

**Direct C3-(sp<sup>2</sup>)-H Alkenylation and C(γ-sp<sup>3</sup>)-H  
Arylation of Five Membered Heteroaryl Compounds  
via Palladium Catalysis: An Access to Novel  
Compounds with Photophysical Properties**

विद्या वाचस्पति की  
उपाधि की अपेक्षाओं की आंशिक पूर्ति में प्रस्तुत शोध प्रबंध

**A thesis**

**submitted in partial fulfillment of the requirements  
of the degree of Doctor of Philosophy**

**द्वारा / By**

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**Indian Institute of Science Education and Research Pune**

**2023**

*This thesis is dedicated to...*

*My parents*

*And*

*My beloved family*



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## CERTIFICATE

This is to certify that the research work incorporated in this thesis entitled “*Direct C3-(sp<sup>2</sup>)-H Alkenylation and C(γ-sp<sup>3</sup>)-H Arylation of Five Membered Heteroaryl Compounds via Palladium Catalysis: An Access to Novel Compounds with Photophysical Properties*” submitted by **Javed Yasin Shaikh** and the research was carried out by the candidate at Indian Institute of Science Education and Research (IISER), Pune, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other University or institution.

**Date:** 31/10/2023

**Place:** Pune (Maharashtra)

**Prof. Ramakrishna G. Bhat**

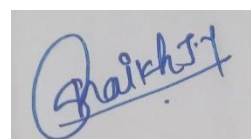
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## List of Abbreviations

|                   |                                        |
|-------------------|----------------------------------------|
| Å                 | angstrom (s)                           |
| AcOH              | acetic acid (glacial)                  |
| ACN               | acetonitrile                           |
| Ac <sub>2</sub> O | acetic anhydride                       |
| Ag                | argentums (Silver)                     |
| aq.               | aqueous                                |
| Ar                | aryl/heteroaryl                        |
| atm               | atmosphere                             |
| Bn                | benzyl                                 |
| bs                | broad singlet                          |
| BQ                | benzoquinone                           |
| C                 | carbon                                 |
| °C                | degree Celsius                         |
| Calcd.            | calculated                             |
| Cat.              | catalytic                              |
| cm <sup>-1</sup>  | wavenumber(s)                          |
| Cu                | copper                                 |
| CDCl <sub>3</sub> | Deuterated chloroform                  |
| CT                | charge transfer                        |
| δ                 | chemical shift                         |
| d                 | day (s); doublet (spectral)            |
| DCC               | <i>N, N'</i> -dicyclohexylcarbodiimide |
| DCM               | dichloromethane                        |
| DCE               | dichloroethane                         |
| DMA               | dimethyl actamide                      |
| dd                | doublet of doublet                     |
| DFT               | density functional theory              |
| DMF               | dimethylformamide                      |
| DMSO              | dimethylsulfoxide                      |
| DG                | directing group                        |

|                        |                                        |
|------------------------|----------------------------------------|
| DSC                    | differential scanning calorimetry      |
| dr                     | diastereomeric ratio                   |
| <i>ee</i>              | enantiomeric excess                    |
| equiv.                 | equivalent                             |
| ESI                    | electrospray ionisation                |
| Et                     | ethyl                                  |
| EtOAc                  | ethyl acetate                          |
| EWG                    | electron withdrawing group             |
| EDG                    | electron donating group                |
| FWHM                   | full width at half maxima              |
| FTIR                   | Fourier transform infrared             |
| g                      | gram(s)                                |
| H                      | hydrogen                               |
| h                      | hour(s)                                |
| HFIP                   | hexafluoro isopropanol                 |
| HPLC                   | high performance liquid chromatography |
| HRMS                   | high resolution mass spectrometry      |
| Hz                     | hertz                                  |
| <sup>i</sup> Pr        | isopropyl                              |
| <sup>i</sup> Bu        | isobutyl                               |
| IQE                    | internal quantum efficiency            |
| ICT                    | intramolecular charge transfer         |
| <i>J</i>               | spin coupling constant                 |
| kcal                   | kilocalories                           |
| $\lambda_{\text{max}}$ | wavelength                             |
| L                      | ligand                                 |
| m                      | multiplet (in NMR)                     |
| m                      | meta                                   |
| M                      | molar (mol L <sup>-1</sup> )           |
| <i>m/z</i>             | mass- to-charge ratio                  |
| Me                     | methyl                                 |
| mg                     | milligram                              |
| min                    | minute(s)                              |



|                |                                          |
|----------------|------------------------------------------|
| mL             | millilitres                              |
| μL             | microlitre                               |
| ms             | millisecond                              |
| MS             | molecular sieves                         |
| mmol           | millimole                                |
| mol            | mole                                     |
| m.p.           | melting point                            |
| MeOH           | methanol                                 |
| N              | nitrogen                                 |
| NMR            | nuclear magnetic resonance               |
| NR             | no reaction                              |
| O              | oxygen                                   |
| o              | ortho                                    |
| OAc            | acetate                                  |
| OTf            | trifluoromethane sulfonate               |
| ORTEP          | oak ridge thermal-ellipsoid plot program |
| OLED's         | organic light emitting diodes            |
| p              | para                                     |
| P              | phosphorus                               |
| Ph             | phenyl                                   |
| ppm            | parts per million                        |
| PXRD           | powder X-ray diffraction                 |
| Pd             | palladium                                |
| PL             | photoluminescence                        |
| PAHs           | poly aromatic hydrocarbons               |
| q              | quartet                                  |
| QY             | quantum yield                            |
| R <sub>f</sub> | retention factor                         |
| rt             | room temperature                         |
| RB             | round bottom flask                       |
| S              | sulphur                                  |
| s              | singlet (NMR)                            |
| t              | triplet (NMR)                            |
| t-, tert-      | tertiary (branched alkyl chain)          |

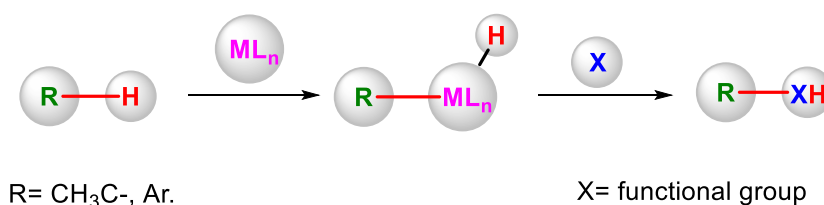
|             |                                                         |
|-------------|---------------------------------------------------------|
| td          | triplet of doublet                                      |
| <i>t</i> Bu | tertiary butyl                                          |
| THF         | tetrahydrofuran                                         |
| TFA         | trifluoroacetic acid                                    |
| TFE         | trifluoroethanol                                        |
| TLC         | thin-layer chromatography                               |
| TMS         | trimethylsilyl                                          |
| TS          | transition state                                        |
| Ts          | tosyl                                                   |
| TIPS        | triisopropyl silane                                     |
| TDG         | transient directing group                               |
| TPA         | triphenyl amine                                         |
| TRPL        | time-resolved photo luminescence                        |
| UV          | ultraviolet                                             |
| X           | heteroatom                                              |
| XRD         | X-ray diffraction                                       |
| $\delta$    | chemical shift in ppm downfield<br>from trimethylsilane |

## SYNOPSIS

The thesis entitled “*Direct C3-(sp<sup>2</sup>)-H Alkenylation and C(γ-sp<sup>3</sup>)-H Arylation of Five Membered Heteroaryl Compounds via Palladium Catalysis: An Access to Novel Compounds with Photophysical Properties*” comprises of five main chapters

### **Chapter 1: *Transition Metal Catalyzed C-H Bond Activation Reactions and its Applications in Development of Organic Fluorescent Materials***

This introductory chapter presents a brief overview on the C-H bond activation processes catalyzed by transition metals. Over the years, the transition metal catalyzed C-H activation has appeared one of the most versatile and efficient strategies for the construction of carbon–carbon and carbon–heteroatom bonds to access useful compounds. In principle the C-H activation relies on the inert C-H bonds activation of the organic substrates via insertion of suitable transition metal catalysts such as palladium, rhodium, ruthenium, nickel, cobalt, iridium etc subsequently leading to breaking of the inert C-H bond and to form the C-[M] bond. This complex further reacts with the suitable located reactive functional group to form the final functionalized product.



**Scheme 1.1** General C–H activation reaction with transition metal.

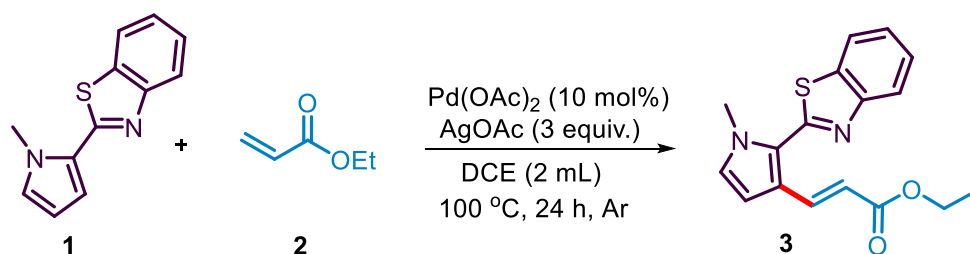
This introductory chapter describes the basics of C-H bond activation reaction, the difference between C-H activation and C-H functionalization reactions. It also highlights the different mechanistic pathways of C-H activation reactions. The different types of the C-H activation reactions including the non-directed, directed C-H activation, directing group assisted C-H activation reactions have been presented. Finally, this chapter highlights some of the applications of C-H bond activation strategies catalyzed by transition-metal for the development of some of organic fluorescent materials that are traditionally difficult to synthesise. Some of the well-known organic fluorescent materials have the excellent photophysical properties and high chemical stability with a broader applications in material

chemistry and the utility of C-H activation strategy for the construction of newer compounds, functionalized materials is highly desirable.

## Chapter 2: *Palladium Catalyzed C3-(sp<sup>2</sup>)-H Alkenylation of Pyrroles: A Direct Access to Novel Organic Thermally Activated Delayed Fluorescence (TADF) Materials*

This chapter presents the design and development of a novel, regio- and chemo-selective protocol for the direct C3-(sp<sup>2</sup>)-H alkenylation of pyrroles via palladium catalysis to access novel organic thermally activated delayed fluorescence (TADF) materials. The chapter begins with a brief account on the importance of pyrroles and benzothiazoles. Many of the compounds having these core scaffolds are known to elicit bio-activity as well as they are known to be pharmaceutically active compounds and organic functional materials. Owing to the importance of all these, it was hypothesized that the alkenylation of the pyrroles by employing the benzothiazole moiety as a directing group (pyrrole-benzothiazole hybrid molecule) would be very interesting and this has been rarely explored in the literature.

Looking at the limited synthetic strategies using benzothiazole moiety as a directing group, we planned the synthesis of pyrrole-benzothiazole hybrid molecule and further direct alkenylation so as to access the novel compounds with an extended delocalization to harness the photophysical properties. In this regard, a simple and efficient method has been developed for the synthesis of C3-(sp<sup>2</sup>)-H alkenylated pyrrole-benzothiazole scaffold **3** starting from the 2-*N*-methylpyrrole benzo[d]thiazoles **1** and alkyl/aryl acrylates **2** via palladium catalysis (Scheme 2.1). Based on the exhaustive screening, pyrrole derivative **1** (0.1 mmol), acrylate **2** (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (0.3 mmol) in DCE (2 mL) at 100 °C under Ar has proved to be the optimized reaction condition.



**Scheme 2.1** C3-(sp<sup>2</sup>)-H alkenylated pyrrole-benzothiazole scaffold in presence of palladium catalyst

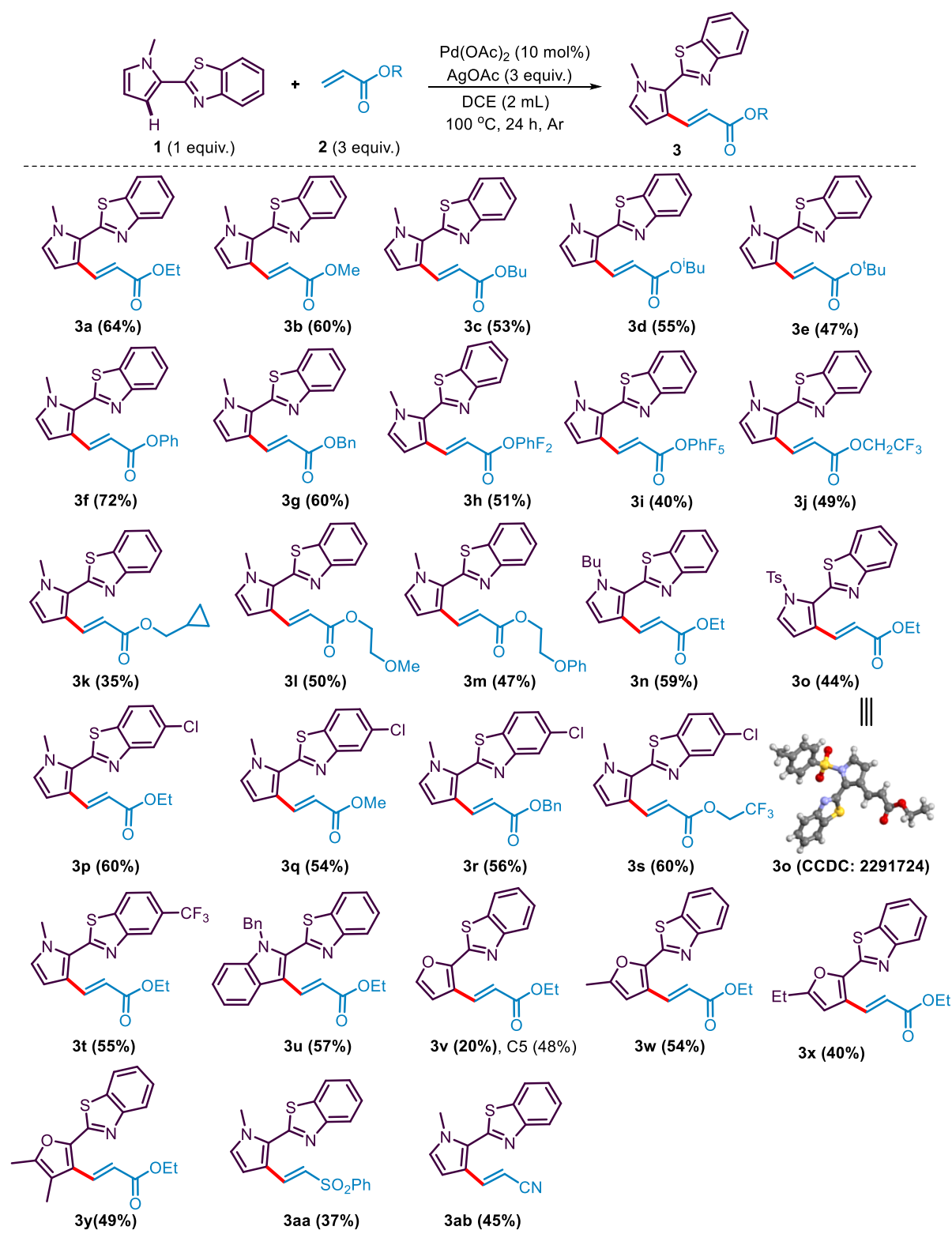
Having standardized the optimum reaction condition, the substrate scope of 2-*N*-methylpyrrole benzo[d]thiazoles (**1a-1m**) with various acrylates (**2**) was investigated to obtain the corresponding alkenylated pyrrole-benzothiazole derivatives (**3a-3m**) in moderate to good yields (See Table 2.1).

Later, different substituted 2-*N*-alkylpyrrole benzo[d]thiazoles (**1n-1t**) were treated with different acrylates (**2**) to obtain the corresponding derivatives (**3n-3t**) in moderate to good yields (See Table 2.1). Also, different 2-hetero benzo[d]thiazoles (**1u-1y**) reacted with various acrylates (**2**) to furnish the corresponding derivatives (**3u-3y**) in moderate to good yields (Table 2.1). The 2-*N*-methyl pyrrole benzo[d]thiazoles (**1z-1aa**) also reacted smoothly with phenyl vinyl sulphone (**2a**) and acrylonitrile (**2b**) to furnish the corresponding derivatives (**3aa-3ab**) in modest yields (see Table 2.1). In order to have the mechanistic insights into the reaction pathway, we have synthesized and characterized the palladium intermediate, and it was found that this intermediate reacts with ethyl acrylate under optimized reaction condition.

Similarly, we further synthesized a few compounds having an extended electronic conjugation to explore the photophysical properties. The 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole **1a** and 2-(1-butyl-1H-pyrrol-2-yl)benzo[d]thiazole **1b** upon treatment with 2-oxo-2-phenylethyl acrylate and substituted 2-oxo-2-phenylethyl acrylate (**2m** and **2p**) furnished the corresponding derivatives **3am** and **3ap** respectively in moderate yields (see Table 2.2).

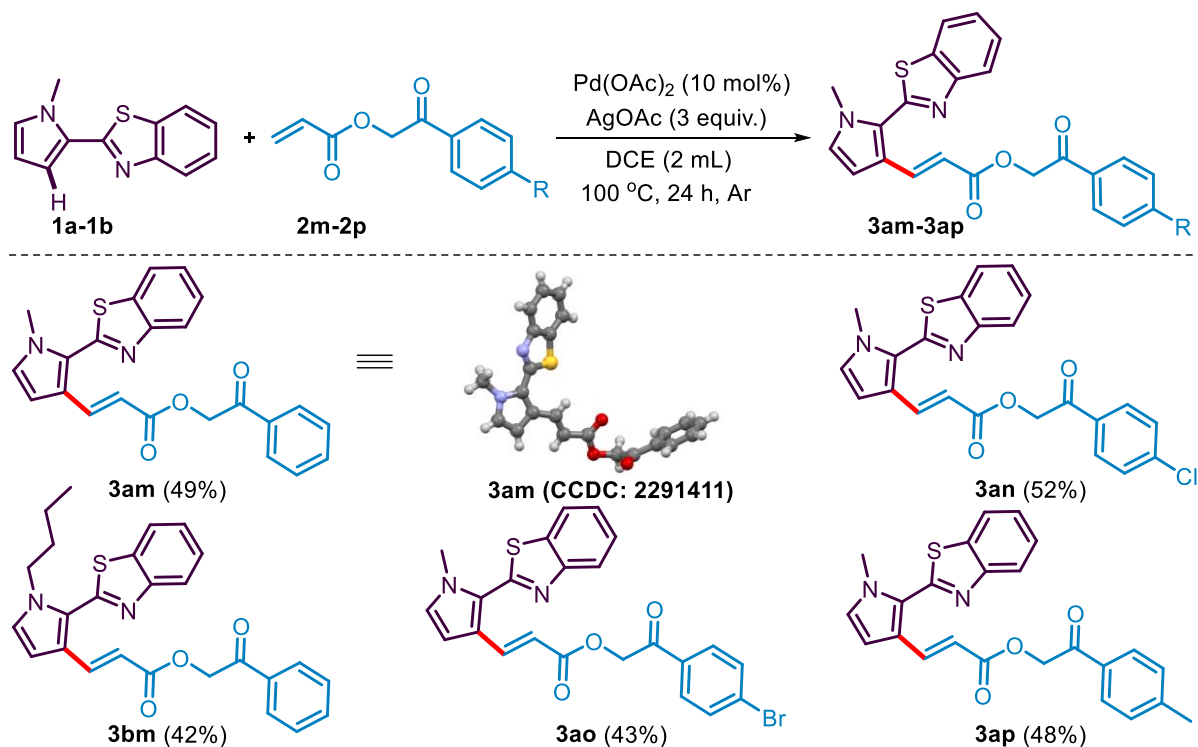
We further carried out the detailed photophysical studies of a few designed and synthesized compounds (**3am-3ap**) and interestingly they proved to be luminogens. The studies clearly showed that these novel molecules are thermally activated delayed fluorescence materials (TADF) and they proved to be blue emitting TADF materials (~ms lifetime). A detailed and systematic investigation has been carried out to study the photophysical properties and this has been further validated by the time dependent (TD) density functional theory (DFT) calculations.

**Table 2.1** Substrate scope of C3-alkenylation of 2-hetero-arylbenzo[d]thiazoles<sup>a, b</sup>



<sup>[a]</sup>Optimized reaction conditions: **1** (0.1 mmol), **2** (0.3 mmol),  $\text{Pd}(\text{OAc})_2$  (10 mol%),  $\text{AgOAc}$  (0.3 mmol), DCE (2 mL), 100 °C, Ar, 24 h. <sup>[b]</sup>Isolated yields based on **1** using column chromatography.

**Table 2.2** Alkenylation of 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole with 2-oxo-2-phenylethyl acrylate



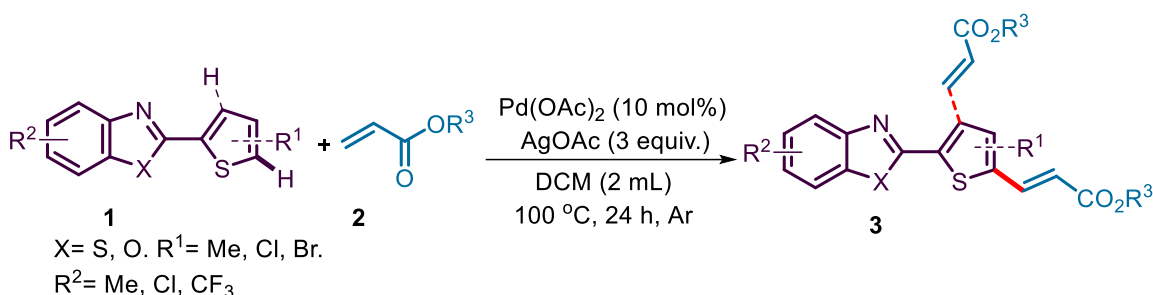
<sup>[a]</sup>**Optimized reaction conditions:** **1** (0.1 mmol), **2** (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (0.3 mmol), DCE (2 mL), 100 °C, Ar, 24 h. <sup>[b]</sup>Isolated yields based on **1** using column chromatography.

In conclusion, we have developed an efficient method for C3-(sp<sup>2</sup>)-H alkenylation of 2-*N*-alkylpyrrolebenzo[d]thiazole derivatives with a wide range of acrylates by exploring the benzothiazole as a directing group. This method proved to be highly regio- and chemo-selective to afford *E*-alkenylation products at C3 position. Further this pyrrole-benzothiazole hybrid scaffold has been effectively utilized to access C3 alkenylated novel luminogens and are proved to be thermally activated delayed fluorescence materials (TADF).

### Chapter 3: Palladium (II) Catalyzed Regioselective C5 and C3-(sp<sup>2</sup>)-H Alkenylation of 2-Thiophenebenzothiazoles

This chapter describes the development of a regioselective C5 and C3-(sp<sup>2</sup>)-H alkenylation of 2-thiophenebenzothiazoles/oxazoles via palladium catalysis. The chapter begins with a brief account on the importance of five membered heterocyclic compounds as a core scaffold that are usually found in numerous bioactive compounds, pharmaceutical

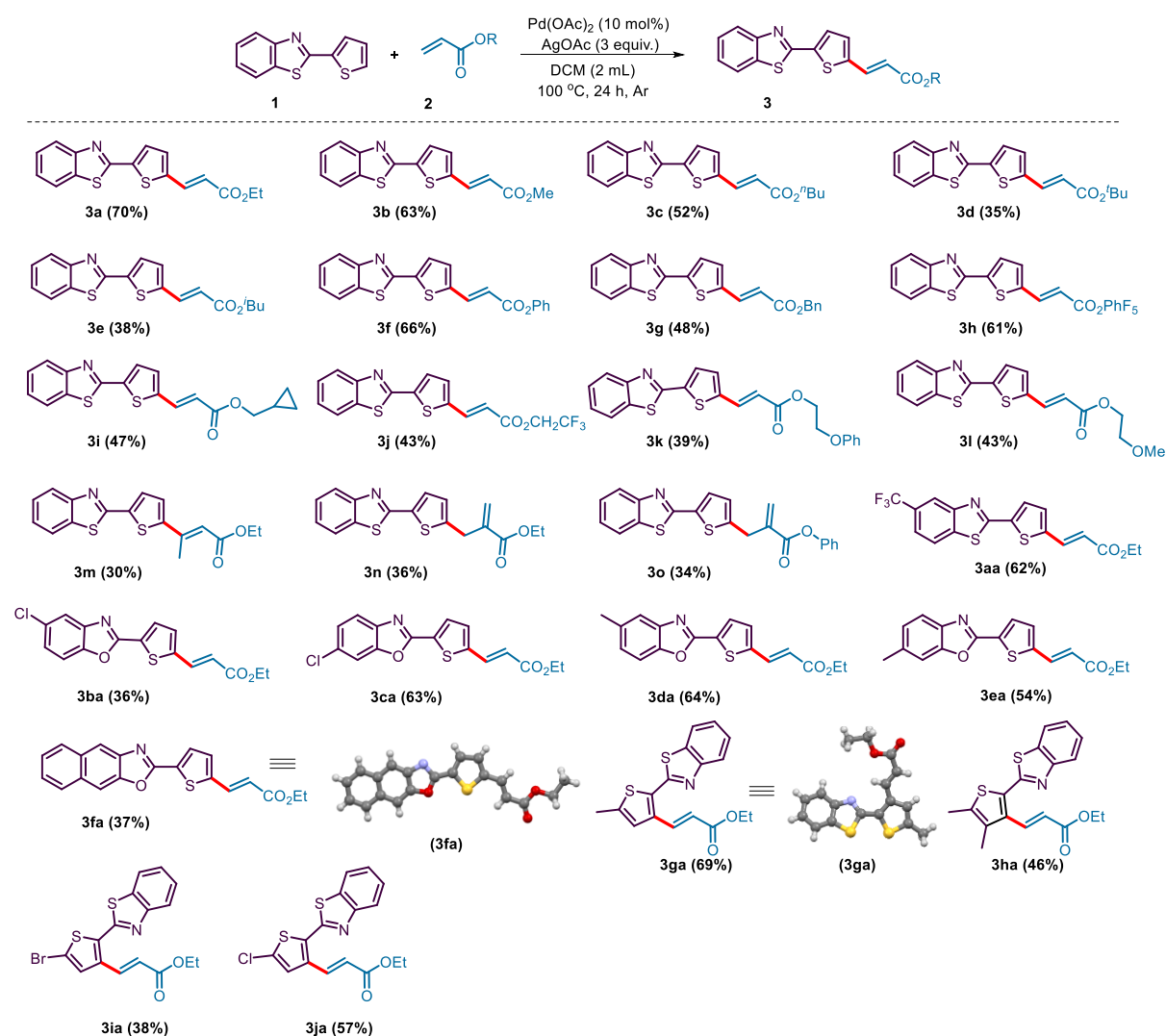
compounds, and natural products. Especially the thiophene derivatives are the essential building blocks for a variety of biologically active compounds and organic functional materials. This chapter illustrates the importance of thiophene and benzothiazole compounds along with a few traditional methods for the alkenylation of the thiophenes. It gives a brief account on the palladium-catalyzed intermolecular dehydrogenative Heck reaction (DHR) or Fujiwara Moritani reaction of diverse aromatic and heteroaromatic compounds with various olefins. The alkenylation of the heterocyclic scaffolds in presence of benzothiazole moiety via DHR reaction or Fujiwara Moritani reaction is always challenging and specially without the assistance from benzothiazole as a directing group would be really difficult and interesting. In this regard, a straightforward approach has been developed for the synthesis of C5 and C3-(sp<sup>2</sup>)-H alkenylated 2-thiophenebenzothiazoles **3** starting from the 2-thiophenebenzothiazole **1** and acrylates **2** via palladium catalysis (Scheme 3.1).



**Scheme 3.1** Regioselective C5 and C3 alkenylation of 2-thiophenebenzothiazoles.

Based on the exhaustive screening the **1a** (0.1 mmol), **2a** (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (0.3 mmol) in DCM 100 °C under inert atmosphere proved to be optimized reaction condition. Having obtained the standard optimal reaction conditions, the substrate scope of 2-(thiophen-2-yl)benzo[d]thiazole (**1**) with different acrylates (**2a-2m**) was investigated to obtain the corresponding alkenylated derivatives (**3a-3m**) in moderate to good yields (see Table 3.1). Further 2-(thiophen-2-yl)benzo[d]thiazole (**1**) reacts efficiently with ethyl methacrylate (**2n**) as well as phenyl methacrylate (**2o**) to furnish interestingly the isomerised products (**3an** and **3ao**) respectively albeit in low yields (see Table 3.1).



**Table 2.** Alkenylation of 2-thiophene benzo[d]thiazoles/oxazoles.<sup>a,b</sup>

<sup>a</sup>Optimized reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (0.3 mmol), DCM (2 mL), 100 °C, Ar, 24 h. <sup>b</sup>Isolated yields based on **1a** using column chromatography.

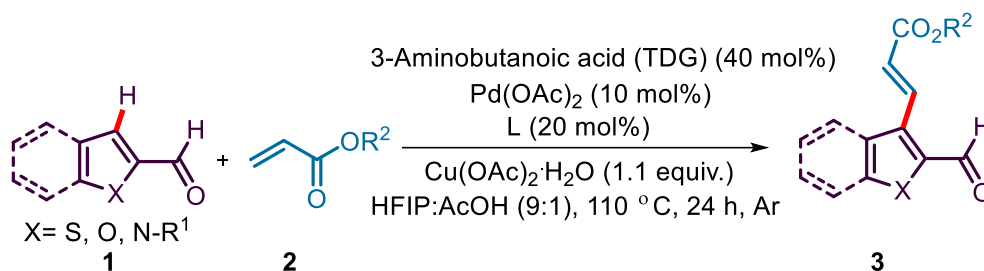
Later, few different substituted benzothiazole/oxazoles containing thiophene compounds (**1a-1e**) upon treatment with ethyl acrylate (**2a**) under the optimized reaction conditions furnished the corresponding derivatives (**3aa-3ae**) in good yields (see Table 3.1). Also, the reaction of 2-(thiophen-2-yl)naphtho[2,3-d]oxazole (**1f**) with ethyl acrylate (**2a**) led to the formation of the corresponding derivative (**3fa**) in low yield (see Table 3.1). Furthermore, the C5 methyl and C5 halo substituted thiophene derivatives (**1g-1j**) reacted with ethyl acrylate (**2a**) to furnish the corresponding products (**3ga-3ja**) in moderate to good yields (see Table 3.1).

In conclusion we have developed an efficient protocol for direct C5 and C3-(sp<sup>2</sup>)-H alkenylation of 2-heteroarylbenzothiazoles with various acrylates via palladium catalysis. This protocol gave an access to C-5 and C-3 *E*-alkenylated thiophene derivatives with high regio-

and chemo-selectivity. The broad substrate scope with good functional group tolerance has also been demonstrated.

#### Chapter 4: *Transient Directing Group enabled C3-(sp<sup>2</sup>)-H Alkenylation of Five Membered Heterocyclic Aldehydes: An Access to Mechanochromic Luminogen*

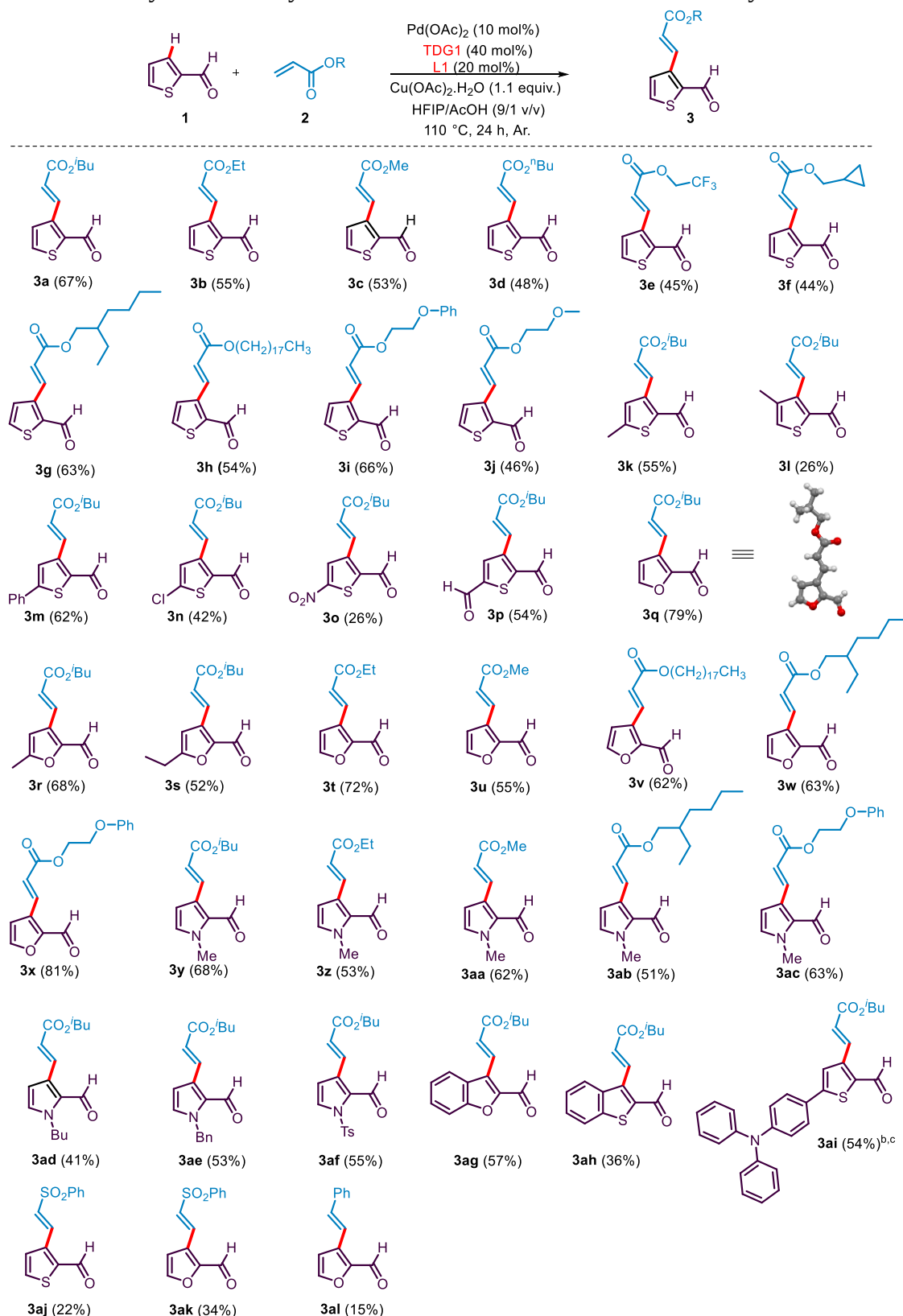
This chapter presents the development of C3-(sp<sup>2</sup>)-H alkenylation of five membered heterocyclic aldehydes in presence of transient directing group (TDGs) and palladium catalyst. The chapter begins with a brief account on the importance of five membered heterocyclic scaffolds and C3-alkenylated five membered heterocyclic compounds. It also discusses the selective C3 alkenylation of the five membered heterocyclic scaffolds in the presence of more reactive C2 and C5 positions. The significance of the transient directing group and transient directing group enabled C3 alkenylation over the traditional methods that have certain limitations such as the need for pre-functionalized starting materials, the installation and removal of directing groups and multi-step synthesis have been highlighted as well. Owing to the importance of the scaffold and looking at the literature a simple and effective procedure has been created for the synthesis of C3-(sp<sup>2</sup>)-H alkenylated heteroarene-2-carboxaldehyde **3** starting from the heteroarene-2-carboxaldehyde **1** and isobutyl acrylates **2** with 3-aminobutanoic acid as a transient directing group (TDG), 5-(trifluoromethyl)-2-pyridone as an external ligand (L) and palladium acetate as a catalyst (Scheme 4.1).



**Scheme 4.1** C3 alkenylation of five-membered heteroarene-2-carboxaldehyde

Based on the exhaustive screening, compound **1** (0.2 mmol), **2** (0.6 mmol), Pd(OAc)<sub>2</sub> (10 mol %), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (1.1 eq.), TDG (40 mol%), L (20 mol%) in HFIP/AcOH (9:1 v/v, 1 mL) at 110 °C for 24 h under inert atmosphere (Argon) has proved to be the optimal reaction condition. Having obtained the optimal reaction conditions, the substrate scope of thiophene-2-carboxaldehyde **1** with a wide range of acrylates (**2**) has been investigated to obtain the corresponding products (**3a-3j**) in moderate to good yields (see Table 4.1).

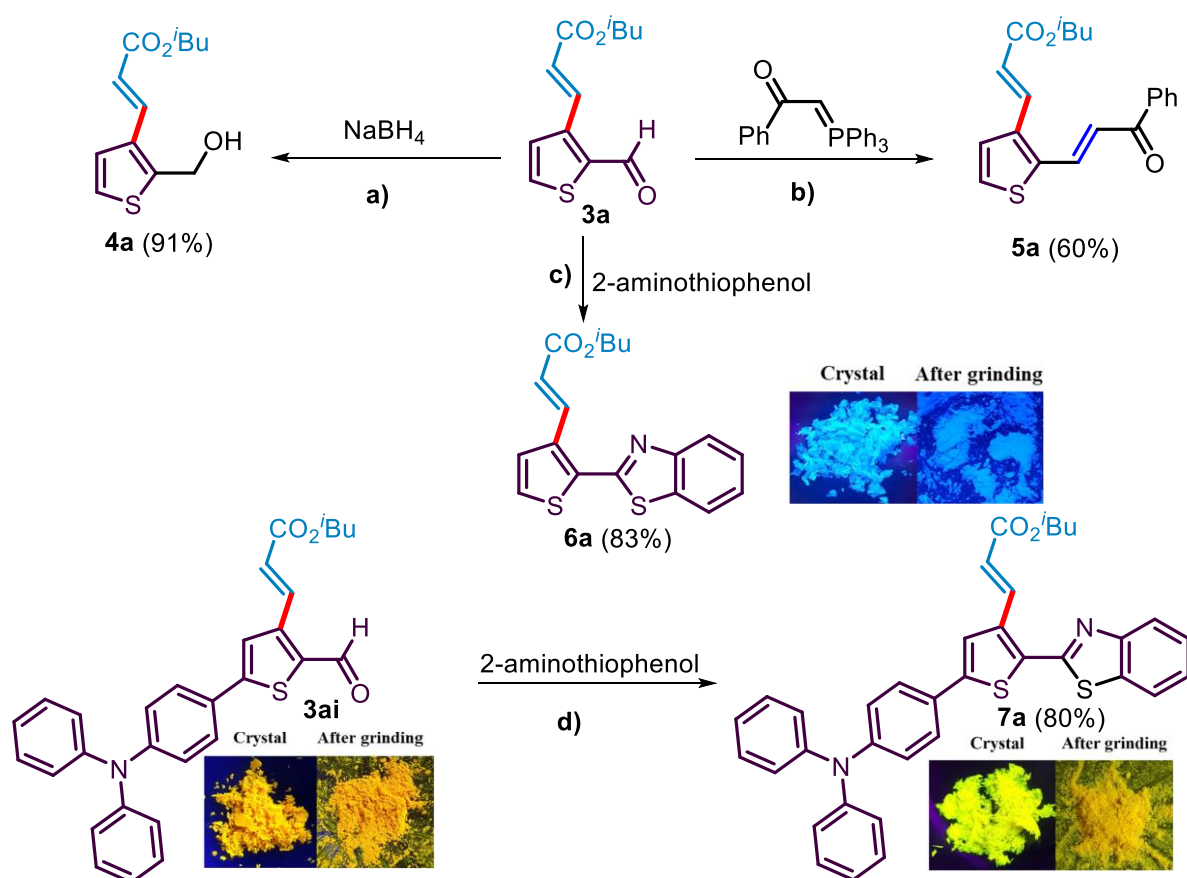
**Table 4.1** A library of C3 alkenylated five-membered heteroarene carbaldehydes



[a] **Optimized reaction conditions:** **1a** (0.2 mmol), **2a** (0.6 mmol), Pd catalyst (10 mol%), **TDG1** (40 mol%), Ligand **L1** (20 mol%), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.22 mmol), HFIP (0.9 mL) AcOH (0.1 mL), 110 °C, Ar, 24 h; [b] Isolated yields after column chromatography; [c] (0.25 mmol), [d] HFIP (1.8 mL) AcOH (0.2 mL).

Further the thiophene-2-carboxaldehyde (**1**) containing electron-withdrawing and -donating groups at the C4 and C5 reacted with isobutyl acrylate (**2**) to afford the corresponding compounds (**3k-3p**) in moderate yields (see Table 4.1). The furan-2-carboxaldehyde (**1q-1x**) and pyrrole-2-carboxaldehyde (**1y-1af**) having different substituents reacted smoothly with various acrylates **2** to furnish the corresponding derivatives (**3q-3af**) in moderate to good yields (see Table 4.1). The benzofuran and benzothiophene aldehydes (**1ag-1ah**) smoothly reacted with iso-butyl acrylate (**2**) to produce the corresponding products (**3ag-3ah**) in moderate yields (see Table 4.1). The triphenylamine (TPA) containing thiophene-2-carboxaldehyde (**1ai**) reacted smoothly with isobutyl acrylate (**2**) to form the corresponding product (**3ai**) in moderate yield (54% see Table 4.1). Furthermore, the other electron-deficient alkene, phenyl vinyl sulphone (**2**) also reacted with thiophene-2-carboxaldehyde and furan-2-carboxaldehyde (**1**) under the optimized reaction conditions to furnish the corresponding C-3 alkenylated products (**3aj-3ak**) in low yield (34 % Table 4.1). Furan-2-carboxaldehyde **1** also reacted with styrene **2** to furnish the corresponding C3-alkenylated product (**3al**) albeit in poor yield (15%, Table 4.1).

**Table 4.2.** Selective synthetic transformations

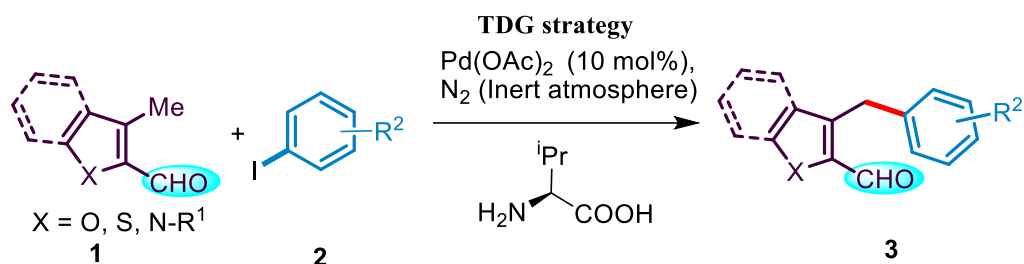


Additionally, we investigated the derivatization of C3-alkenylated thiophene-2-carboxaldehyde as an application to this protocol. The reduction of **3a** as well as the Wittig reaction of **3a** afforded the corresponding derivatives (**4a-5a**) in good to excellent yields (see Table 4.2). Further we demonstrated some applications of the synthesized compounds and the overall protocol. From the compounds **3a** and **3i** we synthesized the corresponding compounds **6a**, **7a** respectively via employing the functional group transformation of an aldehyde into a benzothiazole moiety using the 2-aminothiophenol (Table 4.2c, d). The compounds **3ai**, **6a**, **7a** proved to show photophysical properties and detailed studies of these synthesized luminogens (**3ai**, **6a**, **7a**) showed that among all compound **7a** proved to be best for the mechanochromic properties (Table 4.2, d).

In conclusion we have developed a strategy for the direct selective C3 alkenylation of five membered heterocyclic aldehydes with a wide range of acrylates by employing a  $\beta$ -amino acid as a transient directing group (TDG) and 5-(Trifluoromethyl)-2-pyridone as an external ligand, via palladium catalysis. This protocol is very convenient and practical with a wide substrate scope with good functional group tolerance. The method is also very useful to construct the new mechanochromic luminogenic material.

## Chapter 5: *Transient-Ligand-Enabled Direct $\gamma$ -C(sp<sup>3</sup>)-H Arylation of 3-Methylheteroarene-2-Carbaldehydes to Access Different Derivatives of Hetero-Benzyl Scaffolds*

This chapter discloses the  $\gamma$ -C(sp<sup>3</sup>)-H arylation of 3-methylheteroarene-2-carbaldehydes with various aryl/heteroaryl iodide in presence of  $\alpha$ -amino acid as a transient directing group and palladium catalyst. The chapter gives a brief account on the importance of the  $\beta$ -benzyl-substituted five-membered heterocyclic compounds. The significance of this method over the traditional methods and importance of transient directing group (TDG) over the other directing groups, certain limitations of traditional strategies such as the need for pre-functionalized starting materials, the installation and removal of directing groups and multi-step synthesis etc have been highlighted. In this regard, a straightforward and efficient method has been developed for the synthesis of  $\gamma$ -C(sp<sup>3</sup>)-H arylated heteroarene-2-carbaldehydes **3** starting from the 3-methylheteroarene-2-carbaldehydes **1** and aryl iodides **2** by using L-valine (**L**) as a transient directing group (TDG) in presence of palladium catalyst (Scheme 5.1).



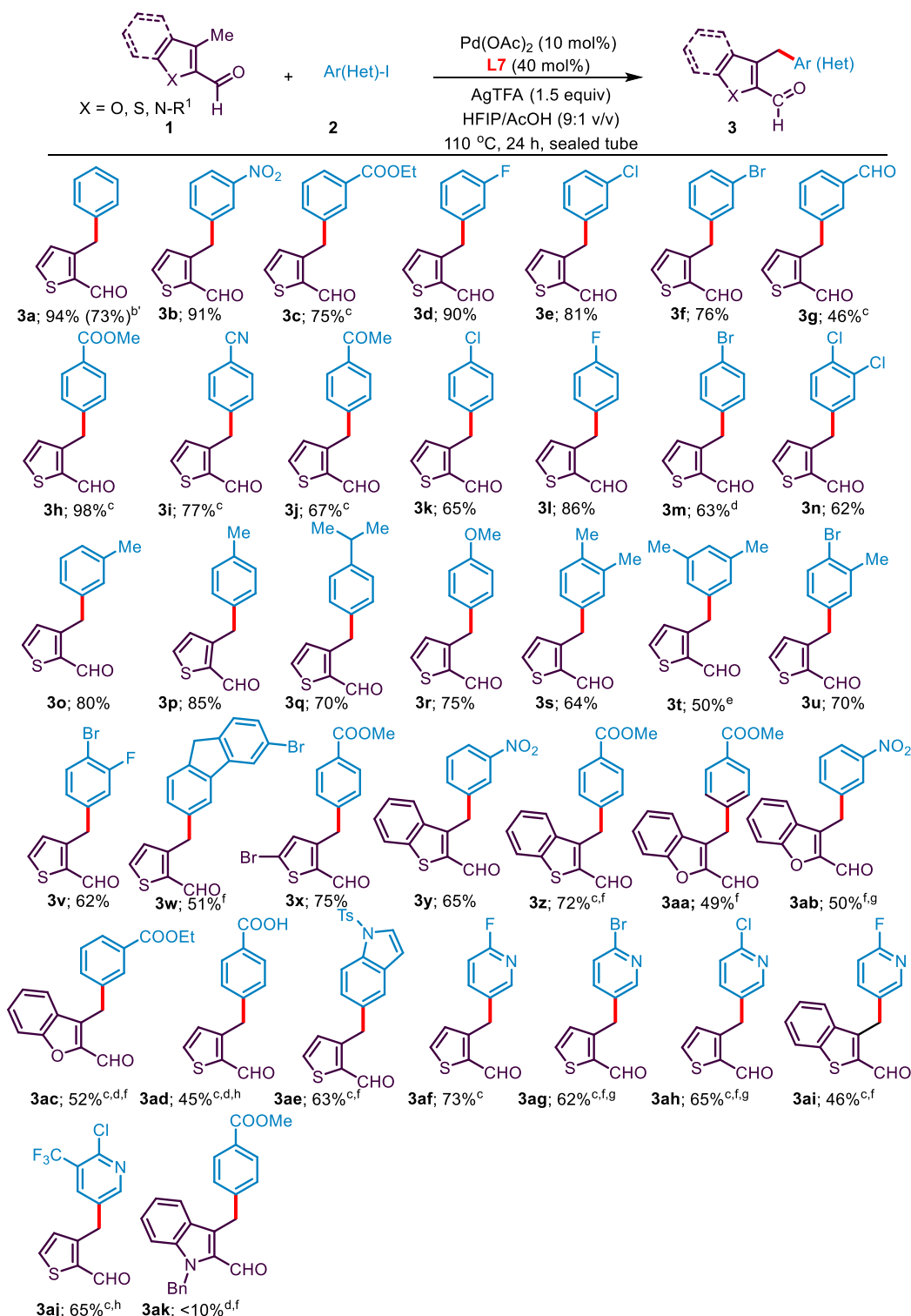
**Scheme 5.1** Selective direct  $\gamma\text{-C}(\text{sp}^3)\text{H}$  arylation of 3-methylheterocyclic aldehydes.

Based on the exhaustive screening, **1** (1 equiv.), **2** (1.5 equiv.) in presence of  $\text{Pd}(\text{OAc})_2$  (10 mol%), AgTFA (1.5 equiv.) and L-valine **L** (40 mol%) in HFIP/AcOH (9:1) at 110 °C for 24 h under inert atmosphere (Argon) has demonstrated the optimal reaction condition. When the optimal reaction conditions have been achieved, the substrate scope of 3-methylthiophene-2-carbaldehyde **1** with a wide variety of aryl iodides (**2**) having electron donating as well as electron withdrawing groups, halides at different positions of phenyl ring has been investigated to obtain the corresponding derivatives (**3a-3w**) in good to excellent yields (up to 98%, Table 5.1).

Further, the direct arylation of 5-bromothiophene-2-carbaldehyde, 3-methyl benzothiophene carbaldehyde and 3-methyl benzofuran 2-carbaldehyde **1** with various aryl/heteroaryl iodides **2** has been carried out to furnish the corresponding derivatives (**3x-3ad**, **3ai**) in moderate to good yields (up to 75%, Table 5.1).

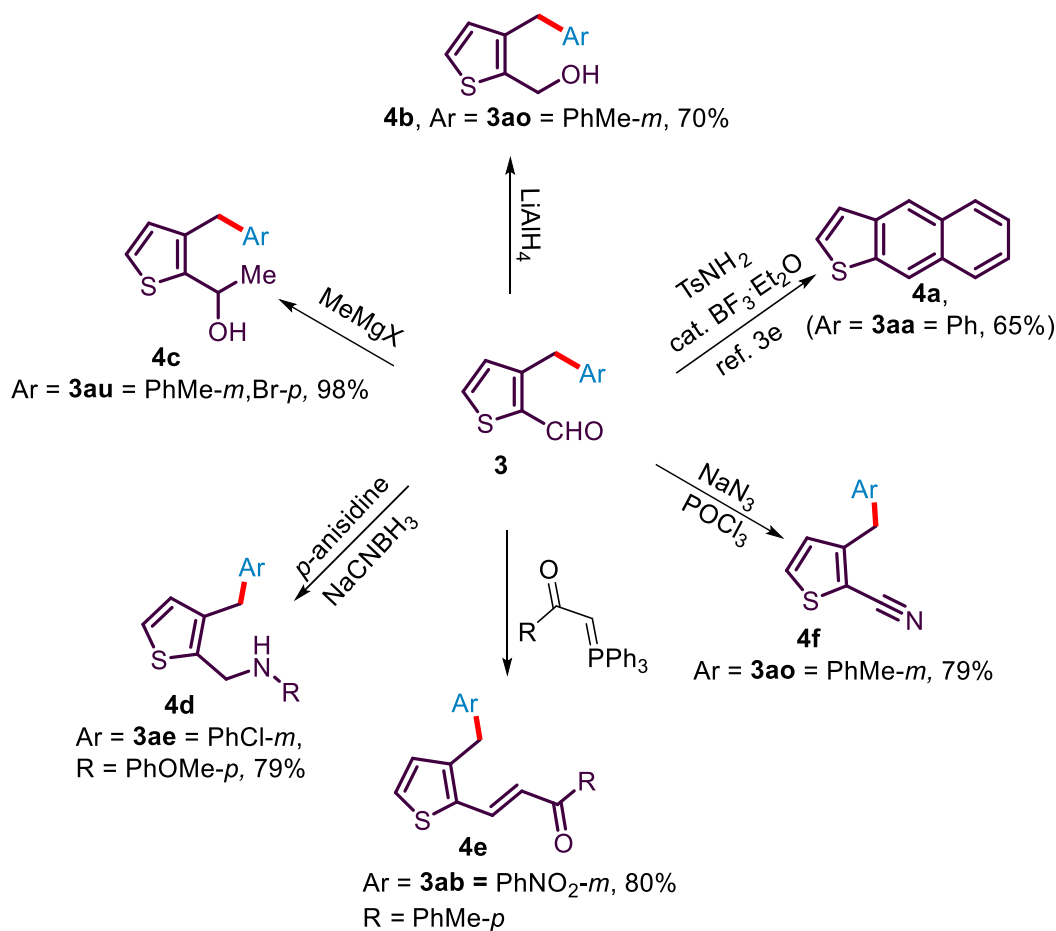
The reactions of 3-methylthiophene-2-carbaldehyde **1** with different heteroaryl iodides **2** afforded the corresponding derivatives (**3ae-3aj**) in moderate to good yields (up to 73%, Table 5.1). The 3-methylindole-2-carbaldehyde **1** reacted with iodobenzene **2** to form the final product (**3ak**) in low yield (see Table 5.1). Later, we carried out few synthetic transformations of benzyl-heteroaryl carbaldehydes (**3**) as an application of this developed protocol. The 3-benzyl-substituted thiophene-2-carbaldehydes (**3a**, **3b**, **3e**, **3o**, **3u**) has been subjected to few different synthetic transformations following the known procedures furnished the corresponding compounds (**4a-4f**) in good to excellent yields (see Table 5.2).

**Table 5.1.** A library of 3-benzyl-substituted five-membered heteroarene carbaldehydes



<sup>a</sup>Optimized reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol),  $\text{Pd}(\text{OAc})_2$  (0.02 mmol), AgTFA (0.3 mmol), **L7** (0.08 mmol), HFIP (1.44 mL), HOAc (0.16 mL), 110 °C, 24 h. <sup>b</sup>Isolated yields; <sup>b</sup>0.3 g scale; <sup>c</sup>**1** (0.24 mmol), **2** (0.2 mmol); <sup>d</sup>36 h, <sup>e</sup>30 h; <sup>f</sup> $\text{Pd}(\text{OAc})_2$  (0.03 mmol); AgTFA (0.4 mmol), 113 °C; <sup>g</sup>40 h; <sup>h</sup> $\text{Pd}(\text{OAc})_2$  (0.03 mmol) and AgTFA (0.6 mmol)

## 5.5 Application to the strategy



In conclusion we have developed a straightforward and efficient strategy for the  $\gamma\text{-C}(\text{sp}^3)\text{-H}$  arylation of 3-methylheteroarene-2-carbaldehydes with a wide range of aryl/heteroaryl iodides in presence of  $\alpha$ -amino acid as a transient directing group (TDG) via palladium catalysis. The method provides a library of  $\beta$ -benzyl-substituted five-membered heterocyclic carbaldehydes in good to excellent yields. The high functional group tolerance, broad substrate scope and smooth arylation with pyridine-based hetero-aryl iodides are the key strengths of this method.

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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)*



# 1

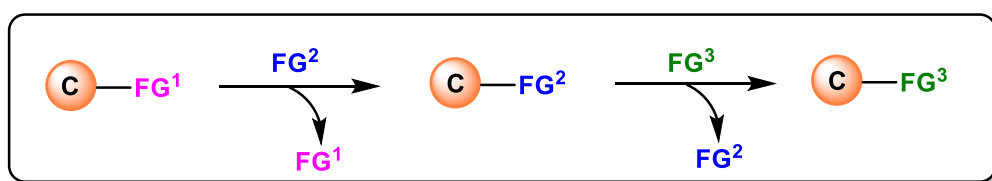
## Transition Metal Catalyzed C-H Bond Activation Reactions and their Applications in the Development of Organic Fluorescent Materials

***Abstract:** The construction of C-C bond remains to be one of the very important challenges and it is crucial in the synthesis of organic molecules. Among the several C-C bond forming reactions, the transition metal catalyzed C-H activation has become one of the most versatile and efficient approaches for the construction of carbon-carbon and carbon-heteroatom bonds in organic synthetic chemistry. A brief history of C-H activation, its various advantages over the traditional methods, different type of reaction mechanisms and the types of the C-H activation reactions have been discussed in this chapter. The various applications of the C-H activation for the developments of the organic fluorescent materials and its photophysical studies have also been presented.*

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## 1.1 Introduction

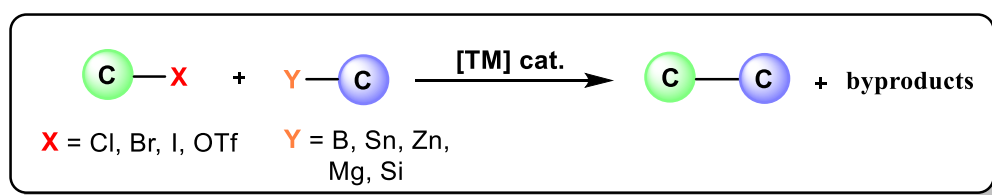
Journey of organic synthesis is almost 200 years old when Friedrich Wöhler in the year 1828 prepared the urea and oxalic acid for the first time from inorganic compounds and did not rely on living beings. The designing of synthetic strategies for the construction of the C-C bonds that are ubiquitous in almost all organic compounds and undoubtedly it is one of the most important and challenging tasks.<sup>1</sup> However, the most desirable and significant aim of the organic synthesis is to convert easily accessible feedstock chemicals into useful ones via easy as well as less number of steps preferably. Traditionally, the synthetic conversion follows the sequential functional groups interconversion (Scheme 1.1). However, the sequences of functional group interconversion have their own drawbacks and flaws such as the generation of considerable amount of the waste, as the starting compounds must lose one functional group in exchange for an another. Furthermore, a lot of work goes into designing, installing, and protecting-deprotecting of functional group etc adds on extra steps as overall as well cost. Therefore, the discovery of novel, efficient and shorter approaches for building complex organic compounds is an important and exciting area of research in catalysis.



**Scheme 1.1** Functional group interconversion in organic synthesis.

In the past century, significant developments have been made in organic synthesis by improving synthetic strategies via novel disconnection approaches, use of new reagents and catalysts. Among these, transition-metal catalyzed cross-coupling reactions have gained notable attention for the efficient carbon-carbon (C-C) and carbon-heteroatom bond forming reactions.<sup>2</sup>

Despite their effectiveness and diversity in synthesis, the cross-coupling reactions typically require the pre-functionalized starting materials to explore the coupling with organometallic reagents. Some of the common examples are the organoboron reagents in Suzuki-Miyaura<sup>3a,b</sup> and other traditional organometallic reagents (Sn, Zn, Mg, Si)<sup>3c,d</sup> though very useful and extensively used, it also limits the step-economic performance for synthesis of complex organic compounds (Scheme 1.2). Usually, the reaction of pre-functionalized organic halides with organometallic reagents in presence of stoichiometric amount of base leads to some undesired by-products along with the desired products.

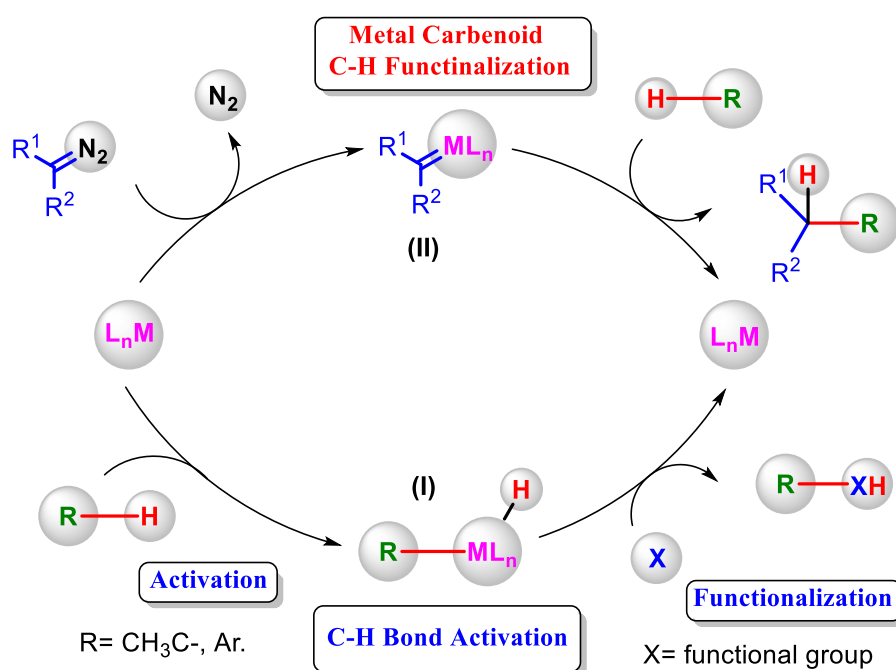


**Scheme 1.2** Transition metal catalyzed cross-coupling reactions.

To address some of the problems associated with cross-coupling reactions, the transition metal catalyzed C-H bond activation has emerged as an attractive alternative for the effective formation of C-C bonds. This strategy effectively reduced the amount of toxic by-product generation and aided in the development of relatively easier, quicker and environmentally friendly procedures for organic synthesis.<sup>4</sup> The C-H activation usually avoids the use of pre-functionalized starting materials or at least one pre-functionalized starting materials so as to achieve an efficient overall synthetic transformation. The C-H activation relatively leads to a minimal waste generation via directly functionalizing ubiquitous unreactive C-H bond of the molecule to construct the useful compounds in less number of steps. Due to the robustness of the C-H bond activation, undoubtedly this approach has been forefront of organic synthesis over the years.

If one gleans through the literature there have been articles on the C-H functionalization has well and it is important to know the subtle difference between the C-H bond activation and C-H bond functionalization though the net result is the C-H bond functionalization. In C-H bond activation the inert C-H bonds of the organic substrates initially interacts with transition metal catalyst such as palladium, rhodium, ruthenium, nickel, cobalt, iridium etc. This activates the inactive C-H bond leading to the insertion of metal between the C-H bond as C-[M]-H bond (**I**) (Scheme 1.3). Finally, this complex **I** reacts with the reactive substrate affording the desired product. The activation of inactive bond via metal catalyst is known as C-H bond activation.

However, in case of C-H bond functionalization, an activated molecule (high energy) such as diazo compound is opted and this upon reaction with metal catalyst forms the energetically unfavourable metal-carbenoid (**II**) by the extrusion of N<sub>2</sub> (Scheme 1.3). This intermediate **II** further reacts with neutral/activated/unactivated C-H bond of the substrate to finally afford the desired C-H insertion or C-H bond functionalized product without formation of any C-[M] bond (Scheme 1.3).<sup>4c</sup>

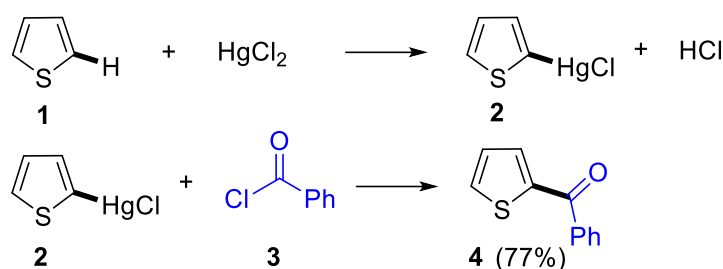


**Scheme 1.3** C–H activation versus metal carbenoid C–H functionalization

The C-H bonds are unreactive or inert due to their high bond dissociation energy (BDE) and acidity.<sup>5a</sup> The BDEs for aliphatic (sp<sup>3</sup>) C-H bond is 88-105 kcal/mol and its pK<sub>a</sub> values are 41-56, while the BDE of aromatic (sp<sup>2</sup>) C-H bond is ~ 111 kcal/mol and its pK<sub>a</sub> value is ~ 40.<sup>5b</sup> Due to the ubiquitous nature of C-H bonds in innumerable organic compounds, controlling the regioselectivity becomes one of the major challenges in C-H bond functionalization.<sup>6</sup> Some of these challenges have been overcome by using the suitable catalyst and directing groups (DGs). In most of the cases directing group (DG) is covalently attached to the substrates, that initially coordinates to the metal catalyst and brings it to the close proximity of C-H bond that need to be functionalized.<sup>7</sup> This synthetic strategy not only ensures the desired site selectivity, but also most of the time increases the reactivity of the transition metal catalyst in cleaving the C-H bonds successfully. A brief history of development of C-H bond activation has been described in details below.

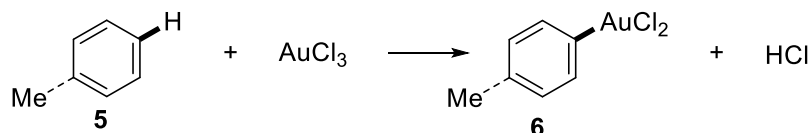
## 1.2 Origin: Pioneering studies of C-H Activation

In 1892 Volhard carried out the first conversion of a generally non-acidic  $sp^2$  C-H bond of the thiophene **1** to the corresponding **2** via carbon-metal bond. This upon subsequent reaction with benzoyl chloride **3** to afford the product **4** (Scheme 1.4).<sup>8</sup> It has been shown for the first time that thiophene **1** could be metalated with mercury salts at the C2 or C5 position to form the 2-chloro-mercuriothiophene **2** which can react with a carbon electrophile.



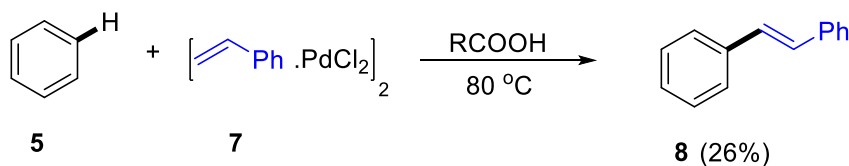
**Scheme 1.4** Volhard's first example of metalation of thiophene with mercury compounds.

Later, in 1931 Kharasch reported the first C-H activation by using a transition metal salt such as  $AuCl_3$  in stoichiometric amounts that metalates arenes **5** under mild conditions. This reaction proved to be highly regioselective to form only *p*-tolylgold dichloride **6** in the auration of toluene **5** (17% Scheme 1.5).<sup>9</sup>



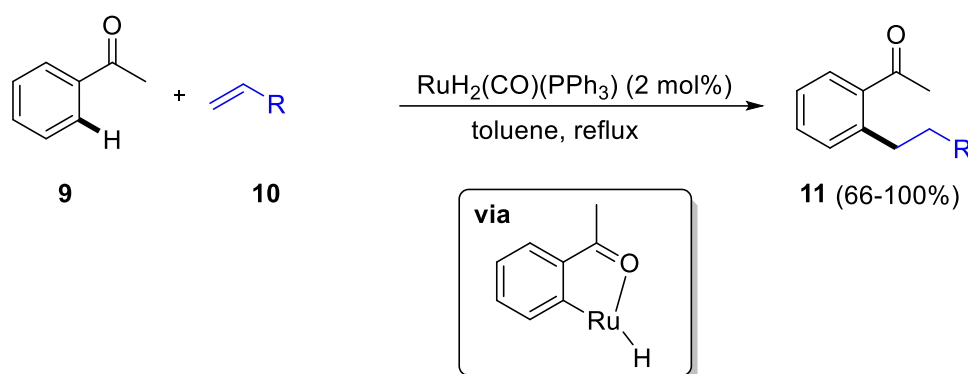
**Scheme 1.5** Kharasch reported the first C-H activation by a transition metal.

In 1967 Fujiwara and Moritani reported the very interesting the direct coupling of aromatic C-H bond with the olefinic C-H bond to construct the carbon-carbon bond in presence of palladium chloride (Scheme 1.6).<sup>10</sup> The reaction of benzene **5** with styrene palladium complex **7** in presence of acetic acid afforded the desired alkenylated product **8** albeit in lower yield (26%, Scheme 1.6).



**Scheme 1.6** Palladium catalyzed Fujiwara and Moritani reaction.

In 1993, Murai and coworkers reported the ruthenium catalyzed selective *ortho*-alkylation of the aromatic ketones. The aromatic ketones **9** upon treatment with various alkenes **10** in presence of ruthenium catalyst afforded the desired *o*-alkylated products **11** in good to excellent yields (Scheme 1.7). The keto group in the aromatic ketones **9** acts as a directing group so as to coordinate with ruthenium metal thus generating a five membered cyclo-metalated species which acts as a reactive intermediate to afford the final product (Scheme 1.7).<sup>11</sup>



**Scheme 1.7** Ruthenium catalyzed *ortho*-alkylation of the aromatic ketones

Over the years various research groups have greatly contributed for the C-H activation and the field has progressed well to execute the novel C-H activation of different aromatic and aliphatic compounds. There are innumerable examples of different C-H activation reactions with various substrates utilizing different catalysts, oxidant, directing groups (DGs) under various reaction conditions.

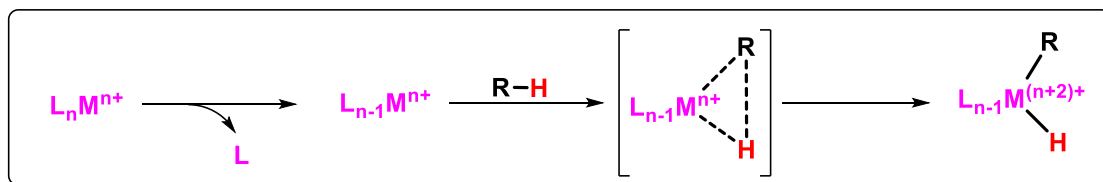
### 1.3 Different Mechanisms of C-H Activation reactions

The mechanisms of C-H activation reactions vary depending on the substrates and transition metal complex that have been used and some of the major types of mechanism have been described below.<sup>12</sup>

#### a) Oxidative addition (O.A.):<sup>12</sup>

Traditionally, the ligands would separate from metal complexes like  $\text{ML}_n$  to generate  $\text{ML}_{n-1}$  to create a vacant coordination site. Through this vacant or unoccupied coordinating site, the unactivated C-H bond would be interacting to form the metal complex by forming the M-C and M-H bond. Such C-H activation reactions are typically seen with electron-rich metal

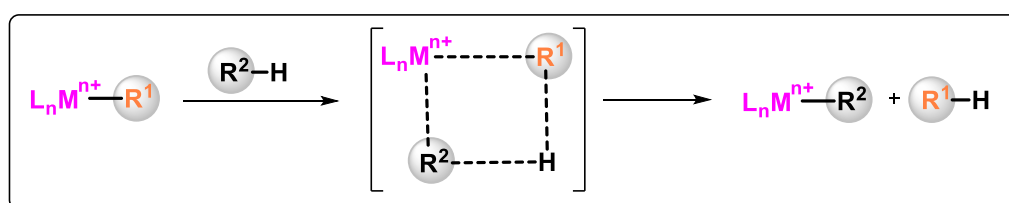
complexes. Usually, this electron-rich metal complex interacts with an inert C-H bond to form a reactive organometallic species. In oxidative addition the oxidation state and co-ordination number of the central metal atom increases by two units. The oxidative addition step is generally occurring in catalytic cycle (see Scheme 1.8).



**Scheme 1.8** General mechanism of oxidative addition

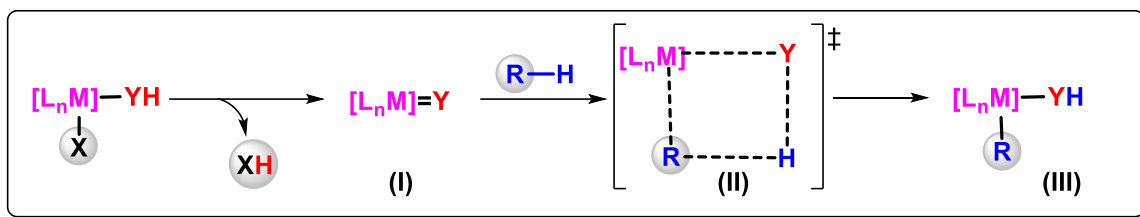
**b) Sigma bond metathesis and 1-2 addition reaction:<sup>12</sup>**

In sigma bond metathesis the mechanism goes through the four membered transition state and a reactive organometallic compound is formed. In this reaction the oxidation state of the metal does not change, and it would remain same all over the reaction as this is believed to proceed via concerted pathway (Scheme 1.9). However, sigma bond metathesis generally occurs for the early transition metals when the electrons are not available for oxidative addition. A few examples for the late transition metals are also found in the literature.



**Scheme 1.9** General mechanism of sigma bond metathesis

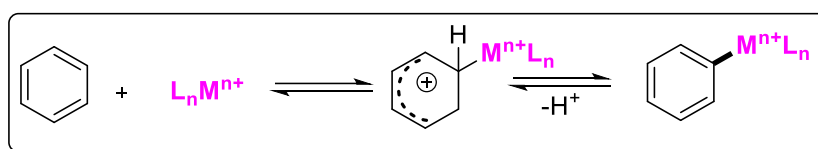
Both oxidative addition and sigma bond metathesis are similar to the 1,2-addition reaction across M=X bonds (X = ligands). However, the 1,2-addition reaction are generally occurring in early transition metals. In this mechanism the reactive intermediate  $L_n M=Y$  (**I**) is formed after the removal of the XH. Then the substrate (R-H) react with the intermediate ( $L_n M=Y$ ) **I** and the C-H fragment will add across to the double bond of this intermediate to form the intermediate with M-C bond (**III**) via four membered transition state (**II**) (Scheme 1.10).



**Scheme 1.10** General mechanism of 1,2-addition reaction

**c) Electrophilic aromatic substitution ( $S_{\text{E}}\text{AR}$ ):** <sup>12</sup>

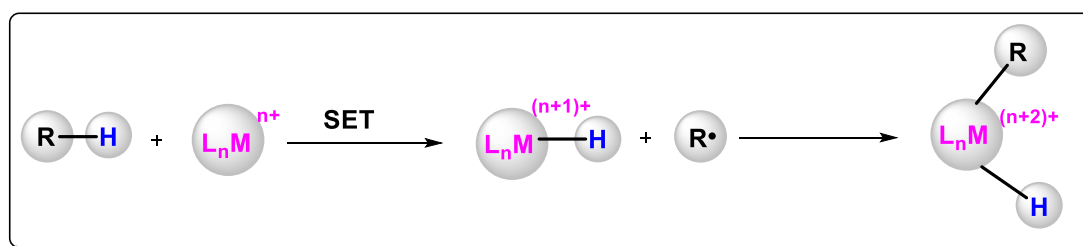
Electrophilic aromatic substitution ( $S_{\text{E}}\text{AR}$ ) occurs between the electron rich aromatic compounds and higher oxidation state transition metals. Due to an empty d-orbital, the transition metal catalyst behaves like an electrophile and then it undergoes electrophilic aromatic substitution with the aromatic moiety. It is important to note that the oxidation state of the metal remains the same during the overall process (Scheme 1.11).



**Scheme 1.11** General mechanism for the electrophilic aromatic substitution reaction

**d) Single electron transfer (SET):** <sup>12e</sup>

In the single electron transfer (SET) process, the homolytic breaking of the C-H bond (R-H) occurs to form the  $L_n\text{M-H}$  intermediate along with the generation of carbon centred radical ( $\text{R}\cdot$ ). This radical recombines with metal centre of  $L_n\text{M-H}$  complex to generate the metal oxidized species via the oxidative addition of R-H (Scheme 1.12). Usually, the a few first-row transition metal catalysts show this kind of radical mechanism (Ni, Cu, Fe, Mn).

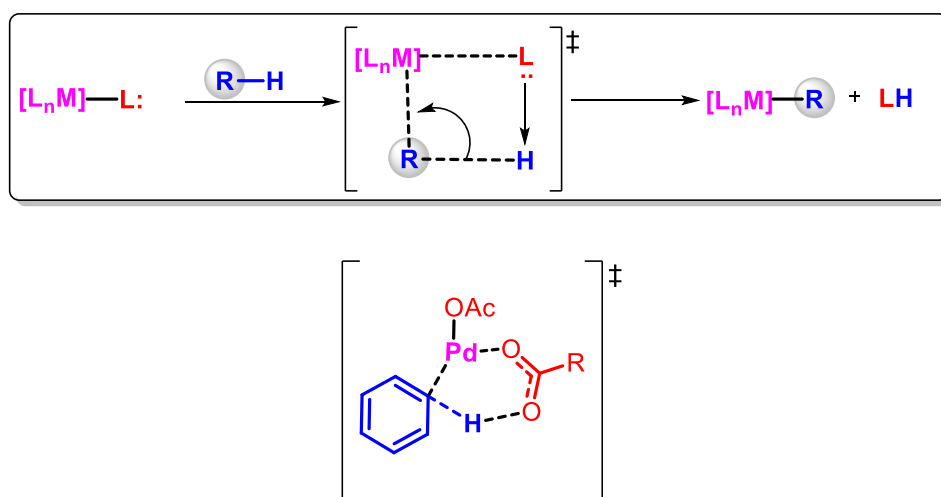


**Scheme 1.12** General mechanism for the single electron transfer (SET) pathway.



### e) Concerted Metalation Deprotonation (CMD):<sup>12</sup>

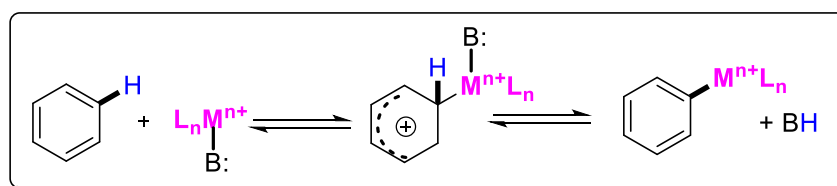
The concerted metalation deprotonation (CMD) is the most common type of mechanism of C-H bond activation reaction. However, the CMD pathway takes place via the single cyclic transition state by the cleavage of C-H bond of the substrate (R-H) to form the  $L_nM$ -C bond. In this reaction the ligand which is associated with the metal acts as an internal base (for e.g., carboxylate and carbonate ligand) and deprotonates the C-H bond of the substrate (R-H) bound to the metal complex to simultaneously form the  $L_nM$ -C bond. Moreover, the CMD pathway is more common for high valent, late transition metals such as Pd, Rh, Ru, Co, Ir, etc. The computational calculation studies that the CMD pathway has the lowest energy transition state. Over the past two decades, catalytic C-H activation to achieve the C-H bond functionalization has become increasingly common due to this mechanism (Scheme 1.13).



**Scheme 1.13** Mechanisms of C-H activation reaction via CMD pathway.

### f) Base assisted intramolecular electrophilic substitution (BIES):<sup>12</sup>

Usually, base assisted intramolecular electrophilic substitution (BIES) are common with the electron-rich aromatic rings. A proton is abstracted by the base leading to the formation of an  $L_nM$ -C bond. In terms of reaction conditions, a BIES pathway and CMD pathway are seen to be identical but they are mechanistically distinct (Scheme 1.14)



**Scheme 1.14** Mechanisms of C-H activation reaction via BIES pathway

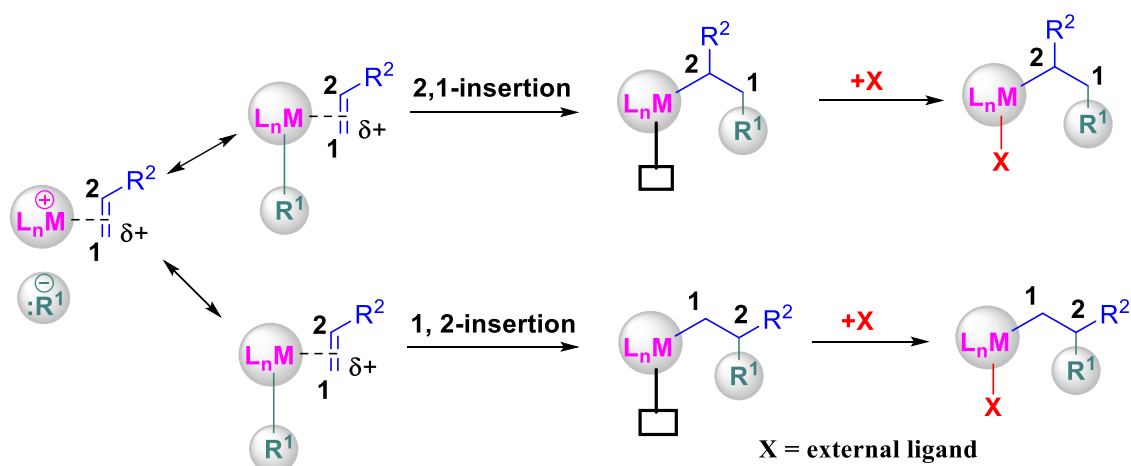
### 1.3.1 Some of the other Elementary steps in catalytic cycles of C-H activation reaction mechanism

There are three common basic or elementary steps in case of organometallic catalytic cycle associated so as to complete the catalytic cycle of C-H activation process.<sup>13</sup> These steps are as follows:

- Migratory insertion of olefins (1,2 insertion vs 2,1 insertion)
- $\beta$ -hydride elimination
- Reductive elimination

#### a) Migratory insertion of olefins (1,2 insertion vs 2,1 insertion):<sup>13a-d</sup>

In insertion step, the electron deficient metal complex first coordinates with olefins intermolecularly then this complex further undergoes the (2,1 or 1,2) migratory insertion of the M-C bond ( $R^1$  group in Scheme 1.15) to the olefin and metal to the olefin (across the double bonds of the olefin) intramolecularly. However, the electron deficient olefins undergo the 2,1-insertion pathway selectively due to the electronic and steric reason. After the insertion reaction the vacant coordination site (coordinative unsaturation) that is generated on the metal complex will be filled by the external ligand (Scheme 1.15).

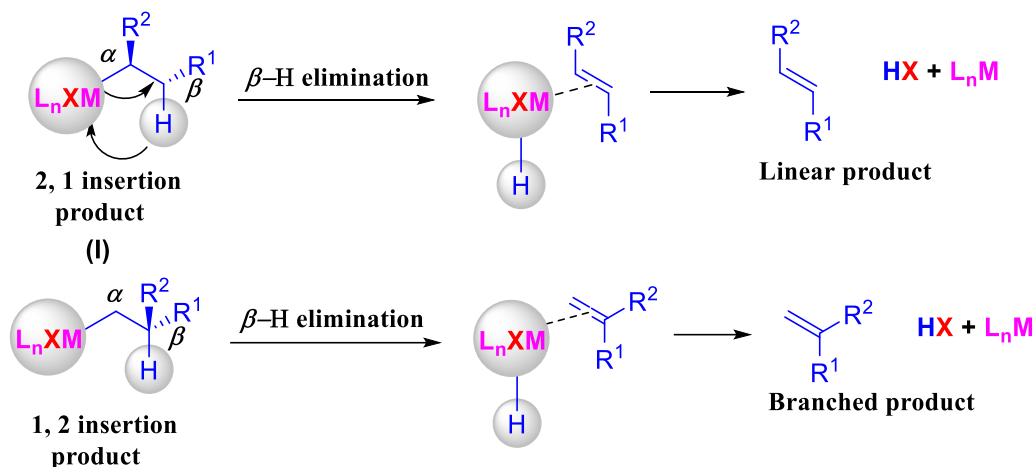


**Scheme 1.15** General mechanism of migratory insertion reaction

#### b) $\beta$ -hydride elimination:<sup>13e-f</sup>

The alkyl groups attached to metal centre undergo a process known as  $\beta$ -hydride elimination (hydrogen  $\beta$  to the metal) leading to an intermediate complex **I** in which metal is bound to hydrogen (metal hydride) as well as coordinated to the alkene. Generally, for this process the

hydrogen must be present on the  $\beta$ -carbon of the alkyl groups. This is also a microscopic reversal reaction of olefin insertion into M-H bond. This process is believed to proceed through a four-centre transition state finally affording the olefin (linear or branched) (Scheme 1.16). The metal complex must have an vacant coordination site for the favourable  $\beta$ -hydride elimination and if there is no vacant site available, a ligand must be removed for facilitating the reaction.

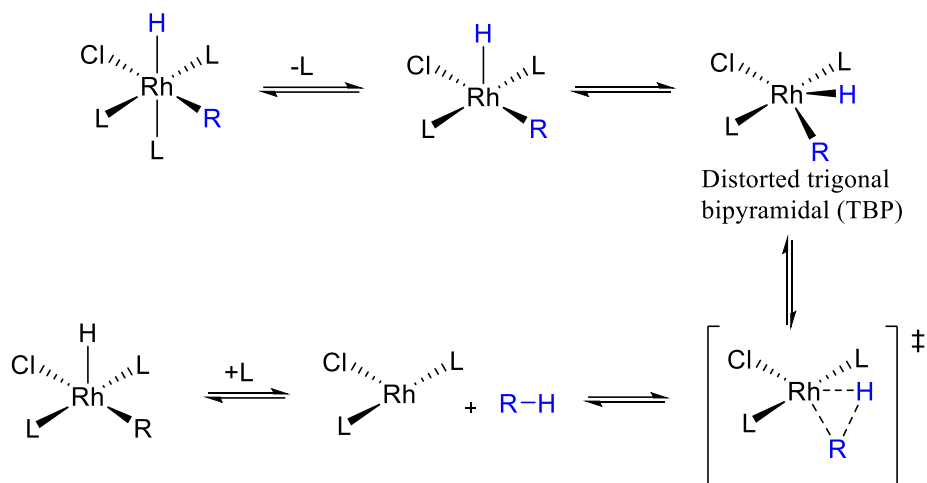


**Scheme 1.16** General mechanism of  $\beta$ -hydride elimination reaction.

### c) Reductive elimination reaction:<sup>13g-j</sup>

Finally, the reductive elimination is the final step in catalytic cycle of the C-H activation reaction to complete the catalytic cycle. It is a reversal of the oxidative addition reaction. In this reaction the oxidation state and coordination number of the metal is reduced by two units (Scheme 1.17). However, the reductive elimination is more common in metals which having higher oxidation states and ligand electronic and steric factors affect the rate of the reductive elimination too. The groups must be *cis*-oriented with each other so as to facilitate the reductive elimination. This reaction pathway is much more common for  $d^8$  metals such as Pd(II), Ni(II) and  $d^6$  metals Pt(IV), Rh(III) and Ir(III).

The different C-H bond activation reactions have been developed by using a range of transition metals including Pd, Rh, Ru, Ni, Co, Ir, Cu, Fe catalyst depending upon the substrates and reactivity.



**Scheme 1.17** Schematic general mechanism for the reductive elimination in octahedral complex.

However, across these metal catalysts, palladium has been used frequently for carbon-carbon and carbon-heteroatom bond formation due to various interesting properties of palladium that favour the facile transformations. In this thesis the C-H activation reactions have been presented that occurs through palladium catalytic cycle that is believed to undergo via CMD pathway.

#### 1.4 Types of C-H Activation:

Over the years synthetic organic community has been focussing on the C-H bond activation and a lot of attention has been given to improvise the strategies and to utilize the same for molecules of industrial relevance. Based on the studies, the C-H bond activation can be distinguished into two major types: A) Non-directed C-H activation and B) Directed or Directing group assisted C-H activation

##### A) Non-directed C-H activation:

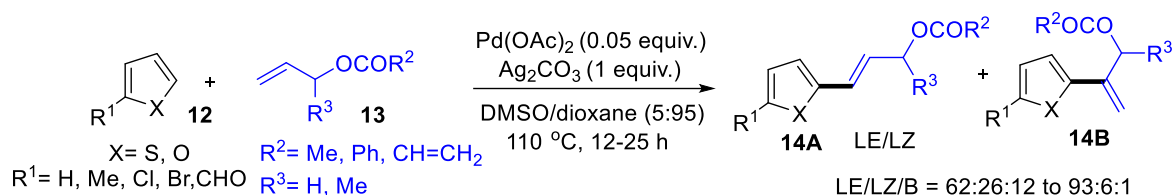
The C-H activation reaction of the substrates has been carried out without the use of any directing groups. This non-directed C-H activation has been further classified into two types based on the nature of substrates and ligand environment on the metal catalyst: a) Innate C-H activation and b) Direct C-H activation and they have been briefly discussed below.

##### a) Innate C-H activation:

In case of innate C-H activation, the steric and electronic factors (inherent bias) of substrates decide the C-H bond cleavage and the subsequent C-H bond functionalizations.<sup>14a</sup> However,

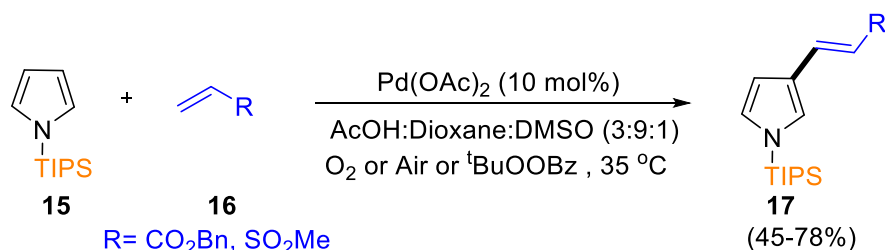
this type of C-H activation is relatively more common in heterocyclic compounds. A few examples of the heterocyclic compounds are given below. In case of the five membered heterocyclic compounds the C2 or C5 positions are more reactive as they are electronically rich and having more acidic C-H bond at that positions.

The Liu and coworkers have reported the cross coupling of the thiophene and furan compounds **12** with allyl ester **13** in presence of palladium catalyst to get the C5 linear **14A** and branched alkenylated product **14B** via  $\beta$ -H elimination (Scheme 1.18).<sup>14b</sup>



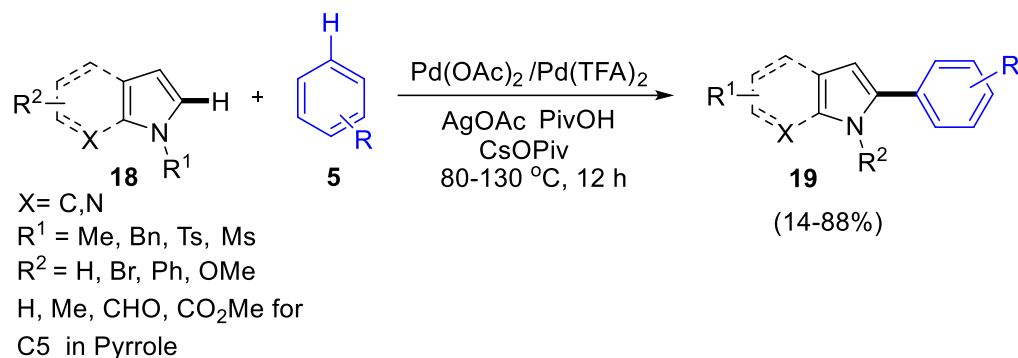
**Scheme 1.18** Palladium catalyzed C-H alkenylation of thiophene and furan derivatives at C5 position.

The presence of the sterically bulky group such as triisopropylsilyl (TIPS) group on the nitrogen of the pyrrole moiety directs the selectivity of the C-H activation towards C3 position. Gaunt and coworkers reported the selective C3 alkenylation of N-TIPS pyrroles **15** with various alkenes **16** in presence of palladium catalyst to furnish the final C-3 alkenylated products **17** in good yields (up to 78%, Scheme 1.19).<sup>15</sup>



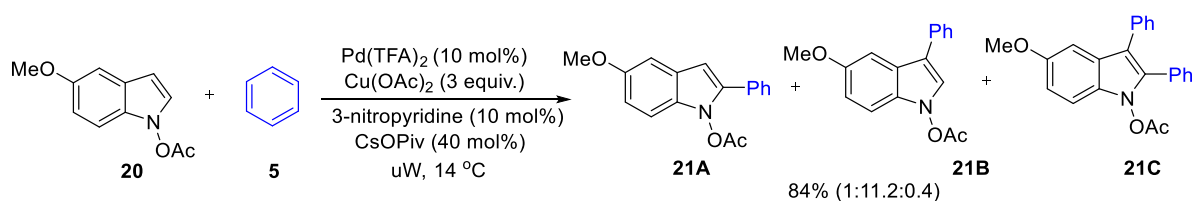
**Scheme 1.19** Palladium catalyzed regioselective C3 alkenylation of N-TIPS derivatives of pyrrole.

However, the sterically less bulky group on pyrroles favours the C-H functionalization at electronically activated C2 or C5 positions. In 2013 the Laha and coworkers reported the regioselective C2 arylation of 7-azaindoles, indoles and pyrrole compounds **18** with various arenes **5** in presence of palladium catalyst to afford the C2 arylated products **19** in low to good yields (up to 88%, Scheme 1.20).<sup>16</sup>



**Scheme 1.20** Palladium catalyzed regioselective C5 arylation of pyrroles.

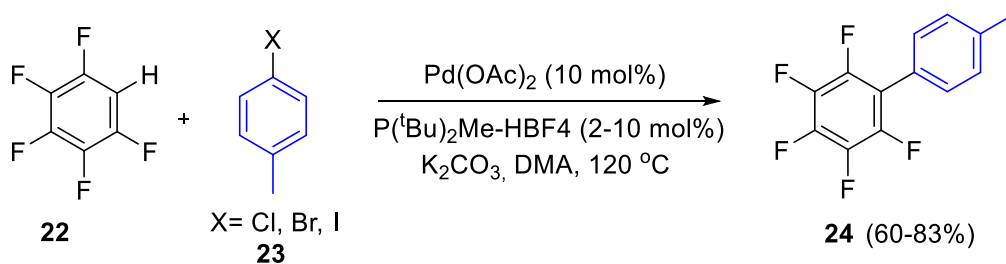
Fagnou and coworker reported the arylation of the indoles derivatives **20** with benzene **5** in presence of palladium catalyst. The arylation takes place on the C2 and C3 positions as these positions are electronically more reactive to afford the corresponding products **21A-C** (Scheme 1.21).<sup>17</sup>



**Scheme 1.21** Palladium catalyzed C-H arylation of indole derivatives at C2 and C3 positions.

These kinds of reactions are quite prevalent for the cross dehydrogenative coupling reactions (CDC) and are highly atom-efficient.

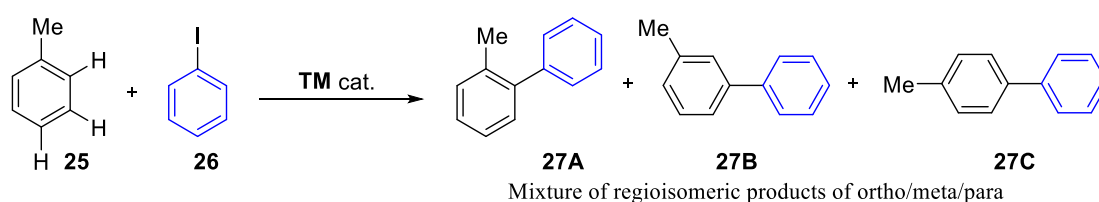
Similarly, the electron deficient benzene ring can also be activated and functionalized using palladium catalyst. In 2006 the Fagnou and coworkers reported the intermolecular direct arylation of perfluorobenzenes **22** with aryl halides **23** in presence of palladium catalyst to afford the final functionalized product **24** in moderate to good yields (up to 83% Scheme 1.22).<sup>18</sup>



**Scheme 1.22** Arylation of electron deficient pentafluorobenzenes.

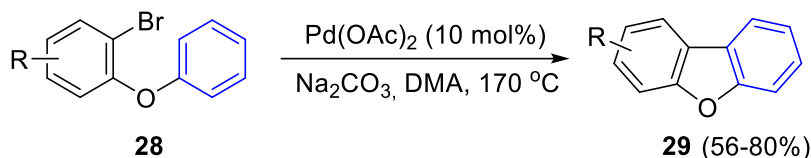
## b) Direct C-H activation:

It is extremely difficult to directly activate an inert C–H bond, although this has been achieved with the help of substrate design and ligand environment on the metal catalyst. The Fujiwara and Moritani reported the olefination of the aromatic C–H bond (See, Scheme 1.4) and this has been one of the earliest examples of the direct C–H bond activation reaction with olefins. The direct arylation of aromatic C–H bonds of arenes **25** with aryl halides **26** to access biaryl compounds (**27A**, **B**, **C**) has been most extensively studied method of C–H activation reactions (Scheme 1.23).<sup>19</sup>



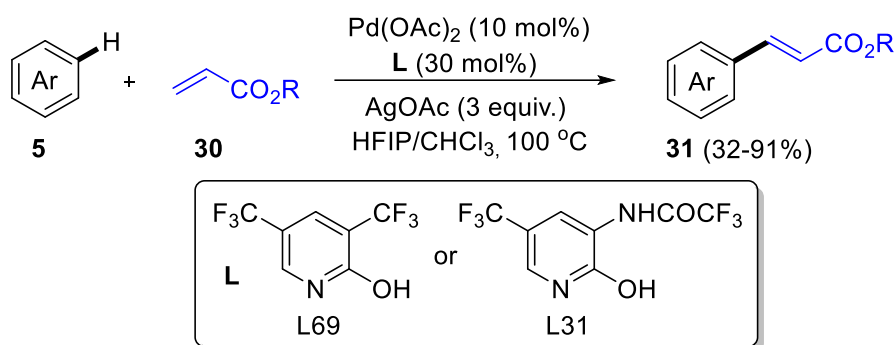
**Scheme 1.23** Non directed direct C–H activation

Further Ames and coworkers reported the intramolecular direct C–H activation. In this reaction first carbon halogen bond of the ether substrates **28** undergoes the oxidative addition followed by intramolecular C–H bond activation of the nearby hydrogen to form the final products **29** in moderate to good yields (up to 80%, Scheme 1.24).<sup>20</sup>



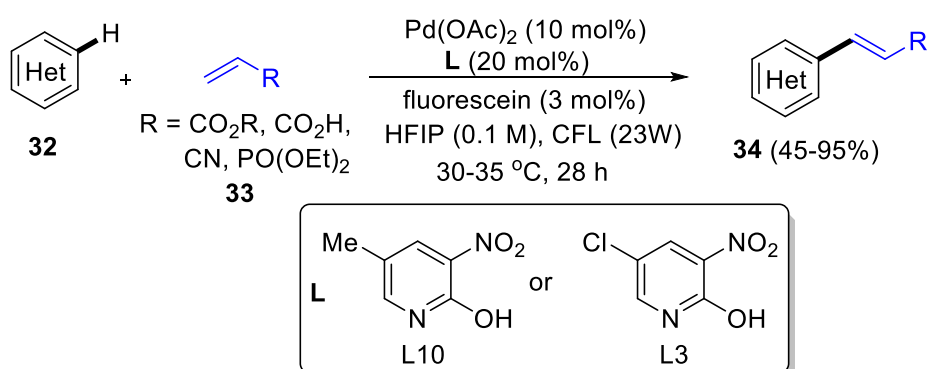
**Scheme 1.24** Palladium catalyzed intramolecular C–H bond activation

Recently, the Yu and coworkers reported the ligand-accelerated (non-directed) direct C–H bond functionalization of arenes under mild reaction condition. In this reaction the pyridone ligand first binds to the palladium catalyst to develop the novel catalyst system which in turn accelerates the olefination reaction (Scheme 1.25).<sup>21</sup> The aromatic and heteroaromatic compounds **5** react with various alkenes **30** in presence of palladium catalyst and pyridone ligand to furnish the final alkenylated products **31** in low to excellent yields (up to 91% yield).



**Scheme 1.25** Palladium catalyzed ligand-accelerated direct C-H olefination

Very recently the Maiti and coworkers have also reported the ligand-accelerated (non-directed) direct C–H bond functionalization of arenes under photocatalytic conditions (Scheme 1.26).<sup>22</sup> The aromatic and heteroaromatic compounds **32** react with various alkenes **33** in presence of palladium catalyst and pyridone ligands (L10, L3 inset, Scheme 1.26) under photocatalytic conditions to afford the final alkenylated products **34** in moderate to excellent yields (up to 95% yield).



**Scheme 1.26** Palladium catalyzed ligand-accelerated direct C-H olefination under photocatalytic conditions

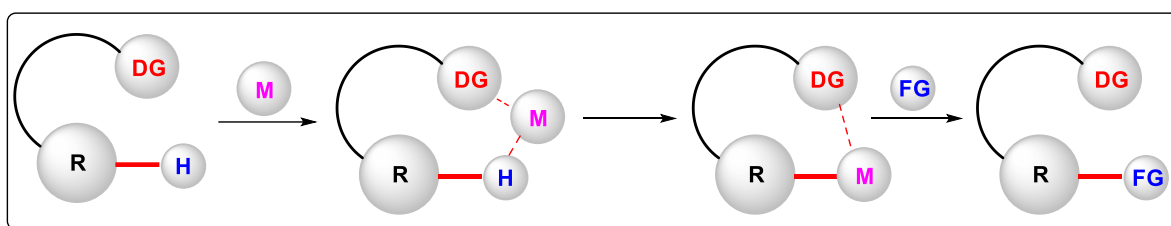
However, the ligand-accelerated non-directed direct C-H activation has some advantages but there are certain limitations too for the non-directed C-H bond activation approach (innate and direct C-H activation). The low functional group tolerance, lack of site selectivity, unusual reactivity and high catalyst loading are some of the limitations in some cases.

To overcome some of these limitations, attention has been made to switch towards directed or directing group assisted C-H activation strategy.



## B) Directed or Directing group (DG) assisted C-H activation:

The directing group (DG) assisted C-H activation method has the excellent site selectivity and wide applicability for C-H bond activation compared to other methods. This strategy completely revolutionized the field of C-H activation. In this method the directing group (DG) is covalently attached to the substrates and the DG initially coordinates or chelates with metal catalyst and brings metal catalyst in close proximity to the nearby C-H bond selectively that need to be functionalized (Scheme 1.27).<sup>11, 23</sup>



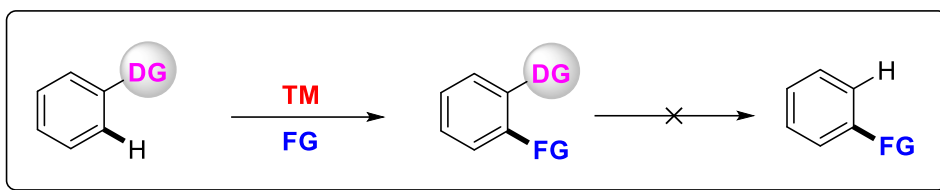
**Scheme 1.27** General mechanism for directing group assisted C-H activation

In 1993, Murai and coworkers were one of the earliest to report the ruthenium catalyzed directing group (DG) (ketone acted as DG) assisted C-H activation to achieve the direct alkylation (see Scheme 1.7). However, depending on the nature of the directing groups, the strategy can be further classified into the four types.

- a) Non removable directing group
- b) Removable directing group
- c) Traceless directing group
- d) Transient directing group

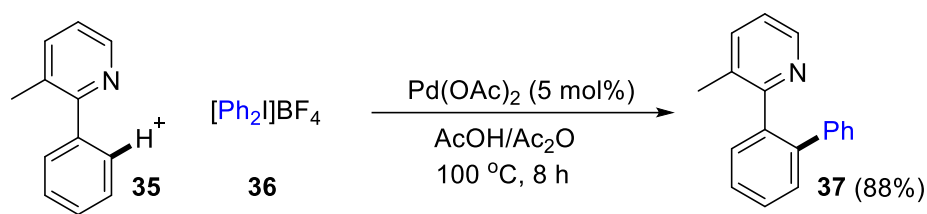
### a) Non-removable directing group:

The non-removable directing groups remain intact to the substrates even after C-H activation process is complete and it is difficult to remove these directing groups from the final products. This type of directing group is already present in the substrates and are covalently attached to it. However, with help of this covalently bound directing groups, the  $sp^2$  and  $sp^3$  C-H activation of the aromatic and aliphatic compounds have been reported earlier (Scheme 1.28).<sup>7c, 24</sup>



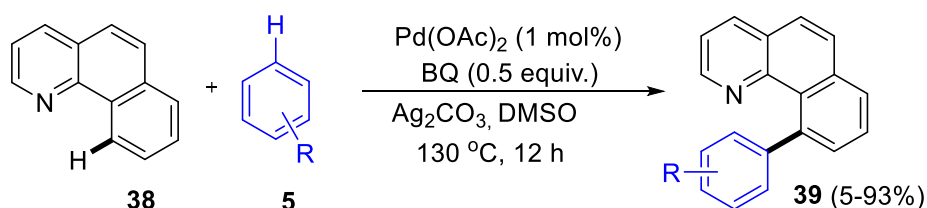
**Scheme 1.28** General mechanism for non-removable directing group

The palladium catalyzed C-H arylation of the 2-aryl pyridines has been reported by the Sanford and coworkers. In this reaction the 2-aryl pyridines **35** react with hypervalent iodine arylating agent **36** to furnish the final arylated product **37** in good yields (up to 88%, Scheme 1.29).<sup>25</sup> The pyridine is a non-removable directing group that directs the C-H activation to the *ortho* position of the arene moiety. This reaction is believed to proceed via 5 membered cyclic transition state (Scheme 1.29).<sup>26</sup> Usually *ortho*-C-H activation requires the 5-7 membered cyclic transition state.



**Scheme 1.29** Palladium catalyzed C-H arylation of arene derivatives with non-removable directing group

In 2007, Sanford and coworker further reported the regioselective cross coupling reaction of the benzo[h]quinoline **38** with various arenes **5** in presence of palladium catalyst to obtain the final arylated product **39** in low to excellent yields (up to 93%, Scheme 1.30).<sup>26</sup>

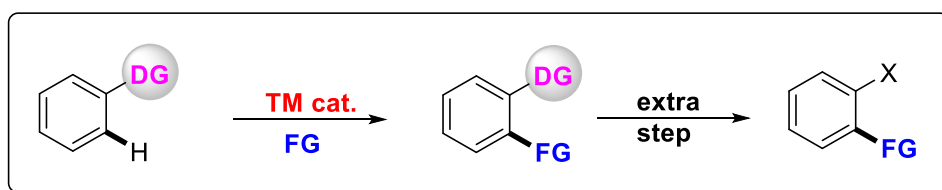


**Scheme 1.30** Palladium catalyzed highly regioselective arylation of benzo[h]quinoline

However, the disadvantage of the non-removable directing groups is that the DG is intact with the substrate even after C-H functionalization. In some cases the DG would remain on the final biological scaffold as a redundant group affecting the overall bioactivity.

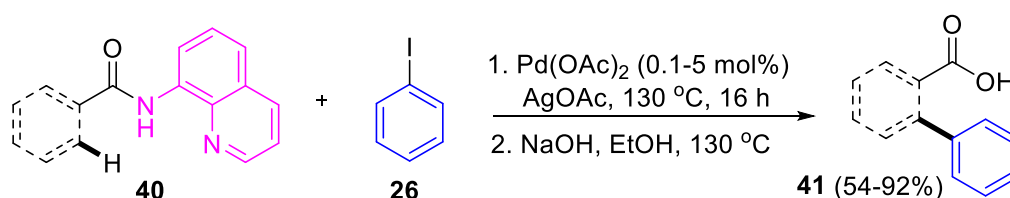
## b) Removable/Modifiable directing group:

In the removable directing group strategy, the directing group can be installed into the system (substrate molecule) particularly for the C-H activation and it can be chemically removed or de-installed from the system after the desired C-H activation is complete (Scheme 1.31).<sup>27</sup> A wide range of Lewis-basic functional groups such as pyridines, esters, amides, and imines, as well as bidentate DGs that act as monodentate directing group. These DGs have been extensively as well as successfully utilized for the  $sp^2$  C-H activation (at *ortho*, *meta*, *para* positions) of the aromatic, heteroaromatic and  $sp^3$  C-H activation ( $\alpha$ ,  $\beta$ ,  $\gamma$ , positions) of the aliphatic compounds by many research groups across the world.



**Scheme 1.31** General mechanism for removable directing group

Daugulis and coworkers have reported the  $sp^2$  and  $sp^3$  C-H arylations of the benzamides derivatives **40** derived using 8-amino quinoline as a removable directing group (forms amide as shown in **40**) with aryl iodide **26** in presence of palladium acetate to afford the final arylated products **41** in moderate to excellent yields (up to 92%, Scheme 1.32).<sup>28</sup>

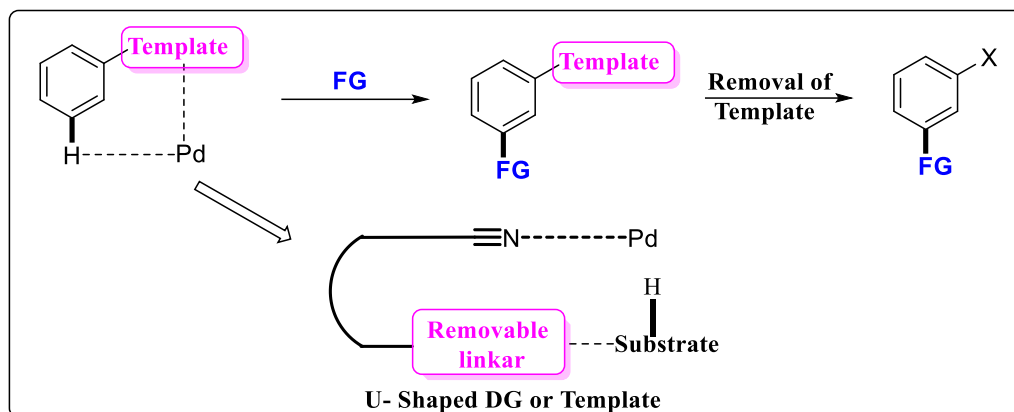


**Scheme 1.32** Palladium catalyzed *ortho* C-H arylations of benzamide derivatives

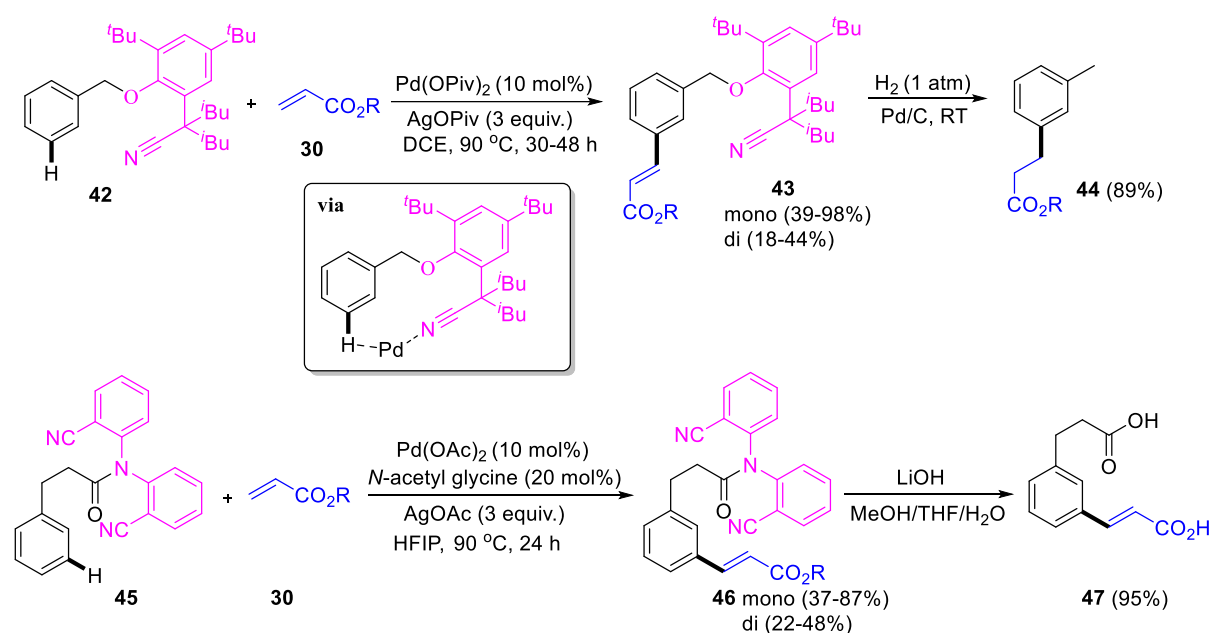
In spite of the widespread usage of *ortho* C-H bond activation via five to seven membered metallacycle, the distal C-H bond activation at the *meta* and *para* positions of aromatic compounds are challenging due to the unstable formation of macrocyclic transition state thus making it unfavourable.

In 2012, Yu and coworkers have reported the successful *meta*  $sp^2$  C-H activation of the aromatic compound using the U-shaped nitrile containing removable directing group (Scheme 1.33, 1.34).<sup>29</sup> This C-H activation is believed to undergo via 12 membered cyclic transition state.

Usually, *meta*-C-H activation requires the 12 or 13 membered cyclic transition state for the fruitful transformation.



**Scheme 1.33** General mechanism for the distal *meta*-C-H activation with removable directing group or Template

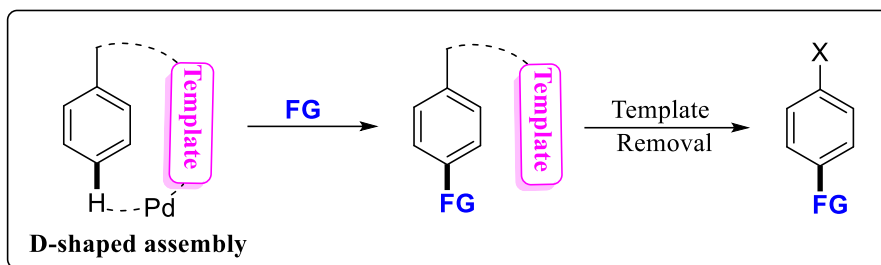


**Scheme 1.34** Template-directed *meta*-C-H olefination of toluene and hydrocinnamic acid derivatives

In this transformation, the starting substrates **42/45** independently react with acrylates **30** in presence of palladium catalyst such as Pd(OAc)<sub>2</sub> to furnish the final *meta*-alkenylated products **43/46** respectively in moderate to excellent yields (Scheme, 1.34).

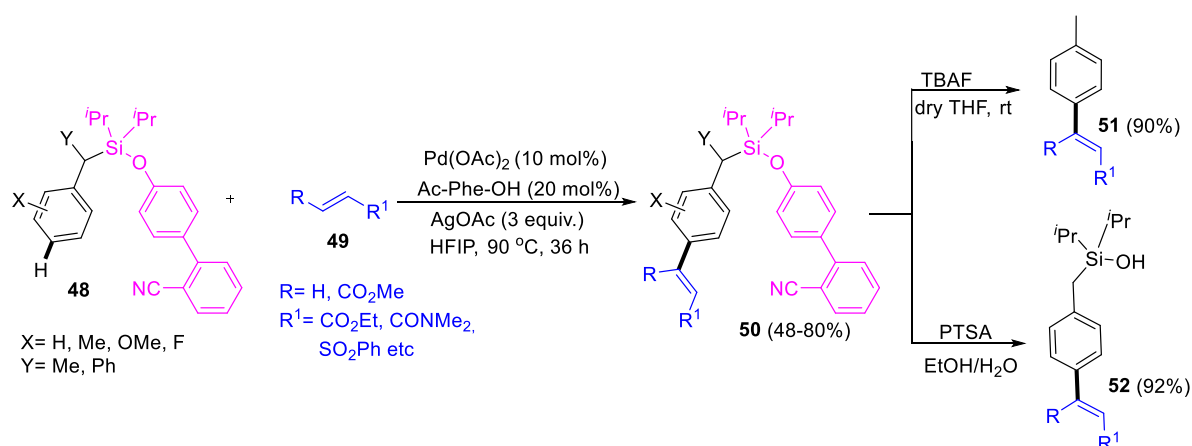
Maiti and coworkers reported for the *para*-C-H activation of aromatic compounds by elegantly designing the D-shaped nitrile containing removable directing group. This activation reaction

believed to proceed via 16 membered cyclic transition state (Scheme 1.35 and Scheme 1.36).<sup>30</sup> Usually para-C-H activation requires the 16-17 membered cyclic transition state and is really challenging achieve.



**Scheme 1.35** General mechanism for template directed distal *para*-C-H activation

The starting compound inbuilt with the D-shaped nitrile containing removable directing group **48** reacted with various alkenes **49** in presence of palladium acetate as a catalyst to afford the final *para*-alkenylated product **50** in moderate to good yields (Scheme 1.36).

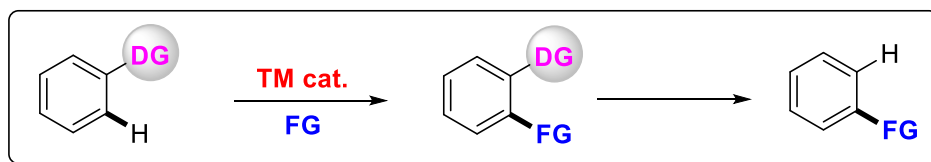


**Scheme 1.36** Template directed distal *para*-C-H olefination of aromatic compounds with Palladium catalyst

Later, different research groups have explored this field for further activation reactions. Though the removable directing groups have many advantages, however, they too have some of the limitations such as the installation and de-installation or removal of the directing groups adding extra steps and making it not attractive for the atom economic transformation.

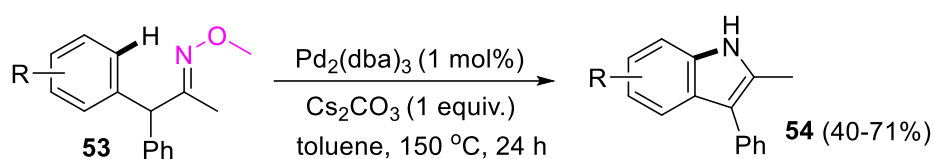
### c) Traceless directing group:

In traceless directing group strategy, the directing group gets detached from the substrate or gets converted in to another functional group after the C-H activation process (Scheme 1.37).<sup>27a,31</sup>



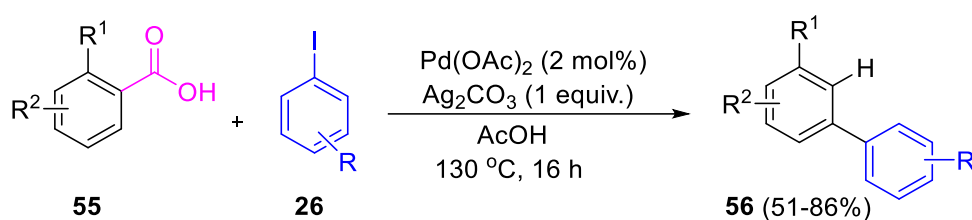
**Scheme 1.37** General mechanism of traceless directing group

Hartwig and coworkers reported the C-H amination of the aromatic compounds **53** in presence of palladium catalyst such as  $\text{Pd}(\text{dba})_3$  to afford the corresponding indole derivatives **54** in moderate to good yields (Scheme 1.38).<sup>32</sup> In this reaction the acetoxy group acts as DG and upon the C-H activation part of the DG becomes the part of the product and partly gets detached.



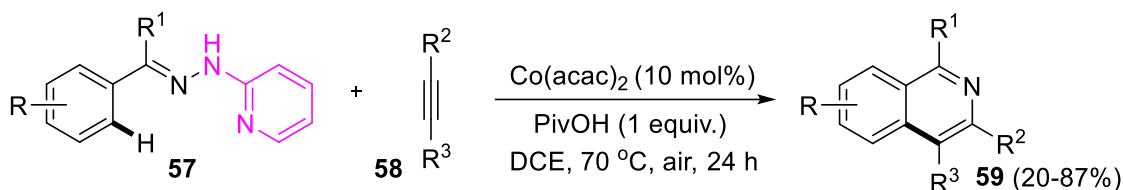
**Scheme 1.38** Palladium catalyzed C-H amination of aromatic compounds in presence of traceless directing group.

In 2006, Larrosa and coworkers reported the *ortho*-arylation of the substituted benzoic acids **55** with various aryl iodides **26** via palladium catalysis to furnish the corresponding decarboxylative arylated products **56** in moderate to good yields (up to 86%, Scheme 1.39).<sup>33</sup> This was the first report on the arylation wherein, the carboxylic acid (in situ DG) is ultimately removed *in situ*.



**Scheme 1.39** Palladium catalyzed *ortho*-arylation of the substituted benzoic acid with concomitant decarboxylation.

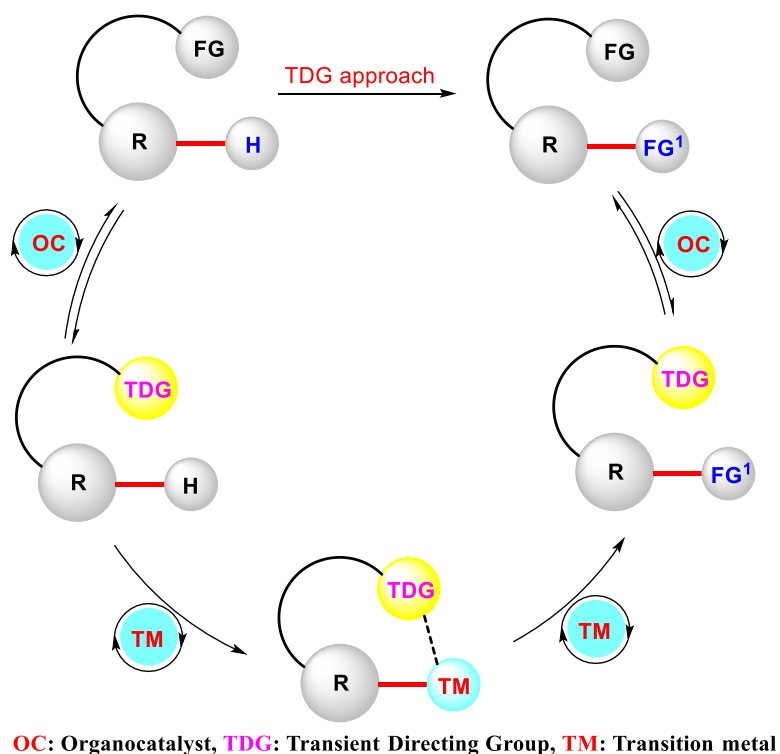
In 2016 Zhu and coworkers reported the traceless bidentate directing group enabled direct synthesis of heterocyclic compounds such as isoquinolines in presence of cobalt catalyst (Scheme 1.40).<sup>34</sup> The starting compound **57** reacts with various alkynes **58** to give the final isoquinoline derivatives **59** in low to very good yields.



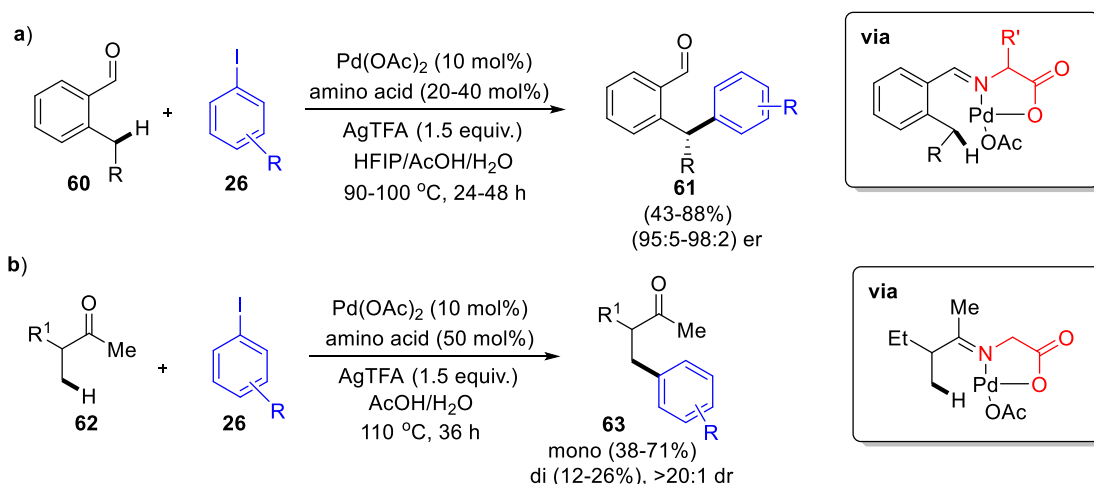
**Scheme 1.40** Synthesis of isoquinoline derivatives in presence of cobalt catalyst.

#### d) Transient directing group (TDGs):

The transient directing group (TDG) is generated *in situ* by the reversible binding of the ligand or organocatalyst with the suitable functional group of a substrate in catalytic amount. The *in situ* generated transient directing group in turn coordinates to the metal catalyst for facilitating the C-H activation. The advantage of this method is that the directing group is formed *in situ* and it doesn't need any installation and removal of the directing group without and it does affect the functionality of the substrate as well. TDGs are a potentially effective method for accelerating C-H functionalization in a single step. The formation of the TDGs are highly reversible and the catalytic ligand must not interfere with the C-H functionalization process. General schematic mechanism of the transient directing group mediated C-H activation has been depicted (Scheme 1.41).<sup>35</sup>



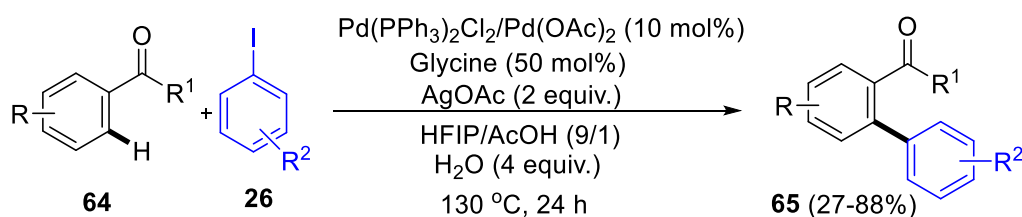
**Scheme 1.41** General mechanism of TDGs mediated C-H activation



**Scheme 1.42** (a) Palladium-catalyzed benzylic C(sp<sup>3</sup>)-H arylation of aldehydes (b) β-C(sp<sup>3</sup>)-H arylations of aliphatic ketones

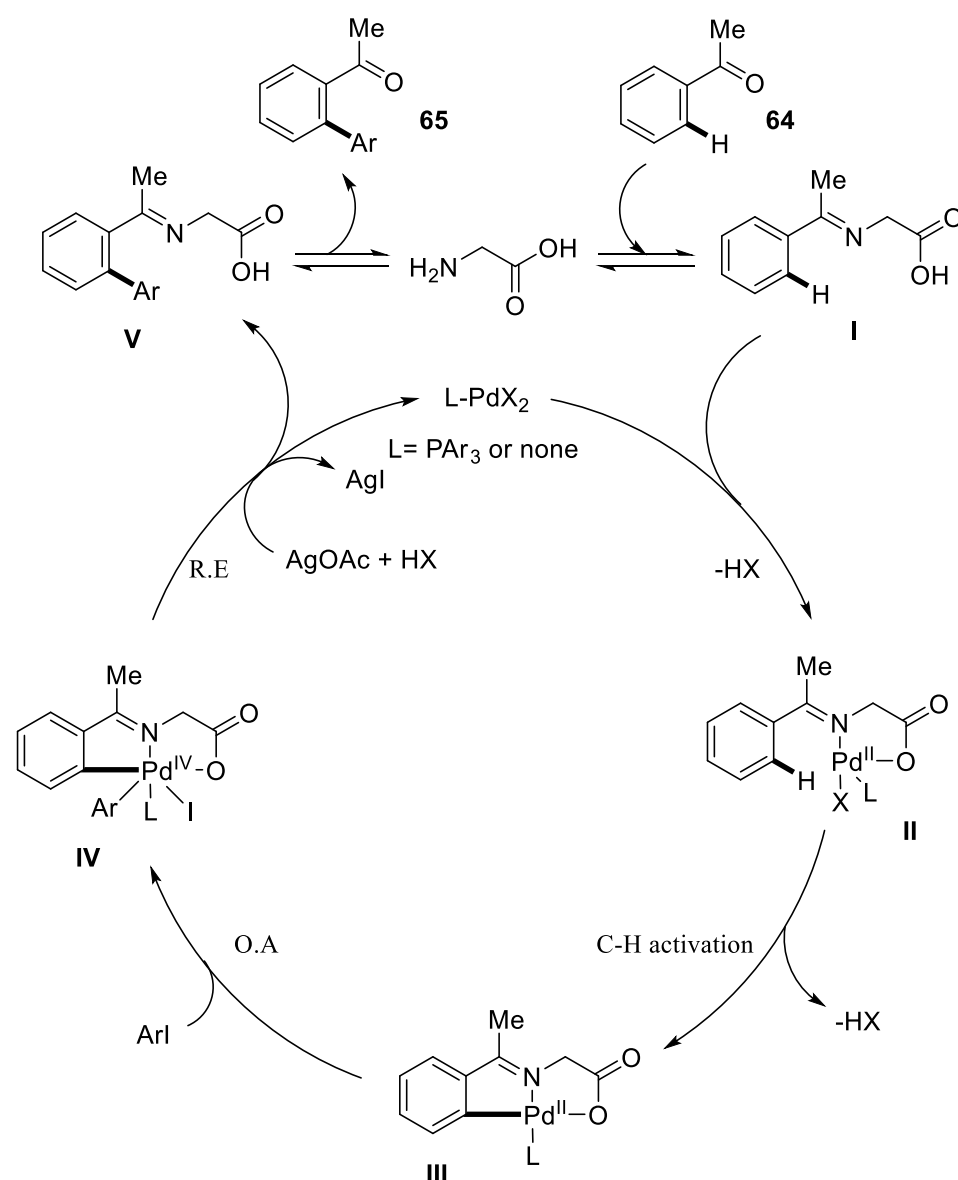
In 2016, Yu and coworkers reported the first examples for benzylic C(sp<sup>3</sup>)-H arylations of o-tolualdehyde derivatives **60** and the β-C(sp<sup>3</sup>)-H arylation of aliphatic ketones **62** with aryl iodides **26** in presence of palladium catalyst and the amino acid as TDG to obtain the final arylated products **61**, **63** respectively in moderate to good yields (Scheme 1.42). In this reactions the catalytic amounts of amino acids such glycine and tert-butyl leucine have been effectively explored as TDGs and they bind with aromatic aldehydes or aliphatic ketones to generate the imine *in situ* which in turn acts as a transient directing group for the effective C-H activation (Scheme 1.42).<sup>35a</sup>

In 2017 Jin, Xu and coworkers reported the direct *ortho*-arylation of aromatic ketones **64** using aryl iodides **26** in presence of glycine as a transient directing group via palladium catalysis to afford the final arylated products **65** in modest to good yields (Scheme 1.43). The catalytic amount of the glycine reacts with aromatic ketones and generates the imine *in situ* which acts as a transient directing group, and it binds to the metal and drive the reaction further. (Scheme 1.43).<sup>36</sup>



**Scheme 1.43** Transient directing group enabled *ortho*-arylation of aromatic ketones





**Scheme 1.44** Proposed reaction mechanism

The mechanism of this *ortho*-arylation has been depicted in Scheme 1.44. In this reaction the aromatic ketone **64** first reacts with glycine and in-situ generates the imine intermediate **I** which acts as a transient directing group (TDG). Further this imine intermediate **I** binds to palladium catalyst to form the intermediate **II** and this intermediate further undergoes the C-H activation process to form the cyclopalladated intermediate complex (**III**). Next the aryl iodide undergoes the oxidative addition reaction on the intermediate complex **III** to form the intermediate **IV** and reductive elimination of this intermediate to form the arylated intermediate **V**. Further in-situ removal of the imine to gives the final arylated product **65**. The silver acetate re-oxidized the palladium catalyst for further catalytic process.

This TDG approach has been recognised as a significant tool for several functional modifications of C-H bonds, including arylation, alkylation, halogenation, amination, and many more. Although the TDGs processes offer a simple and hassle-free synthetic pathway, however, it is only limited to various aromatic and aliphatic aldehydes, ketones, amines, and phenol derivatives.

We have also explored the TDGs mediated C-H activation reaction strategies for accessing useful compounds.

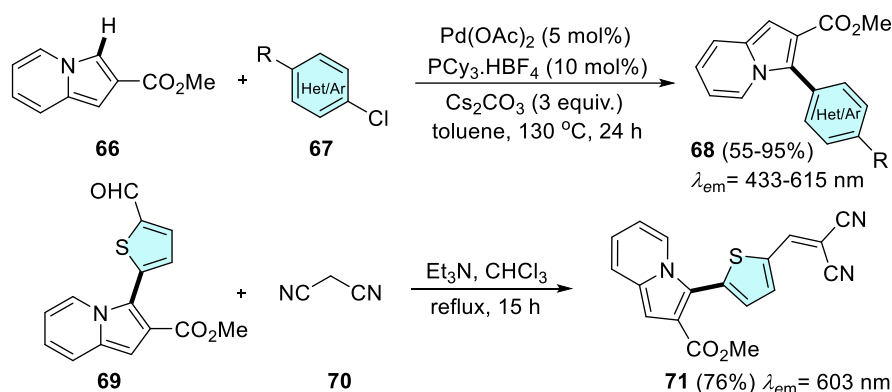
### **1.5 Applications of the C-H activation:**

Over the past few decades, synthetic strategies relying on the C-H bond activation have emerged significantly and the C-H activation has grown as one of the most exciting and rapidly developing areas of organic synthesis. This C-H activation strategy has a remarkable role in the development of many impressive number of transformations that are intended to directly install new C-C or C-X bonds with an ease that were tedious via traditional methods. The use of these novel C-H activation strategies have found applications in the synthesis of natural products, biologically active compounds, polymers, dyes, organic functional materials and also in late-stage functionalization of many useful compounds.<sup>37</sup> Also, the application of C-H activation for accessing useful organic fluorescent materials have been explored over the past ten years. Using this strategy a variety of organic fluorescent materials have been made via the construction of C-C bonds relying on the C-H activation.<sup>38</sup>

#### **1.5.1 Applications of the C-H activation in development of organic fluorescent materials:**

The transition-metal-catalyzed C-H bond activation method provides a distinctive, simple, and atom-efficient strategy for the synthesis of organic fluorescent compounds that are usually difficult to be synthesized using standard synthetic methods. The organic fluorescent materials have excellent photophysical properties and high chemical stability thus they show a broad applications in security systems, memory devices, chemosensors, field-effect transistors, bioprobes, organic light-emitting diodes, electroluminescent materials, and in mechanochromic materials.<sup>38</sup>

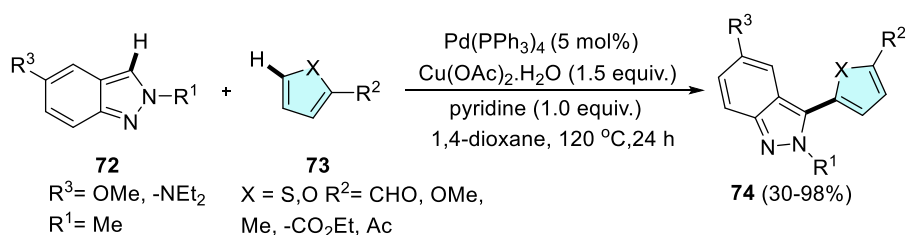
In 2012 Lan, You and coworkers reported the palladium catalyzed direct C-H bond arylation or heteroarylation of the *N*-heteroarenes **66** with a wide range of aryl or heteroaryl chlorides **67** to furnish a library of organic fluorophores **68** in moderate to excellent yields (Scheme 1.45).<sup>39</sup>



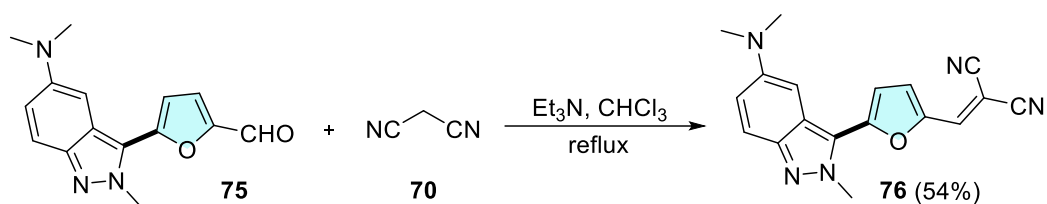
**Scheme 1.45** Palladium-Catalyzed arylation/heteroarylation of N-Heteroarenes with aryl/heteroaryl chlorides

These fluorescent materials usually show solid-state emission from blue emission to red emission (405-615 nm). Additionally, by using this procedure, novel bioimaging fluorescent probe (**71**) has been synthesized. This molecule has also been explored for the marking of human malignant melanoma A375 cells (Scheme 1.45).

In 2016, You, Gao and coworkers reported an oxidative cross coupling of electron-deficient 2H-indazoles **72** with electron-rich heteroarenes **73** in presence of palladium catalyst for the development of a large library of donor-acceptor-type bi-heteroaryl fluorophores **74** (Scheme 1.46).<sup>40</sup> These fluorophores display continuously tuneable full-color emissions with excellent quantum yields and significant Stokes shifts in solution. The donor-acceptor skeleton has been constructed using this strategy to access novel near-infrared-emitting dyes that show emission wavelength over the 700 nm. Additionally, the near-infrared-emitting dye **76** has also shown to be a very efficient fluorescent probe that targets mitochondria (Scheme 1.47).<sup>40</sup>

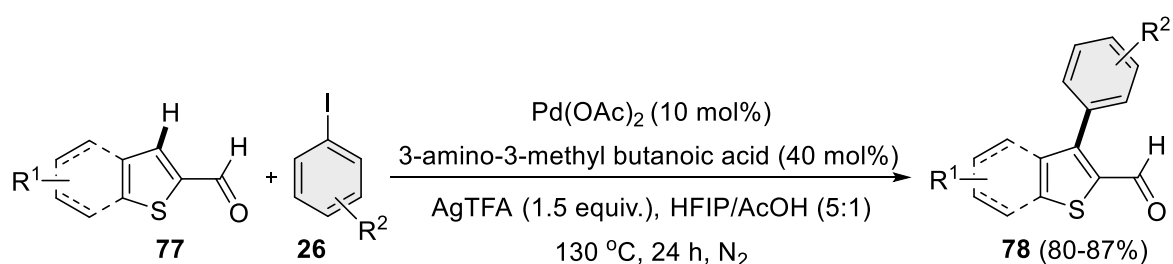


**Scheme 1.46** Oxidative C–H/C–H cross-coupling of 2H-indazoles with various heteroarenes in presence of Palladium catalyst



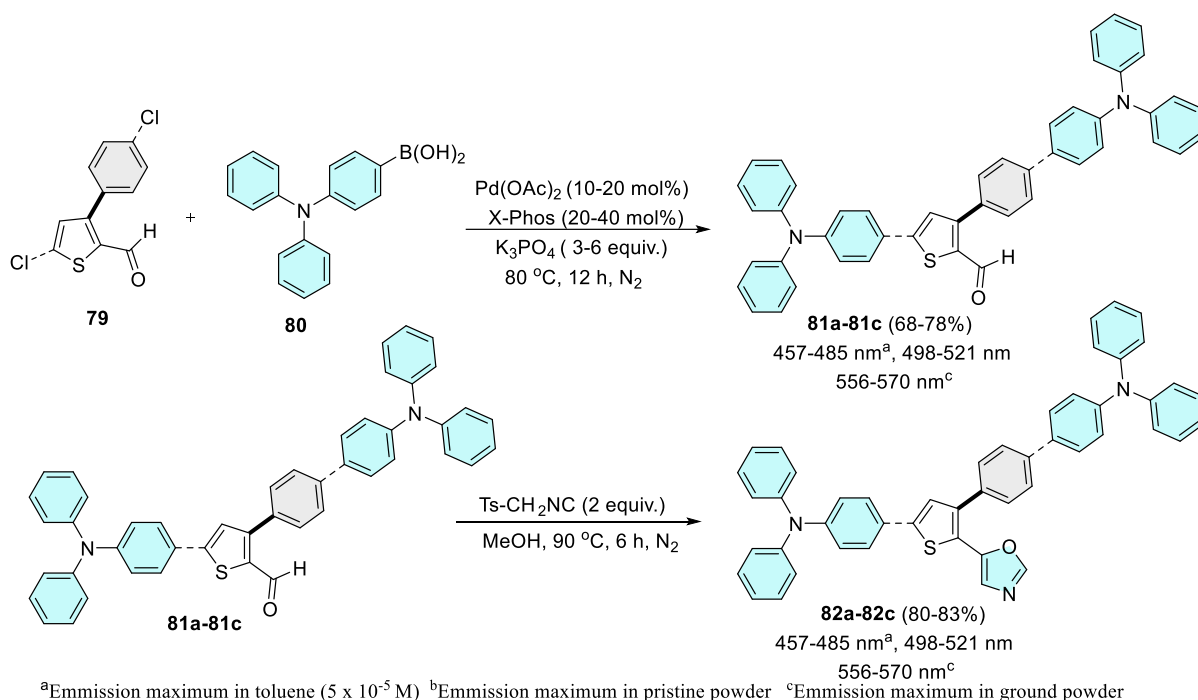
**Scheme 1.47** Synthesis of the near-infrared fluorophore dye **73**

In 2018 Ge and coworkers reported the ortho arylation of the five membered heterocyclic carbonyl compounds **77** with various aryl iodides **26** via TDG mediated palladium catalysis to access arylated products **78** in moderate to good yields (Scheme 1.48).<sup>41</sup> They also developed a range of blue- and red-shifted mechanochromic materials via the C-H arylation of thiophene aldehydes followed by Suzuki cross coupling reaction. Additionally, for the development of D-A-type dyes the triphenylamine (TPA) as the donor (D) unit and an aldehyde or oxazole moiety as the acceptor (A) has been used in order to further understand mechanochromic regularity (Scheme 1.49).<sup>41</sup> These mechanochromic fluorescent materials are smart stimuli-responsive materials and they find potential use in mechanical sensors, security systems, deformation detectors and memory devices.

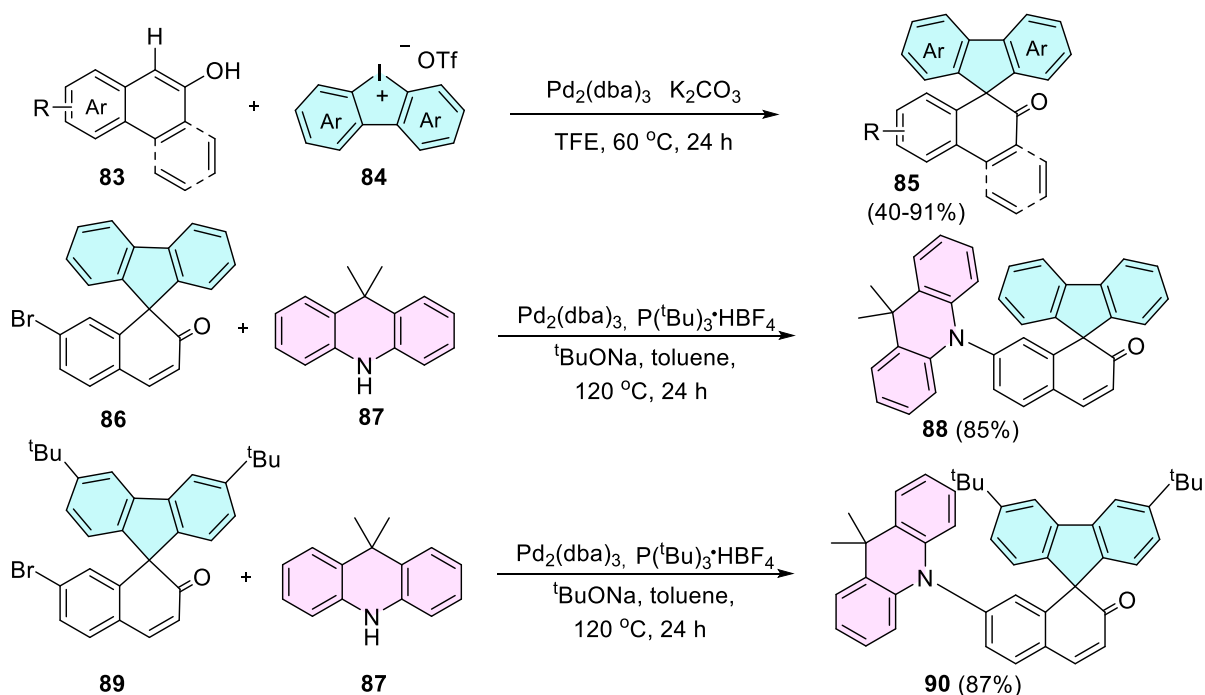


**Scheme 1.48** Synthesis of 3-Aryl-(2-aldehyde)thiophenes in presence of palladium catalyst

Recently, You and coworkers reported for the palladium catalyzed C-H spiroannulation of naphthols **83** with cyclic diaryliodonium salts **84** to synthesize the spirofluorenyl naphthalenones **85** in moderate to excellent yields (Scheme 1.50).<sup>42</sup> Additionally, D-A type thermally activated delayed fluorescent (TADF) materials have been synthesized using the spirofluorenyl naphthalenone unit as the acceptor.



**Scheme 1.49** Suzuki cross-coupling reaction to build TPA-containing compounds.



**Scheme 1.50** C–H spiroannulation of naphthols with cyclic diaryl-iodonium salts in presence of palladium catalyst.

The TADF materials have the great potential to achieve 100% internal quantum efficiency. Due to this these type of compounds have received a lot of attention in the field of organic light emitting diodes (OLEDs). Owing to the importance, two new TADF host materials **88**, **90** have been synthesized via Buchwald Hartwig coupling.

Inspired by the C-H activation as well as many interesting fluorescent compounds, thesis has been aimed to develop a few C-H bond activation strategies to construct interesting compounds that may have different photophysical studies (applications of organic fluorescent materials) and have been described in detail in the subsequent chapters.

## **1.6 Conclusions:**

In conclusion the C-H bond activation has been proven to be very efficient and important strategy for the construction of the carbon-carbon bond to access useful organic compounds. Though cross-coupling reactions have been used extensively for the construction of carbon-carbon bond, but do they have limitations such as requirement of pre-functionalized substrates and often many substrates are commercially not available. Alternatively, the C-H bond activation provides an effective and efficient platform to construct many useful organic compounds without relying heavily on pre-functionalized materials. This chapter has presented a brief history of C-H bond activation reactions. The chapter has also given an account on different reaction mechanisms and details on different types of the C-H bond activations. Different reactions such as arylation, alkenylation, alkylation reaction via C-H bond activation have been presented. The various applications of the C-H bond activation reactions especially the development of fluorescent materials and its photophysical properties have been briefly discussed.

Inspired by the C-H activation as well as many interesting fluorescent compounds, thesis has been constructed on the development of C-H bond activation strategies to access interesting compounds that may have different photophysical studies. Palladium catalyzed alkenylations and arylations of the inert C-H bond of the different five membered heterocyclic scaffolds and have been developed and also designed and developed fluorescent materials along with their photophysical studies. These works have been discussed and described in detail in the subsequent chapters.

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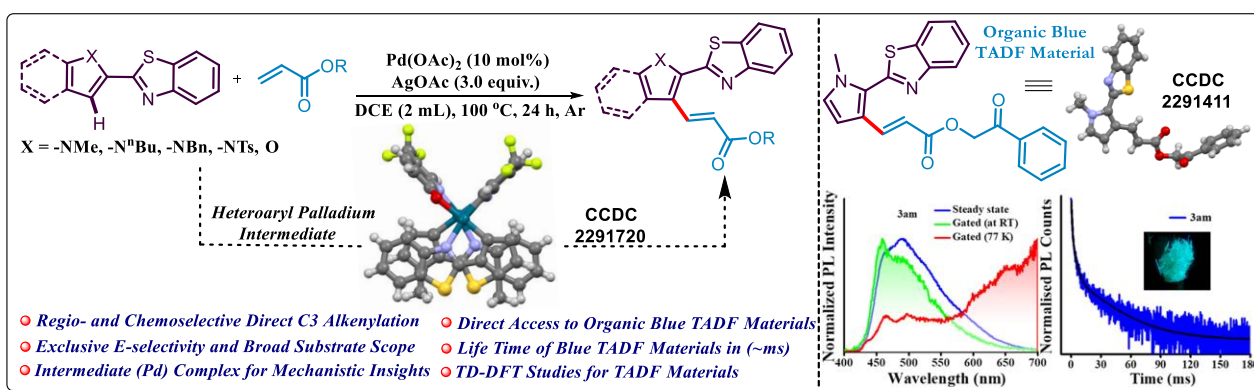
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## Palladium Catalyzed C3-(sp<sup>2</sup>)-H Alkenylation of Pyrroles: A Direct Access to Novel Organic Thermally Activated Delayed Fluorescence (TADF) Materials

### Abstract:

The direct C3-(sp<sup>2</sup>)-H alkenylation of five membered heteroarenes by using benzothiazole as a directing group in presence of palladium (II) catalyst has been successfully developed. The various acrylates undergo the oxidative coupling with a broad range 2-N-alkylpyrroles to produce highly regio- and chemo selective C3 alkenylated products with an exclusive E-selectivity. To gain the insights into the reaction mechanism, an essential intermediate (pd) complex has been isolated and characterised. This methodology gives the direct access to novel organic thermally activated delayed fluorescence materials (TADF). These compounds have been found to be blue emitting TADF materials (~ms lifetime). The photophysical properties have been studied in-depth and the results have been further supported by time-dependent (TD) the density functional theory (DFT) calculations.



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## 2.1 Introduction

The five membered heteroarene compounds are very important as this class of compounds is found in the many active drugs and pharmaceutically active compounds.<sup>1</sup> Among the five membered heterocycles, the pyrrole is one of the most significant core scaffolds and is prevalent in many pharmaceutically active compounds, including commercially available drugs like tolmetin, atorvastatin, and ketorolac.<sup>2,3</sup> Additionally, as a core scaffold, pyrrole scaffold is present in a variety of natural products, bioactive compounds, polymers, and dyes.<sup>2,3</sup> Furthermore the histone deacetylase inhibitor and the pyrrole barbiturates also contain C3-alkenylated pyrrole framework. It is also interesting to note that a few organic functional materials also have pyrrole scaffold as a core unit.<sup>2,3</sup> Intriguingly, like pyrroles, benzothiazole derived compounds are also known to be bioactive and pharmaceutically active<sup>4</sup>. The benzothiazole scaffold has also been explored in organic functional materials, optical research and used as fluorescence probes<sup>5,6</sup> because of its fluorescence properties. Besides its biological activity and fluorescence properties, benzothiazole has also been investigated as a directing group (DG).<sup>4,7</sup>

In light of the significance and potential applications of both of these compounds (pyrrole and benzothiazole), we intended to develop and construct hybrid molecules having both pyrrole and benzothiazole moieties. We further hypothesised that the photophysical properties of this hybrid core scaffold could be tapped by having an extended delocalization by the addition of an olefinic moiety on this hybrid compounds. In this regard, we planned to construct the pyrrole-benzothiazole hybrid framework first and followed by the alkenylation depending on a few parameters. We carefully looked into the development of a strategy to construct a pyrrole-benzothiazole hybrid framework and also to investigate the potency of benzothiazole as a DG for the direct alkenylation at appropriate position.

In this regard we also gleaned through the literature for the alkenylation of heteroarenes. The transition metal catalyzed alkenylation of five membered heteroarenes has recently emerged as one of the most atom- and step-efficient methods in the organic synthesis.<sup>8</sup> Despite this, the selective C3 alkenylation of the pyrrole compounds has been very challenging due to its low

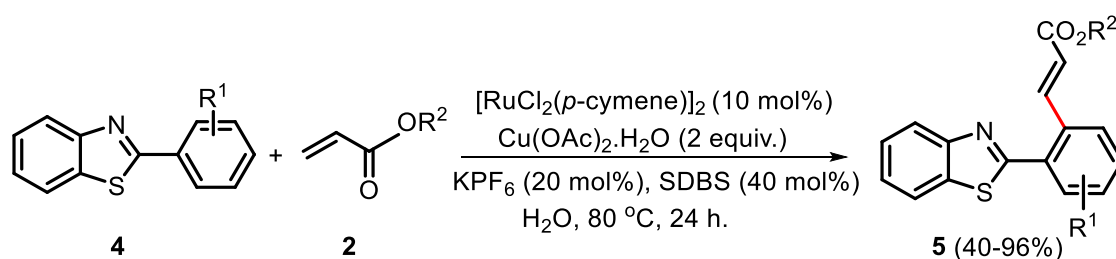
reactivity at this position in contrast to the more reactive C2 and C5 positions since they are located at the  $\alpha$ -position of the nitrogen in pyrroles.<sup>9</sup>

In spite of their important role in pharmaceuticals and their usefulness in chemical synthesis, surprisingly only a few synthetic methods have been reported in the literature for the direct C3-alkenylated pyrrole derivatives. Although these methods have their own merits, but they also have certain limitations such as the requirement of the pre-functionalized starting materials, the need for bulky functional groups on the nitrogen, the employment of stoichiometric quantities of expensive reagents, and also multi-step procedures to achieve the target compounds.<sup>7,10-12.</sup>

It is also significant to note that the alkenylation of the pyrrole compounds by utilizing the benzothiazole moiety as a directing group has been seldom studied in the scientific literature to the best of our knowledge. There are a very few reports on the benzothiazole moiety as a directing group for the C-H bond functionalization of aromatic/heteroaromatic compounds.

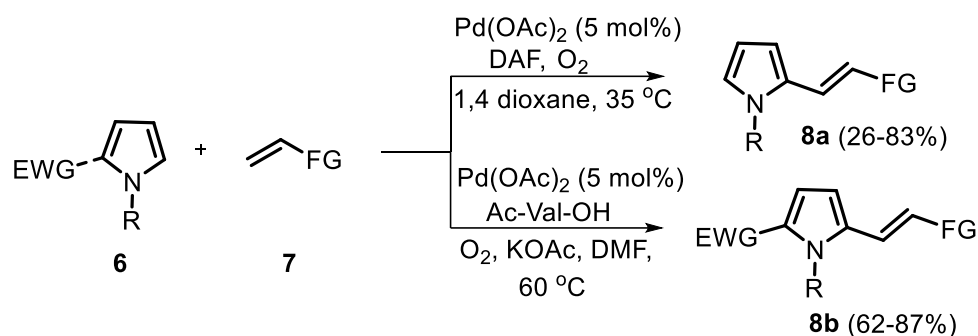
## 2.2 Recent approaches for the *ortho*-C(sp<sup>2</sup>)-H alkenylation of aromatic compounds by using the benzothiazole moiety as a directing group.

There are limited reports on the benzothiazole moiety as a directing group for the C-H bond functionalization of aromatic/heteroaromatic compounds. In 2017, Peng and coworkers reported the *ortho*-alkenylation of the 2-aryl benzo[d]thiazole compounds **4** with different acrylates **2** in presence of ruthenium (II) catalyst along with copper acetate monohydrate as an oxidant, KPF<sub>6</sub> additive, sodium dodecylbenzenesulfonate (SDBS) as a phase transfer catalyst (PTCs) in water at an elevated temperature (80 °C) to afford corresponding *ortho*-alkenylated products **5** in moderate to excellent yields (up to 96%, Scheme 2.1).<sup>4</sup>



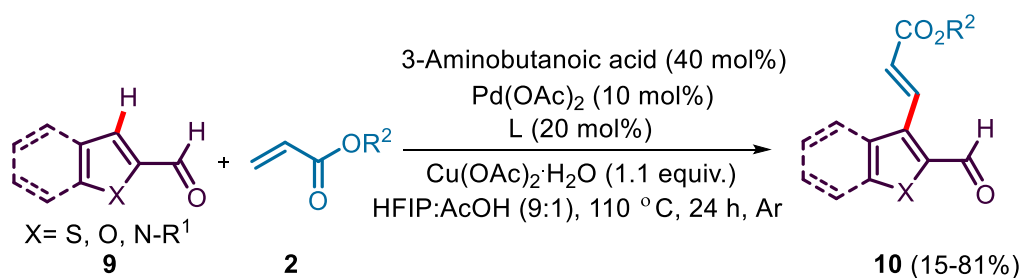
**Scheme 2.1** Alkenylation of the 2-arylbenzo[d]thiazole in presence of ruthenium catalyst.

Further for the pyrrole compounds alkenylation the Joo and coworkers in 2018 reported for the C2 and C5 alkenylation of the pyrroles **6** with various electron deficient olefins **7** in presence of electronically matching ligands and palladium acetate as a catalyst to form the alkenylated pyrrole compounds **8** (**8a-8b**) in moderate to good yields (up to 87% Scheme 2.2).<sup>7a</sup>



**Scheme 2.2** Alkenylation of the pyrroles in presence of electronically matching ligands.

In 2023 Bhat and coworkers reported for the C3 alkenylation of the heterocyclic aldehydes (including pyrrole-2-carboxaldehyde) **9** with various acrylates **2** in presence of 3-aminobutanoic acid as a transient directing group (TDG) and 2-pyridone as an external ligand (L) and palladium acetate catalyst, copper acetate monohydrate as an oxidant and HFIP:AcOH solvent at 110 °C to afford the C3 alkenylated heterocyclic products **10** in moderate to good yields (up to 81% Scheme 2.3).



**Scheme 2.3** C3- alkenylation of heterocyclic aldehydes (Pyrrole-2-aldehydes).

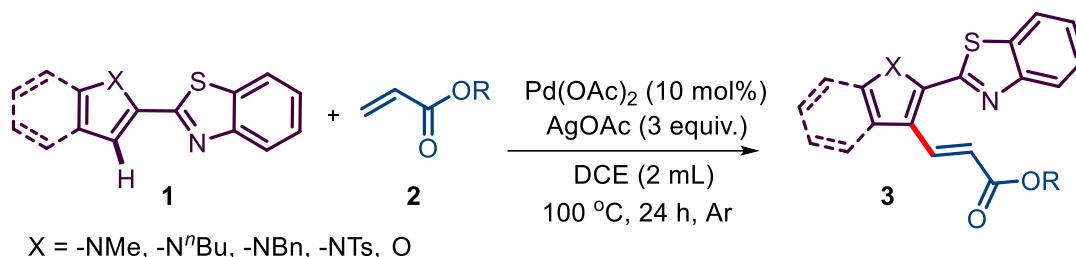
Surprisingly, till date there are not reports for the direct C3-alkenylation of pyrroles by using benzothiazole as a directing group with different acrylates via palladium catalysis to the best of our knowledge.

### 2.3 Our hypothesis and synthetic design

We were more interested in creating the pyrrole-benzothiazole hybrid molecule with the alkenyl functionality after considering the limited synthetic methods that use the benzothiazole moiety as a directing group. This would also present an opportunity for the development of synthetic methods and would provide new compounds with extensive delocalization to take advantage of the photophysical properties and potentially powerful bioactivity.

Herein, in this chapter we have described the first palladium-catalyzed direct C3-alkenylation of 2-*N*-alkylpyrrole benzo[d]thiazoles using a variety of acrylates and by exploring the

potential of benzothiazole as a directing group (DG) to access the compounds with blue TADF properties for the first time. We hypothesized that the 2-*N*-alkylpyrrole benzo[*d*]thiazoles **1** would react with a variety of acrylates **2** in presence of palladium catalyst under suitable reaction conditions to furnish the desired C3-alkenylated product **3** (Scheme 2.4).



**Scheme 2.4** C3-alkenylation of 2-heteroaryl benzo[*d*]thiazole in presence of palladium catalyst.

## 2.4 Results and Discussion

In order to investigate the potential for the direct C3-alkenylation of pyrrole compounds, we commenced the reaction with 2-(1-methyl-1H-pyrrol-2-yl)benzo[*d*]thiazole **1a** (0.1 mmol) and ethyl acrylate **2a** (0.3 mmol) as a model substrates. Fortunately, after the initial screening, we obtained the desired C3-alkenylated product ethyl(*E*)-3-(2-(benzo[*d*]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl) acrylate **3aa** in moderate yield (64% yield, Table 2.1, Entry 1) along with the C3/C5 -dialkenylated product **3aa'** albeit in poor yield (10%, Table 2.1, Entry 1) in presence of Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (0.3 mmol) in DCE (2 mL) at an elevated temperature (100 °C) under inert atmosphere. After the several screenings, Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (3 equiv.) in DCE solvent under inert atmosphere at 100 °C proved to be the initial optimization condition.

After this initial success, we continued to improvise the reaction conditions by screening the various catalysts, oxidants, and solvents (See, Appendix-IIA, Table 1-3, page no. 73-74). Among these, the reaction of **1a** and **2a** in the presence of Pd(OAc)<sub>2</sub>, AgOAc in DCE at a 100 °C temperature proved to be the most optimized reaction condition to furnish the desired product **3aa** in the highest yield. (See, Table 2.1, Entry 1 and Appendix IIA, Table 1-3, page no. 73-74). Further we also observed that the reaction did work in the absence of the palladium catalyst while maintaining the other optimized reaction conditions (Table 2.1, Entry 2). When the reaction was performed in the absence of AgOAc, the desired C3-alkenylation product **3aa** furnished the in poor yield (10 % Table 2.1, Entry 3). These results clearly indicated that Pd(OAc)<sub>2</sub> and AgOAc oxidant are essential for the desired transformation.



Later the reaction was conducted at relatively lower temperature (90 °C) as well as at higher temperature (110 °C). We observed that reactions led to the formation of the desired C3 alkenylated product **3aa** in reduced yields (Table 2.1, Entries 4, 5). Further, we carried out the reaction in an air atmosphere and we observed the decrease in the yield of desired alkenylated product **3aa** (45%, Table 2.1, Entry 6).

**Table 2.1.** Optimization of Reaction Conditions<sup>(a)</sup>

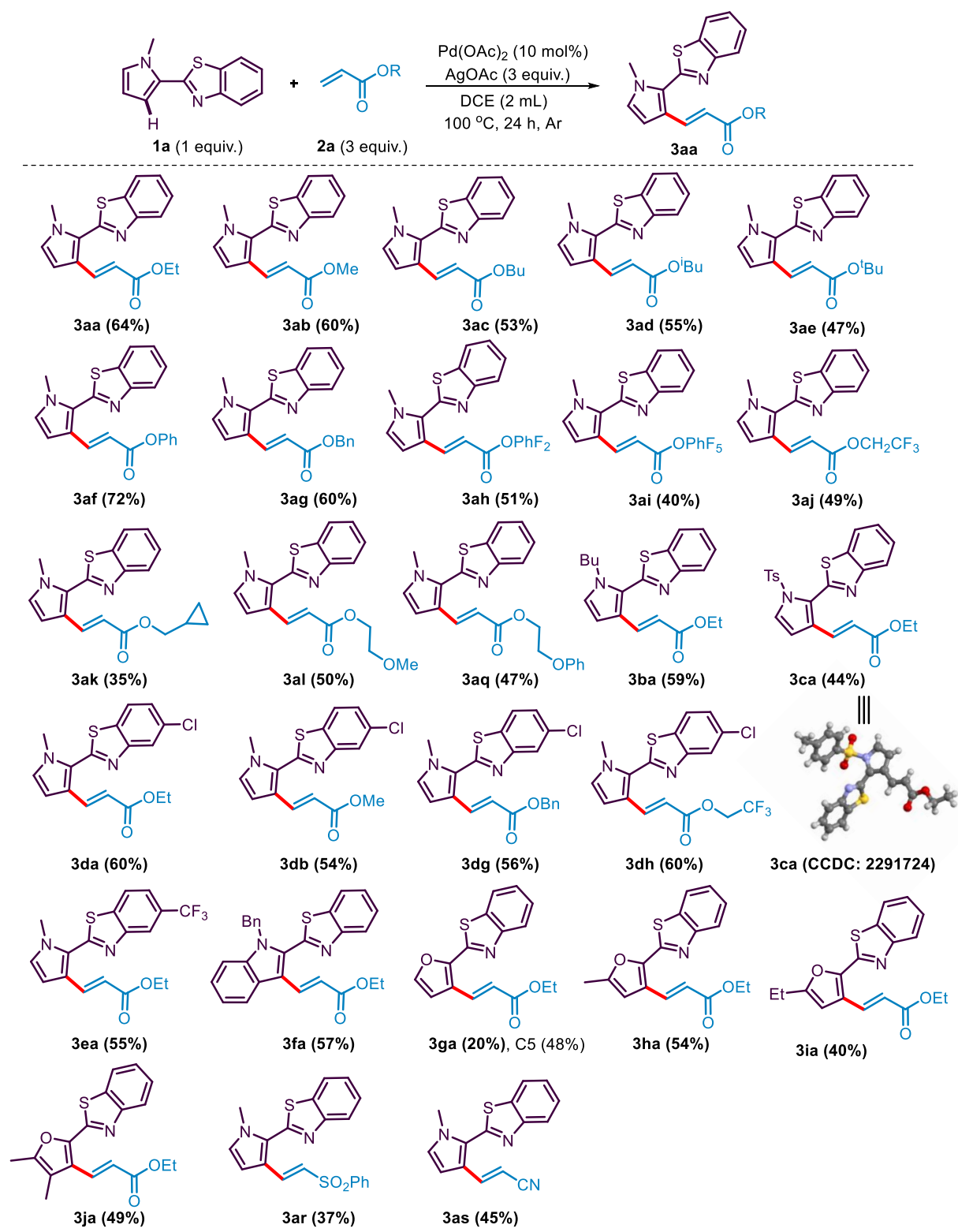
| Entry | Deviation from standard conditions   | Yield(%) <sup>b</sup> |             |
|-------|--------------------------------------|-----------------------|-------------|
|       |                                      | <b>3aa</b>            | <b>3aa'</b> |
| 1     | None                                 | 64                    | 10          |
| 2     | Without Pd(OAc) <sub>2</sub>         | N.R.                  | -           |
| 3     | Without AgOAc                        | 10                    | -           |
| 4     | Temperature 90 °C instead of 100 °C  | 56                    | 8           |
| 5     | Temperature 110 °C instead of 100 °C | 54                    | 7           |
| 6     | Air instead of Argon atmosphere      | 45                    | 5           |

<sup>[a]</sup>Standard conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (0.3 mmol), DCE (2 mL), 100 °C, Ar, 24 h; <sup>[b]</sup>Isolated yields of **1a** after column chromatography; N.R.- No Reaction.

With optimized reaction conditions in hand, we further explored the substrate scope of 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole **1a** with a broad range of acrylates **2** (Table 2.2). The reaction of **1a** with a range of acrylates (**2a-2l**, **2q**) having aliphatic, cyclic, linear chain and aromatic groups proceeded smoothly to afford the corresponding C3-alkenylated derivatives (**3aa-3al**, **3aq**) in modest to good yields respectively (up to 72%, Table 2.2). Additionally, the electron-donating and electron-withdrawing groups containing *N*-protected pyrroles (**1b**, **1c**) also reacted easily with ethyl acrylate (**2a**) to furnish the corresponding desired alkenylated products (**3ba**, **3ca**) in modest yields (Table 2.2). The reaction of chloro- and trifluoromethyl-substituted benzothiazoles (**1d-1e**) with various acrylates (**2b**, **2g**, **2h** and **2a**) has also been investigated under the optimized conditions to obtain the corresponding compounds (**3db-3ea**) in moderate yields (Table 2.2).

Further the reaction of 2-(1-benzyl-1H-indol-2-yl)benzo[d]thiazole **1f** with ethyl acrylate **2a** furnished the corresponding alkenylated product **3fa** in moderate yield (Table 2.2). The reaction of pyrrole and indole with free N-H moiety did not give the desired products under the optimized reaction conditions.

**Table 2.2.** Alkenylation of 2-hetero-arylbenzo[d]thiazoles<sup>a, b</sup>



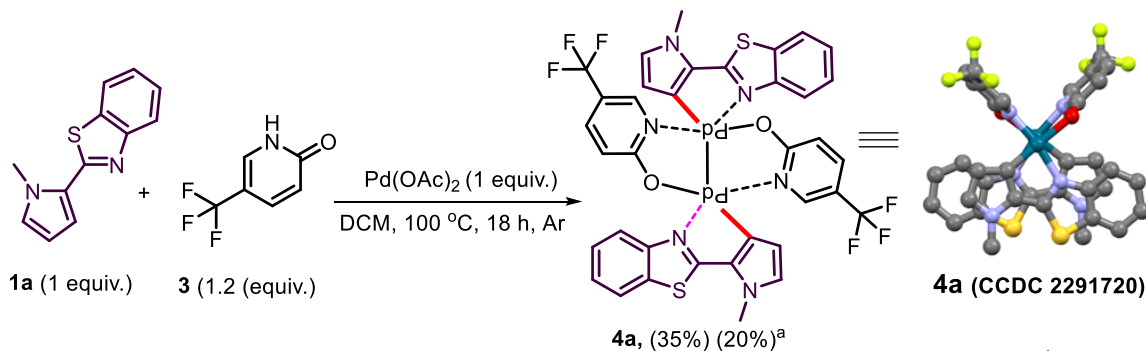
<sup>[a]</sup>Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (0.3 mmol), DCE (2 mL), 100 °C, Ar, 24 h. <sup>[b]</sup>Isolated yields based on **1a** using column chromatography.

Later, the reaction of 2-(furan-2-yl)benzo[d]thiazole **1g** with ethyl acrylate **2a** afforded the desired C3 alkenylated product **3ga** in modest yield along with C5-alkenylated product **3ga'** (Table 2.2). Further different substituted furan derivatives (**1h-1j**) also reacted well with ethyl acrylate (**2a**) to furnish the corresponding C3 alkenylated products (**3ha-3ja**) in moderate yields (Table 2.2). Fortunately, the reactions of 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole (**1a**) with other electron deficient alkenes (**2r-2s**) also worked smoothly under the optimized reaction conditions to afford the C3-alkenylated products (**3ar-3as**) in modest yields (up to 45%, Table 2.2). We also observed the formation of dialkenylated products in very small amounts (< 6%) along with desired product.

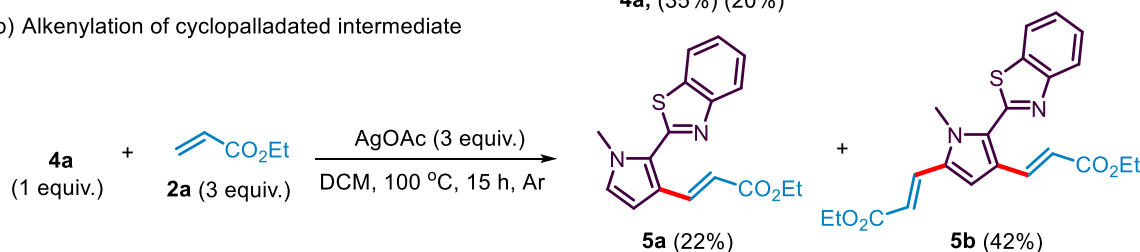
Later, we planned to utilize a suitable ligand to capture the cyclopalladated intermediate from the reaction mixture in order to have some mechanistic insight. Delightfully, after the several attempts, we isolated the cyclopalladated intermediate **4a** from the reaction of 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole **1a** and palladium acetate in the presence of stoichiometric amount of 5-(trifluoromethyl)-2-pyridone ligand **3** (Scheme 2.5a).

Later, we carried out the alkenylation reaction of this intermediate (**4a**) with ethyl acrylate **2a** under optimized reaction condition to furnish the corresponding C3 alkenylated product **5a** (22%) along with C3/C5 di-alkenylated product **5b** (42% yield) (Scheme 2.5b).

(a) Synthesis of cyclopalladated intermediate **4a** and crystallographic structure of intermediate **4a**.



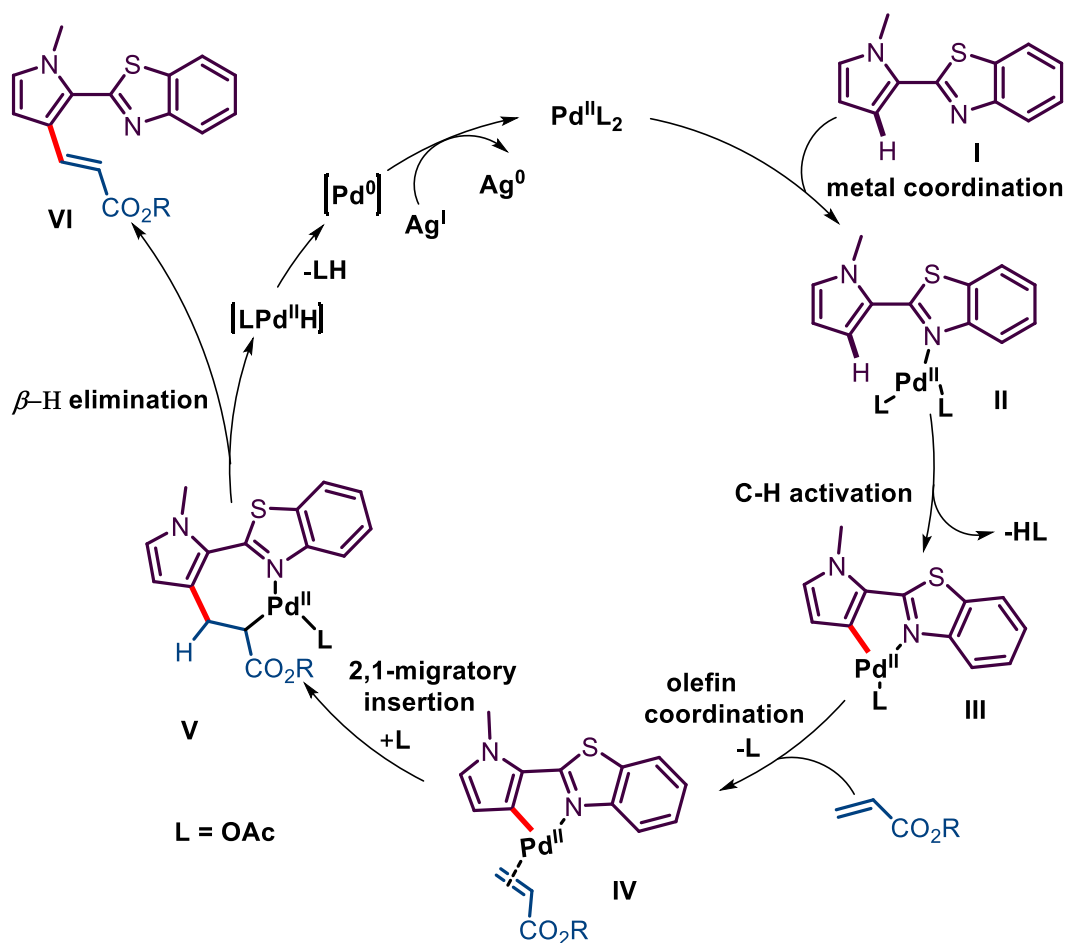
(b) Alkenylation of cyclopalladated intermediate



<sup>a</sup>Reaction carried out in DCE

**Scheme 2.5.** Mechanistic insights into the palladium catalyzed alkenylation

Based on the observed results (Scheme 2.5) and other literature reports,<sup>13</sup> a plausible catalytic cycle has been shown for this transformation (Scheme 2.6).

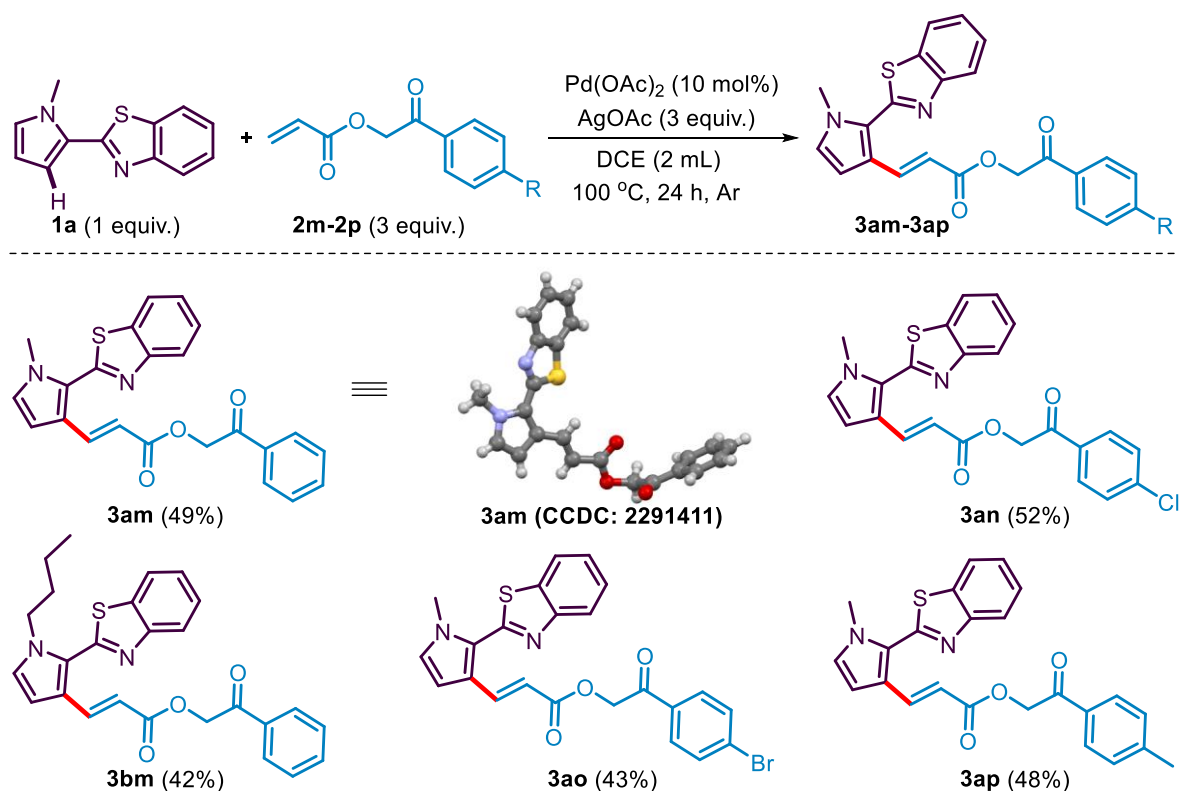


**Scheme 2.6** Plausible Mechanism

In this mechanism the compound **I** coordinate with palladium acetate to form the complex **II**, and this complex (**II**) undergoes the C-H activation via concerted metalation deprotonation (CMD) pathway to form the five membered cyclopalladated intermediate complex **III** (Scheme 2.6) Further this intermediate complex (**III**) undergoes olefin coordination and 2,1 migratory insertion of the olefins with palladium via the complex **IV** and **V**. Next the  $\beta$ -hydride elimination of the complex **V** could give the final alkenylated product **VI**. Further the removal of the  $\text{-LH}$  and reoxidation of the  $\text{Pd}(0)$  catalyst to  $\text{Pd}(\text{II})$  with silver acetate has been successfully carried out.

After showing the practicability of the protocol, as intended initially, we planned to construct few compounds having an extended electronic conjugation. In this regard, the 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole **1a** was treated with 2-oxo-2-phenylethyl acrylate **2m** to obtain 2-oxo-2-phenylethyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate **3am** in

moderate yield (Scheme 2.7). Next, the reaction of **1a** with different halo groups and methyl group substituted 2-oxo-2-phenylethyl acrylates (**2m-2p**) were carried out to obtain the corresponding C3-alkenylated products (**3am-3ap**) in moderate yields (Scheme 2.7). Additionally, the reaction of 2-(1-butyl-1H-pyrrol-2-yl)benzo[d]thiazole **1b** with 2-oxo-2-phenylethyl acrylate **2m** under the optimized reaction condition afforded the corresponding C3-alkenylated product **3bm** in moderate yield (42%, Scheme 2.7).



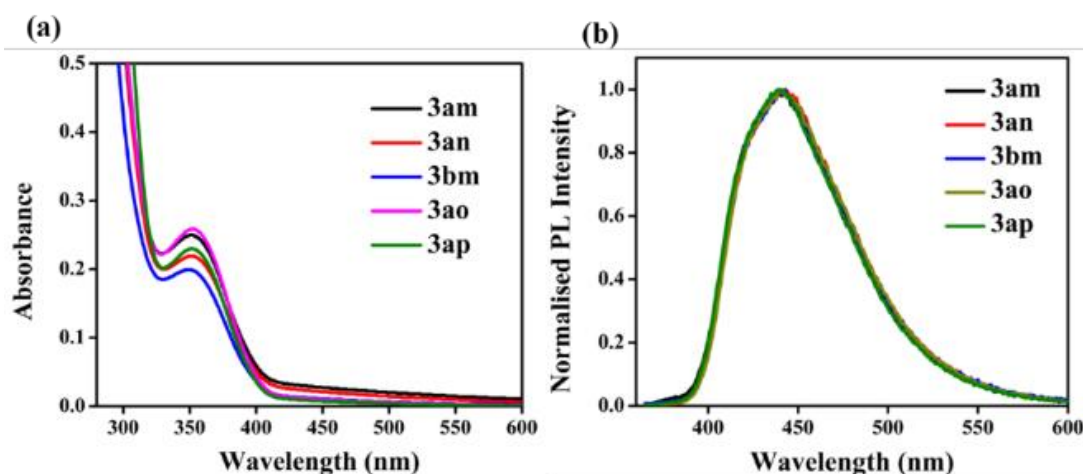
<sup>[a]</sup> **Reaction conditions:** **1a** (0.1 mmol), **2a** (0.3 mmol),  $\text{Pd}(\text{OAc})_2$  (10 mol%),  $\text{AgOAc}$  (0.3 mmol), DCE (2 mL), 100 °C, Ar, 24 h. <sup>[b]</sup> Isolated yields based on **1a** using column chromatography.

**Scheme 2.7** Alkenylation of 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole with 2-oxo-2-phenylethyl acrylate<sup>a, b</sup>

Recently, multifunctional organic luminescent materials with delayed fluorescence and phosphorescence properties have revolutionised the field of optoelectronics. For the applications in lighting, displays, sensing, imaging, and energy conversion devices, these materials offer a flexible platform.<sup>14</sup> In particular, TADF makes it possible for non-emissive triplet excitons to be effectively converted into emissive singlet excitons that achieve the internal quantum efficiency (IQE) (100%) quantitatively without the requirement of any heavy atoms.<sup>15-17</sup> This finding has significantly changed organic electronics by resolving the long-standing issue of underutilizing triplet excitons potential.

In the past few years the TADF-OLED performance has improved significantly by the careful designing of molecules. In particular the blue and sky-blue TADF emitters are inexpensive, extremely effective, and suitable for steady display lighting devices.<sup>18-19</sup> The blue or sky-blue light emitting molecules are very important because they have potential ability for both lighting and display applications.

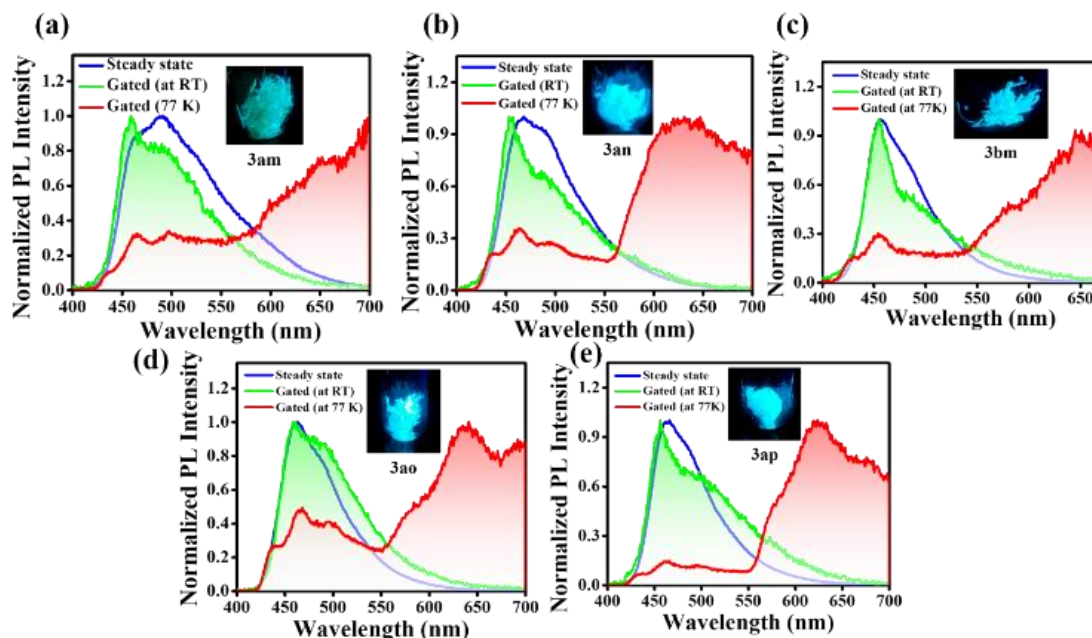
It is also crucial that due to their poor efficiency and insufficient stability, neither fluorescent nor the phosphorescent emitters are appropriate for the blue OLEDs applications. On the other hand, TADF emitters hold enormous promise for producing low-cost, very efficient, and stable blue OLEDs because of their inherent ability for both high efficiency and stability. Due to its significance, we investigated the proposed and synthesized compounds (**3am-3ap**) photophysical properties and found that they do show the luminogenic properties. Further we found that all of these luminogens (**3am-3ap**) exhibit a significant band in their absorption spectrum at around 355 nm in diluted THF solution (Figure 2.1a). We hypothesize that this absorption band might be ascribed to the S0-S1 transition during photoexcitation by TD-DFT computation at the B3LYP/6-31 G (d, p) level (See Appendix IIA, Figure 4, page no. 77).



**Fig.2.1:** (a) Absorption and (b) Emission spectra of all the luminogens (**3am-3ap**) in dilute THF solution (10  $\mu$ m).

Their absorption spectrum remained identical because the energy of the S0-S1 transition is nearly constant for all luminogens (**3am-3ap**). Furthermore, the emission spectra of all these compounds (**3am-3ap**) in THF are also similar with a maximum at around 440 nm (Figure 2.1b). Additionally, the crystals of all of these compounds (**3am-3ap**) emitted a cyan-to-cyan-green emission when exposed to UV light (Figure 2.2). Further, we collected the time-gated emission spectra with a 50  $\mu$ s time delay to look for any delayed emission processes (Figure

2.2). The gated emission spectra of all of these luminogens (**3am-3ap**) were well-matched and in accordance with their steady-state emission spectra (Figure 2.2). This result clearly suggested the presence of thermally activated delayed fluorescence (TADF).



**Fig 2.2** Steady-state and time-gated (at RT & at 77K) emission spectra of all five molecules. All the time-gated emission spectra were collected using 50  $\mu$ s of detector delay and 20 ms of the sample window.

Additionally, the time-resolved photo luminescence (TRPL) experiments have shown that the luminogens (**3am-3ap**) display prompt fluorescence in nanosecond time-scale (See Appendix-IIA, Figure 1, page no. 75) and a very long-lived delayed fluorescence in millisecond regime (See Appendix IIA, Figure 2, page no. 75). Further the detailed information regarding the lifetime and quantum yield of the luminogens (**3am-3ap**) has been shown in Table 2.3. It is important to note that the temperature plays a crucial role for the TADF to occur along with nature of the compounds. The process can be effectively inhibited by reducing the temperature to 77 K and the resulting emission can be seen as phosphorescence. All the luminogens (**3am-3ap**) showed a major emission band in the 425-575 nm region at room temperature with a 50  $\mu$ s detector delay which overlaps with the steady-state emission.

**Table 2.3.** Averaged prompt fluorescence lifetime, delayed fluorescence lifetime, and PL quantum yield of crystals (**3am** to **3ap**).

| <i>Compound</i> | <i>Prompt fluorescence lifetime (in ns)</i> | <i>Delayed fluorescence lifetime (in ms)</i> | <i>Quantum yield (<math>\phi</math>)</i> |
|-----------------|---------------------------------------------|----------------------------------------------|------------------------------------------|
| <b>3am</b>      | 0.4                                         | 20                                           | 0.16                                     |
| <b>3an</b>      | 0.9                                         | 15                                           | 0.08                                     |
| <b>3bm</b>      | 0.5                                         | 41                                           | 0.08                                     |
| <b>3ao</b>      | 0.5                                         | 16                                           | 0.11                                     |
| <b>3ap</b>      | 0.7                                         | 14                                           | 0.07                                     |

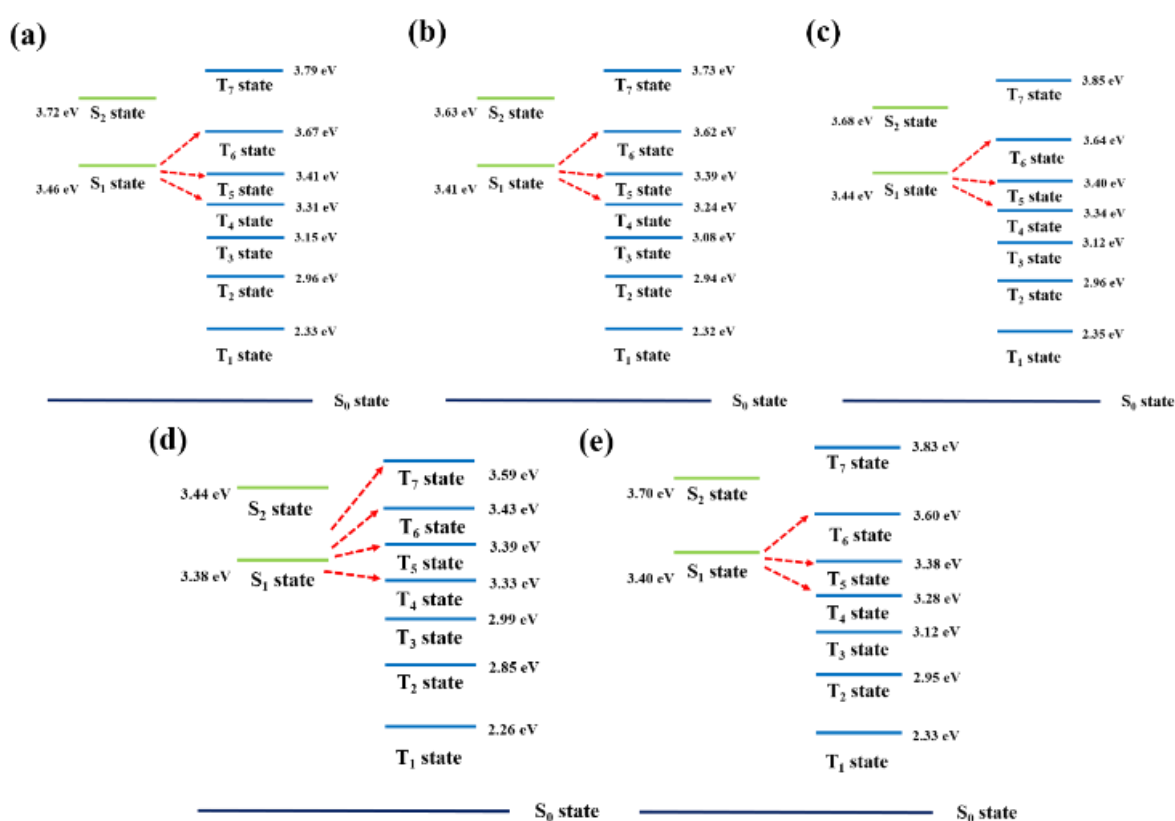
This observation has clearly supported the TADF process. Intriguingly, when the temperature was reduced to 77 K, the intensity of TADF emission of compound (**3am-3ap**) found to be reduced significantly and a low-energy phosphorescent band largely dominated ( $> 600$  nm) the emission spectrum, thus supporting the thermal up-conversion process (Figure 2.2). The similar trends have been observed in 1 wt% (**3am-3ap**) doped PMMA films (Table 2.4, and See Appendix-IIA, Figure 5, page no. 78), but the delayed fluorescence lifetime of all the molecules (**3am-3ap**) have been comparatively shorter in the film state (See Appendix-IIA, Figure 7, page no. 80).

**Table 2.4.** Averaged prompt fluorescence lifetime, delayed fluorescence lifetime, and PL quantum yield of 1 wt% emitter-doped PMMA films (**3am** to **3ap**).

| <i>Compound name</i> | <i>Prompt fluorescence lifetime (in ns)</i> | <i>Delayed fluorescence lifetime (in ms)</i> | <i>Quantum yield (<math>\phi</math>)</i> |
|----------------------|---------------------------------------------|----------------------------------------------|------------------------------------------|
| <b>3am</b>           | 0.6                                         | 0.6                                          | 0.35                                     |
| <b>3an</b>           | 0.7                                         | 0.8                                          | 0.24                                     |
| <b>3bm</b>           | 0.6                                         | 0.7                                          | 0.22                                     |
| <b>3ao</b>           | 0.3                                         | 0.7                                          | 0.21                                     |
| <b>3ap</b>           | 0.4                                         | 0.7                                          | 0.16                                     |



Further the TD-DFT calculation has been carried out on equal number of singlet and triplet state energies to have a detailed information on the excited singlet and triplet states (see Appendix-IIA, page no. 76-86 for more details). It is interesting to note that all singlet and triplet states found to have the same relative energies. This indicates that substitution on the compounds has an insignificant effect on the excited singlet and triplet state energy for the molecules (**3am-3ap**). Interestingly, after carefully looking into the excited state energies, it has been found that the  $S_1$  state of all the luminogens (**3am-3ap**) is close (within 0.3 eV energy range) to three triplet states ( $T_4$ - $T_6$ ). Such closely spaced singlet and triplet states could result in a quicker RISC process that would help the TADF process (Figure 2.3).



**Fig.2.3:** TD-DFT (50-50) calculation of molecules (a) **3an** (b) **3ao** (c) **3bn** (d) **3ap** and (e) **3aq** at the B3LYP/ 6-31G (d, p) level of theory (for **3ap**, the Br atom was treated with GenECP pseudopotential).

Delightfully, it has been shown that these new C3-alkenylated pyrrole-benzothiazole hybrid compounds have intriguing thermally activated delayed fluorescence (TADF) properties in the ~ sub-millisecond to ~ millisecond time scale with emission in the blue to cyan colour region.

## 2.5 Conclusions

In summary, we have successfully utilized the benzothiazole as a directing group for the direct and selective C3-(sp<sup>2</sup>)-H alkenylation of 2-*N*-alkylpyrrolebenzo[d] thiazole compounds with a variety of acrylates. This protocol proved to be highly regio- and chemo-selective to furnish the *E*-alkenylation products at C3 position with a broad substrate scope as well as good functional group tolerance. We have also developed a strategy for the synthesis of C3 alkenylated pyrrole-benzothiazole hybrid scaffold. The C3 alkenylated novel luminogens have been successfully obtained using the pyrrole-benzothiazole hybrid scaffold and some these molecules proved to be thermally activated delayed fluorescence materials (TADF). We have also successfully isolated and characterized cyclopalladated intermediate that also have an insight into the plausible mechanistic pathway.

### 2.6.1. General Experimental Information:

**Reagent Information:** All reactions were carried out with distilled and dried solvents using oven-dried glass wares under dry Argon atmosphere, unless otherwise stated. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin layer chromatography (TLC) was performed using silica gel 60 GF254 pre-coated aluminum backed plates (2.5 mm) with detection by UV light. Visualization was accomplished by irradiation with a UV light at 254 nm followed by KMnO<sub>4</sub> solution as staining agents. Column chromatography was performed using silica gel (100-200 mesh) eluting with petroleum ether and ethyl acetate/DCM. Petroleum ether and ethyl acetate mixture was used as gradient elution for column chromatography.

**Analytical Information:** All the isolated compounds were characterized by <sup>1</sup>H (Proton) and <sup>13</sup>C{<sup>1</sup>H} (carbon) NMR spectra and they were recorded on 400 MHz Bruker Advance III HD Ascend 400 MHz spectrophotometers. All the NMR (Nuclear Magnetic resonance) Spectra were recorded in CDCl<sub>3</sub>. The NMR spectra were recorded using tetramethylsilane (TMS) as an internal standard. <sup>1</sup>H NMR spectra were recorded at 400 MHz and <sup>13</sup>C{<sup>1</sup>H} NMR spectra were recorded at 100 MHz and 150 MHz (Bruker) unless otherwise noted. The chemical shifts (δ) are reported in ppm downfield from CDCl<sub>3</sub> (δ = 7.26 ppm) for <sup>1</sup>H NMR and in relative to the central CDCl<sub>3</sub> resonance (δ = 77.16 ppm) for <sup>13</sup>C{<sup>1</sup>H} NMR spectroscopy. <sup>1</sup>H NMR spectral data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*) and integration. Coupling constants (*J*) are reported in Hertz (Hz). <sup>13</sup>C{<sup>1</sup>H} NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by High Resolution Mass Spectrometer (HRMS) using ESI TOF. Melting points were measured (Büchi B-540 apparatus) in an open glass capillary and values are uncorrected. The single crystal X-ray diffraction (SCXRD) measurements were carried out by using the Bruker KAPPA APEX III CCD diffractometer with Cu/K radiation source (1.54184 Å). Steady-state solution-based absorption spectra are recorded on Shimadzu, UV-2600 UV spectrophotometer. Steady-state emission spectra and time-gated emission spectra of all the samples in solution and solid state are carried out using Fluoromax-4C spectrofluorimeter and Fluorolog-3 phosphorimeter (HORIBA), respectively. Time-resolved PL decay profiles have been recorded either using a diode-laser source (for a total time window <50 μs) or a microsecond flash lamp source (of 1.5-2.5 μs bandwidth and in cases where the total time window > 50 μs) in Edinburgh FLS980

instruments. The absolute quantum yield of all the compounds were measured with an integrating sphere coupled with the Fluoromax-4 spectrofluorimeter (Horiba Jobin Yvon).

### 2.6.2 General Experimental procedures

All the starting compounds (**1a-1j**) have been synthesized using the literature procedure<sup>20,21</sup> and all the 2-oxo-2-phenylethyl acrylate and substituted 2-oxo-2-phenylethyl acrylate (**2m-2p**) have been synthesized using the literature procedures.

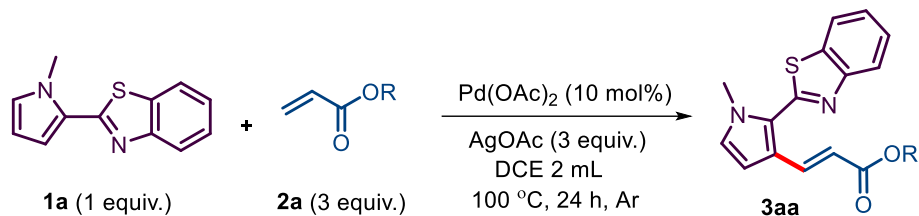
### 2.6.3 General Procedures A for synthesis of of hetroarylbenzo[d] thiazole.(**1a-1j**):<sup>20,21</sup>

An oven-dried round-bottom flask (50 mL) charged with 2-aminothiophenol (83.33  $\mu$ L, 0.8 mmol, 1 equiv.), heterocyclic aldehyde (0.96 mmol, 1.2 equiv.), sodium metabisulfite (182.22 mg, 0.96 mmol, 1.2 equiv.) and DMF (15 mL). Then the reaction mixture was heated under reflux for 2 h. After the completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool down to room temperature and was diluted with EtOAc (30 mL). It was washed with brine (10 mL x 3) and the organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and was filtered. The filtrate was further concentrated under vacuo. The resultant residue was purified by column chromatography over silica gel (EtOAc/Petroleum ether) to obtain the desired product.

### 2.6.4 General Procedures B for synthesis of 2-oxo-2-phenylethyl acrylate and substituted 2-oxo-2-phenylethyl acrylate (**2m-2p**):

An oven-dried round-bottom flask (50 mL) charged with acrylic acid (952.4  $\mu$ L, 13.88 mmol, 1 equiv.), phenacyl bromide (12.49 mmol, 0.9 equiv.), potassium carbonate (2.30 g, 27.75 mmol, 1.2 equiv.) in ACN solvent (25 mL). The reaction mixture was heated to 80 °C and stirred this reaction mixture over night. The reaction mixture was cooled to room temperature, diluted with brine, and extracted with EtOAc (15 mL x 2). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and was filtered and concentrated under vacuo. The resultant residue was purified by column chromatography over silica gel (EtOAc/petroleum ether) to obtain the desired product.

### 2.6.5. General Procedures for Pd(II)-catalyzed C3-(sp<sup>2</sup>)-H Alkenylation of 2-*N*-alkylpyrrolebenzo[d] thiazole.



### 2.6.6. General Procedure C:

A 15 mL dry pressure tube equipped with a stir bar was charged with 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole **1a** (21.43 mg, 0.1 mmol, 1.0 equiv.), ethyl acrylate **2a** (30.04 mg, 0.3 mmol, 3 equiv.), Pd(OAc)<sub>2</sub> (2.25 mg, 0.01 mmol, 0.1 equiv.), AgOAc (50.07 mg, 0.3 mmol, 3 equiv.), and followed by the addition of the solvent DCE (2 mL) at room temperature. Then the resulting reaction mixture was degassed under Argon atmosphere for 2 min and stirred vigorously at room temperature for 10 min. Then the reaction mixture heated to 100 °C for 24 h. After which, the reaction mixture was cooled to room temperature, followed by the dilution with EtOAc (15 mL) and subsequently it was filtered through pad of celite. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel to furnish the desired product **3aa** in 64% yield (20 mg) as a yellow solid.

### 2.6.7. Synthesis of cyclopalladated intermediate

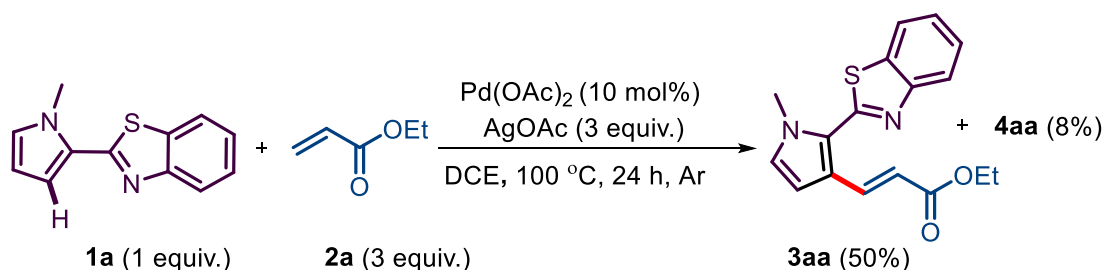
#### General Procedure D for synthesis of cyclopalladated intermediate (**4a**):

A 15 mL dry pressure tube equipped with a stir bar was charged with 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole **1a** (45 mg, 0.21 mmol, 1.0 equiv.), 5-(trifluoromethyl)pyridin-2-ol **3a** (34.25 mg, 0.3 mmol, 3 equiv.), Pd(OAc)<sub>2</sub> (47.15 mg, 0.21 mmol, 1 equiv.), followed by the addition of the solvent DCM (4.5 mL) at room temperature. Then the resulting reaction mixture was degassed under Argon atmosphere for 2 min and stirred vigorously at room temperature for 10 min. Then the reaction mixture heated to 100 °C for 18 h. After which, the reaction mixture was cooled to room temperature, followed by the dilution with EtOAc (15 mL) and subsequently it was filtered through pad of celite. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel to furnish the desired product **4a** in 35% yield (71 mg) as a Brown solid.

### 2.6.8. General Procedure E for alkenylation reaction of cyclopalladated intermediate:

A 15 mL dry pressure tube equipped with a stir bar was charged with palladium complex **4a** (71 mg, 0.075 mmol, 1.0 equiv.), ethyl acrylate **2a** (23.83  $\mu$ L, 0.022 mmol, 3 equiv.), AgOAc (37.34mg, 0.022 mmol, 3 equiv.), and followed by the addition of the solvent DCM (2 mL) at room temperature. Then the resulting reaction mixture was degassed under Argon atmosphere for 2 min and stirred vigorously at room temperature for 10 min. Then the reaction mixture heated to 100 °C for 18 h. After which, the reaction mixture was cooled to room temperature, followed by the dilution with EtOAc (15 mL) and subsequently it was filtered through pad of celite. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel to furnish the desired product **5a** in 22% yield (5.2mg) as a yellow solid along with di-alkenylated product **5b** in 42% yield (13mg) as a yellow solid.

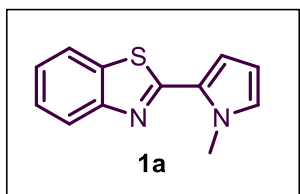
### 2.6.9. Scaleup reaction (1.5 millimole):



A 30 mL dry pressure tube equipped with a stir bar was charged with 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole **1a** (321 mg, 1.5 mmol, 1.0 equiv.), ethyl acrylate **2a** (490.11  $\mu$ L, 4.5 mmol, 3 equiv.), Pd(OAc)<sub>2</sub> (33.63 mg, 0.15 mmol, 0.1 equiv.), AgOAc (750.10 mg, 4.5 mmol, 3 equiv.), and followed by the addition of the solvent DCE (7.5 mL) at room temperature. Then the resulting reaction mixture was degassed under Argon atmosphere for 2 min and stirred vigorously at room temperature for 10 min. Then the reaction mixture heated to 100 °C for 24 h. After which, the reaction mixture was cooled to room temperature, followed by the dilution with EtOAc (25 mL) and subsequently it was filtered through pad of celite. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel to furnish the desired product **3aa** in 50% yield (235 mg) as a yellow solid.

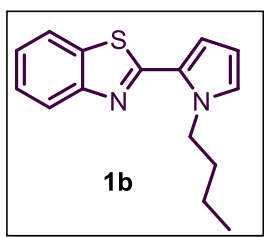
## 2.6.10. Experimental Data:

### 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole (**1a**):



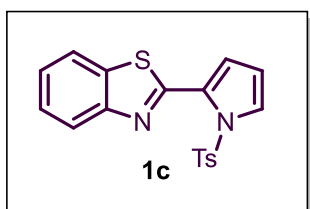
The compound **1a** was obtained by following the general procedure A and it was purified by column chromatography over silica gel to obtain the compound **1a** as yellow solid (70%, 360 mg), m.p. = 57 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 5:95, DCM/ petroleum ether 50:50).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.92 (d,  $J$  = 8.1 Hz, 1H), 7.78 (d,  $J$  = 7.9 Hz, 1H), 7.43 – 7.36 (m, 1H), 7.30 – 7.24 (m, 1H), 6.80 (dd,  $J$  = 3.9, 1.7 Hz, 1H), 6.78 – 6.76 (m, 1H), 6.18 (dd,  $J$  = 3.9, 2.6 Hz, 1H), 4.11 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  160.5, 154.4, 134.0, 128.0, 126.6, 126.0, 124.5, 122.5, 121.2, 114.9, 108.8, 37.2. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_{11}\text{N}_2\text{S}$ : 215.0643; found, 215.0643.

### 2-(1-butyl-1H-pyrrol-2-yl)benzo[d]thiazole (**1b**):



The compound **1b** was obtained by following the general procedure A and it was purified by column chromatography over silica gel to obtain the compound **1b** as brown oil (61 %, 127 mg),  $R_f$  = 0.49 (EtOAc/petroleum ether = 3:97).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.91 (dd,  $J$  = 8.2, 1.1 Hz, 1H), 7.80 (dd,  $J$  = 8.0, 1.2 Hz, 1H), 7.41 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.32 – 7.26 (m, 1H), 6.84 (t,  $J$  = 2.2 Hz, 1H), 6.81 (dd,  $J$  = 3.9, 1.7 Hz, 1H), 6.19 (dd,  $J$  = 3.9, 2.6 Hz, 1H), 4.62 – 4.52 (m, 2H), 1.81 (p,  $J$  = 7.5 Hz, 2H), 1.42 – 1.33 (m, 2H), 0.94 (t,  $J$  = 7.4 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  160.4, 154.5, 134.0, 127.2, 126.0, 125.9, 124.5, 122.6, 121.2, 115.2, 108.8, 49.0, 33.7, 20.0, 13.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_{17}\text{N}_2\text{S}$ : 257.1112; found, 257.1110.

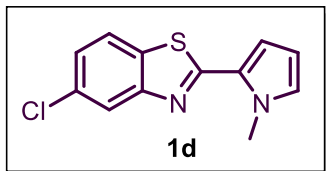
### 2-(1-tosyl-1H-pyrrol-2-yl)benzo[d]thiazole (**1c**):



The compound **1c** was obtained by following the general procedure A and it was purified by column chromatography over silica gel to obtain the compound **1c** as yellow solid (60 %, 170 mg), m.p. = 133 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 15:85).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.95 (d,  $J$  = 8.2 Hz, 1H), 7.86 (d,  $J$  = 8.4 Hz, 3H), 7.64 (dd,  $J$  = 3.3, 1.7 Hz, 1H), 7.51 – 7.45 (m, 1H), 7.41 – 7.36 (m, 1H), 7.28 (d,  $J$  = 8.1 Hz, 2H), 6.76 (dd,  $J$  = 3.5, 1.8 Hz, 1H), 6.38 (t,  $J$  = 3.4 Hz, 1H), 2.40 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  157.4, 153.4, 145.3, 136.1, 135.7, 129.5, 128.4, 127.5, 127.0, 126.3,

125.5, 123.3, 121.5, 120.2, 111.8, 21.8. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{18}H_{15}N_2O_2S_2$ : 355.0575; found, 355.0570.

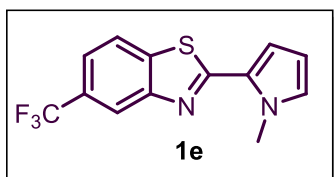
#### 5-chloro-2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole (**1d**):



The compound **1d** was obtained by following the general procedure A and it was purified by column chromatography over silica gel to obtain the compound **1d** as brown solid (77 %, 120 mg), m.p. = 80 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 6:94).  $^1H$

NMR (400 MHz, Chloroform-*d*)  $\delta$  7.90 (d,  $J$  = 2.0 Hz, 1H), 7.69 (d,  $J$  = 8.4 Hz, 1H), 7.26 (dd,  $J$  = 8.2, 1.8 Hz, 1H), 6.83 – 6.79 (m, 2H), 6.19 (dd,  $J$  = 3.7, 2.8 Hz, 1H), 4.11 (s, 3H).  $^{13}C\{^1H\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  162.3, 155.4, 132.3, 132.0, 128.6, 126.3, 124.9, 122.3, 121.8, 115.5, 109.1, 37.4. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{12}H_{10}ClN_2S$ : 249.0253; found, 249.0250.

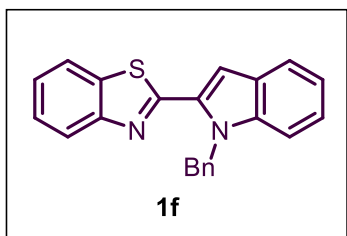
#### 2-(1-methyl-1H-pyrrol-2-yl)-5-(trifluoromethyl)benzo[d]thiazole (**1e**):



The compound **1e** was obtained by following the general procedure A and it was purified by column chromatography over silica gel to obtain the compound **1e** as yellow solid (65 %, 95 mg), m.p. = 78 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 4:96).  $^1H$

NMR (400 MHz, Chloroform-*d*)  $\delta$  8.17 (s, 1H), 7.88 (d,  $J$  = 8.3 Hz, 1H), 7.52 (d,  $J$  = 8.3 Hz, 1H), 6.88 – 6.80 (m, 2H), 6.21 (dd,  $J$  = 3.9, 2.6 Hz, 1H), 4.13 (s, 3H).  $^{13}C\{^1H\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  162.4, 154.2, 137.5, 128.9, 126.1, 125.8, 123.1, 121.7, 120.9 (q,  $J$  = 3.6 Hz), 119.5 (q,  $J$  = 4.1 Hz), 115.9, 109.2, 37.4.  $^{19}F$  NMR (377 MHz, Chloroform-*d*)  $\delta$  -61.7. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{13}H_{10}F_3N_2S$ : 283.0517; found, 283.0516.

#### 2-(1-benzyl-1H-indol-2-yl)benzo[d]thiazole (**1f**):



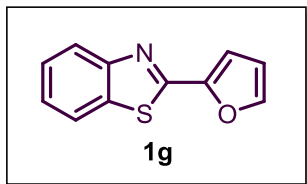
The compound **1f** was obtained by following the general procedure A and it was purified by column chromatography over silica gel to obtain the compound **1f** as white solid (90 %, 95 mg), m.p. = 154 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 3:97).  $^1H$

NMR (400 MHz, Chloroform-*d*)  $\delta$  7.96 (d,  $J$  = 7.7 Hz, 1H), 7.84 (d,  $J$  = 7.9 Hz, 1H), 7.68 (d,  $J$  = 7.9 Hz, 1H), 7.43 (ddd,  $J$  = 8.3, 7.3, 1.3 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.27 – 7.12 (m, 8H), 6.18 (s, 2H).  $^{13}C\{^1H\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  160.4, 154.3, 139.6, 138.5, 134.5, 132.0, 128.6, 127.6, 127.2, 126.8, 126.3, 125.4, 124.5,



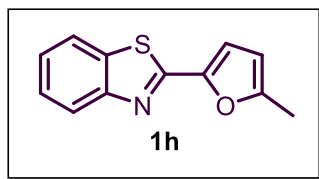
123.4, 121.7, 121.3, 120.9, 111.0, 108.1, 48.4. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{22}H_{17}N_2S$ : 341.1112; found, 341.1115.

### 2-(furan-2-yl)benzo[d]thiazole (**1g**):



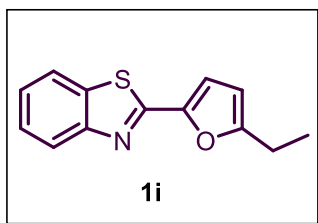
The compound **1g** was obtained by following the general procedure A and it was purified by column chromatography over silica gel to obtain the compound **1g** as white solid (68 %, 110 mg), m.p. = 104 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 7:93).  $^1H$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.05 (d,  $J$  = 8.2 Hz, 1H), 7.88 (d,  $J$  = 7.8 Hz, 1H), 7.60 (d,  $J$  = 2.0 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.37 (ddd,  $J$  = 8.2, 7.2, 1.2 Hz, 1H), 7.19 (d,  $J$  = 3.6 Hz, 1H), 6.59 (dd,  $J$  = 3.5, 1.8 Hz, 1H).  $^{13}C\{^1H\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  157.7, 153.9, 148.9, 144.8, 134.4, 126.6, 125.3, 123.2, 121.7, 112.7, 111.6. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{11}H_8NOS$ : 202.0327; found, 202.0319.

### 2-(5-methylfuran-2-yl)benzo[d]thiazole (**1h**):



The compound **1h** was obtained by following the general procedure A and it was purified by column chromatography over silica gel to obtain the compound **1h** as brown solid (70 %, 120 mg), m.p. = 102 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 6:94).  $^1H$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.02 (d,  $J$  = 8.2 Hz, 1H), 7.83 (d,  $J$  = 8.0 Hz, 1H), 7.44 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 7.32 (ddd,  $J$  = 8.2, 7.2, 1.2 Hz, 1H), 7.05 (d,  $J$  = 3.4 Hz, 1H), 6.16 (d,  $J$  = 3.4 Hz, 1H), 2.41 (s, 3H).  $^{13}C\{^1H\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  157.8, 155.6, 153.9, 147.1, 134.1, 126.4, 124.9, 122.9, 121.5, 113.1, 109.0, 14.0. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{12}H_{10}NOS$ : 216.0483; found, 216.0488.

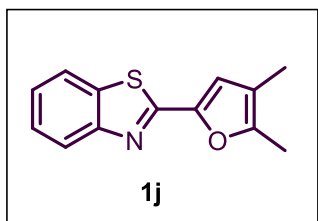
### 2-(5-ethylfuran-2-yl)benzo[d]thiazole (**1i**):



The compound **1i** was obtained by following the general procedure A and it was purified by column chromatography over silica gel to obtain the compound **1i** as brown solid (61 %, 112 mg), m.p. = 84 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 5:95).  $^1H$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.03 (d,  $J$  = 8.2 Hz, 1H), 7.85 (d,  $J$  = 8.0 Hz, 1H), 7.46 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.34 (ddd,  $J$  = 8.2, 7.2, 1.2 Hz, 1H), 7.09 (d,  $J$  = 3.4 Hz, 1H), 6.19 (d,  $J$  = 3.4 Hz, 1H), 2.78 (q,  $J$  = 7.5 Hz, 2H), 1.31 (t,  $J$  = 7.6 Hz, 3H).  $^{13}C\{^1H\}$  NMR (101 MHz, Chloroform-*d*)  $\delta$  161.3, 158.0, 154.0, 147.1, 134.2, 126.5, 125.0, 123.0, 121.6,

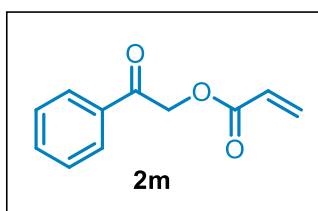
112.0, 107.4, 21.8, 12.1. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{13}H_{12}NOS$ : 230.0640; found, 230.0642.

### 2-(4,5-dimethylfuran-2-yl)benzo[d]thiazole (**1j**):



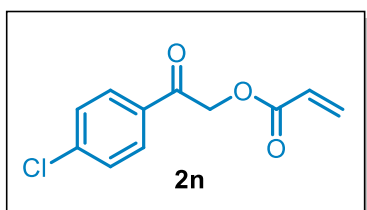
The compound **1j** was obtained by following the general procedure A and it was purified by column chromatography over silica gel to obtain the compound **1j** as brown solid (63 %, 115mg), m.p. = 128 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 5:95).  $^1H$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.01 (d,  $J$  = 8.2 Hz, 1H), 7.84 (d,  $J$  = 7.9 Hz, 1H), 7.45 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.33 (ddd,  $J$  = 8.2, 7.2, 1.2 Hz, 1H), 6.96 (s, 1H), 2.34 (s, 3H), 2.02 (s, 3H).  $^{13}C$   $\{^1H\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  158.0, 154.0, 151.4, 145.8, 134.2, 126.4, 124.9, 122.9, 121.5, 117.7, 115.5, 11.9, 10.0. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{13}H_{12}NOS$ : 230.0640; found, 230.0648.

### 2-oxo-2-phenylethyl acrylate (**2m**):



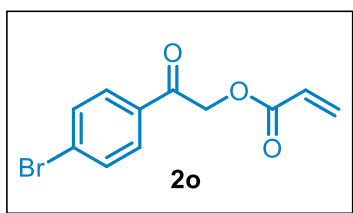
The compound **2m** was obtained by following the general procedure B and it was purified by column chromatography over silica gel to obtain the compound **2m** as colourless liquid (76 %, 2 g),  $R_f$  = 0.49 (EtOAc/petroleum ether = 5:95).  $^1H$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.95 – 7.91 (m, 2H), 7.64 – 7.59 (m, 1H), 7.52 – 7.47 (m, 2H), 6.54 (dd,  $J$  = 17.4, 1.3 Hz, 1H), 6.29 (dd,  $J$  = 17.4, 10.4 Hz, 1H), 5.95 (dd,  $J$  = 10.4, 1.4 Hz, 1H), 5.43 (s, 2H).  $^{13}C$   $\{^1H\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  192.1, 165.6, 134.3, 134.0, 132.2, 129.0, 127.9, 127.6, 66.2. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{11}H_{11}O_3$ : 191.0708; found, 191.0715.

### 2-(4-chlorophenyl)-2-oxoethyl acrylate (**2n**):



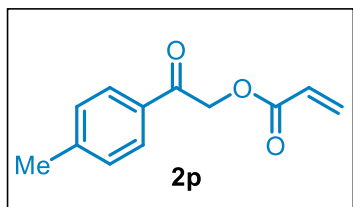
The compound **2n** was obtained by following the general procedure B and it was purified by column chromatography over silica gel to obtain the compound **2n** as white solid (78 %, 2.44 g), m.p. = 69 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 5:95).  $^1H$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.89 – 7.85 (m, 2H), 7.48 – 7.44 (m, 2H), 6.53 (dd,  $J$  = 17.3, 1.3 Hz, 1H), 6.27 (dd,  $J$  = 17.3, 10.4 Hz, 1H), 5.95 (dd,  $J$  = 10.4, 1.3 Hz, 1H), 5.38 (s, 2H).  $^{13}C$   $\{^1H\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  191.3, 165.5, 133.0, 132.4, 132.3, 129.4, 129.3, 127.5, 66.0. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{11}H_{10}ClO_3$ : 225.0318; found, 225.0310.

### 2-(4-bromophenyl)-2-oxoethyl acrylate (**2o**):



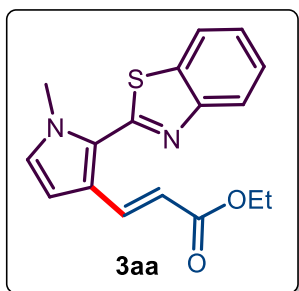
The compound **2o** was obtained by following the general procedure B and it was purified by column chromatography over silica gel to obtain the compound **2o** as yellow solid (74 %, 2.76 g), m.p. = 66 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 5:95).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.81 – 7.77 (m, 2H), 7.65 – 7.61 (m, 2H), 6.53 (dd,  $J$  = 17.3, 1.3 Hz, 1H), 6.27 (dd,  $J$  = 17.3, 10.4 Hz, 1H), 5.95 (dd,  $J$  = 10.5, 1.3 Hz, 1H), 5.37 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  191.1, 165.5, 140.5, 132.6, 132.4, 129.3, 129.3, 127.5, 66.0. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{11}\text{H}_{10}\text{BrO}_3$ : 268.9813; found, 268.9818.

### 2-oxo-2-(p-tolyl)ethyl acrylate (**2p**):



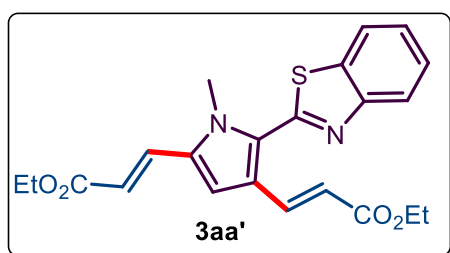
The compound **2p** was obtained by following the general procedure B and it was purified by column chromatography over silica gel to obtain the compound **2p** as white solid (70 %, 2 g), m.p. = 61 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 5:95).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.86 – 7.80 (m, 2H), 7.31 – 7.25 (m, 2H), 6.54 (dd,  $J$  = 17.4, 1.4 Hz, 1H), 6.29 (dd,  $J$  = 17.4, 10.4 Hz, 1H), 5.94 (dd,  $J$  = 10.4, 1.4 Hz, 1H), 5.41 (s, 2H), 2.42 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  191.7, 165.7, 145.0, 132.2, 131.9, 129.7, 128.0, 127.7, 66.1, 21.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_{13}\text{O}_3$ : 205.0865; found, 205.0862.

### Ethyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (**3aa**) :



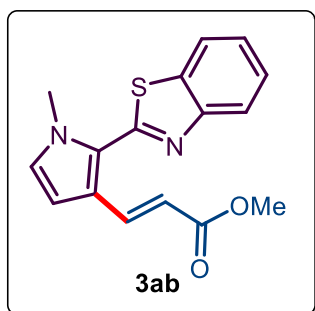
The compound **3aa** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3aa** as yellow solid (64%, 20mg), m.p. = 109 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 8:92).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.13 (d,  $J$  = 15.5 Hz, 1H), 8.08 (d,  $J$  = 8.1 Hz, 1H), 7.93 (d,  $J$  = 8.0 Hz, 1H), 7.52 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.42 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 6.79 (d,  $J$  = 2.9 Hz, 1H), 6.52 (d,  $J$  = 2.9 Hz, 1H), 6.28 (d,  $J$  = 15.5 Hz, 1H), 4.24 (q,  $J$  = 7.1 Hz, 2H), 3.96 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  167.8, 157.1, 153.7, 137.6, 135.5, 127.6, 127.5, 126.5, 125.4, 123.5, 123.4, 121.5, 116.7, 106.9, 60.3, 36.9, 14.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_2\text{S}$ : 313.1011; found, 313.1007.

**Diethyl 3,3'-(5-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrole-2,4-diyl)(2*E*,2'*E*)-diacrylate (3aa')**



**(3aa')**: The compound **3aa'** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3aa'** as yellow solid (10%, 4mg), m.p. = 117 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 18:82). <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  8.13 (ddd,  $J$  = 8.2, 1.2, 0.6 Hz, 1H), 7.99 (d,  $J$  = 15.6 Hz, 1H), 7.95 (ddd,  $J$  = 7.9, 1.3, 0.6 Hz, 1H), 7.65 (d,  $J$  = 15.7 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.48 – 7.44 (m, 1H), 6.97 (s, 1H), 6.38 (d,  $J$  = 15.7 Hz, 1H), 6.30 (d,  $J$  = 15.6 Hz, 1H), 4.31 – 4.21 (m, 4H), 3.98 (s, 3H), 1.36 – 1.31 (m, 6H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, Chloroform-*d*)  $\delta$  167.4, 167.1, 156.3, 153.6, 136.5, 135.8, 133.7, 131.2, 130.7, 126.8, 125.8, 123.7, 123.6, 121.6, 118.3, 117.9, 108.6, 60.8, 60.5, 33.3, 14.5, 14.5. HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>S: 410.1300; found, 410.1305.

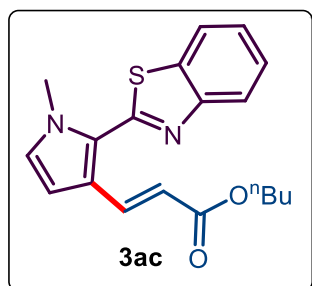
**Methyl (E)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (3ab):**



The compound **3ab** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ab** as yellow solid (60%, 18mg), m.p. = 117 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 14:86). <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  8.13 (d,  $J$  = 15.6 Hz, 2H), 8.09 (ddd,  $J$  = 8.2, 1.2, 0.6 Hz, 2H), 7.93 (ddd,  $J$  = 7.9, 1.3, 0.6 Hz, 1H),

7.52 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.42 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 6.80 (d,  $J$  = 2.9 Hz, 1H), 6.52 (d,  $J$  = 2.9 Hz, 1H), 6.28 (d,  $J$  = 15.6 Hz, 1H), 3.96 (s, 3H), 3.78 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, Chloroform-*d*)  $\delta$  168.2, 157.1, 153.7, 137.8, 137.8, 135.5, 127.6, 125.4, 123.4, 121.5, 116.2, 116.2, 107.0, 51.6, 36.9. HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub>S: 299.0854; found, 299.0845.

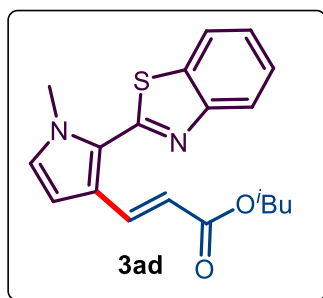
**Butyl (E)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (3ac):**



The compound **3ac** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ac** as yellow oil (53%, 18mg).  $R_f$  = 0.49 (EtOAc/petroleum ether = 9:91). <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)  $\delta$  8.14 (d,  $J$  = 15.6 Hz, 1H), 8.08 (d,  $J$  = 8.1 Hz, 1H), 7.92 (d,  $J$  = 8.0 Hz, 1H), 7.52 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.41 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 6.79 (d,  $J$  = 2.9 Hz, 1H), 6.52 (d,  $J$  = 2.9 Hz, 1H), 6.28 (d,  $J$  =

15.6 Hz, 1H), 4.19 (t,  $J = 6.6$  Hz, 2H), 3.96 (s, 3H), 1.71 – 1.63 (m, 2H), 1.51 – 1.39 (m, 2H), 0.96 (t,  $J = 7.4$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  167.9, 157.1, 153.6, 137.5, 135.5, 127.6, 127.5, 126.5, 125.4, 123.6, 123.4, 121.5, 116.7, 106.9, 64.2, 37.0, 31.0, 19.4, 13.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_2\text{S}$ : 341.1323; found, 341.1315.

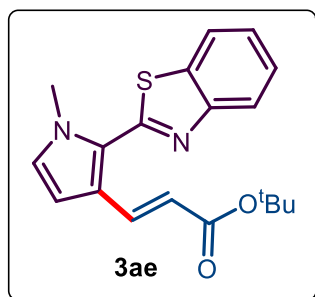
**Isobutyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (**3ad**):**



The compound **3ad** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ad** as yellow oil (55%, 19mg).  $R_f = 0.49$  (EtOAc/petroleum ether = 9:91).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.16 (d,  $J = 15.6$  Hz, 1H), 8.08 (d,  $J = 7.9$  Hz, 1H), 7.93 (d,  $J = 8.0$  Hz, 1H), 7.52 (ddd,  $J = 8.3, 7.2, 1.3$  Hz, 1H), 7.42

(ddd,  $J = 8.2, 7.2, 1.2$  Hz, 1H), 6.80 (d,  $J = 2.9$  Hz, 1H), 6.53 (d,  $J = 2.9$  Hz, 1H), 6.29 (d,  $J = 15.6$  Hz, 1H), 3.97 (d,  $J = 6.2$  Hz, 2H), 3.97 (s, 3H), 2.07 – 1.94 (m, 1H), 0.98 (d,  $J = 6.7$  Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  167.9, 157.1, 153.6, 137.6, 135.4, 127.6, 127.5, 126.6, 125.4, 123.6, 123.4, 121.5, 116.7, 106.9, 70.5, 37.0, 28.0, 19.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_2\text{S}$ : 341.1323; found, 341.1332.

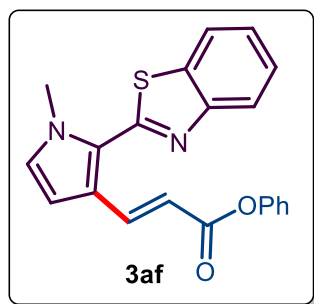
**Tert-butyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (**3ae**):**



The compound **3ae** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ae** as yellow oil (47%, 16mg).  $R_f = 0.49$  (EtOAc/petroleum ether = 10:90).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.11 – 8.05 (m, 2H), 7.91 (d,  $J = 7.9$  Hz, 1H), 7.51 (ddd,  $J = 8.3, 7.2, 1.3$  Hz, 1H), 7.41 (ddd,  $J = 8.3, 7.2, 1.2$  Hz, 1H),

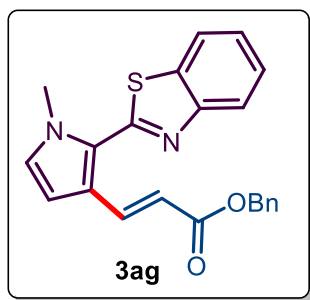
6.78 (d,  $J = 2.9$  Hz, 1H), 6.51 (d,  $J = 2.9$  Hz, 1H), 6.22 (d,  $J = 15.5$  Hz, 1H), 3.96 (s, 3H), 1.52 (s, 9H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  167.2, 157.3, 153.6, 136.6, 135.4, 127.6, 127.4, 126.5, 125.3, 123.7, 123.3, 121.5, 118.5, 106.8, 80.2, 37.0, 28.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_2\text{S}$ : 341.1323; found, 341.1312.

**Phenyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (**3af**) :**



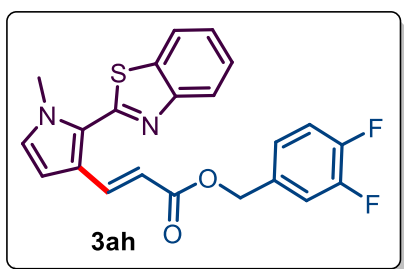
The compound **3af** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3af** as yellow solid (72%, 26mg), m.p. = 157 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 18:82).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.32 (d,  $J$  = 15.5 Hz, 1H), 8.09 (ddd,  $J$  = 8.2, 1.2, 0.6 Hz, 1H), 7.91 (ddd,  $J$  = 8.0, 1.3, 0.6 Hz, 1H), 7.51 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.43 – 7.36 (m, 3H), 7.24 – 7.19 (m, 1H), 7.19 – 7.15 (m, 2H), 6.82 (d,  $J$  = 2.9 Hz, 1H), 6.60 (d,  $J$  = 2.9 Hz, 1H), 6.46 (d,  $J$  = 15.5 Hz, 1H), 3.96 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  166.2, 156.8, 153.6, 151.2, 139.6, 135.5, 129.4, 128.0, 127.8, 126.6, 125.7, 125.5, 123.5, 123.2, 121.9, 121.5, 115.4, 107.1, 36.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{21}\text{H}_{17}\text{N}_2\text{O}_2\text{S}$ : 361.1010; found, 361.1011.

**Benzyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (**3ag**):**



The compound **3ag** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ag** as yellow solid (61%, 23mg), m.p. = 110 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 16:84).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.21 (d,  $J$  = 15.5 Hz, 1H), 8.08 (d,  $J$  = 8.2 Hz, 1H), 7.92 (d,  $J$  = 8.0 Hz, 1H), 7.52 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.44 – 7.39 (m, 3H), 7.38 – 7.31 (m, 3H), 6.79 (d,  $J$  = 2.9 Hz, 1H), 6.51 (d,  $J$  = 2.9 Hz, 1H), 6.33 (d,  $J$  = 15.5 Hz, 1H), 5.24 (s, 2H), 3.95 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  167.6, 157.0, 153.6, 138.2, 136.6, 135.5, 128.7, 128.7, 128.2, 128.2, 127.7, 127.7, 126.6, 125.4, 123.4, 121.5, 116.1, 106.7, 66.1, 36.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}_2\text{S}$ : 375.1167; found, 375.1157.

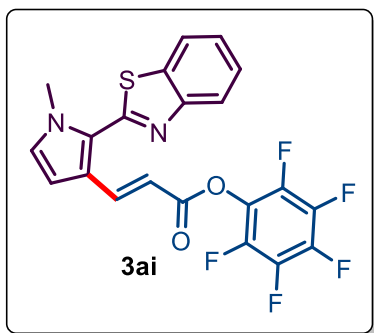
**3,4-difluorobenzyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (**3ah**) :**



The compound **3ah** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ah** as yellow solid (51%, 21mg), m.p. = 162 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 15:85).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.24 (d,  $J$  = 15.5 Hz, 1H), 8.09 (d,  $J$  = 8.2 Hz, 1H), 7.94 (d,  $J$  = 8.0 Hz, 1H), 7.52 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.42 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 6.96 – 6.91 (m, 2H), 6.81 (d,  $J$  = 2.9 Hz, 1H), 6.54 (d,  $J$  = 2.9 Hz, 1H), 6.32 (d,  $J$

= 15.5 Hz, 1H), 5.20 (s, 2H), 3.96 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  167.1, 164.4 (d,  $J$  = 12.7 Hz), 162.0 (d,  $J$  = 12.7 Hz), 156.9, 153.6, 140.6 (t,  $J$  = 9.2 Hz), 138.9, 135.4, 127.9, 127.7, 126.6, 125.5, 123.5, 123.2, 121.5, 115.4, 110.6 (d,  $J$  = 7.1 Hz), 110.4 (d,  $J$  = 7.0 Hz), 107.0, 103.4 (t,  $J$  = 25.3 Hz), 64.6, 37.0.  $^{19}\text{F}$  NMR (377 MHz, Chloroform-*d*)  $\delta$  -109.47. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{22}\text{H}_{17}\text{F}_2\text{N}_2\text{O}_2\text{S}$ : 411.0979; found, 411.0978.

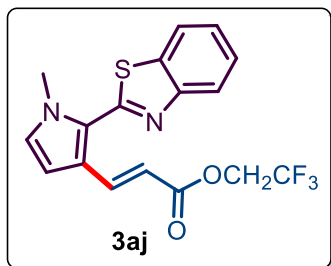
**Perfluoro phenyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (3ai):**



The compound **3aa** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3aa** as yellow semi-solid (40%, 18mg).  $R_f$  = 0.49 (EtOAc/petroleum ether = 16:84).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.37 (d,  $J$  = 15.5 Hz, 1H), 8.11 (d,  $J$  = 8.2 Hz, 1H), 7.94 (d,  $J$  = 8.0 Hz, 1H), 7.54 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.44 (ddd,  $J$  = 8.3, 7.2, 1.2

Hz, 1H), 6.85 (d,  $J$  = 2.9 Hz, 1H), 6.62 (d,  $J$  = 2.9 Hz, 1H), 6.44 (d,  $J$  = 15.5 Hz, 1H), 3.97 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  163.4, 156.5, 153.6, 142.5, 139.2, 136.7, 135.5, 128.9, 128.0, 126.8, 125.7, 125.7, 123.6, 122.8, 121.6, 121.5, 111.8, 107.3, 36.9.  $^{19}\text{F}$  NMR (377 MHz, Chloroform-*d*)  $\delta$  -152.47 (d,  $J$  = 16.3 Hz, 2F), -158.88 (t,  $J$  = 21.7 Hz, 1F), -162.88 (dd,  $J$  = 20.7, 18.3 Hz, 2F). HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{21}\text{H}_{12}\text{F}_5\text{N}_2\text{O}_2\text{S}$ : 451.0540; found, 451.0548.

**2,2,2-trifluoroethyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (3aj):**

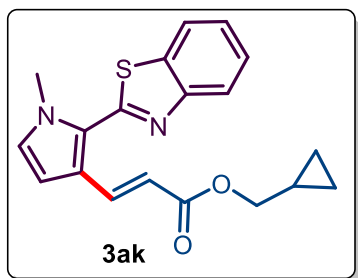


The compound **3aj** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3aj** as yellow solid (49%, 18mg), m.p. = 130 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 8:92).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.25 (d,  $J$  = 15.5 Hz, 1H),

8.10 (d,  $J$  = 8.2 Hz, 1H), 7.94 (d,  $J$  = 8.0 Hz, 1H), 7.53 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.43 (ddd,  $J$  = 8.2, 7.2, 1.2 Hz, 1H), 6.81 (d,  $J$  = 2.9 Hz, 1H), 6.55 (d,  $J$  = 2.9 Hz, 1H), 6.31 (d,  $J$  = 15.5 Hz, 1H), 4.57 (q,  $J$  = 8.5 Hz, 2H), 3.96 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  166.0, 156.7, 153.7, 140.3, 135.5, 128.3, 127.8, 126.7, 125.5, 123.5, 123.4 (q,  $J$  = 277.3 Hz), 123.0, 121.5, 113.9, 107.1, 60.3 (q,  $J$  = 36.4 Hz), 37.0.  $^{19}\text{F}$  NMR (377 MHz, Chloroform-*d*)  $\delta$  -73.70. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_2\text{O}_2\text{S}$ : 367.0728; found, 367.0718.



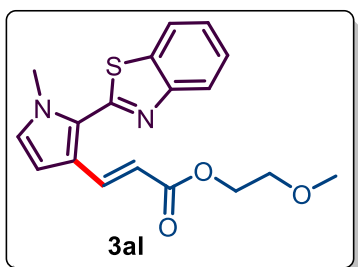
**Cyclopropyl methyl (E)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (3ak):**



**(3ak):** The compound **3ak** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ak** as yellow solid (35%, 12mg).  $R_f$  = 0.49 (EtOAc/petroleum ether = 11:89).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.15 (d,  $J$  = 15.6 Hz, 1H), 8.09 (d,  $J$  = 8.1 Hz, 1H), 7.93 (d,  $J$  = 8.0 Hz, 1H), 7.52

(ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.42 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 6.80 (d,  $J$  = 2.9 Hz, 1H), 6.53 (d,  $J$  = 2.9 Hz, 1H), 6.32 (d,  $J$  = 15.5 Hz, 1H), 4.02 (d,  $J$  = 7.3 Hz, 2H), 3.96 (s, 3H), 1.23 – 1.16 (m, 1H), 0.61 – 0.56 (m, 2H), 0.34 – 0.30 (m, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  167.9, 157.1, 153.7, 137.7, 135.5, 127.6, 126.6, 125.4, 123.6, 123.4, 121.5, 121.4, 116.6, 114.6, 107.0, 69.1, 37.0, 10.1, 3.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_2\text{S}$ : 339.1167; found, 339.1169.

**2-methoxyethyl (E)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (3al):**

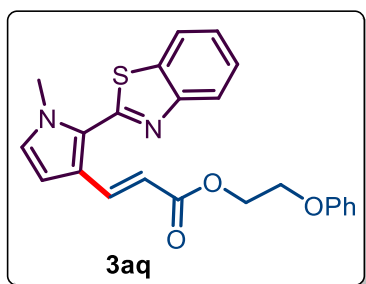


The compound **3al** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3al** as yellow solid (50%, 17mg), m.p. = 86 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 38:62).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.16 (d,  $J$  = 15.5

Hz, 1H), 8.08 (d,  $J$  = 8.2 Hz, 1H), 7.92 (d,  $J$  = 8.0 Hz, 1H), 7.52 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.41 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 6.79 (d,  $J$  = 2.9 Hz, 1H), 6.52 (d,  $J$  = 2.9 Hz, 1H), 6.34 (d,  $J$  = 15.5 Hz, 1H), 4.34 (t,  $J$  = 4.0 Hz, 2H), 3.95 (s, 3H), 3.66 (t,  $J$  = 4.0 Hz, 2H), 3.41 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  167.7, 157.0, 153.6, 138.1, 135.5, 127.7, 127.6, 126.5, 125.4, 123.4, 123.4, 121.5, 116.1, 107.0, 70.8, 63.5, 59.2, 36.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$ : 343.1116; found, 343.1112.

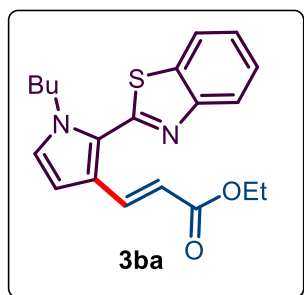


**2-phenoxyethyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (**3aq**):**



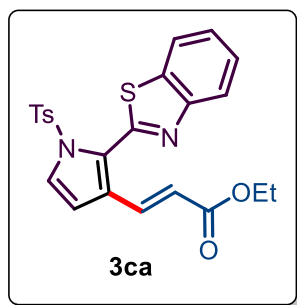
The compound **3aq** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3aq** as yellow solid (47%, 19mg), m.p. = 79 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 25:75).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.18 (d,  $J$  = 15.5 Hz, 1H), 8.07 (d,  $J$  = 8.2 Hz, 1H), 7.88 (d,  $J$  = 8.0 Hz, 1H), 7.51 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.41 (ddd,  $J$  = 8.2, 7.2, 1.2 Hz, 1H), 7.30 – 7.26 (m, 2H), 6.98 – 6.92 (m, 3H), 6.79 (d,  $J$  = 2.9 Hz, 1H), 6.52 (d,  $J$  = 2.9 Hz, 1H), 6.32 (d,  $J$  = 15.5 Hz, 1H), 4.54 (t,  $J$  = 4.0 Hz, 2H), 4.23 (t,  $J$  = 4.0 Hz, 2H), 3.95 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  167.6, 158.7, 157.0, 153.6, 138.4, 135.5, 129.6, 127.7, 127.7, 126.6, 125.4, 123.42, 123.4, 121.5, 121.2, 115.9, 114.8, 107.0, 66.2, 62.8, 36.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$ : 405.1273; found, 405.1271.

**Ethyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-1-butyl-1H-pyrrol-3-yl)acrylate (**3ba**):**



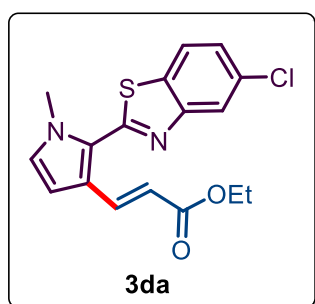
The compound **3ba** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ba** as yellow solid (59%, 21mg), m.p. = 85 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 8:92).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.10 (d,  $J$  = 15.5 Hz, 1H), 8.08 (d,  $J$  = 8.0 Hz, 1H), 7.93 (d,  $J$  = 7.9 Hz, 1H), 7.52 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.42 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 6.84 (d,  $J$  = 2.8 Hz, 1H), 6.52 (d,  $J$  = 2.8 Hz, 1H), 6.27 (d,  $J$  = 15.5 Hz, 1H), 4.39 – 4.31 (m, 2H), 4.24 (q,  $J$  = 7.1 Hz, 2H), 1.69 (p,  $J$  = 7.5 Hz, 2H), 1.31 (t,  $J$  = 7.1 Hz, 3H), 1.31 – 1.22 (m, 2H), 0.86 (t,  $J$  = 7.4 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  167.8, 157.1, 153.7, 137.6, 135.6, 126.9, 126.5, 126.5, 125.3, 123.5, 123.4, 121.5, 116.4, 106.9, 60.3, 48.8, 33.5, 19.9, 14.5, 13.7. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2\text{S}$ : 355.1480; found, 355.1480.

### Ethyl (E)-3-(5-(benzo[d]thiazol-2-yl)-1-tosyl-1H-pyrrol-2-yl)acrylate (**3ca**):



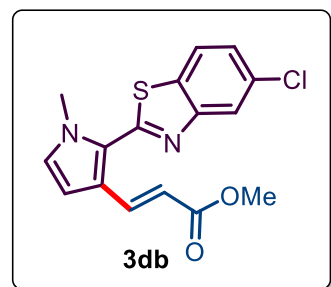
The compound **3ca** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ca** as yellow solid (44%, 20 mg), m.p. = 120 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 30:70).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.06 (d,  $J$  = 8.2 Hz, 1H), 7.97 (d,  $J$  = 7.9 Hz, 1H), 7.67 (d,  $J$  = 8.4 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.53 (d,  $J$  = 3.5 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.41 (d,  $J$  = 15.8 Hz, 1H), 7.26 (s, 3H), 6.62 (d,  $J$  = 3.4 Hz, 1H), 6.22 (d,  $J$  = 15.8 Hz, 1H), 4.15 (q,  $J$  = 7.1 Hz, 2H), 2.42 (s, 3H), 1.23 (t,  $J$  = 7.2 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (150 MHz, Chloroform-*d*)  $\delta$  166.7, 155.5, 152.9, 145.9, 137.1, 135.4, 135.0, 129.9, 128.1, 127.9, 126.8, 126.7, 126.2, 125.8, 123.9, 121.8, 120.2, 109.7, 60.6, 21.9, 14.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}_4\text{S}_2$ : 453.0942; found, 453.0944.

### Ethyl (E)-3-(2-(5-chlorobenzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (**3da**):



The compound **3da** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3da** as yellow solid (60%, 21mg).  $R_f$  = 0.49 (EtOAc/petroleum ether = 10:90), m.p. = 126 °C,  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.13 (d,  $J$  = 15.5 Hz, 1H), 8.06 (d,  $J$  = 1.9 Hz, 1H), 7.83 (d,  $J$  = 8.5 Hz, 1H), 7.39 (dd,  $J$  = 8.5, 2.0 Hz, 1H), 6.81 (d,  $J$  = 2.9 Hz, 1H), 6.52 (d,  $J$  = 2.9 Hz, 1H), 6.29 (d,  $J$  = 15.5 Hz, 1H), 4.25 (q,  $J$  = 7.1 Hz, 2H), 3.97 (s, 3H), 1.33 (t,  $J$  = 7.1 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  167.7, 159.0, 154.5, 137.3, 133.6, 132.6, 128.1, 127.0, 125.8, 124.0, 123.1, 122.2, 117.2, 107.2, 60.4, 37.2, 14.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{16}\text{ClN}_2\text{O}_2\text{S}$ : 347.0621; found, 347.0629.

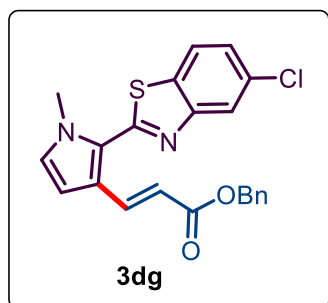
### Methyl (E)-3-(2-(5-chlorobenzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (**3db**):



The compound **3db** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3db** as yellow solid (54%, 18 mg), m.p. = 149 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 13:87).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.12 (d,  $J$  = 15.5 Hz, 1H), 8.07 (d,  $J$  = 1.9 Hz, 1H), 7.83 (d,  $J$  = 8.5 Hz, 1H), 7.39 (dd,  $J$  = 8.5, 2.0 Hz, 1H), 6.81 (d,  $J$  = 2.9 Hz, 1H), 6.52 (d,  $J$  = 2.9 Hz, 1H), 6.29 (d,  $J$  = 15.5 Hz, 1H), 3.97 (s, 3H), 3.79 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  168.1, 158.9, 154.5,

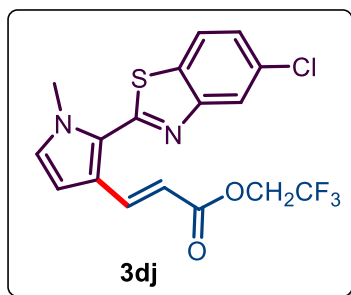
137.5, 133.6, 132.6, 128.1, 127.1, 125.8, 123.9, 123.1, 122.2, 116.7, 107.2, 51.7, 37.2. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{16}H_{14}ClN_2O_2S$ : 333.0464; found, 333.0457.

**Benzyl (*E*)-3-(2-(5-chlorobenzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (**3dg**):**



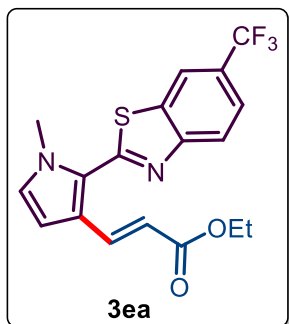
The compound **3dg** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3dg** as yellow solid (56%, 23 mg), m.p. = 149 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 12:88).  $^1H$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.21 (d,  $J$  = 15.5 Hz, 1H), 8.05 (d,  $J$  = 1.9 Hz, 1H), 7.82 (d,  $J$  = 8.5 Hz, 1H), 7.45 – 7.30 (m, 6H), 6.80 (d,  $J$  = 2.9 Hz, 1H), 6.52 (d,  $J$  = 2.9 Hz, 1H), 6.34 (d,  $J$  = 15.5 Hz, 1H), 5.24 (s, 2H), 3.96 (s, 3H).  $^{13}C\{^1H\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  167.4, 158.7, 154.3, 137.8, 136.4, 133.4, 132.5, 128.6, 128.1, 128.1, 128.0, 127.1, 125.7, 123.8, 123.0, 122.0, 116.5, 107.1, 66.1, 37.1. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{22}H_{18}ClN_2O_2S$ : 409.0777; found, 409.0775.

**2,2,2-trifluoroethyl (*E*)-3-(2-(5-chlorobenzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (**3dj**):**



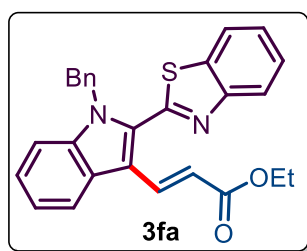
The compound **3dj** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3dj** as yellow solid (60%, 24 mg), m.p. = 114 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 10:80).  $^1H$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.24 (d,  $J$  = 15.5 Hz, 1H), 8.07 (d,  $J$  = 1.9 Hz, 1H), 7.84 (d,  $J$  = 8.5 Hz, 1H), 7.40 (dd,  $J$  = 8.5, 2.0 Hz, 1H), 6.82 (d,  $J$  = 2.9 Hz, 1H), 6.55 (d,  $J$  = 2.9 Hz, 1H), 6.32 (d,  $J$  = 15.5 Hz, 1H), 4.58 (q,  $J$  = 8.5 Hz, 2H), 3.97 (s, 3H).  $^{13}C\{^1H\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  165.9, 158.5, 154.5, 139.9, 133.6, 132.8, 128.2, 126.0, 123.4, 123.4 (d,  $J$  = 277.3 Hz), 123.2, 122.2, 114.4, 107.3, 60.4 (q,  $J$  = 36.4 Hz), 37.2, 29.9.  $^{19}F$  NMR (377 MHz, Chloroform-*d*)  $\delta$  -73.71. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{17}H_{13}ClF_3N_2O_2S$ : 401.0338; found, 401.0337.

**Ethyl (E)-3-(1-methyl-2-(6-(trifluoromethyl)benzo[d]thiazol-2-yl)-1H-pyrrol-3-yl)acrylate (3ea):**



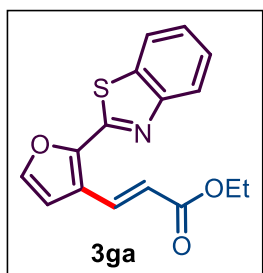
The compound **3ea** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ea** as yellow solid (55%, 21mg), m.p. = 132 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 18:82).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.33 (d,  $J$  = 1.8 Hz, 1H), 8.15 (d,  $J$  = 15.5 Hz, 1H), 8.03 (d,  $J$  = 8.4 Hz, 1H), 7.64 (dd,  $J$  = 8.5, 1.7 Hz, 1H), 6.83 (d,  $J$  = 2.9 Hz, 1H), 6.53 (d,  $J$  = 2.9 Hz, 1H), 6.31 (d,  $J$  = 15.6 Hz, 1H), 4.26 (q,  $J$  = 7.1 Hz, 2H), 4.00 (s, 3H), 1.33 (t,  $J$  = 7.1 Hz, 3H).  $^{19}\text{F}$  NMR (377 MHz, Chloroform-*d*)  $\delta$  -61.67.  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  167.7, 159.2, 153.2, 138.6, 137.1, 129.2 (q,  $J$  = 32.7 Hz), 128.3, 126.7, 124.3 (d,  $J$  = 272.2 Hz), 124.3, 122.1, 121.6 (q,  $J$  = 3.5 Hz), 120.5 (q,  $J$  = 4.0 Hz), 117.5, 107.3, 60.5, 37.3, 14.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{18}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_2\text{S}$ : 381.0885; found, 381.0884.

**Ethyl (E)-3-(2-(benzo[d]thiazol-2-yl)-1-benzyl-1H-indol-3-yl)acrylate (3fa):**



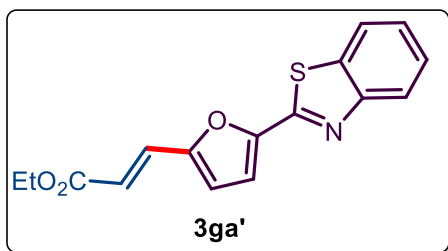
The compound **3fa** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3fa** as yellow solid (57%, 25 mg), m.p. = 94 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 18:82).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.28 (d,  $J$  = 16.0 Hz, 1H), 8.14 (d,  $J$  = 7.9 Hz, 1H), 8.05 (d,  $J$  = 7.1 Hz, 1H), 7.92 (d,  $J$  = 8.1 Hz, 1H), 7.54 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.45 (ddd,  $J$  = 8.2, 7.2, 1.2 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.33 – 7.27 (m, 2H), 7.21 – 7.15 (m, 3H), 7.01 (dd,  $J$  = 7.4, 2.1 Hz, 2H), 6.68 (d,  $J$  = 15.9 Hz, 1H), 5.80 (s, 2H), 4.28 (q,  $J$  = 7.1 Hz, 2H), 1.34 (t,  $J$  = 7.2 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  168.0, 156.6, 153.6, 138.6, 137.3, 137.2, 136.4, 134.3, 128.8, 127.6, 126.8, 126.6, 126.0, 125.6, 125.1, 124.1, 122.4, 121.6, 121.6, 117.4, 115.0, 111.5, 60.4, 48.4, 14.6. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{27}\text{H}_{23}\text{N}_2\text{O}_2\text{S}$ : 439.1480; found, 439.1483.

**Ethyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)furan-3-yl)acrylate (**3ga**):**



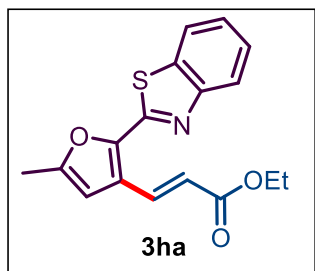
The compound **3ga** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ga** as yellow solid (20%, 6 mg), m.p. = 96 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 15:85).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.67 (d,  $J$  = 16.0 Hz, 1H), 8.13 (d,  $J$  = 8.2 Hz, 1H), 7.92 (d,  $J$  = 8.0 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.41 (ddd,  $J$  = 8.2, 7.2, 1.2 Hz, 1H), 6.80 (d,  $J$  = 1.9 Hz, 1H), 6.40 (d,  $J$  = 16.1 Hz, 1H), 4.31 (q,  $J$  = 7.1 Hz, 2H), 1.37 (t,  $J$  = 7.1 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  166.8, 156.7, 154.1, 147.3, 144.5, 134.8, 134.2, 126.6, 125.6, 123.8, 122.9, 121.5, 121.4, 110.3, 60.6, 14.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{14}\text{NO}_3\text{S}$ : 300.0694; found, 300.0692.

**Ethyl (*E*)-3-(5-(benzo[d]thiazol-2-yl)furan-2-yl)acrylate (**3ga'**):**



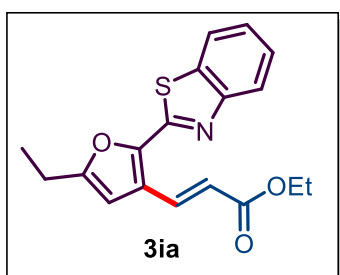
The compound **3ga** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ga** as yellow solid (20%, 6 mg), m.p. = 128 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 18:82).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.07 (d,  $J$  = 8.0 Hz, 1H), 7.92 (d,  $J$  = 8.5 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.48 (d,  $J$  = 15.8 Hz, 1H), 7.42 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 7.26 (d,  $J$  = 3.6 Hz, 1H), 6.78 (d,  $J$  = 3.6 Hz, 1H), 6.55 (d,  $J$  = 15.8 Hz, 1H), 4.28 (q,  $J$  = 7.1 Hz, 2H), 1.35 (t,  $J$  = 7.2 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  166.8, 156.8, 154.0, 152.7, 150.3, 134.7, 130.1, 126.9, 125.8, 123.5, 121.8, 118.5, 116.8, 113.4, 60.9, 14.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{14}\text{NO}_3\text{S}$ : 300.0694; found, 300.0695.

### Ethyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-5-methylfuran-3-yl)acrylate (**3ha**):



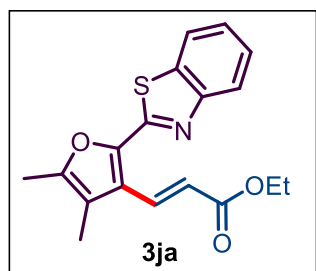
The compound **3ha** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ha** as yellow solid (54%, 17mg), m.p. = 97 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 14:86).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.61 (d,  $J$  = 16.0 Hz, 1H), 8.10 (d,  $J$  = 8.2 Hz, 1H), 7.90 (d,  $J$  = 8.0 Hz, 1H), 7.50 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 7.38 (ddd,  $J$  = 8.2, 7.1, 1.1 Hz, 1H), 6.40 (s, 1H), 6.32 (d,  $J$  = 16.0 Hz, 1H), 4.30 (q,  $J$  = 7.1 Hz, 2H), 2.42 (s, 3H), 1.37 (t,  $J$  = 7.1 Hz, 3H).  $^{13}\text{C}$  { $^1\text{H}$ } NMR (100 MHz, Chloroform-*d*)  $\delta$  167.0, 156.9, 155.4, 154.2, 146.2, 135.2, 134.2, 126.6, 125.4, 124.2, 123.7, 121.6, 121.1, 106.6, 60.7, 14.5, 13.9. HRMS (ESI):  $m/z$  [ $\text{M} + \text{H}$ ] $^+$  calcd for  $\text{C}_{17}\text{H}_{16}\text{NO}_3\text{S}$ : 314.0851; found, 314.0841.

### Ethyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-5-ethylfuran-3-yl)acrylate (**3ia**):



The compound **3ia** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ia** as yellow solid (40%, 13 mg), m.p. = 136 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 14:86).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.63 (d,  $J$  = 16.0 Hz, 1H), 8.10 (d,  $J$  = 8.1 Hz, 1H), 7.90 (d,  $J$  = 7.9 Hz, 1H), 7.49 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 7.38 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 6.41 (s, 1H), 6.34 (d,  $J$  = 16.0 Hz, 1H), 4.30 (q,  $J$  = 7.1 Hz, 2H), 2.76 (q,  $J$  = 7.5 Hz, 2H), 1.37 (t,  $J$  = 7.2 Hz, 3H), 1.33 (t,  $J$  = 7.6 Hz, 3H).  $^{13}\text{C}$  { $^1\text{H}$ } NMR (100 MHz, Chloroform-*d*)  $\delta$  167.0, 160.9, 157.0, 154.3, 146.1, 135.3, 134.2, 126.6, 125.4, 124.0, 123.7, 121.5, 121.0, 105.1, 60.6, 21.6, 14.5, 11.9. HRMS (ESI):  $m/z$  [ $\text{M} + \text{H}$ ] $^+$  calcd for  $\text{C}_{18}\text{H}_{18}\text{NO}_3\text{S}$ : 328.1007; found, 328.1005.

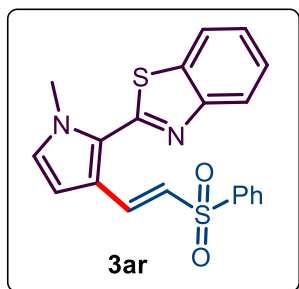
### Ethyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-4,5-dimethylfuran-3-yl)acrylate (**3ja**):



The compound **3ja** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ja** as yellow solid (49%, 16 mg), m.p. = 115 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 10:80).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.67 (d,  $J$  = 16.4 Hz, 1H), 8.09 (d,  $J$  = 8.2 Hz, 1H), 7.89 (d,  $J$  = 8.0 Hz, 1H), 7.48 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.37 (ddd,  $J$

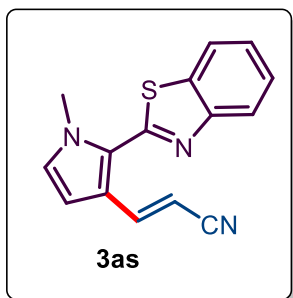
= 8.1, 7.2, 1.2 Hz, 1H), 6.54 (d,  $J$  = 16.4 Hz, 1H), 4.31 (q,  $J$  = 7.1 Hz, 2H), 2.35 (s, 3H), 2.17 (s, 3H), 1.38 (t,  $J$  = 7.1 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  167.4, 157.2, 154.2, 151.4, 145.8, 136.0, 134.2, 126.5, 125.3, 123.6, 123.3, 121.4, 121.0, 116.7, 60.6, 14.5, 11.8, 10.7. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{18}\text{H}_{18}\text{NO}_3\text{S}$ : 328.1007; found, 328.1002.

**(*E*)-2-(1-methyl-3-(2-(phenylsulfonyl)vinyl)-1H-pyrrol-2-yl)benzo[d]thiazole (3ar):**



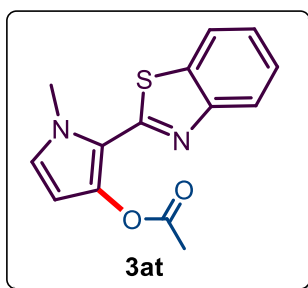
The compound **3ar** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ar** as yellow solid (37%, 14 mg), m.p. = 143 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 40:60).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.13 (d,  $J$  = 15.0 Hz, 1H), 8.11 (d,  $J$  = 7.9 Hz, 1H), 7.98 – 7.93 (m, 3H), 7.63 – 7.54 (m, 1H), 7.55 – 7.50 (m, 3H), 7.46 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 6.79 (d,  $J$  = 3.0 Hz, 1H), 6.65 (d,  $J$  = 15.0 Hz, 1H), 6.41 (d,  $J$  = 2.9 Hz, 1H), 3.95 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  156.4, 153.6, 141.6, 136.0, 135.5, 133.1, 129.3, 128.6, 127.8, 127.6, 126.8, 125.7, 124.8, 123.6, 121.7, 121.0, 107.3, 37.0. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_2\text{S}_2$ : 381.0731; found, 381.0728.

**(*E*)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylonitrile (3as):**



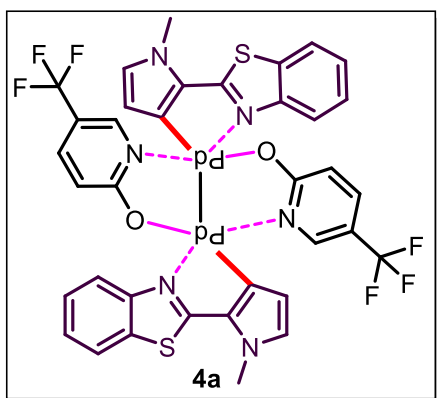
The compound **3as** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3as** as yellow solid (45%, 12 mg), m.p. = 134 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 25:75).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.11 (d,  $J$  = 8.2 Hz, 1H), 7.95 (d,  $J$  = 8.0 Hz, 1H), 7.84 (d,  $J$  = 16.2 Hz, 1H), 7.55 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.45 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 6.81 (d,  $J$  = 3.0 Hz, 1H), 6.47 (d,  $J$  = 2.9 Hz, 1H), 5.65 (d,  $J$  = 16.2 Hz, 1H), 3.95 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  156.3, 153.6, 143.6, 135.3, 127.8, 127.5, 126.8, 125.7, 123.6, 122.8, 121.5, 119.5, 106.2, 93.5, 36.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_{12}\text{N}_3\text{S}$ : 266.0752; found, 266.0751.

### 2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl acetate (**3at**):



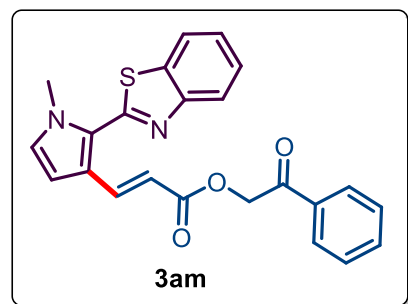
The compound **3at** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3at** as yellow semi-solid (22%, 6 mg).  $R_f = 0.49$  (EtOAc/petroleum ether = 15:85).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  7.96 (d,  $J = 8.1$  Hz, 1H), 7.86 (d,  $J = 7.9$  Hz, 1H), 7.44 (ddd,  $J = 8.3, 7.2, 1.3$  Hz, 1H), 7.33 (ddd,  $J = 8.3, 7.2, 1.2$  Hz, 1H), 6.71 (d,  $J = 3.0$  Hz, 1H), 6.22 (d,  $J = 3.0$  Hz, 1H), 4.14 (s, 3H), 2.44 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  168.8, 156.8, 153.0, 139.5, 133.8, 129.0, 126.1, 125.2, 124.5, 122.6, 121.2, 102.0, 38.6, 21.6. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_2\text{S}$ : 273.0698; found, 273.0693.

### Palladium complex Intermediate (**4a**):



The complex compound **4a** was obtained by following the general procedure D and it was purified by column chromatography over silica gel to obtain the compound **4a** as brown solid (35%, 71mg), m.p. = 230 °C,  $R_f = 0.49$  (EtOAc/petroleum ether = 40:60).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.57 (s, 1H), 7.85 (d,  $J = 7.6$  Hz, 1H), 7.53 – 7.50 (m, 1H), 7.48 (dd,  $J = 9.1, 2.7$  Hz, 1H), 7.12 – 7.05 (m, 2H), 6.71 (d,  $J = 9.1$  Hz, 1H), 5.67 (d,  $J = 2.4$  Hz, 1H), 4.75 (d,  $J = 2.4$  Hz, 1H), 3.39 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  172.6, 162.9, 149.9, 148.8, 135.0, 134.2, 130.5, 128.8, 127.0, 126.6, 123.1, 120.7, 120.1, 117.3, 113.5, 113.1, 112.9, 34.7.  $^{19}\text{F}$  NMR (377 MHz, Chloroform- $d$ )  $\delta$  -61.12. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{36}\text{H}_{27}\text{F}_6\text{N}_6\text{O}_2\text{Pd}_2\text{S}_2$ : 964.9; found, 964.4.

### 2-oxo-2-phenylethyl (E)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (**3am**):

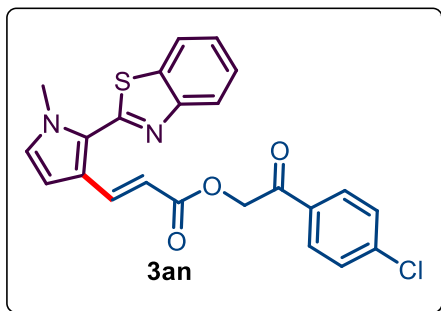


The compound **3am** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3am** as yellow solid (49%, 20 mg), m.p. = 157 °C,  $R_f = 0.49$  (EtOAc/petroleum ether = 25:75).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.24 (d,  $J = 15.5$  Hz, 1H), 8.08 (d,  $J = 8.2$  Hz, 1H), 7.97 – 7.93 (m, 2H), 7.91 (d,  $J = 8.0$  Hz, 1H), 7.62 – 7.57 (m, 1H), 7.53 – 7.46 (m,



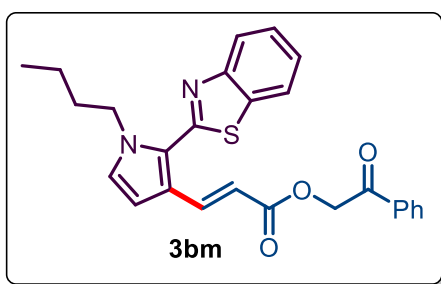
3H), 7.41 (ddd,  $J = 8.2, 7.2, 1.2$  Hz, 1H), 6.81 (d,  $J = 2.9$  Hz, 1H), 6.57 (d,  $J = 2.8$  Hz, 1H), 6.44 (d,  $J = 15.5$  Hz, 1H), 5.44 (s, 2H), 3.96 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  192.9, 167.0, 157.0, 153.6, 139.2, 135.5, 134.6, 133.9, 129.0, 128.0, 127.9, 127.7, 126.6, 125.4, 123.4, 123.3, 121.5, 115.1, 107.1, 66.1, 36.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$ : 403.1116; found, 403.1104.

**2-(4-chlorophenyl)-2-oxoethyl (E)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (3an):**



The compound **3an** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3an** as yellow solid (52%, 23 mg), m.p. = 145 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 24:76).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.23 (d,  $J = 15.5$  Hz, 1H), 8.09 (d,  $J = 8.2$  Hz, 1H), 7.94 – 7.87 (m, 3H), 7.52 (ddd,  $J = 8.3, 7.2, 1.3$  Hz, 1H), 7.48 – 7.44 (m, 2H), 7.42 (ddd,  $J = 8.3, 7.2, 1.2$  Hz, 1H), 6.82 (d,  $J = 2.9$  Hz, 1H), 6.57 (d,  $J = 2.9$  Hz, 1H), 6.42 (d,  $J = 15.5$  Hz, 1H), 5.38 (s, 2H), 3.96 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  191.9, 167.0, 156.9, 153.7, 140.4, 139.4, 135.5, 132.9, 129.4, 129.3, 128.0, 127.7, 126.6, 125.4, 123.5, 123.3, 121.5, 114.9, 107.1, 66.0, 36.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{18}\text{ClN}_2\text{O}_3\text{S}$ : 437.0727; found, 437.0713.

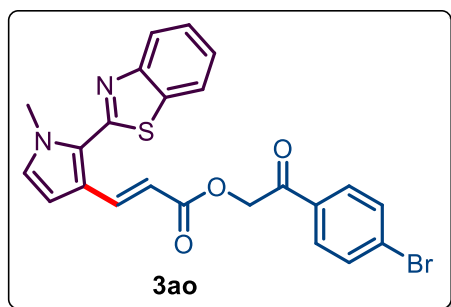
**2-oxo-2-phenylethyl(E)-3-(2-(benzo[d]thiazol-2-yl)-1-butyl-1H-pyrrol-3-yl)acrylate (3bm):**



The compound **3bm** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3bm** as yellow solid (42%, 19 mg), m.p. = 129 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 22:78).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.20 (d,  $J = 15.5$  Hz, 1H), 8.08 (d,  $J = 8.2$  Hz, 1H), 7.97 – 7.90 (m, 3H), 7.62 – 7.57 (m, 1H), 7.54 – 7.46 (m, 3H), 7.41 (ddd,  $J = 8.2, 7.2, 1.2$  Hz, 1H), 6.86 (d,  $J = 2.8$  Hz, 1H), 6.57 (d,  $J = 2.8$  Hz, 1H), 6.43 (d,  $J = 15.5$  Hz, 1H), 5.43 (s, 2H), 4.35 (t,  $J = 7.3$  Hz, 2H), 1.70 (p,  $J = 7.4$  Hz, 2H), 1.32 – 1.26 (m, 2H), 0.87 (t,  $J = 7.4$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  192.9, 167.1, 157.0, 153.7, 139.3, 134.6, 133.9, 129.0, 128.0, 126.6, 126.5, 125.4, 123.5, 123.3, 121.5, 114.9, 107.1, 66.1,

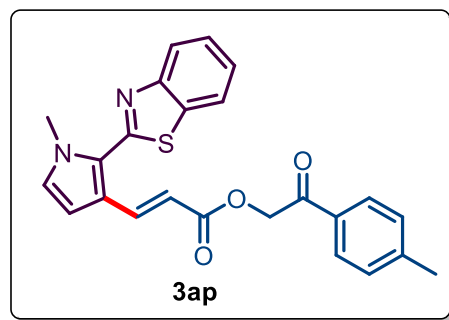
48.8, 33.5, 19.9, 13.7. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{26}H_{25}N_2O_3S$ : 445.1586; found, 445.1584.

**2-(4-bromophenyl)-2-oxoethyl (E)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (3ao):**



The compound **3ao** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ao** as yellow solid (43%, 21mg), m.p. = 164 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 25:75).  $^1H$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.23 (d,  $J$  = 15.5 Hz, 1H), 8.09 (d,  $J$  = 8.2 Hz, 1H), 7.92 (d,  $J$  = 8.0 Hz, 1H), 7.81 (d,  $J$  = 8.6 Hz, 2H), 7.63 (d,  $J$  = 8.6 Hz, 2H), 7.52 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.42 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 6.82 (d,  $J$  = 2.9 Hz, 1H), 6.57 (d,  $J$  = 2.9 Hz, 1H), 6.42 (d,  $J$  = 15.5 Hz, 1H), 5.38 (s, 2H), 3.96 (s, 3H).  $^{13}C$   $\{^1H\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  192.1, 167.0, 156.9, 153.7, 139.4, 135.5, 133.3, 132.3, 129.5, 129.1, 128.0, 127.7, 126.6, 125.4, 123.5, 123.3, 121.5, 114.9, 107.1, 66.0, 36.9. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{24}H_{18}BrN_2O_3S$ : 481.0221; found, 481.0217.

**2-oxo-2-(p-tolyl)ethyl (E)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate (3ap):**

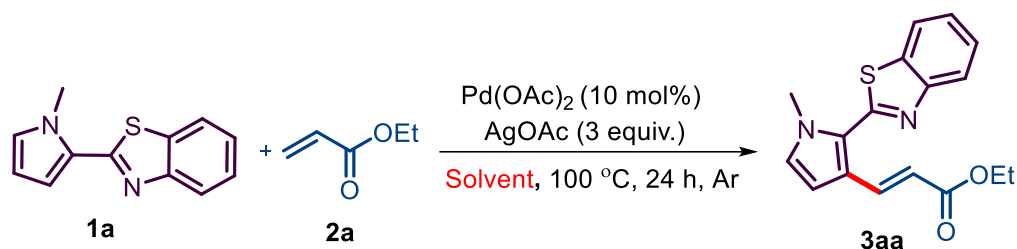


The compound **3ap** was obtained by following the general procedure C and it was purified by column chromatography over silica gel to obtain the compound **3ap** as yellow solid (48%, 20 mg), m.p. = 155 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 26:74).  $^1H$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.24 (d,  $J$  = 15.5 Hz, 1H), 8.08 (d,  $J$  = 8.2 Hz, 1H), 7.92 (d,  $J$  = 8.0 Hz, 1H), 7.85 (d,  $J$  = 8.2 Hz, 2H), 7.51 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.41 (ddd,  $J$  = 8.2, 7.2, 1.2 Hz, 1H), 7.29 – 7.26 (m, 2H), 6.81 (d,  $J$  = 2.9 Hz, 1H), 6.57 (d,  $J$  = 2.9 Hz, 1H), 6.44 (d,  $J$  = 15.5 Hz, 1H), 5.41 (s, 2H), 3.96 (s, 3H), 2.41 (s, 3H).  $^{13}C$   $\{^1H\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  192.5, 167.1, 157.0, 153.7, 144.8, 139.1, 135.5, 132.1, 129.6, 128.1, 127.9, 127.7, 126.6, 125.4, 123.4, 123.4, 121.5, 115.2, 107.1, 66.1, 36.9, 21.9. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{24}H_{21}N_2O_3S$ : 417.1273; found, 417.1272.

## 2.7. Appendix IIA

### 2.7.1. Optimization of Reaction Conditions

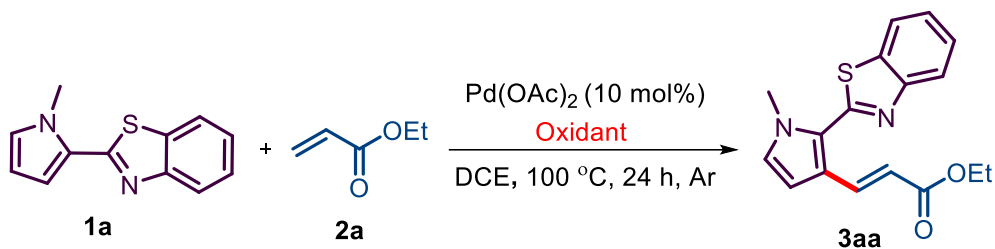
**Table 1. Optimization by varying different solvents:**



| Entry | <i>Pd</i> catalyst        | <i>2a</i> (equiv.) | Oxidants       | Solvent | Yield <i>3aa</i> (%) <sup>b</sup> |
|-------|---------------------------|--------------------|----------------|---------|-----------------------------------|
| 1     | $\text{Pd}(\text{OAc})_2$ | 3                  | $\text{AgOAc}$ | DCE     | 64                                |
| 2     | $\text{Pd}(\text{OAc})_2$ | 3                  | $\text{AgOAc}$ | ACN     | 33                                |
| 3     | $\text{Pd}(\text{OAc})_2$ | 3                  | $\text{AgOAc}$ | Dioxane | 57                                |
| 4     | $\text{Pd}(\text{OAc})_2$ | 3                  | $\text{AgOAc}$ | DCM     | 61                                |
| 5     | $\text{Pd}(\text{OAc})_2$ | 3                  | $\text{AgOAc}$ | DMF     | 44                                |
| 6     | $\text{Pd}(\text{OAc})_2$ | 3                  | $\text{AgOAc}$ | THF     | 53                                |
| 7     | $\text{Pd}(\text{OAc})_2$ | 3                  | $\text{AgOAc}$ | HFIP    | 45                                |
| 8     | $\text{Pd}(\text{OAc})_2$ | 3                  | $\text{AgOAc}$ | Toluene | 43                                |

<sup>a</sup>Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), *Pd* catalyst (10 mol%),  $\text{AgOAc}$  (0.3 mmol), Solvent (2 mL), 100 °C, Ar, 24 h. <sup>b</sup>Isolated yields based on **1a** using column chromatography. N.R.- No Reaction.

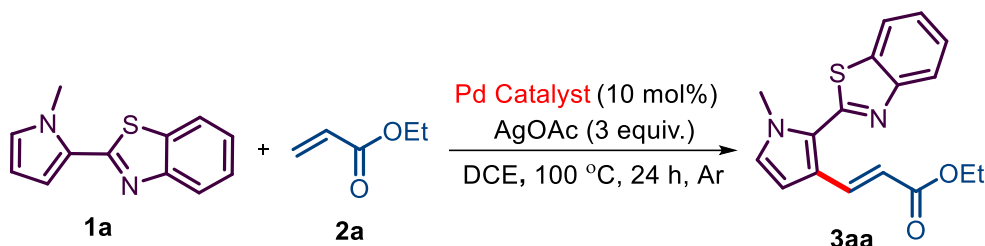
**Table 2. Optimization by varying different oxidants:**



| Entry | Pd catalyst               | 2a (equiv.) | Oxidants                                           | Solvent | Yield 3aa (%) <sup>b</sup> |
|-------|---------------------------|-------------|----------------------------------------------------|---------|----------------------------|
| 1     | $\text{Pd}(\text{OAc})_2$ | 3           | AgTFA                                              | DCE     | 45                         |
| 2     | $\text{Pd}(\text{OAc})_2$ | 3           | AgOTf                                              | DCE     | N.R.                       |
| 3     | $\text{Pd}(\text{OAc})_2$ | 3           | $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ | DCE     | 35                         |
| 4     | $\text{Pd}(\text{OAc})_2$ | 3           | $\text{Cu}(\text{OAc})_2$                          | DCE     | 27                         |

<sup>a</sup>Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol),  $\text{Pd}(\text{OAc})_2$  (10 mol%), Oxidant (0.3 mmol), DCE (2 mL), 100 °C, Ar, 24 h. <sup>b</sup>Isolated yields based on **1a** using column chromatography. N.R.- No Reaction.

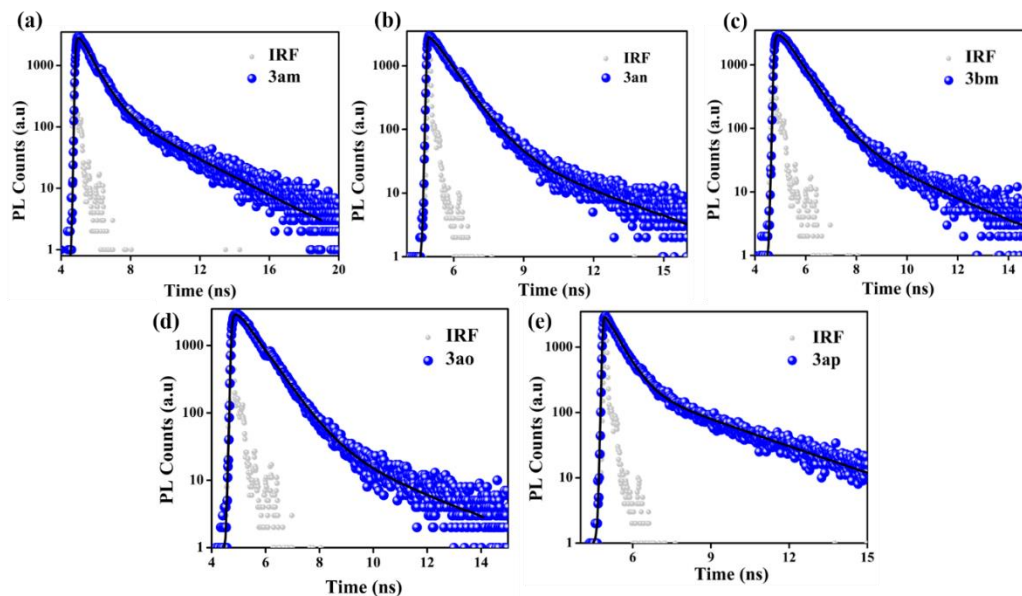
**Table 3. Optimization by varying palladium catalyst:**



| Entry | Pd catalyst                             | 2a (equiv.) | Oxidants | Solvent | Yield 3aa (%) <sup>b</sup> |
|-------|-----------------------------------------|-------------|----------|---------|----------------------------|
| 1     | $\text{Pd}(\text{TFA})_2$               | 3           | AgOAc    | DCE     | 50                         |
| 2     | $\text{PdCl}_2$                         | 3           | AgOAc    | DCE     | 47                         |
| 3     | $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ | 3           | AgOAc    | DCE     | 53                         |
| 4     | $\text{PdCl}_2(\text{PhCN})_2$          | 3           | AgOAc    | DCE     | 51                         |
| 5     | $\text{PdCl}_2(\text{PPh}_3)_2$         | 3           | AgOAc    | DCE     | 30                         |
| 6     | $\text{Pd}(\text{PPh}_3)_4$             | 3           | AgOAc    | DCE     | 10                         |

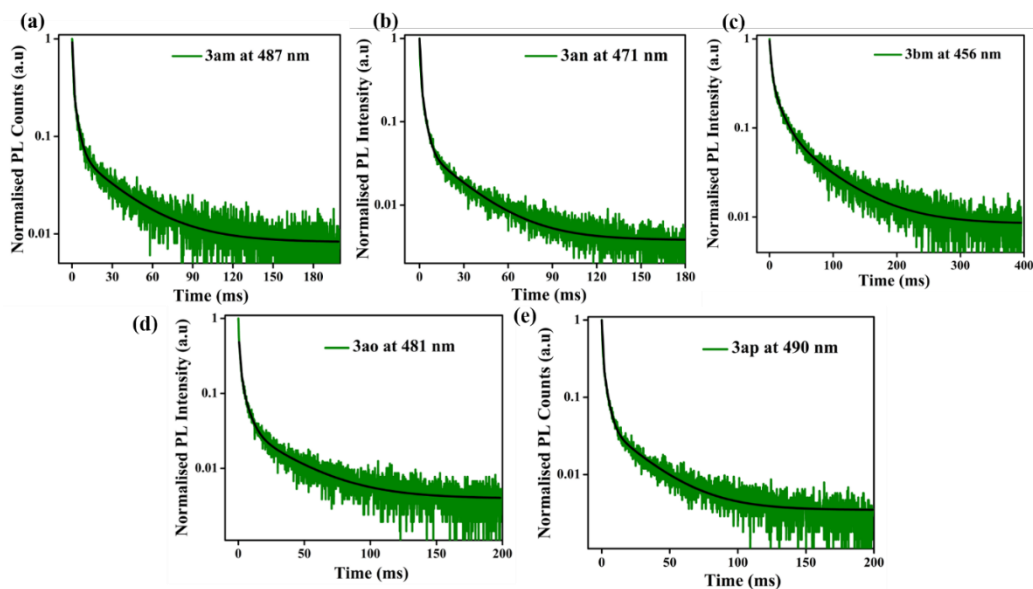
<sup>a</sup>Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Pd catalyst (10 mol%), AgOAc (0.3 mmol), DCE (2 mL), 100 °C, Ar, 24 h. <sup>b</sup>Isolated yields based on **1a** using column chromatography. N.R.- No Reaction.

### 2.7.2. Prompt fluorescence lifetime of crystals:



**Figure 1:** Prompt fluorescence lifetime of crystals (a) **3am**, (b) **3an**, (c) **3bm**, (d) **3ao** and (e) **3ap**.

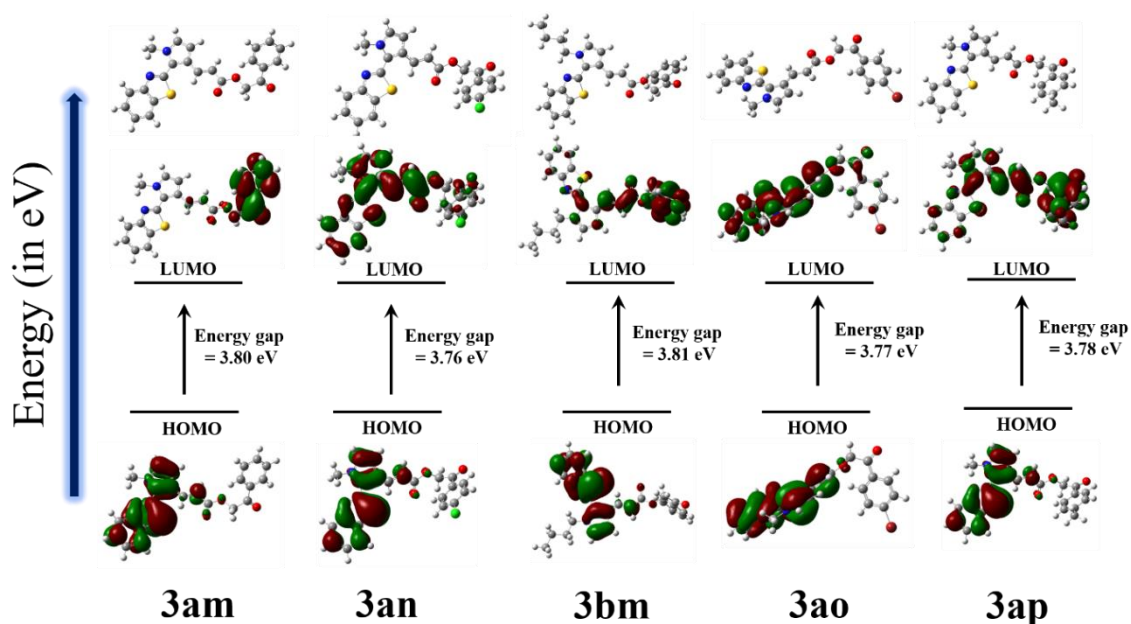
### 2.7.3. Delayed fluorescence lifetime of crystals:



**Figure 2:** Delayed fluorescence lifetime of crystals (a) **3am**, (b) **3an**, (c) **3bm**, (d) **3ao** and (e) **3ap**.

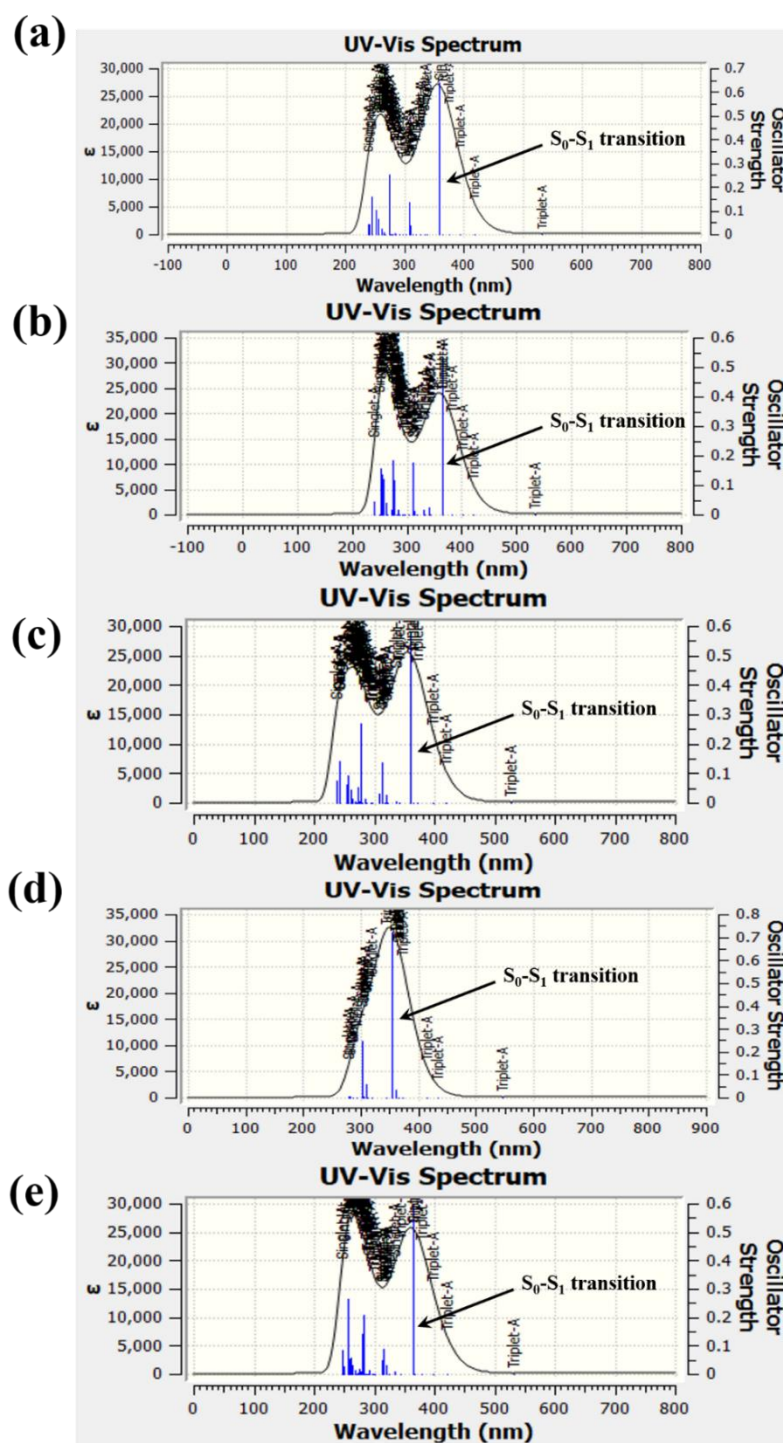
#### 2.7.4. Density Functional Theory (DFT) calculation

Quantum chemical calculations are performed using the Gaussian 09 program<sup>[22]</sup> using a high-performance cluster facility provided by IISER Pune. Initially, geometry optimization of all the luminogens is carried out in the gas phase and the nature of the stationary point (minima on the PE surface) is confirmed by frequency analysis<sup>[23-24]</sup> at the B3LYP/6-31G (d, p) level. Furthermore, TD-DFT calculations are carried out to visualize the spatial distribution of HOMOs and LUMOs as well as to get the energy information of several excited singlet and triplet states on equal no. of singlet and triplet states (td (50-50, n-states=10)) by B3LYP functional using TD-SCF method.



**Figure 3:** HOMO and LUMO molecular orbitals, their energy gaps along with the ground state optimized geometries of molecules 3am-3ap.

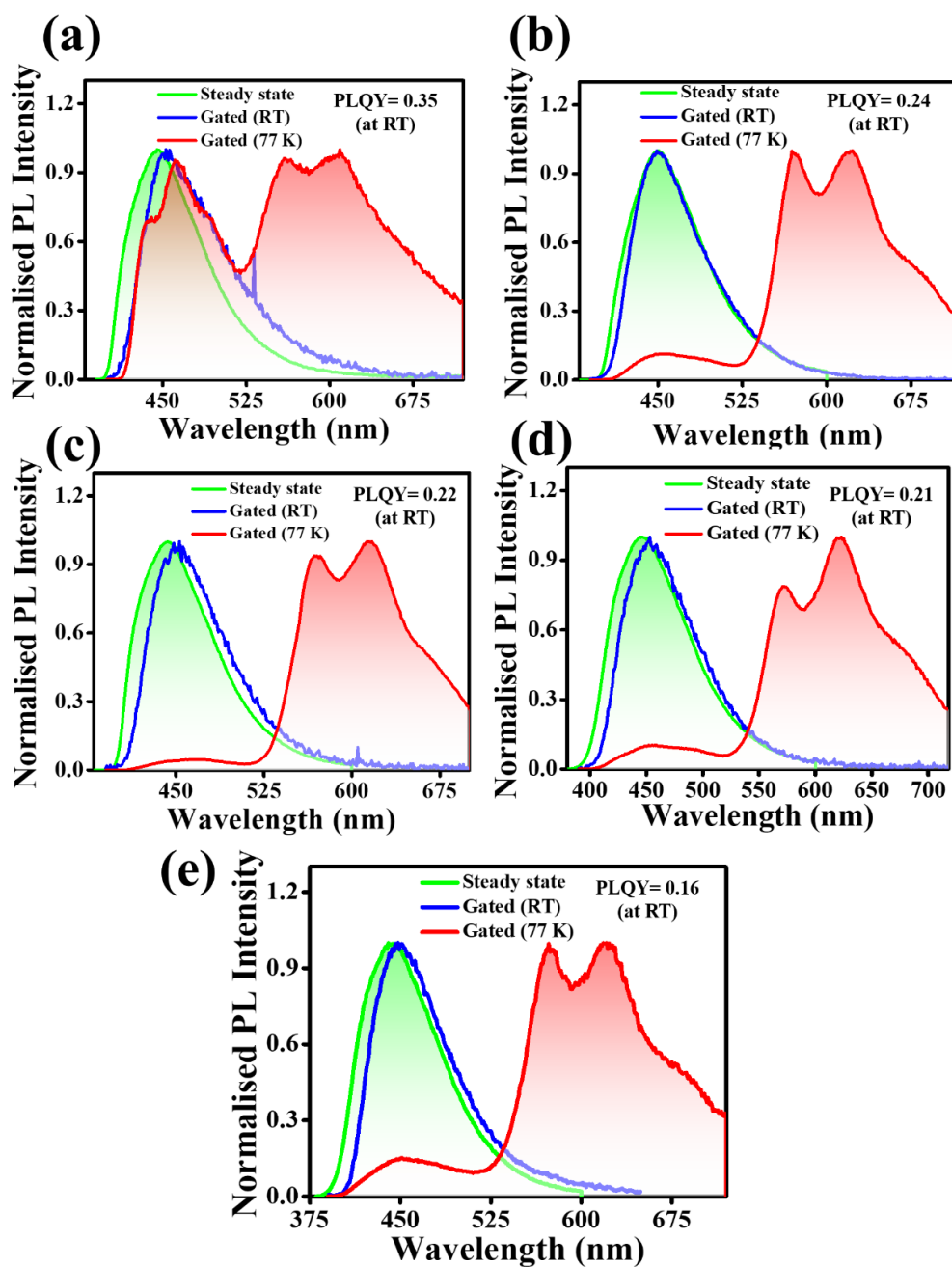
### 2.7.5. Simulated absorption spectra from TD-DFT calculation.



**Figure 4:** Simulated absorption spectra of all five molecules 3am-3ap obtained from TD-DFT calculation.



## 2.7.6 Steady state emission spectra and gated emission spectra:



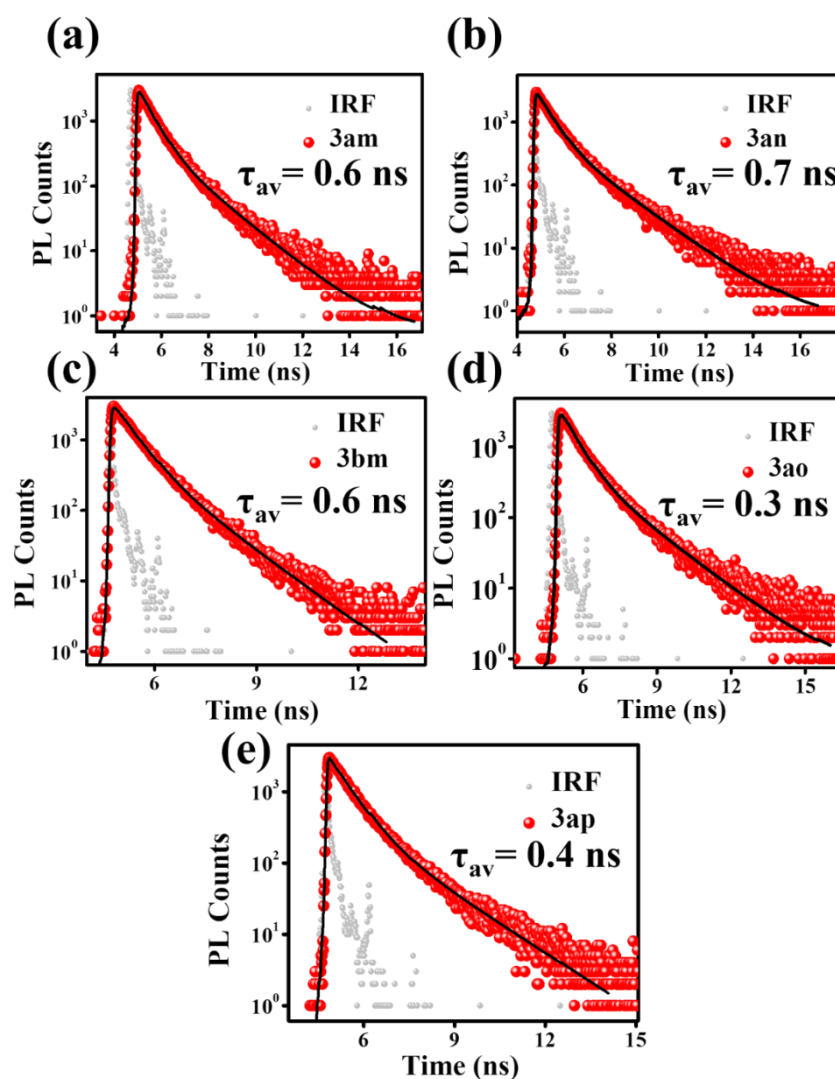
**Figure 5:** Steady state (at 300 K) emission spectra, gated emission spectra at 300 K (50  $\mu$ s delay and 20 ms sample window), and at 77 K (50  $\mu$ s delay and 20 ms sample window).



### 2.7.7. Fabrication of emitter-doped PMMA films

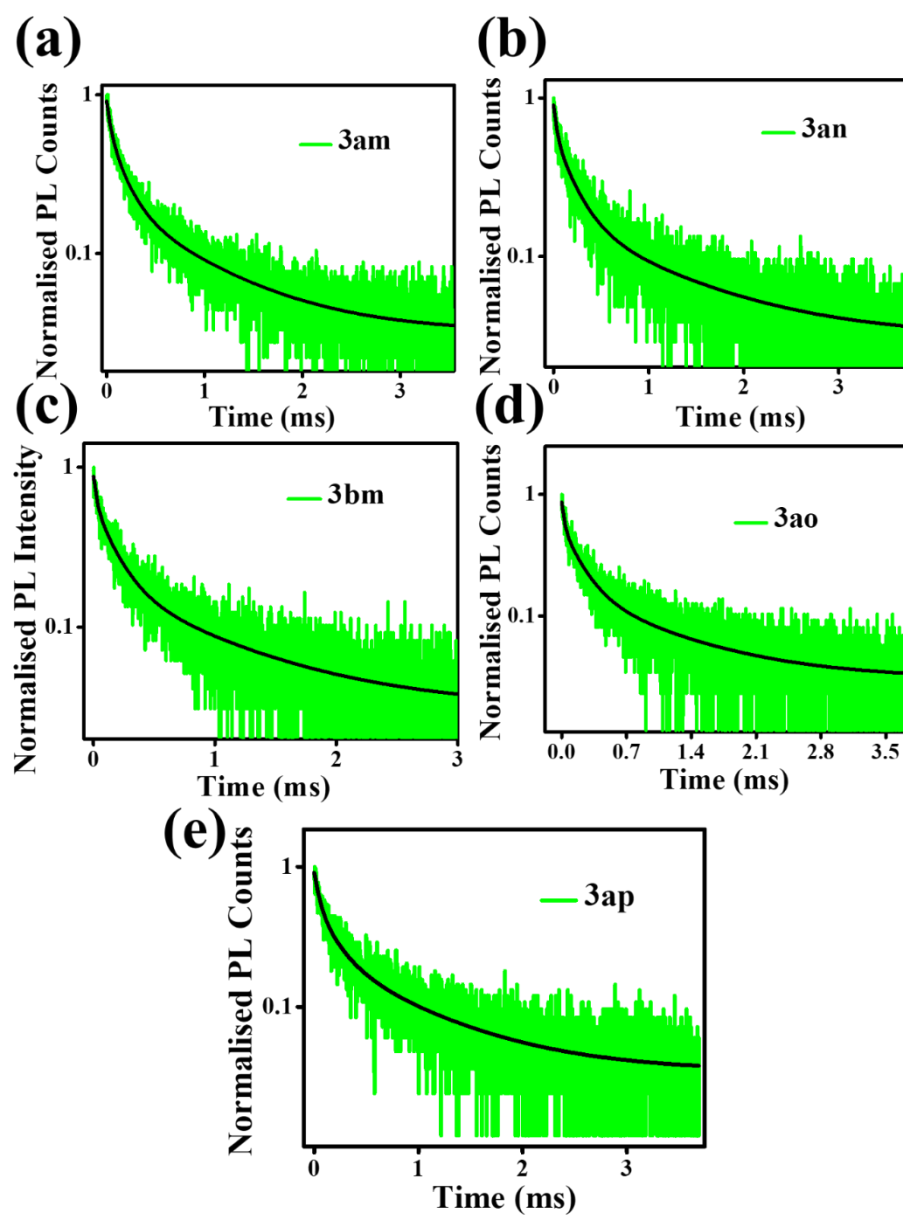
Quantitative amounts of PMMA are dissolved in spectroscopic grade chloroform by heating at 50°C for 10 minutes and followed by sonication for another 5 minutes. Thereafter, a quantitative amount of emitters has been added to the PMMA solution and 0.2 ml of the resulting solution is used for spin-coating on a quartz plate at 2000 rpm for 30 seconds. The quartz plate was then kept in high vacuum for another 20 minutes prior to photophysical studies.

### 2.7.8. Prompt fluorescence lifetimes ( $\tau_{PF}$ ) of 1 wt % emitter-doped PMMA films:



**Figure 6:** Prompt fluorescence lifetimes ( $\tau_{PF}$ ) of 1 wt % emitter-doped PMMA films of (a) 3am, (b) 3an, (c) 3bm, (d) 3ao, and (e) 3ap.

### 2.7.9. Delayed fluorescence lifetimes ( $\tau_{DF}$ ) of 1 wt % emitter-doped PMMA films:



**Figure 7:** Delayed fluorescence lifetimes ( $\tau_{DF}$ ) of 1 wt % emitter-doped PMMA films of (a) 3am, (b) 3an, (c) 3bm, (d) 3ao, and (e) 3ap.

#### 2.7.10. Co-ordinates of ground state optimized geometry of 3am:

|   |           |           |           |
|---|-----------|-----------|-----------|
| C | -6.638000 | -2.817000 | 0.608000  |
| C | -7.274000 | -1.670000 | 1.116000  |
| C | -6.643000 | -0.433000 | 1.089000  |
| C | -5.353000 | -0.339000 | 0.542000  |
| C | -4.725000 | -1.502000 | 0.032000  |
| C | -5.358000 | -2.747000 | 0.064000  |
| N | -4.608000 | 0.821000  | 0.462000  |
| C | -3.440000 | 0.611000  | -0.080000 |
| S | -3.144000 | -1.081000 | -0.587000 |
| C | -2.455000 | 1.649000  | -0.316000 |
| N | -2.824000 | 2.973000  | -0.477000 |
| C | -1.699000 | 3.726000  | -0.697000 |
| C | -0.596000 | 2.911000  | -0.679000 |
| C | -1.048000 | 1.582000  | -0.435000 |
| C | -4.175000 | 3.527000  | -0.474000 |
| C | -0.218000 | 0.410000  | -0.269000 |
| C | 1.096000  | 0.327000  | -0.570000 |
| C | 1.832000  | -0.920000 | -0.320000 |
| O | 3.139000  | -0.791000 | -0.702000 |
| O | 1.385000  | -1.946000 | 0.159000  |
| C | 3.945000  | -1.968000 | -0.539000 |
| C | 5.419000  | -1.607000 | -0.718000 |
| C | 6.037000  | -0.527000 | 0.110000  |
| O | 6.083000  | -2.255000 | -1.513000 |
| C | 7.375000  | -0.191000 | -0.152000 |
| C | 8.018000  | 0.784000  | 0.603000  |
| C | 7.334000  | 1.430000  | 1.637000  |
| C | 6.006000  | 1.099000  | 1.909000  |

C 5.356000 0.128000 1.148000

**2.7.11. Co-ordinates of ground state optimized geometry of 3an:**

C -5.430000 -3.646000 -1.368000

C -6.555000 -2.838000 -1.127000

C -6.415000 -1.550000 -0.628000

C -5.127000 -1.060000 -0.361000

C -4.002000 -1.885000 -0.607000

C -4.143000 -3.179000 -1.114000

N -4.843000 0.201000 0.124000

C -3.559000 0.390000 0.263000

S -2.544000 -1.018000 -0.177000

C -2.969000 1.611000 0.780000

N -3.666000 2.445000 1.634000

C -2.865000 3.507000 1.973000

C -1.650000 3.377000 1.347000

C -1.690000 2.179000 0.577000

C -5.014000 2.256000 2.160000

C -0.652000 1.688000 -0.299000

C 0.620000 2.143000 -0.345000

C 1.567000 1.587000 -1.316000

O 2.789000 2.185000 -1.184000

O 1.337000 0.709000 -2.130000

C 3.813000 1.822000 -2.124000

C 5.073000 1.362000 -1.386000

C 5.019000 0.163000 -0.497000

O 6.112000 1.984000 -1.549000

C 6.119000 -0.078000 0.342000

C 6.150000 -1.188000 1.176000

C 5.070000 -2.074000 1.161000

C 3.971000 -1.864000 0.329000

|    |          |           |           |
|----|----------|-----------|-----------|
| C  | 3.947000 | -0.742000 | -0.496000 |
| Cl | 5.100000 | -3.483000 | 2.208000  |

**2.7.12. Co-ordinates of ground state optimized geometry of 3bm:**

|   |           |           |           |
|---|-----------|-----------|-----------|
| C | -4.490000 | -4.852000 | 0.283000  |
| C | -5.282000 | -4.080000 | 1.152000  |
| C | -5.034000 | -2.726000 | 1.330000  |
| C | -3.976000 | -2.129000 | 0.627000  |
| C | -3.187000 | -2.917000 | -0.247000 |
| C | -3.434000 | -4.281000 | -0.422000 |
| N | -3.612000 | -0.800000 | 0.721000  |
| C | -2.584000 | -0.524000 | -0.034000 |
| S | -1.962000 | -1.910000 | -0.984000 |
| C | -1.989000 | 0.793000  | -0.161000 |
| N | -2.730000 | 1.953000  | 0.001000  |
| C | -1.899000 | 3.033000  | -0.178000 |
| C | -0.630000 | 2.591000  | -0.458000 |
| C | -0.658000 | 1.169000  | -0.450000 |
| C | -4.172000 | 2.028000  | 0.292000  |
| C | 0.476000  | 0.288000  | -0.625000 |
| C | 1.695000  | 0.655000  | -1.076000 |
| C | 2.773000  | -0.334000 | -1.174000 |
| O | 3.909000  | 0.249000  | -1.660000 |
| O | 2.704000  | -1.512000 | -0.868000 |
| C | 5.045000  | -0.599000 | -1.894000 |
| C | 6.284000  | -0.036000 | -1.189000 |
| C | 6.285000  | 0.128000  | 0.295000  |
| O | 7.259000  | 0.257000  | -1.864000 |
| C | 7.321000  | 0.884000  | 0.868000  |
| C | 7.390000  | 1.055000  | 2.246000  |

|   |           |           |          |
|---|-----------|-----------|----------|
| C | 6.429000  | 0.461000  | 3.071000 |
| C | 5.403000  | -0.302000 | 2.511000 |
| C | 5.324000  | -0.466000 | 1.128000 |
| C | -4.783000 | 3.407000  | 0.043000 |
| C | -6.301000 | 3.391000  | 0.272000 |
| C | -6.947000 | 4.762000  | 0.052000 |

### 2.7.13. Co-ordinates of ground state optimized geometry of 3ao:

|   |           |           |           |
|---|-----------|-----------|-----------|
| C | 6.704000  | 1.663000  | -3.031000 |
| C | 7.181000  | 2.386000  | -1.924000 |
| C | 6.659000  | 2.175000  | -0.655000 |
| C | 5.642000  | 1.222000  | -0.487000 |
| C | 5.171000  | 0.500000  | -1.611000 |
| C | 5.694000  | 0.715000  | -2.888000 |
| N | 5.027000  | 0.921000  | 0.712000  |
| C | 4.108000  | 0.006000  | 0.569000  |
| S | 3.921000  | -0.613000 | -1.100000 |
| C | 3.316000  | -0.526000 | 1.663000  |
| N | 3.786000  | -0.523000 | 2.963000  |
| C | 2.843000  | -1.095000 | 3.780000  |
| C | 1.759000  | -1.470000 | 3.028000  |
| C | 2.032000  | -1.117000 | 1.675000  |
| C | 5.081000  | -0.048000 | 3.441000  |
| C | 1.134000  | -1.264000 | 0.553000  |
| C | -0.011000 | -1.981000 | 0.549000  |
| C | -0.854000 | -2.016000 | -0.650000 |
| O | -1.956000 | -2.795000 | -0.435000 |
| O | -0.639000 | -1.439000 | -1.703000 |
| C | -2.849000 | -3.005000 | -1.541000 |
| C | -4.280000 | -2.625000 | -1.148000 |

|    |           |           |           |
|----|-----------|-----------|-----------|
| C  | -4.591000 | -1.223000 | -0.738000 |
| O  | -5.150000 | -3.481000 | -1.190000 |
| C  | -5.844000 | -0.977000 | -0.154000 |
| C  | -6.212000 | 0.307000  | 0.230000  |
| C  | -5.316000 | 1.357000  | 0.016000  |
| C  | -4.071000 | 1.142000  | -0.571000 |
| C  | -3.709000 | -0.151000 | -0.944000 |
| Br | -5.810000 | 3.126000  | 0.537000  |

#### 2.7.14. Co-ordinates of ground state optimized geometry of 3ap:

|   |           |           |           |
|---|-----------|-----------|-----------|
| C | -5.652000 | -3.551000 | -0.907000 |
| C | -6.689000 | -2.600000 | -0.852000 |
| C | -6.425000 | -1.273000 | -0.531000 |
| C | -5.102000 | -0.889000 | -0.257000 |
| C | -4.068000 | -1.857000 | -0.315000 |
| C | -4.332000 | -3.190000 | -0.642000 |
| N | -4.696000 | 0.393000  | 0.058000  |
| C | -3.406000 | 0.462000  | 0.243000  |
| S | -2.543000 | -1.094000 | 0.074000  |
| C | -2.698000 | 1.678000  | 0.607000  |
| N | -3.309000 | 2.679000  | 1.340000  |
| C | -2.412000 | 3.701000  | 1.534000  |
| C | -1.219000 | 3.379000  | 0.933000  |
| C | -1.375000 | 2.094000  | 0.333000  |
| C | -4.666000 | 2.685000  | 1.882000  |
| C | -0.396000 | 1.392000  | -0.467000 |
| C | 0.904000  | 1.737000  | -0.606000 |
| C | 1.791000  | 0.955000  | -1.475000 |
| O | 3.050000  | 1.487000  | -1.475000 |
| O | 1.489000  | -0.041000 | -2.113000 |

|   |          |           |           |
|---|----------|-----------|-----------|
| C | 4.040000 | 0.880000  | -2.325000 |
| C | 5.325000 | 0.621000  | -1.533000 |
| C | 5.293000 | -0.270000 | -0.339000 |
| O | 6.364000 | 1.144000  | -1.917000 |
| C | 6.411000 | -0.289000 | 0.514000  |
| C | 6.438000 | -1.122000 | 1.625000  |
| C | 5.358000 | -1.975000 | 1.919000  |
| C | 4.252000 | -1.961000 | 1.058000  |
| C | 4.212000 | -1.119000 | -0.054000 |
| C | 5.389000 | -2.864000 | 3.138000  |



## 2.8. HPLC Data:

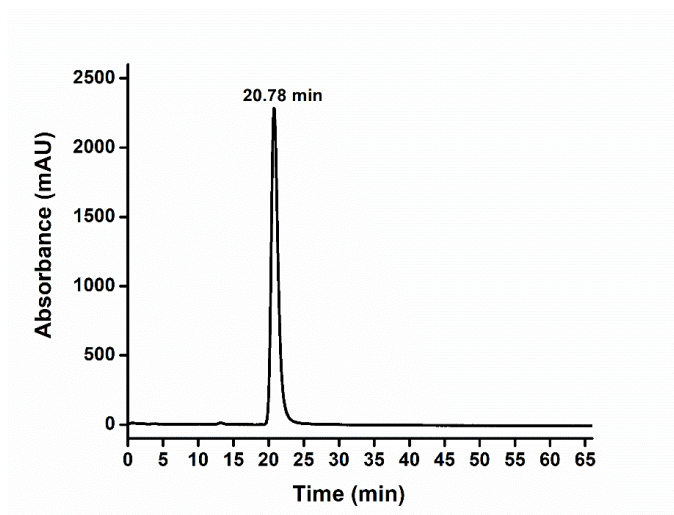
HPLC of all the five compounds (**3am-3ap**) did with

CHIRALPAK IA column,

Hexane/IPA= 70/30,

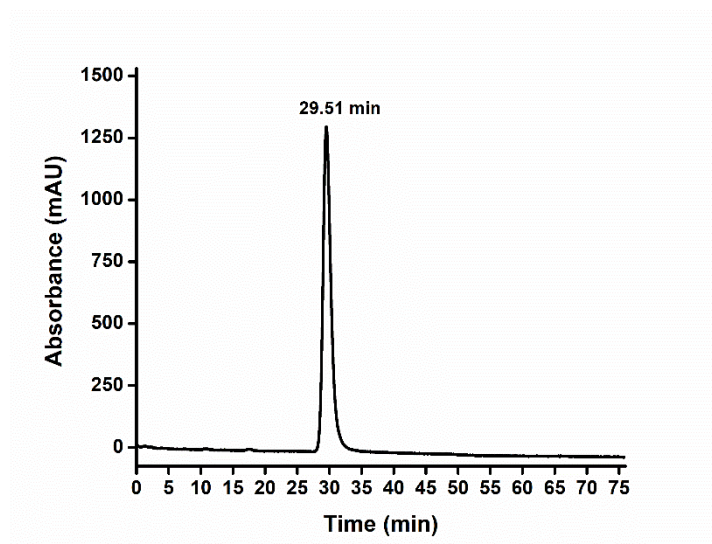
Flow rate = 0.5 mL/min,  $\lambda$  = 254 nm

### 1) HPLC Data of compound **3am**:



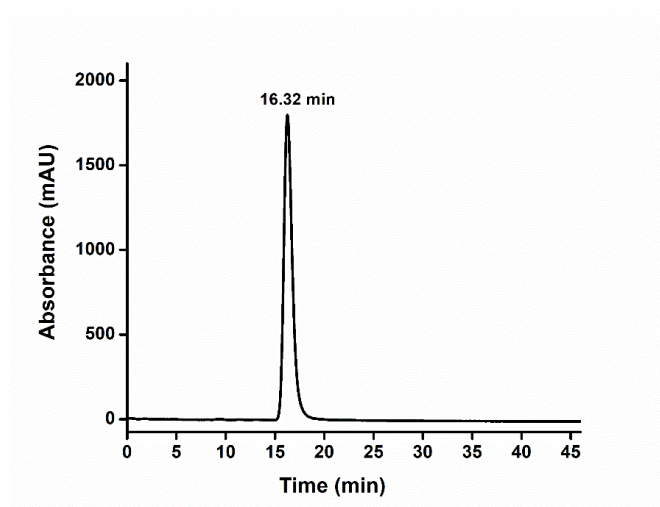
| # | Time  | Area      | Area% | Height  | Height % |
|---|-------|-----------|-------|---------|----------|
| 1 | 20.78 | 15628.207 | 100   | 227.909 | 100      |

### 2) HPLC Data of compound **3an**:



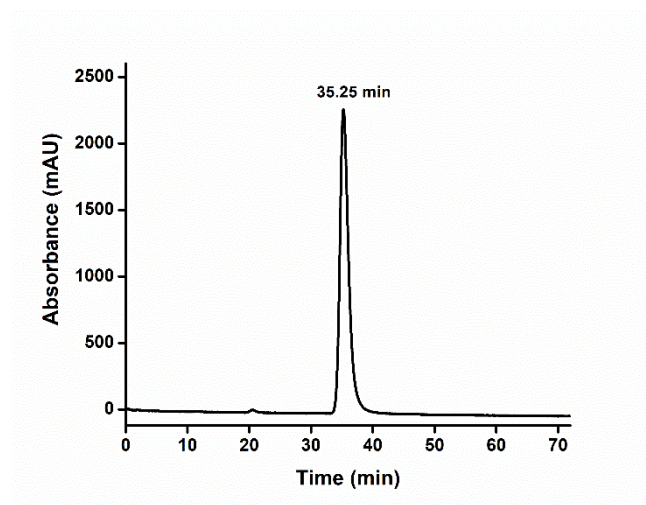
| # | Time  | Area     | Area% | Height | Height % |
|---|-------|----------|-------|--------|----------|
| 1 | 29.51 | 5630.123 | 100   | 68.394 | 100      |

3) HPLC Data of compound **3bm**:



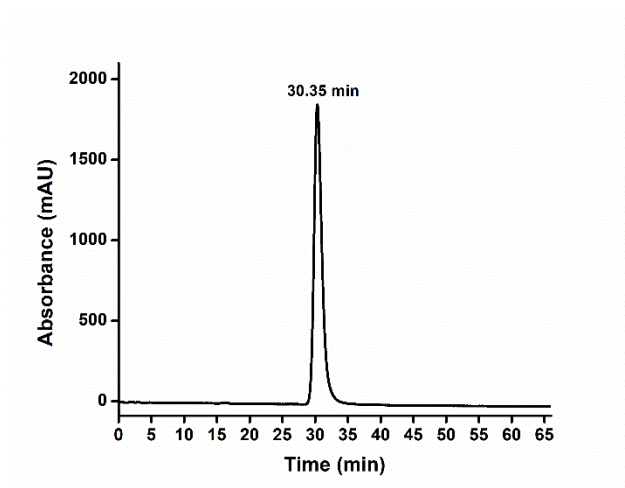
| # | Time  | Area      | Area% | Height  | Height % |
|---|-------|-----------|-------|---------|----------|
| 1 | 16.32 | 10882.640 | 100   | 180.039 | 100      |

4) HPLC Data of compound **3ao**:



| # | Time  | Area      | Area% | Height  | Height % |
|---|-------|-----------|-------|---------|----------|
| 1 | 35.25 | 11181.555 | 100   | 113.997 | 100      |

5) HPLC Data of compound **3ap**:



| # | Time  | Area      | Area% | Height  | Height % |
|---|-------|-----------|-------|---------|----------|
| 1 | 30.35 | 15898.495 | 100   | 186.067 | 100      |

2.9. Appendix IIB:  $^1\text{H}$ ,  $^{13}\text{C}$  spectral data of representative compounds

| Compound No. | Figure II.X                   | Data                                               | Page No |
|--------------|-------------------------------|----------------------------------------------------|---------|
| <b>3aa</b>   | Figure II.1 and II.2          | $^1\text{H}$ and $^{13}\text{C}$                   | 90      |
| <b>3ac</b>   | Figure II.3 and II.4          | $^1\text{H}$ and $^{13}\text{C}$                   | 91      |
| <b>3ga</b>   | Figure II.5 and II.6          | $^1\text{H}$ and $^{13}\text{C}$                   | 92      |
| <b>4a</b>    | Figure II.7 and II.8 and II.9 | $^1\text{H}$ , $^{13}\text{C}$ and $^{19}\text{F}$ | 93-94   |
| <b>3am</b>   | Figure II.10 and II.11        | $^1\text{H}$ and $^{13}\text{C}$                   | 95      |
| <b>3ca</b>   | Figure II.12                  | ORTEP plot                                         | 96      |
| <b>4a</b>    | Figure II.13                  | ORTEP plot                                         | 96      |
| <b>3am</b>   | Figure II.14                  | ORTEP plot                                         | 97      |

Figure II.1  $^1\text{H}$  NMR spectrum of **3aa**,  $\text{CDCl}_3$ , 400 MHz

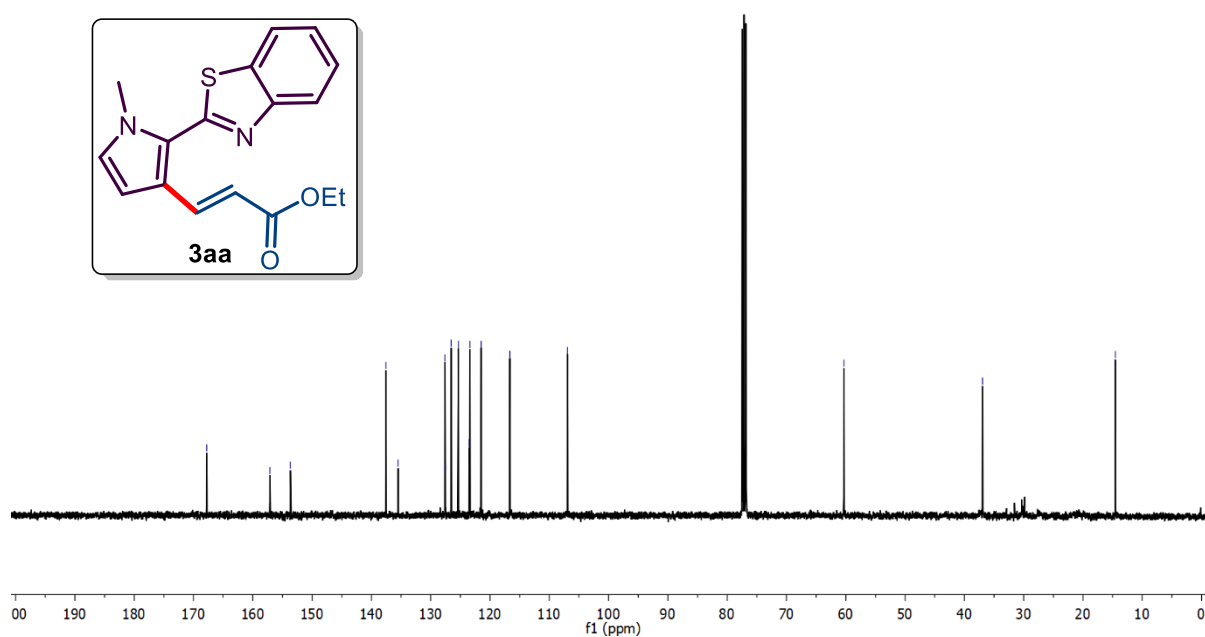
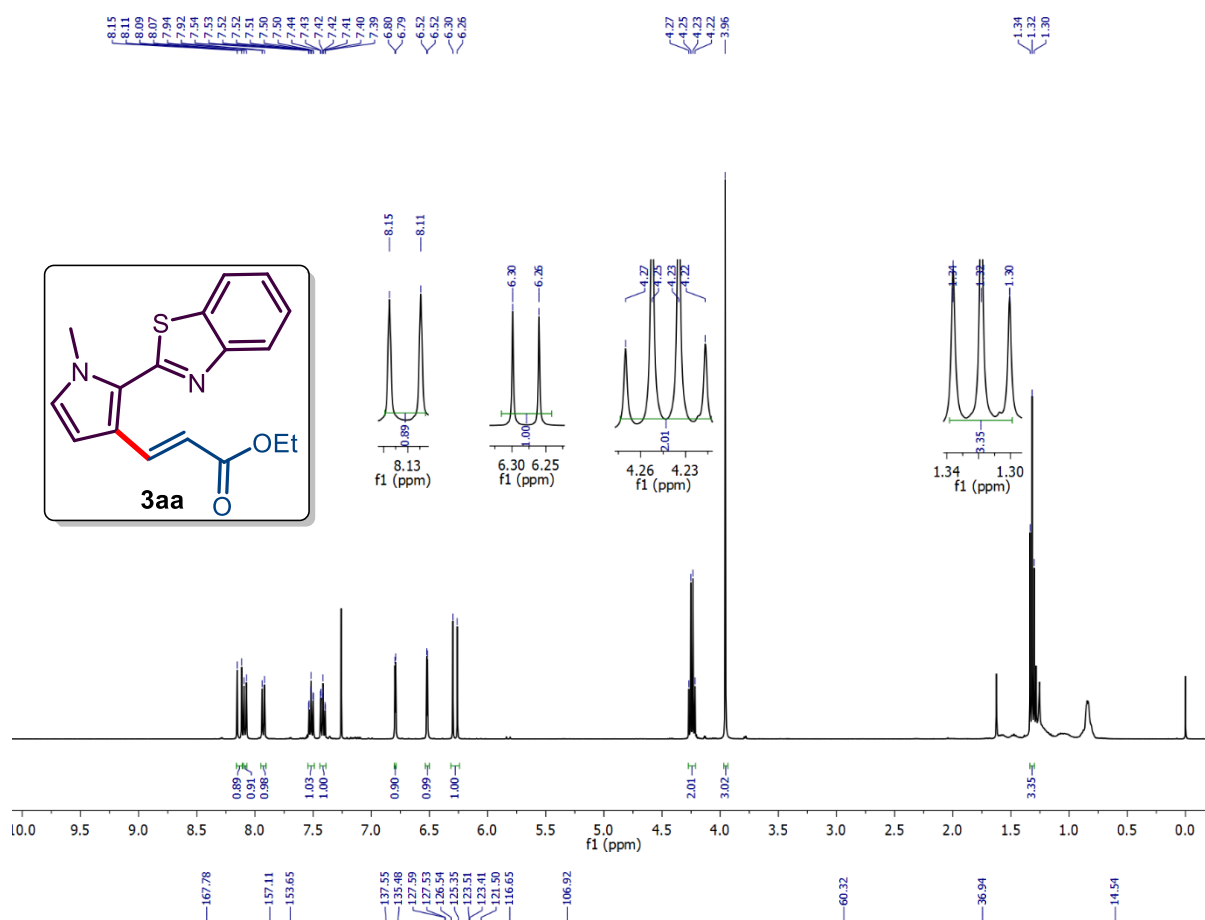


Figure II.2  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3aa**,  $\text{CDCl}_3$ , 400 MHz

Figure II.3  $^1\text{H}$  NMR spectrum of **3ca**,  $\text{CDCl}_3$ , 400 MHz

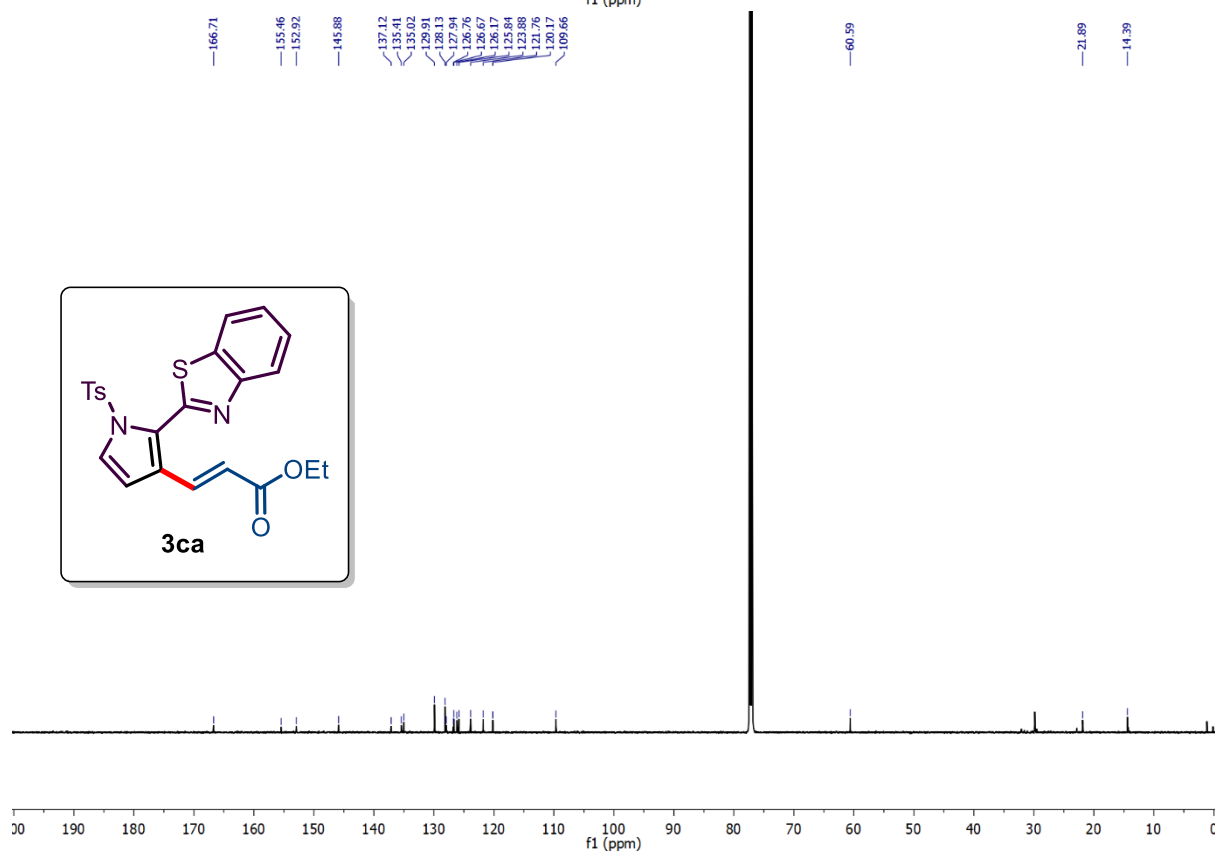
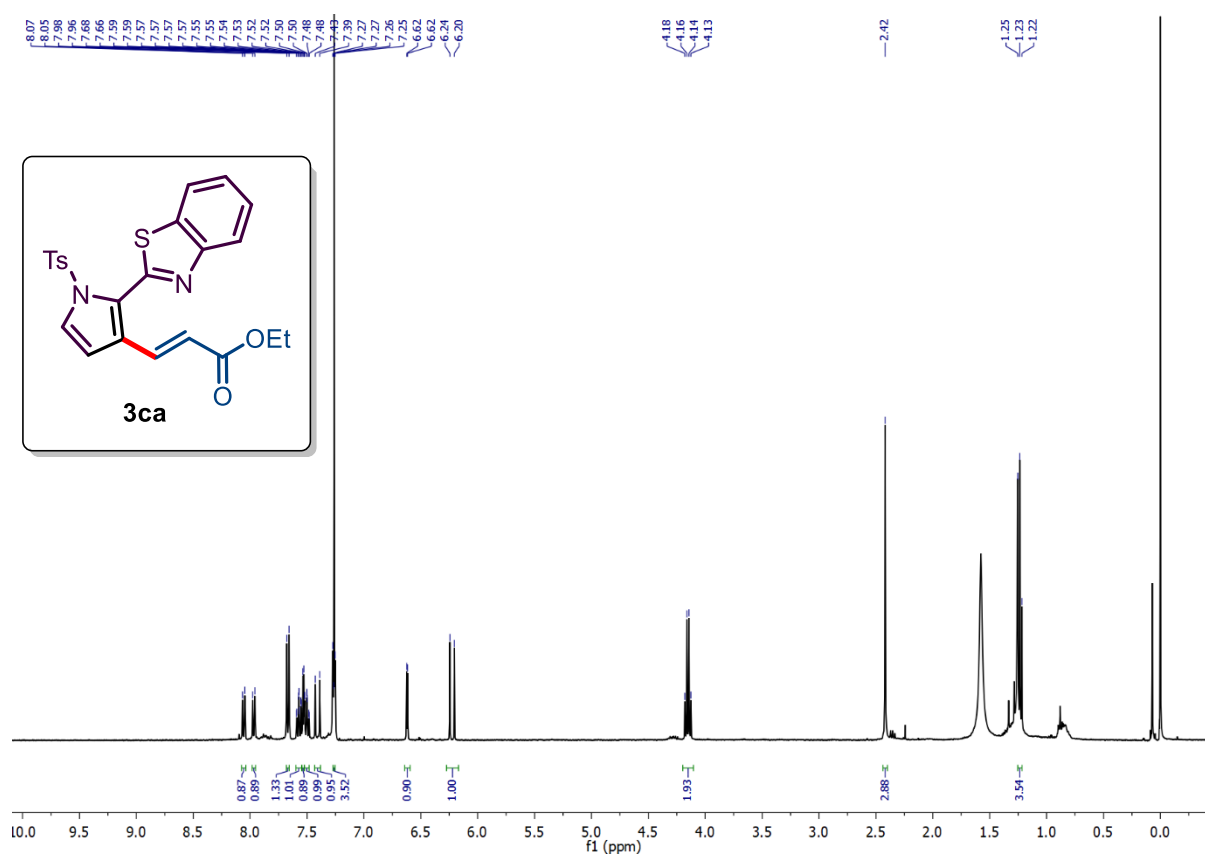


Figure II.4  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3ca**,  $\text{CDCl}_3$ , 400 MHz

Figure II.5  $^1\text{H}$  NMR spectrum of **3ga**,  $\text{CDCl}_3$ , 400 MHz

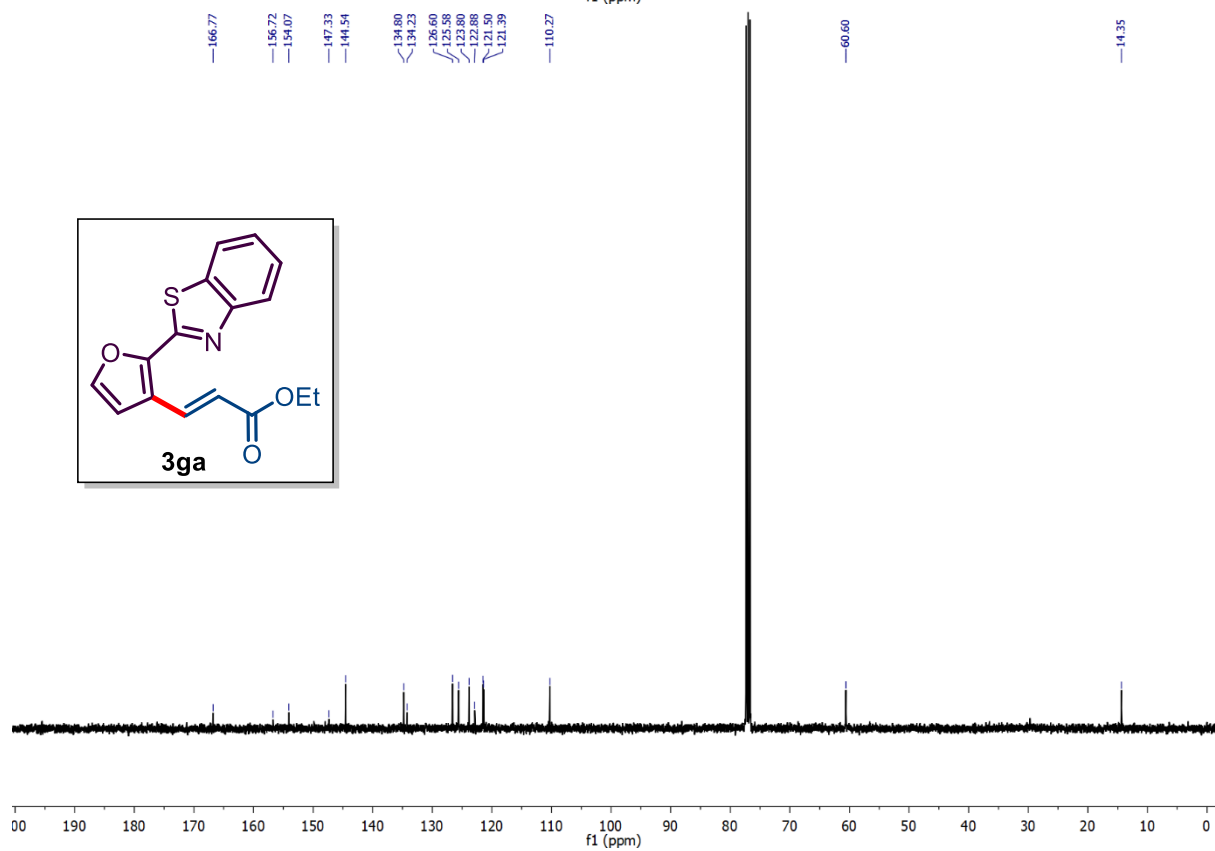
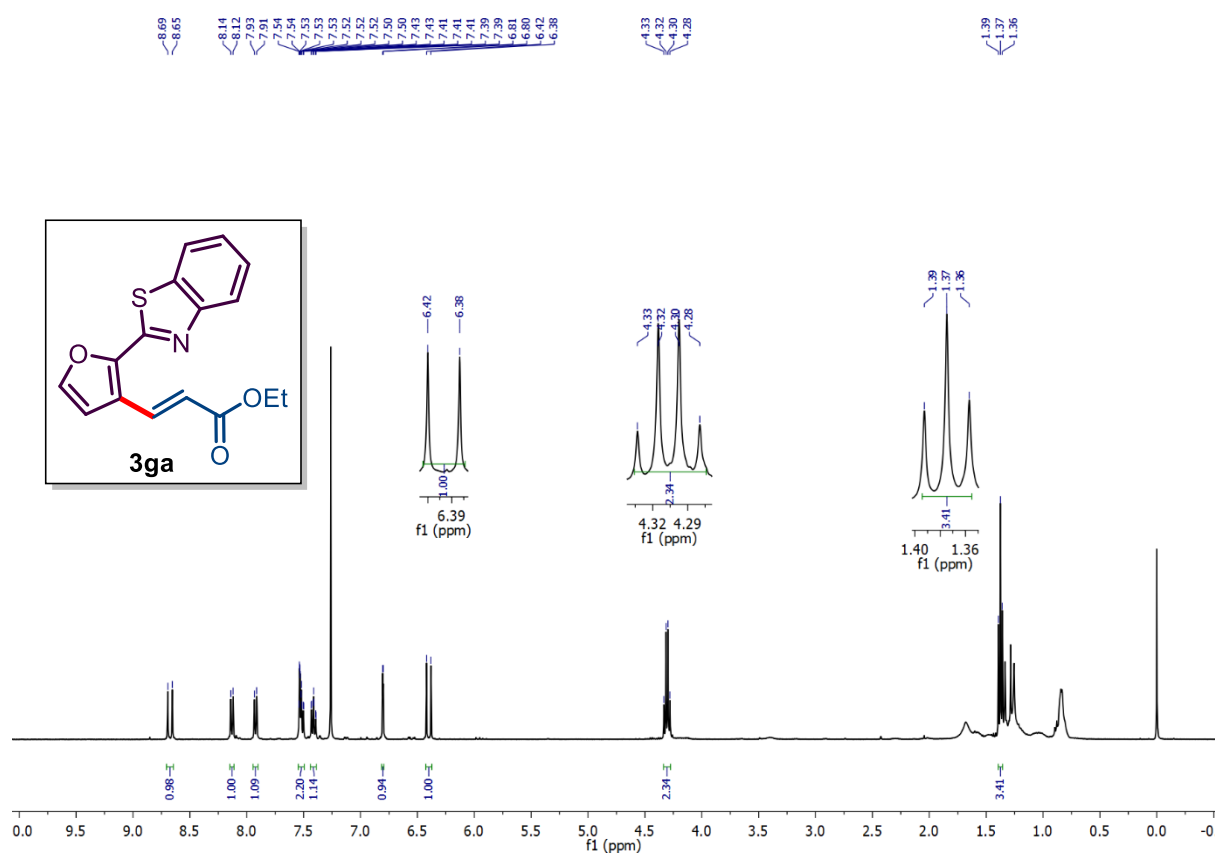
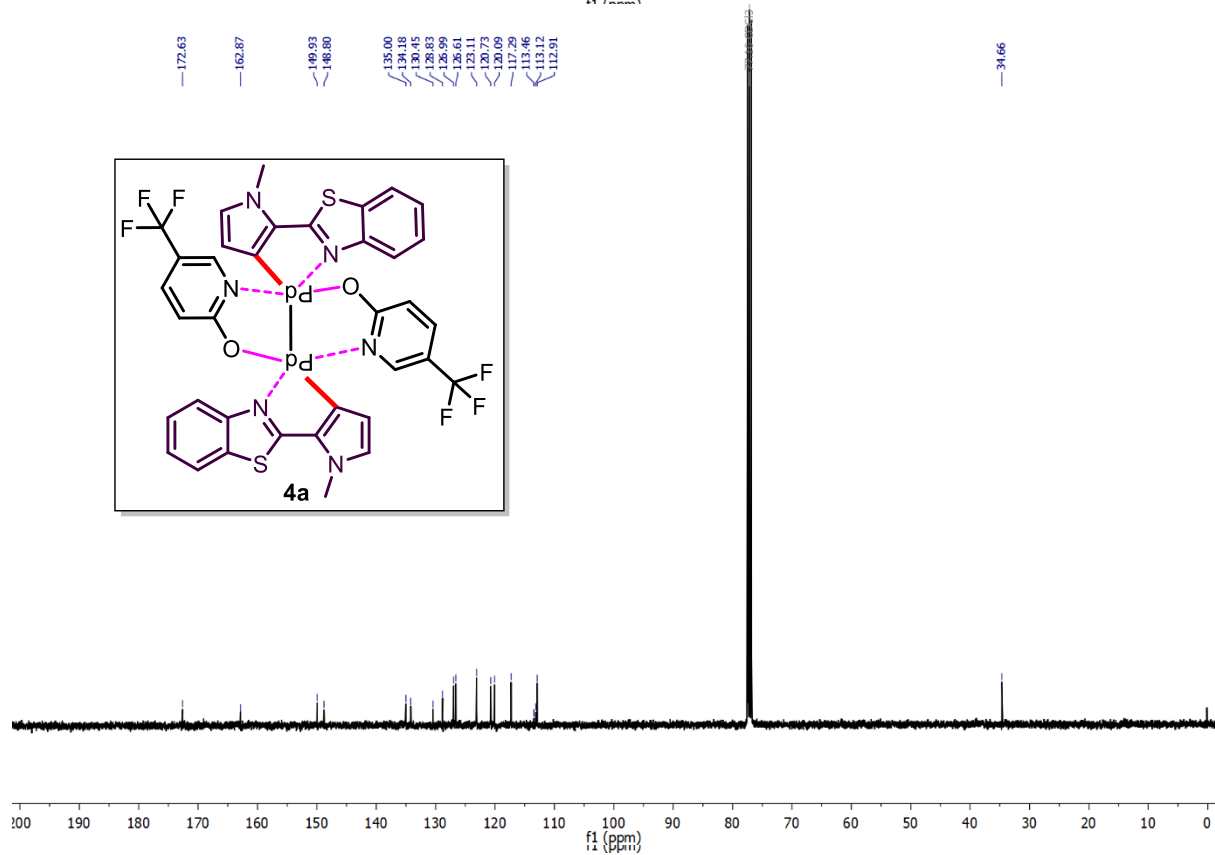
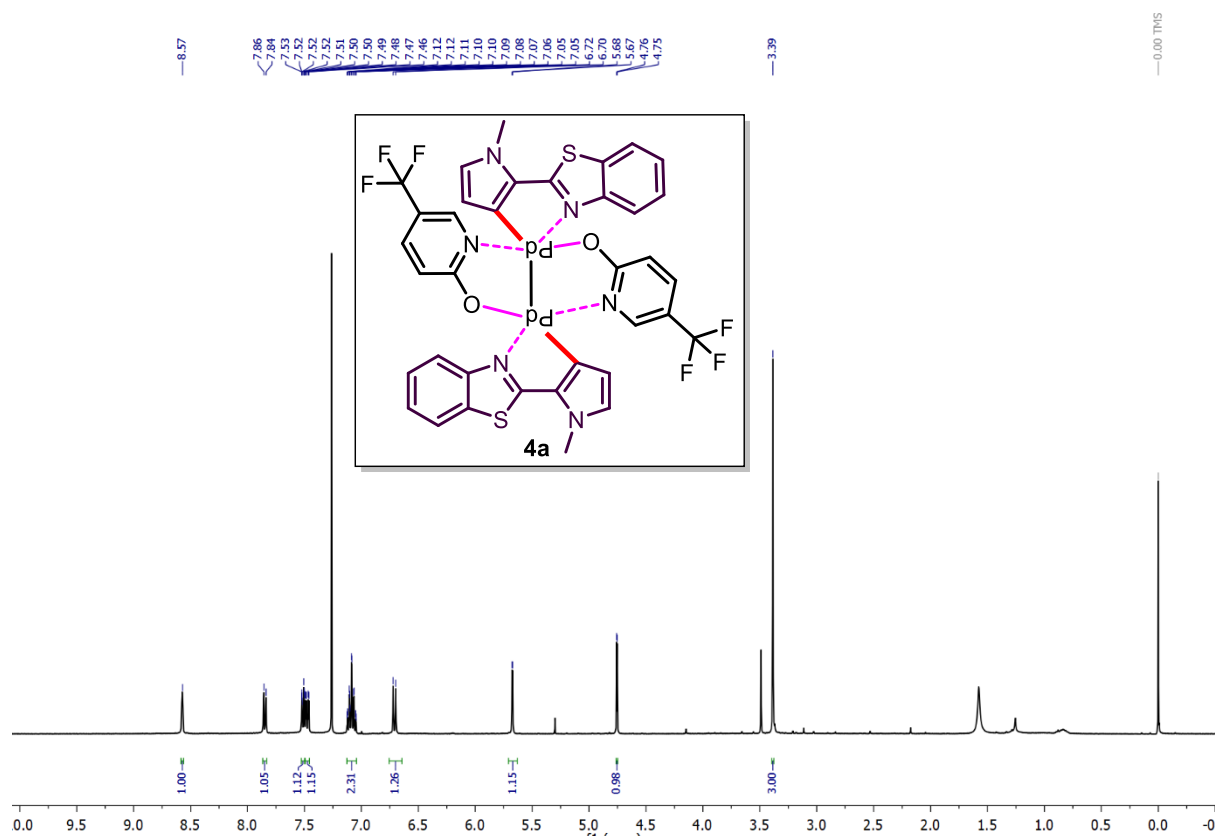


Figure II.6  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3ga**,  $\text{CDCl}_3$ , 400 MHz

**Figure II.7**  $^1\text{H}$  NMR spectrum of **4a**,  $\text{CDCl}_3$ , 400 MHz



**Figure II.8**  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **4a**,  $\text{CDCl}_3$ , 400 MHz

**Figure II.9**  $^{19}\text{F}$  NMR spectrum of **4a**,  $\text{CDCl}_3$ , 400 MHz

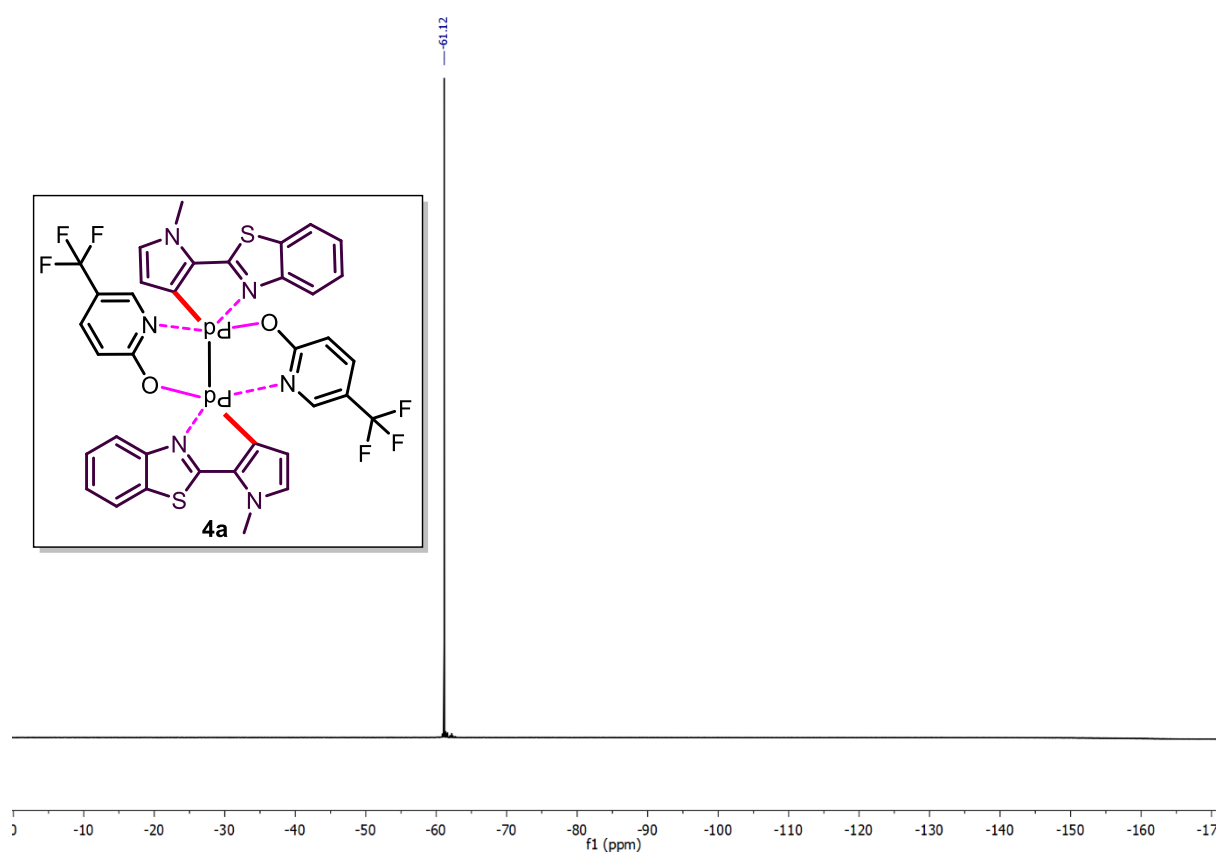




Figure II.10  $^1\text{H}$  NMR spectrum of **3am**,  $\text{CDCl}_3$ , 400 MHz

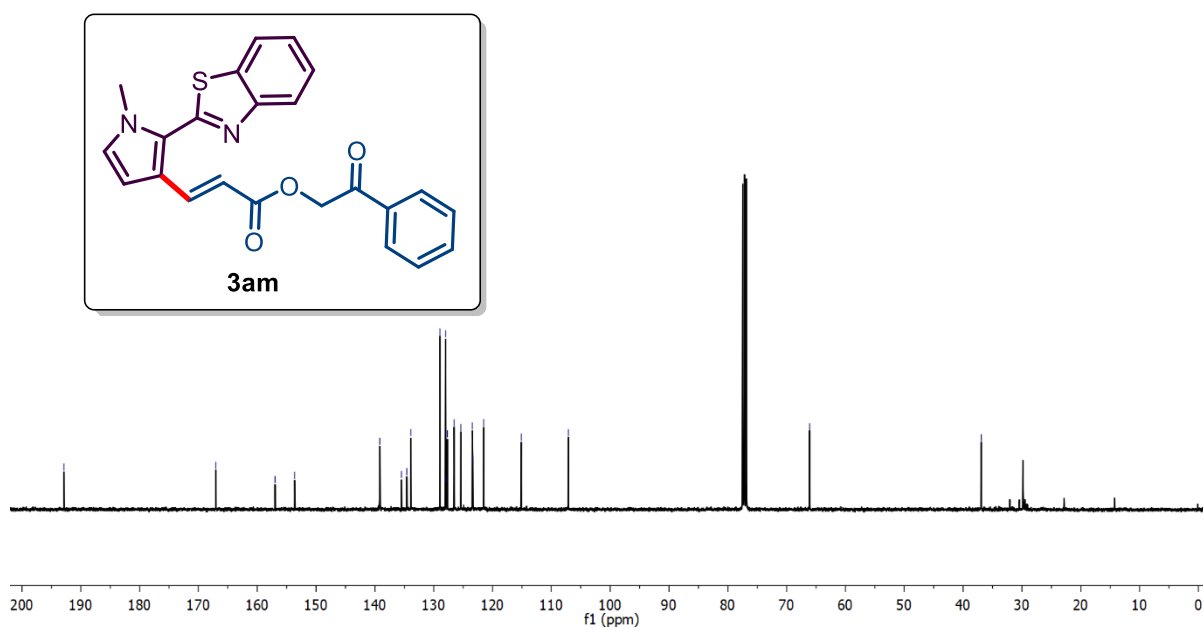
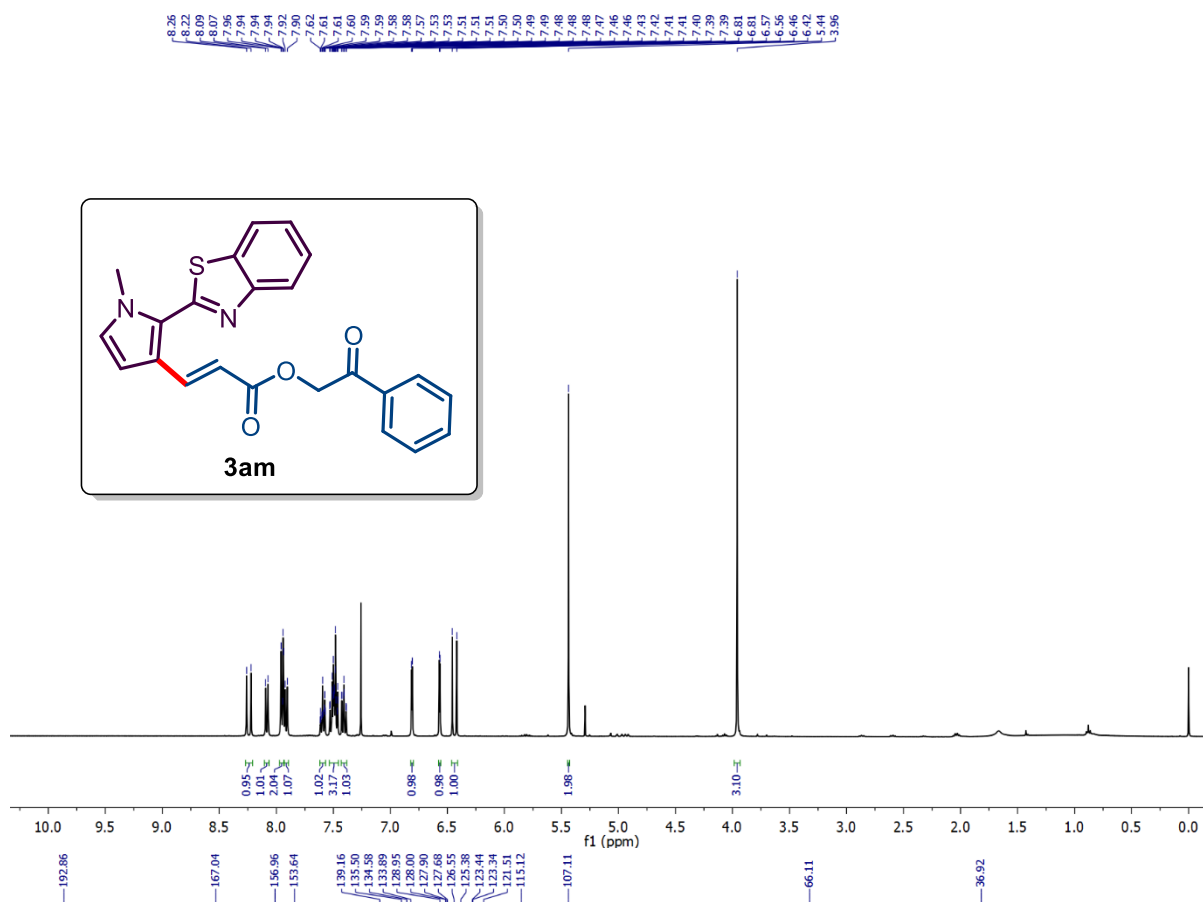
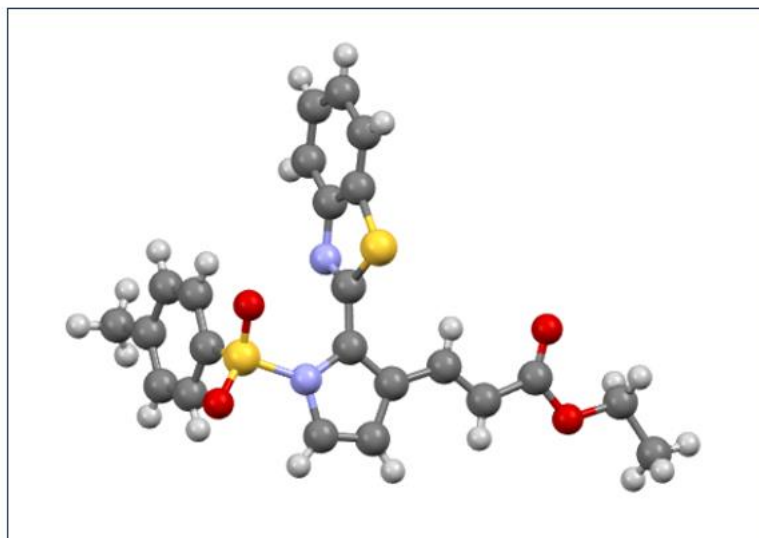
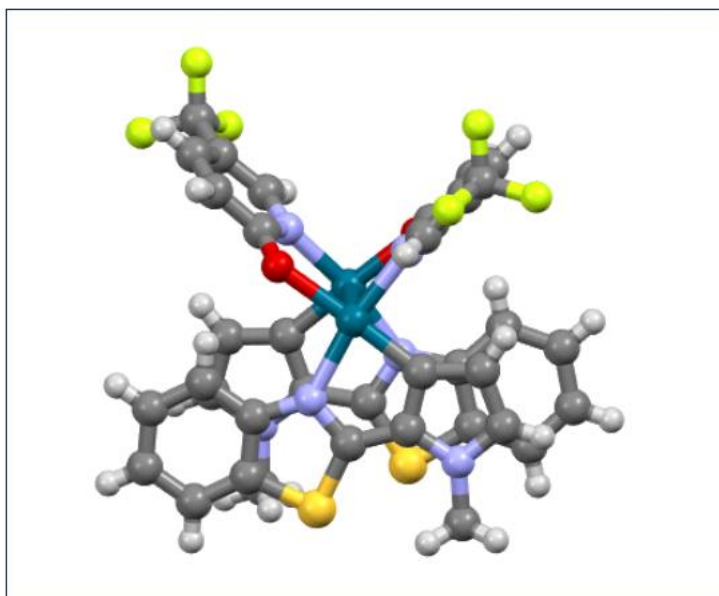


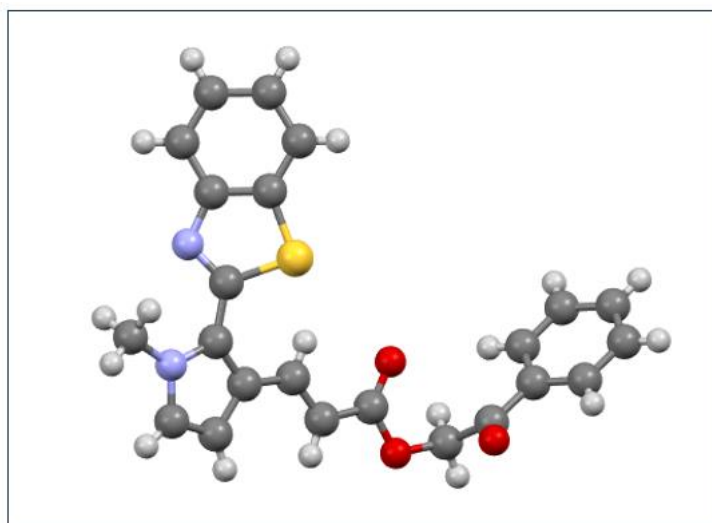
Figure II.11  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3am**,  $\text{CDCl}_3$ , 400 MHz



**Figure III.12** ORTEP plot (thermal ellipsoids set at 50% probability) of the structures obtained from single crystal X-ray diffraction analyses of **3ca**



**Figure III.13** ORTEP plot (thermal ellipsoids set at 50% probability) of the structures obtained from single crystal X-ray diffraction analyses of **4a**



**Figure III.14** ORTEP plot (thermal ellipsoids set at 50% probability) of the structures obtained from single crystal X-ray diffraction analyses of **3am**

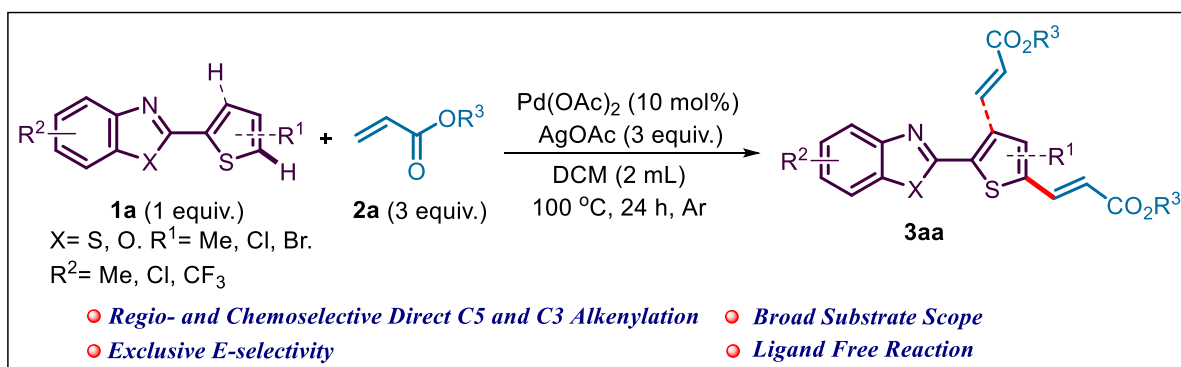
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**Abstract:** The direct regioselective C5 and C3-(sp<sup>2</sup>)-H alkenylation of 2-thiophene benzothiazoles has been successfully developed via palladium (II) catalysis. A wide range of acrylates have been explored and they found to undergo oxidative dehydrogenative coupling (DHR) with the 2-(thiophen-2-yl)benzo[d]thiazole to furnish the regio- and chemo-selective C5 and C3-alkenylated products with an exclusive E-selectivity. This strategy provides a straightforward and efficient way to develop the direct C5 and C3 alkenylated thiophene derivatives with a broad substrate scope in modest to good yields.



Shaikh, J. Y.; Bhowmick, A.; Chatterjee, A.; Laha D.; Bhat R. G, Manuscript is about to be communicated

### 3.1 Introduction

The selective C-H bond activation and subsequent functionalization of selective C-H bond in presence of multiple C-H bonds via transition metal catalysis has become an important topic of research in organic synthesis. The C-H activation has grown rapidly due their synthetic utility and advantages over the traditional metal-catalyzed cross-coupling reactions as they don't require two pre-functionalized starting materials. Also they can be utilized for the late stage modification and some of these strategies proved to be atom as well as step efficient.<sup>1,2</sup> Additionally, as an application, the direct C-H activation of heteroaromatic compounds has proven to be efficient and advantageous as the five membered heterocyclic scaffolds are ubiquitously found bioactive molecules, natural products and also their derivatives have been explored as pharmaceutical compounds.<sup>3</sup> The heteroarenes such as thiophene is also significant and prevalent scaffold that serves as the fundamental building block for a variety of biologically active compounds and organic functional materials.<sup>3,4</sup>

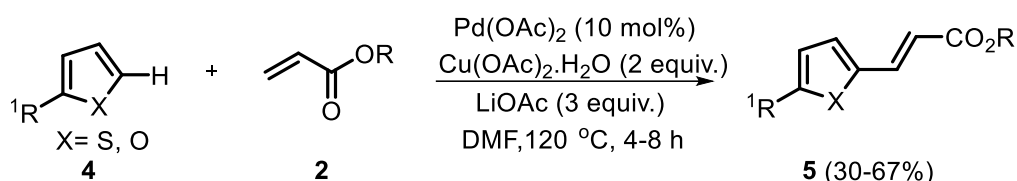
The functionalization of thiophene and its derivatives is usually difficult, especially for the selective functionalization of thiophenes with olefin moieties. Some of few traditional methods for alkenylation of the thiophene moieties include formylation followed by the Wittig reaction and cross coupling reactions etc.<sup>5,6</sup> Even though these methods are very useful and extensively used, however there associated drawbacks, such as the necessity of pre-functionalized starting materials, the use of expensive reagents in stoichiometric amounts and multi-step synthesis, inability of late-stage modifications etc. However, in the recent years a lot of interest in the palladium-catalyzed intermolecular dehydrogenative Heck reaction (DHR)<sup>7</sup> or Fujiwara Moritani reaction<sup>8</sup> has been focused by many research groups. In these strategies a diverse range of aromatic and heteroaromatic compounds with various olefins have been significantly explored.

Also, the alkenylation of the heterocyclic scaffolds with various alkenes has been successfully developed by several research groups.<sup>9,10</sup> Over the years, the C-H activation has been explored for the synthesis of alkenylated aromatic/heteroaromatic substrates using easily accessible alkenes<sup>11</sup> by employing a variety of directing groups<sup>12</sup> and an external ligand.<sup>13</sup> Some of the representative recent examples have been highlighted below.



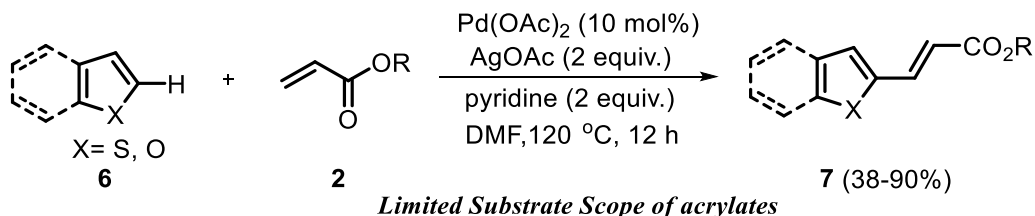
### 3.2 Recent approaches for the C5/C2 (sp<sup>2</sup>)-H bond activation in five-membered heterocyclic compounds

Miura, Satoch and coworker in 2008 reported for the oxidative vinylation of the heterocyclic compounds **4** with electron deficient alkenes **2** in presence of palladium catalyst such as Pd(OAc)<sub>2</sub>, copper acetate monohydrate under weakly basic condition in DMF solvent at 120 °C to furnish the corresponding alkenylated products **5** in moderate to good yields (up to 67% Scheme 3.1).<sup>10a</sup>



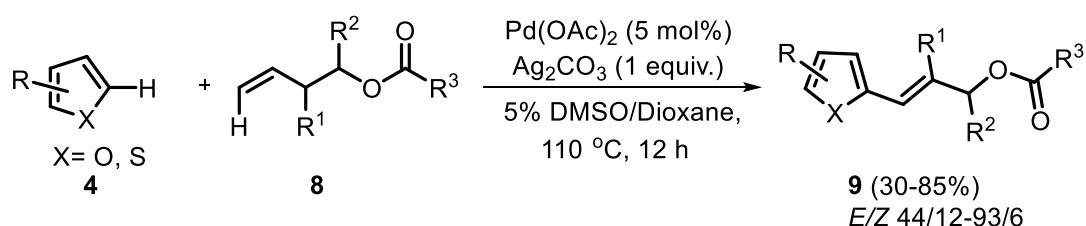
**Scheme 3.1** Alkenylation of the heterocyclic compounds under weakly basic conditions

In 2009 Zhang and coworkers reported the alkenylation of heterocyclic compounds **6** with electron deficient alkenes **2** in presence of palladium catalyst such as Pd(OAc)<sub>2</sub>, silver acetate as an oxidant, pyridine as base in DMF solvent at 120 °C to gives the corresponding alkenylated products **7** in moderate to good yields (up to 90% Scheme 3.1).<sup>10b</sup>



**Scheme 3.2** Alkenylation of heterocyclic compounds.

Later in 2011, Liu and coworkers reported the olefination of the five membered heterocycles **4** using allyl esters **8** in presence of palladium catalyst such as Pd(OAc)<sub>2</sub>, Ag<sub>2</sub>CO<sub>3</sub> as an oxidant, in DMSO/dioxane solvent at 110 °C to led the corresponding *E/Z* alkenylated products **9** in moderate to good yields (up to 85%, Scheme 3.2).<sup>14</sup>



**Scheme 3.3** Alkenylation of heterocyclic compounds with allyl esters.

### 3.3 Rationale for the work:

Despite the progress in the direct alkenylation strategies and available protocols, there are some limitations, such as the narrow substrate scope with electron-deficient olefins etc. Additionally, benzothiazole moiety is a prominent scaffold that is also found in many pharmaceuticals and optical research materials due to its fluorescent properties and its use as a directing group for the C-H bond functionalization of aromatic/heteroaromatic compounds.<sup>15,16</sup> As a result, it has always been difficult to perform the C5 and C3-(sp<sup>2</sup>)-H alkenylation of 2-(thiophen-2-yl)benzo[d]thiazole/oxazoles in presence of transition metal catalysts using a variety of acrylates. Looking at the challenges associated with this and available literature reports, it is important to investigate the alkenylation reaction of 2-thiophene benzo[d]thiazoles/oxazoles with different acrylates under practical conditions. Also, it is important to highlight that the effective regioselective C5 and C3-(sp<sup>2</sup>)-H alkenylation of 2-(thiophen-2-yl)benzo[d]thiazole/oxazoles with a wide range of acrylates via palladium catalysis has not reported till date to the best of our knowledge.

Based on our earlier experience and continuous interest in the alkenylation of heteroarenes via C-H bond activation via palladium catalysis, we hypothesized that under suitable reaction conditions with different acrylates, one could directly access the desired C5 and C3 alkenylated 2-thiophene benzo[d]thiazoles/oxazoles

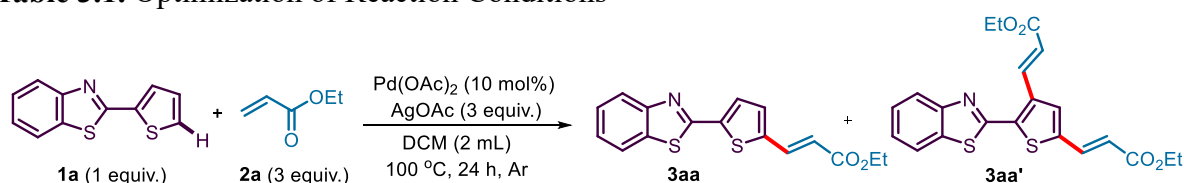
### 3.4 Results and Discussion

In order to explore the feasibility of the hypothesis, we began with 2-(thiophen-2-yl)benzo[d]thiazole **1a** (0.1 mmol) with ethyl acrylate **2a** (0.3 mmol) as model substrates in the presence of palladium catalyst Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (3 equiv.) in DCM (2 mL) at 100 °C for 24 h under inert environment (Ar). We gratifyingly observed the formation of ethyl (*E*)-3-(5-(benzo[d]thiazol-2-yl)thiophen-2-yl)acrylate **3aa** in 70 % yield (Table 1, Entry 1) along with dialkenylated product diethyl 3,3'-(5-(benzo[d]thiazol-2-yl)thiophene-2,4-diyl)(2*E*,2'*E*)-diacrylate **3aa'** in poor yield (18 % yield). This initial optimized condition proved to be encouraging.

With these initial results in hand, we began to explore the reaction conditions further by screening a variety of solvents for improving the yields. Among all solvents, DCM proved to be the best solvent for this desired transformation (See, Appendix-III A, Table 1, page no. 120). We further screened several oxidants as well as different palladium catalysts such as Pd(II) to Pd(0). We observed that among all Pd(OAc)<sub>2</sub> and AgOAc proved to be efficient catalyst and

oxidant for this reaction (See, Appendix-III A, Table 2, 3, page no. 120-121). Furthermore, we noticed that the reaction did not proceed in the absence of a palladium catalyst (Table 1, Entry 2). Also, the reaction in the absence of AgOAc afforded the desired product **3aa** in low yield (15%, Table 1, Entry 3). Further, the reduction in the stoichiometric amount of **2a** (3 equiv. to 2 equiv.) led to the reduction in the yield of desired product **3aa** (60%, Table 1, Entry 4). We also carried out the reaction by varying the temperature to study the effect of temperature on the overall transformation. We observed that the desired alkenylated product **3aa** was obtained in relatively lower yields when the temperature was varied (low to high, 59-57 °C) (Table 1, Entries 5-6). Later, the reaction of **1a** and **2a** under an open atmosphere (air) while maintaining the remaining optimized conditions led to the desired product **3aa** in modest yield (47% , Table 1, Entry 15). After the systematic screening, the reaction of 2-(thiophen-2-yl)benzo[d]thiazole **1a** (0.1 mmol) with ethyl acrylate **2a** (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (0.3 mmol) in DCM (2 mL) at 100 °C under inert atmosphere (Ar) for 24 h has the best optimized reaction conditions to afford the desired product.

**Table 3.1.** Optimization of Reaction Conditions<sup>(a)</sup>



| Entry | Deviation from standard conditions   | Yield(%) <sup>b</sup> |      |
|-------|--------------------------------------|-----------------------|------|
|       |                                      | 3aa                   | 3aa' |
| 1     | None                                 | 70                    | 18   |
| 2     | Without Pd(OAc) <sub>2</sub>         | N.R.                  | -    |
| 3     | Without AgOAc                        | 15                    | -    |
| 4     | 2a (2 equiv.) instead of (3 equiv.)  | 60                    | 15   |
| 5     | Temperature 90 °C instead of 100 °C  | 59                    | 15   |
| 6     | Temperature 110 °C instead of 100 °C | 57                    | 13   |
| 7     | Air instead of Argon atmosphere      | 47                    | 9    |

<sup>[a]</sup>Standard conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (0.3 mmol), DCM (2 mL), 100 °C, Ar, 24 h; <sup>[b]</sup>Isolated yields of **1a** after column chromatography; N.R.- No Reaction.

Having obtained the optimized reaction conditions, we expand the substrate scope of 2-(thiophen-2-yl)benzo[d]thiazole **1a** using a wide range of acrylates **2**. We observed that 2-(thiophen-2-yl)benzo[d]thiazole **1a** reacted smoothly with a wide range of acrylates (**2a-2l**) having aliphatic as well aromatic groups (ester moiety) to afford the corresponding derivatives (**3aa-3al**) in moderate to good yields (up to 70%, Table 3.2). The ethyl crotonate **2m** also reacted well to produce the desired product (**3am**) with a lower yield (28%).

Interestingly the ethyl methacrylate (**2n**) and phenyl methacrylate (**2o**) also reacted well under the optimized reaction conditions to give the corresponding isomerised products (**3an-3ao**) in lower yields (up to 36%, Table 3.2). Further the trifluoromethylated (CF<sub>3</sub>) benzothiazole containing thiophene compound (**1b**) also reacted with ethyl acrylate (**2a**) furnished the desired alkenylated product (**3ba**) in good yield (62%, Table 3.2).

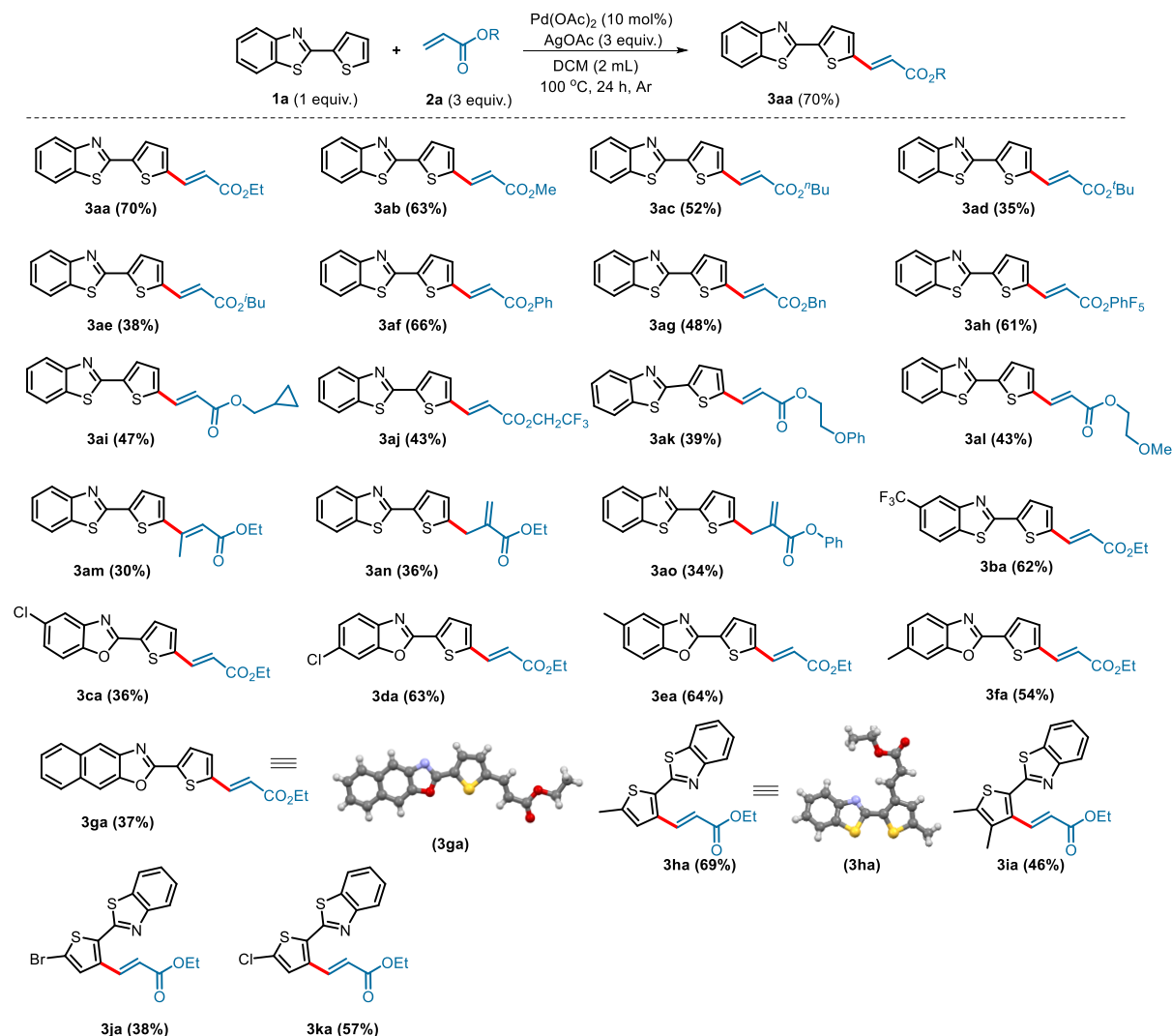
The chloro and methyl substituted benzo[d]oxazole substituted thiophene compounds (**1c-1f**) also reacted efficiently with ethyl acrylate (**2a**) to furnish the required C5 alkenylated products (**3ca-3fa**) in moderate to good yields (up to 64%, Table 3.2). The 2-(thiophen-2-yl)naphtho[2,3-d]oxazole (**1g**) also reacted well with ethyl acrylate (**2a**) to furnish the desired C5 alkenylated product (**3ga**) in modest yield (37%, Table 3.2). We have also characterized the **3ga** by single crystal X-ray analysis and the molecule structure unambiguously proved the structure and alkenylation site (C5-alkenylation, see Table 3.2). In this reactions the thiophene gives the C5 alkenylated product regioselectivity because may be the thiophene undergoes the electrophilic metalations preferentially at the C5 positions.

When the more reactive C5 positions are substituted with alkyl or halo groups the alkenylation occurs regioselectivity at the C3 positions may be because of the benzothiazole group. Later, we explored the reaction of C5-methyl and C5-halo substituted thiophene-benzothiazoles (**1h-1k**) with ethyl acrylate (**2a**) under optimized reaction condition to afford the corresponding C3-alkenylated products (**3ha-3ka**) in moderate to good yields. Along with the desired C5 alkenylated product we have observed the formation of the (C5/C3) dialkenylated products in small amount (<12%).

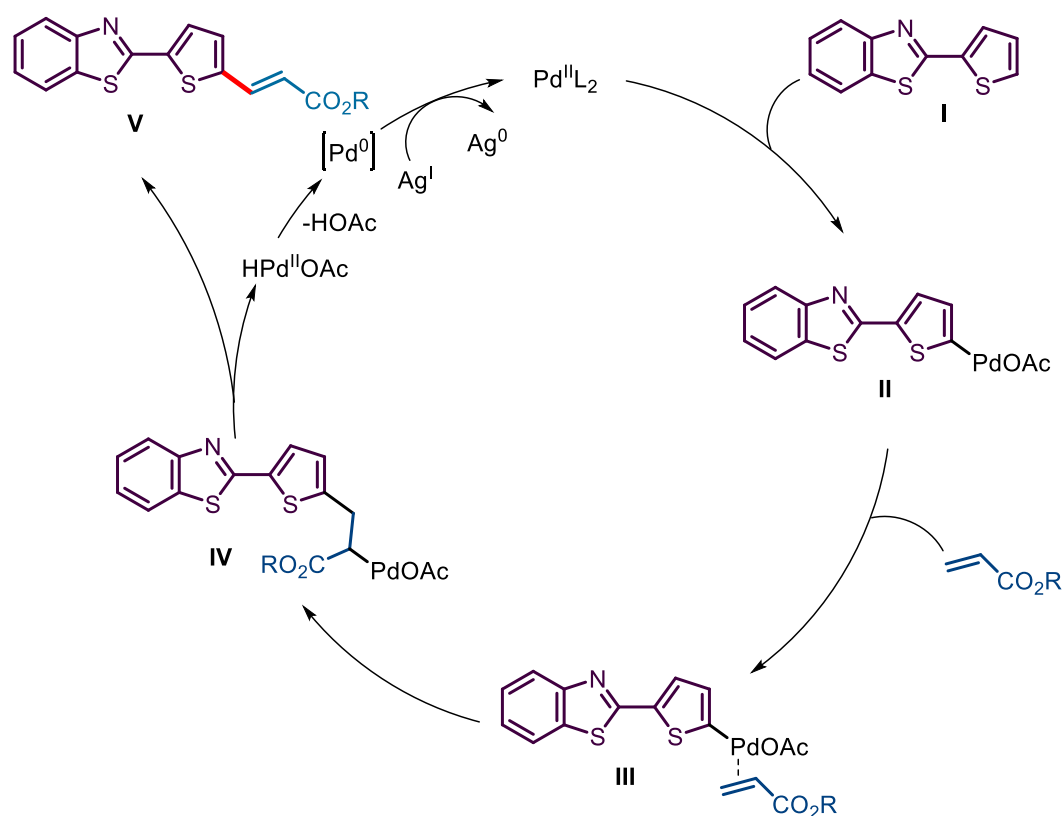
Further in the reaction mechanism initially the palladium catalyst undergoes the electrophilic metalation with compound **I** to further form the intermediate complex **II** which inserts in to the alkenes to give the intermediate **III**. Further this intermediate undergoes 2,1 migratory insertion to form the intermediate **IV** and further subsequent  $\beta$ -hydride elimination to afford the C5 alkenylated product **V**. Finally, the elimination of acetic acid from palladium catalyst followed

by the oxidation of Pd(0) to Pd(II) by silver acetate as an oxidant regenerates the catalyst thus completing the catalytic cycle.

**Table 3.2.** Alkenylation of substituted 2-thiophene benzo[d]thiazoles/oxazoles. <sup>a,b</sup>



<sup>a</sup>Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (0.3 mmol), DCM (2 mL), 100 °C, Ar, 24 h. <sup>b</sup>Isolated yields based on **1a** using column chromatography.



**Scheme 3.4** Plausible Mechanism.

### 3.5 Conclusions:

In summary we have developed an efficient method for the direct C5 and C3-( $\text{sp}^2$ )-H alkenylation of 2-heteroarylbenzothiazoles with a wide range of the acrylates via palladium catalysis. This protocol provides the regio- and chemo-selective *E*-alkenylation products at C5 and C3 position. Also, in the absence of C5-H for the C-H activation, the reaction afforded the corresponding and C3-alkenylated products. A wide range of substrate scope with good functional group tolerance has been demonstrated for this alkenylation strategy.

## 3.6 Experimental Section

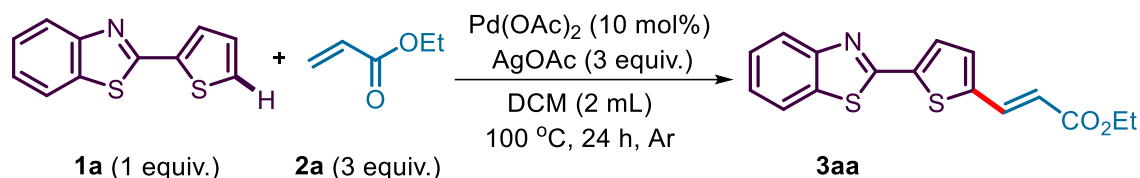
### 3.6.1 General Information

All reactions were carried out with distilled and dried solvents using oven-dried glass wares under dry Argon atmosphere, unless otherwise stated. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin layer chromatography (TLC) was performed using silica gel 60 GF254 pre-coated aluminum backed plates (2.5 mm) with detection by UV light. Visualization was accomplished by irradiation with a UV light at 254 nm followed by 2,4-DNP (Dinitrophenylhydrazine) and KMnO<sub>4</sub> solution as staining agents. Column chromatography was performed using silica gel (100-200 mesh) eluting with petroleum ether and ethyl acetate/DCM. Petroleum ether and ethyl acetate mixture was used as gradient elution for column chromatography. All the isolated compounds were characterized by <sup>1</sup>H (Proton) and <sup>13</sup>C{<sup>1</sup>H} (carbon) NMR spectra and they were recorded on 400 MHz Bruker Advance III HD Ascend 400 MHz spectrophotometers. All the NMR (Nuclear Magnetic resonance) Spectra were recorded in CDCl<sub>3</sub>. The NMR spectra were recorded using tetramethylsilane (TMS) as an internal standard. <sup>1</sup>H NMR spectra were recorded at 400 MHz and <sup>13</sup>C{<sup>1</sup>H} NMR spectra were recorded at 100 MHz (Bruker) unless otherwise noted. The chemical shifts (δ) are reported in ppm downfield from CDCl<sub>3</sub> (δ = 7.26 ppm) for <sup>1</sup>H NMR and in relative to the central CDCl<sub>3</sub> resonance (δ = 77.16 ppm) for <sup>13</sup>C{<sup>1</sup>H} NMR spectroscopy. <sup>1</sup>H NMR spectral data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*) and integration. Coupling constants (*J*) are reported in Hertz (Hz). <sup>13</sup>C{<sup>1</sup>H} NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by High Resolution Mass Spectrometer (HRMS) using ESI TOF. Melting points were measured (Büchi B-540 apparatus) in an open glass capillary and values are uncorrected. The single crystal X-ray diffraction (SCXRD) measurements were carried out by using the Bruker KAPPA APEX III CCD diffractometer with Cu/K radiation source (1.54184 Å).

### 3.6.2. General Experimental procedures

All the starting compounds(**1a-1j**) have been synthesized using the literature procedure<sup>15a</sup>

### 3.6.3. General Procedures for Pd(II)-catalyzed C5 (sp<sup>2</sup>)-H Alkenylation of 2-*N*-alkylpyrrolebenzo[d] thiazole.



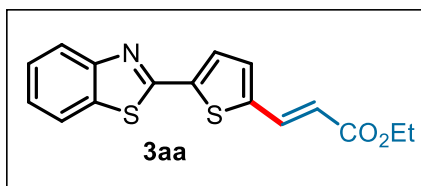
#### General Procedure A:

A 15-mL dry sealed tube equipped with a stir bar was charged with 2-(thiophen-2-yl)benzo[d]thiazole **1a** (21.43 mg, 0.1 mmol, 1.0 equiv.), ethyl acrylate **2a** (31.95  $\mu$ L, 0.3 mmol, 3 equiv.), Pd(OAc)<sub>2</sub> (2.25 mg, 0.01 mmol, 0.1 equiv.), AgOAc (50.07 mg, 0.3 mmol, 3 equiv.), and followed by the addition of the solvent DCM (2 mL) at room temperature. Then the resulting reaction mixture was degassed under Argon atmosphere for 2 min and stirred vigorously at room temperature for 10 min. Then reaction mixture heated to 100 °C for 24 h. After which, the reaction mixture was cooled to room temperature, followed by the dilution with EtOAc (15 mL) and subsequently it was filtered through pad of celite. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel to furnish the desired product **3aa** in 70% yield (22 mg) as a yellow solid.



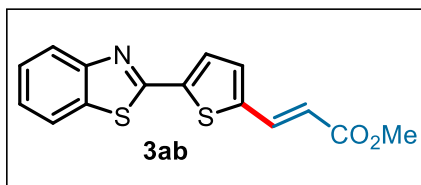
### 3.6.4. Experimental Data:

#### Ethyl (*E*)-3-(5-(benzo[d]thiazol-2-yl)thiophen-2-yl)acrylate (**3aa**):



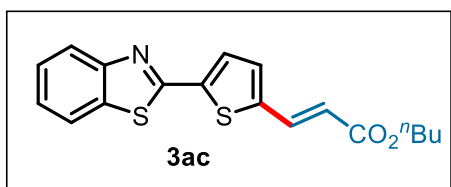
The compound **3aa** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3aa** as yellow solid (70%, 22 mg).  $R_f = 0.49$  (EtOAc/petroleum ether 9:91)  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.97 (d,  $J = 8.2$  Hz, 1H), 7.78 (d,  $J = 8.0$  Hz, 1H), 7.68 (d,  $J = 15.9$  Hz, 1H), 7.42 (ddd,  $J = 8.3, 7.2, 1.2$  Hz, 1H), 7.34 – 7.29 (m, 1H), 7.17 (d,  $J = 4.0$  Hz, 1H), 6.26 (d,  $J = 15.7$  Hz, 1H), 4.20 (q,  $J = 7.1$  Hz, 2H), 1.27 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  166.5, 160.4, 153.6, 142.6, 139.2, 136.3, 135.0, 131.4, 129.0, 126.7, 125.7, 123.3, 121.6, 118.9, 60.8, 14.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{13}\text{NO}_2\text{S}_2$  316.0466; found 316.0460.

#### Methyl (*E*)-3-(5-(benzo[d]thiazol-2-yl)thiophen-2-yl)acrylate (**3ab**):



The compound **3ab** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ab** as yellow solid (63%, 19 mg).  $R_f = 0.49$  (EtOAc/petroleum ether 14:86)  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.04 (d,  $J = 8.1$  Hz, 1H), 7.86 (dd,  $J = 8.1, 1.2$  Hz, 1H), 7.76 (d,  $J = 15.7$  Hz, 1H), 7.56 (d,  $J = 3.9$  Hz, 1H), 7.49 (ddd,  $J = 8.3, 7.2, 1.3$  Hz, 1H), 7.39 (td,  $J = 7.7, 7.3, 1.2$  Hz, 1H), 7.25 (d,  $J = 4.0$  Hz, 1H), 6.34 (d,  $J = 15.7$  Hz, 1H), 3.81 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  167.0, 160.5, 153.8, 142.6, 139.5, 136.7, 135.0, 131.6, 129.1, 126.8, 125.8, 123.4, 121.7, 118.5, 52.0. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_{12}\text{NO}_2\text{S}_2$  302.0309; found 302.0315.

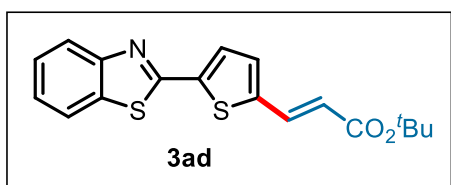
#### Butyl (*E*)-3-(5-(benzo[d]thiazol-2-yl)thiophen-2-yl)acrylate (**3ac**):



The compound **3ac** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ac** as yellow solid (52%, 18mg).  $R_f = 0.49$  (EtOAc/petroleum ether 6:94)  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.04 (d,  $J = 8.2$  Hz, 1H), 7.86 (d,  $J = 8.0$  Hz, 1H), 7.75 (d,  $J = 15.7$  Hz, 1H), 7.56 (d,  $J = 3.9$  Hz, 1H), 7.49 (ddd,  $J = 8.3, 7.3, 1.3$  Hz, 1H), 7.39 (ddd,  $J = 8.3, 7.3, 1.2$  Hz, 1H), 7.25 (d,  $J = 3.9$  Hz, 1H), 6.33 (d,  $J = 15.8$

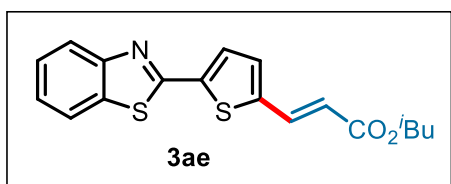
Hz, 1H), 4.22 (t,  $J = 6.7$  Hz, 2H), 1.75 – 1.64 (m, 2H), 1.51 – 1.37 (m, 2H), 0.97 (t,  $J = 7.4$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  166.7, 160.5, 153.8, 142.7, 139.4, 136.4, 135.0, 131.5, 129.1, 126.8, 125.8, 123.4, 121.7, 119.1, 64.8, 30.9, 19.3, 13.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{18}\text{H}_{18}\text{NO}_2\text{S}_2$  344.0779; found 344.0779.

**Tert-butyl (*E*)-3-(5-(benzo[d]thiazol-2-yl)thiophen-2-yl)acrylate (**3ad**):**



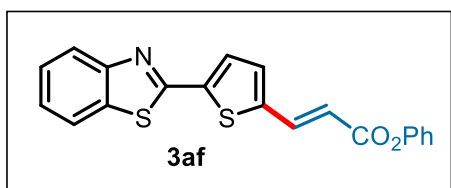
The compound **3ad** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ad** as yellow solid (35%, 12mg).  $R_f = 0.49$  (EtOAc/petroleum ether 6:94).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.04 (d,  $J = 8.2$  Hz, 1H), 7.86 (d,  $J = 8.0$  Hz, 1H), 7.66 (d,  $J = 15.7$  Hz, 1H), 7.56 (d,  $J = 3.9$  Hz, 1H), 7.49 (ddd,  $J = 8.3$ , 7.2, 1.3 Hz, 1H), 7.39 (ddd,  $J = 8.3$ , 7.2, 1.2 Hz, 1H), 7.23 (d,  $J = 3.9$  Hz, 1H), 6.27 (d,  $J = 15.7$  Hz, 1H), 1.54 (s, 9H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  165.9, 160.6, 153.8, 143.0, 139.0, 135.4, 135.0, 131.1, 129.1, 126.8, 125.8, 123.4, 121.7, 121.1, 81.1, 28.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{18}\text{H}_{18}\text{NO}_2\text{S}_2$  344.0779; found 344.0775.

**Isobutyl (*E*)-3-(5-(benzo[d]thiazol-2-yl)thiophen-2-yl)acrylate (**3ae**):**



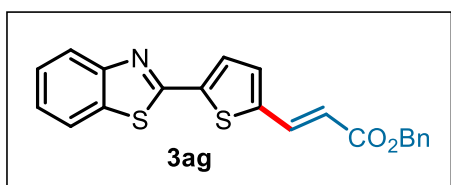
The compound **3ae** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ae** as yellow solid (38%, 13mg).  $R_f = 0.49$  (EtOAc/petroleum ether 7:93).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.04 (ddd,  $J = 8.2$ , 1.3, 0.6 Hz, 1H), 7.86 (ddd,  $J = 8.0$ , 1.3, 0.6 Hz, 1H), 7.76 (dd,  $J = 15.8$ , 0.7 Hz, 1H), 7.57 (d,  $J = 3.9$  Hz, 1H), 7.50 (ddd,  $J = 8.3$ , 7.2, 1.2 Hz, 1H), 7.39 (ddd,  $J = 8.4$ , 7.2, 1.2 Hz, 1H), 7.26 (d,  $J = 4.2$  Hz, 1H), 6.35 (d,  $J = 15.7$  Hz, 1H), 4.00 (d,  $J = 6.7$  Hz, 2H), 2.06 – 1.97 (m, 1H), 0.99 (d,  $J = 6.7$  Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  166.7, 160.5, 153.8, 142.7, 139.4, 136.4, 135.0, 131.5, 129.1, 126.8, 125.8, 123.4, 121.7, 119.0, 71.0, 28.0, 19.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{18}\text{H}_{18}\text{NO}_2\text{S}_2$  344.0779; found 344.0782.

**Phenyl (*E*)-3-(5-(benzo[d]thiazol-2-yl)thiophen-2-yl)acrylate (**3af**):**



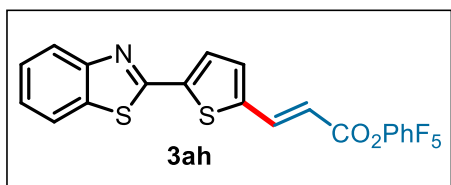
The compound **3af** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3af** as yellow solid (66%, 24mg).  $R_f = 0.49$  (EtOAc/petroleum ether 4:96).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.06 (d,  $J = 8.1$  Hz, 1H), 7.94 (d,  $J = 15.7$  Hz, 1H), 7.88 (d,  $J = 7.8$  Hz, 1H), 7.61 (d,  $J = 3.9$  Hz, 1H), 7.51 (ddd,  $J = 8.3$ , 7.2, 1.3 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.33 (d,  $J = 3.9$  Hz, 1H), 7.26 (m, 1H), 7.18 (d,  $J = 7.5$  Hz, 2H), 6.53 (d,  $J = 15.7$  Hz, 1H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  165.1, 160.4, 153.8, 150.8, 142.3, 140.1, 138.2, 135.0, 132.2, 129.6, 129.2, 126.9, 126.0, 125.9, 123.4, 121.7, 121.7, 117.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{14}\text{NO}_2\text{S}_2$  364.0466; found 364.0475.

**Benzyl (*E*)-3-(5-(benzo[d]thiazol-2-yl)thiophen-2-yl)acrylate (**3ag**):**



The compound **3ag** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ag** as yellow solid (48%, 18mg).  $R_f = 0.49$  (EtOAc/petroleum ether 6:94).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.04 (d,  $J = 8.2$  Hz, 1H), 7.87 (d,  $J = 9.1$  Hz, 1H), 7.80 (d,  $J = 15.7$  Hz, 1H), 7.57 (d,  $J = 3.9$  Hz, 1H), 7.50 (ddd,  $J = 8.3$ , 7.2, 1.3 Hz, 1H), 7.46 – 7.33 (m, 7H), 7.26 (d,  $J = 3.9$  Hz, 1H), 6.38 (d,  $J = 15.7$  Hz, 1H), 5.26 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  166.4, 160.4, 153.8, 142.6, 139.6, 137.0, 136.0, 135.0, 131.7, 129.1, 128.8, 128.5, 128.5, 126.8, 125.8, 123.4, 121.7, 118.5, 66.7. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{21}\text{H}_{16}\text{NO}_2\text{S}_2$  378.0622; found 378.0614.

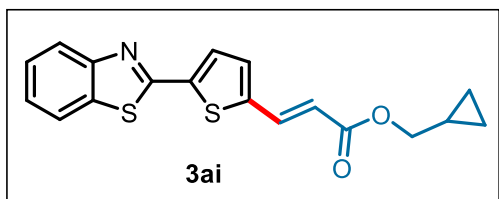
**Perfluorophenyl (*E*)-3-(5-(benzo[d]thiazol-2-yl)thiophen-2-yl)acrylate (**3ah**):**



The compound **3ah** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ah** as yellow solid (61%, 28mg).  $R_f = 0.49$  (EtOAc/petroleum ether 4:96).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.06 (d,  $J = 8.1$  Hz, 1H), 8.00 (d,  $J = 15.7$  Hz, 1H), 7.61 (d,  $J = 4.0$  Hz, 1H), 7.54 – 7.47 (m, 2H), 7.44 – 7.36 (m, 2H), 6.51 (d,  $J = 15.7$  Hz, 1H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  162.4, 160.0, 153.8, 142.8, 141.4, 140.9, 140.3, 139.3, 136.8, 135.7, 135.1, 133.4, 129.2, 127.0, 126.1, 123.6, 121.8,

117.1, 114.4.  $^{19}\text{F}$  NMR (377 MHz, Chloroform-*d*)  $\delta$  -152.41, -158.01, -162.31. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_9\text{F}_5\text{NO}_2\text{S}_2$  453.9995; found 453.9989.

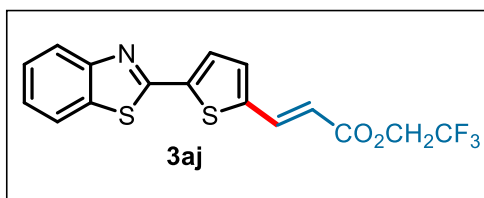
**Cyclopropylmethyl (*E*)-3-(5-(benzo[d]thiazol-2-yl)thiophen-2-yl)acrylate (**3ai**):**



The compound **3ai** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ai** as yellow solid (47%, 16mg).  $R_f$  =

0.49 (EtOAc/petroleum ether 7:93).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.04 (d,  $J$  = 8.2 Hz, 1H), 7.86 (d,  $J$  = 8.0 Hz, 1H), 7.77 (d,  $J$  = 15.7 Hz, 1H), 7.57 – 7.55 (m, 1H), 7.49 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.26 (d,  $J$  = 4.2 Hz, 1H), 6.37 (d,  $J$  = 15.7 Hz, 1H), 4.05 (d,  $J$  = 7.3 Hz, 2H), 1.21 (m, 1H), 0.61 (m, 2H), 0.37 – 0.32 (m, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  166.7, 160.5, 153.8, 142.7, 139.4, 136.5, 135.0, 131.5, 129.1, 126.8, 125.8, 123.4, 121.7, 119.0, 69.7, 10.0, 3.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{18}\text{H}_{16}\text{NO}_2\text{S}_2$  342.0622; found 342.0614.

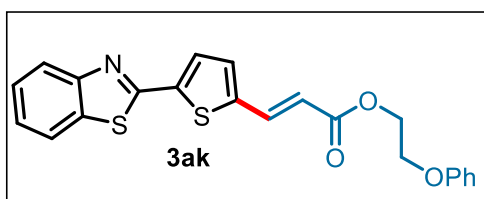
**2,2,2-trifluoroethyl (*E*)-3-(5-(benzo[d]thiazol-2-yl)thiophen-2-yl)acrylate (**3aj**):**



The compound **3aj** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3aj** as yellow solid (43%, 16 mg).  $R_f$  = 0.49

(EtOAc/petroleum ether 6:94).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.05 (d,  $J$  = 8.2 Hz, 1H), 7.88 – 7.82 (m, 2H), 7.58 (d,  $J$  = 3.9 Hz, 1H), 7.50 (ddd,  $J$  = 8.2, 7.2, 1.3 Hz, 1H), 7.40 (ddd,  $J$  = 8.2, 7.3, 1.3 Hz, 1H), 7.31 (d,  $J$  = 3.9 Hz, 1H), 6.36 (d,  $J$  = 15.7 Hz, 1H), 4.60 (q,  $J$  = 8.4 Hz, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  164.8, 160.2, 153.7, 141.8, 140.4, 138.7, 135.0, 132.5, 129.1, 126.9, 125.9, 123.4, 121.7, 116.3, 60.8, 60.4, 60.0. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{11}\text{F}_3\text{NO}_2\text{S}_2$  370.0183; found 370.0182.

**2-phenoxyethyl (*E*)-3-(5-(benzo[d]thiazol-2-yl)thiophen-2-yl)acrylate (**3ak**):**

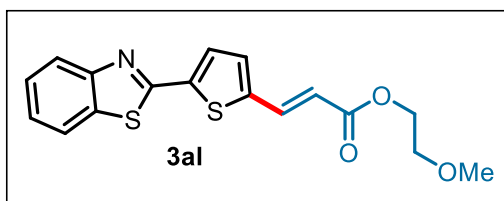


The compound **3ak** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ak** as yellow solid (39%, 16mg).  $R_f$  =

0.49 (EtOAc/petroleum ether 23:77).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.04 (d,  $J$  = 7.8 Hz,

1H), 7.86 (d,  $J = 7.4$  Hz, 1H), 7.78 (d,  $J = 15.7$  Hz, 1H), 7.56 (d,  $J = 3.9$  Hz, 1H), 7.49 (ddd,  $J = 8.3, 7.2, 1.3$  Hz, 1H), 7.42 – 7.36 (m, 1H), 7.33 – 7.28 (m, 2H), 7.25 (d,  $J = 3.9$  Hz, 1H), 6.99 – 6.94 (m, 3H), 6.37 (d,  $J = 15.7$  Hz, 1H), 4.59 – 4.55 (m, 2H), 4.28 – 4.24 (m, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  166.5, 158.6, 153.8, 142.5, 137.1, 135.0, 131.8, 129.7, 129.1, 126.8, 125.8, 123.4, 121.7, 121.4, 118.3, 114.8, 66.0, 63.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{22}\text{H}_{18}\text{NO}_3\text{S}_2$  408.0728; found 408.0733.

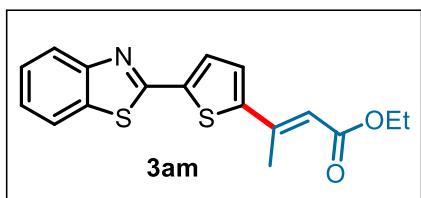
### 2-methoxyethyl (*E*)-3-(5-(benzo[d]thiazol-2-yl)thiophen-2-yl)acrylate (**3al**):



The compound **3al** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3al** as yellow solid (43%, 15mg).  $R_f =$

0.49 (EtOAc/petroleum ether 28:72).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.05 (d,  $J = 7.8$  Hz, 1H), 7.87 (d,  $J = 8.0$  Hz, 1H), 7.79 (d,  $J = 15.7$  Hz, 1H), 7.57 (d,  $J = 3.9$  Hz, 1H), 7.50 (ddd,  $J = 8.3, 7.3, 1.3$  Hz, 1H), 7.44 – 7.36 (m, 1H), 7.27 (d,  $J = 3.9$  Hz, 1H), 6.39 (d,  $J = 15.7$  Hz, 1H), 4.41 – 4.34 (m, 2H), 3.72 – 3.64 (m, 2H), 3.43 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  166.6, 160.5, 153.8, 142.6, 139.6, 136.9, 135.0, 131.7, 129.1, 126.8, 125.8, 123.4, 121.7, 118.5, 70.7, 63.9, 59.2. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{16}\text{NO}_3\text{S}_2$  346.0572; found 346.0575.

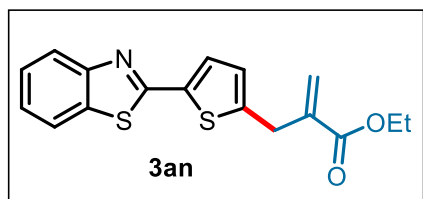
### Ethyl (*E*)-3-(5-(benzo[d]thiazol-2-yl)thiophen-2-yl)but-2-enoate (**3am**):



The compound **3am** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3am** as yellow solid (30%, 10mg).  $R_f =$

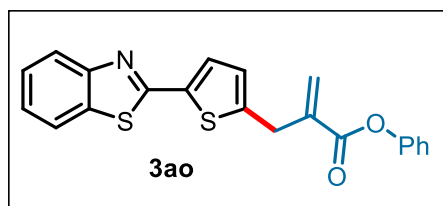
0.49 (EtOAc/petroleum ether 7:93).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.03 (d,  $J = 7.8$  Hz, 1H), 7.86 (d,  $J = 8.0$  Hz, 1H), 7.58 (d,  $J = 4.0$  Hz, 1H), 7.49 (ddd,  $J = 8.3, 7.2, 1.3$  Hz, 1H), 7.39 (ddd,  $J = 8.3, 7.2, 1.2$  Hz, 1H), 7.33 (d,  $J = 4.0$  Hz, 1H), 6.36 (d,  $J = 1.3$  Hz, 1H), 4.23 (q,  $J = 7.1$  Hz, 2H), 2.63 (d,  $J = 1.3$  Hz, 3H), 1.33 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  166.6, 160.7, 153.8, 148.9, 146.9, 138.2, 135.0, 129.0, 127.2, 126.8, 125.7, 123.3, 121.7, 116.1, 60.3, 17.3, 14.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{16}\text{NO}_2\text{S}_2$  330.0622; found 330.0622.

### Ethyl 2-((5-(benzo[d]thiazol-2-yl)thiophen-2-yl)methyl)acrylate (**3an**):



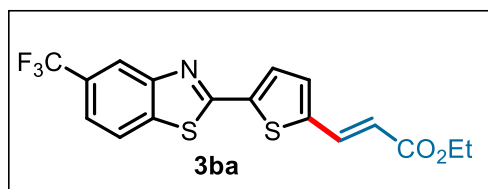
The compound **3an** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3an** as yellow solid (36%, 12mg).  $R_f = 0.49$  (EtOAc/petroleum ether 9:91).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.99 (d,  $J = 8.2$  Hz, 1H), 7.83 (d,  $J = 7.9$  Hz, 1H), 7.50 (d,  $J = 3.7$  Hz, 1H), 7.46 (ddd,  $J = 8.3, 7.2, 1.3$  Hz, 1H), 7.35 (ddd,  $J = 8.3, 7.2, 1.2$  Hz, 1H), 6.89 (d,  $J = 3.8$  Hz, 1H), 6.32 (d,  $J = 1.0$  Hz, 1H), 5.70 (d,  $J = 1.3$  Hz, 1H), 4.23 (q,  $J = 7.1$  Hz, 2H), 3.87 (s, 2H), 1.30 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  166.6, 160.5, 153.8, 142.6, 139.6, 137.0, 135.0, 131.7, 129.1, 126.8, 125.8, 123.4, 121.7, 118.5, 70.7, 63.9, 59.2. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{16}\text{NO}_2\text{S}_2$  330.0622; found 330.0615.

### Phenyl 2-((5-(benzo[d]thiazol-2-yl)thiophen-2-yl)methyl)acrylate (**3ao**):



The compound **3ao** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ao** as yellow solid (34%, 13mg).  $R_f = 0.49$  (EtOAc/petroleum ether 7:93).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.00 (d,  $J = 8.2$  Hz, 1H), 7.84 (d,  $J = 8.0$  Hz, 1H), 7.52 (d,  $J = 3.7$  Hz, 1H), 7.46 (ddd,  $J = 8.3, 7.2, 1.3$  Hz, 1H), 7.37 (dddd,  $J = 11.7, 8.2, 6.7, 1.6$  Hz, 3H), 7.27 – 7.19 (m, 2H), 7.10 (dd,  $J = 8.6, 1.2$  Hz, 2H), 6.95 (d,  $J = 3.7$  Hz, 1H), 6.56 (d,  $J = 0.7$  Hz, 1H), 5.90 (d,  $J = 1.1$  Hz, 1H), 3.98 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  164.9, 161.5, 153.8, 150.9, 145.9, 138.5, 136.1, 134.7, 129.6, 128.9, 127.3, 126.5, 126.1, 125.3, 123.0, 121.7, 121.6, 33.0. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{21}\text{H}_{16}\text{NO}_2\text{S}_2$  378.0622; found 378.0612.

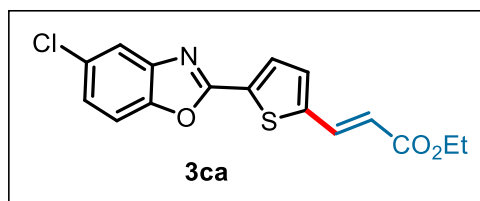
### Ethyl (*E*)-3-(5-(5-(trifluoromethyl)benzo[d]thiazol-2-yl)thiophen-2-yl)acrylate (**3ba**):



The compound **3ba** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ba** as yellow solid (62%, 24mg).  $R_f = 0.49$  (EtOAc/petroleum ether 7:93).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.30 – 8.29 (m, 1H), 7.97 (d,  $J = 8.4$  Hz, 1H), 7.76 (d,  $J = 15.7$  Hz, 1H), 7.64 – 7.61 (m, 1H), 7.60 (d,  $J = 3.9$  Hz, 1H), 7.27 (d,  $J = 3.9$  Hz, 1H), 6.36 (d,  $J = 15.7$  Hz, 1H), 4.28 (q,  $J = 7.1$  Hz, 2H), 1.35 (t,  $J =$

7.2 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  166.5, 162.5, 153.4, 143.6, 138.5, 138.4, 136.2, 131.4, 129.9, 129.4, 124.2 (d,  $J = 272.2$  Hz), 122.3, 122.1 (q,  $J = 3.4$  Hz), 120.5 (q,  $J = 4.0$  Hz), 119.6, 61.0, 14.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{13}\text{F}_3\text{NO}_2\text{S}_2$  384.0340; found 384.0348.

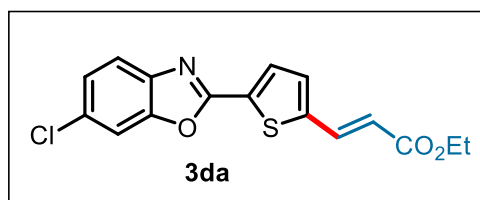
**Ethyl (*E*)-3-(5-(5-chlorobenzo[d]oxazol-2-yl)thiophen-2-yl)acrylate (3ca):**



The compound **3ca** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ca** as yellow solid (36%, 12 mg).  $R_f = 0.49$

(EtOAc/petroleum ether 10:90).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.81 (d,  $J = 3.9$  Hz, 1H), 7.76 (d,  $J = 15.8$  Hz, 1H), 7.70 (d,  $J = 1.8$  Hz, 1H), 7.46 (d,  $J = 8.7$  Hz, 1H), 7.32 (dd,  $J = 8.6$ , 2.1 Hz, 1H), 7.29 (d,  $J = 3.9$  Hz, 1H), 6.35 (d,  $J = 15.8$  Hz, 1H), 4.28 (q,  $J = 7.2$  Hz, 2H), 1.35 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  166.4, 159.5, 149.2, 144.2, 143.2, 136.0, 131.4, 131.0, 130.7, 130.6, 125.9, 120.1, 119.8, 111.4, 61.0, 14.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{13}\text{ClNO}_3\text{S}$  334.0305; found 334.0315.

**Ethyl (*E*)-3-(5-(6-chlorobenzo[d]oxazol-2-yl)thiophen-2-yl)acrylate (3da):**

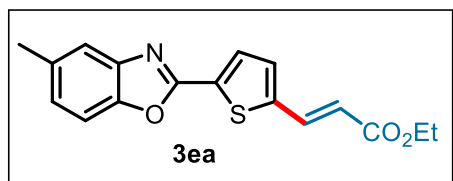


The compound **3da** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3da** as yellow solid (63%, 21mg).  $R_f = 0.49$

(EtOAc/petroleum ether 10:90).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.81 (d,  $J = 3.9$  Hz, 1H), 7.77 (d,  $J = 15.7$  Hz, 1H), 7.65 (d,  $J = 8.5$  Hz, 1H), 7.57 (d,  $J = 1.8$  Hz, 1H), 7.35 (dd,  $J = 8.5$ , 1.9 Hz, 1H), 7.30 (d,  $J = 3.9$  Hz, 1H), 6.36 (d,  $J = 15.8$  Hz, 1H), 4.28 (q,  $J = 7.1$  Hz, 2H), 1.35 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  166.4, 150.8, 144.1, 140.9, 136.0, 131.4, 131.3, 130.9, 130.8, 125.9, 120.6, 119.8, 111.4, 61.0, 14.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{13}\text{ClNO}_3\text{S}$  334.0305; found 334.0306.

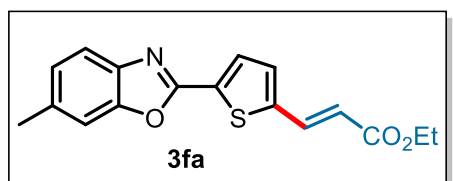


**Ethyl (*E*)-3-(5-(5-methylbenzo[d]oxazol-2-yl)thiophen-2-yl)acrylate (**3ea**):**



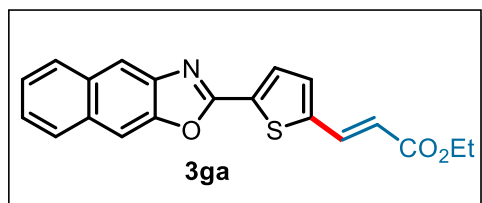
The compound **3ea** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ea** as yellow solid (64%, 20mg).  $R_f = 0.49$  (EtOAc/petroleum ether 11:89).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.80 – 7.74 (m, 2H), 7.53 – 7.51 (m, 1H), 7.42 (d,  $J = 8.3$  Hz, 1H), 7.29 (d,  $J = 3.9$  Hz, 1H), 7.17 (d,  $J = 8.3$  Hz, 1H), 6.34 (d,  $J = 15.7$  Hz, 1H), 4.28 (q,  $J = 7.2$  Hz, 2H), 2.48 (s, 3H), 1.35 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  166.5, 158.3, 148.9, 143.5, 142.3, 136.2, 135.0, 131.7, 131.4, 130.3, 126.9, 120.1, 119.4, 110.0, 60.9, 21.7, 14.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{16}\text{NO}_3\text{S}$  314.0851; found 314.0855.

**Ethyl (*E*)-3-(5-(6-methylbenzo[d]oxazol-2-yl)thiophen-2-yl)acrylate (**3fa**):**



The compound **3fa** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3fa** as yellow solid (54%, 17mg).  $R_f = 0.49$  (EtOAc/petroleum ether 11:89).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.79 – 7.74 (m, 2H), 7.61 (d,  $J = 8.1$  Hz, 1H), 7.36 – 7.34 (m, 1H), 7.29 (d,  $J = 3.9$  Hz, 1H), 7.18 (d,  $J = 8.1$  Hz, 1H), 6.34 (d,  $J = 15.7$  Hz, 1H), 4.28 (q,  $J = 7.2$  Hz, 2H), 2.51 (s, 3H), 1.35 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  166.5, 157.8, 151.0, 143.3, 139.9, 136.4, 136.2, 131.7, 131.4, 130.1, 126.4, 119.5, 119.3, 110.8, 60.9, 22.0, 14.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{16}\text{NO}_3\text{S}$  314.0851; found 314.0848.

**Ethyl (*E*)-3-(5-(naphtho[2,3-*d*]oxazol-2-yl)thiophen-2-yl)acrylate (**3ga**):**

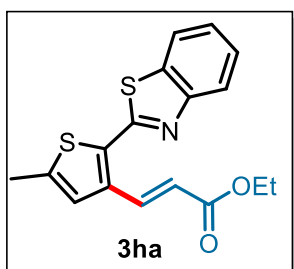


The compound **3ga** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ga** as yellow solid (37%, 13 mg).  $R_f = 0.49$  (EtOAc/petroleum ether 8:92).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.17 (s, 1H), 8.02 – 7.98 (m, 1H), 7.97 – 7.93 (m, 1H), 7.92 (s, 1H), 7.91 (d,  $J = 3.9$  Hz, 1H), 7.79 (d,  $J = 15.7$  Hz, 1H), 7.56 – 7.44 (m, 3H), 7.33 (d,  $J = 3.9$  Hz, 1H), 6.38 (d,  $J = 15.8$  Hz, 1H), 4.29 (q,  $J = 7.2$  Hz, 2H), 1.36 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  166.3, 149.4, 144.4, 141.8, 135.9, 131.9, 131.7, 131.4, 131.3, 131.0, 128.6, 127.9, 127.0, 125.7, 124.9, 119.7, 117.4,



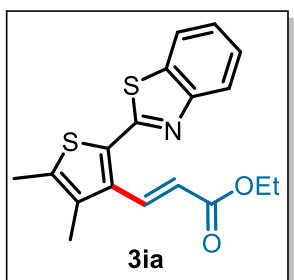
106.4, 60.9, 14.3. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{20}H_{16}NO_3S$  350.0851; found 350.0851.

**Ethyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-5-methylthiophen-3-yl)acrylate (**3ha**):**



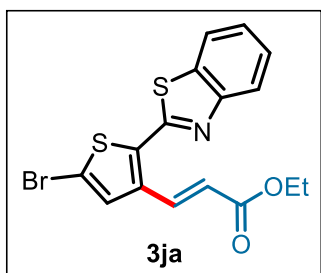
The compound **3ha** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ha** as yellow solid (69%, 23mg).  $R_f$  = 0.49 (EtOAc/petroleum ether 7:93).  $^1H$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.47 (d,  $J$  = 15.8 Hz, 1H), 8.08 (d,  $J$  = 8.2 Hz, 1H), 7.87 (d,  $J$  = 8.0 Hz, 1H), 7.49 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 7.38 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 7.04 (s, 1H), 6.37 (d,  $J$  = 15.8 Hz, 1H), 4.29 (q,  $J$  = 7.1 Hz, 2H), 2.52 (s, 3H), 1.36 (t,  $J$  = 7.1 Hz, 3H).  $^{13}C\{^1H\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  167.2, 159.5, 153.6, 143.5, 137.0, 136.7, 135.3, 135.0, 126.7, 125.5, 125.4, 123.5, 121.5, 121.2, 60.8, 15.7, 14.5. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{17}H_{16}NO_2S_2$  330.0622; found 330.0628.

**Ethyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-4,5-dimethylthiophen-3-yl)acrylate (**3ia**):**



The compound **3ia** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ia** as yellow solid (46%, 16mg).  $R_f$  = 0.49 (EtOAc/petroleum ether 6:94).  $^1H$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.25 (d,  $J$  = 16.3 Hz, 1H), 8.06 (ddd,  $J$  = 8.2, 1.2, 0.7 Hz, 1H), 7.86 (ddd,  $J$  = 8.0, 1.3, 0.7 Hz, 1H), 7.48 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.37 (ddd,  $J$  = 8.0, 7.2, 1.2 Hz, 1H), 6.32 (d,  $J$  = 16.3 Hz, 1H), 4.32 (q,  $J$  = 7.1 Hz, 2H), 2.44 (s, 3H), 2.24 (s, 3H), 1.38 (t,  $J$  = 7.1 Hz, 3H).  $^{13}C\{^1H\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  167.0, 160.1, 153.4, 138.5, 137.9, 136.9, 135.5, 134.1, 132.7, 126.6, 125.3, 123.5, 123.3, 121.5, 60.9, 14.5, 14.2, 14.0. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{18}H_{18}NO_2S_2$  344.0779; found 344.0784.

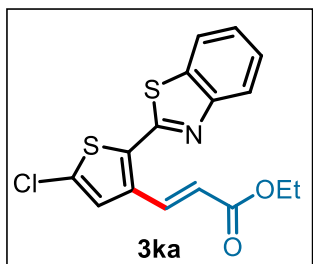
**Ethyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-5-bromothiophen-3-yl)acrylate (**3ja**):**



The compound **3ja** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ja** as yellow solid (38%, 15mg).  $R_f$  = 0.49 (EtOAc/petroleum ether 6:94).  $^1H$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.37 (d,  $J$  = 15.9 Hz, 1H), 8.09 (d,  $J$  = 8.1 Hz, 1H), 7.90 (d,  $J$  = 8.0 Hz, 1H), 7.52 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.42 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 7.33 (s, 1H), 6.38 (d,  $J$  = 15.7 Hz, 1H), 4.30 (q,  $J$  = 7.1 Hz, 2H),

1.36 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  166.7, 158.0, 153.3, 136.8, 135.6, 135.5, 129.9, 128.6, 127.0, 126.0, 123.7, 122.5, 121.6, 117.0, 61.0, 14.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{13}\text{BrNO}_2\text{S}_2$  393.9571; found 393.9562.

**Ethyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-5-chlorothiophen-3-yl)acrylate (3ka):**



The compound **3ka** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ka** as yellow solid (57%, 20mg).

$R_f = 0.49$  (EtOAc/petroleum ether 6:94).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.36 (d,  $J = 15.7$  Hz, 1H), 8.09 (d,  $J = 8.2$  Hz, 1H),

7.90 (d,  $J = 9.2$  Hz, 1H), 7.52 (ddd,  $J = 8.3, 7.2, 1.3$  Hz, 1H), 7.42 (ddd,  $J = 8.3, 7.2, 1.2$  Hz, 1H), 7.19 (s, 1H), 6.37 (d,  $J = 15.7$  Hz, 1H), 4.30 (q,  $J = 7.1$  Hz, 2H), 1.36 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform- $d$ )  $\delta$  166.7, 158.1, 153.3, 135.9, 135.8, 135.7, 135.4, 134.1, 127.0, 126.1, 126.0, 123.7, 122.5, 121.6, 61.0, 14.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{13}\text{ClNO}_2\text{S}_2$  350.0076; found 350.0081.

### 3.7. Appendix IIIA

#### 3.7.1. Optimization of Reaction Conditions

**Table 1. Optimization by varying different solvents:**

| Entry | Pd Catalyst          | 2a (equiv.) | Oxidants | Solvent | Yield |      |
|-------|----------------------|-------------|----------|---------|-------|------|
|       |                      |             |          |         | 3aa   | 3aa' |
| 1     | Pd(OAc) <sub>2</sub> | 3           | AgOAc    | DCM     | 70    | 18   |
| 2     | Pd(OAc) <sub>2</sub> | 3           | AgOAc    | DCE     | 55    | >13  |
| 3     | Pd(OAc) <sub>2</sub> | 3           | AgOAc    | Dioxane | 57    | >13  |
| 4     | Pd(OAc) <sub>2</sub> | 3           | AgOAc    | ACN     | 29    | -    |
| 5     | Pd(OAc) <sub>2</sub> | 3           | AgOAc    | DMF     | 45    | -    |
| 6     | Pd(OAc) <sub>2</sub> | 3           | AgOAc    | THF     | 52    | >12  |
| 7     | Pd(OAc) <sub>2</sub> | 3           | AgOAc    | HFIP    | 45    | >6   |
| 8     | Pd(OAc) <sub>2</sub> | 3           | AgOAc    | Toluene | 47    | >10  |

<sup>[a]</sup>Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (0.3 mmol), Solvent (2 mL), 100 °C, Ar, 24 h; <sup>[b]</sup>Isolated yields of **1a** after column chromatography; N.R.- No Reaction.

**Table 2. Optimization by varying different oxidants:**

| Entry | Pd Catalyst          | 2a (equiv.) | Oxidants                               | Solvent | Yield |      |
|-------|----------------------|-------------|----------------------------------------|---------|-------|------|
|       |                      |             |                                        |         | 3aa   | 3aa' |
| 1     | Pd(OAc) <sub>2</sub> | 3           | AgTFA                                  | DCM     | 45    | 10   |
| 2     | Pd(OAc) <sub>2</sub> | 3           | AgOTf                                  | DCM     | N.R.  | -    |
| 3     | Pd(OAc) <sub>2</sub> | 3           | Ag <sub>2</sub> CO <sub>3</sub>        | DCM     | 10    | -    |
| 4     | Pd(OAc) <sub>2</sub> | 3           | AgNO <sub>3</sub>                      | DCM     | N.R.  | -    |
| 5     | Pd(OAc) <sub>2</sub> | 3           | Cu(OAc) <sub>2</sub> .H <sub>2</sub> O | DCM     | 35    | -    |
| 6     | Pd(OAc) <sub>2</sub> | 3           | Cu(OAc) <sub>2</sub>                   | DCM     | 26    | -    |

<sup>[a]</sup>Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol%), Oxidants (0.3 mmol), DCM (2 mL), 100 °C, Ar, 24 h; <sup>[b]</sup>Isolated yields of **1a** after column chromatography; N.R.- No Reaction.

**Table 3. Optimization by varying palladium catalyst:**

| Entry | Pd Catalyst                                        | 2a (equiv.) | Oxidants | Solvent | Yield |      |
|-------|----------------------------------------------------|-------------|----------|---------|-------|------|
|       |                                                    |             |          |         | 3aa   | 3aa' |
| 1     | Pd(TFA) <sub>2</sub>                               | 3           | AgOAc    | DCM     | 50    | >12  |
| 2     | PdCl <sub>2</sub>                                  | 3           | AgOAc    | DCM     | 47    | >10  |
| 3     | PdCl <sub>2</sub> (ACN) <sub>2</sub>               | 3           | AgOAc    | DCM     | 53    | >12  |
| 4     | PdCl <sub>2</sub> (PhCN) <sub>2</sub>              | 3           | AgOAc    | DCM     | 51    | >12  |
| 5     | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | 3           | AgOAc    | DCM     | 30    | -    |
| 6     | Pd(PPh <sub>3</sub> ) <sub>4</sub>                 | 3           | AgOAc    | DCM     | N.R   | -    |

<sup>[a]</sup>Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (0.3 mmol), DCM (2 mL), 100 °C, Ar, 24 h; <sup>[b]</sup>Isolated yields of **1a** after column chromatography; N.R.- No Reaction.

### 3.8. Appendix IIIB: $^1\text{H}$ , $^{13}\text{C}$ spectral data of representative compounds

| Compound No. | Figure III.X             | Data                             | Page No |
|--------------|--------------------------|----------------------------------|---------|
| <b>3aa</b>   | Figure III.1 and III.2   | $^1\text{H}$ and $^{13}\text{C}$ | 123     |
| <b>3ag</b>   | Figure III.3 and III.4   | $^1\text{H}$ and $^{13}\text{C}$ | 124     |
| <b>3ao</b>   | Figure III.5 and III.6   | $^1\text{H}$ and $^{13}\text{C}$ | 125     |
| <b>3ea</b>   | Figure III.7 and III.8   | $^1\text{H}$ and $^{13}\text{C}$ | 126     |
| <b>3ha</b>   | Figure III.9 and III.10  | $^1\text{H}$ and $^{13}\text{C}$ | 127     |
| <b>3ka</b>   | Figure III.11 and III.12 | $^1\text{H}$ and $^{13}\text{C}$ | 128     |
| <b>3ga</b>   | Figure III.12            | ORTEP plot                       | 129     |
| <b>3ha</b>   | Figure III.13            | ORTEP plot                       | 129     |

Figure III.1  $^1\text{H}$  NMR spectrum of **3aa**,  $\text{CDCl}_3$ , 400 MHz

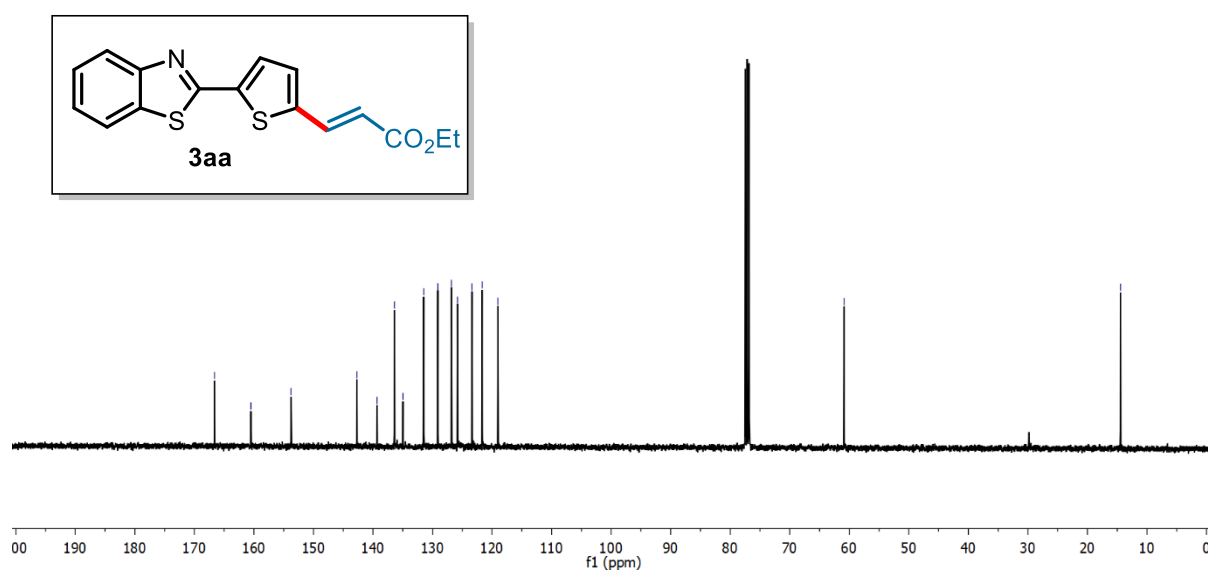
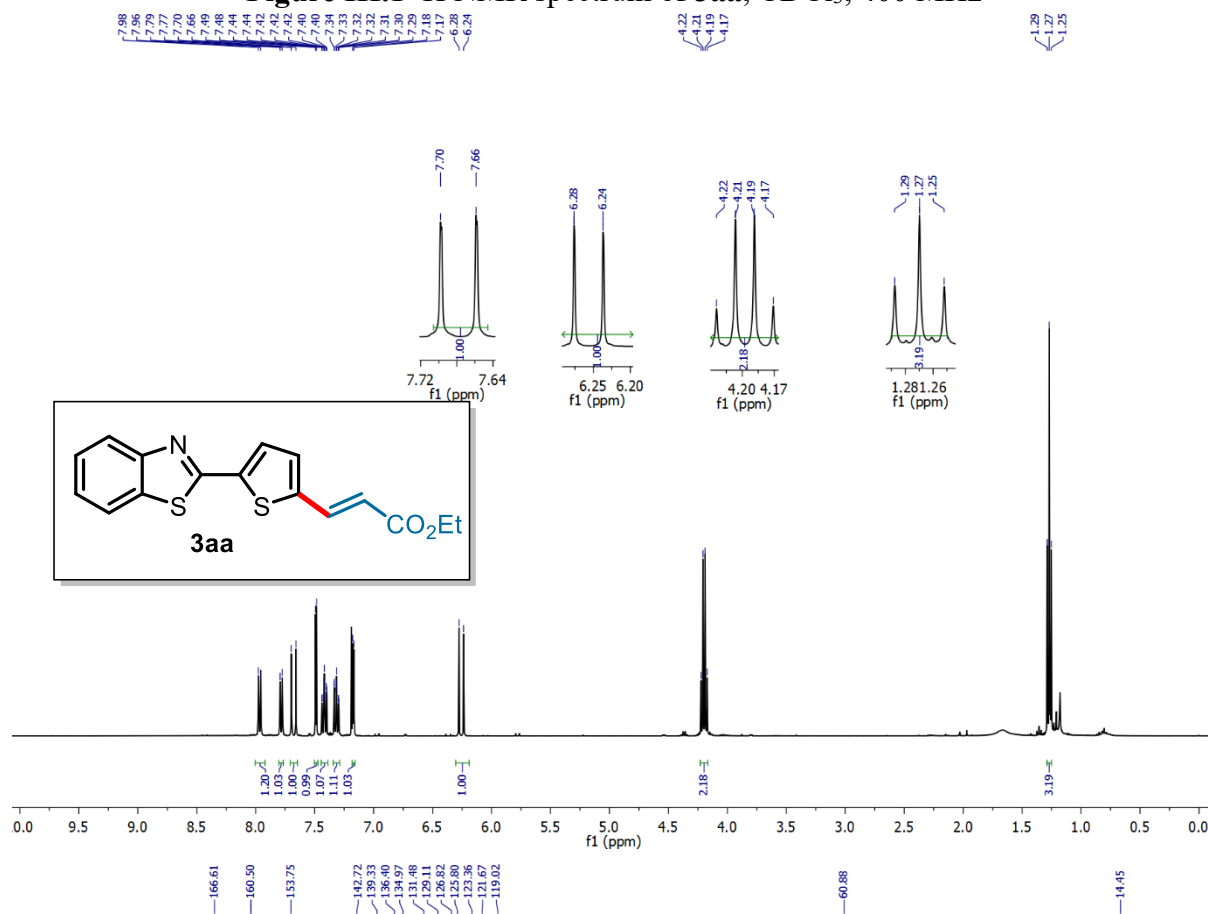
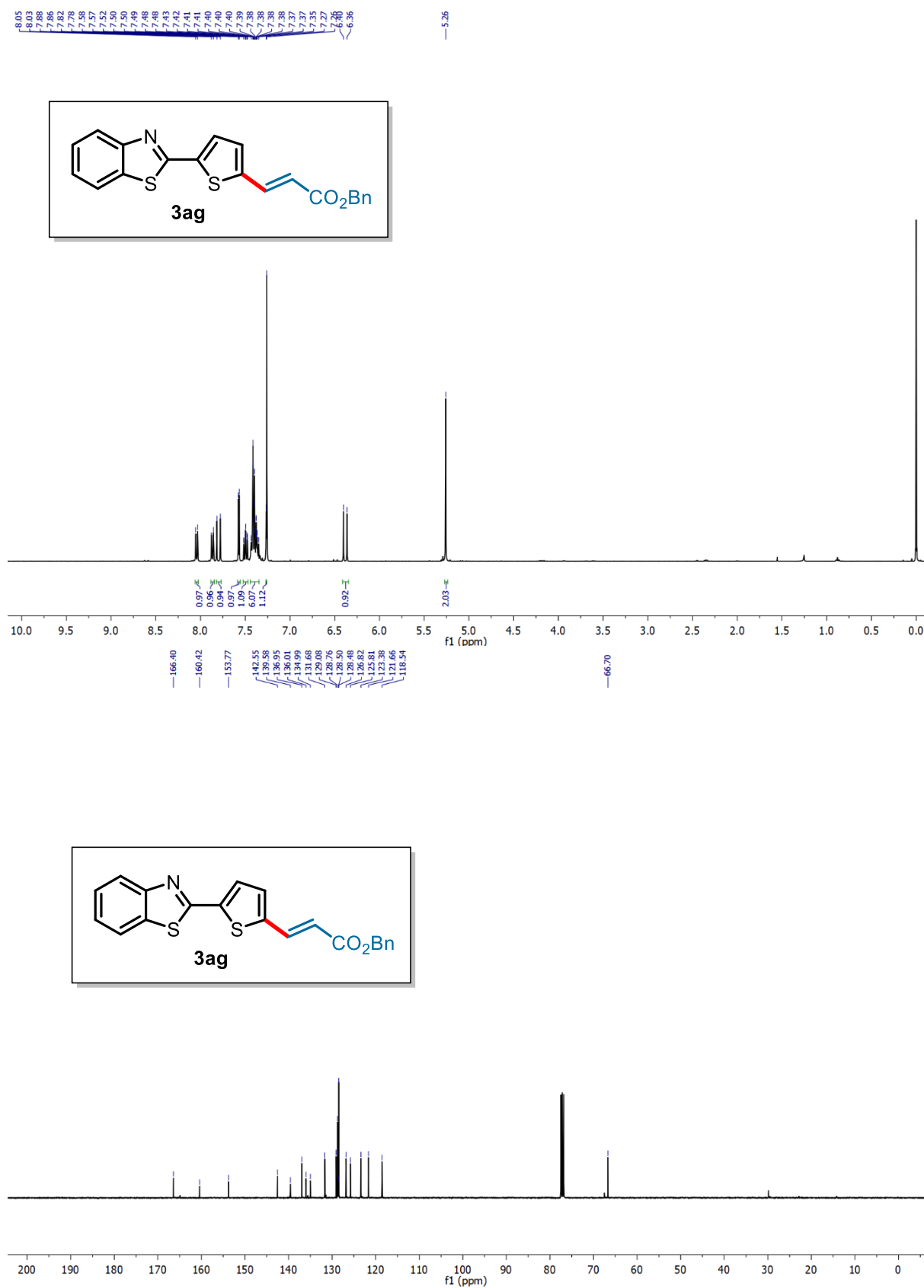
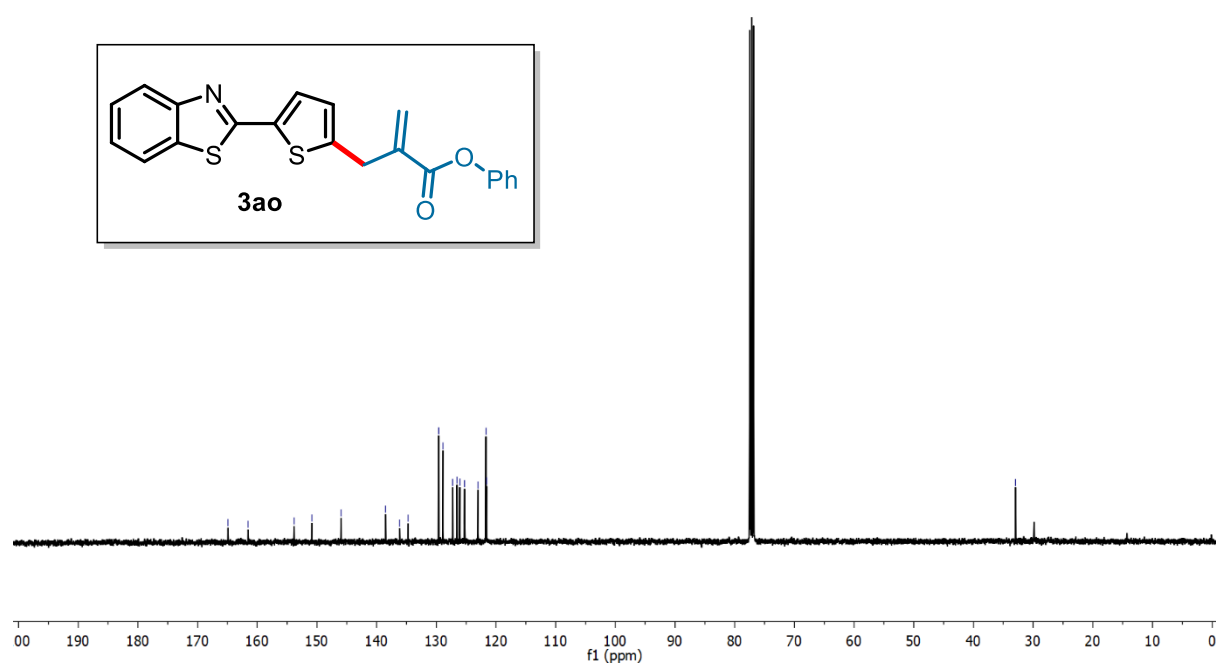
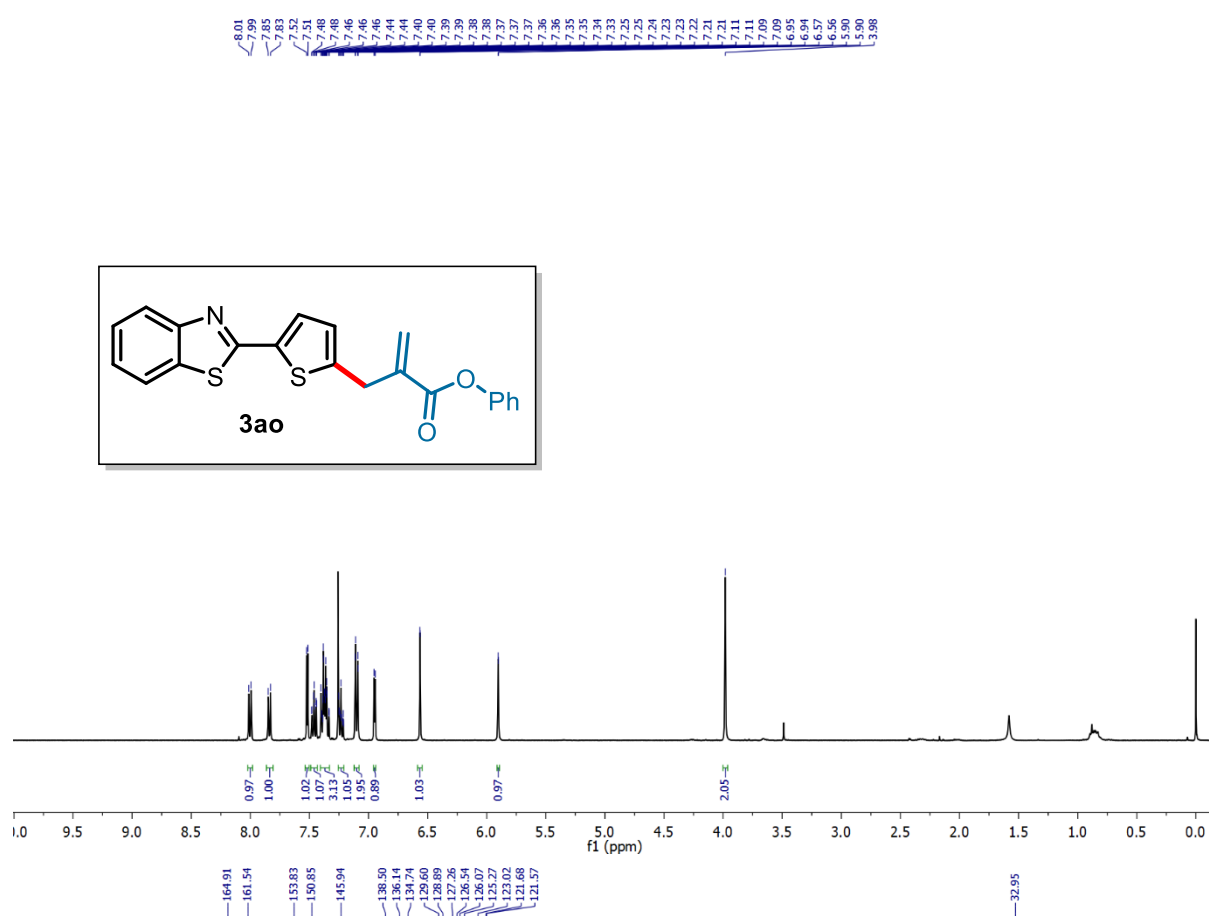


Figure III.3  $^{13}\text{C}$  NMR spectrum of **3ag**,  $\text{CDCl}_3$ , 400 MHz



**Figure III.4**  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3ag**, CDCl<sub>3</sub>, 400 MHz

**Figure III.5**  $^1\text{H}$  NMR spectrum of **3ao**,  $\text{CDCl}_3$ , 400 MHz



**Figure III.6**  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3ao**,  $\text{CDCl}_3$ , 400 MHz



Figure III.7  $^1\text{H}$  NMR spectrum of **3ea**,  $\text{CDCl}_3$ , 400 MHz

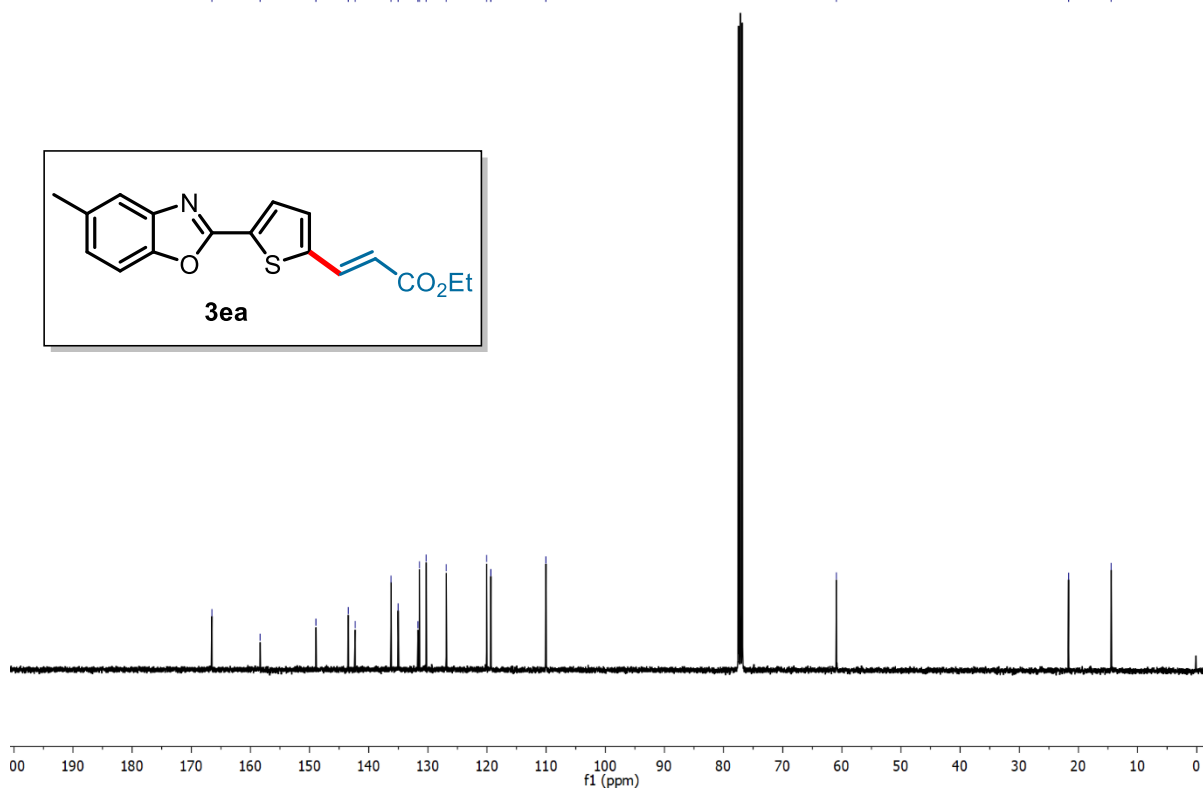
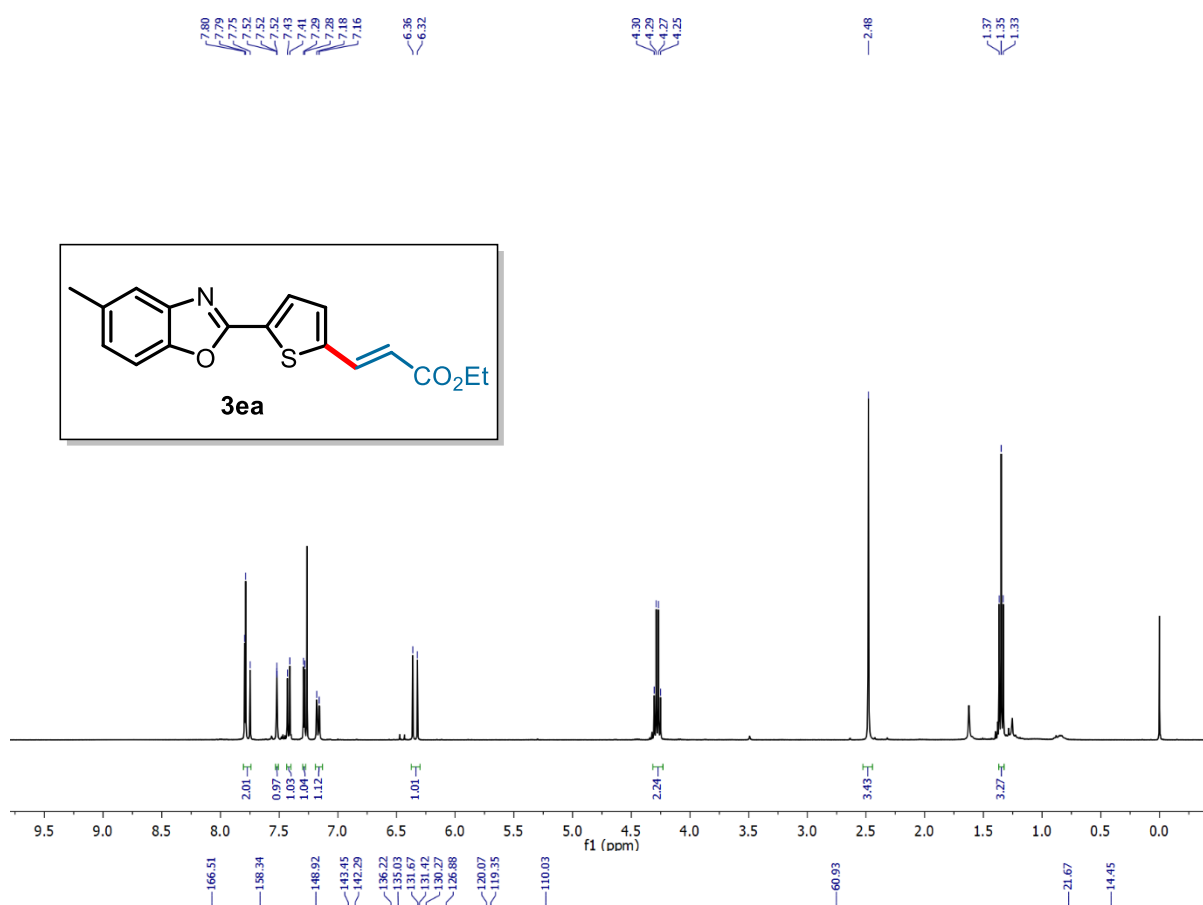


Figure III.8  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3ea**,  $\text{CDCl}_3$ , 400 MHz

Figure III.9  $^1\text{H}$  NMR spectrum of **3ha**,  $\text{CDCl}_3$ , 400 MHz

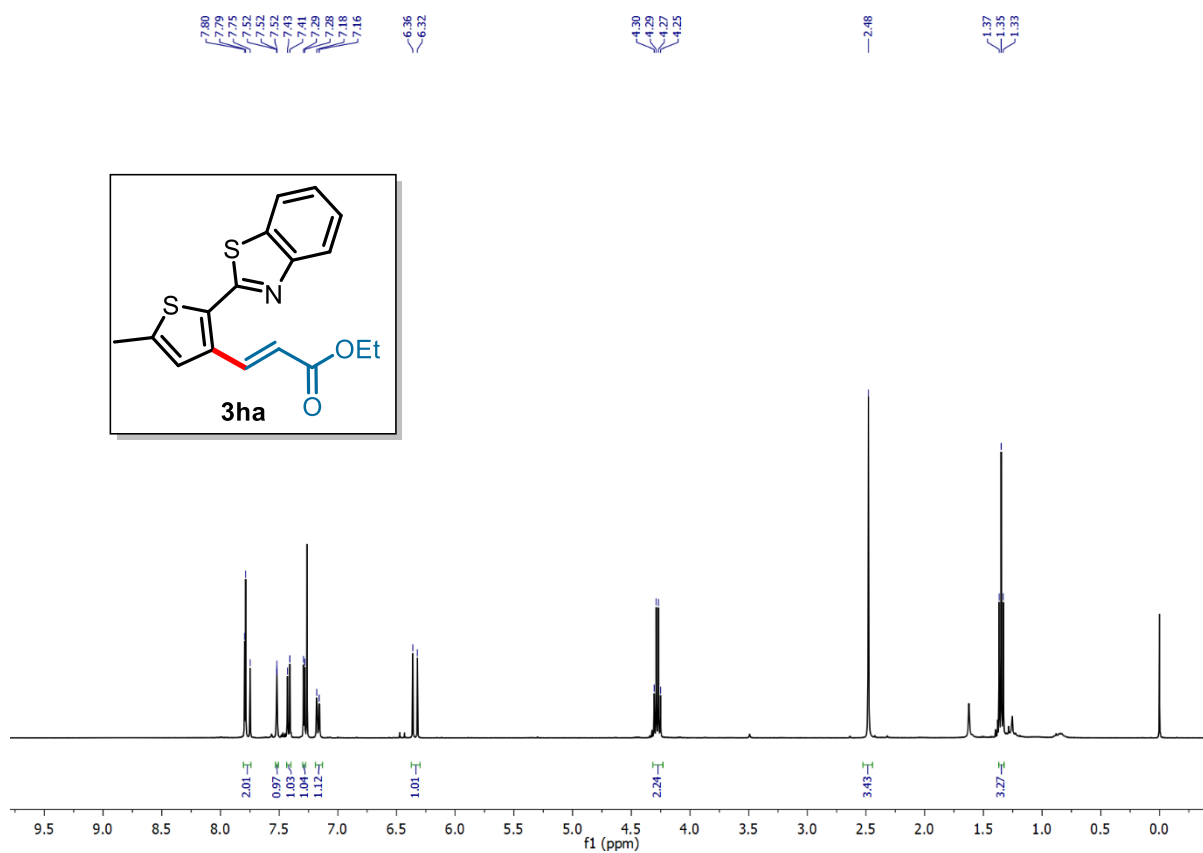
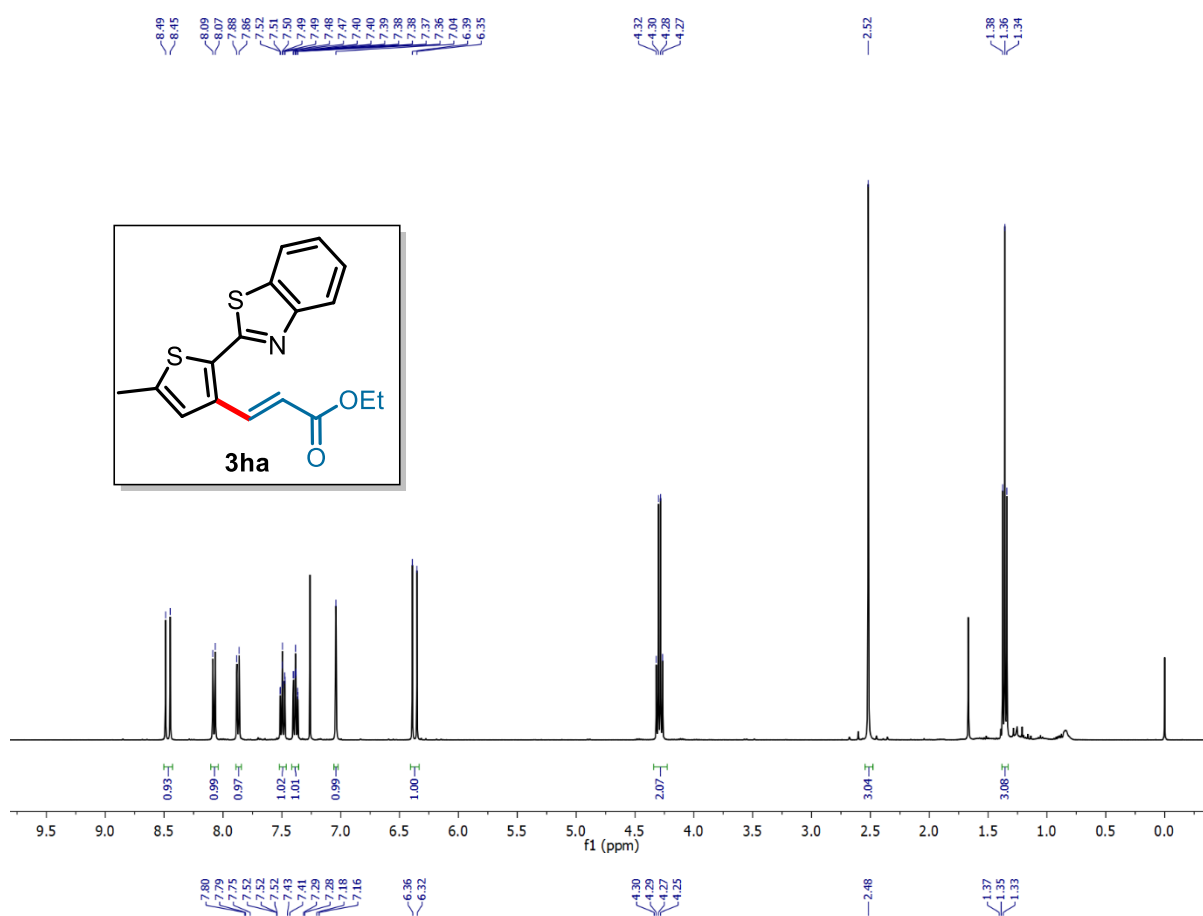


Figure III.10  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR spectrum of **3ha**,  $\text{CDCl}_3$ , 400 MHz

Figure III.11  $^1\text{H}$  NMR spectrum of **3ka**,  $\text{CDCl}_3$ , 400 MHz

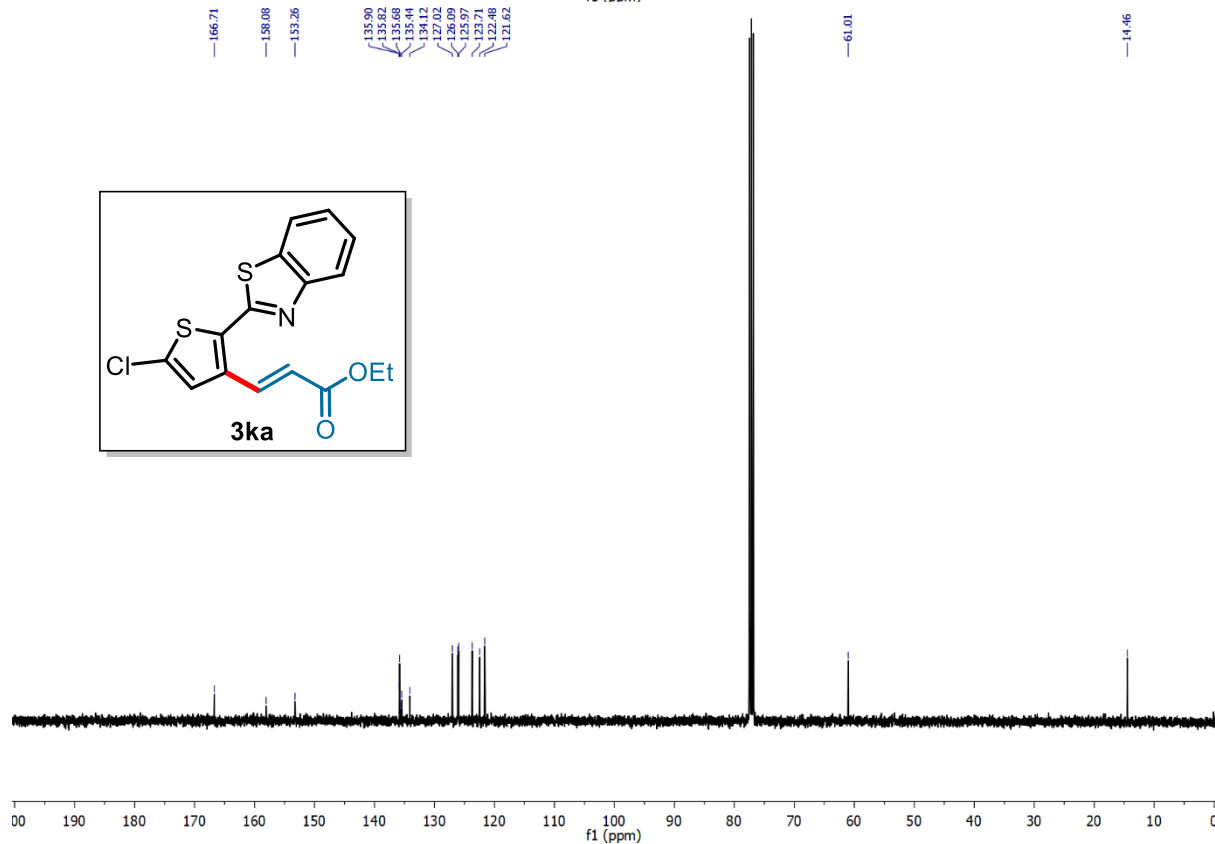
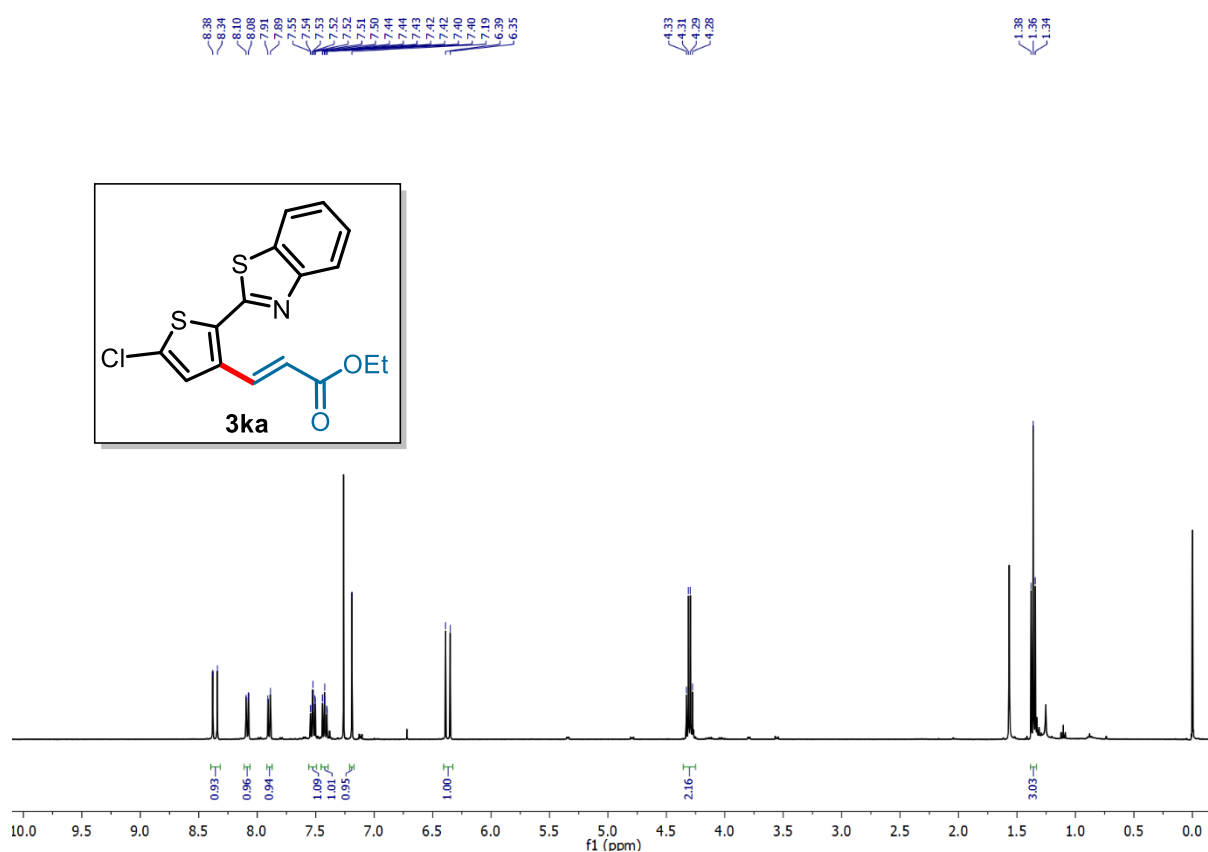
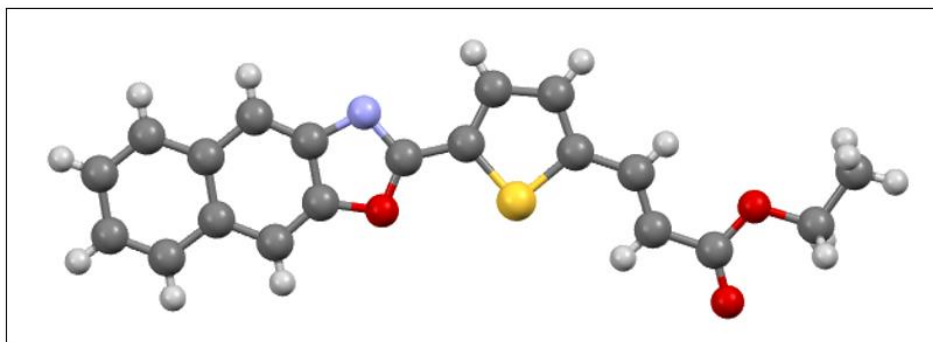
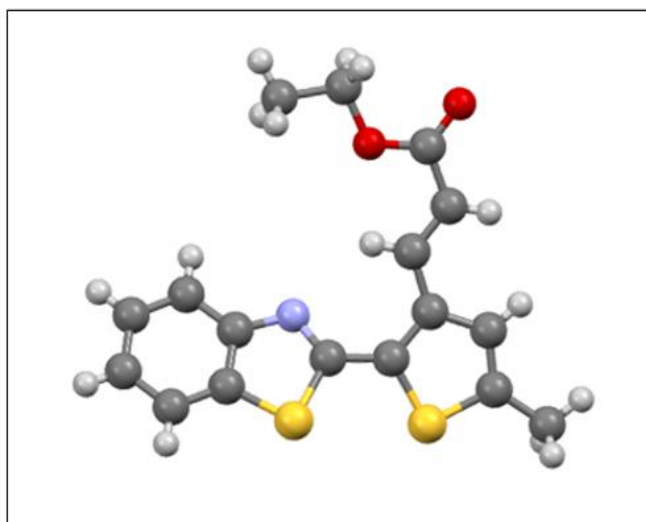


Figure III.12  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3ka**,  $\text{CDCl}_3$ , 400 MHz



**Figure III.13** ORTEP plot (thermal ellipsoids set at 50% probability) of the structures obtained from single crystal X-ray diffraction analyses of **3ga**



**Figure III.14** ORTEP plot (thermal ellipsoids set at 50% probability) of the structures obtained from single crystal X-ray diffraction analyses of **3ha**

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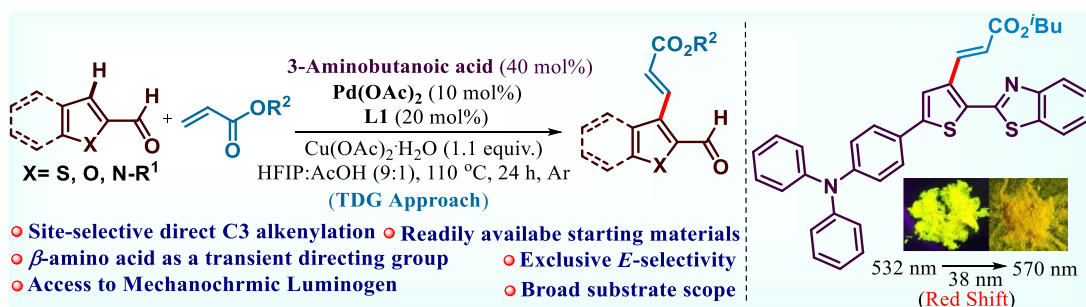
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## Transient Directing Group enabled C3-(sp<sup>2</sup>)-H alkenylation of Five Membered Heterocyclic Aldehydes: An Access to Mechanochromic Luminogen

### Abstract:

The direct site selective C3-(sp<sup>2</sup>)-H alkenylation of five membered heterocyclic carbaldehydes has been developed using 3-aminobutanoic acid as a catalytic transient directing group with Pd(II) catalyst. The various acrylates reacts with a wide range of heterocyclic carbaldehydes to produce highly site-selective C3 alkenylated products. This protocol provides a wide substrate scope with good functional group tolerance and features an exclusive E-selective C3 alkenylation products in good to excellent yields. This methodology provides an easy access to build the new and efficient mechanochromic luminogenic material.

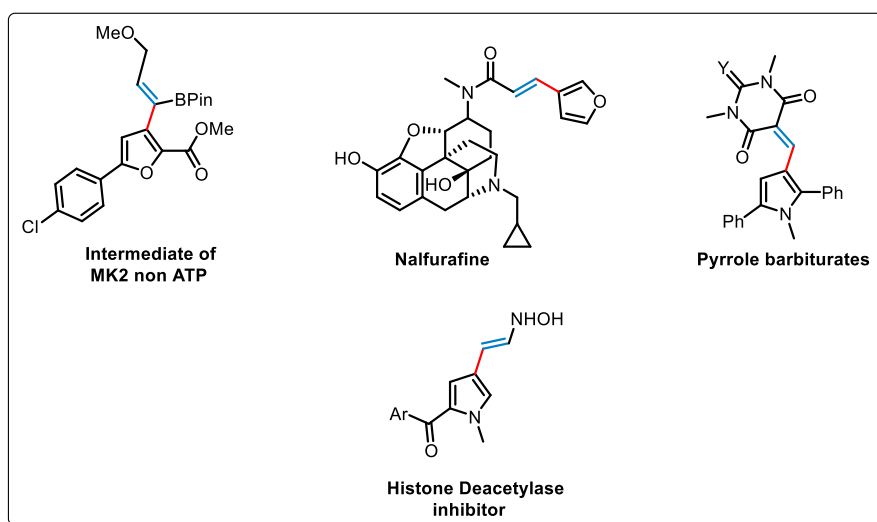


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<https://doi.org/10.1002/adsc.202300528>



## 4.1 Introduction

The alkenyl substituted five-membered heterocyclic compounds are found in a wide range of natural products, pharmaceutically active ingredients, polymers, dyes and organic materials (Figure 4.1).<sup>1,2</sup> The development of concise and practical protocols for the synthesis of functionalized heterocyclic scaffolds has received a lot of attention due to their significance in organic synthesis and medicinal chemistry. The transition metal catalyzed alkenylation of five membered heterocyclic scaffolds has emerged as one of the important and most step- and atom-efficient methods in the organic synthesis in recent years.<sup>3</sup>



**Figure 4.1** Some of the representative examples of C3-alkenylated heterocyclic scaffolds

However, in the five membered heterocyclic scaffolds the selective alkenylation at the C3/ $\beta$ -position is quite difficult due to its low reactivity at this position in comparison to other reactive positions (C2 and/or C5). Since five membered heterocyclic rings are chemically more reactive at the C2 and/or C5 positions ( $\alpha$ -positions), therefore palladium catalyzed alkenylation of five membered heterocyclic compounds is typically occurs at these reactive positions.<sup>4</sup> Even though C3-alkenylated heterocyclic scaffold is extremely important, yet there are limited literature reports available for the synthesis of C3-alkenylated five membered heterocyclic scaffolds.

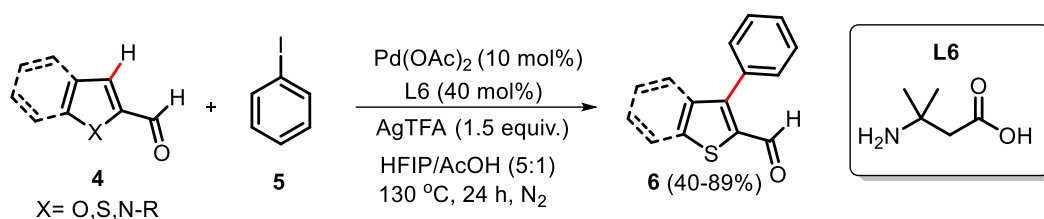
Some of the few available procedures rely on cross coupling reactions,<sup>5</sup> C-H activation strategies employing various directing groups (fixed at C2 position) such as carboxylic acid,<sup>6</sup> and acyl moiety<sup>6</sup> for the alkenylation of heterocyclic scaffold at C3-position. Several other procedures for the direct C3-alkenylation rely on removable directing groups such as imines<sup>7</sup> and amides.<sup>8</sup> Though some of these methods have been employed, yet they have set of limitations too such as the need for the pre-functionalized starting materials, the installation and removal of directing groups, the inability to tolerate functional groups on substrates, the use of stoichiometric amounts of expensive reagents and multi-step approaches to access desired molecules.

In order to address some of the enduring issues, as an alternative it would be extremely desirable to develop the transient directing group (TDG) enabled method for the direct functionalization of the significantly less reactive C3-(sp<sup>2</sup>)-H bond of five membered heterocyclic scaffold in the presence of transition metal catalyst. Over the past few years, the C-H activation technique using a transient directing group (TDG) has gained a great popularity and increased promise. The advantage of the transient directing group is that it easily installed as well as removed later *in situ* without affecting the functionality of the substrate. Also, transient directing group (TDG) can be used in catalytic amount. The transient directing group that is generated *in situ* by the binding to suitable functional group of the substrate and ligand subsequently coordinates to the metal in a reversible pathway.<sup>9</sup>

#### **4.2 Recent approaches for the $\beta$ -C(sp<sup>2</sup>)-H bond activation in five-membered heterocyclic carbonyl compounds**

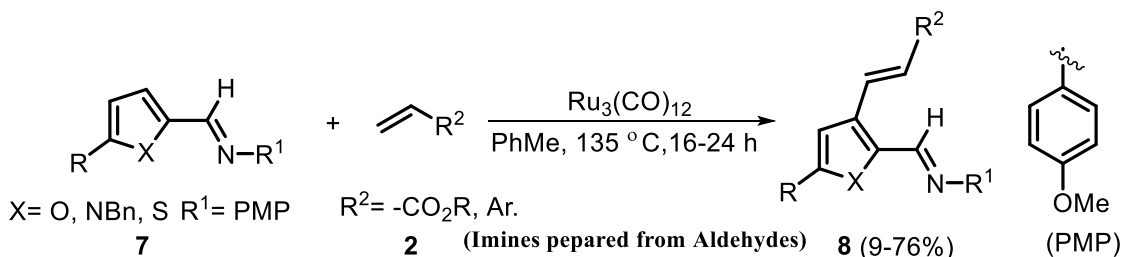
Many research groups have explored the C-H activation of different carbonyl compounds using transient directing groups.<sup>10</sup> In 2017 Ge and coworkers reported the  $\beta$ -C(sp<sup>2</sup>)-H arylation of five-membered heterocyclic carbonyl compounds **4** with the various aryl iodide **5** in presence of palladium catalyst, AgTFA as an oxidant, HFIP/AcOH solvent at 130 °C temperature by employing 3-amino-3-methylbutanoic acid **L6** as TDG to afford the  $\beta$ -C(sp<sup>2</sup>)-H arylation product **6** of the corresponding aldehydes in moderate to good yields (up to 89% Scheme 4.1).<sup>11</sup>

Likewise, our research group has also revealed that C(sp<sup>3</sup>)-H arylation of 3-methylheterocyclic carbonyl scaffolds via TDG-mediated palladium catalysis.<sup>12</sup>



**Scheme 4.1** The  $\beta\text{-C}(\text{sp}^2)\text{-H}$  arylation of five-membered heteroarene carbaldehyde.

Oble and coworkers recently reported the C3-alkenylation of 2 carboxaldimine heterocyclopentadienes **7** with electron poor alkenes **2** in presence of  $\text{Ru}(0)$  catalyst in toluene at  $135\text{ }^\circ\text{C}$  temperature to furnish the C3-alkenylation product **8** in modest to good yields (up to 76%). However, it is important to note that the protocol relied on heterocyclic scaffold having imine as a directing group which is in turn has been prepared from corresponding aldehydes (Scheme 4.2).<sup>7</sup>



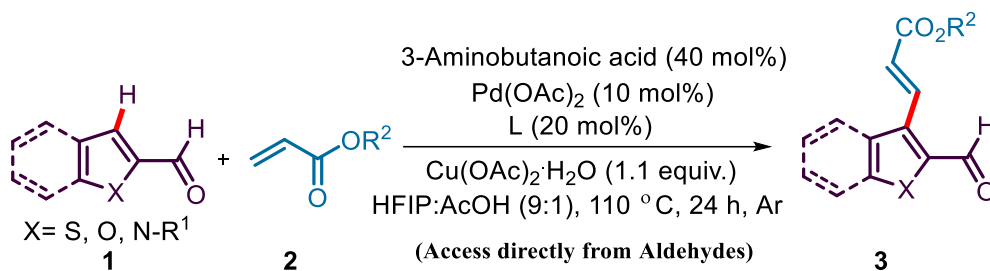
**Scheme 4.2** C3-alkenylation of 2 carboxaldimine heterocyclopentadienes.

There is no direct C3-alkenylation of five-membered heterocyclic carbonyl compounds via TDG approach till date to the best of our knowledge.

### 4.3 Our hypothesis and synthetic design

Looking into the significance of the C3-alkenylation of five-membered heterocyclic carbonyl compounds and based on the available methods as well as limitation, we hypothesized that the heteroarene-2-carbaldehydes could be explored for the direct alkenylation employing the TDG approach via palladium catalysis under suitable reaction conditions.

Here in this chapter, we have described the C3-alkenylation of five-membered heterocyclic carbonyl compounds **1** using 3-amino butanoic acid as a transient directing group (TDG) and 5-(trifluoromethyl)-2-pyridone as an external ligand (**L**) which further reacts with variety of acrylates **2** via palladium catalysis to furnish the desired C3- alkenylation heterocyclic scaffold **3** in moderate to good yields (in Scheme 4.3).<sup>13</sup>



**Scheme 4.3** C3 alkenylation of five-membered heteroarene-2-carboxaldehyde.

#### 4.4 Results and Discussion

In order to explore the hypothesis and to investigate the potential for direct alkenylation of five-membered heterocyclic carbonyl compounds, we commenced with a model reaction of thiophene-2-carboxaldehyde **1a** (0.2 mmol) and isobutyl acrylate **2a** (0.6 mmol) with Pd(OAc)<sub>2</sub> (10 mol%) Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (1 equiv.), 3-aminobutanoic acid as **TDG1** (20 mol%), in HFIP/AcOH (9/1, 1 mL) at 110 °C for 24 h under argon atmosphere. We gratifyingly observed the formation of isobutyl (*E*)-3-(2-formylthiophen-3-yl)acrylate **3aa** albeit in modest yield (38%, Table 4.1, Entry 1).

With this encouraging initial lead, we continued with the further optimization of this model reaction using an additional ligand (5-(trifluoromethyl)-2-pyridone) **L1** (20 mol%) to furnish the corresponding **3aa** with an increased yield (47%, Table 4.1, Entry 2). We further optimized the reaction by increasing the mole percentage of **TDG1** to 40 mol% (Table 4.1, Entry 3). Interestingly, we observed an increase in the yield of **3aa** (57%, Table 4.1, Entry 3). However, further increasing in the **TDG1** loading (60 mol%) reduced the yield of **3aa** (Table 4.1, Entry 4). Later, an increase in the molar equivalent of **2a** (2 to 3 equiv.) improved the yield of **3aa** (62%, Table 4.1, Entry 5). Next, we noticed that the yield of **3aa** was reduced by the addition of 40 mol% of 5-(Trifluoromethyl)-2-pyridone **L1** as a ligand (Table 4.1, Entry 6). After screening the reaction with several oxidants, Cu(OAc)<sub>2</sub>·H<sub>2</sub>O proved to be the most effective oxidant for the desired transformation (Table 4.1, Entries 7-9). We also observed that with the increase in the stoichiometric quantity of the oxidant Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (1 equiv. to 1.1 equiv.), the yield of **3aa** was increased (67%, Table 4.1, Entry 10).

In further optimization, we screened various TDGs and among them 3-aminobutanoic acid (**TDG1**) emerged as the most effective transient directing group for the effective transformation (See Appendix IVA, Table 1, page no. 166). However, the usage of TDG4 (an  $\alpha$ -amino acid)

made the reaction ineffective and it is likely that an  $\beta$ -amino acid favours the development of the [5,6]-bicyclic palladium transition state, which is not achievable in case of an  $\alpha$ -amino acid.

In addition, we screened the reaction with several ligands (**L1-L10**), and **L1** (5-(trifluoromethyl)-2-pyridone) turned out to be the best for the desired transformation (See Appendix IVA, Table 2, page no. 166). We further investigated the reaction using other solvents and we found that the HFIP/AcOH (9:1 v/v, 1 mL) mixture proved to be the optimum solvent mixture for this transformation (Table 4.1, Entry 10 and Entries 13-17).

Later, changing the HFIP/AcOH ratio from 9:1 v/v to 6:4 v/v led to a decrease in the yield of **3aa** (Table 1, see Entries 11, 12). Based on the observations and results HFIP/AcOH (9:1 v/v, 1 mL) proved to be the ideal solvent ratio for the desired transformation. We also changed the catalyst loading [5–15 mol% of Pd(OAc)<sub>2</sub>] and found that 10 mol% of catalyst is the most effective for the transformation (See Appendix IVA, Table 3, page no. 167). The further elevating reaction temperature (120 °C) did not have significant effect on the outcome of the yield, while lowering the temperature (100 °C) reduced yield of the product **3aa** further (Table 4.1, Entries 18–19). The reaction worked smoothly under the inert atmosphere (absence of air or oxygen) indicating that air (or oxygen) has no role in the overall outcome of the reaction and not acting as an oxidant (Table 4.1, Entry 20). Further, we screened the various palladium catalysts, among all Pd(OAc)<sub>2</sub> (10 mol%) proved to be the best catalyst for the desired transformation (Table 4.1, Entries 21–24). The reaction in the absence of the catalyst or oxidant or **TDG1** did not afford the desired product **3aa** (Table 1, Entries 26-28) thus proving that all these are essential for the desired reaction and they have a role in the overall transformation. Based on systematic and exhaustive screening, **1a** (0.2 mmol), **2a** (0.6 mmol), Pd(OAc)<sub>2</sub> (10 mol%), Cu(OAc)<sub>2</sub>.H<sub>2</sub>O (1.1 equiv.), **TDG1** (40 mol%) and **L1** (20 mol%), HFIP/AcOH (9:1 v/v, 1 mL) at 110 °C for 24 h under inert atmosphere (Argon) has turned out to be optimum reaction condition.

After obtaining the optimal reaction conditions, we set out to investigate the practicality and generality of the strategy using thiophene-2-carboxaldehyde **1a** with a wide range of acrylates **2** for exploring the greater substrate scope (Table 4.2). Under the optimized reaction conditions, a variety of acrylates (**2a-2j**) with distinct moieties (linear chain and cyclic) reacted efficiently to furnish the related products (**3aa-3aj**) with good to moderate yields (up to 67%, Table 4.2).

**Table 4.1.** Reaction Conditions Optimization.<sup>[a]</sup>

1a (1 equiv.) + 2a (2 equiv.) → 3aa

**TDG1**

**L1**

| Entry           | Pd Source                            | TDG (mol%)       | Additive                                  | L (mol%)       | 2a (equiv.) | Solvent                           | Yield 3aa (%) <sup>b</sup> |
|-----------------|--------------------------------------|------------------|-------------------------------------------|----------------|-------------|-----------------------------------|----------------------------|
| 1               | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (20) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | -              | 2           | HFIP/AcOH (9:1, v/v)              | 38                         |
| 2               | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (20) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 2           | HFIP/AcOH (9:1, v/v)              | 47                         |
| 3               | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 2           | HFIP/AcOH (9:1, v/v)              | 57                         |
| 4               | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (60) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 2           | HFIP/AcOH (9:1, v/v)              | 45                         |
| 5               | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | HFIP/AcOH (9:1, v/v)              | 62                         |
| 6               | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (40) | 3           | HFIP/AcOH (9:1, v/v)              | 53                         |
| 7               | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(TFA) <sub>2</sub> ·xH <sub>2</sub> O   | <b>L1</b> (20) | 3           | HFIP/AcOH (9:1, v/v)              | 61                         |
| 8               | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub>                      | <b>L1</b> (20) | 3           | HFIP/AcOH (9:1, v/v)              | 40                         |
| 9               | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | AgOAc                                     | <b>L1</b> (20) | 3           | HFIP/AcOH (9:1, v/v)              | 38                         |
| <b>10</b>       | <b>Pd(OAc)<sub>2</sub></b>           | <b>TDG1</b> (40) | <b>Cu(OAc)<sub>2</sub>·H<sub>2</sub>O</b> | <b>L1</b> (20) | <b>3</b>    | <b>HFIP/AcOH (9:1, v/v)</b>       | <b>67</b>                  |
| 11              | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | HFIP/AcOH (8:2, v/v)              | 59                         |
| 12              | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | HFIP/AcOH (6:4, v/v)              | 50                         |
| 13              | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | HFIP (1 mL)                       | 30                         |
| 14              | Pd(TFA) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | AcOH (1 mL)                       | N.R.                       |
| 15              | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | HFIP/AC <sub>2</sub> O (9:1, v/v) | 57                         |
| 16              | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | HFIP/TFA (9:1, v/v)               | N.R.                       |
| 17              | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | TFE/AcOH (9:1, v/v)               | 55                         |
| 18 <sup>c</sup> | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | HFIP/AcOH (9:1, v/v)              | 65                         |
| 19 <sup>d</sup> | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | HFIP/AcOH (9:1, v/v)              | 58                         |
| 20 <sup>e</sup> | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | HFIP/AcOH (9:1, v/v)              | 51                         |
| 21              | Pd(TFA) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | HFIP/AcOH (9:1, v/v)              | 53                         |
| 22              | PdCl <sub>2</sub> (ACN) <sub>2</sub> | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | HFIP/AcOH (9:1, v/v)              | 40                         |
| 23              | PdCl <sub>2</sub>                    | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | HFIP/AcOH (9:1, v/v)              | 45                         |
| 24              | Pd(PPh <sub>3</sub> ) <sub>4</sub>   | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | HFIP/AcOH (9:1, v/v)              | >10                        |
| 25              | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | -              | 3           | HFIP/AcOH (9:1, v/v)              | 50                         |
| 26              | -                                    | <b>TDG1</b> (40) | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | HFIP/AcOH (9:1, v/v)              | N.R.                       |
| 27              | Pd(OAc) <sub>2</sub>                 | -                | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O    | <b>L1</b> (20) | 3           | HFIP/AcOH (9:1, v/v)              | N.R.                       |
| 28              | Pd(OAc) <sub>2</sub>                 | <b>TDG1</b> (40) | -                                         | <b>L1</b> (20) | 3           | HFIP/AcOH (9:1, v/v)              | N.R.                       |

(a) **Reaction conditions:** **1a** (0.2 mmol), **2a** (0.6 mmol), Pd catalyst (10 mol%), **TDG1** (20-60 mol%), Ligand **L1** (20-40 mol%), oxidant (0.3 mmol), solvent (1 mL), 110 °C, Ar, 24 h. (b) Isolated yields after column chromatography. (c) 120 °C. (d) 100 °C. (e) Under air, TDG: Transient Directing group, HFIP: 1,1,3,3 Hexafluoro-2-propanol, AcOH: acetic acid, AC<sub>2</sub>O: acetic anhydride, TFA: trifluoroacetic acid, TFE: trifluoroethanol.

Additionally, iso-butyl acrylate (**2a**) smoothly reacted with a thiophene-2-carboxaldehydes (**1b-1f**) containing electron withdrawing as well electron donating groups at

the C4 and C5 positions to produce there corresponding compounds (**3ba-3fa**) in moderate yields (Table 4.2). Interestingly, the reaction of iso-butyl acrylate **2a** with 2, 5-thiophene-dicarboxaldehyde **1g** furnished the corresponding mono C3-alkenylated compound **3ga** in moderate yield (54%, Table 4.2). Further, we investigated the reactivity of furfural **1i** and substituted furfurals (**1j-1k**) with various acrylates (**2a-2i**) to obtain the selective C3-alkenylated products (**3ia-3ja-3ki-3ii**) in good to excellent yields respectively in all the cases (up to 81% see Table 4.2).

Additionally, reaction of several *N*-protected pyrrole-2-carboxaldehydes (**1l-1o**) were also explored with various acrylates to afford the corresponding products (**3la-3oa**) in good yields (up to 68%, Table 4.2).

Later the molecular structure of **3ia** was unambiguously confirmed by the single crystal X-ray diffraction analysis (CCDC:2240028).<sup>14</sup> This clearly proved the selective C-H functionalization at the C3 position.

However, under similar reaction condition, the unprotected indole and pyrrole with free NH did not produce the final products. The benzofuran and benzothiophene carbonyl compounds (**1p-1q**) reacted efficiently with iso-butyl acrylate (**2a**) to furnish the desired products (**3pa-3qa**) in moderate yields (see Table 4.2).

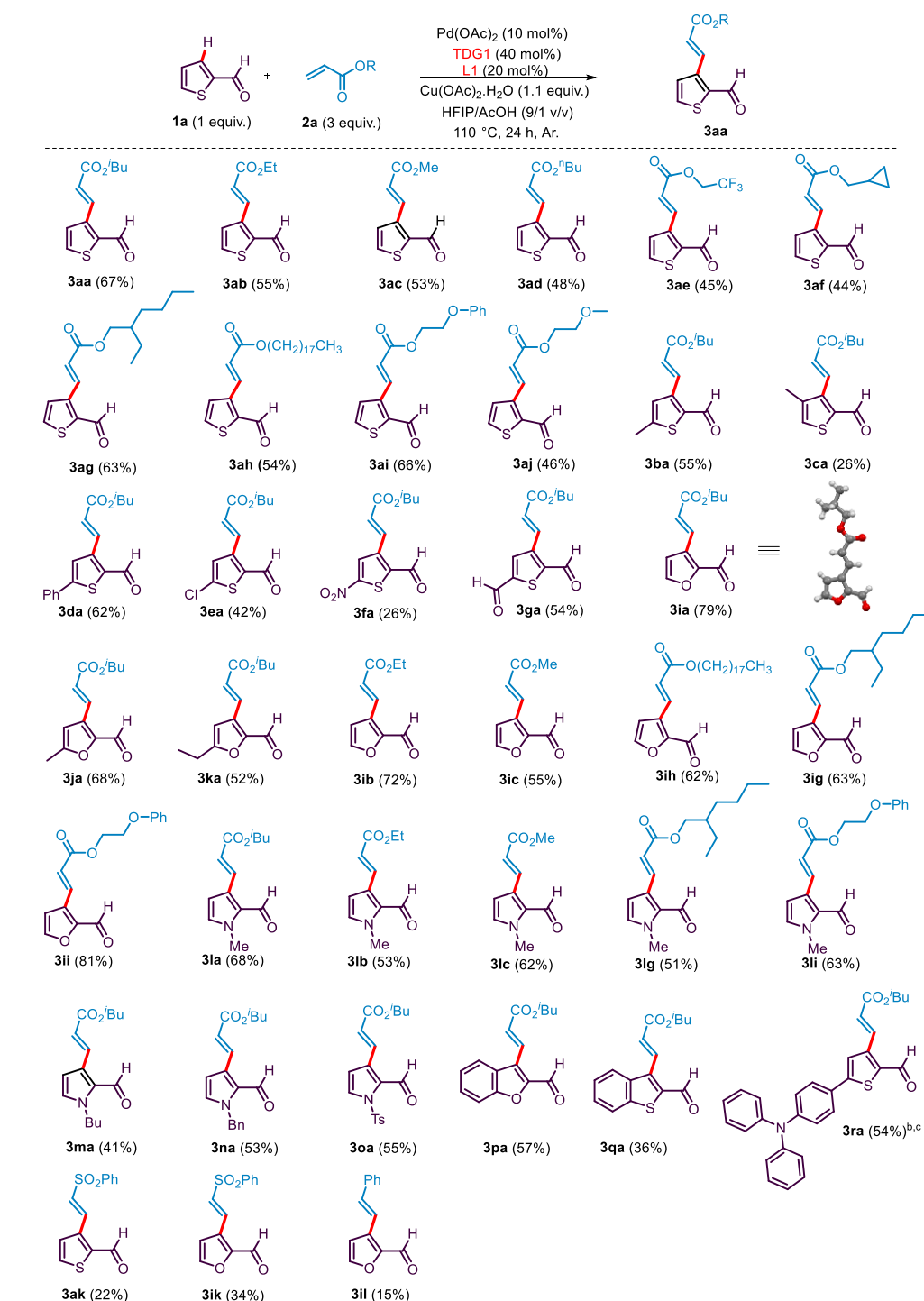
Under optimum reaction conditions, the other electron-deficient alkene such as phenyl vinyl sulphone **2k** also reacted smoothly with thiophene-2-carboxaldehyde **1a** as well as furan-2-carboxaldehyde **1i** to furnish the corresponding C-3 alkenylated products **3ak** and **3ik** respectively in low to modest yields (Table 4.2). Further, furan-2-carboxaldehyde **1i** on treatment with styrene **2l** afforded the corresponding C3-alkenylated product (**3il**) albeit in poor yield (Table 4.2). However, the different Michael acceptor type alkenes (acryl amide, enone and enals, methacrylate etc) did not react under similar reaction conditions.

Overall, the protocol proved to be quite general and worked well for the selective C3-alkenylation of heterocyclic aldehydes at optimum reaction conditions with different acrylates, few sulfones and an alkene. We did not observe the possible C3, C5-dialkenylated products and the protocol afforded the C3-alkenylation products exclusively. Further a plausible mechanism of this reaction has been proposed (See Appendix IVA, page no. 167)<sup>15</sup>

Additionally, we investigated the derivatization of C3-alkenylated thiophene-2-carboxaldehyde as an application to this method. The reduction reaction of **3aa** in presence of NaBH<sub>4</sub> afforded the corresponding product **4a** in excellent yield (91%, Scheme 4.4a).<sup>16</sup> Further

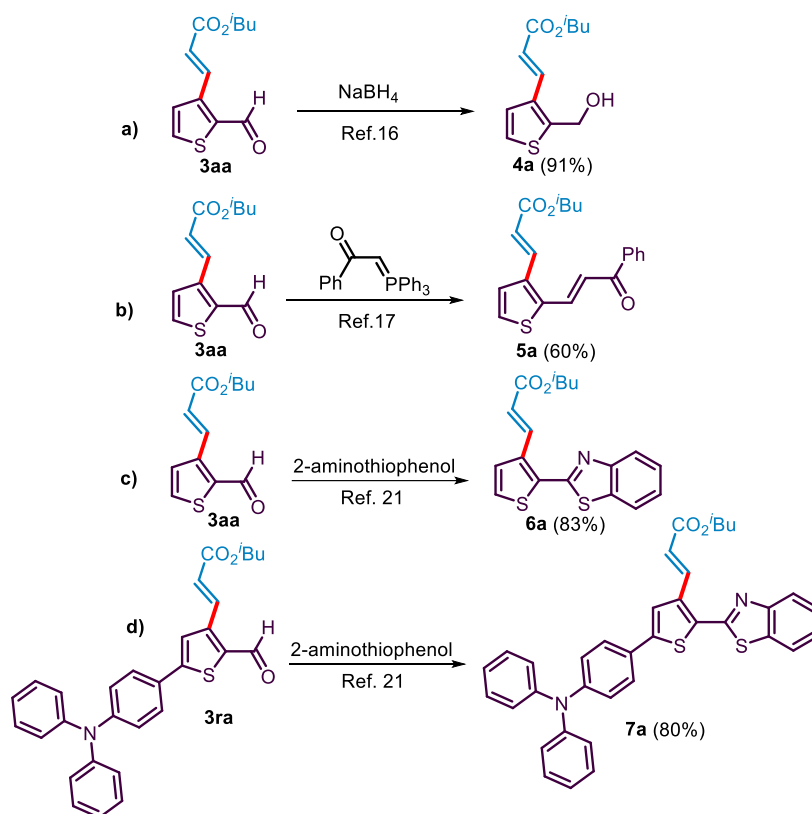
we carried out the Wittig reaction with **3aa** to obtain the corresponding  $\alpha,\beta$  unsaturated carbonyl compound **5a** (60%, Scheme 4.4b).<sup>17</sup>

**Table 4.2.** A library of C3 alkenylated five-membered heteroarene carbaldehydes



<sup>[a]</sup> **Reaction conditions:** **1a** (0.2 mmol), **2a** (0.6 mmol), Pd(OAc)<sub>2</sub> (10 mol%), 3-aminobutanoic acid TDG1 (40 mol%), 5-(Trifluoromethyl)-2-pyridone Ligand L1 (20 mol%), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.22 mmol), HFIP (0.9 mL) AcOH (0.1 mL), 110 °C, Ar, 24 h; <sup>[b]</sup> Isolated yields after column chromatography; <sup>[c]</sup>(0.25 mmol), <sup>[d]</sup>HFIP (1.8 mL) AcOH (0.2 mL).





**Scheme 4.4.** Selective synthetic transformations

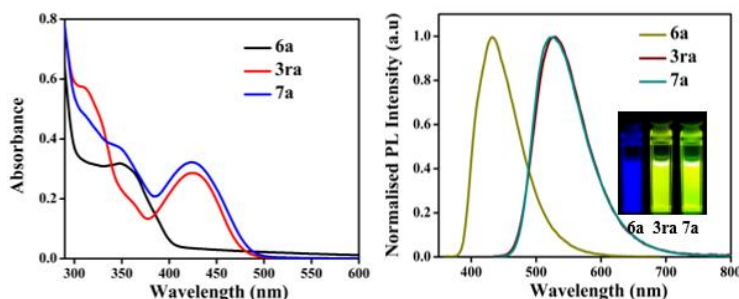
After successfully developing the method, we further planned to further investigate the luminogenic properties of some of these novel compounds by examining their structural framework. Such type of compounds with extended conjugation have numerous uses in the fields of sensing and imaging and organic solid state multi-stimuli responsive materials have gained popularity over the past ten years.<sup>18</sup> When external mechanical force are applied to such kind of materials, they are known to show changes in their properties such as their colour, their luminescence properties such as emission color and intensity which refers mechanochromism. Due to their freedom to change the dihedral angle between the donor and acceptor moieties, donor-acceptor based organic molecules with higher degrees of flexibility, twisting, and non-covalent interactions in the crystalline packing network are more likely to display stimuli-responsive behaviour.<sup>19</sup>

Particularly, due to the presence of extremely flexible three phenyl rings, triphenylamine moiety with propeller-shaped structure is thought to be one of the greatest building blocks for creating novel mechanochromic luminogens.

Inspired this, in order to make such kind of mechanochromic luminogens, we further explored the synthesis of TPA-containing compound **3ra** using the optimised methodology. Following

our optimized reaction conditions, the precursor of **3ra** has been synthesized starting from **1r** and this in turn has been synthesized by the Suzuki cross-coupling reaction.<sup>20</sup> Additionally, we synthesized compounds **6a** and **7a** by employing the functional group transformation of an aldehyde into a benzothiazole moiety using the 2-aminothiophenol, starting from **3aa** and **3ra**, respectively (Scheme 4.4c, d).<sup>21</sup>

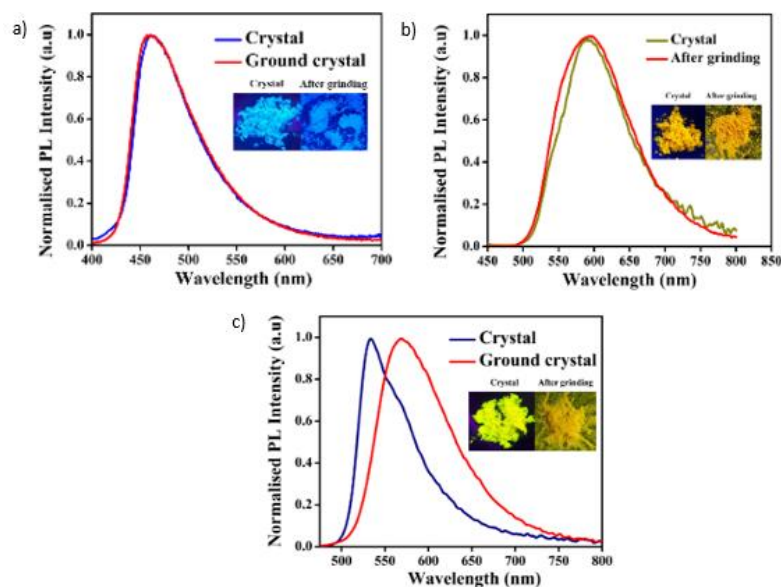
After synthesizing the potential luminogens **6a**, **3ra** and **7a**, we measured their UV-visible absorption spectra in a dilute solution (10  $\mu$ M) of toluene (See Figure 4.2). The intramolecular charge transfer (ICT) transitions from the electron-rich triphenylamine to the electron-deficient C3 alkenyl moiety is believed to be responsible for the lowest energy broad absorption band (in the 380–500 nm area) in **3ra** and **7a**. The high energy absorption band (in 300 nm - 360 nm region) may be due to the molecular  $\pi$ - $\pi^*$  transition. However, in **6a**, we did not observe such ICT transition possibly due to the absence of the triphenylamine moiety and only the molecular  $\pi$ - $\pi^*$  transition occurs in the same region as that of **3ra** and **7a**. Only one emission band has been observed in the steady state PL (photoluminescence) spectra of all the luminogens in toluene. Compounds **3ra** and **7a** in toluene showed green emission with the absorption maxima at  $\sim$  525 nm, while compound **6a** showed blue emission with a maxima at about  $\sim$  430 nm. From **6a** (75 nm) to the other two luminogens (90 nm), the FWHM (Full Width at Half Maxima) varied as well.



**Figure 4.2** Absorption and emission spectra of **6a**, **3ra**, and **7a** in toluene (10  $\mu$ M) of each compound. Emission spectra were collected upon excitation at 380 nm.

Due to the possibility of charge transfer between the triphenylamine and C3 alkenyl moieties in **3ra** and **7a**, the greater emission band-width in these molecules could be attributed to the higher charge-transfer character of the S1 state. The result of emission colour under external stimuli has been significantly influenced by the molecular flexibility and arrangement in crystalline lattice. As the triphenylamine moiety is extremely flexible and has a propeller-like structure, it can be employed as a good building block for creating novel mechanochromic

luminogens. The excited state charge transfer emission in a D-A (donor-acceptor) structure is largely dependent on the dihedral angle between the donor and acceptor moieties. In a flexible luminogen, external stimuli (pressure, temperature, organic vapour treatment) can change the



**Figure 4.3** Emission spectra and UV irradiated (365 nm) photos (given in inset) before and after grinding of a) **6a** b) **3ra** c) **7a**

dihedral angle, changing the emission colour. The compound **6a** containing crystals showed the cyan-blue emission (QY= 0.17) with emission maxima at ~460 nm. Further we observed that in **6a** the emission colour did not change after severe grinding. Similarly, the yellow emission of compound **3ra** crystals (QY=0.27) was unaffected by vigorous grinding, while the FWHM of the emission has been increased from 108 nm to 122 nm in its ground form.

This result indicated that the amorphization or involvement of structurally unordered state due to grinding. It's interesting to note that in **7a** when the green emitting crystals (QY= 0.16, maximum at 532 nm) were slightly ground, the emission maxima had a 38 nm redshift and the ground powder displayed strong yellow emission (maximum at 570 nm, Figure 4.3).

In the crystals **7a**, the emission has a low band-width (67 nm) as well as structured, whereas the ground form of **7a** has a wide (95 nm) and unstructured band-width. This alternating of the emission maxima and emission feature could be attributed to more charge transfer character in ground form of the compound **7a** as well as an increase in orbital overlap between the donor and acceptor moieties after mechanical grinding.

In order to understand further and have more insights, powder X-ray diffraction of (**6a**, **3ra**, **7a**) has been carried out to gain deep understanding of the structure-property relationship of these luminogens. All the PXRD patterns of luminogens (**6a**, **3ra**, **7a**) showed sharp and intense reflection peaks in their crystalline states (See Appendix IVA, page no. 168). Except for the compound **6a**, the intensity and sharpness of the reflection peaks of other two compounds (**7a**, **3ra**) diminished significantly after the grinding treatment. In fact, a broad halo was observed after grinding **7a** thus indicating a change from the ordered crystalline state to the disordered amorphous state. Even if the crystallinity of **3ra** was being modulated, the energy change caused by this was insufficient to change its visual emission color. In compound **7a** such transition may result in a different metastable state with changeable energy to adjust its emission colour from green to bright yellow.

The ability of mechanochromic luminogens to revert to their original crystalline state is of the utmost importance. Looking at this, we carefully dissolved the amorphous powder of **7a** in DCM and later its slow evaporation regenerated its original crystalline state. The PXRD patterns and steady state emission spectra of the re-grown crystals of **7a** completely matched with the original crystals after the DCM dissolution thus validating our results (See Appendix IVA, page no. 168). The DSC profile of both the crystals and ground powder of **6a** revealed essentially no change, thus indicating that no significant phase transition occurred in this instance (See Appendix IVA, page no. 168).

However, two other luminogens (**3ra** and **7a**) displayed interesting behaviour. Two exothermic peaks at 73 °C and 92 °C in crystal **3ra** shifted to 71 °C and 90 °C, respectively, in the ground form. This outcome indicated that this compound exhibited a phase transition behaviour. The transition has been significantly more distinct in case of **7a** and the crystals showed three exothermic peaks at 64 °C, 96 °C, and 130 °C. The peak at 64 °C and 130 °C vanished after grinding, whereas one of the peaks at 96 °C shifted to 90 °C. This result definitely an indication of a phase transition that eventually brought to an alternation in the energy state and mechanochromic activity.

## 4.5 Conclusions

In conclusion, an efficient and novel synthetic strategy has been developed by employing the  $\beta$ -amino acid as a transient directing group (TDG) and 5-(Trifluoromethyl)-2-pyridone as an external ligand (L) via Pd(II)-catalysis for the selective C3 alkenylation of five membered heterocyclic carbonyl compounds with a wide range of acrylates. This method proved to be highly site-selective for the C3 alkenylation of the five membered heterocyclic carbonyl compounds along with the good functional group tolerance. The protocol also gave an access to novel as well as effective mechanochromic luminogenic materials and developed an easy method to make more such type of compounds.

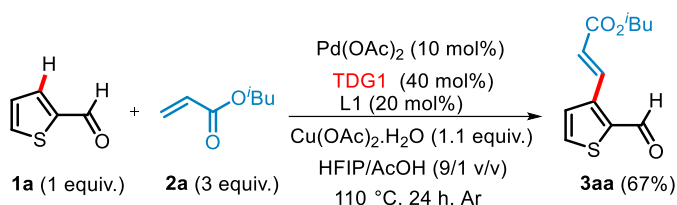
## 4.6 Experimental Section

### 4.6.1 General Information

All reactions were carried out with distilled and dried solvents using oven-dried glass wares under dry Argon atmosphere, unless otherwise stated. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin layer chromatography (TLC) was performed using silica gel 60 GF254 pre-coated aluminum backed plates (2.5 mm) with detection by UV light. Visualization was accomplished by irradiation with a UV light at 254 nm followed by 2,4-DNP (Dinitrophenylhydrazine) and KMnO<sub>4</sub> solution as staining agents. Column chromatography was performed using silica gel (100-200 mesh) eluting with petroleum ether and ethyl acetate/DCM. Petroleum ether and ethyl acetate mixture was used as gradient elution for column chromatography. All the isolated compounds were characterized by <sup>1</sup>H (Proton) and <sup>13</sup>C{<sup>1</sup>H} (carbon) NMR spectra and they were recorded on 400 MHz Bruker Advance III HD Ascend 400 MHz spectrophotometers. All the NMR (Nuclear Magnetic resonance) Spectra were recorded in CDCl<sub>3</sub>. The NMR spectra were recorded using tetramethyl silane (TMS) as an internal standard. <sup>1</sup>H NMR spectra were recorded at 400 MHz and <sup>13</sup>C{<sup>1</sup>H} NMR spectra were recorded at 100 MHz (Bruker) unless otherwise noted. The chemical shifts ( $\delta$ ) are reported in ppm downfield from CDCl<sub>3</sub> ( $\delta$  = 7.26 ppm) for <sup>1</sup>H NMR and in relative to the central CDCl<sub>3</sub> resonance ( $\delta$  = 77.16 ppm) for <sup>13</sup>C{<sup>1</sup>H} NMR spectroscopy. <sup>1</sup>H NMR spectral data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet), coupling constants (J) and integration. Coupling constants (J) are reported in Hertz (Hz). <sup>13</sup>C{<sup>1</sup>H} NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by High Resolution Mass Spectrometer (HRMS) using ESI TOF. Melting points were measured (Büchi B-540 apparatus) in an open glass capillary and values are uncorrected. The DSC data were recorded using TA Discover 250 second-generation differential scanning calorimeter under nitrogen atmosphere. The powder X-ray diffraction (PXRD) measurement was recorded by Bruker D8 advance X-ray diffractometer with CuK $\alpha$  radiation. The single crystal X-ray diffraction (SCXRD) measurements were carried out by using the Bruker KAPPA APEX III CCD diffractometer with Cu/K radiation source (1.54184 Å). The steady state absorption and emission spectra were recorded using the UV-Vis spectrophotometer (Shimadzu, UV-2600) and Fluoromax-4 spectrofluorimeter (Horiba Jobin Yvon) respectively. The absolute quantum yield of all the compounds were measured with an integrating sphere coupled with the Fluoromax-4 spectrofluorimeter (Horiba Jobin Yvon).

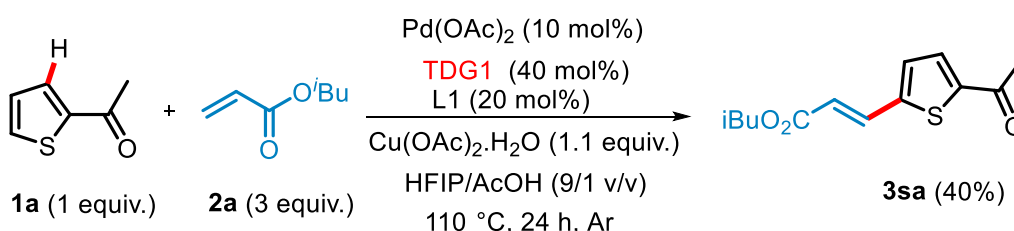
Starting materials *n*-alkyl pyrrole-2-carboxaldehyde (**1m**, **1n**, **1o**),<sup>22</sup> 5-phenylthiophene-2-carbaldehyde (**1d**),<sup>23</sup> 5-(4-(diphenylamino)phenyl)thiophene-2-carbaldehyde (**1r**),<sup>20</sup> have been synthesized using the literature procedures

#### 4.6.2 General Procedures for Pd(II)-catalyzed C3-(sp<sup>2</sup>)-H Alkenylation of 2-heterocyclic aldehyde to access the compound **3aa**:



A 15 mL oven dried Sealed tube with screwcap equipped with a stir bar and charged with thiophene-2-carboxaldehyde **1a** (19  $\mu$ L, 0.2 mmol, 1.0 equiv.), isobutyl acrylate **2a** (86.41  $\mu$ L, 0.6 mmol, 3 equiv.), Pd(OAc)<sub>2</sub> (4.5 mg, 0.01 mmol, 0.1 equiv.), Cu(OAc)<sub>2</sub>.H<sub>2</sub>O (43.94 mg, 0.3 mmol, 1.1 equiv.), 3-aminobutanoic acid as a **TDG1** (8.25mg, 0.04 mmol, 0.4 equiv.), Ligand **L1** (6.5 mg, 0.02 mmol, 0.2 equiv.) and then add the mixture of solvent HFIP (0.9 mL) and AcOH (0.1 mL) at room temperature. Next, resulting reaction mixture was purged with Argon and degassed for 2 min, then close the cap and stirred the mixture vigorously at room temperature for 10 min. The the reaction was mixture then heated to 110 °C for 24 h. After, the completion of the reaction (monitored using TLC), the reaction mixture was cooled to room temperature and it was diluted with EtOAc (15 mL) and subsequently it was filtered through pad of celite. The filtrate was concentrated under vacuo and the residue was purified by column chromatography on silica gel to furnish the desired product **3aa** as a yellow liquid (67%, 32 mg).

#### 4.6.3 Reaction with Five membered heterocyclic ketone compound:



#### 4.6.4 General Procedure B for synthesis of 5-(4-(diphenylamino)phenyl)thiophene-2-carbaldehyde (**1r**)<sup>20</sup>:

The 50 mL round bottom flask was charged with 5-bromothiophene-2- carbaldehyde (95.52 mg, 0.5 mmol), 4-(Diphenylamino)phenylboronic acid (159 mg, 0.55 mmol), caesium carbonate (325.82 mg, 1.0 mmol), [Pd(PPh<sub>3</sub>)<sub>4</sub>] (28.89 mg, 0.25 mmol), THF (9 mL), and water (1 mL). The reaction mixture was degassed and it was stirred for 30 min at room temperature. Later the reaction mixture was heated to 66 °C for 2 h in argon atmosphere, the reaction mixture was then refluxed (at 80 °C) for 16 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and was diluted with DCM and water and the reaction mixture was extracted with DCM (20 mL x 2) then combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuo. The resultant residue was further purified by column chromatography over silica gel (DCM/Petroleumether = 40:60) to afford the desired product (**1r**) as a yellow solid (142 mg, 80%).

#### 4.6.5 General Procedure C for synthesis of Isobutyl (*E*)-3-(2-(hydroxymethyl)thiophen-3-yl)acrylate (**4a**)<sup>16</sup> :

The 25 mL dry round bottom flask was charged with **3aa** (36 mg, 0.15 mmol) and MeOH (5 mL) as solvent. The reaction mixture was cooled to 0 °C and sodium borohydride (8.57mg, 0.227 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. Following the completion of the reaction (monitored by TLC), the reaction mixture was quenched with water (5 mL) and the reaction mixture was further stirred for 30 min. The resulting reaction mixture was extracted with ethyl acetate (15 mL x 2). The combined organic layer was washed with brine solution (15 mL x 2) and dried over anhydrous sodium sulphate. Later, the it as evaporated under vacuo. The residue was purified by column chromatography over silica gel (EtOAc/petroleum ether = 20:80) to obtain the desired product (**4a**) as a colourless oil (91%, 33 mg)

#### 4.6.6 General Procedure D for synthesis of Isobutyl (*E*)-3-(2-((*E*)-3-oxo-3-phenylprop-1-en-1-yl)thiophen-3-yl)acrylate (**5a**)<sup>17</sup>:

A 25 mL round bottom flask was charged with **3aa** (50 mg, 0.21 mmol), and 1-Phenyl-3-(2-thienyl)-2-propen-1-one (100 mg, 0.262 mmol), toluene (5 mL) as solvent. The reaction mixture was refluxed overnight. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled down to room temperature and the solvent removed under vacuo. The residue was purified by column chromatography over silica gel (EtOAc/ petroleum ether as an eluent, 15:85) to get the desired product (**5a**) as a yellow oil (60%, 43 mg).



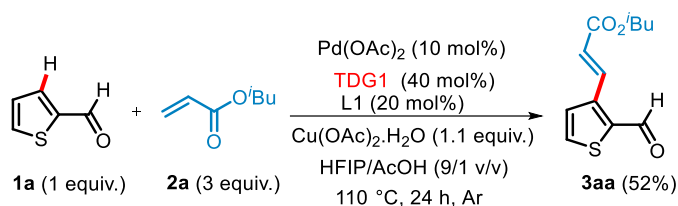
#### 4.6.7 General Procedure E for synthesis of Isobutyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)thiophen-3-yl)acrylate (**6a**)<sup>21</sup>:

An oven dried round bottom flask (50 mL) was charged with **3aa** (95 mg, 0.399 mmol), 2-aminothiophenol (37.81  $\mu$ L, 0.362 mmol), sodium metabisulfite (83 mg, 0.435 mmol) and DMF (15 mL). The reaction mixture was heated under reflux for 2 h. After the completion of the reaction (monitored by TLC), the mixture was allowed to cool to room temperature and was diluted with EtOAc (30 mL) and the reaction mixture was washed with brine (10 mL x 3) and the resultant organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the filtrate was concentrated using rotary evaporated under vacuum. The resultant residue was purified by column chromatography (DCM/Petroleum ether = 50:50) to obtain the desired product (**6a**) as yellow solid (103 mg, 83%).

#### 4.6.8 General Procedure F for synthesis of Isobutyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-5-(4-(diphenylamino)phenyl)thiophen-3-yl)acrylate (**7a**)<sup>21</sup>:

50 mL oven dried round bottom flask charged with compound **3ra** (90 mg, 0.187 mmol), 2-aminothiophenol (17.72  $\mu$ L, 0.170 mmol), sodium metabisulfite (38.75 mg 0.204 mmol) and DMF (15 mL). Then the reaction mixture was heated under reflux for 2 h. After the completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool down to room temperature and was diluted with EtOAc (30 mL). It was washed with brine (10 mL x 3) and the organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and was filtered. The filtrate was further concentrated under vacuo. The resultant residue was purified by column chromatography over silica gel (DCM/Petroleum ether = 70:30) to obtain the desired product **7a** as yellow solid (80 mg, 80%).

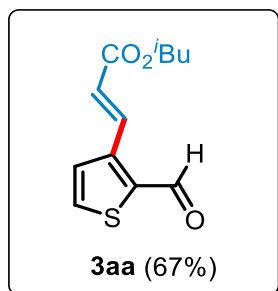
#### 4.6.9 Scaleup reaction (2 millimole):



A 30 mL Sealed tube with screwcap equipped with a stir bar was charged with thiophene-2-carboxaldehyde **1a** (208.3  $\mu\text{L}$ , 2.23 mmol, 1.0 equiv.), isobutyl acrylate **2a** (963  $\mu\text{L}$ , 6.69 mmol, 3 equiv.),  $\text{Pd}(\text{OAc})_2$  (50 mg, 0.223 mmol, 0.1 equiv.),  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (489.57 mg, 2.45 mmol, 1.1 equiv.), 3-aminobutanoic acid as a **TDG1** (91.95 mg, 0.89 mmol, 0.4 equiv.), Ligand **L1** (72.7 mg, 0.45 mmol, 0.2 equiv.) followed by the addition of the mixture of solvent HFIP (4.5 mL) and AcOH (0.5 mL) at room temperature. Then the resulting reaction mixture was degassed under Argon atmosphere for 2 min and stirred vigorously at room temperature for 10 min. Then the reaction mixture was heated to 110 °C for 24 h. After, the completion of the reaction (monitored using TLC), the reaction mixture was cooled to room temperature and it was diluted with EtOAc (30 mL) and subsequently it was filtered through pad of celite. The filtrate was concentrated under vacuo and the residue was purified by column chromatography on silica gel to furnish the desired product **3aa** as a yellow liquid (52%, 275 mg)

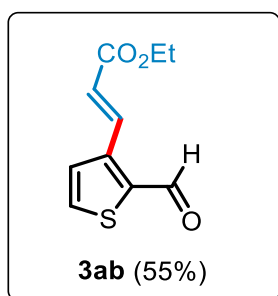
#### 4.6.10 Experimental Data:

##### Isobutyl (*E*)-3-(2-formylthiophen-3-yl)acrylate (**3aa**):



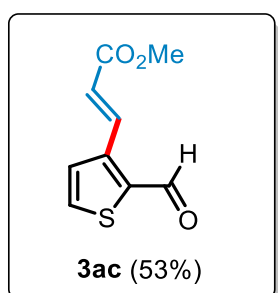
The compound **3aa** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3aa** as pale-yellow oil (67%, 32 mg).  $R_f$  = 0.49 (EtOAc/petroleum ether 14:86),  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.23 (s, 1H), 8.18 (d,  $J$  = 15.9 Hz, 1H), 7.71 (d,  $J$  = 5.2 Hz, 1H), 7.41 (d,  $J$  = 5.1 Hz, 1H), 6.48 (d,  $J$  = 15.8 Hz, 1H), 4.02 (d,  $J$  = 6.7 Hz, 2H), 2.03 (m, 1H), 0.99 (d,  $J$  = 6.7 Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  181.7, 166.5, 143.1, 141.4, 134.7, 133.9, 127.2, 123.4, 71.2, 27.9, 19.2. HRMS (ESI):  $m/z$  [ $\text{M} + \text{Na}$ ] $^+$  calcd for  $\text{C}_{12}\text{H}_{14}\text{NaO}_3\text{S}$ : 261.0561; found, 261.0557

##### Ethyl (*E*)-3-(2-formylthiophen-3-yl)acrylate (**3ab**):



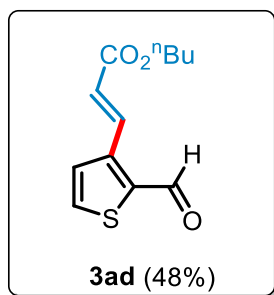
The compound **3ab** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ab** as yellow oil (55%, 23 mg).  $R_f$  = 0.49 (EtOAc/petroleum ether 16:84).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.23 (s, 1H), 8.16 (d,  $J$  = 15.8 Hz, 1H), 7.70 (d,  $J$  = 5.2 Hz, 1H), 7.39 (d,  $J$  = 5.1 Hz, 1H), 6.46 (d,  $J$  = 15.8 Hz, 1H), 4.29 (q,  $J$  = 7.1 Hz, 2H), 1.35 (t,  $J$  = 7.1 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  181.8, 166.4, 143.1, 141.5, 134.7, 134.0, 127.2, 123.5, 61.2, 14.4. HRMS (ESI):  $m/z$  [ $\text{M} + \text{H}$ ] $^+$  calcd for  $\text{C}_{10}\text{H}_{11}\text{O}_3\text{S}$ : 211.0429; found, 211.0435

##### Methyl (*E*)-3-(2-formylthiophen-3-yl)acrylate (**3ac**):



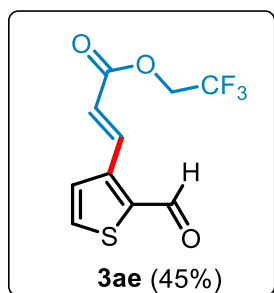
The compound **3ac** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ac** as light-yellow solid (53%, 21 mg).  $R_f$  = 0.49 (EtOAc/petroleum ether 20:80),  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.22 (s, 1H), 8.18 (d,  $J$  = 15.9 Hz, 1H), 7.71 (d,  $J$  = 5.2 Hz, 1H), 7.40 (d,  $J$  = 5.1 Hz, 1H), 6.47 (d,  $J$  = 15.9 Hz, 1H), 3.84 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  181.7, 166.8, 142.9, 141.5, 134.7, 134.2, 127.2, 123.0, 52.2. HRMS (ESI):  $m/z$  [ $\text{M} + \text{H}$ ] $^+$  calcd for  $\text{C}_9\text{H}_9\text{O}_3\text{S}$ : 197.0272; found, 197.0275

### Butyl (*E*)-3-(2-formylthiophen-3-yl)acrylate (**3ad**):



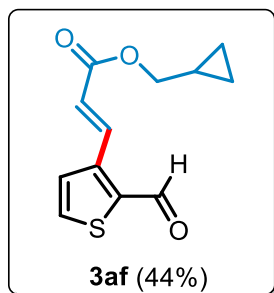
The compound **3ad** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ad** as yellow oil (48%, 23 mg).  $R_f = 0.49$  (EtOAc/petroleum ether 14:86).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.23 (s, 1H), 8.16 (d,  $J = 15.8$  Hz, 1H), 7.71 (d,  $J = 5.2$  Hz, 1H), 7.40 (d,  $J = 5.1$  Hz, 1H), 6.46 (d,  $J = 15.8$  Hz, 1H), 4.24 (t,  $J = 6.7$  Hz, 2H), 1.74 – 1.67 (m, 2H), 1.49 – 1.39 (m, 2H), 0.97 (t,  $J = 7.4$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  181.6, 166.5, 143.1, 141.5, 134.7, 133.9, 127.2, 123.5, 65.1, 30.8, 19.3, 13.7. HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{12}\text{H}_{14}\text{NaO}_3\text{S}$ : 261.0561; found, 261.0550

### 2,2,2-trifluoroethyl (*E*)-3-(2-formylthiophen-3-yl)acrylate (**3ae**):



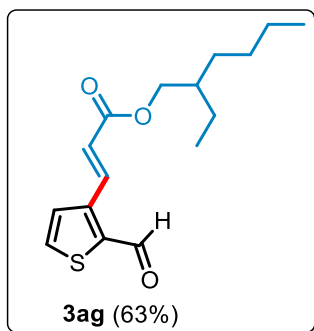
The compound **3ae** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ae** as yellow oil (45%, 24 mg).  $R_f = 0.49$  (EtOAc/petroleum ether 14:86).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.22 (s, 1H), 8.29 (d,  $J = 15.9$  Hz, 1H), 7.74 (d,  $J = 5.2$  Hz, 1H), 7.43 (d,  $J = 5.2$  Hz, 1H), 6.52 (d,  $J = 15.9$  Hz, 1H), 4.62 (q,  $J = 8.4$  Hz, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  181.6, 164.7, 142.2, 142.0, 136.5, 134.8, 127.2, 123.1 (q,  $J = 277.3$  Hz), 120.9, 60.8 (q,  $J = 36.8$  Hz).  $^{19}\text{F}$  NMR (377 MHz, Chloroform-*d*)  $\delta$  -73.68. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{10}\text{H}_8\text{F}_3\text{O}_3\text{S}$ : 265.0146; found, 265.0139.

### Cyclopropyl methyl (*E*)-3-(2-formylthiophen-3-yl)acrylate (**3af**):



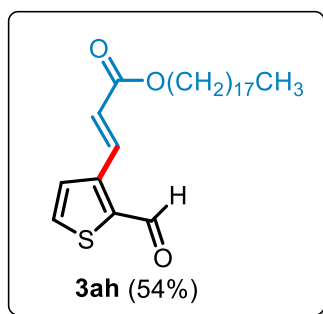
The compound **3af** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3af** as yellow oil (44%, 21 mg).  $R_f = 0.49$  (EtOAc/petroleum ether 18:82).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.24 (s, 1H), 8.18 (d,  $J = 15.8$  Hz, 1H), 7.71 (d,  $J = 5.1$  Hz, 1H), 7.40 (d,  $J = 5.1$  Hz, 1H), 6.50 (d,  $J = 15.8$  Hz, 1H), 4.07 (d,  $J = 7.3$  Hz, 2H), 1.25 – 1.15 (m, 1H), 0.65 – 0.60 (m, 2H), 0.36 – 0.32 (m, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  181.8, 166.5, 143.1, 141.5, 134.7, 134.0, 127.2, 123.5, 70.0, 10.0, 3.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{12}\text{H}_{12}\text{NaO}_3\text{S}$ : 259.0405; found, 259.0402.

### 2-ethylhexyl (*E*)-3-(2-formylthiophen-3-yl)acrylate (**3ag**):



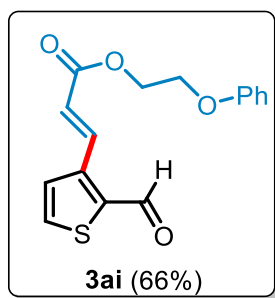
The compound **3ag** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ag** as yellow oil (63%, 37 mg)  $R_f$  = 0.49 (EtOAc/petroleum ether 12:88),  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.23 (s, 1H), 8.17 (d,  $J$  = 15.8 Hz, 1H), 7.71 (d,  $J$  = 5.1 Hz, 1H), 7.41 (d,  $J$  = 5.1 Hz, 1H), 6.47 (d,  $J$  = 15.9 Hz, 1H), 4.16 (dd,  $J$  = 5.9, 2.8 Hz, 2H), 1.67 (m, 1H), 1.43 (m, 2H), 1.39 – 1.34 (m, 2H), 1.34 – 1.31 (m, 4H), 0.93 (t,  $J$  = 7.5 Hz, 3H) 0.91 (t,  $J$  = 7.5 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  181.7, 166.6, 143.1, 141.5, 134.7, 133.9, 127.2, 123.5, 67.6, 39.0, 30.6, 29.1, 24.0, 23.1, 14.2, 11.1. HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{16}\text{H}_{22}\text{NaO}_3\text{S}$ : 317.1187; found, 317.1180.

### Octadecyl (*E*)-3-(2-formylthiophen-3-yl)acrylate (**3ah**):



The compound **3ah** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ah** as white solid (54%, 45 mg), m.p. = 91 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether 6:94)  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.23 (s, 1H), 8.16 (d,  $J$  = 15.8 Hz, 1H), 7.70 (d,  $J$  = 5.2 Hz, 1H), 7.39 (d,  $J$  = 5.1 Hz, 1H), 6.46 (d,  $J$  = 15.8 Hz, 1H), 4.23 (t,  $J$  = 6.7 Hz, 2H), 1.42 – 1.25 (m, 30H), 0.90 – 0.85 (m, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  181.7, 134.7, 133.9, 127.2, 123.5, 65.4, 32.1, 29.8, 29.8, 29.8, 29.7, 29.7, 29.5, 29.4, 28.8, 26.1, 22.8, 14.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{26}\text{H}_{42}\text{NaO}_3\text{S}$ : 457.2752 ; found, 457.2755

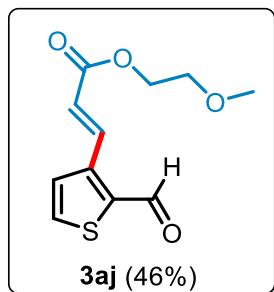
### 2-phenoxyethyl (*E*)-3-(2-formylthiophen-3-yl)acrylate (**3ai**):



The compound **3ai** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ai** as yellow oil (66%, 40 mg).  $R_f$  = 0.49 (EtOAc/petroleum ether 33:67),  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.20 (s, 1H), 8.19 (d,  $J$  = 15.8 Hz, 1H), 7.70 (d,  $J$  = 5.2 Hz, 1H), 7.38 (d,  $J$  = 5.1 Hz, 1H), 7.30 (dd,  $J$  = 8.7, 7.4 Hz, 2H), 6.98 – 6.93 (m, 3H), 6.50 (d,  $J$  = 15.8 Hz, 1H), 4.59 (t,  $J$  = 4.0 Hz, 2H), 4.26 (t,  $J$  = 4.0 Hz, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  181.7, 166.3, 158.6, 142.8, 141.7, 134.7, 134.6, 129.7, 127.2, 122.8,

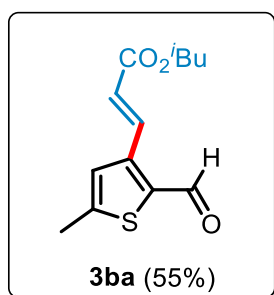
121.4, 114.8, 65.9, 63.5. HRMS (ESI):  $m/z$   $[M + Na]^+$  calcd for  $C_{16}H_{14}NaO_4S$ : 325.0510; found, 325.0508.

### 2-methoxyethyl (*E*)-3-(2-formylthiophen-3-yl)acrylate (**3aj**):



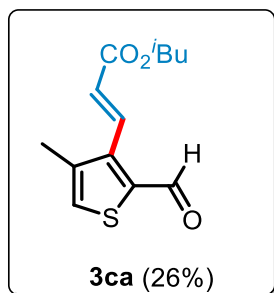
The compound **3aj** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3aj** as yellow oil (46%, 22 mg).  $R_f$  = 0.49 (EtOAc/petroleum ether 38:62),  $^1H$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.23 (s, 1H), 8.20 (d,  $J$  = 15.8 Hz, 1H), 7.71 (d,  $J$  = 5.2 Hz, 1H), 7.39 (d,  $J$  = 5.1 Hz, 1H), 6.52 (d,  $J$  = 15.8 Hz, 1H), 4.43 – 4.36 (t,  $J$  = 6.0 Hz, 2H), 3.72 – 3.65 (t,  $J$  = 4.0 Hz, 2H), 3.43 (s, 3H).  $^{13}C\{^1H\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  181.7, 166.4, 142.9, 141.6, 134.7, 134.4, 127.2, 122.9, 70.5, 64.1, 59.2. HRMS (ESI):  $m/z$   $[M + Na]^+$  calcd for  $C_{11}H_{12}NaO_4S$ : 263.0353; found, 263.0342.

### Isobutyl (*E*)-3-(2-formyl-5-methylthiophen-3-yl)acrylate (**3ba**):



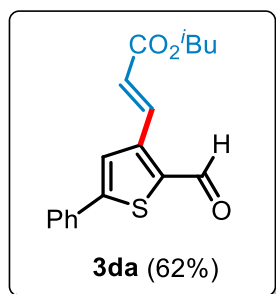
The compound **3ba** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ba** as white solid (55%, 28 mg), m.p. = 66 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether 14:86).  $^1H$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.13 (s, 1H), 8.09 (d,  $J$  = 15.8 Hz, 1H), 7.08 (s, 1H), 6.41 (d,  $J$  = 15.8 Hz, 1H), 4.01 (d,  $J$  = 6.7 Hz, 2H), 2.55 (s, 3H), 2.02 (m, 1H), 0.99 (d,  $J$  = 6.7 Hz, 6H).  $^{13}C\{^1H\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  181.2, 166.6, 150.7, 143.6, 139.9, 134.0, 125.6, 123.1, 71.2, 27.9, 19.2, 16.4. HRMS (ESI):  $m/z$   $[M + Na]^+$  calcd for  $C_{13}H_{16}NaO_3S$ : 275.0717; found, 275.0710

### Isobutyl (*E*)-3-(2-formyl-4-methylthiophen-3-yl)acrylate (**3ca**):



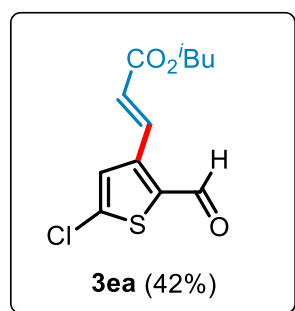
The compound **3ca** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ca** as pale-yellow oil (26%, 13 mg).  $R_f$  = 0.49 (EtOAc/petroleum ether 12:88).  $^1H$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.06 (s, 1H), 7.95 (d,  $J$  = 16.1 Hz, 1H), 7.39 (s, 1H), 6.31 (d,  $J$  = 16.1 Hz, 1H), 4.03 (d,  $J$  = 6.7 Hz, 2H), 2.35 (s, 3H), 2.03 (m, 1H), 0.99 (d,  $J$  = 6.7 Hz, 6H).  $^{13}C\{^1H\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  182.4, 166.1, 142.9, 142.0, 139.3, 135.2, 131.2, 125.8, 71.2, 27.8, 19.1, 15.7. HRMS (ESI):  $m/z$   $[M + Na]^+$  calcd for  $C_{13}H_{16}NaO_3S$ : 275.0717; found, 275.0719.

### Isobutyl (*E*)-3-(2-formyl-5-phenylthiophen-3-yl)acrylate (**3da**):



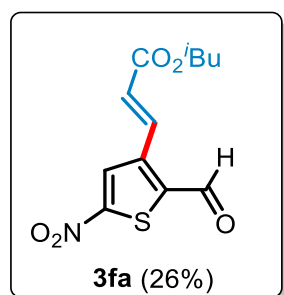
The compound **3da** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3da** as yellow solid (62%, 39 mg), m.p.=131 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether = 12:88).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.20 (s, 1H), 8.15 (d,  $J$  = 15.9 Hz, 1H), 7.68 – 7.65 (m, 2H), 7.57 (s, 1H), 7.46 – 7.42 (m, 3H), 6.53 (d,  $J$  = 15.8 Hz, 1H), 4.03 (d,  $J$  = 6.6 Hz, 2H), 2.03 (m, 1H), 1.00 (d,  $J$  = 6.7 Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  181.4, 166.4, 153.3, 143.9, 140.2, 133.9, 132.5, 130.0, 129.4, 126.5, 123.5, 122.5, 71.2, 27.9, 19.2. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{18}\text{H}_{19}\text{O}_3\text{S}$ : 315.1055; found, 315.1052

### Isobutyl (*E*)-3-(5-chloro-2-formylthiophen-3-yl)acrylate (**3ea**):



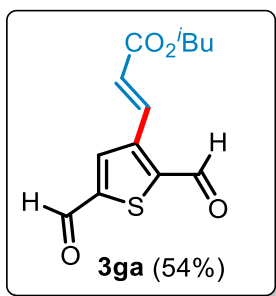
The compound **3ea** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ea** as yellow solid (42%, 23 mg), m.p.=67 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether 12:88).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.12 (s, 1H), 8.04 (d,  $J$  = 15.8 Hz, 1H), 7.23 (s, 1H), 6.41 (d,  $J$  = 15.8 Hz, 1H), 4.02 (d,  $J$  = 6.7 Hz, 2H), 2.02 (m, 1H), 0.99 (d,  $J$  = 6.7 Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  180.5, 166.1, 142.8, 141.5, 140.2, 132.8, 126.3, 124.3, 71.4, 27.9, 19.2. HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{12}\text{H}_{13}\text{ClNaO}_3\text{S}$ : 295.0172; found, 295.0164.

### Isobutyl (*E*)-3-(2-formyl-5-nitrothiophen-3-yl)acrylate(**3fa**):



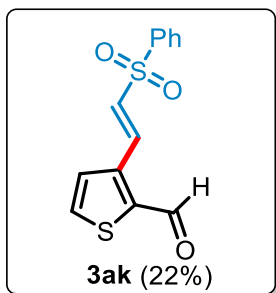
The compound **3fa** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3fa** as colourless oil (26%, 15 mg).  $R_f$  = 0.49 (EtOAc/petroleum ether 20:80).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.28 (s, 1H), 8.12 (s, 1H), 8.09 (d,  $J$  = 16.0 Hz, 1H), 6.55 (d,  $J$  = 15.8 Hz, 1H), 4.04 (d,  $J$  = 6.7 Hz, 2H), 2.03 (m, 1H), 0.99 (d,  $J$  = 6.7 Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  181.7, 165.7, 157.0, 143.5, 141.2, 132.2, 126.5, 125.8, 71.6, 27.9, 19.2. HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{12}\text{H}_{13}\text{NNaO}_5\text{S}$ : 306.0411; found, 306.0409.

### Isobutyl (*E*)-3-(2,5-diformylthiophen-3-yl)acrylate (**3ga**):



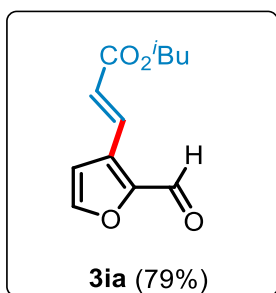
The compound **3ga** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ga** as yellow solid (54%, 29 mg) m.p.=103 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether 24:76).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.30 (s, 1H), 10.02 (s, 1H), 8.17 (d,  $J$  = 15.9 Hz, 1H), 8.02 (s, 1H), 6.55 (d,  $J$  = 15.9 Hz, 1H), 4.04 (d,  $J$  = 6.7 Hz, 2H), 2.03 (m, 1H), 1.00 (d,  $J$  = 6.8 Hz, 6H).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  183.1, 182.3, 166.0, 148.3, 145.7, 142.6, 133.6, 133.2, 124.7, 71.4, 27.9, 19.2. HRMS (ESI):  $m/z$  [ $\text{M} + \text{H}$ ] $^+$  calcd for  $\text{C}_{13}\text{H}_{15}\text{O}_4$ : 267.0691; found, 267.0680.

### (*E*)-3-(2-(phenylsulfonyl)vinyl)thiophene-2-carbaldehyde (**3ak**):



The compound **3ak** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ak** as colourless oil (22%, 12 mg)  $R_f$  = 0.49 (EtOAc/petroleum ether 45:65).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.20 (s, 1H), 8.19 (d,  $J$  = 15.3 Hz, 1H), 7.97 (dd,  $J$  = 7.0, 1.6 Hz, 2H), 7.71 (d,  $J$  = 5.1 Hz, 1H), 7.66 (d,  $J$  = 7.4 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.30 (d,  $J$  = 5.1 Hz, 1H), 6.93 (d,  $J$  = 15.3 Hz, 1H).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  181.3, 142.5, 140.1, 140.0, 134.8, 134.0, 132.3, 131.9, 129.7, 128.1, 127.5. HRMS (ESI):  $m/z$  [ $\text{M} + \text{H}$ ] $^+$  calcd for  $\text{C}_{13}\text{H}_{11}\text{O}_3\text{S}_2$ : 279.0149; found, 279.0141.

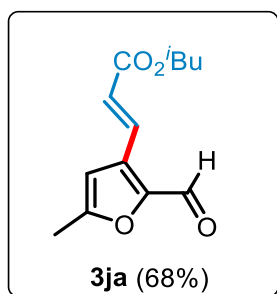
### Isobutyl (*E*)-3-(2-formylfuran-3-yl)acrylate (**3ia**):



The compound **3ia** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ia** as white solid (79%, 35 mg) m.p.= 96 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether 20:80).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.94 (s, 1H), 8.07 (d,  $J$  = 16.0 Hz, 1H), 7.63 (d,  $J$  = 1.9 Hz, 1H), 6.79 (d,  $J$  = 1.9 Hz, 1H), 6.46 (d,  $J$  = 16.0 Hz, 1H), 4.01 (d,  $J$  = 6.7 Hz, 2H), 2.08 – 1.96 (m, 1H), 0.99 (d,  $J$  = 6.7 Hz, 6H).  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  178.5, 166.2, 149.5, 147.8, 132.0, 130.2, 124.4, 110.5, 71.1, 27.9, 19.2. HRMS (ESI):  $m/z$  [ $\text{M} + \text{Na}$ ] $^+$  calcd for  $\text{C}_{12}\text{H}_{14}\text{NaO}_4$ : 245.0790; found, 245.0775.

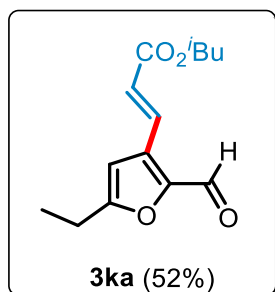


### Isobutyl (*E*)-3-(2-formyl-5-methylfuran-3-yl)acrylate (**3ja**):



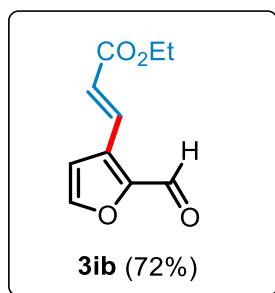
The compound **3ja** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ja** as yellow oil (68%, 32 mg)  $R_f = 0.49$  (EtOAc/petroleum ether 16:84).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.83 (s, 1H), 7.98 (d,  $J = 15.9$  Hz, 1H), 6.42 (s, 1H), 6.40 (d,  $J = 15.9$  Hz, 1H), 4.00 (d,  $J = 6.7$  Hz, 2H), 2.42 (s, 3H), 2.02 (m, 1H), 0.98 (d,  $J = 6.7$  Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  177.2, 166.3, 159.3, 148.7, 132.3, 132.1, 124.0, 107.0, 71.1, 27.9, 19.2, 14.1. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{17}\text{O}_4$ : 237.1121; found, 237.1127.

### Isobutyl (*E*)-3-(5-ethyl-2-formylfuran-3-yl)acrylate (**3ka**):



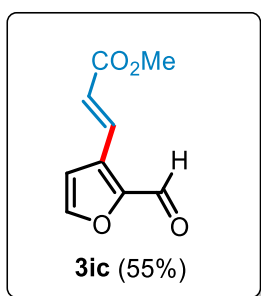
The compound **3ka** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ka** as reddish oil (52%, 26 mg).  $R_f = 0.49$  (EtOAc/petroleum ether 12:88).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.84 (s, 1H), 8.0 (d,  $J = 15.9$  Hz, 1H), 6.43 (s, 1H), 6.42 (d,  $J = 15.9$  Hz, 1H), 4.0 (d,  $J = 6.7$  Hz, 2H), 2.75 (q,  $J = 7.6$  Hz, 2H), 2.08 – 1.96 (m, 1H), 1.31 (t,  $J = 7.6$  Hz, 3H), 0.98 (d,  $J = 6.7$  Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  177.3, 166.3, 164.7, 148.5, 132.2, 132.2, 123.9, 105.5, 71.1, 27.9, 21.8, 19.2, 11.6. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{19}\text{O}_4$ : 251.1278; found, 251.1283.

### Ethyl (*E*)-3-(2-formylfuran-3-yl)acrylate (**3ib**):



The compound **3ib** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ib** as white solid (72%, 28 mg) m.p. = 86 °C,  $R_f = 0.49$  (EtOAc/petroleum ether 22:78).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.94 (s, 1H), 8.05 (d,  $J = 15.9$  Hz, 1H), 7.63 (d,  $J = 1.8$  Hz, 1H), 6.78 (d,  $J = 1.9$  Hz, 1H), 6.45 (d,  $J = 16.0$  Hz, 1H), 4.28 (q,  $J = 7.1$  Hz, 2H), 1.35 (t,  $J = 7.2$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  178.5, 166.1, 149.4, 147.7, 132.0, 130.2, 124.4, 110.5, 61.0, 14.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{10}\text{H}_{11}\text{O}_4$ : 195.0657; found, 195.0659.

### Methyl (*E*)-3-(2-formylfuran-3-yl)acrylate (**3ic**):

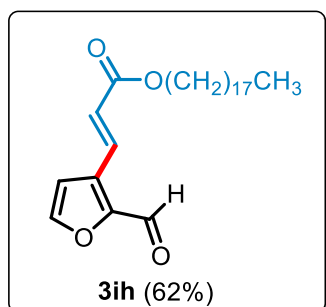


The compound **3ic** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ic** as white solid (55%, 20 mg). m.p. = 107 °C  $R_f$  = 0.49 (EtOAc/petroleum ether 21:79).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.94 (s, 1H), 8.07 (d,  $J$  = 16.0 Hz, 1H), 7.63 (d,  $J$  = 1.9 Hz, 1H), 6.79 (d,  $J$  = 1.8 Hz, 1H), 6.45 (d,  $J$  = 16.0 Hz, 1H), 3.83 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$

NMR (100 MHz, Chloroform-*d*)  $\delta$  178.6, 166.6, 149.5, 147.8, 132.3, 130.0, 123.9, 110.5, 52.1.

HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_9\text{H}_9\text{O}_4$ : 181.0501; found, 181.0510

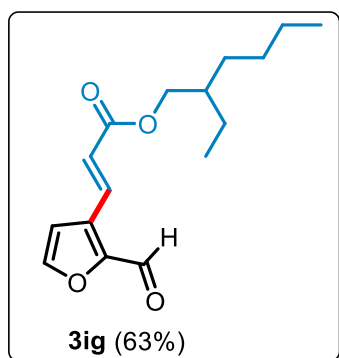
### Octadecyl (*E*)-3-(2-formylfuran-3-yl)acrylate (**3ih**):



The compound **3ih** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ih** as a white solid (62%, 54 mg). m.p. = 90 °C,  $R_f$  = 0.49 (EtOAc/petroleum ether 8:92).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.93 (s, 1H), 8.05 (d,  $J$  = 16.0 Hz, 1H), 7.63 (d,  $J$  = 1.8 Hz, 1H), 6.78 (d,  $J$  = 1.8 Hz, 1H), 6.45 (d,  $J$  = 16.0 Hz, 1H), 4.21 (t,  $J$  = 6.8 Hz, 2H), 1.70 (p,  $J$  = 7.0 Hz,

2H), 1.42 – 1.26 (m, 30H), 0.88 (t,  $J$  = 6.8 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  178.4, 147.7, 131.9, 124.4, 110.5, 65.3, 32.1, 29.8, 29.8, 29.8, 29.7, 29.7, 29.5, 29.4, 28.8, 26.1, 22.8, 14.2. HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{26}\text{H}_{42}\text{NaO}_4$ : 441.2980 ; found, 441.2983

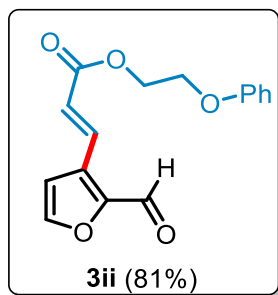
### 2-ethylhexyl (*E*)-3-(2-formylfuran-3-yl)acrylate (**3ig**):



The compound **3ig** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ig** as yellow oil (63%, 35 mg).  $R_f$  = 0.49 (EtOAc/petroleum ether 15:85).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.93 (s, 1H), 8.06 (d,  $J$  = 16.0 Hz, 1H), 7.63 (d,  $J$  = 1.8 Hz, 1H), 6.79 (d,  $J$  = 1.8 Hz, 1H), 6.45 (d,  $J$  = 16.0 Hz, 1H), 4.14 (dd,  $J$  = 5.8, 2.5 Hz, 2H), 1.70 – 1.63 (m, 1H), 1.45 –

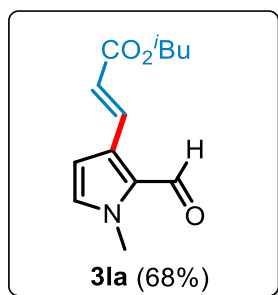
1.38 (m, 2H), 1.36 – 1.29 (m, 6H), 0.96 – 0.90 (m, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  178.4, 166.3, 149.4, 147.7, 131.9, 130.2, 124.4, 110.4, 67.5, 38.9, 30.5, 29.0, 23.9, 23.1, 14.1, 11.1. HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{16}\text{H}_{22}\text{NaO}_4$ : 301.1415; found, 301.1412

### 2-phenoxyethyl (*E*)-3-(2-formylfuran-3-yl)acrylate (**3ii**):



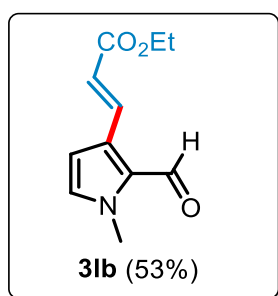
The compound **3ii** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ii** as yellow oil (81%, 49 mg).  $R_f = 0.49$  (EtOAc/petroleum ether 24:76).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.91 (s, 1H), 8.09 (d,  $J = 16.0$  Hz, 1H), 7.62 (d,  $J = 1.6$  Hz, 1H), 7.34 – 7.24 (m, 3H), 7.01 – 6.89 (m, 5H), 6.77 (d,  $J = 1.6$  Hz, 1H), 6.49 (d,  $J = 16.0$  Hz, 1H), 4.58 (t,  $J = 6.0$  Hz, 2H), 4.25 (t,  $J = 4.0$  Hz, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  178.4, 165.9, 158.5, 149.4, 147.6, 132.6, 129.6, 129.6, 123.6, 121.3, 114.7, 110.4, 65.8, 63.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{15}\text{O}_5$ : 287.0919; found, 287.0909

### Isobutyl (*E*)-3-(2-formyl-1-methyl-1H-pyrrol-3-yl)acrylate (**3la**):



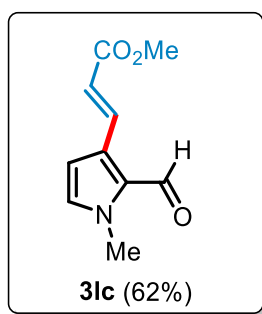
The compound **3la** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3la** as yellow oil (68%, 32 mg).  $R_f = 0.49$  (EtOAc/petroleum ether 25:75).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.99 (s, 1H), 7.99 (d,  $J = 15.7$  Hz, 1H), 6.84 (d,  $J = 2.7$  Hz, 1H), 6.46 (d,  $J = 2.7$  Hz, 1H), 6.33 (d,  $J = 15.7$  Hz, 1H), 3.99 (d,  $J = 6.7$  Hz, 2H), 3.95 (s, 3H), 2.01 (m, 1H), 0.98 (d,  $J = 6.7$  Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  178.5, 167.2, 134.2, 131.9, 131.5, 129.2, 119.4, 107.1, 70.8, 37.4, 28.0, 19.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{18}\text{NO}_3$ : 236.1281; found, 236.1286.

### Ethyl (*E*)-3-(2-formyl-1-methyl-1H-pyrrol-3-yl)acrylate (**3lb**):



The compound **3lb** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3lb** as yellow oil (53%, 22 mg).  $R_f = 0.49$  (EtOAc/petroleum ether = 24:76).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.99 (s, 1H), 7.98 (d,  $J = 15.7$  Hz, 1H), 6.84 (d,  $J = 2.6$  Hz, 1H), 6.45 (d,  $J = 2.7$  Hz, 1H), 6.31 (d,  $J = 15.7$  Hz, 1H), 4.26 (q,  $J = 7.1$  Hz, 2H), 3.95 (s, 3H), 1.33 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  178.5, 167.1, 134.3, 131.9, 131.5, 129.2, 119.4, 107.1, 60.7, 37.4, 14.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{11}\text{H}_{14}\text{NO}_3$ : 208.0973; found, 208.0975

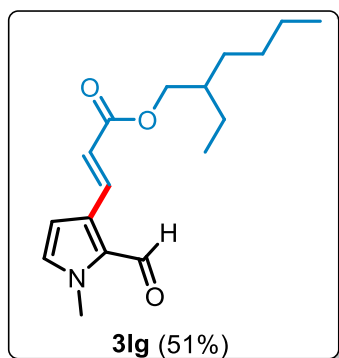
### Methyl (*E*)-3-(2-formyl-1-methyl-1H-pyrrol-3-yl)acrylate (**3lc**):



The compound **3lc** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3lc** as yellow oil (62%, 24 mg).  $R_f = 0.49$  (EtOAc/petroleum ether 24:76).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.99 (s, 1H), 7.99 (d,  $J = 15.7$  Hz, 1H), 6.84 (d,  $J = 2.6$  Hz, 1H), 6.45 (d,  $J = 2.4$  Hz, 1H), 6.31 (d,  $J = 15.7$  Hz, 1H), 3.95 (s, 3H), 3.80 (s, 3H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  178.5, 167.5, 134.5, 131.9, 131.3, 129.3, 118.9, 107.2, 51.9, 37.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{10}\text{H}_{12}\text{NO}_3$ : 194.0817; found, 194.0820

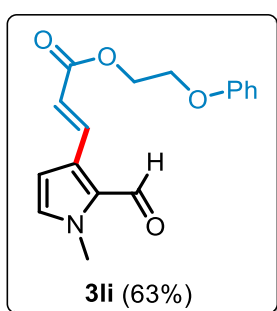
### 2-ethylhexyl (*E*)-3-(2-formyl-1-methyl-1H-pyrrol-3-yl)acrylate (**3lg**):



The compound **3lg** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3lg** as yellow oil (51%, 30 mg).  $R_f = 0.49$  (EtOAc/petroleum ether 15:85).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.99 (s, 1H), 7.97 (d,  $J = 15.7$  Hz, 1H), 6.84 (d,  $J = 2.6$  Hz, 1H), 6.46 (d,  $J = 2.4$  Hz, 1H), 6.32 (d,  $J = 15.7$  Hz, 1H), 4.12 (dd,  $J = 5.9, 3.0$  Hz, 2H), 3.95 (s, 3H), 1.68 – 1.62 (m, 1H), 1.43 – 1.38 (m, 2H), 1.36 – 1.30 (m, 6H), 0.92 (m, 6H).

$^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  178.5, 167.3, 134.2, 131.9, 131.5, 129.2, 119.5, 107.2, 67.2, 39.0, 37.4, 30.6, 29.1, 24.0, 23.1, 14.2, 11.2. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{26}\text{NO}_3$ : 292.1912; found, 292.1906.

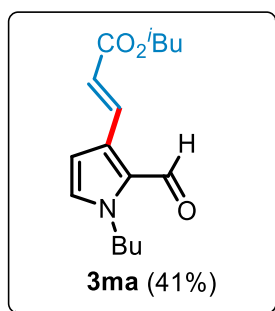
### 2-phenoxyethyl (*E*)-3-(2-formyl-1-methyl-1H-pyrrol-3-yl)acrylate (**3li**):



The compound **3li** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3li** as yellow oil (63%, 38 mg).  $R_f = 0.49$  (EtOAc/petroleum ether 30:70).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.97 (s, 1H), 8.00 (d,  $J = 15.7$  Hz, 1H), 7.32 – 7.28 (m, 2H), 6.99 – 6.93 (m, 3H), 6.83 (d,  $J = 2.6$  Hz, 1H), 6.44 (d,  $J = 2.7$  Hz, 1H), 6.35

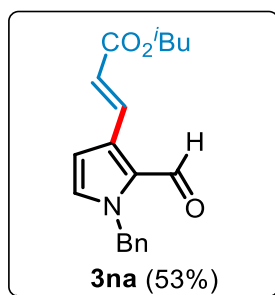
(d,  $J = 15.7$  Hz, 1H), 4.56 (t,  $J = 4.0$  Hz, 2H), 4.25 (t,  $J = 6.0$  Hz, 2H), 3.94 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  178.5, 167.0, 158.6, 135.0, 131.9, 131.2, 129.7, 129.3, 121.3, 118.7, 114.8, 107.2, 66.1, 63.1, 37.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{17}\text{H}_{17}\text{NNaO}_4$ : 322.1055; found, 322.1052

### Isobutyl (*E*)-3-(1-butyl-2-formyl-1H-pyrrol-3-yl) acrylate (**3ma**):



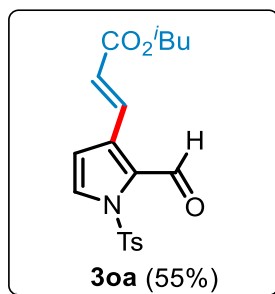
The compound **3ma** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ma** as yellow oil (41%, 23 mg).  $R_f = 0.49$  (EtOAc/petroleum ether 14:86).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.98 (s, 1H), 7.99 (d,  $J = 15.6$  Hz, 1H), 6.89 (d,  $J = 2.8$  Hz, 1H), 6.46 (d,  $J = 2.7$  Hz, 1H), 6.32 (d,  $J = 15.7$  Hz, 1H), 4.30 (t,  $J = 7.2$  Hz, 2H), 3.99 (d,  $J = 6.7$  Hz, 2H), 2.05 – 1.96 (m, 1H), 1.77 – 1.69 (m, 2H), 1.36 – 1.29 (m, 2H), 0.98 (d,  $J = 6.7$  Hz, 6H), 0.93 (t,  $J = 7.4$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  178.1, 167.2, 134.4, 131.8, 131.1, 128.5, 119.3, 107.2, 70.8, 49.6, 33.4, 28.0, 19.8, 19.3, 13.8. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{24}\text{NO}_3$ : 278.1753; found, 278.1756.

### Isobutyl (*E*)-3-(1-benzyl-2-formyl-1H-pyrrol-3-yl)acrylate (**3na**):



The compound **3na** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3na** as brown oil (53%, 33 mg).  $R_f = 0.49$  (EtOAc/petroleum ether 15:85).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.98 (s, 1H), 8.00 (d,  $J = 15.7$  Hz, 1H), 7.34 – 7.27 (m, 3H), 7.14 (d,  $J = 6.5$  Hz, 2H), 6.93 (d,  $J = 2.8$  Hz, 1H), 6.51 (d,  $J = 2.8$  Hz, 1H), 6.34 (d,  $J = 15.7$  Hz, 1H), 5.55 (s, 2H), 3.99 (d,  $J = 6.6$  Hz, 2H), 2.01 (m, 1H), 0.98 (d,  $J = 6.7$  Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  178.3, 167.0, 137.0, 134.2, 132.0, 131.2, 128.9, 128.6, 128.1, 127.4, 119.7, 107.7, 70.8, 52.6, 27.9, 19.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{22}\text{NO}_3$ : 312.1594; found, 312.1599.

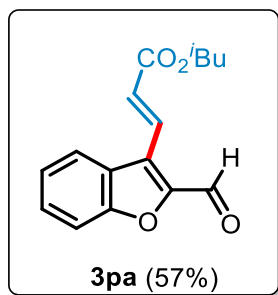
### Isobutyl (*E*)-3-(2-formyl-1-tosyl-1H-pyrrol-3-yl)acrylate (**3oa**):



The compound **3oa** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3oa** as yellow oil (55%, 41 mg).  $R_f = 0.49$  (EtOAc/petroleum ether 25:75).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.29 (s, 1H), 8.16 (d,  $J = 16.1$  Hz, 1H), 7.77 (d,  $J = 8.4$  Hz, 2H), 7.56 (d,  $J = 3.3$  Hz, 1H), 7.34 (d,  $J = 8.0$  Hz, 2H), 6.63 (d,  $J = 3.3$  Hz, 1H), 6.37 (d,  $J = 16.1$  Hz, 1H), 3.97 (d,  $J = 6.6$  Hz, 2H), 2.43 (s, 3H), 1.99 (m, 1H), 0.96 (d,  $J = 6.7$  Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  180.4, 166.4, 146.5, 135.1, 134.9, 133.4,

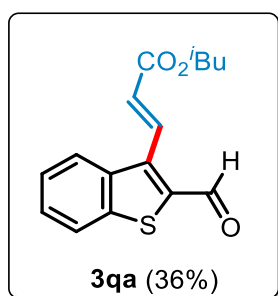
130.5, 129.5, 128.7, 127.4, 123.8, 110.4, 70.9, 27.9, 21.8, 19.2. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{19}H_{22}NO_5S$ : 376.1215; found, 376.1218.

#### Isobutyl (*E*)-3-(2-formylbenzofuran-3-yl)acrylate (**3pa**):



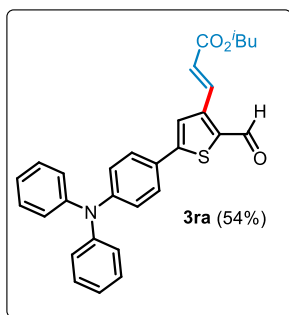
The compound **3pa** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3pa** as yellow solid (57%, 31 mg). m.p.= 86 °C  $R_f$  = 0.49 (EtOAc/petroleum ether 15:85).  $^1H$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.19 (s, 1H), 8.29 (d,  $J$  = 16.2 Hz, 1H), 7.98 (d,  $J$  = 8.0 Hz, 1H), 7.68 – 7.53 (m, 2H), 7.44 (ddd,  $J$  = 8.1, 7.0, 1.2 Hz, 1H), 6.86 (d,  $J$  = 16.2 Hz, 1H), 4.06 (d,  $J$  = 6.7 Hz, 2H), 2.05 (m, 1H), 1.02 (d,  $J$  = 6.7 Hz, 6H).  $^{13}C\{^1H\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  180.0, 166.3, 155.7, 149.6, 132.1, 129.7, 125.2, 125.1, 125.1, 124.7, 123.2, 113.2, 71.3, 28.0, 19.3. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{16}H_{17}O_4$ : 273.1127; found, 273.1116

#### Isobutyl (*E*)-3-(2-formylbenzo[b]thiophen-3-yl)acrylate (**3qa**):



The compound **3qa** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3qa** as yellow oil (36%, 21 mg).  $R_f$  = 0.49 (EtOAc/petroleum ether 12:88).  $^1H$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.33 (s, 1H), 8.23 (d,  $J$  = 16.0 Hz, 1H), 8.06 (d,  $J$  = 7.9 Hz, 1H), 7.91 (d,  $J$  = 8.1 Hz, 1H), 7.54 (dddd,  $J$  = 21.8, 8.2, 7.1, 1.3 Hz, 2H), 6.57 (d,  $J$  = 16.0 Hz, 1H), 4.07 (d,  $J$  = 6.7 Hz, 2H), 2.06 (m, 1H), 1.02 (d,  $J$  = 6.7 Hz, 6H).  $^{13}C\{^1H\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  183.9, 166.0, 142.0, 141.5, 139.5, 138.0, 134.2, 128.8, 127.1, 125.9, 124.8, 123.6, 71.4, 27.9, 19.3. HRMS (ESI):  $m/z$   $[M + Na]^+$  calcd for  $C_{16}H_{16}NaO_3S$ : 311.0717; found, 311.0716.

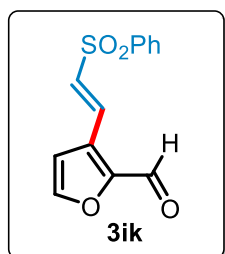
#### Isobutyl (*E*)-3-(5-(4-(diphenylamino)phenyl)-2-formylthiophen-3-yl)acrylate (**3ra**):



The compound **3ra** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ra** as reddish brown solid (54%, 52 mg).  $R_f$  = 0.49 (DCM/petroleum ether 70:30).  $^1H$  NMR (400 MHz, Chloroform-*d*)  $\delta$  10.17 (s, 1H), 8.13 (d,  $J$  = 15.9 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.45 (s, 1H), 7.30 (dd,  $J$  = 8.5, 7.3 Hz, 4H), 7.18 – 7.03 (m, 8H), 6.51 (d,  $J$  = 15.8 Hz, 1H), 4.03 (d,  $J$  = 6.7 Hz, 2H), 2.02 (m, 1H), 1.00 (d,  $J$  = 6.7 Hz, 6H).

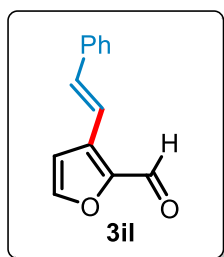
$^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  181.2, 166.5, 153.6, 149.7, 147.0, 144.2, 139.1, 134.1, 129.7, 127.4, 125.5, 125.4, 124.2, 123.3, 122.3, 121.1, 71.2, 28.0, 19.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{30}\text{H}_{28}\text{NO}_3\text{S}$ : 482.1790; found, 482.1788

**(*E*)-3-(2-(phenylsulfonyl)vinyl)furan-2-carbaldehyde (3ik):**



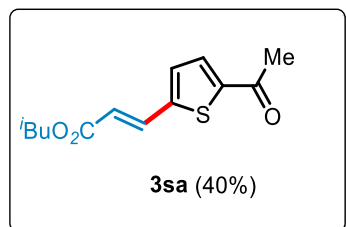
The compound **3ik** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3ik** as yellow oil (34%, 17 mg).  $R_f$  = 0.49 (EtOAc /petroleum ether 8:92).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.93 (s, 1H), 8.05 (d,  $J$  = 15.4 Hz, 1H), 8.00 – 7.93 (m, 2H), 7.66 – 7.62 (m, 2H), 7.62 – 7.53 (m, 2H), 7.03 (d,  $J$  = 15.4 Hz, 1H), 6.70 (d,  $J$  = 1.9 Hz, 1H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  178.9, 149.9, 147.6, 139.9, 133.8, 133.3, 130.2, 129.5, 128.0, 127.9, 111.0. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{11}\text{O}_4\text{S}$ : 263.0378; found, 263.0374

**(*E*)-3-styrylfuran-2-carbaldehyde (3il):**



The compound **3il** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3il** as yellow oil (15%, 6 mg).  $R_f$  = 0.49 (EtOAc /petroleum ether 30:70)  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  9.93 (s, 1H), 7.64 – 7.53 (m, 4H), 7.41 – 7.36 (m, 2H), 7.34 – 7.30 (m, 1H), 7.14 (d,  $J$  = 16.3 Hz, 1H), 6.86 (d,  $J$  = 1.8 Hz, 1H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  178.7, 147.9, 147.6, 136.2, 135.3, 129.1, 128.9, 128.8, 127.0, 116.6, 109.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{11}\text{O}_2$ : 199.0759; found, 199.0754

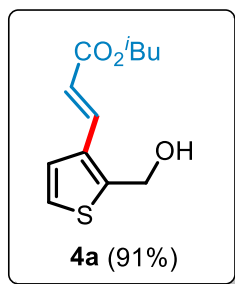
**Isobutyl (*E*)-3-(2-acetylthiophen-3-yl)acrylate (3sa):**



The compound **3sa** was obtained by following the General Procedure A and it was purified by column chromatography over silica gel to obtain the compound **3sa** as yellow oil (40%, 20 mg).  $R_f$  = 0.49 (EtOAc/petroleum ether 20:80).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.72 (d,  $J$  = 15.8 Hz, 1H), 7.61 (d,  $J$  = 3.9 Hz, 1H), 7.25 (d,  $J$  = 3.9 Hz, 1H), 6.40 (d,  $J$  = 15.8 Hz, 1H), 4.00 (s, 2H), 2.56 (s, 3H), 2.01 (m, 1H), 0.98 (d,  $J$  = 6.7 Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  190.6, 166.4, 146.7, 145.6, 136.2, 132.9, 130.8, 120.7, 71.1, 27.9, 26.9, 19.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{17}\text{O}_3\text{S}$ : 253.0892; found, 253.0898.

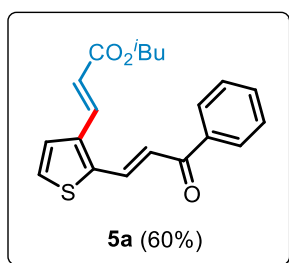


### Isobutyl (*E*)-3-(2-(hydroxymethyl)thiophen-3-yl)acrylate (**4a**):



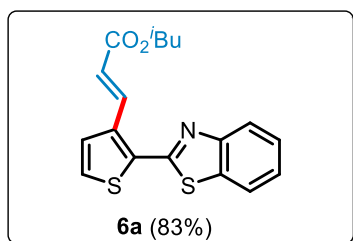
The compound **4a** was obtained by following the General Procedure C and it was purified by column chromatography over silica gel to obtain the compound **4a** as colourless oil (33 mg, 91%)  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  7.74 (d,  $J$  = 15.8 Hz, 1H), 7.25 (d,  $J$  = 1.6 Hz, 2H), 6.27 (d,  $J$  = 15.8 Hz, 1H), 4.95 (s, 2H), 3.98 (d,  $J$  = 6.7 Hz, 2H), 2.07 (s, 1H), 2.00 (m, 1H), 0.98 (d,  $J$  = 6.7 Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  167.6, 145.4, 135.7, 133.7, 125.9, 125.3, 118.7, 70.9, 57.8, 28.0, 19.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{12}\text{H}_{16}\text{NaO}_3\text{S}$ : 263.0717; found, 263.0706.

### Isobutyl (*E*)-3-(2-((*E*)-3-oxo-3-phenylprop-1-en-1-yl)thiophen-3-yl)acrylate (**5a**)<sup>5</sup>:



The compound **5a** was obtained by following the General Procedure D and it was purified by column chromatography over silica gel to obtain the compound **5a** as yellow oil (43 mg, 60%)  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.12 (d,  $J$  = 15.3 Hz, 1H), 7.98 – 7.92 (m, 2H), 7.87 (d,  $J$  = 15.8 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.47 – 7.42 (m, 2H), 7.33 (d,  $J$  = 15.2 Hz, 1H), 7.31 (d,  $J$  = 5.3 Hz, 1H), 7.25 (d,  $J$  = 5.4 Hz, 1H), 6.29 (d,  $J$  = 15.7 Hz, 1H), 3.95 (d,  $J$  = 6.8 Hz, 2H), 1.96 (m, 1H), 0.92 (d,  $J$  = 6.7 Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  189.5, 166.9, 140.7, 139.5, 138.0, 134.6, 133.7, 133.2, 128.9, 128.6, 128.1, 126.9, 122.8, 120.9, 71.1, 28.0, 19.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{21}\text{O}_3\text{S}$ : 341.1211; found, 341.1205.

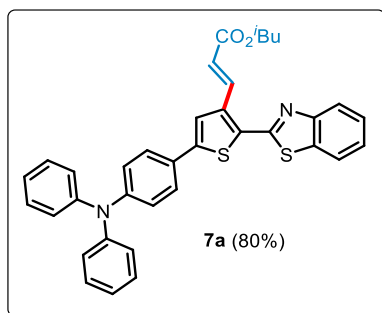
### Isobutyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)thiophen-3-yl)acrylate (**6a**)<sup>5</sup>:



The compound **6a** was obtained by following the General Procedure E and it was purified by column chromatography over silica gel to obtain the compound **6a** as yellow solid (83%, 103 mg). m.p. = 76 °C  $R_f$  = 0.49 (DCM /petroleum ether 50:50).  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)  $\delta$  8.56 (d,  $J$  = 15.8 Hz, 1H), 8.08 (d,  $J$  = 8.0 Hz, 1H), 7.87 (d,  $J$  = 7.6 Hz, 1H), 7.50 (ddd,  $J$  = 8.3, 7.2, 1.3 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.36 (d,  $J$  = 5.3 Hz, 1H), 6.44 (d,  $J$  = 15.8 Hz, 1H), 4.03 (d,  $J$  = 6.6 Hz, 2H), 2.04 (m, 1H), 1.02 (d,  $J$  = 6.7 Hz, 6H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz, Chloroform-*d*)  $\delta$  167.1, 159.5, 153.6, 137.0, 136.9, 136.7, 135.5, 128.6, 127.3, 126.9, 125.8, 123.7, 121.6, 121.6, 70.9, 28.0, 19.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{18}\text{H}_{18}\text{NO}_2\text{S}_2$ : 344.0779; found, 344.0777



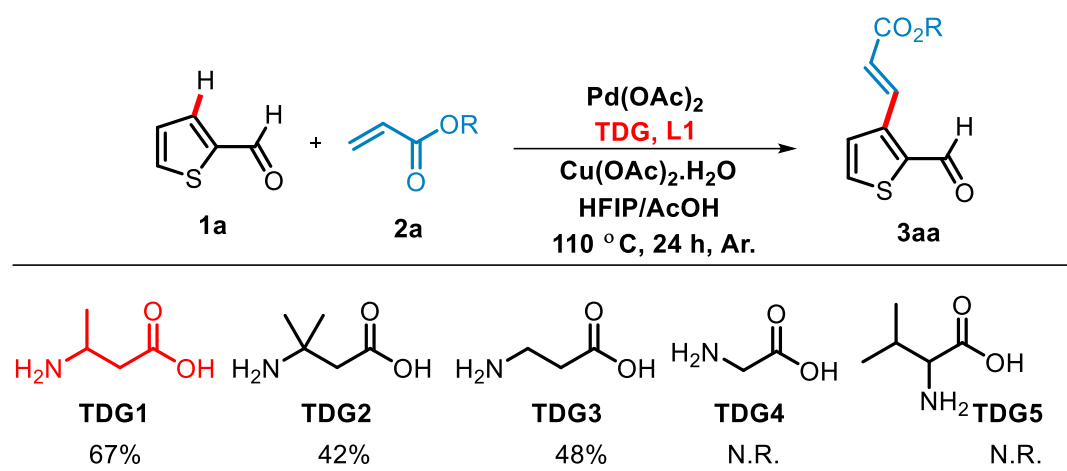
**Isobutyl (E)-3-(2-(benzo[d]thiazol-2-yl)-5-(4-(diphenylamino)phenyl)thiophen-3-yl)acrylate (7a):**



The compound **7a** was obtained by following the General Procedure F and it was purified by column chromatography over silica gel to obtain the compound **7a** as yellow solid (80%, 80 mg).  $R_f$  = 0.49 (DCM/petroleum ether 70:50).  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )  $\delta$  8.55 (d,  $J$  = 15.9 Hz, 1H), 8.09 (d,  $J$  = 8.3 Hz, 1H), 7.89 (d,  $J$  = 7.7 Hz, 1H), 7.54 – 7.49 (m, 3H), 7.46 (s, 1H), 7.40 (ddd,  $J$  = 8.3, 7.2, 1.2 Hz, 1H), 7.30 (dd,  $J$  = 8.5, 7.3 Hz, 4H), 7.15 (dd,  $J$  = 8.6, 1.2 Hz, 4H), 7.11 – 7.06 (m, 4H), 6.49 (d,  $J$  = 15.8 Hz, 1H), 4.04 (d,  $J$  = 6.5 Hz, 2H), 2.09 – 2.02 (m, 1H), 1.03 (d,  $J$  = 6.7 Hz, 6H).  $^{13}\text{C}$  { $^1\text{H}$ } NMR (100 MHz, Chloroform- $d$ )  $\delta$  167.1, 161.6, 159.4, 153.6, 148.8, 147.3, 137.6, 137.1, 135.4, 134.9, 129.6, 127.0, 126.9, 126.3, 125.6, 125.2, 123.8, 123.5, 123.0, 121.7, 121.5, 121.5, 71.0, 28.0, 19.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{36}\text{H}_{31}\text{N}_2\text{O}_2\text{S}_2$ : 587.1827; found, 587.1815

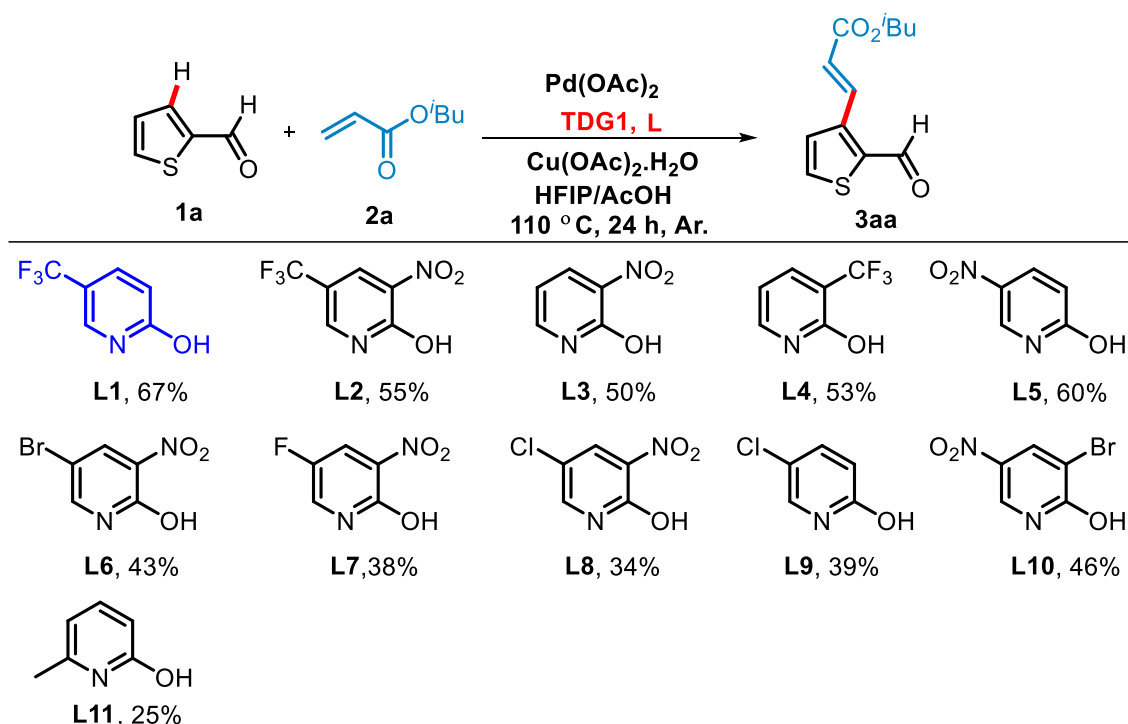
## 4.7 Appendix IVA

### 4.7.1 Table 1. Screening of different transient directing groups (TDGs)



<sup>a</sup>Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), Pd catalyst (10 mol%), **TDG1-TDG5** (40 mol%), Ligand **L1** (20 mol%),  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (0.22 mmol), HFIP (0.9 mL) AcOH (0.1 mL),  $110^\circ\text{C}$ , Ar, 24 h. <sup>b</sup>Isolated yields after column chromatography.

### 4.7.2 Table 2. Screening of different Ligands (L)<sup>a, b</sup>



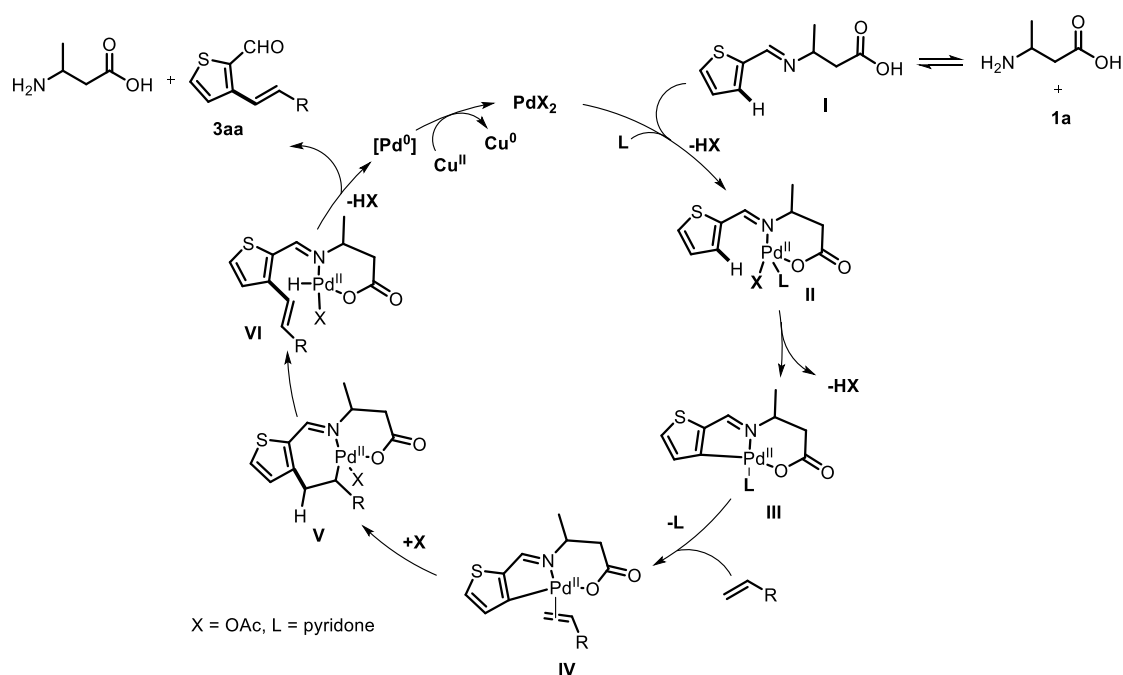
<sup>a</sup>Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), Pd catalyst (10 mol%), **TDG1** (40 mol%), Ligand **L1-L11** (20 mol%),  $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$  (0.22 mmol), HFIP (0.9 mL) AcOH (0.1 mL),  $110^\circ\text{C}$ , Ar, 24 h. <sup>b</sup>Isolated yields after column chromatography.

#### 4.7.3 Table 3. Screening of catalyst loading<sup>a,b</sup>:

| Entry | Pd Source                         | TDG (mol%) | Additive                               | L (mol%) | 2a (equiv.) | Solvent              | Yield 3a (%) <sup>b</sup> |
|-------|-----------------------------------|------------|----------------------------------------|----------|-------------|----------------------|---------------------------|
| 1     | Pd(OAc) <sub>2</sub><br>(10 mol%) | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v) | 67                        |
| 2     | Pd(OAc) <sub>2</sub><br>(5 mol%)  | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v) | 40                        |
| 3     | Pd(OAc) <sub>2</sub><br>(15 mol%) | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v) | 56                        |

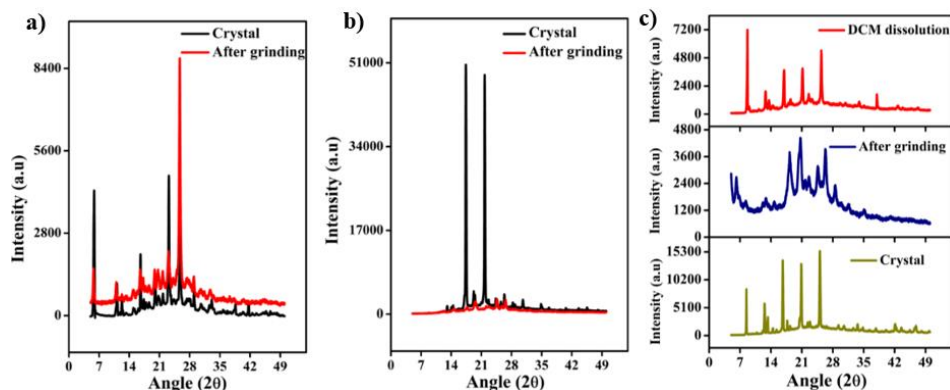
<sup>a</sup>Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), Pd catalyst (5-15 mol%), **TDG1** (40 mol%), Ligand **L1** (20 mol%), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.22 mmol), HFIP (0.9 mL) AcOH (0.1 mL), 110 °C, Ar, 24 h. <sup>b</sup>Isolated yields after column chromatography.

#### 4.7.4 Plausible mechanism:



#### 4.7.5 The powder XRD patterns of 6a, 3ra, 7a in different states:

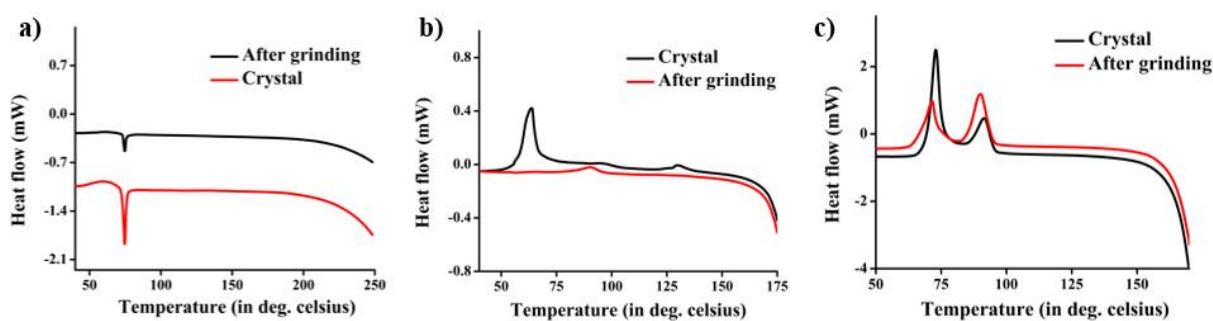
The powder X-ray diffraction (PXRD) measurements were performed by Bruker D8 advance X-ray diffractometer with CuK $\alpha$  as radiation source.



**Fig IVA.1** PXRD patterns of a) 6a, b) 3ra, and c) 7a in different forms.

#### 4.7.6 The DSC trace of 6a, 3ra, 7a in different states

The DSC experiment was carried out by using TA Discover 250 second-generation Differential Scanning Calorimeter under nitrogen atmosphere followed by heating from -10 to 250 °C at the heating rate of 10 °C min<sup>-1</sup>, and simultaneously cooling was also performed at the same rate. The DSC was calibrated with indium standards before measurement. The sample (2-3 mg) was taken in aluminium pan, sealed the pan and measured at the heating rate of 10 °C min<sup>-1</sup>.



**Fig IVA.2** The DSC traces of a) 6a, b) 3ra, c) 7a in different forms at a rate of 10 °C /min.

#### 4.8 Appendix IVB: $^1\text{H}$ , $^{13}\text{C}$ spectral data of representative compounds

| Compound No. | Figure IV.X                      | Data                                                 | Page No |
|--------------|----------------------------------|------------------------------------------------------|---------|
| <b>3aa</b>   | Figure IV.1 and IV.2             | $^1\text{H}$ and $^{13}\text{C}$                     | 170     |
| <b>3ae</b>   | Figure IV.3 and IV.4<br>IV.5     | $^1\text{H}$ and $^{13}\text{C}$ and $^{19}\text{F}$ | 171-172 |
| <b>3ag</b>   | Figure IV.6 and IV.7             | $^1\text{H}$ and $^{13}\text{C}$                     | 173     |
| <b>3ga</b>   | Figure IV.8 and IV.9             | $^1\text{H}$ and $^{13}\text{C}$                     | 174     |
| <b>3ra</b>   | Figure IV.10 and IV.11           | $^1\text{H}$ and $^{13}\text{C}$                     | 175     |
| <b>7a</b>    | Figure IV.12 and Figure<br>IV.13 | $^1\text{H}$ and $^{13}\text{C}$                     | 176     |

Figure IV.1  $^1\text{H}$  NMR spectrum of **3aa**,  $\text{CDCl}_3$ , 400 MHz

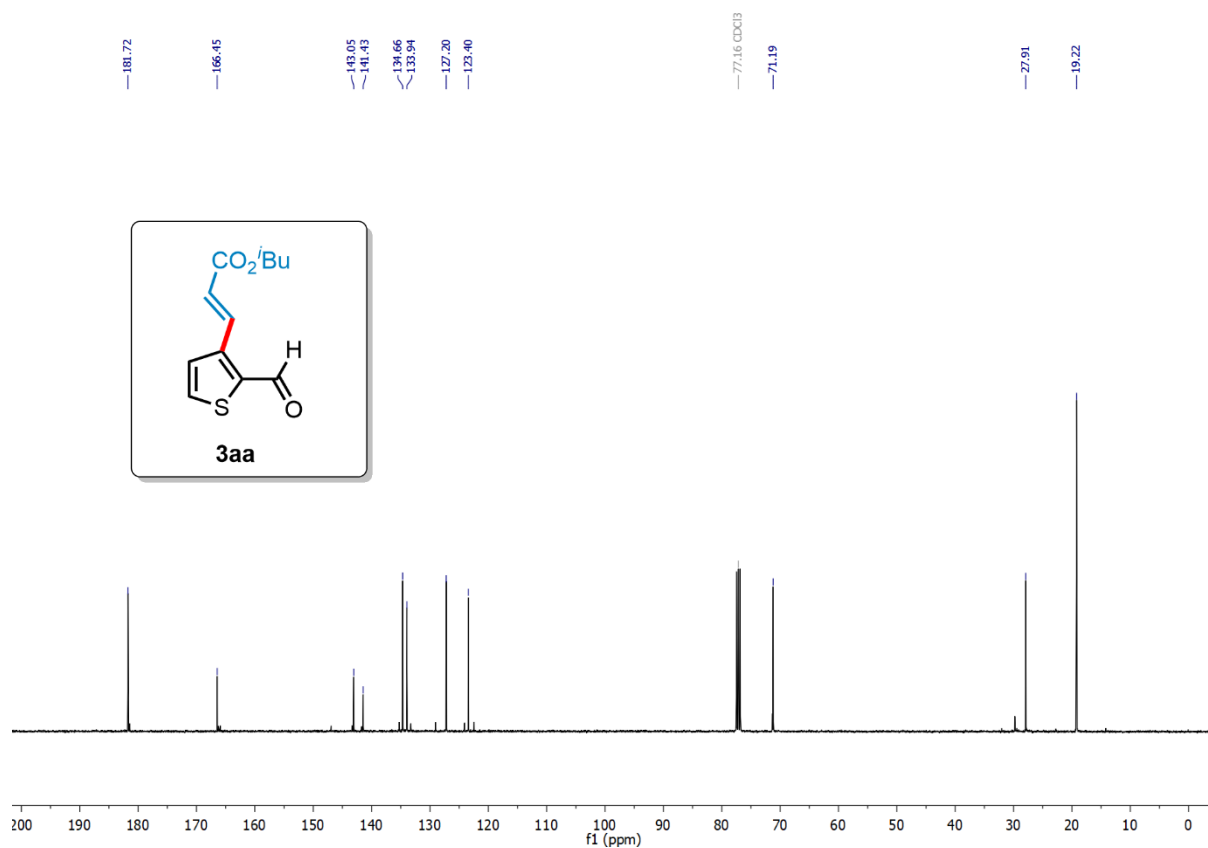
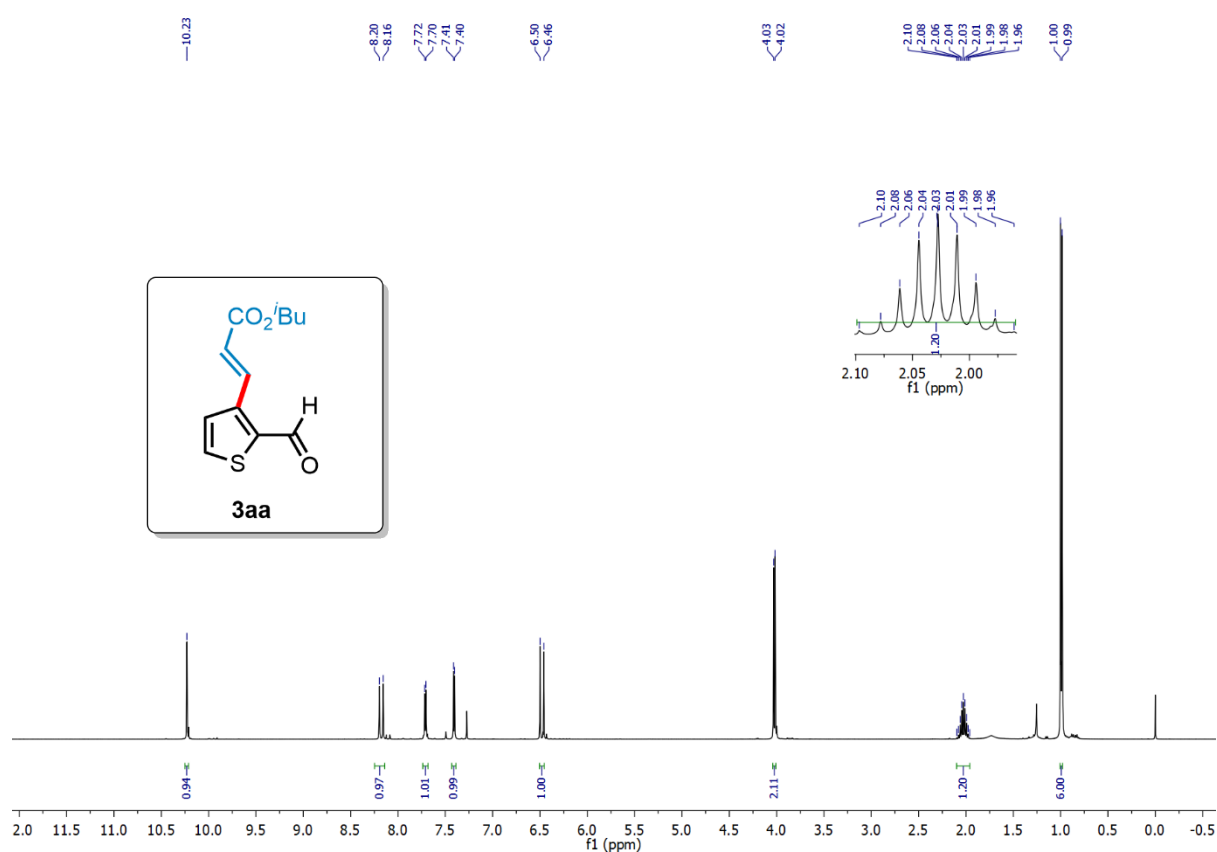


Figure IV. 2  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3aa**,  $\text{CDCl}_3$ , 400 MHz

Figure IV.3  $^1\text{H}$  NMR spectrum of **3ae**,  $\text{CDCl}_3$ , 400 MHz

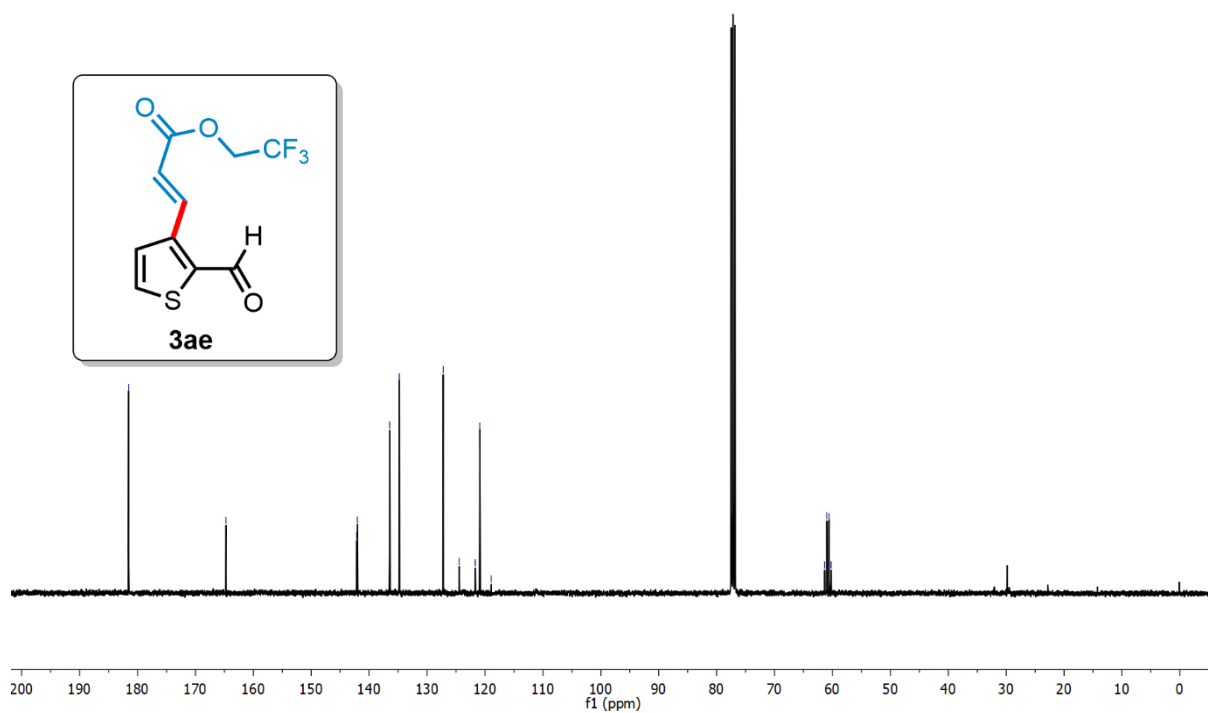
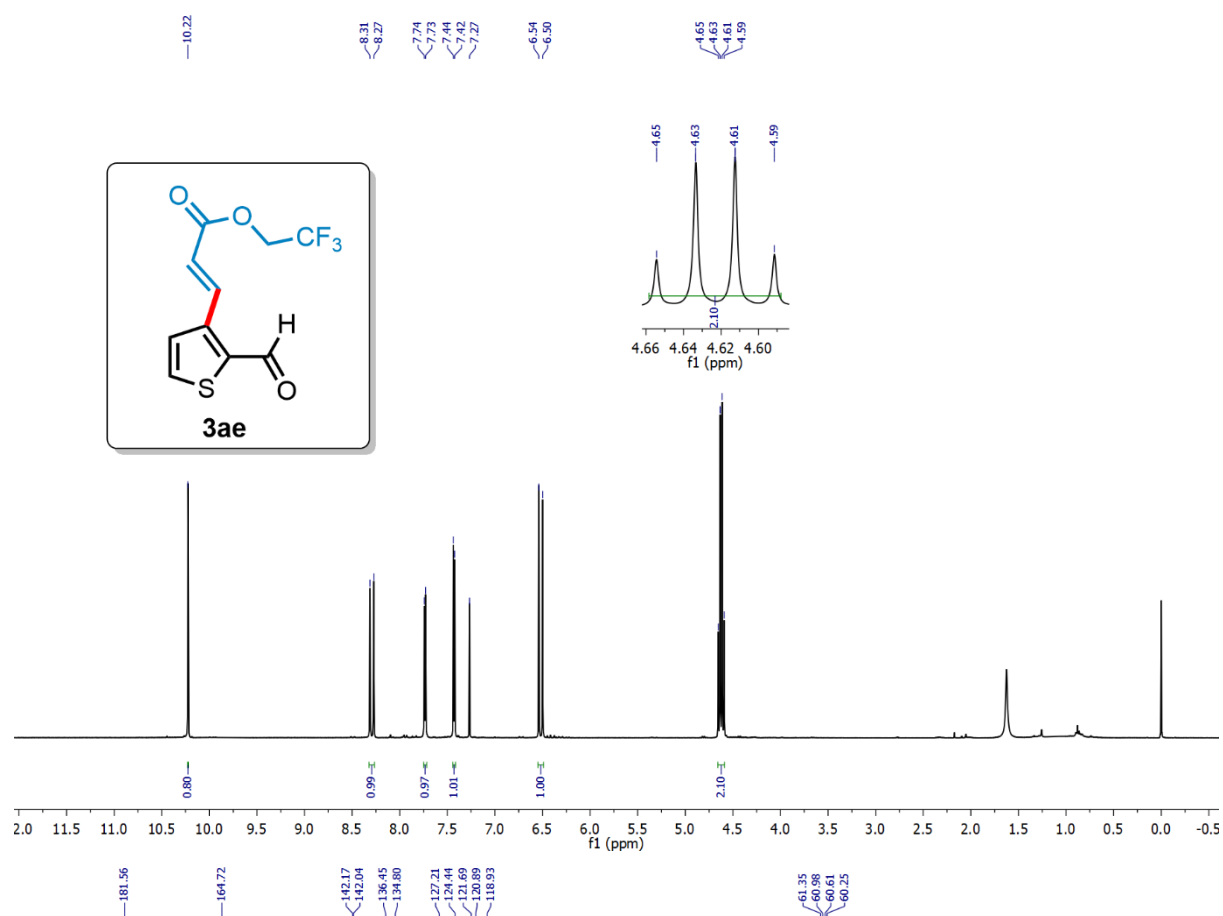


Figure IV.4  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3ae**,  $\text{CDCl}_3$ , 400 MHz

**Figure IV.5**  $^{19}\text{F}$  NMR spectrum of **3ae**,  $\text{CDCl}_3$ , 400 MHz

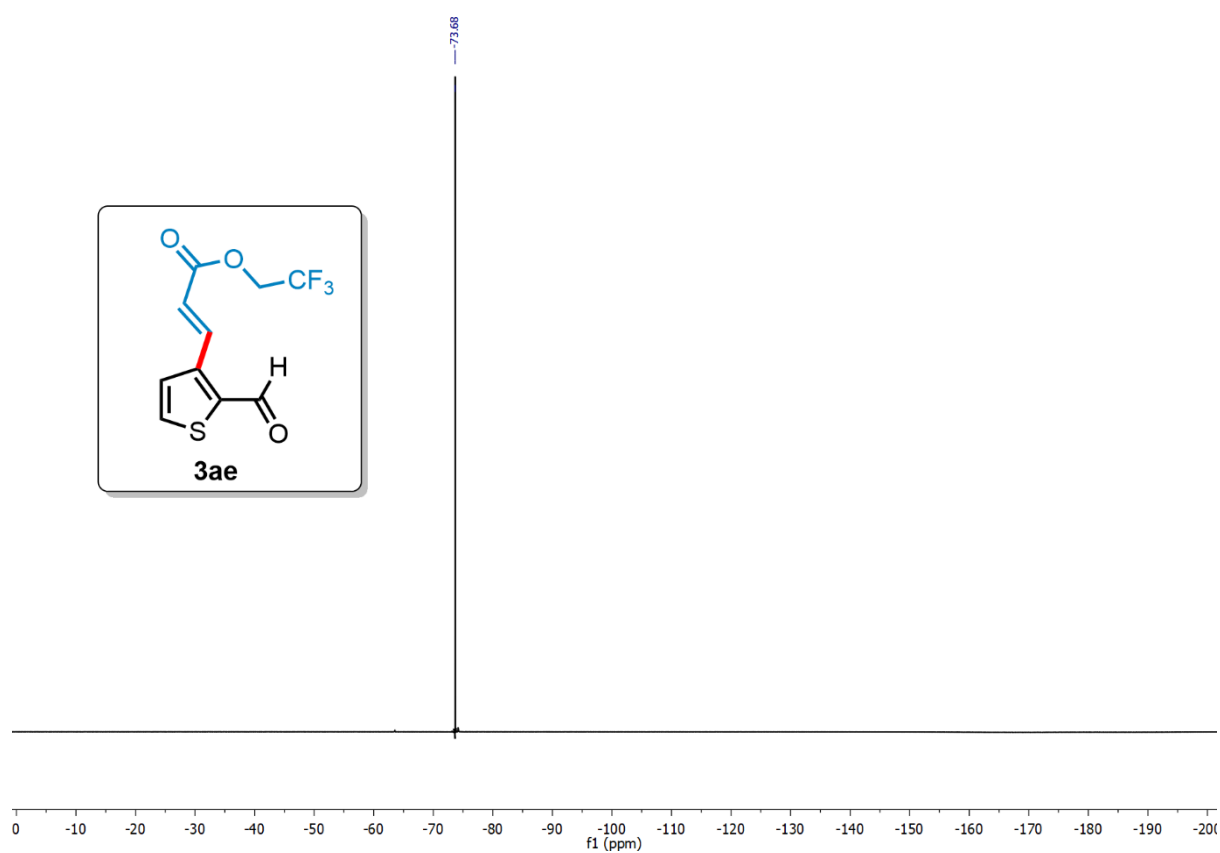




Figure IV.6  $^1\text{H}$  NMR spectrum of **3ag**,  $\text{CDCl}_3$ , 400 MHz

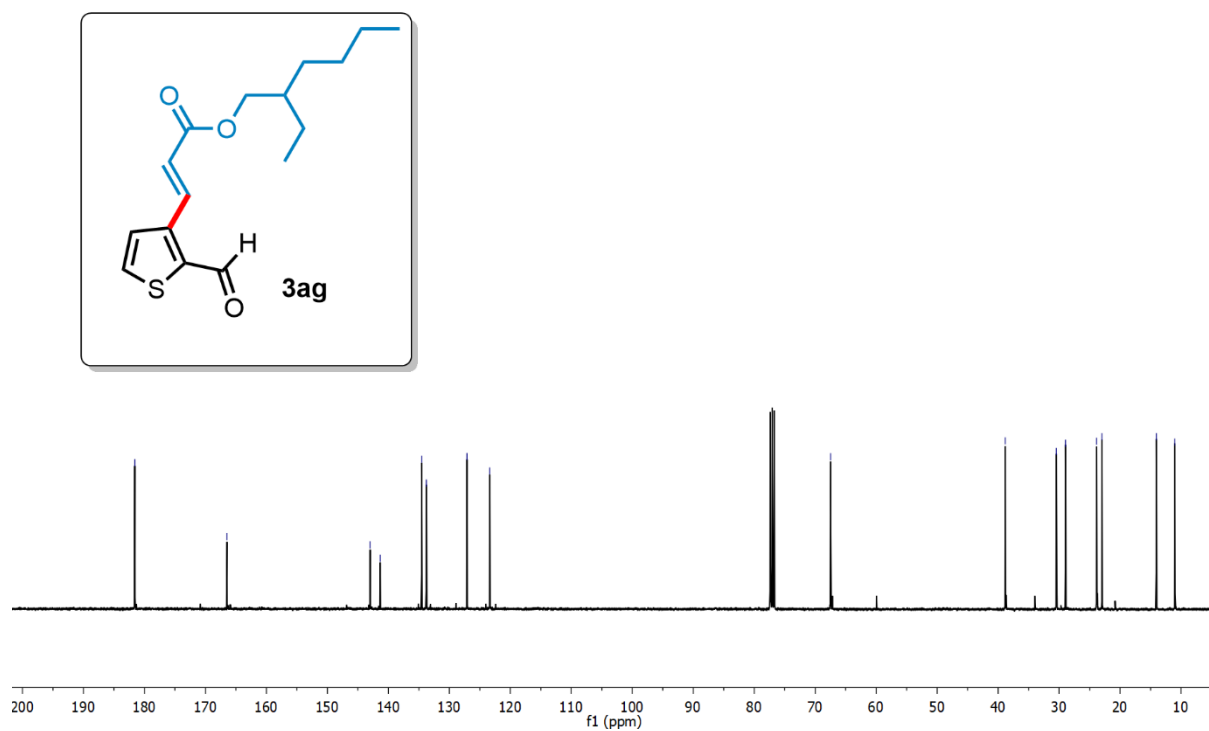
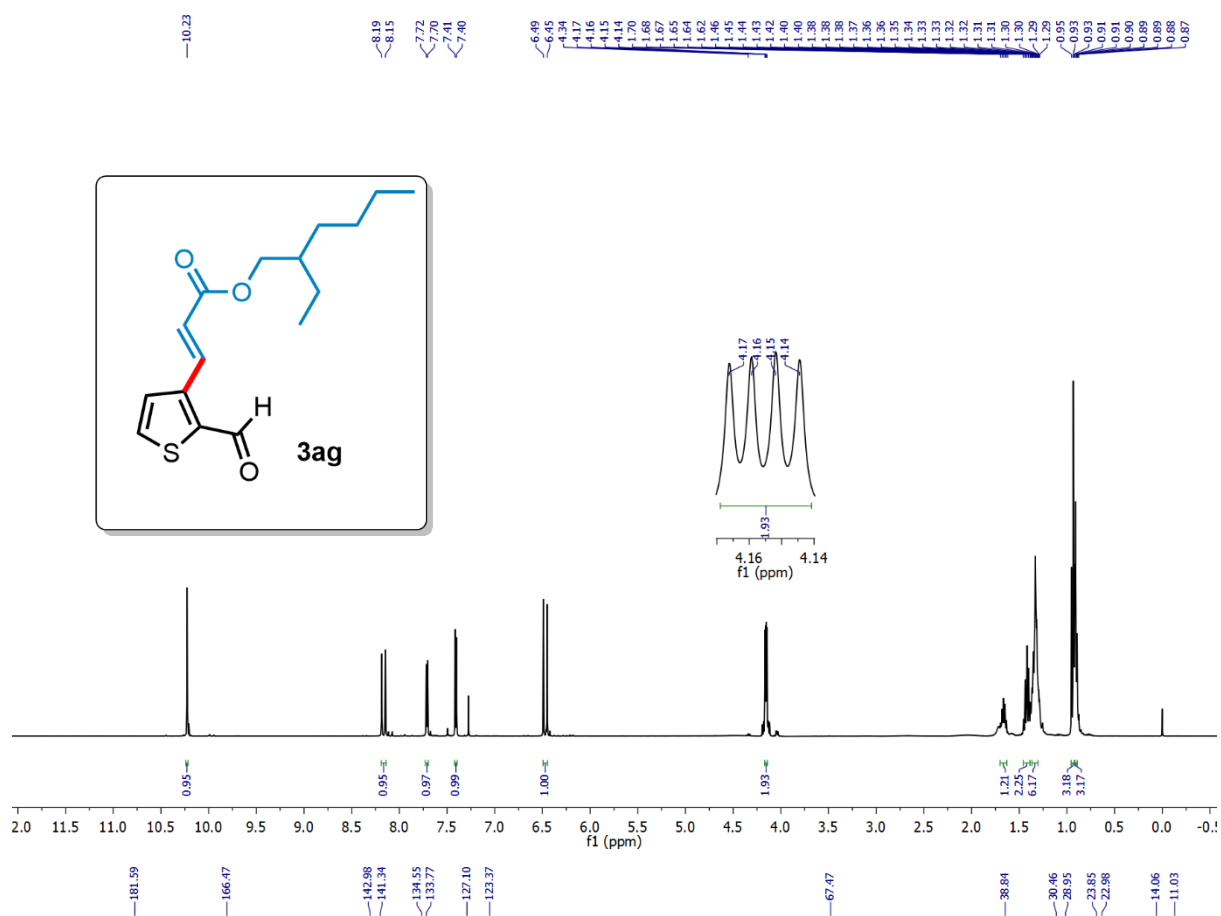
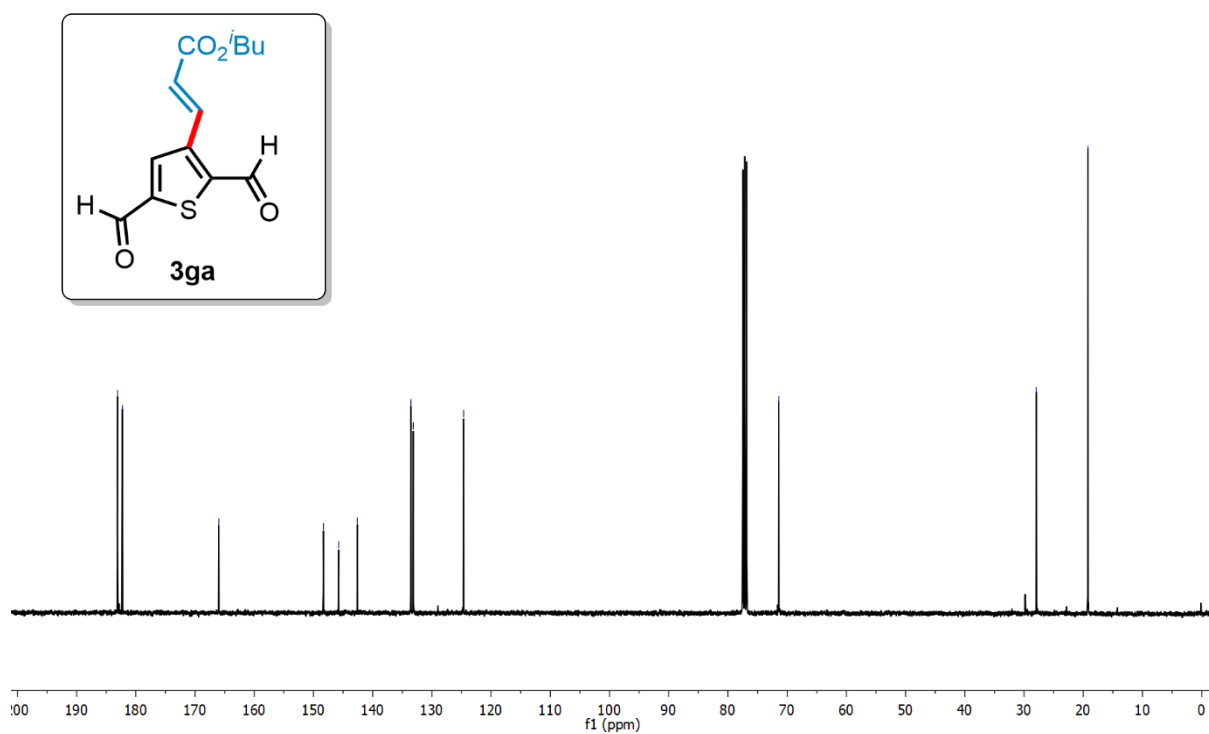
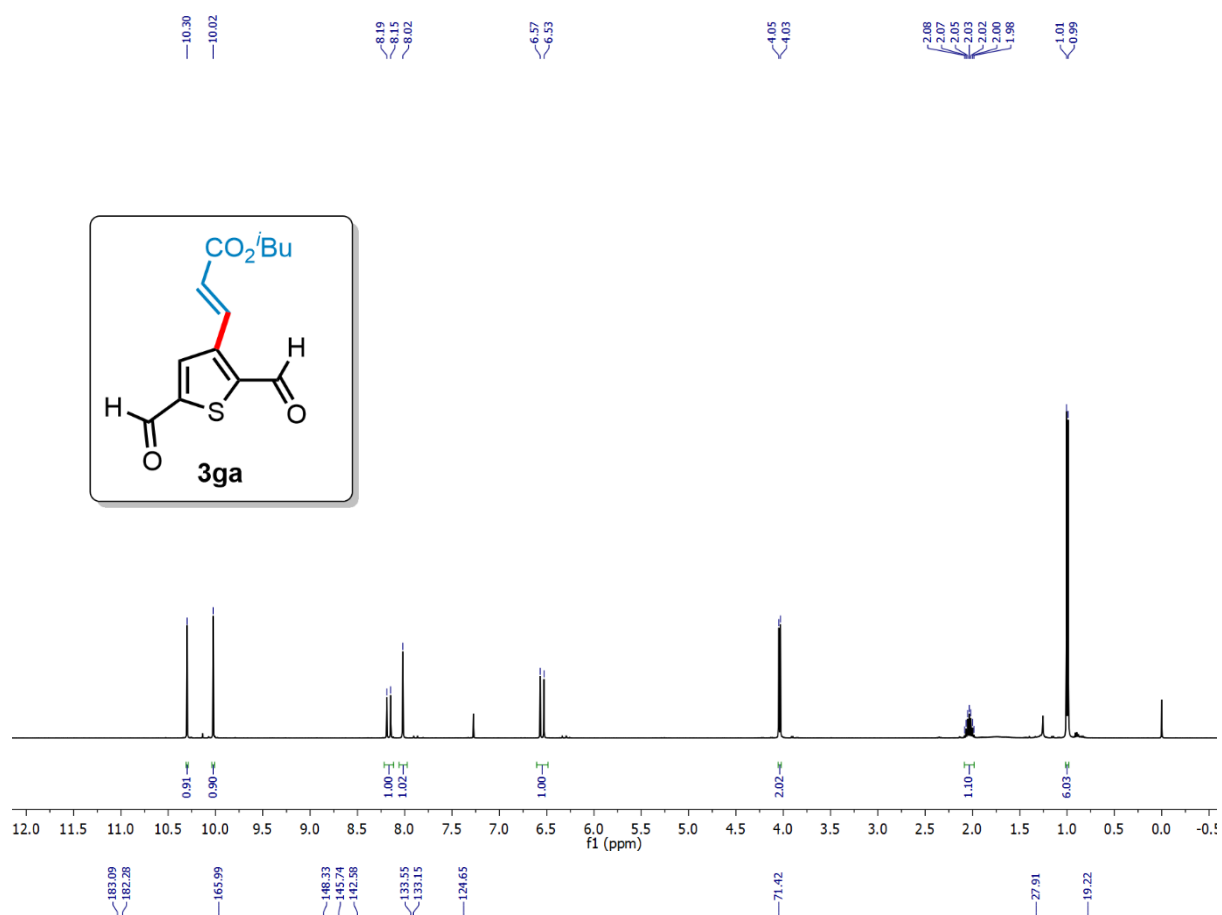


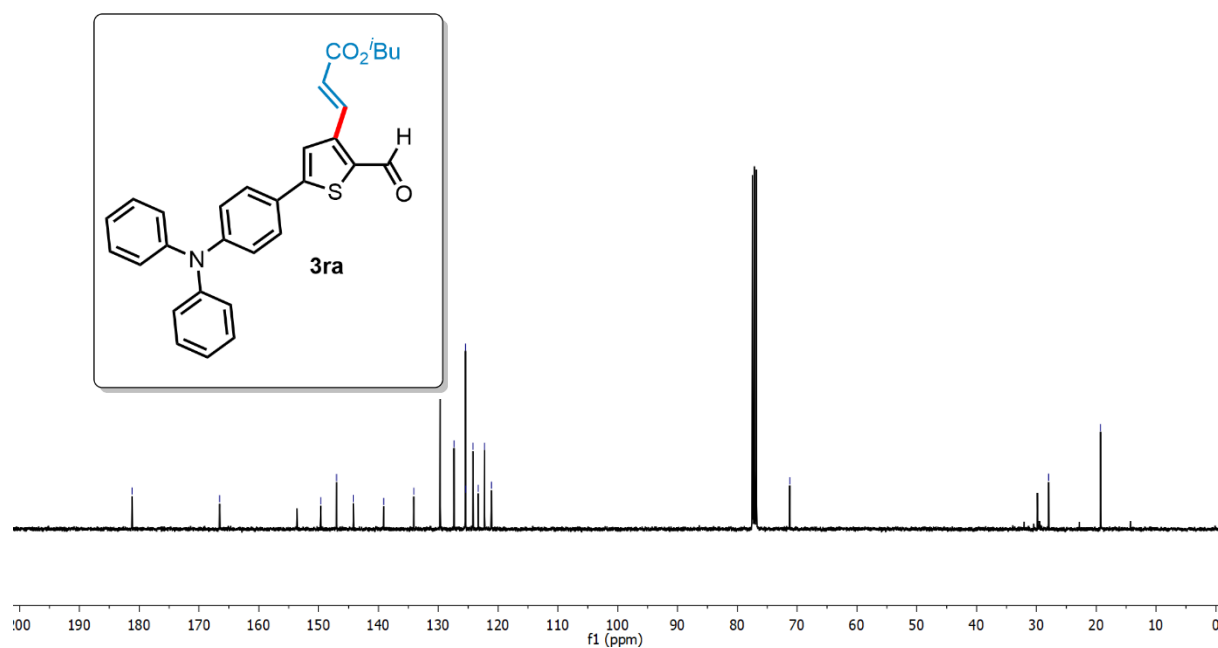
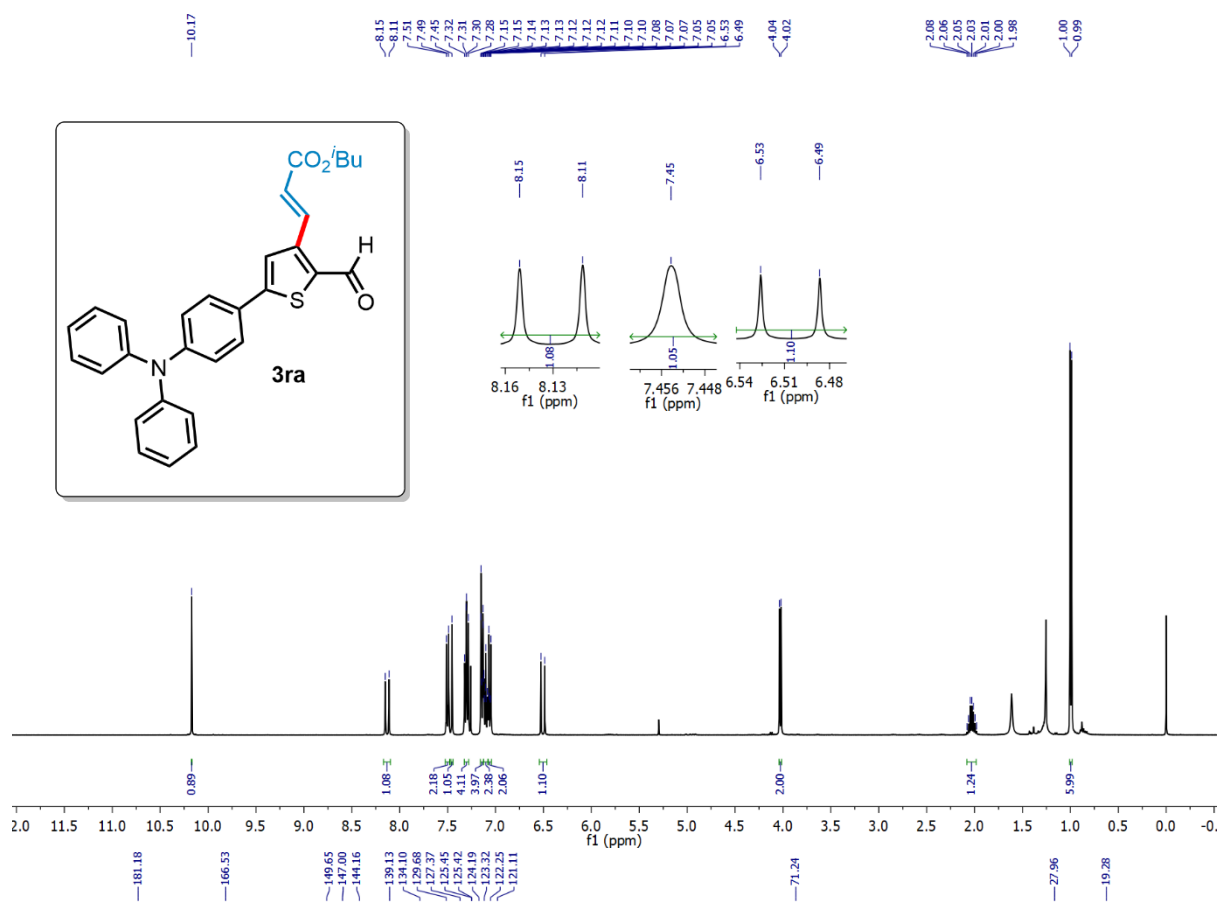
Figure IV. 7  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3ag**,  $\text{CDCl}_3$ , 400 MHz

**Figure IV.8**  $^1\text{H}$  NMR spectrum of **3ga**,  $\text{CDCl}_3$ , 400 MHz



**Figure IV.9**  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3ga**,  $\text{CDCl}_3$ , 400 MHz

**Figure IV.10**  $^1\text{H}$  NMR spectrum of **3ra**,  $\text{CDCl}_3$ , 400 MHz



**Figure IV. 11**  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3ra**,  $\text{CDCl}_3$ , 400 MHz

Figure IV. 12  $^1\text{H}$  NMR spectrum of **7a**,  $\text{CDCl}_3$ , 400 MHz

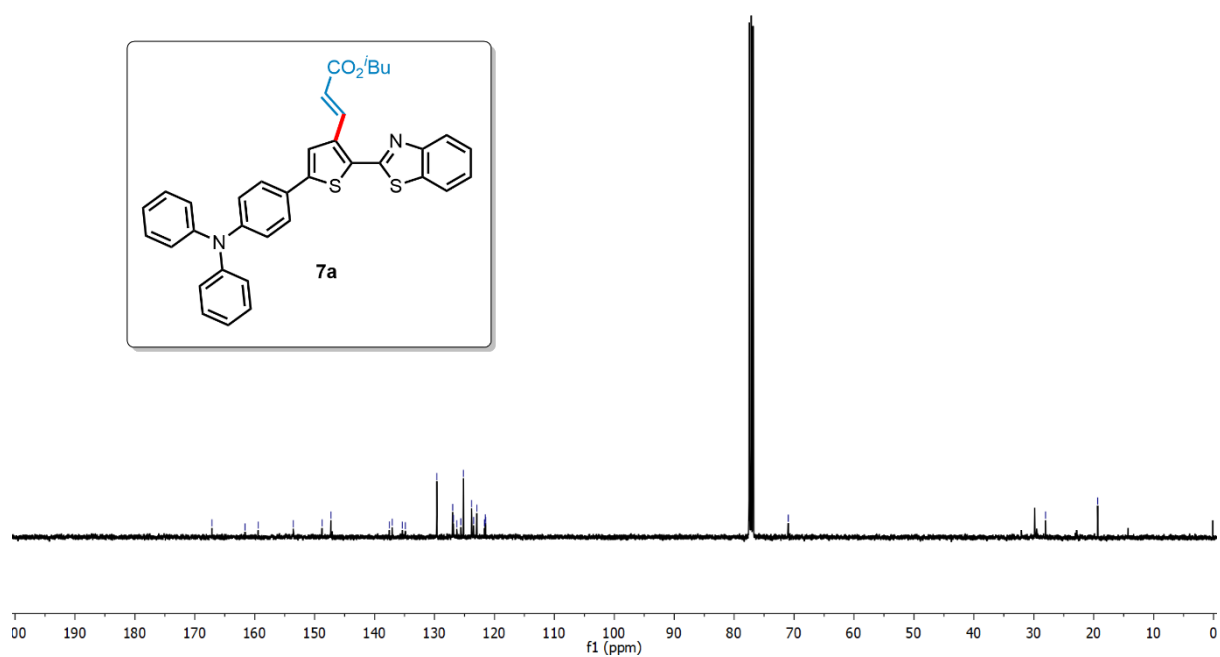
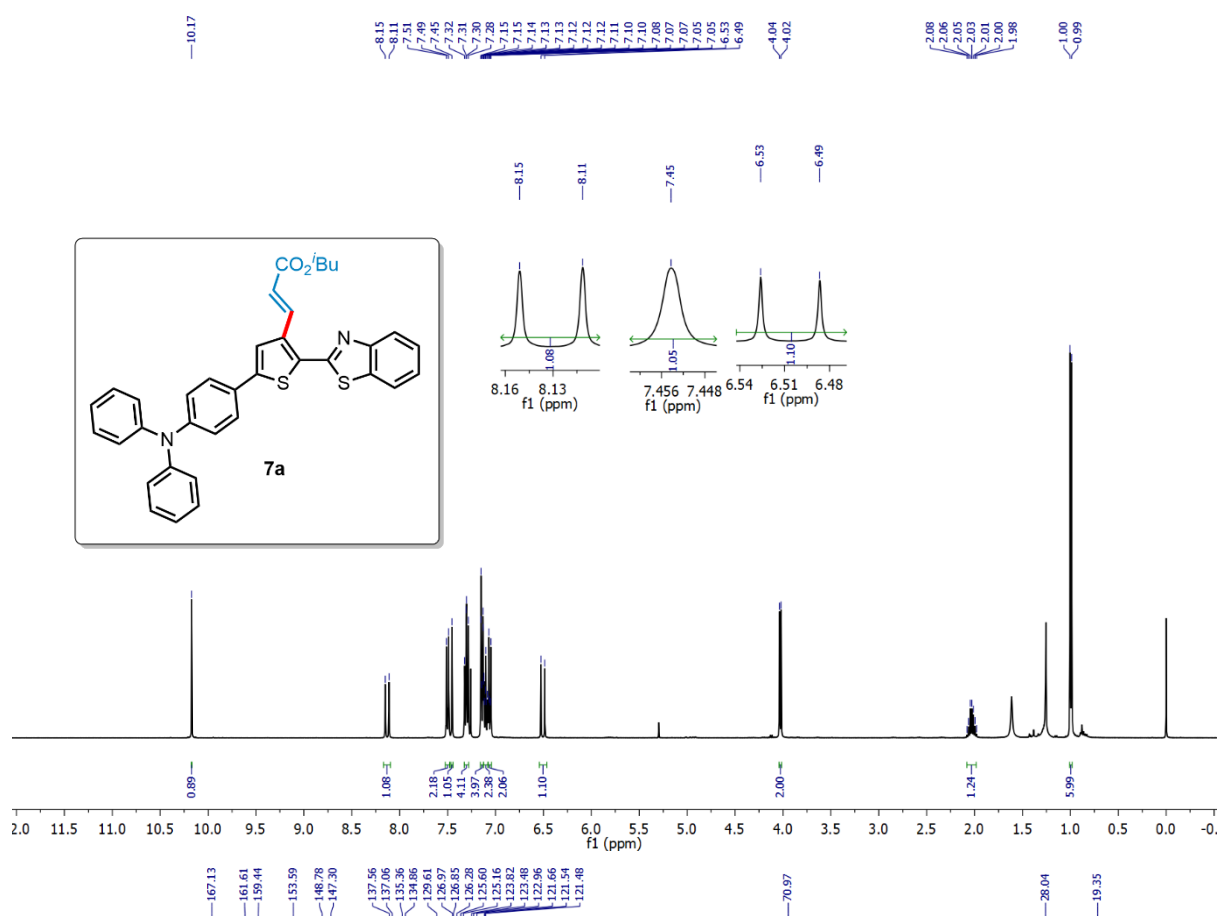


Figure IV. 13  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3a**,  $\text{CDCl}_3$ , 400 MHz

## References

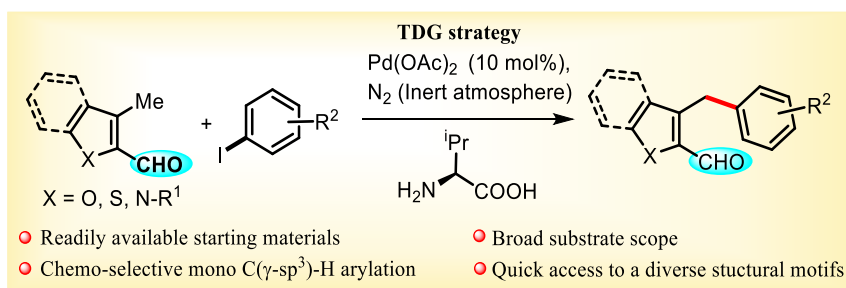
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## Transient Direct Group (TDGs) Enabled Direct $\gamma$ -C(sp<sup>3</sup>)-H Arylation of 3-Methylheteroarene-2-Carbaldehydes to Access Different Derivatives of Hetero-Benzyl Scaffolds

**Abstract:** TDGs enabled selective arylation of 3-methylheteroarene-2-carbaldehydes at the  $\gamma$ -C(sp<sup>3</sup>)-H position via palladium catalysis has been developed for the synthesis of  $\beta$ -benzyl-substituted five-membered heterocyclic carbaldehydes. A wide range of 3-methylheteroarene carbaldehydes and various aryl iodides, such as derivatives of iodo pyridine that are less reactive, under the reaction conditions afforded an extensive collection of functionalized compounds with great selectivity and good to outstanding yields. Also, as an application of this protocol, some of functionalized compounds using this strategy have been effectively used for the synthesis of valuable synthetic intermediates.



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## 5.1 Introduction

The  $\beta$ -benzyl-substituted five-membered heterocyclic compounds are significant class of compounds and that are frequently utilised as essential intermediates or building blocks for the synthesis of polycyclic aromatic hydrocarbons,<sup>1</sup> bioactive chemicals,<sup>2</sup> and compounds with fused rings.<sup>3-4</sup> Remarkably, despite their immense significance and usefulness, there are surprisingly little literature reports accessible for the synthesis of the same. Among these methods are the traditional coupling reactions,<sup>3a,b,4a</sup> the Domino reaction<sup>5</sup>, and the Vilsmeier strategy<sup>3c</sup> for formylation of 3-benzyl-heteroaromatic compounds.

Though some of these strategies are useful, however it lacked the quick access and were limited to narrow substrate scope thus making it constrained for the wider practicality. Also, some of the methods now in use rely on stoichiometric amount of relatively expensive reagents and have limitations such as low substrate group tolerance, multi-step synthetic strategy, and use of commercially available pre-functionalized starting materials.

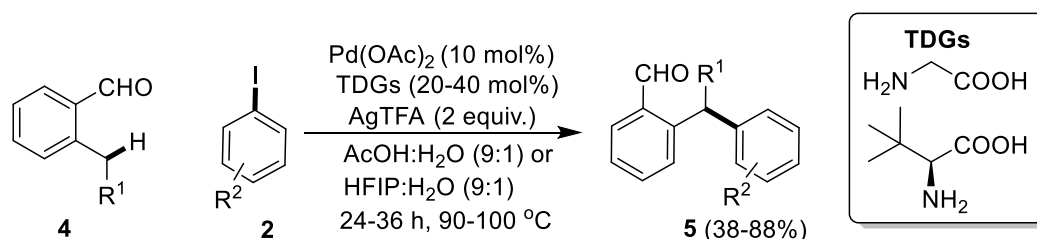
The C-H activation strategy has been proved to be a potent tool in organic synthetic transformations over the past two decades.<sup>6</sup> Typically, in order to achieve high reactivities and controlled selectivity, these methods depend on the non-removable or removable directing groups (DGs) which are covalently linked to the substrates and form a bidentate coordination with a transition metal.<sup>7</sup> However, the major disadvantage of this method is the requirement of installation and de-installation of the directing group that requires the extra steps and many a times, these extra processes are also incompatible with the other functional groups and could be problematic for the late-stage modifications. Despite these limitations, much progress has been achieved in order to accomplish the challenging distal C-H activation or  $\gamma$ -C(sp<sup>3</sup>)-H activation as well.<sup>7c,d</sup>

## 5.2 Recent approaches for the C-H bond activation

Recently the transient directing group (TDG) enabled C-H activation has emerged as an appealing and alternative strategy.<sup>8</sup> These reactions proceed via an in-situ interaction of the ligand with the reactive substrate followed by the reversible coordination to the metal. The TDG has the inherent advantages of free installation (in situ) and simple ligand removal

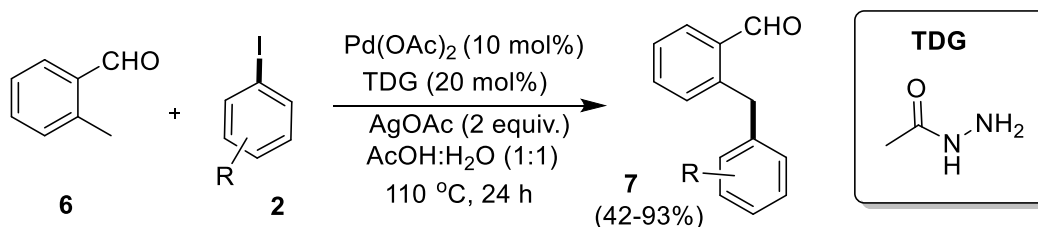
without impairing substrate functionality. For the efficient C-H functionalization of carbonyl compounds<sup>9</sup> and free amino derivatives, several groups have successfully employed and investigated novel as well as modified temporary directing groups.<sup>10</sup> The Yu and coworkers initially identified the glycine as a transient directing group,<sup>11</sup> amino acids have been discovered as easily accessible and effective TDGs that break the C-H bonds without the requirement of removable/non-removable DGs on the substrate.<sup>12,13</sup>

In 2016, Yu and coworkers for the first time described the efficient procedure for the palladium catalyzed direct benzylic C(sp<sup>3</sup>)-H arylation of benzaldehydes **4** with a wide range of aryl iodides **2** in presence of palladium catalyst such as Pd(OAc)<sub>2</sub>, AgTFA as an oxidant, in AcOH/H<sub>2</sub>O or HFIP/H<sub>2</sub>O solvent mixture at an elevated temperature (90-100 °C) by exploring the strength of  $\alpha$ -amino acids such as glycine and tert-butyl leucine as TDGs. The method afforded the benzylic C(sp<sup>3</sup>)-H arylation (enantioselective) products **5** in moderate to good yields (up to 88%) with high enantiomeric ratio (98:2 er) (Scheme 5.1)<sup>11</sup>



**Scheme 5.1** Palladium catalyzed C(sp<sup>3</sup>)H arylation of substituted benzaldehydes.

In 2016, Hu and coworkers also reported the C(sp<sup>3</sup>)-H arylation of various benzaldehydes **6** at the benzylic position with the wide range of aryl iodide **2** and Pd(OAc)<sub>2</sub> as a catalyst, AgOAc as an oxidant in AcOH/H<sub>2</sub>O solvent by using acetohydrazide as a TDG to furnish the desired products benzylic C(sp<sup>3</sup>)-H arylation products **7** in good to excellent yields (up to 93%, Scheme 5.2).<sup>13</sup>



**Scheme 5.2** C(sp<sup>3</sup>)-H arylation of different benzaldehydes at the benzylic position.

Tang et al. recently synthesised only two exemplary cases to get polycyclic aromatic hydrocarbons (PAHs)<sup>1</sup> by the use of aryl diiodides in the glycine-enabled ortho-C(sp<sup>3</sup>)-H

arylation of thiophene aldehydes. However, this strategy has not proved to be highly efficient or suitable to various substrates.<sup>14</sup> The protocol was limited to two substrates and did not show practicability and generality.

Despite recent advancements in TDG strategy for the arylations, the development of new transition metal catalyzed strategies for the selective arylation of benzylic  $\gamma$ -C(sp<sup>3</sup>)-H bonds of 3-methyl substituted heterocyclic carbonyl compounds remains to be a challenging task and highly desirable. Owing to the importance of the heterocyclic framework, their great synthetic utility and also looking at the available reports, exploring the newer strategy for selective  $\gamma$ -C(sp<sup>3</sup>)-H arylation and the substrate scope is highly desirable.

To our knowledge, no report on the practical method with wider substrate scope or detailed investigation available for the quick access to such kind of functionalized compounds via the direct  $\gamma$ -C(sp<sup>3</sup>)-H arylation of five-membered heterocyclic carbonyl compounds using a transient directing group approach. Therefore, the TDG-enabled strategy would be the most straightforward and effective way to gain access to a wide range of hetero-benzyl derivatives. We hypothesized under suitable catalytic conditions along with an amino acid may result in the  $\gamma$ -C(sp<sup>3</sup>)-H arylation.

Here in this chapter, we have described the development of TDG-enabled method for the selective direct  $\gamma$ -C(sp<sup>3</sup>)-H arylation of 3-methylheteroarene-2-carbaldehydes with variety of arene iodides to access via palladium catalysis to access desired  $\gamma$ -C(sp<sup>3</sup>)-H arylated products.

### 5.3 Results and Discussion

In order to explore our hypothesis, we commenced with the arylation of 3-methylthiophene-2-carbaldehyde **1a** using iodobenzene **2a** as a model substrate. A number of amino acids (**L1–L9**) were evaluated as TDGs in conjunction with a number of additional variables, including catalysts, additives, solvents, and solvent concentrations. etc. (Table 5.1).

First, we investigated the arylation of **1a** with iodobenzene **2a** in a combination of acetic acid and water, employing the ligands **L1–L3** as TDGs in presence of palladium acetate as a catalyst (Table 5.1, Entries 1-3) in accordance with the previously reported methods for the aryl diiodides.<sup>1,14</sup> Further, we explored the reaction by utilizing the glycine **L3** as a TDG in acetic acid/water (9:1) with Pd(OAc)<sub>2</sub> (10 mol%) and AgTFA (2 equiv.) to furnish the final product 3-benzylthiophene-2-carbaldehyde (**3aa**) in moderate yield (Table 5.1, Entries 1-3). In order to better optimise the reaction conditions, we looked into the arylation of **1a** with

iodobenzene **2a** in the presence of ligands **L2**, **L3**, and **L4** in a novel solvent system (HFIP:AcOH, 9:1) to produce the corresponding product **3aa** in 20, 55, and 5% yields, respectively. (Table 5.1, Entries 4-6).

The ineffectiveness of the ligands **L2** and **L4** ( $\beta$ -amino acids) is likely caused by the unfavourable [6,6]-bicyclic palladium intermediate that develops during the reaction. Interestingly, ligands **L1** and **L3** also showed poor efficacy for the heterocyclic scaffold even in the solvent system of the previously investigated procedures for benzaldehyde direct benzylic C(sp<sup>3</sup>)-H arylation (Table 5.1, Entries 1 and 3).<sup>11,12</sup>

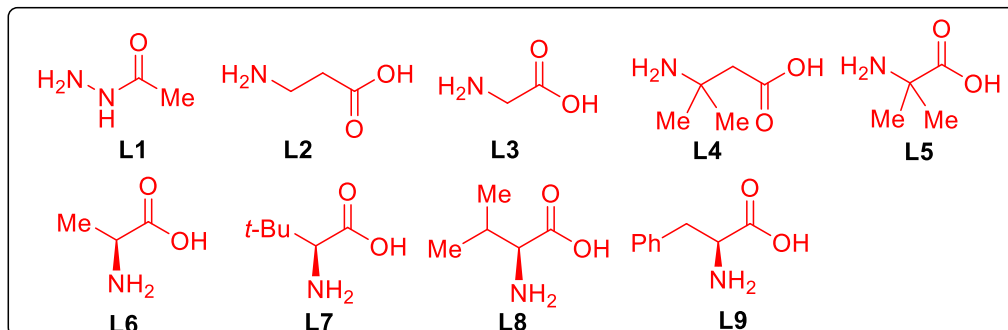
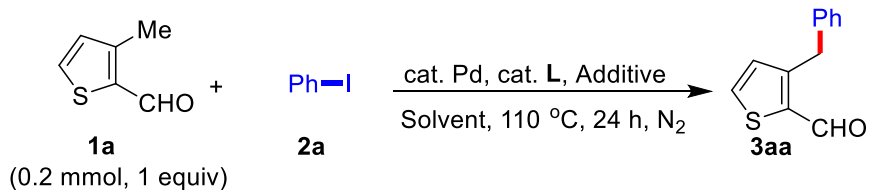
Later on, we intended to test several  $\alpha$ -amino acids for the potential and successful chemo-selective C( $\gamma$ )-H arylation because of their inherent reactivity and reasonably effective rigidity (or an angle). Accordingly, we used a number of  $\alpha$ -amino acids (**L5–L9**) as TDGs to arylate **1a** using iodobenzene **2a** (2 equiv.) (Table 5.1, Entries 7–11). L-valine (**L8**, 40 mol%) was shown to be the most effective TDG among all of them in the presence of Pd(OAc)<sub>2</sub> (10 mol%) and AgTFA (2 equiv.) in HFIP:AcOH (9:1) solvent combination to afford the desired product **3aa** in 93% yield (Table 5.1, Entry 10).

Next, **1a** was arylated separately in HFIP and AcOH to produce the final product **3aa** with yields of 37% and 75%, respectively (Table 5.1, Entries 12–13). In order to enhance the reaction conditions, we screened the reaction by taking into account many factors, including solvent ratios (HFIP/AcOH and AcOH/H<sub>2</sub>O), solvent quantity, catalyst {[Pd(TFA)<sub>2</sub>]}, additive (AgOAc), and the stoichiometric amount of iodobenzene **2a** (0.8 - 2 equiv.) (Table 5.1, Entries 14-23). These outcomes showed that HFIP/AcOH (9:1) combination is more favourable for the efficient transformations.

Under the same reaction conditions, we found that the arylation of **1a** did not occur in the absence of the palladium catalyst, AgTFA, and ligand **L8** (L-Valine), respectively (Table 5.1, Entries 24-26). These results clearly shows that the palladium catalyst [Pd(OAc)<sub>2</sub>], additive (AgTFA) and ligand **L8** are necessarily required for the intended transformation.

After a thorough screening looking into several parameters **1a** (1 equiv.), PhI **2a** (1.5 equiv.) in presence of Pd(OAc)<sub>2</sub> (10 mol%), AgTFA (1.5 equiv.) and L-valine **L8** (40 mol%) in HFIP/AcOH (9:1) at 110 °C for 24 h proved to be the optimum reaction condition (Table 5.1, Entry 19).

#### Table 5.1 Optimization of Reaction Conditions<sup>a</sup>



| Entry           | Pd Catalyst                | L (mol%)       | Additive     | <b>2a</b> (equiv.) | Solvent                          | Yield <b>3aa</b> (%) <sup>b</sup> |
|-----------------|----------------------------|----------------|--------------|--------------------|----------------------------------|-----------------------------------|
| 1               | Pd(OAc) <sub>2</sub>       | <b>L1</b> (20) | AgOAc        | 3                  | AcOH/H <sub>2</sub> O (1:1, v/v) | traces                            |
| 2               | Pd(OAc) <sub>2</sub>       | <b>L2</b> (40) | AgTFA        | 2                  | HFIP/AcOH (5:1, v/v)             | traces                            |
| 3               | Pd(OAc) <sub>2</sub>       | <b>L3</b> (40) | AgTFA        | 2                  | AcOH/H <sub>2</sub> O (9:1, v/v) | 53                                |
| 4               | Pd(OAc) <sub>2</sub>       | <b>L2</b> (40) | AgTFA        | 2                  | HFIP/AcOH (9:1, v/v)             | 20                                |
| 5               | Pd(OAc) <sub>2</sub>       | <b>L3</b> (40) | AgTFA        | 2                  | HFIP/AcOH (9:1, v/v)             | 55                                |
| 6               | Pd(OAc) <sub>2</sub>       | <b>L4</b> (40) | AgTFA        | 2                  | HFIP/AcOH (9:1, v/v)             | <5                                |
| 7               | Pd(OAc) <sub>2</sub>       | <b>L5</b> (40) | AgTFA        | 2                  | HFIP/AcOH (9:1, v/v)             | 59                                |
| 8               | Pd(OAc) <sub>2</sub>       | <b>L6</b> (40) | AgTFA        | 2                  | HFIP/AcOH (9:1, v/v)             | 60                                |
| 9               | Pd(OAc) <sub>2</sub>       | <b>L7</b> (40) | AgTFA        | 2                  | HFIP/AcOH (9:1, v/v)             | 68                                |
| 10              | Pd(OAc) <sub>2</sub>       | <b>L8</b> (40) | AgTFA        | 2                  | HFIP/AcOH (9:1, v/v)             | 93                                |
| 11              | Pd(OAc) <sub>2</sub>       | <b>L9</b> (40) | AgTFA        | 2                  | HFIP/AcOH (9:1, v/v)             | 38                                |
| 12              | Pd(OAc) <sub>2</sub>       | <b>L8</b> (40) | AgTFA        | 2                  | HFIP (1.6 mL)                    | 37                                |
| 13              | Pd(OAc) <sub>2</sub>       | <b>L8</b> (40) | AgTFA        | 2                  | AcOH (1.6 mL)                    | 75                                |
| 14              | Pd(OAc) <sub>2</sub>       | <b>L8</b> (40) | AgTFA        | 2                  | HFIP/AcOH (6:1, v/v)             | 70                                |
| 15              | Pd(OAc) <sub>2</sub>       | <b>L8</b> (40) | AgTFA        | 2                  | HFIP/AcOH (3:1, v/v)             | 75                                |
| 16              | Pd(TFA) <sub>2</sub>       | <b>L8</b> (40) | AgTFA        | 2                  | HFIP/AcOH (9:1, v/v)             | 80                                |
| 17 <sup>c</sup> | Pd(OAc) <sub>2</sub>       | <b>L8</b> (40) | AgOAc        | 2                  | HFIP/AcOH (9:1, v/v)             | 71                                |
| 18              | Pd(OAc) <sub>2</sub>       | <b>L8</b> (40) | AgTFA        | 2                  | HFIP/AcOH (9:1, v/v)             | 72                                |
| <b>19</b>       | <b>Pd(OAc)<sub>2</sub></b> | <b>L8 (40)</b> | <b>AgTFA</b> | <b>1.5</b>         | <b>HFIP/AcOH (9:1, v/v)</b>      | <b>94</b>                         |
| 20 <sup>d</sup> | Pd(OAc) <sub>2</sub>       | <b>L8</b> (40) | AgTFA        | 1                  | HFIP/AcOH (9:1, v/v)             | 70                                |
| 21              | Pd(OAc) <sub>2</sub>       | <b>L8</b> (40) | AgTFA        | 0.8                | HFIP/AcOH (9:1, v/v)             | 78                                |
| 22              | Pd(OAc) <sub>2</sub>       | <b>L8</b> (40) | AgTFA        | 1.5                | AcOH/H <sub>2</sub> O (9:1, v/v) | 47                                |
| 23              | Pd(OAc) <sub>2</sub>       | <b>L8</b> (40) | AgTFA        | 1.5                | AcOH/H <sub>2</sub> O (5:1, v/v) | 54                                |
| 24              | -                          | <b>L8</b> (40) | AgTFA        | 1.5                | HFIP/AcOH (9:1, v/v)             | NR                                |
| 25              | Pd(OAc) <sub>2</sub>       | <b>L8</b> (40) | -            | 1.5                | HFIP/AcOH (9:1, v/v)             | 15                                |
| 26              | Pd(OAc) <sub>2</sub>       | -              | AgTFA        | 1.5                | HFIP/AcOH (9:1, v/v)             | NR                                |

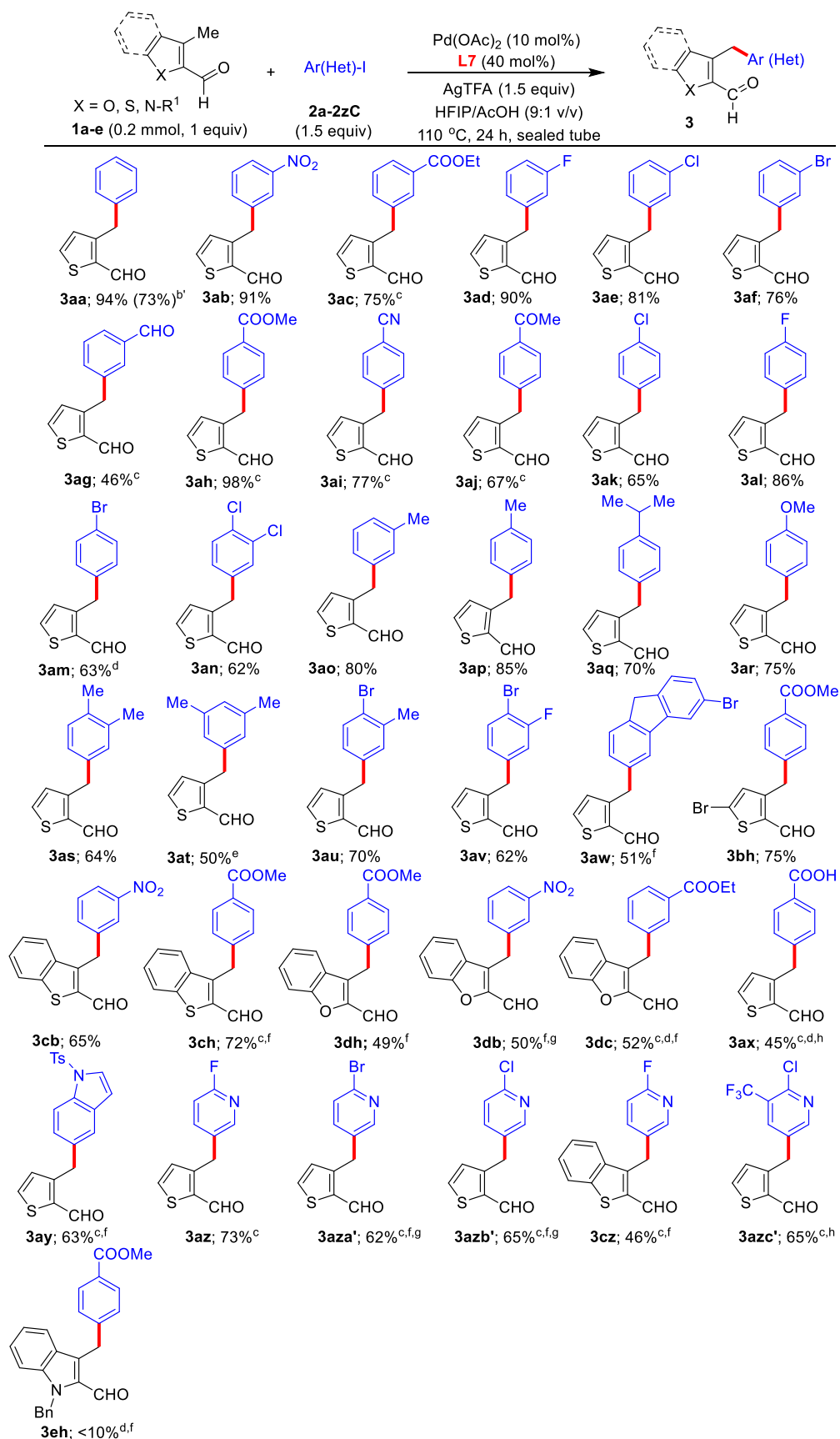
<sup>a</sup>Reaction conditions: **1a** (0.2 mmol), PhI (**2a**), Pd catalyst (10 mol%), Ligand **L** (20-40 mol%), additive (0.3 mmol), solvent (1.6 mL), 110 °C, N<sub>2</sub>, 24 h. <sup>b</sup>Isolated yields based on **1a** using column chromatography. <sup>c</sup>HFIP (0.72 mL)/AcOH (0.08 mL). <sup>d</sup>Isolated yield based on **2a**.

Having obtained the optimized reaction condition, we carried out the arylation of 3-methylthiophene-2-carbaldehyde **1a** with a variety of aryl/heteroaryl iodides **2** to further investigate the reaction and wider substrate scope of this strategy (Table 5.2). The reaction of **1a** with various aryl iodides (**2a-2v**) having electron releasing as well as electron withdrawing groups proceeded effectively to afford the corresponding 3-benzylthiophene derivatives (**3aa-3av**) in moderate to excellent yields (46-98%, Table 5.2). Additionally, the reaction of **1a** with di-substituted aryl iodides (**2n, 2s-v**) containing electron donating and electron withdrawing groups as well as 3-bromo-6-iodo-9H-fluorene **2w** under the optimized reaction conditions afforded the desired products (**3an, 3as-3aw**) respectively in moderate to good yields (50-70%, Table 5.2).

Further, in order to broaden the substrate scope of this strategy, we carried out the direct arylation of 5-bromothiophene-2-carbaldehyde **1b**, 3-methyl benzothiophene carbaldehyde **1c** and 3-methyl benzofuran 2-carbaldehyde **1d** with various aryl/heteroaryl iodides. The arylation of these heterocyclic aldehydes (**1b-1d**) with different aryl iodides (**2b, 2h, 2c, 2z**) under the optimized reaction conditions furnished the corresponding derivatives (**3bh, 3cb, 3ch, 3dh, 3db, 3dc, 3cz**) respectively in moderate to good yields (up to 75 % Table 5.2). Moreover, the different substituted aryl iodides such as 4-iodobenzoic acid (**2x**) which contains free carboxylic acid, 5-iodo-1-tosyl-1H-indole (**2y**) and 5-iodopyridine derivatives (**2z-2zc'**) reacted smoothly to furnish the desired  $\gamma$ -C(sp<sup>3</sup>)-H arylated products (**3ax-3azc'**) in moderate to good yields (Table 5.2). Unfortunately, even under optimal reaction conditions, indole-2-carbaldehyde **1e** reacted slowly to produce the final product **3eh** in a very low yield. (<10%). Despite our repeated attempts, we are unable to isolate the pure compound **3eh**.

Later, for the practicability of protocol we scaled up the reactions (0.3–0.5 g quantity) to obtain the final products **3aa** and **3ab** in good yields (up to 73%, see Table 5.2). Strong electron-withdrawing groups (EWGs) like nitro, nitrile, ester, aldehyde, and keto groups, as well as electron-deactivating halo groups (EDHs) like F, Cl, and Br, were able to withstand the optimised reaction conditions and compounds containing these functional groups also underwent a smooth reaction to yield the corresponding functionalized products in moderate to very good yields. It's also important to highlight that the under the optimized reaction conditions even the less reactive iodo pyridine derivatives reacted smoothly to afford the desired compounds (**3az-3azc'**, Table 5.2). Also, this synthetic strategy gave an access to compounds relatively in better yields in comparison to earlier method (See Appendix VA, page no. 207).

**Table 5.2.** Arylations of the five membered heterocyclic carbonyl compounds.

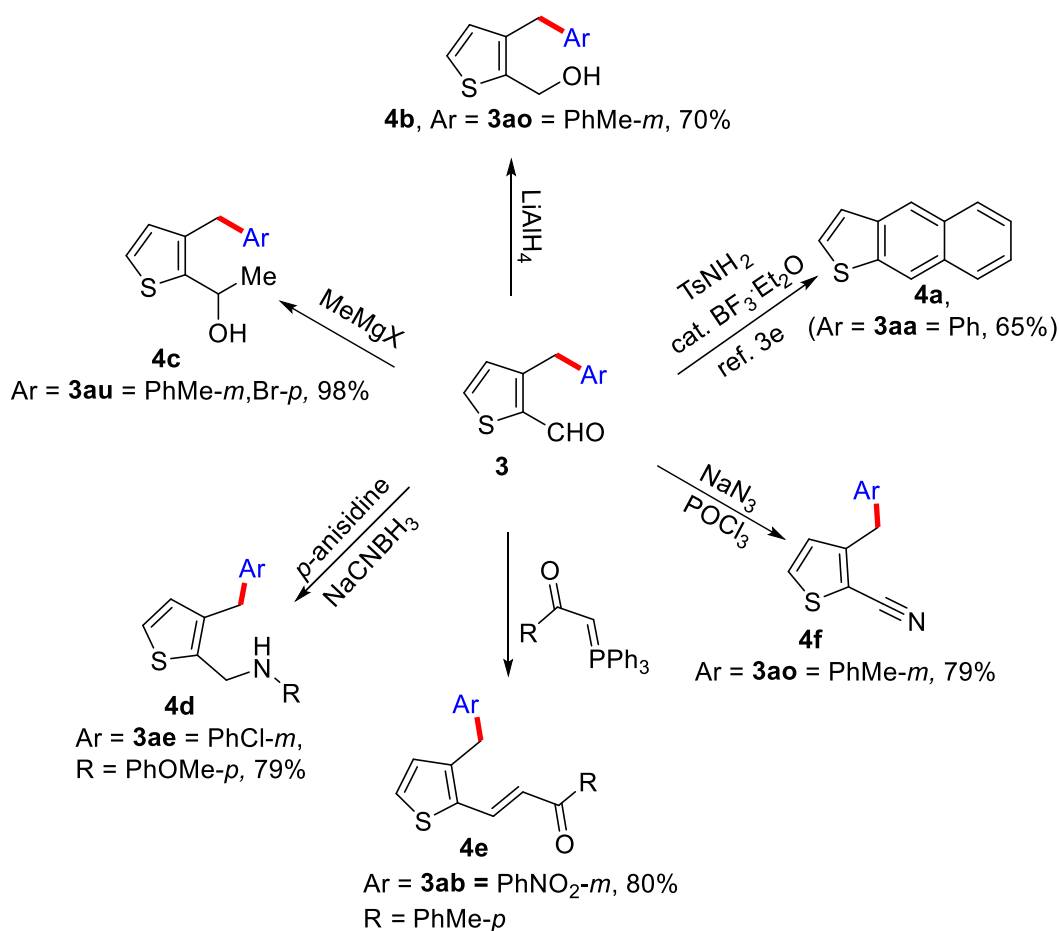


<sup>a</sup>Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), Pd(OAc)<sub>2</sub> (0.02 mmol), AgTFA (0.3 mmol), **L7** (0.08 mmol), HFIP (1.44 mL), HOAc (0.16 mL), 110 °C, 24 h. <sup>b</sup>Isolated yields; <sup>b</sup>0.3 g scale; <sup>c</sup>1 (0.24

mmol), **2** (0.2 mmol); <sup>d</sup>36 h, <sup>e</sup>30 h; <sup>f</sup>Pd(OAc)<sub>2</sub> (0.03 mmol); AgTFA (0.4 mmol), 113 °C; <sup>g</sup>40 h; <sup>h</sup>Pd(OAc)<sub>2</sub> (0.03 mmol) and AgTFA (0.6 mmol)

As discussed, the benzyl-heteroaryl carbaldehydes have been explored as active synthetic intermediates for various useful synthetic transformations. As an application of this protocol, we successfully employed the compounds synthesized (**3aa**, **3ao**, **3au**, **3ae**, **3ab**) for the synthesis of different very important and useful molecules (Scheme 5.3). By following the reported methods, the condensation process of **3aa** was carried out with TsNH<sub>2</sub> and BF<sub>3</sub>. Et<sub>2</sub>O and to furnish the fused naphtho-thiophene compound **4a** in good yield (65% yield, Scheme 5.3).<sup>4b</sup>

#### 5.4 Application to the strategy



**Scheme 5.3** Few synthetic transformations.

It is important to highlight here that we could achieve the synthesis of the compound **4a** relatively in fewer number of steps compared to the earlier described method.<sup>4b</sup> Furthermore, this synthetic approach makes it very simple to obtain benzothiophene compounds as well.<sup>3b</sup> Later we explored the reduction of reaction **3ao** with lithium aluminium



hydride and the Grignard reaction to the compound **3au** with MeMgBr to obtain the corresponding products **4b** and **4c** in good to excellent yields, respectively (70% and 98% Scheme 5.3).

Further the reductive amination of compound **3ab** was carried out with p-anisidine and NaCNBH<sub>3</sub> to furnish the corresponding amine product **4d** in 79% yield. (Scheme 5.4). Additionally, we also performed the Schmidt-type reaction with **3ao** and the Wittig reaction with **3ae** to get the relevant  $\alpha,\beta$ -unsaturated carbonyl compounds **4e** and 2-cyano-3-benzyl thiophene compound **4f** in good yields, respectively. (Scheme 5.3).

The develop synthetic protocol has been proved to be practical and has the potential to furnish a wide variety of structural motifs that are essential intermediates for the synthesis of many useful organic compounds, bio-active molecules and pharmaceuticals.

## 5.5 Conclusions

In conclusion, by employing L-valine as a transient directing group via palladium catalysis, we have created an efficient and straightforward synthetic method for the direct  $\gamma$ -C(sp<sup>3</sup>)-H arylation of 3-methylheteroarene-2-carbaldehydes with a range of aryl iodides. The different 3-methylheteroaryl carbonyl compounds reacts efficiently with a variety of aryl iodides under the reaction condition afforded the large number of  $\beta$ -benzyl-substituted five-membered heterocyclic carbonyl derivatives in good to excellent yields with high regio- and chemo-selectivity. The main advantages and features of this synthetic approach are its high functional group tolerance, wide substrate application, and smooth arylation of even comparatively less reactive pyridine-based hetero-aryl iodides.

## 5.6 Experimental Section

### 5.6.1 General Information.

All compounds have uncorrected melting points. IR spectra of compounds were recorded as thin films or KBr pellets.  $^1\text{H}$  and  $^{13}\text{C}\{^1\text{H}\}$  NMR spectra of all the compounds were recorded on 400 MHz and 100 MHz spectrometers, respectively (using TMS as an internal standard). HRMS measurements were obtained from TOF mass analyzer using electrospray ionization (ESI-TOF). Column chromatography was carried out by using 100-200 mesh silica gel. All the reactions were performed in anhydrous solvent under a nitrogen atmosphere.

Starting compounds (3-methylheteroaryl-2-carbaldehydes (**1a**, **1c**) and aryl iodides (**2a-2x**, **2y-2zc'**) were commercially bought from Sigma-Aldrich, Alfa Aesar, Avra Synthesis Pvt. Ltd., etc. and were utilized as such without any further purifications. Further, 5-bromo-3-methylthiophene-2-carbaldehyde (**1b**)<sup>15</sup> and 5-iodo-1-tosyl-1H-indole (**2y**)<sup>16</sup> compounds were known in literature and synthesized them by following reported literature procedures<sup>15,16</sup>

### 5.6.2 General Procedures for *ortho*-C(sp<sup>3</sup>)-H Arylation of 3-Methylheteroarene-2-carbaldehydes Using a Transient Directing Group.

#### General Procedure A:

A 15-mL dry pressure tube equipped with a stir bar was charged with 3-methylthiophene-2-carbaldehyde **1a** (25.2 mg, 0.20 mmol, 1.0 equiv.), iodobenzene **2a** (61.1 mg, 0.3 mmol, 1.5 equiv.), Pd(OAc)<sub>2</sub> (4.5 mg, 0.02 mmol, 0.1 equiv.), **L8** (9.36 mg, 0.08 mmol, 0.4 equiv.), AgTFA (61.4 mg, 0.3 mmol, 1.5 equiv.), and followed by the addition of the mixture of (1.44 mL) and AcOH (0.16 mL) at room temperature. Then the resulting reaction mixture was degassed under N<sub>2</sub> atmosphere for 2 min and stirred vigorously at room temperature for 15 min. Then the reaction mixture was heated to 110 °C for 24 h. After which, the reaction mixture was cooled to room temperature, followed by the dilution with EtOAc (15 mL) and subsequently it was filtered through pad of celite. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel to furnish the desired product **3aa** in 94% yield (38 mg) as yellow oil.

#### 5.6.3 General Procedure B:

A 15 mL dry pressure tube equipped with a stir bar was charged with ethyl 3-iodobenzoate **2c** (56 mg, 0.2 mmol, 1.0 equiv.), 3-methylthiophene-2-carbaldehyde **1a** (30.7 mg, 0.24 mmol, 1.2 equiv.), Pd(OAc)<sub>2</sub> (4.5 mg, 0.02 mmol, 0.1 equiv.), **L8** (9.36 mg, 0.08 mmol, 0.4 equiv.),

AgTFA (61.4 mg, 0.3 mmol, 1.5 equiv.), and followed by the addition of the mixture of HFIP (1.44 mL) and AcOH (0.16 mL) at room temperature. Then the resulting reaction mixture was degassed under N<sub>2</sub> atmosphere for 2 min and it was stirred vigorously at room temperature for 15 min followed heating at 110 °C for 24 h. After which the reaction mixture was cooled to room temperature followed by dilution with EtOAc (15 mL). Later, the reaction mixture was filtered through pad of celite and the filtrate was then concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the desired product **3ac** in 75% yield (41 mg) as brown coloured semi solid.

Following General Procedure B, the compounds **3ac**, **3ag-aj**, **3dh**, **3ay-3azc'** were synthesized (as shown in Scheme 2)

### 5.6.3a Procedure for the LAH Reduction<sup>17a</sup> and followed by PCC-based Oxidation<sup>17b</sup> and Synthesis of 3-Methylbenzofuran-2-carbaldehyde (**1d**).

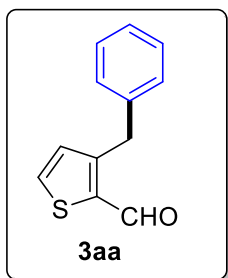
In 50 mL round bottom flask add the 3-methylbenzofuran-2-carboxylic acid (400 mg, 2.27 mmol, 1 equiv.) and dry THF (15 mL) solvent under Ar atmosphere. Stirred the reaction mixture at 0 °C and then add the LiAlH<sub>4</sub> (4.54 mmol, 2 equiv.). After that mixture was allowed to attain room temperature and stirred overnight. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled down to 0 °C and quenched carefully with sat. NH<sub>4</sub>Cl solution (10 mL). Further the mixture was extracted with ethyl acetate (2 x 30 mL) and then the organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuo to obtain the corresponding crude alcohol which was used for the next step for the PCC oxidation reaction without any further purification. To another dry 100 mL RB flask containing the above crude alcoholic solution in DCM (15 mL) was charged with pyridinium chlorochromate (3.40 mmol, 1.5 equiv.) at 0-5 °C under nitrogen atmosphere and allowed to stir at room temperature for 5 h. After the completion of reaction (monitored by TLC), the solvent was distilled off completely under vacuum to obtain the corresponding crude aldehyde and purified the crude compound by column chromatography over silica gel (EtOAc/petroleum ether = 10:90) to obtain 3-methylbenzofuran-2-carbaldehyde (**1d**) as a white solid: R<sub>f</sub> = 0.49 (EtOAc/petroleum ether = 10:90), mp: 86-88 °C; 210 mg (60% yield); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.34 (s, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.44 (dd, J = 8.0, 7.1 Hz, 1H), 2.79 (s, 3H). <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 184.1 143.1, 142.2, 140.2, 137.6, 128.5, 124.9, 124.0, 123.4, 12.2.

### 5.6.3b Procedure for N-benylation<sup>18</sup> of 3-Methyl-1H-indole-2-carbaldehyde and Synthesis of 1-Benzyl-3-methyl-1H-indole-2-carbaldehyde (**1e**).

In a 50 mL R.B. stirred solution of NaH (3.14 mmol, 2 equiv.) in dry THF (10 mL) was charged 3-methyl-1H-indole-2-carbaldehyde (250 mg, 1.57 mmol, 1 equiv.) at 0 °C under Ar and stirred at the same temperature for 10-15 minutes. Then, benzyl bromide (1.1 equiv) was charged gradually at 0-5 °C, the reaction mixture was allowed to room temperature and stirred overnight at 25-30 °C. After the complete consumption of starting material (monitored by TLC), the reaction mass was cooled down to 5 °C and quenched carefully with few drops of MeOH followed by the addition of water (10 mL). The mixture was extracted with EtOAc (2 x 25 mL) and combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The corresponding crude product was purified by silica chromatography (EtOAc/petroleum ether = 15:85) to obtain 1-benzyl-3-methyl-1H-indole-2-carbaldehyde (**1e**) as a pale yellow solid: R<sub>f</sub> = 0.49 (EtOAc/petroleum ether = 15:85), mp: 80-82 °C; 313 mg (80% yield); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.15 (s, 1H), 7.72-7.70 (m, 1H), 7.39-7.30 (m, 2H), 7.25-7.13 (m, 4H), 7.08-7.05 (m, 2H), 5.78 (s, 2H), 2.65 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 181.3, 139.6, 138.2, 130.6, 128.6, 127.6, 127.3, 127.2, 127.2, 126.6, 121.4, 120.4, 110.8, 47.8, 8.7. HRMS (ESI): m/z [M + H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>16</sub>NO: 250.1231; found 250.1218.

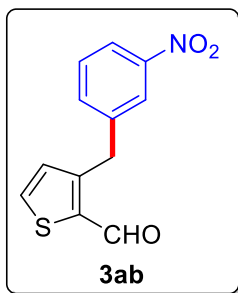
## 5.6.4 Experimental Data

### 3-Benzylthiophene-2-carbaldehyde (3aa).



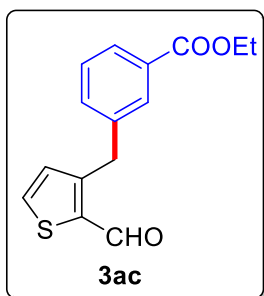
Following the general procedure A described above, **3aa** was obtained after purification by column chromatography on silica gel as a yellow oil:  $R_f$  = 0.49 (EtOAc:Hexane = 10:90), 38 mg (94% yield); FTIR ( $\text{cm}^{-1}$ ): 3028, 1652, 1424, 1225;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.08 (s, 1H), 7.63 (dd,  $J$  = 5.0, 1.0 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.25 – 7.15 (m, 3H), 6.93 (d,  $J$  = 5.0 Hz, 1H), 4.33 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.5, 150.1, 139.2, 138.9, 134.7, 131.5, 128.9, 128.7, 126.8, 34.6. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_{11}\text{OS}$ : 203.0531; found 203.0532.

### 3-(3-Nitrobenzyl)thiophene-2-carbaldehyde (3ab).



Following the general procedure A described above, **3ab** was obtained after purification by column chromatography on silica gel as a yellow brownish solid:  $R_f$  = 0.46 (EtOAc:Hexane = 12:88), mp: 86-88 °C; 45 mg (91% yield); FTIR ( $\text{cm}^{-1}$ ): 3099, 1658, 1526, 1350, 717;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.05 (s, 1H), 8.12 – 8.06 (m, 2H), 7.72 (d,  $J$  = 5.0 Hz, 1H), 7.56 – 7.47 (m, 2H), 6.97 (d,  $J$  = 5.0 Hz, 1H), 4.48 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.1, 148.6, 147.3, 141.3, 138.3, 135.2, 134.9, 131.3, 129.8, 123.6, 122.0, 34.2. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_{10}\text{NO}_3\text{S}$ : 248.0381; found 248.0384.

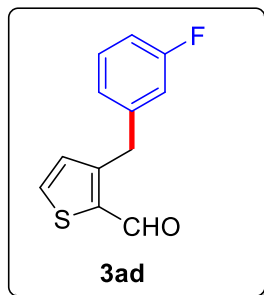
### Ethyl 3-((2-formylthiophen-3-yl)methyl)benzoate (3ac).



Following the general procedure B described above, **3ac** was obtained after purification by column chromatography on silica gel as a brown colour semi solid:  $R_f$  = 0.46 (EtOAc:Hexane = 12:88), 41 mg (75% yield); FTIR ( $\text{cm}^{-1}$ ): 2982, 1712, 1656, 1273, 1188 ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.08 (s, 1H), 7.93 – 7.89 (m, 2H), 7.65 (d,  $J$  = 5.0 Hz, 1H), 7.38 – 7.36 (m, 2H), 6.92 (d,  $J$  = 5.0 Hz, 1H), 4.38 (s, 2H), 4.35 (q,  $J$  = 7.1 Hz, 2H), 1.38 (t,  $J$  = 7.2 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.3, 166.5,

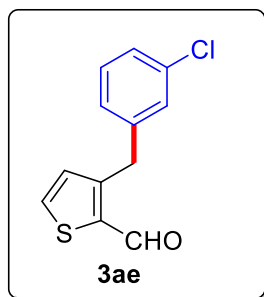
149.1, 139.6, 138.2, 134.9, 133.8, 131.4, 131.1, 129.8, 128.9, 128.1, 61.2, 34.3, 14.4. HRMS (ESI):  $m/z$   $[M + Na]^+$  calcd for  $C_{15}H_{14}NaO_3S$ : 297.0561; found 297.0559.

### 3-(3-Fluorobenzyl)thiophene-2-carbaldehyde (3ad).



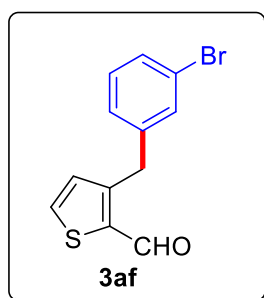
Following the general procedure A described above, **3ad** was obtained after purification by column chromatography on silica gel as a yellow oil:  $R_f$  = 0.49 (EtOAc:Hexane = 10:90), 40 mg (90% yield); FTIR ( $cm^{-1}$ ): 2924, 1658, 1526, 1242, 737;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  10.06 (s, 1H), 7.67 – 7.66 (m, 1H), 7.30-7.24 (m, 1H), 6.94 (d,  $J$  = 5.0 Hz, 1H), 6.98 – 6.86 (m, 3H), 4.34 (s, 2H).  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  182.3, 163.2 (d,  $J_{C-F}$  = 246.6 Hz), 148.8, 141.7 (d,  $J_{C-F}$  = 7.2 Hz), 138.3, 134.9, 131.4, 130.4 (d,  $J_{C-F}$  = 8.3 Hz), 124.8 (d,  $J_{C-F}$  = 2.9 Hz), 115.7 (d,  $J_{C-F}$  = 21.6 Hz), 113.8 (d,  $J_{C-F}$  = 21.0 Hz), 34.2 (d,  $J_{C-F}$  = 1.8 Hz). HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{12}H_{10}FOS$ : 221.0436; found 221.0433.

### 3-(3-Chlorobenzyl)thiophene-2-carbaldehyde (3ae).



Following the general procedure A described above, **3ae** was obtained after purification by column chromatography on silica gel as a yellow oil:  $R_f$  = 0.48 (EtOAc:Hexane = 10:90), 38 mg (81% yield); FTIR ( $cm^{-1}$ ): 1737, 1428, 1227, 724;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  10.06 (s, 1H), 7.67 – 7.66 (m, 1H), 7.26 – 7.16 (m, 3H), 7.08 – 7.06 (m, 1H), 6.93 (d,  $J$  = 5.0 Hz, 1H), 4.32 (s, 2H).  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  182.3, 148.7, 141.2, 138.2, 134.9, 134.7, 131.4, 130.2, 128.8, 127.1, 126.9, 34.2. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{12}H_{10}ClOS$ : 237.0141; found 237.0147.

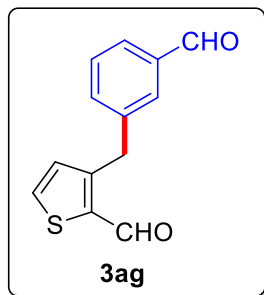
### 3-(3-Bromobenzyl)thiophene-2-carbaldehyde (3af).



Following the general procedure A described above, **3af** was obtained after purification by column chromatography on silica gel as a brown colour semi solid:  $R_f$  = 0.49 (EtOAc:Hexane = 10:90), 42 mg (76% yield); FTIR ( $cm^{-1}$ ): 2924, 1658, 1470, 1229, 720;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  10.05 (s, 1H), 7.66 (d,  $J$  = 4.9 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.18 (t,  $J$  = 7.7 Hz, 1H), 7.13 – 7.10 (m, 1H), 6.93 (d,  $J$  = 5.0 Hz, 1H), 4.31 (s, 2H).  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  182.3, 148.7, 141.5, 138.3, 134.9, 131.7,

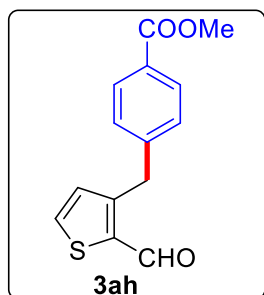
131.4, 130.5, 130.0, 127.4, 122.9, 34.2. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{12}H_{10}BrOS$ : 280.9636; found 280.9635.

### 3-(3-Formylbenzyl)thiophene-2-carbaldehyde (3ag).



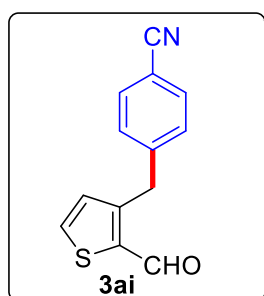
Following the general procedure B described above, **3ag** was obtained after purification by column chromatography on silica gel as a yellow semi solid:  $R_f$  = 0.49 (EtOAc:Hexane = 14:86), 21 mg (46% yield); FTIR ( $cm^{-1}$ ): 3098, 1693, 1654, 1425, 1230;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  10.07 (s, 1H), 9.99 (s, 1H), 7.77 – 7.73 (m, 1H), 7.72 (s, 1H), 7.68 (d,  $J$  = 4.9 Hz, 1H), 7.51 – 7.46 (m, 2H), 6.95 (d,  $J$  = 5.0 Hz, 1H), 4.44 (s, 2H).  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  192.2, 182.2, 148.5, 140.5, 138.3, 136.9, 135.0, 134.8, 131.4, 129.6, 129.5, 128.6, 34.3. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{13}H_{11}O_2S$ : 231.0480; found 231.0481.

### Methyl 4-((2-formylthiophen-3-yl)methyl)benzoate (3ah).



Following the general procedure B described above, **3ah** was obtained after purification by column chromatography on silica gel as a brown solid:  $R_f$  = 0.48 (EtOAc:Hexane = 13:87), mp: 54-56 °C; 50 mg (98% yield); FTIR ( $cm^{-1}$ ): 2923, 1717, 1660, 1523, 1281;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  10.06 (s, 1H), 7.98 (d,  $J$  = 8.4 Hz, 2H), 7.66 (d,  $J$  = 5.0 Hz, 1H), 7.26 (d,  $J$  = 8.6 Hz, 2H), 6.92 (d,  $J$  = 5.0 Hz, 1H), 4.40 (s, 2H), 3.90 (s, 3H).  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  182.2, 166.9, 148.5, 144.5, 138.3, 134.9, 131.4, 130.2, 128.8, 128.7, 52.2, 34.5. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{14}H_{13}O_3S$ : 261.0585; found 261.0588.

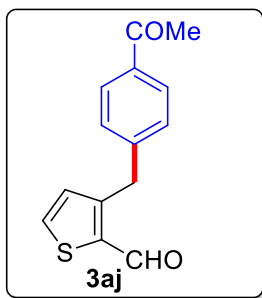
### 4-((2-Formylthiophen-3-yl)methyl)benzonitrile (3ai).



Following the general procedure B described above, **3ai** was obtained after purification by column chromatography on silica gel as yellow crystalline solid:  $R_f$  = 0.49 (EtOAc:Hexane = 15:85), mp: 103-105 °C; 35 mg (77% yield); FTIR ( $cm^{-1}$ ): 1736, 1646, 2224, 1424, 1280;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  10.03 (s, 1H), 7.71 (d,  $J$  = 5.0 Hz, 1H), 7.60

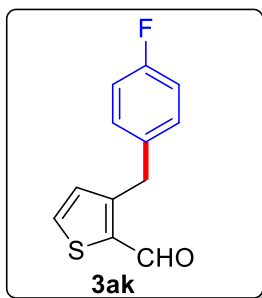
(d,  $J = 8.3$  Hz, 2H), 7.31 (d,  $J = 8.4$  Hz, 2H), 6.94 (d,  $J = 5.0$  Hz, 1H), 4.42 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.1, 147.3, 144.7, 138.3, 135.1, 132.7, 131.3, 129.5, 118.8, 110.7, 34.6. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{10}\text{NOS}$ : 228.0483; found 228.0481.

### 3-(4-Acetylbenzyl)thiophene-2-carbaldehyde (3aj).



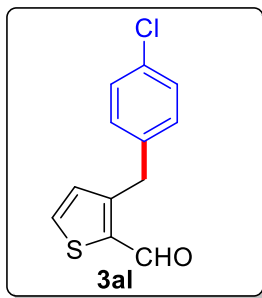
Following the general procedure B described above, **3aj** was obtained after purification by column chromatography on silica gel as a brown solid:  $R_f = 0.49$  (EtOAc:Hexane = 20:80), mp: 61-63 °C; 33 mg (67% yield); FTIR ( $\text{cm}^{-1}$ ): 2924, 1665, 1527, 1423, 1266;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.06 (s, 1H), 7.90 (d,  $J = 8.3$  Hz, 2H), 7.68 (d,  $J = 5.0$  Hz, 1H), 7.29 (d,  $J = 8.4$  Hz, 2H), 6.94 (d,  $J = 5.0$  Hz, 1H), 4.41 (s, 2H), 2.58 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  197.7, 182.2, 148.4, 144.7, 138.3, 135.8, 134.9, 131.4, 129.0, 128.9, 34.5, 26.7. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{13}\text{O}_2\text{S}$ : 245.0636; found 245.0637.

### 3-(4-Fluorobenzyl)thiophene-2-carbaldehyde (3ak).



Following the general procedure A described above, **3ak** was obtained after purification by column chromatography on silica gel as a yellow oil:  $R_f = 0.49$  (EtOAc:Hexane = 10:90), 38 mg (86% yield); FTIR ( $\text{cm}^{-1}$ ): 2926, 1732, 1511, 1225;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.06 (s, 1H), 7.65 (d,  $J = 5.0$  Hz, 1H), 7.16 – 7.13 (m, 2H), 7.01 – 6.96 (m, 2H), 6.91 (d,  $J = 5.0$  Hz, 1H), 4.31 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.4, 161.7 (d,  $J_{\text{C-F}} = 245.3$  Hz), 149.7, 138.1, 134.9 (d,  $J_{\text{C-F}} = 3.0$  Hz), 134.9, 131.4, 130.2 (d,  $J_{\text{C-F}} = 8.0$  Hz), 115.7 (d,  $J_{\text{C-F}} = 21.4$  Hz), 33.7. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_{10}\text{FOS}$ : 221.0436; found 221.0433.

### 3-(4-Chlorobenzyl)thiophene-2-carbaldehyde (3al).

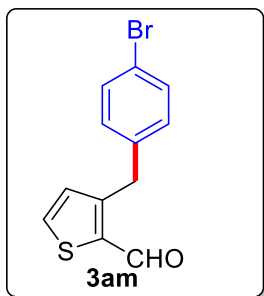


Following the general procedure A described above, **3al** was obtained after purification by column chromatography on silica gel as a brown semi solid:  $R_f = 0.49$  (EtOAc:Hexane = 10:90), 31 mg (65% yield); FTIR ( $\text{cm}^{-1}$ ): 3099, 1653, 1422, 1296, 1091  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.05 (s, 1H), 7.66 – 7.64 (m, 1H), 7.27 (d,  $J = 8.4$  Hz, 2H), 7.12 (d,  $J = 8.6$  Hz, 2H), 6.91 (d,  $J = 5.0$  Hz, 1H), 4.31 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$



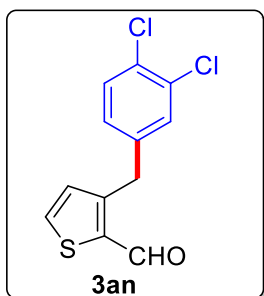
NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  182.3, 149.1, 138.2, 137.7, 134.9, 132.7, 131.4, 130.1, 129.0, 33.9. HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>10</sub>ClOS: 237.0141; found 237.0139.

### 3-(4-Bromobenzyl)thiophene-2-carbaldehyde (**3am**).



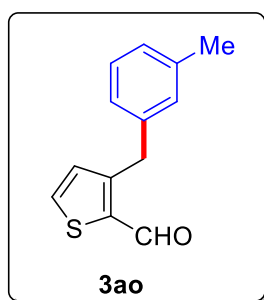
Following the general procedure A described above, **3am** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f$  = 0.49 (EtOAc:Hexane = 10:90), mp: 81-83 °C; 35 mg (63% yield); FTIR (cm<sup>-1</sup>): 3098, 1657, 1486, 1297, 744; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  10.05 (s, 1H), 7.65 (d,  $J$  = 5.0 Hz, 1H), 7.42 (d,  $J$  = 8.4 Hz, 2H), 7.06 (d,  $J$  = 8.6 Hz, 2H), 6.91 (d,  $J$  = 5.0 Hz, 1H), 4.29 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  182.3, 149.0, 138.3, 138.2, 134.9, 131.9, 131.4, 130.5, 120.7, 34.0. HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>10</sub>BrOS: 280.9636; found 280.9625.

### 3-(3,4-Dichlorobenzyl)thiophene-2-carbaldehyde (**3an**).



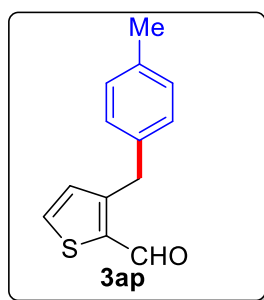
Following the general procedure A described above, **3an** was obtained after purification by column chromatography on silica gel as a brown solid:  $R_f$  = 0.49 (EtOAc/Hexane = 12:88), mp: 50-52 °C; 33 mg (62% yield); FTIR (cm<sup>-1</sup>): 3096, 1659, 1423, 1228; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  10.04 (s, 1H), 7.69 (d,  $J$  = 4.9 Hz, 1H), 7.37 (d,  $J$  = 8.2 Hz, 1H), 7.27 (d,  $J$  = 2.1 Hz, 1H), 7.03 (dd,  $J$  = 8.2, 2.1 Hz, 1H), 6.93 (d,  $J$  = 5.0 Hz, 1H), 4.31 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  182.1, 147.9, 139.5, 138.3, 135.0, 132.9, 131.3, 130.9, 130.8, 130.6, 128.2, 33.7. HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>9</sub>Cl<sub>2</sub>OS: 270.9751; found 270.9756.

### 3-(3-Methylbenzyl)thiophene-2-carbaldehyde (**3ao**).



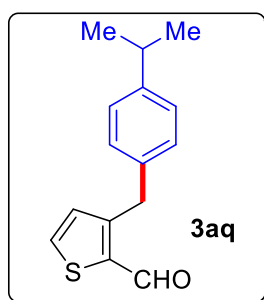
Following the general procedure A described above, **3ao** was obtained after purification by column chromatography on silica gel as a brownish yellow oil:  $R_f = 0.49$  (EtOAc:Hexane = 09:91), 34 mg (80% yield); FTIR ( $\text{cm}^{-1}$ ): 2921, 1659, 1488, 1229;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.09 (s, 1H), 7.63 (d,  $J = 5.0$  Hz, 1H), 7.21- 7.17 (m, 1H), 7.04 (d,  $J = 7.5$  Hz, 1H), 6.99 (s, 1H), 6.98 (d,  $J = 7.7$  Hz, 1H), 6.94 (d,  $J = 5.0$  Hz, 1H), 4.29 (s, 2H), 2.32 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.6, 150.3, 139.1, 138.6, 138.1, 134.7, 131.5, 129.5, 128.8, 127.6, 125.7, 34.5, 21.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{13}\text{OS}$ : 217.0687; found 217.0692.

### 3-(4-Methylbenzyl)thiophene-2-carbaldehyde (**3ap**).



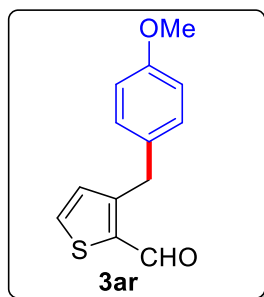
Following the general procedure A described above, **3ap** was obtained after purification by column chromatography on silica gel as a brown oil:  $R_f = 0.49$  (EtOAc:Hexane = 09:91), 37 mg (85% yield); FTIR ( $\text{cm}^{-1}$ ): 3018, 1656, 1424, 1226, 767;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.08 (s, 1H), 7.62 (d,  $J = 5.0$  Hz, 1H), 7.11 (d,  $J = 8.0$  Hz, 2H), 7.07 (d,  $J = 8.1$  Hz, 2H), 6.93 (d,  $J = 5.0$  Hz, 1H), 4.29 (s, 2H), 2.32 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.5, 150.5, 138.1, 136.4, 136.2, 134.7, 131.5, 129.6, 128.6, 34.2, 21.1. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{13}\text{OS}$ : 217.0687; found 217.0690.

### 3-(4-Isopropylbenzyl)thiophene-2-carbaldehyde (**3aq**).



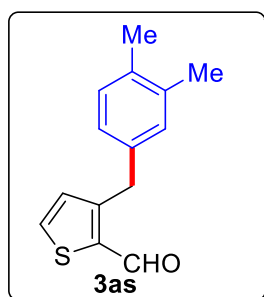
Following the general procedure A described above, **3aq** was obtained after purification by column chromatography on silica gel as a brownish yellow oil:  $R_f = 0.49$  (EtOAc:Hexane = 09:91), 34 mg (70% yield); FTIR ( $\text{cm}^{-1}$ ): 2960, 1659, 1425, 1227, 734;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.09 (s, 1H), 7.63 (d,  $J = 5.0$  Hz, 1H), 7.16 (d,  $J = 8.1$  Hz, 2H), 7.10 (d,  $J = 8.3$  Hz, 2H), 6.95 (d,  $J = 5.0$  Hz, 1H), 4.30 (s, 2H), 2.91 – 2.84 (m, 1H), 1.24 (s, 3H), 1.22 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.57, 150.44, 147.5, 138.2, 136.6, 134.6, 131.6, 128.6, 126.9, 34.1, 33.8, 24.1. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_{17}\text{OS}$ : 245.1000; found 245.0994.

### 3-(4-Methoxybenzyl)thiophene-2-carbaldehyde (**3ar**).



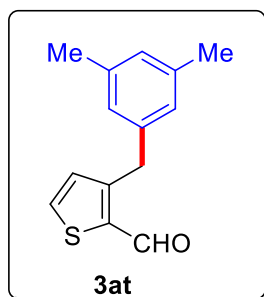
Following the general procedure A described above, **3ar** was obtained after purification by column chromatography on silica gel as a brown oil:  $R_f$  = 0.49 (EtOAc:Hexane = 12:88), 35 mg (75% yield); FTIR ( $\text{cm}^{-1}$ ): 2925, 1656, 1511, 1244, 1033;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.08 (s, 1H), 7.62 (d,  $J$  = 5.0 Hz, 1H), 7.10 (d,  $J$  = 8.8 Hz, 2H), 6.92 (d,  $J$  = 5.0 Hz, 1H), 6.84 (d,  $J$  = 8.7 Hz, 2H), 4.27 (s, 2H), 3.78 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.5, 158.5, 150.7, 138.0, 134.7, 131.5, 131.3, 129.7, 114.3, 55.4, 33.7. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{13}\text{O}_2\text{S}$ : 233.0636; found 233.0643.

### 3-(3,4-Dimethylbenzyl)thiophene-2-carbaldehyde (**3as**).



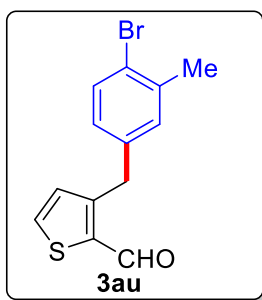
Following the general procedure A described above, **3as** was obtained after purification by column chromatography on silica gel as a brown semi solid:  $R_f$  = 0.49 (EtOAc:Hexanes = 09:91), 29 mg (64% yield); FTIR ( $\text{cm}^{-1}$ ): 2925, 1738, 1437, 1371, 1130, 697;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.08 (s, 1H), 7.61 (d,  $J$  = 5.0 Hz, 1H), 7.06 (d,  $J$  = 7.6 Hz, 1H), 6.95 (s, 1H), 6.94 (d,  $J$  = 5.0 Hz, 1H), 6.91 (d,  $J$  = 7.7 Hz, 1H), 4.25 (s, 2H), 2.22 (s, 3H), 2.22 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.6, 150.7, 138.1, 137.1, 136.6, 135.1, 134.6, 131.5, 130.1, 129.9, 126.0, 34.1, 19.9, 19.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{15}\text{OS}$ : 231.0844; found 231.0845.

### 3-(3,5-dimethylbenzyl)thiophene-2-carbaldehyde (**3at**).



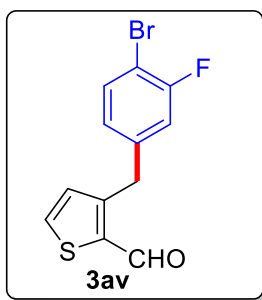
Following the general procedure A described above, **3at** was obtained after purification by column chromatography on silica gel as a brown oil:  $R_f$  = 0.49 (EtOAc:Hexane = 09:91), 23 mg (50% yield); FTIR ( $\text{cm}^{-1}$ ): 2919, 1714, 1424, 1227, 728;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.09 (s, 1H), 7.63 (d,  $J$  = 5.0 Hz, 1H), 6.95 (d,  $J$  = 5.0 Hz, 1H), 6.87 (s, 1H), 6.79 (s, 2H), 4.25 (s, 2H), 2.28 (s, 3H), 2.28 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.6, 150.5, 139.1, 138.5, 138.1, 134.7, 131.5, 128.5, 126.5, 34.4, 21.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{15}\text{OS}$ : 231.0844; found 231.0840.

### 3-(4-Bromo-3-methylbenzyl)thiophene-2-carbaldehyde (**3au**).



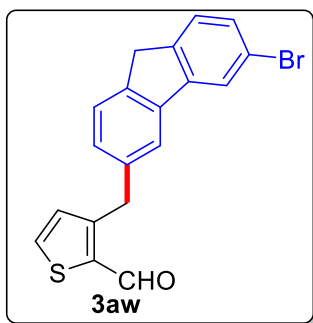
Following the general procedure A described above, **3au** was obtained after purification by column chromatography on silica gel as a yellow semi solid:  $R_f = 0.49$  (EtOAc:Hexane = 10:90), 41 mg (70% yield); FTIR ( $\text{cm}^{-1}$ ): 2923, 1734, 1661, 1474, 1227;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.06 (s, 1H), 7.65 (d,  $J = 5.0$  Hz, 1H), 7.44 (d,  $J = 8.1$  Hz, 1H), 7.05 (s, 1H), 6.92 (d,  $J = 5.0$  Hz, 1H), 6.87 (d,  $J = 7.6$  Hz, 1H), 4.25 (s, 2H), 2.35 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.3, 149.3, 138.5, 138.4, 138.1, 134.8, 132.8, 131.4, 131.2, 127.7, 123.2, 33.9, 23.0. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{12}\text{BrOS}$ : 294.9792; found 294.9785.

### 3-(4-Bromo-3-fluorobenzyl)thiophene-2-carbaldehyde (**3av**).



Following the general procedure A described above, **3av** was obtained after purification by column chromatography on silica gel as a brownish yellow solid:  $R_f = 0.49$  (EtOAc:Hexane = 12:88), mp: 61-63 °C; 37 mg (62% yield); FTIR ( $\text{cm}^{-1}$ ): 3100, 1661, 1528, 1424, 1235;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.03 (s, 1H), 7.68 (d,  $J = 4.9$  Hz, 1H), 7.47 (dd,  $J = 8.1, 7.2$  Hz, 1H), 6.96 (d,  $J = 2.0$  Hz, 1H), 6.93 (d,  $J = 4.9$  Hz, 1H), 6.89 – 6.86 (m, 1H), 4.31 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.1, 159.3 (d,  $J_{\text{C-F}} = 248.0$  Hz), 147.9, 141.0 (d,  $J_{\text{C-F}} = 6.5$  Hz), 138.3, 135.0, 133.8, 131.3, 125.6 (d,  $J_{\text{C-F}} = 3.5$  Hz), 116.9 (d,  $J_{\text{C-F}} = 22.5$  Hz), 107.2 (d,  $J_{\text{C-F}} = 20.9$  Hz), 33.9 (d,  $J_{\text{C-F}} = 1.5$  Hz). HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_9\text{BrFOS}$ : 298.9542; found 298.9533.

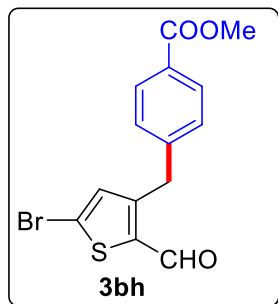
### 3-((6-Bromo-9H-fluoren-3-yl)methyl)thiophene-2-carbaldehyde (**3aw**).



Following the general procedure A described above, **3aw** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f = 0.49$  (EtOAc:Hexane = 10:90), mp: 173-175 °C; 37 mg (51% yield); FTIR ( $\text{cm}^{-1}$ ): 3072, 2925, 1663, 1423, 746;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.12 (s, 1H), 7.68 (d,  $J = 7.8$  Hz, 1H), 7.66 (s, 1H), 7.66 – 7.64 (m, 1H), 7.60 (d,  $J = 8.1$  Hz, 1H), 7.48 (d,  $J = 8.1$  Hz, 1H), 7.34 (s, 1H), 7.22 (d,  $J = 7.8$  Hz, 1H), 6.97 (d,  $J = 5.0$  Hz, 1H), 4.40 (s, 2H), 3.84 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.5, 150.1, 145.3, 143.7, 140.4,

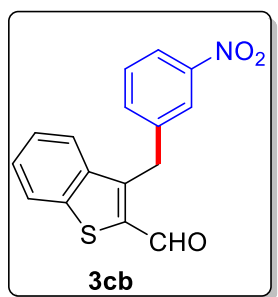
139.5, 138.4, 138.2, 134.8, 131.5, 130.1, 128.4, 127.7, 125.4, 121.2, 120.6, 120.3, 36.8, 34.7. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{19}H_{14}BrOS$ : 368.9949; found 368.9950.

### Methyl 4-((5-bromo-2-formylthiophen-3-yl)methyl)benzoate (**3bh**).



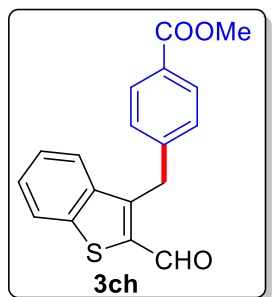
Following the general procedure A described above, **3bh** was obtained after purification by column chromatography on silica gel as a yellow crystalline solid:  $R_f$  = 0.49 (EtOAc:Hexane = 12:88), mp: 131-133 °C; 51 mg (75% yield); FTIR ( $cm^{-1}$ ): 3002, 1717, 1664, 1419, 1280;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  9.96 (s, 1H), 7.96 (d,  $J$  = 8.4 Hz, 2H), 7.72 (s, 1H), 7.24 (d,  $J$  = 8.6 Hz, 2H), 4.43 (s, 2H), 3.90 (s, 3H).  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  181.8, 166.9, 146.4, 143.2, 139.1, 132.5, 130.2, 128.8, 128.5, 115.8, 52.3, 33.6. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{14}H_{12}BrO_3S$ : 338.9691; found 338.9686.

### 3-(3-Nitrobenzyl)benzo[b]thiophene-2-carbaldehyde (**3cb**).



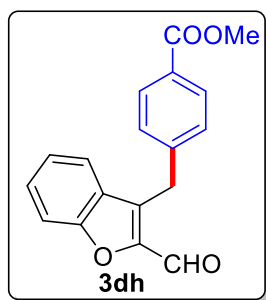
Following the general procedure A described above, **3cb** was obtained after purification by column chromatography on silica gel as a light yellow solid:  $R_f$  = 0.49 (EtOAc:Hexane = 14:86), mp: 171-173 °C; 38 mg (65% yield); FTIR ( $cm^{-1}$ ): 2924, 1712, 1524, 1349, 1205;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  10.32 (s, 1H), 8.11 (s, 1H), 8.10 – 8.07 (m, 1H), 7.93 (d,  $J$  = 8.2 Hz, 1H), 7.78 (d,  $J$  = 8.2 Hz, 1H), 7.55 – 7.39 (m, 4H), 4.75 (s, 2H).  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  183.8, 148.7, 142.7, 142.1, 140.6, 139.2, 139.1, 134.3, 129.9, 128.7, 125.6, 124.3, 123.8, 123.2, 122.2, 31.9. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{16}H_{12}NO_3S$ : 298.0538; found 298.0542.

### Methyl 4-((2-formylbenzo[b]thiophen-3-yl)methyl)benzoate (**3ch**).



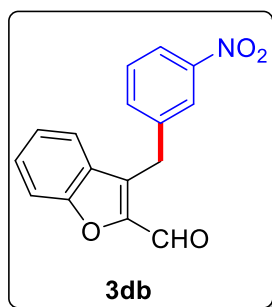
Following the general procedure B described above, **3ch** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f$  = 0.49 (EtOAc:Hexane = 12:88), mp: 132-134 °C; 44 mg (72% yield); FTIR ( $cm^{-1}$ ): 3067, 1719, 1663, 1436, 1282;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  10.32 (s, 1H), 7.94 (d,  $J$  = 8.3 Hz, 2H), 7.90 (d,  $J$  = 8.2 Hz, 1H), 7.77 (d,  $J$  = 8.2 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.39 – 7.35 (m, 1H), 7.26 (d,  $J$  = 8.4 Hz, 2H), 4.68 (s, 2H), 3.88 (s, 3H).  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  184.0, 166.8, 143.8, 143.4, 142.6, 139.5, 139.1, 130.3, 128.9, 128.5, 128.3, 125.3, 124.5, 123.6, 52.3, 32.3. HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{18}H_{15}O_3S$ : 311.0742; found 311.0732

### Methyl 4-((2-formylbenzofuran-3-yl)methyl)benzoate (**3dh**).



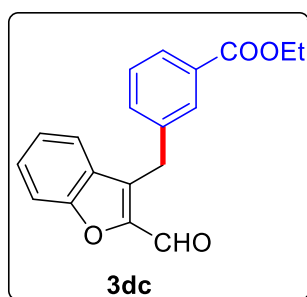
Following the general procedure A described above, **3dh** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f$  = 0.49 (EtOAc:Hexane = 14:86), mp: 129-131 °C; 29 mg (49% yield); FTIR ( $\text{cm}^{-1}$ ): 2945, 1720, 1663, 1436, 1283;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.32 (s, 1H), 7.95 (d,  $J$  = 8.4 Hz, 2H), 7.91 – 7.89 (m, 1H), 7.78 – 7.75 (m, 1H), 7.52 – 7.48 (m, 1H), 7.39 – 7.35 (m, 1H), 7.26 (d,  $J$  = 8.6 Hz, 2H), 4.68 (s, 2H), 3.88 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  184.0, 166.8, 143.8, 143.4, 142.6, 139.5, 139.1, 130.3, 128.9, 128.6, 128.3, 125.3, 124.5, 123.6, 52.3, 32.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{18}\text{H}_{15}\text{O}_4$ : 295.0926; found 295.0918

### 3-(3-Nitrobenzyl)benzofuran-2-carbaldehyde (**3db**).



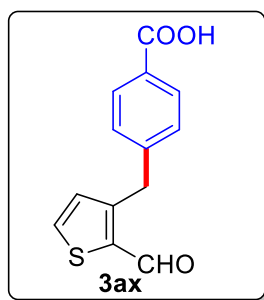
Following the general procedure A described above, **3db** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f$  = 0.49 (EtOAc:Hexane = 15:85), mp: 175-177 °C; 28 mg (50% yield); FTIR ( $\text{cm}^{-1}$ ): 3059, 1661, 1529, 1352, 1211;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.32 (s, 1H), 8.11 (s, 1H), 8.10 – 8.07 (m, 1H), 7.94 – 7.92 (m, 1H), 7.79 – 7.77 (m, 1H), 7.55 – 7.39 (m, 4H), 4.75 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  183.8, 148.7, 142.7, 142.0, 140.7, 139.2, 139.1, 134.3, 129.9, 128.7, 125.6, 124.3, 123.8, 123.2, 122.2, 31.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{12}\text{NO}_4$ : 282.0722; found 282.0727

### Ethyl 3-((2-formylbenzofuran-3-yl)methyl)benzoate (**3dc**).



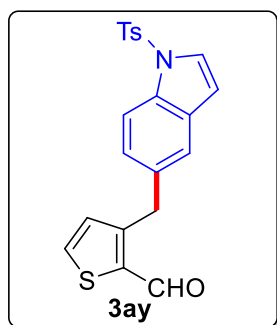
Following the general procedure A described above, **3dc** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f$  = 0.49 (EtOAc:Hexanes = 15:85), mp: 91-93 °C; 32 mg (52% yield); FTIR ( $\text{cm}^{-1}$ ): 2981, 1714, 1661, 1558, 1278;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.34 (s, 1H), 7.97 (s, 1H), 7.91 – 7.88 (m, 2H), 7.81 – 7.79 (m, 1H), 7.51 – 7.47 (m, 1H), 7.39 – 7.28 (m, 3H), 4.68 (s, 2H), 4.36 (q,  $J$  = 7.1 Hz, 2H), 1.37 (t,  $J$  = 7.1 Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  184.1, 166.5, 143.8, 142.6, 139.5, 139.1, 138.9, 132.5, 131.2, 129.4, 129.1, 128.5, 128.2, 125.3, 124.6, 123.6, 61.3, 32.2, 14.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{17}\text{O}_4$ : 309.1127; found 309.1122.

#### 4-((2-Formylthiophen-3-yl)methyl)benzoic acid (**3ax**).



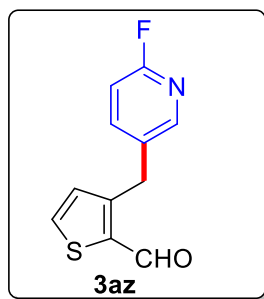
Following the general procedure B described above, **3ax** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f$  = 0.49 (EtOAc:Hexane = 50:50), mp: 169-171 °C; 22 mg (45% yield); FTIR ( $\text{cm}^{-1}$ ): 2943, 1656, 1450, 1020;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3 + \text{CD}_3\text{OD}$ )  $\delta$  10.05 (s, 1H), 7.99 (d,  $J$  = 8.3 Hz, 2H), 7.77 (d,  $J$  = 4.9 Hz, 1H), 7.29 (d,  $J$  = 8.3 Hz, 2H), 6.99 (d,  $J$  = 5.0 Hz, 1H), 4.43 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3 + \text{CD}_3\text{OD}$ )  $\delta$  182.7, 168.4, 149.2, 144.3, 137.7, 135.1, 131.2, 130.0, 128.7, 128.3, 34.0. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{11}\text{O}_3\text{S}$ : 247.0429; found 247.0436.

#### 3-((1-Tosyl-1H-indol-5-yl)methyl)thiophene-2-carbaldehyde (**3ay**).



Following the general procedure B described above, **3ay** was obtained after purification by column chromatography on silica gel as a yellowish semi solid:  $R_f$  = 0.49 (EtOAc:Hexanes = 20:80), 49 mg (63% yield); FTIR ( $\text{cm}^{-1}$ ): 3056, 1735, 1427, 1265;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.06 (s, 1H), 7.90 (d,  $J$  = 8.5 Hz, 1H), 7.75 (d,  $J$  = 8.4 Hz, 2H), 7.62 (d,  $J$  = 4.9 Hz, 1H), 7.54 (d,  $J$  = 3.7 Hz, 1H), 7.30 (s, 1H), 7.22 (d,  $J$  = 8.1 Hz, 2H), 7.14 (d,  $J$  = 8.6 Hz, 1H), 6.92 (d,  $J$  = 5.0 Hz, 1H), 6.57 (d,  $J$  = 3.7 Hz, 1H), 4.38 (s, 2H), 2.34 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.5, 150.2, 145.2, 138.1, 135.4, 134.7, 134.4, 133.7, 131.6, 131.3, 130.1, 127.0, 126.9, 125.4, 121.2, 113.9, 108.9, 34.4, 21.7. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{21}\text{H}_{18}\text{NO}_3\text{S}_2$ : 396.0728; found 396.0729.

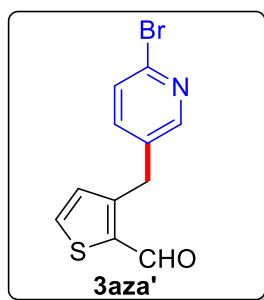
#### 3-((6-Fluoropyridin-3-yl)methyl)thiophene-2-carbaldehyde (**3az**).



Following the general procedure B described above, **3az** was obtained after purification by column chromatography on silica gel as a brownish yellow solid:  $R_f$  = 0.49 (EtOAc:Hexane = 20:80), mp: 47-49 °C; 32 mg (73% yield); FTIR ( $\text{cm}^{-1}$ ): 3098, 1657, 1482, 1242;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.05 (s, 1H), 8.11 (s, 1H), 7.70 (d,  $J$  = 5.0 Hz, 1H), 7.63 – 7.58 (m, 1H), 6.94 (d,  $J$  = 5.0 Hz, 1H), 6.88 (dd,  $J$  = 8.4, 3.0 Hz, 1H), 4.36 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.1, 162.7 (d,  $J_{\text{C-F}}$  = 238.7 Hz), 147.6, 147.3 (d,  $J_{\text{C-F}}$  = 14.6 Hz), 141.4 (d,  $J_{\text{C-F}}$  = 7.8 Hz), 138.1, 135.2, 132.6 (d,  $J_{\text{C-F}}$  = 4.6 Hz), 131.2, 109.7 (d,  $J_{\text{C-F}}$  = 37.5 Hz), 30.9 (d,  $J_{\text{C-F}}$  = 1.4 Hz). HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{11}\text{H}_9\text{FNOS}$ : 222.0389; found 222.0393.

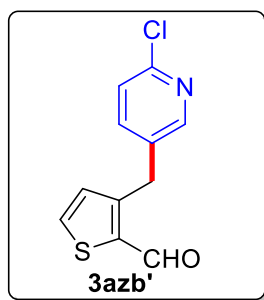


### 3-((6-Bromopyridin-3-yl)methyl)thiophene-2-carbaldehyde (**3aza'**).



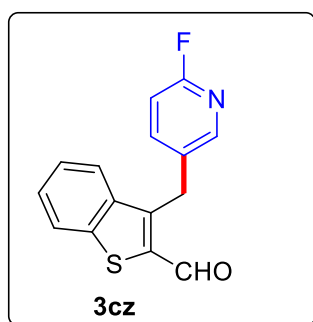
Following the general procedure B described above, **3aza'** was obtained after purification by column chromatography on silica gel as a brown solid:  $R_f = 0.49$  (EtOAc:Hexane = 20:80), mp: 58-60 °C; 34 mg (62% yield); FTIR ( $\text{cm}^{-1}$ ): 3089, 1659, 1448, 1294, 1087;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.03 (s, 1H), 8.27 (d,  $J = 2.4$  Hz, 1H), 7.70 (d,  $J = 4.9$  Hz, 1H), 7.42 (d,  $J = 8.1$  Hz, 1H), 7.37 (dd,  $J = 8.2, 2.5$  Hz, 1H), 6.93 (d,  $J = 5.0$  Hz, 1H), 4.33 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.0, 150.2, 146.9, 140.5, 138.9, 138.1, 135.2, 134.3, 131.2, 128.2, 31.2. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{11}\text{H}_9\text{BrNOS}$ : 281.9588; found 281.9589.

### 3-((6-Chloropyridin-3-yl)methyl)thiophene-2-carbaldehyde (**3azb'**).



Following the general procedure B described above, **3azb'** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f = 0.49$  (EtOAc:Hexane = 20:80), mp: 59-61 °C; 30 mg (65% yield); FTIR ( $\text{cm}^{-1}$ ): 3094, 1660, 1460, 1234, 1023;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.96 (s, 1H), 8.22 (d,  $J = 2.5$  Hz, 1H), 7.63 (d,  $J = 4.9$  Hz, 1H), 7.39 (dd,  $J = 8.2, 2.5$  Hz, 1H), 7.19 (d,  $J = 8.2$  Hz, 1H), 6.86 (d,  $J = 5.0$  Hz, 1H), 4.28 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.0, 150.0, 149.7, 147.1, 139.1, 138.1, 135.2, 133.9, 131.2, 124.4, 31.2. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{11}\text{H}_9\text{ClNOS}$ : 238.0093; found 238.0097.

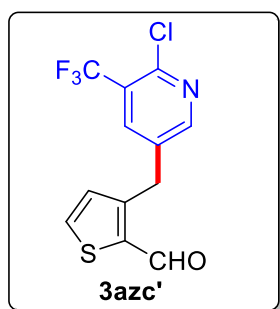
### 3-((6-Fluoropyridin-3-yl)methyl)benzo[b]thiophene-2-carbaldehyde (**3cz**).



Following the general procedure B described above, **3cz** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f = 0.49$  (EtOAc:Hexane = 20:80), mp: 130-132 °C; 25 mg (46% yield); FTIR ( $\text{cm}^{-1}$ ): 3074, 1664, 1483, 1245;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.32 (s, 1H), 8.17 (s, 1H), 7.92 (d,  $J = 8.2$  Hz, 1H), 7.79 (d,  $J = 8.1$  Hz, 1H), 7.56 – 7.50 (m, 2H), 7.44 – 7.40 (m, 1H), 6.83 (dd,  $J = 8.5, 2.9$  Hz, 1H), 4.63 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  183.7, 162.8 (d,  $J_{\text{C-F}} = 239.1$  Hz), 147.0 (d,  $J_{\text{C-F}} = 14.7$  Hz), 142.7, 142.2, 140.8 (d,  $J_{\text{C-F}} = 7.9$  Hz), 139.2, 138.9, 131.9 (d,  $J_{\text{C-F}} = 4.7$  Hz), 128.7, 125.6, 124.3, 123.8, 109.9 (d,  $J_{\text{C-F}} = 37.6$  Hz), 28.8 (d,  $J_{\text{C-F}} = 1.4$  Hz). HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_{11}\text{FNOS}$ : 272.0545; found 272.0547.

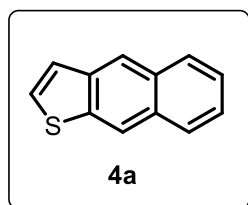


### 3-((6-Chloro-5-(trifluoromethyl)pyridin-3-yl)methyl)thiophene-2-carbaldehyde (**3azc'**).



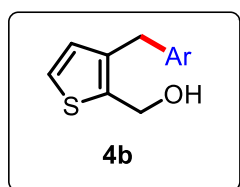
Following the general procedure B described above, **3azc'** was obtained after purification by column chromatography on silica gel as a brown solid:  $R_f$  = 0.49 (EtOAc:Hexane = 20:80), mp: 53-55 °C; 39 mg (65% yield); FTIR ( $\text{cm}^{-1}$ ): 3086, 1662, 1427, 1237, 1142;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.00 (s, 1H), 8.45 (d,  $J$  = 2.3 Hz, 1H), 7.84 (d,  $J$  = 2.3 Hz, 1H), 7.76 (d,  $J$  = 5.0 Hz, 1H), 6.98 (d,  $J$  = 5.0 Hz, 1H), 4.44 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.0, 152.3, 147.3, 145.4, 138.1, 136.8 (q,  $J_{\text{C-F}}$  = 5.0 Hz), 135.5, 134.2, 131.2, 125.3 (d,  $J_{\text{C-F}}$  = 33.2 Hz), 122.1 (d,  $J_{\text{C-F}}$  = 273.0 Hz), 31.2. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_8\text{ClF}_3\text{NOS}$ : 305.9967; found 305.9965.

#### 5.6.4a Procedure for the synthesis of naphtho[2,3-b]thiophene (**4a**).<sup>3b</sup>



An oven dried round bottom flask (25 mL) was charged with **1a** (30.4 mg, 0.15 mmol), tosylamine **2a** (25.7 mg, 0.15 mmol) and toluene (2 mL).  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (30 mol%) was then added to the mixture and the solution was stirred at room temperature for 2 h (Scheme 3). Then, the reaction mixture was purified by column chromatography (EtOAc:Hexane = 25:75) to obtain the white solid **4a**:  $R_f$  = 0.49 (EtOAc:Hexane = 15:85), mp: 188-190 °C; 18 mg (65% yield); FTIR ( $\text{cm}^{-1}$ ): 3054, 2927, 1729, 1267, 1447;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.37 (s, 1H), 8.32 (s, 1H), 7.98 – 7.90 (m, 2H), 7.50 (d,  $J$  = 5.6 Hz, 1H), 7.48 – 7.45 (m, 2H), 7.42 (d,  $J$  = 5.7 Hz, 1H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  139.0, 138.3, 131.1, 131.1, 128.4, 128.3, 127.4, 125.4, 125.1, 123.6, 121.9, 120.8. HRMS (ESI):  $m/z$   $[\text{M}]^+$  calcd for  $\text{C}_{12}\text{H}_8\text{S}$ : 184.0347; found 184.0353.

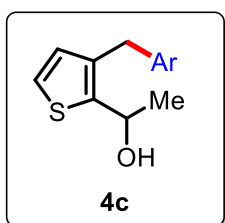
#### 5.6.4b (3-(3-Methylbenzyl)thiophen-2-yl)methanol (**4b**)<sup>19</sup>.



To an oven dried two-necked round bottom flask was charged with a stir bar,  $\text{LiAlH}_4$  (0.22 mmol, 1.5 equiv.) and solution of 3-(3-methylbenzyl)thiophene-2-carbaldehyde **3ao** (0.15 mmol, 1 equiv.) were added in THF (3 mL) at 0 °C under argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred overnight. After the complete consumption of starting material (monitored by TLC), the reaction mixture was cooled down to 0 °C and quenched carefully with 2 M HCl. The reaction mixture was extracted with EtOAc (2x15 mL) and the combined organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The resulting residue was purified by silica chromatography (EtOAc/Hexane = 20:80)

to afford the corresponding alcohol product **4b** as a yellow semi solid:  $R_f = 0.49$  (EtOAc:Hexane = 20:80), 22 mg (70% yield); FTIR ( $\text{cm}^{-1}$ ): 2920, 1605, 1441, 1264;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.19 – 7.15 (m, 2H), 7.02 – 6.94 (m, 3H), 6.83 (d,  $J = 5.1$  Hz, 1H), 4.77 (s, 2H), 3.94 (s, 2H), 2.30 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  140.6, 138.4, 138.4, 137.6, 130.0, 129.3, 128.6, 127.1, 125.6, 124.3, 57.9, 34.3, 21.6. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{15}\text{OS}$ : 219.0799; found 219.0809

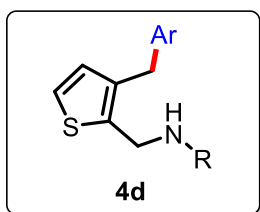
#### 5.6.4c Procedure for the synthesis of 1-(3-(4-Bromo-3-methylbenzyl)thiophen-2-yl)ethanol (**4c**)<sup>20</sup>.



In an oven dried two-necked round bottom flask charged with a stir bar, 3 M MeMgBr solution in THF (0.1 mL, 0.3 mmol, 2 equiv.) was added to a solution of 3-(4-bromo-3-methylbenzyl)thiophene-2-carbaldehyde **3au** (0.15 mmol, 1 equiv.) in THF (3 mL) at  $-78^\circ\text{C}$  under argon atmosphere.

The reaction mixture was continued to stir at  $-78^\circ\text{C}$  for 1 h. After the completion of reaction (monitored by TLC), the reaction mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  solution (5 mL) and extracted with EtOAc (2 x 15 mL). The combined organic layers was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo* and purified by column chromatography using silica gel (EtOAc:Hexane = 15:85) to furnish the desired product **4c** as yellow semi solid:  $R_f = 0.49$  (EtOAc:Hexane = 12:88), 45 mg (98% yield); FTIR ( $\text{cm}^{-1}$ ): 2970, 1473, 1375, 1026;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 (d,  $J = 8.1$  Hz, 1H), 7.16 (d,  $J = 5.1$  Hz, 1H), 7.02 (s, 1H), 6.82 (d,  $J = 8.1$  Hz, 1H), 6.75 (d,  $J = 5.1$  Hz, 1H), 5.21 (q,  $J = 6.4$  Hz, 1H), 3.90 (s, 2H), 2.34 (s, 3H), 1.82 (brs, 1H), 1.55 (d,  $J = 6.4$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  144.1, 139.9, 138.1, 135.9, 132.5, 131.1, 129.7, 127.6, 123.5, 122.6, 64.5, 33.7, 25.4, 23.0. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{16}\text{BrOS}$ : 312.0007; found 312.0017

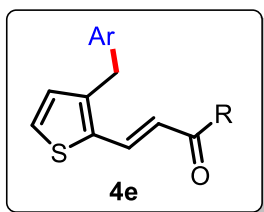
#### 5.6.4d N-((3-(3-Chlorobenzyl)thiophen-2-yl)methyl)-4-methoxyaniline (**4d**)<sup>21</sup>.



To the solution of 3-(3-chlorobenzyl)thiophene-2-carbaldehyde **3ae** (0.15 mmol, 1 equiv.) in DCM (3 mL) was added the corresponding amine (0.15 mmol, 1 equiv.) and sodium sulphate (0.90 mmol, 6 equiv.) under a nitrogen atmosphere and the reaction mixture was stirred at rt for 2 h. Then,  $\text{NaCNBH}_3$  (0.22 mmol, 1.5 equiv.) was added at  $0^\circ\text{C}$  and the reaction mixture was allowed to warm to room temperature and stirred for overnight. After the completion of

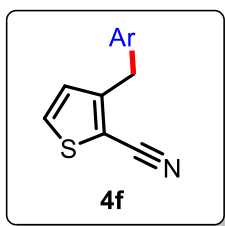
reaction (monitored by TLC), the reaction was quenched by adding water (7 mL). The resulting mixture was extracted with EtOAc (2x15 mL) and combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under *vacuo*. The resulting residue was purified by silica chromatography (EtOAc:Hexane = 20:80) to afford the corresponding alcohol product. Following the general procedure described above, **4d** was obtained after purification by column chromatography on silica gel as a brownish semi solid:  $R_f$  = 0.49 (EtOAc:Hexanes = 15:85), 40 mg (79% yield); FTIR (cm<sup>-1</sup>): 2922, 1511, 1238, 1036; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.22 – 7.18 (m, 2H), 7.15 (d,  $J$  = 5.1 Hz, 1H), 7.13 – 7.12 (m, 1H), 7.04 – 7.02 (m, 1H), 6.81 (d,  $J$  = 5.1 Hz, 1H), 6.77 (d,  $J$  = 9.0 Hz, 2H), 6.57 (d,  $J$  = 9.0 Hz, 2H), 4.35 (s, 2H), 3.95 (s, 2H), 3.74 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  152.8, 142.6, 141.9, 137.5, 136.3, 134.5, 129.9, 129.7, 128.7, 126.8, 126.6, 123.8, 115.0, 114.7, 55.9, 42.8, 34.1. HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>19</sub>ClNOS: 344.0876; found 344.0870.

#### 5.6.4e Procedure for the synthesis of (*E*)-3-(3-(3-Nitrobenzyl)thiophen-2-yl)-1-(*p*-tolyl)prop-2-en-1-one (**4e**).<sup>22</sup>



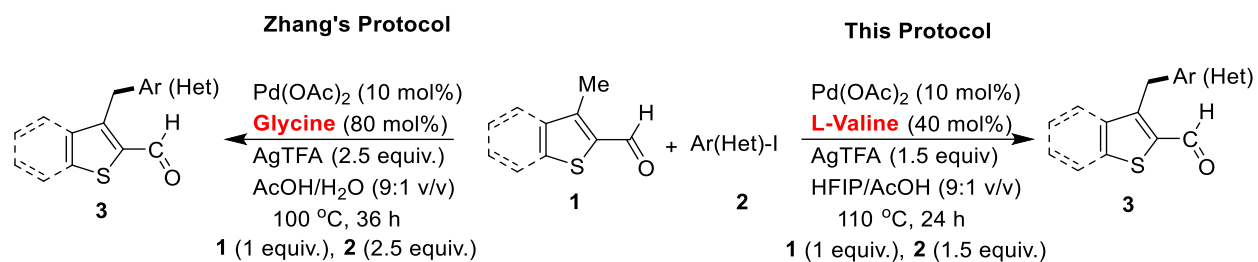
3-(3-Nitrobenzyl)thiophene-2-carbaldehyde **3ab** (0.15 mmol, 1.0 equiv.) and 1-(*p*-tolyl)-2-(triphenylphosphoranylidene)ethanone (0.18 mmol, 1.2 equiv.) were dissolved in toluene (3 mL) and refluxed for 12 h. After the completion of the reaction (monitored by TLC), the solvent was removed under *vacuo* and the residue was purified by column chromatography to furnish the desired product **4e** as yellow solid:  $R_f$  = 0.49 (EtOAc:Hexane = 12:88), mp: 128-130 °C; 43 mg (80% yield); FTIR (cm<sup>-1</sup>): 3096, 1654, 1582, 1526, 1345; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.09 – 8.01 (m, 3H), 7.91 (d,  $J$  = 8.2 Hz, 2H), 7.51 – 7.44 (m, 2H), 7.38 (d,  $J$  = 10.1 Hz, 1H), 7.35 (s, 1H), 7.30 (d,  $J$  = 7.9 Hz, 2H), 6.85 (d,  $J$  = 5.2 Hz, 1H), 4.23 (s, 2H), 2.44 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  189.2, 148.6, 144.0, 143.0, 141.1, 136.1, 135.6, 134.9, 134.2, 130.7, 129.7, 129.5, 128.7, 128.1, 123.5, 121.8, 121.4, 34.1, 21.8. HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>21</sub>H<sub>18</sub>NO<sub>3</sub>S: 364.1007; found 364.1012.

#### 5.6.4f Procedure for the synthesis of 3-(3-Methylbenzyl)thiophene-2-carbonitrile (**4f**).<sup>23</sup>



To a stirred mixture of 3-(3-methylbenzyl)thiophene-2-carbaldehyde **3ao** (0.15 mmol, 1 equiv.) and sodium azide (0.15 mmol, 1 equiv.), phosphorus oxychloride (0.75 mmol, 5 equiv.) was added (in the open vessel with a guard tube) and stirred for 1 h at room temperature. After completion of reaction (monitored by TLC), the reaction mixture was quenched with crushed ice. Then the reaction mixture was extracted with ethyl acetate (15 mL), and washed with sodium bicarbonate solution (15 mL), water (15 mL) and brine solution (15 mL). The organic layer was separated and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under vacuo and the residue was purified by column chromatography using silica gel to give the desired product **4f** as yellow liquid: *R<sub>f</sub>* = 0.49 (EtOAc:Hexanes = 14:86), 25 mg (79% yield); FTIR (cm<sup>-1</sup>): 2921, 2215, 1605, 1415; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.45 (d, *J* = 5.1 Hz, 1H), 7.22-7.18 (m, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.05 – 7.00 (m, 1H), 6.88 (d, *J* = 5.1 Hz, 1H), 4.08 (s, 2H), 2.33 (s, 3H). <sup>13</sup>C {<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 153.0, 138.7, 138.4, 132.1, 129.6, 129.1, 128.8, 127.7, 125.8, 114.4, 106.1, 36.0, 21.5. HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>12</sub>NS: 214.0690; found 214.0679.

## 5.7 Appendix-VA: Comparison of yields for the C( $\gamma$ -sp<sup>3</sup>)-H arylation heterocyclic carbonyl compounds



| Entry | Zhang's protocol <sup>4</sup> | Yield (%) | This protocol | (Yield %) |
|-------|-------------------------------|-----------|---------------|-----------|
| 1     | <b>3ab</b>                    | 22        | <b>3ab</b>    | 91        |
| 2     | <b>3ar</b>                    | 28        | <b>3ar</b>    | 75        |
| 3     | <b>3cb</b>                    | Trace     | <b>3cb</b>    | 65        |
| 4     | <b>3az</b>                    | 6         | <b>3az</b>    | 73        |
| 5     | <b>3cz</b>                    | Trace     | <b>3cz</b>    | 46        |

## 5.8 Appendix VB: <sup>1</sup>H, <sup>13</sup>C spectral data of representative compounds

| Compound No. | Figure V.X                     | Data                               | Page No |
|--------------|--------------------------------|------------------------------------|---------|
| <b>3aa</b>   | Figure V.1 and V.2             | <sup>1</sup> H and <sup>13</sup> C | 208     |
| <b>3ac</b>   | Figure V.3 and V.4             | <sup>1</sup> H and <sup>13</sup> C | 209     |
| <b>3ch</b>   | Figure V.5 and V.6             | <sup>1</sup> H and <sup>13</sup> C | 210     |
| <b>3az</b>   | Figure V.7 and V.8             | <sup>1</sup> H and <sup>13</sup> C | 211     |
| <b>4d</b>    | Figure V.9 and<br>Figure V.10  | <sup>1</sup> H and <sup>13</sup> C | 212     |
| <b>4e</b>    | Figure V.11 and<br>Figure V.12 | <sup>1</sup> H and <sup>13</sup> C | 213     |

Figure V. 1  $^1\text{H}$  NMR spectrum of **3aa**,  $\text{CDCl}_3$ , 400 MHz

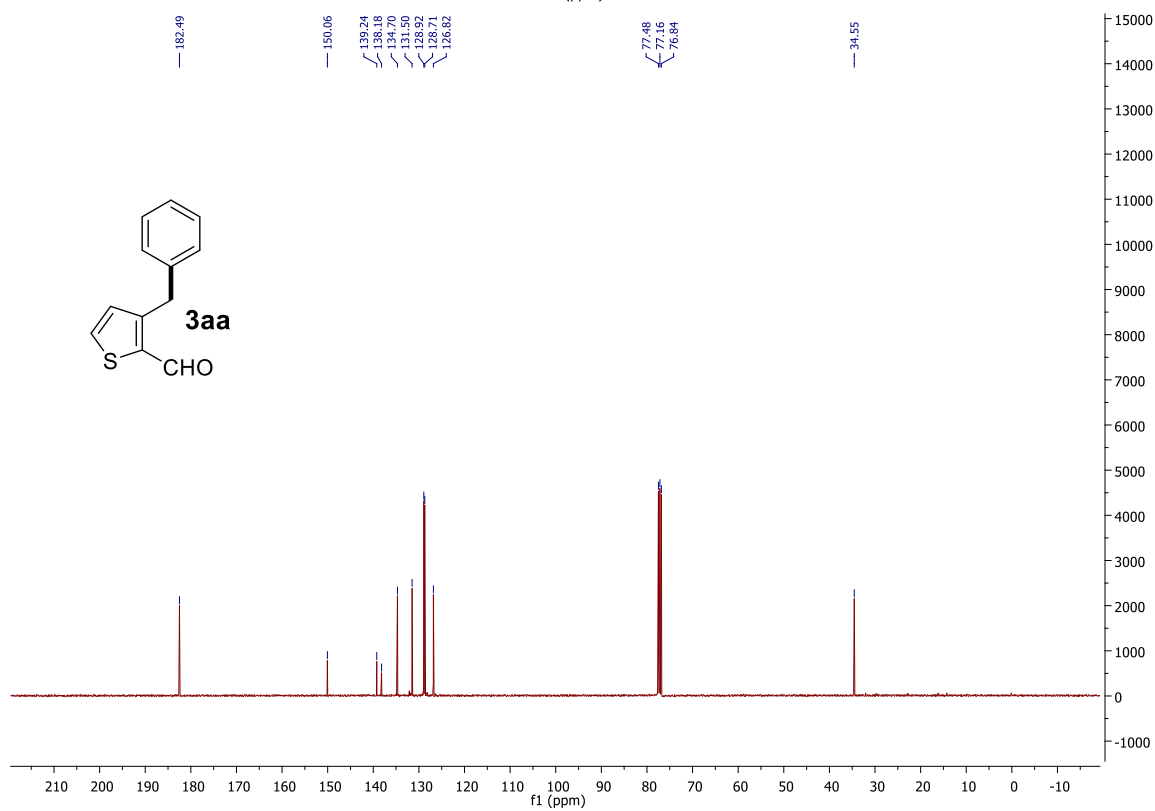
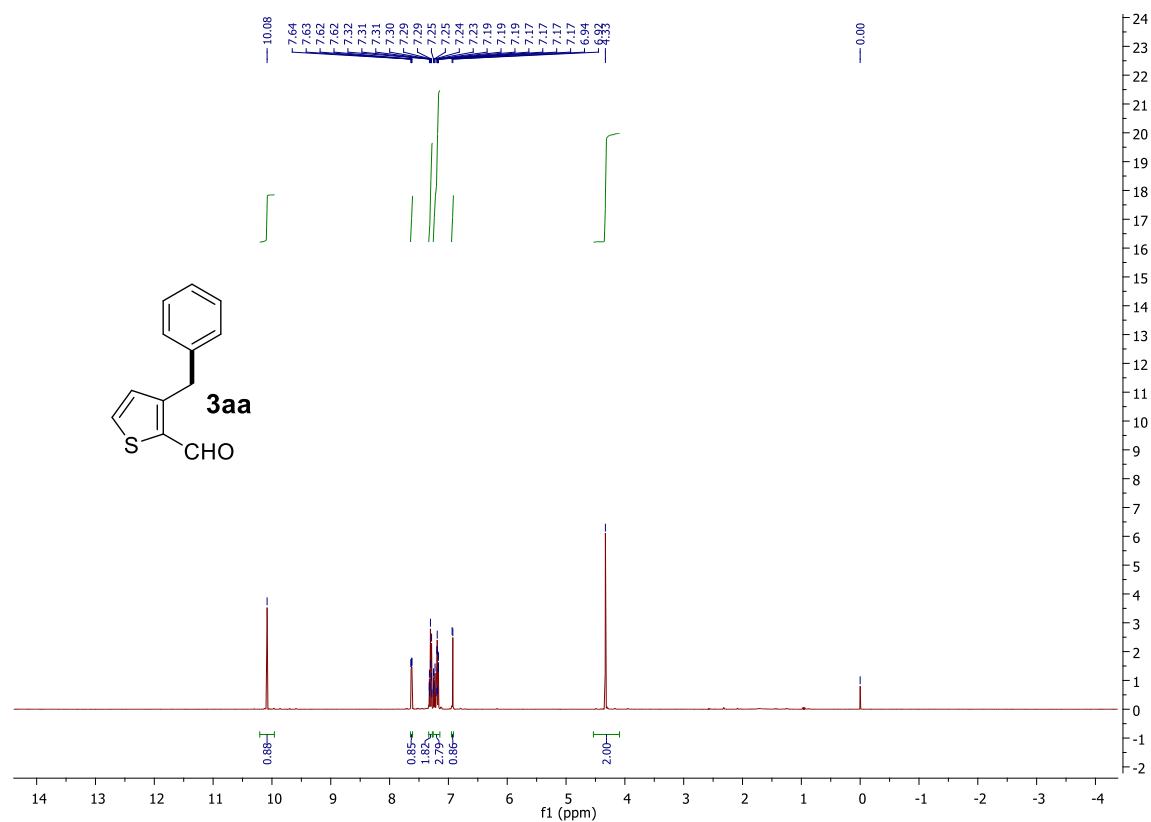


Figure V. 2  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3aa**,  $\text{CDCl}_3$ , 400 MHz

Figure V. 3  $^1\text{H}$  NMR spectrum of **3ac**,  $\text{CDCl}_3$ , 400 MHz

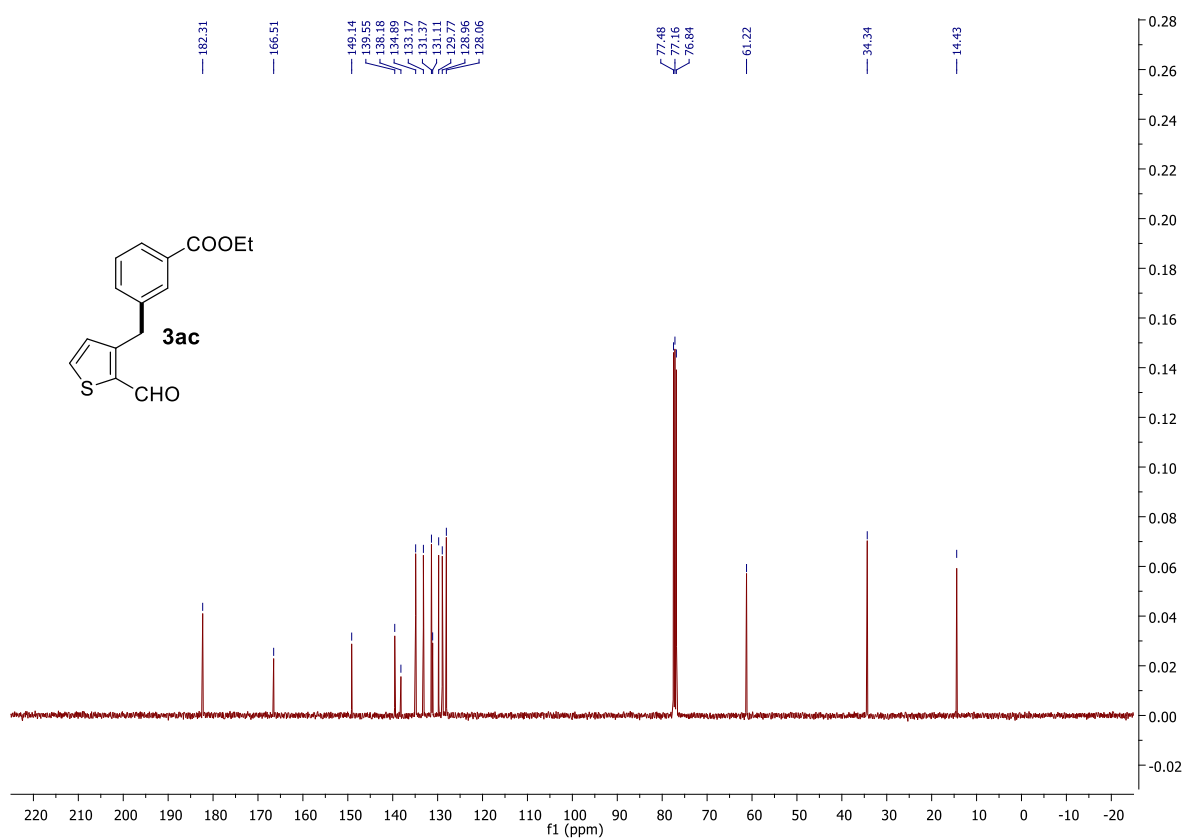
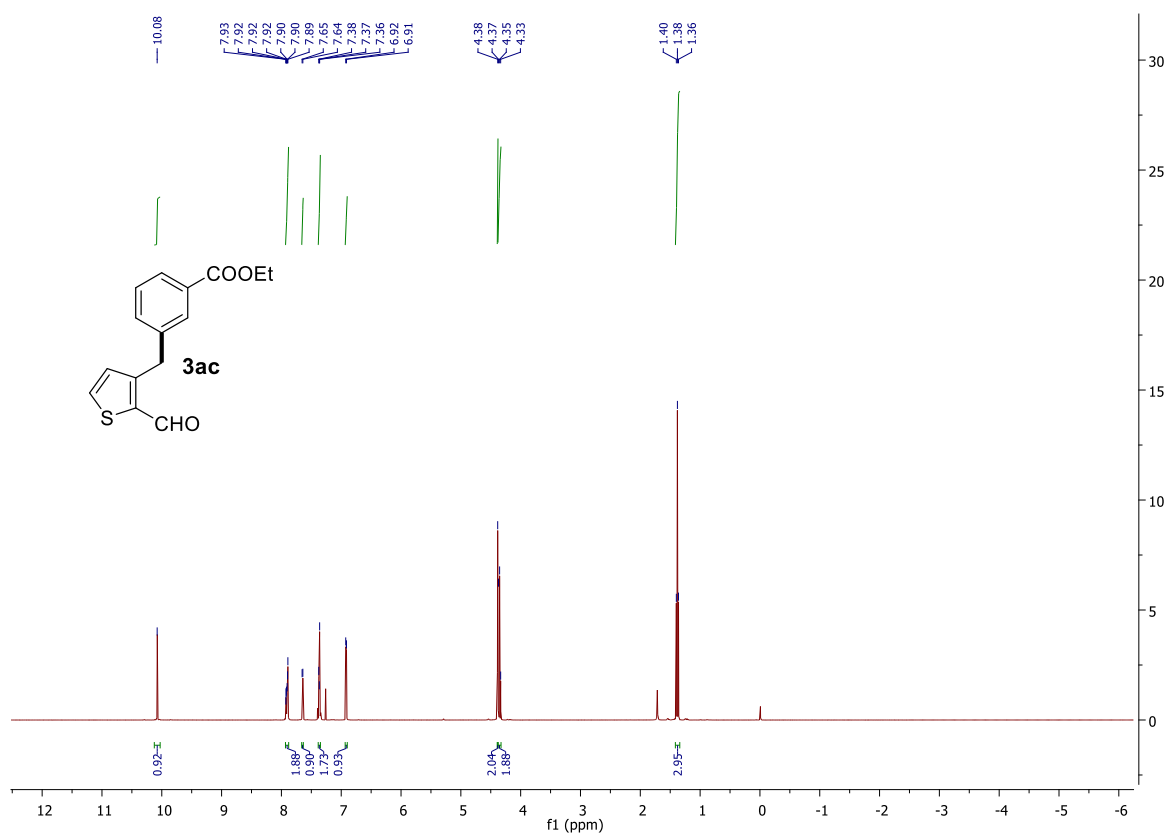


Figure V. 4  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3ac**,  $\text{CDCl}_3$ , 400 MHz

Figure V. 5  $^1\text{H}$  NMR spectrum of **3ch**,  $\text{CDCl}_3$ , 400 MHz

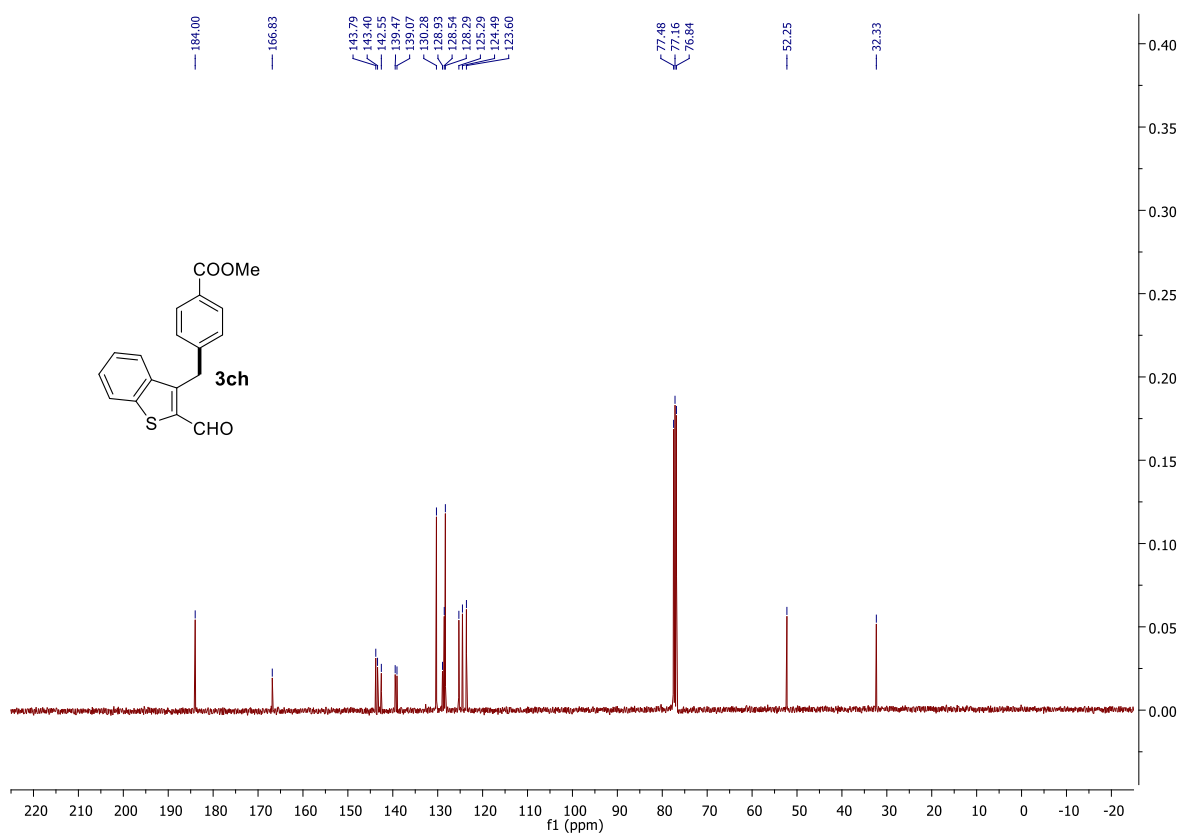
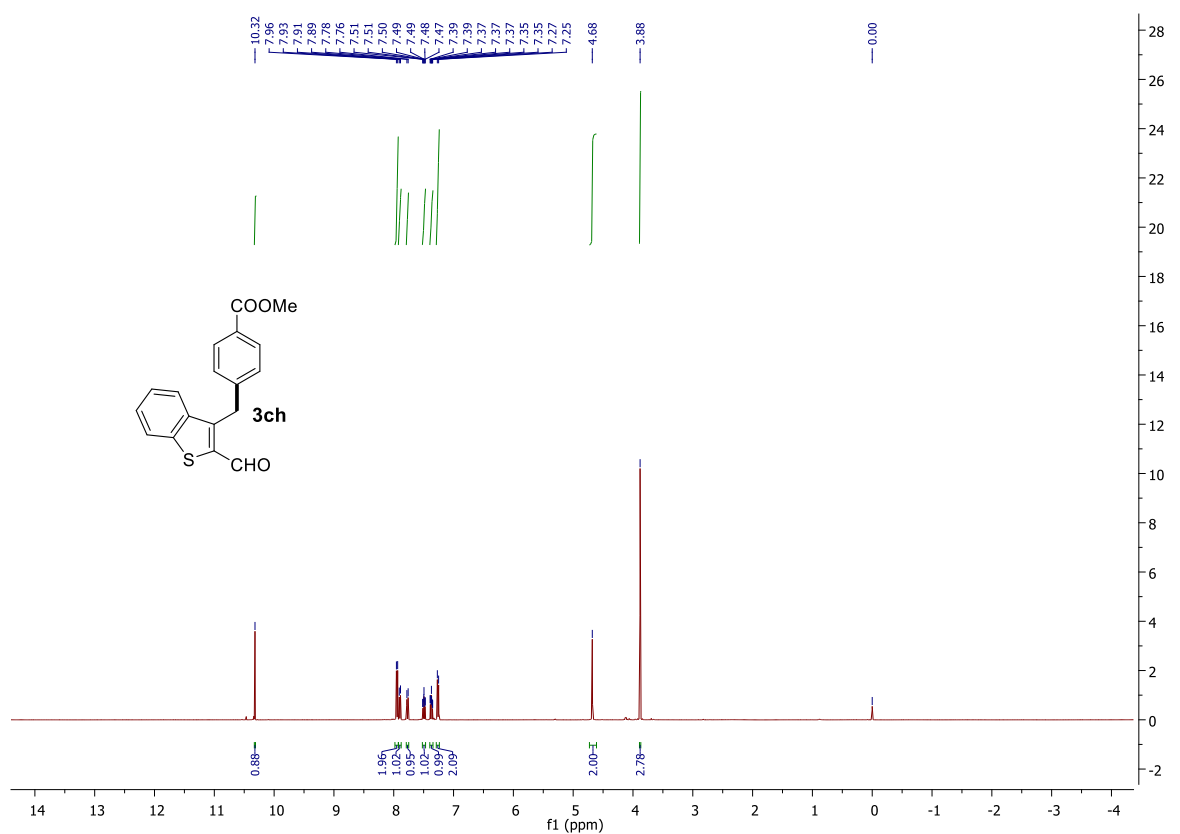


Figure V. 6  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3ch**,  $\text{CDCl}_3$ , 400 MHz



Figure V. 7  $^1\text{H}$  NMR spectrum of **3az**,  $\text{CDCl}_3$ , 400 MHz

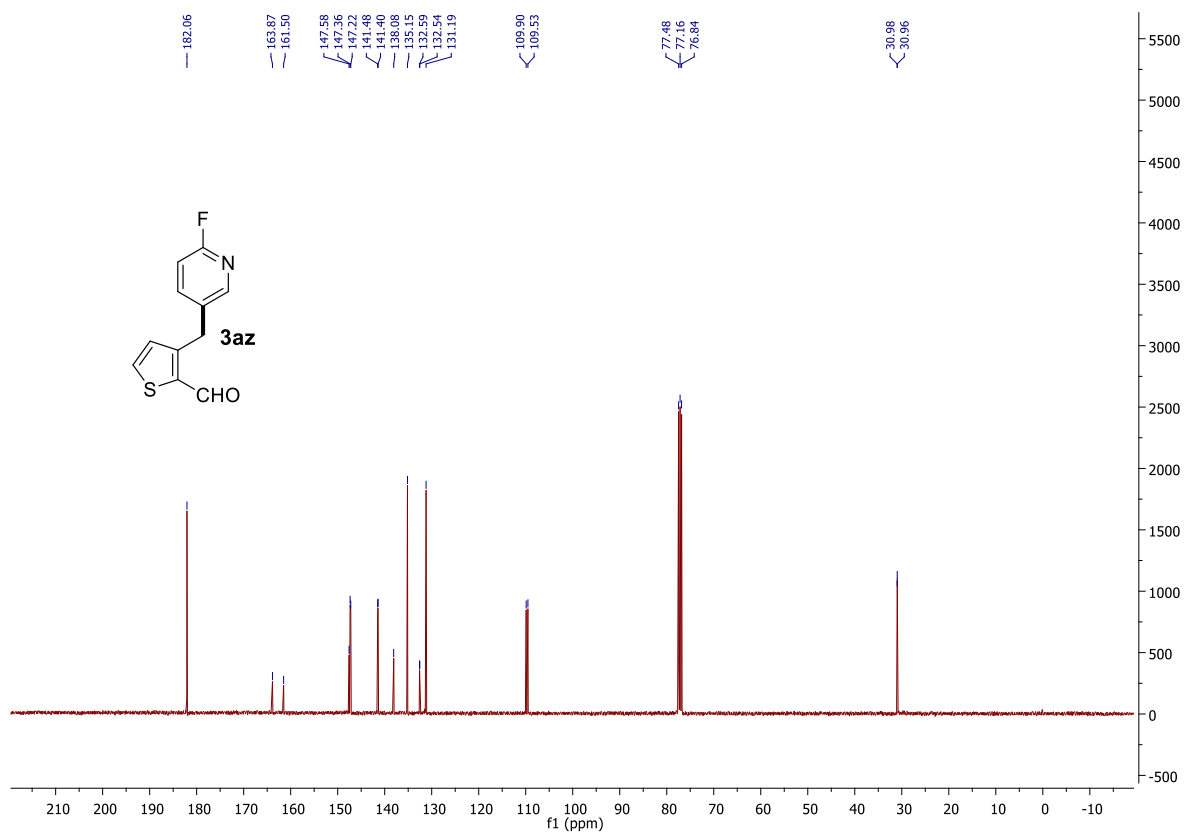
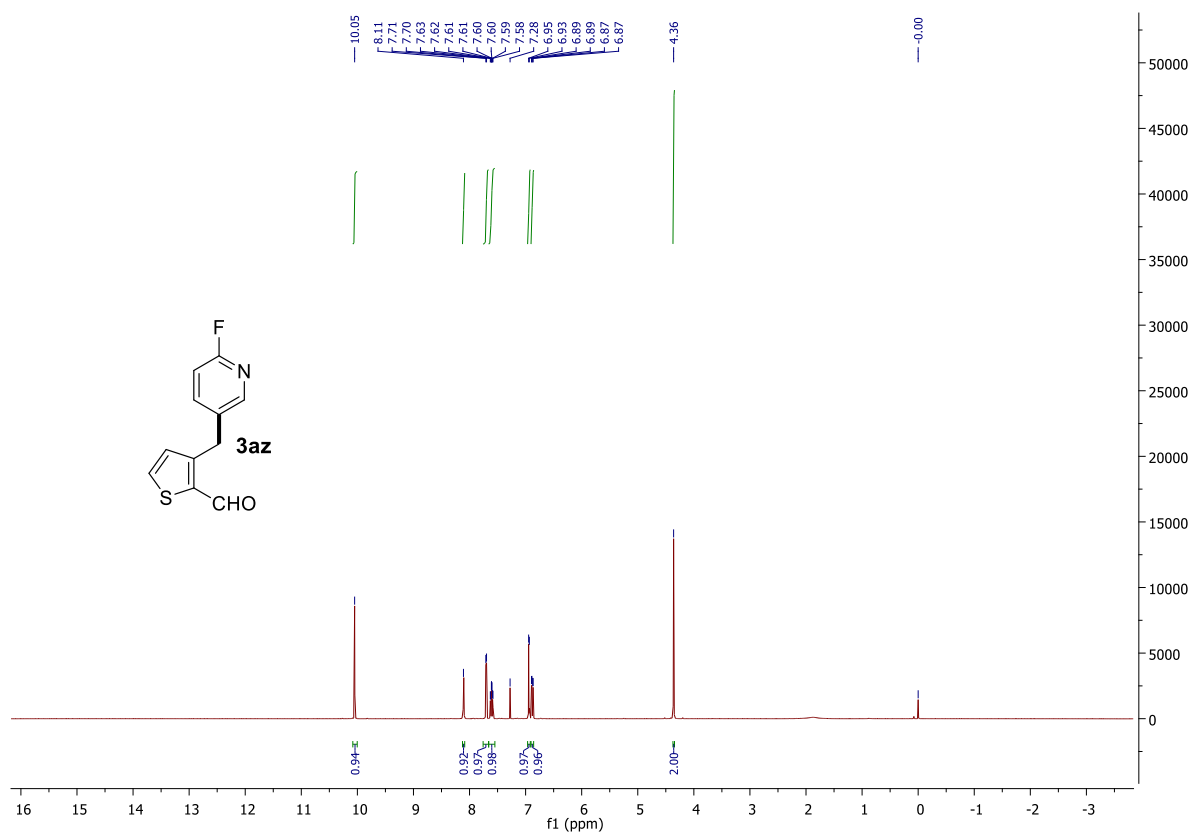


Figure V. 8  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **3az**,  $\text{CDCl}_3$ , 400 MHz

Figure V. 9  $^1\text{H}$  NMR spectrum of **4d**,  $\text{CDCl}_3$ , 400 MHz

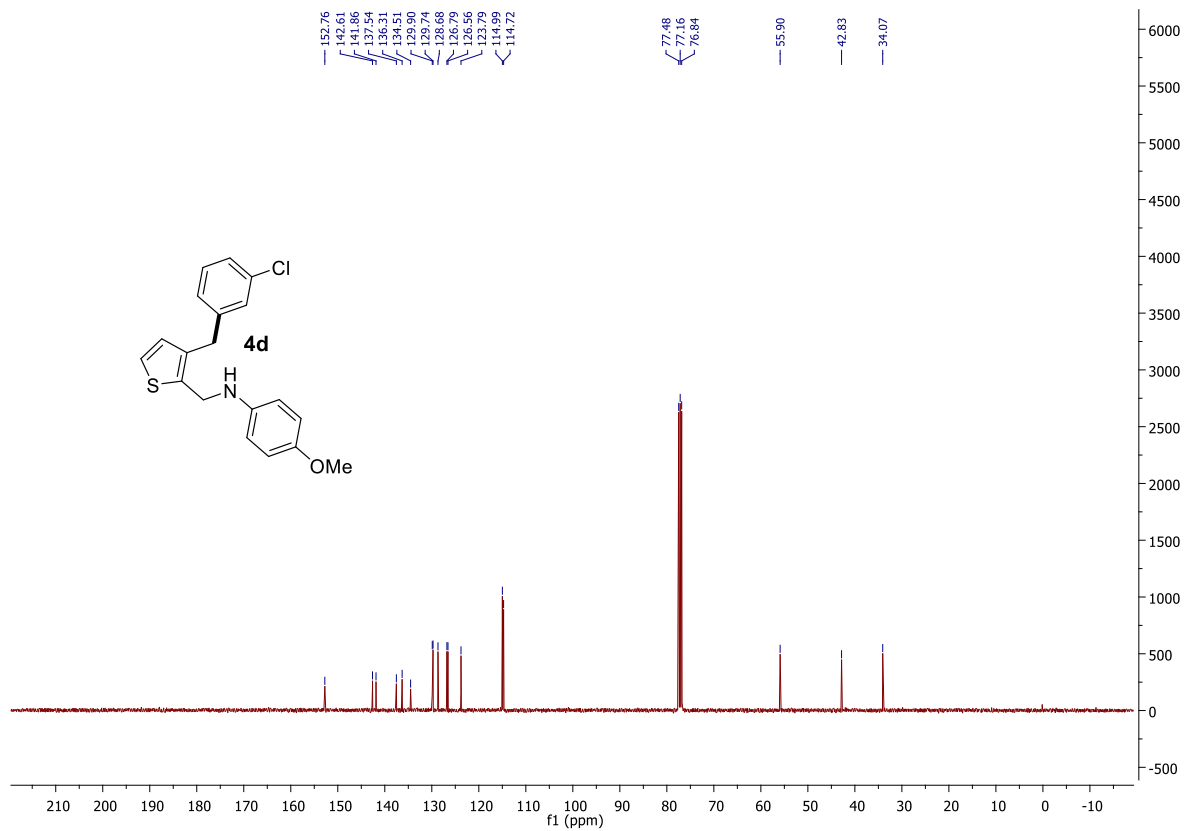
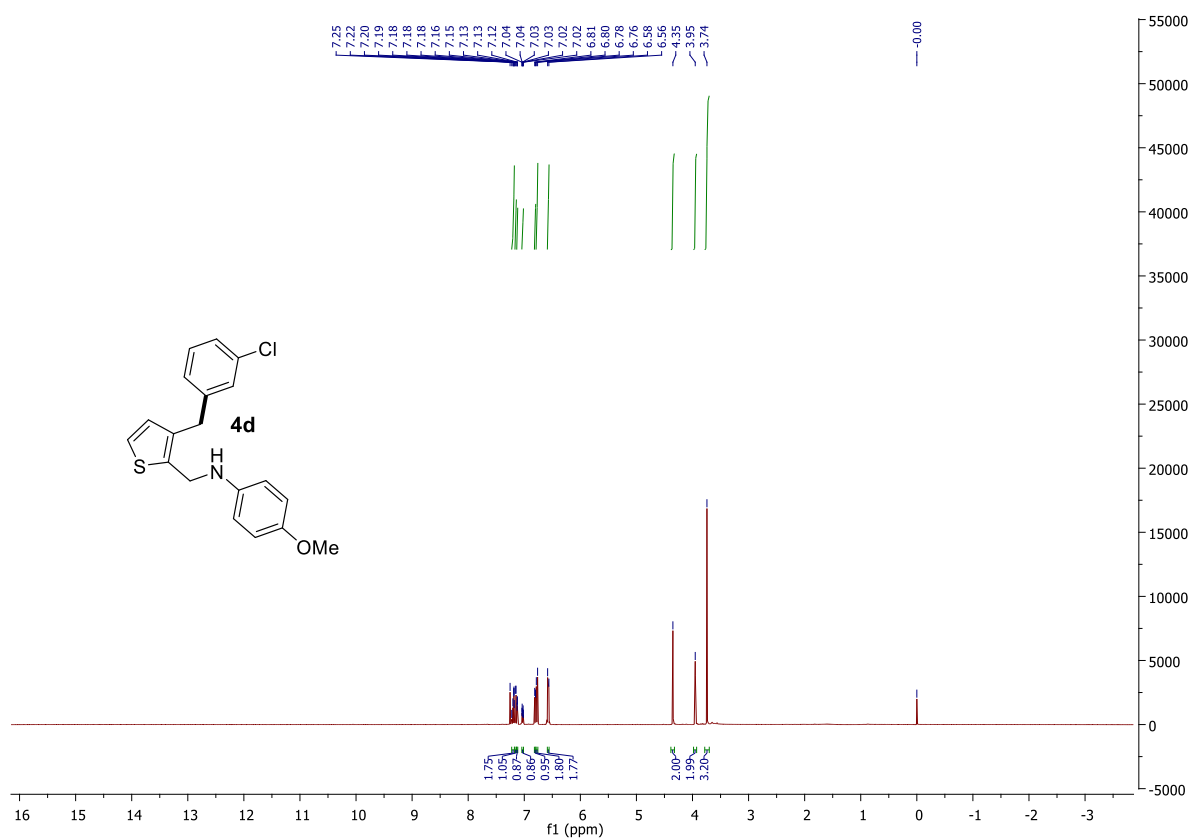


Figure V. 10  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **4d**,  $\text{CDCl}_3$ , 400 MHz

Figure V. 11  $^1\text{H}$  NMR spectrum of **4e**,  $\text{CDCl}_3$ , 400 MHz

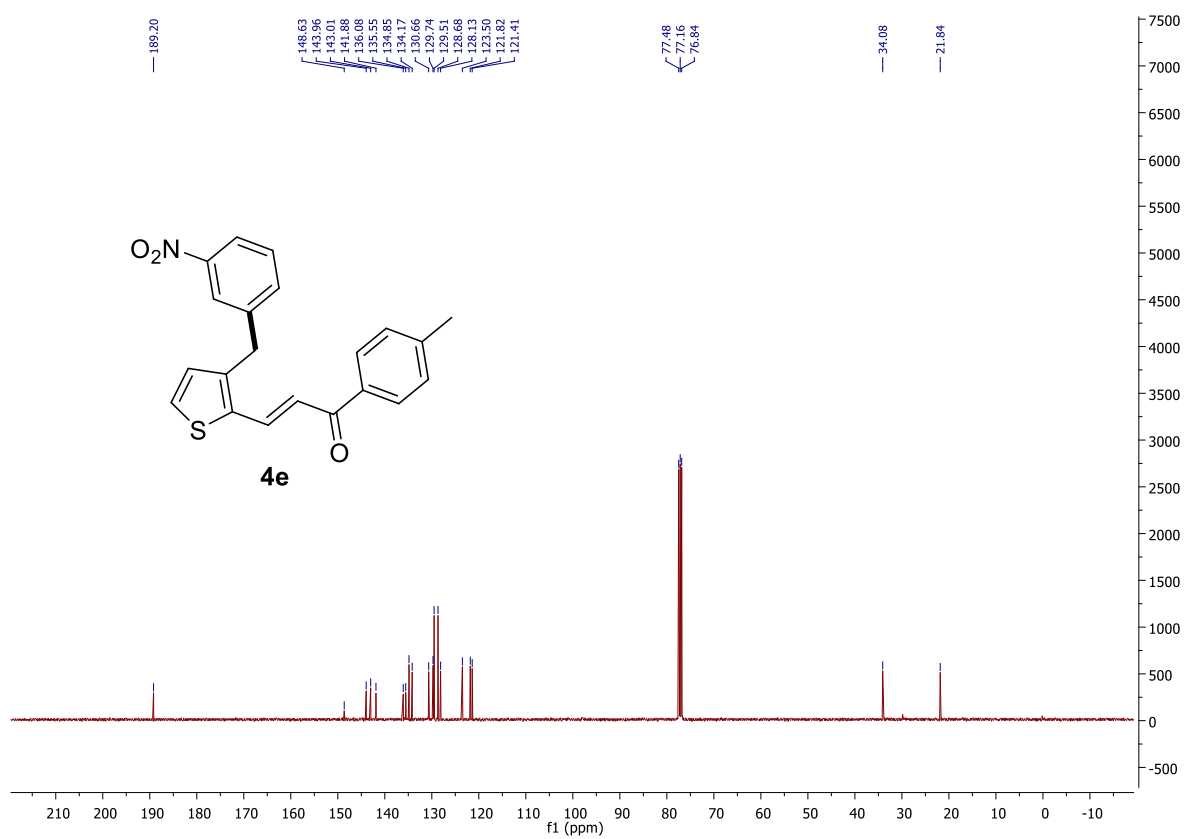
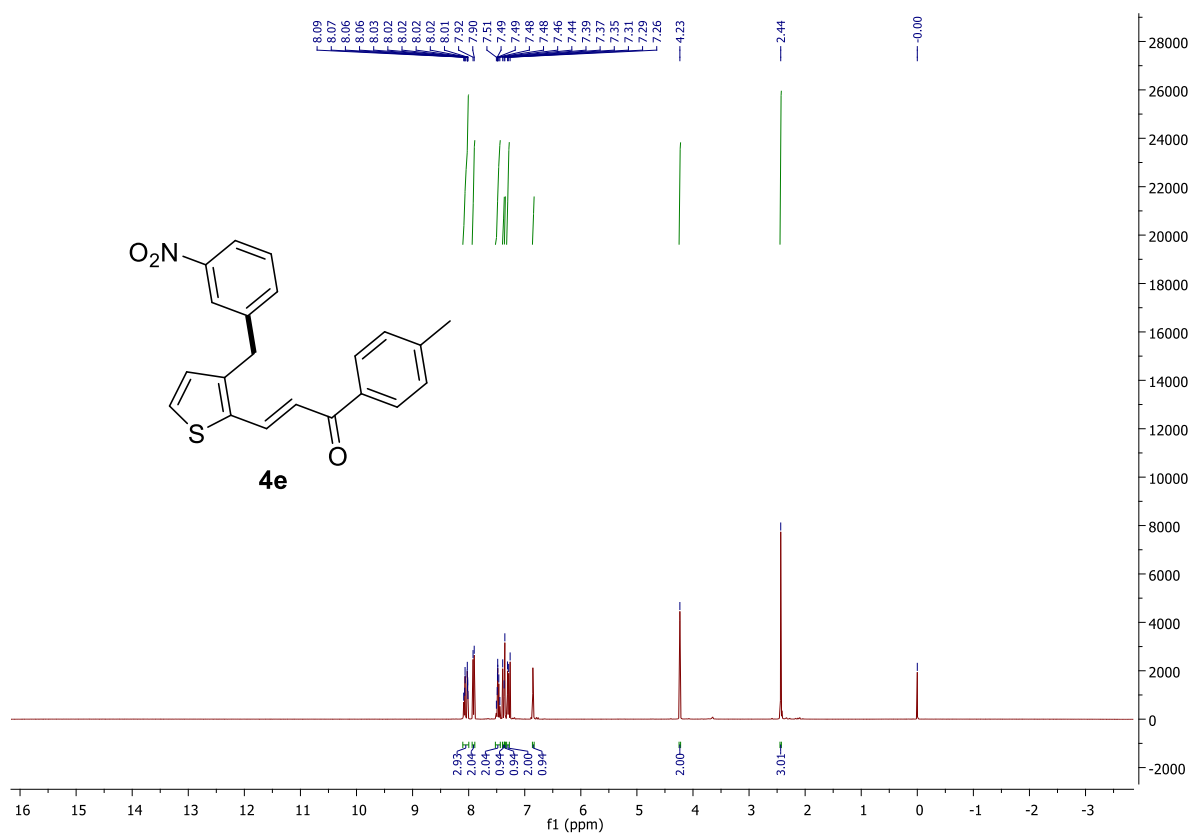


Figure V. 12  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum of **4e**,  $\text{CDCl}_3$ , 400 MHz

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### Chapter 5

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Chennakesava Reddy, Javed Y. Shaikh, and Ramakrishna G. Bhat\*

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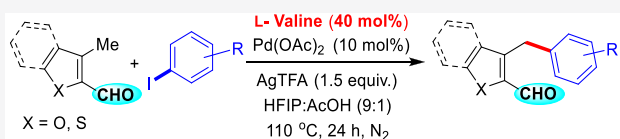
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**ABSTRACT:** An efficient and straightforward method has been developed for the synthesis of  $\beta$ -benzyl-substituted 5-membered heterocyclic carbaldehydes via transient directing-group-enabled direct  $\gamma$ -C(sp<sup>3</sup>)-H arylation of 3-methylheteroarene-2-carbaldehydes. A wide range of 3-methylheteroarene carbaldehydes undergo coupling with a variety of aryl iodides, including less reactive iodo pyridine derivatives to provide a library of highly selective functionalized products in good to excellent yields. Some of these products have been successfully utilized in synthesizing useful synthetic intermediates.



- Readily available starting materials
- Chemoselective mono  $\gamma$ -C(sp<sup>3</sup>)-H arylation
- High tolerance with less reactive iodypyridines
- Broad substrate scope
- Quick access to a diverse structural motifs
- 37 examples with yields up to 98%

## INTRODUCTION

$\beta$ -Benzyl-substituted 5-membered heterocyclic scaffolds are an important class of compounds and are extensively used as key intermediates for the synthesis of bioactive<sup>1</sup> and fused-ring compounds<sup>2,3</sup> as well as polycyclic aromatic hydrocarbons (PAHs).<sup>4</sup> Although this class of compounds is of high significance, only a few literature reports for the synthesis are known. Some of these include the Suzuki–Miyaura cross-coupling reaction of (3-formyl-2-heteroaryl)boronic acid with benzyl halides,<sup>2b,3a</sup> Vilsmeier-type formylation of 3-benzyl-heteroaromatic compounds,<sup>2c</sup> domino reaction of 1,3-enynes with mercaptoacetaldehydes,<sup>5</sup> and the Stille-type coupling reaction of 3-bromo-2-heterocarbaldehyde with tributyl(1-phenylvinyl)stannane.<sup>2a</sup> Regardless of these reports, the effective methodology for a rapid synthesis of these useful motifs with a broad substrate scope is very much limited. Many of the available methods have limitations such as poor substrate tolerance, multistep syntheses, and the requirement of commercially unavailable prefunctionalized starting materials as well as stoichiometric use of relatively expensive reagents.

During the past two decades, the C–H activation strategy has emerged as a powerful tool in organic synthetic transformations.<sup>6</sup> In general, most of the strategies require a covalently attached directing group (DG) on the substrate that forms a bidentate coordination with a transition metal to facilitate high reactivity and controlled selectivity.<sup>7</sup> The preinstallation of an auxiliary as DG in the substrate and the subsequent removal of DG post functionalization constitute additional two steps in the overall synthetic transformation. In spite of this limitation, significant progress has been made on the relatively challenging  $\gamma$ -C(sp<sup>3</sup>)-H or distal C–H activation.<sup>7c,d</sup>

Employing an auxiliary as the transient directing group has become an emerging and attractive strategy in the field of C–H activation in recent times. The transient directing-group (TDG)-enabled C–H activation reactions<sup>8</sup> proceed through in situ binding of ligand with the reacting substrate followed by coordination to the metal in a reversible manner. The TDG bears intrinsic advantages of free installation and effortless removal of ligand without disturbing the functionality of the substrate. In this direction, various groups have disclosed the use of new as well as modified transient directing groups for the C–H functionalization of carbonyl compounds<sup>9</sup> and free amino derivatives.<sup>10</sup>

Since Yu's first remarkable discovery of glycine as a transient directing group,<sup>11</sup> amino acids have emerged as efficient TDGs for the selective cleavage of the C–H bond. This leads to effective C(sp<sup>2</sup>)-H functionalization and C(sp<sup>3</sup>)-H arylation of carbonyl compounds.<sup>12,13</sup> In 2016, for the first time, Yu and co-workers<sup>11</sup> as well as Hu and co-workers<sup>13</sup> independently reported the effective method for the direct benzylic C(sp<sup>3</sup>)-H arylation of benzaldehydes by employing  $\alpha$ -amino acids and acetohydrazide, respectively, as TDGs (Scheme 1a).

Very recently, Zhang and co-workers have performed glycine-enabled *ortho*-C(sp<sup>3</sup>)-H arylation of thiophene aldehydes with aryl diiodides to synthesize just two representative examples to access polycyclic aromatic hydrocarbons (PAHs).<sup>4</sup> However, we observed that this reported

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Table 1. Optimization of Reaction Conditions<sup>a</sup>

$\text{1a} + \text{2a} \xrightarrow[\text{Solvent, 110 } ^\circ\text{C, 24 h, N}_2]{\text{cat. Pd, cat. L, Additive}} \text{3aa}$

(0.2 mmol, 1 equiv)

L1, L2, L3, L4, L5, L6, L7, L8, L9

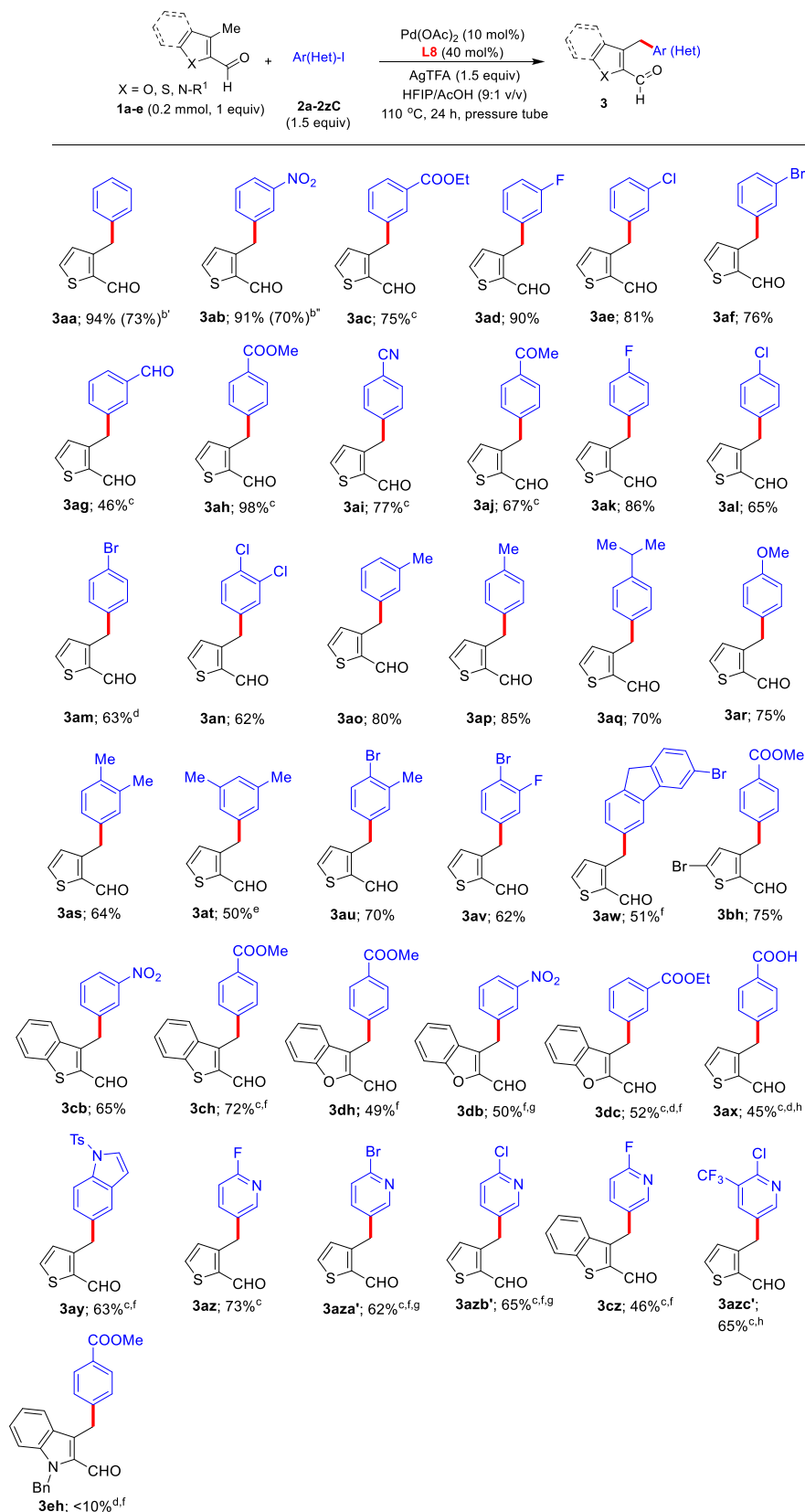
| Entry           | Pd Catalyst                | L (mol%)       | Additive     | 2a (equiv.) | Solvent                          | Yield 3aa (%) <sup>b</sup> |
|-----------------|----------------------------|----------------|--------------|-------------|----------------------------------|----------------------------|
| 1               | Pd(OAc) <sub>2</sub>       | L1 (20)        | AgOAc        | 3           | AcOH/H <sub>2</sub> O (1:1, v/v) | traces                     |
| 2               | Pd(OAc) <sub>2</sub>       | L2 (40)        | AgTFA        | 2           | HFIP/AcOH(5:1, v/v)              | traces                     |
| 3               | Pd(OAc) <sub>2</sub>       | L3 (40)        | AgTFA        | 2           | AcOH/H <sub>2</sub> O (9:1, v/v) | 53                         |
| 4               | Pd(OAc) <sub>2</sub>       | L2 (40)        | AgTFA        | 2           | HFIP/AcOH (9:1, v/v)             | 20                         |
| 5               | Pd(OAc) <sub>2</sub>       | L3 (40)        | AgTFA        | 2           | HFIP/AcOH (9:1, v/v)             | 55                         |
| 6               | Pd(OAc) <sub>2</sub>       | L4 (40)        | AgTFA        | 2           | HFIP/AcOH (9:1, v/v)             | <5                         |
| 7               | Pd(OAc) <sub>2</sub>       | L5 (40)        | AgTFA        | 2           | HFIP/AcOH (9:1, v/v)             | 59                         |
| 8               | Pd(OAc) <sub>2</sub>       | L6 (40)        | AgTFA        | 2           | HFIP/AcOH (9:1, v/v)             | 60                         |
| 9               | Pd(OAc) <sub>2</sub>       | L7 (40)        | AgTFA        | 2           | HFIP/AcOH (9:1, v/v)             | 68                         |
| 10              | Pd(OAc) <sub>2</sub>       | L8 (40)        | AgTFA        | 2           | HFIP/AcOH (9:1, v/v)             | 93                         |
| 11              | Pd(OAc) <sub>2</sub>       | L9 (40)        | AgTFA        | 2           | HFIP/AcOH (9:1, v/v)             | 38                         |
| 12              | Pd(OAc) <sub>2</sub>       | L8 (40)        | AgTFA        | 2           | HFIP (1.6 mL)                    | 37                         |
| 13              | Pd(OAc) <sub>2</sub>       | L8 (40)        | AgTFA        | 2           | AcOH (1.6 mL)                    | 75                         |
| 14              | Pd(OAc) <sub>2</sub>       | L8 (40)        | AgTFA        | 2           | HFIP/AcOH (6:1, v/v)             | 70                         |
| 15              | Pd(OAc) <sub>2</sub>       | L8 (40)        | AgTFA        | 2           | HFIP/AcOH (3:1, v/v)             | 75                         |
| 16              | Pd(TFA) <sub>2</sub>       | L8 (40)        | AgTFA        | 2           | HFIP/AcOH (9:1, v/v)             | 80                         |
| 17 <sup>c</sup> | Pd(OAc) <sub>2</sub>       | L8 (40)        | AgOAc        | 2           | HFIP/AcOH (9:1, v/v)             | 71                         |
| 18              | Pd(OAc) <sub>2</sub>       | L8 (40)        | AgTFA        | 2           | HFIP/AcOH (9:1, v/v)             | 72                         |
| <b>19</b>       | <b>Pd(OAc)<sub>2</sub></b> | <b>L8 (40)</b> | <b>AgTFA</b> | <b>1.5</b>  | <b>HFIP/AcOH (9:1, v/v)</b>      | <b>94</b>                  |
| 20              | Pd(OAc) <sub>2</sub>       | L8 (40)        | AgTFA        | 1           | HFIP/AcOH (9:1, v/v)             | 70                         |
| 21 <sup>d</sup> | Pd(OAc) <sub>2</sub>       | L8 (40)        | AgTFA        | 0.8         | HFIP/AcOH (9:1, v/v)             | 78                         |
| 22              | Pd(OAc) <sub>2</sub>       | L8 (40)        | AgTFA        | 1.5         | AcOH/H <sub>2</sub> O (9:1, v/v) | 47                         |
| 23              | Pd(OAc) <sub>2</sub>       | L8 (40)        | AgTFA        | 1.5         | AcOH/H <sub>2</sub> O (5:1, v/v) | 54                         |
| 24              | -                          | L8 (40)        | AgTFA        | 1.5         | HFIP/AcOH (9:1, v/v)             | NR                         |
| 25              | Pd(OAc) <sub>2</sub>       | L8 (40)        | -            | 1.5         | HFIP/AcOH (9:1, v/v)             | 15                         |
| 26              | Pd(OAc) <sub>2</sub>       | -              | AgTFA        | 1.5         | HFIP/AcOH (9:1, v/v)             | NR                         |

<sup>a</sup>Reaction conditions: **1a** (0.2 mmol), PhI (**2a**), Pd catalyst (10 mol %), ligand L (20–40 mol %), additive (0.3 mmol), solvent (1.6 mL), 110 °C, N<sub>2</sub>, 24 h. <sup>b</sup>Isolated yields based on **1a** using column chromatography. <sup>c</sup>HFIP (0.72 mL)/AcOH (0.08 mL). <sup>d</sup>Isolated yield based on **2a**.

the optimum reaction conditions to furnish the desired product **3eh** in a very poor yield (~10%). In spite of our repeated attempts, we could not isolate pure **3eh** using column chromatography. Further, the practicality of this protocol has been established by scaling up (0.3–0.5 g) the reactions to afford the desired products **3aa** and **3ab** in good yields (see Table 2).

The electron-deactivating halo groups (F, Cl, Br); strong EWGs such as nitro, nitrile, ester, aldehyde, and keto groups; and EDGs such as methyl, isopropyl, and methoxy tolerated the optimized reaction conditions to afford the corresponding functionalized products smoothly. The protocol worked smoothly with relatively less reactive iodo pyridine derivatives.

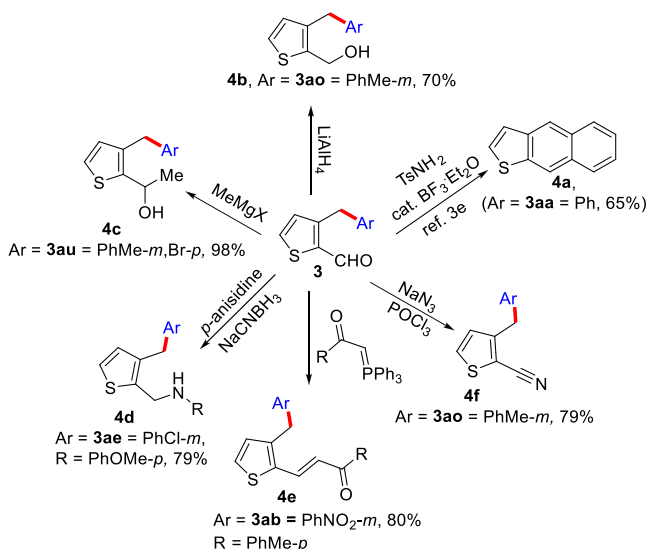
Owing to the importance of benzyl-heteroaryl carbaldehydes as active synthetic intermediates, we successfully utilized them

Table 2. Library of 3-Benzyl-Substituted 5-Membered Heteroarene Carbaldehydes<sup>a,b</sup>

<sup>a</sup>Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), Pd(OAc)<sub>2</sub> (0.02 mmol), AgTFA (0.3 mmol), L8 (0.08 mmol), HFIP (1.44 mL), AcOH (0.16 mL), 110 °C, 24 h. <sup>b</sup>Isolated yields; <sup>b</sup>0.3 g scale; <sup>b</sup>0.5 g scale. <sup>c</sup>**1** (0.24 mmol), **2** (0.2 mmol). <sup>d</sup>36 h. <sup>e</sup>30 h. <sup>f</sup>Pd(OAc)<sub>2</sub> (0.03 mmol); AgTFA (0.4 mmol), 113 °C. <sup>g</sup>40 h. <sup>h</sup>Pd(OAc)<sub>2</sub> (0.03 mmol) and AgTFA (0.6 mmol).

(**3aa**, **3ao**, **3au**, **3ae**, **3ab**) for synthesizing very useful compounds as an application to this strategy (Scheme 2).

**Scheme 2.** Some of the Selective Synthetic Transformations as an Application to the Strategy



The functionalized fused compound **4a** was synthesized starting from **3aa** following the reported procedure.<sup>3b</sup> The fused naphtho-thiophene **4a** was obtained in 65% yield through the condensation reaction of **3aa** in the presence of  $\text{TsNH}_2$  and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ . It is very important to note that we could synthesize **4a** in fewer synthetic steps than the reported procedure.<sup>3b</sup>

Likewise, benzothiophene derivatives can be easily synthesized using this protocol.<sup>2b</sup> The LAH reduction of **3ao** and the Grignard addition of  $\text{MeMgBr}$  with **3au** afforded the corresponding alcohols **4b** and **4c** in 70 and 98% yields, respectively. The reductive amination of **3ae** in the presence of *p*-anisidine and  $\text{NaCNBH}_3$  gave the corresponding substituted amine **4d** in 79% yield. The reaction of **3ab** with the Wittig reagent and the reaction of **3ao** under Schmidt-type reaction conditions afforded the corresponding  $\alpha,\beta$ -unsaturated carbonyl compound **4e** and 2-cyano 3-benzylthiophene derivative **4f**, respectively (Scheme 2). There is a great scope of this strategy to generate a diverse range of structural motifs as crucial intermediates for biologically active molecules, target organic synthesis, and pharmaceuticals.

## CONCLUSIONS

In summary, we have developed an efficient and straightforward palladium-catalyzed strategy for the direct arylation of unactivated  $\gamma\text{-C}(\text{sp}^3)\text{-H}$  bond of 3-methylheteroarene-2-carbaldehydes with a variety of aryl iodides by employing (*S*)-2-amino-3-methylbutanoic acid (*L*-valine) as a transient ligand. The highly regio- and chemoselective reaction of various 3-methylheteroarene carbaldehydes with a wide range of aryl iodides facilitated a straightforward access to a library of  $\beta$ -benzyl-substituted 5-membered heterocyclic carbaldehydes in good to excellent yields. The main importance of this strategy is the high functional group tolerance, broad substrate scope, and the smooth arylation of even relatively less reactive pyridine-based heteroaryl iodides. A further investigation to

synthesize different functionalized heterocycles and enantioselective bioactive intermediates is under progress.

## EXPERIMENTAL SECTION

**General Information.** All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF<sub>254</sub> precoated aluminum backed plates (2.5 mm) with detection by UV light. Column chromatography was performed using silica gel (100–200 mesh) eluting with petroleum ether and ethyl acetate. Melting points of the compounds are uncorrected. IR spectra of compounds were recorded as thin films or KBr pellets. Unless otherwise specified, proton ( $^1\text{H}$ ) and proton-decoupled carbon [ $^{13}\text{C}\{^1\text{H}\}$ ] NMR spectra were recorded operating at 400 MHz for proton and 100 MHz for carbon nuclei. For  $^1\text{H}$  NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. Chemical shifts ( $\delta$ ) are reported in ppm downfield from  $\text{CDCl}_3$  ( $\delta = 7.26$  ppm) for  $^1\text{H}$  NMR and relative to the central  $\text{CDCl}_3$  resonance ( $\delta = 77.16$  ppm) for  $^{13}\text{C}$  NMR spectroscopy. Mass samples were analyzed by high-resolution mass spectrometry (HRMS) using electrospray ionization (ESI-TOF). All of the reactions were performed in anhydrous solvent under a nitrogen atmosphere.

Starting materials (3-methylheteroaryl-2-carbaldehydes (**1a**, **1c**)) and aryl iodides (**2a–x**, **2y–zc'**) were commercially obtained from Sigma-Aldrich, Alfa Aesar, Avra Synthesis Pvt. Ltd., etc. and were utilized as such without further purification. Further, 5-bromo-3-methylthiophene-2-carbaldehyde (**1b**)<sup>15</sup> and 5-iodo-1-tosyl-1H-indole (**2y**)<sup>16</sup> compounds were synthesized by following literature procedures.<sup>15,16</sup>

**Synthetic Procedure for the LAH Reduction<sup>17a</sup> of 3-Methylbenzofuran-2-carboxylic Acid Followed by Pyridinium Chlorochromate (PCC)-Based Oxidation<sup>17b</sup> and Synthesis of 3-Methylbenzofuran-2-carbaldehyde (**1d**).** To a stirred solution of 3-methylbenzofuran-2-carboxylic acid (400 mg, 2.27 mmol, 1 equiv) in tetrahydrofuran (THF; 15 mL) at 0 °C under Ar was added  $\text{LiAlH}_4$  (4.54 mmol, 2 equiv). Then, the mixture was allowed to warm to room temperature and stirred overnight at 25–30 °C. After the complete consumption of the starting material (monitored by TLC), the reaction mass was cooled to 0 °C and quenched carefully with sat.  $\text{NH}_4\text{Cl}$  solution (10 mL). The mixture was extracted with  $\text{EtOAc}$  (2  $\times$  30 mL) and combined organic phase and dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo to obtain the corresponding crude alcohol, which was used as such for the next step PCC oxidation reaction without any further purification. To another dry 100 mL round-bottom (RB) flask containing the above crude alcoholic solution in dichloromethane (DCM; 15 mL) was charged pyridinium chlorochromate (3.40 mmol, 1.5 equiv) at 0–5 °C under a nitrogen atmosphere and stirred at room temperature (RT) for 5 h. After the completion of reaction (monitored by TLC), the solvent was distilled off completely under vacuum to obtain the corresponding crude aldehyde, and the crude was purified by silica chromatography ( $\text{EtOAc}$ /petroleum ether = 10:90) to obtain 3-methylbenzofuran-2-carbaldehyde (**1d**) as a white solid:  $R_f = 0.49$  ( $\text{EtOAc}$ /petroleum ether = 10:90), mp: 86–88 °C; 210 mg (60% yield);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.34 (s, 1H), 7.89 (d,  $J = 7.6$  Hz, 1H), 7.86 (d,  $J = 8.1$  Hz, 1H), 7.53–7.49 (m, 1H), 7.44 (dd,  $J = 8.0, 7.1$  Hz, 1H), 2.79 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  184.1, 143.1, 142.2, 140.2, 137.6, 128.5, 124.9, 124.0, 123.4, 12.2.

**Synthetic Procedure for N-benzylation<sup>18</sup> of 3-Methyl-1H-indole-2-carbaldehyde and Synthesis of 1-Benzyl-3-methyl-1H-indole-2-carbaldehyde (**1e**).** To a stirred solution of  $\text{NaH}$  (3.14 mmol, 2 equiv) in dry THF (10 mL) was charged 3-methyl-1H-indole-2-carbaldehyde (250 mg, 1.57 mmol, 1 equiv) at 0 °C under Ar and stirred at the same temperature for 10–15 min. Then, benzyl bromide (1.1 equiv) was charged gradually at 0–5 °C, and the reaction mixture was allowed to warm to room temperature and stirred overnight at 25–30 °C. After the complete consumption of the starting material (monitored by TLC), the reaction mass was cooled to 5 °C and quenched carefully with few drops of MeOH followed by the addition



of water (10 mL). The mixture was extracted with EtOAc (2 × 25 mL), and the combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The corresponding crude product was purified by silica chromatography (EtOAc/petroleum ether = 15:85) to obtain 1-benzyl-3-methyl-1H-indole-2-carbaldehyde (**1e**) as a pale yellow solid: *R*<sub>f</sub> = 0.49 (EtOAc/petroleum ether = 15:85), mp: 80–82 °C; 313 mg (80% yield); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.15 (s, 1H), 7.72–7.70 (m, 1H), 7.39–7.30 (m, 2H), 7.25–7.13 (m, 4H), 7.08–7.05 (m, 2H), 5.78 (s, 2H), 2.65 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 181.3, 139.6, 138.2, 130.6, 128.6, 127.6, 127.3, 127.2, 126.6, 121.41, 120.43, 110.80, 47.8, 8.7. HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>16</sub>NO: 250.1231; found, 250.1218.

**General Procedures for  $\gamma$ -C(sp<sup>3</sup>)–H Arylation of 3-Methylheteroarene-2-carbaldehydes Using a Transient Directing Group.** *General Procedure A.* A 15 mL dry pressure tube equipped with a stir bar was charged with 3-methylthiophene-2-carbaldehyde **1a** (25.2 mg, 0.20 mmol, 1.0 equiv), iodobenzene **2a** (61.1 mg, 0.3 mmol, 1.5 equiv), Pd(OAc)<sub>2</sub> (4.5 mg, 0.02 mmol, 0.1 equiv), **L8** (9.36 mg, 0.08 mmol, 0.4 equiv), and AgTFA (61.4 mg, 0.3 mmol, 1.5 equiv), followed by the addition of a mixture of HFIP (1.44 mL) and AcOH (0.16 mL) at room temperature. Then, the resulting reaction mixture was degassed under a N<sub>2</sub> atmosphere for 2 min and stirred vigorously at room temperature for 15 min. Then, the reaction mixture was heated to 110 °C for 24 h in a heating block, after which it was cooled to room temperature, followed by dilution with EtOAc (15 mL) and subsequent filtration through a pad of celite. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel to furnish the desired product **3aa** in 94% yield (38 mg) as a yellow oil.

*General Procedure B.* A 15 mL dry pressure tube equipped with a stir bar was charged with ethyl 3-iodobenzoate **2c** (56 mg, 0.2 mmol, 1.0 equiv), 3-methylthiophene-2-carbaldehyde **1a** (30.7 mg, 0.24 mmol, 1.2 equiv), Pd(OAc)<sub>2</sub> (4.5 mg, 0.02 mmol, 0.1 equiv), **L8** (9.36 mg, 0.08 mmol, 0.4 equiv), and AgTFA (61.4 mg, 0.3 mmol, 1.5 equiv), followed by the addition of a mixture of HFIP (1.44 mL) and AcOH (0.16 mL) at room temperature. Then, the resulting reaction mixture was degassed under a N<sub>2</sub> atmosphere for 2 min and stirred vigorously at room temperature for 15 min followed by heating at 110 °C for 24 h in a heating block, after which the reaction mixture was cooled to room temperature followed by dilution with EtOAc (15 mL). Later, the reaction mixture was filtered through a pad of celite and the filtrate was then concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the desired product **3ac** in 75% yield (41 mg) as brown semisolid.

Following general procedure B, the compounds **3ac**, **3ag–aj**, **3dh**, and **3ay–azc** were synthesized (as shown in Scheme 2).

**3-Benzylthiophene-2-carbaldehyde (3aa).** Following the general procedure A described above, **3aa** was obtained after purification by column chromatography on silica gel as a yellow oil: *R*<sub>f</sub> = 0.49 (EtOAc/petroleum ether = 10:90), 38 mg (94% yield); FTIR (cm<sup>−1</sup>): 3028, 1652, 1424, 1225; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.08 (s, 1H), 7.63 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.34–7.27 (m, 2H), 7.25–7.15 (m, 3H), 6.93 (d, *J* = 5.0 Hz, 1H), 4.33 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 182.5, 150.1, 139.2, 138.9, 134.7, 131.5, 128.9, 128.7, 126.8, 34.6. HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>11</sub>OS: 203.0531; found, 203.0532.

**3-(3-Nitrobenzyl)thiophene-2-carbaldehyde (3ab).** Following the general procedure A described above, **3ab** was obtained after purification by column chromatography on silica gel as a yellow-brownish solid: *R*<sub>f</sub> = 0.46 (EtOAc/petroleum ether = 12:88), mp: 86–88 °C; 45 mg (91% yield); FTIR (cm<sup>−1</sup>): 3099, 1658, 1526, 1350, 717; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.05 (s, 1H), 8.12–8.06 (m, 2H), 7.72 (d, *J* = 5.0 Hz, 1H), 7.56–7.47 (m, 2H), 6.97 (d, *J* = 5.0 Hz, 1H), 4.48 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 182.1, 148.6, 147.3, 141.3, 138.3, 135.2, 134.9, 131.3, 129.8, 123.6, 122.0, 34.2. HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>10</sub>NO<sub>3</sub>S: 248.0381; found, 248.0384.

**Ethyl 3-((2-Formylthiophen-3-yl)methyl)benzoate (3ac).** Following the general procedure B described above, **3ac** was obtained after

purification by column chromatography on silica gel as a brown semisolid: *R*<sub>f</sub> = 0.46 (EtOAc/petroleum ether = 12:88), 41 mg (75% yield); FTIR (cm<sup>−1</sup>): 2982, 1712, 1656, 1273, 1188; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.08 (s, 1H), 7.93–7.89 (m, 2H), 7.65 (d, *J* = 5.0 Hz, 1H), 7.38–7.36 (m, 2H), 6.92 (d, *J* = 5.0 Hz, 1H), 4.38 (s, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 182.3, 166.5, 149.1, 139.6, 138.2, 134.9, 133.8, 131.4, 131.1, 129.8, 128.9, 128.1, 61.2, 34.3, 14.4. HRMS (ESI): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>15</sub>H<sub>14</sub>NaO<sub>3</sub>S: 297.0561; found, 297.0559.

**3-(3-Fluorobenzyl)thiophene-2-carbaldehyde (3ad).** Following the general procedure A described above, **3ad** was obtained after purification by column chromatography on silica gel as a yellow oil: *R*<sub>f</sub> = 0.49 (EtOAc/petroleum ether = 10:90), 40 mg (90% yield); FTIR (cm<sup>−1</sup>): 2924, 1658, 1526, 1242, 737; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.06 (s, 1H), 7.67–7.66 (m, 1H), 7.30–7.24 (m, 1H), 6.94 (d, *J* = 5.0 Hz, 1H), 6.98–6.86 (m, 3H), 4.34 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 182.3, 163.2 (d, *J*<sub>C–F</sub> = 246.6 Hz), 148.8, 141.7 (d, *J*<sub>C–F</sub> = 7.2 Hz), 138.3, 134.9, 131.4, 130.4 (d, *J*<sub>C–F</sub> = 8.3 Hz), 124.8 (d, *J*<sub>C–F</sub> = 2.9 Hz), 115.7 (d, *J*<sub>C–F</sub> = 21.6 Hz), 113.8 (d, *J*<sub>C–F</sub> = 21.0 Hz), 34.2 (d, *J*<sub>C–F</sub> = 1.8 Hz). HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>10</sub>FOS: 221.0436; found, 221.0433.

**3-(3-Chlorobenzyl)thiophene-2-carbaldehyde (3ae).** Following the general procedure A described above, **3ae** was obtained after purification by column chromatography on silica gel as a yellow oil: *R*<sub>f</sub> = 0.48 (EtOAc/petroleum ether = 10:90), 38 mg (81% yield); FTIR (cm<sup>−1</sup>): 1737, 1428, 1227, 724; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.06 (s, 1H), 7.67–7.66 (m, 1H), 7.26–7.16 (m, 3H), 7.08–7.06 (m, 1H), 6.93 (d, *J* = 5.0 Hz, 1H), 4.32 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 182.3, 148.7, 141.2, 138.2, 134.9, 134.7, 131.4, 130.2, 128.8, 127.1, 126.9, 34.2. HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>10</sub>ClOS: 237.0141; found, 237.0147.

**3-(3-Bromobenzyl)thiophene-2-carbaldehyde (3af).** Following the general procedure A described above, **3af** was obtained after purification by column chromatography on silica gel as a brown semisolid: *R*<sub>f</sub> = 0.49 (EtOAc/petroleum ether = 10:90), 42 mg (76% yield); FTIR (cm<sup>−1</sup>): 2924, 1658, 1470, 1229, 720; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.05 (s, 1H), 7.66 (d, *J* = 4.9 Hz, 1H), 7.38–7.33 (m, 2H), 7.18 (t, *J* = 7.7 Hz, 1H), 7.13–7.10 (m, 1H), 6.93 (d, *J* = 5.0 Hz, 1H), 4.31 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 182.3, 148.7, 141.5, 138.3, 134.9, 131.7, 131.4, 130.5, 130.0, 127.4, 122.9, 34.2. HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>10</sub>BrOS: 280.9636; found, 280.9635.

**3-(3-Formylbenzyl)thiophene-2-carbaldehyde (3ag).** Following the general procedure B described above, **3ag** was obtained after purification by column chromatography on silica gel as a yellow semisolid: *R*<sub>f</sub> = 0.49 (EtOAc/petroleum ether = 14:86), 21 mg (46% yield); FTIR (cm<sup>−1</sup>): 3098, 1693, 1654, 1425, 1230; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.07 (s, 1H), 9.99 (s, 1H), 7.77–7.73 (m, 1H), 7.72 (s, 1H), 7.68 (d, *J* = 4.9 Hz, 1H), 7.51–7.46 (m, 2H), 6.95 (d, *J* = 5.0 Hz, 1H), 4.44 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 192.2, 182.2, 148.5, 140.5, 138.3, 136.9, 135.0, 134.8, 131.4, 129.6, 129.5, 128.6, 34.3. HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>11</sub>O<sub>2</sub>S: 231.0480; found, 231.0481.

**Methyl 4-((2-Formylthiophen-3-yl)methyl)benzoate (3ah).** Following the general procedure B described above, **3ah** was obtained after purification by column chromatography on silica gel as a brown solid: *R*<sub>f</sub> = 0.48 (EtOAc/petroleum ether = 13:87), mp: 54–56 °C; 50 mg (98% yield); FTIR (cm<sup>−1</sup>): 2923, 1717, 1660, 1523, 1281; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.06 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 5.0 Hz, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 5.0 Hz, 1H), 4.40 (s, 2H), 3.90 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 182.2, 166.9, 148.5, 144.5, 138.3, 134.9, 131.4, 130.2, 128.8, 128.7, 52.2, 34.5. HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>13</sub>O<sub>3</sub>S: 261.0585; found, 261.0588.

**4-((2-Formylthiophen-3-yl)methyl)benzonitrile (3ai).** Following the general procedure B described above, **3ai** was obtained after purification by column chromatography on silica gel as a yellow crystalline solid: *R*<sub>f</sub> = 0.49 (EtOAc/petroleum ether = 15:85), mp: 103–105 °C; 35 mg (77% yield); FTIR (cm<sup>−1</sup>): 1736, 1646, 2224, 1424, 1280; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.03 (s, 1H), 7.71 (d, *J*

= 5.0 Hz, 1H), 7.60 (d,  $J$  = 8.3 Hz, 2H), 7.31 (d,  $J$  = 8.4 Hz, 2H), 6.94 (d,  $J$  = 5.0 Hz, 1H), 4.42 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.1, 147.3, 144.7, 138.3, 135.1, 132.7, 131.3, 129.5, 118.8, 110.7, 34.6. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{10}\text{NOS}$ : 228.0483; found, 228.0481.

**3-(4-Acetylbenzyl)thiophene-2-carbaldehyde (3aj).** Following the general procedure B described above, **3aj** was obtained after purification by column chromatography on silica gel as a brown solid:  $R_f$  = 0.49 (EtOAc/petroleum ether = 20:80), mp: 61–63 °C; 33 mg (67% yield); FTIR ( $\text{cm}^{-1}$ ): 2924, 1665, 1527, 1423, 1266;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.06 (s, 1H), 7.90 (d,  $J$  = 8.3 Hz, 2H), 7.68 (d,  $J$  = 5.0 Hz, 1H), 7.29 (d,  $J$  = 8.4 Hz, 2H), 6.94 (d,  $J$  = 5.0 Hz, 1H), 4.41 (s, 2H), 2.58 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  197.7, 182.2, 148.4, 144.7, 138.3, 135.8, 134.9, 131.4, 129.0, 128.9, 34.5, 26.7. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{13}\text{O}_2\text{S}$ : 245.0636; found, 245.0637.

**3-(4-Fluorobenzyl)thiophene-2-carbaldehyde (3ak).** Following the general procedure A described above, **3ak** was obtained after purification by column chromatography on silica gel as a yellow oil:  $R_f$  = 0.49 (EtOAc/petroleum ether = 10:90), 38 mg (86% yield); FTIR ( $\text{cm}^{-1}$ ): 2926, 1732, 1511, 1225;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.06 (s, 1H), 7.65 (d,  $J$  = 5.0 Hz, 1H), 7.16–7.13 (m, 2H), 7.01–6.96 (m, 2H), 6.91 (d,  $J$  = 5.0 Hz, 1H), 4.31 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.4, 161.7 (d,  $J_{\text{C-F}}$  = 245.3 Hz), 149.7, 138.1, 134.9 (d,  $J_{\text{C-F}}$  = 3.0 Hz), 134.9, 131.4, 130.2 (d,  $J_{\text{C-F}}$  = 8.0 Hz), 115.7 (d,  $J_{\text{C-F}}$  = 21.4 Hz), 33.7. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_9\text{FOS}$ : 221.0436; found, 221.0433.

**3-(4-Chlorobenzyl)thiophene-2-carbaldehyde (3al).** Following the general procedure A described above, **3al** was obtained after purification by column chromatography on silica gel as a brown semisolid:  $R_f$  = 0.49 (EtOAc/petroleum ether = 10:90), 31 mg (65% yield); FTIR ( $\text{cm}^{-1}$ ): 3099, 1653, 1422, 1296, 1091  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.05 (s, 1H), 7.66–7.64 (m, 1H), 7.27 (d,  $J$  = 8.4 Hz, 2H), 7.12 (d,  $J$  = 8.6 Hz, 2H), 6.91 (d,  $J$  = 5.0 Hz, 1H), 4.31 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.3, 149.1, 138.2, 137.7, 134.9, 132.7, 131.4, 130.1, 129.0, 33.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_9\text{ClOS}$ : 237.0141; found, 237.0139.

**3-(4-Bromobenzyl)thiophene-2-carbaldehyde (3am).** Following the general procedure A described above, **3am** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f$  = 0.49 (EtOAc/petroleum ether = 10:90), mp: 81–83 °C; 35 mg (63% yield); FTIR ( $\text{cm}^{-1}$ ): 3098, 1657, 1486, 1297, 744;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.05 (s, 1H), 7.65 (d,  $J$  = 5.0 Hz, 1H), 7.42 (d,  $J$  = 8.4 Hz, 2H), 7.06 (d,  $J$  = 8.6 Hz, 2H), 6.91 (d,  $J$  = 5.0 Hz, 1H), 4.29 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.3, 149.0, 138.3, 138.2, 134.9, 131.9, 131.4, 130.5, 120.7, 34.0. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_9\text{BrOS}$ : 280.9636; found, 280.9625.

**3-(3,4-Dichlorobenzyl)thiophene-2-carbaldehyde (3an).** Following the general procedure A described above, **3an** was obtained after purification by column chromatography on silica gel as a brown solid:  $R_f$  = 0.49 (EtOAc/petroleum ether = 12:88), mp: 50–52 °C; 33 mg (62% yield); FTIR ( $\text{cm}^{-1}$ ): 3096, 1659, 1423, 1228;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.04 (s, 1H), 7.69 (d,  $J$  = 4.9 Hz, 1H), 7.37 (d,  $J$  = 8.2 Hz, 1H), 7.27 (d,  $J$  = 2.1 Hz, 1H), 7.03 (dd,  $J$  = 8.2, 2.1 Hz, 1H), 6.93 (d,  $J$  = 5.0 Hz, 1H), 4.31 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.1, 147.9, 139.5, 138.3, 135.0, 132.9, 131.3, 130.9, 130.8, 130.6, 128.2, 33.7. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_9\text{Cl}_2\text{OS}$ : 270.9751; found, 270.9756.

**3-(3-Methylbenzyl)thiophene-2-carbaldehyde (3ao).** Following the general procedure A described above, **3ao** was obtained after purification by column chromatography on silica gel as a brownish yellow oil:  $R_f$  = 0.49 (EtOAc/petroleum ether = 09:91), 34 mg (80% yield); FTIR ( $\text{cm}^{-1}$ ): 2921, 1659, 1488, 1229;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.09 (s, 1H), 7.63 (d,  $J$  = 5.0 Hz, 1H), 7.21–7.17 (m, 1H), 7.04 (d,  $J$  = 7.5 Hz, 1H), 6.99 (s, 1H), 6.98 (d,  $J$  = 7.7 Hz, 1H), 6.94 (d,  $J$  = 5.0 Hz, 1H), 4.29 (s, 2H), 2.32 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.6, 150.3, 139.1, 138.6, 138.1, 134.7, 131.5, 129.5, 128.8, 127.6, 125.7, 34.5, 21.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{13}\text{OS}$ : 217.0687; found, 217.0692.

**3-(4-Methylbenzyl)thiophene-2-carbaldehyde (3ap).** Following the general procedure A described above, **3ap** was obtained after purification by column chromatography on silica gel as a brown oil:  $R_f$  = 0.49 (EtOAc/petroleum ether = 09:91), 37 mg (85% yield); FTIR ( $\text{cm}^{-1}$ ): 3018, 1656, 1424, 1226, 767;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.08 (s, 1H), 7.62 (d,  $J$  = 5.0 Hz, 1H), 7.11 (d,  $J$  = 8.0 Hz, 2H), 7.07 (d,  $J$  = 8.1 Hz, 2H), 6.93 (d,  $J$  = 5.0 Hz, 1H), 4.29 (s, 2H), 2.32 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.5, 150.5, 138.1, 136.4, 136.2, 134.7, 131.5, 129.6, 128.6, 34.2, 21.1. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{13}\text{OS}$ : 217.0687; found, 217.0690.

**3-(4-Isopropylbenzyl)thiophene-2-carbaldehyde (3aq).** Following the general procedure A described above, **3aq** was obtained after purification by column chromatography on silica gel as a brownish yellow oil:  $R_f$  = 0.49 (EtOAc/petroleum ether = 09:91), 34 mg (70% yield); FTIR ( $\text{cm}^{-1}$ ): 2960, 1659, 1425, 1227, 734;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.09 (s, 1H), 7.63 (d,  $J$  = 5.0 Hz, 1H), 7.16 (d,  $J$  = 8.1 Hz, 2H), 7.10 (d,  $J$  = 8.3 Hz, 2H), 6.95 (d,  $J$  = 5.0 Hz, 1H), 4.30 (s, 2H), 2.91–2.84 (m, 1H), 1.24 (s, 3H), 1.22 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.57, 150.44, 147.5, 138.2, 136.6, 134.6, 131.6, 128.6, 126.9, 34.1, 33.8, 24.1. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_{17}\text{OS}$ : 245.1000; found, 245.0994.

**3-(4-Methoxybenzyl)thiophene-2-carbaldehyde (3ar).** Following the general procedure A described above, **3ar** was obtained after purification by column chromatography on silica gel as a brown oil:  $R_f$  = 0.49 (EtOAc/petroleum ether = 12:88), 35 mg (75% yield); FTIR ( $\text{cm}^{-1}$ ): 2925, 1656, 1511, 1244, 1033;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.08 (s, 1H), 7.62 (d,  $J$  = 5.0 Hz, 1H), 7.10 (d,  $J$  = 8.8 Hz, 2H), 6.92 (d,  $J$  = 5.0 Hz, 1H), 6.84 (d,  $J$  = 8.7 Hz, 2H), 4.27 (s, 2H), 3.78 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.5, 158.5, 150.7, 138.0, 134.7, 131.5, 131.3, 129.7, 114.3, 55.4, 33.7. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{13}\text{O}_2\text{S}$ : 233.0636; found, 233.0643.

**3-(3,4-Dimethylbenzyl)thiophene-2-carbaldehyde (3as).** Following the general procedure A described above, **3as** was obtained after purification by column chromatography on silica gel as a brown semisolid:  $R_f$  = 0.49 (EtOAc/petroleum ether = 09:91), 29 mg (64% yield); FTIR ( $\text{cm}^{-1}$ ): 2925, 1738, 1437, 1371, 1130, 697;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.08 (s, 1H), 7.61 (d,  $J$  = 5.0 Hz, 1H), 7.06 (d,  $J$  = 7.6 Hz, 1H), 6.95 (s, 1H), 6.94 (d,  $J$  = 5.0 Hz, 1H), 6.91 (d,  $J$  = 7.7 Hz, 1H), 4.25 (s, 2H), 2.22 (s, 3H), 2.22 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.6, 150.7, 138.1, 137.1, 136.6, 135.1, 134.6, 131.5, 130.1, 129.9, 126.0, 34.1, 19.9, 19.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{15}\text{OS}$ : 231.0844; found, 231.0845.

**3-(3,5-Dimethylbenzyl)thiophene-2-carbaldehyde (3at).** Following the general procedure A described above, **3at** was obtained after purification by column chromatography on silica gel as a brown oil:  $R_f$  = 0.49 (EtOAc/petroleum ether = 09:91), 23 mg (50% yield); FTIR ( $\text{cm}^{-1}$ ): 2919, 1714, 1424, 1227, 728;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.09 (s, 1H), 7.63 (d,  $J$  = 5.0 Hz, 1H), 6.95 (d,  $J$  = 5.0 Hz, 1H), 6.87 (s, 1H), 6.79 (s, 2H), 4.25 (s, 2H), 2.28 (s, 3H), 2.28 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.6, 150.5, 139.1, 138.5, 138.1, 134.7, 131.5, 128.5, 126.5, 34.4, 21.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{15}\text{OS}$ : 231.0844; found, 231.0840.

**3-(4-Bromo-3-methylbenzyl)thiophene-2-carbaldehyde (3au).** Following the general procedure A described above, **3au** was obtained after purification by column chromatography on silica gel as a yellow semisolid:  $R_f$  = 0.49 (EtOAc/petroleum ether = 10:90), 41 mg (70% yield); FTIR ( $\text{cm}^{-1}$ ): 2923, 1734, 1661, 1474, 1227;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.06 (s, 1H), 7.65 (d,  $J$  = 5.0 Hz, 1H), 7.44 (d,  $J$  = 8.1 Hz, 1H), 7.05 (s, 1H), 6.92 (d,  $J$  = 5.0 Hz, 1H), 6.87 (d,  $J$  = 7.6 Hz, 1H), 4.25 (s, 2H), 2.35 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.3, 149.3, 138.5, 138.4, 138.1, 134.8, 132.8, 131.4, 131.2, 127.7, 123.2, 33.9, 23.0. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{12}\text{BrOS}$ : 294.9792; found, 294.9785.

**3-(4-Bromo-3-fluorobenzyl)thiophene-2-carbaldehyde (3av).** Following the general procedure A described above, **3av** was obtained after purification by column chromatography on silica gel as a brownish yellow solid:  $R_f$  = 0.49 (EtOAc/petroleum ether = 12:88), mp: 61–63 °C; 37 mg (62% yield); FTIR ( $\text{cm}^{-1}$ ): 3100, 1661, 1528, 1424, 1235;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.03 (s, 1H), 7.68 (d,  $J$  = 4.9 Hz, 1H), 7.47 (dd,  $J$  = 8.1, 7.2 Hz, 1H), 6.96 (d,  $J$  = 2.0 Hz,



1H), 6.93 (d,  $J = 4.9$  Hz, 1H), 6.89–6.86 (m, 1H), 4.31 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.1, 159.3 (d,  $J_{\text{C-F}} = 248.0$  Hz), 147.9, 141.0 (d,  $J_{\text{C-F}} = 6.5$  Hz), 138.3, 135.0, 133.8, 131.3, 125.6 (d,  $J_{\text{C-F}} = 3.5$  Hz), 116.9 (d,  $J_{\text{C-F}} = 22.5$  Hz), 107.2 (d,  $J_{\text{C-F}} = 20.9$  Hz), 33.9 (d,  $J_{\text{C-F}} = 1.5$  Hz). HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_9\text{BrFOS}$ : 298.9542; found, 298.9533.

**3-((6-Bromo-9H-fluoren-3-yl)methyl)thiophene-2-carbaldehyde (3aw).** Following the general procedure A described above, **3aw** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f = 0.49$  (EtOAc/petroleum ether = 10:90), mp: 173–175 °C; 37 mg (51% yield); FTIR ( $\text{cm}^{-1}$ ): 3072, 2925, 1663, 1423, 746;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.12 (s, 1H), 7.68 (d,  $J = 7.8$  Hz, 1H), 7.66 (s, 1H), 7.66–7.64 (m, 1H), 7.60 (d,  $J = 8.1$  Hz, 1H), 7.48 (d,  $J = 8.1$  Hz, 1H), 7.34 (s, 1H), 7.22 (d,  $J = 7.8$  Hz, 1H), 6.97 (d,  $J = 5.0$  Hz, 1H), 4.40 (s, 2H), 3.84 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.5, 150.1, 145.3, 143.7, 140.4, 139.5, 138.4, 138.2, 134.8, 131.5, 130.1, 128.4, 127.7, 125.4, 121.2, 120.6, 120.3, 36.8, 34.7. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{14}\text{BrOS}$ : 368.9949; found, 368.9950.

**Methyl 4-((5-Bromo-2-formylthiophen-3-yl)methyl)benzoate (3bh).** Following the general procedure A described above, **3bh** was obtained after purification by column chromatography on silica gel as a yellow crystalline solid:  $R_f = 0.49$  (EtOAc/petroleum ether = 12:88), mp: 131–133 °C; 51 mg (75% yield); FTIR ( $\text{cm}^{-1}$ ): 3002, 1717, 1664, 1419, 1280;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.96 (s, 1H), 7.96 (d,  $J = 8.4$  Hz, 2H), 7.72 (s, 1H), 7.24 (d,  $J = 8.6$  Hz, 2H), 4.43 (s, 2H), 3.90 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  181.8, 166.9, 146.4, 143.2, 139.1, 132.5, 130.2, 128.8, 128.5, 115.8, 52.3, 33.6. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{12}\text{BrO}_3\text{S}$ : 338.9691; found, 338.9686.

**3-(3-Nitrobenzyl)benzo[b]thiophene-2-carbaldehyde (3cb).** Following the general procedure A described above, **3cb** was obtained after purification by column chromatography on silica gel as a light yellow solid:  $R_f = 0.49$  (EtOAc/petroleum ether = 14:86), mp: 171–173 °C; 38 mg (65% yield); FTIR ( $\text{cm}^{-1}$ ): 2924, 1712, 1524, 1349, 1205;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.32 (s, 1H), 8.11 (s, 1H), 8.10–8.07 (m, 1H), 7.93 (d,  $J = 8.2$  Hz, 1H), 7.78 (d,  $J = 8.2$  Hz, 1H), 7.55–7.39 (m, 4H), 4.75 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  183.8, 148.7, 142.7, 142.1, 140.6, 139.2, 139.1, 134.3, 129.9, 128.7, 125.6, 124.3, 123.8, 123.2, 122.2, 31.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{12}\text{NO}_3\text{S}$ : 298.0538; found, 298.0542.

**Methyl 4-((2-Formylbenzo[b]thiophen-3-yl)methyl)benzoate (3ch).** Following the general procedure B described above, **3ch** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f = 0.49$  (EtOAc/petroleum ether = 12:88), mp: 132–134 °C; 44 mg (72% yield); FTIR ( $\text{cm}^{-1}$ ): 3067, 1719, 1663, 1436, 1282;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.32 (s, 1H), 7.94 (d,  $J = 8.3$  Hz, 2H), 7.90 (d,  $J = 8.2$  Hz, 1H), 7.77 (d,  $J = 8.2$  Hz, 1H), 7.51–7.47 (m, 1H), 7.39–7.35 (m, 1H), 7.26 (d,  $J = 8.4$  Hz, 2H), 4.68 (s, 2H), 3.88 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  184.0, 166.8, 143.8, 143.4, 142.6, 139.5, 139.1, 130.3, 128.9, 128.5, 128.3, 125.3, 124.5, 123.6, 52.3, 32.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{18}\text{H}_{15}\text{O}_3\text{S}$ : 311.0742; found, 311.0732.

**Methyl 4-((2-Formylbenzofuran-3-yl)methyl)benzoate (3dh).** Following the general procedure A described above, **3dh** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f = 0.49$  (EtOAc/petroleum ether = 14:86), mp: 129–131 °C; 29 mg (49% yield); FTIR ( $\text{cm}^{-1}$ ): 2945, 1720, 1663, 1436, 1283;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.32 (s, 1H), 7.95 (d,  $J = 8.4$  Hz, 2H), 7.91–7.89 (m, 1H), 7.78–7.75 (m, 1H), 7.52–7.48 (m, 1H), 7.39–7.35 (m, 1H), 7.26 (d,  $J = 8.6$  Hz, 2H), 4.68 (s, 2H), 3.88 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  184.0, 166.8, 143.8, 143.4, 142.6, 139.5, 139.1, 130.3, 128.9, 128.6, 128.3, 125.3, 124.5, 123.6, 52.3, 32.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{18}\text{H}_{15}\text{O}_4$ : 295.0926; found, 295.0918.

**3-(3-Nitrobenzyl)benzofuran-2-carbaldehyde (3db).** Following the general procedure A described above, **3db** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f = 0.49$  (EtOAc/petroleum ether = 15:85), mp: 175–177 °C; 28 mg (50% yield); FTIR ( $\text{cm}^{-1}$ ): 3059, 1661, 1529, 1352, 1211;  $^1\text{H}$

NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.32 (s, 1H), 8.11 (s, 1H), 8.10–8.07 (m, 1H), 7.94–7.92 (m, 1H), 7.79–7.77 (m, 1H), 7.55–7.39 (m, 4H), 4.75 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  183.8, 148.7, 142.7, 142.0, 140.7, 139.2, 139.1, 134.3, 129.9, 128.7, 125.6, 124.3, 123.8, 123.2, 122.2, 31.9. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{12}\text{NO}_4$ : 282.0722; found, 282.0727.

**Ethyl 3-((2-Formylbenzofuran-3-yl)methyl)benzoate (3dc).** Following the general procedure A described above, **3dc** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f = 0.49$  (EtOAc/petroleum ether = 15:85), mp: 91–93 °C; 32 mg (52% yield); FTIR ( $\text{cm}^{-1}$ ): 2981, 1714, 1661, 1558, 1278;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.34 (s, 1H), 7.97 (s, 1H), 7.91–7.88 (m, 2H), 7.81–7.79 (m, 1H), 7.51–7.47 (m, 1H), 7.39–7.28 (m, 3H), 4.68 (s, 2H), 4.36 (q,  $J = 7.1$  Hz, 2H), 1.37 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  184.1, 166.5, 143.8, 142.6, 139.5, 139.1, 138.9, 132.5, 131.2, 129.4, 129.1, 128.5, 128.2, 125.3, 124.6, 123.6, 61.3, 32.2, 14.4. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{17}\text{O}_4$ : 309.1127; found, 309.1122.

**4-((2-Formylthiophen-3-yl)methyl)benzoic acid (3ax).** Following the general procedure B described above, **3ax** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f = 0.49$  (EtOAc/petroleum ether = 50:50), mp: 169–171 °C; 22 mg (45% yield); FTIR ( $\text{cm}^{-1}$ ): 2943, 1656, 1450, 1020;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3 + \text{CD}_3\text{OD}$ )  $\delta$  10.05 (s, 1H), 7.99 (d,  $J = 8.3$  Hz, 2H), 7.77 (d,  $J = 4.9$  Hz, 1H), 7.29 (d,  $J = 8.3$  Hz, 2H), 6.99 (d,  $J = 5.0$  Hz, 1H), 4.43 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3 + \text{CD}_3\text{OD}$ )  $\delta$  182.7, 168.4, 149.2, 144.3, 137.7, 135.1, 131.2, 130.0, 128.7, 128.3, 34.0. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{11}\text{O}_3\text{S}$ : 247.0429; found, 247.0436.

**3-((1-Tosyl-1H-indol-5-yl)methyl)thiophene-2-carbaldehyde (3ay).** Following the general procedure B described above, **3ay** was obtained after purification by column chromatography on silica gel as a yellowish semisolid:  $R_f = 0.49$  (EtOAc/petroleum ether = 20:80), 49 mg (63% yield); FTIR ( $\text{cm}^{-1}$ ): 3056, 1735, 1427, 1265;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.06 (s, 1H), 7.90 (d,  $J = 8.5$  Hz, 1H), 7.75 (d,  $J = 8.4$  Hz, 2H), 7.62 (d,  $J = 4.9$  Hz, 1H), 7.54 (d,  $J = 3.7$  Hz, 1H), 7.30 (s, 1H), 7.22 (d,  $J = 8.1$  Hz, 2H), 7.14 (d,  $J = 8.6$  Hz, 1H), 6.92 (d,  $J = 5.0$  Hz, 1H), 6.57 (d,  $J = 3.7$  Hz, 1H), 4.38 (s, 2H), 2.34 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.5, 150.2, 145.2, 138.1, 135.4, 134.7, 134.4, 133.7, 131.6, 131.3, 130.1, 127.0, 126.9, 125.4, 121.2, 113.9, 108.9, 34.4, 21.7. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{21}\text{H}_{18}\text{NO}_3\text{S}_2$ : 396.0728; found, 396.0729.

**3-((6-Fluoropyridin-3-yl)methyl)thiophene-2-carbaldehyde (3az).** Following the general procedure B described above, **3az** was obtained after purification by column chromatography on silica gel as a brownish yellow solid:  $R_f = 0.49$  (EtOAc/petroleum ether = 20:80), mp: 47–49 °C; 32 mg (73% yield); FTIR ( $\text{cm}^{-1}$ ): 3098, 1657, 1482, 1242;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.05 (s, 1H), 8.11 (s, 1H), 7.70 (d,  $J = 5.0$  Hz, 1H), 7.63–7.58 (m, 1H), 6.94 (d,  $J = 5.0$  Hz, 1H), 6.88 (dd,  $J = 8.4, 3.0$  Hz, 1H), 4.36 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.1, 162.7 (d,  $J_{\text{C-F}} = 238.7$  Hz), 147.6, 147.3 (d,  $J_{\text{C-F}} = 14.6$  Hz), 141.4 (d,  $J_{\text{C-F}} = 7.8$  Hz), 138.1, 135.2, 132.6 (d,  $J_{\text{C-F}} = 4.6$  Hz), 131.2, 109.7 (d,  $J_{\text{C-F}} = 37.5$  Hz), 30.9 (d,  $J_{\text{C-F}} = 1.4$  Hz). HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{11}\text{H}_6\text{FNOS}$ : 222.0389; found, 222.0393.

**3-((6-Bromopyridin-3-yl)methyl)thiophene-2-carbaldehyde (3aza').** Following the general procedure B described above, **3aza'** was obtained after purification by column chromatography on silica gel as a brown solid:  $R_f = 0.49$  (EtOAc/petroleum ether = 20:80), mp: 58–60 °C; 34 mg (62% yield); FTIR ( $\text{cm}^{-1}$ ): 3089, 1659, 1448, 1294, 1087;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.03 (s, 1H), 8.27 (d,  $J = 2.4$  Hz, 1H), 7.70 (d,  $J = 4.9$  Hz, 1H), 7.42 (d,  $J = 8.1$  Hz, 1H), 7.37 (dd,  $J = 8.2, 2.5$  Hz, 1H), 6.93 (d,  $J = 5.0$  Hz, 1H), 4.33 (s, 2H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.0, 150.2, 146.9, 140.5, 138.9, 138.1, 135.2, 134.3, 131.2, 128.2, 31.2. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{11}\text{H}_6\text{BrNOS}$ : 281.9588; found, 281.9589.

**3-((6-Chloropyridin-3-yl)methyl)thiophene-2-carbaldehyde (3azb').** Following the general procedure B described above, **3azb'** was obtained after purification by column chromatography on silica gel as a yellow solid:  $R_f = 0.49$  (EtOAc/petroleum ether = 20:80), mp:

59–61 °C; 30 mg (65% yield); FTIR (cm<sup>-1</sup>): 3094, 1660, 1460, 1234, 1023; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.96 (s, 1H), 8.22 (d, *J* = 2.5 Hz, 1H), 7.63 (d, *J* = 4.9 Hz, 1H), 7.39 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 5.0 Hz, 1H), 4.28 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 182.0, 150.0, 149.7, 147.1, 139.1, 138.1, 135.2, 133.9, 131.2, 124.4, 31.2. HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>9</sub>ClNOS: 238.0093; found, 238.0097.

**3-((6-Fluoropyridin-3-yl)methyl)benzo[b]thiophene-2-carbaldehyde (3cz).** Following the general procedure B described above, **3cz** was obtained after purification by column chromatography on silica gel as a yellow solid: *R*<sub>f</sub> = 0.49 (EtOAc/petroleum ether = 20:80), mp: 130–132 °C; 25 mg (46% yield); FTIR (cm<sup>-1</sup>): 3074, 1664, 1483, 1245; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.32 (s, 1H), 8.17 (s, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.56–7.50 (m, 2H), 7.44–7.40 (m, 1H), 6.83 (dd, *J* = 8.5, 2.9 Hz, 1H), 4.63 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 183.7, 162.8 (d, *J*<sub>C–F</sub> = 239.1 Hz), 147.0 (d, *J*<sub>C–F</sub> = 14.7 Hz), 142.7, 142.2, 140.8 (d, *J*<sub>C–F</sub> = 7.9 Hz), 139.2, 138.9, 131.9 (d, *J*<sub>C–F</sub> = 4.7 Hz), 128.7, 125.6, 124.3, 123.8, 109.9 (d, *J*<sub>C–F</sub> = 37.6 Hz), 28.8 (d, *J*<sub>C–F</sub> = 1.4 Hz). HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>11</sub>FNOS: 272.0545; found, 272.0547.

**3-((6-Chloro-5-(trifluoromethyl)pyridin-3-yl)methyl)thiophene-2-carbaldehyde (3azc').** Following the general procedure B described above, **3azc'** was obtained after purification by column chromatography on silica gel as a brown solid: *R*<sub>f</sub> = 0.49 (EtOAc/petroleum ether = 20:80), mp: 53–55 °C; 39 mg (65% yield); FTIR (cm<sup>-1</sup>): 3086, 1662, 1427, 1237, 1142; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.00 (s, 1H), 8.45 (d, *J* = 2.3 Hz, 1H), 7.84 (d, *J* = 2.3 Hz, 1H), 7.76 (d, *J* = 5.0 Hz, 1H), 6.98 (d, *J* = 5.0 Hz, 1H), 4.44 (s, 2H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 182.0, 152.3, 147.3, 145.4, 138.1, 136.8 (q, *J*<sub>C–F</sub> = 5.0 Hz), 135.5, 134.2, 131.2, 125.3 (d, *J*<sub>C–F</sub> = 33.2 Hz), 122.1 (d, *J*<sub>C–F</sub> = 273.0 Hz), 31.2. HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>8</sub>ClF<sub>3</sub>NOS: 305.9967; found, 305.9965.

**Scale-Up Procedure for the Synthesis of 3-Benzylthiophene-2-carbaldehyde (3aa).** A 30 mL dry pressure tube equipped with a stir bar was charged with 3-methylthiophene-2-carbaldehyde **1a** (0.3 g, 2.38 mmol, 1.0 equiv), iodobenzene **2a** (0.727 g, 3.57 mmol, 1.5 equiv), Pd(OAc)<sub>2</sub> (0.053 g, 0.24 mmol, 0.1 equiv), **L8** (0.111 g, 0.95 mmol, 0.4 equiv), and AgTFA (0.730 g, 3.57 mmol, 1.5 equiv), followed by the addition of a mixture of HFIP (12.96 mL) and AcOH (1.44 mL) at room temperature. Then, the resulting reaction mixture was degassed under a N<sub>2</sub> atmosphere for 2 min and stirred vigorously at room temperature for 15 min. Then, the reaction mixture was heated to 110 °C for 24 h in a heating block, after which the reaction mixture was cooled to room temperature, followed by dilution with EtOAc (25 mL) and subsequent filtration through a pad of celite. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel to furnish the desired product **3aa** in 73% yield (0.35 g) as a yellow oil.

**Scale-Up Procedure for the Synthesis of 3-(3-Nitrobenzyl)thiophene-2-carbaldehyde (3ab).** A 30 mL dry pressure tube equipped with a stir bar was charged with 3-methylthiophene-2-carbaldehyde **1a** (0.5 g, 3.96 mmol, 1.0 equiv), 1-iodo-3-nitrobenzene **2b** (1.48 g, 5.94 mmol, 1.5 equiv), Pd(OAc)<sub>2</sub> (0.088 g, 0.40 mmol, 0.1 equiv), **L8** (0.185 g, 1.59 mmol, 0.4 equiv), and AgTFA (1.22 g, 5.94 mmol, 1.5 equiv), followed by the addition of a mixture of HFIP (14.40 mL) and AcOH (1.60 mL) at room temperature. Then, the resulting reaction mixture was degassed under a N<sub>2</sub> atmosphere for 2 min and stirred vigorously at room temperature for 15 min. Then, the reaction mixture was heated to 110 °C for 24 h in a heating block, after which the reaction mixture was cooled to room temperature, followed by dilution with EtOAc (30 mL) and subsequent filtration through a pad of celite. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel to furnish the desired product **3ab** in 70% yield (0.69 g) as a yellow-brownish solid.

**Procedure for the Synthesis of Naphtho[2,3-*b*]thiophene (4a).<sup>3b</sup>** An oven-dried round-bottom flask (25 mL) was charged with **1a** (30.4 mg, 0.15 mmol), tosylamine **2a** (25.7 mg, 0.15 mmol), and toluene (2 mL). BF<sub>3</sub>·Et<sub>2</sub>O (30 mol %) was then added to the mixture, and the solution was stirred at room temperature for 2 h. Then, the

reaction mixture was purified by column chromatography (EtOAc/petroleum ether = 25:75) to obtain a white solid **4a**: *R*<sub>f</sub> = 0.49 (EtOAc/petroleum ether = 15:85), mp: 188–190 °C; 18 mg (65% yield); FTIR (cm<sup>-1</sup>): 3054, 2927, 1729, 1267, 1447; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.37 (s, 1H), 8.32 (s, 1H), 7.98–7.90 (m, 2H), 7.50 (d, *J* = 5.6 Hz, 1H), 7.48–7.45 (m, 2H), 7.42 (d, *J* = 5.7 Hz, 1H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 139.0, 138.3, 131.1, 131.1, 128.4, 128.3, 127.4, 125.4, 125.1, 123.6, 121.9, 120.8. HRMS (ESI): *m/z* [M]<sup>+</sup> calcd for C<sub>12</sub>H<sub>8</sub>S: 184.0347; found, 184.0353.

**(3-(3-Methylbenzyl)thiophen-2-yl)methanol (4b).<sup>19</sup>** In an oven-dried two-neck round-bottom flask charged with a stir bar, LiAlH<sub>4</sub> (0.22 mmol, 1.5 equiv) and a solution of 3-(3-methylbenzyl)thiophene-2-carbaldehyde **3ao** (0.15 mmol, 1 equiv) were added in THF (3 mL) at 0 °C under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred overnight. After the complete consumption of the starting material (monitored by TLC), the reaction mixture was cooled to 0 °C and quenched carefully with 2 M HCl. The reaction mixture was extracted with EtOAc (2 × 15 mL), and the combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The resulting residue was purified by silica chromatography (EtOAc/petroleum ether = 20:80) to afford the corresponding alcohol product **4b** as a yellow semisolid: *R*<sub>f</sub> = 0.49 (EtOAc/petroleum ether = 20:80), 22 mg (70% yield); FTIR (cm<sup>-1</sup>): 2920, 1605, 1441, 1264; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.19–7.15 (m, 2H), 7.02–6.94 (m, 3H), 6.83 (d, *J* = 5.1 Hz, 1H), 4.77 (s, 2H), 3.94 (s, 2H), 2.30 (s, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 140.6, 138.4, 138.4, 137.6, 130.0, 129.3, 128.6, 127.1, 125.6, 124.3, 57.9, 34.3, 21.6. HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>13</sub>OS: 219.0799; found, 219.0809.

**Procedure for the Synthesis of 1-(3-(4-Bromo-3-methylbenzyl)thiophen-2-yl)ethanol (4c).<sup>20</sup>** In an oven-dried two-neck round-bottom flask charged with a stir bar, 3 M MeMgBr solution in THF (0.1 mL, 0.3 mmol, 2 equiv) was added to a solution of 3-(4-bromo-3-methylbenzyl)thiophene-2-carbaldehyde **3au** (0.15 mmol, 1 equiv) in THF (3 mL) at –78 °C under an argon atmosphere. The reaction mixture was continued to stir at –78 °C for 1 h. After the completion of reaction (monitored by TLC), the reaction mixture was quenched with a saturated NH<sub>4</sub>Cl solution (5 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo and purified by column chromatography using silica gel (EtOAc/petroleum ether = 15:85) to furnish the desired product **4c** as a yellow semisolid: *R*<sub>f</sub> = 0.49 (EtOAc/petroleum ether = 12:88), 45 mg (98% yield); FTIR (cm<sup>-1</sup>): 2970, 1473, 1375, 1026; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.41 (d, *J* = 8.1 Hz, 1H), 7.16 (d, *J* = 5.1 Hz, 1H), 7.02 (s, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.75 (d, *J* = 5.1 Hz, 1H), 5.21 (q, *J* = 6.4 Hz, 1H), 3.90 (s, 2H), 2.34 (s, 3H), 1.82 (brs, 1H), 1.55 (d, *J* = 6.4 Hz, 3H). <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>) δ 144.1, 139.9, 138.1, 135.9, 132.5, 131.1, 129.7, 127.6, 123.5, 122.6, 64.5, 33.7, 25.4, 23.0. HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>16</sub>BrOS: 312.0007; found, 312.0017.

**N-((3-(3-Chlorobenzyl)thiophen-2-yl)methyl)-4-methoxyaniline (4d).<sup>21</sup>** To a solution of 3-(3-chlorobenzyl)thiophene-2-carbaldehyde **3ae** (0.15 mmol, 1 equiv) in DCM (3 mL) was added the corresponding amine (0.15 mmol, 1 equiv) and sodium sulfate (0.90 mmol, 6 equiv) under a nitrogen atmosphere, and the reaction mixture was stirred at RT for 2 h. Then, NaCNBH<sub>3</sub> (0.22 mmol, 1.5 equiv) was added at 0 °C and the reaction mixture was allowed to warm to room temperature and stirred for overnight. After the completion of reaction (monitored by TLC), the reaction was quenched by adding water (7 mL). The resulting mixture was extracted with EtOAc (2 × 15 mL), and the combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuo. The resulting residue was purified by silica chromatography (EtOAc/petroleum ether = 20:80) to afford the corresponding alcohol product. Following the general procedure described above, **4d** was obtained after purification by column chromatography on silica gel as a brownish semisolid: *R*<sub>f</sub> = 0.49 (EtOAc/petroleum ether = 15:85), 40 mg (79% yield); FTIR (cm<sup>-1</sup>): 2922, 1511, 1238, 1036; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.22–7.18 (m, 2H), 7.15 (d, *J* = 5.1 Hz, 1H), 7.13–7.12 (m, 1H), 7.04–7.02 (m, 1H), 6.81 (d, *J* = 5.1 Hz, 1H),



6.77 (d,  $J = 9.0$  Hz, 2H), 6.57 (d,  $J = 9.0$  Hz, 2H), 4.35 (s, 2H), 3.95 (s, 2H), 3.74 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  152.8, 142.6, 141.9, 137.5, 136.3, 134.5, 129.9, 129.7, 128.7, 126.8, 126.6, 123.8, 115.0, 114.7, 55.9, 42.8, 34.1. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{19}\text{ClNOS}$ : 344.0876; found, 344.0870.

**Procedure for the Synthesis of (E)-3-(3-(3-Nitrobenzyl)thiophene-2-yl)-1-(p-tolyl)prop-2-en-1-one (4e).**<sup>22</sup> 3-(3-Nitrobenzyl)thiophene-2-carbaldehyde **3ab** (0.15 mmol, 1.0 equiv) and 1-(p-tolyl)-2-(triphenylphosphoranylidene)ethanone (0.18 mmol, 1.2 equiv) were dissolved in toluene (3 mL) and refluxed for 12 h. After the completion of reaction (monitored by TLC), the solvent was removed under vacuo and the residue was purified by column chromatography to furnish the desired product **4e** as a yellow solid:  $R_f = 0.49$  (EtOAc/petroleum ether = 12:88), mp: 128–130 °C; 43 mg (80% yield); FTIR ( $\text{cm}^{-1}$ ): 3096, 1654, 1582, 1526, 1345;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.09–8.01 (m, 3H), 7.91 (d,  $J = 8.2$  Hz, 2H), 7.51–7.44 (m, 2H), 7.38 (d,  $J = 10.1$  Hz, 1H), 7.35 (s, 1H), 7.30 (d,  $J = 7.9$  Hz, 2H), 6.85 (d,  $J = 5.2$  Hz, 1H), 4.23 (s, 2H), 2.44 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  189.2, 148.6, 144.0, 143.0, 141.1, 136.1, 135.6, 134.9, 134.2, 130.7, 129.7, 129.5, 128.7, 128.1, 123.5, 121.8, 121.4, 34.1, 21.8. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{21}\text{H}_{18}\text{NO}_3\text{S}$ : 364.1007; found, 364.1012.

**Procedure for the Synthesis of 3-(3-Methylbenzyl)thiophene-2-carbonitrile (4f).**<sup>23</sup> To a stirred mixture of 3-(3-methylbenzyl)thiophene-2-carbaldehyde **3ao** (0.15 mmol, 1 equiv) and sodium azide (0.15 mmol, 1 equiv), phosphorus oxychloride (0.75 mmol, 5 equiv) was added (in the open vessel with a guard tube) and stirred for 1 h at room temperature. After the completion of reaction (monitored by TLC), the reaction mixture was quenched with crushed ice. Then, the reaction mixture was extracted with ethyl acetate (15 mL) and washed with sodium bicarbonate solution (15 mL), water (15 mL), and brine solution (15 mL). The organic layer was separated and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was removed under vacuo, and the residue was purified by column chromatography using silica gel to give the desired product **4f** as a yellow liquid:  $R_f = 0.49$  (EtOAc/petroleum ether = 14:86), 25 mg (79% yield); FTIR ( $\text{cm}^{-1}$ ): 2921, 2215, 1605, 1415;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45 (d,  $J = 5.1$  Hz, 1H), 7.22–7.18 (m, 1H), 7.06 (d,  $J = 8.0$  Hz, 1H), 7.05–7.00 (m, 1H), 6.88 (d,  $J = 5.1$  Hz, 1H), 4.08 (s, 2H), 2.33 (s, 3H).  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  153.0, 138.7, 138.4, 132.1, 129.6, 129.1, 128.8, 127.7, 125.8, 114.4, 106.1, 36.0, 21.5. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{12}\text{NS}$ : 214.0690; found, 214.0679.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.0c00154>.

Copies of  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra of compounds **1d–e**, **3aa–aw**, **3bh**, **3cb**, **3ch**, **3dh**, **3db**, **3dc**, **3ax**, **3ay**, **3az**, **3aza'**, **3azb'**, **3cz**, **3azc'**, and **4a–f** (PDF)

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### Notes

The authors declare no competing financial interest.

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# Transient Directing Group Enabled C3-( $sp^2$ )–H Alkenylation of Five Membered Heterocyclic Aldehydes: An Access to Mechanochromic Luminogen

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**Abstract:** The palladium (II) catalyzed direct C3-( $sp^2$ )–H alkenylation of five membered heterocyclic aldehydes has been developed using 3-aminobutanoic acid as a catalytic transient directing group. A wide range of heterocyclic aldehydes reacted with various acrylates to afford highly site-selective C3-alkenylated products. This method features an exclusive *E*-selective alkenylation at the C3-position of heterocyclic aldehydes with a broad substrate scope. The protocol also proved to be useful to construct the mechanochromic luminogen.

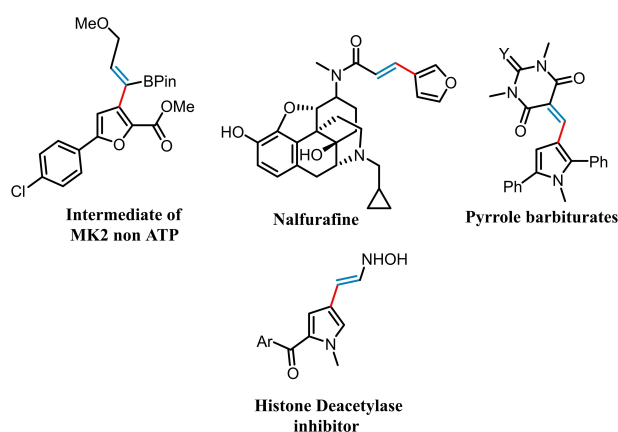
**Keywords:** Palladium; C–H activation; alkenylation; heterocyclic aldehydes; mechanochromism

## Introduction

The alkenyl substituted five membered heterocyclic scaffolds are widely present in a large number of natural products, pharmaceutically active compounds, polymers, dyes and organic functional materials (Figure 1).<sup>[1,2]</sup> Owing to the importance of this scaffold in organic synthesis and medicinal chemistry, great efforts have been devoted for the development of efficient and succinct protocols for the construction as well as functionalization of heterocyclic scaffolds. In recent years, the transition metal catalyzed alkenylation of five membered heterocyclic scaffolds has become one of the important and most atom- and step-economical approaches in organic synthesis.<sup>[3]</sup>

The selective C3-alkenylation of five membered heterocyclic scaffolds is quite challenging due to the intrinsic low reactivity at this position. Generally, the palladium catalyzed alkenylation of five membered heterocyclic compounds occurs at C2 and/or C5 positions ( $\alpha$ -positions) because five membered heterocyclic rings are chemically more reactive at this position.<sup>[4]</sup>

In spite of the great significance of C3 alkenylated heterocyclic scaffolds, interestingly only a few literature



**Figure 1.** Representative compounds with C3-alkenylated heterocyclic scaffold.

reports are available for the synthesis of C3 or  $\beta$ -alkenylated five membered heterocyclic derivatives. Some of these protocols relied on cross coupling reactions,<sup>[5]</sup> C–H activation strategy using different directing groups (fixed at C2 position) such as carboxylic acid,<sup>[6]</sup> acyl moiety<sup>[6]</sup> for the direct alkenylation of



heterocyclic scaffold at C3-position. While some of the other protocols for the direct C3-alkenylation relied on the removable directing groups such as imines<sup>[7]</sup> and amides.<sup>[8]</sup> However, some of these useful methods have certain limitations such as requirement of pre-functionalized starting materials, installation and de-installation of directing group, poor substrate functional group tolerance, the use of stoichiometric amount of expensive reagents, and also multi-step strategy to access target compounds. In this regard, development of transient directing group (TDG) enabled strategy for the direct functionalization of relatively less reactive C3-(*sp*<sup>2</sup>)-H bond of five membered heterocyclic scaffold in presence of transition metal catalyst is highly desirable to overcome some of the perennial problems.

The C-H activation strategy using a transient directing group (TDG) has become increasingly promising and popular over the last few years. The transient directing group are formed *in situ* by the binding of ligand with the substrate which further coordinates to the metal in reversible fashion and it has advantage of easy installation and subsequent removal without affecting functionality of the substrate.<sup>[9]</sup> In this regard different research groups have reported the use of transient directing groups for the C-H functionalization of various carbonyl compounds.<sup>[9a,b,10]</sup> In 2017 Ge and co-workers have reported the  $\beta$ -C(*sp*<sup>2</sup>)-H arylation of five-membered heterocyclic carbonyl compounds by using 3-amino-3-methylbutanoic acid as TDG.<sup>[11]</sup> Similarly, our research group has reported the direct  $\gamma$ -C(*sp*<sup>3</sup>)-H arylation of 3-methylheteroarene-2-carbaldehydes via TDG mediated strategy using  $\alpha$ -amino acid.<sup>[12]</sup> Very recently Oble and co-workers have reported the C3-alkenylation of 2-carboxaldimine heterocyclopentadienes (prepared from corresponding aldehydes) using Ru(0) as a catalyst (Scheme 1A).<sup>[7]</sup> To the

best of our knowledge, there is no report on TDG mediated direct C3-alkenylation of five-membered heterocyclic aldehydes till date.

Herein we report the very first transient directing group (TDG) enabled site-selective direct C3 alkenylation of five-membered heteroarene-2-carboxaldehydes via palladium catalysis (Scheme 1B).<sup>[13]</sup>

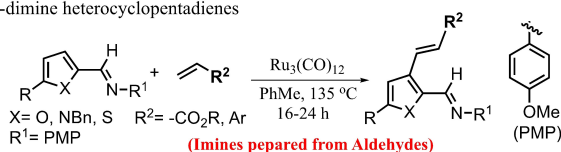
## Results and Discussion

In order to explore the possibility of direct alkenylation of five-membered heterocyclic carbonyl compounds, we commenced with the model reaction of thiophene-2-carboxaldehyde **1a** (0.2 mmol) with isobutyl acrylate **2a** (0.6 mmol) in presence of Pd(OAc)<sub>2</sub> (10 mol%), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (1 equiv.), **TDG1** (20 mol%), HFIP/AcOH (9/1, 1 mL) at 110 °C for 24 h under argon atmosphere. Interestingly, we observed the formation of isobutyl (*E*)-3-(2-formylthiophen-3-yl)acrylate **3aa** in 38% yield (Table 1, Entry 1). With this initial lead, we further carried out this model reaction with an additional ligand **L1** (20 mol%) to obtain **3aa** with an improved yield (47%, Table 1, Entry 2). Further we optimized the reaction by increasing the **TDG1** loading (40 mol%, Table 1, Entry 3). Gratifyingly we observed improvement in the yield of **3aa** (57%, Table 1, Entry 3). However, the further increase in the loading of **TDG1** (60 mol%) resulted in decrease of yield of **3aa** (Table 1, Entry 4). Later, increase in the molar equivalent of **2a** (2 to 3 equiv.) enhanced the yield of **3aa** (62%, Table 1, Entry 5). Subsequently, we observed that the increase in the ligand loading of 5-(trifluoromethyl)-2-pyridone **L1** (40 mol%) decreased the yield of **3aa** (Table 1, Entry 6). We further screened the reaction using different oxidants and we observed that among all, Cu(OAc)<sub>2</sub>·H<sub>2</sub>O proved to be the best for the desired transformation (Table 1, Entries 7–9). We observed that increase in the stoichiometric amount of oxidant Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (1 equiv. to 1.1 equiv.) enhanced the yield of **3aa** (67%, Table 1, Entry 10).

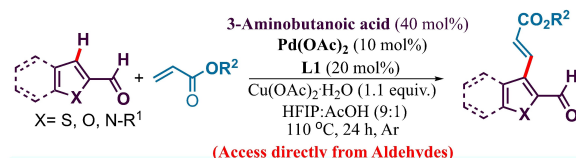
In order to optimize further we screened different TDGs and among all, **TDG1** proved to be efficient (See Table S1, ESI). We noticed that reaction did not work in presence of TDG4 ( $\alpha$ -amino acid) and probably  $\beta$ -amino acid favors the formation of [5,6]-bicyclic palladium transition state, which is not possible with  $\alpha$ -amino acid. Further, we screened the reaction using various ligands (**L1**–**L11**) and among all, **L1** proved to be best for the desired transformation (See Table S2, ESI).

We further screened the reaction using different solvents and we observed that among all, HFIP/AcOH mixture proved to be most advantageous (Table 1, Entry 10 and Entries 13–17). Later changing the ratio of HFIP/AcOH from 9:1 v/v to 6:4 v/v resulted in the reduction in the yield of **3aa** (Table 1, see Entries 11, 12).

**A. Previous work:** Ru(0) catalyzed C3 (*sp*<sup>2</sup>) C-H alkenylation of 2-carboxal-dimine heterocyclopentadienes



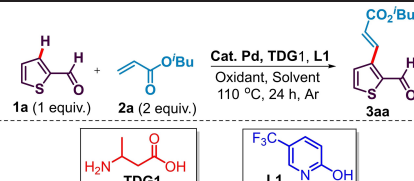
**B. Present work:** Pd(II) catalyzed and TDG enabled C3-(*sp*<sup>2</sup>)-H alkenylation of five membered heterocyclic aldehydes-Access to luminogenic material



**Key Features:**

- Site-selective direct C3 alkenylation
- Readily available starting materials
- $\beta$ -amino acid as a transient directing group
- Exclusive *E*-selectivity
- Access to Mechanochromic Luminogen
- Broad substrate scope

**Scheme 1.** C3-(*sp*<sup>2</sup>)-H alkenylation of five-membered heterocyclic scaffolds.

**Table 1.** Optimization of Reaction Conditions.<sup>[a]</sup>


| Entry           | Pd Source                            | TDG (mol%) | Additive                                | L (mol%) | 2a (equiv.) | Solvent                           | Yield 3aa (%) <sup>b</sup> |
|-----------------|--------------------------------------|------------|-----------------------------------------|----------|-------------|-----------------------------------|----------------------------|
| 1               | Pd(OAc) <sub>2</sub>                 | TDG1 (20)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | -        | 2           | HFIP/AcOH (9:1, v/v)              | 38                         |
| 2               | Pd(OAc) <sub>2</sub>                 | TDG1 (20)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 2           | HFIP/AcOH (9:1, v/v)              | 47                         |
| 3               | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 2           | HFIP/AcOH (9:1, v/v)              | 57                         |
| 4               | Pd(OAc) <sub>2</sub>                 | TDG1 (60)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 2           | HFIP/AcOH (9:1, v/v)              | 45                         |
| 5               | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v)              | 62                         |
| 6               | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (40)  | 3           | HFIP/AcOH (9:1, v/v)              | 53                         |
| 7               | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(TFA) <sub>2</sub> ·xH <sub>2</sub> O | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v)              | 61                         |
| 8               | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub>                    | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v)              | 40                         |
| 9               | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | AgOAc                                   | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v)              | 38                         |
| 10              | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v)              | 67                         |
| 11              | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP/AcOH (8:2, v/v)              | 59                         |
| 12              | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP/AcOH (6:4, v/v)              | 50                         |
| 13              | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP (1 mL)                       | 30                         |
| 14              | Pd(TFA) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | AcOH (1 mL)                       | N.R.                       |
| 15              | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP/Ac <sub>2</sub> O (9:1, v/v) | 57                         |
| 16              | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP/TFA (9:1, v/v)               | N.R.                       |
| 17              | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | TFE/AcOH (9:1, v/v)               | 55                         |
| 18 <sup>c</sup> | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v)              | 65                         |
| 19 <sup>d</sup> | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v)              | 58                         |
| 20 <sup>e</sup> | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v)              | 51                         |
| 21              | Pd(TFA) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v)              | 53                         |
| 22              | PdCl <sub>2</sub> (ACN) <sub>2</sub> | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v)              | 40                         |
| 23              | PdCl <sub>2</sub>                    | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v)              | 45                         |
| 24              | Pd(PPh <sub>3</sub> ) <sub>4</sub>   | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v)              | >10                        |
| 25              | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | -        | 3           | HFIP/AcOH (9:1, v/v)              | 50                         |
| 26              | -                                    | TDG1 (40)  | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v)              | N.R.                       |
| 27              | Pd(OAc) <sub>2</sub>                 | -          | Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O  | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v)              | N.R.                       |
| 28              | Pd(OAc) <sub>2</sub>                 | TDG1 (40)  | -                                       | L1 (20)  | 3           | HFIP/AcOH (9:1, v/v)              | N.R.                       |

<sup>[a]</sup> Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), Pd catalyst (10 mol%), **TDG1** (20–60 mol%), Ligand **L1** (20–40 mol%), oxidant (0.3 mmol), solvent (1 mL), 110 °C, Ar, 24 h.

<sup>[b]</sup> yields of isolated compounds after column chromatography.

<sup>[c]</sup> 120 °C.

<sup>[d]</sup> 100 °C.

<sup>[e]</sup> Under air, TDG: Transient Directing group, HFIP: 1,1,3,3-Hexafluoro-2-propanol, AcOH: acetic acid, Ac<sub>2</sub>O: acetic anhydride, TFA: trifluoroacetic acid, TFE: trifluoroethanol.

The result indicated that HFIP/AcOH (9:1 v/v, 1 mL) is the optimum solvent ratio for the desired reaction.

We also varied the catalyst loading [5–15 mol% of Pd(OAc)<sub>2</sub>] and observed that 10 mol% of catalyst proved to be optimum for the transformation (see Table S3, ESI). We noticed that the lowering or raising the reaction temperature from 110 °C reduced the yield of the product **3aa** (Table 1, Entries 18–19). The reaction worked smoothly under inert atmosphere thus indicating that air (or oxygen) has no role in the outcome of the reaction (Table 1, Entry 20).

Additionally, we screened four different palladium catalysts and among all Pd(OAc)<sub>2</sub> (10 mol%) proved to be optimum catalyst for the desired transformation (Table 1, Entries 21–24). The reaction in the absence of

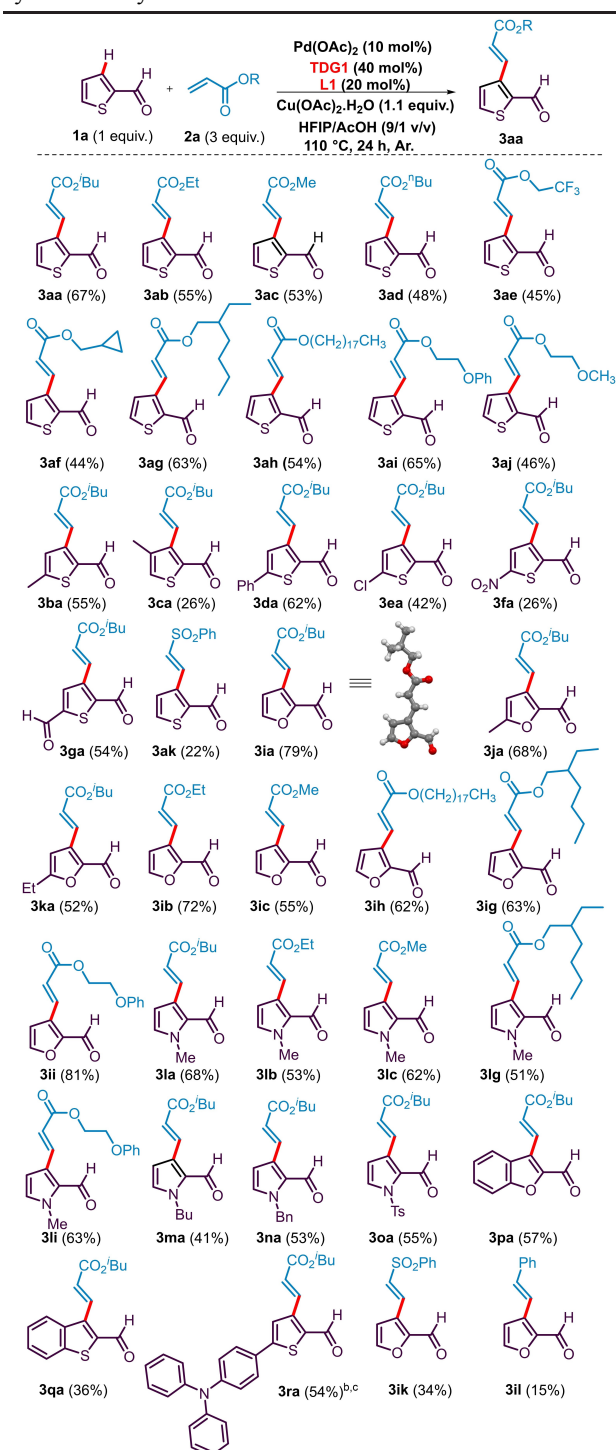
catalyst, oxidant and **TDG1** did not afford the desired product **3aa** (Table 1, Entries 26–28). Based on the exhaustive screening, compound **1a** (0.2 mmol), **2a** (0.6 mmol), Pd(OAc)<sub>2</sub> (10 mol%), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (1.1 equiv.), **TDG1** (40 mol%), **L1** (20 mol%) in HFIP/AcOH (9:1 v/v, 1 mL) at 110 °C for 24 h under inert atmosphere (Argon) proved to be the optimum reaction condition.

Having optimized the reaction conditions, we set out to explore the strategy with thiophene-2-carboxaldehyde **1a** with a broad range of acrylates **2** for the wider substrate scope (Table 2). A variety of acrylates (**2a–2j**) bearing different moieties (linear chain as well as cyclic) reacted under the optimum reaction conditions to afford the corresponding products (**3aa–3aj**) with moderate to good yields respectively (up to 67%, Table 2). Furthermore, a thiophene-2-carboxaldehyde bearing electron donating as well as electron withdrawing groups either at C4 and C5 positions (**1b–1f**) reacted smoothly with *iso*-butyl acrylate (**2a**) to furnish the corresponding products (**3ba–3fa**) in moderate yields (Table 2). Interestingly, 2, 5-thiophene-di-carboxaldehyde **1g** upon treatment with *iso*-butyl acrylate **2a** afforded the corresponding mono C3-alkenylated product **3ga** in moderate yield. Further, we explored the reactivity of furfural **1i** as well as substituted furfural (**1j–1k**) by treating with different acrylates (**2a–2i**). In all the cases the corresponding selective C3-alkenylated products (**3ia–3ka–3ii**) were obtained in good to excellent yields (Table 2).

Further different *N*-protected pyrrole-2-carboxaldehydes (**1l–1o**) also reacted smoothly with different acrylates to furnish the corresponding products (**3la–3oa**) in good yields (Table 2). Further, the molecular structure of **3ia** was unambiguously established by single crystal X-ray analysis.<sup>[14]</sup> However, the indole and free N–H pyrrole compounds did not give the desired products under optimized reaction conditions.

Even the benzofuran and benzothiophene carbonyl compounds (**1p–1q**) reacted with *iso*-butyl acrylate (**2a**) smoothly to afford the corresponding products (**3pa–3qa**) in moderate yields. The other electron deficient alkene phenyl vinyl sulphone **2k** also reacted efficiently with thiophene carboxaldehyde **1a** and furan carboxaldehyde **1i** under optimized reaction condition to furnish the corresponding C-3 alkenylated products (**3ak–3ik**) though in lower yields (Table 2). The styrene **2l** also reacted with furan-2-carboxaldehyde **1i** to afford the corresponding product **3il** albeit in poor yield (Table 2). However, other alkenes (cyclohexene, acryl amide, enone and enals, methacrylates etc.) did not react under the optimized reaction condition.

Overall, we observed that the protocol proved to be selective for the C3-alkenylation of heterocyclic aldehydes under the standard optimum reaction conditions. We did not observe even trace amount of C3, C5 dialkenylated products and the protocol afforded ex-

**Table 2.** A library of C3-alkenylated five-membered heterocyclic carbonyl scaffolds.<sup>[a,b]</sup>

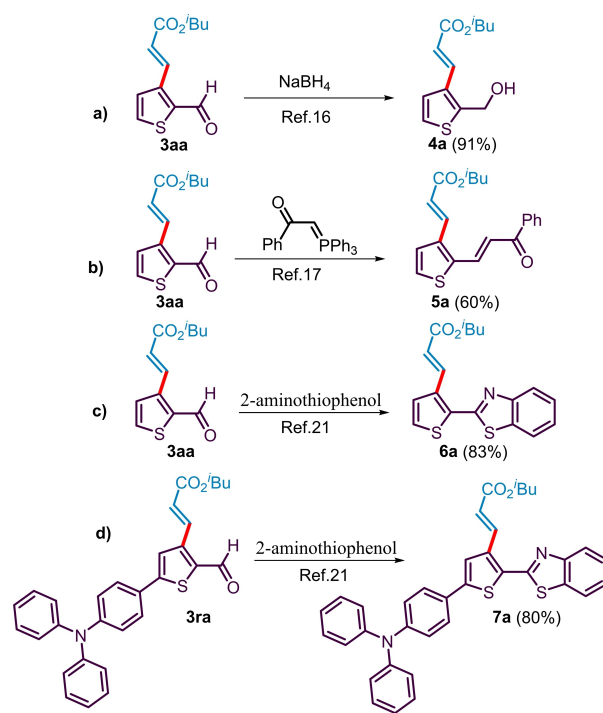
clusively C3-alkenylation products. A plausible reaction mechanism of this transformation has been proposed (See ESI, Page S8).<sup>[15]</sup>

Further we examined the derivatization of C3 alkenylated thiophene-2-carboxaldehyde as an application to this strategy. The reaction of **3aa** with NaBH<sub>4</sub> afforded the corresponding reduction product **4a** in excellent yield (91%, Scheme 2a).<sup>[16]</sup>

Later, we employed the **3aa** for the Wittig reaction to obtain the corresponding  $\alpha,\beta$  unsaturated carbonyl compound **5a** (60%, Scheme 2b).<sup>[17]</sup>

After having established the synthetic strategy successfully, we planned to explore the luminogenic property of some of these new compounds by looking at their structural framework. The organic solid state multi-stimuli responsive materials have been increasingly in demand in the last decade for their various applications in the field of sensing and imaging.<sup>[18]</sup> However, these materials change their luminescence properties such as emission color and intensity when applied to the external mechanical force known as mechanochromism.

Donor-acceptor based organic molecules with higher degree of flexibility, twisting and non-covalent interactions in the crystalline packing network are prone to exhibit stimuli-responsive behavior due to their freedom to alter the dihedral angle between the donor and acceptor moieties.<sup>[19]</sup> Specially, electron rich triphenylamine moiety with propeller shaped structure is considered to be one of the best building blocks for designing

**Scheme 2.** Selective synthetic transformations.



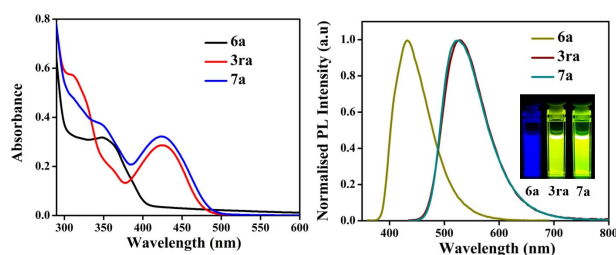
novel mechanochromic luminogens due to the presence of very flexible three phenyl rings. Owing to the importance of mechanochromic luminogens, we planned to explore further utility of this novel strategy for the mechanochromic studies.

In order to synthesize luminogen, we commenced with the synthesis of TPA containing compound **3ra** following the optimized protocol (Table 2). The precursor of **3ra** was synthesized from **1r** which is synthesized via Suzuki cross-coupling reaction<sup>[20]</sup> subsequently following our optimized reaction condition. Later, we synthesized compounds **6a** and **7a** starting from **3aa** and **3ra** respectively via the functional group transformation from aldehyde into the benzothiazole moiety using the 2-aminothiophenol (Scheme 2c, d).<sup>[21]</sup>

Having synthesized the potential luminogens, we recorded the UV-visible absorption spectra of **6a**, **3ra** and **7a** in dilute solution (10  $\mu$ M) in toluene (See Figure 2). In **3ra** and **7a** the lowest energy broad absorption band (in the 380–500 nm region) and this can be ascribed to the ICT (intramolecular charge transfer) transition from the electron-rich triphenylamine to the electron deficient C3-alkenyl moieties.

The high energy absorption band (in 300 nm–360 nm region) may be attributed to the molecular  $\pi$ – $\pi^*$  transition. Noticeably, in **6a**, due to the absence of the triphenylamine moiety, such ICT transition band is not present and only the molecular  $\pi$ – $\pi^*$  transition takes place in the same region as that of **3ra** and **7a**. The steady state PL (photoluminescence) spectra of all the luminogens in toluene showed only a single emission band. While the compound **6a** in toluene exhibited blue emission with maxima at  $\sim$  430 nm, whereas, compounds **3ra** and **7a** in toluene exhibited green emission with the maxima at  $\sim$  525 nm. The FWHM (Full Width at Half Maxima) also varied from **6a** (75 nm) to the other two luminogens ( $\sim$  90 nm).

The higher emission band-width in **3ra** and **7a** is due to higher charge-transfer character of the  $S_1$  state owing to the possibility of charge transfer between the triphenylamine and C3-alkenyl moieties in these molecules.

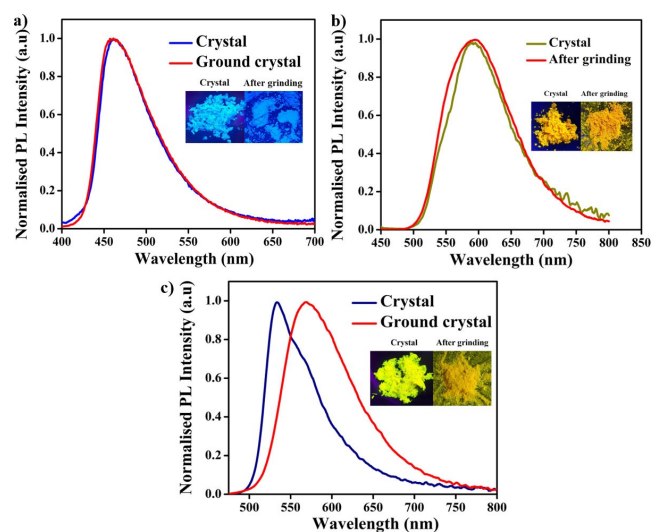


**Figure 2.** Absorption and emission spectra of **6a**, **3ra**, and **7a** in toluene (10  $\mu$ M) of each compound. Emission spectra were collected upon excitation at 380 nm.

Molecular flexibility and arrangement in crystalline lattice play a significant role for the outcome of emission color under external stimuli. Triphenylamine moiety can be used as a suitable building block for designing novel mechanochromic luminogens, owing to its super flexible propeller like structure. In a D-A (donor-acceptor) architecture, the excited state charge transfer emission is largely dependent on the dihedral angle between the donor and acceptor moieties, and in a flexible luminogen, external stimuli (pressure, temperature, organic vapor treatment) can alter the dihedral angle thus altering the emission color.

The crystals of **6a** exhibited the cyan-blue emission (QY=0.17) with emission maxima at  $\sim$ 460 nm. After vigorous grinding, we observed that the emission color did not change. Similarly, compound **3ra** upon vigorous grinding, the yellow emission of the crystals (QY=0.27) was unaltered, although FWHM of the emission changed from 108 nm in crystal to 122 nm in its ground form. This result suggested that involvement of structurally unordered state or amorphization due to grinding. Intriguingly, in **7a**, upon slight grinding of the green emitting crystals (QY=0.16, maxima at  $\sim$ 532 nm), the emission maxima had 38 nm red shift and the ground powder exhibited bright yellow emission (maxima at  $\sim$ 570 nm, Figure 3)

In **7a** crystals, the emission was structured with a narrow band-width (67 nm) whereas, the ground form of **7a** was found to be unstructured and broad (95 nm). Such alternation of the emission maxima as well as the emission feature may be attributed to more charge transfer character in ground form **7a** and also due to an increase in the orbital overlap between the donor and the acceptor moieties upon mechanical grinding.



**Figure 3.** Emission spectra and UV irradiated (365 nm) photos (given in inset) before and after grinding of a) **6a** b) **3ra** c) **7a**.

To gain an in-depth understanding of the structure-property relationship of these luminogens, powder X-ray diffraction was performed. PXRD patterns of all the luminogens in crystalline state exhibited sharp and intense reflection peaks (See ESI, Page S9). Apart from **6a**, in other two cases, upon grinding treatment the intensity and sharpness of those reflection peaks were largely reduced. In fact, after grinding **7a** a broad halo appeared thus suggesting a transformation from ordered crystalline state to the disordered amorphous state. Although in **3ra** a modulation of crystallinity was taking place, but the energy change due to this was not enough to alter its visual emission color. In compound **7a**, such transformation may lead to a separate metastable state with variable energy to tune its emission color from green to bright yellow.

The utmost importance of mechanochromic luminogens is its reversibility to its original crystalline state. In this regard, we have carefully dissolved the amorphous powder (**7a**) in DCM and further its slow evaporation furnished the original crystalline state. After the DCM dissolution, the PXRD patterns and the steady state emission spectra of the re-grown crystals totally matched with the original crystals thus supporting our observations. In **6a**, the DSC profile of both the crystals and ground powder showed almost no change, suggesting no major phase transition happening in this case (See ESI, Page S10). Intriguingly, other two luminogens (**3ra**, **7a**) behaved differently. In crystal **3ra**, two exothermic peaks at 73 °C and 92 °C shifted to 71 °C and 90 °C respectively in its ground form. This result suggested a phase transition behavior in this molecule. In case of **7a**, the transition was much clearer and the crystals exhibited three exothermic peaks at 64 °C, 96 °C and 130 °C. Upon grinding, the peak at 64 °C and 130 °C disappeared, while, at 96 °C one of the peaks got shifted to 90 °C. This clearly indicated a phase transition that finally leads to the alternation of its energy state and mechanochromic activity.

## Conclusion

In summary, we have developed a protocol for the direct site selective C3-alkenylation of five membered heterocyclic carbonyl compounds with a variety of acrylates via palladium catalysis. This strategy has been accomplished relying on the strength of  $\beta$ -amino acid as a transient directing group and 5-(trifluoromethyl)-2-pyridone as an external ligand. A wide substrate scope with good functional group tolerance has been demonstrated. The protocol also proved to be useful to build a mechanochromic luminogenic material.

## Experimental Section

A 15 mL dry pressure tube with screwcap equipped with a stir bar was charged with thiophene-2-carboxaldehyde **1a** (19  $\mu$ L,

0.2 mmol, 1.0 equiv.), isobutyl acrylate **2a** (86.41  $\mu$ L, 0.6 mmol, 3 equiv.), Pd(OAc)<sub>2</sub> (4.5 mg, 0.01 mmol, 0.1 equiv.), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (43.94 mg, 0.3 mmol, 1.1 equiv.), 3-aminobutanoic acid as a **TDG1** (8.25 mg, 0.04 mmol, 0.4 equiv.), Ligand **L1** (6.5 mg, 0.02 mmol, 0.2 equiv.) followed by the addition of the mixture of solvent HFIP (0.9 mL) and AcOH (0.1 mL) at room temperature. Then the resulting reaction mixture was degassed under argon atmosphere for 2 min and stirred vigorously at room temperature for 10 min. The reaction mixture was heated to 110 °C for 24 h. After, completion of the reaction (monitored using TLC), the reaction mixture was cooled to room temperature and it was diluted with EtOAc (15 mL) and subsequently it was filtered through a pad of celite. The filtrate was concentrated under vacuo and the residue was purified by column chromatography on silica gel to furnish the desired product **3aa** as a yellow oil (67%, 32 mg).

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# Palladium Catalyzed C3-(sp<sup>2</sup>)-H Alkenylation of Pyrroles: A Direct Access to Novel Organic Thermally Activated Delayed Fluorescence (TADF) Materials

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**Abstract:** A Pd (II)-catalyzed direct C3-(sp<sup>2</sup>)-H alkenylation of heteroarenes using benzothiazole as a directing group has been successfully achieved. A wide range of 2-*N*-alkylpyrroles undergo an oxidative coupling with a variety of acrylates to furnish highly regio- and chemo-selective *E*-alkenylation products at C3 position. An important intermediate complex has been isolated and characterized so as to have an insight into the mechanism. This convenient protocol proved to be practical to access novel thermally activated delayed fluorescence materials (TADF). These molecules proved to be blue emitting TADF materials (~ms life time). A detailed and systematic investigation has been carried out to study the photophysical properties and this has been further validated by the time dependent (TD) density functional theory (DFT) calculations.

## Introduction

The five membered heterocyclic scaffold has a great significance as it is found in many pharmaceutically active compounds and therapeutic agents.<sup>[1]</sup> Among many heteroarenes, pyrrole is one of the most important core scaffolds that is prominently present in pharmaceutically active compounds, marketed drugs such as tolmetin, atorvastatin and ketorolac. Also, many natural products, bioactive molecules, polymers, dyes contain pyrrole as a core scaffold.<sup>[2,3]</sup> Importantly, the histone deacetylase inhibitor and pyrrole barbiturates contain the C3-alkenylated pyrrole core as well.<sup>[2,3]</sup> Few organic functional materials also contain pyrrole framework.<sup>[2,3]</sup> Interestingly, benzothiazole derived compounds are known to be biologically active<sup>[4]</sup> and core to some of the pharmaceuticals. Also, due to fluorescence properties, the benzothiazole scaffold has been explored in optical research and utilized in fluorescence probes.<sup>[5,6]</sup> Looking at the importance and applications of these compounds, we planned to design and synthesize the hybrid molecules containing both pyrrole and benzothiazole moieties. We also hypothesized that having an extended delocalization by introducing an olefinic moiety may enhance the photophysical properties of this hybrid core scaffold (Scheme 1b). In order to construct this proposed hybrid framework, we planned to build the pyrrole-benzothiazole core first followed by the

alkenylation based on few parameters. Along with its biological potency and optical properties, benzothiazole has also been explored as a directing group (DG) for C-H activation.<sup>[4,7]</sup> In this regard, we planned to build the pyrrole-benzothiazole hybrid framework and explore the strength of benzothiazole (as a DG) for the direct alkenylation at suitable position. In the last few years, the transition metal catalyzed alkenylation of five membered heteroarenes have emerged among the most atom- and step-economical approaches in organic synthesis.<sup>[8]</sup> However, the selective C3-alkenylation of the pyrrole derivatives is relatively difficult due to its low reactivity at this position compared to more reactive C2 and C5 positions as they are located at  $\alpha$ -position of the nitrogen in pyrroles.<sup>[9]</sup> Despite their high significance in pharmaceuticals and their utility in organic synthesis, only a few literature reports are available for the direct C3-alkenylated pyrrole derivatives.<sup>[7,10-12]</sup> Though some of these methods have their own merits, however some of these have limitations such as relying on pre-functionalized starting materials, necessity of bulky group on the nitrogen and multi-step approaches to access target compounds.<sup>[7,10-12]</sup>

Interestingly, the alkenylation of the pyrroles by using benzothiazole moiety as a directing group has been rarely explored in the literature. Also there are limited reports on the use of benzothiazole moiety as a directing group for the C-H bond functionalization of aromatic/heteroaromatic compounds.<sup>[4,7]</sup> In 2017, Peng and coworkers disclosed the *ortho*-alkenylation of the aromatic compounds using benzothiazole as a directing group.<sup>[4]</sup>

Looking at the limited synthetic strategies using benzothiazole moiety as a directing group, we became more interested to construct the pyrrole-benzothiazole hybrid molecule along with the alkenyl functionality. This would give an opportunity to develop synthetic strategy as well as furnish novel compounds with an extended delocalization to harness the photophysical properties and possible potent bioactivity.

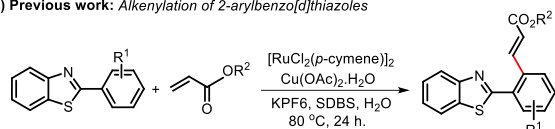
However, the transition metal catalyzed C3-(sp<sup>2</sup>)-H alkenylation of 2-*N*-alkylpyrrole benzo[d]thiazoles with a variety of acrylates using benzothiazole moiety as a directing group is

always challenging and there are no literature precedence. Hence it is desirable to explore the C3-alkenylation of 2-*N*-alkylpyrrole benzo[d]thiazoles subsequently to construct the target molecule. To the best of our knowledge there are no reports on C3-alkenylation of 2-*N*-alkylpyrrole benzo[d]thiazoles with different acrylates in presence of palladium or other metal catalysts and this framework is not known in the literature.

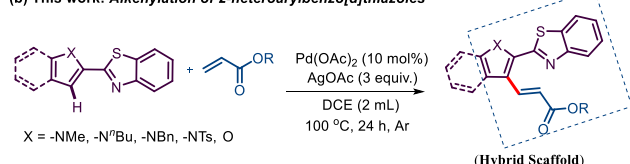
Herein, we report the direct C3-alkenylation of 2-*N*-alkylpyrrole benzo[d]thiazoles with a series of acrylates with a varied electronic properties via palladium catalysis for the very first time to access molecules with blue TADF properties (Scheme 1b).

**Scheme 1.** Benzothiazole directed C3-(sp<sup>2</sup>)-H alkenylation

(a) **Previous work:** Alkenylation of 2-arylbenzo[d]thiazoles



(b) **This work:** Alkenylation of 2-heteroarylbenzo[d]thiazoles



## Result and Discussion

In order to achieve the hypothesized hybrid target molecule, we commenced with the 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole **1a** (0.1 mmol) and ethyl acrylate **2a** (0.3 mmol) as a model substrates. Gratifyingly, we obtained the corresponding desired C3-alkenylation product ethyl(*E*)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl) acrylate **3aa** in moderate yield (64% yield, Table 1, Entry 1) along with the C3/C5-dialkenylated product **3aa'** albeit in poor yield (10%, Table 1, Entry 1). Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (3 equiv.) in DCE solvent under inert atmosphere at an elevated temperature proved to be the initial optimization condition (Table 1, Entry 1).

With this initial success, we further carried out the optimization of the reaction condition by screening various catalysts, oxidants and solvents (See ESI, Table S1-S3, Page S5-S6). Among all, the reaction of **1a** and **2a** in presence of Pd(OAc)<sub>2</sub>, AgOAc in DCE at an elevated temperature proved to be the most optimum reaction condition to obtain the desired product **3aa** in highest yield (See, Table 1, Entry 1, and ESI, Table S1-S3, Page S5-S6). We observed that the reaction did not proceed in the absence of Pd-catalyst while maintaining other optimized reaction conditions (Table 1, Entry 2). The reaction in the absence of AgOAc furnished the desired C3-alkenylation product **3aa** in poor yield (10%, Table 1, Entry 3). These results clearly indicate that

Pd-catalyst and AgOAc as an oxidant are necessary and they synergistically work so as to achieve the desired transformation.

Further lowering the temperature (90 °C) as well as elevating the reaction temperature (110 °C) led to the desired C3-alkenylated product **3aa** in relatively diminished yield (Table 1, Entries 4, 5). Further the reaction in presence of air furnished the desired alkenylated product **3aa** in modest yield (45%, Table 1, Entry 6).

**Table 1.** Optimization of Reaction Conditions<sup>(a)</sup>

| Entry | Deviation from standard conditions   | Yield(%) <sup>b</sup> |             |
|-------|--------------------------------------|-----------------------|-------------|
|       |                                      | <b>3aa</b>            | <b>3aa'</b> |
| 1     | None                                 | 64                    | 10          |
| 2     | Without Pd(OAc) <sub>2</sub>         | N.R.                  | -           |
| 3     | Without AgOAc                        | 10                    | -           |
| 4     | Temperature 90 °C instead of 100 °C  | 56                    | 8           |
| 5     | Temperature 110 °C instead of 100 °C | 54                    | 7           |
| 6     | Air instead of Argon atmosphere      | 45                    | 5           |

<sup>[a]</sup>Standard conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Pd catalyst (10 mol%), AgOAc (0.3 mmol), DCE (2 mL), 100 °C, Ar, 24 h; <sup>[b]</sup>Isolated yields of **1a** after column chromatography; N.R.: No Reaction.

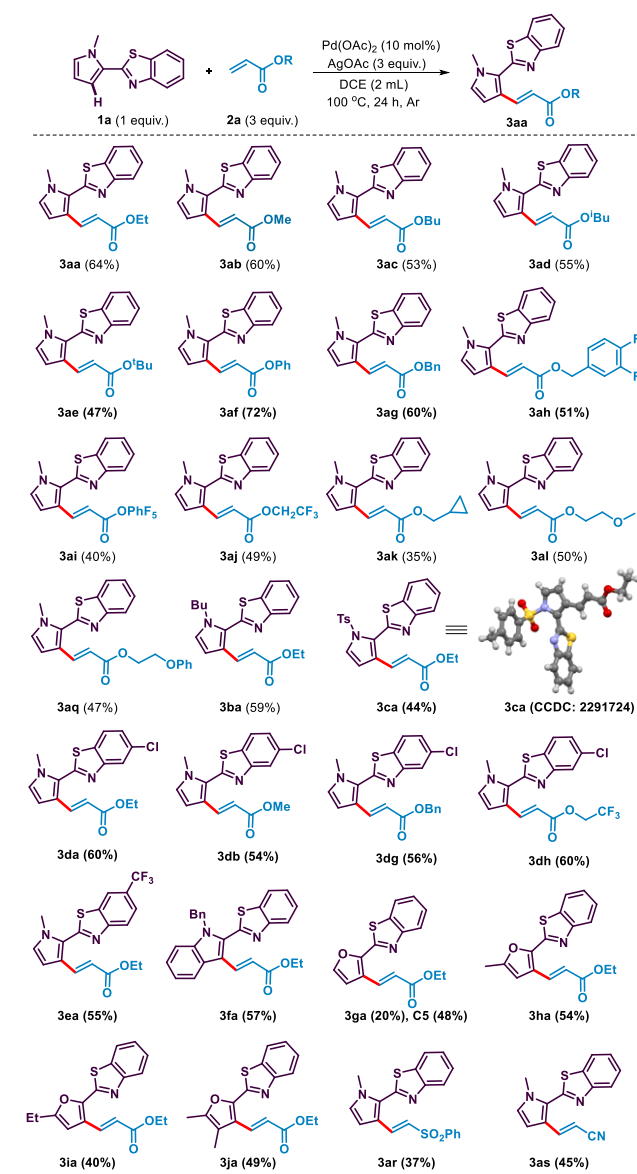
Having optimized the reaction conditions, we further explored the substrate scope of 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole with a broad range of acrylates (Table 2). The reaction of **1a** with a variety of acrylates (**2a-2l**, **2q**) having aliphatic, cyclic as well as linear chain moieties and aromatic groups underwent reaction smoothly to afford the corresponding C3-alkenylated derivatives (**3aa-3al**, **3aq**) in moderate to good yields respectively (up to 72%, Table 2).

Furthermore, the electron donating as well as electron withdrawing group containing *N*-protected pyrroles (**1b-1c**) reacted smoothly with ethyl acrylate **2a** to furnish the corresponding products (**3ba-3ca**) in moderate yields (Table 2). Further we explored the reaction of chloro and trifluoromethyl substituted benzothiazoles (**1d-1e**) with different acrylates (**2b**, **2g**, **2h**, **2a**) to furnish the corresponding products (**3db-3ea**) in moderate yields (Table 2). The reaction of 2-(1-benzyl-1H-indol-2-yl)benzo[d]thiazole **1f** with ethyl acrylate **2a** led to the formation of corresponding alkenylated product **3fa** in moderate yield (Table 2). As expected the reaction of free pyrrole and indole with unprotected N-H group did not give the desired product under similar reaction conditions.

Further the reaction of 2-(furan-2-yl)benzo[d]thiazole **1g** with ethyl acrylate **2a** furnished the desired C3 alkenylated product **3ga** in modest yield along with C5-alkenylated product (Table 2). Few substituted furan derivatives (**1h-1j**) also reacted smoothly with ethyl acrylate **2a** to afford corresponding C3-alkenylated products (**3ha-3ja**) in moderate yields (Table 2).

Gratifyingly, the reactions of 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole **1a** with other electron deficient alkenes (**2r-2s**) also worked well under the reaction conditions to afford the C3-alkenylated products (**3ar-3as**) in moderate yields (up to 45% Table 2). Along with the desired products, we also noticed the formation of dialkynelated products in very small amounts (< 6%)

**Table 2.** Alkenylation of 2-hetero-arylbenzo[d]thiazoles<sup>a, b</sup>

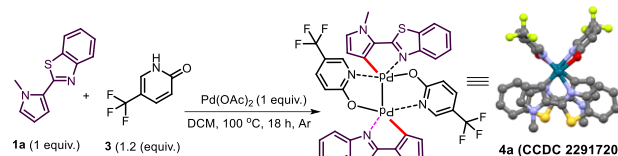


<sup>[a]</sup>Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Pd catalyst (10 mol%), Oxidant (0.3 mmol), solvent (2 mL), 100 °C, Ar, 24 h. <sup>[b]</sup>Isolated yields based on **1a** using column chromatography.

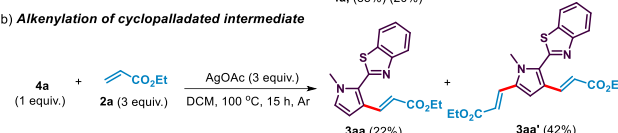
Later in order to have some mechanistic insight, we planned to utilize suitable ligand so as to trap the cyclopalladated intermediate from the reaction mixture. Gratifyingly, we isolated the cyclopalladated intermediate **4a** from the reaction of 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole **1a**, and palladium acetate in presence of stoichiometric amount of 5-(trifluoromethyl)-2-pyridone ligand **3** (Scheme 2a).

**Scheme 2.** Mechanistic insights for the palladium catalyzed alkenylation

(a) Synthesis of cyclopalladated intermediate **4a** and crystallographic structure of intermediate **4a**



(b) Alkenylation of cyclopalladated intermediate



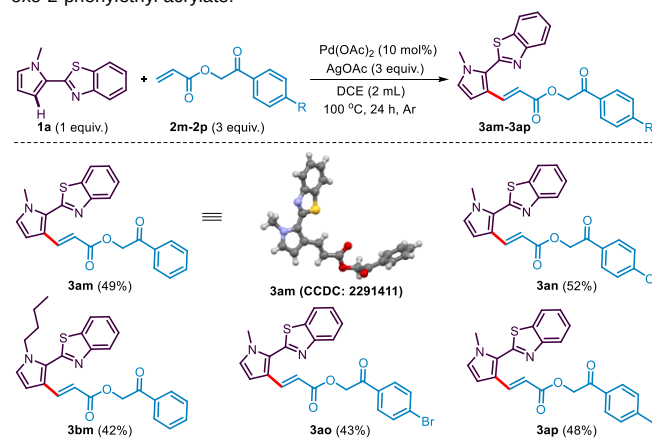
<sup>a</sup>Reaction carried out in DCE

We further subjected this intermediate **4a** for the alkenylation under the optimized reaction condition to afford the corresponding C3-alkenylated product **3aa** (22%) along with dialkynelated product **3aa'** (C3/C5, 42% yield, Scheme 2b).

A plausible catalytic cycle has been depicted for this transformation based on the observed results (Scheme 2) and prior literature reports<sup>[13]</sup> (See ESI, Page S7).

As aimed at the beginning, we further planned to synthesize few compounds having an extended electronic conjugation. 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole **1a** was treated with 2-oxo-2-phenylethyl acrylate **2m** to obtain 2-oxo-2-phenylethyl (*E*)-3-(2-(benzo[d]thiazol-2-yl)-1-methyl-1H-pyrrol-3-yl)acrylate **3am** in moderate yield (Scheme 3). Later, the reaction of **1a** with different halo and methyl group substituted 2-oxo-2-phenylethyl acrylates (**2m-2p**) afforded the corresponding C3-alkenylated products (**3am-3ap**) in moderate yields (Scheme 3).

**Scheme 3.** Alkenylation of 2-(1-methyl-1H-pyrrol-2-yl)benzo[d]thiazole with 2-oxo-2-phenylethyl acrylate: <sup>a, b</sup>



<sup>[a]</sup> Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol%), AgOAc (0.3 mmol), DCE (2 mL), 100 °C, Ar, 24 h. <sup>[b]</sup> Isolated yields based on **1a** using column chromatography.

Also, the treatment of 2-(1-butyl-1H-pyrrol-2-yl)benzo[d]thiazole **1b** with 2-oxo-2-phenylethyl acrylate **2m** under the optimized

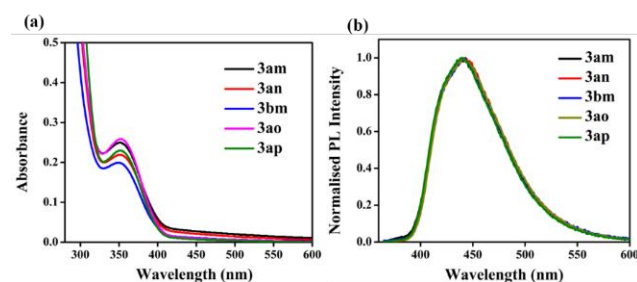


reaction conditions furnished the C3-alkenylated product **3bm** in moderate yield (42%, Scheme 3).

Multi-functional organic luminescent materials exhibiting the delayed fluorescence and phosphorescence properties have transformed the field of optoelectronics recently. These materials provide a versatile platform for applications in lighting, display, sensing, imaging and energy conversion devices.<sup>[14]</sup> Particularly, TADF enables the efficient conversion of non-emissive triplet excitons into emissive singlet excitons thus achieving nearly quantitative (100%) internal quantum efficiency (IQE) without the need for any heavy atoms.<sup>[15-17]</sup> This discovery has made a profound impact on organic electronics by addressing the long-standing issue of not exploring the potential of triplet excitons.

In recent years, there has been a significant progress in improving the performance of TADF-OLEDs through careful molecular designing. Most importantly, the blue and sky-blue TADF emitters have been proven to be low-cost, highly efficient, for the stable display illumination devices.<sup>[18-19]</sup> Molecules that emit blue or sky-blue light are very remarkable as they have potential capability for the display as well as lighting applications. It is also important to note that neither fluorescent nor phosphorescent emitters are suitable for blue OLEDs applications due to their low efficiency and unsatisfactory stability. TADF emitters on the other hand show a great promise to furnish the low-cost, highly efficient and stable blue OLEDs due to their inherent potential for high efficiency and stability.

Owing to this importance, we explored the photophysical properties of designed and synthesized compounds (**3am-3ap**) and gratifyingly they proved to be luminogens. We observed that the absorption spectra of all these luminogens (**3am-3ap**) in dilute THF solution have a major band at approximately 355 nm (Figure 1a). Through TD-DFT calculation at the B3LYP/6-31 G (d, p) level we believe that this absorption band could be attributed to the  $S_0-S_1$  transition upon photoexcitation (See ESI, Figure S4, Page S10).

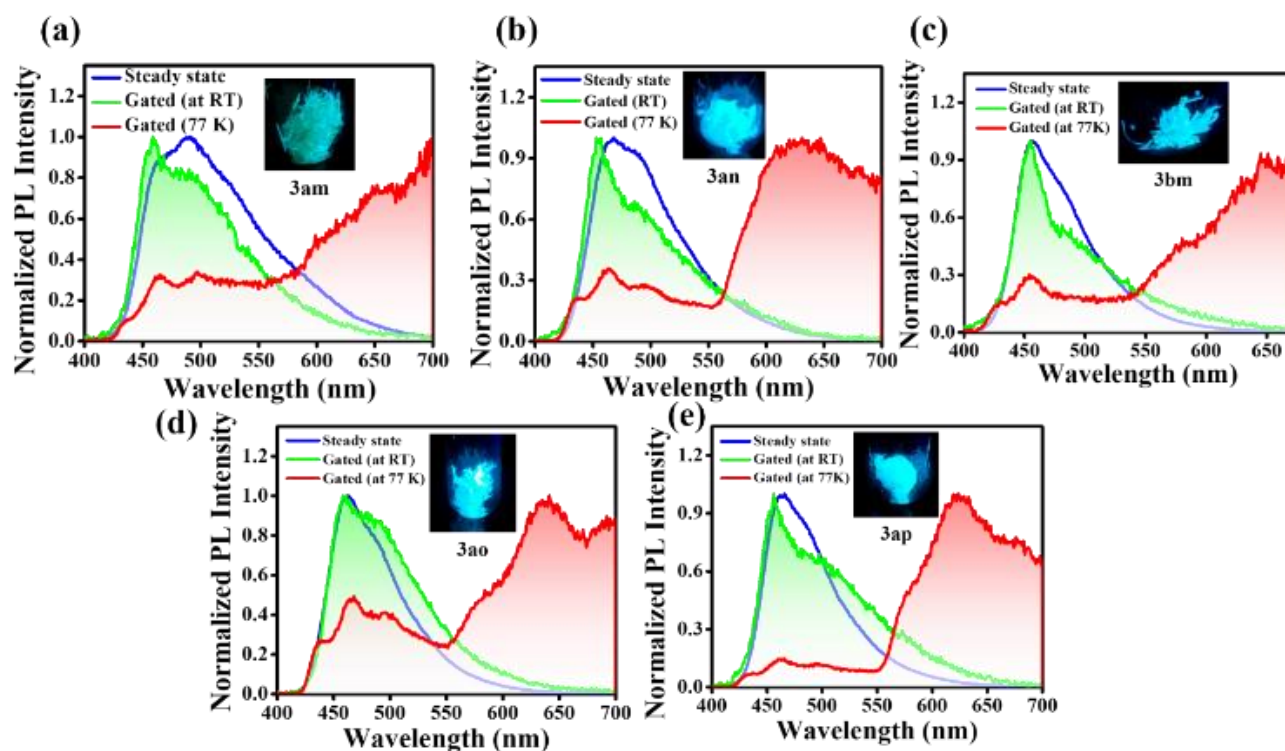


**Fig.1:** (a) Absorption and (b) Emission spectra of all the luminogens (**3am-3ap**) in dilute THF solution (10  $\mu$ m).

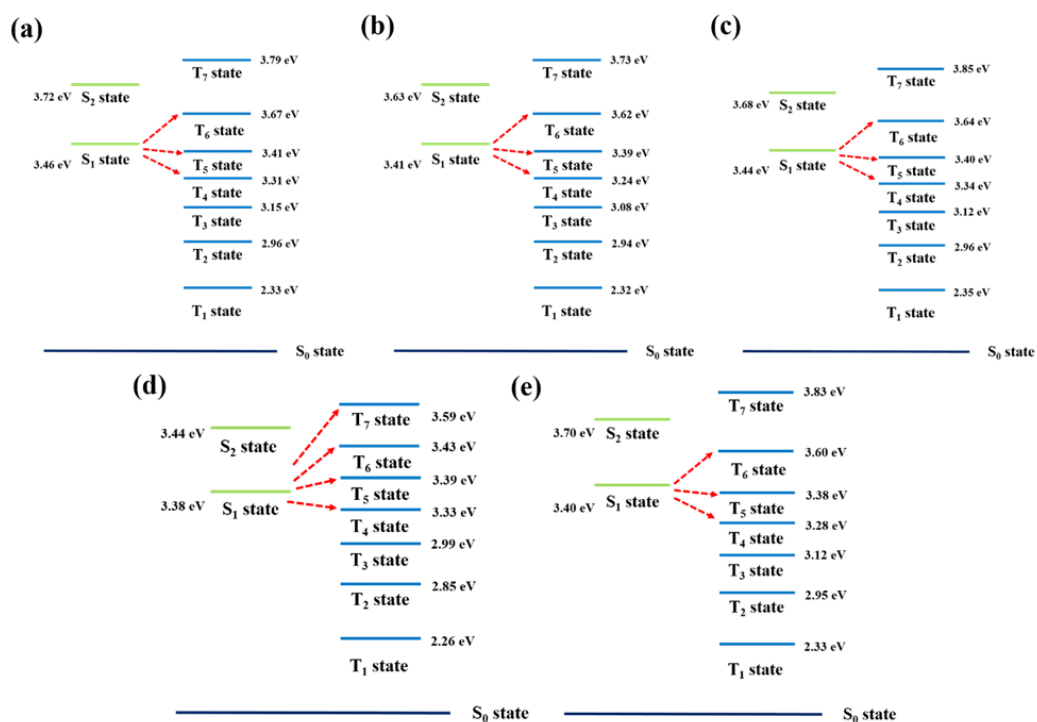
Since the energy of the  $S_0-S_1$  transition is almost the same for all the luminogens (**3am-3ap**), their absorption spectra remained unchanged. In addition, all these compounds (**3am-3ap**) in THF showed a similar emission spectrum with a maximum of about 440 nm (Figure 1b). Further, when exposed to UV light, crystal of all these compounds (**3am-3ap**) emitted a cyan-to-cyan-green emission (Figure 2).

In order to identify any delayed emission processes, we collected the time-gated emission spectrum with a 50  $\mu$ s time delay (Figure 2). The gated emission spectra of all the luminogens (**3am-3ap**) matched well and were in accordance with the steady-state emission spectra of these luminogens (**3am-3ap**) (Figure 2). This clearly indicated the presence of thermally activated delayed fluorescence (TADF). Further, the time-resolved photoluminescence (TRPL) studies have revealed that the luminogens (**3am-3ap**) exhibit prompt fluorescence in nanosecond time-scale (See ESI, Figure S1, Page S8) and a very long-lived delayed fluorescence in millisecond regime (See ESI, Figure S2, Page S8). The detailed information about the lifetime and quantum yield of the luminogens (**3am-3ap**) is summarized in Table 3. It is important to note that temperature plays a crucial role for the outcome of photophysical properties of these luminogens. The TADF process can be effectively inhibited by reducing the temperature to 77K and the resulting emission can be seen as phosphorescence. At room temperature, with a 50  $\mu$ s detector delay, all luminogens showed a major emission band in the 425-575 nm region which overlaps with the steady-state emission thus clearly supporting the TADF process (Figure 2).

Interestingly, when the temperature was reduced to 77 K, the intensity of TADF emission of compounds (**3am-3ap**) has been found to reduce significantly and a low-energy phosphorescent band largely dominated ( $> 600$  nm) the emission spectrum, thus supporting the thermal up-conversion process (Figure 2). Similar trends are observed in 1 wt% (**3am-3ap**) doped PMMA films (see ESI, Figure S5, Page S11), but the delayed fluorescence lifetime of all the molecules (**3am-3ap**) have been found to be comparatively shorter in the film state (Table 4, Also, see ESI, Figure S7, Page S13). Further the TD-DFT calculation on equal number of singlet and triplet state energies have been carried out to have a detailed information on the excited singlet and triplet states (see ESI for more details). Interestingly, the relative energies of all the singlet and triplet states have been found to be the same. This suggests substitution on the compounds (**3am-3ap**) has insignificant effect on the excited singlet and triplet state energies.



**Fig 2.** Steady-state and time-gated (at RT & at 77K) emission spectra of all five molecules. All the time-gated emission spectra were collected using 50  $\mu$ s of detector delay and 20 ms of the sample window.



**Fig.3:** TD-DFT (50-50) calculation of molecules (a) **3am** (b) **3an** (c) **3bm** (d) **3ao** and (e) **3ap** at the B3LYP/ 6-31G (d, p) level of theory (for **3ao**, the Br atom was treated with GenECP pseudopotential).

**Table 3.** Averaged prompt fluorescence lifetime, delayed fluorescence lifetime, and PL quantum yield of crystals (**3am** to **3ap**).

| Compound   | Prompt fluorescence lifetime (in ns) | Delayed fluorescence lifetime (in ms) | Quantum yield ( $\phi$ ) |
|------------|--------------------------------------|---------------------------------------|--------------------------|
| <b>3am</b> | 0.4                                  | 20                                    | 0.16                     |
| <b>3an</b> | 0.9                                  | 15                                    | 0.08                     |
| <b>3bm</b> | 0.5                                  | 41                                    | 0.08                     |
| <b>3ao</b> | 0.5                                  | 16                                    | 0.11                     |
| <b>3ap</b> | 0.7                                  | 14                                    | 0.07                     |

Intriguingly, careful evaluation of the excited state energies revealed that the  $S_1$  state of all the luminogens (**3am-3ap**) is close (within 0.3 eV energy range) to three triplet states ( $T_4$ - $T_6$ ). Such a close-lying singlet as well as triplet states could lead to the faster RISC process which could further assist in the TADF process (Figure 3).

**Table 4.** Averaged prompt fluorescence lifetime, delayed fluorescence lifetime, and PL quantum yield of 1 wt% emitter-doped PMMA films (**3am** to **3ap**).

| Compound name | Prompt fluorescence lifetime (in ns) | Delayed fluorescence lifetime (in ms) | Quantum yield ( $\phi$ ) |
|---------------|--------------------------------------|---------------------------------------|--------------------------|
| <b>3am</b>    | 0.6                                  | 0.6                                   | 0.35                     |
| <b>3an</b>    | 0.7                                  | 0.8                                   | 0.24                     |
| <b>3bm</b>    | 0.6                                  | 0.7                                   | 0.22                     |
| <b>3ao</b>    | 0.3                                  | 0.7                                   | 0.21                     |
| <b>3ap</b>    | 0.4                                  | 0.7                                   | 0.16                     |

These novel C3-alkenylated pyrrole-benzothiazole hybrid compounds have been proven to exhibit interesting thermally activated delayed fluorescence (TADF) properties in ~sub-milli-second to ~mili-second time scale with an emission in the blue to cyan color region. These newly introduced chromophores could further aid in the design and development of newer blue or sky-blue TADF luminogens in the future.

## Conclusions

In summary, we have developed the C3-( $sp^2$ )-H alkenylation of 2-*N*-alkylpyrrolebenzo[d]thiazole compounds with a variety of acrylates by using benzothiazole as a directing group. This method provides highly stereo- and regio-selective *E*-alkenylation products at C3 position with a broad substrate scope with a good functional group tolerance. The pyrrole-benzothiazole hybrid scaffold has been effectively utilized to access C3 alkenylated novel luminogens that are proved to be thermally activated delayed fluorescence materials (TADF).

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**Keywords:** palladium . C-H activation . alkenylation . pyrrole scaffolds . TADF materials.

## Data availability

General information, detailed experimental procedures, characterization data for all new compounds, and NMR spectra are in the ESI. Data for the crystal structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under the deposition number **3ca** (CCDC: 2291724) **3am** (CCDC: 2291411) **4a** (CCDC 2291720)

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### Author Contributions

J. Y.S conceived the project, optimized the reaction, performed the investigation on the control experiments, other spectroscopic techniques, the scope of the reaction, the purification of final compounds, and the first draft of the manuscript and prepared ESI.

A. B. synthesized compounds and purified. A. C. carried out the measurement of all the photophysical properties and theoretical analysis using DFT and wrote the related part of manuscript. D.L. made few compounds, purified the starting materials and helped in solving single crystal X-ray data. R. G. B. supervised the project, edited the manuscript and proofread the experimental part.

## Conflicts of interest

"There are no conflicts to declare".

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