prepared in situ starting from aldehyde **2** and fluorinated hemiacetal **18**. The Michael addition of this intermediate **19** to *α,β*-unsaturated aldehydes **20** followed by the subsequent lactol formation and oxidation affords the desired lactone **21**.



Scheme 4.5: NHC and amine catalyzed synthesis of *γ*-butyrolactone by Han and coworkers.

Recently, Pan and co-workers[6a] developed a two steps co-operative strategy for the synthesis of enantiopure *γ*-butyrolactone **6** (Scheme 4.6) starting from *α*-hydroxy ketone **3**

and α,β-unsaturated aldehyde **20**. In this method, the primary amine catalyst (**CHT**) forms an enamine intermediate by reacting with α-hydroxy ketone **3**, while the secondary amine catalyst **P** activates α,β-unsaturated aldehyde **20**. The Michael addition of enamine to the unsaturated aldehyde **20** leads to cyclic hemiacetal which upon oxidation with PCC afforded the substituted γ-butyrolactone derivatives **6**. However, this multistep method proved to be suitable only for aromatic α-hydroxy ketone **3** and aromatic Michael acceptors **20** and the aliphatic α-hydroxy ketone and aliphatic Michael acceptors did not furnish the expected results.



Scheme 4.6: Organocatalytic asymmetric Michael-hemiacetalization reaction by Pan and co-workers.

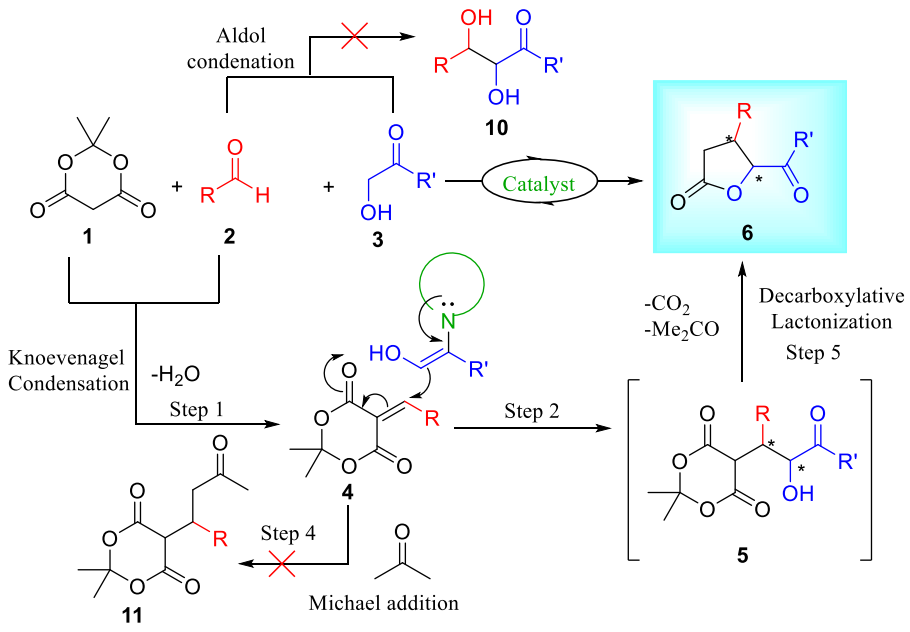
Several multistep catalytic approaches have been developed for the construction of γ-butyrolactone scaffold.[4-6] However, some of the major drawbacks of these methodologies are the use of heavy and expensive transitional metal catalysts (Ir, Ru, Au, Cr etc), expensive ligands and commercially unavailable pre-functionalized starting materials. Very few available organocatalytic protocols are limited to either highly reactive fluorinated ketones or aromatic α-hydroxy ketone and aromatic Michael acceptors as substrates.[5] Evidently, enantiopure synthesis of γ-butyrolactones that avoids pre-functionalized starting materials, complicated multistep operations that involves easily and commercially available starting materials, and relatively less reactive simple ketones is much more challenging and demanding to pursue.

Some of these synthetic challenges strongly encouraged us to explore the synthesis of enantiopure lactones by more convenient and practical approach. One-pot multicomponent organocatalytic approach to obtain the enantiopure γ-butyrolactones in a cost effective and efficient manner is highly desirable and challenging. Remarkably, to the best of our knowledge, enantioselective organocatalytic multicomponent synthesis of γ-butyrolactone

remained an unmet challenge till date. Keeping all these parameters in mind, we ventured into developing a novel and more convenient strategy to synthesize γ-butyrolactones. We have been focusing on the novel use of Meldrum's acid **1** in organic synthesis as an ongoing research programme in our laboratory. In this regard, we became interested in evaluating the scope of Meldrum's acid **1** in enantioselective organocatalytic multicomponent reaction for the the construction of very useful and biologically relevant lactone scaffold.[6]

4.3 Our hypothesis and synthetic planning

Meldrum's acid **1** is a valuable and easily available starting material and finds a great utility in organic synthesis. It has also been utilized efficiently in variety of multicomponent processes.[7,8] Owing its easy accessibility and reactivity, its derivative: *α,β*-unsaturated alkylidene Meldrum's acid **4** acts as an excellent Michael acceptor in 1,4-conjugate addition reactions[7a,9] unlike its acyclic analogues such as benzylidene malonate esters, *α,β*-unsaturated ketones. By taking all these facts into consideration, we hypothesized a novel three component chemoselective domino Knoevenagel-Michael-lactonization sequence as shown in scheme 4.7. However, our proposed multicomponent synthetic route has few daunting chemoselectivity challenges to be met practically as depicted in scheme 4.7.



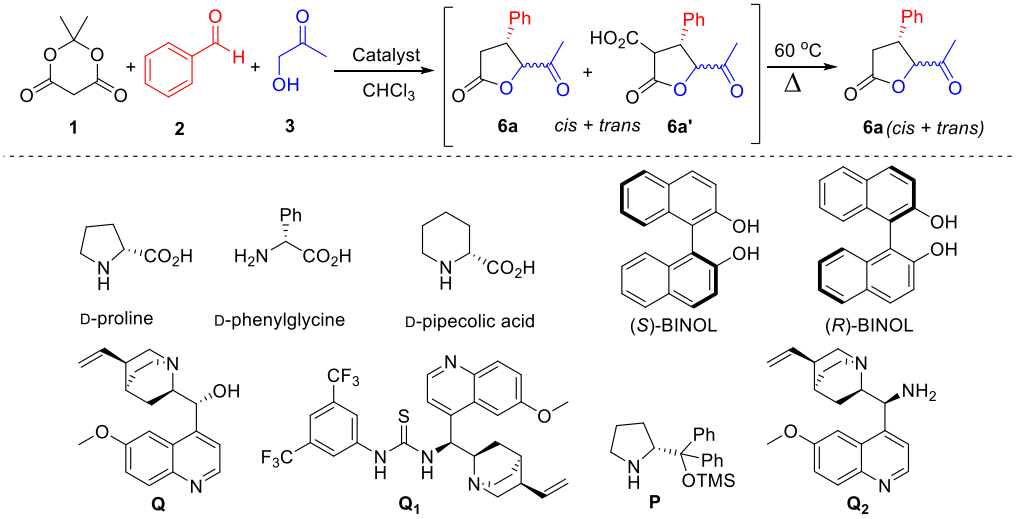
Scheme 4.7: Proposed one pot synthesis of enantiopure γ-butyrolactone via Knoevenagel-Michael-lactonization sequence

Some of the important challenges are: (1) the Knoevenagel condensation reaction should rapidly lead to alkylidene Meldrum's acid **4** (step 1) (Scheme 4.7); (2) very importantly, 1,4-Michael addition (step 2) has to be dominant over aldol condensation[10] (step 3); (3) by-product, acetone should barely take part in the reaction to avoid the formation of side product **11**[8a] (step 4), i.e. 1,4-Michael addition on product **4**; (4) finally, the lactonization should happen in one pot (step 5) under ambient temperature. Looking at the importance of γ-butyrolactones and to access them through a one pot strategy, we ventured into validate our hypothesis by exploring the proposed reaction.

4.4 Results and discussion

Keeping all the reaction possibilities in mind, initially we planned to explore the reaction by using proline as a catalyst as it has widely been used in aminocatalysis.[11] Initially, a model reaction was performed by using Meldrum's acid **1**, benzaldehyde **2a** and hydroxyacetone **3a** in presence of catalytic amount of D-proline (20 mol%) in chloroform at room temperature. Gratifyingly, the desired lactone **6a** was obtained but as two separable diastereomers (1:2.1 *dr*), albeit in poor enantioselectivity at room temperature (Table 4.1, entry 1). It is interesting note that Knoevenagel condensation, Michael addition, lactonization and decarboxylation took place in one pot at room temperature to afford the desired product **6a**.The structures of both *cis* and *trans* diastereomers (**6**a$_{cis}$ and **6a**$_{trans}$) were confirmed by ^{1}H, ^{13}C NMR spectral analysis and single-crystal X-ray diffraction data (see Experimental Section, Page 146).[12] The low enantioselectivity of the product **6a** may be attributed to either inadequate steric bulk of proline or less efficient steric interactions. Initially, we believed that epimerization of *cis*-lactone **6**a$_{cis}$ would have resulted in poor diastereoselective outcome. However, this possibility was ruled out as we did not observe any epimerization of *cis*-lactone of **6a** under the similar reaction conditions even after prolonged reaction time. Subsequently, lowering the reaction temperature to 0 ^{o}C turned out to be extremely disadvantageous (Table 4.1, entry 2). This initial exciting breakthrough for the one pot lactonization encouraged us to screen some more efficient catalyst systems. Recently, it has been demonstrated that combining additional supplemental co-catalyst along with amino acid catalyst is hugely beneficial in enhancing the effective stereo interactions.[13] In this regard, we planned to introduce a cinchona based thiourea-amino acid catalytic assembly with an aim to have high stereo control in this reaction. Various catalyst assemblies have been explored for achieving higher enantioselectivity. However, all these catalyst modules did not enhance the enantioselectivity (Table 4.1, entries 3-7).

Table 4.1: Optimization of proposed synthesis of *γ*-butyrolactone



Entry	Catalyst (mol%)	Additive (mol%)	Yield[b] (%)	*dr* (*trans*: *cis*) [c]	*ee* (%) (*trans*/*cis*)[d]
1	D-Pro(20)	-	63	1:2.1	24/26
2[a]	D-Pro(20)	-	Trace	nd	nd
3	D-Pro(20)	Q1(20)	64	1:2.1	nd/24
4	L-Pro(20)	Q1(20)	60	1:2.1	nd /21
5	L-Pro(20)	(*S*)-BINOL(20)	55	1:2	nd /25
6	L-Pro(20)	(*R*)-BINOL(20)	50	1:2	nd /25
7	D-Phg(20)	Q1(20)	8	nd	nd
8	D-Pip(20)	-	Trace	nd	nd
9	P (20)	-	-		-
10	-	Q1(20)	-	-	-
11	Q2(20)	-	70	2.5:1	89/
12	Q2(20)	TFA (40)	79	2.5:1	91/58
13[a]	Q2(20)	TFA (40)	Trace	nd	nd
14[e]	**Q2(5)**	**TFA (10)**	**78**	**2.5:1**	**91/58**
15[e]	Q2(10)	TFA (20)	78	2.5:1	91/58

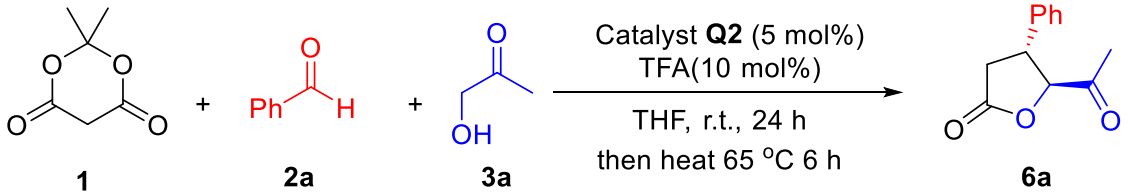
Reaction Conditions: Meldrum's acid **1** (1 equiv.), benzaldehyde **2a** (1.05 equiv.), hydroxyacetone **3a** (3 equiv.) catalyst (5-20 mol%), additive (10-40 mol%), in $CHCl_3$ at rt, 24 h, [a]reactions were carried out at 0 °C, [b]isolated yield after purification by column chromatography, [c]*dr* was calculated based isolated yields [d]*ee* was determined by HPLC, [e]reaction was stirred for 24 h followed by heating at 60 °C for 6 h for the decarboxylation.

Surprisingly, additional amino acid based catalyst (D-pipecolic acid or P) and thiourea catalyst **Q1** were found to be extremely ineffective in terms of reactivity (Table 4.1, entries 8-10).Based on these studies, we surmised that quinine based bifunctional diamine **Q2** may prove to be more potential to serve as a good catalyst. Chiral cinchona derived bifunctional (diamine) catalysts are believed to invoke favorable stereo interactions due to their intrinsic ability to simultaneously form enamine and hydrogen bonding with high degree of conformational flexibility. To our delight, promising results were obtained in the presence of quinine based bifunctional primary amine catalyst **Q2** (20 mol%) by affording the desired product **6a** in 70% yield with good stereoselectivity (Table 4.1, entry 11). While the two fold addition of TFA (40 mol%) along with the catalyst **Q2** (20 mol%) marginally enhanced the yield and enantioselectivity of desired product **6a** (Table 4.1, entry 12) . Presumably TFA might have reduced the unanticipated acid-base interaction between catalyst **Q2** and Meldrum's acid **1**.

Further reduction in catalytic loading (5 and 10 mol%, entries 14, 15) afforded the desired product **6a** along with the undecarboxylated intermediate **6a'** (detected by HRMS) at room temperature (see Table 4.1, entries 14, 15), unlike in case of higher catalytic loading (20 mol%) wherein, decarboxylation took place without heating (see Table 4.1, entry 12). We observed the incomplete decarboxylation even after prolonged reaction time (48 h). Further, in order to decarboxylate the intermediate **6a'**, the reaction mixture was heated at 60 ^{o}C for 6 h for the complete decarboxylation to afford the product **6a** in 78% yield without any erosion of enantioselectivity (91% *ee*). Based on these results, to avoid higher catalytic loading, we decided to use 5 mol% of catalyst **Q2** followed by heating as initial optimized reaction conditions for the substrate scope.

Encouraged by the initial results, further we screened various solvents under initial optimized reaction condition (Table 4.2). Interestingly, THF was found to be the best solvent for the desired transformation (**6a**, 78% yield, 94% *ee*). On the other hand polar solvents such as DMF, DMSO and H_2O had a detrimental effect on the reaction.

Table 4.2: Solvents screening



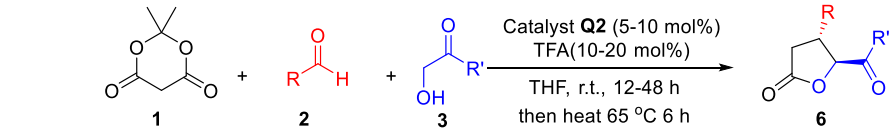
1 + 2a + 3a → 6a

Sr. No.	Solvent	Yield(%)[c]	*dr*	*ee*(%)[d]
1	$CHCl_3$[a]	74	2.1:1	86
2	EtOAc	56	2:1	62
3	Toluene	62	2.3:1	82
4	**THF**	**78**	**2.5:1**	**94**
5	ACN	44	2:1	66
6	DMF	Trace	-	-
7	DMSO	Trace	-	-
8	H_2O	Trace	-	-
9	CH_2Cl_2[b]	72	2.2:1	82
10	MTBE	70	2.2:1	89

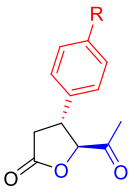
Reaction conditions: Meldrum's acid **1** (1 equiv.), benzaldehyde **2a** (1.05 equiv.), hydroxyacetone **3a** (3 equiv.) catalyst (5 mol%), TFA (10 mol%), in solvents screened in above table at rt, 24 h followed by heating at 65 °C, [a]heated at 60 °C, [b]heated at 38 °C, [c]isolated yield after column chromatography, [d]*ee* determined by chiral HPLC.

Having obtained the optimized reaction conditions in hand (5 mol% **Q2**, 10 mol% TFA in THF at room temperature for 24 h followed heating at 65 °C for 6 h in one pot), further the scope of Knoevenagel-Michael-lactonization was investigated using various aldehydes and α-hydroxy ketones. It was observed that aromatic aldehydes containing electron donating as well as withdrawing functional groups reacted smoothly under the optimized reaction conditions to afford the corresponding lactones (**6b-6j,** Table 4.3) in good yields with high to excellent enantioselectivity (up to 99% *ee*).

Table 4.3: One Pot Enantiopure Synthesis of γ-butyrolactones[a-e]

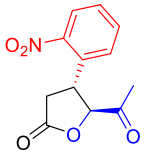


1 2 3 6

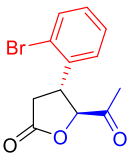


1.5 gram scale
6a, R = H, 75% yield, 94% *ee* (58%), *dr* 2.5:1

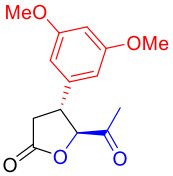
6a, R = H, 78% yield, 94% *ee* (58%), *dr* 2.5:1
6b, R = OMe, 76% yield, 91% *ee* (87%), *dr* 1.5:1
6c, R = Me, 65% yield, >99% *ee* (91%),*dr* 1.8:1
6d, R = F, 82% yield, >99% *ee* (98%), *dr* 1.7:1
6e, R = Cl, 61% yield, 91% *ee* (87%), *dr* 1.6:1
6f, R = CN, 86% yield, 97% *ee* (87%), *dr* > 20:1
6g, R = CF_3, 55% yield, >99% *ee* (96%), *dr* 3.5:1



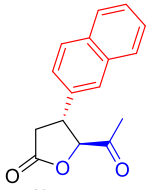
6h, 51% yield, 86% *ee* *dr* >20:1



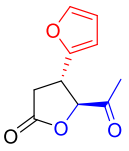
6i, 65% yield, 91% *ee* *dr* >20:1



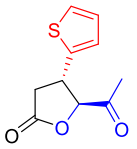
6j, 81% yield, 94% *ee* (91%) *dr* 2.4:1



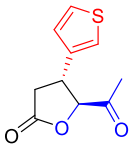
6k, 65% yield, 94% *ee* (93%) *dr* 1.5:1



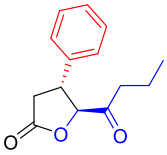
6l, 59% yield, 87% *ee* (67%) *dr* 3.5:1



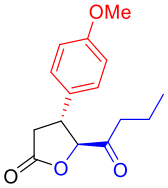
6m, 64% yield, 90% *ee* (94%) *dr* 1.1:1



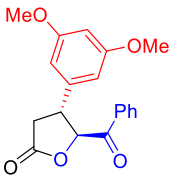
6n, 59% yield, 94% *ee* (95%) *dr* 1.2:1



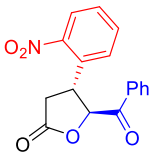
6o, 64% yield,[b] 91% *ee*(83%) *dr* 6:1



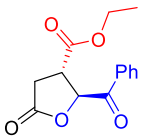
6p, 58% yield,[b] >99% *ee*(94%) *dr* 5:1



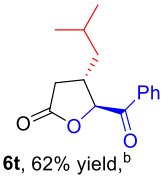
6q, 69% yield,[b] 80% *ee* *dr* >20:1



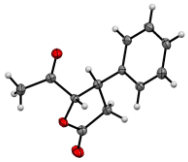
6r, 59% yield,[b] 61% *ee*(4%) *dr* 3:1



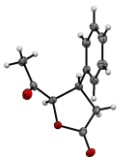
6s, 64% yield,[b] 67% *ee*(75%) *dr* >10:1



6t, 62% yield,[b] 70% *ee* *dr* >20:1



$6a_{trans}$



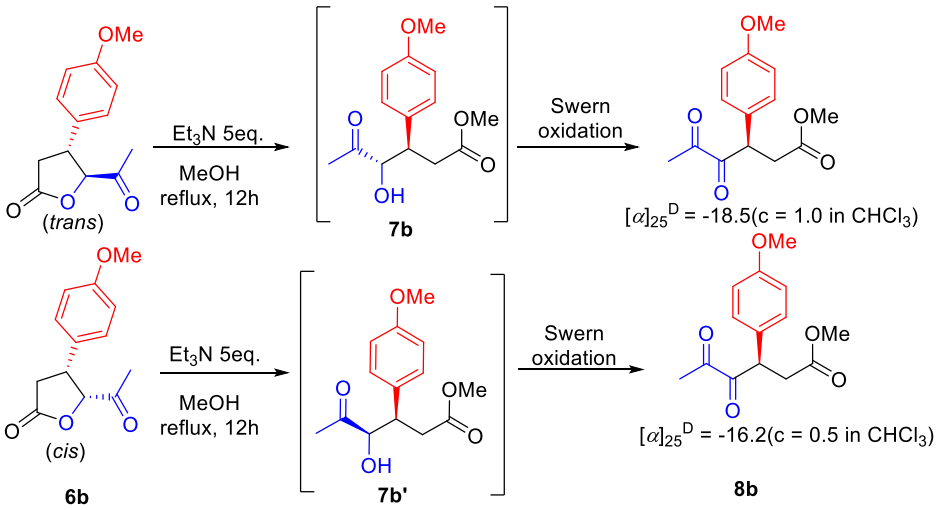
$6a_{cis}$

[a]Reaction conditions: Meldrum's acid **1** (1 equiv.), aldehyde **2** (1.05 equiv.), α-hydroxy ketone **3** (3 equiv.), **Q2** (5 mol%), TFA as additive (10 mol%), in THF at rt, 24 h then heat at 65 °C in one pot; [b]10 mol% of catalyst **Q2** and TFA (20 mol%) were used for the complete conversion, [c]isolated yield after purification by column chromatography, [d]*dr* was calculated based on isolated yields [e]*ee* was determined by HPLC; *ee* of *cis*-isomer is given in parenthesis.

Naphthaldehyde **2k** under the reaction conditions afforded the corresponding lactone **6k** in good yield and excellent enantioselectivity (65%, 94% *ee*). Similarly, heteroaromatic aldehydes such as furfural **2l** and thiophene 2/3-aldehydes (**2m** and **2n**) afforded the corresponding lactones **6l**, **6m** and **6n** respectively (up to 64% yield, up to 94% *ee*, Table 4.3). In order to have generality of the method and for wider practicability, we planned to explore the reactions of 1-hydroxyl-2-pentanone **3b** and 2-hydroxyacetophenone **3c.** Under

the optimized reaction conditions **3b** reacted smoothly with aldehydes **2a**, **2b** and Meldrum's acid **1** to afford the corresponding lactones **6o** and **6p** in moderate to good yields with excellent enantioselectivity (up to >99% *ee*, see, Table 4.3). Likewise, the reaction of 2-hydroxyacetophenone **3c** with aldehydes **2j** and **2h** afforded the corresponding products **6q**, and **6r** respectively in moderate to good yield with good enantioselectivity (up to 80% *ee*, see, Table 4.3). Interestingly, it is very significant to note that the reaction of aliphatic aldehydes such as ethyl glyoxalate **2o** and isovaleraldehyde **2p** with 2-hydroxyacetophenone **3b** afforded the corresponding lactones **6s** and **6t** in good enantioselectivity (up to 70% *ee*, see, Table 4.3)

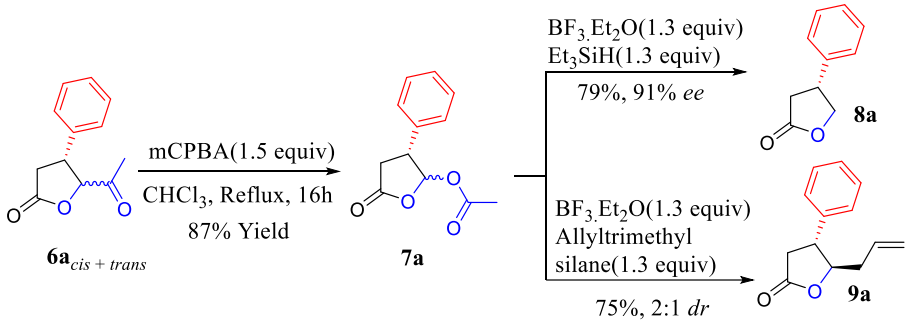
We observed that steric and electronic factors did not have any significant effect on the efficiency and yield of the reaction. A wide variety of aldehydes and different functional groups tolerated the reaction conditions. In order to have some insight into stereochemical outcome of the transformation and mechanistic aspects, we carried out few experiments on lactone **6b**. Esterification followed by oxidation of two separate diastereomers of **6b** (*cis* and *trans*) afforded the corresponding diketo compound **8b** via the intermediates (**7b** and **7b'**, Scheme 4.8).



Scheme 4.8: Esterification followed by oxidation of γ-butyrolactone **6b**

Specific rotation of **8b** revealed that only one face of alkylidene Meldrum's acid **4** is interacting with both *re* and *si* face of hydroxyacetone enamine (**ENM**). To assign the absolute configuration, the product **6a**$_{cis+trans}$ was subjected to Baeyer-Villiger oxidation followed by reduction of **7a** (Scheme 4.9). By comparing the specific rotation of product **8a** with the literature value, the absolute configuration of **6a** was assigned as '*R*' at benzylic

position (β) (observed specific rotation $[\alpha]_D^{25}$ = – 41.0 º(c 1.0, $CHCl_3$), literature $[\alpha]_D^{25}$ = – 27.7º (c 4.0, $CHCl_3$) for '*R*' configuration).[14]

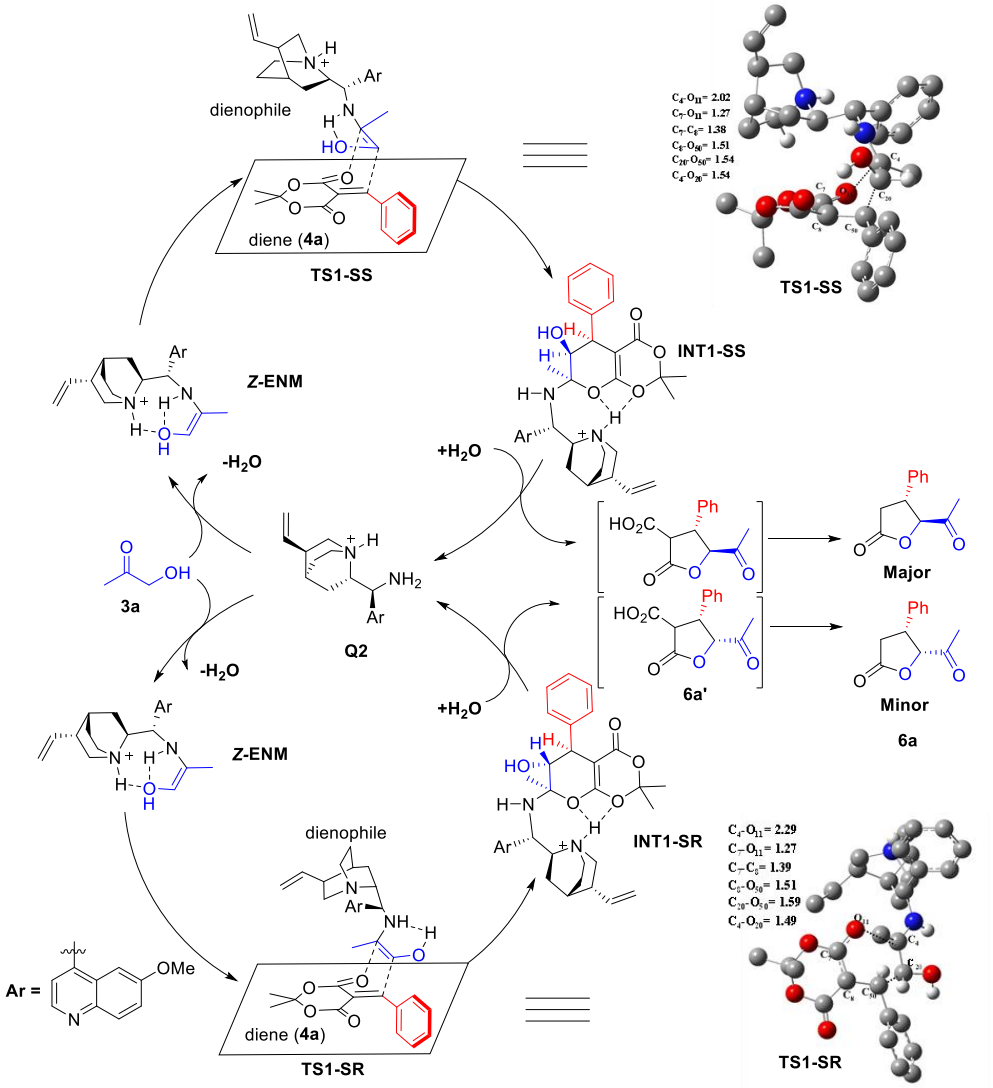


Scheme 4.9: Reduction and allylation of butyrolactone **6a**

Further, to make this protocol more practical and to demonstrate the synthetic utility of the products, synthetically useful allyl lactone **9a** was synthesized starting from compound **7a** in a shorter pathway (Scheme 4.9)**.** Further, to demonstrate the practical utility of this protocol, lactone **6a** was synthesized on a gram scale in good yield (75%) without the erosion of enantioselectivity (94% *ee*).

To have a better understanding of the mechanism and stereoselectivity of reaction catalyzed by chiral cinchona catalyst **Q2**, we planned to investigate the intermediates and transition states (TS) that are involved in the catalytic cycle by density functional theory (DFT) calculations (see pages 147-156). The proposed catalytic cycle is outlined in scheme 4.10. Initially protonated primary amine **Q2** catalyzes Knoevenagel condensation to afford the corresponding heterodiene **4a**. Further this reacts with enamine (***Z*-ENM** and ***E*-ENM** as dienophile) via [4+2]-hetero-Diels-Alder cycloaddition pathway. DFT calculations revealed that *Z*-enamine (***Z*- ENM**) is 7.059 kcal.mol^{-1} more stable than *E*-enamine (***E*-ENM**) due to favorable hydrogen bonding. It is important to note that under experimental conditions, we obtained only *RS* and *RR* lactones selectively. Calculations were carried out to determine the role of TS's on the outcome of stereochemistry of the lactones. This was further unambiguously supported by single crystal X-ray analysis and specific rotation. Keeping this in view, we computationally studied the attack of only ***Z*-ENM** (both *re* and *si faces*) to the only *si* face of heterodiene **4a** in detail for the outcome of *RS* and *RR* lactones (see Experimental Section pages 147-156). Transition state TS1-*SS* (*si* face of **4a** and *si* face of ***Z*-ENM**) is 5.534 kcal.mol^{-1} more stable than TS1-*SR* (*si* face of **4a** and *re* face of ***Z*-ENM**, see page 147). TS1-*SS* leads to more stable major product lactone **6a**-*RS* (10.69 kcal.mol^{-1} more

stable than **6a**-*RR* lactone) through a series of transition states and intermediates for the stepwise mechanism. These DFT calculations strongly support the experimental results and high stereoselectivity (Theoretical *ee* = 99% is in very good agreement with the experimental *ee* = 94%).



Scheme 4.10: Proposed catalytic cycle. [a,b,c]

[a]Selected bond distances are in Å; [b]relative free energies given in kcal·mol^{-1}; M06-2X/6-311++G(d,p)/SMD//M06-2X/6-31G(d); [c]most of the H-atoms have been omitted for the sake of clarity.

4.5 Conclusions

In conclusion, we have developed a novel, robust and a straightforward protocol for the highly enantiopure synthesis of γ-butyrolactones via one-pot organocatalytic multicomponent reaction (OMCR) strategy. Potential of OMCR is explored for the first time for the rapid access of enantiopure lactone scaffolds starting from commercially available simple starting materials. Experimental observation was further supported by the computational studies. More importantly protocol avoids the use of pre-functionalized substrates, additional base and expensive transition metals. The reaction proved to be highly enantioselective and reproducible on a gram scale and is proved to be practical to access synthetically useful enantiopure lactones.

4.6 Experimental section

General methods

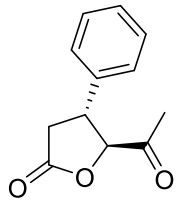
Unless otherwise stated, all reagents were purchased from commercial suppliers and used further without purification. Meldrum's acid was purchased from Spectrochem. Aldehydes and ketones were purchased from Aldrich, Spectrochem and Alfa-aeser. Catalyst was prepared and characterized by using reported procedure.[16] All reactions were carried out in oven dried glassware. Thin-layer chromatography (TLC) was performed using silica gel 60 GF254 pre-coated aluminum backed plates (2.5 mm). Visualization was accomplished by irradiation with UV light at 254 nm and/or ninhydrin stain. Column chromatography was performed using silica gel (200-300 mesh) eluting with petroleum ether and ethyl acetate. NMR spectra were recorded with tetramethylsilane as the internal standard. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz (Bruker and Jeol). Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.16 ppm) for ^{13}C NMR spectroscopy. Coupling constants (*J*) are given in Hz. IR spectra were obtained using a FT-IR spectrophotometer as neat and are reported in cm^{-1}. Mass samples were analyzed by High-resolution mass spectrometry using ESI TOF. Optical rotations were measured at 589 nm at 25 °C. Enantiomeric excess was determined by HPLC analysis on Chiralpak IA, Chiralpak IE and chiral columns by using *n*-hexane, *n*-hepatne and isopropanol as eluents.

General procedure for the enantioselective three-component reaction

In a glass vial equipped with a teflon-coated stir bar, 9-amino(9-deoxy)*epi*quinine **Q2** (0.04 mmol, 11.2 mg, 5 mol%) was dissolved in 1.0 mL of THF. After addition of TFA (0.07 mmol, 5.3 mmL, 10 mol%), the reaction mixture was stirred for 15 minutes. Then Meldrum's acid **1** (100 mg, 0.7 mmol, 1 equiv.), benzaldehyde **2a** (74.3 mmL, 0.73 mmol, 1.05 equiv.) and hydroxyacetone **3a** (145.6 mmL, 2.1 mmol, 3 equiv.) were added subsequently and stirred for 24 h or as indicated in the manuscript. Upon complete consumption of Meldrum's acid, the reaction mixture was heated at 65° C for 6 hours to decarboxylate the acid intermediate. The crude product **6a** was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as an eluent. Compound **6a** was obtained as solid in 78% yield.

*In the case of lactones **6o**-**6t** 10 mol% of catalyst **Q2** and 20 mol% of TFA were used.

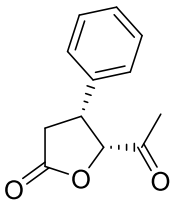
(4*R*,5*S*)-5-acetyl-4-phenyldihydrofuran-2(3H)-one (6a-*trans*)



6a-*trans*

Compound **6a** was synthesized following the general procedure. Compound **6a** was obtained as white solid in 78% (110 mg, *trans*/*cis*; 2.5:1); m.p. 85-88 °C, R_f = 0.44 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 2H), 7.34 – 7.32 (m, 1H), 7.27 – 7.25 (m, 2H), 4.85 (d, *J* = 6.2 Hz, 1H), 3.74 (dd, *J* = 15.1, 7.7 Hz, 1H), 3.00 (dd, *J* = 18.0, 9.4 Hz, 1H), 2.72 (dd, *J* = 18.0, 7.4 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 174.8, 139.5, 129.5, 128.2, 127.0, 87.9, 43.3, 36.1, 26.9; FTIR cm^{-1} (neat) 1783.73, 1721.78, 1609.66, 1496.48, 1453.64, 1416.84, 1361.98, 1277.89, 1185.01, 1142.16, 1058.39, 968.79, 924.74, 876.85, 756.25, 698.59, 640.47. HRMS (ESI TOF) *m/z* calcd. For $C_{12}H_{12}O_3$ + H $[M + H]^+$ 205.0859, found 205.0863. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 16.9 min (major) and t_R= 17.4 min (minor). *ee* = 94%. Specific rotation $[\alpha]_D^{25}$ = +34.2 (c = 1.0, $CHCl_3$).

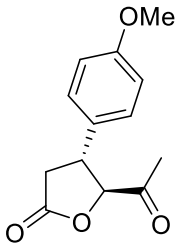
(4*R*, 5*R*)-5-acetyl-4-phenyldihydrofuran-2(3H)-one (6a-*cis*)



6a-*cis*

m.p. 115-118 ^{o}C. R_f = 0.23 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 3H), 7.15 (dd, *J* = 7.9, 1.4 Hz, 2H), 5.08 (d, *J* = 7.4 Hz, 1H), 4.05 (td, *J* = 7.8, 5.7 Hz, 1H), 3.01 – 2.89 (m, 2H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0, 175.7, 136.0, 129.3, 128.5, 127.7, 85.7, 44.2, 34.6, 28.1; FTIR cm^{-1} (neat) 1783.86, 1722.03, 1607.21, 1496.57, 1454.36, 1416.69, 1359.13, 1310.33, 1218.82, 1147.14, 1055.96, 1007.56, 971.42, 923.31, 872.50, 748.74, 700.11, 667.56. HRMS (ESI TOF) *m/z* calcd. For $C_{12}H_{12}O_3$ + H $[M + H]^+$ 205.0859, found 205.0863. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 92:08, flow rate = 0.5 mL/min, λ = 210 nm, t_R = 14.4 min (major) and t_R= 16.2 min (minor). *ee* = 58%. Specific rotation $[\alpha]_D^{25}$ = -91.8 (c = 2.0, $CHCl_3$).

(4*R*,5*S*)-5-acetyl-4-(4-methoxyphenyl)dihydrofuran-2(3H)-one (6b-*trans*)



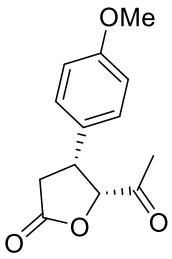
6b-*trans*

Compound **6b** was synthesized following the general procedure. Compound **6b** was obtained as white solid in 76% (124 mg, trans/cis; 1.5:1).

m.p. 91-94 ^{o}C. R_f = 0.25 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.79 (d, *J* = 6.6 Hz, 1H), 3.79 (s, 3H), 3.69 – 3.63 (m, 1H), 2.95 (dd, *J* = 17.9, 9.3 Hz, 1H), 2.68 (dd, *J* = 17.9, 7.8 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 174.8, 159.4, 131.2, 128.1, 114.8, 88.1, 55.4, 42.8, 36.2, 26.8; FTIR cm^{-1} (neat) 1773.56, 1722.08, 1605.54, 1509.71, 1449.72, 1419.19, 1357.11, 1331.34, 1291.98, 1247.41, 1155.70, 1054.93, 1021.10, 960.84, 929.69, 875.95, 827.34, 763.81, 706.51. HRMS (ESI TOF) *m/z* calcd. For $C_{13}H_{14}O_4$ + Na $[M + Na]^+$ 257.0784, found 257.0789. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 96:04, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 37.6 min (major) and t_R= 43.7 min (minor). *ee* = 91%. Specific rotation $[\alpha]_D^{25}$ = +38.9 (c = 1.0, $CHCl_3$).

Molecular structures of $\mathbf{6a_{cis}}$ and $\mathbf{6_{trans}}$ were unambiguously determined by single crystal X-ray analysis. It was very interesting note that methyl proton of lactone-*cis* isomers (derived from hydroxyacetone and aromatic aldehydes) resonated in the up field region of ^{1}H-NMR spectrum due to the high shielding of methyl protons by phenyl ring current.

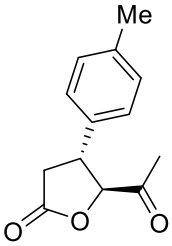
(4*R*,5*R*)-5-acetyl-4-(4-methoxyphenyl) dihydrofuran-2(3H)-one (6b-*cis*)



6b-*cis*

m.p. 133-137 ^{o}C. R_f = 0.13 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.04 (d, *J* = 7.3 Hz, 1H), 4.03 – 3.96 (m, 1H), 3.78 (s, 3H), 2.95 (dd, *J* = 17.5, 8.4 Hz, 1H), 2.85 (dd, *J* = 17.5, 5.6 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 175.9, 159.6, 128.8, 127.7, 114.6, 85.8, 55.4, 43.4, 34.7, 28.2; FTIR cm^{-1} (neat) 2926.60, 2229.84, 1782.31, 1720.58, 1611.35, 1513.49, 1460.07, 1418.72, 1358.63, 1302.96, 1251.59, 1149.91, 1051.19, 971.01, 873.31, 835.38, 782.70, 733.08, 702.69. HRMS (ESI TOF) *m/z* calcd. For $C_{13}H_{14}O_4$ + Na $[M + Na]^+$ 257.0784, found 257.0789. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 96:04, flow rate = 0.5 mL/min, λ = 210 nm, t_R = 28.1 min (major) and t_R= 32.1 min (minor). *ee* = 87%. Specific rotation $[\alpha]_D^{25}$ = -74.6 (c = 1.0, $CHCl_3$).

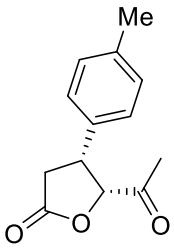
(4*R*,5*S*)-5-acetyl-4-(p-tolyl)dihydrofuran-2(3H)-one (6c-*trans*)



6c-*trans*

Compound 6c was synthesized following the general procedure. Compound **6c** was obtained as colorless viscous oil in 65% (99 mg, trans/cis; 1.8:1). R_f = 0.44 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.12 (m, 4H), 4.81 (d, *J* = 6.5 Hz, 1H), 3.68 (dd, *J* = 16.2, 7.2 Hz, 1H), 2.98 (dd, *J* = 18.0, 9.3 Hz, 1H), 2.70 (dd, *J* = 18.0, 7.6 Hz, 1H), 2.33 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 174.9, 138.0, 136.3, 130.1, 126.9, 88.0, 43.0, 36.2, 26.8, 21.1; FTIR cm^{-1} (neat) 1783.05, 1721.32, 1516.09, 1419.27, 1358.68, 1312.16, 1152.26, 1053.18, 1009.23, 971.95, 873.65, 822.28, 753.41, 666.82. HRMS (ESI TOF) *m/z* calcd. For $C_{13}H_{14}O_3$ + Na $[M + Na]^+$ 241.0835, found 241.0834. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 96:04, flow rate = 0.5 mL/min, λ = 210 nm, t_R = 31.0 min (major) *ee* = 84%. Specific rotation $[\alpha]_D^{25}$ = +40.2 (c = 1.0, $CHCl_3$).

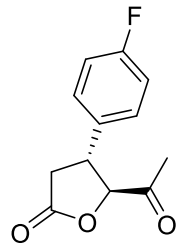
(4*R*,5*R*)-5-acetyl-4-(p-tolyl)dihydrofuran-2(3H)-one (6c-*cis*)



6c-*cis*

R_f = 0.22 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 7.9 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 5.06 (d, *J* = 7.4 Hz, 1H), 2.95 (dd, *J* = 17.5, 8.4 Hz, 1H), 2.86 (dd, *J* = 17.5, 5.7 Hz, 2H), 2.31 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 175.9 , 138.3, 132.8, 129.9, 127.5, 85.8, 43.8, 34.6, 28.2, 21.1; FTIR cm^{-1} (neat) 2924.69, 1785.62, 1721.38, 1516.21, 1419.14, 1359.08, 1315.27, 1163.44, 1054.88, 1012.68, 973.35, 874.83, 822.29. HRMS (ESI TOF) *m/z* calcd. For $C_{13}H_{14}O_3$ + Na $[M + Na]^+$ 241.0835, found 241.0834. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 96:04, flow rate = 0.5 mL/min, λ = 210 nm, t_R = 23.9 min (major) and t_R= 27.7 min (minor). *ee* = 91%. Specific rotation $[\alpha]_D^{25}$ = -88.6 (c = 1.0, $CHCl_3$).

(4*R*,5*S*)-5-acetyl-4-(4-fluorophenyl)dihydrofuran-2(3H)-one (6d-*trans*)

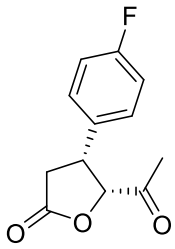


6d-*trans*

Compound **6d** was synthesized following the general procedure. Compound **6d** was obtained as colorless viscous oil in 82% (127 mg, *trans/cis*; 1.7:1).

R_f = 0.43 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 2H), 7.13 – 6.98 (m, 2H), 4.79 (d, *J* = 6.4 Hz, 1H), 3.78 – 3.72 (m, 1H), 3.00 (dd, *J* = 18.0, 9.3 Hz, 1H), 2.69 (dd, *J* = 18.0, 7.6 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 174.5, 162.4(d, *J* = 247.3 Hz), 135.1(d, *J* = 3.4 Hz), 128.7(d, *J* = 8.2 Hz), 116.4(d, *J* = 21.6 Hz), 87.9(d, *J* = 1.3 Hz), 42.5, 36.1, 26.8; FTIR cm^{-1} (neat) 1786.05, 1723.80, 1604.91, 1511.70, 1418.59, 1361.98, 1281.38, 1226.74, 1144.86, 1059.17, 968.08, 879.58, 835.54, 748.75, 667.43. HRMS (ESI TOF) *m/z* calcd. For $C_{12}H_{11}FO_3$ + H $[M + H]^+$ 223.0765, found 223.0768. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 96:04, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 13.8 min (minor) and t_R= 14.9 min (major). *ee* = >99%. Specific rotation $[\alpha]_D^{25}$ = +28.5 (c = 2.0, $CHCl_3$).

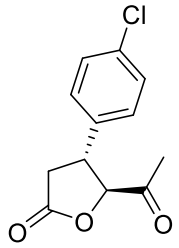
(4*R*,5*R*)-5-acetyl-4-(4-fluorophenyl)dihydrofuran-2(3H)-one (6d-*cis*)



6d-*cis*

R_f = 0.23 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.11 (m, 2H), 7.05 – 7.01 (m, 2H), 5.05 (d, *J* = 7.3 Hz, 1H), 4.07 – 4.01 (m, 1H), 2.99 (dd, *J* = 17.5, 8.5 Hz, 1H), 2.85 (dd, *J* = 17.5, 5.0 Hz, 1H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.1, 175.4, 162.6(d, *J* = 248.2 Hz), 131.9(d, *J* = 3.2 Hz), 129.4(d, *J* = 8.2 Hz), 116.3(d, *J* = 21.6 Hz), 85.6, 43.4, 34.9, 28.2; FTIR cm^{-1} (neat) 1782.95, 1721.08, 1605.31, 1511.22, 1420.03, 1359.36, 1306.14, 1227.53, 1154.61, 1054.08, 1008.43, 971.73, 837.30, 782.68, 710.16. HRMS (ESI TOF) *m/z* calcd. For $C_{12}H_{11}FO_3$ + H $[M + H]^+$ 223.0765, found 223.0770. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 96:04, flow rate = 0.5 mL/min, λ = 210 nm, t_R = 11.2 min (minor) and t_R= 12.1 min (major). *ee* = 98%. Specific rotation $[\alpha]_D^{25}$ = -90.6 (c = 1.0, $CHCl_3$).

(4*R*,5*S*)-5-acetyl-4-(4-chlorophenyl)dihydrofuran-2(3H)-one (6e-*trans*)

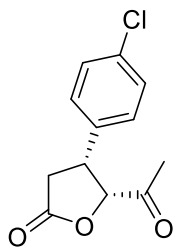


6e-*trans*

Compound **6e** was synthesized following the general procedure. Compound **6e** was obtained as semisolid in 61% (101 mg, *trans/cis*; 1.6:1).

R_f = 0.44 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 4.78 (d, *J* = 6.4 Hz, 1H), 3.76 – 3.70 (m, 1H), 2.99 (dd, *J* = 18.0, 9.4 Hz, 1H), 2.68 (dd, *J* = 18.0, 7.6 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 174.4, 137.8, 134.1, 129.6, 128.4, 87.7, 42.6, 36.0, 26.9; FTIR cm^{-1} (neat) 1784.52, 1721.76, 1608.39, 1493.05, 1415.44, 1361.15, 1276.85, 1183.01, 1142.34, 1057.71, 1014.64, 966.84, 878.40, 826.35, 753.78, 666.2. HRMS (ESI TOF) *m/z* calcd. For $C_{12}H_{11}ClO_3$ + Na $[M + Na]^+$ 261.0289, found 261.0293. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 96:04, flow rate = 0.5 mL/min, λ = 210 nm, t_R = 16.5 min (minor) and t_R= 17.3 min (major). *ee* = 91%. Specific rotation $[\alpha]_D^{25}$ = +25.5 (c = 1.0, $CHCl_3$).

(4*R*,5*R*)-5-acetyl-4-(4-chlorophenyl)dihydrofuran-2(3H)-one (6e-*cis*)

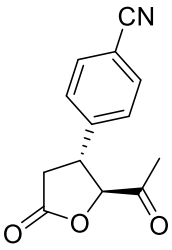


6e-*cis*

m.p. 117-120 ^{o}C. R_f = 0.26 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 5.06 (d, *J* = 7.3 Hz, 1H), 4.05 – 4.00 (m, 1H), 2.99 (dd, *J* = 17.5, 8.6 Hz, 1H), 2.84 (dd, *J* = 17.5, 5.0 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 175.3, 134.6, 134.5, 129.5, 129.1, 85.5, 43.5, 34.9, 28.3; FTIR cm^{-1} (neat) 1775.45, 1718.71, 1596.75, 1491.67, 1419.39, 1355.75, 1295.80, 1170.11,

1094.19, 1058.47, 1009.60, 975.13, 877.54, 835.51, 758.43, 703.41. HRMS (ESI TOF) *m/z* calcd. For $C_{12}H_{11}ClO_3$ + Na $[M + Na]^+$ 261.0289, found 261.0293. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 96:04, flow rate = 0.5 mL/min, λ = 210 nm, t_R = 13.9 min (major) and t_R= 15.2 min (minor). *ee* = 87%. Specific rotation $[\alpha]_D^{25}$ = -25.7 (c = 1.0, $CHCl_3$).

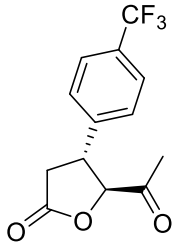
4-((2*S*,3*R*)-2-acetyl-5-oxotetrahydrofuran-3-yl)benzonitrile (6f-*trans*)



6f-*trans*

Compound **6f** was synthesized following the general procedure. Compound **6f** was obtained as colorless viscous oil in 85% (135 mg, trans/cis; >20:1). R_f = 0.19 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 4.78 (d, *J* = 6.3 Hz, 1H), 3.88 – 3.82 (m, 1H), 3.03 (dd, *J* = 18.0, 9.4 Hz, 1H), 2.71 (dd, *J* = 18.0, 7.5 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 173.8, 144.7, 133.2, 128.1, 118.3, 112.3, 87.1, 42.9, 35.7, 26.9; FTIR cm^{-1} (neat) 1785.46, 1722.32, 1610.55, 1508.61, 1417.29, 1361.94, 1278.20, 1183.15, 1143.10, 1059.62, 966.79, 879.17, 837.44, 749.73, 704.46, 666.25. HRMS (ESI TOF) *m/z* calcd. For $C_{13}H_{11}NO_3$ + Na $[M + Na]^+$ 252.0631, found 252.0636. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 85:15, flow rate = 0.5 mL/min, λ = 210 nm, t_R = 27.6 min (minor) and t_R= 28.9 min (major). *ee* = 97%. Specific rotation $[\alpha]_D^{25}$ = +33.6 (c = 1.0, $CHCl_3$).

(4*R*,5*S*)-5-acetyl-4-(4-(trifluoromethyl)phenyl)dihydrofuran-2(3H)-one (6g-*trans*)

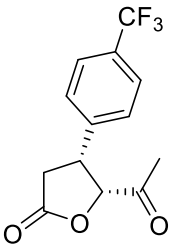


6g-*trans*

Compound **6g** was synthesized following the general procedure. Compound **6g** was obtained as semisolid in 55% (104 mg, trans/cis; 3.5:1). R_f = 0.49 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 4.81 (d, *J* = 6.2 Hz, 1H), 3.85 (dt, *J* = 9.3, 7.1 Hz, 1H), 3.03 (dd, *J* = 18.0, 9.4 Hz, 1H), 2.73 (dd, *J* = 18.0, 7.4 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 174.1, 143.5, 130.5 (q, *J* = 32.8 Hz), 127.6, 126.4 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 272.2 Hz), 87.4, 42.9, 35.9, 26.9; FTIR cm^{-1} (neat) 1787.90, 1724.66, 1620.14, 1421.10, 1363.40, 1322.84, 1115.69, 1059.72, 967.04, 878.54, 838.46, 755.72, 708.12, 669.05, 638.45. HRMS (ESI TOF) *m/z* calcd. For $C_{13}H_{11}F_3O_3$ + H $[M + H]^+$ 273.0733, found 273.0736. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-hexane/*i*-PrOH

= 80:20, flow rate = 0.5 mL/min, λ = 210 nm, t_R = 19.2 min (major). *ee* = 95%. Specific rotation $[\alpha]_D^{25}$ = +13.6 (c = 1.0, $CHCl_3$, with trace of *cis* isomer).

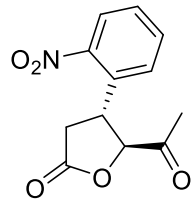
(4*R*,5*R*)-5-acetyl-4-(4-(trifluoromethyl)phenyl)dihydrofuran-2(3H)-one (6g-*cis*)



6g-*cis*

m.p. 120-124 °C. R_f = 0.25 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 5.10 (d, *J* = 7.3 Hz, 1H), 4.14 – 4.09 (m, 1H), 3.04 (dd, *J* = 17.6, 8.6 Hz, 1H), 2.88 (dd, *J* = 17.6, 4.6 Hz, 1H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 175.1, 140.5, 130.8 (q, *J* = 32.9 Hz), 128.2, 126.2 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 272.2 Hz), 85.4, 43.8, 35.0, 28.3. FTIR cm^{-1} (neat) 1778.43, 1724.57, 1617.04, 1426.45, 1329.47, 1158.68, 1109.85, 1061.63, 1012.02, 970.91, 846.42, 784.39, 704.34. HRMS (ESI TOF) *m/z* calcd. For $C_{13}H_{11}F_3O_3$ + H $[M + H]^+$ 273.0733, found 273.0736. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-hxane/*i*-PrOH = 80:20, flow rate = 0.5 mL/min, λ = 210 nm, t_R = 13.9 min (major) and t_R= 16.5 min (minor). *ee* = 96%. Specific rotation $[\alpha]_D^{25}$ = +3.0 (c = 1.0, $CHCl_3$, with trace of *trans* isomer).

(4*R*, 5*S*)-5-acetyl-4-(2-nitrophenyl)dihydrofuran-2(3H)-one (6h-*trans*)

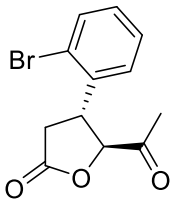


6h-*trans*

Compound **6h** was synthesized following the general procedure. Compound **6h** was obtained as colorless viscous oil in 51% (88 mg, trans/cis; >20:1).

R_f = 0.28 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.68 (td, *J* = 7.7, 1.3 Hz, 1H), 7.53 – 7.46 (m, 2H), 4.96 (d, *J* = 4.4 Hz, 1H), 4.31 (dt, *J* = 9.4, 4.7 Hz, 1H), 3.10 (dd, *J* = 18.2, 9.4 Hz, 1H), 2.66 (dd, *J* = 18.2, 5.0 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 174.6, 149.3, 134.6, 134.2, 129.2, 128.0, 125.5, 86.7, 38.2, 35.2, 26.9; FTIR cm^{-1} (neat) 1785.43, 1723.03, 1609.49, 1576.17, 1523.95, 1418.36, 1350.10, 1143.86, 1057.79, 966.98, 856.81, 746.09, 709.28, 672.27. HRMS (ESI TOF) *m/z* calcd. For $C_{12}H_{11}NO_5$ + Na $[M + Na]^+$ 272.0529, found 272.0529. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 85:15, flow rate = 0.5 mL/min, λ = 210 nm, t_R = 13.5 min (minor) and t_R= 21.8 min (major). *ee* = 86%. Specific rotation $[\alpha]_D^{25}$ = +15.6 (c = 1.0, $CHCl_3$).

(4*R*, 5*S*)-5-acetyl-4-(2-bromophenyl)dihydrofuran-2(3H)-one (6i-*trans*)

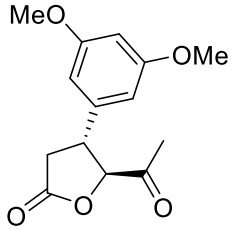


6i-*trans*

Compound **6i** was synthesized following the general procedure. Compound **6i** was obtained as white solid in 65% (128 mg, trans/cis; >20:1).

m.p. 82-85 ^{o}C. R_f = 0.52 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (td, *J* = 7.7, 1.3 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.28 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.17 (ddd, *J* = 8.0, 7.2, 1.8 Hz, 1H), 4.92 (d, *J* = 4.9 Hz, 1H), 4.21 (dt, *J* = 9.5, 5.2 Hz, 1H), 3.00 (dd, *J* = 18.0, 9.4 Hz, 1H), 2.63 (dd, *J* = 18.0, 5.5 Hz, 1H), 2.32 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 174.8, 138.6, 133.7, 129.6, 128.6, 127.6, 124.0, 86.4, 42.1, 34.7, 26.7. FTIR cm^{-1} (neat) 1784.54, 1722.39, 1473.43, 1422.34, 1360.53, 1142.88, 1057.39, 1024.25, 966.53, 874.13, 755.47, 666.45. HRMS (ESI TOF) *m/z* calcd. For $C_{12}H_{11}BrO_3$ + Na $[M + Na]^+$ 304.9784, found 304.9782. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 96:04, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 17.4 min (minor) and t_R= 19.3 min (major). *ee* = 91%. Specific rotation $[\alpha]_D^{25}$ = +12.3 (c = 1.0, $CHCl_3$).

(4*R*,5*S*)-5-acetyl-4-(3,5-dimethoxyphenyl)dihydrofuran-2(3H)-one (6j-*trans*)

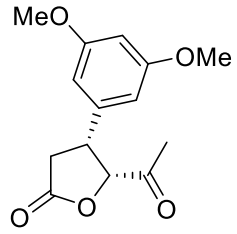


6j-*trans*

Compound **6j** was synthesized following the general procedure. Compound **6j** was obtained as colorless viscous oil in 81% (148 mg, trans/cis; 2.4:1).

R_f = 0.26 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (s, 3H), 4.84 (d, *J* = 6.2 Hz, 1H), 3.77 (s, 6H), 3.62 (ddd, *J* = 12.7, 7.5, 4.5 Hz, 1H), 2.95 (dd, *J* = 18.1, 9.4 Hz, 1H), 2.69 (dd, *J* = 18.1, 7.2 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 174.8, 161.5, 141.9, 105.1, 99.4, 87.6, 55.5, 43.3, 35.9, 26.8; FTIR cm^{-1} (neat) 1785.90, 1725.35, 1598.32, 1464.47, 1429.13, 1358.33, 1302.33, 1200.38, 1150.01, 1061.84, 927.30, 840.36, 746.77, 689.35. HRMS (ESI TOF) *m/z* calcd. For $C_{14}H_{16}O_5$ + Na $[M + Na]^+$ 287.0890, found 287.0888. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 96:04, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 40.3 min (major) and t_R= 46.8 min (minor). *ee* = 94%. Specific rotation $[\alpha]_D^{25}$ = +23.6 (c = 1.0, $CHCl_3$).

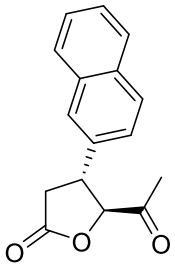
(4*R*,5*R*)-5-acetyl-4-(3,5-dimethoxyphenyl)dihydrofuran-2(3H)-one (6j-*cis*)



6j-*cis*

R_f = 0.16 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (t, *J* = 2.1 Hz, 1H), 6.27 (d, *J* = 2.2 Hz, 2H), 5.05 (d, *J* = 7.5 Hz, 1H), 3.99 – 3.93 (m, 1H), 3.75 (s, 6H), 2.96 – 2.82 (m, 2H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 175.5, 161.4, 138.3, 105.9, 99.9, 85.5, 55.5, 44.4, 34.5, 28.2; FTIR cm^{-1} (neat) 1784.73, 1722.58, 1597.34, 1464.00, 1431.20, 1356.44, 1303.11, 1201.05, 1149.75, 1055.89, 1011.40, 973.24, 929.39, 840.72, 750.33, 699.04. HRMS (ESI TOF) *m/z* calcd. For $C_{14}H_{16}O_5$ + H $[M + H]^+$ 265.1071, found 265.1076. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 96:04, flow rate = 0.5 mL/min, λ = 210 nm, t_R = 26.6 min (major) and t_R= 30.8 min (minor). *ee* = 91%. Specific rotation $[\alpha]_D^{25}$ = -52.4 (c = 1.0, $CHCl_3$).

(4*R*,5*S*)-5-acetyl-4-(naphthalen-2-yl)dihydrofuran-2(3H)-one (6k-*trans*)

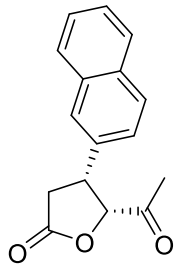


6k-*trans*

Compound **6k** was synthesized following the general procedure. Compound **6k** was obtained as white solid in 65% (115 mg, trans/cis; 1.5:1).

m.p. 126-128 ^{o}C. R_f = 0.41 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 1H), 7.85 – 7.80 (m, 2H), 7.70 (d, *J* = 1.3 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.36 (dd, *J* = 8.5, 1.9 Hz, 1H), 4.94 (d, *J* = 6.2 Hz, 1H), 3.90 (dt, *J* = 9.3, 6.9 Hz, 1H), 3.05 (dd, *J* = 18.0, 9.4 Hz, 1H), 2.82 (dd, *J* = 18.0, 7.3 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 174.8, 136.7, 133.5, 132.9, 129.6, 127.9, 127.8, 126.9, 126.6, 126.1, 124.4, 87.8, 43.4, 36.0, 26.9; FTIR cm^{-1} (neat) 1782.75, 1722.18, 1602.31, 1417.04, 1361.32, 1270.76, 1142.09, 1059.38, 967.30, 894.36, 860.79, 817.36, 741.59, 704.23. HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{14}O_3$ + Na $[M + Na]^+$ 277.0835, found 277.0834. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 96:04, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 19.3 min (major) and t_R= 20.5 min (minor). *ee* = 94%. Specific rotation $[\alpha]_D^{25}$ = +39.9 (c = 1.0, $CHCl_3$).

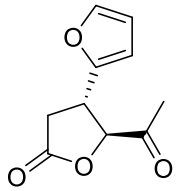
(4*R*,5*R*)-5-acetyl-4-(naphthalen-2-yl)dihydrofuran-2(3H)-one (6k-*cis*)



6k-*cis*

m.p. 167-169 ^{o}C. R_f = 0.28 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 9.7, 6.6 Hz, 3H), 7.62 (d, *J* = 0.9 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.25 (dd, *J* = 8.3, 1.6 Hz, 1H), 5.16 (d, *J* = 7.4 Hz, 1H), 4.22 (dd, *J* = 13.9, 7.5 Hz, 1H), 3.24 – 2.81 (m, 2H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 175.7, 133.4, 133.3, 133.0, 129.2, 128.0, 127.8, 126.9, 126.8, 126.7, 125.4, 85.8, 44.3, 34.8, 28.3; FTIR cm^{-1} (neat) 1781.96, 1721.98, 1600.11, 1506.78, 1417.88, 1361.15, 1319.07, 1161.25, 1057.23, 966.24, 864.72, 822.52, 749.63, 666.51. HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{14}O_3$ + Na [M + Na]$^{+}$ 277.0835, found 277.0840. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-heptane /*i*-PrOH = 96:04, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 17.5 min (major) and t_R= 19.2 min (minor). *ee* = 93%. Specific rotation $[\alpha]_D^{25}$ = -88.2 (c = 1.0, $CHCl_3$).

(4*S*,5*S*)-5-acetyl-4-(furan-2-yl)dihydrofuran-2(3H)-one (6l-*trans*)

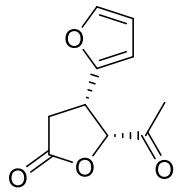


6l-*trans*

Compound **6l** was synthesized following the general procedure. Compound **6l** was obtained as colorless viscous oil in 59% (79 mg, trans/cis; 3.5:1).

R_f = 0.44 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.34 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.23 (d, *J* = 3.3 Hz, 1H), 4.88 (d, *J* = 6.3 Hz, 1H), 3.85 (dd, *J* = 14.6, 8.3 Hz, 1H), 2.93 – 2.80 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.5, 174.1, 151.2, 142.9, 110.8, 107.4, 85.1, 36.9, 33.2, 26.9; FTIR cm^{-1} (neat) 1783.28, 1722.63, 1613.10, 1506.48, 1418.41, 1361.71, 1143.92, 1061.97, 1012.35, 970.10, 933.86, 872.13, 814.09, 742.34. HRMS (ESI TOF) *m/z* calcd. For $C_{10}H_{10}O_4$ + Na [M + Na]$^{+}$ 217.0471, found 217.0471. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL/min, λ = 210 nm, t_R = 16.3 min (major) and t_R= 22.4 min (minor). *ee* = 87%. Specific rotation $[\alpha]_D^{25}$ = +54.2 (c = 2.0, $CHCl_3$).

(4*S*,5*R*)-5-acetyl-4-(furan-2-yl)dihydrofuran-2(3H)-one (6l-*cis*)

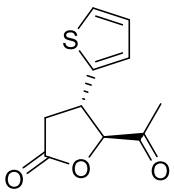


6l-*cis*

R_f = 0.26 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 1.9, 0.7 Hz, 1H), 6.32 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.18 (d, *J* = 3.3 Hz, 1H), 4.99 (d, *J* = 7.4 Hz, 1H), 4.12 (q, *J* = 7.4 Hz, 1H), 2.88 (d, *J* = 7.4 Hz, 2H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 174.7, 149.2, 143.0, 111.0, 108.6, 83.9, 38.1, 32.7, 26.9; FTIR cm^{-1} (neat)

1785.21, 1724.46, 1505.38, 1418.56, 1361.75, 1148.98, 1058.67, 1014.98, 969.72, 877.48, 818.74, 742.38, 667.75, 629.00. HRMS (ESI TOF) *m/z* calcd. For $C_{10}H_{10}O_4$ + Na $[M + Na]^+$ 217.0471, found 217.0471. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL/min, λ = 210 nm, t_R = 15.5 min (minor) and t_R= 15.9 min (major). *ee* = 70%. Specific rotation $[\alpha]_D^{25}$ = -31.6 (c = 2.0, $CHCl_3$).

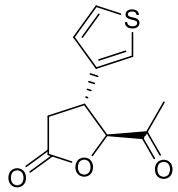
(4*S*,5*S*)-5-acetyl-4-(thiophen-2-yl)dihydrofuran-2(3H)-one (6m-*trans*)



6m-*trans*

Compound **6m** was synthesized following the general procedure. Compound **6m** was obtained as colorless viscous oil in 64% (93 mg, trans/cis; 1.1:1). R_f = 0.42 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 4.6, 1.9 Hz, 1H), 7.00 – 6.98 (m, 2H), 4.83 (d, *J* = 6.6 Hz, 1H), 4.07 (td, *J* = 8.5, 6.8 Hz, 1H), 3.04 (dd, *J* = 17.8, 9.1 Hz, 1H), 2.79 (dd, *J* = 17.8, 8.0 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 173.8, 141.9, 127.5, 125.4, 125.2, 87.8, 38.7, 36.8, 27.0; FTIR cm^{-1} (neat) 1783.98, 1721.46, 1417.12, 1360.36, 1312.89, 1151.66, 1054.08, 970.13, 847.43, 706.94. HRMS (ESI TOF) *m/z* calcd. For $C_{10}H_{10}O_3S$ + H $[M + H]^+$ 211.0423, found 211.0427. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 16.3 min (major) and t_R= 17.4 min (minor). *ee* = 90%. Specific rotation $[\alpha]_D^{25}$ = +40.0 (c = 1.0, $CHCl_3$, with trace of *trans* isomer).

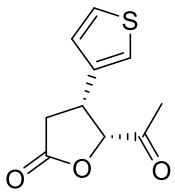
(4*R*,5*S*)-5-acetyl-4-(thiophen-3-yl)dihydrofuran-2(3H)-one (6n-*trans*)



6n-*trans*

Compound **6n** was synthesized following the general procedure. Compound **6n** was obtained as colorless viscous oil in 59% (86 mg, trans/cis; 1.2:1). R_f = 0.44 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 5.0, 2.9 Hz, 1H), 7.16 – 7.15 (m, 1H), 7.01 (dd, *J* = 5.0, 1.4 Hz, 1H), 4.79 (d, *J* = 6.4 Hz, 1H), 3.86 (dd, *J* = 15.8, 7.2 Hz, 1H), 2.96 (dd, *J* = 17.8, 9.1 Hz, 1H), 2.70 (dd, *J* = 17.8, 7.6 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 174.6, 139.8, 127.7, 125.9, 121.9, 87.4, 38.7, 35.6, 26.8; FTIR cm^{-1} (neat) 1782.04, 1721.34, 1611.28, 1416.59, 1360.75, 1138.72, 1057.72, 970.25, 864.09, 751.48, 701.62, 650.02. HRMS (ESI TOF) *m/z* calcd. For $C_{10}H_{10}O_3S$ + H $[M + H]^+$ 211.0423, found 211.0428. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 20.0 min (major) and t_R= 25.2 min (minor). *ee* = 94%. Specific rotation $[\alpha]_D^{25}$ = +32.4 (c = 1.0, $CHCl_3$).

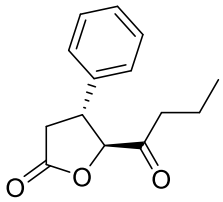
(4*R*,5*R*)-5-acetyl-4-(thiophen-3-yl)dihydrofuran-2(3H)-one (6n-*cis*)



6n-*cis*

R_f = 0.28 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 5.0, 2.9 Hz, 1H), 7.09 (dd, *J* = 2.8, 1.0 Hz, 1H), 6.90 (dd, *J* = 5.0, 1.4 Hz, 1H), 5.01 (d, *J* = 7.0 Hz, 1H), 4.17 (dd, *J* = 15.0, 7.5 Hz, 1H), 2.96 (dd, *J* = 17.3, 8.3 Hz, 1H), 2.84 (dd, *J* = 17.3, 5.2 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 175.6, 136.8, 127.4, 126.8, 122.9, 85.1, 40.0, 35.2, 27.8; FTIR cm^{-1} (neat) 1780.60, 1719.79, 1416.29, 1360.92, 1318.59, 1248.72, 1153.99, 1054.06, 1005.14, 971.65, 860.61, 790.77, 704.23, 632.32. HRMS (ESI TOF) *m/z* calcd. For $C_{10}H_{10}O_3S$ + H $[M + H]^+$ 211.0423, found 211.0428. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 16.0 min (major) and t_R= 17.8 min (minor). *ee* = 95%. Specific rotation $[\alpha]_D^{25}$ = -26.2 (c = 1.0, $CHCl_3$, with trace amount of *trans* isomer).

(4*R*,5*S*)-5-butyryl-4-phenyldihydrofuran-2(3H)-one (6o-*trans*)

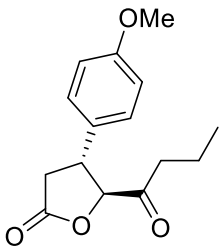


6o-*trans*

Compound **6q** was synthesized following the general procedure. Compound **6q** was obtained as colorless viscous oil in 64% (103 mg, trans/cis; 6:1).

R_f = 0.7 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (ddd, *J* = 7.5, 6.2, 1.4 Hz, 2H), 7.33 – 7.28 (m, 1H), 7.26 – 7.22 (m, 2H), 4.83 (d, *J* = 6.0 Hz, 1H), 3.75 – 3.69 (m, 1H), 2.98 (dd, *J* = 18.0, 9.4 Hz, 1H), 2.70 (dd, *J* = 18.0, 7.1 Hz, 1H), 2.54 (td, *J* = 7.1, 1.5 Hz, 2H), 1.67 – 1.58 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 175.0, 139.8, 129.5, 128.2, 127.0, 87.7, 43.3, 41.4, 36.0, 16.6, 13.7. FTIR cm^{-1} (neat) 2963.60, 2877.43, 1785.90, 1721.37, 1603.57, 1496.67, 1456.92, 1376.42, 1280.75, 1192.36, 1139.53, 1042.34, 889.52, 760.45, 700.03. HRMS (ESI TOF) *m/z* calcd. For $C_{14}H_{16}O_3$ + Na $[M + Na]^+$ 255.0996, found 255.0998. The enantiomeric excess was determined by HPLC analysis using Chiralpak IE, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 23.7 min (major) and t_R= 26.5 min (minor). *ee* = 91%. Specific rotation $[\alpha]_D^{25}$ = +40.3 (c = 1.0, $CHCl_3$, with trace of *cis* isomer).

(4*R*,5*S*)-5-butyryl-4-(4-methoxyphenyl)dihydrofuran-2(3H)-one (6p-*trans*+*cis*)

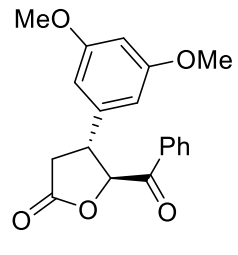


6p-*trans*+*cis*

Compound **6r** was synthesized following the general procedure. Compound **6r** was obtained as colorless viscous oil in 58% (106 mg, trans/cis; 5:1). Diastereomers were inseparable.

R_f = 0.7 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.13 (m, 2H), 6.90 – 6.83 (m, 2H), 4.79 (d, *J* = 6.4 Hz, 1H), 3.79 (s, 3H), 3.77 – 3.63 (m, 1H), 2.96 (dd, *J* = 18.0, 9.3 Hz, 1H), 2.67 (dd, *J* = 18.0, 7.5 Hz, 1H), 2.53 (td, *J* = 7.0, 1.8 Hz, 2H), 1.62 (dd, *J* = 14.6, 7.3 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 206.1, 175.0, 168.6, 159.8, 159.3, 131.4, 129.6, 129.3, 128.1, 114.7, 114.5, 87.8, 85.5, 61.0, 55.4, 49.4, 43.3, 42.7, 41.3, 36.1, 28.6, 16.5, 15.7, 13.7, 13.4. FTIR cm^{-1} (neat) 2927.12, 2853.49, 1788.15, 1721.77, 1664.99, 1601.01, 1512.49, 1459.21, 1367.99, 1292.90, 1250.62, 1174.75, 1030.01, 981.67, 898.48, 829.46, 758.91, 699.30. HRMS (ESI TOF) *m/z* calcd. For $C_{15}H_{18}O_4$ + Na $[M + Na]^+$ 285.1102, found 285.1114. The enantiomeric excess was determined by HPLC analysis using Chiralpak IE, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL/min, λ = 254 nm, t_R= 36.6 min (major). *ee* = >99%. Specific rotation $[\alpha]_D^{25}$ = +31.0 (c = 1.0, $CHCl_3$, with trace of *cis* isomer).

(4*R*,5*S*)-5-benzoyl-4-(3,5-dimethoxyphenyl)dihydrofuran-2(3H)-one (6q-*trans*)

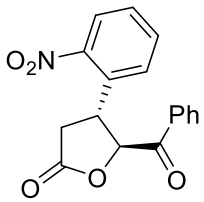


6q-*trans*

Compound **6t** was synthesized following the general procedure. Compound **6t** was obtained as colorless viscous oil in 69% (156 mg, trans/cis; >20:1).

m.p. 121-124 ^{o}C. R_f = 0.55 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.90 (m, 2H), 7.65 – 7.61 (m, 1H), 7.52 – 7.46 (m, 2H), 6.42 – 6.40 (m, 1H), 6.39 (d, *J* = 2.2 Hz, 2H), 5.78 (d, *J* = 3.7 Hz, 1H), 3.82 – 3.76 (m, 1H), 3.78 (s, 6H), 3.04 (dd, *J* = 18.0, 9.5 Hz, 1H), 2.67 (dd, *J* = 18.0, 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 175.6, 161.7, 143.0, 134.6, 133.6, 129.2, 129.0, 104.9, 99.6, 84.2, 55.5, 43.4, 35.1. FTIR cm^{-1} (neat) 2925.78, 2853.59, 1685.68, 1592.65, 1456.76, 1427.76, 1354.33, 1275.63, 1238.86, 1202.82, 1156.65, 1098.25, 1064.72, 973.72, 927.91, 835.63, 757.76, 688.30. HRMS (ESI TOF) *m/z* calcd. For $C_{19}H_{18}O_5$ + Na $[M + Na]^+$ 349.1046, found 349.1040. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 21.2 min (minor) and t_R= 23.4 min (major). *ee* = 80%. Specific rotation $[\alpha]_D^{25}$ = +65.7 (c = 1.0, $CHCl_3$).

(4*R*,5*S*)-5-benzoyl-4-(2-nitrophenyl)dihydrofuran-2(3H)-one (6r-*trans*+*cis*)

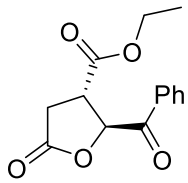


6r-*trans*+*cis*

Compound **6u** was synthesized following the general procedure. Compound **6u** was obtained as colorless viscous oil in 59% (132 mg, trans/cis; 3:1).

R_f = 0.3 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.90 (m, 2H), 7.72 (td, *J* = 7.7, 1.4 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.52 (ddd, *J* = 8.7, 7.4, 1.4 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.25 – 7.19 (m, 1H), 5.85 (d, *J* = 2.7 Hz, 1H), 4.50 (dt, *J* = 9.6, 2.9 Hz, 1H), 3.26 (dd, *J* = 18.2, 9.6 Hz, 1H), 2.70 (dd, *J* = 18.2, 3.2 Hz, 1H). 13C NMR (100 MHz, $CDCl_3$) δ 195.6, 193.1, 174.9, 174.7, 150.0, 149.0, 135.4, 134.7, 134.6, 134.2, 134.1, 133.5, 133.4, 129.1, 129.0, 129.0, 128.6, 128.6, 128.1, 128.0, 127.7, 127.7, 125.3, 124.9, 82.9, 79.6, 40.6, 37.9, 35.0, 31.9. HRMS (ESI TOF) *m/z* calcd. For C17H13NO5 + Na $[M + Na]^+$ 334.0686, found 334.0681. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-hexane /*i*-PrOH = 90:10, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 52.5 min (minor) and t_R= 64.6 min (major). *ee* = 61%. Specific rotation $[\alpha]_D^{25}$ = +15.5 (c = 2.0, $CHCl_3$, with trace of *cis* isomer).

Ethyl (2*S*,3*S*)-2-benzoyl-5-oxotetrahydrofuran-3-carboxylate (6s-*trans*)

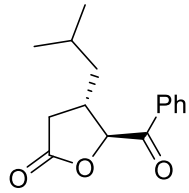


6s-*trans*

Compound **6v** was synthesized following the general procedure. Compound **6v** was obtained as colorless viscous oil in 64% (117 mg, trans/cis; >10:1).

R_f = 0.35 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.69 – 7.64 (m, 1H), 7.55 – 7.51 (m, 2H), 6.04 (d, *J* = 3.8 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.70 (ddd, *J* = 9.8, 4.6, 3.8 Hz, 1H), 2.97 (dd, *J* = 18.1, 4.8 Hz, 1H), 2.84 (dd, *J* = 18.2, 10.0 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 174.0, 170.8, 134.8, 133.4, 129.4, 129.2, 79.5, 62.6, 42.0, 30.1, 14.2. HRMS (ESI TOF) *m/z* calcd. For $C_{14}H_{14}O_5$ + Na $[M + Na]^+$ 285.0733, found 285.0730. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 19.8 min (minor) and t_R= 20.8 min (major). *ee* = 67%. Specific rotation $[\alpha]_D^{25}$ = +46.7 (c = 1.0, $CHCl_3$, with trace of *cis* isomer).

(4*S*,5*S*)-5-benzoyl-4-isobutyldihydrofuran-2(3H)-one (6t-*trans*)



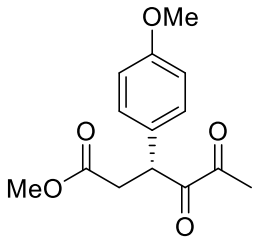
6t-*trans*

Compound **6w** was synthesized following the general procedure. Compound **6w** was obtained as colorless viscous oil in 62% (106 mg, trans/cis; >20:1).

R_f = 0.7 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dt, *J* = 8.5, 1.6 Hz, 2H), 7.66 – 7.62 (m, 1H), 7.54 – 7.50 (m, 2H), 5.39 (d, *J* = 3.6 Hz, 1H), 2.81 – 2.70 (m, 2H), 2.30 – 2.23 (m, 1H), 1.72 – 1.60 (m, 1H), 1.60 – 1.52 (m, 1H), 1.51 – 1.42 (m, 1H), 0.91 (t, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 176.0, 134.4, 134.2, 129.1, 128.9, 83.5, 43.3, 36.2, 33.5, 26.0, 22.9, 22.1. FTIR cm^{-1} (neat) 2957.02, 2872.38, 1782.03, 1690.68, 1595.27, 1452.33, 1417.52, 1374.52, 1245.67, 1156.56, 1064.06, 981.05, 940.35, 875.48, 843.70, 776.13, 699.62, 654.77. HRMS (ESI TOF) *m/z* calcd. For $C_{15}H_{18}O_3$ + H $[M + H]^+$ 247.1329, found 247.1338. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-hexane /*i*-PrOH = 80:20, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 13.0 min (minor) and t_R= 13.7 min (major). *ee* = 70%. Specific rotation $[\alpha]_D^{25}$ = +42.2 (c = 1.0, $CHCl_3$).

Determination of Absolute configuration:

Synthesis of Methyl (*R*)-3-(4-methoxyphenyl)-4,5-dioxohexanoate (8b)

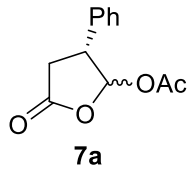


8b

To a solution of butyrolactone **6b** (100 mg, 427 µmol) in 10.0 mL methanol was added Et_3N (300 mmL, 2.1 mmol), and the reaction was refluxed for 12 h. The reaction was then cooled and methanol was evaporated on rotatory evaporator. The resdiual methanol was removed azeotropically with hexanes (2 x 20 mL), producing crude alcohol 7b which was used without purification. In a flame dried 50 mL round bottomed flask, under an atmosphere of nitrogen, dimethylsulfoxide (61 mmL, 854 µmol, 2.0 eq) was added dropwise at −78°C to a solution of oxalylchloride (55 mmL, 640 µmol, 1.5 eq) in 7 mL of dry dichloromethane. The resulting colourless solution was stirred for 5 min and a solution of alcohol 7b in 3 mL of dry dichloromethane was added dropwise via cannula at −78°C. After stirring for an additional 15 min, at this temperature, triethylamine (240 mmL, 1.7 mmol, 4 eq) was added dropwise and the reaction mixture was slowly warmed to room temperature (30 min). It was quenched by adding 50 mL of a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with dichloromethane (3 x 20 mL), the combined organic layers were washed with water (2 X 30 mL) and brine (1 x 30 mL), dried over

sodium sulfate, filtered and concentrated in vacuo. Crude product was purified column chromatography on silica gel using petroleum ether/ethyl(88/12) acetate as eluent. Product obtained as colorless liquid with 78% yield (88 mg). R_f = 0.65 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.94 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.77 (s, 3H), 3.65 (s, 3H), 3.23 (dd, *J* = 17.2, 10.6 Hz, 1H), 2.70 (dd, *J* = 17.2, 4.9 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 196.5, 172.4, 159.4, 129.9, 127.0, 114.7, 55.4, 52.1, 45.1, 37.0, 24.5. FTIR cm^{-1} (neat) 2925.15, 2849.29, 1716.63, 1678.39, 1606.19, 1511.45, 1440.03, 1359.77, 1305.57, 1251.42, 1174.93, 1112.76, 1031.77, 912.24, 835.89. HRMS (ESI TOF) *m/z* calcd. For $C_{14}H_{16}O_5$ + Na $[M + Na]^+$ 287.0895, found 287.0898. Specific rotation $[\alpha]_D^{25}$ = -18.5 (c = 1.0, $CHCl_3$).

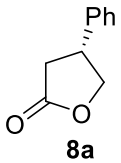
(3*R*)-5-oxo-3-phenyltetrahydrofuran-2-yl acetate (7a)



7a

To a solution of butyrolactone 6a (500 mg, 2.45 mmol) in 20 mL chloroform was added meta-chloroperoxybenzoic acid (845 mg, 4.90 mmol, 2 eq), and the reaction was refluxed for 12 h. The reaction was then cooled and chloroform was evaporated on rotatory evaporator. Reaction mixture was dissolved in ethyl acetate and washed with saturated aq.$NaHCO_3$ followed by brine and dried over sodium sulphate. Crude product was purified column chromatography on silica gel using petroleum ether/ethyl(85/15) acetate as eluent. Product obtained as colorless liquid with 85% yield (458 mg). R_f = 0.53 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 3H), 7.21 – 7.19 (m, 2H), 6.50 (d, *J* = 2.0 Hz, 1H), 3.66 (ddd, *J* = 9.2, 3.9, 2.0 Hz, 1H), 3.16 (dd, *J* = 18.1, 9.2 Hz, 1H), 2.67 (dd, *J* = 18.1, 4.0 Hz, 1H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 169.1, 138.3, 129.4, 128.2, 126.78, 99.7, 46.0, 34.3, 21.0. FTIR cm^{-1} (neat) 1794.22, 1755.51, 1498.35, 1452.44, 1421.70, 1367.79, 1333.95, 1210.74, 1134.99, 1074.34, 1041.84, 975.49, 943.22, 900.88, 841.13, 759.20, 697.79, 644.13. HRMS (ESI TOF) *m/z* calcd. For $C_{12}H_{12}O_4$ + Na $[M + Na]^+$ 243.0628, found 243.0639.

(*R*)-4-phenyldihydrofuran-2(3H)-one (8a)

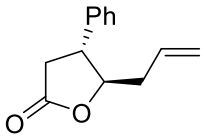


8a

To a stirred solution of 7a (100 mg, 0.45 mmol) in dichloromethane (3 mL) at −78 °C were added successively $BF_3{\cdot}O(C_2H_5)_2$ (0.6 mmol) and Et_3SiH (0.6 mmol) and the reaction mixture was stirred for 30 min maintaining the temperature, after which the reaction mixture was allowed to warm to room temperature. After completion of reaction(monitored by TLC), the reaction mixture was quenched with ethylenediamine (to remove starting material 7a) and saturated $NaHCO_3$,

extracted with dichloromethane, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give 8a. Crude product was purified column chromatography on silica gel using petroleum ether/ethyl (86/14) acetate as eluent. Product obtained as colorless liquid with 75% yield (55 mg). R_f = 0.53 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 2H), 7.34 – 7.28 (m, 1H), 7.26 – 7.22 (m, 2H), 4.67 (dd, *J* = 9.0, 7.9 Hz, 1H), 4.27 (dd, *J* = 9.1, 8.0 Hz, 1H), 3.84 – 3.75 (m, 1H), 2.93 (dd, *J* = 17.5, 8.7 Hz, 1H), 2.68 (dd, *J* = 17.5, 9.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 139.5, 129.3, 127.8, 126.8, 74.2, 41.2, 35.8. FTIR cm^{-1} (neat) 2910.63, 1770.55, 1494.27, 1454.61, 1420.05, 1356.12, 1165.11, 1016.55, 944.76, 903.69, 851.66, 816.28, 757.68, 697.95, 640.73. HRMS (ESI TOF) *m/z* calcd. For $C_{10}H_{10}O_2$ + Na $[M + Na]^+$ 185.0573, found 185.0572. The enantiomeric excess was determined by HPLC analysis using Chiralpak IA, *n*-hexane /*i*-PrOH = 95:05, flow rate = 0.5 mL/min, λ = 254 nm, t_R = 24.2 min (minor) and t_R= 25.5 min (major). *ee* = 93%. Specific rotation $[\alpha]_D^{25}$ = -41.0 (c = 1.0, $CHCl_3$).

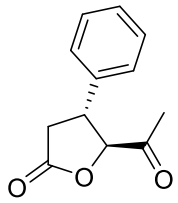
(4*R*,5*R*)-5-allyl-4-phenyldihydrofuran-2(3H)-one (9a)



9a

To a stirred solution of 7a (100 mg, 0.45 mmol) in dichloromethane (3 mL) at −78 °C were added successively $BF_3{\cdot}O(C_2H_5)_2$ (0.6 mmol) and allyltrimethylsilane (0.6 mmol) and the reaction mixture was stirred for 30 min maintaining the temperature, after which the reaction mixture was allowed to warm to room temperature. After completion of reaction(monitored by TLC), the reaction mixture was quenched with ethylenediamine (to remove starting material 7a) and saturated $NaHCO_3$, extracted with dichloromethane, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give 9a. Crude product was purified column chromatography on silica gel using petroleum ether/ethyl (87/13) acetate as eluent. Product obtained as colorless liquid with 55% yield (51 mg). R_f = 0.65 (pet ether/ethyl acetate 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.14 (m, 7H), 5.85 – 5.54 (m, 1H), 5.19 – 5.17 (m, 1H), 5.06 – 4.95 (m, 1H), 4.53 (ddd, *J* = 8.1, 6.7, 4.6 Hz, 1H), 3.39 (dt, *J* = 9.9, 8.5 Hz, 1H), 2.95 (dd, *J* = 17.7, 8.8 Hz, 1H), 2.76 (dd, *J* = 17.8, 10.2 Hz, 1H), 2.54 (dddd, *J* = 12.7, 6.5, 3.7, 1.2 Hz, 1H), 2.42 (ddd, *J* = 14.8, 7.9, 3.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 175.7, 139.0, 137.9, 133.0, 132.3, 129.3, 129.0, 128.0, 127.9, 127.9, 127.4, 119.2, 118.3, 86.0, 83.4, 46.5, 44.5, 37.7, 37.4, 35.9, 35.7. FTIR cm^{-1} (neat) 2922.75, 1775.85, 1642.73, 1497.59, 1454.70, 1421.65, 1341.20, 1188.68, 1093.32, 986.51, 917.43, 760.65, 701.99, 667.79. HRMS (ESI TOF) *m/z* calcd. For $C_{13}H_{14}O_2$ + Na $[M + Na]^+$ 225.0886, found 225.0884. Specific rotation $[\alpha]_D^{25}$ = -40.9 (c = 0.5, $CHCl_3$, with trace of *cis* isomer).

Gram Scale Synthesis of 6a



6a (*trans* + *cis*)

Following general procedure by using Meldrum's acid (1.5 g, 10.4 mmol, 1equiv.), benzaldehyde (1.17 mL, 11.45 mmol, 1.1 equiv.), hydroxyacetone (2.14 mL, 31.2 mmol, 3 equiv.), Q2 (168.31 g, 0.52 mmol, 5 mol%), TFA (79.64 µL, 1.04 mmol, 10 mol%). After completion of the reaction (Confirmed by TLC), product was purified by column chromatography (as slurry) without work up. The product was purified on silica gel using petroleum ether/ethyl acetate (85:15). Compound **6a** (trans + cis) was obtained as white solid in 75% yield (1.59 g) without loss of enantioselectivity (95% ee).

4.7 Appendix IV: ^{1}H, ^{13}C and HPLC spectral data of representative compounds

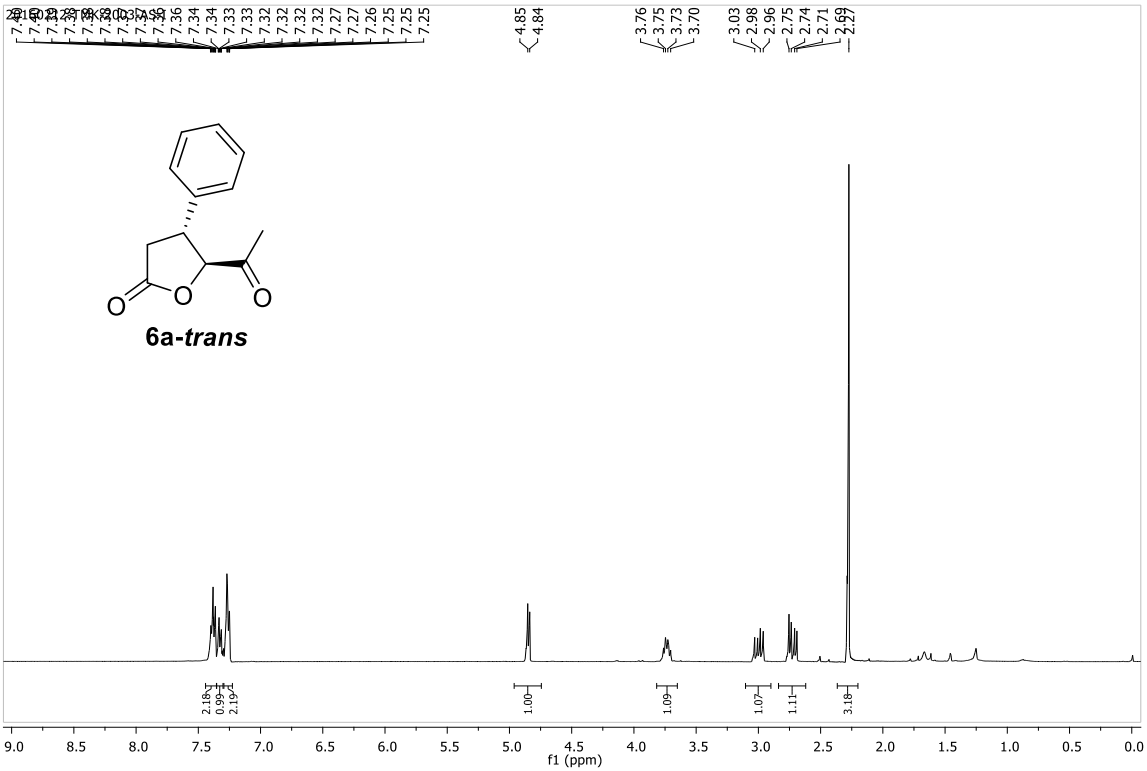


Figure AIV.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **6a$_{trans}$**

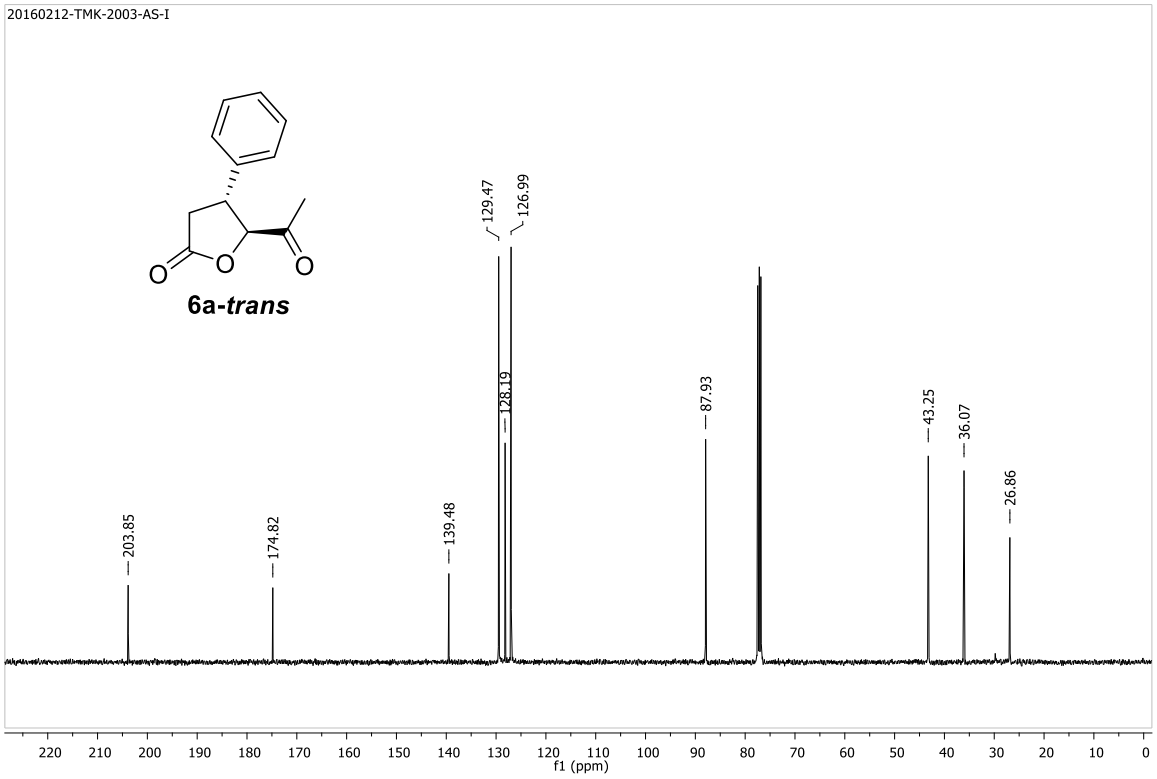
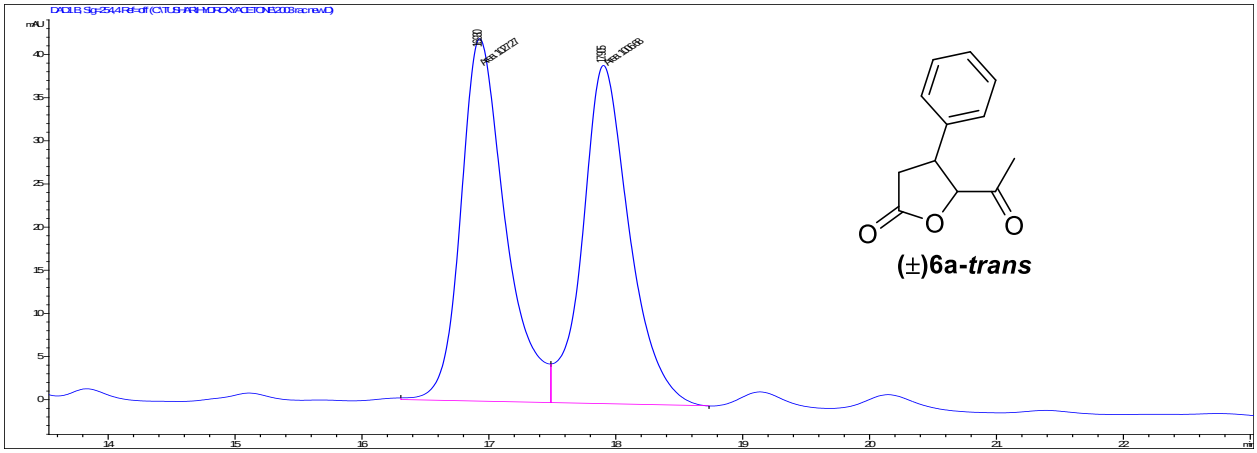
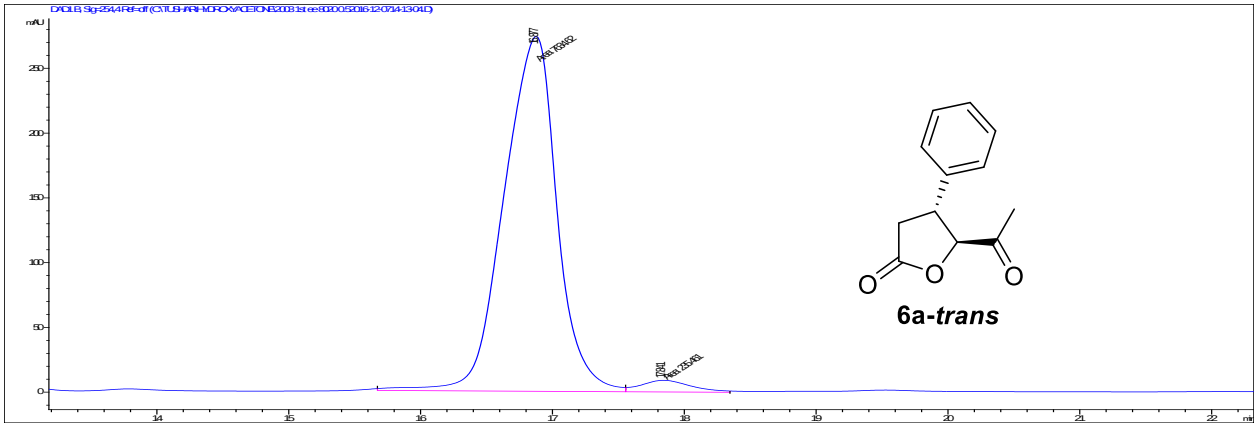


Figure AIV.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **6b$_{trans}$**



Signal 1: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.930	MF	0.4075	1027.27429	42.01900	50.5062
2	17.905	FM	0.4281	1006.68317	39.19172	49.4938
Totals :				2033.95746	81.21072	



Signal 1: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.877	MF	0.4645	7634.61865	273.95303	97.0082
2	17.841	FM	0.4384	235.46097	8.95155	2.9918
Totals :				7870.07962	282.90458	

Figure AIV.3: HPLC profile of compound **6a$_{trans}$**

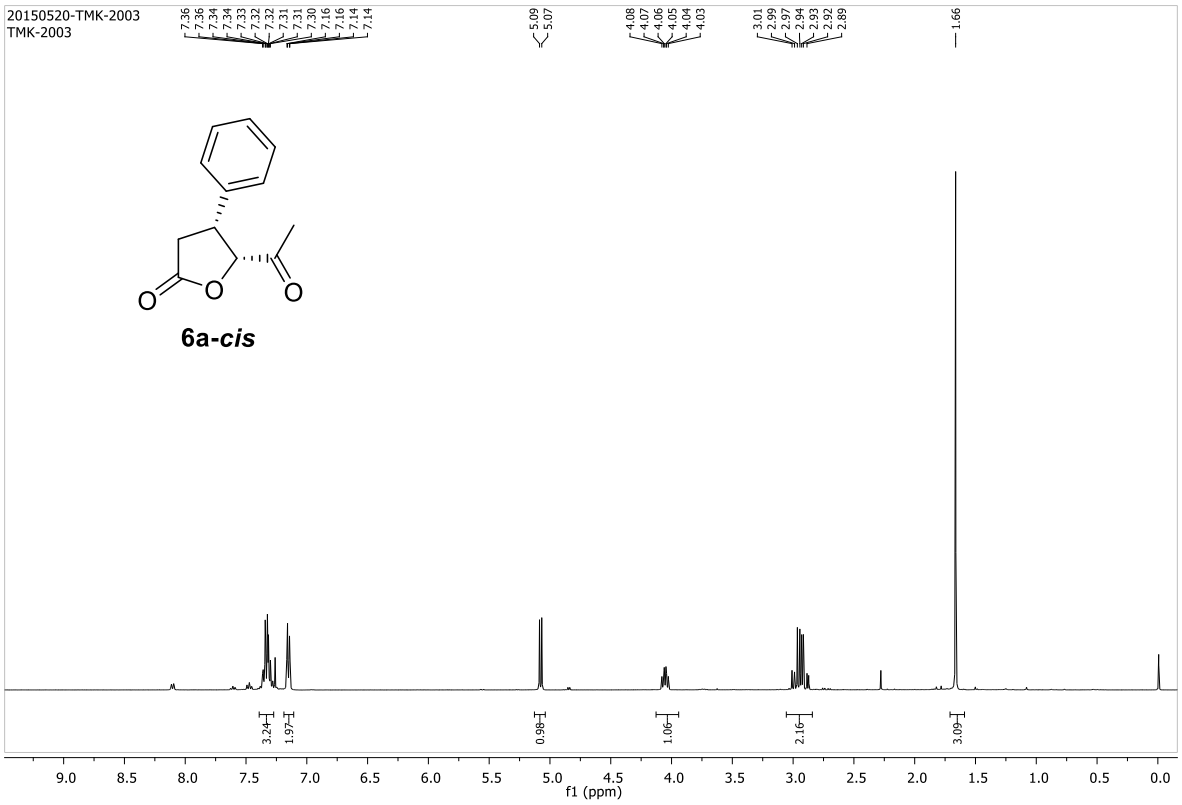


Figure AIV.4: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **6a$_{cis}$**

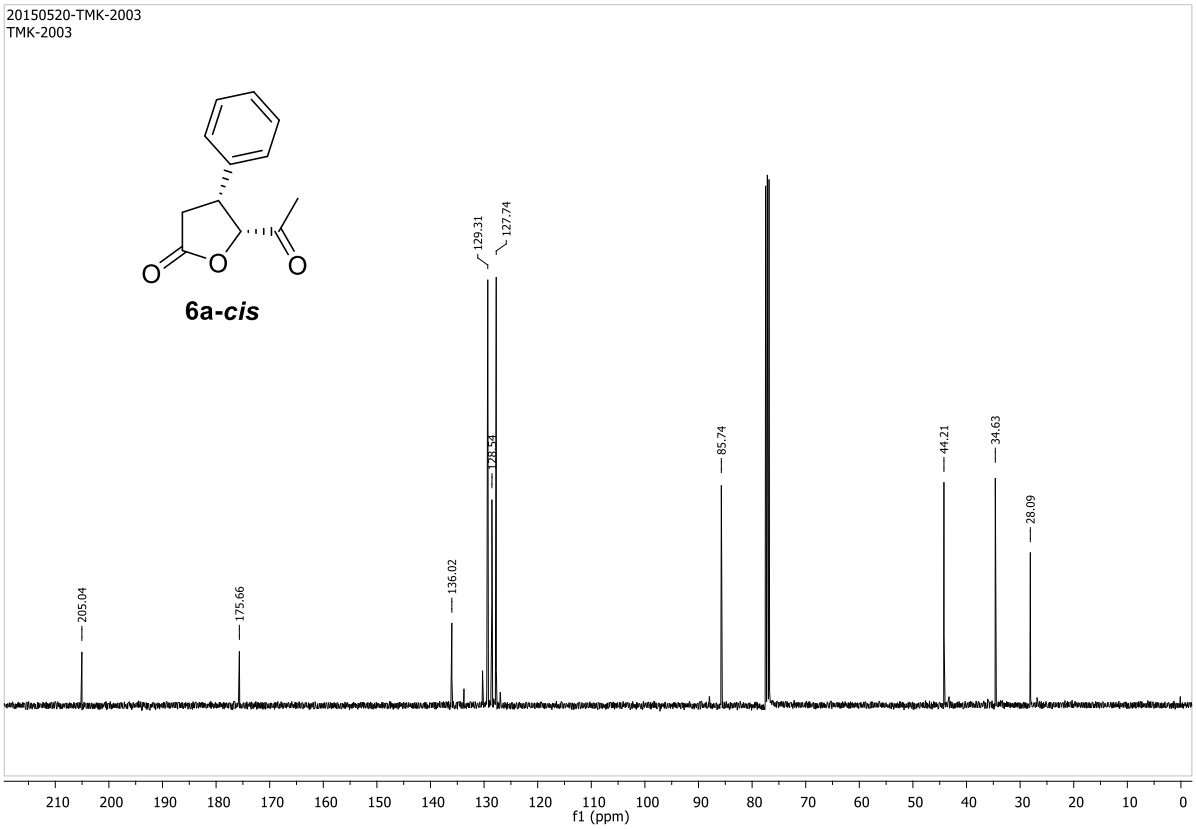
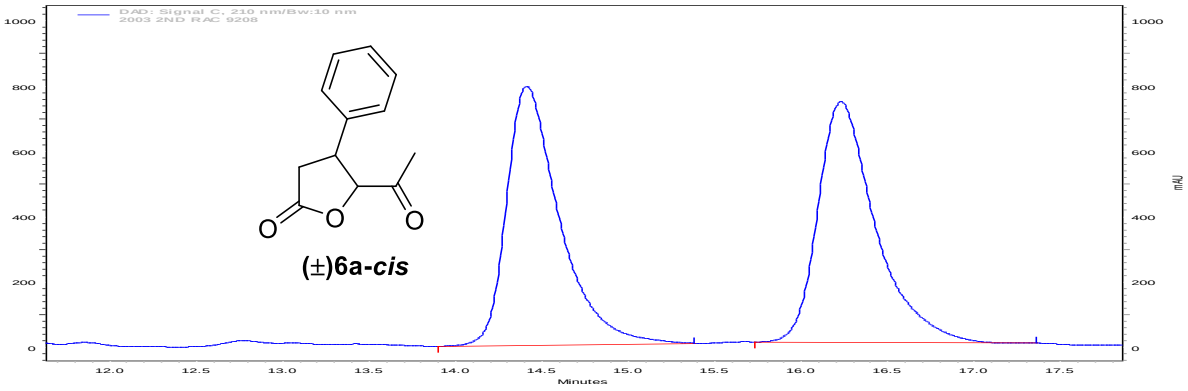
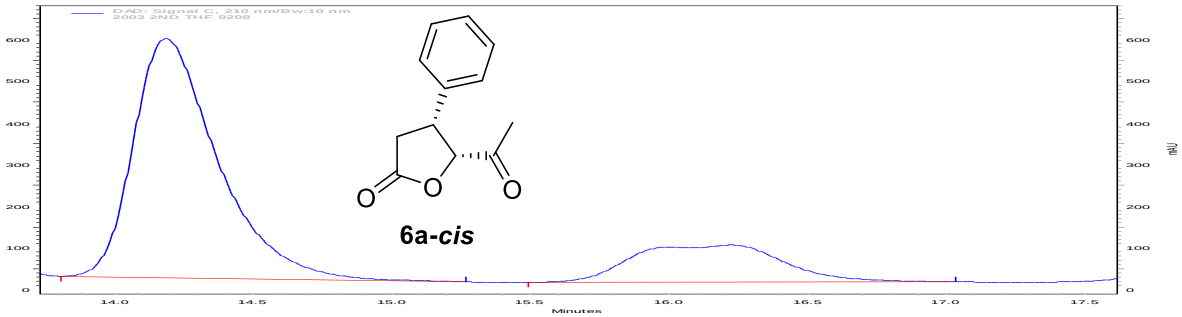


Figure AIV.5: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **6b$_{cis}$**



DAD: Signal B, 210 nm/Bw:8 nm Results

Retention Time	Area	Area %	Height	Height %
14.407	35378001	49.69	1662211	51.82
16.227	35817308	50.31	1545289	48.18
Totals	71195309	100.00	3207500	100.00



DAD: Signal C, 210 nm/Bw:10 nm Results

Retention Time	Area	Area %	Height	Height %
14.187	25420179	78.34	1202580	86.58
16.220	7027181	21.66	186416	13.42
Totals	32447360	100.00	1388996	100.00

Figure AIV.6: HPLC profile of compound **$6a_{cis}$**

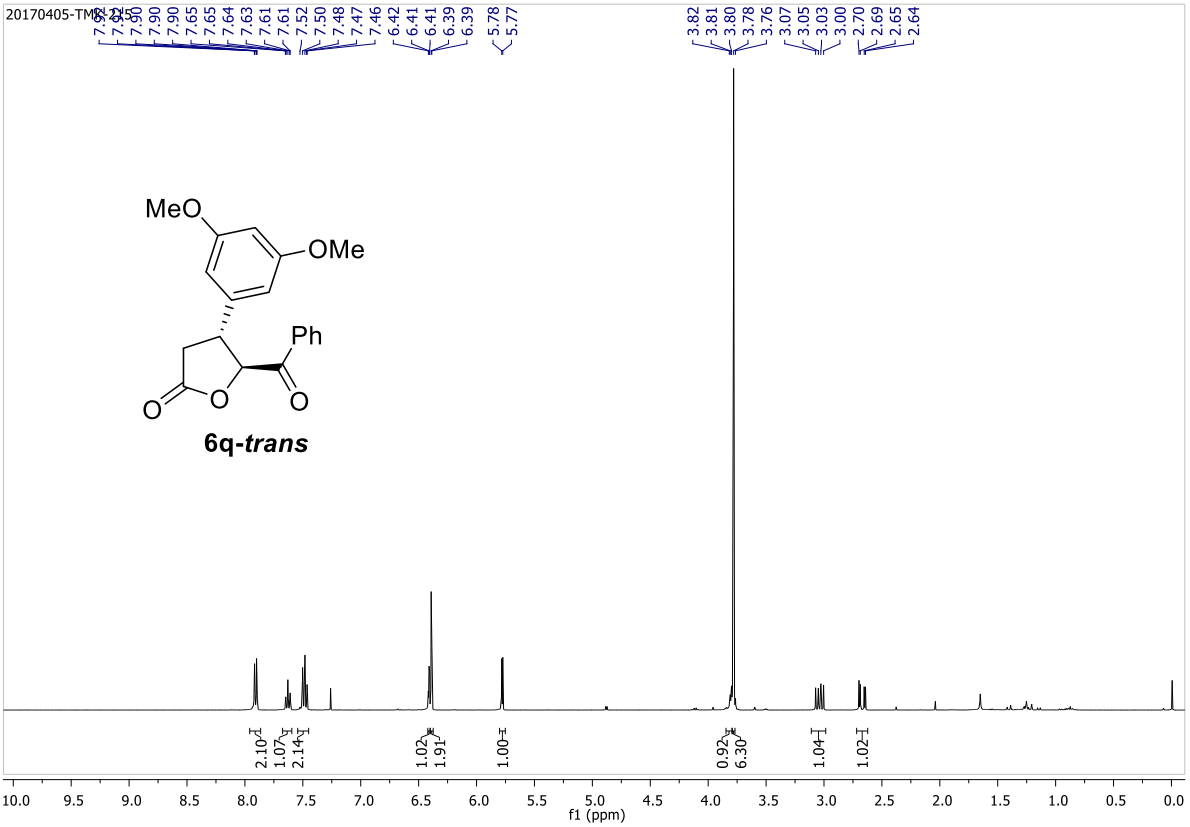


Figure AIV.7: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **6q$_{trans}$**

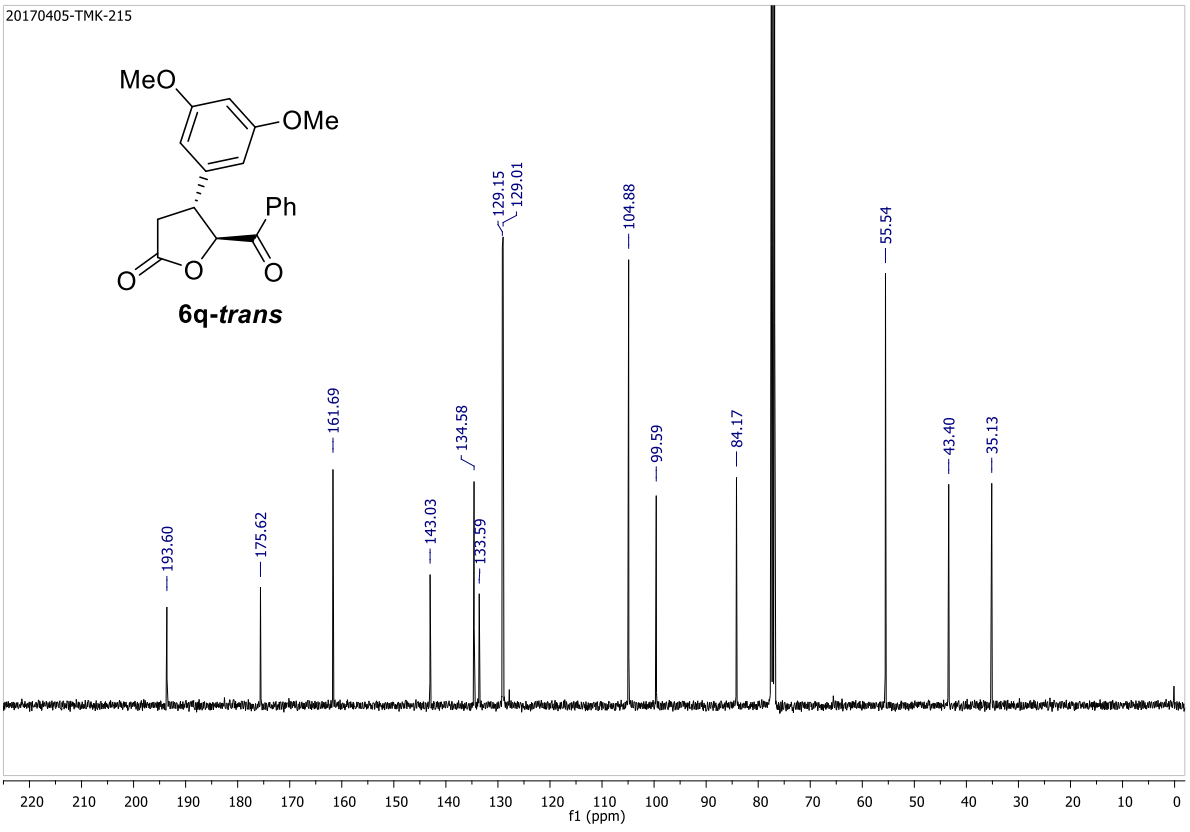
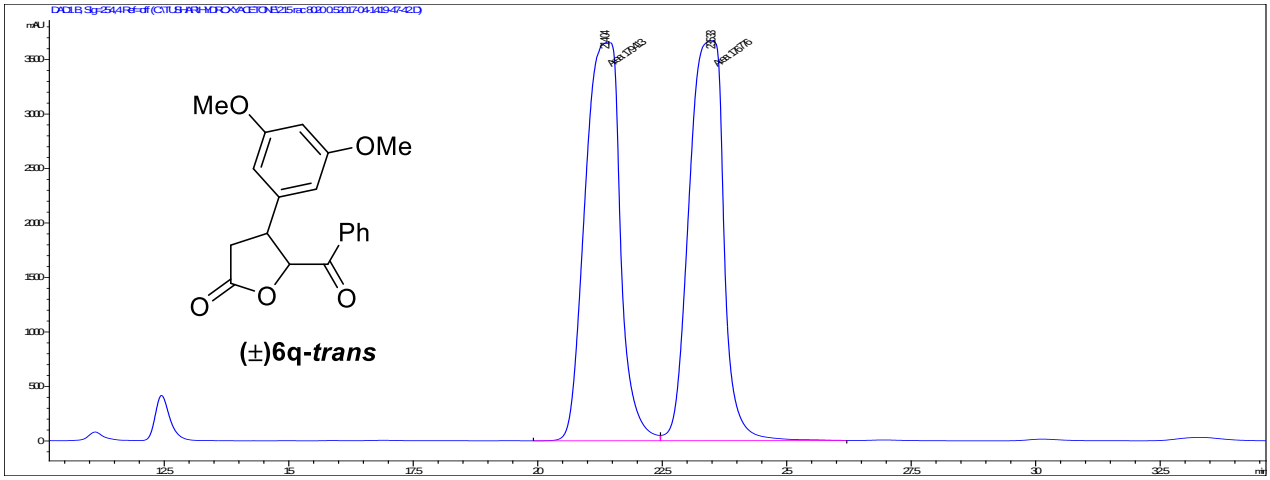
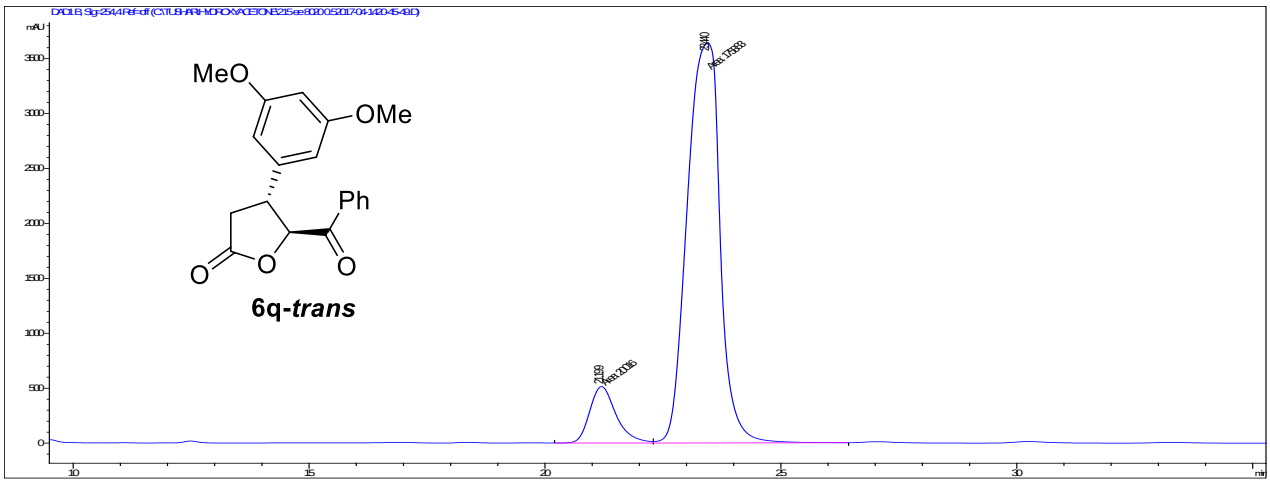


Figure AIV.8: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **6q$_{trans}$**



Signal 1: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.404	MF	0.8170	1.79413e5	3660.07861	50.3702
2	23.533	FM	0.8019	1.76776e5	3674.00464	49.6298
Totals :				3.56189e5	7334.08325	



Signal 1: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.199	MF	0.6496	2.00160e4	513.56549	10.2175
2	23.440	FM	0.8044	1.75883e5	3644.01172	89.7825
Totals :				1.95899e5	4157.57721	

Figure AIV.9: HPLC profile of compound **6q$_{trans}$**

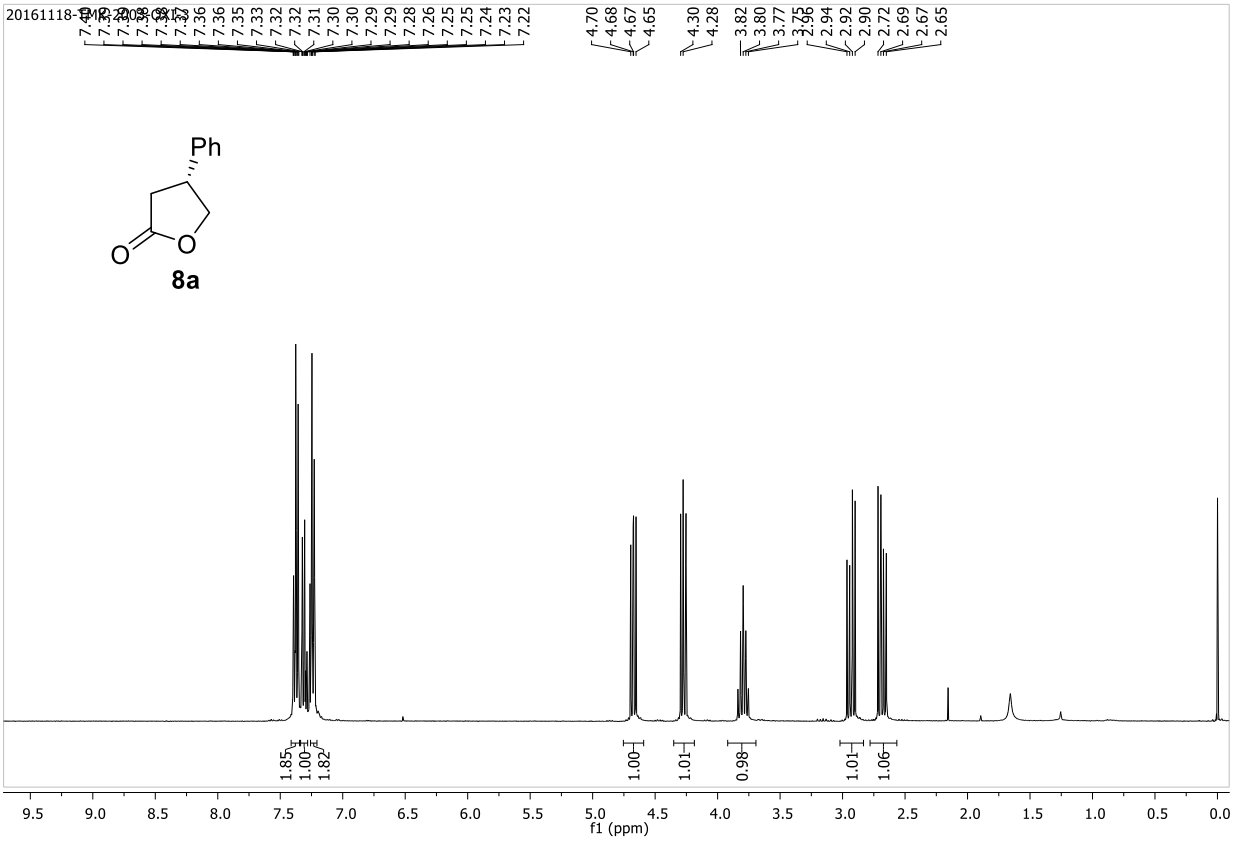


Figure AIV.10: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8a**

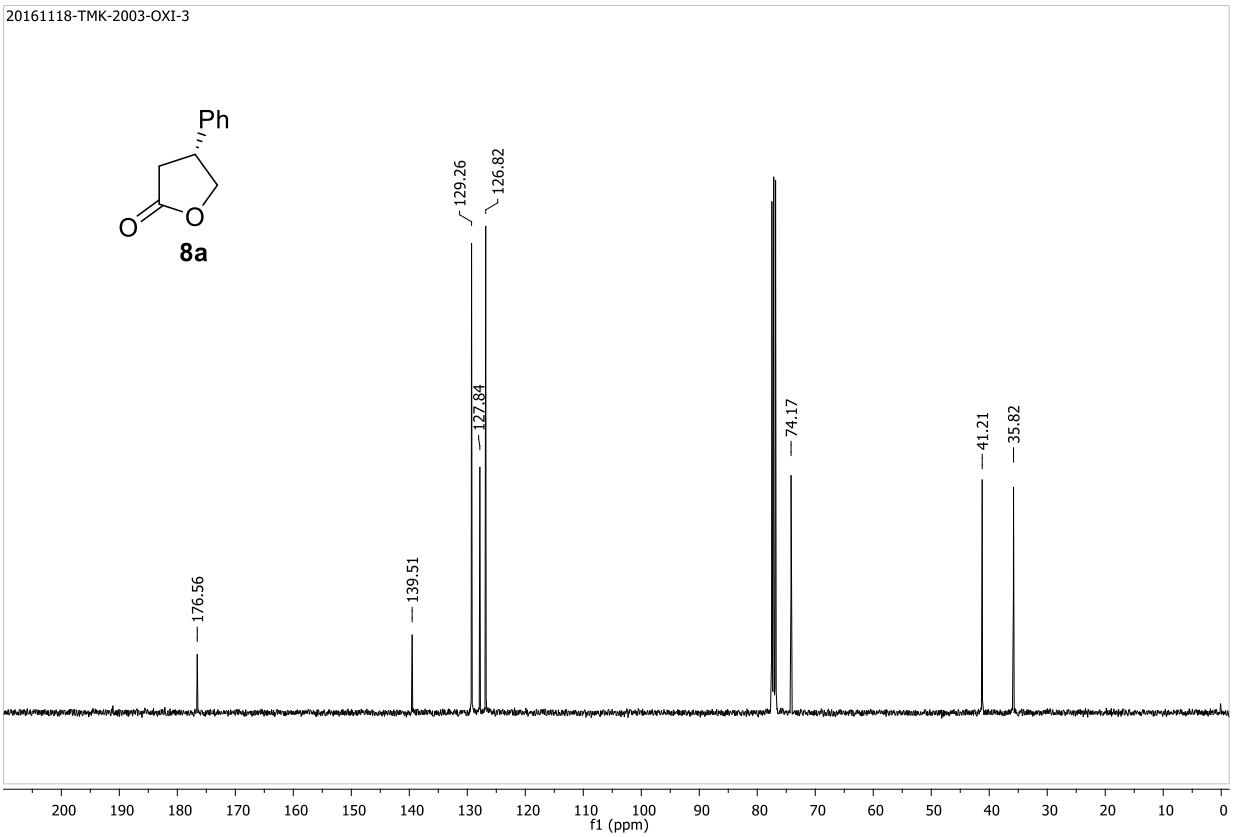
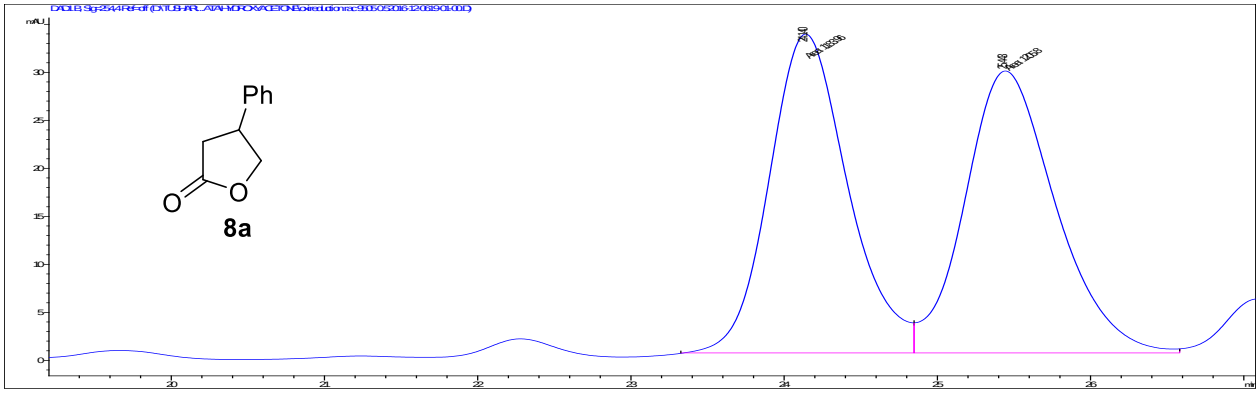
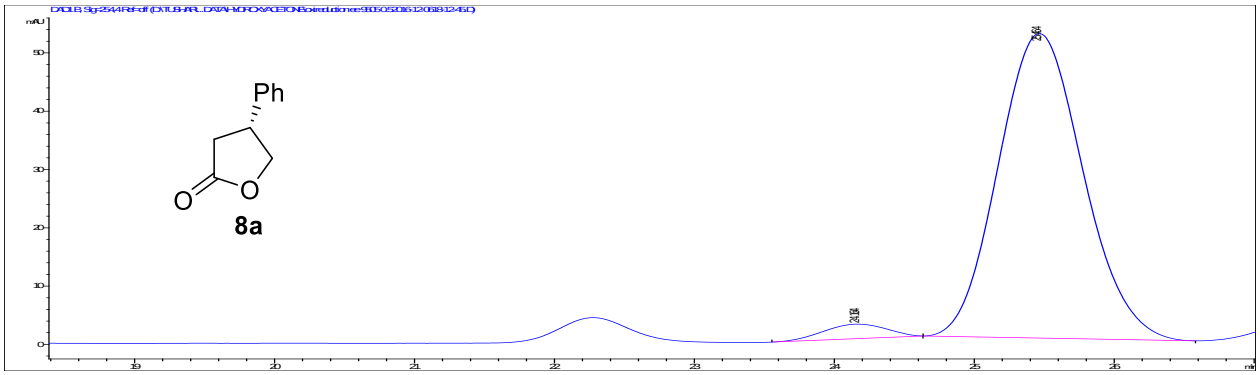


Figure AIV.11: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **8a**



Signal 1: DAD1 B, Sig=254,4 Ref=off

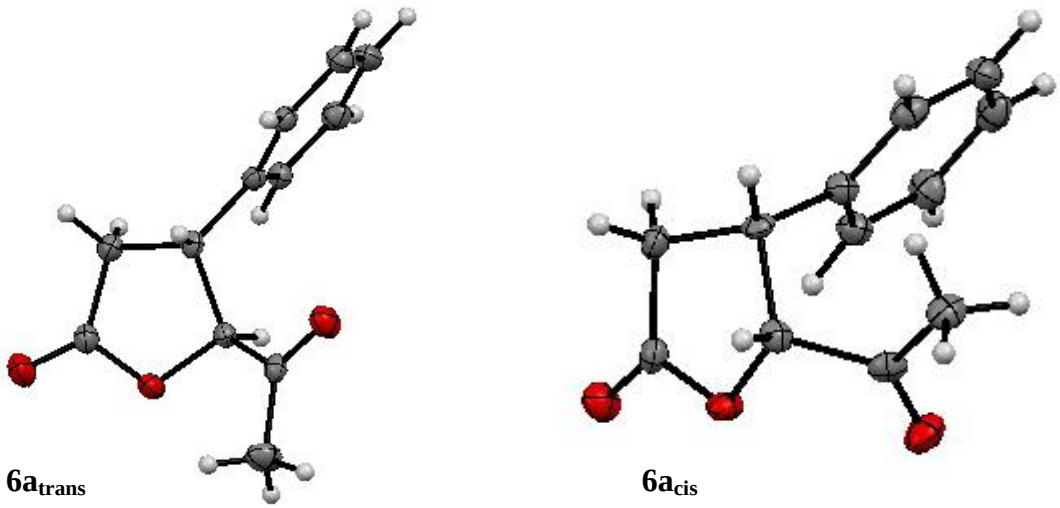
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.140	MF	0.5941	1183.96204	33.21460	49.5432
2	25.443	FM	0.6845	1205.79504	29.36101	50.4568
Totals :				2389.75708	62.57560	



Signal 1: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.164	BB	0.4874	77.45628	2.48692	3.4081
2	25.464	BB	0.6601	2195.25610	52.25633	96.5919
Totals :				2272.71238	54.74325	

Figure AIV.12: HPLC profile of compound **8a**



6a$_{trans}$ **6a$_{cis}$**

Figure AIV.13: X-ray single crystal structures of compounds **6a$_{trans}$** and **6a$_{cis}$**

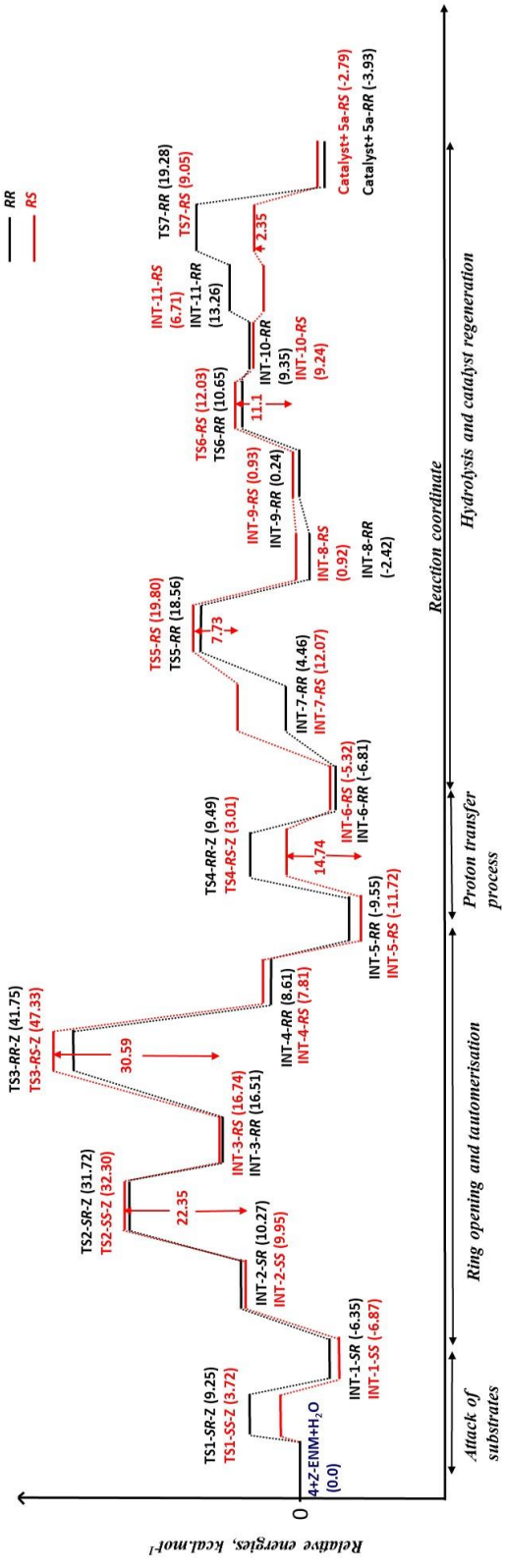
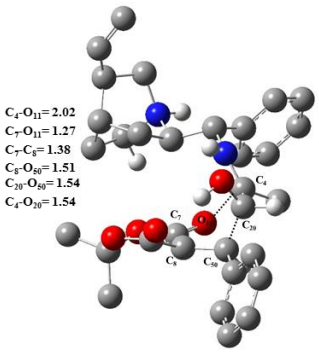
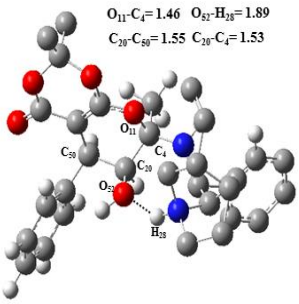


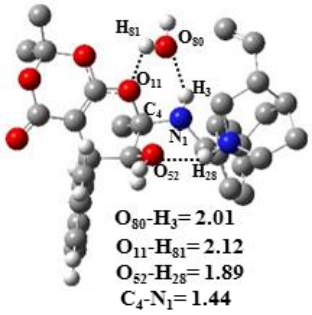
Figure AIV 14: Relative energy profiles for the cycloaddition reaction followed by ring opening and hydrolysis for regeneration of the catalyst (values of ΔG are given in parentheses). Product **6a**$_{\mathbf{trans}}$ is generated along the red pathway. Product **6a**$_{\mathbf{cis}}$ is generated along the black pathway.



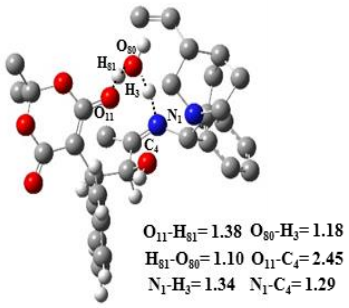
TS1-*SS*



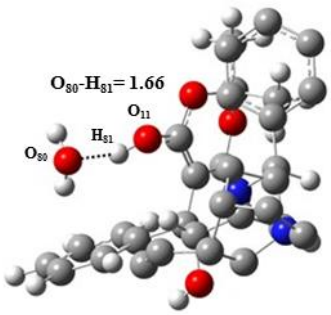
INT-1-*SS*



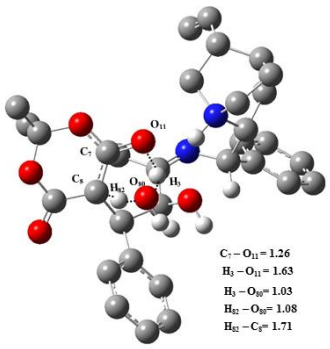
INT-2-*SS*



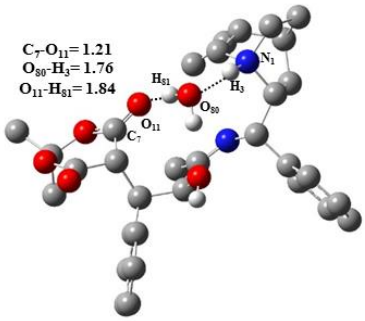
TS2-*SS*



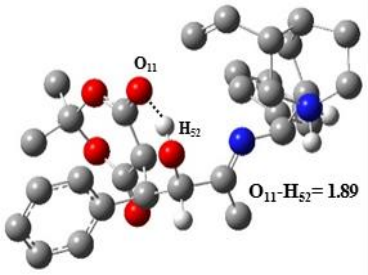
INT-3-*RS*



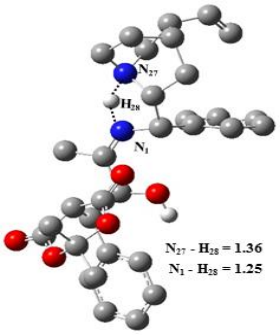
TS3-*RS*



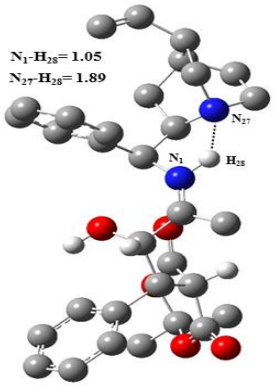
INT-4-*RS*



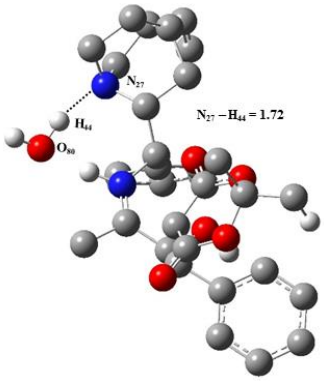
INT-5-*RS*



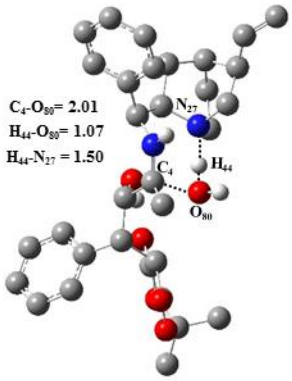
TS4-*RS*



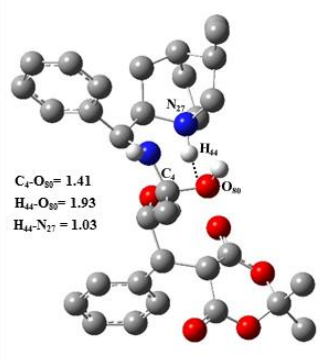
INT-6-*RS*



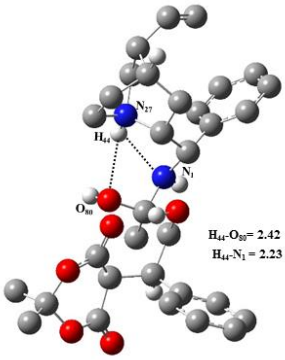
INT-7-*RS*



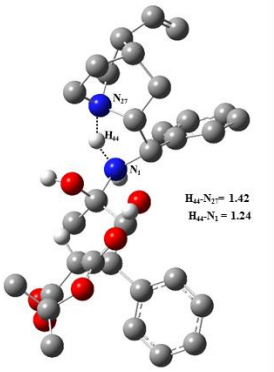
TS5-*RS*



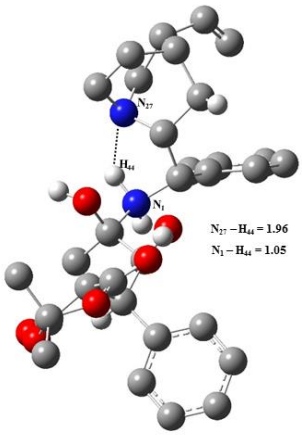
INT-8-*RS*



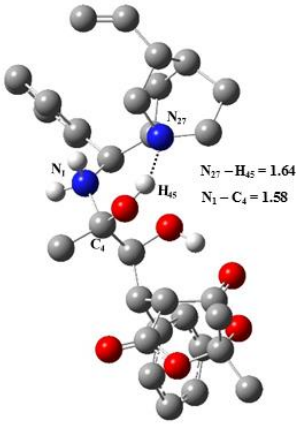
INT-9-*RS*



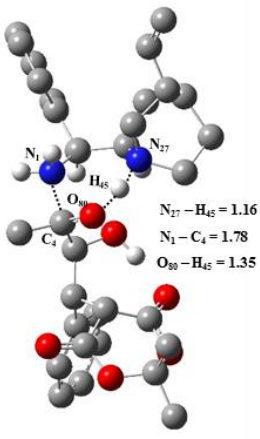
TS6-*RS*



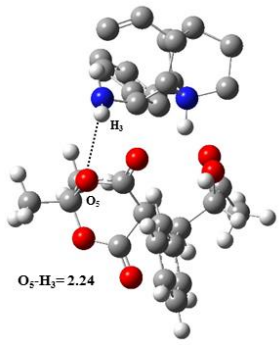
INT-10-*RS*



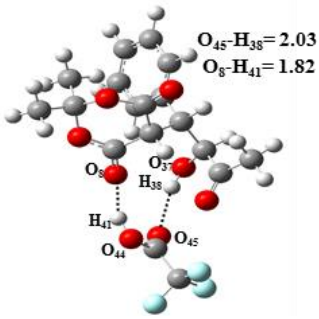
INT-11-*RS*



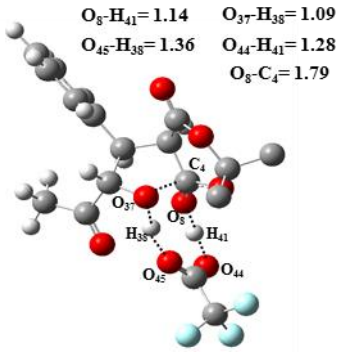
TS7-*RS*



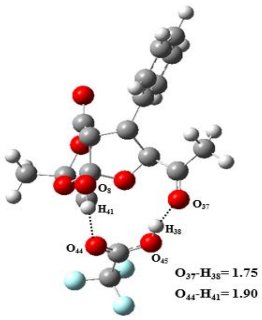
5a-*RS*+CAT



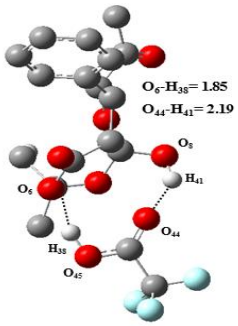
INT-12-*RS*



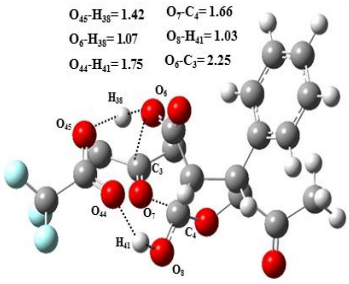
TS8-*RS*



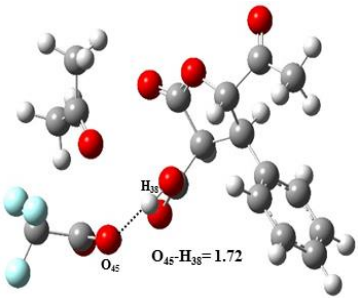
INT-13-*RS*



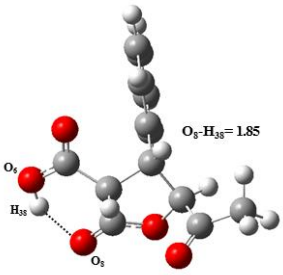
INT-14-*RS*



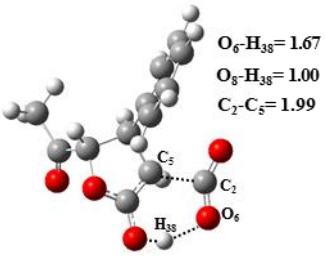
TS9-*RS*



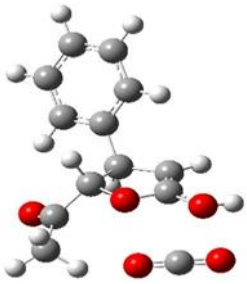
INT-15-*RS* + act



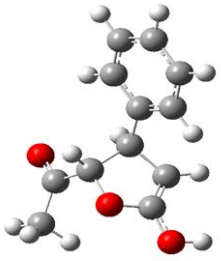
INT-16-*RS*



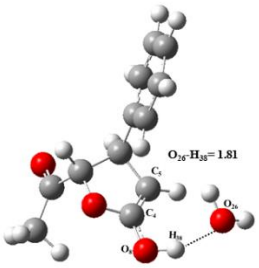
TS10-*RS*



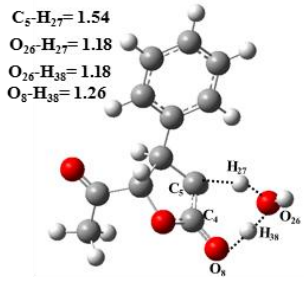
INT-17-*RS*+CO_2



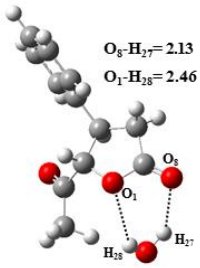
INT-17-*RS*



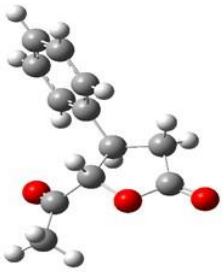
INT-18-*RS*



TS11-*RS*



INT-19-*RS*



6a-*RS* (*trans*)

Figure AIV 15: Optimized geometries and selected geometric parameters for the formation of product $\mathbf{6a_{trans}}$. Some hydrogen atoms not involved in reaction sites are omitted. Distances are in Å

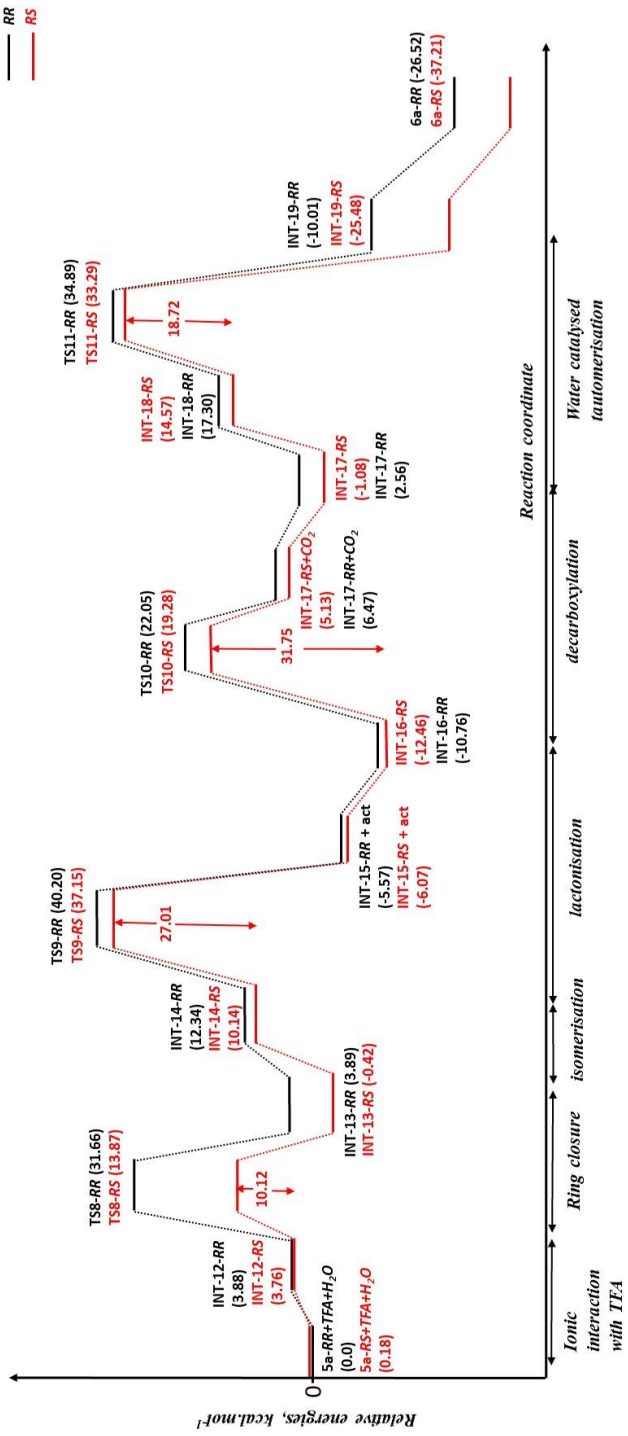
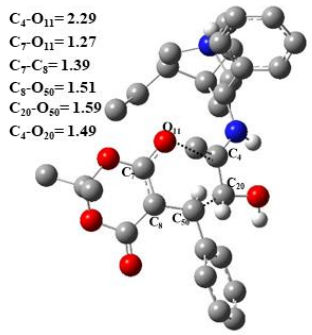
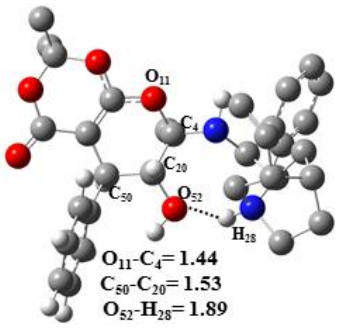


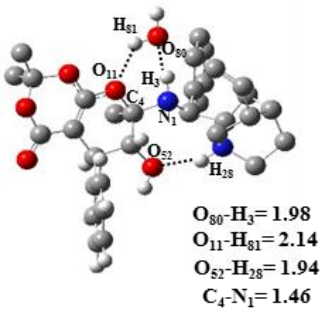
Figure AIV 16: Relative energy profiles for the TFA assisted lactonisation of intermediate **5a** (values of ΔG are given in parentheses). Product $\mathbf{6a_{trans}}$ is generated along the red pathway. Product $\mathbf{6a_{cis}}$ is generated along the black pathway.



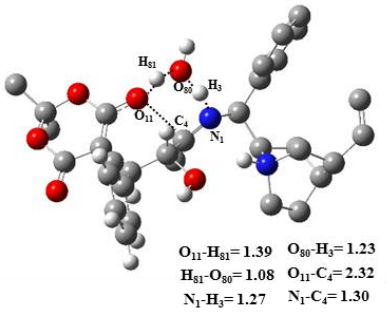
TS1-*SR*



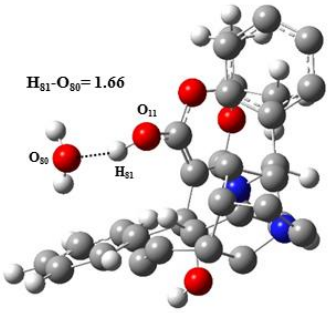
INT-1-*SR*



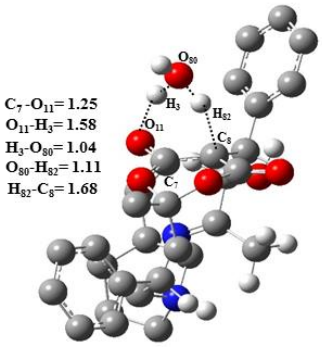
INT-2-*SR*



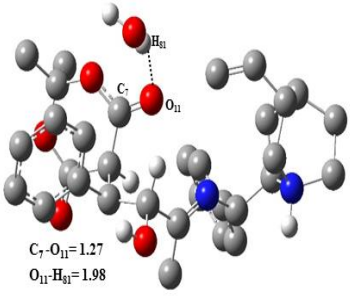
TS2-*SR*



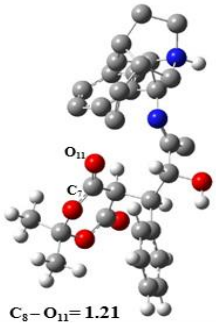
INT-3-*RR*



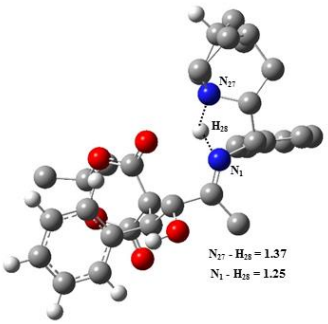
TS3-*RR*



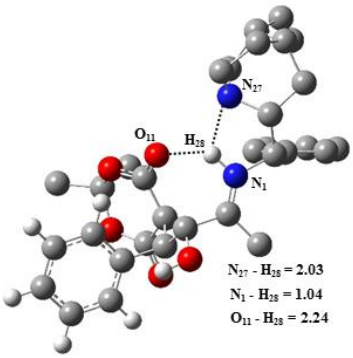
INT-4-*RR*



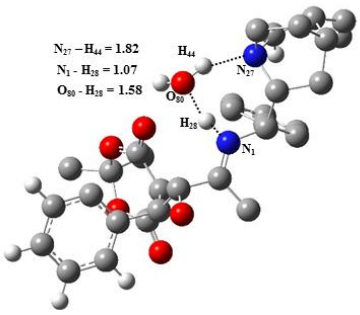
INT-5-*RR*



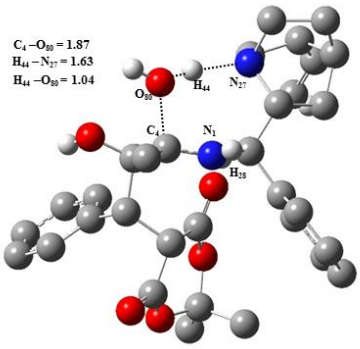
TS4-*RR*



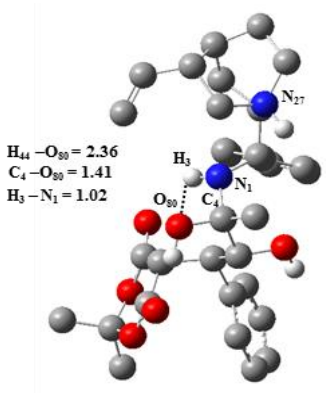
INT-6-*RR*



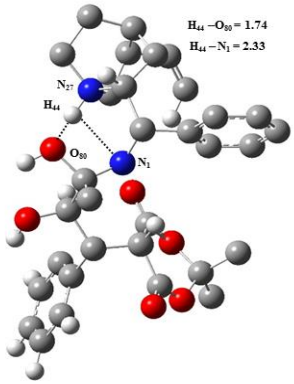
INT-7-*RR*



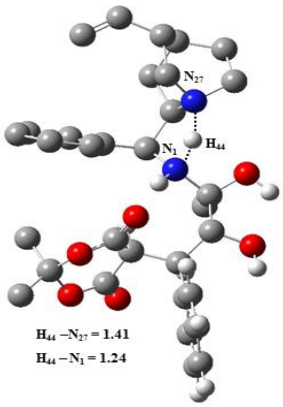
TS5-*RR*



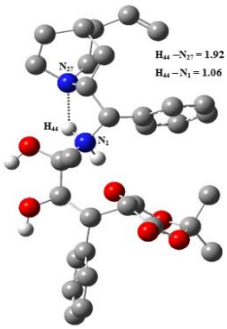
INT-8-*RR*



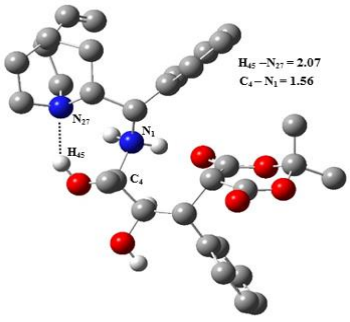
INT-9-*RR*



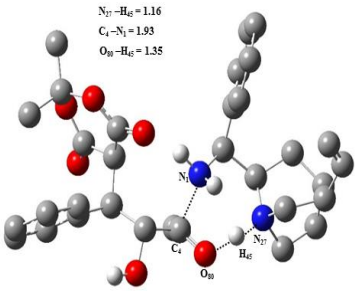
TS6-*RR*



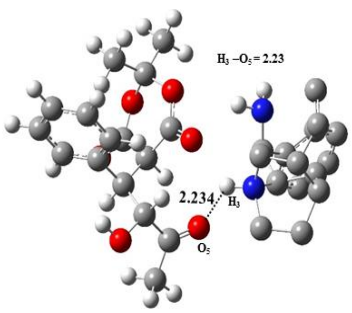
INT-10-*RR*



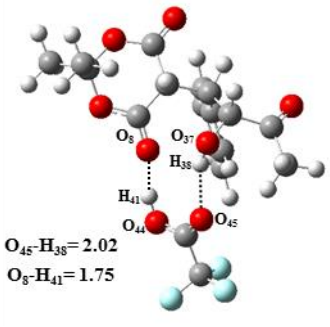
INT-11-*RR*



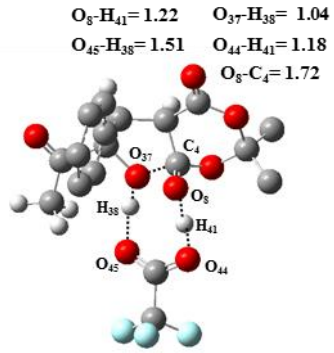
TS7-*RR*



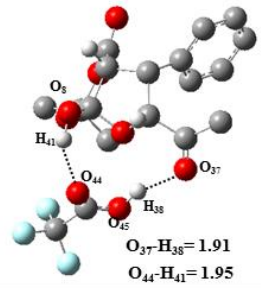
5a-*RR*+CAT



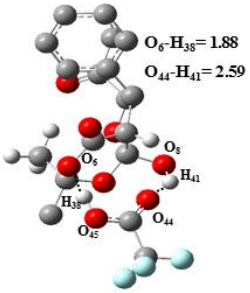
INT-12-*RR*



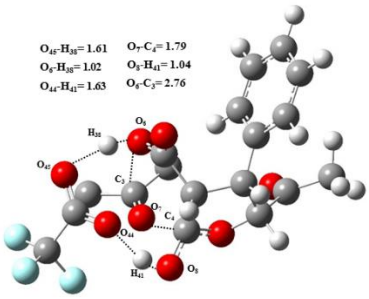
TS8-*RR*



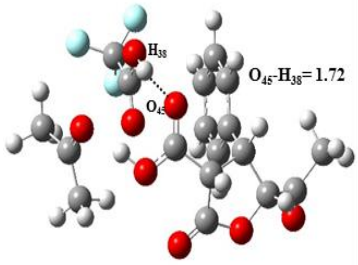
INT-13-*RR*



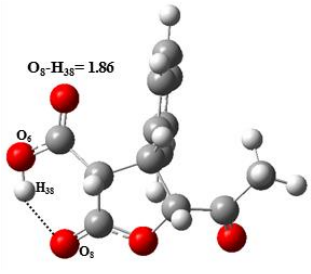
INT-14-*RR*



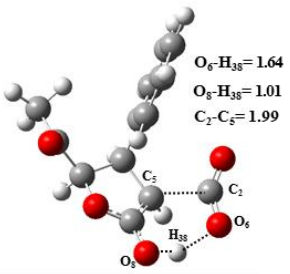
TS9-*RR*



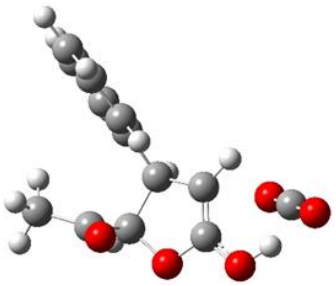
INT-15-*RR*+ act

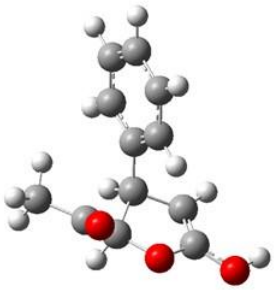


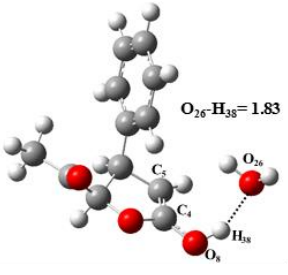
INT-16-*RR*



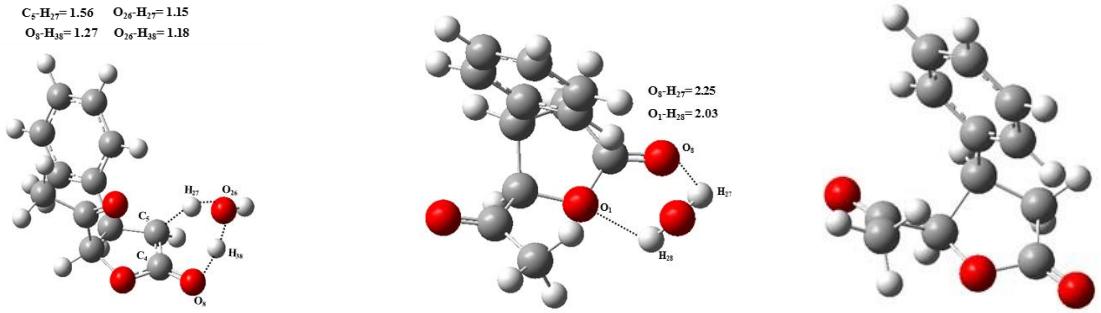
TS10-*RR*







INT-17-*RR*+CO_2 **INT-17-*RR*** **INT-18-*RR***



TS11-*RR* **INT-19-*RR*** **6a-*RR* (*cis*)**

Figure AIV 16: Optimized geometries and selected geometric parameters for the formation of product $\mathbf{6a_{cis}}$. Some hydrogen atoms not involved in reaction sites are omitted. Distances are in Å

4.8 References

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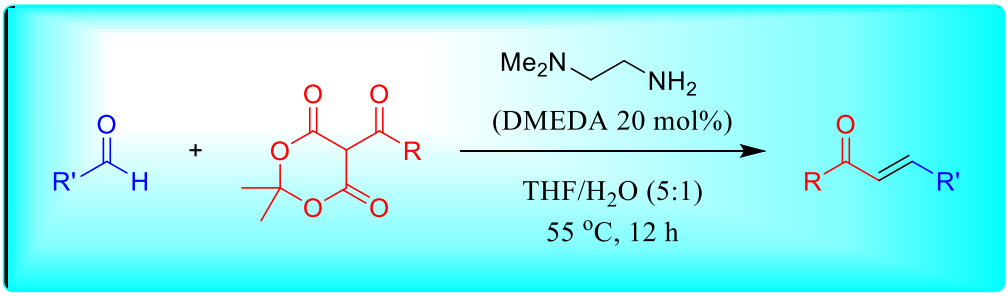
Chapter 5

Direct Organocatalytic Synthesis of α,β-Unsaturated Carbonyl Compounds



5 Direct Organocatalytic Synthesis of *α,β*-Unsaturated Carbonyl Compounds

Operationally simple, robust and straightforward organocatalytic protocol is developed for the synthesis of E-selctive α,β-unsaturated carbonyl compounds. The method utilizes simple and easily accessible starting materials such as Meldrum's acid, aldehyde and simple catalyst. The tandem organocatalytic process utilizes acyl/aroyl Meldrum's acid as a enolate surrogate for the effective Doebner-Knoevenagel type condensation reactions. A wide variety of aldehydes, acids and base sensitive functional groups are well tolerated under the mild reaction conditions.

5.1 Introduction

α,β-unsaturated carbonyl compounds are frequently used as starting materials in various transformations in organic synthesis. The vinylogy due to the vinylogous carbonyl functional group makes them chemically different from their constituents analogous such as simple carbonyl compounds and olefins. Their electronic effects and reactivity patterns are relatively different from that of simple carbonyl compounds due to the presence of vinylogy. Many of the stereoselective chemical transformations make use of *α,β*-unsaturated carbonyl scaffolds to construct a diverse array of organic compounds (Figure 5.1). The *α,β*-unsaturated carbonyl compounds **5** have been utilized for the nucleophilic 1,2-addition and 1,4-Michael addition (conjugate addition) to give the corresponding compounds (**11** and **12**). They are also prone to undergo cascade reaction through simultaneous 1,4-Michael addition and attack on electrophiles to give the corresponding Michael addition products (**13**). Similarly, *α,β*-unsaturated carbonyl compounds **5** have been explored in Diels-Alder and Hetero-Diels-Alder reactions to afford valuable intermediates (**14** and **15**). The reaction *α,β*-unsaturated carbonyl compounds **5** under Click chemistry reaction conditions affords valuable heterocycles (**16**). Corresponding epoxides (**17**) and aziridines (**18**) have been synthesized via epoxidation and aziridination of *α,β*-unsaturated carbonyl compounds **5**. The cascade reactions are particularly very important and play a significant role in the fields of academia and pharmaceutical, polymer and agriculture industries (Figure 5.1).[1]

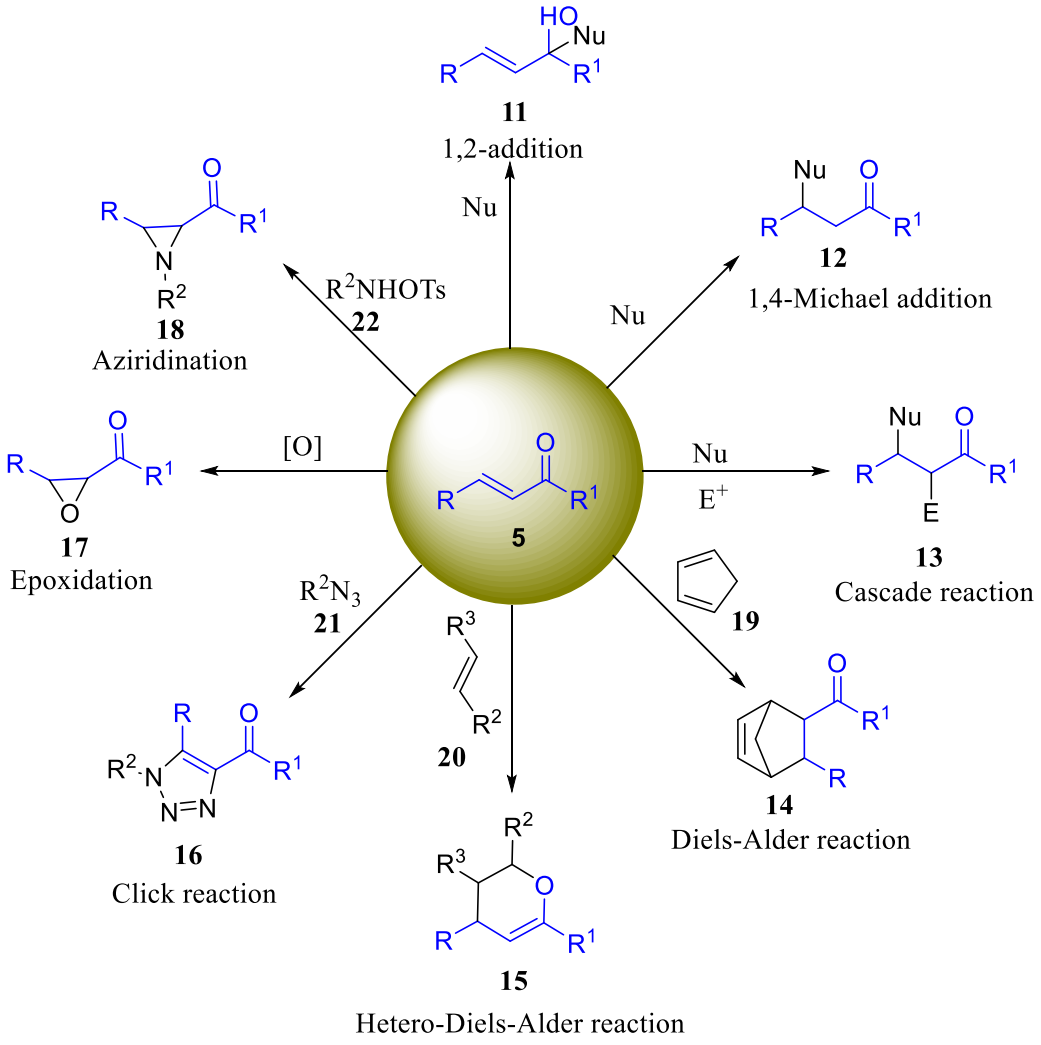
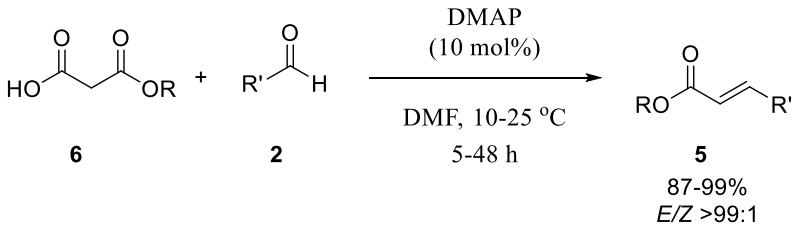


Figure 5.1: Transformations of *α,β*-unsaturated carbonyl compounds

Evidently, a plenty of methods are available in the literature for the synthesis of *α,β*-unsaturated carbonyl compounds owing to their importance. Most frequently used methods include Wittig reaction[2] and Horner–Wadsworth–Emmons reaction.[3] Though these methods are routinely used, they produce a stoichiometric amount of by-products such as triphenylphosphine oxide and other phosphine salts and generate a lot of waste. Doebner-Knoevenagel type reactions[4] which utilize active methylene compounds such as malonic acid half ester,[4a] *β*-keto acid[4d] and trifluoroacetate derivatives[4b] and organocatalytic aldol condensation[4c] are some of the notable methods to synthesize *α,β*-unsaturated carbonyl compounds. Some of these selected methods have been described here.

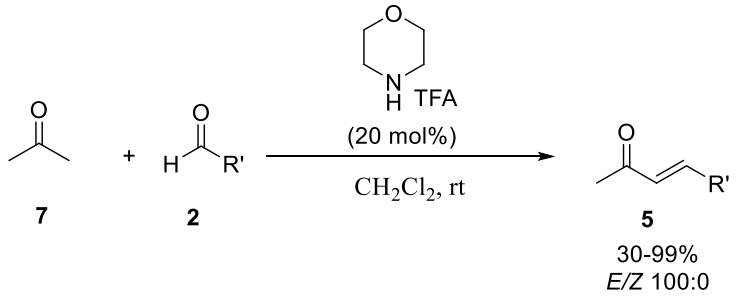
5.2 Previous synthetic approaches to access *α,β*-unsaturated carbonyl compounds

In 2005, List and co-workers[4a] developed an efficient decarboxylative Doebner-Knoevenagel-type reaction to access *α,β*-unsaturated esters. The protocol utilizes aldehyde **2** and malonic acid half esters **6** along with catalytic amount DMAP (Scheme 5.1). This DMAP catalyzed reaction overcame some of the difficulties such as achieving higher *E*/*Z* selectivity and chemoselectivity. The reaction exclusively afforded *α,β*-unsaturated ester **5** and did not yield any undesired *β,γ*-unsaturated ester. This efficient protocol gives an access to *α,β*-unsaturated esters **5** starting from both aliphatic and aromatic substrates in excellent yields (up to 99%) with excellent stereoselectivity (*E/Z* ratio >99:1).



Scheme 5.1: Doebner-Knoevenagel-type reaction by List and co-workers

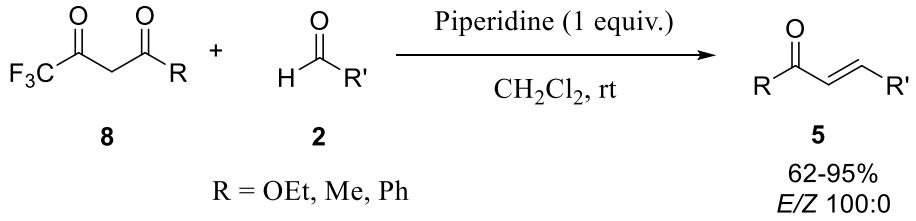
In the year 2010, List and co-workers [4c] reported a protocol to access *α,β*-unsaturated ketones **5** via an aldol condensation reaction of acetone **7** and aldehydes **2** in the presence of catalytic amount of morpholinium trifluoroacetate (20 mol%) (Scheme 5.2). This protocol proved to be efficient and both aliphatic as well as aromatic substrates reacted smoothly under the reaction conditions to afford the corresponding *α,β*-unsaturated ketones **5** in good to excellent yields (up to 99%) and high stereoselectivity.



Scheme 5.2: Aldol condensation reaction by List and co-workers

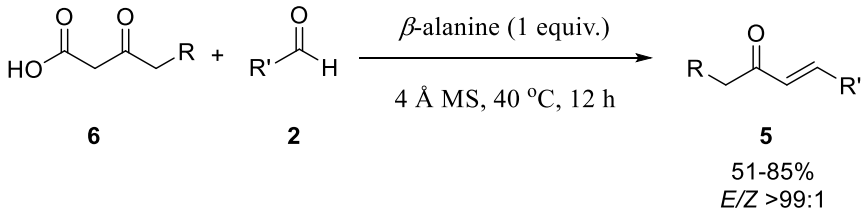
In 2010, China Raju and co-workers[4b] reported piperidine mediated condensation reaction between fluorinated 1,3-diketo compounds **8** and aldehydes **2** for the synthesis of *α,β*-unsaturated ketones **5** (Scheme 5.3). The protocol afforded the desired products in good

to excellent yields (62-95%), however the use of strong base such as piperidine was unavoidable.



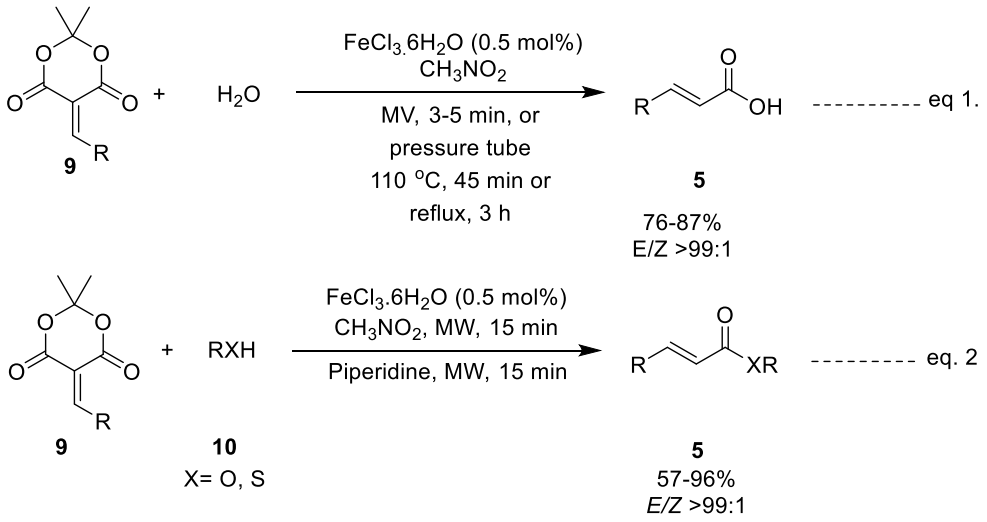
Scheme 5.3: Synthesis of *α,β*-unsaturated ketones and esters by China Raju and co-workers

In 2011, Taddei and co-workers[4d] developed a method for the synthesis of *α,β*-unsaturated ketones **5** starting from *β*-keto acids **6** and aldehydes **2** via Doebner-Knoevenagel-type reaction (Scheme 5.4). The protocol explored the use of relatively milder reagent such as *β*-alanine to afford *α,β*-unsaturated ketones **5** in very good yields (up to 85%) with excellent stereoselectivity (*E/Z* >99:1). However, this method proved to be ineffective for aromatic *β*-keto acids **6**.



Scheme 5.4: Synthesis of *α,β*-unsaturated ketones by Taddei and co-workers

Recently our group[4e,4f] reported microwave assisted $FeCl_3.6H_2O$ catalyzed synthesis of *α,β*-unsaturated carbonyl compounds **5** starting from alkylidene Meldrum's acid **9** (Scheme 5.5). The protocol explored the use of easily accessible alkylidene Meldrum's acid **9** for the synthesis of variety of *α,β*-unsaturated acids (eq. 1 Scheme 5.5), esters and thioesters (eq. 2 Scheme 5.5) with excellent *E*-selectivity (*E/Z* >99:1) in good to excellent yields.



Scheme 5.5: Synthesis of *α,β*-unsaturated acids, esters and thioesters by Bhat and co-workers

Although, various methods are available in the literature, some of these methods either suffer due to limited substrate scope or use of a stoichiometric amount of base. Other synthetic protocols include synthesis of chalcone by various approaches. Some of the methods utilized strong base, Lewis acid such as $TiCl_4$ to promote aldol condensation of ketones,[5] IBX oxidation of ketones to afford *α,β*-unsaturated ketones.[6] Likewise, carbonyl olefination has been explored for the synthesis of *α,β*-unsaturated ketones in presence of catalytic amount of AgI,[7] and BF_3[8] The basic anion-exchange resins were employed to catalyze aldol condensations to afford *α,β*-unsaturated ketones starting from. ketones and aldehydes.[9] Many other approaches utilized metal reagents and catalysts to access *α,β*-unsaturated carbonyl compounds.[10] Nevertheless, operationally simple, practical and straightforward organocatalytic strategy which is devoid of transition metals and that utilizes easily available or less expensive substrates and organocatalyst for the synthesis of *α,β*-unsaturated compounds is highly desirable.

5.3 Our hypothesis and synthetic planning

Earlier, we have explored the reactivity of alkylidene Meldrum's acid **9** in the synthesis *α,β*-unsaturated carboxylic acids, esters and thioesters[4e,4f] As an ongoing research programme, we have been focusing on the novel use of Meldrum's acid in organocatalytic synthesis. During our literature survey, we learnt that acyl/aroyl Meldrum's acids **4** undergoes a slow hydrolysis to afford relatively less stable and reactive *β*-keto acid. Interestingly, this intrinsic reactivity of acyl/aroyl Meldrum's acid **4** has not been well studied and explored to the fullest in organic synthesis for the construction of useful compounds. We

presumed that acyl/aroyl Meldrum's acids **4** can potentially act as a key reagent or as an enolate equivalent for the novel synthesis of *α,β*-unsaturated carbonyl compounds. The tendency and strength of acyl/aroyl Meldrum's acids **4** to deliver a reactive enolate species *in situ* via slow and controlled sequential hydrolysis followed by decarboxylation can be utilized in constructing *α,β*-unsaturated carbonyl scaffold. The successful exploration or utilization of this reactivity of **4** as enolate surrogate may help in avoiding the use of less stable beta-keto acids and half esters as precursors for generating enolates in stepwise manner (Figure 5.2).[4a,4d]

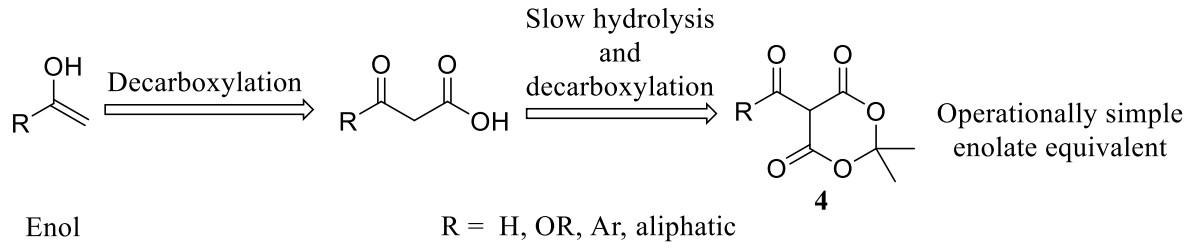


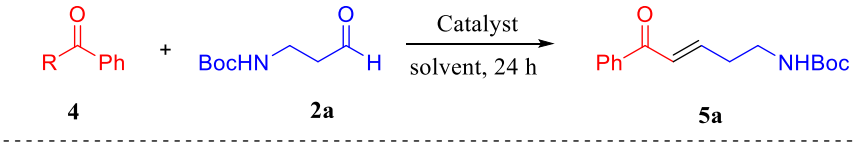
Figure 5.2: Acyl/aroyl Meldrum's acid as enolate equivalent

We believed that aroyl/acyl Meldrum's acids **4** can act as an operationally robust and synthetically simple starting material and it could be effectively utilized in the synthesis of *α,β*-unsaturated carbonyl compounds. In order to validate our hypothesis we planned to carry out a series of systematic experimental studies.

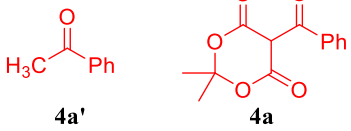
5.4 Results and discussion

In order to execute the plan initially we synthesized corresponding benzoyl Meldrum's acid **4a** (see Experimental section, page 172). However, we became curious to study the reactivity of simple and less reactive aromatic ketone such as acetophenone **4a'** towards organocatalytic aldol condensation, even before exploring the reactivity of benzoyl Meldrum's acid **4a** in the proposed strategy (see, Table 5.1). Initially, a reaction was performed between acetophenone **4a'** and synthetically useful aldehyde such as Boc *β*-alaninal **2a**[11] in presence of catalytic amount of *β*-alanine (20 mol%) in toluene at room temperature (Table 5.1). As anticipated, the reaction did not afford the desired *α,β*-unsaturated ketone **5a** even after stirring the reaction mixture for a prolonged reaction time (48 h, see Table 5.1, entry 1). Similarly, pyrrolidine failed to afford the desired product **5a** (Table 5.1, entry 2). Later, we decided to screen bifunctional diamine catalyst such as *N*,*N*-dimethylethylenediamine (DMEDA).

Table 5.1: Optimization of reaction conditions[a,]

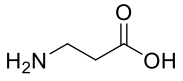


4 **2a** **5a**

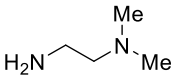


4a' **4a**

Catalysts



β-alanine



N,N-dimethylethylenediamine (DMEDA)

Pyrrolidine

Entry	**4**	Catalyst	Solvent	Temp. (^oC)	Yield[c] (%)	*E:Z*[d]
1	**4a'**[b]	*β*-alanine	Toluene	rt	-	-
2	**4a'**[b]	Pyrrolidine	Toluene	rt	-	-
3	**4a'**[b]	DMEDA	Toluene	rt	Trace	-
4	**4a'**[b]	DMEDA	Toluene	60	Trace	-
5	**4a'**[b]	*β*-alanine	Toluene/H_2O	rt	Trace	-
6	**4a**	*β*-alanine	Toluene/H_2O	60	52	>99:1
7	**4a**	DMEDA	Toluene	60	55	>99:1
8	**4a**	DMEDA	CH_2Cl_2	60	53	>99:1
9	**4a**	DMEDA	$CHCl_3$	60	52	>99:1
10	**4a**	DMEDA	ACN	60	62	>99:1
11	**4a**	DMEDA	EtOAc	60	66	>99:1
12	**4a**	DMEDA	THF	60	62	>99:1
13	**4a**	DMEDA	DMF	60	15	>99:1
14	**4a**	DMEDA	DMSO	60	15	>99:1
15	**4a**	DMEDA	H_2O	60	34	>99:1
16	**4a**	DMEDA	THF/H_2O	55	82	>99:1

Reaction conditions: [a]Benzoyl Meldrum's acid **4a** was freshly prepared by coupling Meldrum's acid **1** (1.0 equiv.) with benzoic acid **3a** (1.0 equiv.) by using coupling reagent DCC (1.4 equiv.) and DMAP (2.0 equiv.) as a base. Freshly prepared **4a** was used immediately without any purification as it is known to hydrolyze with the time. Aldehyde **2a** (1 equiv.), acetophenone/acyl Meldrum's acid **4** (1.5 equiv.), were treated in the presence of 20 mol% of catalyst for 24 h, [b]reactions were stirred for 48 h, [c]isolated yield after purification by column chromatography, [d]*E/Z* ratio determined by ^{1}H NMR spectroscopy.

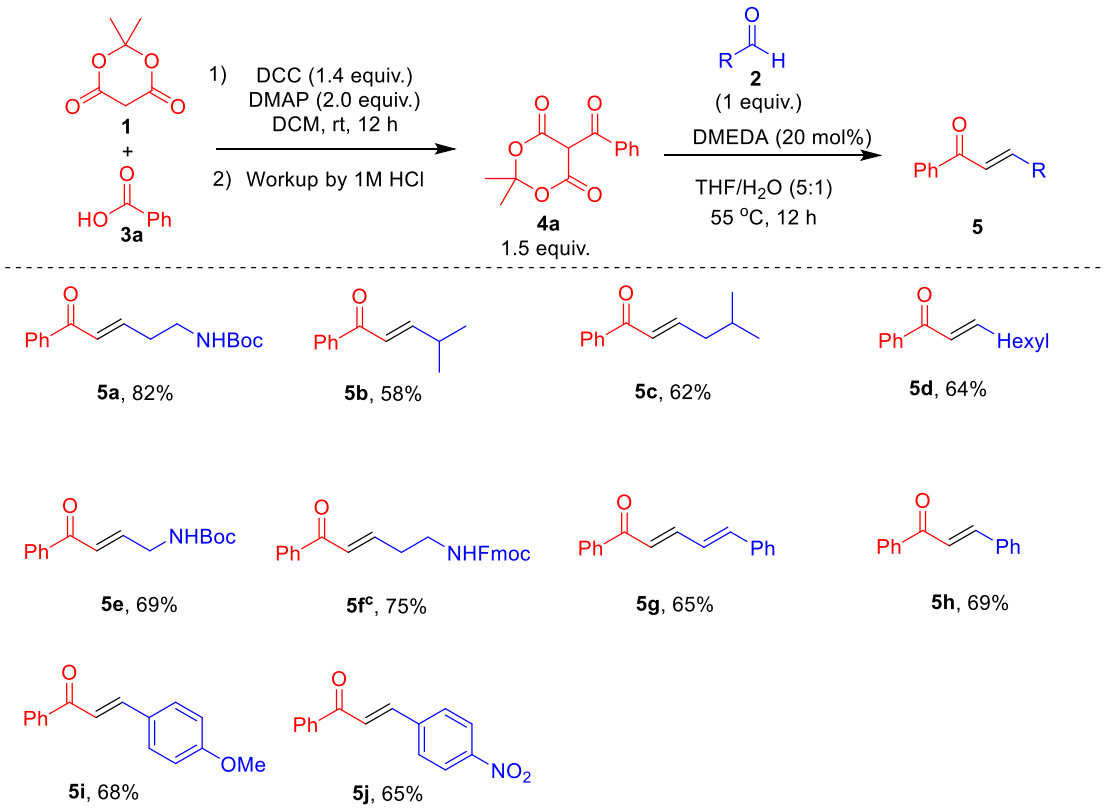
Bifunctional diamine catalysts are known to be highly efficient catalysts in condensation reactions such as aldol and Knoevenagel condensation reactions.[12] However, in the presence DMEDA as a bifunctional diamine catalyst (20 mol%) we observed only a trace amount of desired product **5a** even at elevated temperature and extended reaction time (Table 5.1, entries 3 and 4). This results clearly indicated that probably aromatic ketones are less reactive towards the amine catalysts for the desired transformation. After initial experiments, we turned our attention towards the active methine species such as benzoyl Meldrum's acid **4a** for the desired transformation.

In order execute the proposed reaction, the benzoyl Meldrum's acid **4a** was freshly prepared by coupling Meldrum's **1** acid with benzoic acid **3a** in the presence of coupling reagent DCC (1.4 equiv.) and DMAP (2.0 equiv.) as a base in DCM (see Experimental section, Page 172). As benzoyl Meldrum's acid **4a** is known to decompose slowly over a period of time, it was utilized for the subsequent reaction without any purification. Initially, a model reaction was carried out between aldehyde **2a** (*N*-Boc *β*-alaninal) and benzoyl Meldrum's acid **4a** (1.5 equiv.) in the presence of catalyst *β*-alanine (20 mol%) in toluene/water (5:1) biphasic solvent system at room temperature (water was added to hydrolyze **4a**). However, to our dismay, a trace amount of product **5a** was observed after prolonged reaction time (Table 5.1, entry 5). Instead, compound **4a** slowly underwent hydrolysis followed by decarboxylation to afford acetophenone **4a'** in almost quantitative yields. Gratifyingly, a moderate amount of desired product **5a** was isolated with excellent *E*-selectivity (*E/Z* >99:1) when the reaction was carried out at 60 ^{o}C for 24 hours (Table 5.1, entry 6). Later, we switched towards basic bifunctional diamine catalyst DMEDA. Gratifyingly, the reaction in the presence of DMEDA afforded the desired product **5a** with a marginal increase in the yield and with excellent *E*-selectivity (*E/Z* >99:1, Table 5.1, entry 7). From the initial experiments, *N*,*N*-dimethylethylenediamine (DMEDA) found to be a suitable catalyst. Further, various solvents were screened for the optimizing the reaction conditions in terms of yield of product **5a** (Table 5.1, entries 8-15). It was observed that the solvents such as CH_2Cl_2, $CHCl_3$, acetonitrile, ethyl acetate and THF did not enhance the yield of product **5a** (Table 5.1, entries 8-12). While, polar solvents such as DMSO, DMF and H_2O found to be disadvantageous for the desired transformation (Table 5.1, entries 13-15). Interestingly, THF/Water (5:1) solvent system emerged as most useful for the optimum results by providing the desired product **5a** in 85% yield with excellent *E*-selectivity (*E/Z* >99:1) at 55 ^{o}C (Table 5.1, entry 16). After exhaustive screening benzoyl Meldrum's acid **4a** (1.5 equiv.)

and DMEDA (20 mol%) in THF/water (5:1) biphasic solvent system at 55 ^{o}C emerged as optimum reaction conditions (Table 5.1, entry 16,).

Having obtained optimum reaction conditions in hand, further, we planned to investigate the substrate scope for the synthesis of different *α,β*-unsaturated ketones **5** by using different aldehydes **2** and benzoyl Meldrum's acid **4a.** Initially, simple aliphatic aldehydes (**2b**-**2d**) were explored for the synthesis of the corresponding *α,β*-unsaturated ketones (**5b**-**5d**) under optimum reaction conditions. In all the cases corresponding *α,β*-unsaturated ketones (**5b**-**5d**) were obtained as a single *E*-isomer exclusively in moderate to very good yields (58-64%, see Table 5.2). Probably, lower boiling points of aldehydes (**2b**, **2c**) might have resulted in the corresponding desired products (**5b** and **5c)** in moderate yields.

Table 5.2: Substrate scope[a,b]



Reaction conditions: Unless otherwise noted, benzoyl Meldrum's acid **4a** was freshly prepared by coupling reaction of Meldrum's (1 equiv.) acid with Benzoic acid **3a**, DCC (1.4 equiv.) as coupling reagent, DMAP (2 equiv.) as a base in DCM at room temperature for 12 h followed by workup with 1M HCl. Then aldehyde **2** (1 equiv.), benzoyl Meldrum's acid **5a** (1.5 equiv.), DMEDA (20 mol%) in THF/H_2O (5:1) at 55 ^{o}C for 12 h, [a]isolated yield after purification by column chromatography, [b]*E/Z* ratio are >99:1 for all the products, [c]*β*-alanine (20 mo%) was used as a catalyst.

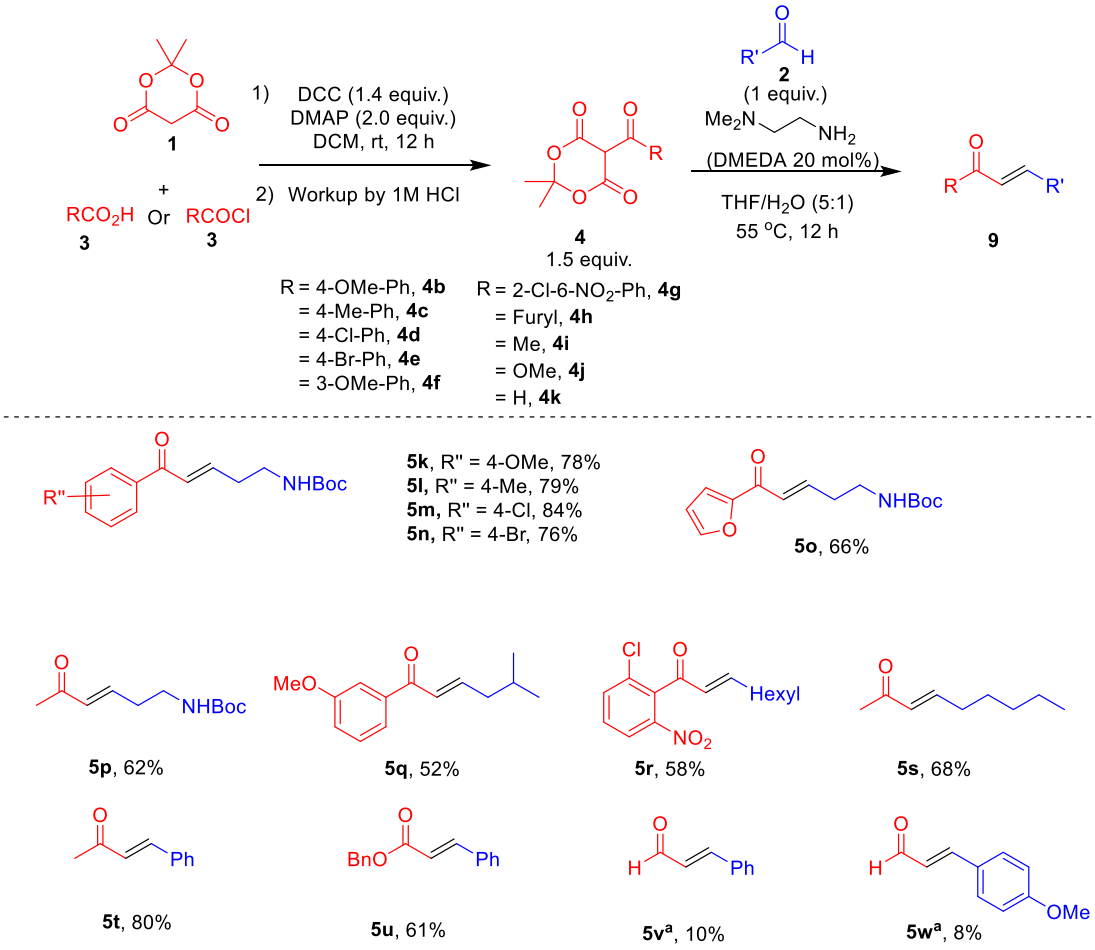
Similarly, the aliphatic aldehyde such as glycinal (**2e**) derived from glycine was successfully utilized in the synthesis of the corresponding *E*-isomer of *α,β*-unsaturated ketone **5e** in good yield (69%). The reaction of Fmoc-protected aldehyde derived from *β*-alanine **2f** under optimum reaction conditions afforded the corresponding *α,β*-unsaturated ketone **5f** in good yield with excellent *E*-selectivity (75%, *E/Z* >99:1, Table 5.2). It is very important to note that highly base sensitive protecting group such as Fmoc (Fluorenylmethyloxycarbonyl) tolerated the reaction conditions well and we did not observe any premature deprotection. Further, the reactivity of benzoyl Meldrum's acid **4a** with respect to various aromatic aldehydes (**2g**-**2j**) was explored under the optimized reaction conditions to afford the corresponding *α,β*-unsaturated ketones (**5g**-**5j**) in good yields with excellent *E*-selectivity (65-69% yields, *E/Z* >99:1). The substituents containing both electron withdrawing and donating groups tolerated the reaction conditions and did not have any significant effect on the yields and rate of the reaction.

In order to make this protocol more practical and general, we planned to explore the reaction with various tricarbonyl derivatives of Meldrum's acid including ester and formyl analogues (**4b**-**4k**, See Table 5.3). Various acyl/aroyl Meldrum acids (**4b**-**4i**) were synthesized (See Experimental section, page 172) and were treated with the different aldehydes (**2a**, **2c**, **2d**, **2h** and **2k**) under optimum reaction conditions. The corresponding *α,β*-unsaturated ketones (**5k**-**5t**) were isolated in moderate to good yields with exclusive *E*-selectivity (52-84%, *E/Z* >99:1, Table 5.3).

Having synthesized *α,β*-unsaturated ketones we turned our attention to synthesize *α,β*-unsaturated aldehydes and esters by using this protocol and to make it really robust and practical procedure. Under the optimized reaction conditions the corresponding ester analog of Meldrum's acid **4j** reacted smoothly to afford the corresponding *α,β*-unsaturated ester **5u** in good yield with excellent *E*-selectivity (61%, *E/Z* >99:1). On the other hand, the aldehyde analog of Meldrum's acid **4k** afforded the corresponding *α,β*-unsaturated aldehydes (**5v**-**5w**) in poor yields with excellent *E*-selectivity (8-10% yield, *E/Z* >99:1).

The method proved to be very simple and practical and afforded the corresponding *α,β*-unsaturated ketones/aldehydes/esters in very high selectivity. We explored the novel utility of acyl/aroyl Meldrum's acid as enolate equivalents for the construction of *α,β*-unsaturated carbonyl scaffold.

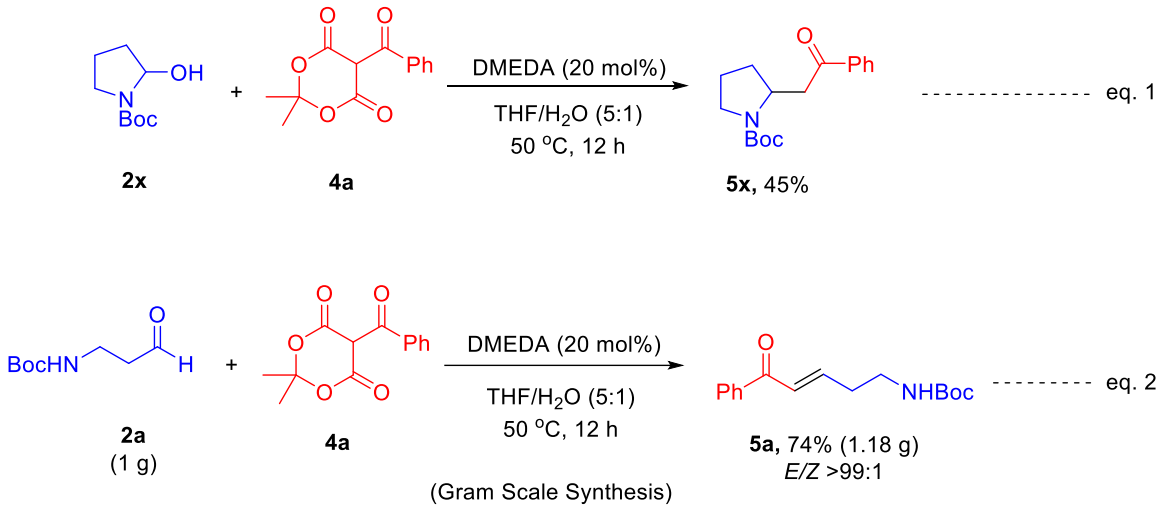
Table 5.3: Substrate scope[a-d]



Reaction conditions: Unless otherwise noted, acyl/aroyl Meldrum's acid (**4b**-**4i**) were freshly prepared by coupling reaction of Meldrum's acid **1** (1 equiv.) with corresponding carboxylic acids **3**, DCC (1.4 equiv.) as coupling reagent, DMAP (2 equiv.) as a base in DCM at room temperature for 12 h followed by workup with 1 M HCl. [a]ester analog **4j** prepared by treatment of benzyl chloroformate with Meldrum's acid **1** in DCM at rt, [b]aldehyde analog of **4k** was prepared by the reaction of triethyl formate and Meldrum's acid **1** followed by treatment with 1M HCl. Then aldehyde **2** (1 equiv.), **4** (1.5 equiv.), DMEDA (20 mol%) in THF/H_2O (5:1) at 55 ^oC for 12 h, [c]isolated yield after purification by column chromatography, [d]*E*/*Z* ratio are >99:1 for all the products.

In order to study the practicality of the protocol further benzoyl Meldrum's acid **4a** was treated with very useful substrate 2-hydroxy pyrrolidine **2x** (eq 1, Scheme 5.5) under optimum reaction conditions. The method proved to work satisfactorily and afforded the corresponding heterocyclic compound **5x** in modest yield (45%, eq 1, Scheme 5.5). It is interesting to note that the tandem aldol condensation/intra-aza-Michael addition happened in one pot to give the corresponding heterocyclic derivative **5x**. Further, in order to study the practicality of the protocol, the compound **5a** was synthesized on a gram scale and method

proved to be scalable (eq. 2, Scheme 5.5). The selectivity was excellent (*E/Z* >99:1) even on larger scale.



Scheme 5.5: Application and gram scale synthesis

5.5 Conclusions

In conclusion, we developed a facile, practical and mild protocol for the synthesis of *α,β*-unsaturated carbonyl compounds. The process utilized simple starting materials accessed through one step from easily and commercially available carboxylic acids and Meldrum's acid. This straightforward protocol tolerated a wide variety of aldehydes and various acyl/aroyl Meldrum's acid derivatives. The effective use ofacyl/aroyl Meldrum's acid derivatives as enolate surrogates has been demonstrated successfully. The method afforded *α,β*-unsaturated carbonyl compounds in moderate to good yields with very high *E*-stereoselectivity. Similarly, mild reaction conditions tolerated acid and base sensitive protecting groups.

5.6 Experimental section

General methods

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without purification. Meldrum's acid was purchased from Spectrochem. Aldehydes, carboxylic acids, and ketones were purchased from Aldrich, Spectrochem and Alfa-aeser. Catalyst was purchased from Sigma-Aldrich. All the reactions were carried out in oven dried glassware. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm). Visualization was accomplished by irradiation with UV light at 254 nm and/or ninhydrin stain. Column chromatography was performed using silica gel (200-300 mesh) eluting with petroleum ether and ethyl acetate. NMR spectra were recorded with tetramethylsilane as the internal standard. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz (Bruker and Jeol). Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.16 ppm) for ^{13}C NMR spectroscopy. Coupling constants (*J*) are given in Hz. IR spectra were obtained using FT-IR spectrophotometer as neat and are reported in cm^{-1}. Mass samples were analyzed by High-resolution mass spectrometer (HRMS) using ESI TOF.

Section I: General procedure for the synthesis of compounds 4a-4k

General Procedure for the synthesis aroyl/acyl Meldrum's acid from carboxylic acid (4b-4i):

Freshly recrystallized Meldrum's acid **1** (1.0 g, 6.9 mmol) and benzoic acid **3a** (0.85 g, 6.9 mmol) were dissolved in dry CH_2Cl_2 (10 mL) and stirred at room temperature for 5 minutes. DMAP (1.7 g, 13.9 mmol) followed by DCC (2.0 g, 9.7 mmol) were added to the reaction mixture and the mixture was stirred for 16 h under nitrogen. A change in color from colorless to brown was noted. After complete consumption of Meldrum's acid **1** (monitored by TLC) solution was quenched with 1 M HCl (10 mL). The organic layer was collected and washed with 1 M HCl (10 mL X 3) followed by with brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. A crude product **4a** (95% yield, 1.64 g) was used immediately without purification (Product **4a** slowly undergoes hydrolysis and decarboxylation to give acetophenone **4a'**).

Likewise, products **4b-4i** were prepared following the similar procedure.

General Procedure for the synthesis ester 4j:

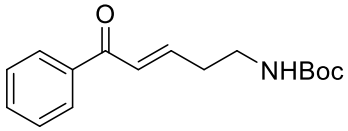
Freshly recrystallized Meldrum's acid **1** (1.0 g, 6.9 mmol) and DMAP (1.7 g, 13.9 mmol) were dissolved in dry CH_2Cl_2 (10 mL) and stirred at room temperature for 5 minutes. Then benzyl chloroformate (0.54 mL, 6.94 mmol) was added dropwise and the mixture was stirred for 12 h under nitrogen. After complete consumption of Meldrum's acid **1** (monitored by TLC) solution was quenched with 1 M HCl (10 mL). The organic layer was collected and washed with 1 M HCl (10 mL X 3) followed by with brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. A crude product **4j** (90% yield, 1.26 g) was used immediately without purification.

Product **4k** (55% yield, 0.66 g) was prepared following the literature procedure.[13]

Section II- General Procedure for the synthesis of *α,β*-unsaturated ketone 5a-5x:

To the vial equipped with magnetic bar, aldehyde **2a** (200 mg, 1.15 mmol) and benzoyl Meldrum's acid **4a** (430 mg, 1.73 mmol) were dissolved in 2 mL THF/H_2O (5:1). Then catalyst DMEDA (24.86 mmL, 0.23 mmol) was added and reaction mixture was allowed to stir for 12 h at 55 ^oC. After complete consumption of aldehyde **4a** (monitored by TLC), reaction mixture was filtered through anhydrous Na_2SO_4 and the residue was purified by column chromatography on silica gel using ethyl acetate in petroleum ether as eluent. The product **5a** was obtained as pale yellow viscous oil in 82% yield (261 mg).

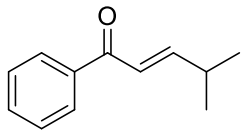
***tert*-butyl *(E)*-(5-oxo-5-phenylpent-3-en-1-yl)carbamate (5a)**



Compound **5a** prepared following the General procedure. Obtained as pale yellow viscous oil in 82% yield (261 mg).

^1H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.91 (m, 2H), 7.59 – 7.53 (m, 1H), 7.46 (dd, *J* = 10.5, 4.7 Hz, 2H), 7.04 – 6.92 (m, 2H), 4.67 (s, 1H), 3.34 (dd, *J* = 12.5, 6.1 Hz, 2H), 2.52 (dd, *J* = 12.4, 6.5 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 156.0, 145.8, 137.8, 132.9, 128.7, 128.7, 127.8, 79.6, 39.3, 33.5, 28.5. HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{21}NO_3 + Na^+$ $[M + Na]^+$ 298.1414, found 298.1428.

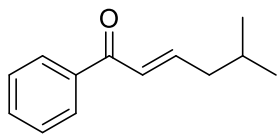
***(E)*-4-methyl-1-phenylpent-2-en-1-one (5b)**



Compound **5b** prepared following the General procedure. Obtained as colorless viscous oil in 58% yield (280 mg).

^1H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.93 (m, 1H), 7.91 (d, *J* = 1.4 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.49 – 7.44 (m, 2H), 7.04 (dd, *J* = 15.5, 6.8 Hz, 1H), 6.82 (dd, *J* = 15.5, 1.3 Hz, 1H), 2.65 – 2.50 (m, 1H), 1.14 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 156.3, 138.2, 132.7, 128.7, 128.6, 123.2, 31.7, 21.5. HRMS (ESI TOF) *m/z* calcd. For $C_{12}H_{14}O + Na^+$ $[M + Na]^+$ 197.0937, found 197.0945.

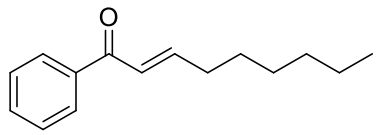
***(E)*-5-methyl-1-phenylhex-2-en-1-one (5c)**



Compound **5c** prepared following the General procedure. Obtained as colorless viscous oil in 62% yield (271 mg).

^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 5.4, 3.3 Hz, 2H), 7.57 – 7.52 (m, 1H), 7.49 – 7.43 (m, 2H), 7.10 – 6.99 (m, 1H), 6.87 (dt, *J* = 15.6, 1.3 Hz, 1H), 2.24 – 2.17 (m, 2H), 1.88 – 1.77 (m, 1H), , 0.96 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 149.1, 138.1, 132.7, 128.7, 128.6, 127.1, 42.2, 28.1, 22.6. HRMS (ESI TOF) *m/z* calcd. For $C_{13}H_{16}O + Na^+$ $[M + Na]^+$ 211.1093, found 211.1101.

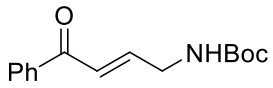
***(E)*-1-phenylnon-2-en-1-one (5d)**



Compound **5d** prepared following the General procedure. Obtained as colorless oil in 64% yield (242 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (m, 2H), 7.57 – 7.50 (m, 1H), 7.49 – 7.42 (m, 2H), 7.06 (dt, *J* = 15.3, 6.9 Hz, 1H), 6.87 (dt, *J* = 15.3, 1.4 Hz, 1H), 2.37 – 2.27 (m, 2H), 1.56 – 1.44 (m, 2H), 1.41 – 1.21 (m, 6H), 0.89 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 150.3, 138.1, 132.7, 128.6, 128.6, 126.0, 33.0, 31.7, 29.0, 28.3, 22.7, 14.2. HRMS (ESI TOF) *m/z* calcd. For $C_{15}H_{20}O + Na^+$ $[M + Na]^+$ 239.1406, found 239.1401.

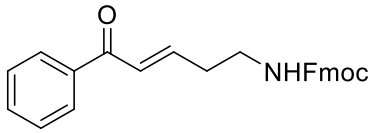
tert-butyl *(E)*-(4-oxo-4-phenylbut-2-en-1-yl)carbamate (5e)



Compound **5e** prepared following the General procedure. Obtained as colorless viscous oil in 69% yield (226 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.4 Hz, 2H), 7.58 – 7.52 (m, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.02 – 6.91 (m, 2H), 4.90 (s, 1H), 4.01 (d, *J* = 3.5 Hz, 2H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 155.8, 145.0, 137.7, 133.0, 128.7, 125.6, 80.0, 42.0, 28.5. HRMS (ESI TOF) *m/z* calcd. For $C_{15}H_{19}NO_3 + Na^+$ $[M + Na]^+$ 284.1257, found 284.1265.

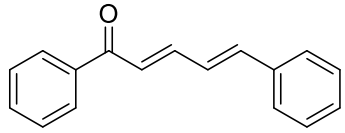
(9H-fluoren-9-yl)methyl *(E)*-(5-oxo-5-phenylpent-3-en-1-yl)carbamate (5f)



Compound **5f** prepared following the General procedure (*β*-alanine used as catalyst instead of DMEDA. Obtained as colorless viscous oil in 75% yield (201 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.89 (m, 2H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.1 Hz, 3H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.32 – 7.25 (m, 2H), 7.03 – 6.94 (m, 2H), 4.95 (s, 1H), 4.42 (d, *J* = 6.8 Hz, 2H), 4.21 (t, *J* = 6.7 Hz, 1H), 3.47 – 3.35 (m, 2H), 2.55 (dd, *J* = 11.7, 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 156.5, 145.5, 144.0, 141.4, 137.7, 133.1, 128.7, 128.7, 127.9, 127.8, 127.2, 125.1, 120.1, 66.8, 47.4, 39.7, 33.4. HRMS (ESI TOF) *m/z* calcd. For $C_{26}H_{23}NO_3 + Na^+$ $[M + Na]^+$ 420.1570, found 420.1586.

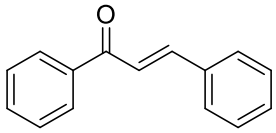
(2*E*,4*E*)-1,5-diphenylpenta-2,4-dien-1-one (5g)



Compound **5g** prepared following the General procedure. Obtained as yellow solid in 65% yield (230 mg).

m.p. 100-101 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.97 (m, 2H), 7.65 – 7.55 (m, 2H), 7.52 – 7.47 (m, 4H), 7.40 – 7.30 (m, 3H), 7.10 (d, *J* = 15.0 Hz, 1H), 7.04 – 7.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 145.3, 142.4, 138.6, 136.5, 133.1, 129.7, 129.3, 129.0, 128.8, 127.7, 127.4, 125.9. HRMS (ESI TOF) *m/z* calcd. For $C_{17}H_{14}O + Na^+$ $[M + Na]^+$ 257.0937, found 257.0948.

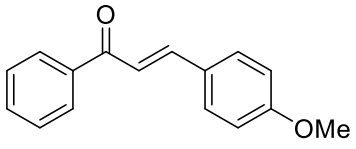
***(E)*-chalcone (5h)**



Compound **5h** prepared following the General procedure. Obtained as pale yellow solid in 69% yield (271 mg).

m.p. 56-58 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dt, *J* = 3.5, 2.2 Hz, 2H), 7.82 (d, *J* = 15.7 Hz, 1H), 7.67 – 7.63 (m, 2H), 7.62 – 7.57 (m, 1H), 7.57 – 7.48 (m, 3H), 7.45 – 7.40 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 145.0, 138.3, 135.0, 132.9, 130.7, 129.0, 128.7, 128.6, 128.6, 122.2. HRMS (ESI TOF) *m/z* calcd. For $C_{15}H_{12}O + Na^+$ $[M + Na]^+$ 231.0780, found 231.0786.

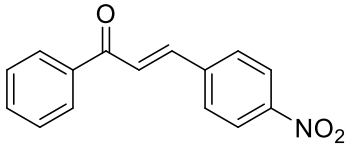
***(E)*-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (5i)**



Compound **5i** prepared following the General procedure. Obtained as pale yellow solid in 68% yield (238 mg).

m.p. 85-88 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.78 (d, *J* = 15.7 Hz, 1H), 7.61 – 7.54 (m, 3H), 7.51 – 7.47 (m, 2H), 7.41 (d, *J* = 15.6 Hz, 1H), 6.94 – 6.92 (m, 2H), 3.84 (s, 3H). ^{13}C NMR (100 MHz $CDCl_3$) δ 190.7, 161.8, 144.9, 138.6, 132.7, 130.4, 128.7, 128.5, 127.7, 119.9, 114.5, 55.5. HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{14}O_2 + Na^+$ $[M + Na]^+$ 261.0886, found 261.0889.

***(E)*-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (5j)**

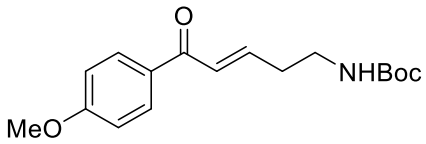


Compound **5j** prepared following the General procedure. Obtained as brown solid in 65% yield (217 mg).

m.p. 160-162 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.25 (m, 2H), 8.05 – 8.02 (m, 2H), 7.84 – 7.76 (m, 3H), 7.67 – 7.60

(m, 2H), 7.52 (dd, *J* = 10.4, 4.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 148.7, 141.6, 141.2, 137.6, 133.5, 129.1, 128.9, 128.7, 125.8, 124.3. HRMS (ESI TOF) *m/z* calcd. For $C_{15}H_{11}NO_3$ + Na^+ $[M + Na]^+$ 276.0631, found 276.0639.

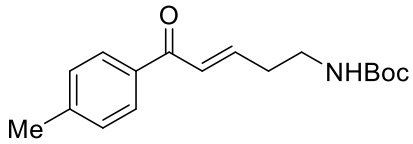
tert-butyl *(E)*-(5-(4-methoxyphenyl)-5-oxopent-3-en-1-yl)carbamate (5k)



Compound **5k** prepared following the General procedure. Obtained as pale yellow viscous oil in 78% yield (275 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.9 Hz, 2H), 7.05 – 6.87 (m, 4H), 4.64 (s, 1H), 3.88 (s, 3H), 3.34 (d, *J* = 6.2 Hz, 2H), 2.51 (d, *J* = 3.9 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 163.5, 155.8, 144.5, 130.9, 130.6, 127.4, 113.8, 79.5, 55.5, 39.2, 33.2, 28.4. HRMS (ESI TOF) *m/z* calcd. For $C_{17}H_{23}NO_4$ + Na^+ $[M + Na]^+$ 328.1519, found 328.1523.

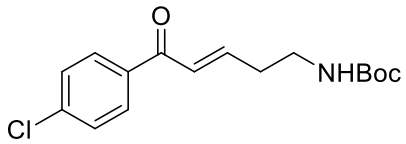
tert-butyl *(E)*-(5-oxo-5-(p-tolyl)pent-3-en-1-yl)carbamate (4l)



Compound **5l** prepared following the General procedure. Obtained as pale yellow viscous oil in 79% yield (264 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.01 – 6.87 (m, 2H), 4.72 (s, 1H), 3.32 (q, *J* = 6.3 Hz, 2H), 2.50 (q, *J* = 6.4 Hz, 2H), 2.40 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 155.9, 145.3, 143.8, 135.1, 129.4, 128.8, 127.7, 79.5, 39.2, 33.3, 28.5, 21.7. HRMS (ESI TOF) *m/z* calcd. For $C_{17}H_{23}NO_3$ + Na^+ $[M + Na]^+$ 312.1570, found 312.1577.

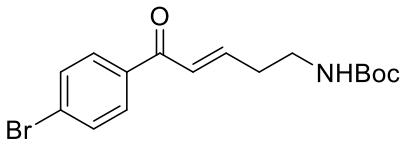
tert-butyl *(E)*-(5-(4-chlorophenyl)-5-oxopent-3-en-1-yl)carbamate (4m)



Compound **5m** prepared following the General procedure. Obtained as pale yellow viscous oil in 84% yield (300 mg).

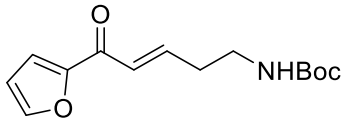
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.05 – 6.84 (m, 2H), 4.66 (s, 1H), 3.34 (q, *J* = 6.2 Hz, 2H), 2.52 (q, *J* = 6.6 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1, 155.8, 146.2, 139.3, 136.0, 130.0, 128.9, 127.2, 79.6, 39.1, 33.4, 28.4. HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{20}ClNO_3$ + Na^+ $[M + Na]^+$ 332.1024, found 332.1030.

tert-butyl *(E)*-(5-(4-bromophenyl)-5-oxopent-3-en-1-yl)carbamate (4n)



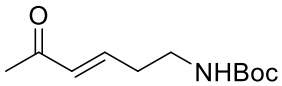
Compound **5n** prepared following the General procedure. Obtained as colorless viscous oil in 76% yield (311 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.74 (m, 2H), 7.65 – 7.53 (m, 2H), 7.07 – 6.83 (m, 2H), 4.66 (s, 1H), 3.34 (q, *J* = 6.2 Hz, 2H), 2.51 (q, *J* = 6.5 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 155.8, 146.3, 136.4, 131.9, 130.1, 127.9, 127.2, 79.5, 39.1, 33.4, 28.4. HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{20}BrNO_3$+Na $[M + Na]^+$ 376.0519, found 376.537.

tert-butyl *(E)*-(5-(furan-2-yl)-5-oxopent-3-en-1-yl)carbamate (4o)



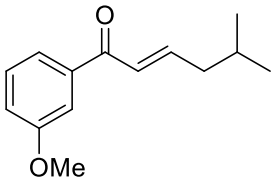
Compound **5o** prepared following the General procedure. Obtained as pale yellow viscous oil in 66% yield (202 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.66 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.15 (dd, *J* = 4.9, 3.8 Hz, 1H), 7.04 (dt, *J* = 15.3, 7.0 Hz, 1H), 6.87 (d, *J* = 15.4 Hz, 1H), 4.65 (s, 1H), 3.34 (dd, *J* = 12.5, 6.1 Hz, 2H), 2.51 (q, *J* = 6.6 Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 156.0, 145.1, 145.0, 134.1, 132.3, 128.4, 127.3, 79.7, 39.2, 33.3, 28.5. HRMS (ESI TOF) *m/z* calcd. For $C_{14}H_{19}NO_4$ + Na^+ $[M + Na]^+$ 288.1206, found 288.1214.

tert-butyl *(E)*-(5-oxohex-3-en-1-yl)carbamate (4p)



Compound **5p** prepared following the General procedure. Obtained as pale yellow viscous oil in 62% yield (153 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 – 6.68 (m, 1H), 6.09 (d, *J* = 16.0 Hz, 1H), 4.66 (s, 1H), 3.27 (d, *J* = 6.2 Hz, 2H), 2.40 (q, *J* = 6.7 Hz, 2H), 2.23 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 156.0, 144.7, 133.0, 79.6, 39.1, 33.4, 28.5, 27.0. HRMS (ESI TOF) *m/z* calcd. For $C_{11}H_{19}NO_3$ + Na^+ $[M + Na]^+$ 236.1257, found 236.1260.

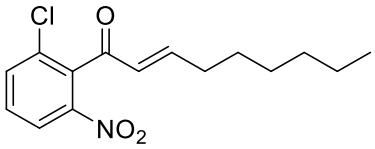
***(E)*-1-(3-methoxyphenyl)-5-methylhex-2-en-1-one (4q)**



Compound **5q** prepared following the General procedure. Obtained as colorless viscous oil in 52% yield (264 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 2H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.06 (ddd, *J* = 22.7, 11.6, 5.0 Hz, 2H), 6.84 (d, *J* = 15.5 Hz, 1H), 3.85 (s, 3H), 2.23 – 2.17 (m, 2H), 1.81 (td, *J* = 13.4, 6.7 Hz, 1H), 0.95 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 159.9, 149.1, 139.5, 129.6, 127.1, 121.2, 119.2,

112.9, 55.5, 42.2, 28.1, 22.6. HRMS (ESI TOF) *m/z* calcd. For $C_{14}H_{18}O_2$ + Na^+ $[M + Na]^+$ 241.1199, found 241.1207.

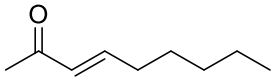
(*E*)-1-(2-chloro-6-nitrophenyl)non-2-en-1-one (4r)



Compound **5r** prepared following the General procedure. Obtained as colorless viscous oil in 58% yield (300 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.22 (m, 2H), 7.61 (dt, *J* = 2.7, 0.8 Hz, 1H), 6.74 (dt, *J* = 15.9, 6.9 Hz, 1H), 6.47 (dt, *J* = 15.7, 1.4 Hz, 1H), 2.34 – 2.27 (m, 2H), 1.48 (dt, *J* = 15.1, 7.4 Hz, 2H), 1.36 – 1.23 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 154.9, 146.4, 140.2, 138.1, 131.5, 129.7, 125.7, 124.3, 33.1, 31.6, 29.0, 27.9, 22.6, 14.2. HRMS (ESI TOF) *m/z* calcd. For $C_{15}H_{18}ClNO_3$ + Na^+ $[M + Na]^+$ 318.0867, found 318.0879.

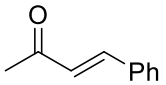
(*E*)-non-3-en-2-one (4s)



Compound **5s** prepared following the General procedure. Obtained as colorless viscous oil in 68% yield (190 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (dt, *J* = 16.0, 6.9 Hz, 1H), 6.07 (dt, *J* = 16.0, 1.5 Hz, 1H), 2.25 – 2.20 (m, 5H), 1.51 – 1.44 (m, 2H), 1.36 – 1.28 (m, 4H), 0.92 – 0.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 148.8, 131.4, 32.5, 31.4, 27.8, 26.9, 22.5, 14.0. HRMS (ESI–TOF) m/z calcd. for $C_9H_{16}O$ + H^+ $[M + H]^+$ 141.1279, found 141.1286.

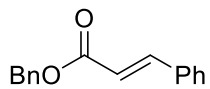
(*E*)-4-phenylbut-3-en-2-one (4t)



Compound **5t** prepared following the General procedure. Obtained as white solid in 80% yield (220 mg).

m.p. = 40-42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.49 (m, 3H), 7.41–7.39 (m, 3H), 6.72 (d, *J* = 16.3 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 143.6, 134.5, 130.6, 129.1, 128.4, 127.2, 27.6. HRMS (ESI–TOF) m/z calcd. for $C_{10}H_{10}O$ + H^+ $[M + H]^+$ 147.0810, found 147.0813.

Benzyl cinnamate (4u)

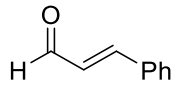


Compound **5u** prepared following the General procedure. Obtained as white solid in 61% yield (274 mg).

m.p. 35–38 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 16.0 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.45 – 7.33 (m, 8H), 6.50 (d, *J* = 16.0 Hz, 1H), 5.27 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 145.3, 136.2, 134.5, 130.5, 129.0, 128.7, 128.4, 128.4, 128.2,

118.0, 66.5. HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{14}O_2$ + Na^+ $[M + Na]^+$ 261.0886, found 261.0889.

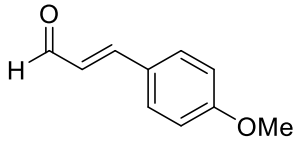
Cinnamaldehyde (4v)



Compound **5v** prepared following the General procedure. Obtained as pale yellow viscous oil in 10% yield (25 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 7.7 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.48 (d, *J* = 16.0 Hz, 1H), 7.46 – 7.40 (m, 3H), 6.72 (dd, *J* = 16.0, 7.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 153.0, 134.1, 131.4, 129.2, 128.7, 128.6. HRMS (ESI TOF) *m/z* calcd. For C_9H_8O + Na^+ $[M + Na]^+$ 155.0467, found 295.1541.

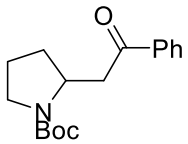
***(E)*-3-(4-methoxyphenyl)acrylaldehyde (4w)**



Compound **5w** prepared following the General procedure. Obtained as colorless viscous oil in 8% yield (19 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, *J* = 7.8 Hz, 1H), 7.54 – 7.50 (m, 2H), 7.42 (d, *J* = 15.8 Hz, 1H), 6.97 – 6.92 (m, 2H), 6.61 (ddd, *J* = 15.7, 7.8, 0.7 Hz, 1H), 3.85 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 162.3, 152.9, 130.5, 126.9, 126.6, 114.7, 55.6. HRMS (ESI TOF) *m/z* calcd. For $C_{10}H_{10}O_2$ + Na^+ $[M + Na]^+$ 185.0573, found 185.0578.

tert-butyl 2-(2-oxo-2-phenylethyl)pyrrolidine-1-carboxylate (4y)



Compound **5x** prepared following the General procedure. Obtained as colorless viscous oil in 45% yield (139 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.95 (m, 2H), 7.60 – 7.51 (m, 1H), 7.46 (m, 2H), 4.33 (ddt, *J* = 10.8, 7.6, 3.2 Hz, 1H), 3.70 (m, 1H), 3.44 – 3.29 (m, 2H), 2.83 (dt, *J* = 19.7, 13.1 Hz, 1H), 2.13 – 1.98 (m, 1H), 1.92 – 1.70 (m, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 198.8, 154.4, 137.0, 133.4, 133.2, 128.7, 128.5, 128.3, 79.9, 79.4, 54.5, 54.3, 46.8, 46.4, 43.9, 43.2, 31.5, 30.5, 28.7, 23.7, 22.9. HRMS (ESI TOF) *m/z* calcd. For $C_{17}H_{23}NO_3$ + H^+ $[M + H]^+$ 290.1751, found 290.1759.

5.7 Appendix V: ^{1}H and ^{13}C spectral data of representative compounds

compound No.	**Figure V.X**	**data**	**Page No.**
5a	Figure AV.1 and AV.2	^{1}H-^{13}C	181
5b	Figure AV.3 and AV.4	^{1}H-^{13}C	182
5f	Figure AV.5 and AV.6	^{1}H-^{13}C	183
5k	Figure AV.7 and AV.8	^{1}H-^{13}C	184
5x	Figure AV.9 and AV.10	^{1}H-^{13}C	185

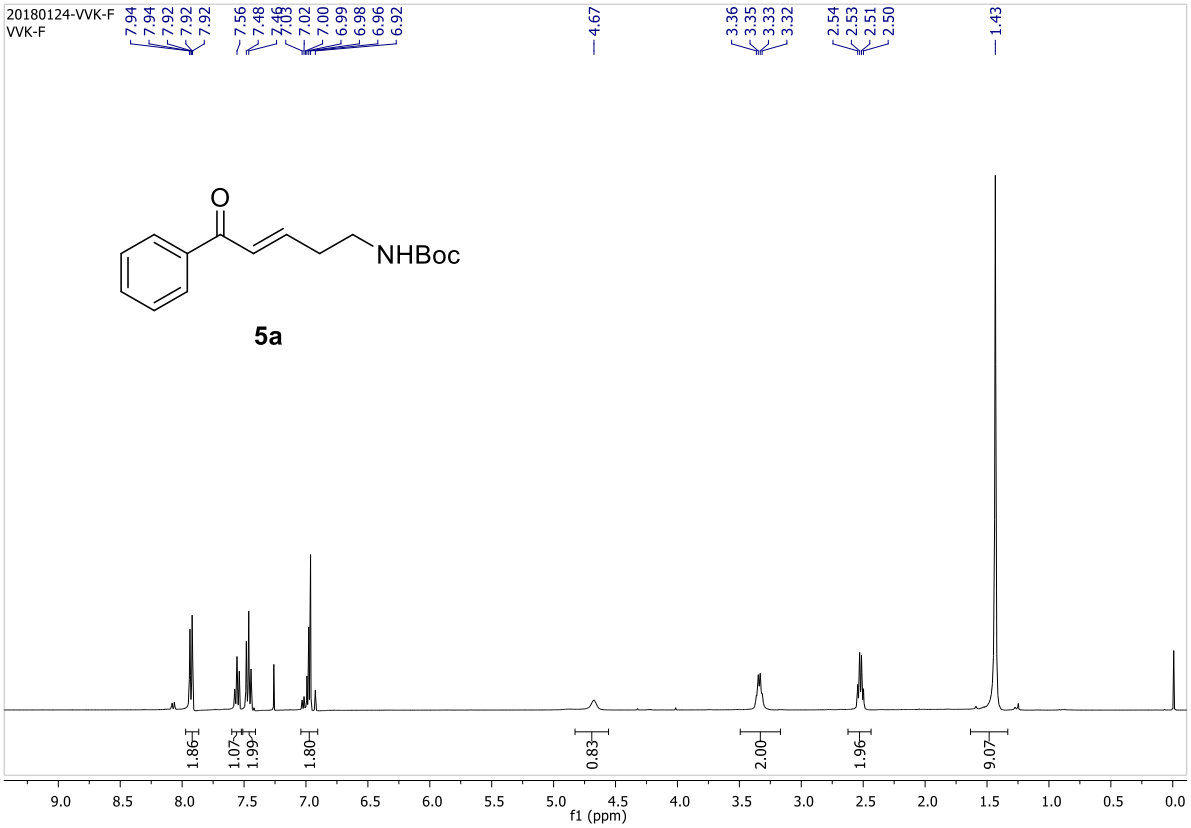


Figure AV.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5a**

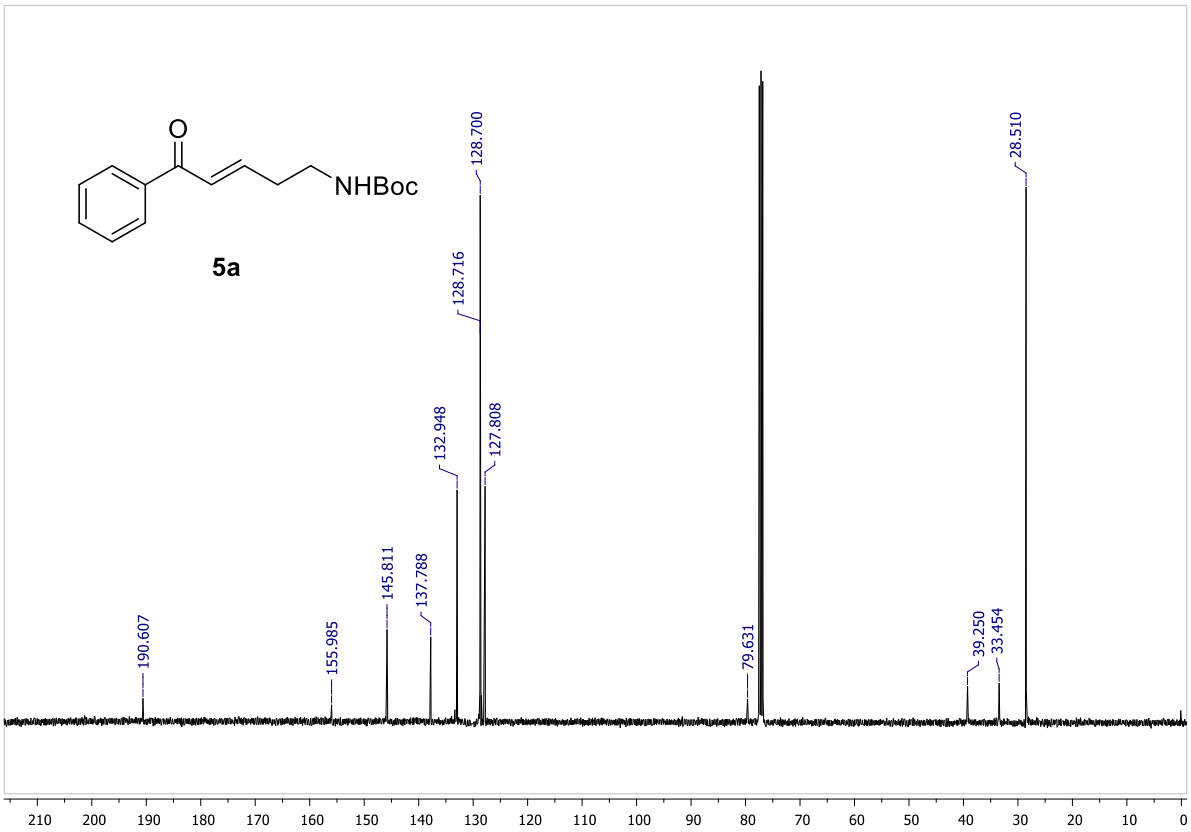


Figure AV.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **5a**

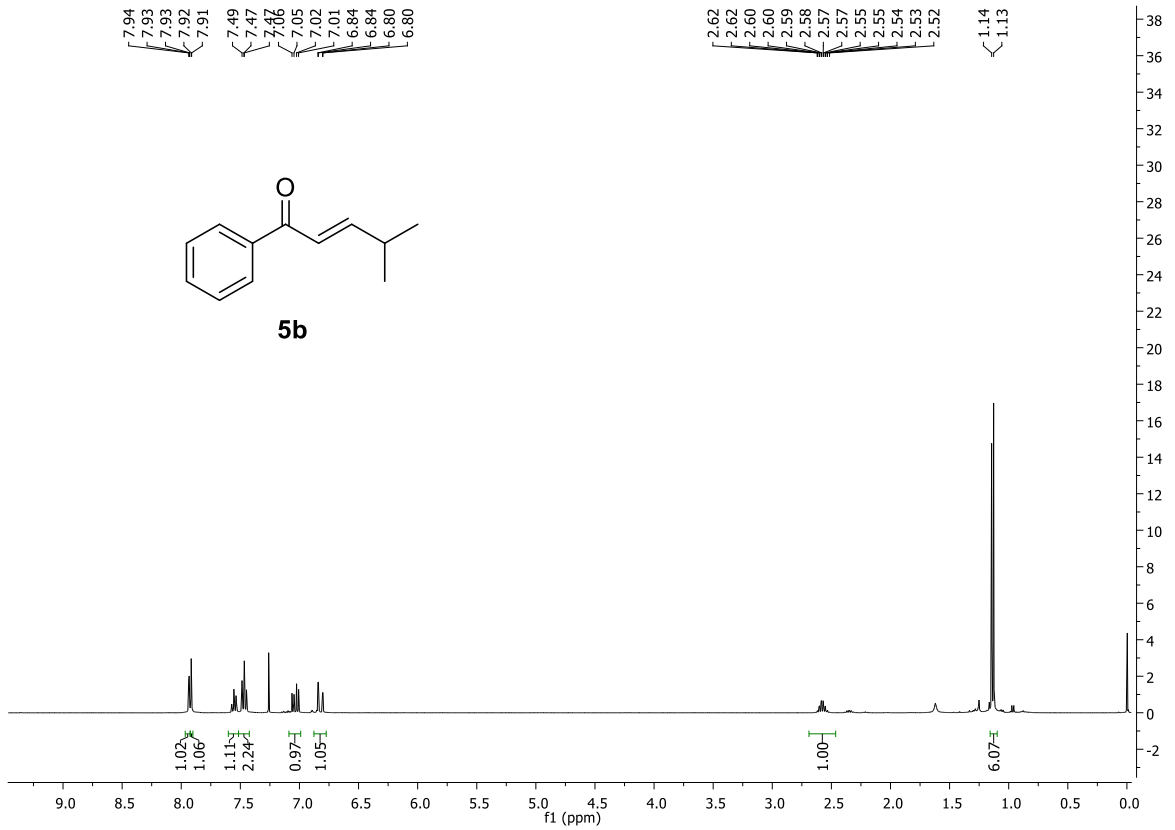


Figure AV.3: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5b**

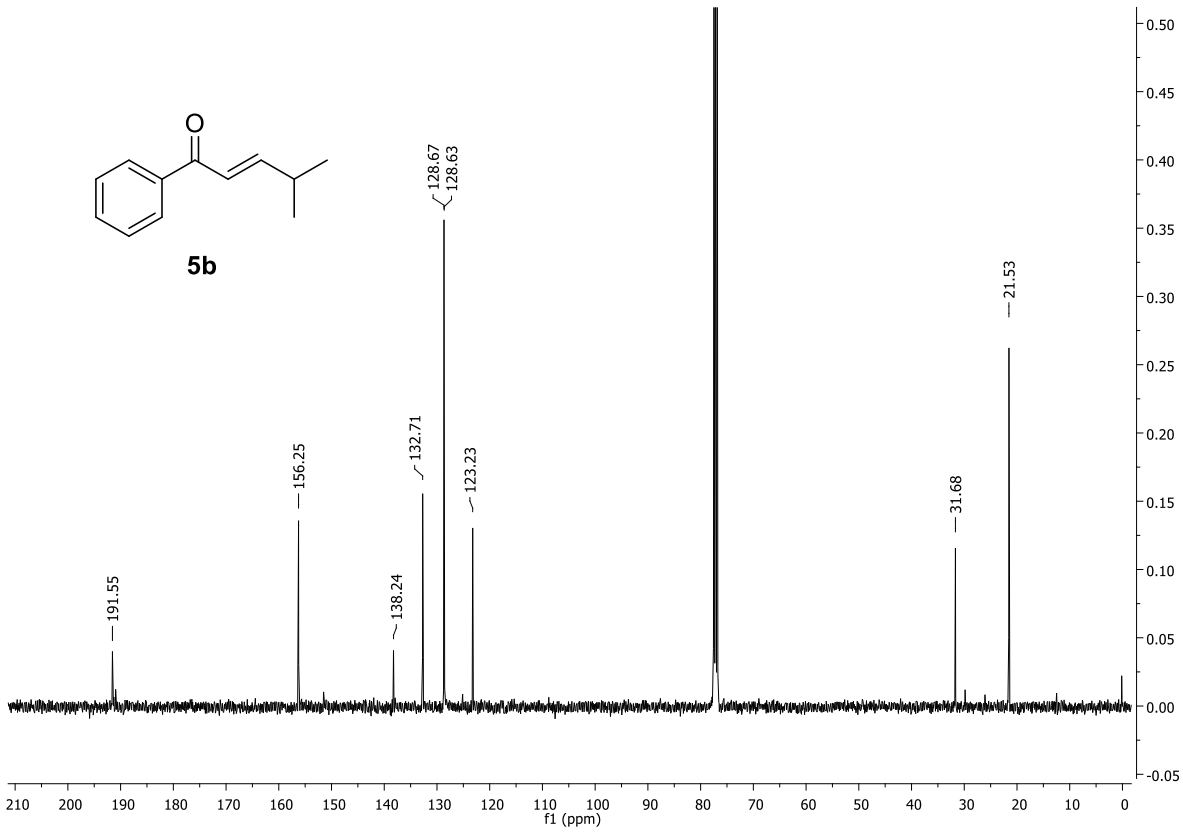


Figure AV.4: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **5b**

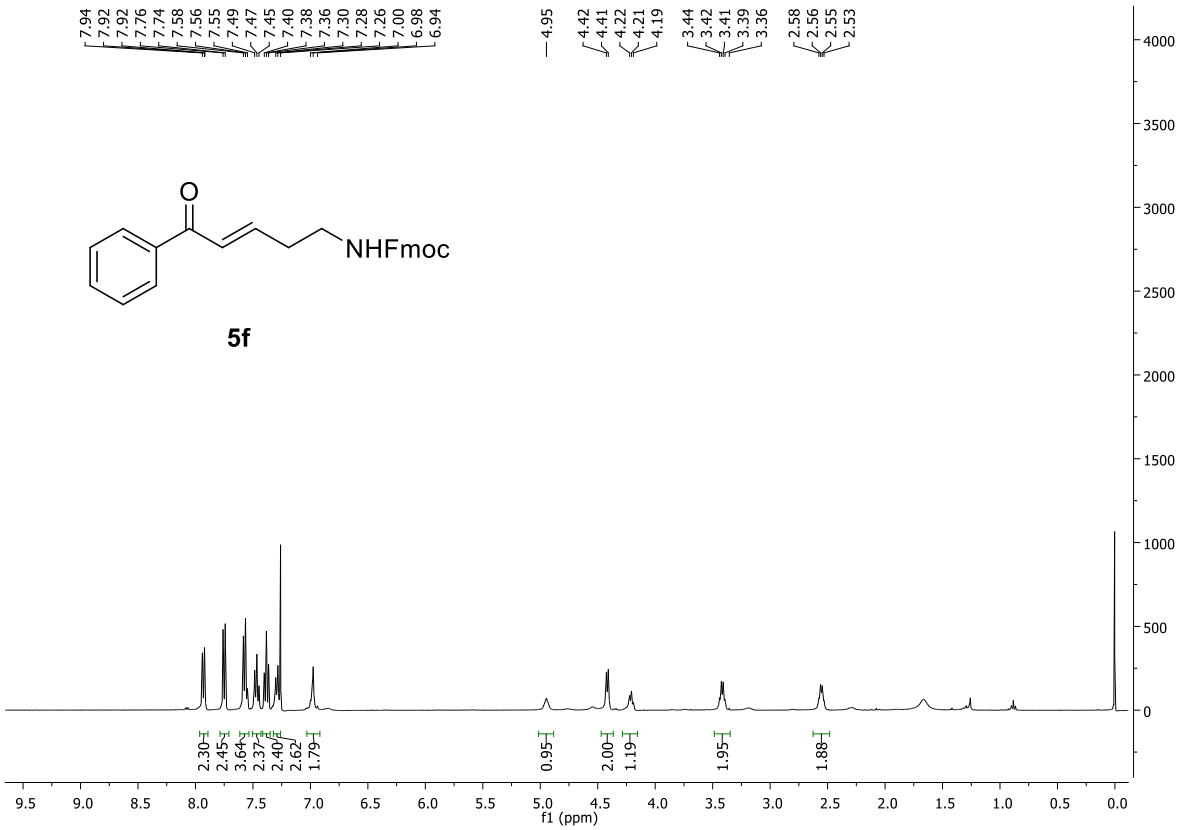


Figure AV.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5f**

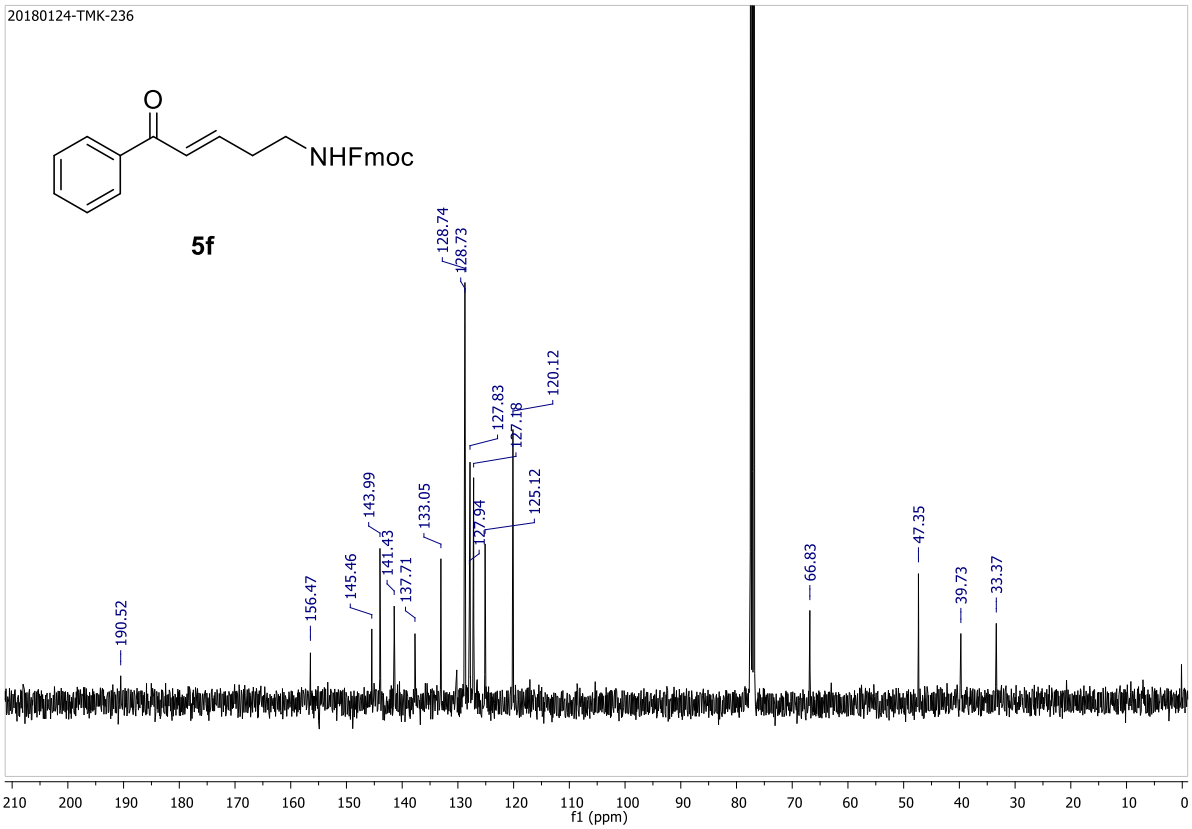


Figure AV.6: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **5f**

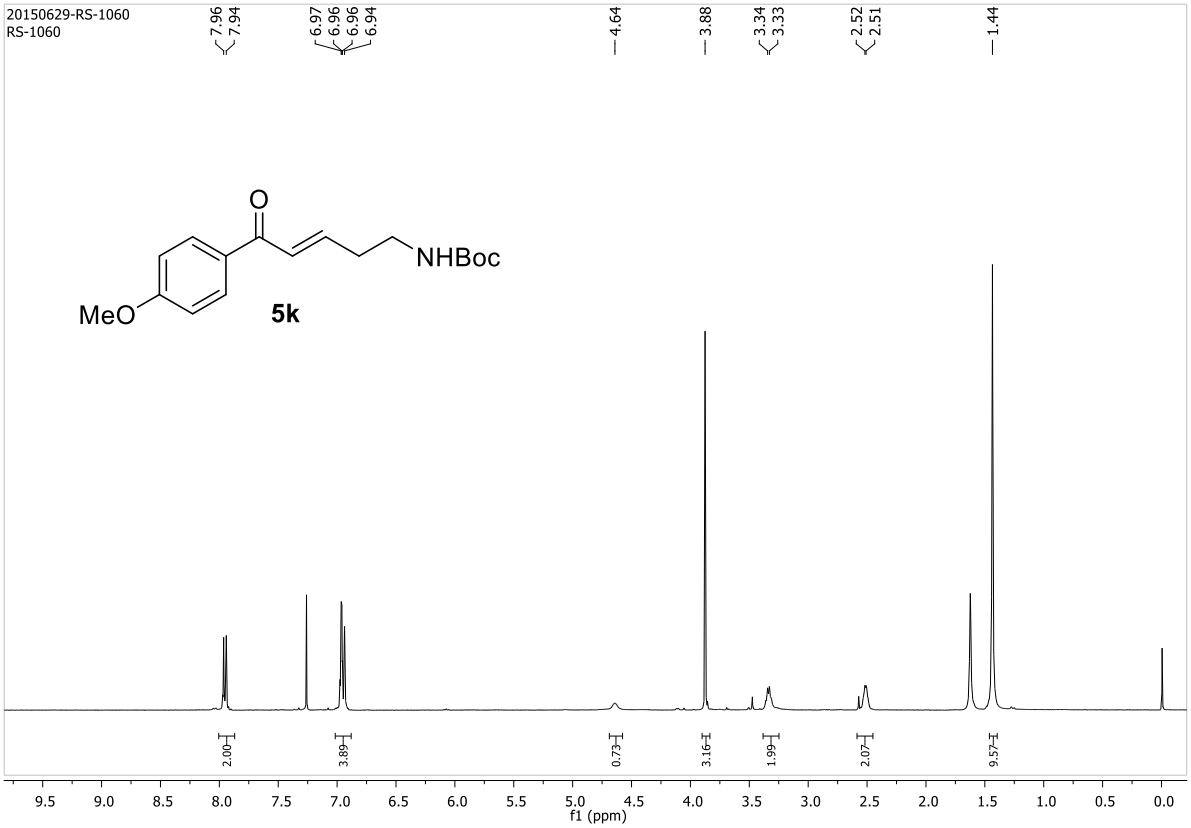


Figure AV.7: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5k**

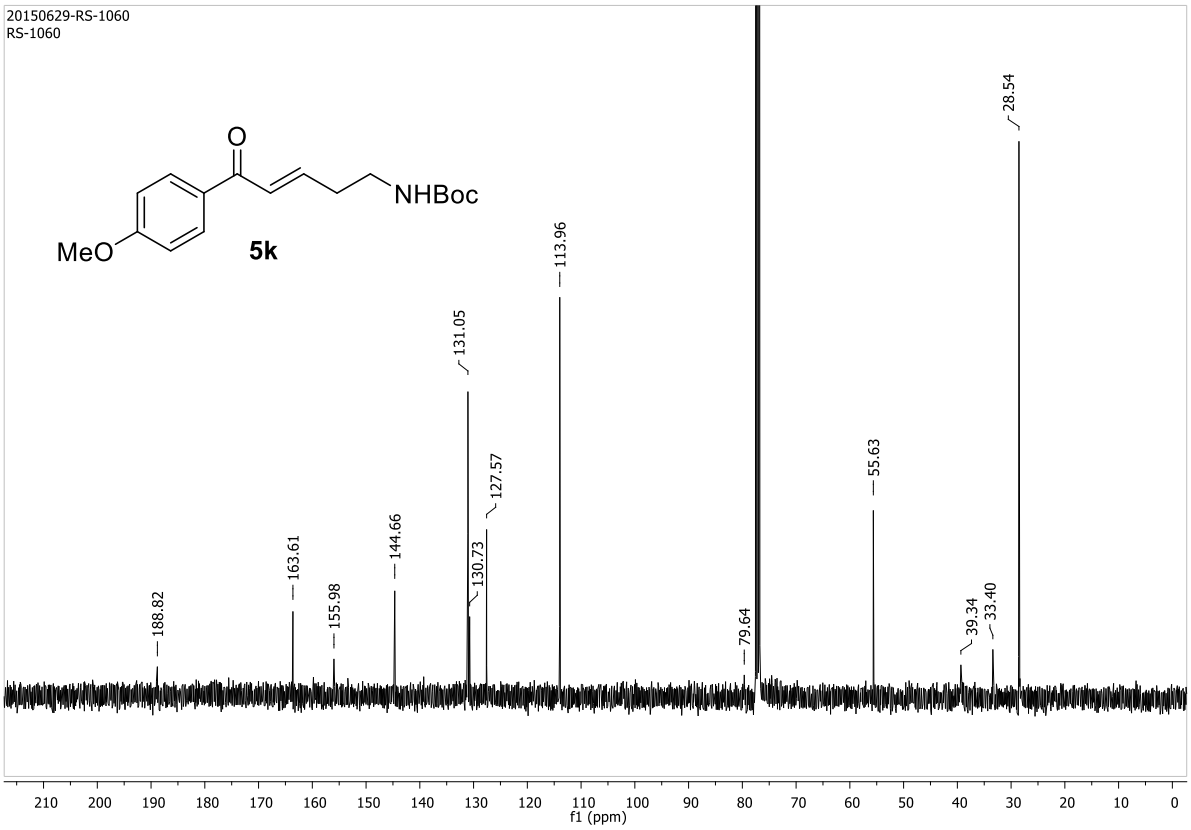


Figure AV.8: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **5k**

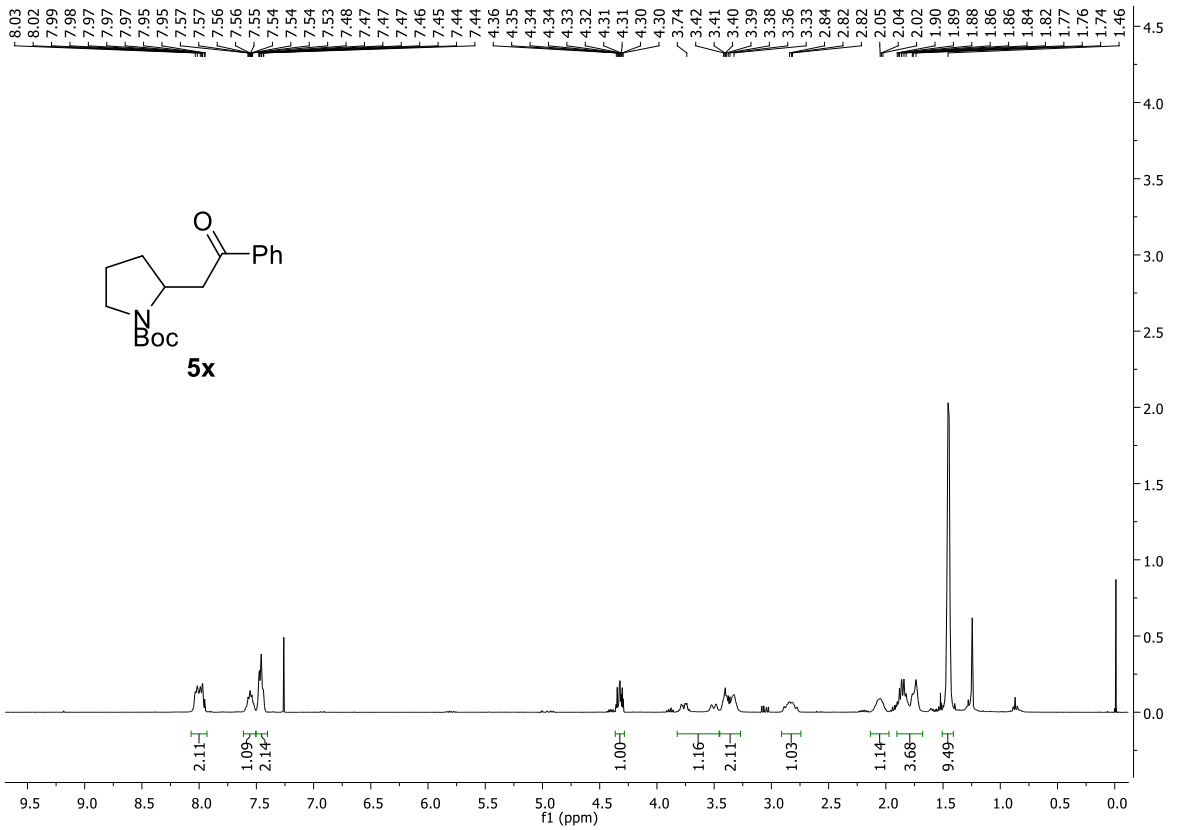


Figure AV.9: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5x**

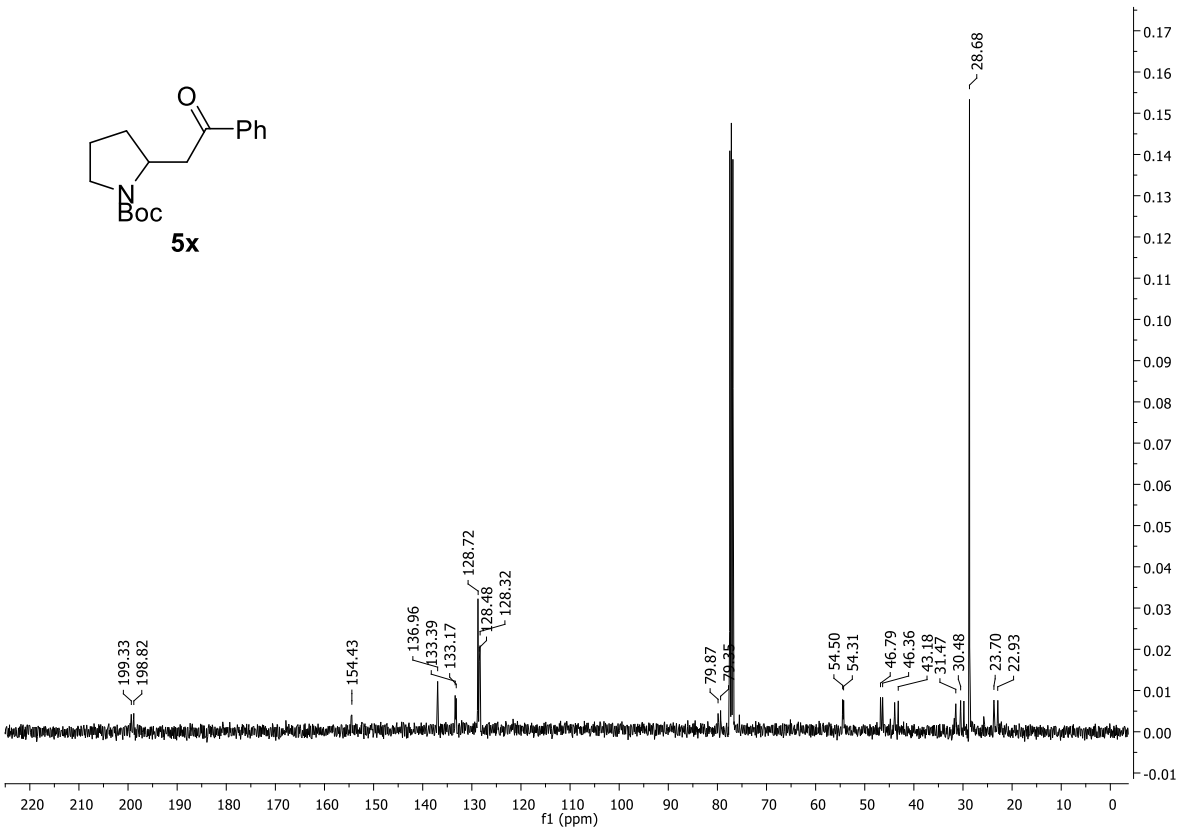


Figure AV.10: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **5x**

5.8 References

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Summary

Organocatalysis is one of the essential pillars in the field of catalysis and is often explored in several synthetic transformations. At the dawn of asymmetric organocatalysis, various research groups independently discovered that organocatalysts possess an unprecedented strength of catalyzing a number of reactions very efficiently and selectively to generate a broad array of diverse optically active compounds. However, to identify suitable catalyst and set of conditions is always crucial for the success of stereoselective transformations. At many instances, the substrate-organocatalysts interactions are more crucial that allow one to design a target oriented synthesis. These interactions help to design various new methods useful not only in academia but in large scale industries, for instance, pharmaceutical, polymer, food etc. Meldrum's acid is one of the efficient substrates that have been explored in the fields of organic synthesis and it has been utilized as a useful platform in numerous organocatalytic approaches. Organocatalytic processes that explore the use of Meldrum's acid have gained a gradual attention in the last decade. In this thesis novel uses of Meldrum's acid have been explored for the efficient organocatalytic transformation to synthesize useful scaffolds such as pyroglutamic acids, *δ*-ketoesters, *γ*-butyrolactones and *α,β*-unsaturated carbonyl compounds.

We developed a novel stereoselective multi-component organocatalytic approach for the synthesis of pyroglutamic acid derivatives using Meldrum's acid, aldehyde and Schiff's base. Similarly, the first enantioselective organocatalytic multicomponent reaction using Meldrum's acid, aldehyde and ketone has been explored for the synthesis of *δ*-ketoesters. We systematically studied an adverse effect of higher catalyst loading and longer reaction time on enantioselectivity in organocatalytic multicomponent reaction. Further, we demonstrated a novel method for the direct organocatalytic multicomponent synthesis of enantiopure γ-butyrolactones via tandem Knoevenagel-Michael-lactonization sequence. Meldrum's acid has also been effectively employed for the direct organocatalytic synthesis of *α,β*-unsaturated carbonyl compounds.

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Direct Organocatalytic Multicomponent Synthesis of Enantiopure γ-Butyrolactones via Tandem Knoevenagel-Michael-Lactonization Sequence

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Abstract: An expedient and straightforward protocol is developed for the synthesis of highly enantiopure synthesis of γ-butyrolactones. For the first time, one pot enantioselective organocatalytic multicomponent reaction (OMCR) is explored to construct functionalized butyrolactones without the use of pre-functionalized substrates and expensive transition metals. The protocol is proved to be reproducible on a gram scale. Density functional theory (DFT) calculations strongly support the mechanism and were in close agreement with the observed high stereoselectivity.

Keywords: Multicomponent reactions; Organocatalysis; γ-Butyrolactones; Enantioselectivity; Hetero-Diels-Alder reaction

Optically active γ-butyrolactone is one of the most abundant structural motifs in a wide array of biologically active natural products.[1] In fact, the γ-butyrolactone core constitutes about 10% of naturally occurring compounds[2] and many of these possess a broad range of biological activities and are known potent anticancer, antibacterial and antifungal agents.[3] In this regard, several multistep catalytic approaches have been explored for the racemic synthesis of γ-butyrolactones.[4] Considering the inevitable importance of γ-lactone scaffold, conspicuous efforts have been devoted towards the enantioselective synthesis of a γ-butyrolactone core with the catalytic approach.[5] Among these many enantioselective methods, most noteworthy are asymmetric transfer hydrogenation (Figure 1a),[5a–c] gold catalyzed lactonization by Lipshutz (see Figure 1b)[5d] and chromium catalyzed γ-butyrolactone synthesis by Yun.[5e] However, some of these methodologies rely on the use of heavy and expensive transitional metal catalysts (Ir, Ru, Au, Cr, etc), very expensive ligands and commercially unavailable pre-functionalized starting materials. Notably, only countable organocatalyzed protocols such as asymmetric cross-benzoin/Michael/acetalization by Han,[5f] cross annulation by Saigo[5g] and Fiksdahl[5h] are limited only to highly reactive fluorinated ketones as substrates (See Figure 1c). Moreover, it is important to note that in other protocols only aromatic hydroxyketones are proved to be efficient precursors for the enantioselective synthesis of γ-butyrolactones and related compounds such as five membered oxygen heterocycles.[6] However, these multistep methods are limited to aromatic hydroxyketones and aromatic Michael acceptors. While the aliphatic hydroxyketones and aliphatic Michael acceptors did not react under the reaction conditions[6a] or they were not explored possibly due to the similar reasons.[6b] However, organocatalyzed enantiopure synthesis of γ-butyrolactones that involves easily and commercially available starting materials, and less reactive simple aliphatic as well as aromatic hydroxyketones in one step is much more challenging and demanding to pursue. Some of these synthetic limitations strongly encouraged us to explore the synthesis of enantiopure lactones by more convenient and practical approach. The key challenges are to avoid pre-functionalized starting materials and expensive transition metal catalysts. One-pot organocatalytic multicomponent reactions can prove to be one of the very important strategies to access the enantiopure γ-butyrolactones in a cost effective and efficient manner.

Remarkably, to the best of our knowledge, one-pot enantioselective organocatalytic multicomponent reaction (OMCR) for the formation of γ-butyrolactone

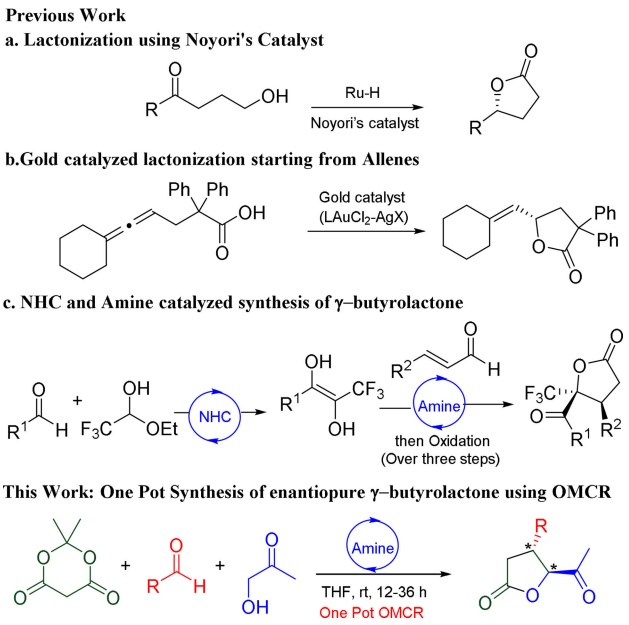
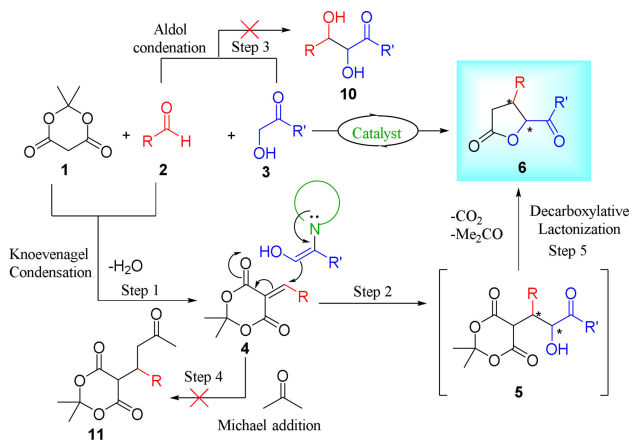


Figure 1. Enantioselective synthesis of γ-butyrolactones.

remains an unmet challenge till date. Keeping all these parameters in mind, we ventured into developing a novel and more convenient strategy to synthesize γ-butyrolactone. Herein, in this paper we report a novel and expedient enantiopure synthesis of γ-butyrolactones achieved by organocatalytic enantioselective tandem three component reaction between Meldrum's acid, aldehyde and hydroxyketone for the first time. Recently our laboratory has shown a considerable interest in Meldrum's acid related synthesis.[7] In our continuing efforts, we became interested to evaluate the scope of Meldrum's acid with the asymmetric catalysis. Meldrum's acid has attracted significant attention as it offers various valuable products[8] and the usefulness of which is efficiently demonstrated in complex multicomponent processes.[9] Undoubtedly, α,β-unsaturated alkylidene Meldrum's acid derivative **4** acts as an excellent Michael acceptor in 1,4-addition reaction[10] and the ensuing intermediates are highly versatile compounds for various new transformations. By taking into account of these, we hypothesized a novel three component chemoselective tandem Knoevenagel-Michael-lactonization sequence as shown in scheme 1. However, our proposed multicomponent synthetic scheme has following daunting chemoselectivity challenges to be met (Scheme 1). Some of them are:(1) the Knoevenagel condensation reaction should rapidly lead to alkylidene Meldrum's acid product **4** (step 1); (2) very importantly, 1,4-Michael addition (step 2) has to be dominant over aldol condensation[11] (step 3); (3) by-product, acetone should barely take part in the reaction to avoid side product **11**[9a] (step 4), i.e. 1,4-Michael addition on intermediate **4**; (4) finally, the lactonization should happen in one pot (step 5) under ambient temperature. Keeping all these possibilities in mind, initially we planned to explore the reaction by using proline as a catalyst as it has widely been used in aminocatalysis.[12]

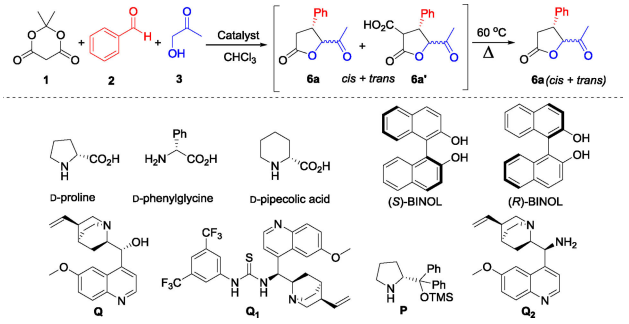


Scheme 1. Proposed one pot synthesis of enantiopure γ-butyrolactone via Knoevenagel-Michael-lactonization.

Initially, a model reaction was performed by using Meldrum's acid **1**, benzaldehyde **2a** and hydroxyacetone **3a** in presence of catalytic amount of D-proline (20 mol%) in chloroform. Gratifyingly, the desired lactone **6a** was obtained but as two separable diastereomers (1:2.1 *d.r.*), albeit in poor enantioselectivity at room temperature (Table 1, entry 1).

The structures of both *cis* and *trans* diastereomers were confirmed by ^{1}H, ^{13}C NMR spectral analysis and single-crystal X-ray diffraction data (see ESI).[13] The low enantioselectivity of the product **6a** may be attributed to either inadequate steric bulk of proline or less efficient steric interactions. Initially, we believed that epimerization of *cis*-lactone would have resulted in poor diastereoselective outcome. However, this possibility was ruled out as we observed no epimerization of *cis*-lactone of **6a** under the similar reaction conditions even after prolonged reaction time. Subsequently, lowering the reaction temperature to 0 °C turned out to be extremely disadvantageous (Table 1, entry 2). This initial exciting breakthrough for the one pot lactonization encouraged us to screen some more efficient catalyst systems. Recently, it has been demonstrated that combining additional supplemental co-catalyst along with amino acids enhances the effective stereo interactions.[14] Therefore, we planned to introduce a cinchona based thiourea-amino acid catalytic assembly with an aim to have high stereocontrol to this reaction. However, all the modules did not enhance the enantioselectivity (Table 1, entries 3–7). The lack of enantioselectivity could be attributed to the unanticipated, but favorable acid-

Table 1. Optimization of Proposed synthesis of γ-butyrolactone.



entry	Catalyst (mol%)	Additive (mol%)	Yield[b] (%)	*d.r.* (*trans*:*cis*)[c]	*ee* (%) (*trans*/*cis*)[d]
1	D-Pro (20)	–	63	1:2.1	24/26
2[a]	D-Pro (20)	–	trace	nd	nd
3	D-Pro (20)	Q1(20)	64	1:2.1	nd/24
4	L-Pro (20)	Q1(20)	60	1:2.1	nd/21
5	L-Pro (20)	(*S*)-BINOL (20)	55	1:2	nd/25
6	L-Pro (20)	(*R*)-BINOL (20)	50	1:2	nd/25
7	D-Phg (20)	Q1(20)	8	nd	nd
8	D-Pip (20)	–	trace	nd	nd
9	P (20)	–	–	–	–
10	–	Q1(20)	–	–	–
11	Q2(20)	–	70	2.5:1	89/57
12	Q2(20)	TFA (40)	79	2.5:1	91/58
13[a]	Q2(20)	TFA (40)	trace	nd	nd
14[e]	**Q2(5)**	**TFA (10)**	**78**	**2.5:1**	**91/58**
15[e]	Q2(10)	TFA (20)	78	2.5:1	91/58

Reaction Conditions: Meldrum's acid **1** (1 equiv.), Benzaldehyde (1.05 equiv.), Hydroxyacetone (3 equiv.) Catalyst (5–20 mol%), Additive (10–40 mol%), in $CHCl_3$ at rt, 24 h,
[a] reactions were carried out at 0 °C,
[b] isolated yield after purification by column chromatography,
[c] *dr* was calculated based isolated yields
[d] *ee* was determined by HPLC,
[e] Reactions were stirred for 24 h followed by heating at 60 °C for 6 h for the decarboxylation.

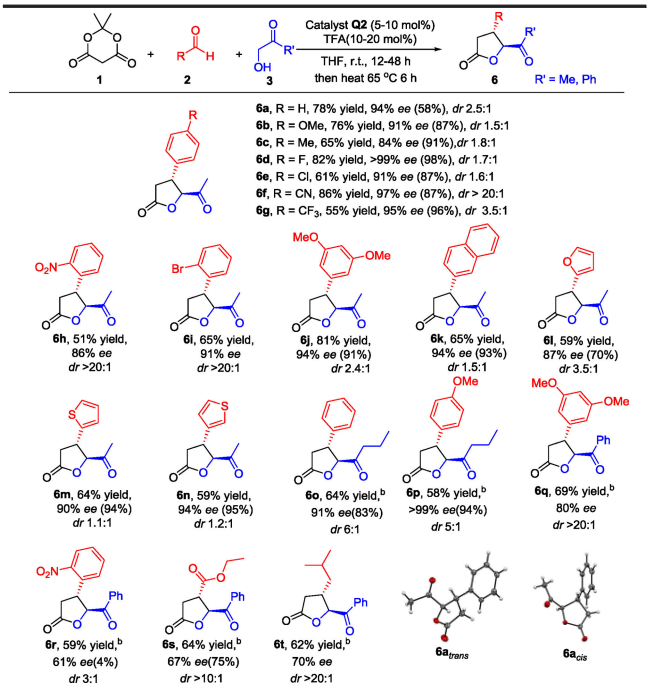
base interaction between Meldrum's acid (pKa 4.9) and thiourea. This might have resulted proline to catalyze the reaction solely. Surprisingly, additional amino acid based catalyst (D-pipecolic acid or P) and thiourea catalyst **Q1** were found to be extremely ineffective in terms of reactivity (Table 1, entry 8–10).

Based on these studies, we surmised that quinine based bifunctional diamine **Q2** may prove to be more potential to serve as a good catalyst. Chiral cinchona diamines are believed to invoke favorable stereo interactions due to their intrinsic ability to simultaneously form enamine and hydrogen bonding with high degree of conformational flexibility. To our delight, promising results were obtained in the presence of quinine based bifunctional primary amine catalyst **Q2** (20 mol%) by affording the desired product **6a** in 70% yield with good stereoselectivity (Table 1, entry 11). It is interesting to note that Knoevenagel condensation, Michael addition, lactonization and decarboxylation took place in one pot at room temperature to afford the desired product **6a**. While the two fold addition of TFA (40 mol%) along with the catalyst **Q2** (20 mol%) marginally enhanced the yield and enantioselectivity of desired product **6a** (Table 1, entry 12). Presumably, TFA might have reduced the unanticipated acid-base interaction between catalyst **Q2** and Meldrum's acid. Further reduction in catalytic loading (5 and 10 mol%, entries 14, 15) afforded the desired product **6a** along with the undecarboxylated intermediate **6a'** (detected by HRMS) at room temperature (see Table 1, entries 14, 15), unlike in case of higher catalytic loading (20 mol%) wherein, decarboxylation took place without heating (see Table 1, entry 12). We observed the incomplete decarboxylation even after prolonged reaction time (48 h). Further, in order to decarboxylate the intermediate **6a**′, the reaction mixture was heated at 60 °C for 6 h for the complete decarboxylation to afford product **6a** in 78% yield without any erosion of enantioselectivity (91% *ee*). Based on these results, to avoid higher catalytic loading, we decided to use 5 mol% of catalyst **Q2** followed by heating for the substrate scope. Encouraged by the initial results, further we screened various solvents under optimized reaction condition (**Q2** 5 mol% followed by heating, see ESI). Interestingly, THF was found to be the best solvent for the desired transformation (**6a**, 78% yield, 94% *ee*). On the other hand polar solvents such as H_2O, DMSO, DMF, EtOH had a detrimental effect on the reaction.

Having obtained the optimized reaction conditions in hand (5 mol% **Q2**, 10 mol% TFA in THF at room temperature for 24 h followed by heating at 65 °C for 6 h in one pot), further the scope of Knoevenagel-Michael-lactonization was investigated using various aldehydes and hydroxyketones. It was observed that aromatic aldehydes containing electron donating as well as withdrawing functional groups reacted smoothly under the optimized reaction conditions to afford the corresponding lactones (**6b–6j,** Table 2) in good yields with high to excellent enantioselectivity (up to 99% *ee*). Naphthaldehyde under the reaction conditions afforded the corresponding lactone **6k** in

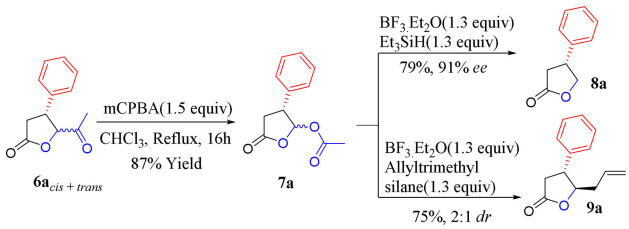
good yield and excellent enantioselectivity (65%, 94% *ee*).

Table 2. One pot enantiopure synthesis of γ-butyrolactones[a–e].



[a] Reaction conditions: Meldrum's acid **1** (1 equiv.), Aldehyde (1.05 equiv.), Hydroxyketone (3 equiv.) **Q2** (5 mol%), TFA as additive (10 mol%), in THF at rt, 24 h then heat at 65 °C in one pot;
[b] 10 mol% of catalyst **Q2** and TFA (20 mol%) were used for the complete conversion,
[c] isolated yield after purification by column chromatography,
[d] *d.r.* was calculated based on isolated yields
[e] *ee* was determined by HPLC; *ee* of *cis*-isomer is given in parenthesis.

Similarly, heteroaromatic aldehydes such as furfural and thiophene 2/3-aldehydes afforded the corresponding lactones **6l**, **6m** and **6n** respectively (up to 94% *ee*, Table 2). In order to have generality of the method and for the wider practicability, we planned to explore the reactions of 1-hydroxy-2-pentanone **3b** and 2-hydroxyacetophenone **3c**. Under the optimized reaction conditions **3b** reacted smoothly with aldehydes **2a, 2b** and Meldrum's acid **1** to afford the corresponding lactones **6o** and **6p** in moderate to good yields with excellent enantioselectivity (see, Table 2). Likewise, the reaction of 2-hydroxyacetophenone **3c** with aldehydes **2j** and **2h** afforded the corresponding products **6q** and **6r** respectively in moderate to good yield with good enantioselectivity. Interestingly, it is very significant to note that the reaction of aliphatic aldehydes such as isovaleraldehyde **2o** and ethyl glyoxalate **2p** with 2-hydroxyacetophenone afforded the corresponding lactones **6s** and **6t** in good enantioselectivity. We observed that steric and electronic factors did not have any significant effect on the efficiency and yield of the reaction. Wide variety of aldehydes and different functional groups tolerated the reaction conditions. In order to have some insight into stereochemical outcome of the transformation and mechanistic aspects, we carried out few experiments on lactone **6b**. Esterification followed by oxidation of two separate diastereomers of **6b** (*cis* and *trans*) afforded the corresponding identical enantiomer (see ESI). This revealed that only one face of alkylidene Meldrum's acid **4** interacted with the both *re* and *si* face of hydroxyacetone enamine (**ENM**). To assign the absolute configuration, the product $\mathbf{6a}_{cis+trans}$ was subjected to Baeyer-Villiger oxidation followed by reduction of **7a** (Scheme 2). By comparing the specific rotation of product **8a** with the literature value, the absolute configuration of **6a** was assigned as '*R*' at benzylic position (observed specific rotation $[\alpha]_{25}^{D} = -41.0$ (*c* 1.0, $CHCl_3$), literature $[\alpha]_{23}^{D} = -27.7$ (*c* 4.0, $CHCl_3$) for '*R*' configuration).[15]

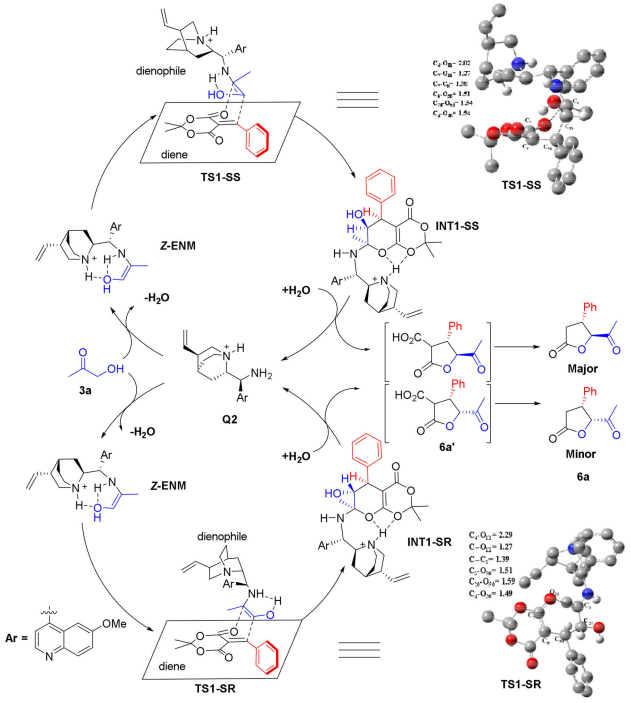


Scheme 2. Reduction and allylation of butyrolactone **6a**.

Further, to make this protocol more practical and to demonstrate the synthetic utility of the products, synthetically useful allyl lactone **9a** was synthesized starting from compound **7a** in a shorter pathway. Further, to demonstrate the practical utility of this protocol, lactone **6a** was synthesized on a gram scale in good yield (75%) without the erosion of enantioselectivity (94% *ee*) (Scheme 2).

To have a better understanding of the mechanism and stereoselectivity of reaction catalyzed by chiral cinchona catalyst **Q2**, we planned to investigate the intermediates and transition states (TS) that are involved in the catalytic cycle by Density Functional Theory (DFT) calculations. The proposed catalytic cycle is outlined in Scheme 3. Initially protonated primary amine **Q2** catalyzes Knoevenagel condensation to afford the corresponding heterodiene **4a**. Further this reacts with enamine (***Z*-ENM** and ***E*-ENM** as dienophile) via [4+2]-hetero-Diels-Alder

cycloaddition pathway. DFT calculations revealed that *Z*-enamine (***Z*- ENM**) is 7.059 kcal mol^{-1} more stable than *E*-enamine (***E*-ENM**) due to favorable hydrogen bonding. It is important to note that under experimental conditions, we obtained only *RS* and *RR* lactones selectively.



[a]Selected bond distances are in Å. [b]Relative free energies given in kcal·mol^{-1}; M06-2X/6-311++G(d,p)/SMD//M06-2X/6-31G(d).
[c]Most of the H-atoms have been omitted for the sake of clarity.

Scheme 3. Proposed catalytic cycle.[a,b,c]

The optimized structures of all the reactants, TS's, intermediates and products are given in ESI. Calculations were carried out to determine the role of TS's on the outcome of stereochemistry of the lactones. This was further unambiguously supported by single crystal X-ray analysis and specific rotation. Keeping this in view, we computationally studied the attack of only ***Z*-ENM** (both *re* and *si faces*) to the only *si* face of heterodiene **4a** in detail for the outcome of *RS* and *RR* lactones (see ESI for data and details). Transition state TS1-*SS* (*si* face of **4a** and *si* face of ***Z*-ENM**) is 5.534 kcal mol^{-1} more stable than TS1-*SR* (*si* face of **4a** and *re* face of ***Z*-ENM**). TS1-*SS* leads to more stable major product lactone **6a**-*RS* (10.69 kcal mol^{-1} more stable than **6a**-*RR* lactone) through a series of transition states and intermediates for the stepwise mechanism (see ESI).

These DFT calculations strongly support the experimental results and high stereoselectivity (Theoretical *ee* = 99% is in very good agreement with the experimental *ee* = 94%).

In conclusion, we developed a novel, robust and a straightforward protocol for the highly enantiopure synthesis of γ-butyrolactones via one-pot organocatalytic multicomponent reaction (OMCR) strategy. Potential of OMCR is explored for the first time for the rapid access of enantiopure lactone scaffolds starting from commercially available simple starting materials. Experimental observation was further supported by the computational studies. More importantly protocol avoids the use of pre-functionalized substrates, additional base and, expensive transition metals. Reaction proved to be highly enantioselective and reproducible on a gram scale and is proved to practical to access synthetically useful lactones.

Experimental Section

In a glass vial equipped with a teflon-coated stir bar, 9-amino (9-deoxy)*epi*quinine Q2 (0.04 mmol, 11.2 mg, 5 mol%) was dissolved in 1.0 mL of THF. After addition of TFA (0.07 mmol, 5.3 µL, 10 mol%), the reaction mixture was stirred for 15 minutes. Then Meldrum's acid 1 (100 mg, 0.7 mmol, 1 equiv.), benzaldehyde (74.3 µL, 0.73 mmol, 1.05 equiv.) and hydroxy acetone (145.6 µL, 2.1 mmol, 3 equiv.) were added subsequently and stirred for 24 h or as indicated in the manuscript. Upon complete consumption of Meldrum's acid, the reaction mixture was heated at 65 °C for 6 hours to decarboxylate the acid intermediate. The crude product 6a was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as an eluent. Compound 6a was obtained as solid in 78% yield.

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Organocatalysis

An Adverse Effect of Higher Catalyst Loading and Longer Reaction Time on Enantioselectivity in an Organocatalytic Multicomponent Reaction

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Abstract: An enantioselective organocatalytic multicomponent reaction of aldehydes, ketones, and Meldrum's acid has been developed. A cinchona-based primary amine (1 mol%) catalyses the multicomponent reaction via the formation of the Knoevenagel product and a chiral enamine to form enantiopure δ-keto Meldrum's acids in a tandem catalytic pathway. An adverse effect of higher catalyst loading and longer reaction time on enantioselectivity was studied. This mild protocol provides an easy access to enantiopure carboxylic acids, esters and amides and the method is scalable on a gram quantity. DFT calculations were carried out on the proposed reaction mechanism and they were in close agreement with the experimental results.

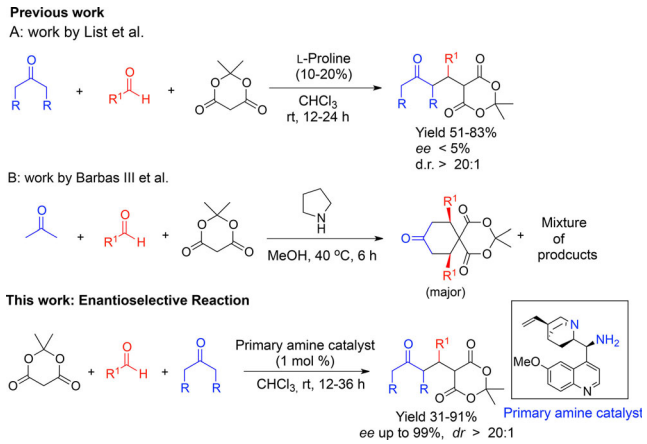

Figure 1. Multicomponent reaction of ketones, aldehydes and Meldrum's acid.

Aminocatalysis is one of the essential pillars in the field of organocatalysis and is often explored in several complex multicomponent reactions.[1–3] At the dawn of asymmetric organocatalysis, various research groups independently discovered that aminocatalysts possess an unprecedented affinity for catalysing a number of diverse multicomponent processes very efficiently and selectively to generate a broad array of diverse optically active compounds.[4] However, to identify a suitable catalyst and a set of conditions is always crucial for the success of enantioselective multicomponent reactions. List and co-worker[5] reported an efficient proline-catalysed three-component Knoevenagel–Michael addition reaction of Meldrum's acid, an aldehyde and a ketone (see Figure 1 A). Although this elegant C–C bond-forming reaction is highly diastereoselective, it lacks enantioselectivity. Furthermore, in addition to the desired reaction sequence, numerous pathways are possible that can compete by leading to the undesired products. For example, Barbas and co-worker[6] demonstrated a similar reaction that furnished four products when pyrrolidine was used as a catalyst (see Figure 1 B).

To our surprise, this highly efficient C–C bond-forming, enantioselective, three-component process still remained an unmet challenge and this encouraged us to investigate an appropriate catalyst system.

We believed that the modularly designed organocatalyst assembly developed by Zhao group[7] or cinchona-based primary amine catalysts[3c] might overcome the ineffective enantiodiscrimination catalysed by proline. In general, it is often assumed that reactions work smoothly when aminocatalysts are employed in the range of 10–30 mol%. However, their counterproductive effects on the chemoselectivity and stereoselectivity are rarely observed and studied.[8] To the best of our knowledge, the counterproductive effects of high-catalyst loading of an aminocatalyst and a longer reaction time in the multicomponent reactions have not been investigated to date. In this communication, we report the very first enantioselective organocatalytic multicomponent reaction of aldehydes, ketones, and Meldrum's acid and the study on the significant effect of low-catalyst loading on the enhancement in the enantioselectivity of multicomponent reaction.

At the outset, we began our investigation by treating Meldrum's acid **1**, benzaldehyde **2a** and acetone **3a** with D-proline and various other catalyst modules (Scheme 1 and see Supporting Information for the screening table). Initial screening with D-proline as well as modularly designed catalysts (D-proline/D-phenylglycine and a chiral thiourea catalyst)[7] afforded the desired product **4a** with extremely poor enantioselectivity (4–5% *ee*). The Hayashi–Jørgensen catalyst and other cat-

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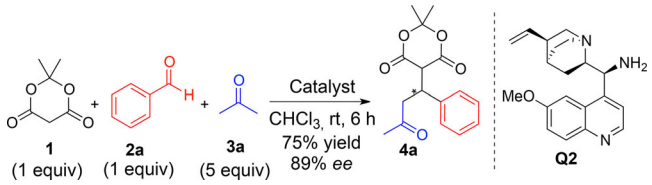


Scheme 1. Bifunctional amine catalysed model reaction.

alyst assemblies comprising chiral thiourea and amino acids, such as D-aspartic acid, D-glutamic acid and D-pipecolic acid, led to unsatisfactory results. After exhaustive screening, we turned our attention towards a cinchona-based, primary amine, bi-functional catalyst **Q2**. The reaction with catalyst **Q2** (10 mol%) gave the desired product **4a** in 75% yield with good enantioselectivity (89% *ee*) in a considerably shorter reaction time than with other catalysts at room temperature (6 h, rt, see Supporting Information). After establishing the suitable catalyst system, the effect of solvents on the enantioselectivity was examined (see Supporting Information). Screening of various solvents revealed that chloroform is the best solvent for the desired transformation. The primary amine catalyst **Q2** (10 mol%) in chloroform at room temperature was established as the optimised reaction conditions.

Having the optimised reaction conditions in hand, we planned to extend the scope of the reaction by using various aldehydes and ketones for the generality of the protocol. Initially, the reaction of Meldrum's acid **1**, 4-methoxybenzaldehyde **2b** and acetone **3a** under optimised reaction conditions afforded the corresponding product **4b** in 50% yield with 72% *ee* after 6 h. However, when we tried to increase the yield by stirring the reaction for an extended period of time, the enantioselectivity was drastically lowered from 72% *ee* at 6 h to 10% *ee* at 48 h. This unanticipated observation indicated the probable negative influence of longer reaction time on the enantioselectivity. In order to validate this finding, the same reaction was repeated and the enantiomeric excess of the product **4b** at different time intervals was recorded as summarised in Figure 2 (black line). Surprisingly, we observed that the initial

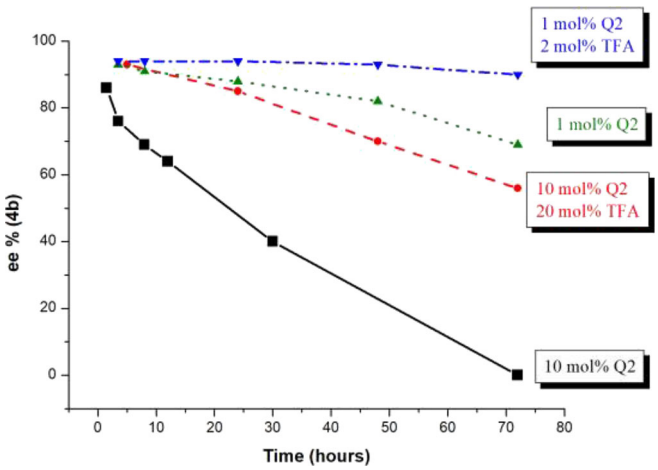
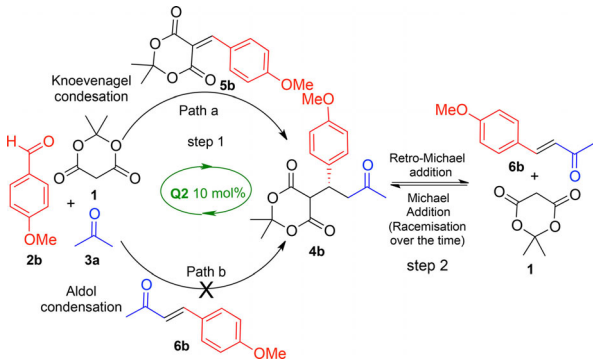


Figure 2. Effect of catalyst loading and time on enantioselectivity of **4b**.

very good enantioselectivity (86% *ee* at 1.5 h) was found to be eroding continuously over a period of time and virtually became racemic after 72 h (Figure 2, black line 10 mol% **Q2**). However, unlike **Q2**, the D-proline-catalysed reaction led to the racemic product in a short period of time (1 h). Prior to unravel the root cause of racemisation over a period of time, it was important to understand the possible pathways of this transformation.

We firmly believed that the three-component reaction of **1**, **2b** and **3a** can proceed via either a Knoevenagel–Michael reaction pathway (path a) or an aldol–Michael reaction pathway (path b) (Scheme 2). In order to investigate the most plausible

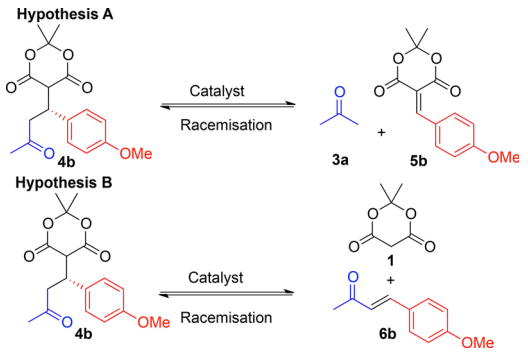


Scheme 2. Possible pathways for the product **4b**.

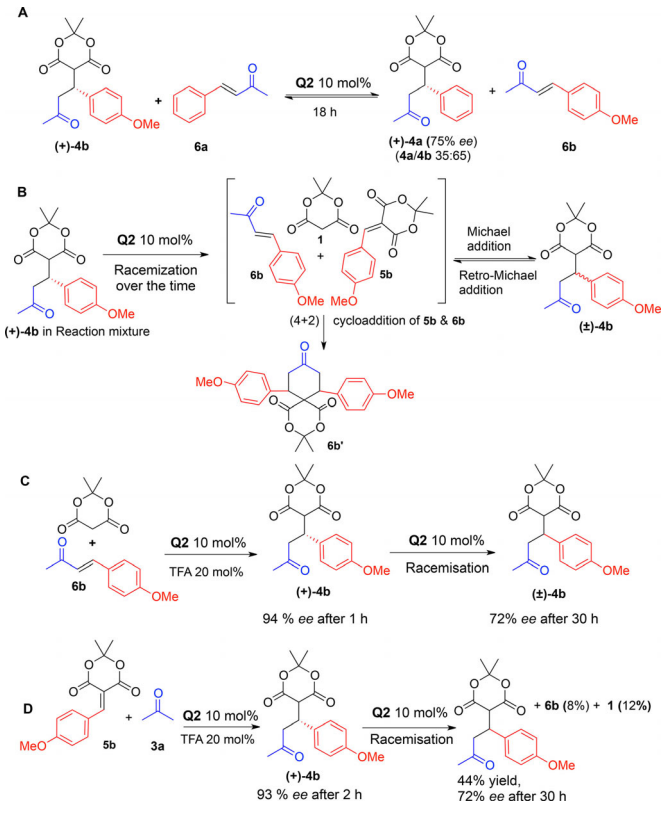
pathway, we carried out the time-dependent ^{1}H NMR experiments of the reaction mixture (see Supporting Information for the stacked spectrum). An intense peak (s, 8.32 ppm) corresponding to alkylidene Meldrum's acid **5b** appeared immediately within 10 minutes. This peak disappeared over a period of time, while the characteristic peak (dd, 3.01 ppm) corresponding to the product **4b** intensified gradually over a period of time (10 min–8 h). Likewise, the time-dependent ^{1}H NMR experiments of the reaction mixture of **4a** gave a similar pattern of results. However, we also noticed that initially absent or insignificant characteristic peaks corresponding to benzylidene acetone (**6a**; d, 6.72 ppm) and 4-methoxybenzylidene acetone (**6b**; d, 6.61 ppm) slowly appeared along with the product peak (see Supporting Information). Based on this interesting observation we surmised that either the initially formed products **4a**/**4b** (by the Knoevenagel–Michael pathway, path a) slowly underwent elimination of **1** thus leading to **6a**/**6b** or aldol condensation competed weakly with the path a. In order to validate further, we carried out the reaction of **2b** and **3a** in the presence of catalyst **Q2** (10 mol%). Interestingly, the anticipated aldol condensation product **6b** was not obtained. Surprisingly, 20 mol% of **1** along with **Q2** (10 mol%) catalysed the formation of **6b** in a trace amount (see Supporting Information, Eq. (2), page S23). These findings unambiguously infer that the reaction proceeds by a Knoevenagel–Michael reaction pathway (path a).

Further, in the quest for finding the reason for the erosion in enantioselectivity over a period of time we conceived two probable hypotheses A and B (Scheme 3). In both the hypotheses, enantiopure compound **4b** may undergo racemising, equi-

librating, retro-Michael/Michael addition. However, based on the earlier NMR experiments, hypothesis A seems to be unlikely as **5b** disappeared over a period of time, while, **6b** formed by means of the racemising, equilibrating, retro-Michael/Michael addition starting from enantiopure **4b**. Further, in order to validate the possible reversible retro-Michael/Michael addition reaction (hypothesis B), we carried out a cross-over experiment of enantiopure product **4b** and benzylidene acetone (**6a**) in the presence of 10 mol% of catalyst **Q2** in chloroform (18 h, Scheme 4A, see Supporting Information). The formation of **6b** and product **4a** unambiguously supported the hypothesis B for the reversible retro-Michael/Michael addition pathway. This clearly gives an insight that compound **4b** undergoes an elimination process to afford **1** and **6b** over a period of time.



Scheme 3. Possible routes for the racemisation.



Scheme 4. Crossover experiment to validate hypothesis B.

Interestingly, longer reaction time also resulted in spiro compound **6b'** ([4+2] through cycloaddition of **5b** and **6b**, 35% yield)[6] along with racemic **4b** (see Scheme 4B) and this finding further supported the hypothesis B.[9] It is possible that the higher concentration of the catalyst **Q2** may be the key factor (acting as a base) for the retro-Michael/Michael addition thus causing erosion of enantiopurity. In order to overcome this problem, we added the acidic additive trifluoroacetic acid (20 mol% TFA, pK_a 0.23) along with the catalyst to reduce the undesirable base effect of the catalyst. However, we observed that the initial excellent enantioselectivity eroded over the time (see red line, Figure 2). Nevertheless, erosion of enantioselectivity was found to be relatively slower than in the presence of sole catalyst **Q2** (see black line, Figure 2).

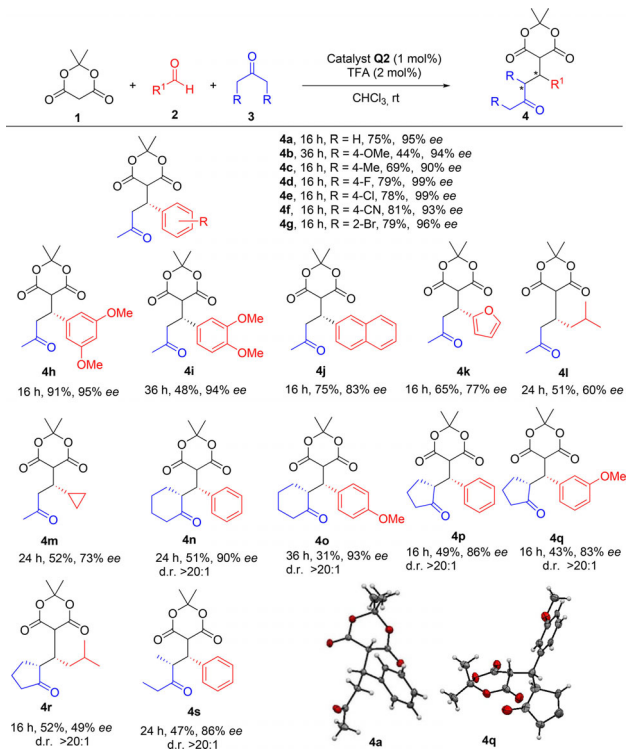
This led us to believe that reducing the catalyst loading instead of compromising the reaction time would be more beneficial. It was gratifying to note that the reaction of **1**, **2b** and **3a** in the presence of 1 mol% of **Q2** in chloroform (24 h) afforded the corresponding product **4b** in excellent enantioselectivity (93% *ee*). However, over a period of time very slow erosion of enantioselectivity was inevitable (see green line, Figure 2). The addition of 2 mol% of TFA along with **Q2** (1 mol%) was found to be highly effective and the enantiopurity of **4b** remained almost unchanged even after prolonged reaction time at 72 h (see blue line, Figure 2).

Based on our experimental observations and literature precedents,[8c,d] we propose that under higher catalyst loading the initially formed enantiopure product **4b**, slowly undergoes an equilibrating retro-Michael/Michael addition process thus leading to racemisation (Step 2, Scheme 2). The more favourable increase in entropy could be the driving force for the irreversible racemisation and would reach the completion when thermodynamic equilibrium is achieved (*ee*≈0%).[10] This assumption was further revalidated by the reaction of **1** and **6b** in presence of 10 mol% of **Q2** and 20 mol% TFA (see Scheme 4C).[11] It is interesting to note that the initially formed enatiomerically pure product (+)-**4b** (94% *ee*) was susceptible to the erosion of enantiopurity over a period of time (30 h, 72% *ee*). Treatment of the isolated enantiopure product (+)-**4b** with 10 mol% of **Q2** over a period of time (72 h) resulted in an almost racemic mixture of (±)-**4b**. On the other hand, under the lower catalytic loading (1 mol% **Q2** and 2 mol% TFA), owing to the slower reaction rate, the Michael addition was favoured over the racemising retro-Michael/Michael pathway (Step 2, Scheme 2), thus affording the enantiomerically pure product (+)-**4b**. Further, the reaction of **5b** with **3a** in the presence of 10 mol% of **Q2** and 20 mol% TFA afforded the enantiopure desired product (+)-**4b** in 2 h. However, prolonging this reaction (40 h) resulted in erosion in enantioselectivity leading to **4b** (72% *ee*) along with small amount of **1** and **6b** (see Scheme 4D). Based on the above experiments and especially from Scheme 4C and D, it can be proposed that enantiopure (+)-**4b** slowly undergoes retro-Michael/Michael reaction equilibrium to give racemic **4b** over a period of time.

Based on the available experimental evidence, the most probable mechanistic pathway for the erosion in the enantioselectivity can be surmised. After re-establishing the optimum

catalytic loading (1 mol% **Q2** and 2 mol% TFA), we explored the generality of the reaction by using various aldehydes and ketones. Aromatic aldehydes, both electron-rich and electron-deficient, were found to be compatible under the optimised reaction conditions by affording the corresponding products (**4a**–**4j**, Table 1) in good yields with excellent enantioselectivity up to 99% *ee*. However, we observed that the reaction of aromatic aldehydes, such as 4-methoxy benzaldehyde and 3,4-dimethoxy benzaldehyde reacted relatively slowly (36 h) to afford **4b** and **4l** in moderate yields.[9] The heteroaromatic aldehyde furfural worked well under the reaction conditions and afforded the corresponding product **4k** in good yield but with lower enantioselectivity (77% *ee*). In order to have a wider scope, we examined the feasibility of the reaction on aliphatic aldehydes. It was found that even enolisable aldehydes were well tolerated in the presence of primary amine catalyst **Q2**, affording the products (**4l** and **4m**) in good yields with moderate enantioselectivity (60–73% *ee*). The scope of the reaction was extended further towards substituted Michael donors such as cyclohexanone, cyclopentanone and 3-pentanone with various aldehydes. In all cases, the corresponding products (**4n**–**4s**) were obtained as single diastereomers with moderate to excellent enantioselectivity (up to 94% *ee*). Notably, this protocol tolerated a wide variety of aldehydes under very mild reaction conditions. The strength and practicality of this protocol was also demonstrated on a gram scale synthesis of product **4a** (74% yield) without loss of enantioselectivity (94% *ee*) under optimised reaction conditions.

Table 1. Substrate scope.[a–d]



[a] Optimised reaction conditions: Meldrum's acid **1** (1 equiv), aldehyde **2** (1.05 equiv), ketone **3** (5 equiv) catalyst **Q2** (1 mol%), TFA as an additive (2 mol%), in chloroform at rt. [b] Isolated yield after purification by column chromatography given in parenthesis. [c] d.r. was calculated based ^{1}H NMR spectroscopy. [d] *ee* was determined by HPLC using chiral column.

In order to show the wider applicability of this protocol we demonstrated enantiopure synthesis of some of the important precursors of many useful molecules such as carboxylic acid, ester and amide starting from **4a** (see page S25 in the Supporting Information). The synthesis of ester also helped to identify the absolute configuration of **4a** (see Supporting Information).[12] Based on these findings the absolute configuration of **4a** was assigned as *R*.

The molecular structure of compounds **4a** and **4q** (relative configuration) were established using single-crystal X-ray diffraction analysis (Table 1).[13]

The proposed mechanism was computationally studied by using density functional theoretical calculations (see Supporting Information for results and details). Initially protonated primary amine **Q2** catalyses the Knoevenagel condensation via iminium ion intermediate I and intermediate II to generate a heterodiene (**5a**). In the second step catalyst **Q2** forms chiral enamine (*S*-ENM) with **3a** that further reacts with the heterodiene (**5a**) by means of a [4+2]-hetero-Diels–Alder cycloaddition pathway.[14] The transition states (TSs) for the [4+2] cycloaddition step could follow the enamine/**5a** *si* facial attack or enamine/**5a** *re* facial attack, thus resulting in TS1-*S* and TS1-*R*, respectively (Figure 3). Of these two TSs formed, TS1-*S* is 7.53 kcal mol^{-1} more stable than the TS1-*R*, resulting in product **4a** (*R* configuration) with high stereoselectivity (theoretical

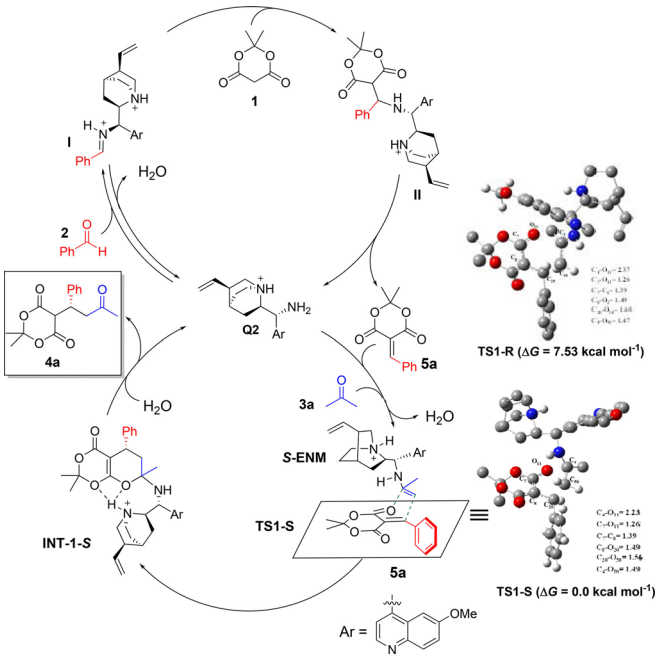


Figure 3. Proposed mechanism: Transition state structures for the addition of enamine *S*-ENM to **5a** (both *si* and *re* face); selected bond lengths are in Å; relative free energies are given in parenthesis (kcal mol^{-1}); M06-2X/6-311++G(d,p)/SMD//M06-2X/6-31G(d). Most of the H atoms have been omitted for the sake of clarity.

ee = 98% is in very good agreement with the experimental *ee* = 95% see Supporting Information).

In conclusion, we have demonstrated a highly enantioselective organocatalytic multicomponent reaction of aldehydes, ketones, and Meldrum's acid for the first time since its discovery. We carried out a systematic study on the adverse effect of higher catalytic loading and longer reaction time on the outcome of enantioselectivity. In order to understand the mechanism of racemisation in depth, further detailed investigation is needed. The protocol is efficient under very low catalyst loading (1 mol%) and is scalable. The protocol is practical as it gives a quick access to very useful precursors and intermediates such as enantiopure δ-keto esters, carboxylic acids and amides. This mild and useful reaction may find a wider application in the future.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: adverse effect · enantioselectivity · hetero-Diels–Alder cycloaddition · multicomponent reaction · organocatalysis

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COMMUNICATION

Organocatalysis

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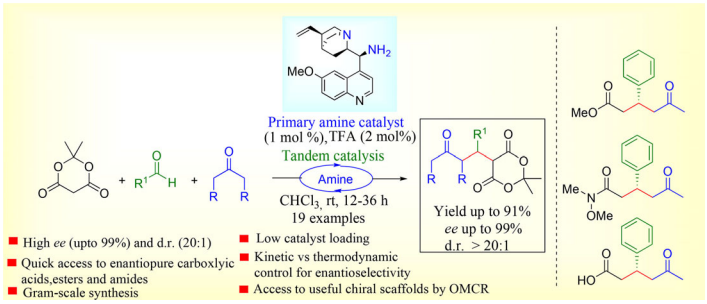
An Adverse Effect of Higher Catalyst Loading and Longer Reaction Time on Enantioselectivity in an Organocatalytic Multicomponent Reaction



Cause and effect: An adverse effect of higher catalyst loading and longer reaction time on enantioselectivity was studied. An enantioselective organocatalytic multicomponent reaction of aldehydes, ketones and Meldrum's acid was developed (up to 99% *ee*). This mild protocol provides an easy access to enantiopure carboxylic acids, esters and amides with high enantioselectivities and the method is scalable.