# Manganese, Nickel and Copper-Catalyzed C−H Bond Alkylation and Alkynylation of (Hetero)arenes

by

**Suryadev Kumar Verma**
(Registration Number: 10CC18A26053)

**A thesis submitted to the**
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under the supervision of
**Dr. Benudhar Punji**

**CSIR-NATIONAL CHEMICAL LABORATORY**
**Pune**

Academy of Scientific and Innovative Research
AcSIR Headquarters, CSIR-HRDC campus
Sector 19, Kamla Nehru Nagar
Ghaziabad, U.P. - 201 002, India

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# Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, **"Manganese, Nickel and Copper-Catalyzed C–H Bond Alkylation and Alkynylation of (Hetero)arenes"** submitted by ***Suryadev Kumar Verma*** to the Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of ***Doctor of Philosophy of Science***, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) etc., used in the thesis from other source(s), have also been duly cited and acknowledged.

Suryadev Kr Verma

**Suryadev Kumar Verma**
Research Student
Date: 26-03-2024

**Dr. Benudhar Punji**
Research Supervisor
Date: 26-03-2024

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I **Suryadev Kumar Verma**, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. **10CC18A26053** hereby undertake that, the thesis entitled "**Manganese, Nickel and Copper-Catalyzed C–H Bond Alkylation and Alkynylation of (Hetero)arenes**" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)*".

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Name : Dr. Benudhar Punji
Date : 26-03-2024
Place : CSIR-NCL, Pune

*Dedicated to the Almighty God and my Parents*

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***Suryadev K. Verma***

**Units**

| | |
|---|---|
| **Å** | Angstrom |
| **$^{o}$C** | Degree Celsius |
| **g** | Gram |
| **mg** | Milligram |
| **h** | Hour |
| **Hz** | Hertz |
| **mL** | Millilitre |
| **µL** | Microlitre |
| **min** | Minutes |
| **MHz** | Mega Hertz |
| **mmol** | Millimole |
| **ppm** | Parts per million |
| **m/z** | Mass to charge ratio |
| **cm** | Centimetre |

**Chemical Notations**

| | |
|---|---|
| **AcOH** | Acetic acid |
| **$Ac_2O$** | Acetic anhydride |
| **Ad** | 1-Adamantane |
| **aq** | Aqueous |
| **br s** | Broad singlet |
| **BHT** | Butylated hydroxytoluene |
| **BDMAE** | Bis(2-dimethylaminoethyl) ether |
| **bpy** | Bipyridine |
| **Calcd** | Calculated |
| **Cat** | Catalyst |
| **$CDCl_3$** | Deuterated chloroform |
| **Conc.** | Concentrated |
| **Cy** | Cyclohexane |
| **DCE** | 1,2-dichloroethane |
| **DG** | Directing group |
| **DMF** | *N*,*N*-Dimethylformamide |
| **DMPU** | 1,3-Dimethyl-2-oxohexahydropyrimidine; *N*,*N*′- |

| | |
|---|---|
| | Dimethylpropylene |
| **DMSO** | Dimethyl sulfoxide |
| **DPEphos** | Bis[(2-diphenylphosphino)phenyl] ether |
| **dppe** | 1,2-Bis(diphenylphosphino)ethane |
| **dppen** | cis-1,2-Bis(diphenylphosphino)ethylene |
| **dppf** | 1,1'-Bis(diphenylphosphino)ferrocene |
| **dppbz** | 1,2-Bis(diphenylphosphanyl)benzene |
| **DTBP** | Di-*tert*-butyl Peroxide |
| **D$^t$BEDA** | *N*,*N*'-Di-tert-butyl ethylenediamine |
| **equiv** | Equivalent |
| **EtOH** | Ethanol |
| **EtOAc** | Ethyl acetate |
| **Galvinoxyl** | 2,6-Di-*tert*-butyl-α-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1- ylidene)-*p*-tolyloxy |
| **$H_2O$** | Water |
| **HRMS** | High resolution mass spectrometry |
| **KHMDS** | Potassium bis(trimethylsilyl)amide |
| **MALDI** | Matrix Assisted Laser Desorption/ionization |
| **NaHMDS** | Sodium bis(trimethylsilyl)amide |
| **$Na_2SO_4$** | Sodium sulfate |
| **NaH** | Sodium hydride |
| **Neocuproine** | 2,9-dimethyl-1,10-phenanthroline |
| **NMR** | Nuclear Magnetic Resonance |
| **OTf** | Trifluoromethanesulfonate |
| **Phen** | 1,10-Phenanthroline |
| **$PPh_3$** | Triphenyl phosphine |
| **rt** | Room temperature |
| **$^t$Bu-bpy** | 4,4'-Di-tert-butyl bipyridine |
| **TEMPO** | (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl |
| **TFE** | Trifluoroethanol |
| **TIPS** | Triisopropylsilyl |
| **TMEDA** | *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine |
| **TLC** | Thin layer chromatography |
| **Xantphos** | 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene |

- All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. Solvents were dried using standard protocols.
- All reactions were carried out in oven-dried glassware in open air or glove box or under a positive pressure of argon unless otherwise mentioned with magnetic stirring.
- Air-sensitive reagents and solutions were transferred *via* syringe or cannula and were introduced to the apparatus *via* rubber septa.
- Progresses of reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with UV light, $KMnO_4$ stain, or Iodine adsorbed on silica gel.
- Column chromatography was performed on silica gel (100-200 or 230-400 mesh size) and neutral alumina.
- Deuterated solvents for NMR spectroscopic analyses were used as received.
- All $^{1}H$ NMR and $^{13}C$ NMR spectra were obtained using a 200 MHz, 400 MHz, and 500 MHz spectrometer. Coupling constants were measured in Hertz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m =multiplet, br = broad.
- HRMS (ESI) were recorded on ORBITRAP mass analyzer (Thermo Scientific, QExactive).
- Chemical nomenclature (IUPAC) and structures were generated using Chem Bio Draw Ultra.

| AcSIR | **Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Sciences** |
|---|---|
| **Name of the Candidate** | **Mr. Suryadev K Verma** |
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| **Laboratory** | CSIR-National Chemical Laboratory |
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| **Research Supervisor** | Dr. Benudhar Punji |

## 1. Introduction

The thesis entitled "Manganese, Nickel and Copper-Catalyzed C–H Bond Alkylation and Alkynylation of (Hetero)Arenes'' is divided into five chapters. Chapter 1 deals with the general introduction of alkylation and alkynylation of phenols, indolines and 2-pyridones using transition metal as a catalyst. Further, we have discussed the importance of 3rd row transition metal for C–H functionalization of (hetero)arenes as well as challenges associated with unactivated alkyl halides for the alkylation strategy. Moreover, we highlight the biological importance of alkylated phenols, indolines and 2-pyridones.[1-11] The detailed literature survey of alkylation and alkynylation of heteroarenes, including mechanistic proposals are briefly discussed. In chapter 2, we demonstrated copper-catalyzed regioselective C–H alkylation of phenols and detailed mechanistic aspects. Some of these phenols and their derivatives widely exist in various bioactive natural products, pharmaceuticals and many newly developed functional materials.[12] In chapter 3, we have demonstrated the Mn(II)-catalyzed C($sp^2$)–H alkylation of indolines and (2-pyridinyl)arenes with unactivated alkyl bromides. These alkylated indolines play an important role in pharmaceuticals, agrochemicals, and biology.[13] In chapter 4, we described the synthesis of quinoline-based (NNP)Ni(II)OAc complex and thorough characterization. The developed nickel complex is employed for C–H alkylation of 2-pyridones with unactivated alkyl halides. Such 2-pyridone motifs are present in numerous bioactive natural products and synthetic compounds.[14] In chapter 5, we presented Ni(II)-catalyzed C-6 selective alkynylation of 2-pyridones using alkynyl bromides. Finally, we summarize the overall thesis work, followed by future directions related to the field.

Dr. Benudhar Punji (Supervisor)

Suryadev K Verma (Candidate)

## 2. Statement of the Problem

The C–H bond alkylation of (hetero)arenes has emerged as a powerful tool in organic chemistry, which helps in the improvement of chemical and biological properties of synthetically important compounds, including their lipophilicity and metabolic stability. Traditionally, C–H bond alkylation and alkynylation of (hetero)arenes are demonstrated using activated coupling partners. Moreover, researchers have used 4d and 5d transition metals as catalyst, and most of these protocols have shown limited substrate scopes, multistep synthetic sequences and undesired products. To overcome these challenges, my thesis deals with the alkylation and alkynylation of (hetero)arenes using unactivated and demanding coupling partners. All the functionalization is demonstrated using earth-abundant and inexpensive 3d transition metals as catalyst.

## 3. Objectives

As discussed in the above section, selective functionalization of inert C($sp^2$)–H bond is restricted to the use of traditional methods or limited to 4d and 5d transition metals and the use of activated coupling partners. Thus, our objective is to investigate the problem related to these precedented approaches and attempt to resolve those by developing suitable catalytic systems and novel reaction methodologies to achieve mild reaction conditions by employing 3d transition metals as a catalyst.

## 4. Methodology and Result

### Chapter 2. Copper-Catalyzed Regioselective C–H Alkylation of Phenol Derivatives with Unactivated Alkyl Chlorides

The alkylated phenolic compounds have versatile applications in natural products pharmaceutical compounds and organic dyes.[15] Thus, the development of an efficient method for *ortho*-alkylation of phenol is highly desirable for sustainable and practical synthesis. The *ortho*-alkylation of phenol has been demonstrated with $\alpha$-diazoester as a coupling partner, wherein the protocol is limited to substrate scope. Therefore, in chapter 2, we have disclosed the *ortho*-alkylation of phenol using unactivated alkyl chloride as a coupling partner in the presence of a copper catalyst (Scheme 1). The reaction provided a broad substrate scope of phenol derivatives and tolerated numerous functionalities such as silyl, aryl ether, aryl thioether, pyrrolyl, indolyl, carbazolyl groups as well as alkyl bearing fatty alcohol, nonyl phenyl ether and vitamin E. Preliminary mechanistic and EPR studies reveal that the Cu(I) is an active catalyst and the alkylation reaction proceed via $2e^-$ oxidative addition process.

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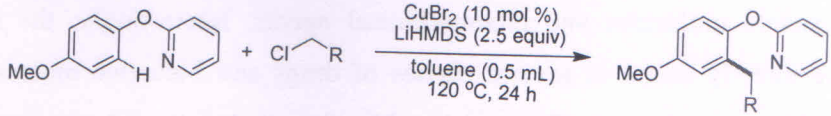
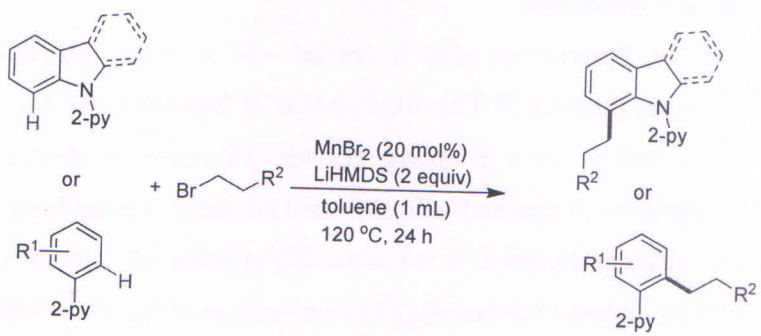
Moreover, the kinetics experiment suggested that the oxidative addition pathway is the rate-limiting step.




**Scheme 1.** Copper-catalyzed regioselective C–H alkylation of phenols.

**Chapter 3. Mn(II)-Catalyzed C($sp^2$)–H Alkylation of Indolines and (2-Pyridinyl)Arenes with Unactivated Alkyl Bromides**

The alkylated indoline compounds are the structural motifs with important applications in pharmaceuticals, agrochemicals, and materials sciences.[16] The literature precedents for this protocol are limited to the use of stoichiometric amounts of Grignard reagent and phosphorus-based ligand. To address these limitations, in this chapter, we developed ligand-free Mn(II)-catalyzed C($sp^2$)–H alkylation of indolines and (2-pyridinyl)arenes with unactivated alkyl bromides (Scheme 2). The reaction provided a broad substrate scope of indolines and (2-pyridinyl)arenes. A range of alkyl bromides were coupled with the tolerance of diverse functionalities, including alkenyl, alkynyl, silyl, aryl ether, pyrrolyl, indolyl, carbazolyl and alkyl bearing fatty alcohol as well as polycyclic-steroid moiety. Mechanistic studies highlight a single electron transfer (SET) pathway for the alkylation involving 1e oxidative addition of alkyl bromide and a rate-limiting C–H metalation.




**Scheme 2.** Mn(II)-catalyzed C($sp^2$)–H alkylation of indolines and (2-pyridinyl)arenes with unactivated alkyl bromides

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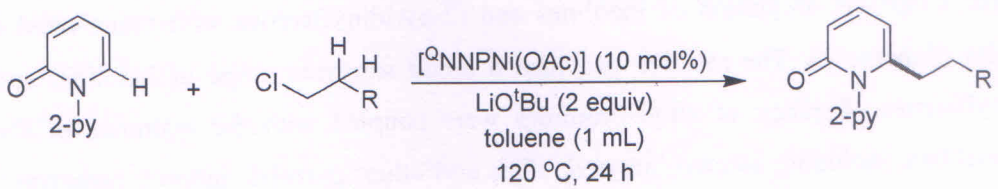
**Chapter 4. Regioselective C(6)–H Alkylation of 2-Pyridones with Unactivated Alkyl Chlorides Using a Well-defined Ni(II)-Catalyst**

The 2-pyridone is one of the most important heteroaromatic rings found in natural products, bioactive molecules and pharmaceutical agents. Interestingly, the alkylated 2-pyridones are directly found in several classes of drugs and bioactive molecules such as ciclopirox, milrinone and camptothecin.[17] Notably, the alkylation of 2-pyridones is mostly explored by using 4d and 5d transition metals as a catalyst, whereas it is not precedented by 3d transition metals. In chapter 4, we discussed the synthesizing of quinoline-based (NNP)Ni(II)X complexes for C–H alkylation of 2-pyridones with unactivated alkyl chlorides (Scheme 3). We have synthesized quinoline-based NNP ligand and its complexes. Further, we developed regio-selective alkylation of 2-pyridones using ($^{Q}$NNP)Ni(II)OAc complex. The protocol provided a wide range of alkylated products including alkenyl, alkynyl, silyl, ethers and heteroaromatics. Notably, biologically relevant molecules such as cholesterol and stigmasterol-derived alkyl chlorides are also tolerated under the reaction condition.




**Scheme 3.** Ni(II)-catalyzed alkylation of 2-pyridones using alkyl chlorides.

**Chapter 5. Nickel-Catalyzed C6 Selective Alkynylation of 2-Pyridones Using Unactivated Alkynyl Bromides**

The alkynylated 2-pyridones play a crucial role in many pharmaceutically active compounds and natural products.[18] The alkynylation of 2-pyridone is not precedented with unactivated alkynyl halide as a coupling partner. However, a rhodium-catalyzed C-6 alkynylation of 2-pyridone is reported with activated alkyne as a coupling partner. In chapter 5, we established Ni(II)-catalyzed C-6 selective alkynylation of 2-pyridones using alkynyl bromide as a coupling partner (Scheme 4). The combination of $Ni(OTf)_2$ with an electron-rich $^{t}$Bu-bpy ligand was found to be an excellent catalyst system for the alkynylation reaction. We have demonstrated substantial substrate scope and investigated detailed reaction mechanism.

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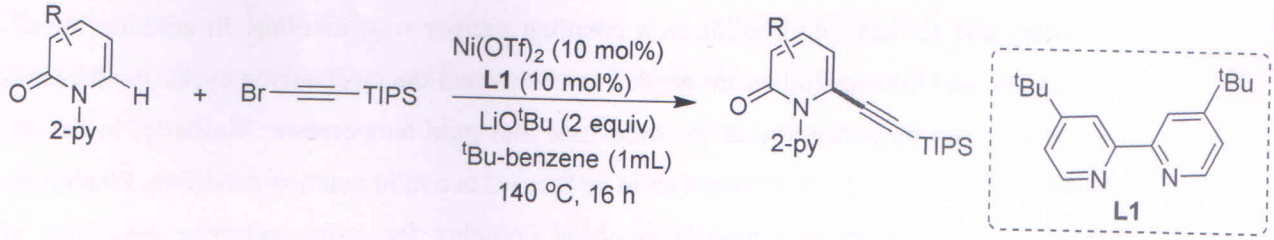


**Scheme 4.** Ni(II)-Catalyzed C-6 Selective Alkynylation of 2-Pyridones Using Alkynyl Bromides

## 5. Summary

Overall, the thesis demonstrates an efficient protocol for the alkylation and alkynylation of (hetero)arenes using 3d transition metals as catalysts. we have described the *ortho*-alkylation of phenoxy pyridine with abundant and inexpensive alkyl chloride as a coupling partner using a copper catalyst. A preliminary mechanistic and kinetic study is performed to understand the catalytic path for the alkylation protocol (chapter 2). Further, we developed a ligand-free Mn(II)-catalyzed C($sp^2$)–H alkylation of indolines and (2-pyridinyl)arenes with unactivated alkyl bromides. The key feature of this protocol is that the reaction does not require a Grignard reagent as a base (Chapter 3). Furthermore, an efficient method was developed for the regioselective alkylation of 2-pyridone using alkyl chloride as a coupling partner in the presence of ($^{Q}$NNP)Ni(II)OAc catalyst. A diverse functional groups and biologically relevant compounds are tolerated under the reaction condition (Chapter 4). In addition, we have demonstrated the Ni(II)-catalyzed C-6 alkynylation of 2-pyridone using unactivated alkynyl bromide as a coupling partner. This methodology showed a variety of scopes of 2-pyridones (chapter 5).

## 6. Future Directions

We have successfully attempted to resolve the problems related to existing methodologies for the alkylation and alkynylation of phenol, indoline and 2-pyridone using 3d transition metals. However, there is a scope to achieve better conditions for C–H functionalization reactions.

In chapter 2, secondary and tertiary alkylation at the *ortho* position of phenol is unsuccessful. This protocol is limited to the use of strong base such as LiHMDS and harsh reaction conditions. Future focus should be given to performing the alkylation reaction of phenol at a mild base as well as mild temperature. In chapter 3, the focus should be given to

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secondary and tertiary alkyl halide as a coupling partner with indoline. In addition, details mechanistic and kinetic studies are needed to understand the mechanistic cycle. In chapter 4, the reaction can be performed at the mild base and mild temperature. Similarly, in the last chapter, alkynylation of 2-pyridone should be focused at a mild reaction condition. Finally, the focus should be given to synthesizing chiral complex for enantioselective alkylation of (hetero)arenes using 3d metals as a catalyst.

## 7. List of Publications

1. **Verma, S.K.**, Punji, B., Copper-Catalyzed Regioselective C–H Alkylation of Phenol Derivatives with Unactivated Alkyl Chlorides (Manuscript communicated)
2. **Verma, S.K.**, Punji, B., Manganese-Catalyzed C($sp^2$)-H Alkylation of Indolines and Arenes with Unactivated Alkyl Bromides, *Chem. Asian J.* **2022** *17*, e202200103.
3. **Verma, S.K.**, Punji, B., Regioselective C(6)–H Alkylation of 2-Pyridones with Unactivated Alkyl Chlorides Using a Well-defined Ni(II)-Catalyst (Ongoing work)
4. **Verma, S.K.**, Punji, B., Nickel-Catalyzed C6 Selective Alkynylation of 2-Pyridones Using Alkynyl Bromides (Ongoing work)
5. Jagtap, R. A., **Verma, S.K.**, and Punji, B., $MnBr_2$-Catalyzed Direct and Site-Selective Alkylation of Indoles and Benzo[h]quinoline, *Org. Lett.* **2020**, *22*, 4643 - 4647

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# TABLE OF CONTENTS

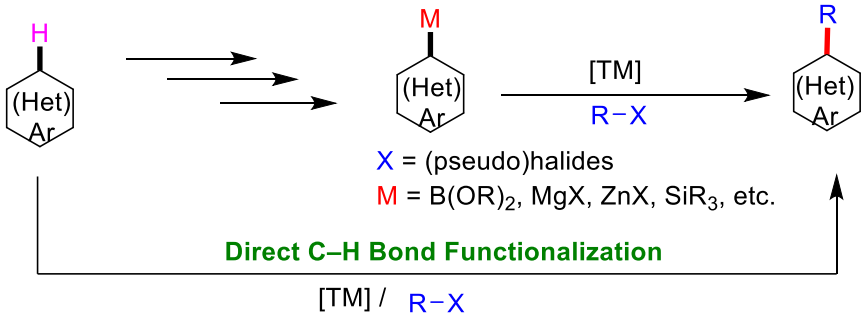
# Chapter 1

# Introduction

Transition metal-catalyzed cross-coupling reactions represent a very economical approach to carbon-carbon bond formation.[1,2] These methodologies are crucial in synthetic organic and material chemistry and find extensive use in pharmaceuticals, agrochemicals, and the fine chemical industry.[3,4] Notably, Numerous cross-coupling reactions employing transition metal in the role of catalysts are used as intermediates in the organic synthesis of numerous drug molecules. Over the past 50 years, the selective modification of C−H bonds applying transition metals as catalysts has developed and expanded extensively.[5,6] The term C−H bond activation typically involves the initial reaction of the C−H bond with a metal catalyst to form an organometallic complex with a C−M bond. In the early 1970s, Shilov and colleagues revealed the first platinum-catalyzed alkane C−H bond functionalizations, specifically achieving platinum-catalyzed chlorination of alkanes.[7,8] Before investigations on the oxidative addition of aliphatic C−H bonds, numerous examples of direct transformation C−H bonds were documented. For instance, a reaction mediated by nickelocene with azobenzene led to the formation of a metallacycle containing a novel nickel-aryl bond.[9] Taking inspiration from these pioneering reports, the area of direct C−H bond functionalization using 3d metals has been steadily and quietly advancing.

Regioselective direct C−H bond activation depicts a significant advancement in organic chemistry. Numerous research groups have pioneered the cleavage of C−H bonds in (hetero)arenes, often followed by cross-coupling reactions. This approach typically requires prefunctionalized substrates and main group organometallic reagents, limiting its applicability (Scheme 1.1).[10-11]

**Traditional Cross-Coupling**




**Scheme 1.1** Traditional cross-coupling *versus* C−H bond activation.

However, direct C−H bond activation and transformation circumvent the need for such reagents, making it a more versatile method for (hetero)arene functionalization. In previous

decades, researchers predominantly employed costly, less abundant, and toxic 4d and 5d transition metals as catalysts for (hetero)arene functionalization. [12-13] To address these limitations, there has been a concerted effort to explore the use of less expensive and more readily available 3d transition metals as catalysts. The effectiveness of 3d transition metals in functionalizing C−H bonds in bio-relevant heteroarenes opens up promising avenues for future research and development.[14-15]

The alkylation of (hetero)arenes is a significant transformation in chemical synthesis. Alkylated (hetero)arenes play a crucial role in various applications, including fine chemicals, drugs and in material science.[16] The regioselective alkylation of (hetero)arenes predominantly relies on the Friedel–Crafts reaction. However, this method faces significant limitations, including harsh reaction conditions, low chemo- and/or regioselectivities along with less reactivity for a specific category of substrates. Another avenue involves a stepwise prefunctionalization of the arene, succeeded by a metal-catalyzed cross-coupling, offering an alternative route with potential advantages.[17,18] Notably, recent advancements in this field have yielded highly efficient processes for directly incorporating alkyl groups onto aromatic frameworks.[19] This approach is more straightforward and appealing as compared to conventional alkylation methods. Alkylating heteroarenes directly presents a significant challenge compared to other functionalization methods due to the *β*-hydride elimination process.[20] To be synthetically valuable, these reactions must also exhibit high regioselectivity. Various alkylating agents, including alkyl halides, alkenes, organometallic reagents, alkanes, epoxides, and alcohols are employed as coupling partners in the direct alkylation of heteroarenes.

Similar to alkylation, the alkynylation of (hetero)arenes acts a pivotal role in organic synthesis, facilitating the preparation of aryl alkynes and enyne skeletons, which serve as intermediates in various natural products, pharmaceuticals, agrochemicals, and organic functionalization materials. Traditionally, alkynylation of (hetero)arenes has been accomplished through Sonogashira cross-coupling reactions, employing terminal alkynes as coupling partners in the presence of palladium catalysts and Cu(I) co-catalysts with amine bases. However, this approach required prefunctionalized substrates, which limits its versatility.[21-22] In recent years, several research groups have focused on developing direct alkynylation of (hetero)arenes using 4d and 5d transition metals, necessitating Cu co-catalysts to activate the alkyne moiety.[23] Presently, there is a growing interest in exploring alkynylation of (hetero)arenes in the presence of 3d metals due to their lower cost, abundance in nature, and less toxicity compared to precious transition metals. However, the alkynylation of

(hetero)arenes remains relatively underdeveloped. Specifically, there is ongoing exploration into 3d transition metal-catalyzed alkynylation of (hetero)arenes using alkynyl bromides or phenylacetylene as coupling partners, which holds promise for advancing this important synthetic transformation.[24,25] In this Chapter, we discuss the precedents on direct C–H bond alkylation and alkynylation catalyzed by 3d transition metal catalysts.

## 1.1 C–H Bond Alkylation (Hetero)Arenes

In pharmaceuticals, agrochemicals, polymers, and material science, the incorporation of an alkyl chain into the (hetero)arenes component plays a pivotal role. Traditional methods for (hetero)arenes alkylation have relied on Friedel-Craft reactions or the coupling of organometallic (hetero)arenes with alkylating agents. [26] However, recent development in C–H bond alkylation has proven highly advantageous, overcoming limitations inherent in classical approaches.[27] Alkylation at a specific position of hetero(arenes) is challenging in the absence of an installing directing group. Particularly, the use of *N*-containing directing groups has enabled for the selective functionalization of (hetero)arenes.[28,29] This progress involves the use of diverse alkylating reagents, including organometallic reagents, alkenes, acids, *N*-tosylhydrazone alkyl, and diazo compounds. This section provides a comprehensive exploration of direct (hetero)arenes alkylation using various alkylating agents.

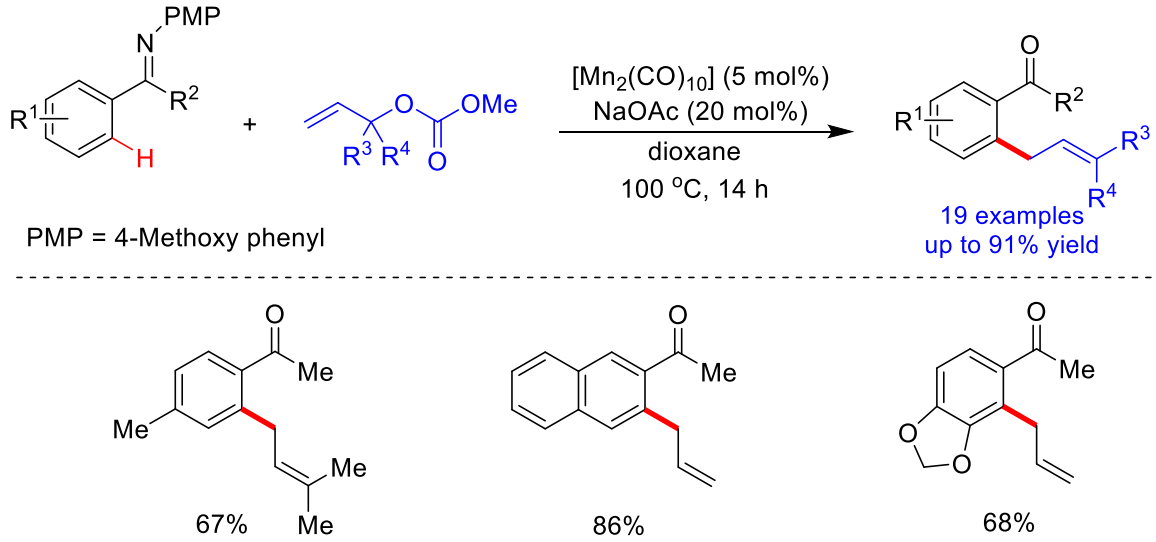
### 1.1.1 C–H BOND ALKYLATION OF ARENES

The direct modification of arene C−H bonds is of great interest in organic synthesis, with regioselective alkylation of arene C−H bonds emerging as a crucial research area over recent decades in organic chemistry. Various groups have developed alkylation methodologies using traditional cross-coupling techniques, along with direct alkylation of arenes employing 4d and 5d transition metals.[30-31] Despite these advancements, these methods are subject to various limitations. Nevertheless, there is increasing interest in the direct alkylation of arenes using 3d transition metals as catalysts. However, this methodology still requires further development.

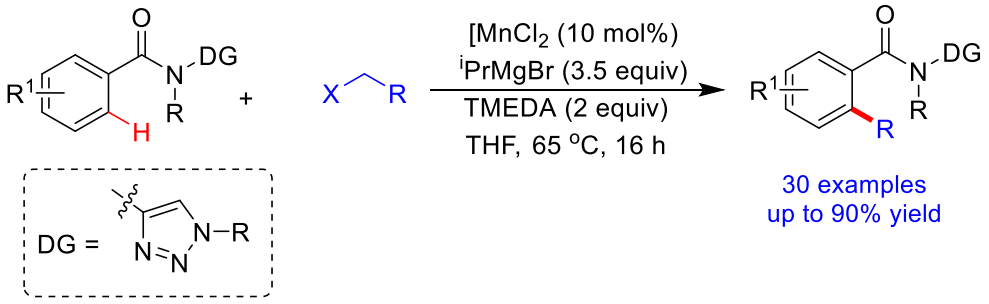
#### 1.1.1.1 Mn-Catalyzed Alkylation

Manganese proves to be a versatile metal, serving as a dynamic catalyst for numerous C–H bond functionalization processes. Given its ability to adopt variable oxidation states spanning from -3 to +7, the utilization of this earth-abundant metal in multiple

functionalizations is highly desirable.[32] This versatility is exemplified through the exploration of high-valent manganese in various transformations such as halogenation, nitration, and oxygenation reactions. Ackermann disclosed a protocol for the allylation of arenes assisted by carboxylates using Mn(I) as a catalyst (Scheme 1.2)[33]. The Mn(I) catalyst serves a pivotal function in the regioselective C−H allylation of arenes. This approach demonstrates a wide substrate scope, tolerating both groups electron-donating as well as withdrawing under optimized conditions. Furthermore, the method has been employed in several synthetically valuable arenes with good results. Further, a similar team has also disclosed Mn-catalyzed alkylation of aromatic amides with *β*-hydrogens containing alkyl halides (Scheme 1.3)[34]. The existence of a Grignard compound and a TAM directing group is necessary for the *ortho*-selective alkylation of aryl amides. This protocol offers an ample substrate scope, facilitated by the easily removable TAM group.



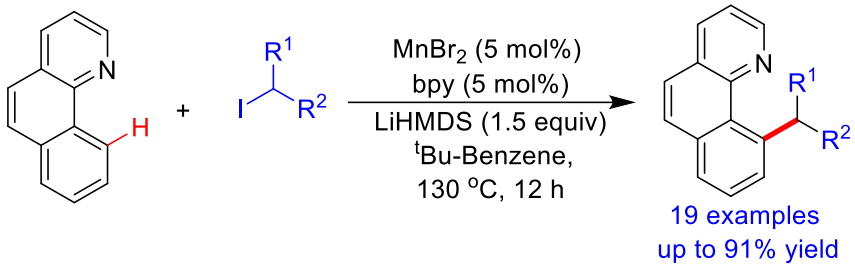

**Scheme 1.2** Mn-catalyzed C($sp^2$)–H alkylation of arenes.




**Scheme 1.3** Mn-catalyzed C($sp^2$)–H alkylation of benzamide using unactivated alkyl halide.

In recent years, Punji and co-workers have revealed a regioselective alkylation method for benzo[*h*]quinoline, employing unactivated alkyl iodide as a coupling partner. The current

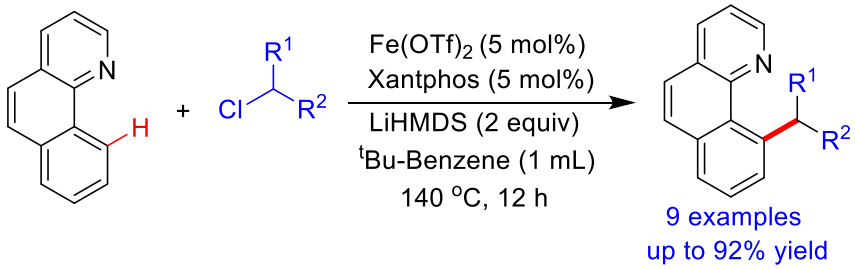
procedure necessitates the use of $MnBr_2$ as a catalyst and bipyridine as a ligand (Scheme 1.4).[35] Notably, the inclusion of LiHMDS is a crucial step in the alkylation process, facilitating the generation of an Mn-amido as an active catalyst. The presence of important functional moieties in the molecule is compatible with the reaction condition. However, the yield of the alkylated product was compromised when alkyl iodide containing other heterocycles was used as coupling partners. Similarly, low yield was predicted in the case of secondary alkyl iodide. In addition, mechanistic and kinetic studies demonstrate that the C–H bond activation step is a reversible step and alkyl iodide undergoes $1e^-$ oxidative addition to the metal.




**Scheme 1.4** Mn-catalyzed C($sp^2$)–H alkylation of benzo[*h*]quinoline.

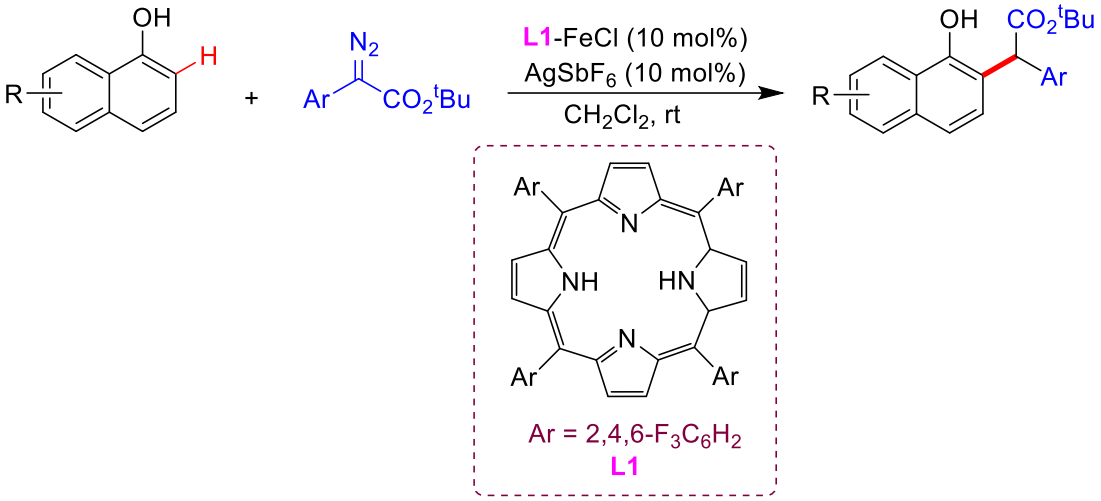
### 1.1.1.2 Fe-Catalyzed Alkylation

Iron is a highly abundant element in the universe, especially among the 3rd-row transition metal elements.[36] Its use as a catalyst in organic transformations is appealing due to its cost-effectiveness, environmentally friendly nature, and less toxicity. However, despite this privilege, the application of iron catalysts in favor of the C–H bond alkylation of arene has been limited. Recently, Punji research team has established an alkylation method for benzo[*h*]quinoline, employing non-activated alkyl chlorides as coupling partners with iron catalyst (Scheme 1.5).[37] In this framework, the utilization of $Fe(OTf)_2$/xantphos catalyst framework significantly influences the generation of the alkylated product of benzo[*h*]quinoline. Notably, the reaction proceeds smoothly when employing polycyclic cholesterol-derived alkyl chloride in the form of a coupling partner, resulting in a good yield of the desired alkylated product.



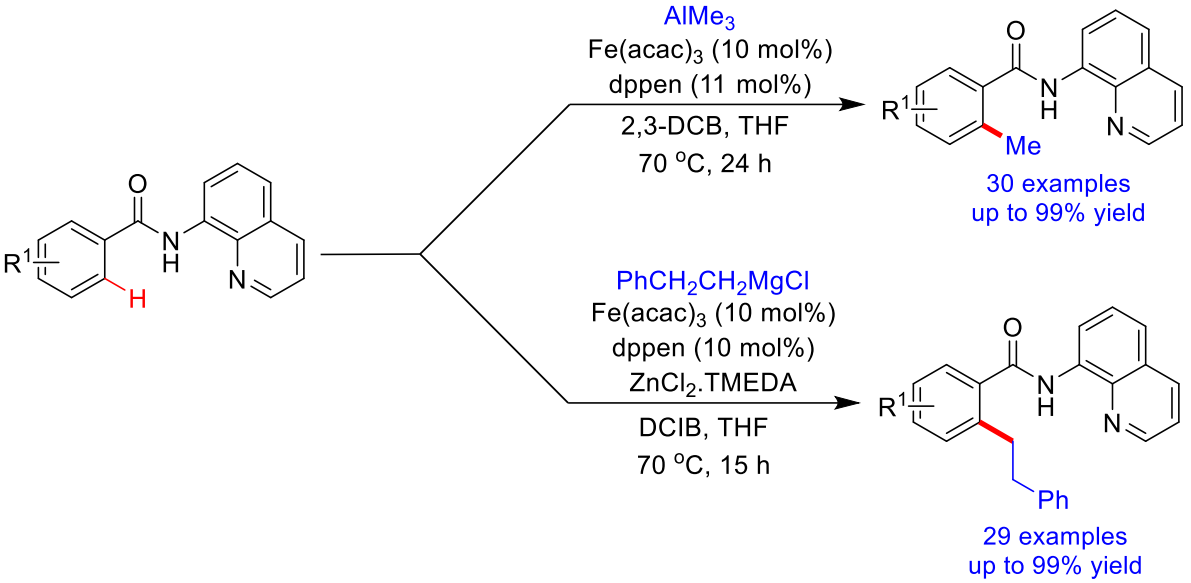

**Scheme 1.5** Fe-catalyzed alkylation by chelation assistane.

Furthermore, in 2021, Liu group successfully demonstrated the direct alkylation of naphthol using *α*-aryl-*α*-diazoacetates as coupling partners with porphyrin iron catalyst system (Scheme 1.6).[38] This innovative methodology yielded good to moderate *ortho*-alkylation of naphthol, displaying excellent chemo-selectivity and site-selectivity. The *ortho* C($sp^2$)–H bond activation in naphthol was facilitated by the coordination between the hydroxy group and the iron catalyst. However, it is important to note that this approach was limited to the C–H bond alkylation of C8-substituted 1-naphthol, Furthermore, various phenol derivatives also failed to couple with *α*-aryl-*α*-diazoacetates under the optimized reaction conditions.



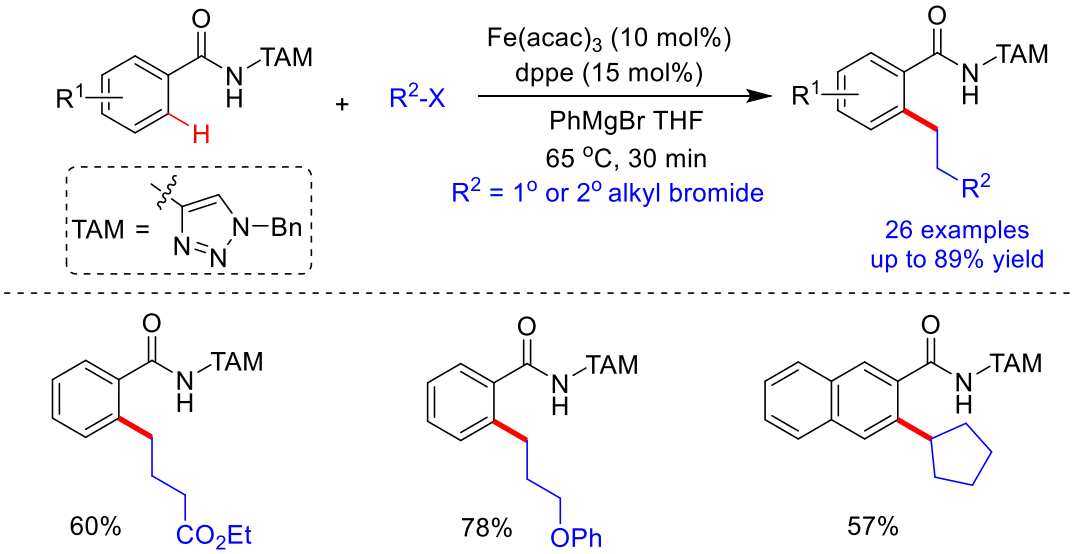

**Scheme 1.6** Fe-catalyzed C($sp^2$)–H alkylation of phenols using *α*-aryl-*α*-diazoacetates.

Nakamura *et. al.* successfully established the iron-catalyzed methylation of benzamide. In their approach, they utilized $AlMe_3$ either as a methylating agent or diamine complex form, in conjunction with a diphosphine and 2,3-dichlorobutane as a stoichiometric oxidant (Scheme 1.7).[39] The reaction demonstrated applicability to various amide substrates, particularly those bearing 8-aminoquinoline as a directing group. The use of the mild aluminum reagent served to prevent the undesired reduction of iron. Concurrently, Matsubara developed an iron-catalyzed direct alkylation reaction of benzamide with primary and secondary alkyl zinc halides.[40] The critical aspect of C–H bond alkylation is the stabilization of the organo (III) species by a dual coordination directing species and a diphosphine ligand. This organo (III) metallic is also accountable for achieving C–H activation, marking a significant advancement in the development of efficient iron catalysis with economic and environmental benefits.




**Scheme 1.7** Fe-catalyzed C($sp^2$)–H alkylation of benzamide.

2016, Ackermann published a comprehensive method for the *ortho* C($sp^2$)–H alkylation in amides containing arene rings with iron catalysts. Interestingly, secondary and primary alkyl halides are smoothly reacted with benzamide (Scheme 1.8).[41] Selective C–H bond activation of (hetero)arenes is accomplished through the utilization of a directing moiety assisted by triazole. The iron/dppe catalyst system is responsible for the alkylation reaction of benzamide. This system also successfully deprotected the TAM directing group under mild optimal conditions.

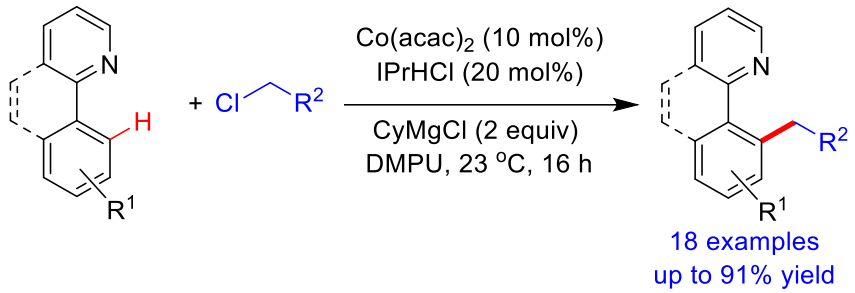



**Scheme 1.8** Fe-catalyzed C($sp^2$)–H alkylation of benzamide using alkyl bromide.

### 1.1.1.3 Co-Catalyzed Alkylation

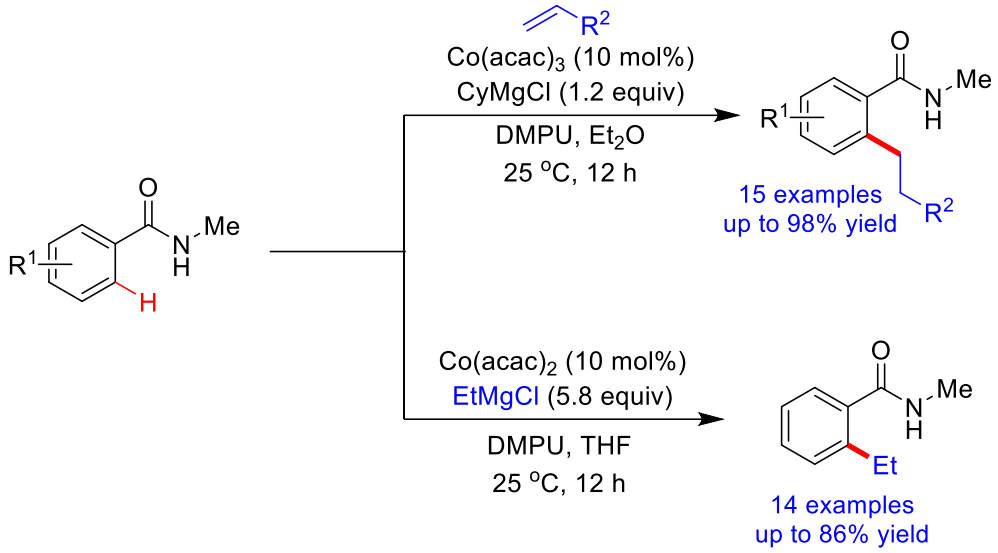
Cobalt, an economically viable and biologically relevant transition metal, has obtained

significant attention for its application in the arenes subjected to C−H alkylation.[42] In 2013, Ackermann group developed the alkylation of benzo[*h*]quinoline under the condition of a Co-catalyst using alkyl chlorides as a coupling partner (Scheme 1.9).[43] The success of this method relies on the inclusion of an *N*-heterocyclic carbene (NHC) ligand, specifically IPr.HCl, along with $Co(acac)_2$. In addition, this protocol also required a higher quantity of Grignard reagent (CyMgCl) under mild reaction conditions. This methodology exhibited high chemo-selectivity and site-selectivity in the alkylation of diversely substituted benzo[*h*]quinoline. Notably, benzo[*h*]quinoline reacted smoothly with more challenging secondary alkyl chloride, providing a good to moderate yield of the desired product. However, it is noteworthy that various types of functional groups are not tolerated in the presence of Grignard reagent. In addition, mechanistic analysis has revealed that carbon radical participates during the mechanistic cycle.



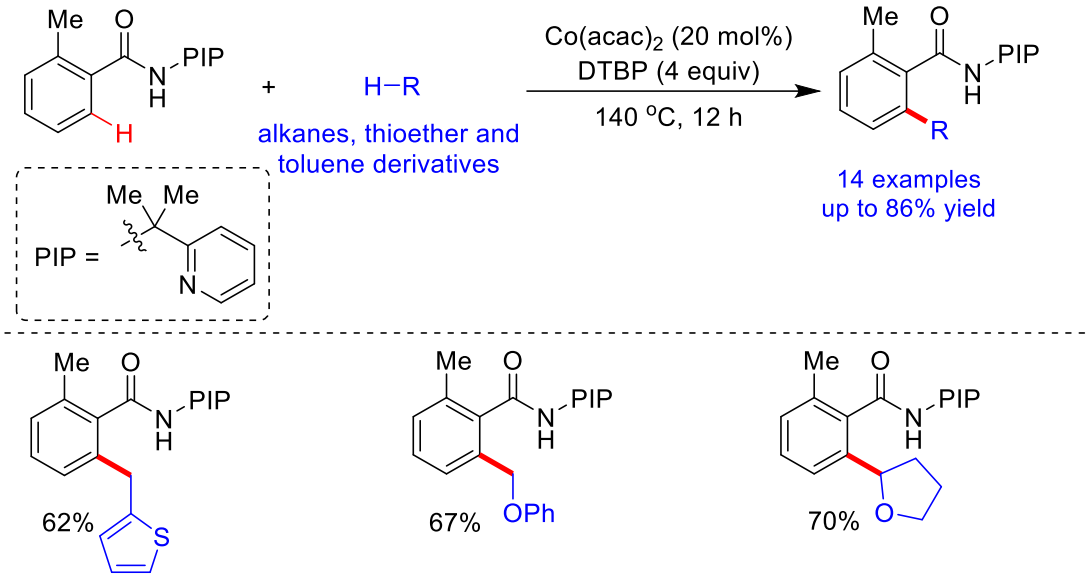

**Scheme 1.9** Co-catalyzed C($sp^2$)–H alkylation of benzo[*h*]quinoline using alkyl chloride.

Nakamura invented a method for *ortho*-privileged alkylation of benzamide using a cobalt catalyst. Alkenes were employed as the alkylating agents in this method (Scheme 1.10).[44] This process, conducted at 25 °C with DMPU as an essential ligand and CyMgCl as a base, obtained selectively *ortho*-alkylated products. This approach showed a wide scope relating to both the alkene and aromatic carboxamide substrates. Additionally, other functional entities like bromine, olefin, amide, and ester are suitable under the reaction parameters. Furthermore, DMPU plays an important role to achieve this transformation. Similarly, the same research group published another study on cobalt-catalyzed *ortho*-selective alkylation of benzamide by introducing a *β*-hydrogen-containing alkyl anion.[45] DMPU also acts a critical role in modulating the reactivity of the alkyl cobalt in this transformation. The method has also demonstrated broad substrate scopes with various functional groups.




**Scheme 1.10** Co-catalyzed alkylation of benzamide using alkene and Grignard reagent.

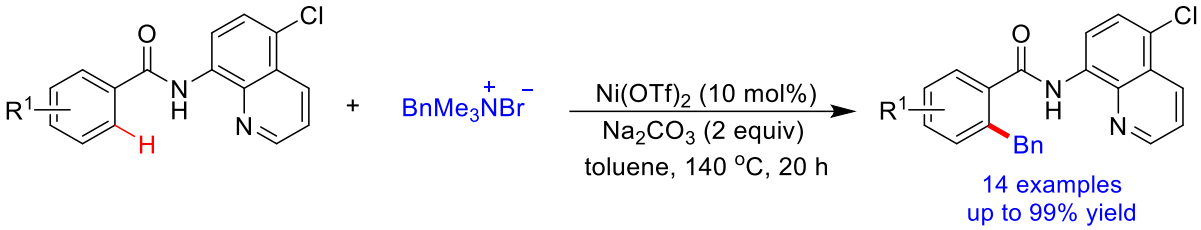
Xu group reported straightforward cobalt-catalyzed methylation and ethylation of aromatic and heteroaromatic carboxamides using triphenylphosphine as a ligand. In this method, they employed an organoaluminium reagent as a coupling partner and 2,3-dichlorobutane as an oxidant.[46] In a novel approach, Li group demonstrated in 2017, the cobalt-catalyzed aromatic carboxamides alkylation using hydrocarbons such as alkanes and toluene as coupling partners. Interestingly, the aromatic carboxamides also react with thioethers in the form of coupling partners. This approach shows a diverse scope encompassing aromatic carboxamides as well as hydrocarbons including alkanes, toluene derivatives, ethers, and thioethers (Scheme 1.11).[47] This methodology has shown a wide scope for benzamides with various types of hydrocarbons, yielding excellent results. Additionally, alkyl derivatives of important functional groups also react with benzamide, giving good yields. Preliminary mechanistic investigation, involving radical trapping experiments, hydrogen/deuterium exchange experiments, and kinetics isotope effects, suggested that the cobalt catalyst facilitated the cleavage of the C($sp^2$)–H bond, while a radical hydrogen atom abstraction step achieved activation of the C($sp^3$)–H bond.



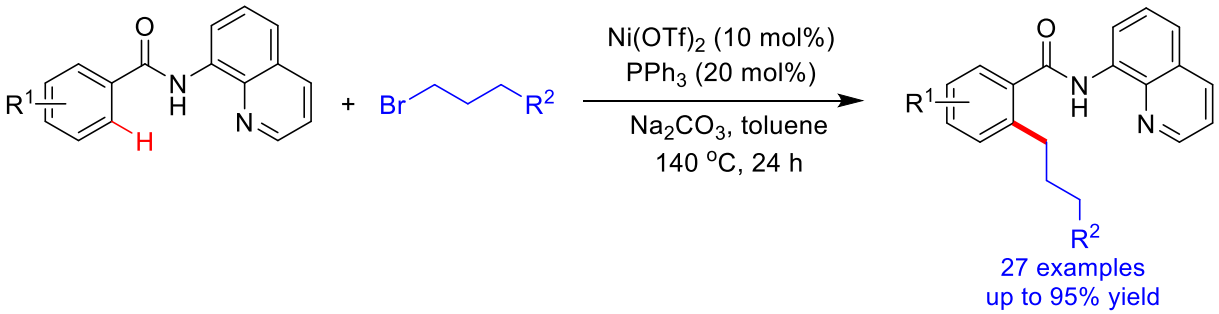

**Scheme 1.11** Co-catalyzed alkylation of benzamide *via* cross-dehydrogenative coupling.

### 1.1.1.4 Ni-Catalyzed Alkylation

Recently, there has been growing attention to the implementation of nickel catalysts in C–H bond alkylation chemistry.[48] Nonetheless, a highly uncommon approach enables the alkyl-substituted arenes in the presence of alkyl halides. However, Chatani applied the advantage of 8-aminoquinolinyl chelation assistance in nickel-catalyzed alkylation. Notably, they described the benzylation of aromatic amides using benzyltrimethylammonium salts as a coupling partner with nickel catalyst (Scheme 1.12)[49]. The reaction was conducted at 140 °C for 20 hours, with noteworthy selectivity for benzylation occurring exclusively at the *ortho* C($sp^2$)–H in aryl amides, without detectable methylation. The presence of the 5-chloro-8-aminoquinoline moiety proved vital for the reaction's success. Importantly, this protocol exhibited tolerance towards diverse functional components, like amine, methoxy, and acetate. Furthermore, another heteroarene amide, such as thiophene, reacted smoothly with benzyltrimethylammonium. The same research group introduced a novel catalytic alkylation system in the benzamide with 8-aminoquinoline as a directing assistance employing nickel catalyst (Scheme 1.13).[50] The reaction exhibits remarkable selectivity, favoring the more accessible C–H bond in the aromatic amides at *meta*-position. Additionally, the reaction demonstrates high compatibility with various functional groups.

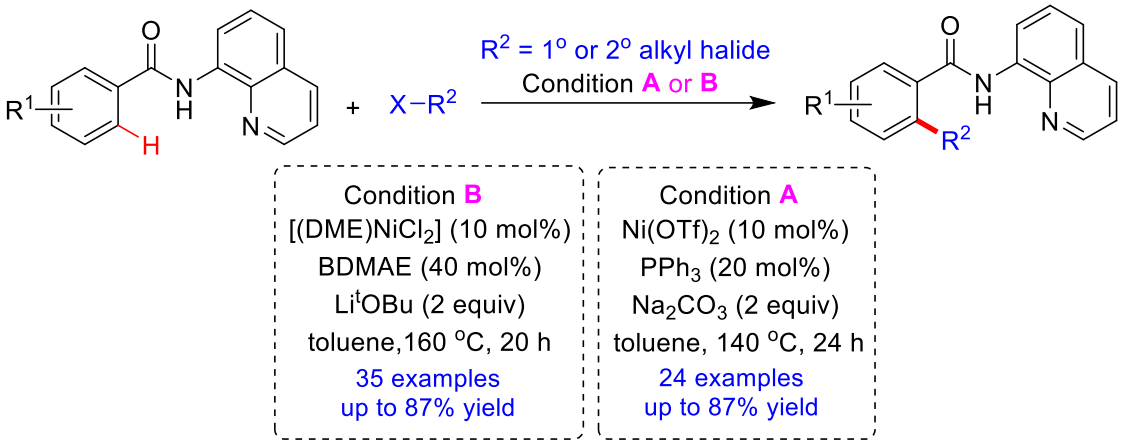



**Scheme 1.12** Ni-catalyzed alkylation of benzamide using benzyltrimethylammonium.




**Scheme 1.13** Ni-catalyzed alkylation of benzamide using bidentate chelation assistance.

In 2014, Ackermann established selective alkylation of aromatic benzamide using more challenging secondary alkyl halides as coupling partners with the involvement of nickel catalyst. The key feature of the alkylation product is the use of the (DME)$NiCl_2$/BDMAE catalyst system.[51] Preliminary mechanistic analysis suggested the dynamic C–H metalation, emphasizing the significance of the reactivity of the C–H bond to be cleaved. Similarly, in 2015, Chatani group disclosed the nickel-catalyzed regioselective alkylation of benzamide using pseudo-alkyl halides in the form of a coupling partner in toluene at 140 °C. This methodology required phosphine-based ligands to achieve the selective desired alkylated product (Scheme 1.14).[52] The reaction demonstrated tolerance towards various functional groups. Moreover, Ni(II) exhibits excellent catalytic activity for this transformation. The researchers have also demonstrated the involvement of Ni(II)/Ni(IV) route in the mechanistic cycle, indicating that the process does not follow a radical pathway (Figure 1.1).




**Scheme 1.14** Ni-catalyzed C($sp^2$)–H alkylation of benzamide using alkyl halide.

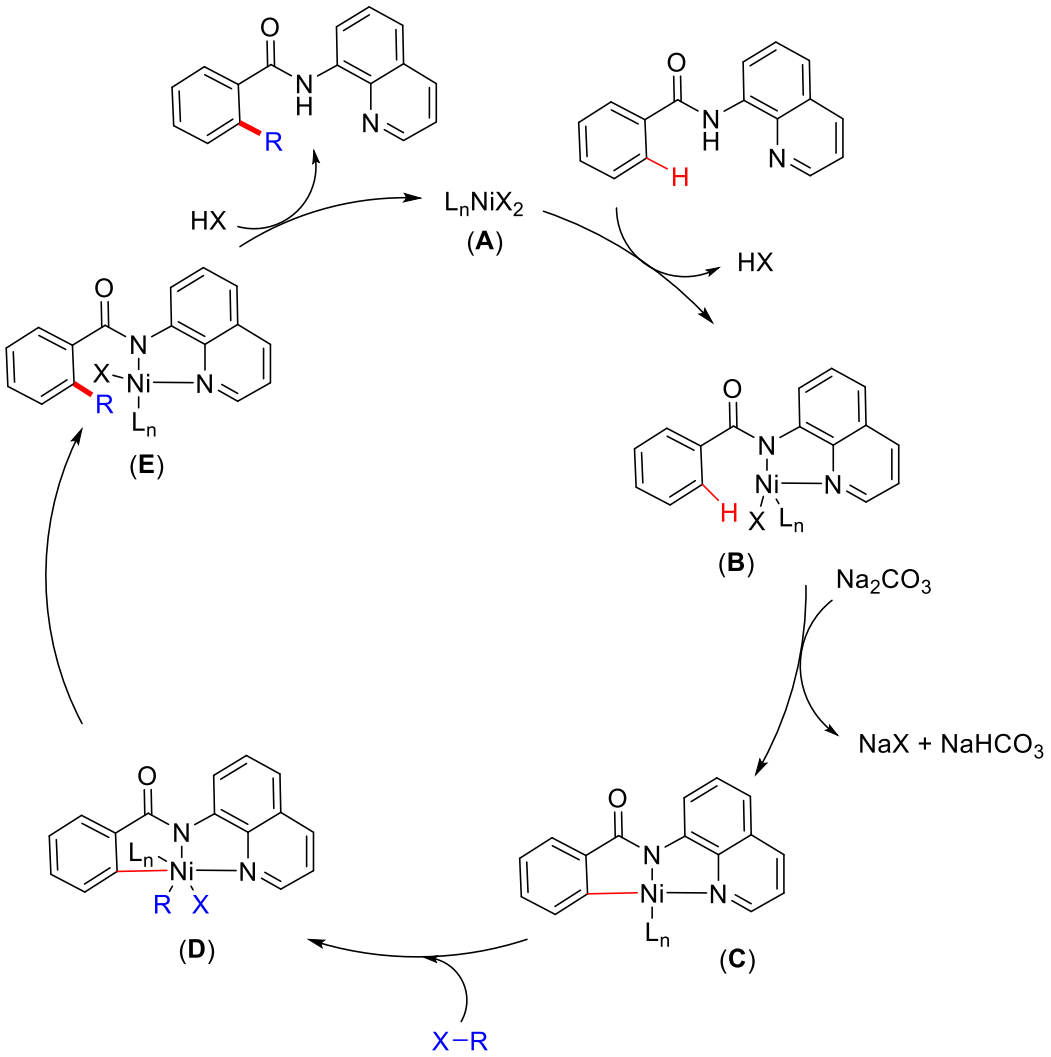
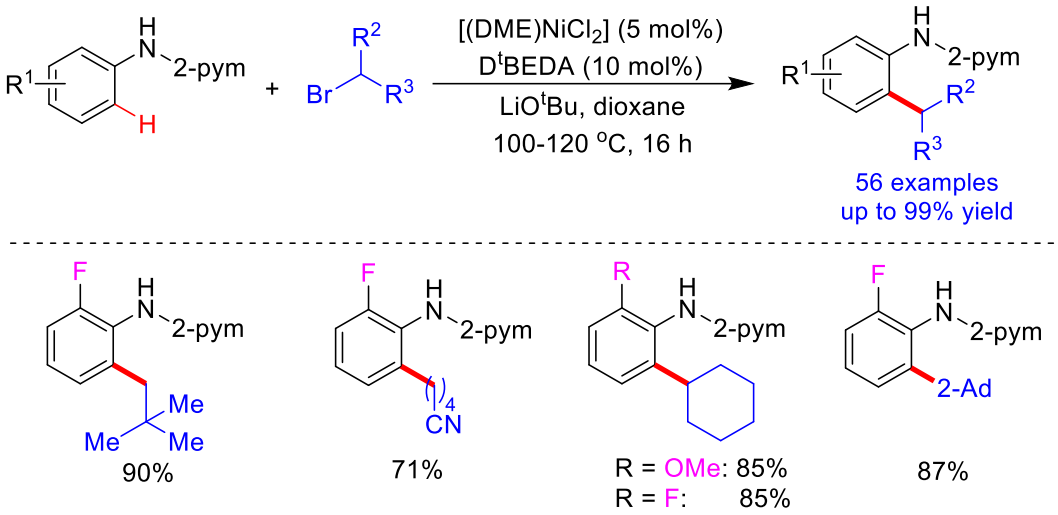



**Figure 1.1** Plausible reaction mechanism for Ni-catalyzed alkylation of amide.

.

Further, Ackermann group demonstrated the alkylation of purine nucleobases, showcasing an extensive array of substrates and excellent compatibility with functional units.[53]Additionally, the same group successfully developed the alkylation of aniline with

mono-chelation assistance. In this study, aniline containing pyrimidine was alkylated with various non-activated alkyl halides utilizing [(DME)$NiCl_2$] as a catalyst and D$^t$BEDA as a ligand (Scheme 1.15).[54] The resulting products represent essential structural features found in numerous bioactive compounds and blockbuster drugs. The cost-effective nickel catalyst demonstrated broad applicability and facilitated C–H alkylation with an excellent level of positional selectivity. Preliminary mechanistic studies suggested that the C–H nickelation step is facile. The same research team has pioneered the Ni-catalyzed alkylation of purine nucleosides using secondary bromides as coupling partners.[55] Their work demonstrates extensive substrate versatility and achieves exceptional levels of chemo-, site-, and regio-selectivity in producing the desired products.




**Scheme 1.15** Ni-catalyzed alkylation of benzamide using secondary alkyl bromide.

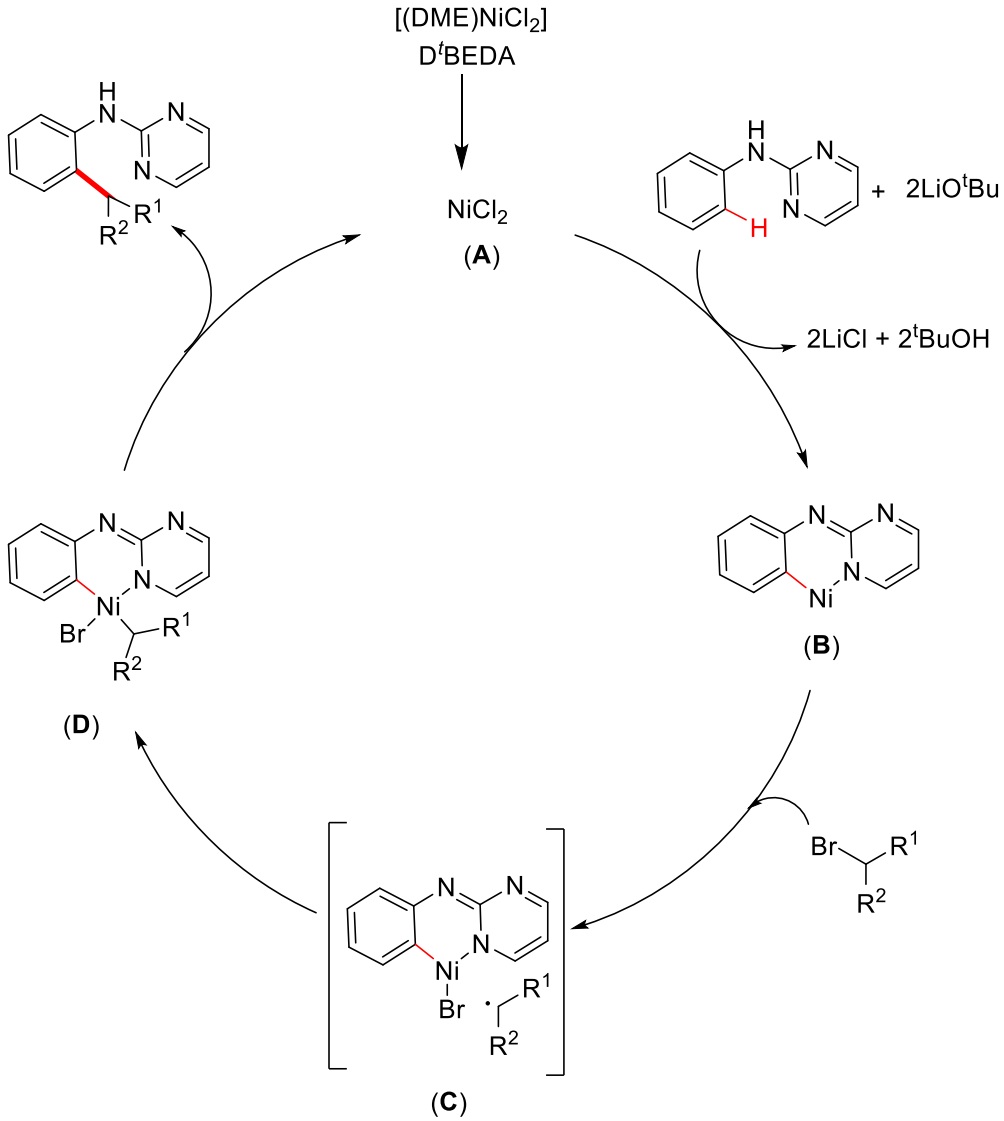
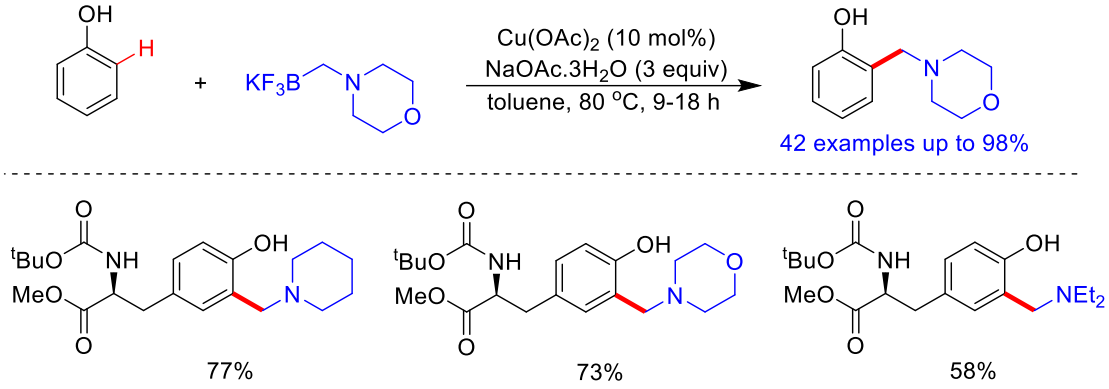



**Figure 1.2** Plausible reaction mechanism for Ni-catalyzed alkylation of aniline.

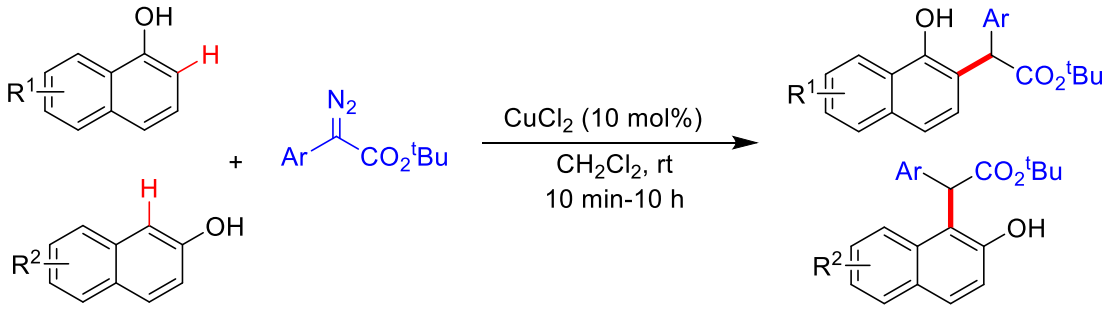
### 1.1.1.5 Cu-Catalyzed Alkylation

Copper catalysts play a crucial role in organic molecule synthesis owing to their readily available oxidation states spanning from 0 to +III. In recent years, C–H functionalization using copper catalyst has found application in diverse organic modifications employing the C–H activation strategy.[56] Nevertheless, the C–H bond alkylation of phenol is relatively underexplored in this context.[57] Wang group has addressed this gap by developing an *ortho*-selective C–H bond aminomethylation of free phenols under moderate reaction parameters (Scheme 1.16).[58] This innovative approach accommodates various substituents on the phenol ring and potassium aminomethyltrifluoroborate, resulting in the final products in good yields. Furthermore, the reaction of amino acids such as the tyrosine derivative Boc-Tyro-OMe with trifluoroborates proceeded smoothly, providing a good yield of the desired products. The

plausible mechanism involves a SET-mediated radical coupling route with a cyclohexane-like transition state can be utilized to explain the heightened *ortho*-selectivity. This strategy offers a direct route to accessing *ortho*-aminomethyl-containing phenols, and bioactive molecules. Inspired by the above group, Liu's research team has successfully established a Cu-catalyzed direct C–H functionalization method for unprotected phenols and naphthols, employing diazoacetates as a coupling partner. The reaction occurs under the specified conditions. (Scheme 1.17).[59] The researchers showcased a broad substrate scope, highlighting exceptional chemo- and site-selectivity in obtaining the desired products. Notably, the authors conducted preliminary mechanistic studies, unveiling a proposed catalytic cycle involving a copper carbene intermediate. This innovative approach boasts several key attributes, including the use of an economical catalyst, easily accessible starting materials, a departure from traditional O–H insertion in favor of unprecedented C–H functionalization, wide substrate compatibility, moderate reaction conditions, and the versatility of the resultant products for various transformations.




**Scheme 1.16** Cu-catalyzed *ortho*-selective aminomethylation of phenol.



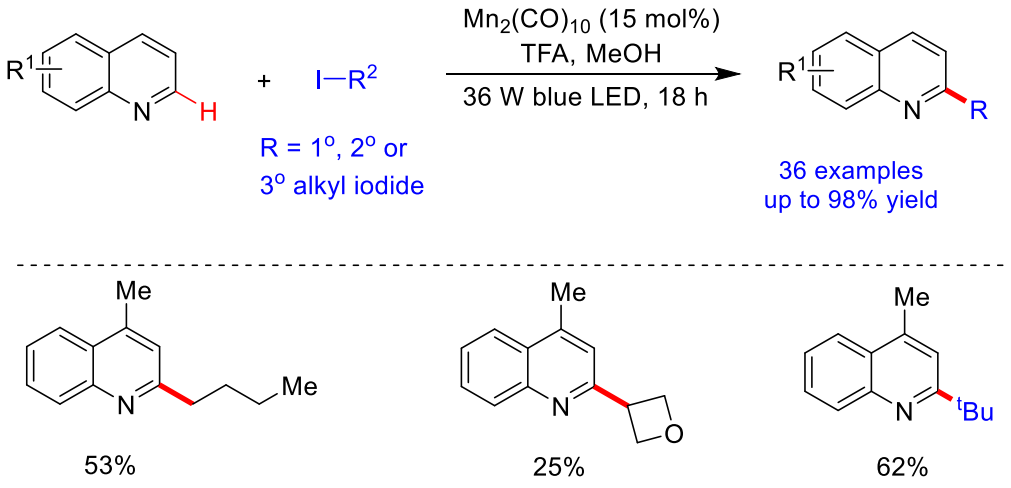

**Scheme 1.17** Cu-catalyzed C($sp^2$)–H alkylation of napthol.

### 1.1.2 C–H BOND ALKYLATION OF HETEROARENES

Heteroarenes containing alkyl groups serve a crucial role in pharmaceuticals, agrochemicals, and polymer chemistry. The incorporation of alkyl substituents into organic molecules enhances lipophilicity. A notable advancement in this domain is the regioselective alkylation of heteroarenes through modification of C–H bond, presenting a substitute for conventional cross-coupling reactions. The current protocol eliminates the need for organometallic alkyl reagents as coupling partners, which can lead to the production of metallic waste. Instead, various types of alkylating reagents, such as alkenes, alkyl halides, alkyl-derived corboxylic acid and diazo compounds, have been used for the direct regioselective alkylation of heteroarenes.

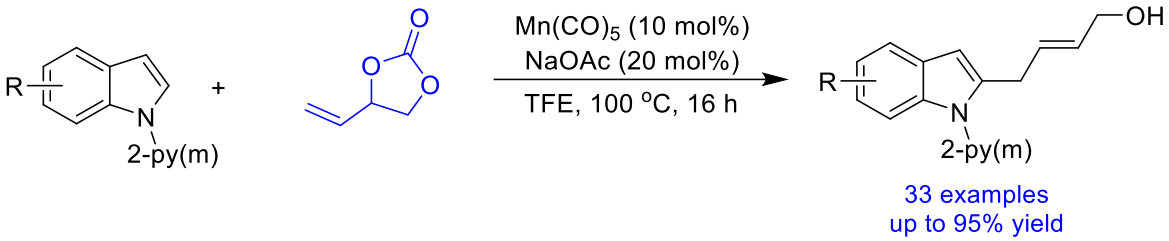
#### 1.1.2.1 Mn-Catalyzed Alkylation

Manganese, being a versatile metal capable of accessing variable diversity of oxidation states from -3 to +7, has proven to act as an effective catalyst for numerous C–H bond functionalizations.[60] Despite its potential, C–H bond alkylation with manganese catalyst has been relatively underdeveloped. Fadeyi group has developed a photoredox alkylation method for quinoline using unactivated alkyl iodides, with earth-abundant and inexpensive manganese as a catalyst (Scheme 1.18).[61] This protocol requires visible light for the alkylation of quinoline and exhibits a diverse range of substrates of alkyl iodides with quinoline, obtaining satisfactory yields of alkylated products. The group has also utilized this technique for the synthesis of complex drug molecules through late-stage functionalization. Additionally, photophysical and DFT investigations have supported a light-mediated mechanism involving a chain reaction.

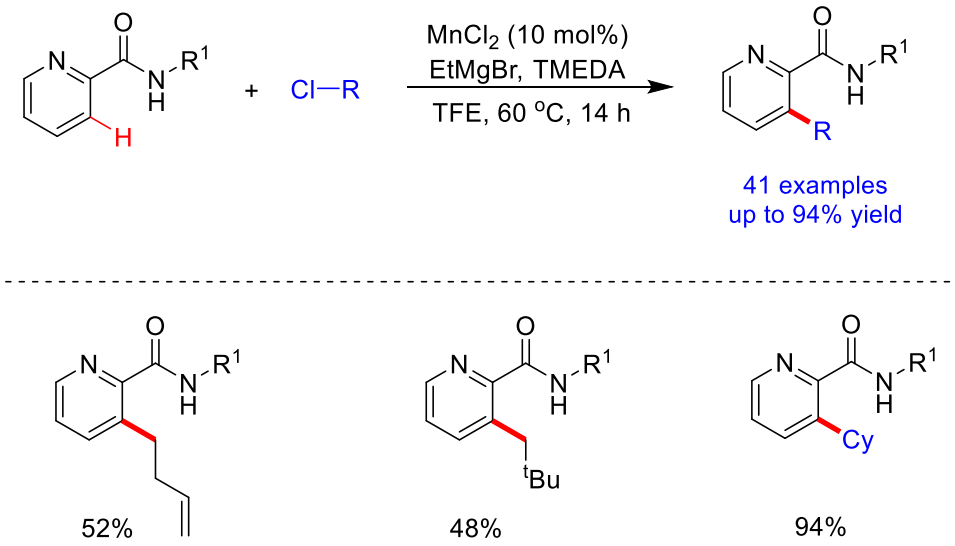



**Scheme 1.18** Mn-catalyzed alkylation of quinoline.

Ackermann has showcased the decarboxylative of indole allylation employing dioxolanones as coupling partners (Scheme 1.19).[62] This method is compatible with water and air, exhibiting C2 position of indole with pyridine or pyrimidine as a directing group. Notably, this protocol does not need a stoichiometric amount of base and operates under favorable reaction conditions. Further, the same group has also shown Mn-catalyzed alkylation of azines using challenging alkyl chlorides as coupling partners (Scheme 1.20).[63] This protocol necessitates a Grignard reagent to facilitate the alkylation process. It applies to both primary as well as secondary alkyl chlorides as coupling partners with indole. The group has successfully conducted gram-scale reactions for alkylation and oxidative azine modification. Mechanistic studies suggest homolytic cleavage of the alkyl halide.



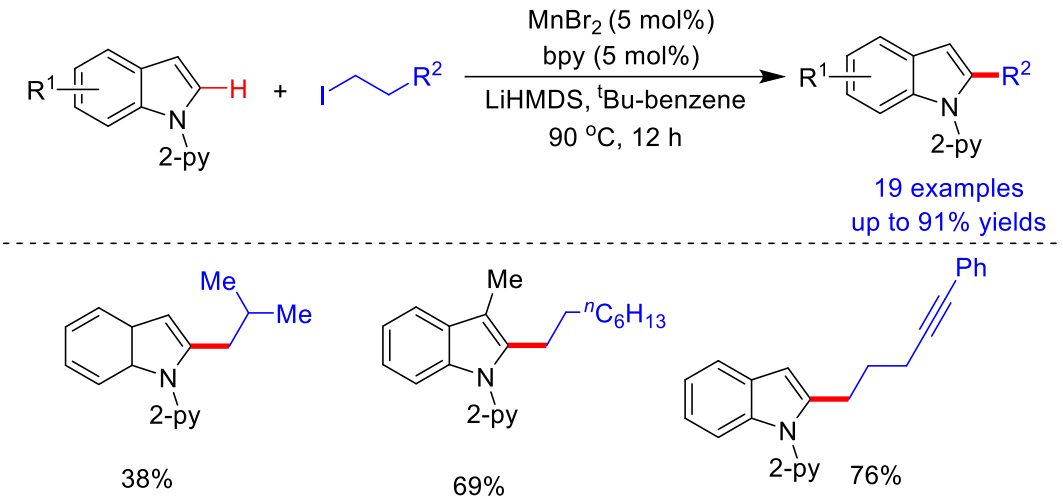

**Scheme 1.19** Mn-catalyzed decarboxylative alkylation of indole.




**Scheme 1.20** Mn-catalyzed alkylation of azines using alkyl chlorides.

In a recent year, a novel method for the direct alkylation of indole has been devised utilizing $MnBr_2$ as a catalyst, with bipyridine serving as a ligand, and unactivated alkyl iodide as the coupling partner (Scheme 1.21).[64] Notably, this protocol employs LiHMDS base instead of a Grignard reagent, offering enhanced efficacy for the alkylation reaction. Intriguingly, the

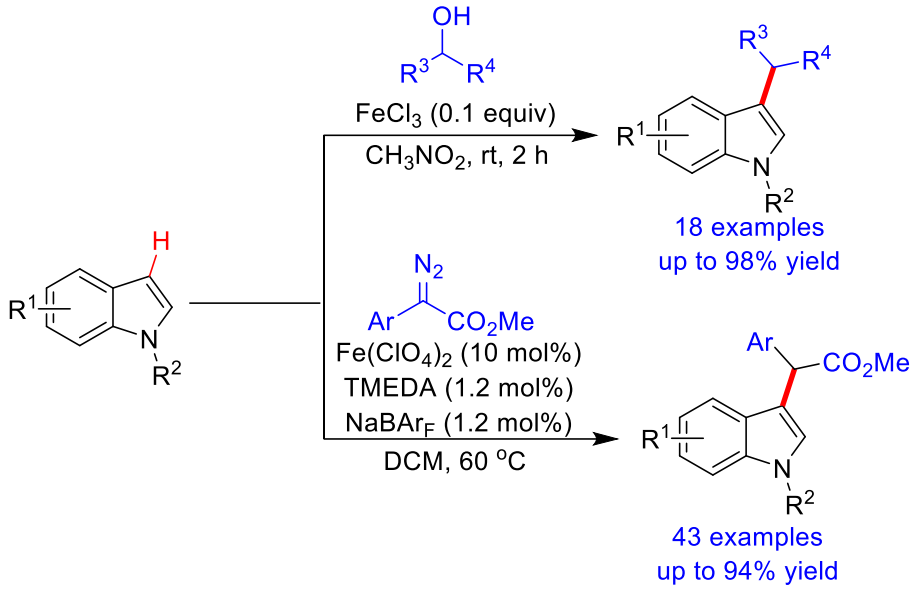
generation of a Mn-amido complex during the reaction between $MnBr_2$ and LiHMDS serves as an active catalyst for this modification. Furthermore, the reaction exhibits remarkable versatility, accommodating crucial functionalities such as heteroarenes, alkynes, phenyl ethers, and silyl-derived alkyl iodides, giving products with satisfactory yields. Mechanistic investigations suggest that the slowest step involves C−H activation, with the inclusion of an alkyl radical species.




**Scheme 1.21** Mn-catalyzed alkylation of indole.

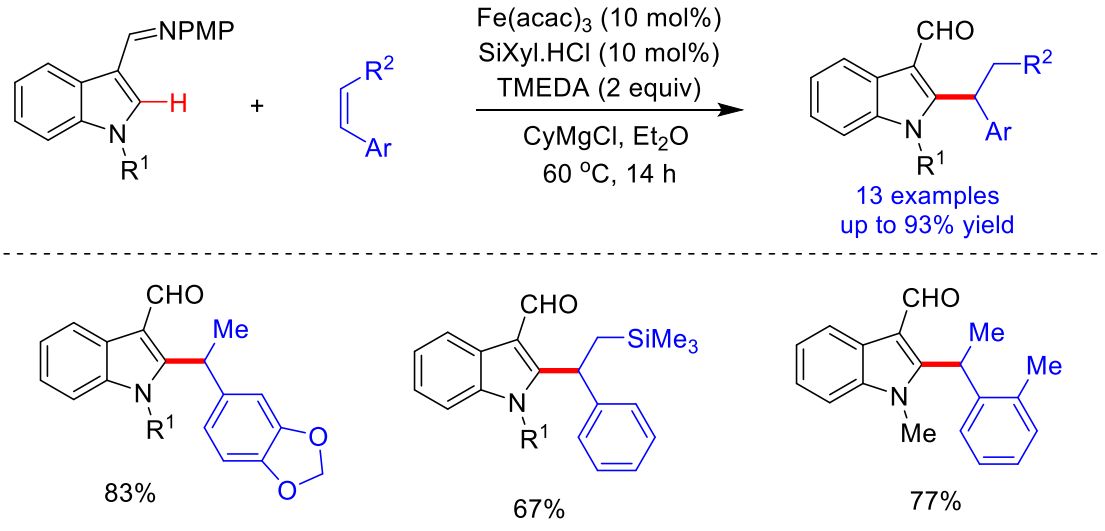
### 1.1.2.2 Fe-Catalyzed Alkylation

Over the past decade, the transformation of C−H bonds with iron catalysts has established diverse applications in various organic transformations employing the C−H activation strategy. However, direct alkylation has remained relatively underdeveloped.[65] Biswas demonstrated Friedel-Craft alkylation of indole at C3 position employing benzylic and allylic alcohols as electrophiles utilizing iron catalyst. The experiment was conducted with a catalytic amount of $FeCl_3$ in nitromethane under mild conditions (Scheme 1.22).[66] Additionally, in 2011, Zhou developed an iron-catalyzed C−H functionalization of indoles with *α*-aryl-*α*-diazoacetates, offering an efficient method for constructing valuable *α*-aryl-*α*-indolylacetate derivatives.[67] Moreover, various substituents on the indole moiety exhibit good compatibility with diazoester as a coupling partner. Mechanistic studies suggest that carbene generation is responsible for the alkylation reaction.




**Scheme 1.22** Fe-catalyzed C3-alkylation of indole.

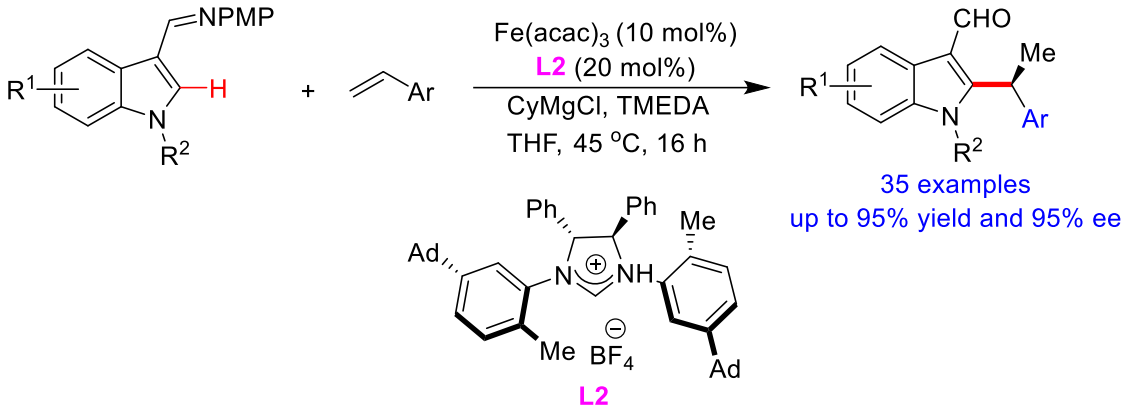
Yoshikai has developed a Fe-catalyzed C2 alkylation of indole using vinyl styrene as a coupling partner (Scheme 1.23).[68] This protocol relies on the iron-NHC system to achieve the desired C2 alkylation of indole. They have demonstrated an ample substrate scope with different types of vinyl arenes with indole, giving good to moderate yields. Furthermore, deuterium labeling experiments support a mechanism involving the C−H bond oxidative addition to the iron center, alkene insertion into the Fe−H bond, and subsequent reductive elimination to generate the active catalyst.




**Scheme 1.23** Fe-catalyzed C2 alkylation of indole.

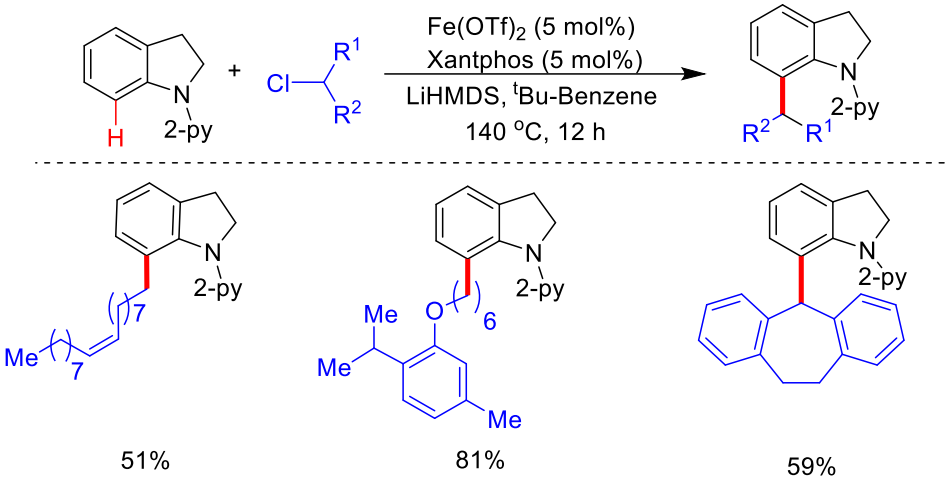
In 2017, the Ackermann group reported a method for the enantioselective branch alkylation of indole. This protocol requires a Grignard reagent to achieve the target product,

and the use of a chiral NHC ligand is necessary to achieve enantioselectivity. The approach shows a wide range of applicable substrates with good enantioselectivity under milder reaction conditions (Scheme 1.24).[69]




**Scheme 1.24** Asymmetric Fe-catalyzed alkylation of indole.

Recently, In 2020, Punji research group devised a strategy for the C7 alkylation of indoline employing cost-effective and abundantly available iron metal. Utilizing $Fe(OTf)_2$ in conjunction with xantphos as a catalytic amount facilitated regio-selective alkylation, even when employing primary and secondary alkyl chlorides as more challenging coupling partners (Scheme 1.25).[37] Notably, various functional group-derived alkyl chlorides, including alkenes, alkynes, ethers, as well as heteroarenes like indole and carbazole, participated in the reaction, affording alkylated products with satisfactory yields. Remarkably, alkyl chlorides derived from polycyclic steroid molecules also proved amenable to the reaction conditions. Deuterium and kinetic studies unveiled that C−H activation constitutes the rate-determining step, with mechanistic experiments indicating Fe(I) as the active catalyst for this alkylation, following a one-electron oxidative addition pathway (Figure 1.3).




**Scheme 1.25** Fe-catalyzed C7 alkylation of indoline using alkyl chloride.

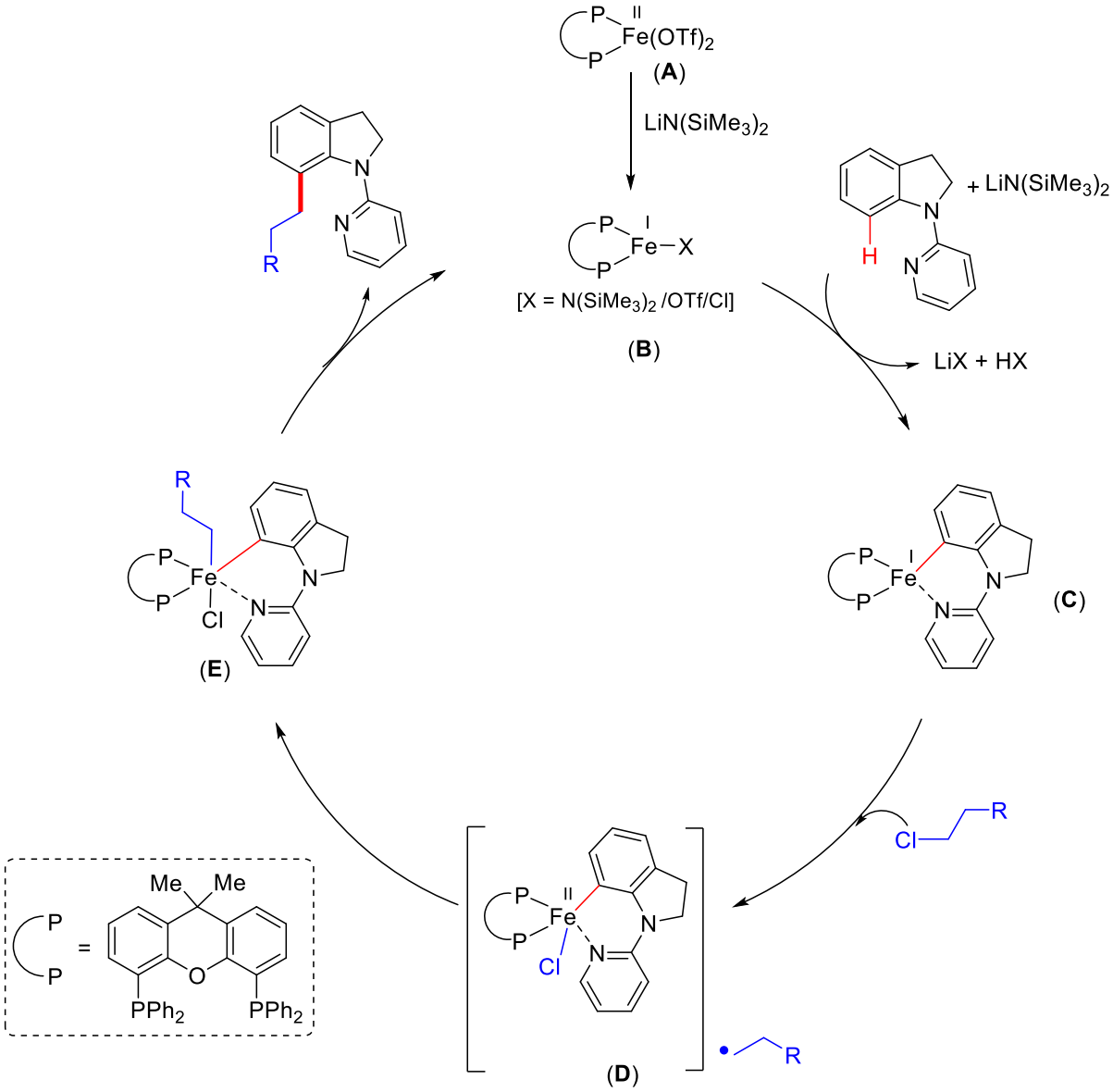
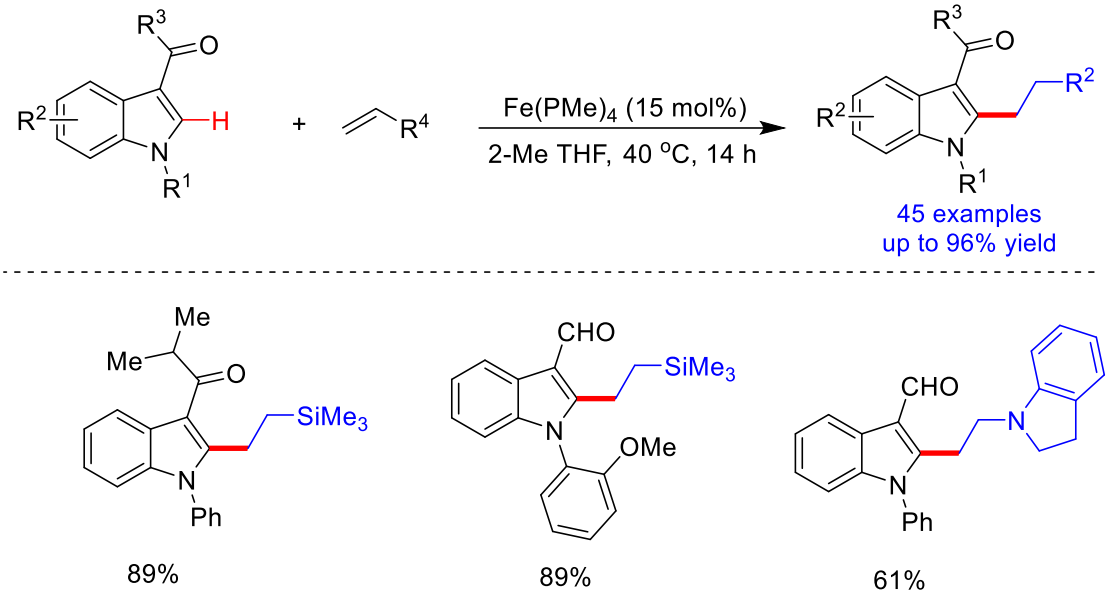



**Figure 1.3** Plausible reaction mechanism for Fe-catalyzed alkylation of indoline.

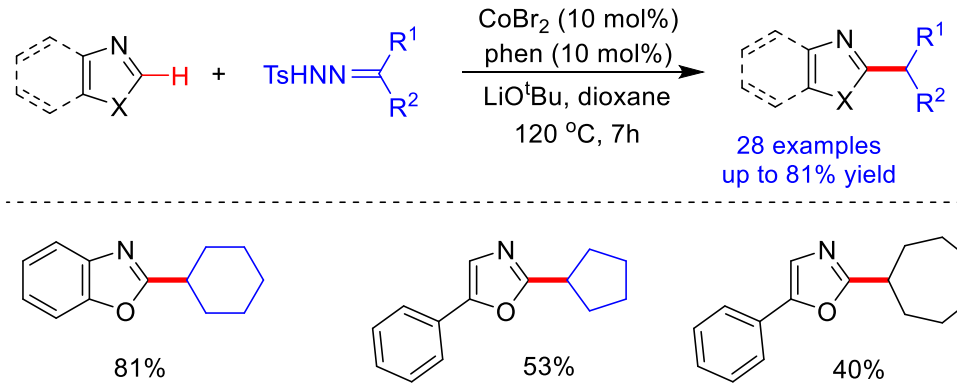
In recent years, Punji group has developed a cost-effective, regioselective alkylation of indole using a carbonyl as a directing group (Scheme 1.26).[70] This methodology is made more reliable by using a renewable solvent or operating in the absence of solvents and additives. The key to achieving C2 alkylation of indole is the use of Fe(0) as a catalyst. This method demonstrates a wide substrate scope of indole with vinyl silane, providing excellent yields. Mechanistic studies indicate that Fe(0)/Fe(II) is involved in the catalytic pathway, involving facile C−H activation and 1,2-alkene insertion.




**Scheme 1.26** Fe-catalyzed C2 alkylation of indole.

### 1.1.2.3 Co-Catalyzed Alkylation

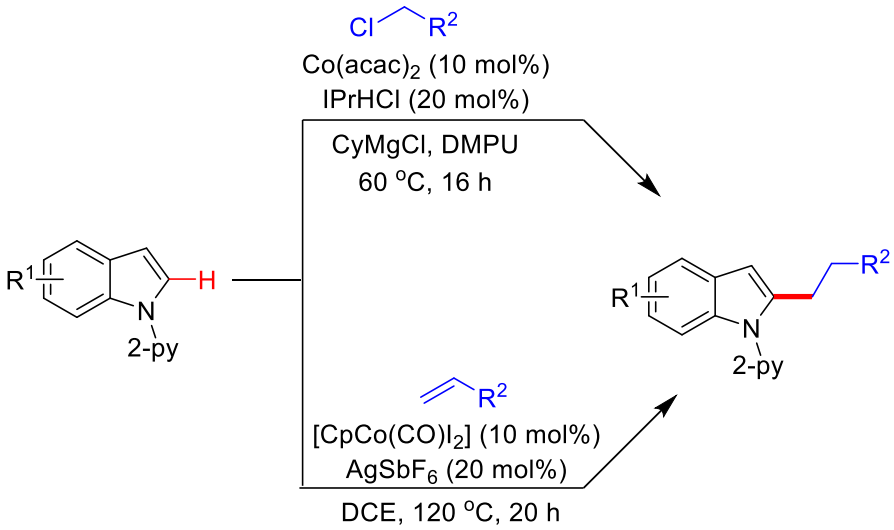
Miura *et. al.* introduced a direct alkylation method for azoles utilizing N-tosylhydrazones, employing the $CoBr_2$/phen catalyst system, and $LiO^tBu$ as the base in dioxane (Scheme 1.27).[71] The standard reaction conditions proved effective for the smooth alkylation of 5-aryloxazoles containing electron-withdrawing groups like chloro, trifluoromethyl, and cyano groups. However, for electron-donating methoxy substituents, more rigorous conditions were necessary, necessitating the use of $NaO^tBu$ as the base.




**Scheme 1.27** Co-catalyzed alkylation of azole.

Ackermann group disclosed a Co-catalyzed alkylation of indole, achieving the alkylation of indole with more challenging *β*-hydrogen-containing alkyl chloride Notably, Grignard reagent and carbene ligand is necessary for the regioselective alkylation of indole. Additionally, this reaction needs low catalyst loading and mild reaction temperature.[72] The C−H bond alkylation demonstrated excellent chemo- and site-selectivities, along with a broad

scope of substrates. Subsequently, a similar group reported *ortho* C−H bond hydroarylation of indole with alkene as a coupling partner in DCE solvent at 120 °C, where different types of functional groups withstood the reaction parameters. Following this report on alkylation using chelation assistance, numerous other research groups presented alkylations of indole with various alkylating agents (Scheme 1.28).[73] Other groups have also developed the alkylation of indole using various alkylating agents with the involvement of cobalt catalyst.[74-75]

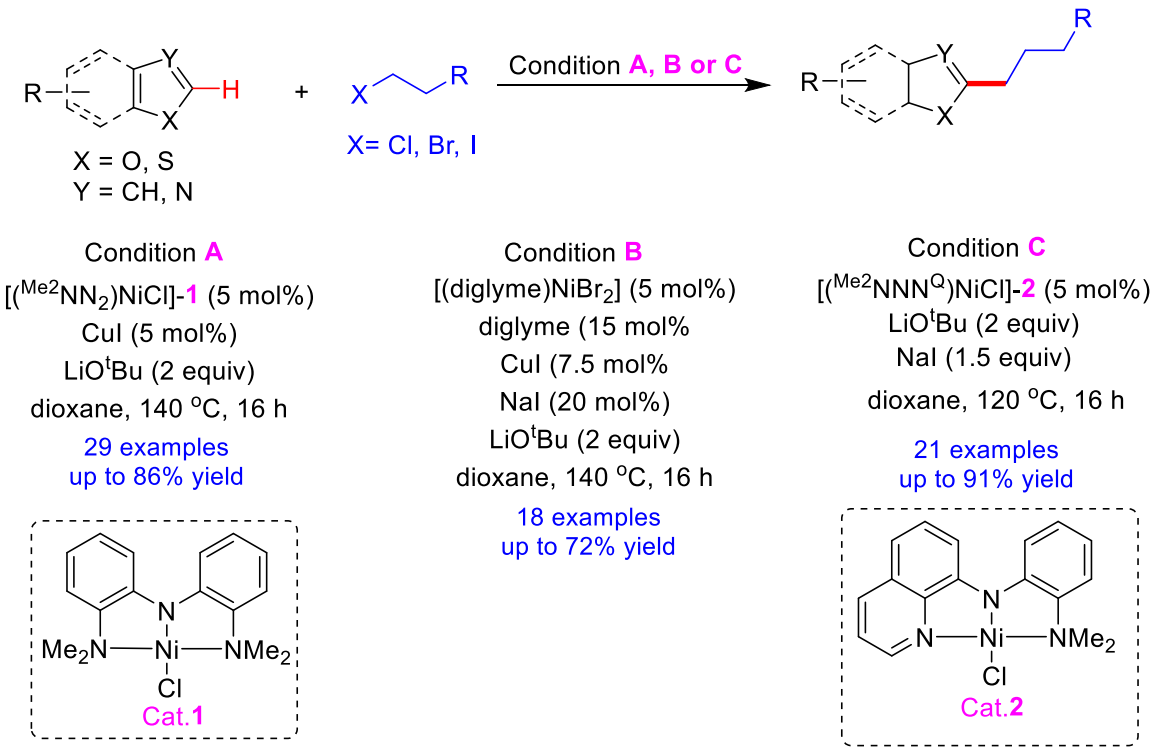



**Scheme 1.28** Co-catalyzed alkylation of indole using alkyl chloride and alkene.

### 1.1.2.4 Ni-Catalyzed Alkylation

Nickel plays a pivotal role in catalyzing the C–H alkylation of azoles and other heteroarenes due to its versatility, high activity, and selectivity, contributing to efficient and sustainable processes in various industries.[76] Its abundance on Earth, cost-effectiveness, and eco-friendly nature make nickel a preferred catalyst for the alkylation of 1,3-azoles with various alkylating agents. In a pioneering study, Hu developed a pincer-based [($Me_2NN_2$)NiCl] (Cat. **1**) catalyst for the alkylation of azoles.[77] This method requires CuI as a co-catalyst to achieve the desired alkylation product. Additionally, different types of azoles, such as benzoxazoles, thiophenes, and oxazoles, are reacted with alkyl halides, including alkyl chlorides and bromides, to obtain significatnt amount of alkylated products. The reaction accepted an array of functional groups including ketone, alkene, cyano, ester, ether, thioether, and other heteroarenes. However, secondary alkyl halides were ineffective under the optimal parameters. Moreover, Ackermann group has successfully established the azoles alkylation reaction.[78] In their method, they utilized nickel as a catalyst along with a catalytic amount of diglyme as a ligand. Additionally, CuI was employed as a co-catalyst for this conversion. Notably, NaI was utilized for halide exchange with alkyl chloride or alkyl bromide, facilitating

their coupling with azoles. The mechanistic investigation suggested that the alkylation reaction undergoes one electron oxidative addition of alkyl halide to the nickel center. This approach aimed to overcome the limitations associated with copper co-catalysts and catalyst decomposition. Inspired by the work of the Hu group, Punji and co-workers have developed a quinoline-based NNN-pincer catalyst, characterized by its well-defined and robust nature. Employing the [($^{Me2}$NNN$^{Q}$)NiCl] complex, they targeted the C−H bond alkylation of azoles using primary alkyl iodide as the reactant. Remarkably, this alkylation was conducted at a lower temperature of 100 °C, compared to previous reactions requiring 140°C, and notably, it does not necessitate CuI as a co-catalyst. The reaction demonstrated broad substrate compatibility under the given conditions. Initial investigations suggest that the alkylation proceeds via a radical pathway, while DFT studies propose an alkylation mechanism involving a Ni(II)/Ni(IV) pathway (Figure 1.4).[79]




**Scheme 1.29** Ni-catalyzed direct alkylation of azoles with unactivated alkyl halides.

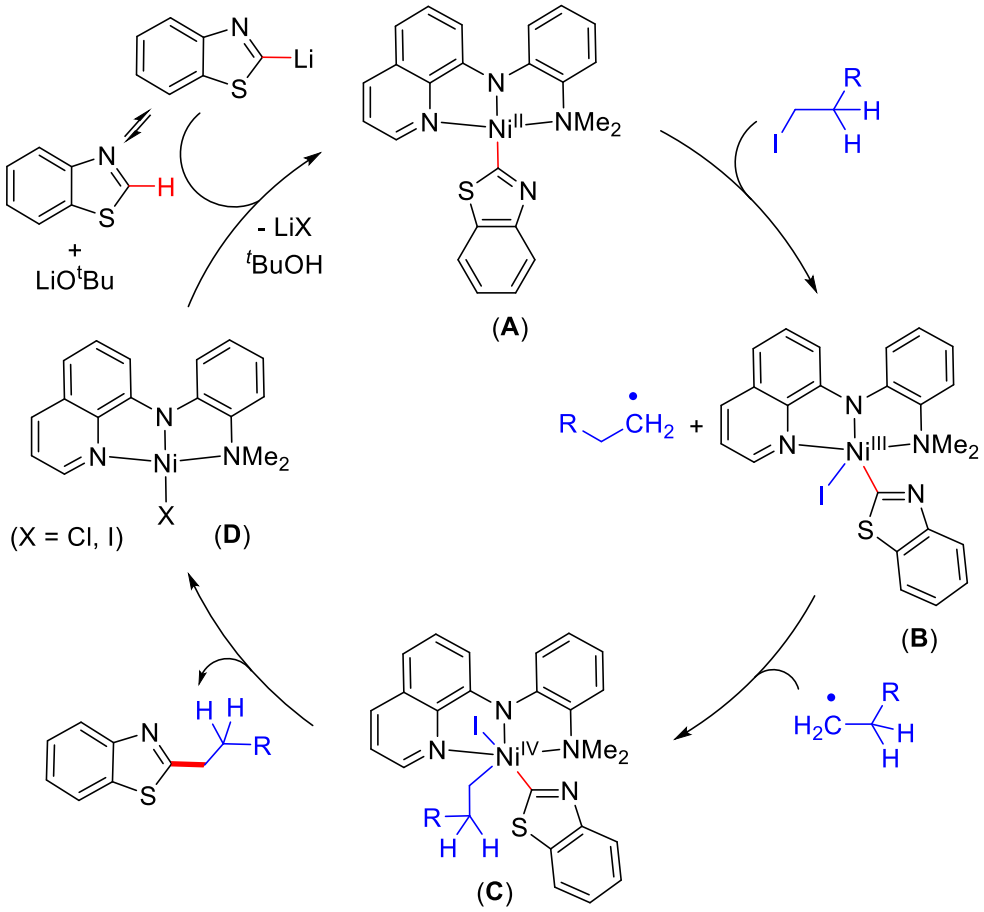
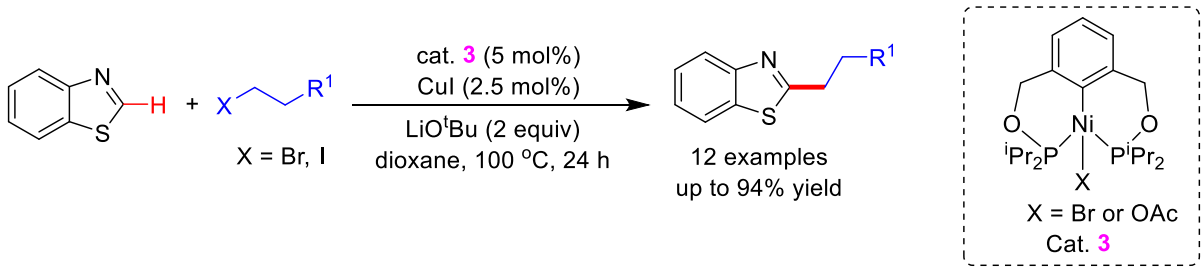



**Figure 1.4** Plausible reaction mechanism for Ni-catalyzed alkylation of azole.

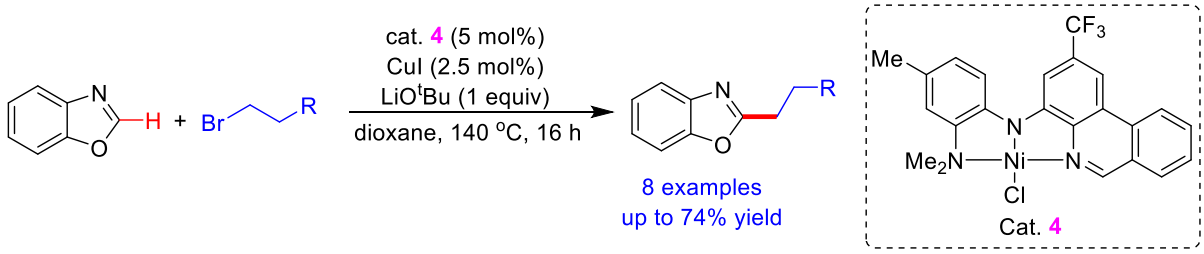
Expanding upon their previous research, Punji group further investigated benzothiazole alkylation using primary bromoalkane and iodoalkane, employing phosphine-based nickelacycles pincer complexes (Scheme 1.30).[80] The phosphine ligand stabilizes the electronic state of nickel, which is crucial for the alkylation reaction of azoles. However, it's important to note that this reaction still requires a copper co-catalyst.




**Scheme 1.30** Alkylation of benzothiazole using nickel pincer complex.

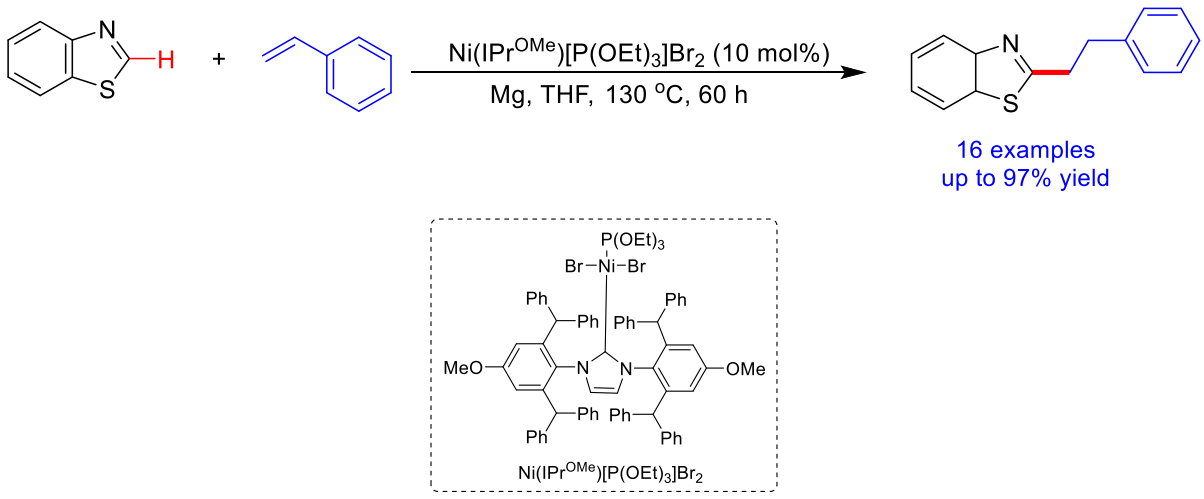
In a recent study, Herbert developed a nickel pincer complex with phenanthridine as the ligand backbone. The NNN-based ligand is crucial for the alkylation reaction of azoles. This catalyst achieved the alkylated azole products in moderate yields at of 140°C (Scheme

1.31).[81] The synthetic pathway to the (NNN)-proligand frameworks allows for the easy incorporation of various substituents. The electron-donating or electron-withdrawing properties of these substituents can be quantified based on the redox behavior of their nickel complexes. The study also involved mechanistic investigations, including the association of catalytic activity with the π-acidity of the benzannulated phenanthridine ligand frameworks.




**Scheme 1.31** Alkylation of benzoxazole using nickel pincer complex.

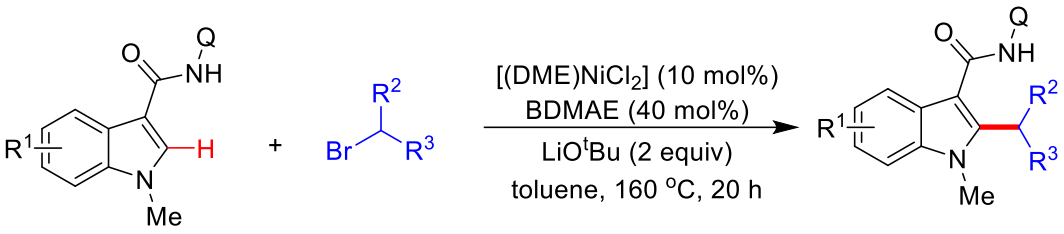
Additionally, Sun group developed a unique heteroleptic Ni(II) complex identified as Ni(NHC)[P(OR)$_3$]Br$_2$. They disclosed its use as the initiative Ni(II)-based precatalyst for hydroarylation of azoles with vinylarenes, employing stoichiometric amounts of magnesium turnings (Scheme 1.32).[82] The NHC-controlled regioselective switch observed in this study is notably uncommon in reported hydroarylation processes. This distinctive feature offers a practical method for synthesizing a diverse array of 2-alkylated benzothiazoles. The analysis also underscores the potential synergistic effects between a phosphite ligand and NHC ligand, showcasing their collaborative role in advancing nickel catalysis.




**Scheme 1.32** Ni-catalyzed alkylation of imidazole using styrene.

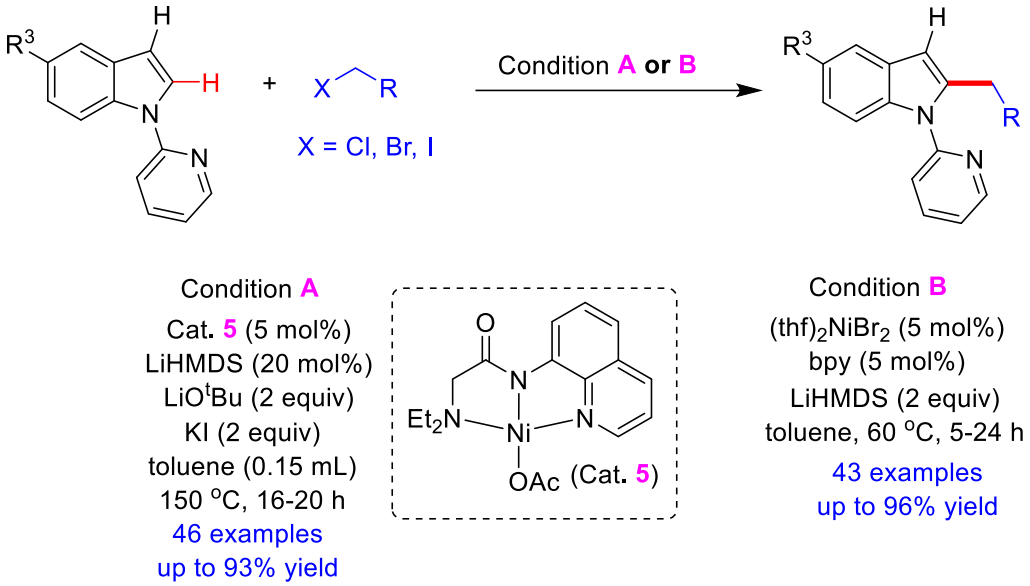
Ackermann developed a regioselective alkylation of indole employing secondary bromoalkane as an electrophile with nickel catalyst. Noteworthy is the incorporation in the 8-aminoquinoline group at the C3 position, serving as a directing group for the selective

alkylation of indole. A diverse array of cyclic or acyclic alkyl bromides reacts with indole, yielding products with satisfactory yields (Scheme 1.33).[83]




**Scheme 1.33** Ni-catalyzed alkylation of indole using bidentate chelation assistance.

Punji and co-workers developed a quinoline-based (NNN)Ni(OAc)-pincer complex for the regioselective alkylation of indole via monodentate chelation assistance. The well-designed quinoline-based NNN ligand provides an electronic environment and stability to the metal, enabling C2 alkylation of indole.[84] Remarkably, this method obviates the need for a bidentate directing group, offering a significant advantage for this transformation. Notably, they employed LiHMDS in catalytic amounts to generate the active amido complex responsible for activating the C2 position of indole. This protocol demonstrated the compatibility of various primary and secondary alkyl halides with indole. The same group has unveiled a Ni-catalyzed regioselective alkylation of indole, employing difficult primary and secondary alkyl chlorides as coupling partners.[85] A pivotal discovery in this protocol is the utilization of LiHMDS, which forms an active Ni(I) catalyst. Notably, the alkylation reaction proceeds under mild conditions (Scheme 1.34). Various functional groups derived from alkyl chlorides, including alkenes, alkynes, phenyl ethers, as well as heteroarenes such as indole, pyrrole, and carbazole, are tolerated under the reaction conditions. Mechanistic studies have indicated Ni(I) as the active catalyst, operating via a 1e oxidative addition pathway (Figure 1.5).




**Scheme 1.34** Ni-catalyzed alkylation of indole using unactivated alkyl halide.

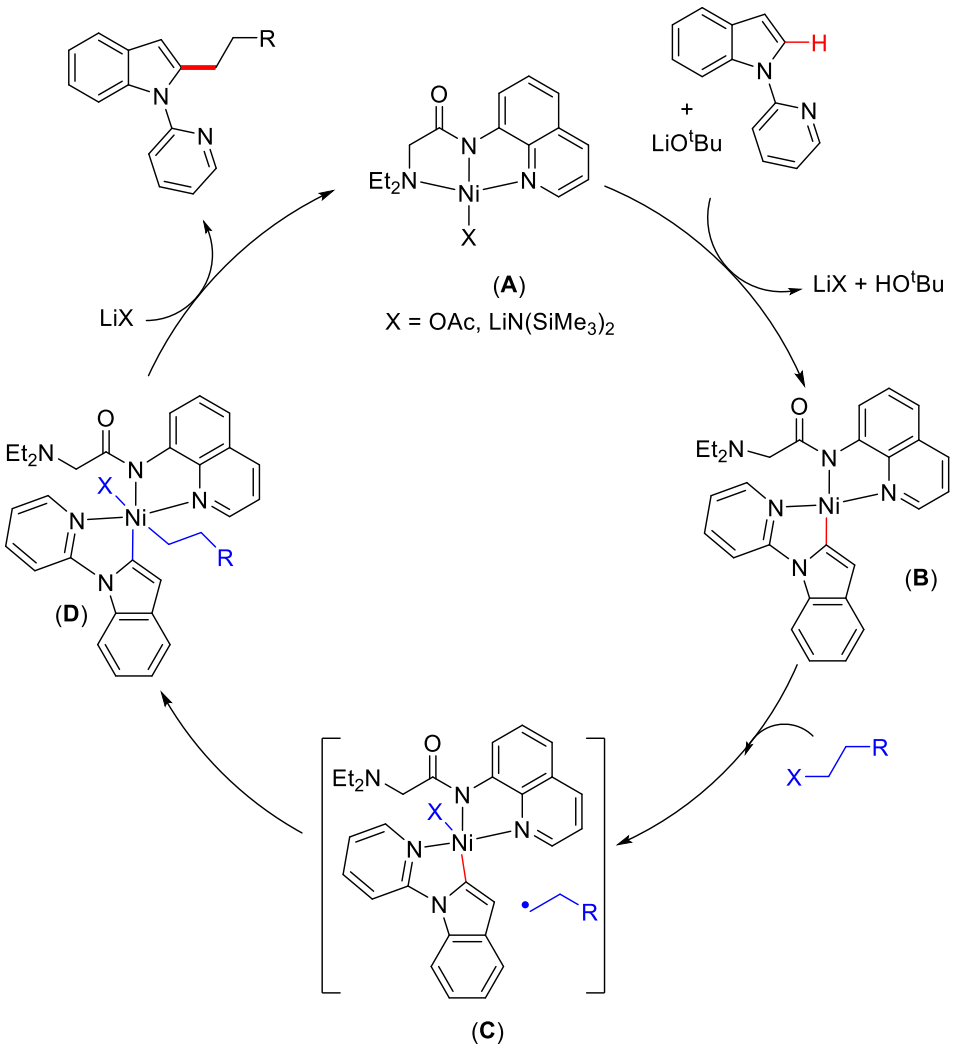
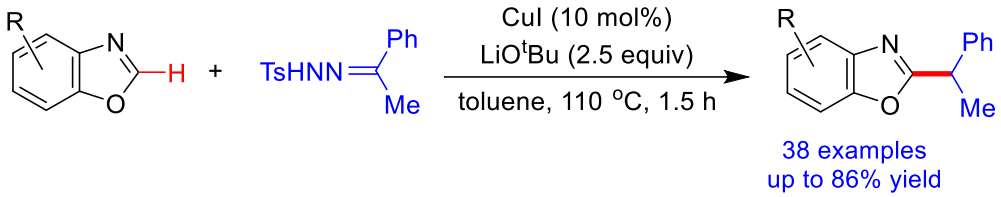



**Figure 1.5** Plausible reaction mechanism for Ni-catalyzed alkylation of indole.

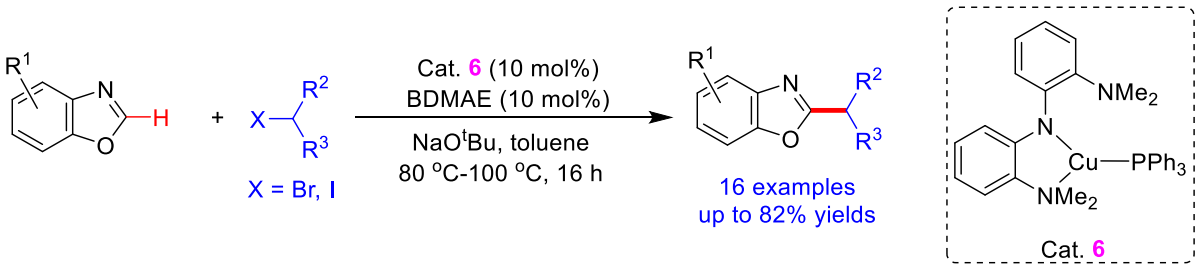
### 1.1.2.5 Cu-Catalyzed Alkylation

Among the 3d transition metals, copper has emerged as a widely employed catalyst for alkylation reactions.[86] In 2011, Wang group demonstrated the alkylation of azoles using hydrazones as coupling partners under the condition of copper catalyst. Copper is indipspensable in the alkylation reaction, which is conducted in toluene at 110°C. This method highlights a good substrate scope with yields varying from satisfactory to moderate. This approach provides an effective method for C–H bond functionalization through the secondary benzyl group, a challenging feat in other transition metal-assisted C−H bond modification techniques. Notably, the proposed key role in this transformation involves Cu carbene migratory insertion (Scheme 1.35).[87] Subsequently, the benzylation of 1,3,4-oxadiazoles was pioneered by the Das group. This protocol utilizes N-tosylhydrazones as coupling partners and copper as a catalyst.[88] Numerous substituted oxadiazoles smoothly underwent the reaction with N-tosylhydrazones, providing good yields of the desired products.




**Scheme 1.35** Alkylation of benzoxazole using copper catalyst

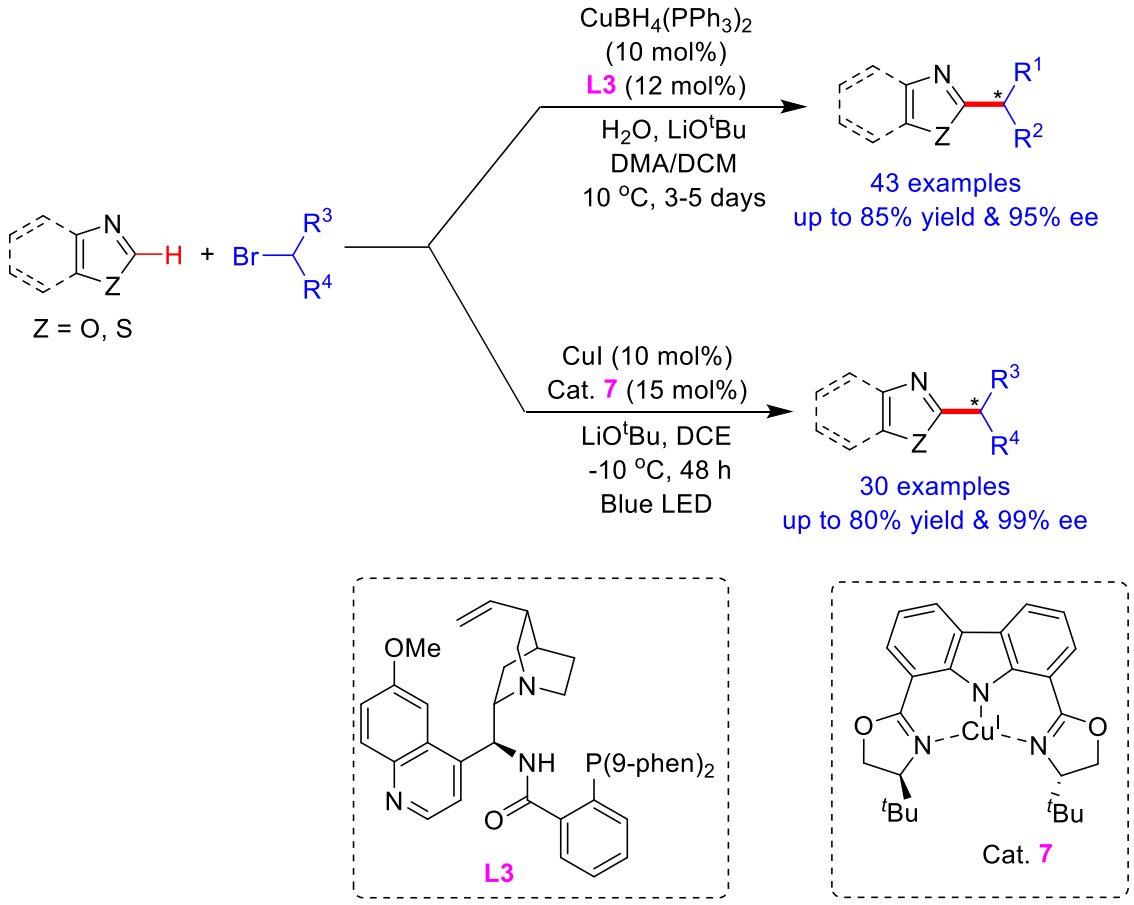
Following the previously described approach, Hu group achieved the first time of azoles alkylation using more challenging 2° alkyl halides as electrophiles. Their method employed a well-defined copper complex, identified as the optimal catalyst system for this protocol, along with catalytic amounts of BDMAE to facilitate the alkylation reaction (Scheme 1.36).[89] Various types of secondary alkyl iodides were successfully utilized as coupling partners with azoles, resulting in satisfactory yields of the desired product.




**Scheme 1.36** Cu-catalyzed alkylation of benzothiazole.

In recent developments, Zhang and Li have made significant strides in enantioselective alkylation, employing racemic alkyl bromide as a coupling partner. The utilization of a

combination of $CuBH_4(PPh_3)_2$ and a chiral ligand has proven pivotal in achieving high enantioselective products. Li's group has demonstrated diverse alkylation of azoles, providing products with 95% enantioselectivity of the desired product.[90] On the other hand, Zhang's approach involves employing a Cu-based NNN chiral complex for the enantioselective alkylation of azoles.[91] Notably, the introduction of a BLUE LED serves a crucial role in the alkylation reaction. Azoles such as benzoxazole and benzothiazole exhibit excellent reactivity with racemic alkyl halide, resulting in good yields and outstanding enantioselectivity. Remarkably, this methodology accommodates different functional groups such as methoxy, fluoro, and ether, further enhancing its applicability (Scheme 1.37).




**Scheme 1.37** Copper-catalyzed enantioselective alkylation of azoles.

### 1.2 C–H Bond Alkynylation of (Hetro)Arene

Alkynylation reactions are highly significant in organic chemistry due to their ability to effectively diversify carbon-carbon triple bonds, offering considerable adaptability in synthetic strategies. Traditionally, methods like Sonogashira coupling have been employed for alkynylation, but they necessitated the use of halogenated substrates, presenting a notable limitation. To address this drawback, the field has noticed the emergence of the C−H bond

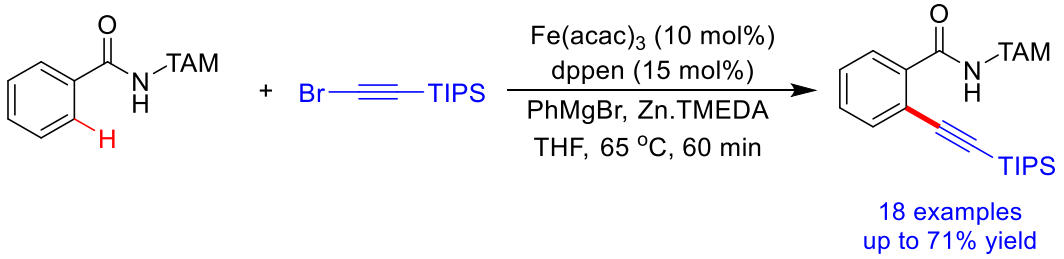
alkynylation using transition metal-catalyst as a more contemporary alternative.[92,93] Notably, the alkynylation of (hetero)arenes *via* C−H activation serves as a crucial intermediate for various organic transformations. Initially, specific directing groups or potent alkynylating agents were required for the synthesis of (hetero)arenes alkynylation. However, recent advancements in transition metal-catalyzed methods have introduced milder conditions and readily available alkynylating agents, offering a more efficient and accessible approach to (hetero)arenes alkynylation.

### 1.2.1 C−H BOND ALKYNYLATION OF ARENES

The direct C−H bonds functionalization holds a significant interest in organic molecule synthesis. Over the last few decades, site-selective alkynylation of arenes C−H bond appeared as a crucial research area in organic chemistry. Several groups have devised alkynylation methodologies through traditional cross-coupling techniques as well as direct alkynylation of arenes using 4d and 5d transition metals.[94,95] However, these methods come with various limitations. Nonetheless, there is a growing interest in direct alkynylation of arenes utilizing 3d transition metals as a catalysts. Notably, this methodology remains relatively underdeveloped.

#### 1.2.1.1 Fe-Catalyzed Alkynylation

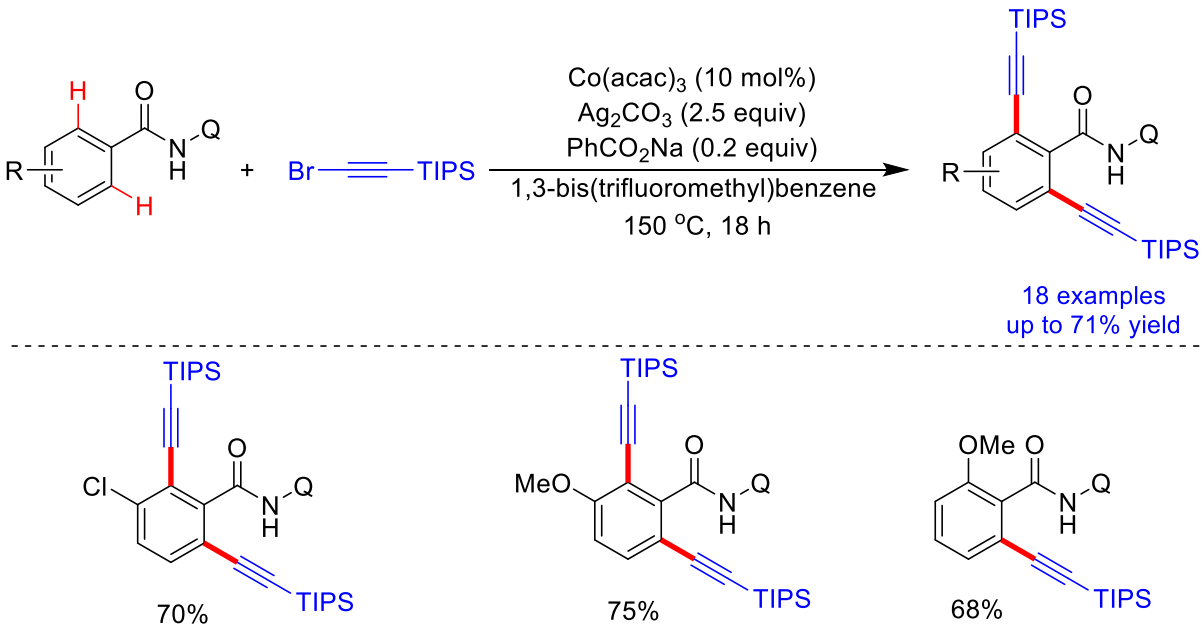
Iron is one of the most prevalent transition metals in the Earth's crust, particularly within the 3$^{rd}$ row. Its utilization as a catalyst for organic transformations is appealing due to its distinctive characteristics, including cost-effectiveness, environmental friendliness, and lower toxicity.[96] Despite these advantages, the application of iron catalysts in the C–H bond alkynylation of arenes has been notably constrained. The pioneering work of Ackermann revealed the iron-catalyzed alkynylation of benzamide, employing a triazole-assisted directing group. Grignard reagent is required for this transformation (Scheme 1.38).[97] This innovative protocol demonstrated the site-selective C−H functionalization of diverse arenes and heteroarenes with exceptional functional group tolerance. Notably, the reaction conditions accommodated *meta*- and *para*-substituents of benzamide. In addition, kinetic isotope effects suggested that the rate-determining step did not participate in C−H activation process.




**Scheme 1.38** Fe-catalyzed alkynylation of benzamide.

### 1.2.1.2 Co-Catalyzed C–H Bond Alkynylation

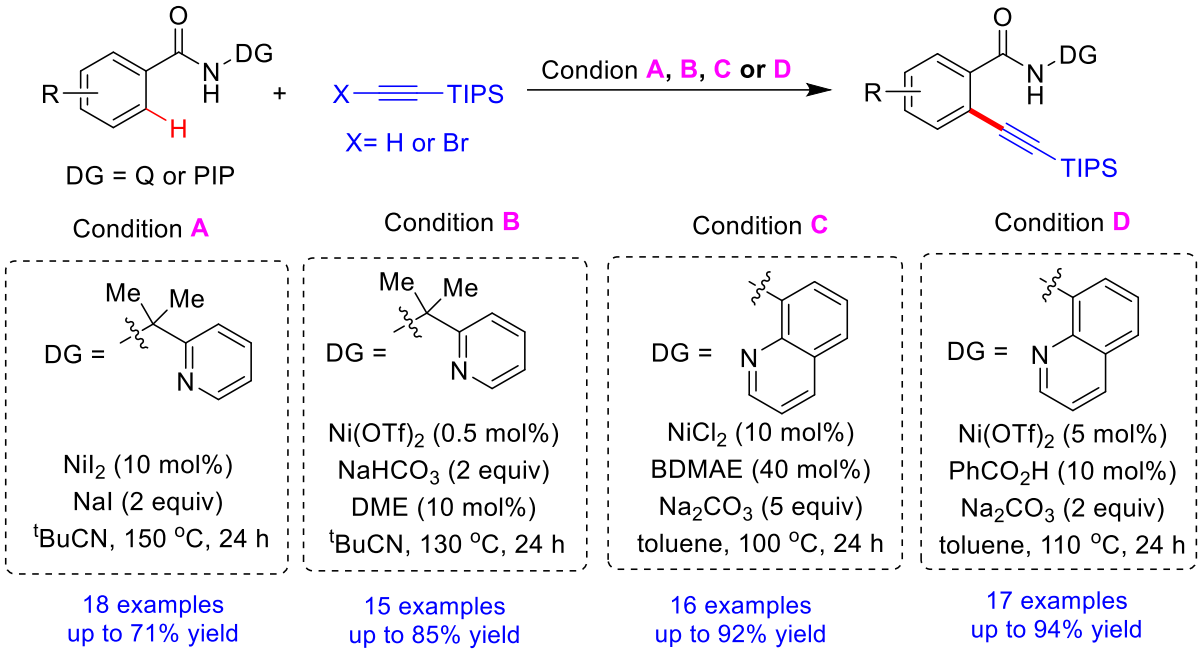
Catalysts based on cobalt are frequently linked to mild reaction conditions and exceptional selectivities.[98] Consequently, the advancement of cobalt catalysts for the selective alkynylation of arenes, including benzamide and related compounds, represents a significant step toward sustainable synthesis. In 2016, Balaraman disclosed a method for di-alkynylation of amides through dual C−H bond activation utilizing a cobalt catalyst. Significantly, this approach employed the use of readily accessible and cost-effective 8-aminoquinoline as a removable directing group (Scheme 1.39).[99] The current procedure has demonstrated remarkable versatility, accommodating both electron-rich and electron-poor groups. Furthermore, the results of radical trapping experiments suggested the formation of an alkynyl radical during the reaction.




**Scheme 1.39** Co-catalyzed alkynylation of benzamide.

### 1.2.1.3 Ni-Catalyzed Alkynylation

In 2015, Shi and team demonstrated a nickel-catalyzed dehydrogenative alkynylation method for benzamide, utilizing unactivated terminal alkyne as a coupling partner under atmospheric pressure of oxygen.[100] The use of catalytic amounts of $O_2$ as the sole oxidant offered a more straightforward and environmentally friendly approach for aryl alkyne synthesis. This protocol demonstrated compatibility with different functional groups, like nitro, ether, and methoxy, within benzamide, providing good yields. Moreover, heteroarene benzamides also smoothly reacted with terminal alkynes under the reaction condition. In the same year, the group disclosed the alkynylation of benzamide using unactivated alkyne bromide as a coupling partner with a lower loading of nickel catalyst.[101] Significantly, the introduction of a directing moiety was crucial for the *ortho*-selective alkynylation of benzamide in both cases. Following these reports, Li and the team developed a Ni-catalyzed alkynylation of benzamide employing a chelated-assisted approach. This approach required BDMAE as an auxiliary ligand for the selective alkynylation of arenes.[102] Remarkably, this approach exhibited an outstanding substrate scope as well as demonstrated smooth reactivity even with heteroarene amides in the presence of alkynyl bromide. Mechanistic investigations examined that C–H activation served as the rate-limiting step, and the SET pathway was deemed less likely. After these reports, Balaraman group explored the alkynylation of benzamide using alkynyl bromide as a coupling partner with a nickel catalyst. The *ortho*-selective alkynylation of benzamide requires the presence quinoline-derived directing group.[103] Various halides containing aromatic amide smoothly reacted with alkynyl bromide under mild reaction conditions, addressing challenges faced by previous approaches in synthesizing such compounds. This methodology exhibited a range of *ortho*-alkynylated products and demonstrated tolerance towards various functional groups (Scheme 1.40).




**Scheme 1.40** Ni-catalyzed alkynylation of benzamide using alkyne and alkynyl bromide.

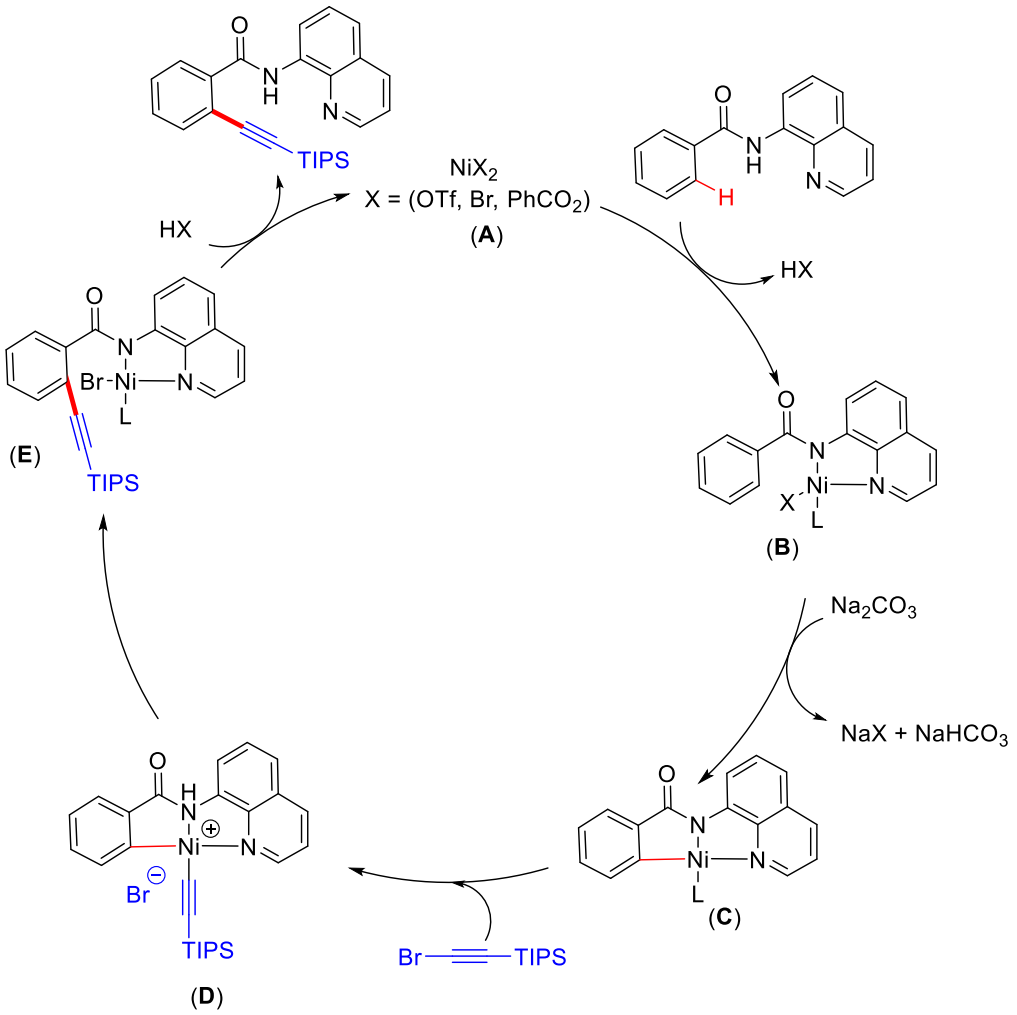
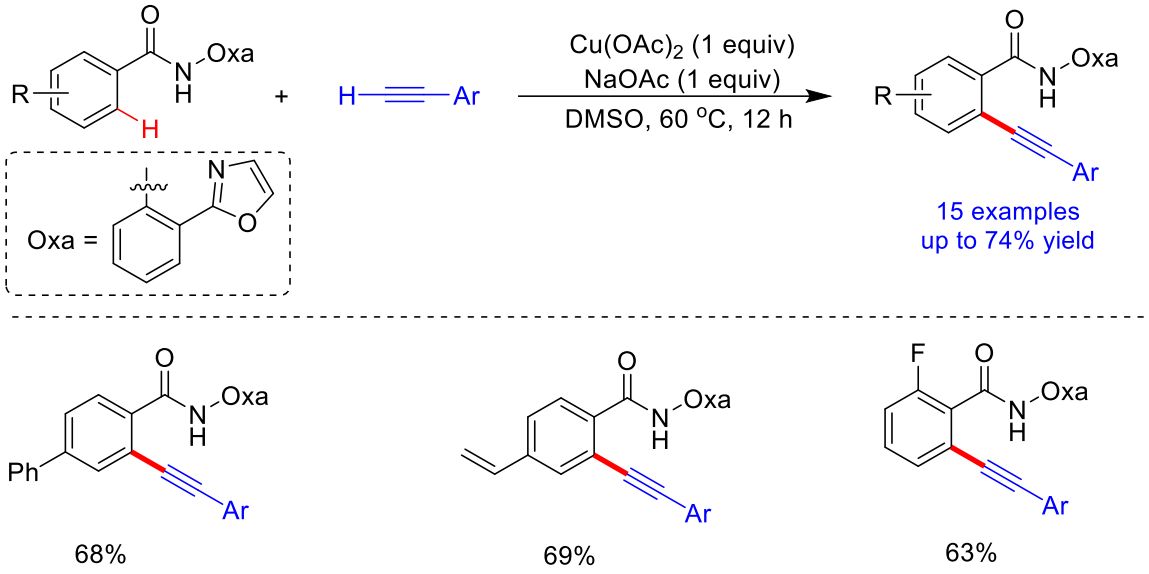



**Figure 1.6** Plausible reaction mechanism for Ni-catalyzed alkynylation of benzamide.

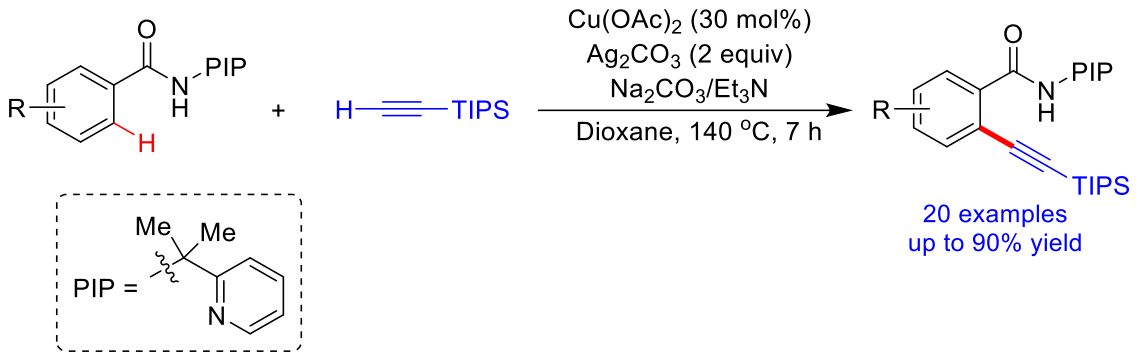
### 1.2.1.4 Cu-Catalyzed Alkynylation

Copper chemistry is highly esteemed due to its ability to readily adopt variable oxidation states ($Cu^0$, $Cu^I$, $Cu^{II}$, and $Cu^{III}$), enabling facile one or two-electron processes.[104] This versatility allows for both SET pathway and two-electron redox pathway through organometallic intermediates. Consequently, these characteristics broaden the scope of functionalizations achievable through copper catalysis. Yu developed a Cu(II)-assisted *ortho*-alkynylation method for (hetero)arenes using terminal alkynes. This transformation utilized a stoichiometric amount of copper catalyst and NaOAc as a base. Importantly, the reaction conditions tolerated both electron-donating as well as withdrawing groups on benzamide (Scheme 1.41).[105] Additionally, a broad array of aryl and terminal alkynes possessing various substituents was identified as a compatible with this reaction. This protocol offers a broadly applicable approach for the preparation of aryl alkynes, serving as a different synthetic strategy to Sonogashira coupling.




**Scheme 1.41** Cu-catalyzed alkynylation of benzamide.

Shi and team developed a method for the *ortho*-alkynylation of aromatic amides using a copper catalyst (Scheme 1.42).[106] They utilized alkynyl bromide as a coupling partner and sodium carbonate as a base in dioxane. The alkynylation reaction requires a stoichiometric amount of silver carbonate. The method is appropriate for important functional groups on the amide and has also been demonstrated with biologically active molecules. The introduction of PIP directing group on benzamide in the presence of copper contributes to the method's high reactivity toward the alkynylation reaction.



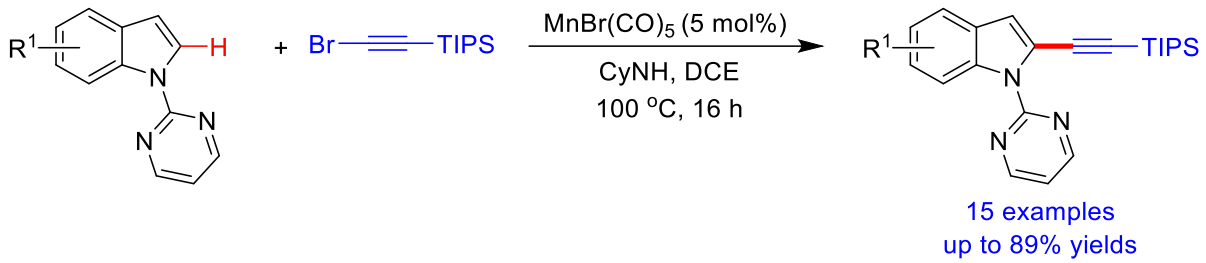

**Scheme 1.42** Cu-catalyzed alkynylation of benzamide using alkyne.

### 1.2.2 C–H BOND ALKYNYLATION OF HETEROARENES

The significance of alkynylation in heteroarenes is evident across pharmaceuticals, natural products, and functional materials. The integration of alkyne groups into heteroarenes plays a crucial role as an intermediate in numerous drug molecules and their derivatives. Consequently, the establishment of an effective method for introducing alkyne groups into diverse heteroarenes has become a focal point in contemporary organic synthesis research. In recent decades, notable improvement has been made in achieving C–H bond alkynylation heteroarenes using alkynylating agents as coupling partners in the presence of 4d and 5d transition metals.[107] Notably, this strategy has facilitated the incorporation of alkyne groups into heteroarenes, contributing to their versatility in various applications. However, the selective alkynylation of heteroarenes remains relatively underexplored with 3d transition metals.

#### 1.2.2.1 Mn-Catalyzed Alkynylation

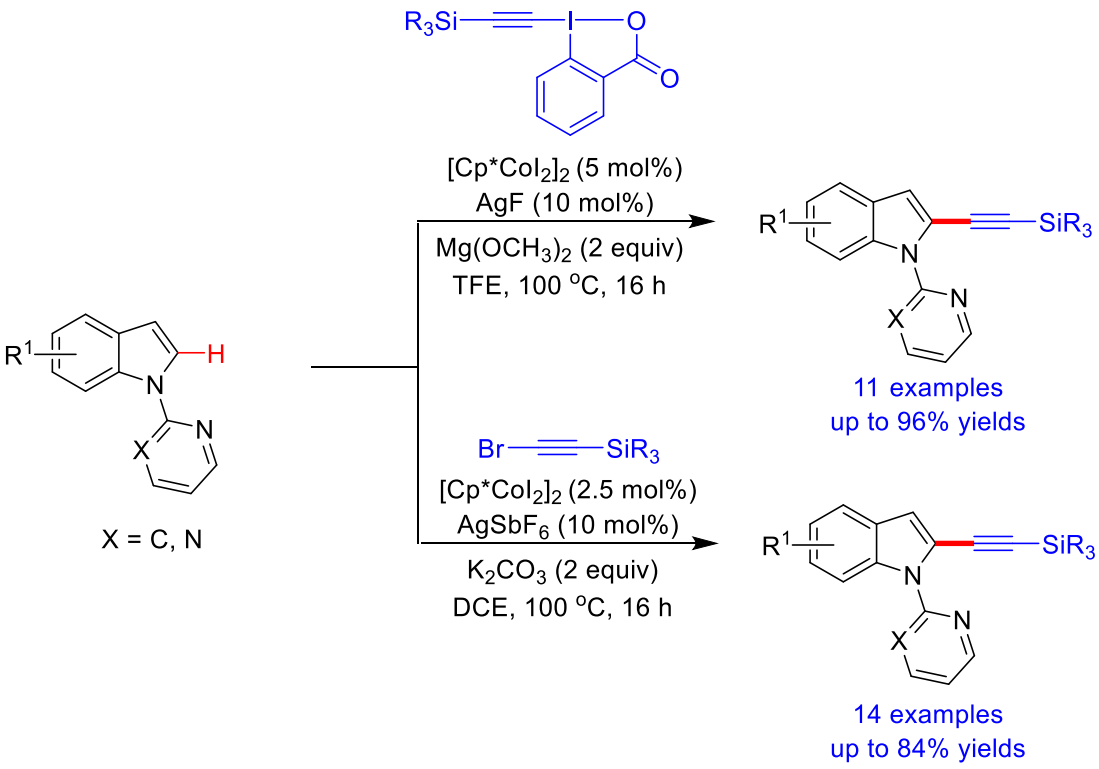
There is a growing interest among researchers in utilizing manganese for the (hetero)arenes C−H bond functionalization.[108] Ackermann disclosed a Mn(I)-catalyzed alkynylation of indole with alkynyl bromide as a coupling partner under mild conditions in DCE solvent (Scheme 1.43).[109] Notably, the presence of 2-pyrimidine as a directing assistant is essential for the transformation. Various scopes have been explored, encompassing indole derivatives with a variety of silyl groups as well as more challenging aryl, alkenyl, and alkynyl substrates. Furthermore, this protocol tolerates indole-derived fluorescent labels, steroids, and amino acids.




**Scheme 1.43** Mn-catalyzed alkynylation of indole using alkynyl bromide.

### 1.2.2.2 Co-Catalyzed Alkynylation

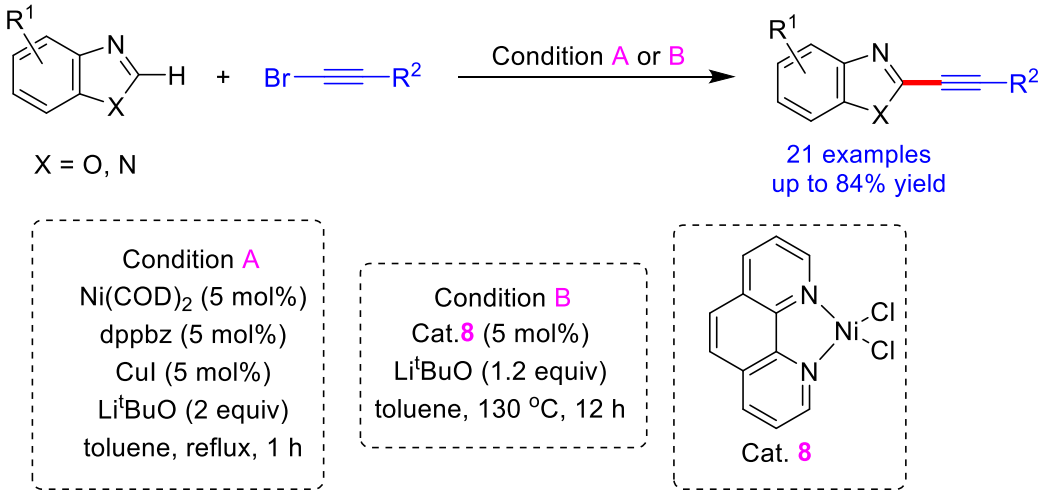
Shi research group has developed a regioselective alkynylation of indole using cobalt as a catalyst, along with hypervalent iodine reagents (Scheme 1.44).[110] This method allows for the incorporation of various substituents on indole molecules such as –OMe, –F, –Br, –$CO_2$Me, and –CN, resulting in good yields of the alkynylated product. Furthermore, the protocol enables the removal of pyrimidine and silyl protecting groups in one pot, providing the deprotected product with good yield. Inspired by Shi group, Ackermann has introduced a Co-catalyzed alkynylation of indole with mono-chelated assistance using alkyne bromide (Scheme 1.44).[111] This reaction proceeds under mild base conditions, such as $K_2CO_3$, and mild reaction parameters. The protocol displays an ample substrate scope, accommodating indole derivatives with various alkynyl bromides, resulting in good yields of desired alkynylation products.




**Scheme 1.44** Co-catalyzed alkynylation of indoles.

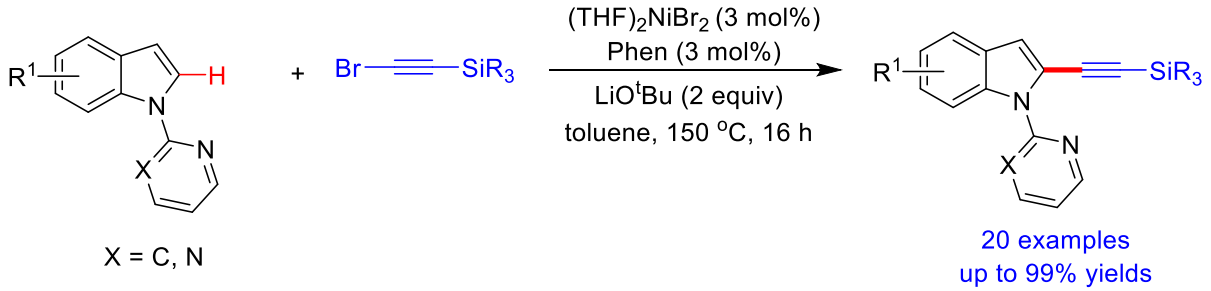
### 1.2.2.3 Ni-Catalyzed Alkynylation

Nickel plays a pivotal role in the C−H alkynylation of azoles due to its variable oxidation states, cost-effectiveness, and eco-friendly properties. [112] Miura demonstrated the Ni-catalyzed alkynylation of azoles, requiring the mixture of $Ni(COD)_2$ and dppbz as catalytic agents for the reaction (Scheme 1.45).[113] Importantly, this protocol is particularly effective with electron-deficient azoles with alkynyl bromides in the form of a coupling partner. Similarly, Punji group has developed a Ni-catalyzed alkynylation of azoles using alkynyl bromide as a coupling partner and $LiO^tBu$ as a base in toluene solvent at 130 °C (Scheme 1.45).[114] They synthesized a well-defined, air-stable catalyst, $(phen)NiCl_2$, and found that a Cu-cocatalyst is not required for this methodology. Various azoles such as benzothiazole and benzoxazole reacted with alkynyl bromide to give a good yield of alkynylated products. The reaction is compatible with electronically diverse groups such as –OMe, –Br, –F, and $–CF_3$ under the given conditions. Mechanistic investigations suggest that the reaction nature is homogeneous and does not involve radicals in the catalytic cycle.




**Scheme 1.45** Ni-catalyzed alkynylation of azoles.

Additionally, Punji has devised a regioselective alkynylation of indole utilizing unactivated silyl alkyne bromide as the coupling partner, facilitated by nickel as a catalyst and phen as a ligand. Crucial functionalities on the indole, including halides, ether, nitrile, and nitro groups, are smoothly coupled with (triisopropylsilyl)alkynyl bromide (Scheme 1.46).[115] Mechanistic examinations show that the reaction undergoes two-electron oxidative addition pathway.




**Scheme 1.46** Ni-catalyzed alkynylation of indoles.

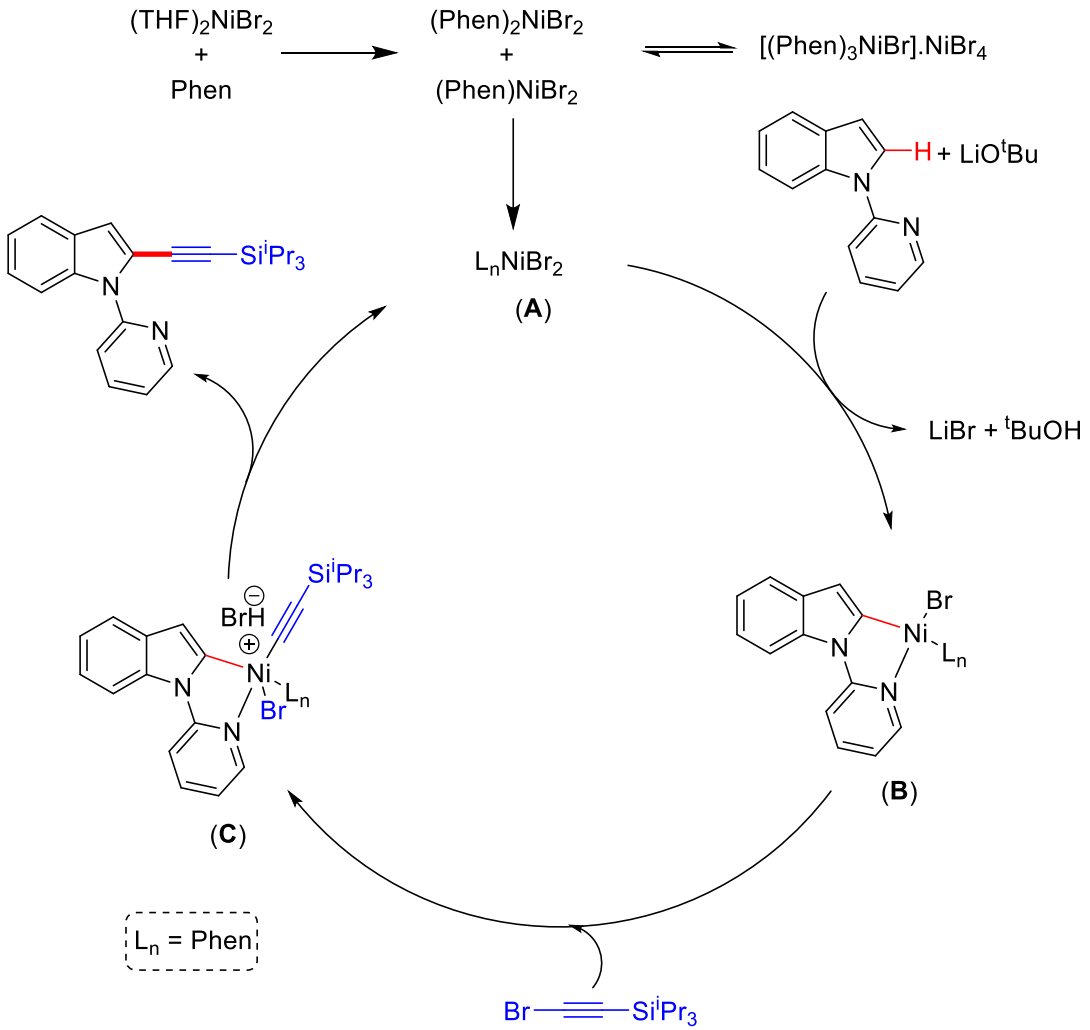
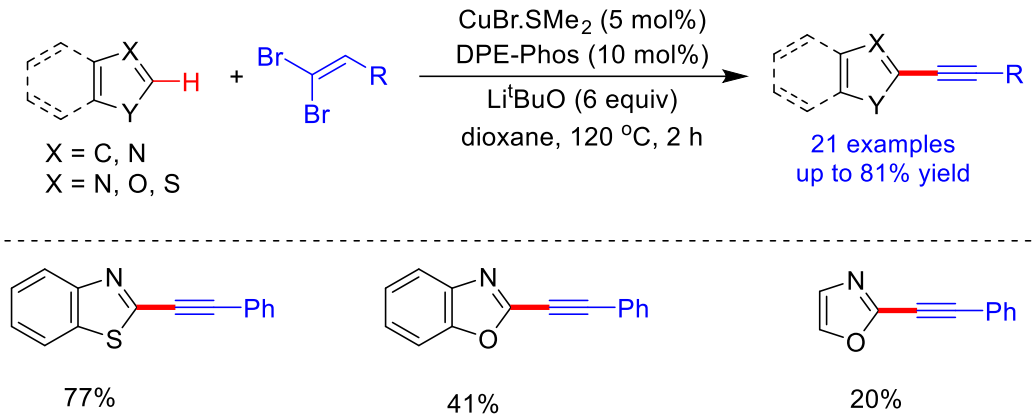



**Figure 1.7** Plausible reaction mechanism for Ni-catalyzed alkynylation of indoles.

### 1.2.2.4 Cu-Catalyzed Alkynylation

In 2010, Piguel showcased the alkynylation of azoles using 1,1-dibromo-1-alkene as a coupling partner in the presence of a copper catalyst (Scheme 1.47).[116] This methodology enabled the synthesis of diverse derivatives of azoles with 1,1-dibromo-1-alkene, yielding satisfactory results under optimized reaction conditions.




**Scheme 1.47** Cu-catalyzed alkynylation of azoles using 1,1-dibromo-1-alkenes.

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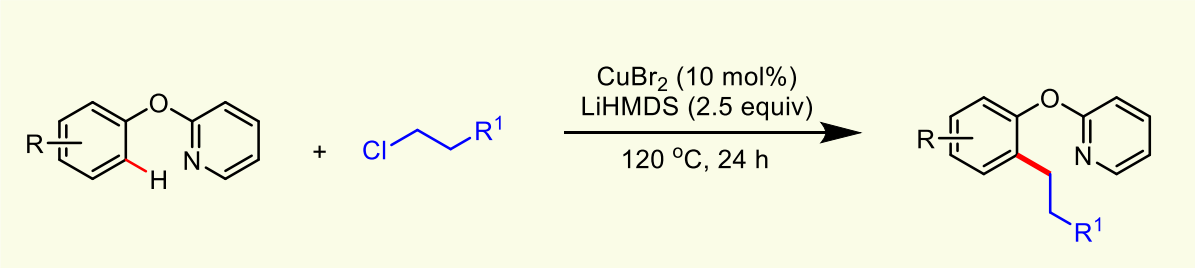
## 1.4 Objectives of the Present Study

In recent years, significant advancements have been made in the field of C–H functionalization of (hetero)arenes using 3d transition metals. These developments include alkylation, arylation, alkenylation, and alkynylation of (hetero)arenes. However, these methods often require activated coupling partners and substrates with a bidentate-chelate auxiliary. Additionally, many protocols rely on Grignard reagents as a base. The main objective of our work was to develop a 3d transition metal-catalyzed C–H functionalization method for (hetero)arenes containing a mono-chelated assistance directing group, using unactivated coupling partners and a user-friendly base. Specifically, we aimed to functionalize phenols and 2-pyridones, which are present in many drug molecules, biologically active compounds, and natural products, using 3d transition metals such as Mn, Ni, and Cu. The results obtained from the present study are discussed in Chapters 2 to 5. In chapter 2, we develop an efficient copper-catalyzed method for the regioselective coupling of unactivated alkyl chlorides with the *ortho* C–H bond of phenol derivatives. The employment of inexpensive, abundant, and non-toxic copper catalysts and widely available unactivated alkyl chlorides make this alkylation protocol highly viable. The reaction is compatible with a variety of simple and functionalized alkyl chlorides as well as with a range of phenol derivatives. The use of LiHMDS base play a critical role in the success of alkylation by generating a Cu-amido complex during the reaction. Detailed mechanistic investigation of the alkylation allowed us to draw a catalytic path that follows the rate-limiting 2e oxidative addition of alkyl chloride. Controlled experiments, kinetic analyses, and EPR studies reveals the participation of a Cu(I) active species, therefore

supporting a Cu(I)/Cu(III) pathway. We trust that the simplicity and uniqueness of the demonstrated sustainable copper-catalyzed protocol would contribute significantly to the investigation and development of many other such processes. Chapter 3 is demonstrates the ligand-free and cost-effective Mn(II)-catalyzed chemo- and regioselective protocol for the C–H bond alkylation of indoline and (2-pyridinyl)arenes. This protocol provides a wide range of alkylated products containing alkenyl, alkynyl, silyl, ethers and heteroaromatic functionalities, including fatty alcohol and cholesterol. Alkylation proceeds either *via* a five-membered or a six-membered metallacycle leading to the desired products. The use of a LiHMDS base is very crucial, as it can produce an active Mn-amido species. A preliminary mechanistic study suggests that the alkylation proceeds through a single electron transfer (SET) process involving the rate-limiting C–H bond metalation of indoline. Chapter 4 disclose the selective C6 C($sp^2$)–H bond alkylation of 2-pyridones with unactivated primary as well as secondary alkyl chloride using a well-designed quinoline-based nickel pincer complex. This protocol shows a broad substrate scope and functional group tolerance. Alkyl halides containing alkenyl, silyl, ether, indolyl, and carbazolyl groups as well as polycyclic-steroid moiety work well under the reaction conditions. Moreover, we perform mechanistic aspects of the reaction including the reaction scope and limitations. Chapter 5 is describes Ni-catalyzed alkynylation of 2-pyridones, employing (triisopropylsilyl)alkynyl bromide as a coupling partner, facilitated by monodentate chelation assistance. Notable features of this protocol include wide substrate scope and outstanding tolerance for diverse functional groups.

# Chapter 2

# Copper-catalyzed Regioselective C–H Alkylation of Phenol Derivatives with Unactivated Alkyl Chlorides




This chapter is adopted from the published article: "Copper-catalyzed regioselective C−H alkylation of phenol derivatives with unactivated alkyl chlorides: Manifesting a Cu(I)/Cu(III) pathway" **Verma, S. K.**; Punji, B., *J. Catal.* **2024**, *430*, 115351.

## 2.1 INTRODUCTION

Phenols are distinctive structural motifs substantially identified in the area of pharmaceuticals, agrochemicals, natural products, and dyes (Figure 2.1).[1-6] Additionally, they are commonly used as basic starting material in various cross-coupling reactions for synthesizing diverse functional molecules.[7,8] Thus, efficient and cost-effective functionalization of phenolic derivatives, particularly by step-economical C–H bond activation, has stimulated substantial attention.[9] The C–H functionalization of phenol and phenolic derivatives has been substantially demonstrated during the past two decades.[10-12] Several of these functionalizations include chemo and regioselective arylation, alkenylation, halogenation, acetoxylation, and nitration of phenols; however, a more challenging alkylation protocol is limited. Amongst the alkylation, diazoesters, alcohols, and alkenes are used as alkylating sources, and the reactions are mostly established with expensive and deleterious 4d and 5d transition metal catalysts (Scheme 2.1a).[13-20] However, the employment of challenging haloalkane as coupling partners in phenols alkylation under base-metal catalysis is unprecedented;[21-23] though few reports are known using simple and activated diazoesters (Scheme 2.1b).[24]

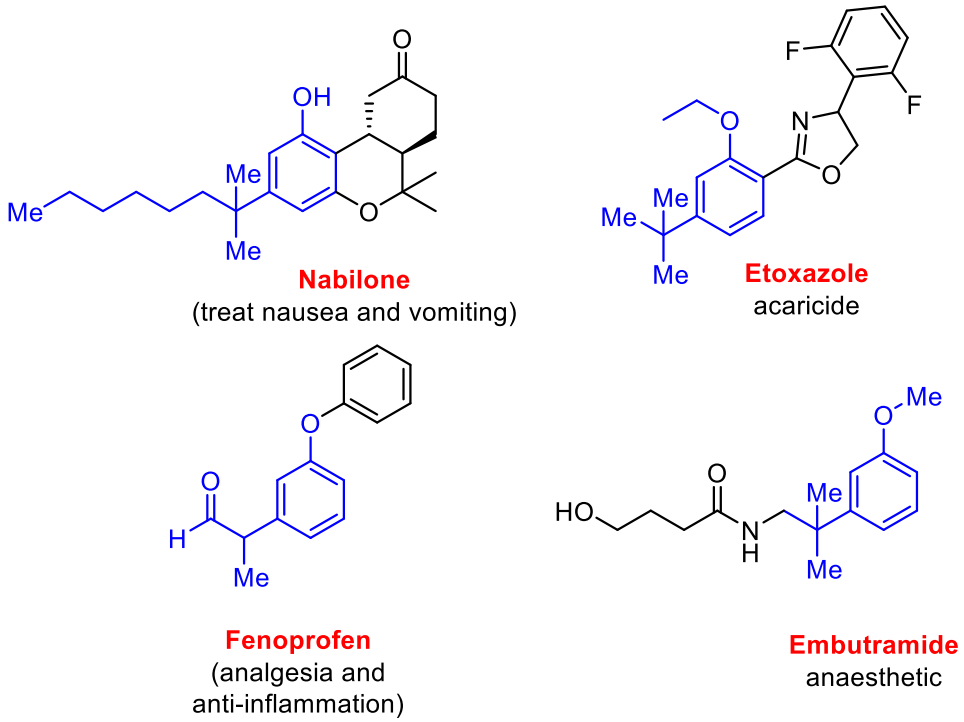
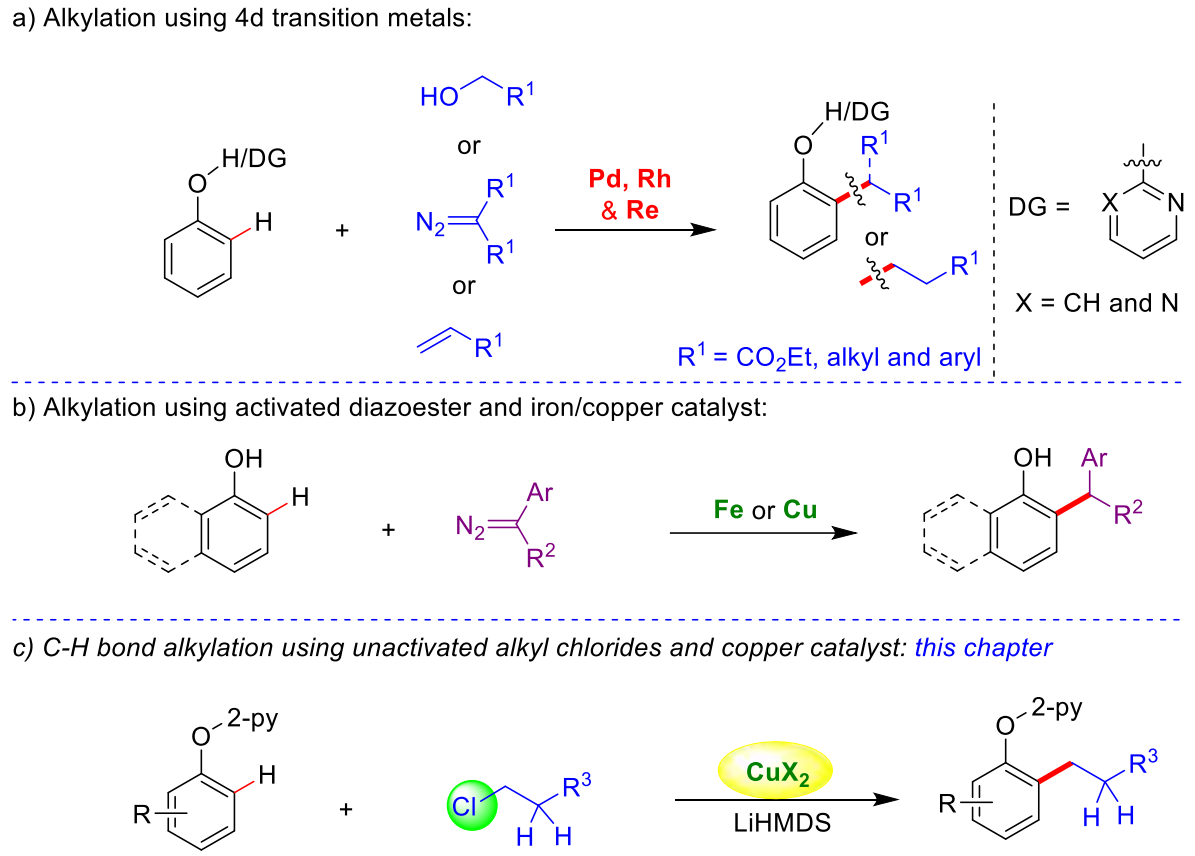



**Figure 2.1** Selected bioactive molecule of phenols.




**Scheme 2.1** Approaches for *ortho*-alkylation of phenol derivatives.

In particular, the alkylation of aromatics using non-activated alkyl halides contaning *β*–hydrogen is limited and highly challenging due to various reasons, including problems in alkyl halide's oxidative addition and undesired side products resulting from *β*-hydride elimination.[25,26] Additionally, the use of inexpensive and low-reactive alkyl chlorides in the *ortho*-alkylation of phenols is unknown. Therefore, implementing the alkyl chlorides within the C–H alkylation of phenols using cost-effective 3d metal catalysts,[27-31] particularly copper,[32-41] would be highly beneficial for the sustainable development of the protocol.

In view of the natural abundance, cost-effectiveness, and low toxicity of copper, copper complexes are widely used as catalysts in various organic transformations. The pioneering work of Ullman and Goldberg demonstrated in the formation of both C–heteroatom and C–C bond formations using copper catalysts.[42] In recent years, copper-catalyzed C–H functionalization of arenes and heteroarenes has been reported by various groups.[43-47] Unfortunately, the C–H modification of phenols by the copper catalyst is very scarce.[48] In a significant development, Zhang and Liu reported the *ortho*-alkylation of phenol with activated *α*-aryl-*α*-diazoester under copper catalysis (Scheme 2.1b).[49] Notably, this protocol

is limited to activated *α*-aryl-substituted diazoesters, and O-substituted phenolic compounds did not engaged in the reaction. To our knowledge, the *ortho*-alkylation of phenol derivatives using unactivated and demanding alkyl halides is unknown. In this Chapter, we demonstrate the first general protocol for the efficient coupling of alkyl chlorides with the *ortho* C–H bond of phenol derivatives using an inexpensive and abundant Cu(II)-catalyst (Scheme 2.1c).

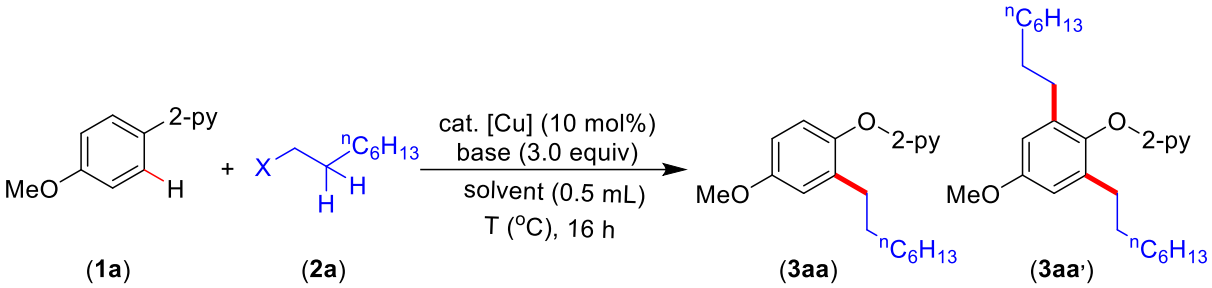
## 2.2 RESULTS AND DISCUSSION

### 2.2.1 Reaction Optimization

We initiated the optimization of reaction parameters for the Cu-catalyzed of phenol *ortho*-alkylation derivatives using 2-(4-methoxyphenoxy)pyridine (**1a**) as a model substrate with octyl halide in the form of coupling partner and lithium bis(trimethylsilyl)amide (LiHMDS) as a base in toluene at 140 $^{o}$C under argon atmosphere. Using 1-iodooctane or 1-bromooctane as the coupling partners provided the desired product **3aa** in 31% and 50%, respectively. Notably, in these cases, a significant quantity of unwanted side products was observed upon the reaction of 1-bromooctane or 1-iodooctane with LiHMDS (Table 2.1, entries 1 and 2). Interestingly, using the more challenging coupling partner, 1-chlorooctane, substantially reduced the side product and delivered product **3aa** in 58% yield (entry 3). Among the various Cu(II) metal precursors screened (entries 4-7), the use of $CuBr_2$ as a catalyst provided marginally better yield for the mono-alkylated product **3aa** (61%), and the *ortho*-dialkylated product obtained in 15%. The Cu(I) salts like CuCl, CuBr, and CuI were also effective catalysts, providing **3aa** in 51-60% yield (entries 8-10). The employment of ancillary nitrogen and phosphorus-based ligands such as bpy, phen, $PPh_3$, dppe, dppf, and xantphos, along with the $CuBr_2$ catalyst, did not show a positive effect on the alkylation process (entries 11-16). In fact, the overall yield of alkylation was reduced in the presence of external ligands, probably due to the undesired extra stability of copper intermediate or difficulty in the approach of 2-pyridinyl-phenoxy (**1a**) towards the ligated copper complex. The attempted alkylation in the presence of moderate inorganic bases, such as $LiO^tBu$, $NaO^tBu$, $KO^tBu$, $Na_2CO_3$, or $K_2CO_3$, did not occur (entries 17-21). The LiHMDS was the only practical base for the reaction, which could be due to the effective formation of active Cu-amido species. In addition to the toluene, the alkylation successfully occurred in various non-polar solvents such as *ortho*-xylene, *meta*-xylene, *para*-xylene, *para*-cymene, and $^t$Bu-benzene, even though the obtained yields were on the lower side (entries 22-26). The alkylation was competitive even with 2.5 equiv each of 1-chlorooctane and LiHMDS (entry 27); however, the yield of **3aa** was slightly reduced by further lowering the amount of 1-

chlorooctane and LiHMDS (entry 28). Notably, the alkylation also proceeded smoothly at 120 °C, providing **3aa** in 62% yield (entry 29). Interestingly, the product yield was improved by performing the reaction at 120 °C for 24 h and afforded **3aa** in 66% yield (entry 30). Further minimizing the catalyst quantity or reaction temperature generated a lower yield of the alkylation product (entries 31 and 32). The alkylation reaction did not occur without a $CuBr_2$ catalyst (entry 33).

Table 2.1 Optimization of Reaction Parameters in Details.[a]



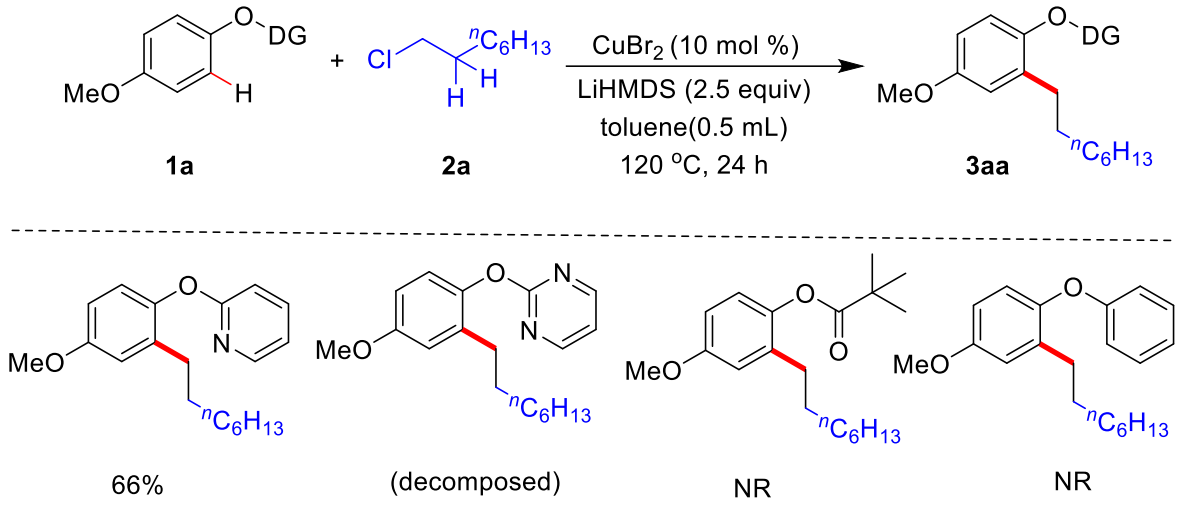

| Entry | X | [Cu] | Base | Solvent | T (°C) | **3aa** (%)[b] | **3aa'**(%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | I | $CuCl_2$ | LiHMDS | toluene | 140 | 31 | -- |
| 2 | Br | $CuCl_2$ | LiHMDS | toluene | 140 | 50 | -- |
| 3 | Cl | $CuCl_2$ | LiHMDS | toluene | 140 | 58 | 15 |
| 4 | Cl | $CuBr_2$ | LiHMDS | toluene | 140 | 61 | 20 |
| 5 | Cl | $Cu(OAc)_2$ | LiHMDS | toluene | 140 | 30 | trace |
| 6 | Cl | $Cu(OTf)_2$ | LiHMDS | toluene | 140 | trace | -- |
| 7 | Cl | $Cu(acac)_2$ | LiHMDS | toluene | 140 | 37 | 10 |
| 8 | Cl | CuCl | LiHMDS | toluene | 140 | 55 | 9 |
| 9 | Cl | CuBr | LiHMDS | toluene | 140 | 60 | 27 |
| 10 | Cl | CuI | LiHMDS | toluene | 140 | 51 | 11 |
| 11 | Cl | $CuBr_2$/bpy | LiHMDS | toluene | 140 | 56 | 15 |
| 12 | Cl | $CuBr_2$/phen | LiHMDS | toluene | 140 | 48 | 20 |
| 13 | Cl | $CuBr_2$/xantphos | LiHMDS | toluene | 140 | 46 | 7 |
| 14 | Cl | $CuBr_2$/dppe | LiHMDS | toluene | 140 | 36 | 4 |
| 15 | Cl | $CuBr_2$/dppf | LiHMDS | toluene | 140 | 38 | 5 |
| 16 | Cl | $CuBr_2$/$PPh_3$ | LiHMDS | toluene | 140 | 59 | 7 |
| 17 | Cl | $CuBr_2$ | $LiO^tBu$ | toluene | 140 | NR | -- |
| 18 | Cl | $CuBr_2$ | $NaO^tBu$ | toluene | 140 | NR | -- |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 19 | Cl | $CuBr_2$ | $KO^tBu$ | toluene | 140 | NR | -- |
| 20 | Cl | $CuBr_2$ | $Na_2CO_3$ | toluene | 140 | NR | -- |
| 21 | Cl | $CuBr_2$ | $K_2CO_3$ | toluene | 140 | NR | -- |
| 22 | Cl | $CuBr_2$ | LiHMDS | *o*-xylene | 140 | 53 | 17 |
| 23 | Cl | $CuBr_2$ | LiHMDS | *m*-xylene | 140 | 43 | 8 |
| 24 | Cl | $CuBr_2$ | LiHMDS | *p*-xylene | 140 | 52 | 14 |
| 25 | Cl | $CuBr_2$ | LiHMDS | *p*-cymene | 140 | 50 | 6 |
| 26 | Cl | $CuBr_2$ | LiHMDS | $^t$Bu-benzene | 140 | 50 | 8 |
| 27 [c] | Cl | $CuBr_2$ | LiHMDS | toluene | 140 | 60 | 20 |
| 28 [d] | Cl | $CuBr_2$ | LiHMDS | toluene | 140 | 55 | 9 |
| 29 [c] | Cl | $CuBr_2$ | LiHMDS | toluene | 120 | 62 | 10 |
| **30[c,e]** | **Cl** | **$CuBr_2$** | **LiHMDS** | **toluene** | **120** | **70 (66)** | **11** |
| 31[c,e] | Cl | $CuBr_2$ | LiHMDS | toluene | 110 | 52 | |
| 32[c,e,f] | Cl | $CuBr_2$ | LiHMDS | toluene | 120 | 43 | 4 |
| 33[c,e] | Cl | -- | LiHMDS | toluene | 120 | NR | -- |

[a] Reaction Conditions: **1a** (0.041 g, 0.204 mmol), **2a** (0.090 g, 0.601 mmol), [Cu] precursor (0.02 mmol, 10 mol%), LiHMDS (0.10 g, 0.60 mmol), solvent (0.5 mL). [b]GC yield using n-dodecane as an internal standard; isolated yield is given in parentheses. [c] Employing 2.5 equiv of LiHMDS and 2.5 equiv of **2a**. [d] Employing 2.0 equiv of LiHMDS and 2.0 equiv of **2a**. [e] Reaction performed for 24 h. [f] 5.0 mol% of $CuBr_2$ was used. All reactions were carried out under argon atmosphere.

### 2.2.2 Effect of Oxygen-Substituents of Phenol on Alkylation

In addition to the 2-pyridinyl as a directing group for the alkylation of 2-(4-methoxyphenoxy)pyridine, other possibilities were investigated (Scheme 2.2). The use of 2-pyrimidinyl as a directing functionality led to the complete decomposition of the starting compound, 2-(4-methoxyphenoxy)pyrimidine. A substrate without a coordinating atom, such as 1-methoxy-4-phenoxybenzene, did not participate in the alkylation. Similarly, a weak coordination directing functionality like –C(O)$^t$Bu in the substrate 4-methoxyphenyl pivalates was unsuitable for the desired alkylation. All these findings suggest that robust directing nitrogen functionality is essential for the regioselective copper-catalyzed *ortho*-alkylation of phenol derivatives.

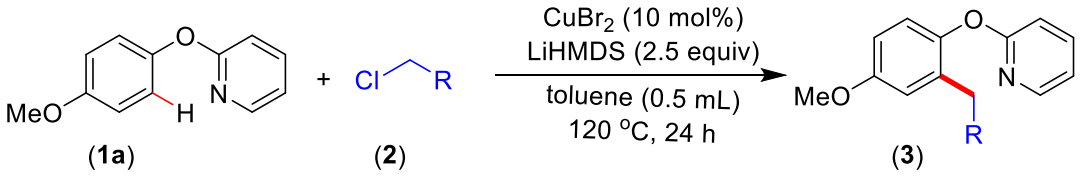


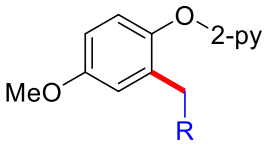

**Scheme 2.2** Effect of directing group on alkylation.

### 2.2.3 Reaction Scope

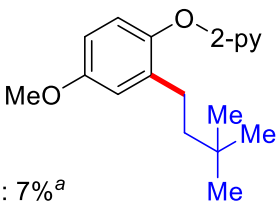
After having optimized reaction conditions in hand for the *ortho*-alkylation of phenoxy-2-pyridine using an inexpensive copper catalyst, we explored the generality of the reaction protocol with various functionalized and alkyl chlorides (Scheme 2.3). Initially, the linear alkyl chlorides using different carbon chain lengths were reacted with substrate **1a** to give desired *ortho*-alkylated products **3aa**-**3ak** in moderate to good yields. In general, the short-chain alkyl chlorides provided slightly higher yields than the long-chain derivatives, probably due to the better solubility of short-chain saturated alkyl partners. The branched *γ*-substituted alkyl chloride reacted with low efficacy to afford mono-alkylated product **3al** in 41%. Similarly, a synthetically important functionality, the silyl group-containing alkylated compound **3am** could be obtained in low yield. The phenyl ring bearing alkyl chloride reacted with **1a** to provide **3an** in 80% yield. Notably, phenyl ether and phenyl thioether-containing alkyl chlorides were smoothly coupled with **1a** to afford corresponding products **3ao**-**3av** in good yields. Important heteroarene functionalities, such as indolyl, pyrrolyl, and carbazolyl-containing alkyl chlorides, reacted moderately with **1a** to afford **3aw**, **3ax**, and **3ay**, respectively. Unfortunately, the alkyl chlorides bearing base-sensitive functionalities, such as acetyl, ester, and nitrile, could not be coupled with **1a**. The oleyl chloride, derived from an unsaturated fatty alcohol, could be coupled with a moderate yield (58%) of **3az**. Interestingly, biologically relevant compounds like nonylphenol (**2A**) and vitamin-E derived (**2B**) alkyl chlorides were compatible with the optimized protocol and provided corresponding coupled products in 60% and 32% yields, respectively. Notably, most alkyl chlorides reacted smoothly and provided exclusively mono-alkylated products. The traces of the *ortho*-dialkylated products were obtained in some instances. Nevertheless, the use of

diverse, cost-effective, and challenging alkyl chlorides in the regioselective C–H alkylation is notable. Moreover, the copper, being inexpensive and environment friendly, makes the overall alkylation process highly user-friendly.

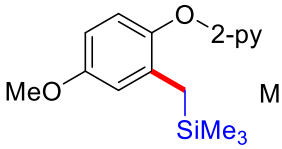


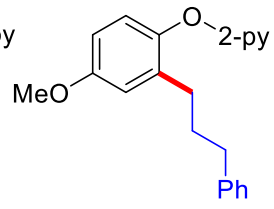

R = $^{n}C_7H_{15}$ (**3aa**): 66% (**3aa'**): 7%[a]
R = $^{n}CH_3$ (**3ab**): 62% (X = Br)
R = $^{n}C_2H_5$ (**3ac**): 66% (X = Br)
R = $^{n}C_3H_7$ (**3ad**): 61%
R = $^{n}C_4H_9$ (**3ae**): 58% (X = Br)
R = $^{n}C_5H_{11}$ (**3af**): 65%
R = $^{n}C_6H_{13}$ (**3ag**): 64% (X = Br)
R = $^{n}C_9H_{19}$ (**3ah**): 49%
R = $^{n}C_{11}H_{23}$ (**3ai**): 45%
R = $^{n}C_{13}H_{27}$ (**3aj**): 48% (*CCDC: 2290347*)
R = $^{n}C_{21}H_{43}$ (**3ak**): 54%



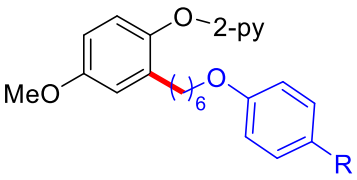

(**3al**): 41%



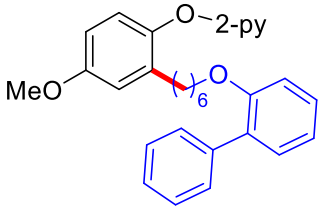

(**3am**): 35%



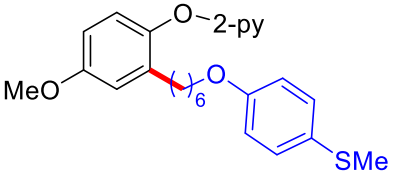

(**3an**): 80%



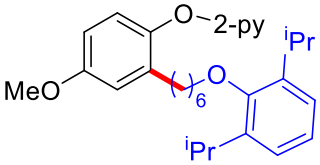

R = H, (**3ao**): 69%
R = OMe, (**3ap**): 57%
R = Ph, (**3aq**): 66%



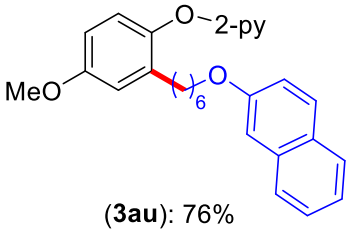

(**3ar**): 61%



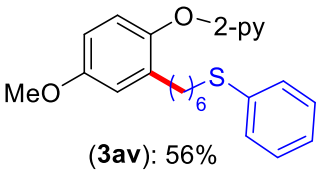

(**3as**): 44%



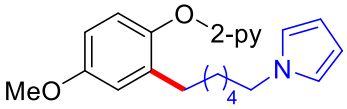

(**3at**): 52%



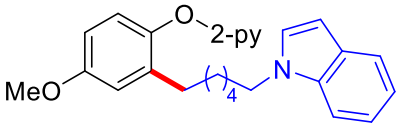

(**3au**): 76%



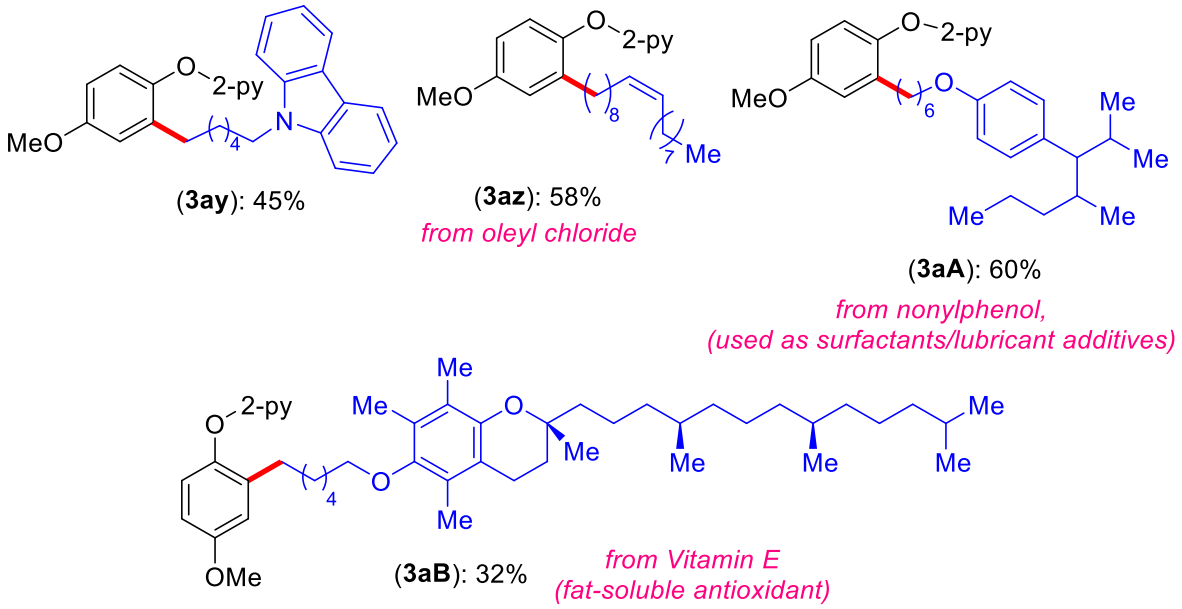

(**3av**): 56%




(**3aw**): 35%



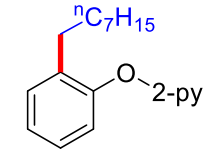

(**3ax**): 38%



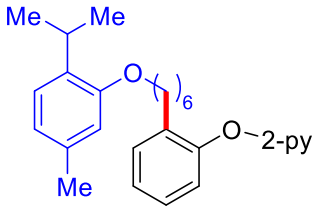

**Scheme 2.3** Substrates scope using various alkyl chlorides. Reaction conditions: **1a** (0.040 g, 0.204 mmol), compound **2** (0.50 mmol), $CuBr_2$ (0.0045 g, 0.02 mmol, 10 mol%), LiHMDS (0.084 g, 0.5 mmol), toluene (0.5 mL). [a]2,2-dialkylated product isolated.

We examined the scope and limitations of diverse 2-phenoxypyridine derivatives for the alkylation strategy (Scheme 2.4). The unsubstituted 2-phenoxypyridine showed good reactivity with 1-chlorooctane and provided the *ortho* mono-alkylated product **3ba** in 66% yield. Moreover, a thymol-derived alkyl chloride coupled with the 2-phenoxypyridine affords 38% of **3bC**. The 4-methylphenoxypyridine (**1c**) reacted smoothly with various linear alkyl chlorides to provide desired *ortho*-alkylated products **3ca**, **3ch**, **3cj**, and **3ck** in good yields. The oleyl chloride reacted with low efficacy to afford a vital compound **3cz** in a 45% yield. The ethyl, octyloxy cyclohexyl, cyclohexyl propyl, *tert*-butyl, adamantyl, nonyl, and phenyl-substitutions at the *para* position of the phenol ring were compatible and delivered expected mono-alkylated products **3da-3ka**. Surprisingly, an alkenyl-substituted phenol gave the alkylated product **3la** in a meager yield, most likely due to the self-polymerization of starting alkenyl phenol. Interestingly, the pterostilbene (**1m**), phenylacetylene substituted phenol (**1n**), and 4-((tetrahydro-2*H*-pyran-2-yl)oxy)phenol (**1o**) could also deliver the desired alkylated products in low to moderate yields. Moreover, the thiomethyl and *N*,*N*-dimethylamino-substituted 2-phenoxypyridine underwent efficient alkylation to provide a reasonable yield of desired products **3pa** and **3qa**. On the other hand, the *ortho/meta*-substituted 2-phenoxypyridine ring afforded a low yield of alkylated products **3ra** and **3sa**,

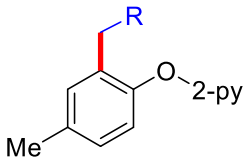
probably due to steric factors. A 2-(naphthalen-1-yloxy)pyridine was also compatible with the alkylation strategy, giving a 24% yield of alkylated product **3ta**. Furthermore, the 2-phenoxypyridines substituted with heteroarenes such as pyridinyl (**1u**), pyrrolyl (**1v**), and indolinyl (**1w**) at the *para* position participated in the alkylation process with moderate activity. Notably, substrate **1u** delivered alkylation at the *ortho* position to 2-pyO (**3ua**), and a 2-py directed alkylation at the ortho to pyridine was not observed. Unfortunately, the phenols bearing electron-withdrawing as well as halide functionalities could not undergo alkylation with alkyl chloride under the optimized conditions.



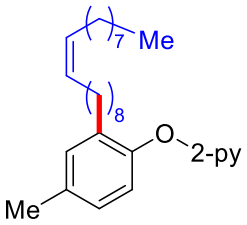
(**3ba**): 66%



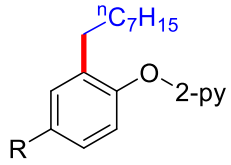
(**3bC**): 38%



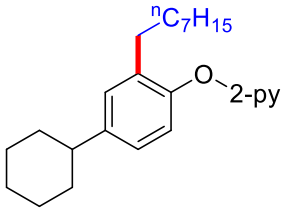
R = $^{n}C_7H_{15}$ (**3ca**): 71%
R = $^{n}C_9H_{19}$ (**3ch**): 56%
R = $^{n}C_{13}H_{27}$ (**3cj**): 60%
R = $^{n}C_{21}H_{43}$ (**3ck**): 66%



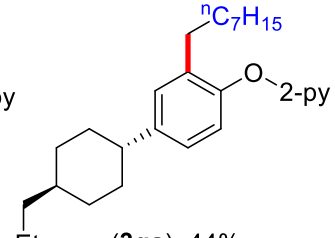
(**3cz**): 45%
*from oleyl chloride*



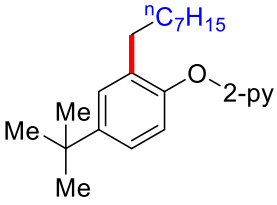
R = $^{n}C_2H_5$ (**3da**): 67%
R = O$^{n}C_8H_{17}$(**3ea**): 53%



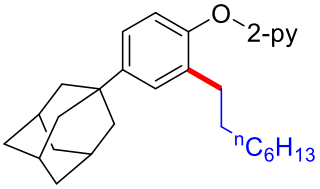
(**3fa**): 57%



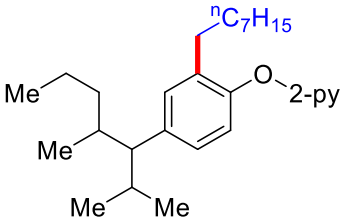
Et (**3ga**): 44%



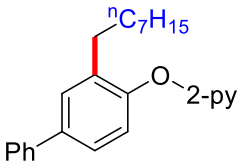
(**3ha**): 55%



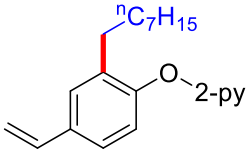
(**3ia**): 42%



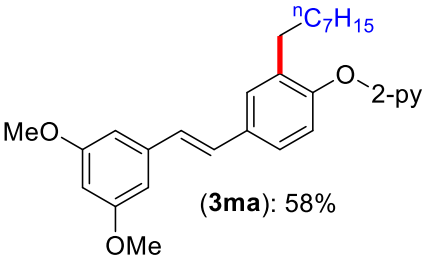
(**3ja**): 38%



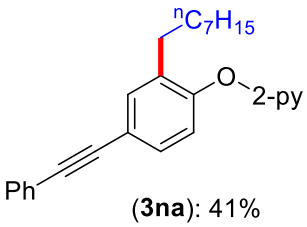
(**3ka**): 73%



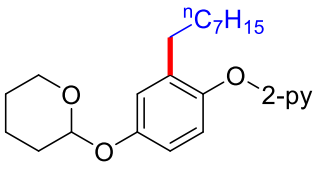
(**3la**): 12%



(**3ma**): 58%

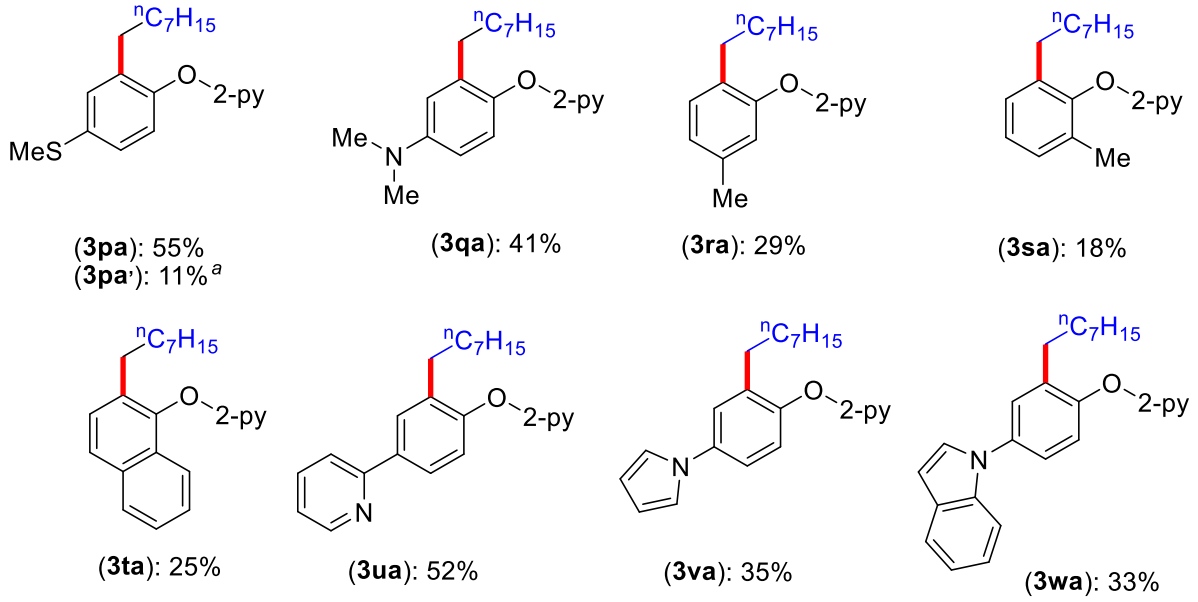


(**3na**): 41%



(**3oa**): 25%

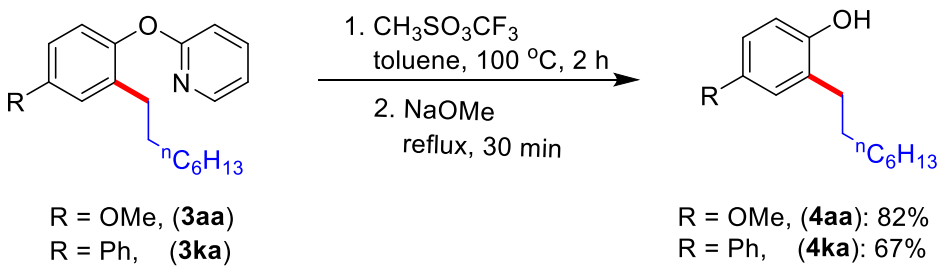
*from Pterostilbene (antioxidant)*




**Scheme 2.4** Scope using substituted phenol derivatives. Reaction conditions: **1** (0.204 mmol), 1-chlorooctane **2a** (0.074 g, 0.5 mmol), $CuBr_2$ (0.0045g, 0.02 mmol, 10 mol%), LiHMDS (0.084 g, 0.5 mmol), toluene (0.5 mL). [a]2,2-dialkylated product isolated.

### 2.2.4 Scale-up and Deprotection of the Directing Group

A gram-scale alkylation of 2-(4-methoxyphenoxy)pyridine (**1a**; 4.97 mmol) with 1-chlorooctane provided 0.89 g (57%) of product **3aa** under the ideal circumstances, which highlights the usefulness of the reaction for probable practical use. It is important to note that the 2-pyridinyl group can be readily deprotected to deliver *ortho*-alkylated phenol derivatives in good yields (Scheme 2.5). Thus, the treatments of **3aa** and **3ka** with MeOTf/NaOMe provided **4aa** and **4ka**. The synthesis of such *ortho*-alkylated phenol is challenging to access by other traditional functionalization methods.




R = OMe, (**3aa**)
R = Ph, (**3ka**)

R = OMe, (**4aa**): 82%
R = Ph, (**4ka**): 67%

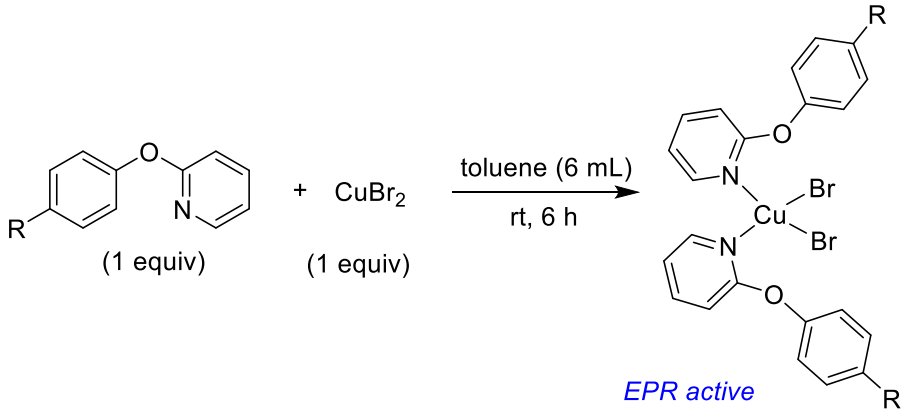
**Scheme 2.5** Deprotection of 2-pyridinyl directing group.

### 2.2.5 Mechanistic Aspects

#### 2.2.5.1 Probing Cu(I) Species

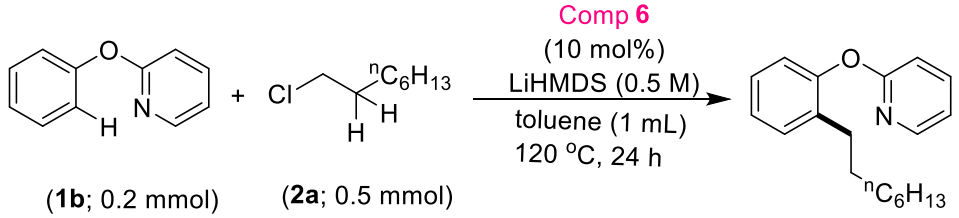
The reaction mechanism was investigated to identify the active Cu-catalytic species and to understand the pathway of the *ortho*-alkylation of phenol. The treatments of compounds **1a** and **1b** with $CuBr_2$ afforded complex $(2\text{-py-}OC_6H_4\text{-}4\text{-}OMe)_2CuBr_2$ (**5**) and $(2\text{-py-}OPh)_2CuBr_2$ (**6**), respectively (Scheme 2.6a), which were structurally characterized by the X-ray diffraction study (Figure 2.2A and 2.2B). The complex **6** serve as catalyst for the alkylation to produce a quantitative yield of **3ba** (Scheme 2.6b). The EPR analysis of complex **6** shows a peak with g-factor 2.06, suggesting unpaired spin residing in an orbital with significant metal character ($d^9$ system) (Figure 2.2C).[54] Interestingly, treatment of $(2\text{-py-}OPh)_2CuBr_2$ (**6**) with LiHMDS resulted in a species that is EPR silent (Scheme 2.6c, Figure 2.2D). Similarly, the EPR measurement of the incomplete catalytic reaction mixture ($CuBr_2$, **1a**, **2a**, and LiHMDS) suggested the absence of an odd-electron species. These observations reveal that the Cu(II) species transformed to Cu(I) intermediate ($d^{10}$ system, EPR silent) with LiHMDS, which is assumed to be an active catalytic species. Notably, the formation of a di-copper(II) species, wherein two Cu(II) centers antiferromagnetically coupled (could be EPR silent), cannot be ruled out. However, the superior reaction rate with Cu(I) than with the Cu(II) catalyst, and the absence of a 1e- radical species during the reaction (discussed vide infra) do not validate a Cu(II)/Cu(III) pathway. In the cyclic voltammetry analysis, the $E^0$ values for complex **5**, complex **6**, $CuBr_2$, and LiHMDS are found to be 0.634 V (Figure 2.2E), 0.601 V, 0.648 V and -0.520 V (Figure 2.2F), respectively.16 As the $E^0$ value of LiHMDS is lower compared to Cu(II) complexes, the electron transfer is feasible from LiHMDS to Cu(II) complexes in generating active Cu(I) complex.[55] To further support these findings, the independent reaction rate was determined using $CuBr_2$ and CuBr as catalysts, wherein the reaction rate with Cu(I)Br was slightly higher (Figure. 2.3). The EPR examination of the reaction mixture also suggested the absence of a probable carbon-centric radical (alkyl radical).

*a) Reactions of **1a** & **1b** with $CuBr_2$: synthesis of complexes **5** and **6***

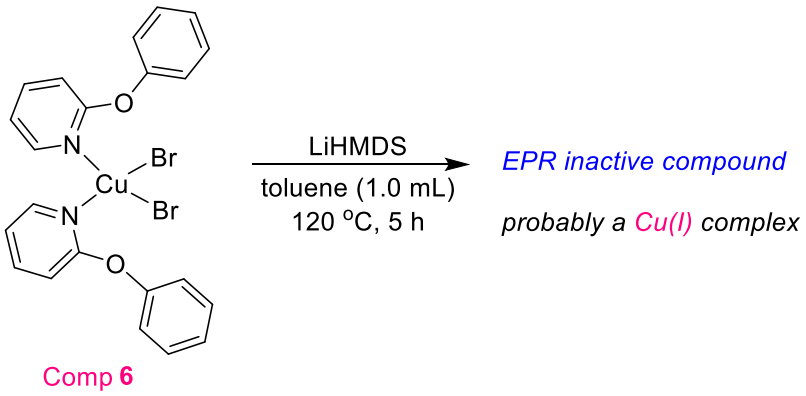



R = OMe (**5**); (2-py-$OC_6H_4$-4-OMe)$_2CuBr_2$ (CCDC: 2291780)
R = H (**6**); (2-py-OPh)$_2CuBr_2$ (CCDC: 2290349)

*b) Use of (2-py-OPh)$_2CuBr_2$ (**6**) as a catalyst*




*c) Reaction of (2-py-OPh)$_2CuBr_2$ (**6**) with LiHMDS*




**Scheme 2.6** Synthesis of (2-aryloxy-pyridine)$_2CuBr_2$ complexes and control experiments.

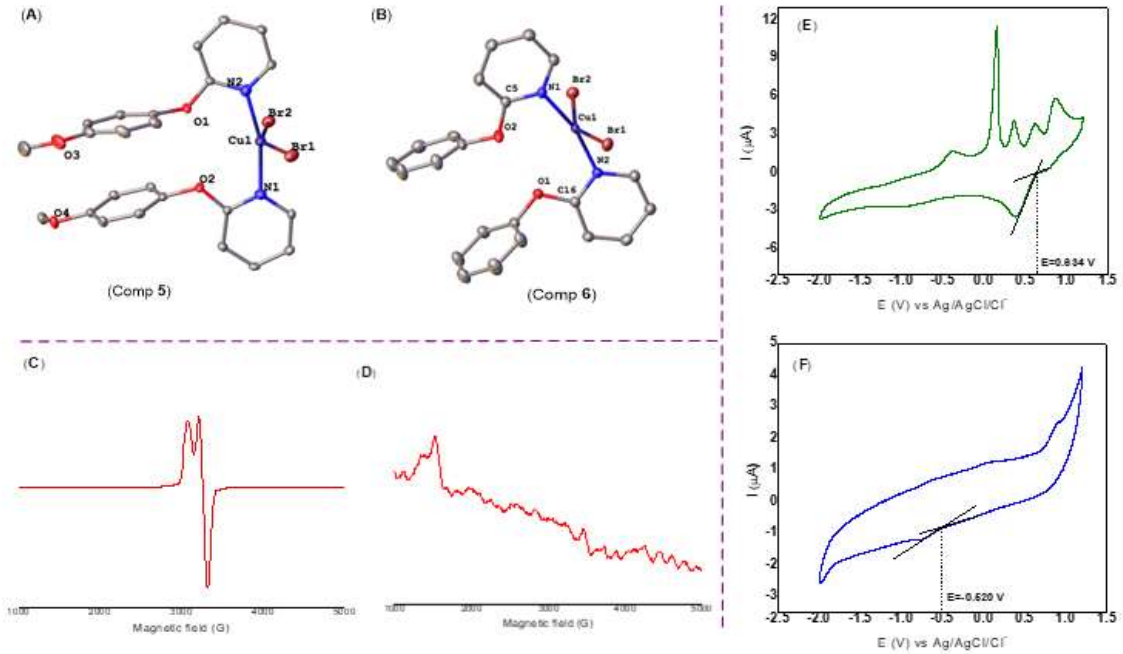
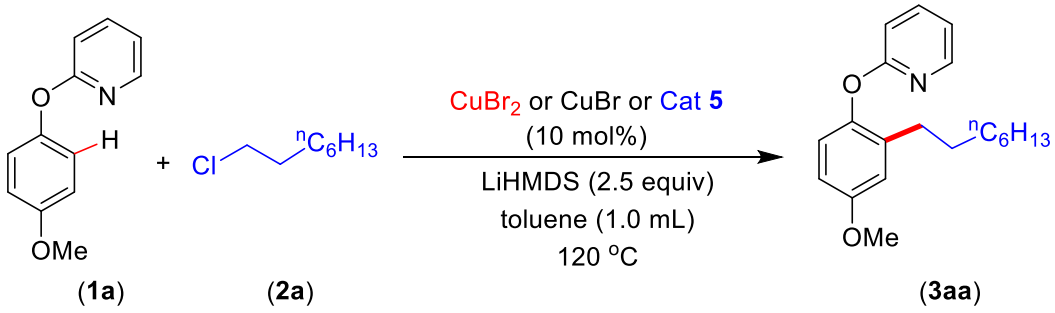



**Figure 2.2** Thermal ellipsoid plot of (2-py-$OC_6H_4$-4-OMe)$_2$$CuBr_2$ (**5**), (B) Thermal ellipsoid plot of (2-py-OPh)$_2$$CuBr_2$ (**6**), (C) EPR spectrum of the complex (2-py-OPh)$_2$$CuBr_2$ (**6**) with the g anisotropy value (g = 2.063), (D) EPR spectrum of (2-py-OPh)$_2$$CuBr_2$ (**6**) + LiHMDS, (E) Cyclic voltammogram of 1.0 mM (2-py-O-$C_6H_4$-4-OMe)$_2$$CuBr_2$ (**5**), (F) Cyclic voltammogram of 1.0 mM LiHMDS



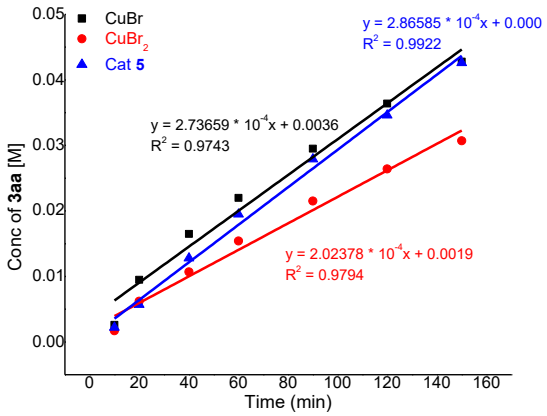
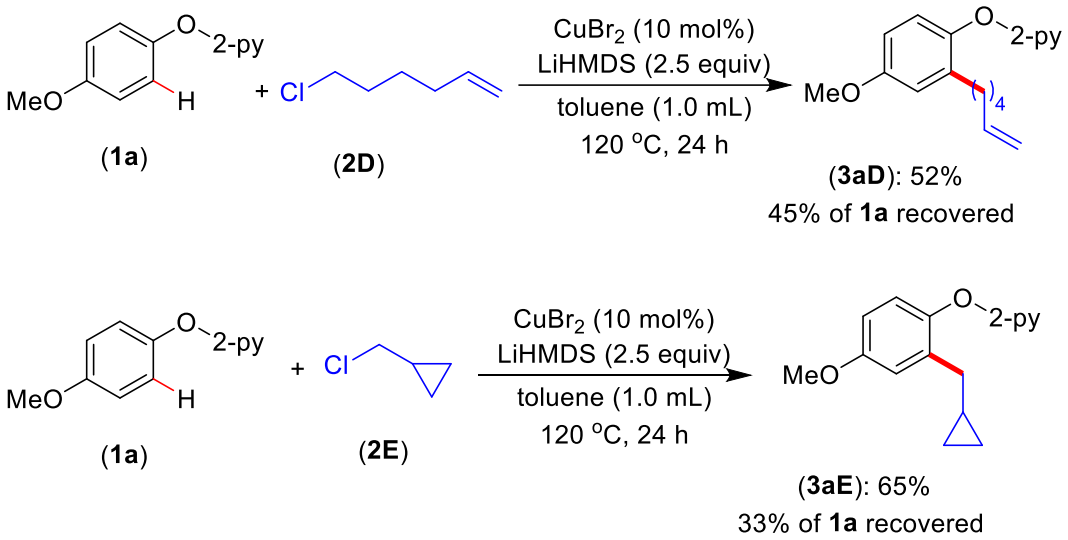




**Figure 2.3** Time-dependent formation of **3aa** using catalysts $CuBr_2$, CuBr and (2-py-$OC_6H_4$-4-OMe)$_2$$CuBr_2$ (Cat **5**)

### 2.2.5.2 Radical Clock Experiments

Radical trapping studies were performed to understand the reactivity pattern of alkyl chloride (Scheme 2.7). Thus, the reactions of **1a** with 6-chlorohex-1-ene and (chloromethyl)cyclopropane with Cu-catalyst under standard conditions provided direct coupled products, **4aD** and **4aE**, respectively. The absence of radical cyclization or radical-induced ring opening supports the non-involvement of an alkyl radical species. Therefore, we assume a plausible two-electron alkyl chloride oxidative addition to an active Cu(I) species.

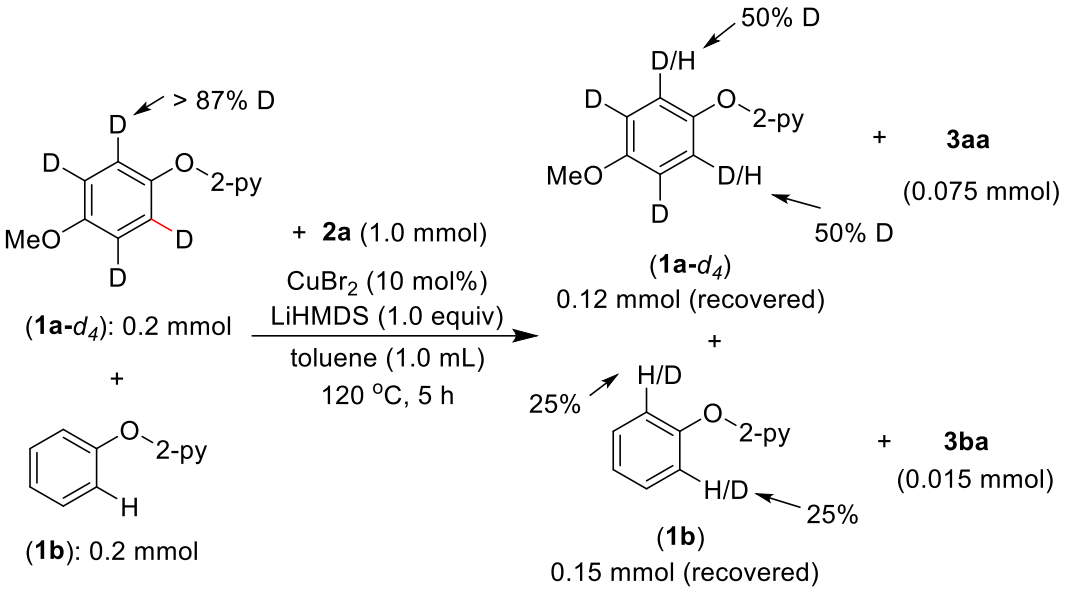



**Scheme 2.7** Radical clock experiment.

### 2.2.5.3 H/D Scrambling Experiment

We have performed the deuterium labelling experiment to understand the nature of cleavage of *ortho*-C($sp^2$)–H in phenol. Thus, a substantial H/D exchange between the **1a**-$d_4$ and **1b** at the *ortho* position of 2-phenoxypyridine was observed (Scheme 2.8), suggesting the reversible nature of the C–H bond cleavage followed by metalation with copper. Therefore, the reaction of 2-(4-methoxyphenoxy-2,3,5,6-*d4*)pyridine (**1a**-$d_4$; 0.041 g, 0.2 mmol), 2-phenoxypyridin (**1b**; 0.034 g, 0.2 mmol), 1-chlorooctane (0.15 g, 1.0 mmol), $CuBr_2$ (0.0089 g, 0.02 mmol), LiHMDS (0.17 g, 1.0 mmol) was performed at 120 °C in a preheated oil bath for 5 hr. At ambient temperature, reaction mixture was quenched with distilled $H_2O$ (10 mL). The crude mixture was then extracted with EtOAc (20 mL x 3). The combined organic extract was dried over $Na_2SO_4$ and the volatiles were evaporated in *vacuo*. The remaining residue was subjected to column chromatography on silica gel (petroleum ether/EtOAc: 10/1) to recover the starting compounds. The $^1$H NMR analysis of the recovered compound **1b**

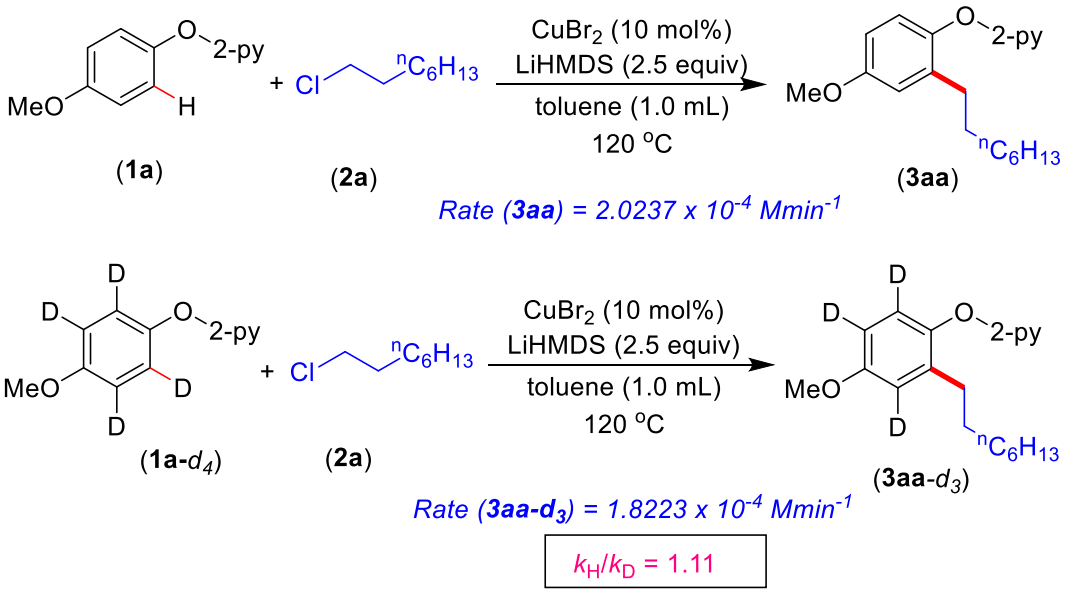
shows 25% incorporation of deuterium at the C(2)–H, whereas compound **1a**-$d_4$ shows 37% loss of deuterium




**Scheme 2.8** Deuterium labeling experiments.

### 2.2.5.4 Kinetic Isotope Effect (KIE) Study

The kinetic isotope effect was carried out to know the pathway of C–H bond cleavage The independent rate measurement of alkylation of **1a** and **1a**-$d_4$ with **2a** provided the KIE value of 1.11 (Scheme 2.9), indicating that the C–H bond metalation of 2-(4-methoxyphenoxy)pyridine is unlikely the rate-limiting step.[56] Therefore, employing 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.2 mmol) or 2-(4-methoxyphenoxy-2,3,5,6-$d_4$)pyridine (**1a**-$d_4$; 0.041 g, 0.2 mmol), 1-chlorooctane (0.075 g, 0.5 mmol), $CuBr_2$ (0.0045 g, 0.02 mmol), LiHMDS (0.084 g, 0.5 mmol) inside the glove-box. The data's were collected till 150 min for **1a**-$d_4$. The final data was obtained by averaging the results of two independent experiments. The initial rate obtained for the coupling 2-(4-methoxyphenoxy)pyridine (**1a**) with 1-chlorooctane is 2.02378 x $10^{-4}$ $Mmin^{-1}$, whereas the rate for the coupling of 2-(4-methoxyphenoxy-2,3,5,6-$d_4$)pyridine (**1a**-$d_4$) with 1-chlorooctane is 1.8223 x $10^{-4}$ $Mmin^{-1}$. Therefore, the $k_H/k_D$ = 2.02378 x $10^{-4}$/1.8223 x $10^{-4}$ = 1.11 (Figure 2.4).




**Scheme 2.9**. Deuterium scrambling experiment.

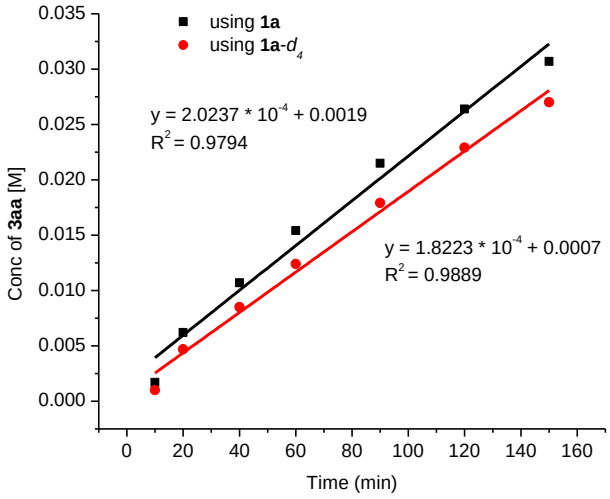



**Figure 2.4** Time-dependent formation of **3aa** using substrates **1a** and **1a**-*d*4.

### 2.2.5.5 Kinetic Analysis for Rate Order Determination

We have determined the rate order of alkylation reaction with various reaction components to obtain additional mechanistic information. The reaction is approximately first-order dependent on substrate **1a** (Figure 2.5), whereas it is fractional order dependent on alkyl chloride (**2a**) and catalyst $CuBr_2$ (Figure 2.6 and Figure 2.8). The first-rate order with **1a** suggests the diverse approach of **1a** interaction with $CuBr_2$ (mono-ligated and bis-ligated). The fractional rate order with catalyst $CuBr_2$ is reason-able as the copper species is involved in multiple steps. However, the fractional rate order on alkyl chloride is attributed to the

probable involvement of C–Cl bond activation in the rate-limiting step. Notably, the alkylation reaction is negative rate order on the concentration of LiHMDS (Figure 2.7), due to the excessive side reaction of LiHMDS with alkyl chloride with the increased concentration of base LiHMDS.

*Rate Order Determination on 2-(4-methoxyphenoxy)pyridine **1a** (Figure 2.5).* To determine the order of the alkylation reaction on 2-(4-methoxyphenoxy)pyridine (**1a**), initial rates at different initial concentrations of **1a** were determined. The final data was obtained by averaging the results of two independent experiments for the same initial concentration.

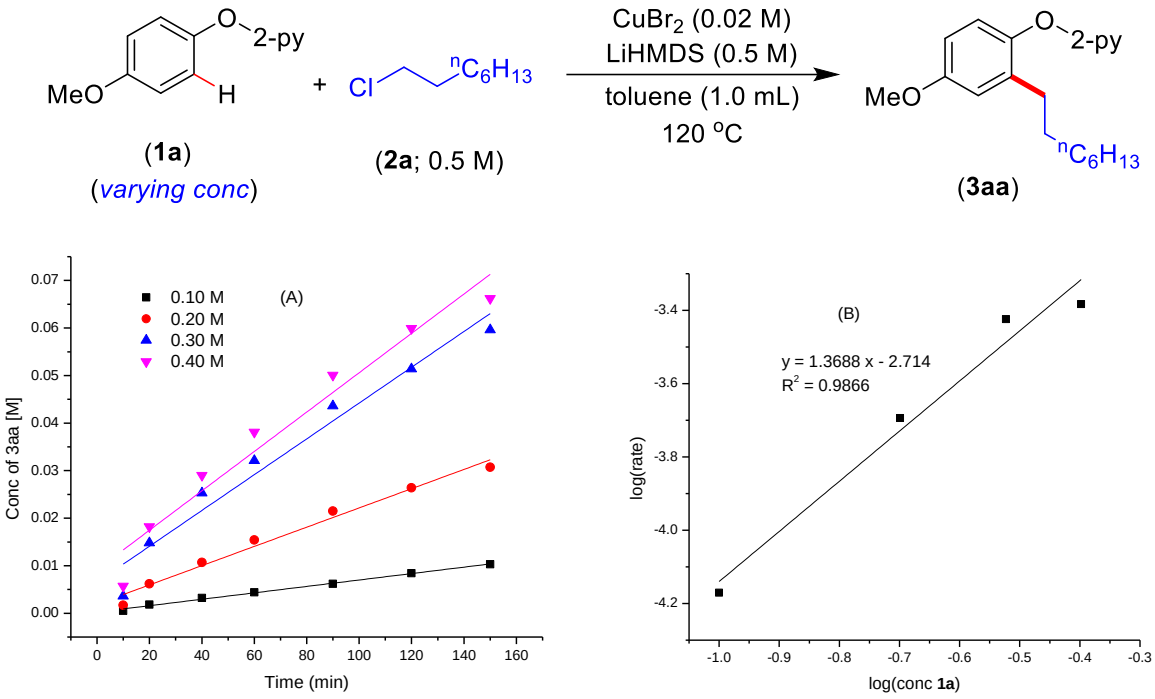



**Figure 2.5** (A) Time-dependent formation of **3aa** at different initial concentration 2-(4-methoxyphenoxy)pyridine, (B) Plot of log(rate) *vs* log(conc **1a**).

*Rate Order Determination on 1-Chlorooctane (**2a**) (Figure 2.6).* To determine the order of the alkylation reaction on 1-chlorooctane, the initial rates at different initial concentrations of 1-chlorooctane were recorded. The final data was obtained by averaging the results of three independent experiments for the same initial concentration.

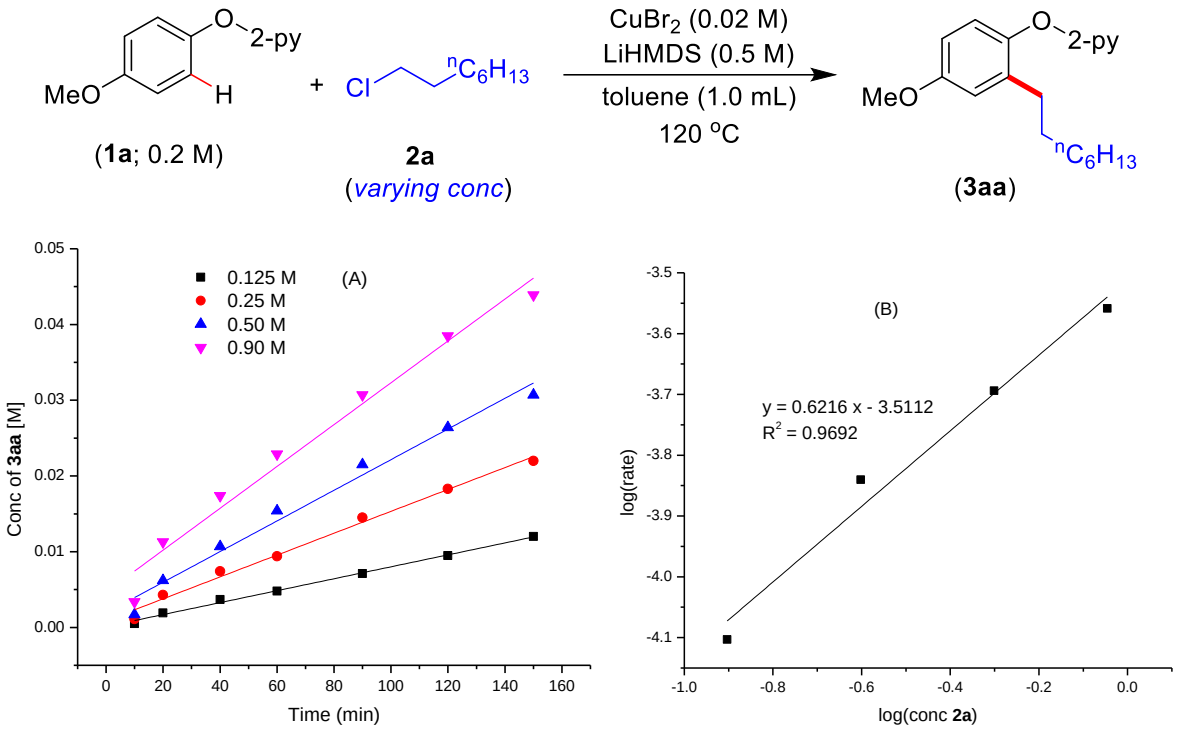
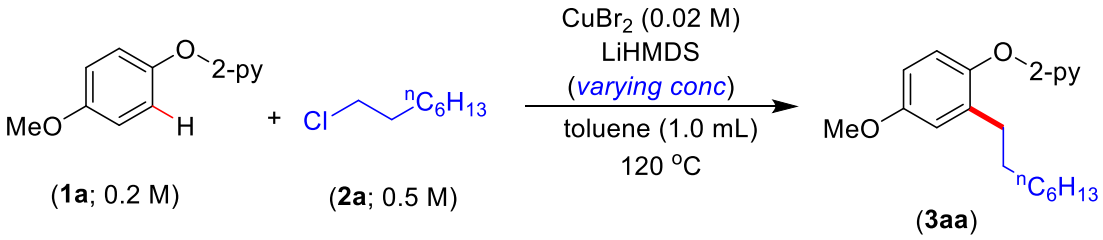



**Figure 2.6** (A) Time-dependent formation of **2a** at different initial concentration of 1-chlorooctane, (B) Plot of log(rate) *vs* log(conc **2a**).

*Rate Order Determination on 1-Chlorooctane (**2a**) (Figure 2.7).* To determine the order of the alkylation reaction on 1-chlorooctane, the initial rates at different initial concentrations of 1-chlorooctane were recorded. The final data was obtained by averaging the results of three independent experiments for the same initial concentration.



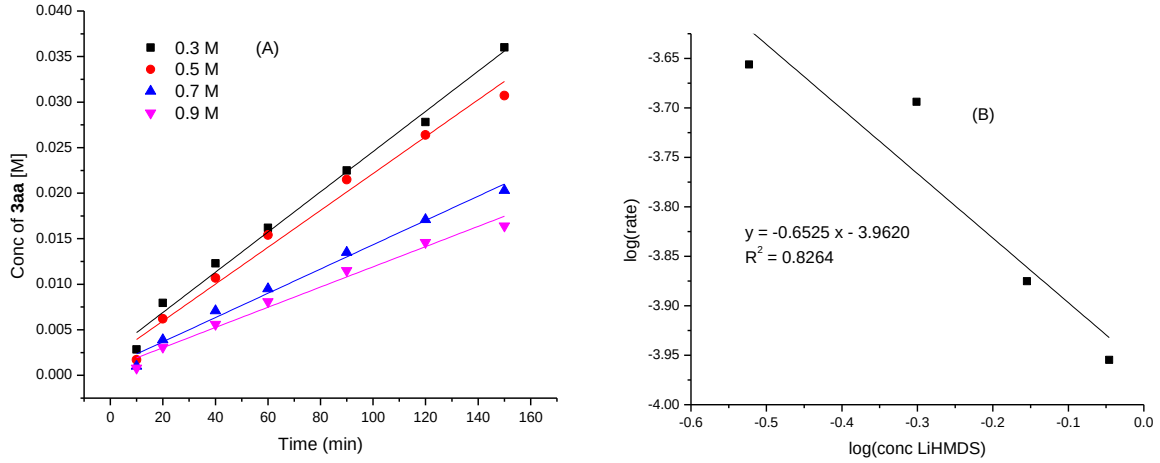
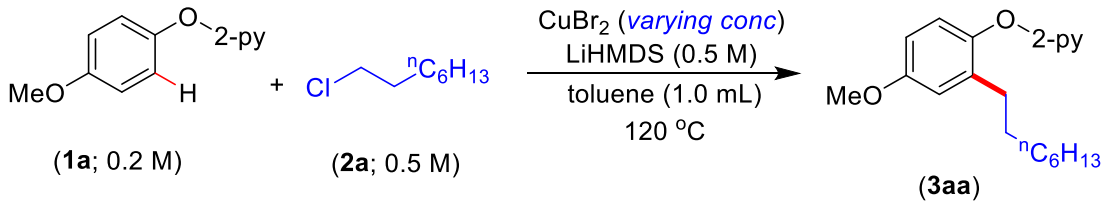



**Figure 2.7** (A) Time-dependent formation of **3aa** at different concentrations of LiHMDS, (B) Plot of log(rate) *vs* log(conc LiHMDS).

*Rate Order Determination on Catalyst (Figure 2.8):* To determine the order of the alkylation reaction on catalyst, the initial rates at different concentrations of catalyst were recorded. The final data was obtained by averaging the results of two independent experiments for same initial concentration.



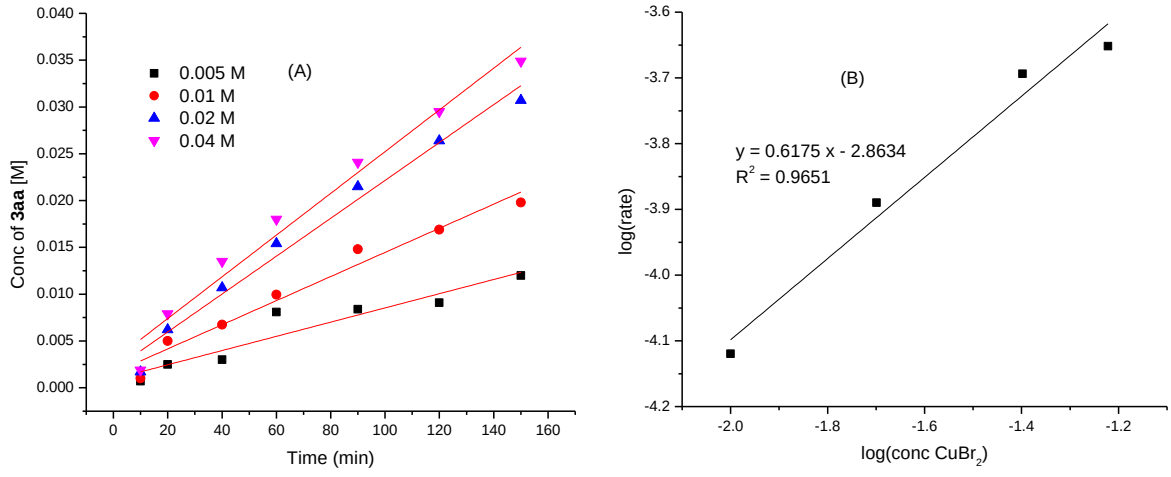




**Figure 2.8** (A) Time-dependent formation of **3aa** at different concentrations of $CuBr_2$, (B) Plot of log(rate) *vs* log(conc $CuBr_2$).

### 2.2.5.6 Rate of Alkylation Reaction with Octyl Chloride and Octyl Bromide

We have determined the independent rate of 1-bromooctane and 1-chlorooctane to find the rate limiting step where we observed the slow reaction of 1-chlorooctane over the 1-bromooctane supports the assumed rate-limiting oxidative cleavage of the C–Cl bond in alkyl chloride. Therefore, Further, the independent rate determination of the alkylation reaction using 1-chlorooctane and 1-bromooctane as coupling partners was 2.19 x 10-4 Mmin-1 and 5.18 x 10-4 Mmin-1 (Figure 2.9). During the alkylation process, the slow reaction of 1-chlorooctane over the 1-bromooctane supports the assumed rate-limiting oxidative cleavage of the C–Cl bond in alkyl chloride.

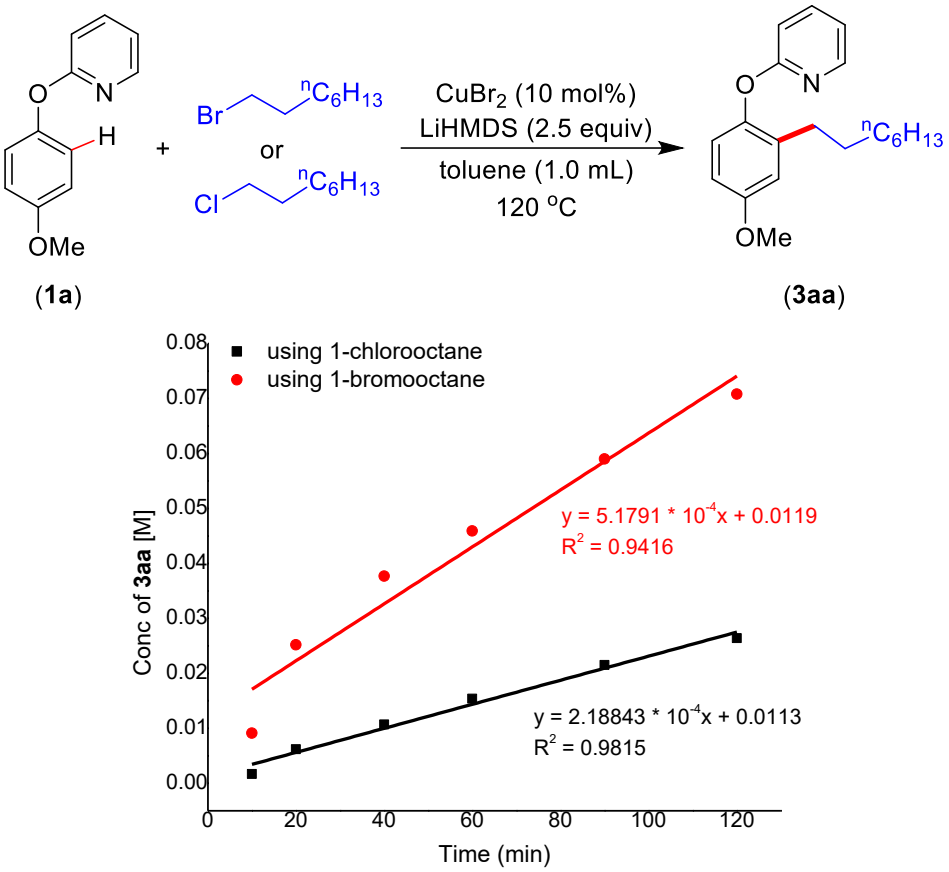



**Figure. 2.9** Time-dependent formation of **3aa** using 1-chlorooctane and 1-bromooctane.

### 2.2.6 Catalytic Cycle

We have designed a proposed catalytic cycle based on our mechanistic findings and literature precedents (Figure 2.10).[38,41,57,58] The 2-py-OAr will first coordinate to Cu(II) species to form (2-py-OAr)$_2$Cu(II)X$_2$, which will reduce to (2-py-OAr)$_2$Cu(I)X [X = halide or N(SiMe$_3$)$_2$] (**A**) in the presence of LiHMDS. The Cu(II) might reduce to Cu(I) via the comproportionation reaction between completely reduced Cu(0) and Cu(II). The Cu(II)

complexes were isolated and structurally characterized, and controlled studies and EPR analysis support the formation of Cu(I) species **A**. The absence of a radical intermediate tentatively rules out the Cu(II)/Cu(III) 1e- oxidation pathway.[59,60] The coordinated 2-py-OAr (**1**) then undergoes facile and reversible *ortho* C–H cleavage to deliver metallacycle intermediate **B**. The deuterium labeling study supported the reversibility of this step, and the formation of intermediate **B** was established by MALDI-TOF analysis. The low-valent and electron-rich Cu(I) species **B** would facilitate the oxidative addition of 1-chloroalkane in the rate-limiting step to produce Cu(III) intermediate **C**. The radical clock experiments and EPR analysis ruled out a one-electron radical path and strongly support the 2e oxidative addition of alkyl chloride. Moreover, the controlled experiments and kinetic analysis endorsed the oxidative addition as the rate-limiting step. After product reductive elimination of **3** from Cu(III) species **C**, the regeneration of active catalyst **A** in the presence of incoming substrate **1**.

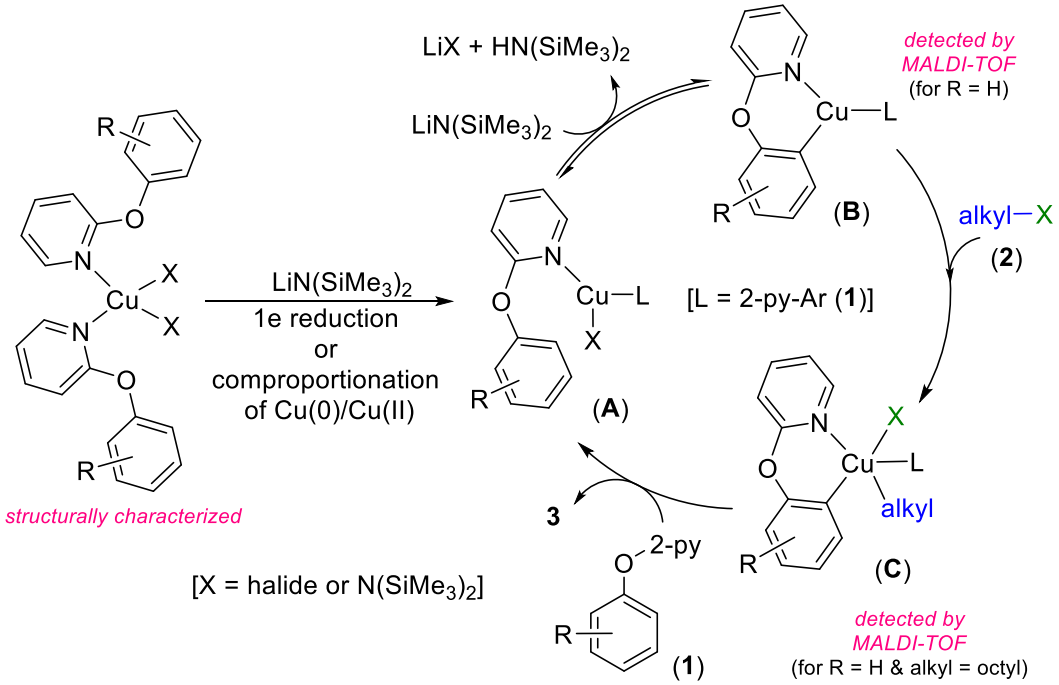



**Figure. 2.10** Plausible pathway for the Cu-catalyzed alkylation.

## 2.3 CONCLUSION

In conclusion, we established an efficient methodology for the regioselective coupling of non-activated alkyl chlorides using Cu-catalyst with the *ortho* C–H bond of phenol derivatives. The employment of inexpensive, abundant, and non-toxic copper catalysts and widely available unactivated alkyl chlorides make this alkylation protocol highly viable. The

reaction is appropriate with a variety of simple and functionalized alkyl chlorides as well as with a range of phenol derivatives. The use of LiHMDS base played a critical role in the success of alkylation by generating a Cu-amido complex during the reaction. Detailed mechanistic analysis of the alkylation approved us to draw a catalytic path that follows the rate-limiting 2e oxidative addition of alkyl chloride. Controlled experiments, kinetic analyses, and EPR studies revealed the participation of a Cu(I) active species, therefore supporting a Cu(I)/Cu(III) pathway. We trust that the simplicity and uniqueness of the manifested sustainable copper-catalyzed protocol would contribute significantly to the investigation and development of many other such processes.

## 2.4 EXPERIMENTAL SECTION

### 2.4.1 General Information

All the manipulations were conducted under an argon atmosphere either in a glove box or using standard Schlenk techniques in pre-dried glassware. The catalytic reactions were performed in flame-dried reaction vessels with a Teflon screw cap under argon atmosphere. Solvents were dried over Na/benzophenone or $CaH_2$ and distilled prior to use. Liquid reagents were flushed with argon prior to use. The alkyl chlorides **2o**,[61] **2r**,[62] **2s**,[61] **2v**,[63] **2w**,[64] **2x**,[65] **2y**,[66] and **2C**[62] and phenol derivatives **1a**,[67] **1b**,[67] **1c**,[67] **1d**,[68] **1f**,[69]**1g**,[69] **1h**,[67] **1k**,[67] **1l**,[68] **1m**,[70] **1p**,[70] **1q**,[71] **1r**,[71] **1s**,[71] **1t**,[71]and **1u**[72] were prepared according to the previously described procedures. All other chemicals were obtained from commercial sources and were used without further purification. High-resolution mass spectrometry (HRMS) mass spectra were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. EPR spectra were recorded on JES - FA200 ESR Spectrometer with X and Q band (Standard Frequency (X band) - 8.75-9.65 GHz) at 77 K. NMR: ($^1$H and $^{13}$C) spectra were recorded at 400 or 500 MHz ($^1$H), 100 or 125 MHz $^{13}$C{$^1$H}, DEPT (distortionless enhancement by polarization transfer)}, respectively in $CDCl_3$ solutions, if not otherwise specified; chemical shifts ($\delta$) are given in ppm. The $^1$H and $^{13}$C{$^1$H} NMR spectra are referenced to residual solvent signals ($CDCl_3$: $\delta$ H = 7.26 ppm, $\delta$ C = 77.2 ppm).

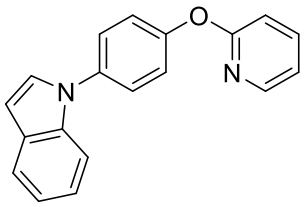
**GC Method.** Gas Chromatography analyses were performed using a Shimadzu GC-2010 gas chromatograph equipped with a Shimadzu AOC-20s auto-sampler and a Restek RTX-5 capillary column (30 m x 0.25 mm x 0.25µm). The instrument was set to an injection volume of 1 µL, an inlet split ratio of 10:1, and inlet and detector temperatures of 250 and 320 °C, respectively. UHP-grade nitrogen ($N_2$) was used as carrier gas with a flow rate of 30 mL/min. The temperature program used for all the analyses is as follows: 80 °C, 1 min; 30

°C/min to 200 °C, 2 min; 30 °C/min to 260 °C, 3 min; 30 °C/min to 300 °C, 3 min. Response factors for all the necessary compounds with respect to standard *n*-dodecane were calculated from the average of three independent GC runs.

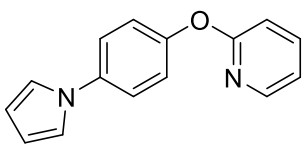
### 2.4.2 Synthesis of Starting Compounds

**Representative Procedure for Synthesis Phenol Derivatives**

**Synthesis of 1-(4-(Pyridin-2-yloxy)phenyl)-*1H*-indole (1w).** A Teflon screw-capped tube equipped with a magnetic stir bar was charged with CuI (0.048 g, 0.25 mmol), 2-picolinic acid (0.063 g, 0.51 mmol) and $K_3PO_4$ (1.07 g, 5.04 mmol). To this mixture, 2-bromopyridine (0.4 g, 2.53 mmol), 4-(*1H*-indol-1-yl)phenol (0.63 g, 3.01 mmol) and, 6 mL DMSO were added. The reaction mixture was heated at 90 $^oC$ for 24 h. At ambient temperature, the reaction mixture was diluted with ethyl acetate and extracted with ethyl acetate (30 mL x 3). The organic extract was washed with $H_2O$ multiple times and dried over $Na_2SO4$ and concentrated under vacuum. The remaining residue was purified by column chromatography on silica gel (petroleum ether/ EtOAc = 5/1) to yield **1w** (0.43 g, 59%) as a yellow solid.

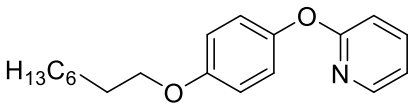



**1-(4-(Pyridin-2-yloxy)phenyl)-*1H*-indole(1w):** $^1$H-NMR (400 MHz,$CDCl_3$): $\delta$ = 8.21 (ddd, *J* = 4.9, 1.9, 0.6 Hz, 1H, Ar–H), 7.68-7.63 (m, 2H, Ar–H), 7.54 (d, *J* = 7.5 Hz, 1H, Ar–H), 7.48-7.45 (m, 2H, Ar–H), 7.29 (d, *J* = 3.3 Hz, 1H, Ar–H),7.26-7.13 (m, 4H, Ar–H), 6.98-6.94 (m, 2H, Ar–H), 6.64 (d, *J* = 3.1 Hz, 1H, Ar–H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 163.5 ($C_q$), 152.5 ($C_q$), 147.7 (CH), 139.7 (CH), 136.3 ($C_q$), 136.0 ($C_q$), 129.3 ($C_q$), 128.1 (CH), 125.7 (2C, CH), 122.4 (CH), 123.3 (2C, CH), 121.2 (CH), 120.4 (CH), 118.9 (CH), 111.9 (CH), 110.6 (CH) 103.6 (CH). HRMS (ESI): *m/z* Calcd for $C_{19}H_{14}ON_2 + H^+$ $[M + H]^+$ 287.1179; Found 287.1179.

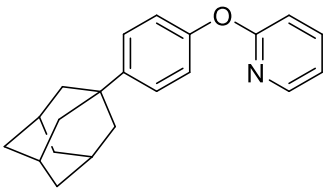



**2-(4-(*1H*-Pyrrol-1-yl)phenoxy)pyridine (1v):** The representative procedure was followed,

using 2-bromopyridine (0.5 g, 3.16 mmol) and 4-(1*H*-pyrrol-1-yl)phenol (0.60 g, 3.77 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **1v** (0.42 g, 56%) as a light yellow solid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.22 (dd, *J* = 5.0, 1.4 Hz, 1H, Ar–H), 7.74-7.69 (m, 1H, Ar–H), 7.44-7.40 (m, 2H, Ar–H), 7.23-7.20 (m, 2H, Ar–H), 7.01 (vt, *J* = 2.1 Hz, 2H, Ar–H), 7.04-7.00 (m, 1H, Ar–H), 6.96 (d, *J* = 8.4 Hz, 1H, Ar–H), 6.35 (vt, *J* = 2.1 Hz, 2H, Ar–H). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 163.7 ($C_q$), 151.9 ($C_q$), 147.8 (CH), 139.7 (CH), 137.7 ($C_q$), 122.4 (2C, CH), 122.1 (2C, CH), 119.8 (2C, CH), 118.8 (CH), 111.8 (CH), 110.4 (2C, CH). HRMS (ESI): *m/z* Calcd for $C_{15}H_{12}ON_2 + H^+$ $[M + H]^+$ 237.1022; Found 237.1022.

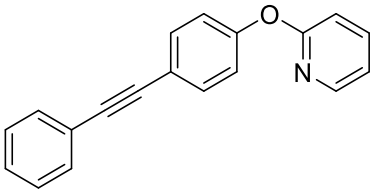



**2-(4-(Octyloxy)phenoxy)pyridine (1e):** The representative procedure was followed, using 2-bromopyridine (0.3 g, 1.89 mmol) and 4-(octyloxy)phenol (0.51 g, 2.29 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **1e** (0.35 g, 62%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.19 (d, *J* = 4.9 Hz, 1H, Ar–H), 7.65 (vt, *J* =7.6 Hz, 1H, Ar–H), 7.04 (d, *J* = 8.5 Hz, 2H, Ar–H), 6.95 (vt, *J* = 5.8 Hz, 1H, Ar–H), 6.91 (d, *J* = 8.9 Hz, 2H, Ar–H), 6.84 (t, *J* = 8.2 Hz, 1H, Ar–H), 3.94 (t, *J* = 6.4 Hz, 2H, $CH_2$), 1.81-1.75 (m, 2H, $CH_2$), 1.48-1.42 (m, 2H, $CH_2$), 1.33-1.26 (m, 8H, $CH_2$), 0.89 (t, *J* = 6.1 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.9 ($C_q$), 156.4 ($C_q$), 148.0 (CH), 147.4 ($C_q$), 139.4 (CH), 122.5 (2C, CH), 118.2 (CH), 115.5 (2C, CH), 111.2 (CH), 68.5 ($CH_2$), 32.0 ($CH_2$), 29.5 (2C, $CH_2$), 29.4 ($CH_2$), 26.3 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{19}H_{25}O_2N + H^+$ $[M + H]^+$ 300.1958; Found 300.1963.

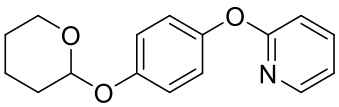



**2-(4-((*3r,5r,7r*)-Adamantan-1-yl)phenoxy)pyridine (1i):** The representative procedure was followed, using 2-bromopyridine (0.3 g, 1.89 mmol) and 4-(*3r,5r,7r*)-adamantan-1-yl)phenol (0.52 g, 2.27 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **1i** (0.38 g, 66%) as a white solid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.21 (dd, *J* = 4.8, 1.6 Hz, 1H, Ar–H), 7.68-7.64 (m, 1H, Ar–H), 7.38 (d, *J* = 8.6 Hz, 2H,

Ar–H). 7.08 (d, *J* = 8.3 Hz, 2H, Ar–H). 6.99-6.96 (m, 1H, Ar–H), 6.88 (d, *J* = 8.3 Hz, 1H, Ar–H), 2.10 (s, 3H, CH), 1.93 (d, *J* = 2.5 Hz, 6H, $CH_2$), 1.78-1.76 (m, 6H, $CH_2$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.2 ($C_q$), 152.0 ($C_q$), 148.0 (CH), 147.8 ($C_q$), 139.5 (CH), 126.3 (2C, CH), 120.7 (2C, CH), 118.4 (CH), 111.6 (CH), 43.5 (3C, $CH_2$), 37.0 (3C, $CH_2$), 36.1 ($C_q$), 29.2 (3C, CH). HRMS (ESI): *m/z* Calcd for $C_{21}H_{23}ON + H^+$ $[M + H]^+$ 306.1852; Found 306.1854.



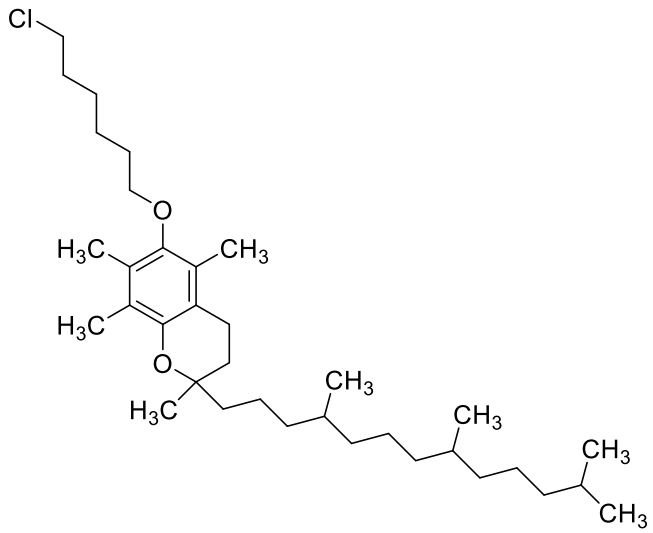

**2-(4-(Phenylethynyl)phenoxy)pyridine (1n):** The representative procedure was followed, using 2-bromopyridine (0.5 g, 3.16 mmol) and 2-(4-(phenylethynyl)phenoxy)pyridine (0.74 g, 3.80 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **1n** (0.5 g, 58%) as a light yellow liquid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.23 (dd, *J* = 5.0, 2.0 Hz, 1H, Ar–H), 7.73-7.69 (m, 1H, Ar–H), 7.58-7.52 (m, 4H, Ar–H), 7.38-7.32 (m, 3H, Ar–H), 7.15-7.11 (m, 2H, Ar–H), 7.04-7.01 (m, 1H, Ar–H), 6.94 (d, *J* = 8.3 Hz, 1H, Ar–H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 163.5 ($C_q$), 154.4 ($C_q$), 148.0 (CH), 139.7 (CH), 133.2 (2C, CH), 131.7 (2C, CH), 128.5 (2C, CH), 128.4 (CH), 123.5 ($C_q$), 121.2 (2C, CH), 119.7 ($C_q$), 119.1 (CH), 112.1 (CH), 89.2 ($C_q$), 89.1 ($C_q$). HRMS (ESI): *m/z* Calcd for $C_{19}H_{13}ON + H^+$ $[M + H]^+$ 272.1070; Found 272.1072.




**2-(4-((Tetrahydro-*2H*-pyran-2-yl)oxy)phenoxy)pyridine (1o):** The representative procedure was followed, using 2-bromopyridine (0.3 g, 1.89 mmol) and 2-(4-((tetrahydro-*2H*-pyran-2-yl)oxy)phenoxy)pyridine (0.44 g, 2.27 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **1o** (0.27 g, 53%) as a light yellow liquid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.19 (dd, *J* = 5.0, 2.0 Hz, 1H, Ar–H), 7.67-7.62 (m, 1H, Ar–H), 7.09-7.04 (m, 4H, Ar–H), 6.97-6.93 (m,1H, Ar–H), 6.85 (d, *J* = 8.3 Hz, 1H, Ar–H), 5.38 (t, *J* = 3.3 Hz, 1H, CH), 3.96-3.91 (m, 1H, CH), 3.63-3.58 (m, 1H, CH), 2.05-1.96 (m, 1H, CH), 1.88-1.84 (m, 2H, $CH_2$), 1.71-1.68 (m, 1H, CH), 1.67-1.57 (m, 2H, $CH_2$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.9 ($C_q$), 154.3 ($C_q$), 148.3 ($C_q$), 148.0 (CH),

139.4 (CH), 122.3 (2C, CH), 118.3 (CH), 117.7 (2C, CH), 111.2 (CH), 97.0 (CH), 62.2 ($CH_2$), 30.6 ($CH_2$), 25.4 ($CH_2$), 19.0 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{16}H_{17}O_3N + H^+$ [M + H]$^+$ 272.1281; Found 272.1283.

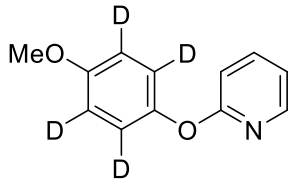
**Procedure for Synthesis of 6-((6-Chlorohexyl)oxy)-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chromane (2B):** In an oven-dried Schlenk flask NaH (50-60% dispersed in mineral oil) (0.11 g, 4.64 mmol) was dissolved in DMF (20 mL) and 2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-ol (0.50 g, 1.09 mmol) was added at 0 $^oC$. The resulting reaction mixture was stirred for 30 min and 1,6-dichlorohexane (0.36 g, 2.32 mmol) was added and continued stirring at room temperature for 12 h. The reaction was quenched with water (15 mL) and extracted with ethyl acetate (20 mL x 3). The organic extract was washed with $H_2O$, the combined organic extract was dried over $Na_2SO_4$ and the volatiles were evaporated in *vacuo*. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 50/1) to yield **2B** (0.29 g, 46%).




**6-((6-Chlorohexyl)oxy)-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chromane (2B):** $^1$H-NMR (500 MHz, $CDCl_3$): 3.64 (t, *J* = 6.6 Hz, 2H, $CH_2$), 3.56 (q, *J* = 6.8 Hz, 2H, $CH_2$, 1H, CH), 2.58 (t, *J* = 6.8 Hz, 2H, $CH_2$), 2.17 (s, 3H, $CH_3$), 2.13 (s, 3H, $CH_3$), 2.09 (s, 3H, $CH_3$), 1.87-1.72 (m, 6H, $CH_2$, 1H, CH), 1.60-1.47 (m, 8H, $CH_2$, 1H, CH), 1.42-1.37 (m, 4H, $CH_2$), 1.29-1.22 (m, 8H, $CH_2$), 1.17-1.06 (m, 2H, $CH_2$, 3H, $CH_3$), 0.89-0.84 (m, 12H, $CH_3$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 148.5, 147.9, 128.0, 125.9, 123.0, 117.7, 74.9, 73.0, 45.2, 45.1 , 40.3, 39.6 , 37.7, 37.6, 37.5 , 33.0, 32.8, 32.6, 30.4 , 28.2, 27.1, 26.3, 25.8, 25.0 , 24.6, 24.1, 22.9, 22.8, 21.2, 20.8, 19.9, 19.8, 12.9, 12.1, 12.

**Procedure for Synthesis of 2-(4-Methoxyphenoxy-2,3,5,6-*d*$_4$)pyridine (1a-*d*$_4$):**

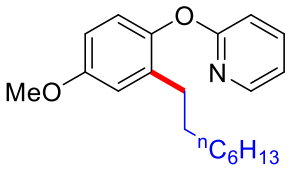
Teflon screw-capped tube equipped with magnetic stir bar was charged with CuI (0.036 g, 0.19 mmol), 2-picolinic acid (0.046 g, 0.374 mmol) and $K_3PO_4$ (0.80 g, 3.77 mmol). To the mixture 2-bromopyridine (0.3 g, 1.90 mmol), 4-methoxyphen-2,3,5,6-*d*$_4$-ol (0.28 g, 2.26 mmol) and 6 mL DMSO were added. The reaction was heated in a pre-heated oil bath at 90 $^oC$ for 24 h. At ambient temperature, the reaction mixture was diluted with ethyl acetate and extracted with ethyl acetate (30 mL x 3). The organic extract was washed with $H_2O$ multiple times and dried over $Na_2SO4$ and concentrated. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 50/1) to yield **1a**-*d*$_4$ (0.35 g, 90%; 87% D) as a yellow solid.



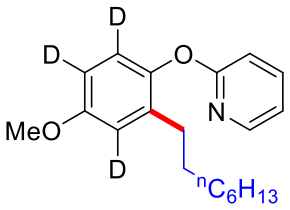

$^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.19 (d, *J* = 4.6 Hz, 1H, Ar–H), 7.65 (vt, *J* = 7.3 Hz, 1H, Ar–H), 7.07 (s, CH/D, Ar–H), 6.97-6.93 (s, 1H, CH/D, Ar–H), 6.87 (d, *J* = 8.4 Hz, 1H, Ar–H), 3.81 (s, 3H, $CH_3$). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.4 ($C_q$), 156.6 ($C_q$), 147.8 (CH), 147.4 ($C_q$), 139.4 (CH), 122.4 (2C, CH/CD), 118.2 (CH), 114.8 (2C, CH/CD), 117.2 (CH), 55.7 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{12}H_7{}^2H_4O_2N + H^+$ $[M + H]^+$ 206.1114; Found 206.1104.

### 2.4.3 Representative Procedure for Alkylation

**Synthesis of 2-(4-Methoxy-2-octylphenoxy)pyridine (3aa):** To a flame-dried screw-cap tube equipped with magnetic stir bar were introduced 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol), 1-chlorooctane (**2a**; 0.075 g, 0.504 mmol), $CuBr_2$ (0.0045 g, 0.02 mmol, 10.0 mol%) and LiHMDS (0.084 g, 0.50 mmol) inside the glove box under argon atmosphere. To the above mixture in the tube was added toluene (0.5 mL). The resultant reaction mixture in the tube was immersed in a preheated oil bath at 120 $^oC$ and stirred for 24 h. At ambient temperature, the reaction mixture was quenched with distilled $H_2O$ (10.0 mL) and the crude product was extracted with EtOAc (15 mL x 3). The combined organic extract was dried over $Na_2SO_4$ and the volatiles were evaporated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) to yield **3aa** (0.042 g, 66%) as a light yellow liquid.

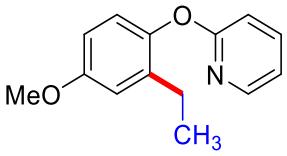



$^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 4.9, 1.5 Hz, 1H, Ar–H), 7.66-7.61 (m, 1H, Ar–H), 6.98 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.93 (vt, $J$ = 6.4 Hz, 1H, Ar–H), 6.83-6.81 (m, 2H, Ar–H), 6.76 (dd, $J$ = 8.1, 3.1 Hz, 1H, Ar–H), 3.81 (s, 3H, $CH_3$), 2.48 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.58-1.51 (m, 2H, $CH_2$), 1.26-1.21 (m, 10H, $CH_2$), 0.86 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.6 ($C_q$), 156.9 ($C_q$), 148.0 (CH), 145.5 ($C_q$), 139.4 (CH), 136.7 ($C_q$), 123.1 (CH), 117.9 (CH), 115.8 (CH), 112.1 (CH), 110.6 (CH), 55.7 ($CH_3$), 32.0 ($CH_2$), 30.6 ($CH_2$), 30.1 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{20}H_{27}O_2N + H^+$ $[M + H]^+$ 314.2115; Found 314.2115.

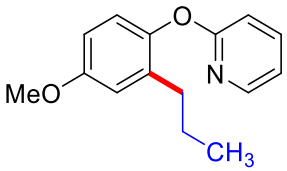



**2-(4-Methoxy-3-octylphenoxy-2,5,6-*d*$_3$)pyridine (3aa-*d*$_3$):** The representative procedure was followed, using 2-(4-methoxyphenoxy-2,3,5,6-*d*$_4$)pyridine (**1a**-*d*$_4$; 0.082 g, 0.40 mmol) and 1-chlorooctane (**2a**; 0.15 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3aa**-*d*$_3$ (0.052 g, 41%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.17 (d, $J$ = 1.9 Hz, CH/CD, Ar–H), 7.63-7.62 (m, 1H, Ar–H), 6.99-6.97 (m, CH/CD, Ar–H), 6.92 (d, $J$ = 1.9 Hz, 1H, Ar–H), 6.82 (d, $J$ = 7.5 Hz, 1H, Ar–H), 6.76 (s, CH/CD, Ar–H), 3.80 (s, 3H, $CH_3$), 2.48 (q, $J$ = 7.8 Hz, 2H, $CH_2$), 1.56-1.51 (m, 2H, $CH_2$), 1.26-1.21 (m, 10H, $CH_2$), 0.86 (t, $J$ = 6.4 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.6 ($C_q$), 156.8 (t, $J$ = 3.4 Hz, $C_q$), 148.0 (CH), 145.5 (d, $J$ = 4.6 Hz, $C_q$), 139.3 (d, $J$ = 10.7 Hz, CH), 136.7 (d, $J$ = 8.4 Hz, $C_q$), 123.1 (d, $J$ = 10.7 Hz, CH), 117.9 (d, $J$ = 14.5 Hz, CH), 115.8 (t, $J$ = 1.5 Hz, CH), 112.0 (dd, $J$ = 9.9, 3.8 Hz, CH), 110.6 (CH), 55.6 ($CH_3$), 32.0 ($CH_2$), 30.5 ($CH_2$), 30.0 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{20}H_{24}{}^{2}H_3O_2N + H^+$ $[M + H]^+$ 317.2303; Found 317.2290.

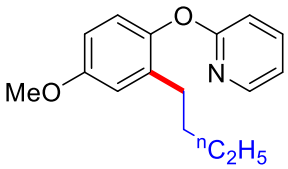
### 2.4.4 Characterization Data of Alkylated Compounds



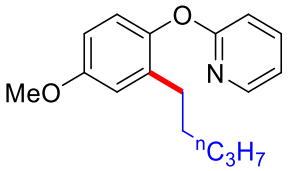

**2-(2-Ethyl-4-methoxyphenoxy)pyridine (3ab):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 1-bromoroethane (**2b**; 0.054 g, 0.50 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3ab** (0.029 g, 62%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (d, $J$ = 3.8 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 6.98 (dd, $J$ = 5.0, 1.4 Hz, 1H, Ar–H), 6.95-6.92 (m, 1H, Ar–H), 6.85-6.82 (m, 2H, Ar–H), 6.77 (dd, $J$ = 8.8, 3.1 Hz, 1H, Ar–H), 3.81 (s, 3H, $CH_3$), 2.49 (q, $J$ = 7.5 Hz, 2H, $CH_2$), 1.16 (t, $J$ = 7.6 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 157.0 ($C_q$), 148.0 (CH), 145.3 ($C_q$), 139.4 (CH), 137.8 ($C_q$), 123.0 (CH), 118.0 (CH), 115.1 (CH), 112.0 (CH), 110.5 (CH), 55.6 ($CH_3$), 23.6 ($CH_2$), 14.2 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{14}H_{15}O_2N + H^+$ $[M + H]^+$ 230.1176; Found 230.1173.



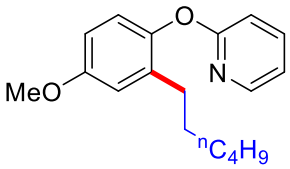

**2-(4-Methoxy-2-propylphenoxy)pyridine (3ac):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 1-bromoropropane (**2c**; 0.062 g, 0.50 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3ac** (0.033 g, 66%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 5.0, 1.6 Hz, 1H, Ar–H), 7.66-7.61 (m, 1H, Ar–H), 6.98 (d, $J$ = 8.6 Hz, 1H, Ar–H), 6.95-6.91 (m, 1H, Ar–H), 6.83-6.81 (m, 2H, Ar–H), 6.77 (dd, $J$ = 8.8, 3.1 Hz, 1H, Ar–H), 3.81 (s, 3H, $CH_3$), 2.48 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 1.64-1.55 (m, 2H, $CH_2$), 0.89 (t, $J$ = 7.4 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 156.8 ($C_q$), 148.0 (CH), 145.6 ($C_q$), 139.4 (CH), 136.3 ($C_q$), 123.0 (CH), 117.9 (CH), 115.8 (CH), 112.1 (CH), 110.6 (CH), 55.6 ($CH_3$), 32.6 ($CH_2$), 23.2 ($CH_2$), 14.2 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{15}H_{17}O_2N + H^+$ $[M + H]^+$ 244.1332; Found 244.1332.



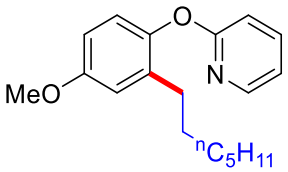

**2-(2-Butyl-4-methoxyphenoxy)pyridine (3ad):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 1-chlorobutane (**2d**; 0.046 g, 0.50 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3ad** (0.032 g, 61%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 4.4, 2.0 Hz, 1H, Ar–H), 7.66-7.61 (m, 1H, Ar–H), 6.98 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.95-6.91 (m, 1H, Ar–H), 6.82 (vt, $J$ = 4.1 Hz, 2H, Ar–H), 6.76 (dd, $J$ = 8.8, 3.0 Hz, 1H, Ar–H), 3.86 (s, 3H, $CH_3$), 2.49 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.58-1.50 (m, 2H, $CH_2$), 1.30-1.25 (m, 2H, $CH_2$), 0.85 (t, $J$ = 7.4 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.6 ($C_q$), 156.6 ($C_q$), 147.9 (CH), 145.3 ($C_q$), 139.4 (CH), 136.6 ($C_q$), 123.1 (CH), 117.9 (CH), 115.8 (CH), 112.1 (CH), 110.6 (CH), 55.6 ($CH_3$), 32.2 ($CH_2$), 30.3 ($CH_2$), 22.6 ($CH_2$), 14.0 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{16}H_{19}O_2N$ + $H^+$ $[M + H]^+$ 258.1489; Found 258.1495.



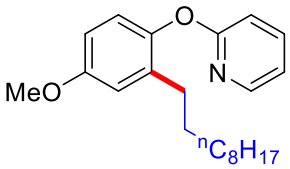

**2-(4-Methoxy-2-pentylphenoxy)pyridine (3ae):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 1-bromopetane (**2e**; 0.076 g, 0.50 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3ae** (0.032 g, 58%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 4.9, 1.4 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 6.98 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.95-6.92 (m, 1H, Ar–H), 6.83-6.81 (m, 2H, Ar–H), 6.77 (dd, $J$ = 8.8, 3.1 Hz, 1H, Ar–H), 3.81 (s, 3H, $CH_3$), 2.48 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.58-1.53 (m, 2H, $CH_2$), 1.26-1.22 (m, 4H, $CH_2$), 0.82 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 156.8 ($C_q$), 148.0 (CH), 145.4 ($C_q$), 139.4 (CH), 136.6 ($C_q$), 123.1 (CH), 117.9 (CH), 115.8 (CH), 112.0 (CH), 110.6 (CH), 55.6 ($CH_3$), 31.7 ($CH_2$), 30.5 ($CH_2$), 29.7 ($CH_2$), 22.6 ($CH_2$), 14.1 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{17}H_{21}O_2N$ + $H^+$ $[M + H]^+$ 272.1645; Found 272.1644.



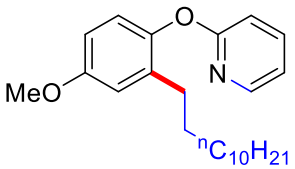

**2-(2-Hexyl-4-methoxyphenoxy)pyridine (3af):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 1-chlorohexane (**2f**; 0.060 g, 0.50 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3af** (0.038 g, 65%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (d, $J$ = 2.5 Hz, 1H, Ar–H), 7.64 (vt, $J$ = 6.9 Hz, 1H, Ar–H), 6.98 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.93 (vt, $J$ = 6.5 Hz, 1H, Ar–H), 6.83-6.81 (m, 2H, Ar–H), 6.76 (dd, $J$ = 8.6, 2.9 Hz, 1H, Ar–H), 3.81 (s, 3H, $CH_3$), 2.48 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 2.50-2.46 (m, 2H, $CH_2$), 1.58-1.51 (m, 2H, $CH_2$), 1.28-1.22 (m, 4H, $CH_2$), 0.83 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.6 ($C_q$), 156.9 ($C_q$), 148.0 (CH), 145.5 ($C_q$), 139.4 (CH), 136.6 ($C_q$), 123.1 (CH), 117.9 (CH), 115.8 (CH), 112.0 (CH), 110.6 (CH), 55.6 ($CH_3$), 31.8 ($CH_2$), 30.6 ($CH_2$), 30.0 ($CH_2$), 29.2 ($CH_2$), 22.7 ($CH_2$), 14.2 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{18}H_{23}O_2N + H^+$ $[M + H]^+$ 286.1802; Found 286.1816.



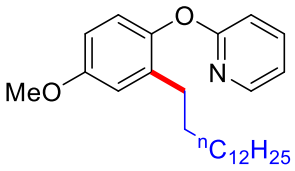

**2-(2-Heptyl-4-methoxyphenoxy)pyridine (3ag):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 1-bromoheptane (**2g**; 0.090 g, 0.50 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3ag** (0.039 g, 64%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 5.0, 1.8 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 6.98 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.95-6.92 (m, 1H, Ar–H), 6.83-6.81 (m, 2H, Ar–H), 6.77 (dd, $J$ = 8.8, 3.1 Hz, 1H, Ar–H), 3.80 (s, 3H, $CH_3$), 2.48 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.58-1.50 (m, 2H, $CH_2$), 1.25-1.20 (m, 8H, $CH_2$), 0.84 (t, $J$ = 6.6 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 156.8 ($C_q$), 148.0 (CH), 145.4 ($C_q$), 139.4 (CH), 136.6 ($C_q$), 123.1 (CH), 117.9 (CH), 115.8 (CH), 112.0 (CH), 110.6 (CH), 55.6 ($CH_3$), 31.9 ($CH_2$), 30.6 ($CH_2$), 30.0 ($CH_2$), 29.5 ($CH_2$), 29.2 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{19}H_{25}O_2N + H^+$ $[M + H]^+$ 300.1958; Found 300.1955.



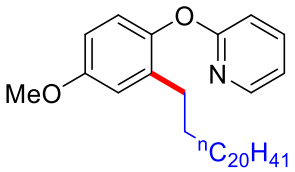

**2-(2-Decyl-4-methoxyphenoxy)pyridine (3ah):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 1-chlorodecane (**2h**; 0.089 g, 0.50 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3ah** (0.034 g, 49%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 5.0, 2.0 Hz, 1H, Ar–H), 7.66-7.61 (m, 1H, Ar–H), 6.98 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.95-6.91 (m, 1H, Ar–H), 6.82 (vt, $J$ = 4.9 Hz, 2H, Ar–H), 6.76 (dd, $J$ = 8.8, 3.0 Hz, 1H, Ar–H), 3.81 (s, 3H, $CH_3$), 2.48 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.59-1.51 (m, 2H, $CH_2$), 1.29-1.21 (m, 14H, $CH_2$), 0.88 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 156.9 ($C_q$), 148.0 (CH), 145.5 ($C_q$), 139.4 (CH), 136.6 ($C_q$), 123.1 (CH), 117.9 (CH), 115.8 (CH), 112.0 (CH), 110.6 (CH), 55.6 ($CH_3$), 32.1 ($CH_2$), 30.6 ($CH_2$), 30.0 ($CH_2$), 29.8 ($CH_2$), 29.7 ($CH_2$), 29.6 ($CH_2$), 29.5 (2C, $CH_2$), 22.8 ($CH_2$), 14.8 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{22}H_{31}O_2N + H^+$ $[M + H]^+$ 342.2428; Found 342.2414.




**2-(2-Dodecyl-4-methoxyphenoxy)pyridine (3ai):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 1-chlorododecane (**2i**; 0.103 g, 0.50 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3ai** (0.034 g, 45%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 4.9, 1.5 Hz, 1H, Ar–H), 7.66-7.61 (m, 1H, Ar–H), 6.98 (d, $J$ = 8.6 Hz, 1H, Ar–H), 6.94-6.91 (m, 1H, Ar–H), 6.84-6.81 (m, 2H, Ar–H), 6.76 (dd, $J$ = 8.8, 3.1 Hz, 1H, Ar–H), 3.80 (s, 3H, $CH_3$), 2.48 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.58-1.51 (m, 2H, $CH_2$), 1.25-1.21 (m, 18H, $CH_2$), 0.88 (t, $J$ = 6.5 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 156.8 ($C_q$), 148.0 (CH), 145.4 ($C_q$), 139.3 (CH), 136.6 ($C_q$), 123.0 (CH), 117.9 (CH), 115.7 (CH), 112.0 (CH), 110.6 (CH), 55.6 ($CH_3$), 32.1 ($CH_2$), 30.6 ($CH_2$), 30.0 ($CH_2$), 29.0 ($CH_2$), 29.8 (2C, $CH_2$), 29.7 ($CH_2$), 29.6 ($CH_2$), 29.5 (2C, $CH_2$), 22.6 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{24}H_{35}O_2N + H^+$ $[M + H]^+$ 370.2741; Found 370.2744.

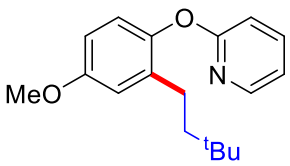



**2-(4-Methoxy-2-tetradecylphenoxy)pyridine (3aj):** The representative procedurewas followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 1-chlorotetradecane (**2j**; 0.120 g, 0.515 mmol) and the reaction mixture was stirred at 140 °C. Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3aj** (0.039 g, 48%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 5.0, 1.6 Hz, 1H, Ar–H), 7.66-7.61 (m, 1H, Ar–H), 6.98 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.95-6.91 (m, 1H, Ar–H), 6.82 (vt, $J$ = 5.5 Hz, 2H, Ar–H), 6.76 (dd, $J$ = 8.8, 3.1 Hz, 1H, Ar–H), 3.81 (s, 3H, $CH_3$), 2.48 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.58-1.51 (m, 2H, $CH_2$), 1.32-1.21 (m, 22H, $CH_2$), 0.88 (t, $J$ = 6.6 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.6 ($C_q$), 156.9 ($C_q$), 148.0 (CH), 145.5 ($C_q$), 139.3 (CH), 136.6 ($C_q$), 123.1 (CH), 117.9 (CH), 115.8 (CH), 112.0 (CH), 110.6 (CH), 55.6 ($CH_3$), 32.1 ($CH_2$), 30.6 ($CH_2$), 30.0 ($CH_2$), 29.9 (2C, $CH_2$), 29.8 (3C, $CH_2$), 29.7 ($CH_2$), 29.6 (2C, $CH_2$), 29.5 ($CH_2$), 22.9 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{26}H_{39}O_2N + H^+$ $[M + H]^+$ 398.3054; Found 398.3073.

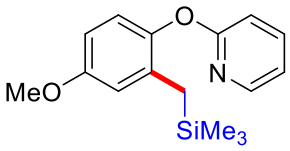



**2-(2-Docosyl-4-methoxyphenoxy)pyridine (3ak):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.081 g, 0.40 mmol) and 1-chlorodocosane (**2k**; 0.35 g, 1.0 mmol) and the reaction mixture was stirred at 140 °C. Purification by column chromatography on silica gel (petroleum ether/EtOAc: 50/1) yielded **3ak** (0.11 g, 54%) as a white solid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (d, $J$ = 4.6 Hz, 1H, Ar–H), 7.63 (t, $J$ = 7.8 Hz, 1H, Ar–H), 6.99 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.93 (vt, $J$ = 6.4 Hz, 1H, Ar–H), 6.83 (d, $J$ = 8.3 Hz, 2H, Ar–H), 6.76 (d, $J$ = 8.8 Hz, 1H, Ar–H), 3.81 (s, 3H, $CH_3$), 2.48 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.56-1.53 (m, 2H, $CH_2$), 1.26-1.21 (m, 38H, $CH_2$), 0.88 (t, $J$ = 5.1 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.6 ($C_q$), 156.9 ($C_q$), 148.0 (CH), 145.5 ($C_q$), 139.3 (CH), 136.6 ($C_q$), 123.1 (CH), 117.9 (CH), 115.8 (CH), 112.1 (CH), 110.6 (CH), 55.6 ($CH_3$), 32.1 ($CH_2$), 30.6 ($CH_2$), 30.0 ($CH_2$), 29.9 (12C, $CH_2$), 29.8 ($CH_2$), 29.7 ($CH_2$), 29.6 (3C, $CH_2$), 22.9 ($CH_2$), 14.3 ($CH_3$). GC-MS for $C_{34}H_{55}NO_2$, 509.5 [$M^+$]. Due to the insolubility of **3ak** in acetonitrile and methanol, we could not get suitable HRMS

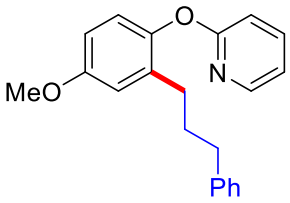
data for this compound, therefore, we have provided GC-MS data.



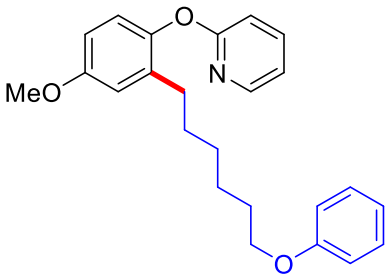

**2-(2-(3,3-Dimethylbutyl)-4-methoxyphenoxy)pyridine (3al):** The representative procedurewas followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.081 g, 0.40 mmol) and 1-chloro-3,3-dimethylbutane (**2l**; 0.12 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3al** (0.047 g, 41%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.17 (dd, $J$ = 4.9, 1.6 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 6.99 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.94-6.91 (m, 1H, Ar–H), 6.84 (d, $J$ = 8.3 Hz, 1H, Ar–H), 6.80 (d, $J$ = 3.0 Hz, 1H, Ar–H), 6.76 (dd, $J$ = 8.6, 3.0 Hz, 1H, Ar–H), 3.81 (s, 3H, $CH_3$), 2.45-2.41 (m, 2H, $CH_2$), 1.44-1.39 (m, 2H, $CH_2$), 0.82 (s, 9H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 156.9 ($C_q$), 147.9 (CH), 145.2 ($C_q$), 139.4 (CH), 137.2 ($C_q$), 123.3 (CH), 117.9 (CH), 115.7 (CH), 112.0 (CH), 110.6 (CH), 55.6 ($CH_3$), 44.7 ($CH_2$), 30.6 ($C_q$), 29.4 (3C, $CH_3$), 26.1 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{18}H_{23}O_2N$ + $H^+$ [M + H]$^+$ 286.1802; Found 286.1799.




**2-(4-Methoxy-2-((trimethylsilyl)methyl)phenoxy)pyridine (3am):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.081 g, 0.40 mmol) and (chloromethyl)trimethylsilane (**2m**; 0.123 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3am** (0.040 g, 35%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 4.8, 1.5 Hz, 1H, Ar–H), 7.64-7.60 (m, 1H, Ar–H), 6.95 (d, $J$ = 8.6 Hz, 1H, Ar–H), 6.92-6.90 (m, 1H, Ar–H), 6.80 (d, $J$ = 8.3 Hz, 1H, Ar–H), 6.67-6.63 (m, 2H, Ar–H), 3.78 (s, 3H, $CH_3$), 1.95 (s, 2H, $CH_2$), –0.01 (s, 9H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.3 ($C_q$), 156.6 ($C_q$), 148.0 (CH), 144.6 ($C_q$), 139.4 (CH), 134.7 ($C_q$), 122.8 (CH), 117.9 (CH), 115.5 (CH), 110.7 (CH), 110.5 (CH), 55.6 ($CH_3$), 21.6 ($CH_2$), –1.2 (3C, $CH_3$). HRMS (ESI): *m/z* Calcd for $C_{16}H_{21}O_2NSi$ + $H^+$ [M + H]$^+$ 288.1414; Found 288.1415.

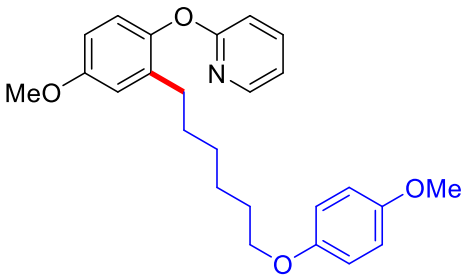



**2-(4-Methoxy-2-(3-phenylpropyl)phenoxy)pyridine (3an):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.040 g, 0.204 mmol) (3-chloropropyl)benzene (**2n**; 0.077 g, 0.50 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3an** (0.050 g, 80%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 5.6, 1.9 Hz, 1H, Ar–H), 7.65-7.60 (m, 1H, Ar–H), 7.22 (vt, $J$ = 7.5 Hz, 2H, Ar–H), 7.16 (d, $J$ = 7.3 Hz, 1H, Ar–H), 7.12-7.08 (m, 2H, Ar–H), 6.89 (d, $J$ = 8.6 Hz, 1H, Ar–H), 6.94-6.91 (m, 2H, Ar–H), 6.81-6.77 (m, 2H, Ar–H), 3.79 (s, 3H, $CH_3$), 2.61-2.52 (m, 4H, $CH_2$), 1.93-1.86 (m, 2H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 156.9 ($C_q$), 147.9 (CH), 145.6 ($C_q$), 142.4 ($C_q$), 139.4 (CH), 136.0 ($C_q$), 128.5 (CH), 128.4 (CH), 125.8 (CH), 123.2 (CH), 122.5 (CH), 118.0 (CH), 115.8 (CH), 114.9 (CH), 112.3 (CH), 110.7 (CH), 55.6 ($CH_3$), 35.7 ($CH_2$), 31.4 ($CH_2$), 30.3 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{21}H_{21}O_2N + H^+$ $[M + H]^+$ 320.1645; Found 320.1643.

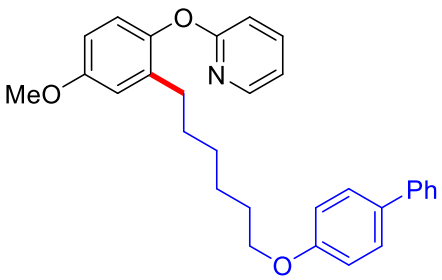



**2-(4-Methoxy-2-(6-phenoxyhexyl)phenoxy)pyridine (3ao):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 1-((6-chlorohexyl)oxy)benzene (**2o**; 0.11 g, 0.517 mmol). Purification by column chromatography on silica gel (petroleum ether/$NEt_3$: 100/1) yielded **3ao** (0.053 g, 69%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.17 (d, $J$ = 2.4 Hz, 1H, Ar–H), 7.63-7.59 (m, 1H, Ar–H), 7.28-7.24 (m, 2H, Ar–H), 6.98 (d, $J$ = 8.6 Hz, 1H, Ar–H), 6.91 (vt, $J$ = 6.4 Hz, 2H, Ar–H), 6.87 (d, $J$ = 8.6 Hz, 2H, Ar–H), 6.83-6.81 (m, 2H, Ar–H), 6.77 (dd, $J$ = 8.8, 3.1 Hz, 1H, Ar–H), 3.89 (t, $J$ = 6.5 Hz, 2H, $CH_2$), 3.79 (s, 3H, $CH_3$), 2.50 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.74-1.67 (m, 2H, $CH_2$), 1.63-1.55 (m, 2H, $CH_2$), 1.43-1.33 (m, 4H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 159.2 ($C_q$), 156.9 ($C_q$), 147.9 (CH), 145.5 ($C_q$), 139.4 (CH), 136.4 ($C_q$), 129.5 (2C, CH), 123.1 (CH), 120.6 (CH), 118.0 (CH), 115.8 (CH), 114.6

(2C, CH), 112.1 (CH), 110.6 (CH), 67.9 ($CH_2$), 55.6 ($CH_3$), 30.5 ($CH_2$), 29.9 ($CH_2$), 29.3 ($CH_2$), 29.2 ($CH_2$), 25.9 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{24}H_{27}O_3N + H^+$ $[M + H]^+$ 378.2064; Found 378.2068.

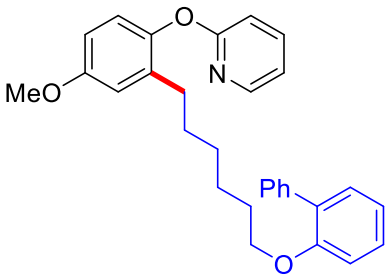



**2-(4-Methoxy-2-(6-(4-methoxyphenoxy)hexyl)phenoxy)pyridine (3ap):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 1-((6-chlorohexyl)oxy)-4-methoxybenzene (**2p**; 0.122 g, 0.50 mmol). Purification by column chromatography on silica gel (petroleum ether/$NEt_3$: 100/1) yielded **3ap** (0.047 g, 57%) as a light yellow liquid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.17 (dd, $J$ = 4.9, 1.6 Hz, 1H, Ar–H), 7.64-7.60 (m, 1H, Ar–H), 6.98 (d, $J$ = 8.6 Hz, 1H, Ar–H), 6.94-6.91 (m, 1H, Ar–H), 6.83-6.81 (m, 6H, Ar–H), 6.77 (dd, $J$ = 8.8, 3.1 Hz, 1H, Ar–H), 3.84 (t, $J$ = 6.6 Hz, 2H, $CH_2$), 3.80 (s, 3H, $CH_3$), 3.76 (s, 3H, $CH_3$), 2.50 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 1.70-1.67 (m, 2H, $CH_2$), 1.63-1.59 (m, 2H, $CH_2$), 1.42-1.32 (m, 4H, $CH_2$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.4 ($C_q$), 157.9 ($C_q$), 153.8 ($C_q$), 153.5 ($C_q$), 148.0 (CH), 145.5 ($C_q$), 139.4 (CH), 136.4 ($C_q$), 123.1 (CH), 117.9 (CH), 115.8 (CH), 115.6 (2C, CH), 114.8 (2C, CH), 112.1 (CH), 110.6 (CH), 68.1 ($CH_2$), 55.9 ($CH_3$), 55.7 ($CH_3$), 30.5 ($CH_2$), 30.0 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 26.0 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{25}H_{29}O_4N + H^+$ $[M + H]^+$ 408.2169; Found 408.2172.

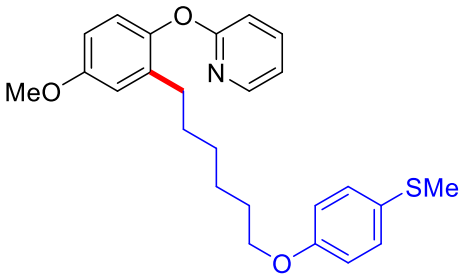



**2-(2-(6-([1,1'-Biphenyl]-4-yloxy)hexyl)-4-methoxyphenoxy)pyridine (3aq):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.081 g, 0.40 mmol) and 4-((6-chlorohexyl)oxy)-1,1'-biphenyl (**2q**; 0.290 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/$NEt_3$: 100/1) yielded **3aq** (0.12 g,

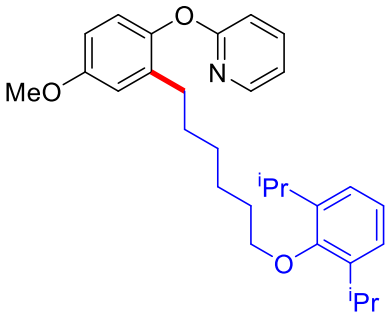
66%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.17 (s, 1H, Ar–H), 7.62 (vt, $J$ = 8.0 Hz, 1H, Ar–H), 7.56-7.50 (m, 4H, Ar–H), 7.41 (vt, $J$ = 7.5 Hz, 2H, Ar–H), 7.29 (vt, $J$ = 7.5 Hz, 1H, Ar–H), 6.99-6.93 (m, 4H, Ar–H), 6.81-6.83 (m, 2H, Ar–H), 6.77 (dd, $J$ = 8.6, 2.9 Hz, 1H, Ar–H), 3.94 (t, $J$ = 6.5 Hz, 2H, $CH_2$), 3.80 (s, 3H, $CH_3$), 2.51 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.77-1.72 (m, 2H, $CH_2$), 1.62-1.58 (m, 2H, $CH_2$), 1.44-1.33 (m, 4H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ =164.4 ($C_q$), 158.9 ($C_q$), 156.9 ($C_q$), 148.0 (CH), 145.5 ($C_q$), 141.1 ($C_q$), 139.4 (CH), 136.4 ($C_q$), 133.7 ($C_q$), 128.9 (2C, CH), 128.3 (2C, CH), 126.9 (2C, CH), 126.8 (CH), 123.1 (CH), 118.0 (CH), 115.9 (CH), 115.0 (2C, CH), 112.2 (CH), 110.6 (CH), 68.2 ($CH_2$), 55.7 ($CH_3$), 30.5 ($CH_2$), 30.0 ($CH_2$), 29.3 (2C, $CH_2$), 26.0 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{30}H_{31}O_3N + H^+$ $[M + H]^+$ 454.2377; Found 454.2369.




**2-(2-(6-([1,1'-Biphenyl]-2-yloxy)hexyl)-4-methoxyphenoxy)pyridine (3ar):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 2-((6-chlorohexyl)oxy)-1,1'-biphenyl (**2r**; 0.145 g, 0.5 mmol). Purification by column chromatography on silica gel (petroleum ether/$NEt_3$: 100/1) yielded **3ar** (0.056 g, 61%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.15 (d, $J$ = 2.0 Hz, 1H, Ar–H), 7.58 (vt, $J$ = 7.9 Hz, 1H, Ar–H), 7.52 (d, $J$ = 7.5 Hz, 2H, Ar–H), 7.37-7.25 (m, 5H, Ar–H), 7.02-6.92 (m, 3H, Ar–H), 6.88 (vt, $J$ = 6.3 Hz, 1H, Ar–H), 6.80-6.74 (m, 3H, Ar–H), 3.88 (t, $J$ = 6.1 Hz, 2H, $CH_2$), 3.79 (s, 3H, $CH_3$), 2.46 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.64-1.61 (m, 2H, $CH_2$), 1.55-1.51 (m, 2H, $CH_2$), 1.32-1.26 (m, 4H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ =164.5 ($C_q$), 156.9 ($C_q$), 156.1 ($C_q$), 148.9 (CH), 145.5 ($C_q$), 139.4 (CH), 138.8 ($C_q$), 136.4 ($C_q$), 131.1 ($C_q$), 131.0 (CH), 129.7 (2C, CH), 128.7 (CH), 127.9 (2C, CH), 126.9 (CH), 123.1 (CH), 120.9 (CH), 117.9 (CH), 115.8 (CH), 112.7 (CH), 112.1 (CH), 110.6 (CH), 68.5 ($CH_2$), 55.6 ($CH_3$), 30.5 ($CH_2$), 29.9 ($CH_2$), 29.1 (2C, $CH_2$), 25.9 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{30}H_{31}O_3N + H^+$ $[M + H]^+$ 454.2377; Found 454.2369.

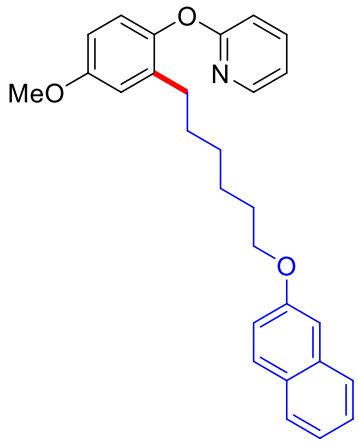



**2-(4-Methoxy-2-(6-(4-(methylthio)phenoxy)hexyl)phenoxy)pyridine (3as):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.081 g, 0.40 mmol) and (6-chlorohexyl)(p-tolyl)sulfane (**2s**; 0.260 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/$NEt_3$: 100/1) yielded **3as** (0.075 g, 44%) as a light yellow liquid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.16 (dd, $J$ = 4.9, 1.8 Hz, 1H, Ar–H), 7.63-7.59 (m, 1H, Ar–H), 7.24 (d, $J$ = 8.8 Hz, 2H, Ar–H), 6.97 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.93-6.91 (m, 1H, Ar–H), 6.82-6.80 (m, 4H, Ar–H), 6.75 (dd, $J$ = 8.8, 3.1 Hz, 1H, Ar–H), 3.86 (t, $J$ = 6.5 Hz, 2H, $CH_2$), 3.79 (s, 3H, $CH_3$), 2.50 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 2.43 (s, 3H, $CH_3$), 2.72-1.67 (m, 2H, $CH_2$), 1.62-1.57 (m, 2H, $CH_2$), 1.40-1.31 (m, 4H, $CH_2$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 157.8 ($C_q$), 156.9 ($C_q$), 147.9 (CH), 145.5 ($C_q$), 139.4 (CH), 136.3 ($C_q$), 130.3 (2C, CH), 128.6 ($C_q$), 123.0 (CH), 117.9 (CH), 115.7 (CH), 115.3 (2C, CH), 112.1 (CH), 110.5 (CH), 68.1 ($CH_2$), 55.6 ($CH_3$), 30.4 ($CH_2$), 29.9 ($CH_2$), 29.2 ($CH_2$), 29.1 ($CH_2$), 25.9 ($CH_2$), 18.2 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{25}H_{29}O_3NS + H^+$ $[M + H]^+$ 424.1941; Found 424.1938.

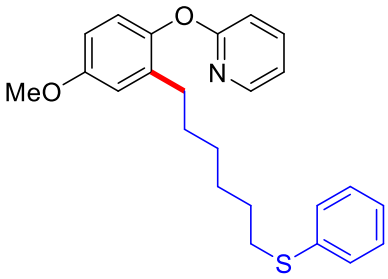



**2-(2-(6-(2,6-Diisopropylphenoxy)hexyl)-4-methoxyphenoxy)pyridine (3at):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.061 g, 0.303 mmol) and 2-((6-chlorohexyl)oxy)-1,3-diisopropylbenzene (**2t**; 0.224 g, 0.75 mmol). Purification by column chromatography on silica gel (petroleum ether/ $NEt_3$: 100/1) yielded **3at** (0.073 g, 52%) as a light yellow liquid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.19 (d, $J$ = 5.0 1.4 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 7.10-7.08 (m, 3H, Ar–H), 7.00 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.95-6.92 (m, 1H, Ar–H), 6.85-6.84 (m, 2H, Ar–H), 6.79 (dd, $J$ = 8.8, 3.0 Hz,

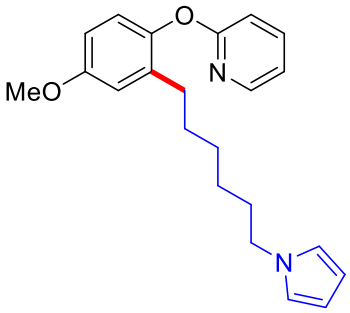
1H, Ar–H), 3.82 (s, 3H, $CH_3$), 3.69 (t, *J* = 6.6 Hz, 2H, $CH_2$), 3.33-3.26 (m, 2H, CH), 2.54 (t, *J* = 7.6 Hz, 2H, $CH_2$), 1.81-1.74 (m, 2H, $CH_2$), 1.67-1.60 (m, 2H, $CH_2$), 1.52-1.44 (m, 2H, $CH_2$) 1.42-1.36 (m, 2H, $CH_2$), 1.22 (t, *J* = 6.9 Hz, 12H, $CH_3$). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 156.9 (2C, $C_q$), 153.6 ($C_q$), 147.9 (CH), 145.5 ($C_q$), 142.0 ($C_q$), 139.4 (CH), 136.4 ($C_q$), 124.5 (2C, CH), 124.1 (CH), 123.1 (CH), 118.0 (CH), 115.8 (CH), 112.1 (CH), 110.6 (CH), 75.0 ($CH_2$), 55.6 ($CH_3$), 30.6 ($CH_2$), 30.5 ($CH_2$), 30.0 ($CH_2$), 29.5 ($CH_2$), 26.5 (2C, CH), 26.1 ($CH_2$), 24.3 (4C, $CH_3$). HRMS (ESI): *m/z* Calcd for $C_{30}H_{39}O_3N + H^+$ $[M + H]^+$ 462.3003; Found 462.2996.




**2-(4-Methoxy-2-(6-(naphthalen-2-yloxy)hexyl)phenoxy)pyridine (3au):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 2-((6-chlorohexyl)oxy)naphthalene (**2u**; 0.132 g, 0.50 mmol). Purification by column chromatography on silica gel (petroleum ether/ $NEt_3$: 100/1) yielded **3au** (0.066 g, 76%) as a light yellow liquid. $^1H$-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, *J* = 5.0, 1.4 Hz, 1H, Ar–H), 7.77-7.71 (m, 3H, Ar–H), 7.64-7.59 (m, 1H, Ar–H), 7.45-741 (m, 1H, Ar–H), 7.35-7.31 (m, 1H, Ar–H), 7.15-7.10 (m, 2H, Ar–H), 6.98 (d, *J* = 8.8 Hz, 1H, Ar–H), 6.93-6.90 (m, 1H, Ar–H), 6.84-6.82 (m, 2H, Ar–H), 6.78 (dd, *J* = 8.8, 3.1 Hz, 1H, Ar–H), 4.02 (t, *J* = 6.6 Hz, 2H, $CH_2$), 3.81 (s, 3H, $CH_3$), 2.53 (t, *J* = 7.5 Hz, 2H, $CH_2$), 1.81-1.75 (m, 2H, $CH_2$), 1.66-1.58 (m, 2H, $CH_2$), 1.49-1.43 (m, 2H, $CH_2$), 1.39-1.36 (m, 2H, $CH_2$). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 157.2 ($C_q$), 156.9 ($C_q$), 148.0 (CH), 145.5 ($C_q$), 139.4 (CH), 136.4 ($C_q$), 134.8 ($C_q$), 129.4 (CH), 129.0 ($C_q$), 127.8 (CH), 126.8 (CH), 126.4 (CH), 123.6 (CH), 123.1 (CH), 119.1 (CH), 118.0 (CH), 115.0 (CH), 112.1 (CH), 110.6 (CH), 106.7 (CH), 68.0 ($CH_2$), 55.6 ($CH_3$), 30.5 ($CH_2$), 29.9 ($CH_2$), 29.2 (2C, $CH_2$), 26.0 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{28}H_{29}O_3N + H^+$ $[M + H]^+$ 428.2220; Found 428.2227.

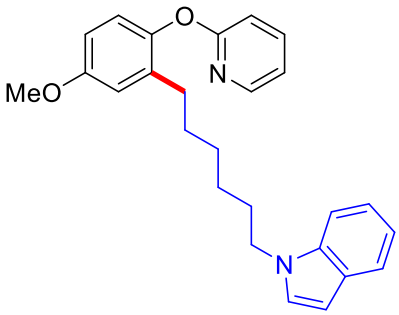



**2-(4-Methoxy-2-(6-(phenylthio)hexyl)phenoxy)pyridine (3av):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and (6-chlorohexyl)(phenyl)sulfane (**2v**; 0.115 g, 0.50 mmol). Purification by column chromatography on silica gel (petroleum ether/$NEt_3$: 100/1) yielded **3av** (0.045 g, 56%) as a light yellow liquid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 5.0, 1.6 Hz, 1H, Ar–H), 7.66-7.61 (m, 1H, Ar–H), 7.32-7.25 (m, 4H, Ar–H), 7.18-7.14 (m, 1H, Ar–H), 6.98 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.95-6.92 (m, 1H, Ar–H), 6.84-6.80 (m, 2H, Ar–H), 6.76 (dd, $J$ = 8.8, 3.1 Hz, 1H, Ar–H), 3.81 (s, 3H, $CH_3$), 2.86 (t, $J$ = 7.4 Hz, 2H, $CH_2$), 2.49 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.62-1.52 (m, 4H, $CH_2$), 1.42-1.34 (m, 2H, $CH_2$), 1.32-1.27 (m, 2H, $CH_2$). $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 156.9 ($C_q$), 148.0 (CH), 145.5 ($C_q$), 139.4 (CH), 137.2 ($C_q$), 136.2 ($C_q$), 129.0 (4C, CH), 125.8 (CH), 123.1 (CH), 118.0 (CH), 115.8 (CH), 112.0 (CH), 110.6 (CH), 55.6 ($CH_3$), 33.6 ($CH_2$), 30.4 ($CH_2$), 30.0 ($CH_2$), 29.1 ($CH_2$), 29.0 ($CH_2$), 28.7 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{24}H_{27}O_2NS + H^+$ $[M + H]^+$ 394.1835; Found 394.1847.

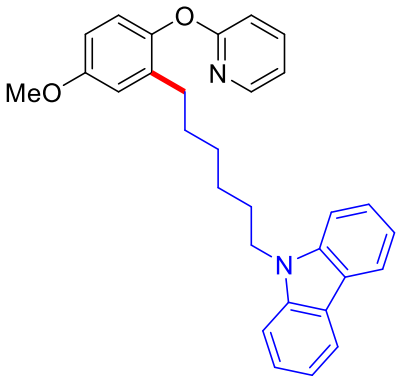



**2-(2-(6-(*1H*-Pyrrol-1-yl)hexyl)-4-methoxyphenoxy)pyridine (3aw):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.081 g, 0.40 mmol) and 1-(6-chlorohexyl)-*1H*-pyrrole (**2w**; 0.185 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/$NEt_3$: 100/1) yielded **3aw** (0.049 g, 35%) as a light yellow liquid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 4.9, 1.9 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 6.98 (d, $J$ = 8.5 Hz, 1H, Ar–H), 6.95-6.92 (m, 1H, Ar–H), 6.83-6.76 (m, 3H, Ar–H), 6.61 (t, $J$ = 2.1 Hz, 2H, Ar–H), 6.12 (t, $J$ = 2.1 Hz, 2H, Ar–H), 3.82-3.79

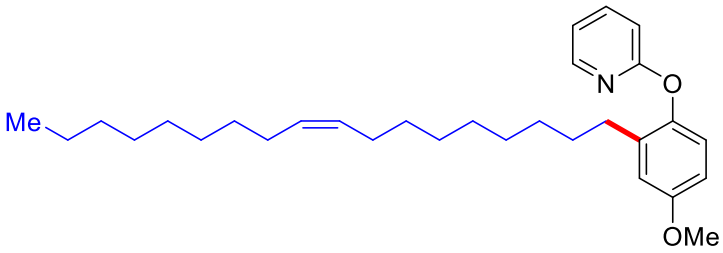
(m, 2H, $CH_2$, 3H, $CH_3$), 2.49 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.73-1.61 (m, 2H, $CH_2$), 1.58-1.52 (m, 2H, $CH_2$), 1.32-1.23 (m, 4H, $CH_2$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 156.9 ($C_q$), 148.0 (CH), 145.5 ($C_q$), 139.5 (CH), 136.3 ($C_q$), 123.1 (CH), 120.6 (CH), 118.0 (CH), 115.8 (2C, CH), 112.1 (CH), 110.6 (CH), 107.9 (2C, CH), 55.6 ($CH_3$), 49.7 ($CH_2$), 31.5 ($CH_2$), 30.4 ($CH_2$), 29.8 ($CH_2$), 29.0 ($CH_2$), 26.6 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{22}H_{26}O_2N_2 + H^+$ $[M + H]^+$ 351.2067; Found 351.2071.




**1-(6-(5-Methoxy-2-(pyridin-2-yloxy)phenyl)hexyl)-*1H*-indole (3ax):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 1-(6-chlorohexyl)-*1H*-indole (**2x**; 0.12 g, 0.508 mmol). Purification by column chromatography on silica gel (petroleum ether/$NEt_3$: 100/1) yielded **3ax** (0.031 g, 38%) as a light yellow liquid. $^1H$-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.17 (dd, $J$ = 4.9, 1.6 Hz, 1H, Ar–H), 7.64-7.58 (m, 2H, Ar–H), 7.31 (d, $J$ = 8.3 Hz, 1H, Ar–H), 7.22-7.17 (m, 1H, Ar–H), 7.12-7.08 (m, 1H, Ar–H), 7.06 (d, $J$ = 3.1 Hz, 1H, Ar–H), 6.98 (d, $J$ = 8.4 Hz, 1H, Ar–H), 6.92-6.89 (m, 1H, Ar–H), 6.80-6.76 (m, 3H, Ar–H), 6.48 (d, $J$ = 2.6 Hz, 1H, Ar–H), 4.06 (t, $J$ = 7.1 Hz, 2H, $CH_2$), 3.80 (s, 3H, $CH_3$), 2.48 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.80-1.73 (m, 2H, $CH_2$), 1.56-1.51 (m, 2H, $CH_2$), 1.31-1.29 (m, 2H, $CH_2$), 0.91-0.84 (m, 2H, $CH_2$). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 156.9 ($C_q$), 148.0 (CH), 145.5 ($C_q$), 139.5 (CH), 136.3 ($C_q$), 136.1 ($C_q$), 128.7 ($C_q$), 127.9 (CH), 123.1 (CH), 121.4 (CH), 121.1 (CH), 119.3 (CH), 118.0 (CH), 115.8 (CH), 112.0 (CH), 110.5 (CH), 109.5 (CH), 101.0 (CH), 55.7 ($CH_3$), 46.5 ($CH_2$), 30.5 ($CH_2$), 30.2 ($CH_2$), 29.8 ($CH_2$), 29.0 ($CH_2$), 26.9 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{22}H_{28}O_2N_2 + H^+$ $[M + H]^+$ 401.2229; Found 401.1499.

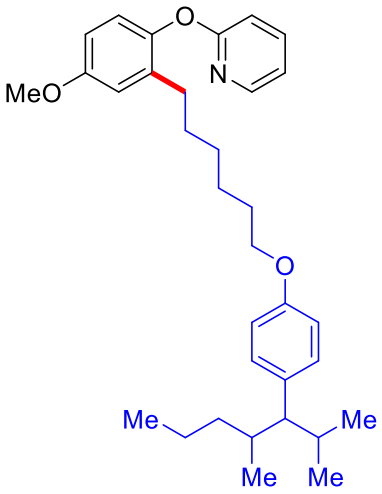



**9-(6-(5-Methoxy-2-(pyridin-2-yloxy)phenyl)hexyl)-9*H*-carbazole (3ay):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 9-(6-chlorohexyl)-9*H*-carbazole (**2y**; 0.145 g, 0.507 mmol). Purification by column chromatography on silica gel (petroleum ether/ $NEt_3$: 100/1) yielded **3ay** (0.041 g, 45%) as a light yellow liquid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.12-8.08 (m, 3H, Ar–H), 7.58-7.54 (m, 1H, Ar–H), 7.46-7.42 (m, 2H, Ar–H), 7.36 (s, 1H, Ar–H), 7.35-7.33 (m, 1H, Ar–H), 7.25-7.19 (m, 3H, Ar–H), 6.96 (d, $J$ = 8.4 Hz, 1H, Ar–H), 6.87-6.84 (m, 1H, Ar–H), 6.76 (s, 2H, Ar–H), 4.26 (t, $J$ = 7.3 Hz, 2H, $CH_2$), 3.78 (s, 3H, $CH_3$), 2.45 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 1.80-1.75 (m, 2H, $CH_2$), 1.55-1.50 (m, 2H, $CH_2$), 1.32-1.27 (m, 4H, $CH_2$). $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 156.9 ($C_q$), 148.0 (CH), 145.5 ($C_q$), 140.6 (2C, $C_q$), 139.4 (CH), 136.2 ($C_q$), 125.7 (2C, CH), 123.1 (CH), 123.0 (2C, $C_q$), 120.5 (2C, CH), 118.9 (2C, CH), 118.0 (CH), 115.8 (CH), 112.2 (CH), 110.6 (CH), 108.8 (2C, CH), 55.6 ($CH_3$), 43.2 ($CH_2$), 30.5 ($CH_2$), 29.9 ($CH_2$), 29.2 ($CH_2$), 29.0 ($CH_2$), 27.0 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{30}H_{30}O_2N_2 + H^+$ $[M + H]^+$ 451.2380; Found 451.2385.




**(*Z*)-2-(2-(Octadec-9-en-1-yl)phenoxy)pyridine (3az):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and (*Z*)-1-chlorooctadec-9-ene (**2z**; 0.144 g, 0.50 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3az** (0.053 g, 58%) as a light yellow liquid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 5.0, 2.0 Hz, 1H, Ar–H), 7.66-7.61 (m, 1H, Ar–H), 6.98 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.95-6.91 (m, 1H, Ar–H), 6.82 (vt, $J$ = 5.6 Hz, 2H,

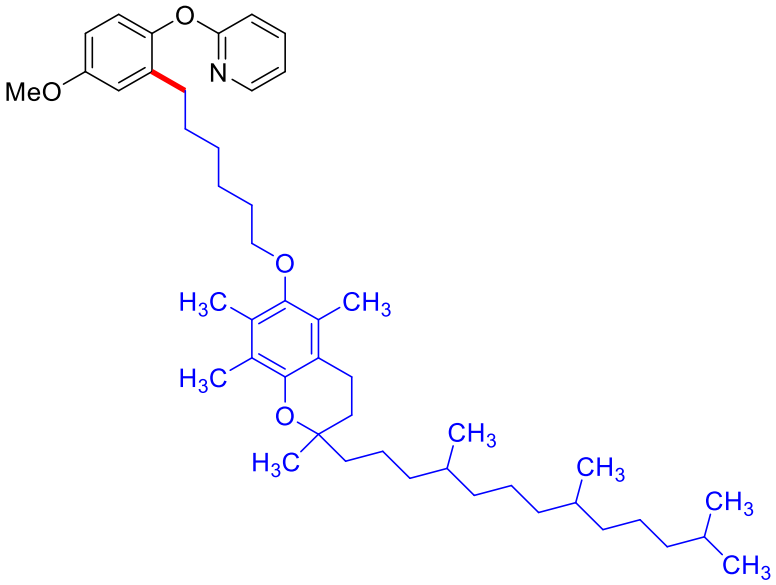
Ar–H), 6.76 (dd, *J* = 8.6, 3.0 Hz, 1H, Ar–H), 5.38-5.30 (m, 2H, CH), 3.81 (s, 3H, $CH_3$), 2.48 (t, *J* = 7.6 Hz, 2H, $CH_2$), 2.03-1.97 (m, 4H, $CH_2$), 1.57-1.51 (m, 2H, $CH_2$), 1.27-1.23 (m, 22H, $CH_2$), 0.88 (t, *J* = 6.8 Hz, 3H, $CH_3$). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.6 ($C_q$), 156.9 ($C_q$), 148.0 (CH), 145.5 ($C_q$), 139.4 (CH), 136.6 ($C_q$), 130.1 (CH), 130.0 (CH), 123.1 (CH), 117.9 (CH), 115.8 (CH), 112.0 (CH), 110.6 (CH), 55.6 ($CH_3$), 32.8 ($CH_2$), 32.1 ($CH_2$), 30.6 ($CH_2$), 30.2 ($CH_2$), 29.9 (2C, $CH_2$), 29.8 ($CH_2$), 29.7 (2C, $CH_2$), 29.6 ($CH_2$), 29.5 (3C, $CH_2$), 27.4 ($CH_2$), 22.9 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{30}H_{45}O_2N + H^+$ $[M + H]^+$ 452.3523; Found 452.3520.



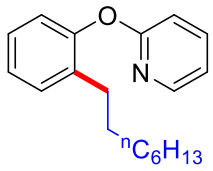

**2-(2-(6-(4-(2,4-Dimethylheptan-3-yl)phenoxy)hexyl)-4-methoxyphenoxy)pyridine (3aA):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.081 g, 0.40 mmol) and 1-((6-chlorohexyl)oxy)-4-(2,4-dimethylheptan-3-yl)benzene (**2A**; 0.338 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 50/1) yielded **3aA** (0.120 g, 60%) as a light yellow liquid. $^1H$-NMR (500 MHz, $CDCl_3$): $\delta$ 8.20 (dd, *J* = 4.8, 1.4 Hz, 1H, Ar–H), 7.64-7.60 (m, 1H, Ar–H), 7.25-7.15 (m, 2H, Ar–H), 6.99 (d, *J* = 8.6 Hz, 1H, Ar–H), 6.94-6.91 (m, 1H, Ar–H), 6.84-6.76 (m, 5H, Ar–H), 3.88 (t, *J* = 6.4 Hz, 2H, $CH_2$), 3.81 (s, 3H, $CH_3$), 2.50 (t, *J* = 7.6 Hz, 2H, $CH_2$), 1.72-1.55 (m, 6H, $CH_2$), 1.46-1.32 (m, 3H, CH, 2H, $CH_2$), 1.28 (d, *J* = 8.5 Hz, 3H, $CH_3$), 1.21 (d, *J* = 4.6 Hz, 2H, $CH_2$), 1.15-1.05 (m, 2H, $CH_2$), 0.90-0.57 (m, 9H, $3CH_3$). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): 164.5, 156.8, 148.0, 145.4, 142.6-139.3 (m), 139.4, 136.4, 127.5-127.1 (m), 123.1, 118.0, 115.8, 113.9-113.6 (m), 112.1, 110.6, 67.8, 55.6, 30.5, 29.8, 29.4, 29.3, 26.0, and multiple peaks for nonylphenol backbone. HRMS (ESI): *m/z* Calcd for $C_{33}H_{45}O_3N + H^+$ $[M + H]^+$ 504.3472; Found 504.3476.

*Note: Due to the nonylphenol backbone (which is mixture of several isomers), the $^{13}C$-NMR*

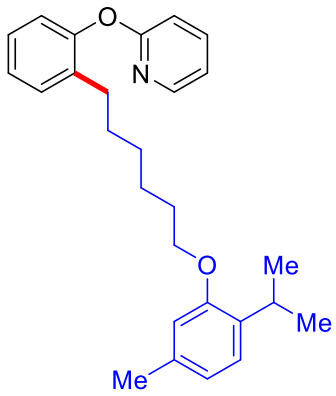
*for nonylphenol moiety show multiple peaks. Thus, we have provided only major peaks in $^{13}C$ NMR.*




**2-(4-Methoxy-2-(6-((2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl)oxy)hexyl)phenoxy)pyridine (3aB):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 6-((6-chlorohexyl)oxy)-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chromane (**2B**; 0.275 g, 0.50 mmol). Purification by column chromatography on silica gel (petroleum ether/$NEt_3$: 100/1) yielded **3aB** (0.046 g, 32%) as a light yellow liquid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (d, $J$ = 3.3 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 6.99 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.95-6.92 (m, 1H, Ar–H), 6.85-6.83 (m, 2H, Ar–H), 6.78 (dd, $J$ = 8.6, 3.0 Hz, 1H, Ar–H), 3.82 (s, 3H, $CH_3$), 3.58 (t, $J$ = 6.6 Hz, 2H, $CH_2$), 2.59-2.50 (m, 4H, $CH_2$), 2.14 (s, 3H, $CH_3$), 2.10 (s, 3H, $CH_3$), 2.08 (s, 3H, $CH_3$), 1.85-1.82 (m, 1H, CH), 1.78-1.70 (m, 4H, $CH_2$), 1.66-1.52 (m, 6H, $CH_2$), 1.48-1.33 (m, 8H, $CH_2$, 1H, CH), 1.27-1.23 (m, 8H, $CH_2$, 1H, CH), 1.15-1.07 (m, 3H, $CH_3$, 2H, $CH_2$), 0.88-0.85 (m, 12H, $CH_3$). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.5, 156.9, 148.6, 148.0, 147.8, 145.5, 139.4, 136.5, 128.0, 126.0, 123.1, 122.9, 118.0, 117.6, 115.8, 112.1, 110.6, 75.0, 73.2, 55.6, 40.3, 39.6, 37.6 (2C), 37.5, 33.0 (2C), 32.9 (2C), 31.5, 30.5, 30.4, 30.0, 29.5, 28.2, 26.2, 25.0, 24.6, 24.1, 22.9, 22.8, 21.2, 20.8, 19.9, 12.9, 12.0 (2C). HRMS (ESI): *m/z* Calcd for $C_{47}H_{71}O_4N^+$ $[M]^+$ 714.5456; Found 714.5446.

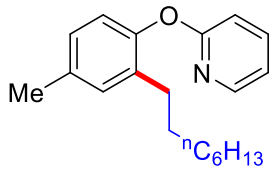



**2-(2-Octylphenoxy)pyridine (3ba):** The representative procedure was followed, using 2-phenoxypyridine (**1b**; 0.035 g, 0.204 mmol) and 1-chlorooctane (**2a**; 0.075 g, 0.504 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3ba** (0.038 g, 66%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (ddd, *J* = 5.0, 2.0, 0.63 Hz, 1H, Ar–H), 7.67-7.63 (m, 1H, Ar–H), 7.28 (dd, *J* = 7.4, 1.5 Hz, 1H, Ar–H), 7.22 (td, *J* = 7.5, 1.9 Hz, 1H, Ar–H), 7.15 (td, *J* = 7.4, 1.4 Hz, 1H, Ar–H), 7.04 (dd, *J* = 7.9, 1.3 Hz, 1H, Ar–H), 6.96-6.93 (m, 1H, Ar–H), 6.84 (d, *J* = 8.4 Hz, 1H, Ar–H), 2.54 (t, *J* = 7.6 Hz, 2H, $CH_2$), 1.58-1.52 (m, 2H, $CH_2$), 1.28-1.21 (m, 10H, $CH_2$), 0.86 (t, *J* = 6.9 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.2 ($C_q$), 152.1 ($C_q$), 148.0 (CH), 139.5 (CH), 135.4 ($C_q$), 130.7 (CH), 127.2 (CH), 125.3 (CH), 122.1 (CH), 118.2 (CH), 110.9 (CH), 32.03 ($CH_2$) 30.4 ($CH_2$), 30.1 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$) 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{19}H_{25}ON + H^+$ $[M + H]^+$ 284.2009; Found 284.2023.

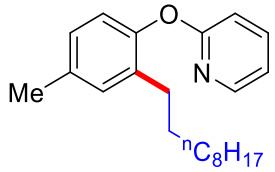



**2-(2-(6-(2-Isopropyl-5-methylphenoxy)hexyl)phenoxy)pyridine (3bC):** The representative procedure was followed, using 2-phenoxypyridine (**1b**; 0.035 g, 0.204 mmol) and 2-((6-chlorohexyl)oxy)-1-isopropyl-4-methylbenzene (**2C**; 0.135 g, 0.503 mmol). Purification by column chromatography on silica gel (petroleum ether/$NEt_3$: 100/1) yielded **3bC** (0.031 g, 38%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.19 (dd, *J* = 4.9, 1.9 Hz, 1H, Ar–H), 7.67-7.62 (m, 1H, Ar–H), 7.30 (dd, *J* = 7.5, 1.6 Hz, 1H, Ar–H), 7.24 (dd, *J* = 7.8, 1.9 Hz, 1H, Ar–H), 7.18-7.14 (m, 1H, Ar–H), 7.08 (d, *J* = 7.6 Hz, 1H, Ar–H), 7.05 (dd, *J* = 7.9, 1.3 Hz, 1H, Ar–H), 6.97-6.93 (m, 1H, Ar–H), 6.85 (d, *J* = 8.3 Hz, 1H, Ar–H), 6.72 (d, *J* = 7.6 Hz, 1H, Ar–H), 6.93 (s, 1H, Ar–H), 3.89 (t, *J* = 6.4 Hz, 2H, $CH_2$), 3.30-3.25 (m, 1H, CH), 2.85 (t, *J* = 7.6 Hz, 2H, $CH_2$), 2.31 (s, 3H, $CH_3$), 1.77-1.70 (m, 2H, $CH_2$), 1.65-1.58 (m, 2H,

$CH_2$), 1.49-1.42 (m, 2H, $CH_2$), 1.40-1.34 (m, 2H, $CH_2$), 1.19 (d, $J$ = 6.9 Hz, 6H, $CH_3$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.2 ($C_q$), 156.3 ($C_q$), 152.2 ($C_q$), 148.0 (CH), 139.5 (CH), 136.4 ($C_q$), 135.2 ($C_q$), 134.2 ($C_q$), 130.7 (CH), 127.3 (CH), 126.0 (CH), 125.3 (CH), 122.2 (CH), 121.0 (CH), 118.2 (CH), 112.3 (CH), 110.9 (CH), 67.9 ($CH_2$), 30.3 ($CH_2$), 30.1 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 26.8 (CH), 26.1 ($CH_2$), 22.9 (2C, $CH_3$), 21.5 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{27}H_{33}O_2N + H^+$ $[M + H]^+$ 404.2584; Found 404.2585.

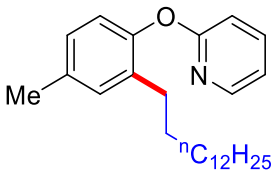



**2-(4-Methyl-2-octylphenoxy)pyridine (3ca):** The representative procedure was followed, using 2-(4-methylphenoxy)pyridine (**1c**; 0.038 g, 0.205 mmol) and 1-chlorooctane (**2a**; 0.075 g, 0.504 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 50/1) yielded **3ca** (0.043 g, 71%) as a light yellow liquid. $^1H$-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 4.9, 1.4 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 7.08 (s, 1H, Ar–H), 7.03 (dd, $J$ = 8.1, 1.8 Hz, 1H, Ar–H), 6.95-6.92 (m, 2H, Ar–H), 6.84 (d, $J$ = 8.3 Hz, 1H, Ar–H), 2.48 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 2.34 (s, $CH_3$), 1.57-1.52 (m, 2H, $CH_2$), 1.28-1.21 (m, 10H, $CH_2$), 0.86 (t, $J$ = 6.9 Hz, 3H, $CH_3$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.4 ($C_q$), 149.7 ($C_q$), 148.0 (CH), 139.4 (CH), 135.1 ($C_q$), 134.8 ($C_q$), 131.3 (CH), 127.8 (CH), 122.0 (CH), 118.0 (CH), 110.7 (CH), 32.0 ($CH_2$), 30.3 ($CH_2$), 30.2 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 22.8 ($CH_2$), 21.2 ($CH_3$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{20}H_{27}ON + H^+$ $[M + H]^+$ 298.2165; Found 298.2164.

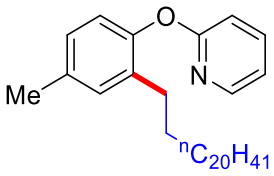



**2-(2-Decyl-4-methylphenoxy)pyridine (3ch):** The representative procedure was followed, using 2-(4-methylphenoxy)pyridine (**1c**; 0.074 g, 0.40 mmol) and 1-chlorodecane (**2h**; 0.18 g, 1.0 mmol) and the reaction mixture was stirred at 140 $^oC$. Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3ch** (0.073 g, 56%) as a light yellow liquid. $^1H$-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 4.5, 1.5 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 7.08 (s, 1H, Ar–H), 7.03 (dd, $J$ = 8.1, 2.0 Hz, 1H, Ar–H), 6.95-6.92 (m, 2H, Ar–H), 6.83 (d, $J$ = 8.3 Hz, 1H, Ar–H), 2.48 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 2.34 (s, 3H,

$CH_3$), 1.58-1.50 (m, 2H, $CH_2$), 1.26-1.21 (m, 14H, $CH_2$), 0.88 (t, $J$ = 6.9 Hz, 3H, $CH_3$). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.4 ($C_q$), 149.7 ($C_q$), 148.0 (CH), 139.4 (CH), 135.1 ($C_q$), 134.8 ($C_q$), 131.3 (CH), 127.8 (CH), 122.0 (CH), 118.0 (CH), 110.8 (CH), 32.1 ($CH_2$), 30.4 ($CH_2$), 30.2 ($CH_2$), 29.8 ($CH_2$), 29.7 (2C, $CH_2$), 25.6 ($CH_2$), 25.5 ($CH_2$), 22.3 ($CH_2$), 21.2 ($CH_3$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{22}H_{31}ON + H^+$ $[M + H]^+$ 326.2478; Found 326.2473.

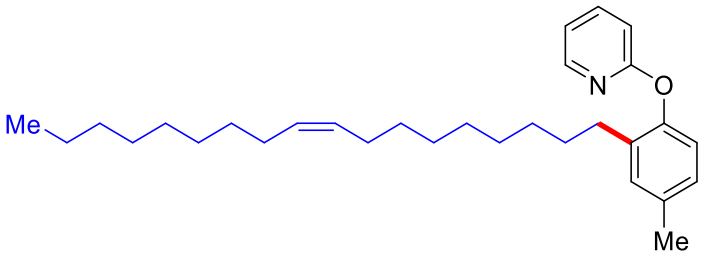



**2-(4-Methyl-2-tetradecylphenoxy)pyridine (3cj):** The representative procedure was followed, using 2-(4-methylphenoxy)pyridine (**1c**; 0.074 g, 0.40 mmol) and 1-chlorotetradecane (**2j**; 0.23 g, 1.0 mmol) and the reaction mixture was stirred at 140 °C. Purification by column chromatography on silica gel (petroleum ether/EtOAc: 50/1) yielded **3cj** (0.092 g, 60%) as a light yellow liquid. $^1H$-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 4.9, 1.6 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 7.08 (s, 1H, Ar–H), 7.03 (dd, $J$ = 8.1, 1.9 Hz, 1H, Ar–H), 6.95-6.92 (m, 2H, Ar–H), 6.83 (d, $J$ = 8.4 Hz, 1H, Ar–H), 2.48 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 2.34 (s, 3H, $CH_3$), 1.57-1.50 (m, 2H, $CH_2$), 1.26-1.21 (m, 22H, $CH_2$), 0.88 (t, $J$ = 6.6 Hz, 3H, $CH_3$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.4 ($C_q$), 149.7 ($C_q$), 148.0 (CH), 139.4 (CH), 135.1 ($C_q$), 134.8 ($C_q$), 131.3 (CH), 127.8 (CH), 122.0 (CH), 118.0 (CH), 110.8 (CH), 32.1 ($CH_2$), 30.4 ($CH_2$), 30.2 ($CH_2$), 29.9 (4C, $CH_2$), 29.8 ($CH_2$), 29.7 (2C, $CH_2$), 29.6 (2C, $CH_2$), 22.8 ($CH_2$), 21.1 ($CH_3$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{26}H_{39}ON + H^+$ $[M + H]^+$ 382.3104; Found 382.3090.

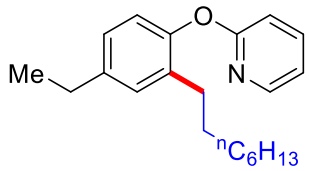



**2-(2-Docosyl-4-methylphenoxy)pyridine (3ck):** The representative procedure was followed, using 2-(4-methylphenoxy)pyridine (**1c**; 0.074 g, 0.40 mmol) and 1-chlorodocosane (**2k**; 0.345 g, 1.0 mmol) and the reaction mixture was stirred at 140 °C. Purification by column chromatography on silica gel (petroleum ether/EtOAc: 50/1) yielded **3ck** (0.13 g, 66%) as a light yellow liquid. $^1H$-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (d, $J$ = 4.8 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 7.09 (s, 1H, Ar–H), 7.04 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.93 (vt, $J$ = 7.6 Hz,

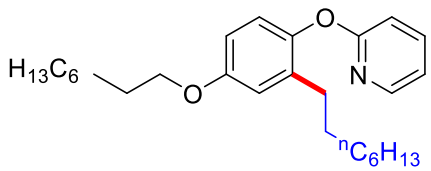
2H, Ar–H), 6.85 (d, *J* = 8.8 Hz, 1H, Ar–H), 2.49 (t, *J* = 8.1 Hz, 2H, $CH_2$), 2.35 (s, 3H, $CH_3$), 1.57-1.53 (m, 2H, $CH_2$), 1.27-1.22 (m, 38H, $CH_2$), 0.90 (t, *J* = 5.5 Hz, 3H, $CH_3$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.4 ($C_q$), 149.7 ($C_q$), 148.0 (CH), 139.3 (CH), 135.1 ($C_q$), 134.8 ($C_q$), 131.3 (CH), 127.8 (CH), 122.0 (CH), 117.9 (CH), 110.7 (CH), 32.1 ($CH_2$), 30.4 ($CH_2$), 30.2 ($CH_2$), 29.9 (15C, $CH_2$), 29.7 (2C, $CH_2$), 29.6 ($CH_2$), 21.2 ($CH_3$), 14.3 ($CH_3$). GC-MS for $C_{34}H_{55}NO$, 493.5 [$M^+$]. Due to the insolubility of **3ck** in acetonitrile and methanol, we could not get suitable HRMS data for this compound, therefore, we have provided GC-MS data.



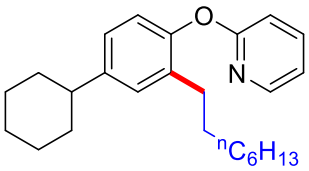

**(*Z*)-2-(4-Methyl-2-(octadec-9-en-1-yl)phenoxy)pyridine (3cz):** The representative procedure was followed, using 2-(4-methylphenoxy)pyridine (**1c**; 0.074 g, 0.40 mmol) and (*Z*)-1-chlorooctadec-9-ene (**2z**; 0.287 g, 1.0 mmol) and the reaction mixture was stirred at 140 $^oC$. Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3cz** (0.078 g, 45%) as a light yellow liquid. $^1H$-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, *J* = 5.0, 1.4 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 7.09 (s, 1H, Ar–H), 7.04 (dd, *J* = 8.1, 1.8 Hz, 1H, Ar–H), 6.95-6.92 (m, 2H, Ar–H), 6.84 (d, *J* = 8.3 Hz, 1H, Ar–H), 5.40-5.34 (m, 2H, CH), 2.50 (t, *J* = 7.6 Hz, 2H, $CH_2$), 2.35 (s, 3H, $CH_3$), 2.03-1.98 (m, 4H, $CH_2$), 1. 57-1.52 (m, 2H, $CH_2$), 1.31-1.24 (m, 22H, $CH_2$), 0.89 (t, *J* = 6.6 Hz, 3H, $CH_3$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.4 ($C_q$), 149.7 ($C_q$), 148.0 (CH), 139.4 (CH), 135.1 ($C_q$), 134.7 ($C_q$), 131.3 (CH), 130.1 (CH), 130.0 (CH), 127.8 (CH), 122.0 (CH), 117.9 (CH), 110.7 (CH), 32.1 ($CH_2$), 30.3 ($CH_2$), 30.2 ($CH_2$), 29.9 (2C, $CH_2$), 29.8 ($CH_2$), 29.7 ($CH_2$), 29.6 (2C, $CH_2$), 29.5 (4C, $CH_2$), 27.4 ($CH_2$), 22.9 ($CH_2$), 21.1 ($CH_3$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{30}H_{45}ON + H^+$ $[M + H]^+$ 436.3574; Found 436.3566.



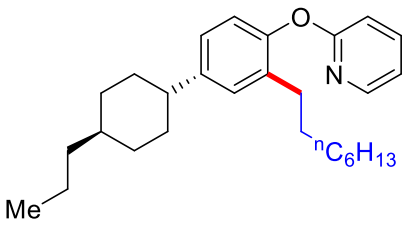

**2-(4-Ethyl-2-octylphenoxy)pyridine (3da):** The representative procedure was followed, using 2-(4-ethylphenoxy)pyridine (**1d**; 0.040 g, 0.201 mmol) and 1-chlorooctane (**2a**; 0.075 g, 0.504 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 50/1) yielded **3da** (0.042 g, 67%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 4.8, 1.5 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 7.10 (s, 1H, Ar–H), 7.06 (dd, $J$ = 8.1, 1.8 Hz, 1H, Ar–H), 6.97-6.92 (m, 2H, Ar–H), 6.83 (d, $J$ = 8.3 Hz, 1H, Ar–H), 2.64 (q, $J$ = 7.6 Hz, 2H, $CH_2$), 2.50 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.58-1.51 (m, 2H, $CH_2$), 1.27-1.21 (m, 10H, $CH_2$, 3H, $CH_3$), 0.86 (t, $J$ = 6.6 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.8 ($C_q$), 149.8 ($C_q$), 148.0 (CH), 141.0 ($C_q$), 139.4 (CH), 135.1 ($C_q$), 130.1 (CH), 126.5 (CH), 121.9 (CH), 118.0 (CH), 110.1 (CH), 32.0 ($CH_2$), 30.4 ($CH_2$), 30.1 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 28.5 ($CH_2$) 22.8 ($CH_2$), 15.9 ($CH_3$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{21}H_{29}ON + H^+$ $[M + H]^+$ 312.2322; Found 312.2324.




**2-(2-Octyl-4-(octyloxy)phenoxy)pyridine(3ea):** The representative procedure was followed, using 2-(4-(octyloxy)phenoxy)pyridine (**1e**; 0.120 g, 0.40 mmol) and 1-chlorooctane (**2a**; 0.150 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 50/1) yielded **3ea** (0.087 g, 53%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (d, $J$ = 4.8, 1H, Ar–H), 7.63 (vt, $J$ = 7.3 Hz, 1H, Ar–H), 6.97-6.91 (m, 2H, Ar–H), 6.82-6.80 (m, 2H, Ar–H), 6.75 (dd, $J$ = 8.8, 2.4 Hz, 1H, Ar–H), 3.94 (t, $J$ = 6.4 Hz, 2H, $CH_2$), 2.47 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.80-1.74 (m, 2H, $CH_2$), 1.56-1.50 (m, 2H, $CH_2$), 1.48-1.43 (m, 2H, $CH_2$), 1.34-1.21 (m, 18H, $CH_2$), 0.94-0.84 (m, 6H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.6 ($C_q$), 156.5 ($C_q$), 148.0 (CH), 145.3 ($C_q$), 139.3 (CH), 136.5 ($C_q$), 123.0 (CH), 117.9 (CH), 116.4 (CH), 112.6 (CH), 110.5 (CH), 68.4 ($CH_2$), 32.0 (2C, $CH_2$), 30.6 ($CH_2$), 30.0 ($CH_2$), 29.6 (3C, $CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 26.3 ($CH_2$), 22.9 ($CH_2$), 22.8 ($CH_2$), 14.3 (2C, $CH_3$). HRMS (ESI): *m/z* Calcd for $C_{27}H_{41}O_2N + H^+$ $[M + H]^+$ 412.3210; Found 412.3195.

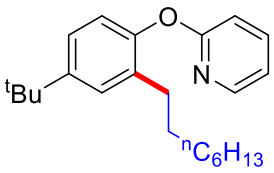



**2-(4-Cyclohexyl-2-octylphenoxy)pyridine (3fa):** The representative procedure was followed, using 2-(4-cyclohexylphenoxy)pyridine (**1f**; 0.051 g, 0.201 mmol) and 1-chlorooctane (**2a**; 0.075 g, 0.504 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 50/1) yielded **3fa** (0.042 g, 57%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.19 (dd, $J$ = 4.9, 1.5 Hz, 1H, Ar–H), 7.66-7.61 (m, 1H, Ar–H), 7.10 (d, $J$ = 2.1 Hz, 1H, Ar–H), 7.05 (d, $J$ = 8.3, 2.1 Hz, 1H, Ar–H), 6.96-6.92 (m, 2H, Ar–H), 6.81 (d, $J$ = 8.4, 1H, Ar–H), 2.51 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.92-1.84 (m, 4H, $CH_2$), 1.77-1.73 (m, 1H, CH), 1.56-1.51 (m, 2H, $CH_2$), 1.44-1.38 (m, 4H, $CH_2$), 1.28-1.21 (m, 12H, $CH_2$), 0.86 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.4 ($C_q$), 150.0 ($C_q$), 148.1 (CH), 144.8 ($C_q$), 139.4 (CH), 134.8 ($C_q$), 129.1 (CH), 125.4 (CH), 121.7 (CH), 118.0 (CH), 110.8 (CH), 44.2 (CH), 34.8 (2C, $CH_2$), 32.0 ($CH_2$), 30.6 ($CH_2$), 30.3 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 27.1 (2C, $CH_2$), 26.4 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{25}H_{35}ON + H^+$ $[M + H]^+$ 366.2791; Found 366.2787.

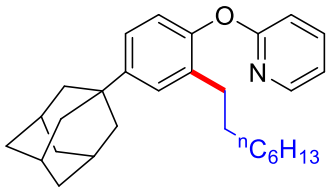



**2-(2-Octyl-4-((1r,4s)-4-propylcyclohexyl)phenoxy)pyridine (3ga):** The representative procedure was followed, using 2-(4-((1s,4r)-4-propylcyclohexyl)phenoxy)pyridine (**1g**; 0.12 g, 0.406 mmol) and 1-chlorooctane (**2a**; 0.15 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 50/1) yielded **3ga** (0.072 g, 44%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.20 (dd, $J$ = 5.0, 1.5 Hz, 1H, Ar–H), 7.66-7.61 (m, 1H, Ar–H), 7.11 (d, $J$ = 2.1 Hz, 1H, Ar–H), 6.93 (dd, $J$ = 8.3, 2.1 Hz, 1H, Ar–H), 6.97-6.92 (m, 2H, Ar–H), 6.82 (d, $J$ = 8.4 Hz, 1H, Ar–H), 2.52 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 2.47-2.43 (m, 1H, CH), 1.95-1.86 (m, 4H, $CH_2$), 1.58-1.54 (m, 2H, $CH_2$), 1.47 (dd, $J$ = 12.8, 2.9 Hz, 2H, $CH_2$), 1.41-1.31 (m, 4H, $CH_2$, 1H, CH), 1.29-1.22 (m, 10H, $CH_2$), 1.11-1.01 (m, 2H, $CH_2$), 0.93-0.85 (m, 6H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.4 ($C_q$), 150.0 ($C_q$), 148.0 (CH), 144.6 ($C_q$), 139.4 (CH), 134.8 ($C_q$), 129.1 (CH), 125.4 (CH), 121.7 (CH), 118.0 (CH), 110.8 (CH), 44.3 (CH), 39.9 ($CH_2$), 37.2 (CH), 34.6 (2C, $CH_2$), 33.8 (2C, $CH_2$),

32.0 ($CH_2$), 30.5 ($CH_2$), 30.3 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 22.8 ($CH_2$), 20.2 ($CH_2$), 14.6 ($CH_3$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{28}H_{41}ON + H^+$ $[M + H]^+$ 408.3261; Found 408.3257.

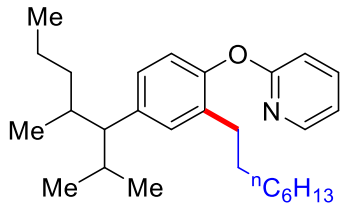



**2-(4-(*tert*-Butyl)-2-octylphenoxy)pyridine (3ha):** The representative procedure was followed, using 2-(4-(*tert*-butyl)phenoxy)pyridine (**1h**; 0.046 g, 0.202 mmol) and 1-chlorooctane (**2a**; 0.075 g, 0.504 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3ha** (0.038 g, 55%) as a light yellow liquid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.20 (dd, *J* = 4.9, 1.4 Hz, 1H, Ar–H), 7.65-7.61 (m, 1H, Ar–H), 7.26 (d, *J* = 2.4 Hz, 1H, Ar–H), 7.23 (dd, *J* = 8.4, 2.5 Hz, 1H, Ar–H), 6.97-6.92 (m, 2H, Ar–H), 6.82 (d, *J* = 8.4 Hz, 1H, Ar–H), 2.53 (t, *J* = 7.6 Hz, 2H, $CH_2$), 1.57-1.52 (m, 2H, $CH_2$), 1.33 (s, 9H, $CH_3$), 1.26-1.21 (m, 10H, $CH_2$), 0.86 (t, *J* = 6.6 Hz, 3H, $CH_3$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.4 ($C_q$), 149.7 ($C_q$), 148.0 (CH), 147.7 ($C_q$), 139.4 (CH), 134.4 ($C_q$), 127.7 (CH), 124.1 (CH), 121.3 (CH), 118.0 (CH), 110.8 (CH), 34.5 ($C_q$), 32.0 ($CH_2$), 31.7 (3C, $CH_3$), 30.8 ($CH_2$), 30.4 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$) 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{23}H_{33}ON + H^+$ $[M + H]^+$ 340.2635; Found 340.2635.



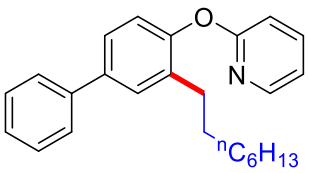

**2-(4-((*3r,5r,7r*)-Adamantan-1-yl)-2-octylphenoxy)pyridine (3ia):** The representative procedure was followed, using 2-(4-((*3r,5r,7r*)-adamantan-1-yl)phenoxy)pyridine (**1i**; 0.122 g, 0.40 mmol) and 1-chlorooctane (**2a**; 0.150 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3ia** (0.070 g, 42%) as a light yellow liquid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.20 (dd, *J* = 5.0, 1.5 Hz 1H, Ar–H), 7.65-7.61 (m, 1H, Ar–H), 7.24 (d, *J* = 2.4 Hz, 1H, Ar–H), 7.20 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar–H), 6.97 (d, *J* = 8.4 Hz, 1H, Ar–H), 6.94-6.92 (m, 1H, Ar–H), 6.81 (d, *J* = 8.3 Hz, 1H, Ar–H), 2.53 (t, *J* = 7.8 Hz, 2H, $CH_2$), 2.10 (s, 3H, CH), 1.93 (d, *J* = 2.5 Hz, 6H, $CH_2$), 1.81-1.73 (m, 6H, $CH_2$), 1.59-1.51 (m, 2H, $CH_2$), 1.28-1.21 (m, 10H, $CH_2$), 0.86 (t, *J* = 6.8 Hz, 3H, $CH_3$).

$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.4 ($C_q$), 149.8 ($C_q$), 148.1 (CH), 145.3 ($C_q$), 139.4 (CH), 134.4 ($C_q$), 127.3 (CH), 123.7 (CH), 121.3 (CH), 118.0 (CH), 110.8 (CH), 43.5 (3C, $CH_2$), 37.0 (3C, $CH_2$), 36.1 ($C_q$), 32.0 ($CH_2$), 30.8 ($CH_2$), 30.4 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.2 (3C, CH), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{29}H_{39}ON$ + $H^+$ $[M + H]^+$ 418.3104; Found 418.3086.



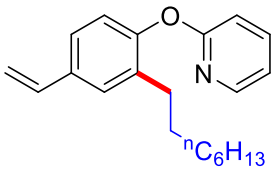

**2-(4-(2,4-Dimethylheptan-3-yl)-2-octylphenoxy)pyridine (3ja):** The representative procedure was followed, using 2-(4-(2,4-dimethylheptan-3-yl)phenoxy)pyridine (**1j**; 0.120 g, 0.403 mmol) and 1-chlorooctane (**2a**; 0.150 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 50/1) yielded **3ja** (0.062 g, 38%) as a light yellow liquid. $^{1}H$-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.20 (s, 1H, Ar–H), 7.65-7.60 (m, 1H, Ar–H), 7.23-7.10 (m, 2H, Ar–H), 6.96-6.93 (m, 2H, Ar–H), 6.80-6.70 (m, 1H, Ar–H), 2.53 (t, *J* = 7.5 Hz, 2H, $CH_2$), 1.56-1.51 (m, 2H, $CH_2$), 1.32-1.21 (m, 3H, CH, 14H, $CH_2$, 3H, $CH_3$), 0.91-0.66 (m, 12H, $4CH_3$). $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.4, 149.7-149.6 (m), 148.1-148.0 (m), 147.1 146.6, 146.4-144.5 (m), 139.4, 134.2-133.8 (m), 129.5-128.3 (m), 125.9-124.7 (m), 121.1-120.7 (m), 118.0, 110.7-110.4 (m), 32.0, 30.7, 29.6, 29.5, 29.4, 22.8, 14.3, and multiple peaks for nonylphenol backbone. HRMS (ESI): *m/z* Calcd for $C_{28}H_{43}ON$ + $H^+$ $[M + H]^+$ 410.3417; Found 410.3421.

*Note: Due to the nonylphenol backbone (which is mixture of several isomers), the $^{13}C$-NMR for nonylphenol moiety show multiple peaks. Thus, we have provided only major peaks in $^{13}C$ NMR.*

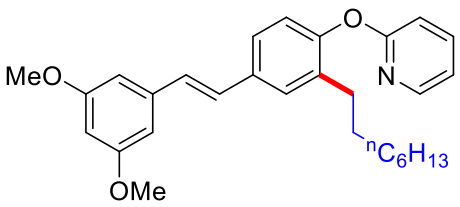



**2-((3-Octyl-[1,1'-biphenyl]-4-yl)oxy)pyridine (3ka):** The representative procedure was followed, using 2-([1,1'-biphenyl]-4-yloxy)pyridine (**1k**; 0.050 g, 0.202 mmol) and 1-chlorooctane (**2a**; 0.075 g, 0.504 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3ka** (0.053 g, 73%) as a light yellow liquid. $^{1}H$-NMR

(400 MHz, $CDCl_3$): $\delta$ = 8.22 (dd, $J$ = 5.0, 1.5 Hz, 1H, Ar–H), 7.71-7.67 (m, 1H, Ar–H), 7.61-7.59 (m, 2H, Ar–H), 7.51 (d, $J$ = 2.3 Hz, 1H, Ar–H), 7.46-7.42 (m, 3H, Ar–H), 7.33 (vt, $J$ = 7.4 Hz, 1H, Ar–H), 7.13 (d, $J$ = 8.3 Hz, 1H, Ar–H), 7.00-6.96 (m, 1H, Ar–H), 6.92 (d, $J$ = 8.3 Hz, 1H, Ar–H), 2.61 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.63-1.60 (m, 2H, $CH_2$), 1.32-1.22 (m, 10H, $CH_2$), 0.86 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.2 ($C_q$), 151.7 ($C_q$), 148.0 (CH), 141.1 ($C_q$), 139.5 (CH), 138.3 ($C_q$), 135.6 ($C_q$), 129.5 (CH), 128.9 (2C, CH), 127.3 (2C, CH), 127.2 (CH), 126.0 (CH), 122.4 (CH), 118.3 (CH), 111.1 (CH), 32.0 ($CH_2$) 30.6 ($CH_2$), 30.2 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{25}H_{29}ON + H^+$ $[M + H]^+$ 360.2322; Found 360.2322.

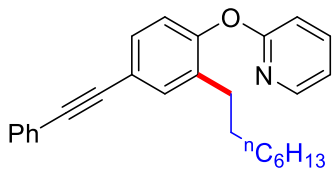



**2-(2-Octyl-4-vinylphenoxy)pyridine (3la):** The representative procedure was followed, using 2-(4-vinylphenoxy)pyridine (**1l**; 0.099 g, 0.502 mmol) and 1-chlorooctane (**2a**; 0.19 g, 1.28 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3la** (0.019 g, 12%) as a light yellow liquid. $^1H$-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 5.0, 1.3 Hz, 1H, Ar–H), 7.66-7.64 (m, 1H, Ar–H), 7.31-7.27 (m, 2H, Ar–H), 7.01 (d, $J$ = 8.3 Hz, 1H, Ar–H), 6.98-6.94 (m, 1H, Ar–H), 6.86 (d, $J$ = 8.3 Hz, 1H, Ar–H), 6.74-6.66 (m, 1H, CH), 5.71 (dd, $J$ = 17.5, 0.8 Hz, 1H, CH), 5.22 (dd, $J$ = 10.9, 0.8 Hz, 1H, CH), 2.53 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.57-1.52 (m, 2H, $CH_2$), 1.26-1.21 (m, 10H, $CH_2$), 0.86 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.2 ($C_q$), 151.8 ($C_q$), 148.1 (CH), 139.5 (CH), 136.6 (CH), 135.4 ($C_q$), 134.8 ($C_q$), 128.7 (CH), 125.0 (CH), 122.2 (CH), 118.3 (CH), 113.4 ($CH_2$), 111.0 (CH), 32.0 ($CH_2$), 30.5 ($CH_2$), 30.2 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{21}H_{27}ON + H^+$ $[M + H]^+$ 310.2165; Found 310.2173.

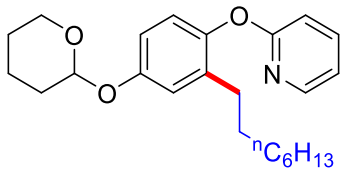



**€-2-(4-(3,5-Dimethoxystyryl)-2-octylphenoxy)pyridine (3ma):** The representative procedure was followed, using €-2-(4-(3,5-dimethoxystyryl)phenoxy)pyridine (**1m**; 0.067 g,

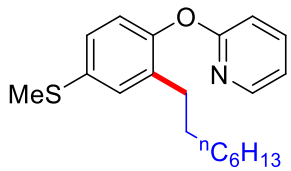
0.201 mmol) and 1-chlorooctane (**2a**; 0.075 g, 0.504 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3ma** (0.052 g, 58%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.21 (dd, $J$ = 5.0, 1.6 Hz, 1H, Ar–H), 7.69-7.65 (m, 1H, Ar–H), 7.43-7.37 (m, 2H, Ar–H), 7.06 (d, $J$ = 6.9 Hz, 1H, Ar–H), 7.03-6.96 (m, 3H, Ar–H), 6.89 (d, $J$ = 8.4 Hz, 1H, Ar–H), 6.69 (d, $J$ = 2.3 Hz, 2H, CH), 6.40 (t, $J$ = 2.3 Hz, 1H, Ar–H), 3.84 (s, 6H, $CH_3$), 2.57 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.62-1.58 (m, 2H, $CH_2$), 1.28-1.38 (m, 10H, $CH_2$), 0.87 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.1 ($C_q$), 161.1 (2C, $C_q$), 151.8 ($C_q$), 148.0 (CH), 139.7 ($C_q$), 139.5 (CH), 135.6 ($C_q$), 134.2 ($C_q$), 130.0 (CH), 128.9 (CH), 128.6 (CH), 125.3 (CH), 122.3 (CH), 118.3 (CH), 111.0 (CH), 104.6 (2C, CH), 100.1 (CH), 55.5 (2C, $CH_3$), 32.0 ($CH_2$), 30.5 ($CH_2$), 30.2 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{29}H_{35}O_3N + H^+$ $[M + H]^+$ 446.2690; Found 446.2697.



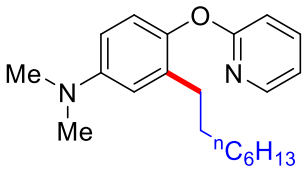

**2-(2-Octyl-4-(phenylethynyl)phenoxy)pyridine (3na):** The representative procedure was followed, using 2-(4-(phenylethynyl)phenoxy)pyridine (**1n**; 0.11 g, 0.405 mmol) and 1-chlorooctane (**2a**; 0.150 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 50/1) yielded **3na** (0.063 g, 41%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.19 (dd, $J$ = 4.8, 1.4 Hz, 1H, Ar–H), 7.71-7.67 (m, 1H, Ar–H), 7.54-7.52 (m, 2H, Ar–H), 7.48 (s, 1H, Ar–H), 7.41 (dd, $J$ = 8.3, 1.8 Hz, 1H, Ar–H), 7.37-7.33 (m, 3H, Ar–H), 7.03-6.98 (m, 2H, Ar–H), 6.89 (d, $J$ = 8.4 Hz, 1H, Ar–H), 2.55 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.60-1.56 (m, 2H, $CH_2$), 1.27-1.22 (m, 10H, $CH_2$), 0.86 (t, $J$ = 6.6 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 163.8 ($C_q$), 152.3 ($C_q$), 148.0 (CH), 139.7 (CH), 135.6 ($C_q$), 134.0 (CH), 131.8 (2C, CH), 130.6 (CH), 128.5 (2C, CH), 128.3 (CH), 123.6 ($C_q$), 122.1 (CH), 120.0 ($C_q$), 118.6 (CH), 111.2 (CH), 89.4 ($C_q$), 89.9 ($C_q$), 32.0 ($CH_2$), 30.2 ($CH_2$), 30.0 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{27}H_{29}ON + H^+$ $[M + H]^+$ 384.2322; Found 384.2321.



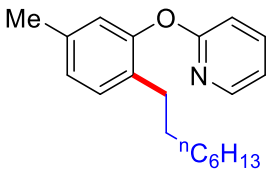
**2-(2-Octyl-4-((tetrahydro-*2H*-pyran-2-yl)oxy)phenoxy)pyridine (3oa):** The representative procedure was followed, using 2-(4-((tetrahydro-*2H*-pyran-2-yl)oxy)phenoxy)pyridine (**1o**; 0.136 g, 0.501 mmol) and 1-chlorooctane (**2a**; 0.19 g, 1.278 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3oa** (0.048 g, 25%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (d, $J$ = 2.6 Hz, 1H, Ar–H), 7.63 (t, $J$ = 8.1 Hz, 1H, Ar–H), 6.97-6.91 (m, 4H, Ar–H), 6.80 (d, $J$ = 8.4 Hz, 1H, Ar–H), 5.38 (s, 1H, CH), 3.95 (t, $J$ = 10.6 Hz, 1H, CH), 3.62 (d, $J$ = 11.3 Hz, 1H, CH), 2.48 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 2.03-1.98 (m, 1H, CH), 1.86 (s, 2H, $CH_2$), 1.67-1.63 (m, 2H, $CH_2$, 1H, CH), 1.58-1.50 (m, 2H, $CH_2$), 1.26-1.20 (m, 10H, $CH_2$), 0.88 (t, $J$ = 6.5 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 154.5 ($C_q$), 148.0 (CH), 146.3 ($C_q$), 139.4 (CH), 136.5 ($C_q$), 122.9 (CH), 118.4 (CH), 117.9 (CH), 114.8 (CH), 110.6 (CH), 97.0 (CH), 62.2 ($CH_2$), 32.0 ($CH_2$), 30.7 ($CH_2$), 30.5 ($CH_2$), 30.0 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 25.1 ($CH_2$), 22.8 ($CH_2$), 19.0 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{24}H_{33}O_3N + H^+$ $[M + H]^+$ 384.2533; Found 384.2548.



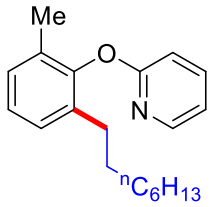
**2-(4-(Methylthio)-2-octylphenoxy)pyridine (3pa):** The representative procedure was followed, using 2-(4-(methylthio)phenoxy)pyridine (**1p**; 0.087 g, 0.40 mmol) and 1-chlorooctane (**2a**; 0.15 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3pa** (0.072 g, 55%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (s, 1H, Ar–H), 7.65 (t, $J$ = 7.3 Hz, 1H, Ar–H), 7.20 (s, 1H, Ar–H), 7.13 (d, $J$ = 8.4 Hz, 1H, Ar–H), 7.00-6.95 (m, 2H, Ar–H), 6.86 (d, $J$ = 8.3 Hz, 1H, Ar–H), 2.53-2.48 (m, 2H, $CH_2$, 3H, $CH_3$), 1.57-1.54 (m, 2H, $CH_2$), 1.26-1.22 (m, 10H, $CH_2$), 0.86 (t, $J$ = 6.4 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.1 ($C_q$), 150.0 ($C_q$), 147.9 (CH), 139.4 (CH), 136.0 ($C_q$), 134.4 ($C_q$), 129.5 (CH), 125.9 (CH), 122.7 (CH), 118.2 (CH), 110.9 (CH), 32.0 ($CH_2$), 30.4 ($CH_2$), 30.0 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 22.8 ($CH_2$), 16.8 ($CH_3$), 14.2 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{20}H_{27}ONS + H^+$ $[M + H]^+$ 330.1886; Found 330.1896.



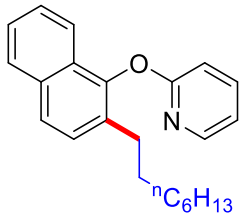

***N,N*-dimethyl-3-octyl-4-(103yridine-2-yloxy)aniline (3qa):** The representative procedure was followed, using *N,N*-dimethyl-4-(103yridine-2-yloxy)aniline (**1q**; 0.065 g, 0.303 mmol) and 1-chlorooctane (**2a**; 0.112 g, 0.753 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3qa** (0.041 g, 41%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 4.9, 1.9 Hz, 1H, Ar–H), 7.63-7.58 (m, 1H, Ar–H), 6.94-6.89 (m, 2H, Ar–H), 6.78 (d, $J$ = 8.3 Hz, 1H, Ar–H), 6.64-6.60 (m, 2H, Ar–H), 2.94 (s, 6H, $CH_3$), 2.47 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.58-1.50 (m, 2H, $CH_2$), 1.26-1.21 (m, 10H, $CH_2$), 0.85 (t, $J$ = 6.9 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 165.0 ($C_q$), 148.5 ($C_q$), 148.0 (CH), 143.1 ($C_q$), 139.2 (CH), 135.8 ($C_q$), 122.7 (CH), 117.7 (CH), 114.7 (CH), 111.7 (CH), 110.3 (CH), 41.3 (2C, $CH_3$), 32.0 ($CH_2$), 31.0 ($CH_2$), 30.4 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{21}H_{30}ON_2$ + $H^+$ $[M + H]^+$ 327.2431; Found 327.2431.



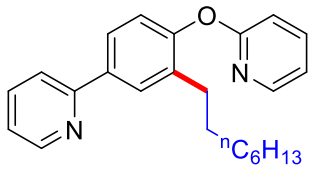

**2-(5-Methyl-2-octylphenoxy)pyridine (3ra):** The representative procedure was followed, using 2-(m-tolyloxy)pyridine (**1r**; 0.074 g, 0.40 mmol) and 1-chlorooctane (**2a**; 0.15 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3ra** (0.035 g, 29%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (s, 1H, Ar–H), 7.65-7.62 (m, 1H, Ar–H), 7.16 (d, $J$ = 7.6, 1H, Ar–H), 6.97-6.92 (m, 2H, Ar–H), 6.85-6.82 (m, 2H, Ar–H), 2.48 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 2.31 (s, 3H, $CH_3$), 1.56-1.48 (m, 2H, $CH_2$), 1.26-1.20 (m, 10H, $CH_2$), 0.85 (t, $J$ = 6.5 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 163.3 ($C_q$), 151.9 ($C_q$), 148.0 (CH), 139.4 (CH), 137.0 ($C_q$), 132.2 ($C_q$), 130.4 (CH), 126.2 (CH), 122.6 (CH), 118.0 (CH), 110.9 (CH), 32.0 ($CH_2$), 30.2 ($CH_2$), 30.0 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$) 22.8 ($CH_2$), 21.1 ($CH_3$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{20}H_{27}ON$ + $H^+$ $[M + H]^+$ 298.2165; Found 298.2163.



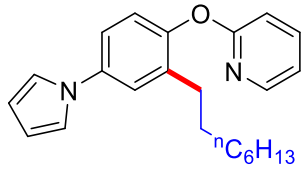

**2-(2-Methyl-6-octylphenoxy)pyridine (3sa):** The representative procedure was followed, using 2-(o-tolyloxy)pyridine (**1s**; 0.074 g, 0.40 mmol) and 1-chlorooctane (**2a**; 0.150 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3sa** (0.021 g, 18%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.16 (dd, $J$ = 5.0, 1.6 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 7.13-7.09 (m, 3H, Ar–H), 6.94-6.91 (m, 1H, Ar–H), 6.80 (d, $J$ = 8.3 Hz, 1H, Ar–H), 2.45 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 2.10 (s, 3H, $CH_3$), 1.56-1.48 (m, 2H, $CH_2$), 1.26-1.20 (m, 10H, $CH_2$), 0.86 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 163.7 ($C_q$), 150.2 ($C_q$), 148.1 (CH), 139.5 (CH), 135.9 ($C_q$), 131.5 ($C_q$), 128.9 (CH), 128.0 (CH), 125.6 (CH), 117.8 (CH), 109.9 (CH), 32.0 ($CH_2$), 30.4 ($CH_2$), 30.1 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 22.8 ($CH_2$), 16.9 ($CH_3$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{20}H_{27}ON + H^+$ $[M + H]^+$ 298.2165; Found 298.2182.




**2-((2-Octylnaphthalen-1-yl)oxy)pyridine (3ta):** The representative procedure was followed, using 2-(naphthalen-1-yloxy)pyridine (**1t**; 0.089 g, 0.402 mmol) and 1-chlorooctane (**2a**; 0.150 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 50/1) yielded **3ta** (0.034 g, 25%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.15 (dd, $J$ = 4.6, 1.5 Hz, 1H, Ar–H), 7.86-7.80 (m, 2H, Ar–H), 7.72 (d, $J$ = 8.4 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 7.44-7.37 (m, 3H, Ar–H), 6.96-6.93 (m, 1H, Ar–H), 6.82 (d, $J$ = 8.4 Hz, 1H, Ar–H), 2.66 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.66-1.58 (m, 2H, $CH_2$), 1.27-1.22 (m, 10H, $CH_2$), 0.87 (t, $J$ = 6.9 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 148.2 (CH), 146.4 ($C_q$), 139.6 (CH), 133.7 ($C_q$), 131.9 ($C_q$), 128.4 (CH), 128.2 ($C_q$), 128.0 (CH), 126.3 (CH), 125.6 (2C, CH), 122.2 (CH), 118.0 (CH), 109.9 (CH), 32.0 ($CH_2$) 30.5 ($CH_2$), 30.2 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{23}H_{27}ON + H^+$ $[M + H]^+$ 334.2165; Found 334.2162.

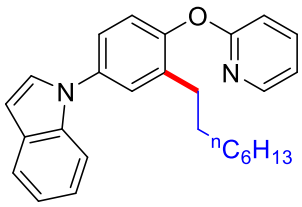


**2-(2-Octyl-4-(105yridine-2-yl)phenoxy)pyridine (3ua):** The representative procedure was followed, using 2-(4-(105yridine-2-yl)phenoxy)pyridine (**1u**; 0.075 g, 0.302 mmol) and 1-chlorooctane (**2a**; 0.112 g, 0.75 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3ua** (0.057 g, 52%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.69-8.68 (m, 1H, Ar–H), 8.21 (dd, $J$ = 5.0, 1.4 Hz, 1H, Ar–H), 7.96 (d, $J$ = 2.3 Hz, 1H, Ar–H), 7.83 (dd, $J$ = 8.4, 2.3 Hz, 1H, Ar–H), 7.74-7.72 (m, 2H, Ar–H), 7.70-7.65 (m, 1H, Ar–H), 7.22-7.19 (m, 1H, Ar–H), 7.15 (d, $J$ = 8.4 Hz, 1H, Ar–H), 7.00-6.96 (m, 1H, Ar–H), 6.90 (d, $J$ = 8.3 Hz, 1H, Ar–H), 2.63 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.67-1.59 (m, 2H, $CH_2$), 1.30-1.21 (m, 10H, $CH_2$), 0.85 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.1 ($C_q$), 157.3 ($C_q$), 153.1 ($C_q$), 149.8 (CH), 148.1 (CH), 139.6 (CH), 136.9 (CH), 136.4 ($C_q$), 135.8 ($C_q$), 129.4 (CH), 125.8 (CH), 122.3 (CH), 122.0 (CH), 120.6 (CH), 118.4 (CH), 111.1 (CH), 32.0 ($CH_2$), 30.7 ($CH_2$), 30.3 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$) 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{24}H_{28}ON_2 + H^+$ $[M + H]^+$ 361.2274; Found 361.2277.

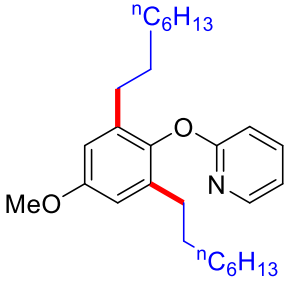


**2-(2-Octyl-4-(*1H*-pyrrol-1-yl)phenoxy)pyridine (3va):** The representative procedure was followed, using 2-(4-(*1H*-pyrrol-1-yl)phenoxy)pyridine (**1v**; 0.095 g, 0.402 mmol) and 1-chlorooctane (**2a**; 0.150 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 50/1) yielded **3va** (0.049 g, 35%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.19 (dd, $J$ = 5.0, 1.5 Hz, 1H, Ar–H), 7.70-7.66 (m, 1H, Ar–H), 7.30 (d, $J$ = 2.3 Hz, 1H, Ar–H), 7.24 (dd, $J$ = 8.5, 2.8 Hz, 1H, Ar–H), 7.09 (d, $J$ = 8.5 Hz, 1H, Ar–H), 7.05 (t, $J$ = 2.3 Hz, 2H, Ar–H), 6.98-6.95 (m, 2H, Ar–H), 6.91 (d, $J$ = 8.3 Hz, 1H, Ar–H), 6.33 (t, $J$ = 2.1 Hz, 1H, Ar–H), 2.57 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.62-1.55 (m, 2H, $CH_2$), 1.30-1.21 (m, 10H, $CH_2$), 0.86 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.0 ($C_q$), 149.8 ($C_q$), 147.9 (CH), 139.6 (CH), 138.0 ($C_q$), 136.8 ($C_q$), 123.2 (CH), 122.9 (CH), 119.8 (2C, CH), 119.5 (CH), 118.4 (CH), 111.1 (CH), 110.3 (2C, CH), 32.0 ($CH_2$), 30.5 ($CH_2$), 30.2 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS

(ESI): *m/z* Calcd for $C_{23}H_{28}ON_2 + H^+$ $[M + H]^+$ 349.2274; Found 349.2277.

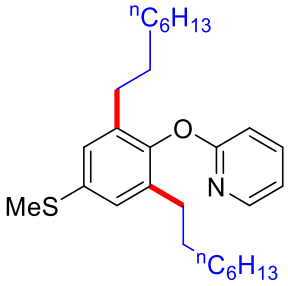



**1-(3-Octyl-4-(106yridine-2-yloxy)phenyl)-*1H*-indole (3wa):** The representative procedure was followed, using 1-(4-(106yridine-2-yloxy)phenyl)-*1H*-indole (**1w**; 0.115 g, 0.402 mmol) and 1-chlorooctane (**2a**; 0.15 g, 1.0 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3wa** (0.053 g, 33%) as a light yellow liquid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 4.9, 1.4 Hz, 1H, Ar–H), 7.71-7.67 (m, 2H, Ar–H), 7.58 (d, $J$ = 8.4 Hz, 1H, Ar–H), 7.42 (d, $J$ = 2.6 Hz, 1H, Ar–H), 7.35-7.32 (m, 2H, Ar–H), 7.24-7.14 (m, 3H, Ar–H), 7.00-6.94 (m, 2H, Ar–H), 6.67 (d, $J$ = 2.9 Hz, 1H, Ar–H), 2.62 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.63-1.58 (m, 2H, $CH_2$), 1.31-1.22 (m, 10H, $CH_2$), 0.86 (t, $J$ = 6.6 Hz, 3H, $CH_3$). $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 163.9 ($C_q$), 150.4 ($C_q$), 147.9 (CH), 139.7 (CH), 136.8 ($C_q$), 136.7 ($C_q$), 136.1 ($C_q$), 129.4 ($C_q$), 128.3 (CH), 126.4 (CH), 123.1 (CH), 123.0 (CH), 122.4 (CH), 121.2 (CH), 120.4 (CH), 118.5 (CH), 111.3 (CH), 110.7 (CH), 103.4 (CH), 32.0 ($CH_2$), 30.5 ($CH_2$), 30.0 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$) 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{27}H_{30}ON_2 + H^+$ $[M + H]^+$ 399.2431.; Found 399.2450.

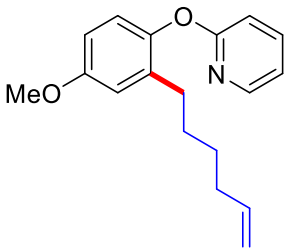



**2-(4-Methoxy-2,6-dioctylphenoxy)pyridine (3aa'):** Yield = 7%, $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.16 (ddd, $J$ = 4.9, 1.9, 0.6 Hz, 1H, Ar–H), 7.65-7.60 (m, 1H, Ar–H), 6.92-6.89 (m, 1H, Ar–H), 6.80 (d, $J$ = 8.4 Hz, 1H, Ar–H), 6.66 (s, 2H, Ar–H), 3.80 (s, 3H, $CH_3$), 2.40 (t, $J$ = 7.8 Hz, 4H, $CH_2$), 1.56-1.50 (m, 4H, $CH_2$), 1.25-1.21 (m, 20H, $CH_2$), 0.86 (t, $J$ = 6.9 Hz, 6H, $CH_3$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.2 ($C_q$), 156.8 ($C_q$), 148.1 (CH), 143.4 ($C_q$), 139.3 (CH), 136.9 (2C, $C_q$), 117.6 (CH), 112.9 (2C, CH), 109.8 (CH), 55.5 ($CH_3$), 32.0 (2C, $CH_2$), 30.8 (2C, $CH_2$), 29.9 (2C, $CH_2$), 29.7 (2C, $CH_2$), 29.5 (2C, $CH_2$) 29.3 (2C,

$CH_2$), 22.8 (2C, $CH_2$), 14.3 (2C, $CH_3$). HRMS (ESI): *m/z* Calcd for $C_{28}H_{43}O_2N$ + $H^+$ $[M + H]^+$ 426.3367; Found 426.3348.

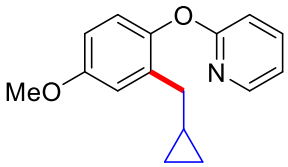



**2-(4-(Methylthio)-2,6-dioctylphenoxy)pyridine (3pa'):** Yield = 11%. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, *J* = 5.0, 1.4 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 7.02 (s, 2H, Ar–H), 6.94-6.91 (m, 1H, Ar–H), 6.81 (d, *J* = 8.3 Hz, 1H, Ar–H), 2.49 (s, $CH_3$), 2.39 (t, *J* = 7.6 Hz, 4H, $CH_2$), 1.54-1.47 (m, 4H, $CH_2$), 1.26-1.20 (m, 20H, $CH_2$), 0.86 (t, *J* = 6.9 Hz, 6H, $CH_3$). $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 163.9 ($C_q$), 148.1 (CH), 147.8 ($C_q$), 139.4 (CH), 136.6 (2C, $C_q$), 134.5 ($C_q$), 126.6 (2C, CH), 117.8 (CH), 110.0 (CH), 32.0 (2C, $CH_2$) 30.7 (2C, $CH_2$), 29.9 (2C, $CH_2$), 29.7 (2C, $CH_2$), 29.5 (2C, $CH_2$), 29.3 (2C, $CH_2$), 22.8 (2C, $CH_2$), 16.7 ($CH_3$), 14.3 (2C, $CH_3$). HRMS (ESI): *m/z* Calcd for $C_{28}H_{43}ONS$ + $H^+$ $[M + H]^+$ 442.3138; Found 442.3147.




**2-(2-(Hex-5-en-1-yl)-4-methoxyphenoxy)pyridine (3aD):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and 6-chlorohex-1-ene (**2D**; 0.060 g, 0.505 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3aD** (0.030 g, 52%) as a light yellow liquid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar–H), 7.66-7.62 (m, 1H, Ar–H), 6.98 (d, *J* = 8.8 Hz, 1H, Ar–H), 6.95-6.92 (m, 1H, Ar–H), 6.84-6.81 (m, 2H, Ar–H), 6.76 (dd, *J* = 8.6, 3.0 Hz, 1H, Ar–H), 5.77-5.69 (m, 1H, CH), 4.97-4.87 (m, 2H, $CH_2$), 3.81 (s, 3H, $CH_3$), 2.50 (t, *J* = 7.6 Hz, 2H, $CH_2$), 2.03-1.98 (m, 2H, $CH_2$), 1.62-1.54 (m, 2H, $CH_2$), 1.41-1.34 (m, 2H, $CH_2$). $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.5 ($C_q$), 156.9 ($C_q$), 148.0 (CH), 145.5 ($C_q$), 139.4 (CH), 139.0 (CH), 136.4 ($C_q$), 123.1 (CH), 117.9 (CH), 115.8 (CH), 114.5 ($CH_2$),

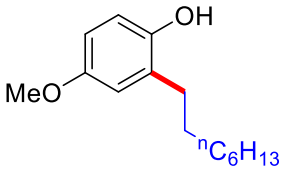
112.0 (CH), 110.6 (CH), 55.6 ($CH_3$), 33.7 ($CH_2$), 30.4 ($CH_2$), 29.5 ($CH_2$), 28.8 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{18}H_{21}O_2N + H^+$ $[M + H]^+$ 284.1645; Found 284.1646.




**2-(2-(Cyclopropylmethyl)-4-methoxyphenoxy)pyridine (3aE):** The representative procedure was followed, using 2-(4-methoxyphenoxy)pyridine (**1a**; 0.041 g, 0.204 mmol) and (chloromethyl)cyclopropane (**2E**; 0.046 g, 0.508 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3aE** (0.034 g, 65%) as a light yellow liquid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.17 (dd, $J$ = 4.8, 1.3 Hz, 1H, Ar–H), 7.66-7.61 (m, 1H, Ar–H), 7.01-6.98 (m, 2H, Ar–H), 6.94-6.91 (m, 1H, Ar–H), 6.82 (d, $J$ = 8.4 Hz, 1H, Ar–H), 6.79 (dd, $J$ = 8.8, 3.0 Hz, 1H, Ar–H), 3.82 (s, 3H, $CH_3$), 2.43 (d, $J$ = 8.8 Hz, 2H, $CH_2$), 1.00-0.95 (m, 1H, CH), 0.49-0.45 (m, 2H, $CH_2$), 0.15-0.11 (m, 2H, $CH_2$). $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.4 ($C_q$), 156.9 ($C_q$), 148.0 (CH), 145.4 ($C_q$), 139.4 (CH), 136.1 ($C_q$), 122.9 (CH), 117.9 (CH), 115.8 (CH), 112.1 (CH), 110.6 (CH), 55.6 ($CH_3$), 34.8 ($CH_2$), 10.6 (CH), 4.9 (2C, $CH_2$). HRMS (ESI): *m/z* Calcd for $C_{16}H_{17}O_2N + H^+$ $[M + H]^+$ 256.1332; Found 256.1330.

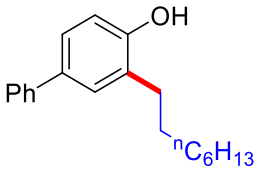
### 2.4.5 Procedure for Removal of Directing Group

**Removal of DG from Phenol (Synthesis of 4aa):** In an oven dried round bottom flask, 2-(4-methoxy-2-octylphenoxy)pyridine (**3aa**: 0.10 g, 0.319 mmol) was introduced and toluene (10 mL) was added into it. Methyl trifluoromethanesulfonate (MeOTf; 0.13 g, 0.792 mmol) was added drop wise *via* a syringe to the reaction mixture and the resultant mixture was stirred at 100 $^o$C under argon atmosphere for 2 h. The reaction mixture was cooled to ambient temperature and the solvent was evaporated under vacuum. The crude product was dissolved in dry MeOH (5 mL) and MeONa (0.14 g, 2.59 mmol) was added and the reaction mixture was heated to reflux for 30 min. At ambient temperature, the volatiles were evaporated under reduced pressure, and the crude product was extracted with EtOAc (30 mL x 3). The combined organic extract was washed with brine, dried over $Na_2SO_4$ and the volatiles were evaporated in *vacuo*. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) to yield **4aa** (0.062 g, 82%) as a light yellow liquid.




**Compound 4aa:** $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 6.70-6.61 (m, 3H, Ar–H), 4.68 (s, 1H, OH), 3.76 (s, 3H, $CH_3$), 2.57 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.61 (t, $J$ = 6.3 Hz, 2H, $CH_2$), 1.33-1.28 (m, 10H, $CH_2$), 0.89 (t, $J$ = 6.5 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 153.8 ($C_q$), 147.6 ($C_q$), 130.1 ($C_q$), 116.0 (2C, CH), 111.7 (CH), 55.9 ($CH_3$), 32.1 ($CH_2$), 30.4 ($CH_2$), 30.0 ($CH_2$), 29.7 (2C, $CH_2$), 29.4 ($CH_2$) 28.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{15}H_{24}O_2$ + $[M]^+$ 236.1771; Found 236.1767.

**Compound 4ka:**




**Procedure:** The procedure similar to the synthesis of **4aa** was followed, using 2-((3-octyl-[1,1'-biphenyl]-4-yl)oxy)pyridine (0.067 g, 0.186 mmol), methyl trifluoromethanesulfonate (MeOTf; 0.075 g, 0.457 mmol) and NaOMe (0.080 g, 1.48 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **4ka** (0.035 g, 67%) as a light yellow solid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 7.57 (d, $J$ = 8.4 Hz, 2H, Ar–H), 7.42 (vt, $J$ = 7.5 Hz, 2H, Ar–H), 7.38 (s, 1H, Ar–H), 7.34-7.29 (m, 2H, Ar–H), 6.85 (d, $J$ = 8.1 Hz, 1H, Ar–H), 4.89 (s, 1H, OH), 2.68 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 1.71-1.64 (m, 2H, $CH_2$), 1.43-1.29 (m, 10H, $CH_2$), 0.90 (t, $J$ = 6.5 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 153.8 ($C_q$), 141.3 ($C_q$), 134.1 ($C_q$), 129.2 (CH), 129.1 ($C_q$), 128.3 (2C, CH), 126.9 (2C, CH), 126.7 (CH), 125.8 (CH), 115.7 (CH), 32.1 ($CH_2$), 30.3 ($CH_2$), 30.0 ($CH_2$), 29.8 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$) 28.9 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{20}H_{26}O$ + $[M]^+$ 282.1978; Found 282.1973.

### 2.4.6 Kinetic Experiments

**Representative Procedure for Reaction Rate Determination:** To a Teflon-screw capped tube equipped with magnetic stir bar was introduced $CuBr_2$ (0.0045 g, 0.02 mmol, 0.02 M), LiHMDS (0.084 g, 0.50 mmol, 0.50 M), 2-(4-methoxyphenoxy)pyridine **1a** (0.041 g, 0.20 mmol, 0.20 M), 1-chlorooctane (0.075 g, 0.50 mmol, 0.50 M) and *n*-dodecane (0.020

mL, 0.088 mmol, 0.088 M, internal standard), and toluene (0.89 mL) was added to make the total volume to 1.0 mL. The reaction mixture was then stirred at 120 $^{o}$C in a pre-heated oil bath. At regular intervals (10, 20, 40, 60, 90, 120, 150 min), the reaction vessel was cooled to ambient temperature and an aliquot of sample was withdrawn to the GC vial. The sample was diluted with ethyl acetate and subjected to GC analysis. The concentration of the product **3aa** obtained in each sample was determined with respect to the internal standard *n*-dodecane. The final data was obtained by averaging the results of two independent experiments (Table 2.2). The data of the concentration of the product *vs* time (min) plot for the early reaction time was drawn. For the calculation of rate, the plot was fitted linear with Origin Pro 8.5, and the reaction rate was determined by the initial rate method. The slope of the linear fitting represents the reaction rate, shown in Table 2.3.

Table 2.2 Concentration of **3aa** Formed using $CuBr_2$, CuBr or Complex **5** at Different Time Intervals.

| Time (min) | Conc. of **3aa** [M] using catalyst | | |
|---|---|---|---|
| | $CuBr_2$ | CuBr | Complex **5** |
| 10 | 0.0017 | 0.0026 | 0.0022 |
| 20 | 0.0062 | 0.0095 | 0.0057 |
| 40 | 0.0107 | 0.0165 | 0.0128 |
| 60 | 0.0154 | 0.022 | 0.0195 |
| 90 | 0.0215 | 0.0295 | 0.0279 |
| 120 | 0.0264 | 0.0364 | 0.0346 |
| 150 | 0.0307 | 0.0428 | 0.0426 |

Table 2.3 Rate of Alkylation Reaction with $CuBr_2$ or CuBr or Complex (**5**).

| Copper catalyst | Amount (g) | Initial Rate [$Mmin^{-1}$] x $10^{-3}$ | $R^2$ |
|---|---|---|---|
| $CuBr_2$ | 0.0045 | 0.2024 ± 0.0119 | 0.9794 |
| CuBr | 0.0029 | 0.2737 ± 0.0181 | 0.9743 |
| Complex **5** | 0.012 | 0.2866 ± 0.00103 | 0.9922 |

**Procedure for Rate Order Determination**

The rate order of the alkylation reaction with various reaction components was

determined by the initial rate method. The data of the concentration of the product *vs* time (min) plot was fitted linear with Origin Pro 8.5. The slope of the linear fitting represents the reaction rate. The order of the reaction was then determined by plotting log(rate) *vs* log(conc) for a particular component.

**Representative Procedure**: *Rate Order Determination on 2-(4-methoxyphenoxy)pyridine **1a** (Table 2.4).* To determine the order of the alkylation reaction on 2-(4-methoxyphenoxy)pyridine (**1a**), initial rates at different initial concentrations of **1a** were determined. The final data was obtained by averaging the results of two independent experiments for the same initial concentration. In standard expriment, a Teflon-screw cap tube equipped with magnetic stir bar was introduced $CuBr_2$ (0.02 mmol, 0.02 M), LiHMDS (0.084 g, 0.5 mmol, 0.5 M), 1-chlorooctane (**2a**; 0.075 g, 0.504 mmol, 0.504 M), specific amount of 2-(4-methoxyphenoxy)pyridine (as shown in Table 2.4), *n*-dodecane (0.02 mL, 0.088 mmol, 0.088 M, internal standard), and toluene (appropriate amount) was added to make the total volume to 1.0 mL. The reaction mixture was then heated at 120 $^{o}$C in a pre-heated oil bath. At regular intervals (10, 20, 40, 60, 90, 120, 150 min), the reaction vessel was cooled to ambient temperature and an aliquot of sample was withdrawn to the GC vial. The sample was diluted with ethyl acetate and subjected to GC analysis. The concentration of the product **3aa** obtained in each sample was determined with respect to the internal standard *n*-dodecane.

Table 2.4 Rate of Alkylation Reaction at Different Initial Concentrations of 2-(4-methoxyphenoxy)pyridine (1a).

| Experiment | Amount of **1a** (g) | Initial Conc. of **1a** [M] | Initial Rate [$Mmin^{-1}$] x $10^{-3}$ | $R^2$ |
|---|---|---|---|---|
| 1 | 0.020 | 0.10 | 0.0676 ± 0.0019 | 0.9979 |
| 2 | 0.040 | 0.20 | 0.2024±0.0119 | 0.9794 |
| 3 | 0.060 | 0.30 | 0.3764 ± 0.0310 | 0.9553 |
| 4 | 0.080 | 0.40 | 0.4140 ± 0.0392 | 0.94 |

*Rate Order Determination on 1-Chlorooctane (**2a**) (Table 2.5).* To determine the order of the alkylation reaction on 1-chlorooctane, the initial rates at different initial concentrations of 1-chlorooctane were recorded. The final data was obtained by averaging the results of three independent experiments for the same initial concentration.

Representative procedure of rate order determination was followed, employing 2-(4-methoxyphenoxy)pyridine (0.20 M), LiHMDS (0.50 mmol, 0.5 M), specific amount of 1-chlorooctane (as shown in Table 2.5), *n*-dodecane (0.02 mL, 0.088 mmol, 0.088 M, internal standard), and toluene (appropriate amount) was added to make the total volume to 1.0 mL.

Table 2.5 Rate of Alkylation Reaction at Different Initial Concentrations of 1-Chlorooctane.

| Experiment | Amount of **2a** (g) | Initial Conc. of **2a** [M] | Initial Rate [$Mmin^{-1}$] x $10^{-3}$ | $R^2$ |
|---|---|---|---|---|
| 1 | 0.019 | 0.125 | 0.0788 ± 0.0023 | 0.9951 |
| 2 | 0.037 | 0.25 | 0.1444 ± 0.0061 | 0.9894 |
| 3 | 0.074 | 0.50 | 0.2024 ± 0.0119 | 0.9794 |
| 4 | 0.134 | 0.90 | 0.2763 ± 0.0190 | 0.9723 |

*Rate Order Determination on LiHMDS (Table 2.6):* To determine the order of the alkylation reaction on base, the initial rates at different concentrations of LiHMDS were recorded. The final data was obtained by averaging the results of three independent experiments for same initial concentration.

Representative procedure of rate order determination was followed, employing 2-(4-methoxyphenoxy)pyridine (0.20 M), 1-chlorooctane (0.50 M) and specific amount of LiHMDS (as shown in Table 2.6) in toluene.

Table 2.6 Rate of Alkylation Reaction at Different Concentrations of LiHMDS.

| Experiment | Amount of LiHMDS (g) | Initial Conc. of LiHMDS [M] | Initial Rate [$Mmin^{-1}$] x $10^{-3}$ | $R^2$ |
|---|---|---|---|---|
| 1 | 0.050 | 0.30 | 0.2208 ± 0.0094 | 0.9892 |
| 2 | 0.084 | 0.50 | 0.2024 ± 0.0119 | 0.9794 |
| 3 | 0.117 | 0.70 | 0.1333 ± 0.0064 | 0.9861 |
| 4 | 0.151 | 0.90 | 0.1109 ± 0.0066 | 0.9789 |

*Rate Order Determination on Catalyst (Table 2.7):* To determine the order of the alkylation reaction on catalyst, the initial rates at different concentrations of catalyst were recorded. The final data was obtained by averaging the results of two independent

experiments for same initial concentration.

Representative procedure of rate order determination was followed, employing 2-(4-methoxyphenoxy)pyridine (0.20 M), 1-chlorooctane (0.50 M), LiHMDS (0.50 M) and specific amount of $CuBr_2$ (as shown in Table 2.7) in toluene.

Table 2.7 Rate of Alkylation Reaction at Different Concentrations of $CuBr_2$.

| Experiment | Amount of $CuBr_2$(g) | Initial Conc. of $CuBr_2$ [M] | Initial Rate [$Mmin^{-1}$] x $10^{-3}$ | $R^2$ |
|---|---|---|---|---|
| 1 | 0.0011 | 0.005 | 0.0759 ± 0.0111 | 0.8837 |
| 2 | 0.0022 | 0.01 | 0.1288 ± 0.0108 | 0.9637 |
| 3 | 0.0045 | 0.02 | 0.2024 ± 0.0119 | 0.9794 |
| 4 | 0.0089 | 0.04 | 0.2228± 0.0156 | 0.9714 |

**Rate of Alkylation Reaction with Octyl Chloride and Octyl Bromide:** Representative procedure of the rate-determination experiment was followed using $CuBr_2$ (0.0045 g, 0.02 mmol, 0.02 M), LiHMDS (0.084 g, 0.5 mmol, 0.50 M), compound 2-(4-methoxyphenoxy)pyridine (0.041 g, 0.20 mmol, 0.2 M), 1-chlorooctane (0.075 g, 0.50 mmol, 0.5 M) or 1-bromooctane (0.097 g, 0.50 mmol, 0.5 M) and *n*-dodecane (0.020 mL, 0.088 mmol, 0.088 M, internal standard), and toluene. The concentration of the product **3aa** obtained in each sample was determined with respect to the internal standard *n*-dodecane (Table 2.8). The data of the concentration of the product *vs* time (min) plot was drawn and fitted linear with Origin Pro 8.5, and the rate was determined by the initial rate method (up to 150 minutes). The slope of the linear fitting represents the reaction rate.

Table 2.8 Rate of Alkylation Reaction with Octyl Chloride and Octyl Bromide.

| 1-Octyl Halides | Amount (g) | Initial Conc. of [M] | Initial Rate [$Mmin^{-1}$] x $10^{-3}$ | $R^2$ |
|---|---|---|---|---|
| 1-chlorooctane | 0.059 | 0.50 | 0.2188 ± 0.0134 | 0.9815 |
| 1-bromooctane | 0.097 | 0.50 | 0.5179 ± 0.0573 | 0.9416 |

### 2.4.7 Procedure for EPR Analysis

To a flame-dried screw-cap tube equipped with magnetic stir bar were introduced 2-phenoxypyridine (**1a**; 0.041 g, 0.204 mmol), 1-chlorooctane (**2a**; 0.075 g, 0.50 mmol), $CuBr_2$

(0.013 g, 0.06 mmol), LiHMDS (0.084 g, 0.50 mmol) inside the glove-box. To the above mixture, toluene (1.0 mL) was added and the resultant reaction mixture was stirred at 120 °C in a preheated oil bath for 3 h. The reaction tube was introduced to the glove box, and the reaction mixture was transferred to an EPR tube and frozen at 100 K, which was then subjected to EPR measurement (Fig 2.11).

Similar procedure was followed to perform the EPR analysis of controlled reaction mixtures, such as (i) complex (**6**) and (ii) complex (**6**) + LiHMDS.

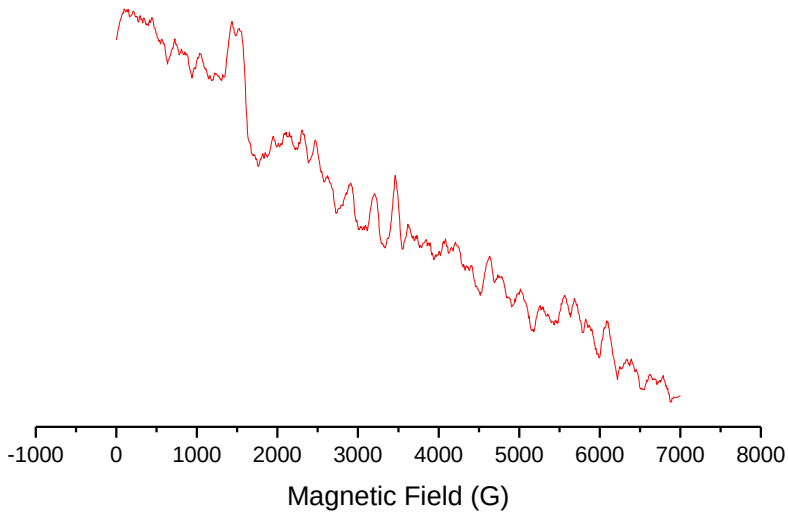



**Figure. 2.11** EPR spectrum of the reaction mixture with 30% $CuBr_2$: (**1a** + **2a** + $CuBr_2$ + LiHMDS).

### 2.4.8 Cyclic Voltammetry

Cyclic voltammetry was carried out using reference 3000 (Gamry instruments) electrochemical workstation in a standard 3 electrode setup. Glassy carbon electrode (2 mm diameter) as working, platinum wire as counter electrode and silver/silver chloride as reference electrode. All the electrodes were cleaned prior to each use. The reference electrode was stored in a 3 M KCl solution to maintain the equilibrium potential. The working electrode was cleaned by manual polishing with 0.05-micron alumina powder prior to experiment. All the experiments were carried out using 100 mM tetra-n-butylammonium perchlorate (TBAP) in dimethyl formamide (DMF) as supporting electrolyte. The concentration of all the analyte was maintained at 1 mM. Prior to experiments, the background signal without analyte was taken to optimize the potential window.

Electrochemical analysis was carried out using cyclic voltammetry to get the insight into the electrode potentials of various reaction components (Figure 2.12). From the cyclic voltammetry analysis, the $E^0$ values for complex (**5**), complex (**6**), $CuBr_2$ and LiHMDS found to be 0.634 V, 0.601 V, 0.648 V and -0.520 V, respectively. As the $E^0$ value of LiHMDS is lower compared to Cu(II) complexes, it can easily act as reducing agent for all of them, making the electron transfer feasible from LiHMDS to Cu(II) complexes**.**

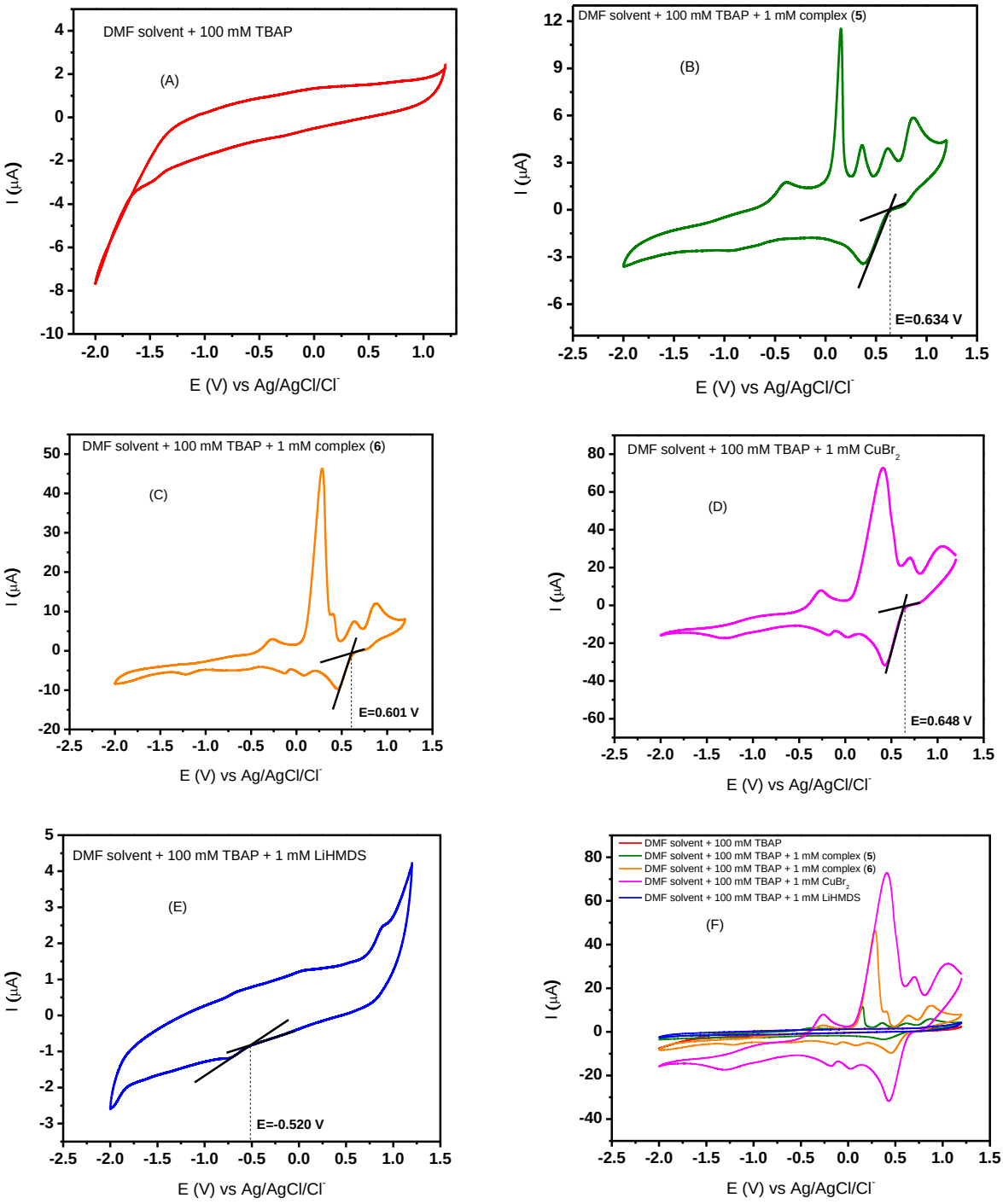



**Figure. 2.12** Cyclic voltammograms of (A) DMF, (B) 1.0 mM complex **5**, (C) complex **6**,

(D) 1.0 mM $CuBr_2$, € 1.0 mM LiHMDS and (F) Combined data; at 100 mV/s scan rate. 100 mM TBAP was used a supporting electrolyte, with Glassy carbon as working electrode, Platinum wire as counter electrode and Ag/AgCl/$Cl^-$ as reference electrode.

### 2.4.9 X-Ray Crystallography

The single-crystal structures of complex **5**, complex **6** and compound **3aj** were solved using X-ray intensity data recorded on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics with X-ray generator power setting at 50 kV and 1.4 mA. The intensity measurements were carried out with Mo (MoKα = 0.71073 Å) microfocus sealed tube diffraction source. For all the compounds, the unit cell parameters were determined using 36 frames (matrix runs). The full intensity data were collected using an optimized strategy that consisted of different sets of ω, ϕ and 2θ with 0.5° width keeping the sample-to-detector distance fixed at 5.00 cm. The exposure time was set at 10-30 sec depending on the diffraction power of the crystals. The whole process of X-ray data acquisition was controlled and monitored by the APEX3[73] program suite. The complete data sets were corrected for Lorentz polarization and absorption effects using the APEX3 package through SAINT and SADABS programs. Using the APEX3 program suite, the structure was solved with the ShelXS-97[74] structure solution program, using direct methods. The model was refined with the version of ShelXL-2013[75] using Least Squares minimization. All the hydrogen atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms. Crystallographic information is available at www.ccdc.cam.ac.uk/data.

Table 2.9 Crystallographic Data for Compounds.

| Identification code | Complex **5** | Complex **6** | **3aj** |
|---|---|---|---|
| Empirical formula | $C_{24}H_{22}Br_2CuO_4N_2$ | $C_{22}H_{18}Br_2CuN_2O_2$ | $C_{26}H_{39}NO_2$ |
| Formula weight | 625.80 | 565.74 | 397.58 |
| Temperature/K | 100(2) | 100.0 | 274(2) |
| Crystal system | triclinic | triclinic | triclinic |
| Space group | *P*-1 | *P*-1 | *P*-1 |
| a/Å | 8.6370(5) | 8.7516(8) | 6.7050(5) |
| b/Å | 16.9845(11) | 9.6873(9) | 10.2382(8) |
| c/Å | 18.0041(12) | 13.3675(14) | 18.5387(14) |
| α/° | 111.386(2) | 74.097(3) | 79.680(2) |

| | | | |
|---|---|---|---|
| β/° | 91.571(2) | 84.403(3) | 89.602(2) |
| γ/° | 97.084(2) | 89.465(3) | 79.478(2) |
| Volume/Å$^3$ | 2433.0(3) | 1084.54(18) | 1230.55(16) |
| Z | 2 | 2 | 2 |
| $\rho_{calc}$g/cm$^3$ | 1.708 | 1.732 | 1.073 |
| μ/mm$^{-1}$ | 4.215 | 4.711 | 0.066 |
| F(000) | 1244.0 | 558.0 | 436.0 |
| Crystal size/mm$^3$ | 0.25 × 0.2 × 0.15 | 0.25 × 0.18 × 0.17 | 0.3 × 0.25 × 0.21 |
| Radiation | MoKα (λ = 0.71073) | MoKα (λ = 0.71073) | MoKα (λ = 0.71073) |
| 2Θ range for data collection/° | 4.174 to 56 | 4.372 to 56.852 | 4.312 to 55.998 |
| Index ranges | -11 ≤ h ≤ 10, -22 ≤ k ≤ 22, -23 ≤ l ≤ 23 | -11 ≤ h ≤ 11, -12 ≤ k ≤ 12, -17 ≤ l ≤ 17 | -8 ≤ h ≤ 8, -13 ≤ k ≤ 13, -24 ≤ l ≤ 24 |
| Reflections collected | 63123 | 60673 | 64602 |
| Independent reflections | 11742 [$R_{int}$ = 0.0741, $R_{sigma}$ = 0.0557] | 5436 [$R_{int}$ = 0.0581, $R_{sigma}$ = 0.0263] | 5912 [$R_{int}$ = 0.0826, $R_{sigma}$ = 0.0398] |
| Data/restraints/parameters | 11742/0/599 | 5436/0/262 | 5912/0/264 |
| Goodness-of-fit on $F^2$ | 1.019 | 1.053 | 1.048 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0400, $wR_2$ = 0.0905 | $R_1$ = 0.0223, $wR_2$ = 0.0540 | $R_1$ = 0.0656, $wR_2$ = 0.1792 |
| Final R indexes [all data] | $R_1$ = 0.0672, $wR_2$ = 0.1052 | $R_1$ = 0.0261, $wR_2$ = 0.0558 | $R_1$ = 0.0992, $wR_2$ = 0.2086 |
| Largest diff. peak/hole / e Å$^{-3}$ | 2.11/-0.67 | 0.45/-0.49 | 0.20/-0.19 |
| CCDC Number | 2291780 | 2290349 | 2290347 |

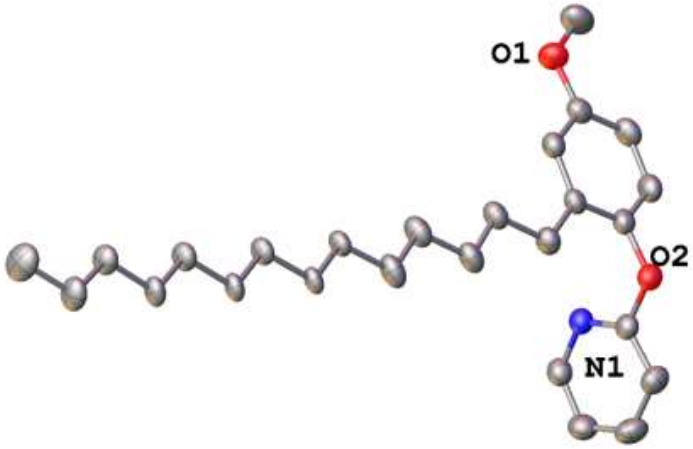
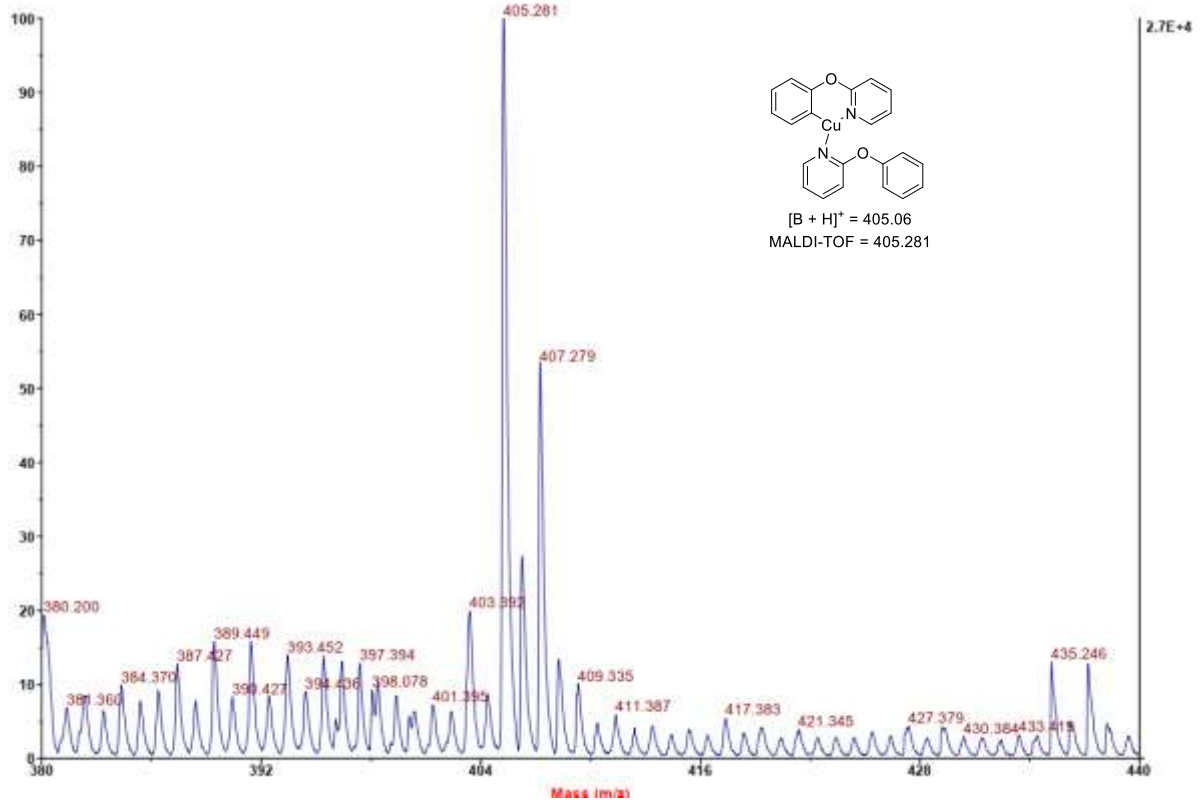
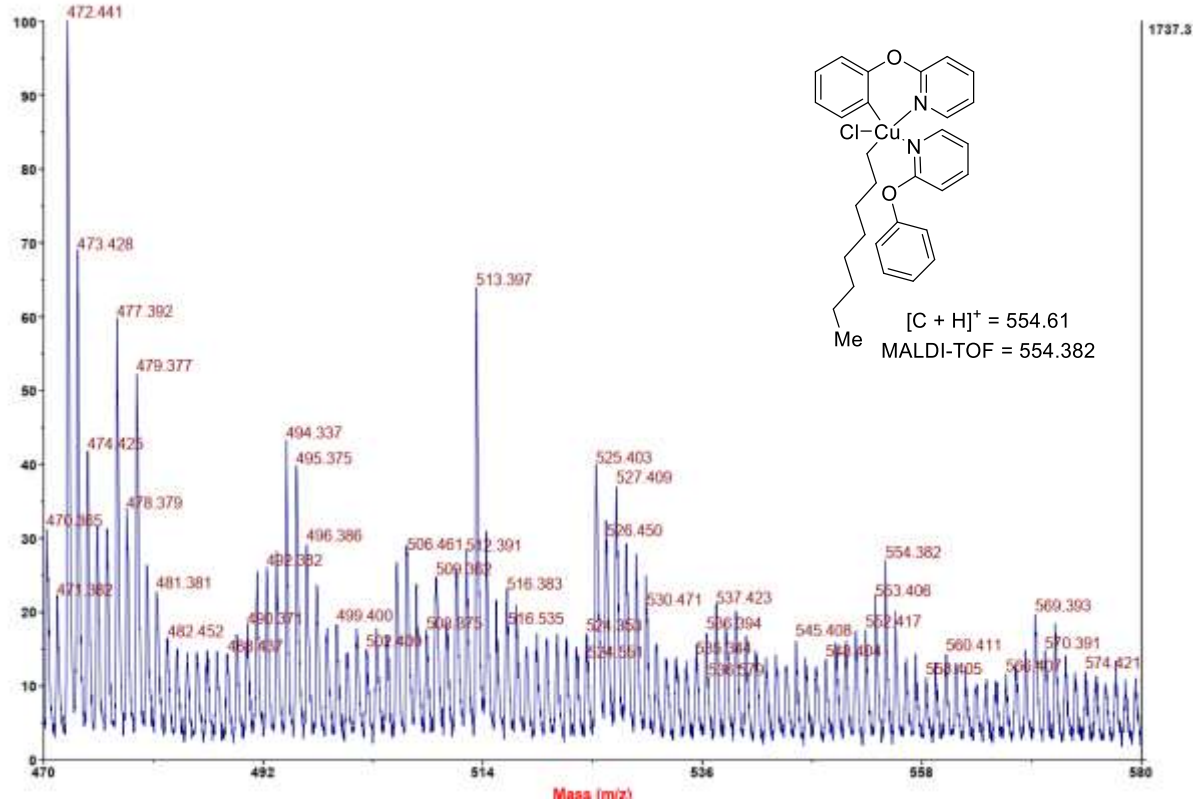


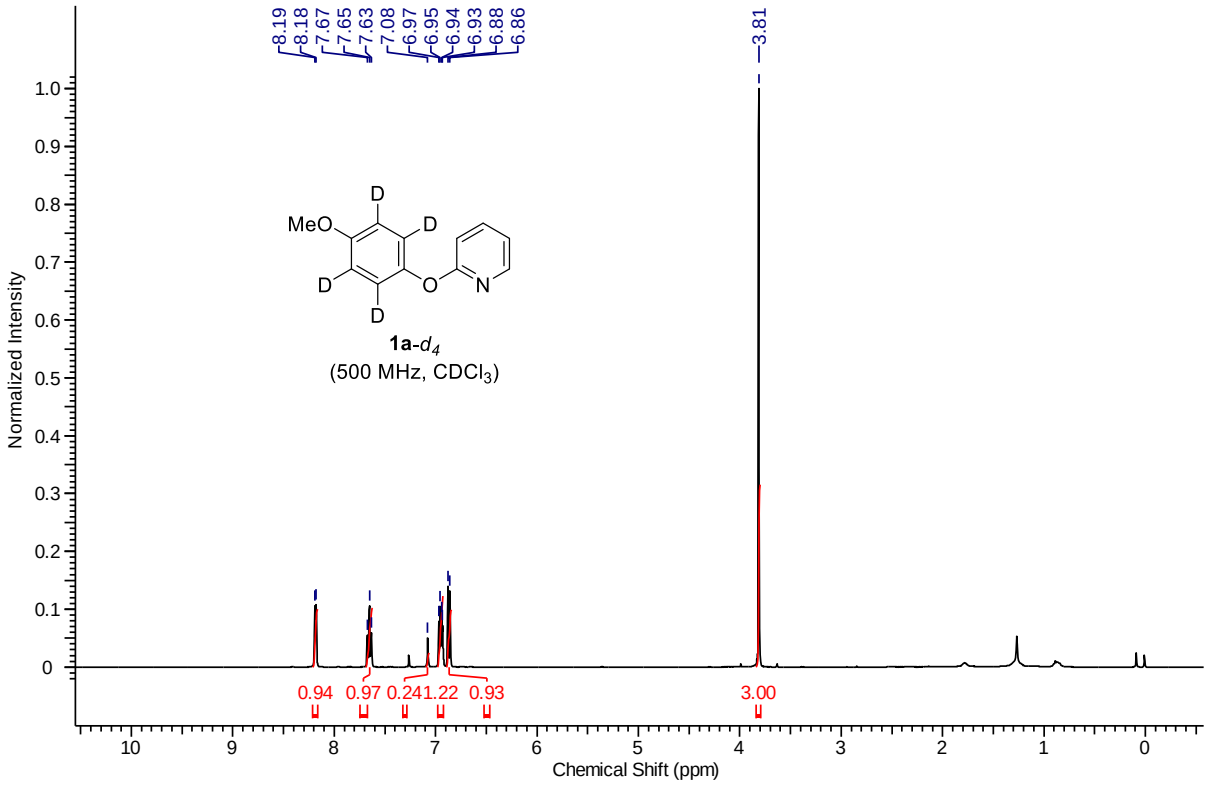

**Figure 2.13** Thermal ellipsoid plot of compound **3aj**.

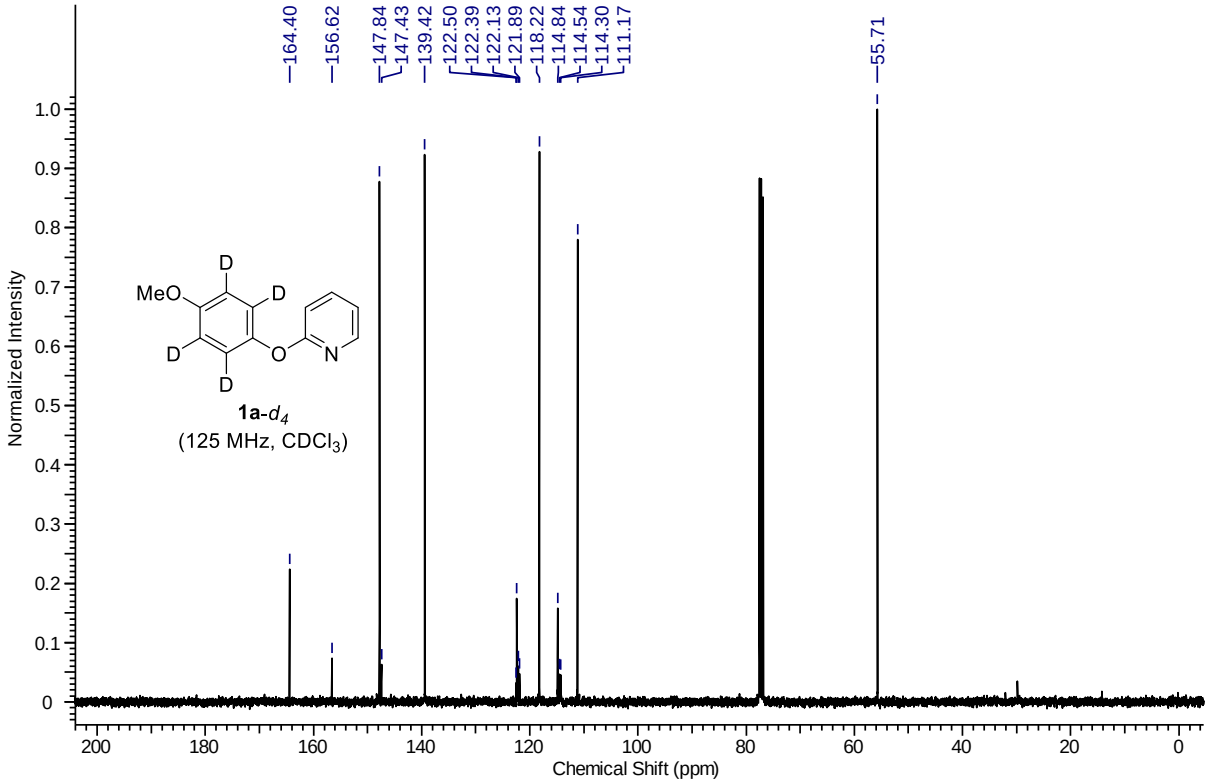
## 2.4.10 MALDI-TOF Spectra of Intermediates

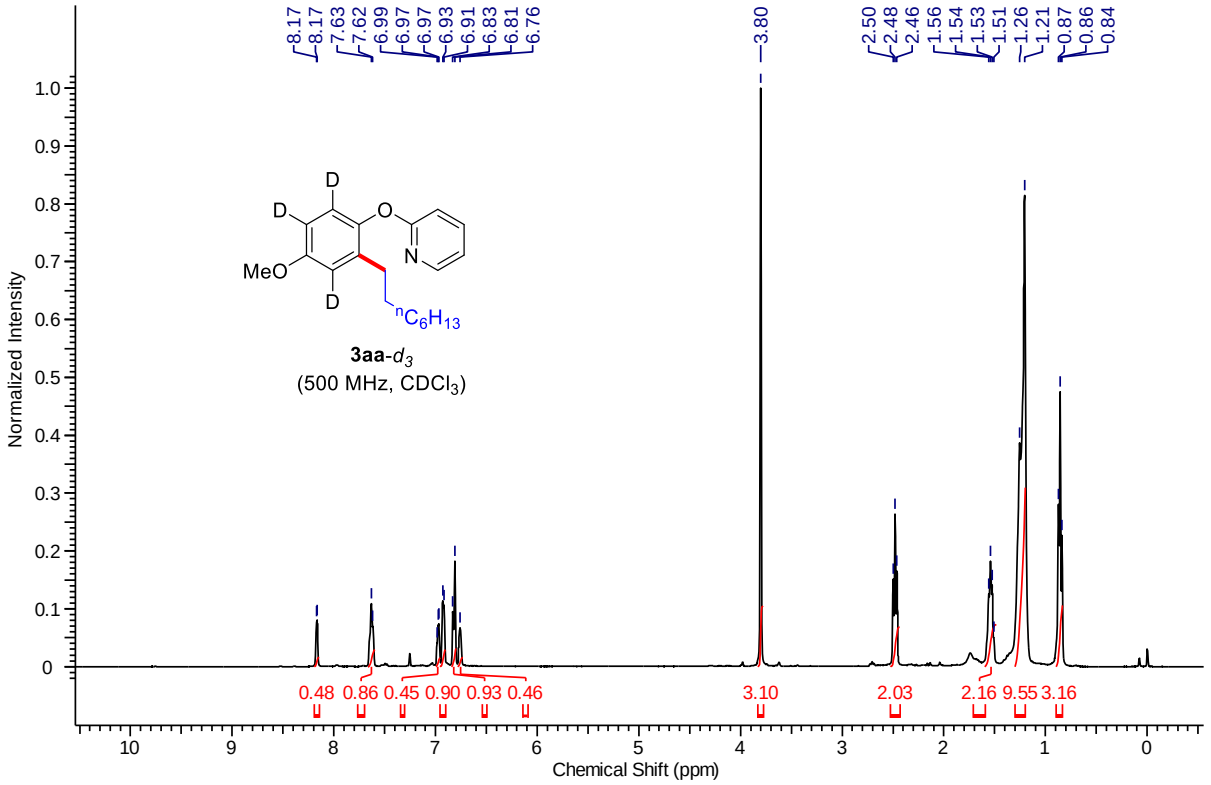


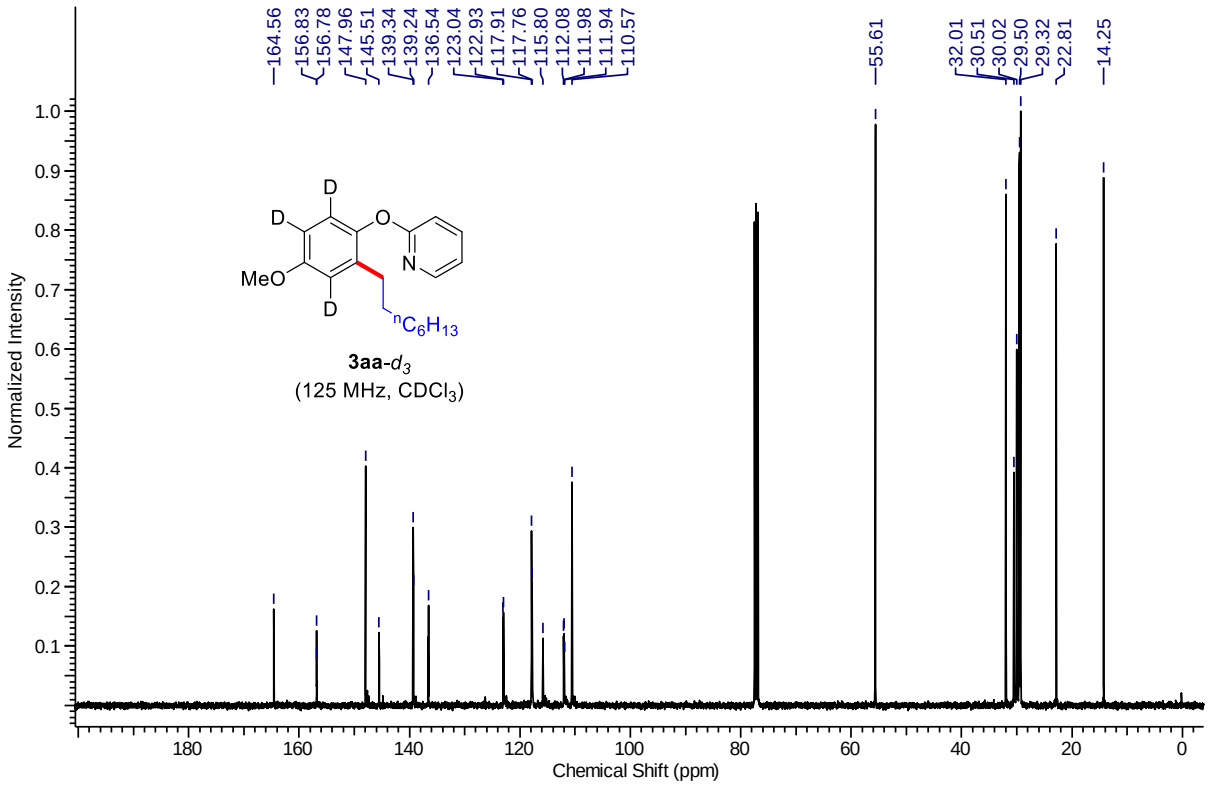



## 2.4.11 $^{1}H$ and $^{13}C\{^{1}H\}$ NMR Spectra of Deuterated Compounds

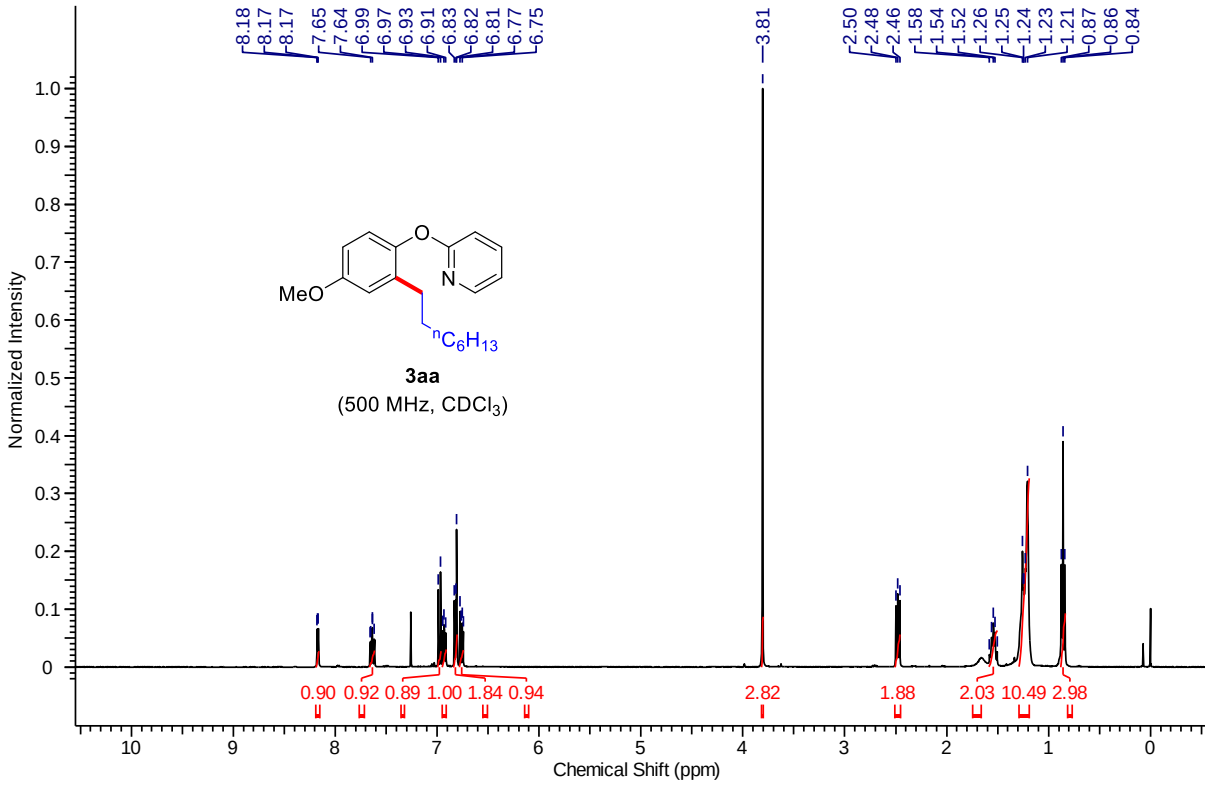


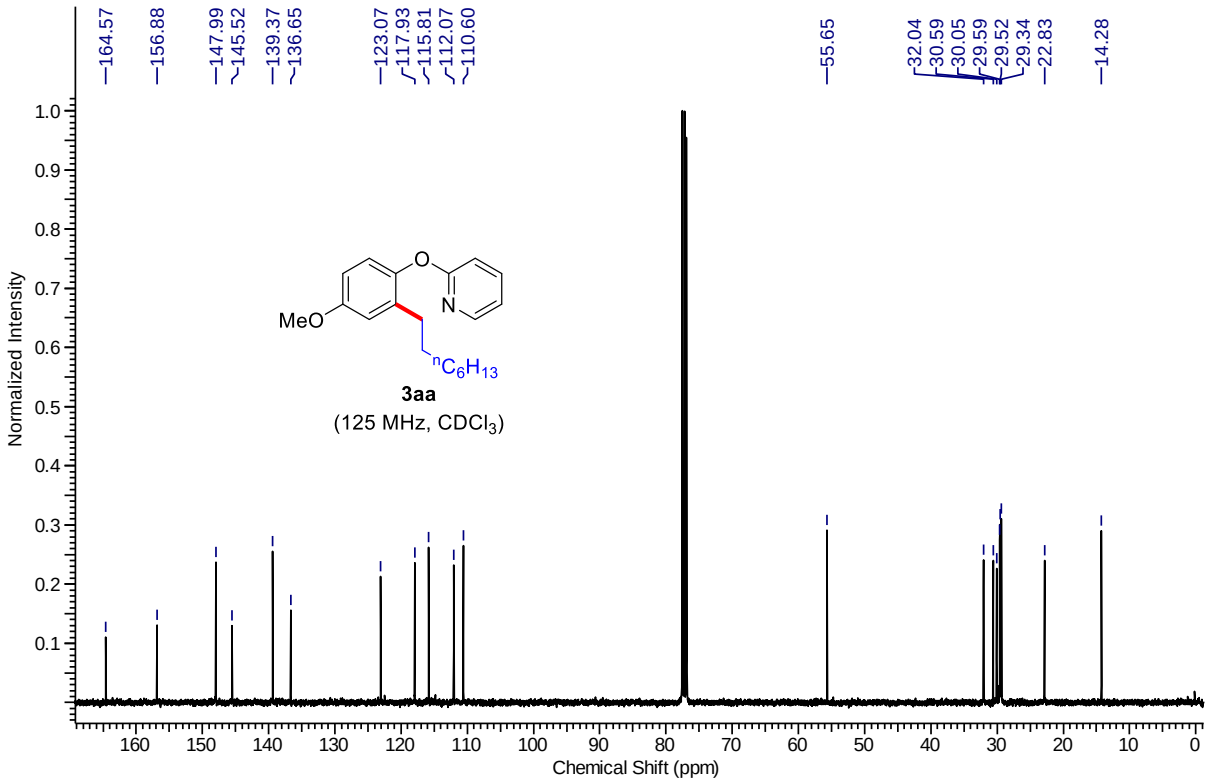




8.17
8.17
7.63
7.62
6.99
6.97
6.97
6.93
6.91
6.83
6.81
6.76
3.80
2.50
2.48
2.46
1.56
1.54
1.53
1.51
1.26
1.21
0.87
0.86
0.84
D
D
O
N
MeO
D
nC6H13
3aa-d3
(500 MHz, CDCl3)
Normalized Intensity
0.48 0.86 0.45 0.90 0.93 0.46
3.10
2.03
2.16 9.55 3.16
Chemical Shift (ppm)


164.56
156.83
156.78
147.96
145.51
139.34
139.24
136.54
123.04
122.93
117.91
117.76
115.80
112.08
111.98
111.94
110.57
55.61
32.01
30.51
30.02
29.50
29.32
22.81
14.25
D
D
O
N
MeO
D
nC6H13
3aa-d3
(125 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)

## 2.4.12 $^{1}H$ and $^{13}C\{^{1}H\}$ NMR Spectra of Selected Alkylated Products



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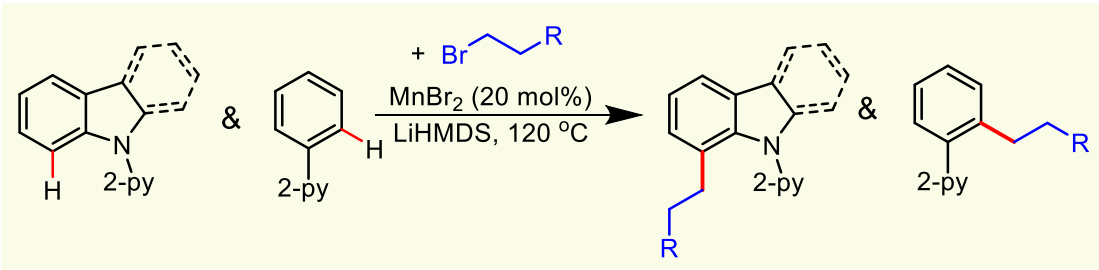
# Chapter 3

# C(sp$^2$)–H Alkylation of Indolines and Arenes with Unactivated Alkyl Bromides Using Mn(II) Catalyst

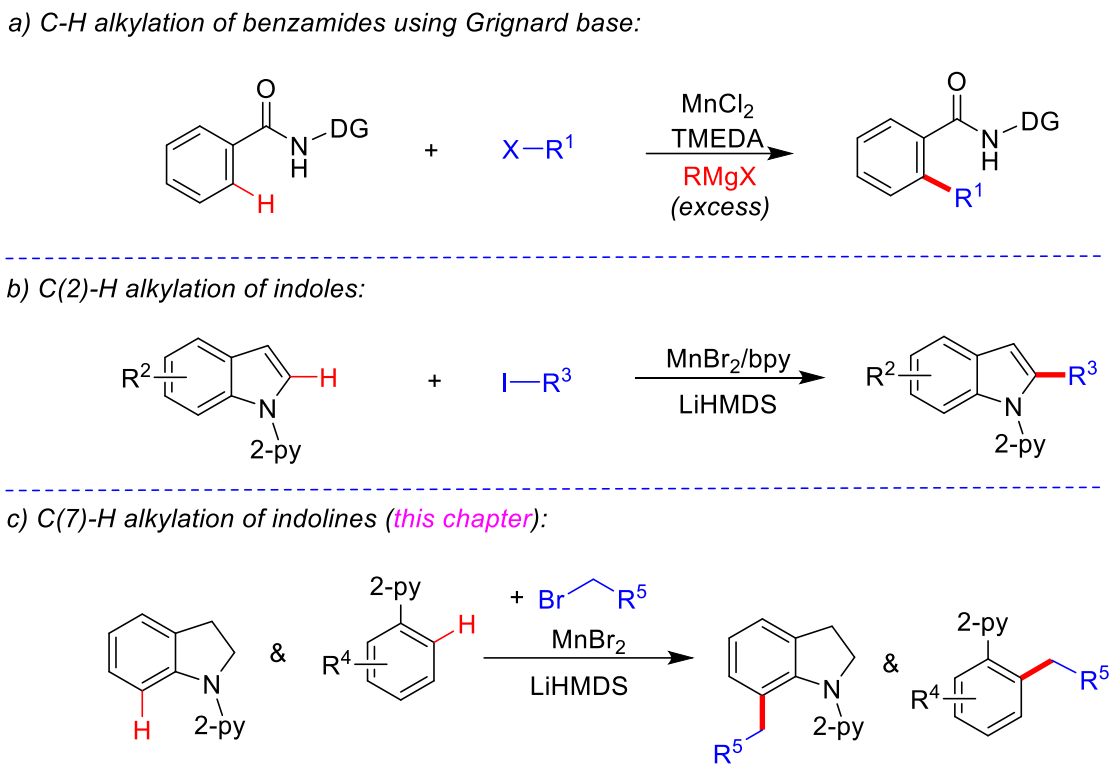



This chapter is adopted from the published article: "Manganese-Catalyzed C(sp$^2$)−H Alkylation of Indolines and Arenes with Unactivated Alkyl Bromides" **Verma, S. K.**; Punji, B., *Chem. Asian J.* **2022**, *17*, e202200103.

## 3.1 INTRODUCTION

Manganese complexes as catalysts are highly appealing in building molecular architecture through C–C bond formation,[1-4] considering the ease of availability, inexpensiveness and distinct characteristic of Mn metal. In recent years, molecular construction *via* the ubiquitous C–H bond modification has given special consideration.[5-9] Therefore, the relatively challenging C–H transformation by employing the 3rd most abundant transition metal, manganese, would be extremely beneficial. Notably, the manganese catalysts in C–H functionalization is under-utilized compared to other metal catalysts,[10-15] though it has a huge potential in environmentally benign and sustainable molecular synthesis.[15-20] The groups of Kuninobu and Takai,[21-22] Wang,[23-27] Ackermann,[28-34] Glorius,[35-37] and others[38-45] have independently established the Mn-catalysis in C–H functionalization, wherein an expensive Mn(I) {*i.e.*, $MnBr(CO)_5$} is used, and the coupling partners are mostly restricted to unsaturated species bearing polar multiple bonds. Particularly, Mn-catalysis in the coupling of C–H bonds with organic halides employing an easily available $Mn(II)X_2$ salt is limited. Ackermann disclosed the alkylation of benzamides with alkyl halides using $MnCl_2$/TMEDA, where a large amount of Grignard reagent is utilized that might limit the practical synthesis (Scheme 3.1a).[46,47] Therefore, developing Mn-catalyzed C–H functionalization methodologies with organic halides using a simple inorganic base is highly attractive. In that direction, recently, we developed the C(2)–H alkylation of indoles with alkyl iodides using a user-friendly LiHMDS, without the Grignard reagent (Scheme 3.1b).[48]

Selective C–H alkylation of heteroarenes, particularly that of indoles and indolines, is significant considering their biological and pharmacological importance.[49-51] In particular, most functionalization in indoles is directed towards the pyrrole-ring (C2 and C3),[52-55] whereas C(7)–H functionalization of benzene-ring in indole/indoline is relatively scant.[56-65] In recent, we shown the C(7)–H alkylation of indolines using a $Fe(OTf)_2$/xantphos catalyst.[66] Though limited reports are established for the C(7)–H transformation of indoles and indolines, the earth-abundant manganese has never been analyzed for the benzenoid-ring C–H functionalization. Thus, a simple and user-friendly approach for the C(7)–H indolines alkylation, without employing a phosphine ligand or Grignard reagent, under low-cost Mn(II) catalysis would be extremely profitable. With this assumption and a step towards sustainable synthesis, in this chapter, we demonstrate the $MnBr_2$-catalyzed C-7 indolines alkylation and related arenes with aliphatic alkyl bromides employing a LiHMDS base (Scheme 3.1c).




**Scheme 3.1** Mn(II)-catalyzed C–H alkylation strategies.

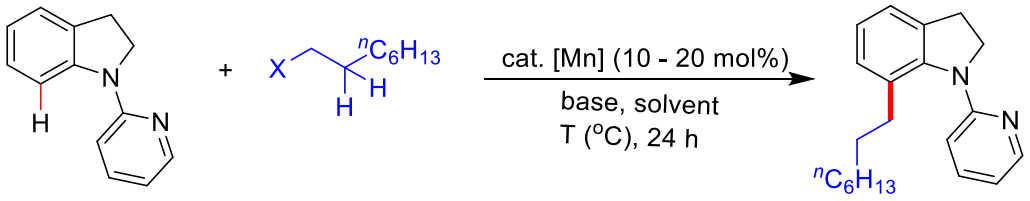
## 3.2 RESULTS AND DISCUSSION

### 3.2.1 Reaction Optimization

The demonstrated Mn-catalyzed C-2 alkylation of indoles with alkyl iodides proceeds through a favorable five-membered metallacycle (Scheme 3.1b);[48] whereas the C-7 alkylation of indoline (**1a**) would occur *via* a less favored six-membered metallacycle intermediate (Scheme 3.1c). In searching for a more facile and straightforward Mn-catalyst for the C-7 alkylation of indoline, we initiated the reaction of **1a** with different 1-octyl halides using 10 mol% of $MnBr_2$ at 120 $^oC$ (Table 3.1). Among the coupling partners, the use of 1-octyl iodide provided a 45% yield of **3aa** (entry 1), whereas 1-octyl bromide afforded 52% and the 1-octyl chloride gave **3aa** in 22% yield (entry 2 and 3). Using the 1-octyl bromide and $MnBr_2$ catalyst, the employment of nitrogen- or phosphine-based ligands, bpy, phen, neocuprione, xantphos, dppm, dppf and $PPh_3$ did not help overall reaction performance that could be due to the undesired stabilization of Mn-species (entries 4-10). Further, the yield of **3aa** is not improved with 15 mol% of $MnBr_2$ (entry 11). Interestingly, with an increase in the $MnBr_2$ loading to 20 mol%, the reaction provided **3aa** in 70% yield with a significant reduction in undesired reaction (entry 12). The inspection of other Mn(II) or Mn(I) precursors like $MnCl_2$, $Mn(OAc)_2$ and $Mn(CO)_5Br$ as catalysts afforded a slightly low yield of **3aa** (entries 13-15). The inorganic bases such as $LiO^tBu$, $NaO^tBu$, $KO^tBu$ and $Li_2CO_3$ were ineffective, whereas a

significant decomposition of **1a** was observed in the presence of NaHMDS (entries 16-20). We assume that the employment of LiHMDS generates an active Mn-amido species that initiates the alkylation, thus, the use Grignard base is not necessary like other Mn-catalyzed C–H transformations.[46,47] As the LiHMDS is needed to activate $MnX_2$ catalyst, and participate in the C–H activation process, more than a stoichiometric amount of base was used. The alkylation in *ortho*-xylene, *para*-xylene, *meta*-xylene or $^{t}$Bu-benzene provided a moderate yield of **3aa** (entries 21-24). Notably, the yield of **3aa** remains the same with 2.5 equivalent of LiHMDS (Scheme 25). The alkylation proceeded efficiently at 120 $^{o}$C; however, further lowering in reaction temperature (100 $^{o}$C) or reaction time led to a low yield (entry 26 and 27). The employment of $MnBr_2$ catalyst was essential, without which the alkylation did not occur (entry 28).

Table 3.1 Optimization of Reaction Parameters.[a]




(**1a**) (**2a**) (**3aa**)

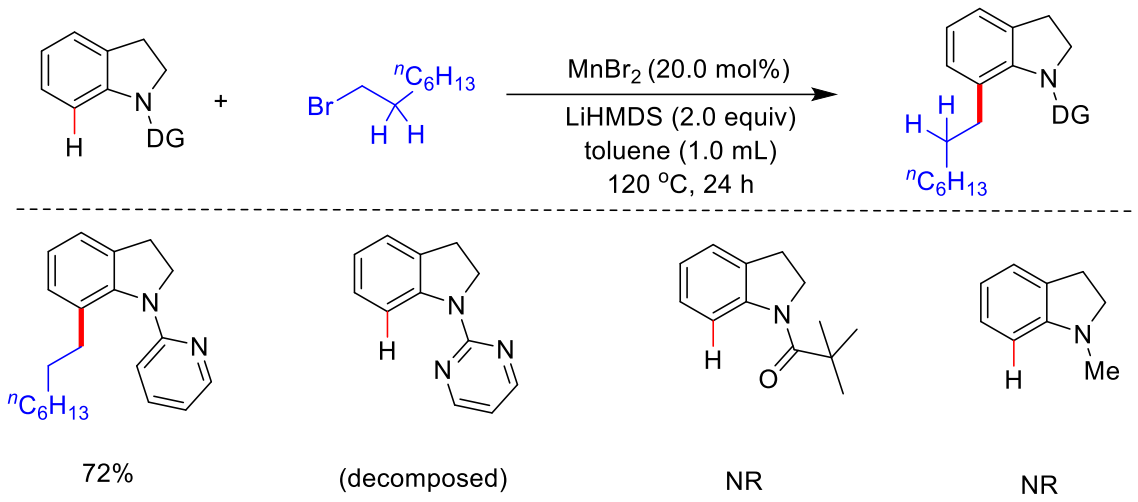
| Entry | X | [Mn] | Base | Solvent | T ($^{o}$C) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | I | $MnBr_2$ | LiHMDS | toluene | 120 | 45 |
| 2 | Br | $MnBr_2$ | LiHMDS | toluene | 120 | 52 |
| 3 | Cl | $MnBr_2$ | LiHMDS | toluene | 120 | 22 |
| 4 | Br | $MnBr_2$/bpy | LiHMDS | toluene | 120 | 32 |
| 5 | Br | $MnBr_2$/phen | LiHMDS | toluene | 120 | 29 |
| 6 | Br | $MnBr_2$/neocuproine | LiHMDS | toluene | 120 | 24 |
| 7 | Br | $MnBr_2$/xantphos | LiHMDS | toluene | 120 | 14 |
| 8 | Br | $MnBr_2$/dppm | LiHMDS | toluene | 120 | 24 |
| 9 | Br | $MnBr_2$/dppf | LiHMDS | toluene | 120 | 15 |
| 10 | Br | $MnBr_2$/$PPh_3$ | LiHMDS | toluene | 120 | 17 |
| 11 | Br | $MnBr_2$ | LiHMDS | toluene | 120 | 58 |
| **12** | **Br** | **$MnBr_2$** | **LiHMDS** | **toluene** | **120** | **72 (70)** |
| 13 | Br | $MnCl_2$ | LiHMDS | toluene | 120 | 60 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 14 | Br | $Mn(OAc)_2$ | LiHMDS | toluene | 120 | 52 |
| 15 | Br | $MnBr(CO)_5$ | LiHMDS | toluene | 120 | 18 |
| 16 | Br | $MnBr_2$ | $LiO^tBu$ | toluene | 120 | trace |
| 17 | Br | $MnBr_2$ | $NaO^tBu$ | toluene | 120 | trace |
| 18 | Br | $MnBr_2$ | $KO^tBu$ | toluene | 120 | NR |
| 19 | Br | $MnBr_2$ | $Li_2CO_3$ | toluene | 120 | NR |
| 20 | Br | $MnBr_2$ | NaHMDS | toluene | 120 | -- |
| 21 | Br | $MnBr_2$ | LiHMDS | $^t$Bu-benzene | 120 | 61 |
| 22 | Br | $MnBr_2$ | LiHMDS | *o*-xylene | 120 | 53 |
| 23 | Br | $MnBr_2$ | LiHMDS | *m*-xylene | 120 | 44 |
| 24 | Br | $MnBr_2$ | LiHMDS | *p*-xylene | 120 | 45 |
| 25[c] | Br | $MnBr_2$ | LiHMDS | toluene | 120 | 70 (68) |
| 26[d] | Br | $MnBr_2$ | LiHMDS | toluene | 120 | 60 |
| 27 | Br | $MnBr_2$ | LiHMDS | toluene | 100 | 51 |
| 28 | Br | -- | LiHMDS | toluene | 120 | NR |

[a] Reaction Conditions: **1a** (0.040 g, 0.204 mmol), **2a** (0.40 mmol), LiHMDS (0.067 g, 0.40 mmol), solvent (1.0 mL). Entries 1-10: 10 mol% $MnBr_2$/ligand was used. Entry 11: 15 mol% of $MnBr_2$ was used. Entries 12-27: 20 mol% of $MnBr_2$ was used. [b] GC yield using *n*-dodecane as internal standard; isolated yield is given in parentheses. [c] Employing 0.50 mmol of LiHMDS. [d] Reaction performed for 16 h.

### 3.2.2 Effect of Nitrogen Substituents of Indoline on the Alkylation

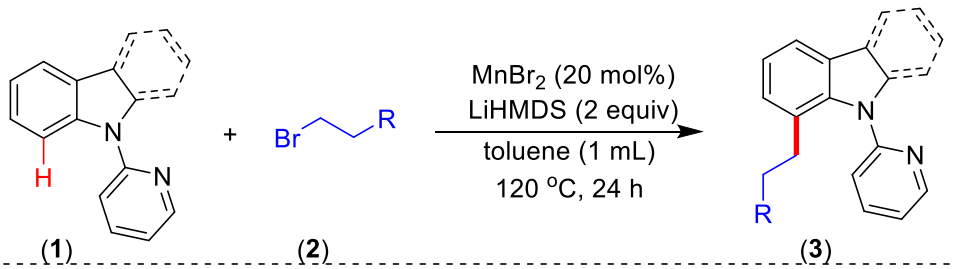
We have investigated the effect of nitrogen substituents of indoline on the C-7 alkylation reaction employing various N-protected indolines with alkyl bromide (Scheme 3.2). The screening of various *N*-substitutions (directing group) suggests that the 2-pyridinyl is an ideal group. In contrast, the indoline having *N*-2-pyrimidinyl or *N*-pivaloyl decomposes under the reaction conditions, and the *N*-Me-indoline did not participate in the reaction.

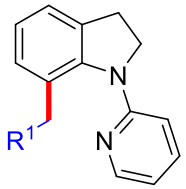



**Scheme 3.2** Effect of directing group on alkylation.

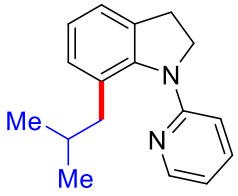
### 3.2.3 Substrate Scope for the Alkylation of Indolines

After a comprehensive screening of reaction parameters, the ligand-free $MnBr_2$-catalyzed protocol was applied to coupling various unactivated primary alkyl bromides with C(7)–H of indoline (Scheme 3.3). The linear alkyl bromides with different length of chain were efficiently coupled with **1a** to give C-7 alkylated compounds **3aa**-**3am** in moderate to good yields. Generally, short-chain length alkyl bromides were more productive than the long-chain alkyl bromides, which could be due to the better solubility of the former. The isobutyl bromide reacted actively to provide **3an** in 56% yield, whereas the sterically demanding neopentyl bromide reacted at a low pace to give **3ao**. In particular, silyl- and aryl-substituted alkyl bromides were smoothly reacted with 2-pyridinyl indoline to provide **3ap** and **3aq**. The 1,6-dibromohexane as a coupling partner selectively reacted to give mono-bromo alkylated **3ar**, albeit in low yield. Internal as well as terminal alkenyl functionalities were well tolerated to provide **3as** and **3at**. Important functionalities, such as phenyl ether (**3au**, **3av**), thymol (**3aw**), and heteroarenes like pyrrolyl (**3ax**), indolyl (**3ay**) and carbazolyl (**3az**) were well tolerated. Unfortunately, the alkyl halides containing base-reactive functionalities like acetyl, ester and nitrile as well as bulky secondary and tertiary alkyl could not participate in the reaction. Similarly, the electrophile-containing sulfur atom failed to react, attributed to the catalyst poisoning due to a sulfur moiety. Notably, the 2-pyridinyl carbazole reacted with 1-octyl bromide to afford selective mono-alkylated **3ba** in 63% yield, even though two C($sp^2$)–H bonds were susceptible for the alkylation. Unfortunately, the attempted C-7 alkylation of 2-methyl-*N*-pyridinyl indole did not occur, which is expected to proceed *via* a similar six-membered metallacycle.

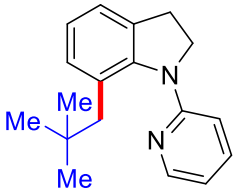


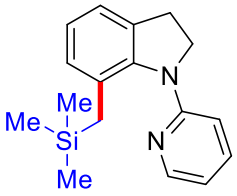
$R^1 = C_7H_{15}$ (**3aa**): 70%
$R^1 = CH_3$ (**3ab**): 68%
$R^1 = C_2H_5$ (**3ac**): 72%
$R^1 = C_3H_7$ (**3ad**): 68%
$R^1 = C_4H_9$ (**3ae**): 74%
$R^1 = C_5H_{11}$ (**3af**): 66%
$R^1 = C_6H_{13}$ (**3ag**): 68%
$R^1 = C_9H_{19}$ (**3ah**): 63%
$R^1 = C_{10}H_{21}$ (**3ai**): 52%
$R^1 = C_{12}H_{25}$ (**3aj**): 53%
$R^1 = C_{13}H_{27}$ (**3ak**): 52%
$R^1 = C_{15}H_{31}$ (**3al**): 58%
$R^1 = C_{17}H_{35}$ (**3am**): 63%



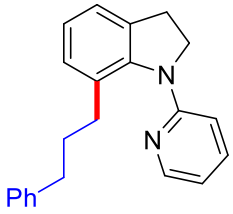
(**3an**): 56%



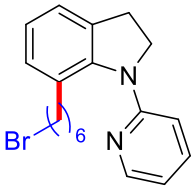
(**3ao**): 28%



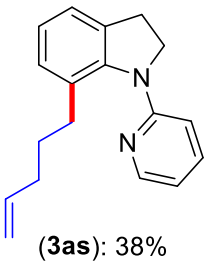
(**3ap**): 51%



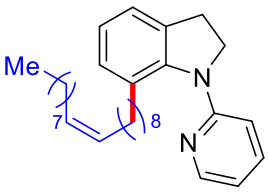
(**3aq**): 75%



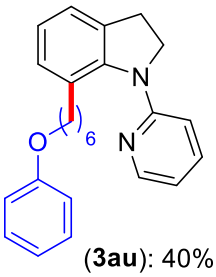
(**3ar**): 28%



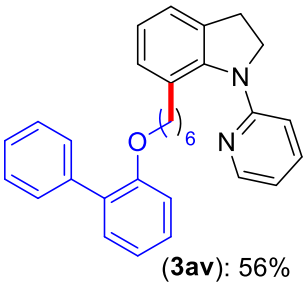
(**3as**): 38%



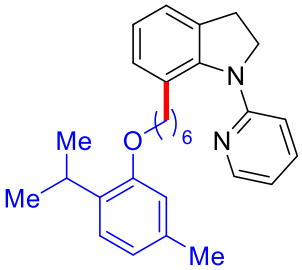
(**3at**): 30%



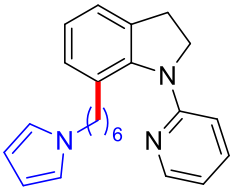
(**3au**): 40%



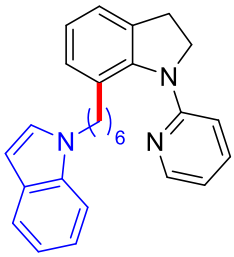
(**3av**): 56%



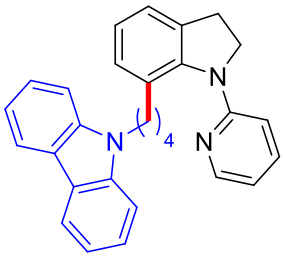
(**3aw**): 45%



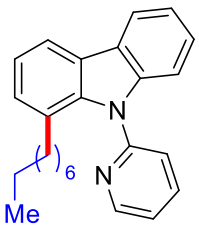
(**3ax**): 34%



(**3ay**): 48%



(**3az**): 31%

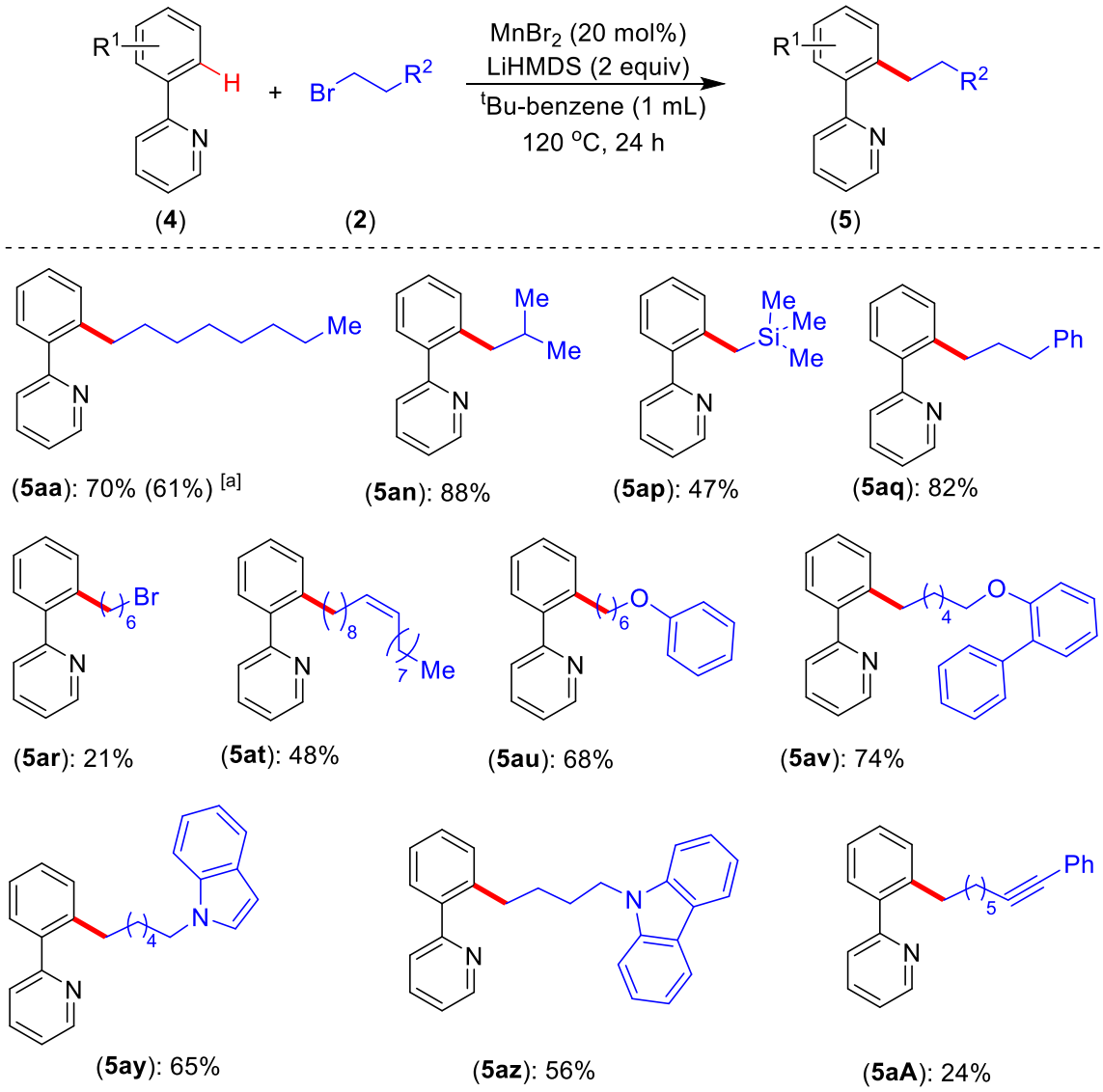


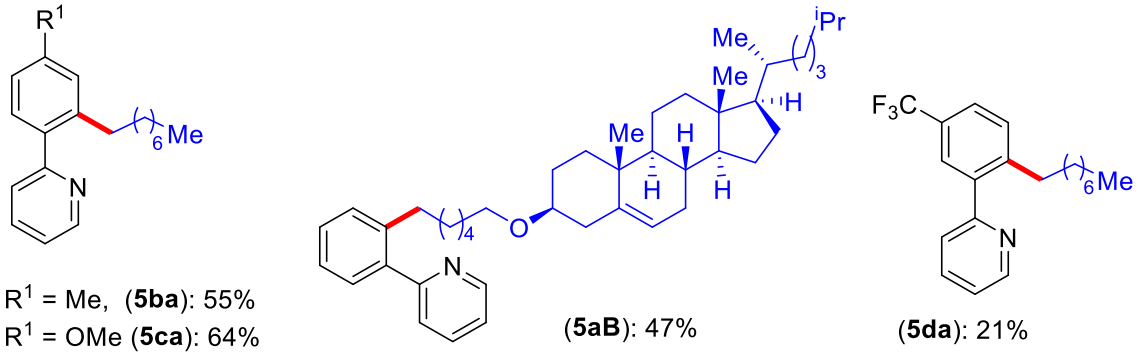
(**3ba**): 63%

**Scheme 3.3** Substrate scope for indoline alkylation.

### 3.2.4 Substrate Scope for Alkylation of (2-Pyridinyl)arenes

The alkylation protocol was extended to the C–H coupling of (2-pyridinyl)arenes with various alkyl bromides in *tert*-butylbenzene (Scheme 3.4). The linear and branched alkyl bromides are efficiently coupled to deliver **5aa**, **5an**, **5ap**, **5aq** in good yields. The synthetically useful bromo, alkenyl and alkynyl functionalities were tolerated (**5ar**, **5at**, **5aA**). Notably, the phenyl ethers and heteroarene-substituted alkyl bromides conveniently coupled with 2-phenyl pyridine and afforded good yields (**5au**, **5av**, **5ay**, **5az**), which were less effective with the 2-pyridinyl indoline. Cholesterol-derived alkyl bromide reacted moderately with 2-phenyl pyridine affording a satisfactory yield of **5aB**. In addition, the substituted 2-pyridinyl arenes underwent alkylation and gave a moderate yield of **5ba-5ca**. Strikingly, selective mono-alkylation was observed in all the (2-pyridinyl)arenes, and the dialkylation was not detected.



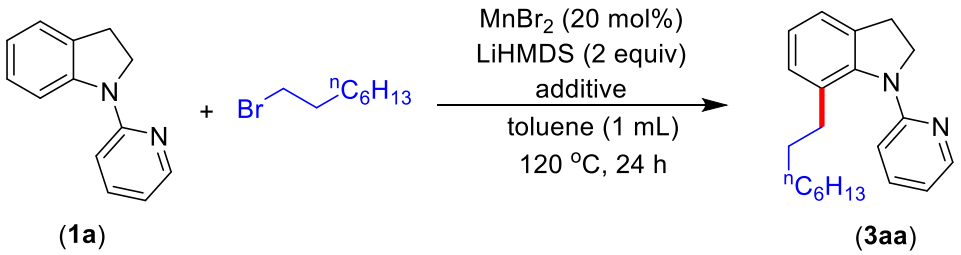



**Scheme 3.4** Substrate scope for alkylation of (2-pyridinyl)arenes.

### 3.2.5 Mechanistic Aspects

#### 3.2.5.1 External Additive Experiments

The alkylation using mercury (500 equiv w.r.t. Mn) afforded a reduced yield of **3aa** (48%), pointing to the presence of homogeneous active catalytic species though a partial formation of heterogeneous species cannot be ruled out. The attempted alkylation of **1a** was completely quenched under the condition of radical scavengers, TEMPO, galvinoxyl or BHT, wherein the compound **1a** was recovered in 95%, 84% and 92%, respectively (Scheme 3.5). These findings highlighted the engagement of radical intermediates during the alkylation.[48,67]



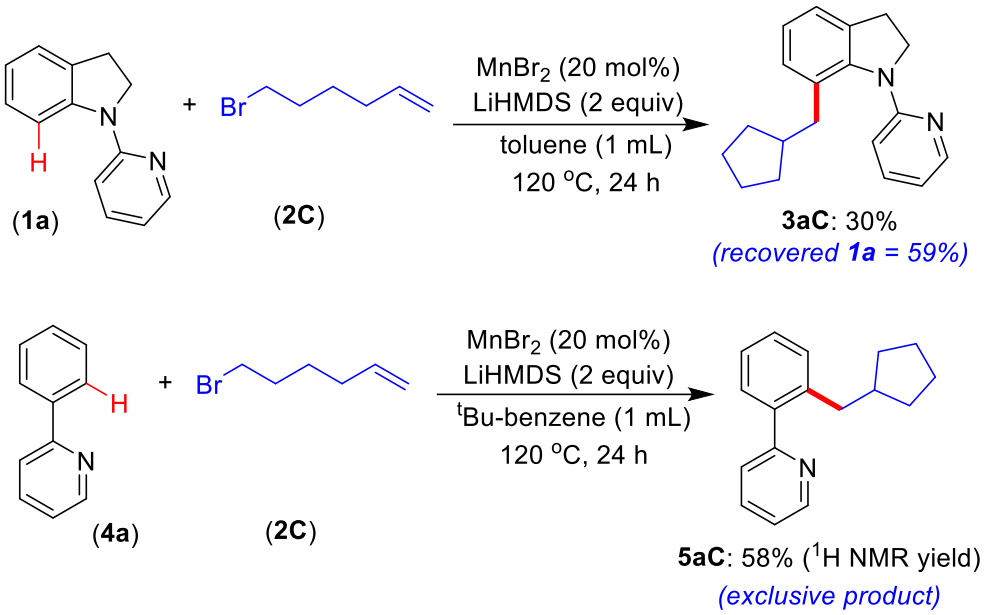

| additive (w.r.t. **1a**) | **3aa** | recovered **1a** |
|---|---|---|
| No additive | 70% | --- |
| TEMPO (2 equiv): | NR | 95% |
| BHT (2 equiv): | NR | 92% |
| Galvinoxyl (2 equiv): | NR | 84% |

**Scheme 3.5** External additive experiments.

#### 3.2.5.2 Radical Clock Experiments

Radical clock experiment was performed to support the preliminary observation of radical pathway for the alkylation reaction (Scheme 3.6). The exclusive rearranged/cyclized products **3aC** and **5aC** were obtained in the reaction of 6-brormohex-1-ene with **1a** and **4a**, respectively (Scheme 3.6). All this experimental evidence suggested the participation of an

alkyl radical species in the alkylation.[48,54,55]




**Scheme 3.6** Radical clock experiments.

### 3.2.6 Kinetic Analysis

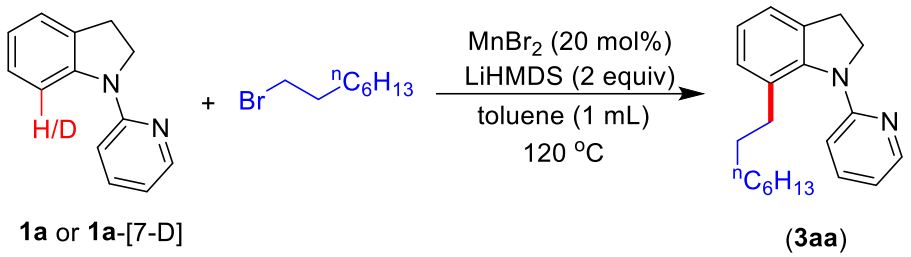
#### 3.2.6.1 Kinetic Isotope Effect (KIE) Study

To determine whether C–H bond activation is involved in the rate-determining step, a kinetic isotope effect (KIE) study can be carried out by employing 1-(pyridin-2-yl)indoline (**1a**, 0.040 g, 0.204 mmol) or 1-(pyridin-2yl)indoline-7-*d* (**1a**-[7-D]; 0.040 g, 0.204 mmol), 1-bromooctane (**2a**, 0.077 g, 0.40 mmol), $MnBr_2$ (0.0086 g, 0.04 mmol, 20 mol%) and LiHMDS (0.067 g, 0.4 mmol) and *n*-dodecane (0.020 mL, 0.088 mmol, internal standard) and toluene (0.91 mL) was added to make the total volume to 1.0 mL inside the glove-box. The reaction mixture was then stirred at 120 °C in a preheated oil bath. At regular intervals (10, 20, 30, 45, 60, 80, 100, 120 min), the reaction vessel was cooled to ambient temperature and an aliquot of sample was withdrawn to the GC vial. The sample was diluted with EtOAc and subjected to GC analysis. The concentration of product **3aa** obtained in each sample was determined with respect to the internal standard *n*-dodecane (Table 3.2). The data of the concentration of the product **3aa** *versus* time (min) plot was drawn (Figure 3.1) with Origin Pro 8.5, and the rate was determined by initial rate method (up to 120 min). The data were taken from the average of two independent experiments. The initial rate obtained for the coupling of 1-(pyridin-2-yl)indoline (**1a**) with 1-bromooctane was 5.86 x $10^{-4}$ $Mmin^{-1}$. Similarly, the rate for the coupling of 1 (pyridin-2-yl)indoline-7-*d* (**1a**-[7-D]) with 1-bromooctane was 1.45 x $10^{-4}$ $Mmin^{-1}$. Therefore, the rate (H)/ rate (D) = 5.86 x $10^{-4}$ /1.45 x

$10^{-4}$ = 4.04. The kinetic isotopes effect suggests the probable involvement of a rate-limiting C–H activation.[68]

Table 3.2. Time Dependent Formation of Product **3aa** from **1a** and **1a**-[7-D].

| Time (min) | Conc. of **3aa** using **1a** [M] | Conc. of **3aa** using **1a**-[7-D] [M] |
|---|---|---|
| 10 | 0.0053 | 0.0010 |
| 20 | 0.0113 | 0.0029 |
| 30 | 0.0176 | 0.0035 |
| 45 | 0.0272 | 0.0057 |
| 60 | 0.0377 | 0.0078 |
| 80 | 0.0497 | 0.0111 |
| 100 | 0.0602 | 0.0140 |
| 120 | 0.0676 | 0.0170 |




**1a** or **1a**-[7-D]

(**3aa**)

rate for **1a** = 5.85 x $10^{-4}$ $Mmin^{-1}$

rate for **1a**-[7-D] = 1.45 x $10^{-4}$ $Mmin^{-1}$

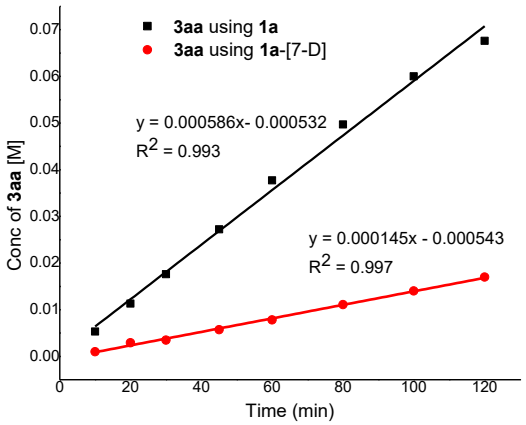



**Figure 3.1** Time-dependent formation of **3aa** using substrates **1a** and **1a**-[7-D].

### 3.2.6.2 Rate Order Determination on Mn-Catalyst

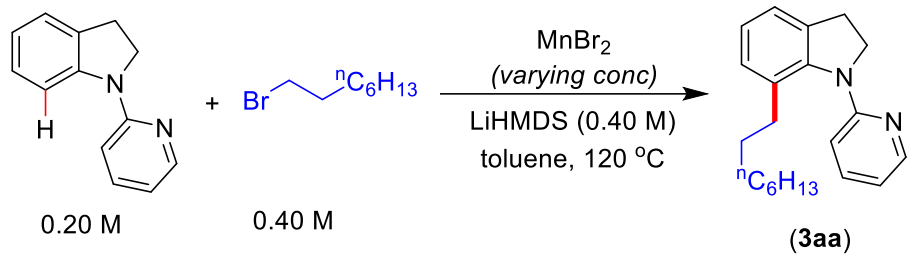
To determine the order of the alkylation reaction on $MnBr_2$, initial rates at different initial concentrations of $MnBr_2$ were determined. The final data was obtained by averaging the results of three independent experiments for the same initial concentration. In standard experiment, a Teflon-screw cap tube equipped with magnetic stir bar was introduced

Substrate **1a** (0.04 g, 0.20 M), LiHMDS (0.067 g, 0.40 mmol, 0.40 M), 1-bromooctane (**2a**; 0.077 g, 0.4 mmol, 0.4 M), specific amount of $MnBr_2$ (as shown in Table 3.3), *n*-dodecane (0.02 mL, 0.088 mmol, 0.088 M, internal standard), and toluene (appropriate amount) was added to make the total volume to 1.0 mL. The reaction mixture was then heated at 120 $^oC$ in a pre-heated oil bath. At regular intervals (10, 20, 30, 45, 60, 80, 100, 120 min), the reaction vessel was cooled to ambient temperature and an aliquot of sample was withdrawn to the GC vial. The sample was diluted with ethyl acetate and subjected to GC analysis. The concentration of the product **3aa** obtained in each sample was determined with respect to the internal standard *n*-dodecane. The kinetic analysis of alkylation indicates the absence of an induction period (Fig 3.2), which supports the direct involvement of Mn(II) active species.

The data of the concentration of the product *vs* time (min) plot was fitted linear with Origin Pro 8.5. The slope of the linear fitting represents the reaction rate. The order of the reaction was then determined by plotting log(rate) *vs* log(conc. $MnBr_2$).

Table 3.3 Rate of Alkylation Reaction at Different Initial Concentrations of $MnBr_2$.

| Experiment | Amount of $MnBr_2$ (g) | Initial Conc. of $MnBr_2$ [M] | Initial Rate [$Mmin^{-1}$] x $10^{-3}$ | $R^2$ |
|---|---|---|---|---|
| 1 | 0.0011 | 0.005 | 0.096 ± 0.0067 | 0.964 |
| 2 | 0.0021 | 0.01 | 0.205 ± 0.0042 | 0.997 |
| 3 | 0.0086 | 0.04 | 0.585 ± 0.0188 | 0.993 |
| 4 | 0.013 | 0.06 | 0.625 ± 0.0326 | 0.981 |



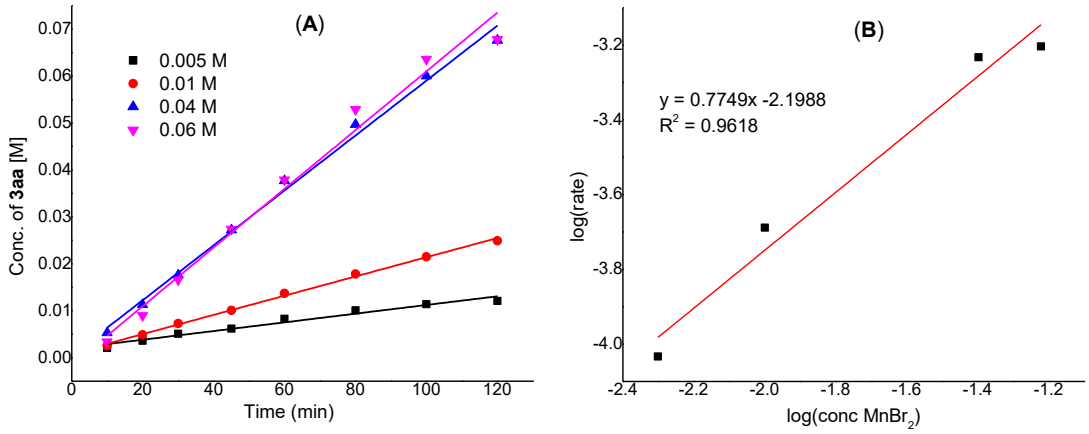



**Figure 3.2** (A) Time-dependent formation of **3aa** at different initial concentrations of $MnBr_2$, (B) Plot of log(rate) *versus* log(conc $MnBr_2$).

### 3.2.7 Plausible Catalytic Cycle

Based on our investigation and literature reports,[46,48] two tentative catalytic cycles were proposed (Path I and Path II; Fig 3.3). The reaction would start by $MnBr_2$ or Mn(II)-amido species that reacts with C(7)–H of **1a** in the rate-determining step to form intermediate **A**. The Mn-intermediate triggers the halide atom transfer (HAT) of **2**, leading to species **B** and alkyl radical (Path I). Controlled and radical clock studies have proved the involvement of alkyl radicals. Radical recombination followed by the reductive elimination from **C** would result in the formation of **3**. Alternately, two molecules of intermediate **A** can participate in homolytic cleavage of the C–Br bond in **2** to generate Mn(III) intermediates **D** and **E** (Path II). Considering the positive fractional rate order of alkylation on catalyst concentrations, this pathway seems more feasible. The reductive elimination of **3** would generate the product (or substrate) coordinated Mn(I) complex **F**. Upon releasing **3**; the Mn(I) can undergo comproportionation with **E** to form active species **A** and $MnX_2$, both of which can re-enter the catalytic cycle.

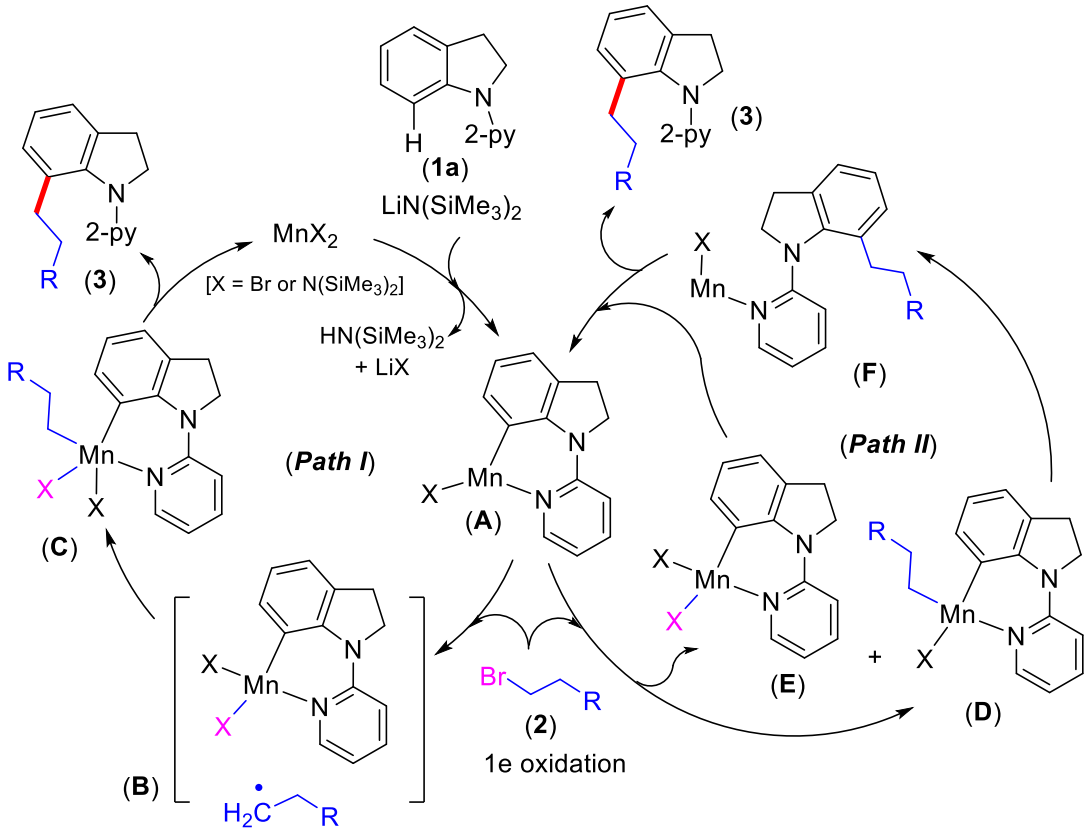



**Figure 3.3** Plausible catalytic cycles.

## 3.3 CONCLUSION

In summary, we have disclosed a ligand-free and cost-effective Mn(II)-catalyzed chemo- and regioselective method for the C($sp^2$)–H bond alkylation of indolines and (2-pyridinyl)arenes. This protocol provided a wide range of alkylated products containing alkenyl, alkynyl, silyl, ethers and heteroaromatic functionalities, including fatty alcohol and cholesterol. Alkylation proceeded either *via* a five-membered or a six-membered metallacycle leading to the desired products. The use of a LiHMDS base is very crucial, as it can produce an active Mn-amido species. A preliminary mechanistic study indicated that the alkylation progresses *via* a single electron transfer (SET) process, which participates in the slow-step metalation of indoline.

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## 3.4 EXPERIMENTAL SECTION

### 3.4.1 General Information

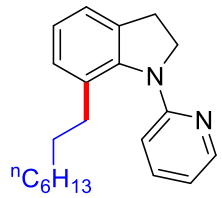
All the manipulations were conducted under an argon atmosphere either in a glove box or using standard Schlenk techniques in pre-dried glasswares. The catalytic reactions were performed in flame-dried reaction vessels with Teflon screw cap. Solvents were dried over Na/benzophenone or $CaH_2$ and distilled prior to use. Liquid reagents were flushed with argon prior to use. The alkyl bromides **2u**,[69] **2v**,[69] **2x**,[70] **2y**,[71] **2z**,[72] **2A**[73]and **2B**[74] were synthesized according to the previously described procedures. All other chemicals were obtained from commercial sources and were used without further purification. High resolution mass spectrometry (HRMS) mass spectra were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. NMR: ($^1$H and $^{13}$C) spectra were recorded at 400 or 500 MHz ($^1$H), 100 or 125 MHz {$^{13}$C, DEPT (distortionless enhancement by polarization transfer)}, 377 MHz ($^{19}$F), respectively in $CDCl_3$ solutions, if not otherwise specified; chemical shifts ($\delta$) are given in ppm. The $^1$H and $^{13}$C NMR spectra are referenced to residual solvent signals ($CDCl_3$: $\delta$ H = 7.26 ppm, $\delta$ C = 77.2 ppm).

**GC Method.** Gas Chromatography analyses were performed using a Shimadzu GC-2010 gas chromatograph equipped with a Shimadzu AOC-20s auto sampler and a Restek RTX-5 capillary column (30 m x 0.25 m x 0.25 µm). The instrument was set to an injection volume of 1 µL, an inlet split ratio of 10:1, and inlet and detector temperatures of 250 and 320 °C, respectively. UHP-grade argon was used as carrier gas with a flow rate of 30 mL/min. The temperature program used for all the analyses is as follows: 80 °C, 1 min; 30 °C/min to 200 °C, 2 min; 30 °C/min to 260 °C, 3 min; 30 °C/min to 300 °C, 3 min. Response factors for all the necessary compounds with respect to standard *n*-dodecane were calculated from the average of three independent GC runs.

### 3.4.2 Representative Procedure for Alkylation A

**Synthesis of 7-octyl-1-(pyridin-2-yl)indoline (3aa):** To a flame-dried screw-cap tube equipped with magnetic stir bar were introduced 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol), 1-bromooctane (**2a**; 0.077 g, 0.40 mmol), $MnBr_2$ (0.0086 g, 0.04 mmol, 20.0 mol %), and LiHMDS (0.067 g, 0.40 mmol) inside the glove box. To the above mixture in the tube was added toluene (1.0 mL). The resultant reaction mixture in the tube was immersed in a preheated oil bath at 120 $^o$C and stirred for 24 h. At ambient temperature, the reaction mixture was quenched with distilled $H_2O$ (10.0 mL) and the crude product was extracted with EtOAc

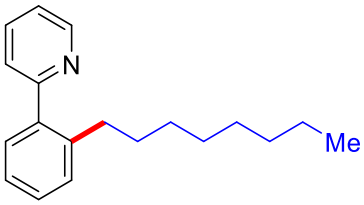
(15 mL x 3). The combined organic extract was dried over $Na_2SO_4$ and the volatiles were evaporated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) to yield **3aa** (0.044 g, 70%) as a light yellow liquid.




$^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.30 (d, $J$ = 4.9 Hz, 1H, Ar–H), 7.47 (t, $J$ = 7.9 Hz, 1H, Ar–H), 7.11 (d, $J$ = 7.1 Hz, 1H, Ar–H), 7.07 (d, $J$ = 7.6 Hz, 1H, Ar–H), 6.97 (vt, $J$ = 7.4 Hz, 1H, Ar–H), 6.77 (vt, $J$ = 5.5 Hz, 1H, Ar–H), 6.64 (d, $J$ = 8.4 Hz, 1H, Ar–H), 4.30 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 3.03 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 2.39 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 1.53-1.49 (m, 2H, $CH_2$), 1.25-1.16 (m, 10H, $CH_2$), 0.86 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 158.4 ($C_q$), 147.9 (CH), 143.7 ($C_q$), 137.2 (CH), 135.0 ($C_q$), 131.2 ($C_q$), 128.2 (CH), 123.7 (CH), 122.5 (CH), 115.5 (CH), 111.5 (CH), 55.2 ($CH_2$), 33.1 ($CH_2$), 32.0 ($CH_2$), 30.1 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.3 (2C, $CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{21}H_{28}N_2 + H^+$ $[M + H]^+$ 309.2325; Found 309.2325.

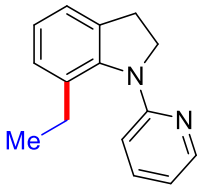
### 3.4.3 Representative Procedure for Alkylation B

**Synthesis of 2-(2-Octylphenyl)pyridine (5aa):** To a flame-dried screw-cap tube equipped with magnetic stir bar were introduced 2-phenylpyridine (**4a**; 0.030 g, 0.20 mmol), 1-bromooctane (**2a**; 0.077 g, 0.40 mmol), $MnBr_2$ (0.0086 g, 0.04 mmol, 20.0 mol%), and LiHMDS (0.067 g, 0.40 mmol) inside the glove box. To the above mixture in the tube was added *tert*-butyl benzene (1.0 mL). The resultant reaction mixture in the tube was immersed in a preheated oil bath at 120 °C and stirred for 24 h. At ambient temperature, the reaction mixture was quenched with distilled $H_2O$ (10.0 mL) and the crude product was extracted with EtOAc (15 mL × 3). The combined organic extract was dried over $Na_2SO_4$ and the volatiles were evaporated in vacuo. The remaining residue was purified by column chromatography on silica gel (petroleum ether/ EtOAc: 10/1) to yield **5aa** (0.038 g, 70%) as a light yellow liquid.

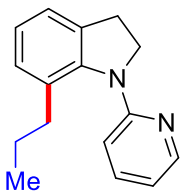



$^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.69 (ddd, $J$ = 4.9, 1.9, 0.9 Hz, 1H, Ar–H), 7.74 (td, $J$ = 7.8, 1.9 Hz, 1H, Ar–H), 7.38 (dt, $J$ = 7.9, 1.0 Hz, 1H, Ar–H), 7.35-7.23 (m, 5H, Ar–H), 2.69 (t, $J$ = 7.9 Hz, 2H, $CH_2$), 1.48-1.41 (m, 2H, $CH_2$), 1.27-1.17 (m, 10H, $CH_2$), 0.86 (t, $J$ = 7.1 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 160.5 ($C_q$), 149.3 (CH), 141,0 ($C_q$), 140.5 ($C_q$), 136.2 (CH), 129.9 (2C, CH), 128.4 (CH), 125.9 (CH), 124.3 (CH), 121.8 (CH), 33.1 ($CH_2$), 32.0 ($CH_2$), 31.4 ($CH_2$), 29.6 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{19}H_{25}N + H^+$ $[M + H]^+$ 268.2060; Found 268.2056.

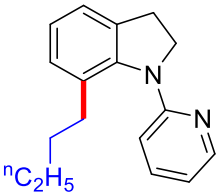
### 3.4.4 Characterization Data for Alkylation



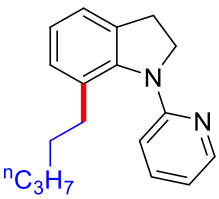

**7-Ethyl-1-(pyridin-2-yl)indoline (3ab):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 1-bromoethane (**2b**; 0.044 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3ab** (0.031 g, 68%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.30 (dd, $J$ = 5.0, 1.1 Hz, 1H, Ar–H), 7.51-7.46 (m, 1H, Ar–H), 7.11 (vt, $J$ = 6.9 Hz, 2H, Ar–H), 7.00 (vt, $J$ = 7.5 Hz, 1H, Ar–H), 6.79-6.76 (m, 1H, Ar–H), 6.63 (d, $J$ = 8.4 Hz, 1H, Ar–H), 4.30 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 3.04 (t, $J$ = 7.9 Hz, 2H, $CH_2$), 2.41 (q, $J$ = 7.5 Hz, 2H, $CH_2$), 1.12 (t, $J$ = 7.5 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 158.7 ($C_q$), 148.1 (CH), 143.7 ($C_q$), 137.1 (CH), 134.9 ($C_q$), 132.3 ($C_q$), 127.3 (CH), 123.7 (CH), 122.5 (CH), 115.6 (CH), 111.4 (CH), 55.2 ($CH_2$), 30.1 ($CH_2$), 25.8 ($CH_2$), 13.6 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{15}H_{16}N_2 + H^+$ $[M + H]^+$ 225.1386; Found 225.1385.



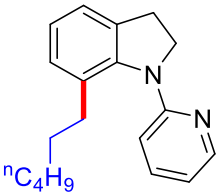
**7-Propyl-1-(pyridin-2-yl)indoline (3ac):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 1-bromopropane (**2c**; 0.049 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3ac** (0.035 g, 72%) as a light-yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.30 (ddd, $J$ = 4.9, 1.1, 0.9 Hz, 1H, Ar–H), 7.50-7.45 (m, 1H, Ar–H), 7.11 (d, $J$ = 7.1 Hz, 1H, Ar–H), 7.06 (d, $J$ = 7.6 Hz, 1H, Ar–H), 6.98 (vt, $J$ = 7.4 Hz, 1H, Ar–H), 6.79-6.75 (m, 1H, Ar–H), 6.64 (d, $J$ = 8.4 Hz, 1H, Ar–H), 4.30 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 3.03 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 2.37 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.59-1.50 (m, 2H, $CH_2$), 0.77 (t, $J$ = 7.3 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 158.7 ($C_q$), 148.3 (CH), 143.9 ($C_q$), 137.0 (CH), 135.0 ($C_q$), 130.9 ($C_q$), 128.1 (CH), 123.5 (CH), 122.5 (CH), 115.6 (CH), 111.3 (CH), 55.1 ($CH_2$), 35.0 ($CH_2$), 30.1 ($CH_2$), 22.5 ($CH_2$), 14.2 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{16}H_{18}N_2$ + $H^+$ $[M + H]^+$ 239.1543; Found 239.1541.



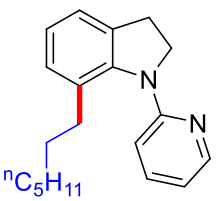

**7-Butyl-1-(pyridin-2-yl)indoline (3ad):** The representative procedure **A** was followed, using 1 (pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 1-bromobutane (**2d**; 0.055 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3ad** (0.035 g, 68%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.30 (ddd, $J$ = 4.9, 1.1, 0.9 Hz, 1H, Ar–H), 7.50-7.45 (m, 1H, Ar–H), 7.11 (d, $J$ = 7.1 Hz, 1H, Ar–H), 7.07 (d, $J$ = 7.6 Hz, 1H, Ar–H), 6.97 (vt, $J$ = 7.4 Hz, 1H, Ar–H), 6.79-6.75 (m, 1H, Ar–H), 6.64 (d, $J$ = 8.4 Hz, 1H, Ar–H), 4.29 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 3.03 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 2.40 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.53-1.46 (m, 2H, $CH_2$), 1.21-1.12 (m, 2H, $CH_2$), 0.77 (t, $J$ = 7.4 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 158.7 ($C_q$), 148.2 (CH), 143.9 ($C_q$), 137.0 (CH), 135.0 ($C_q$), 131.1 ($C_q$), 128.2 (CH), 123.6 (CH), 122.5 (CH), 115.6 (CH), 111.4 (CH), 55.1 ($CH_2$), 32.7 ($CH_2$), 31.5 ($CH_2$), 30.1 ($CH_2$), 22.7 ($CH_2$),14.0 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{17}H_{20}N_2$ + $H^+$ $[M + H]^+$ 253.1699; Found 253.1698.



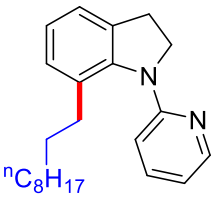
**7-Pentyl-1-(pyridin-2-yl)indoline (3ae):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 1-bromopentane (**2e**; 0.060 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3ae** (0.040 g, 74%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.30 (dd, $J$ = 4.9, 1.6 Hz, 1H, Ar–H), 7.50-7.45 (m, 1H, Ar–H), 7.11 (d, $J$ = 7.1 Hz, 1H, Ar–H), 7.07 (d, $J$ = 7.5 Hz, 1H, Ar–H), 6.98 (vt, $J$ = 7.4 Hz, 1H, Ar–H), 6.78-6.75 (m, 1H, Ar–H), 6.63 (d, $J$ = 8.3 Hz, 1H, Ar–H), 4.29 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 3.03 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 2.39 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.55-1.48 (m, 2H, $CH_2$), 1.22-1.10 (m, 4H, $CH_2$), 0.80 (t, $J$ = 7.0 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 158.7 ($C_q$), 148.2 (CH), 143.8 ($C_q$), 137.0 (CH), 135.0 ($C_q$), 131.1 ($C_q$), 128.1 (CH), 123.6 (CH), 122.5 (CH), 115.6 (CH), 111.4 (CH), 55.1 ($CH_2$), 33.0 ($CH_2$), 31.8 ($CH_2$), 30.1 ($CH_2$), 29.0 ($CH_2$), 22.6 ($CH_2$), 14.2 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{18}H_{23}N_2 + H^+$ $[M + H]^+$ 267.1856; Found 267.1854.



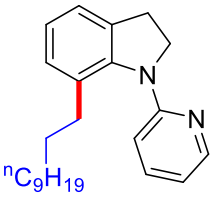

**7-Hexyl-1-(pyridin-2-yl)indoline (3af):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 1-bromohexane (**2f**; 0.066 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3af** (0.038 g, 66%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.30 (dd, $J$ = 5.0, 1.3 Hz, 1H, Ar–H), 7.50-7.46 (m, 1H, Ar–H), 7.11 (d, $J$ = 7.1 Hz, 1H, Ar–H), 7.06 (d, $J$ = 7.5 Hz, 1H, Ar–H), 6.97 (vt, $J$ = 7.4 Hz, 1H, Ar–H), 6.78-6.75 (m, 1H, Ar–H), 6.64 (d, $J$ = 8.4 Hz, 1H, Ar–H), 4.30 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 3.03 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 2.39 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.54-1.46 (m, 2H, $CH_2$), 1.22-1.12 (m, 6H, $CH_2$), 0.81 (t, $J$ = 6.9 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 158.6 ($C_q$), 148.2 (CH), 143.8 ($C_q$), 137.0 (CH), 135.0 ($C_q$), 131.2 ($C_q$), 128.2 (CH), 123.6 (CH), 122.5 (CH), 115.6 (CH), 111.4 (CH), 55.1 ($CH_2$), 33.1 ($CH_2$), 31.8 ($CH_2$), 30.1 ($CH_2$), 29.3 (2C, $CH_2$), 22.7 ($CH_2$), 14.2 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{19}H_{24}N_2 + H^+$ $[M + H]^+$ 281.2012; Found 281.2013.



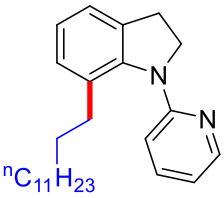
**7-Heptyl-1-(pyridin-2-yl)indoline (3ag):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 1-bromoheptane (**2g**; 0.072 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3ag** (0.041 g, 68%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.30 (dd, $J$ = 5.3, 1.5 Hz, 1H, Ar–H), 7.50-7.45 (m, 1H, Ar–H), 7.11 (d, $J$ = 6.9 Hz, 1H, Ar–H), 7.06 (d, $J$ = 6.9 Hz, 1H, Ar–H), 6.97 (vt, $J$ = 7.6 Hz, 1H, Ar–H), 6.78-6.76 (m, 1H, Ar–H), 6.63 (d, $J$ = 8.4 Hz, 1H, Ar–H), 4.29 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 3.03 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 2.38 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.54-1.47 (m, 2H, $CH_2$), 1.22-1.11(m, 8H, $CH_2$), 0.83 (t, $J$ = 6.9 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 158.6 ($C_q$), 148.2 (CH), 143.8 ($C_q$), 137.0 (CH), 135.0 ($C_q$), 131.1 ($C_q$), 128.1 (CH), 123.5 (CH), 122.5 (CH), 115.6 (CH), 111.4 (CH), 55.1 ($CH_2$), 33.1 ($CH_2$), 31.9 ($CH_2$), 30.1 ($CH_2$), 29.6 ($CH_2$), 29.3 ($CH_2$), 29.2 ($CH_2$), 22.8 ($CH_2$), 14.2 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{20}H_{26}N_2$ + $H^+$ $[M + H]^+$ 295.2169; Found 295.2169.




**7-Decyl-1-(pyridin-2-yl)indoline (3ah):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 1-bromodecane (**2h**; 0.088 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3ah** (0.043 g, 63%) as a light brown liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.30 (d, $J$ = 4.6 Hz, 1H, Ar–H), 7.50-7.45 (m, 1H, Ar–H), 7.11 (d, $J$ = 6.9 Hz, 1H, Ar–H), 7.07 (d, $J$ = 7.6 Hz, 1H, Ar–H), 6.98 (vt, $J$ = 7.9 Hz, 1H, Ar–H), 6.78-6.75 (m, 1H, Ar–H), 6.64 (d, $J$ = 8.4 Hz, 1H, Ar–H), 4.30 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 3.03 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 2.39 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.56-1.47 (m, 2H, $CH_2$), 1.31-1.15 (m, 14H, $CH_2$), 0.88 (t, $J$ = 6.1 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 158.6 ($C_q$), 148.2 (CH), 143.8 ($C_q$), 137.0 (CH), 135.0 ($C_q$), 131.1 ($C_q$), 128.1 (CH), 123.5 (CH), 122.4 (CH), 115.6 (CH), 111.3 (CH), 55.1 ($CH_2$), 33.0 ($CH_2$), 32.1 ($CH_2$), 30.1 ($CH_2$), 29.7 (2C, $CH_2$), 29.6 ($CH_2$), 29.5 (2C, $CH_2$), 29.3 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{23}H_{32}N_2$ + $H^+$ $[M + H]^+$ 337.2638; Found 337.2641.

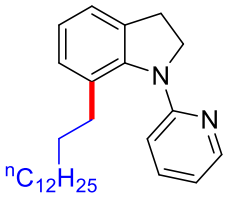



**7-Undecyl-1-(pyridin-2-yl)indoline (3ai):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 1-bromoundecane (**2i**; 0.094 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3ai** (0.037 g, 52%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.29 (ddd, $J$ = 4.9, 2.0, 0.9 Hz, 1H, Ar–H), 7.49-7.45 (m, 1H, Ar–H), 7.11 (d, $J$ = 7.1 Hz, 1H, Ar–H), 7.06 (d, $J$ = 7.6 Hz, 1H, Ar–H), 6.97 (vt, $J$ = 7.5 Hz, 1H, Ar–H), 6.78-6.75 (m, 1H, Ar–H), 6.63 (d, $J$ = 8.3 Hz, 1H, Ar–H), 4.29 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 3.03 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 2.39 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.54-1.47 (m, 2H, $CH_2$), 1.29-1.14 (m, 16H, $CH_2$), 0.88 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 158.7 ($C_q$), 148.3 (CH), 143.9 ($C_q$), 136.9 (CH), 135.0 ($C_q$), 131.1 ($C_q$), 128.1 (CH), 123.5 (CH), 122.5 (CH), 115.6 (CH), 111.4 (CH), 55.1 ($CH_2$), 33.1 ($CH_2$), 32.1 ($CH_2$), 30.1 ($CH_2$), 29.8 (2C, $CH_2$), 29.7 ($CH_2$), 29.6 (2C, $CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 22.9 ($CH_2$) 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{24}H_{34}N_2$ + $H^+$ $[M + H]^+$ 351.2795; Found 351.2799.

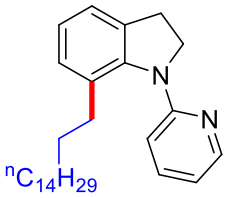



**7-Tridecyl-1-(pyridin-2-yl)indoline (3aj):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 1-bromotridecane (**2j**; 0.11 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3aj** (0.041 g, 53%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.30 (d, $J$ = 4.6 Hz, 1H, Ar–H), 7.50-7.46 (m, 1H, Ar–H), 7.11 (d, $J$ = 7.1 Hz, 1H, Ar–H), 7.06 (d, $J$ = 7.6 Hz, 1H, Ar–H), 6.97 (vt, $J$ = 7.3 Hz, 1H, Ar–H), 6.78-6.75 (m, 1H, Ar–H), 6.64 (d, $J$ = 8.4 Hz, 1H, Ar–H), 4.30 (t, $J$ = 7.0 Hz, 2H, $CH_2$), 3.03 (t, $J$ = 7.7 Hz, 2H, $CH_2$), 2.39 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.52-1.49 (m, 2H, $CH_2$), 1.30-1.15 (m, 20H, $CH_2$), 0.88 (t, $J$ = 6.4 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 158.6 ($C_q$), 148.2 (CH), 143.8 ($C_q$), 136.9 (CH), 135.0 ($C_q$), 131.1 ($C_q$), 128.1 (CH), 123.5 (CH), 122.5 (CH), 115.6 (CH), 111.3 (CH), 55.1 ($CH_2$), 33.0 ($CH_2$), 32.1 ($CH_2$), 30.1 ($CH_2$), 29.9 ($CH_2$), 29.8 (3C, $CH_2$), 29.7 ($CH_2$), 29.6 (2C, $CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 22.9 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z*

Calcd for $C_{26}H_{38}N_2$ + $H^+$ $[M + H]^+$ 379.3108; Found 379.3110.

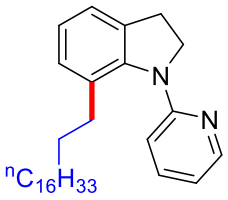



**1-(Pyridin-2-yl)-7-tetradecylindoline (3ak):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 1-bromotetradecane (**2k**; 0.11 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3ak** (0.042 g, 52%) as a light-yellow liquid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.29 (ddd, $J$ = 5.0, 2.0, 0.9 Hz, 1H, Ar–H), 7.50-7.45 (m, 1H, Ar–H), 7.10 (d, $J$ = 7.1 Hz, 1H, Ar–H), 7.06 (d, $J$ = 7.6 Hz, 1H, Ar–H), 6.97 (vt, $J$ = 7.4 Hz, 1H, Ar–H), 6.78-6.75 (m, 1H, Ar–H), 6.63 (d, $J$ = 8.4 Hz, 1H, Ar–H), 4.29 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 3.03 (t, $J$ = 7.9 Hz, 2H, $CH_2$), 2.38 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.54-1.46 (m, 2H, $CH_2$), 1.32-1.14 (m, 22H, $CH_2$), 0.88 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 158.6 ($C_q$), 148.2 (CH), 143.8 ($C_q$), 137.0 (CH), 135.0 ($C_q$), 131.1 ($C_q$), 128.1 (CH), 123.5 (CH), 122.5 (CH), 115.6 (CH), 111.4 (CH), 55.1 ($CH_2$), 33.1 ($CH_2$), 32.1 ($CH_2$), 30.1 ($CH_2$), 29.9 (2C, $CH_2$), 29.8 (3C, $CH_2$), 29.7 ($CH_2$), 29.6 (2C, $CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 22.9 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{27}H_{40}N_2$ + $H^+$ $[M + H]^+$ 393.3271; Found 393.2538.

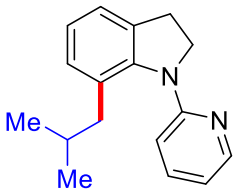



**7-Hexadecyl-1-(pyridin-2-yl)indoline (3al):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 1-bromohexadecane (**2l**; 0.120 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3al** (0.05 g, 58%) as a light yellow liquid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.30 (dd, $J$ = 5.0, 1.1 Hz, 1H, Ar–H), 7.50-7.46 (m, 1H, Ar–H), 7.10 (d, $J$ = 7.1 Hz, 1H, Ar–H), 7.06 (d, $J$ = 7.6 Hz, 1H, Ar–H), 6.97 (vt, $J$ = 7.4 Hz, 1H, Ar–H), 6.79-6.75 (m, 1H, Ar–H), 6.64 (d, $J$ = 8.3 Hz, 1H, Ar–H), 4.30 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 3.03 (t, $J$ = 7.9 Hz, 2H, $CH_2$), 2.38 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.54-1.46 (m, 2H, $CH_2$), 1.32-1.14 (m, 26H, $CH_2$), 0.88 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 158.6 ($C_q$), 148.1 (CH), 143.8 ($C_q$), 137.1 (CH), 135.0 ($C_q$), 131.2 ($C_q$), 128.2 (CH), 123.6 (CH), 122.5 (CH), 115.6

(CH), 111.4 (CH), 55.2 ($CH_2$), 33.1 ($CH_2$), 32.1 ($CH_2$), 30.1 ($CH_2$), 29.9 (4C, $CH_2$), 29.8 (3C, $CH_2$), 29.7 (2C, $CH_2$), 29.6 (2C, $CH_2$), 29.3 ($CH_2$), 22.9 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{29}H_{44}N_2 + H^+$ $[M + H]^+$ 421.3577; Found 421.3577.

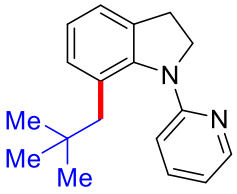



**7-Octadecyl-1-(pyridin-2-yl)indoline (3am):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 1-bromooctadecane (**2m**; 0.13 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3am** (0.058 g, 63%) as a light yellow liquid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.30 (d, *J* = 5.3 Hz, 1H, Ar–H), 7.49-7.45 (m, 1H, Ar–H), 7.11 (d, *J* = 6.9 Hz, 1H, Ar–H), 7.06 (d, *J* = 6.9 Hz, 1H, Ar–H), 6.97 (vt, *J* = 7.6 Hz, 1H, Ar–H), 6.78-6.75 (m, 1H, Ar–H), 6.63 (d, *J* = 8.4 Hz, 1H, Ar–H), 4.29 (t, *J* = 7.6 Hz, 2H, $CH_2$), 3.03 (t, *J* = 8.4 Hz, 2H, $CH_2$), 2.38 (t, *J* = 7.6 Hz, 2H, $CH_2$), 1.52-1.48 (m, 2H, $CH_2$), 1.32-1.15 (m, 30H, $CH_2$), 0.88 (t, *J* = 6.9 Hz, 3H, $CH_3$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 158.7 ($C_q$), 148.3 (CH), 143.9 ($C_q$), 136.9 (CH), 135.0 ($C_q$), 131.2 ($C_q$), 128.2 (CH), 123.5 (CH), 122.5 (CH), 115.6 (CH), 111.3 (CH), 55.1 ($CH_2$), 33.1 ($CH_2$), 32.1 ($CH_2$), 30.1 ($CH_2$), 29.9 (6C, $CH_2$), 29.8 (3C, $CH_2$), 29.7 (2C, $CH_2$), 29.6 (2C, $CH_2$), 29.3 ($CH_2$), 22.9 ($CH_2$) 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{31}H_{48}N_2 + H^+$ $[M + H]^+$ 449.3890; Found 449.2585.

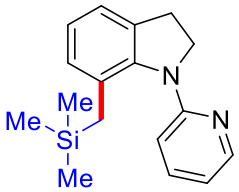



**7-Isobutyl-1-(pyridin-2-yl)indoline (3an):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 1-bromo-2-methylpropane (**2n**; 0.054 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3an** (0.029 g, 56%) as a light yellow liquid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.31 (ddd, *J* = 5.0, 1.9, 0.8 Hz, 1H, Ar–H), 7.50-7.45 (m, 1H, Ar–H), 7.11 (d, *J* = 6.9 Hz, 1H, Ar–H), 7.01-6.94 (m, 2H, Ar–H), 6.78-6.75 (m, 1H, Ar–H), 6.63 (d, *J* = 8.4 Hz, 1H, Ar–H), 4.28 (t, *J* = 7.8 Hz, 2H, $CH_2$), 3.02 (t, *J* = 7.8 Hz, 2H, $CH_2$), 2.31 (d, *J* = 7.1 Hz, 2H, $CH_2$), 1.85-1.78 (m, 1H, CH), 0.70 (d, *J* = 6.6 Hz, 6H, $CH_3$). $^{13}$C{$^1$H}-NMR (100 MHz,

$CDCl_3$): $\delta$ = 158.3 ($C_q$), 148.1 (CH), 144.1 ($C_q$), 137.0 (CH), 135.1 ($C_q$), 130.1 ($C_q$), 129.1 (CH), 123.4 (CH), 122.6 (CH), 115.5 (CH), 111.4 (CH), 55.1 ($CH_2$), 42.7 ($CH_2$), 30.1 ($CH_2$), 28.5 (CH), 22.6 (2C, $CH_3$). HRMS (ESI): *m/z* Calcd for $C_{17}H_{20}N_2$ + $H^+$ $[M + H]^+$ 253.1699; Found 253.1696.

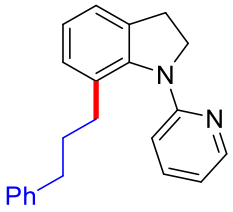



**7-Neopentyl-1-(pyridin-2-yl)indoline (3ao):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 1-bromo-2,2-dimethylpropane (**2o**; 0.060 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3ao** (0.015 g, 28%) as a light yellow liquid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.30 (dd, *J* = 5.0, 1.1 Hz, 1H, Ar–H), 7.48-7.44 (m, 1H, Ar–H), 7.15-1.13 (m, 1H, Ar–H), 6.98-6.95 (m, 2H, Ar–H), 6.77-6.74 (m, 1H, Ar–H), 6.65 (d, *J* = 8.4 Hz, 1H, Ar–H), 4.28 (t, *J* = 7.6 Hz, 2H, $CH_2$), 2.99 (t, *J* = 7.6 Hz, 2H, $CH_2$), 2.39 (s, 2H, $CH_2$), 0.74 (s, 9H, $CH_3$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 158.0 ($C_q$), 147.9 (CH), 144.5 ($C_q$), 137.2 (CH), 135.5 ($C_q$), 131.3 (CH), 128.8 ($C_q$), 123.2 (CH), 123.0 (CH), 115.3 (CH), 111.0 (CH), 54.9 ($CH_2$), 46.9 ($CH_2$), 33.2 ($C_q$), 30.0 ($CH_2$), 29.6 (3C, $CH_3$). HRMS (ESI): *m/z* Calcd for $C_{18}H_{22}N_2$ + $H^+$ $[M + H]^+$ 267.1856; Found 267.1851.

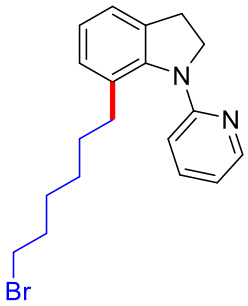



**1-(Pyridin-2-yl)-7-((trimethylsilyl)methyl)indoline (3ap):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.059 g, 0.30 mmol) and 1-(bromomethyl)trimethylsilane (**2p**; 0.10 g, 0.60 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3ap** (0.043 g, 51%) as a light yellow liquid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.31 (ddd, *J* = 5.0, 2.0, 0.9 Hz, 1H, Ar–H), 7.49-7.44 (m, 1H, Ar–H), 7.02 (dd, *J* = 7.3, 1.1 Hz, 1H, Ar–H), 6.92 (t, *J* = 7.6 Hz, 1H, Ar–H), 6.84 (d, *J* = 7.1 Hz, 1H, Ar–H), 6.76-6.73 (m, 1H, Ar–H), 6.62 (d, *J* = 8.4 Hz, 1H, Ar–H), 4.28 (t, *J* =7.6 Hz, 2H, $CH_2$), 2.98 (t, *J* = 7.6 Hz, 2H, $CH_2$), 1.94 (s, 2H, $CH_2$), 0.15 (s,

9H, $CH_3$). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): $\delta$ = 157.8 ($C_q$), 148.3 (CH), 142.9 ($C_q$), 136.9 (CH), 135.5 ($C_q$), 129.5 ($C_q$), 128.6 (CH), 123.7 (CH), 121.0 (CH), 115.2 (CH), 111.0 (CH), 54.9 ($CH_2$), 30.1 ($CH_2$), 24.7 ($CH_2$), –1.4 (3C, $CH_3$). HRMS (ESI): *m/z* Calcd for $C_{17}H_{22}N_2Si$ + $H^+$ $[M + H]^+$ 283.1625; Found 283.1628.

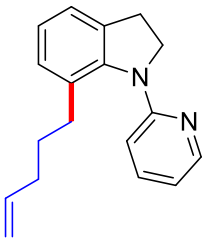



**7-(3-Phenylpropyl)-1-(pyridin-2-yl)indoline (3aq):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and (3-bromopropyl)benzene (**2q**; 0.079 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3aq** (0.048 g, 75%) as a light yellow liquid. $^1H$-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.30 (dd, *J* = 5.0, 1.9 Hz, 1H, Ar–H), 7.50-7.45 (m, 1H, Ar–H), 7.22 (vt, *J* = 7.5 Hz, 2H, Ar–H), 7.13 (vt, *J* = 7.4 Hz, 2H, Ar–H), 7.06 (vt, *J* = 7.3 Hz, 3H, Ar–H), 6.99 (vt, *J* = 7.4 Hz, 1H, Ar–H), 6.80-6.77 (m, 1H, Ar–H), 6.63 (d, *J* = 8.3 Hz, 1H, Ar–H), 4.31 (t, *J* = 7.8 Hz, 2H, $CH_2$), 3.05 (t, *J* = 7.8 Hz, 2H, $CH_2$), 2.46 (t, *J* = 7.9 Hz, 4H, $CH_2$), 1.89-1.81 (m, 2H, $CH_2$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 158.5 ($C_q$), 148.2 (CH), 143.9 ($C_q$), 142.5 ($C_q$), 137.0 (CH), 135.0 ($C_q$), 130.0 ($C_q$), 128.5 (2C, CH), 128.3 (2C, CH), 128.2 (CH), 125.7 (CH), 123.6 (CH), 122.6 (CH), 115.7 (CH), 111.4 (CH), 55.2 ($CH_2$), 35.8 ($CH_2$), 32.9 ($CH_2$), 30.9 ($CH_2$), 30.1 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{22}H_{22}N_2$ + $H^+$ $[M + H]^+$ 315.1856; Found 315.1855.

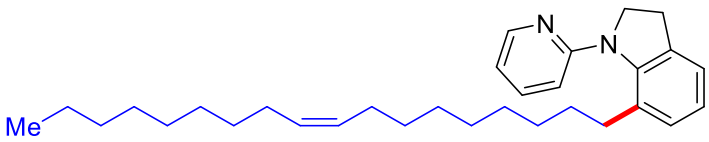



**7-(6-Bromohexyl)-1-(pyridin-2-yl)indoline (3ar):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.059 g, 0.30 mmol) and 1,6-dibromohexane (**2r**; 0.15 g, 0.61 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3ar** (0.030 g, 28%) as a light-yellow liquid. $^1H$-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.30 (d, *J* = 4.8, 1H, Ar–H), 7.51-7.47 (m, 1H, Ar–H), 7.11 (d, *J* = 7.1 Hz, 1H,

Ar–H), 7.03 (d, *J* = 7.6 Hz, 1H, Ar–H), 6.97 (vt, *J* = 7.3 Hz, 1H, Ar–H), 6.80-6.77 (m, 1H, Ar–H), 6.64 (d, *J* = 8.4 Hz, 1H, Ar–H), 4.29 (t, *J* = 7.8 Hz, 2H, $CH_2$), 3.32 (t, *J* = 6.9 Hz, 2H, $CH_2$), 3.04 (t, *J* = 7.8 Hz, 2H, $CH_2$), 2.40 (t, *J* = 7.5 Hz, 2H, $CH_2$), 1.78-1.71 (m, 2H, $CH_2$), 1.55-1.47 (m, 2H, $CH_2$), 1.33-1.26 (m, 2H, $CH_2$), 1.20-1.12 (m, 2H, $CH_2$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 158.6 ($C_q$), 148.2 (CH), 143.9 ($C_q$), 137.1 (CH), 135.1 ($C_q$), 130.8 ($C_q$), 128.2 (CH), 123.6 (CH), 122.6 (CH), 115.7 (CH), 111.4 (CH), 55.2 ($CH_2$), 34.1 ($CH_2$), 33.0 ($CH_2$), 32.8 ($CH_2$), 30.1 ($CH_2$), 30.0 ($CH_2$), 28.6 ($CH_2$), 28.02 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{19}H_{23}N_2Br + H^+$ $[M + H]^+$ 359.1117, 361.1097; Found 359.1112, 361.1090.

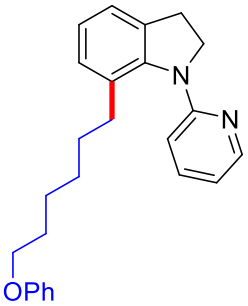



**7-(Pent-4-en-1-yl)-1-(pyridin-2-yl)indoline (3as):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.059 g, 0.30 mmol) and 5-bromopent-1-ene (**2s**; 0.089 g, 0.60 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3as** (0.030 g, 38%) as a light yellow liquid. $^1H$-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.29 (d, *J* = 4.8, 1H, Ar–H), 7.50-7.46 (m, 1H, Ar–H), 7.11 (d, *J* = 7.3 Hz, 1H, Ar–H), 7.06 (d, *J* = 7.5 Hz, 1H, Ar–H), 6.97 (vt, *J* = 7.4 Hz, 1H, Ar–H), 6.79-6.76 (m, 1H, Ar–H), 6.64 (d, *J* = 8.4 Hz, 1H, Ar–H), 5.71-5.60 (m, 1H, CH), 4.91-4.83 (m, 2H, $CH_2$), 4.29 (t, *J* = 7.9 Hz, 2H, $CH_2$), 3.04 (t, *J* = 7.8 Hz, 2H, $CH_2$), 2.42 (t, *J* = 7.6 Hz, 2H, $CH_2$), 1.90 (q, *J* = 7.1 Hz, 2H, $CH_2$), 1.64-1.57 (m, 2H, $CH_2$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 158.6 ($C_q$), 148.3 (CH), 143.9 ($C_q$), 138.7 (CH), 137.0 (CH), 135.1 ($C_q$), 130.6 ($C_q$), 128.2 (CH), 123.5 (CH), 122.6 (CH), 115.6 (CH), 114.6 (CH), 111.4 ($CH_2$), 55.1 ($CH_2$), 33.6 ($CH_2$), 32.6 ($CH_2$), 30.1 ($CH_2$), 28.5 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{18}H_{20}N_2 + H^+$ $[M + H]^+$ 265.1699; Found 265.1698.

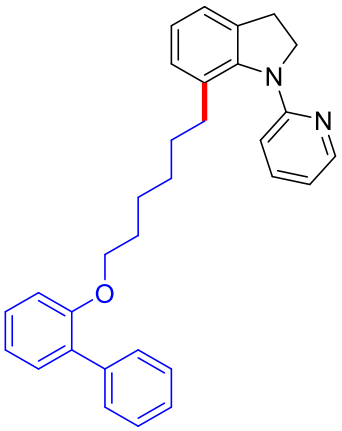



**(Z)-7-(Heptadec-8-en-1-yl)-1-(pyridin-2-yl)indoline (3at):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and (*Z*)-1-bromooctadec-9-ene (**2t**; 0.13 g, 0.40 mmol). Purification by column chromatography on

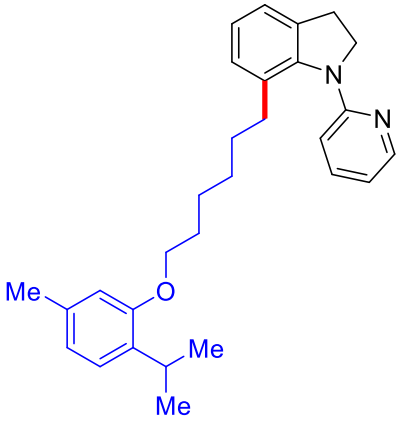
silica gel (petroleum ether/EtOAc: 5/1) yielded **3at** (0.027 g, 30%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.30 (ddd, $J$ = 5.0, 1.9, 0.8 Hz, 1H, Ar–H), 7.50-7.45 (m, 1H, Ar–H), 7.11 (d, $J$ = 7.3 Hz, 1H, Ar–H), 7.06 (d, $J$ = 7.5 Hz, 1H, Ar–H), 6.97 (vt, $J$ = 7.4 Hz, 1H, Ar–H), 6.78-6.75 (m, 1H, Ar–H), 6.64 (d, $J$ = 8.3 Hz, 1H, Ar–H), 5.38-5.29 (m, 2H, CH), 4.29 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 3.03 (t, $J$ = 7.9 Hz, 2H, $CH_2$), 2.39 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 2.05-1.96 (m, 4H, $CH_2$), 1.54-1.47 (m, 2H, $CH_2$), 1.32-1.15 (m, 22H, $CH_2$), 0.88 (t, $J$ = 6.5 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 158.7 ($C_q$), 148.2 (CH), 143.9 ($C_q$), 137.0 (CH), 135.0 ($C_q$), 131.1 ($C_q$), 130.1 (2C, CH), 128.2 (CH), 123.5 (CH), 122.5 (CH), 115.6 (CH), 111.4 (CH), 55.1 ($CH_2$), 33.1 ($CH_2$), 32.1 ($CH_2$), 30.1 ($CH_2$), 30.0 ($CH_2$), 29.9 ($CH_2$), 29.7 ($CH_2$), 29.6 (2C, $CH_2$), 29.5 (4C, $CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 27.4 ($CH_2$), 22.9 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{31}H_{46}N_2$ + $H^+$ $[M + H]^+$ 447.3734; Found 447.3726.



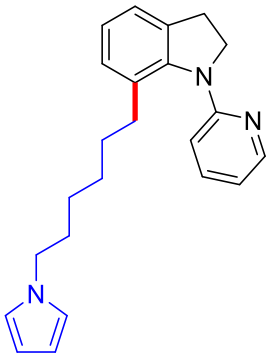

**7-(4-Phenoxyhexyl)-1-(pyridin-2-yl)indoline (3au):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.059 g, 0.30 mmol) and (4-bromohexyl)benzene (**2u**; 0.15 g, 0.60 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3au** (0.045 g, 40%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.29 (dd, $J$ = 5.0, 1.1 Hz, 1H, Ar–H), 7.48-7.44 (m, 1H, Ar–H), 7.28-7.25 (m, 2H, Ar–H), 7.11 (d, $J$ = 7.3 Hz, 1H, Ar–H), 7.06 (d, $J$ = 7.6 Hz, 1H, Ar–H), 6.97 (vt, $J$ = 7.3 Hz, 1H, Ar–H), 6.92 (t, $J$ = 7.3 Hz, 1H, Ar–H), 6.87 (dd, $J$ = 8.0, 0.8 Hz, 2H, Ar–H), 6.76-6.73 (m, 1H, Ar–H), 6.64 (d, $J$ = 8.4 Hz, 1H, Ar–H), 4.29 (t, $J$ = 8.0 Hz, 2H, $CH_2$), 3.86 (t, $J$ = 6.5 Hz, 2H, $CH_2$), 3.03 (t, $J$ = 8.0 Hz, 2H, $CH_2$), 2.42 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.70-1.64 (m, 2H, $CH_2$), 1.57-1.51 (m, 2H, $CH_2$), 1.36-1.30 (m, 2H, $CH_2$), 1.24-1.18 (m, 2H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 159.3 ($C_q$), 158.6 ($C_q$), 148.2 (CH), 143.8 ($C_q$), 137.0 (CH), 135.0 ($C_q$), 130.9 ($C_q$), 129.5 (2C, CH), 128.2 (CH), 123.6 (CH), 122.6 (CH), 120.6 (CH), 115.6 (CH), 114.6 (2C, CH), 111.4 (CH), 67.9 ($CH_2$), 55.1 ($CH_2$), 33.0 ($CH_2$), 30.1 ($CH_2$), 29.3 (2C, $CH_2$), 29.1 ($CH_2$), 25.9 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{25}H_{28}N_2O$ + $H^+$ $[M + H]^+$ 373.2274; Found 373.2276.




**7-(6-([1,1'-Biphenyl]-2-yloxy)hexyl)-1-(pyridin-2-yl)indoline (3av):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 2-((6-bromohexyl)oxy)-1,1'-biphenyl (**2v**; 0.13 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3av** (0.051 g, 56%) as a colorless liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.28 (dd, $J$ = 4.9, 1.5 Hz, 1H, Ar–H), 7.53 (m, 2H, Ar–H), 7.46-7.42 (m, 1H, Ar–H), 7.39-7.25 (m, 5H, Ar–H), 7.11 (d, $J$ = 7.0 Hz, 1H, Ar–H), 7.05-6.93 (m, 4H, Ar–H), 6.76-6.72 (m, 1H, Ar–H), 6.62 (d, $J$ = 8.4 Hz, 1H, Ar–H), 4.28 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 3.87 (t, $J$ = 6.5 Hz, 2H, $CH_2$), 3.03 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 2.38 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.64-1.57 (m, 2H, $CH_2$), 1.53-1.45 (m, 2H, $CH_2$), 1.30-1.22 (m, 2H, $CH_2$), 1.18-1.12 (m, 2H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 158.5 ($C_q$), 156.2 ($C_q$), 148.1 (CH), 143.8 ($C_q$), 138.8 ($C_q$), 137.1 (CH), 135.0 ($C_q$), 131.0 ($C_q$), 131.0 (CH), 130.9 ($C_q$), 129.7 (2C, CH), 128.7 (CH), 128.2 (CH), 127.9 (2C, CH), 126.9 (CH), 123.6 (CH), 122.6 (CH), 120.9 (CH), 115.7 (CH), 112.7 (CH), 111.5 (CH), 68.5 ($CH_2$), 55.2 ($CH_2$), 33.0 ($CH_2$), 30.1 ($CH_2$), 29.1 (3C, $CH_2$), 25.9 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{31}H_{32}N_2O$ + $H^+$ $[M + H]^+$ 449.2587; Found 449.2592.

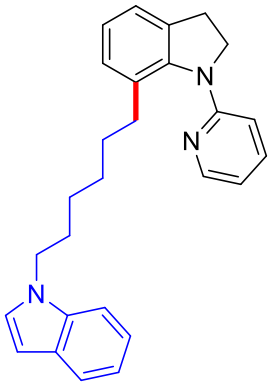


**7-(6-(2-Isopropyl-5-methylphenoxy)hexyl)-1-(pyridin-2-yl)indoline (3aw):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 2-((6-bromohexyl)oxy)-1-isopropyl-4-methylbenzene (**2w**; 0.13 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3aw** (0.039 g, 45%) as a colorless liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.31 (dd, $J$ = 5.0, 1.1 Hz, 1H, Ar–H), 7.50-7.47 (m, 1H, Ar–H), 7.11 (d, $J$ = 7.3 Hz, 1H, Ar–H), 7.08 (d, $J$ = 7.6 Hz, 2H, Ar–H), 6.99 (vt, $J$ = 7.6 Hz, 1H, Ar–H), 6.79-6.72 (m, 2H, Ar–H), 6.65 (t, $J$ = 8.4 Hz, 2H, Ar–H), 4.31 (t, $J$ = 8.0 Hz, 2H, $CH_2$), 3.87 (t, $J$ = 6.5 Hz, 2H, $CH_2$), 3.29-3.24 (m, 1H, CH), 3.05 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 2.43 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 2.32 (s, 3H, $CH_3$), 1.73-1.68 (m, 2H, $CH_2$), 1.59-1.53 (m, 2H, $CH_2$), 1.41-1.35 (m, 2H, $CH_2$), 1.25-1.22 (m, 2H, $CH_2$), 1.20 (d, $J$ = 6.9 Hz, 6H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 158.5 ($C_q$), 156.3 ($C_q$), 148.0 (CH), 143.8 ($C_q$), 137.1 (CH), 136.3 ($C_q$), 135.0 ($C_q$), 134.2 ($C_q$), 130.9 ($C_q$), 128.2 (CH), 125.9 (CH), 123.6 (CH), 122.6 (CH), 121.0 (CH), 115.6 (CH), 112.3 (CH), 111.4 (CH), 67.9 ($CH_2$), 55.2 ($CH_2$), 33.0 ($CH_2$), 30.1 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 29.2 ($CH_2$), 26.8 (CH), 26.1 ($CH_2$), 22.9 (2C, $CH_3$), 21.5 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{29}H_{36}N_2O + H^+$ $[M + H]^+$ 429.2900; Found 429.2904.

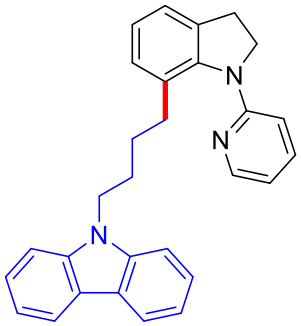



**7-(6-(1*H*-Pyrrol-1-yl)hexyl)-1-(pyridin-2-yl)indoline (3ax):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) 1-(6-bromohexyl)-2*H*-pyrrole (**2x**; 0.092 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3ax** (0.024 g, 34%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.31 (dd, $J$ = 4.9, 1.6 Hz, 1H, Ar–H), 7.51-7.47 (m, 1H, Ar–H), 7.12 (d, $J$ = 7.1 Hz, 1H, Ar–H), 7.04 (d, $J$ = 7.4 Hz, 1H, Ar–H), 6.98 (vt, $J$ = 7.3 Hz, 1H, Ar–H), 6.80-6.77 (m, 1H, Ar–H), 6.65-6.59 (m, 3H, Ar–H), 6.12-6.11 (m, 2H, Ar–H), 4.30 (t, $J$ = 7.9 Hz, 2H, $CH_2$), 3.78 (t, $J$ = 7.1 Hz, 2H, $CH_2$), 3.04 (t, $J$ = 7.9 Hz, 2H, $CH_2$), 2.39 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.69-1.62 (m, 2H, $CH_2$), 1.54-1.47 (m, 2H, $CH_2$), 1.18-1.15 (m, 4H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 158.5 ($C_q$), 148.1 (CH), 143.8 ($C_q$), 137.1 (CH), 135.0

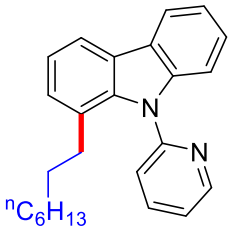
($C_q$), 130.8 ($C_q$), 128.2 (CH), 123.7 (CH), 122.6 (CH), 120.6 (2C, CH), 115.6 (CH), 111.4 (CH), 107.9 (2C, CH), 55.2 ($CH_2$), 49.7 ($CH_2$), 33.0 ($CH_2$), 31.5 ($CH_2$), 30.1 ($CH_2$), 29.1 ($CH_2$), 29.0 ($CH_2$), 26.6 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{23}H_{27}N_3$ + $H^+$ $[M + H]^+$ 346.2278; Found 346.2279.




**7-(6-(Indolin-1-yl)hexyl)-1-(pyridin-2-yl)indoline (3ay):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.059 g, 0.30 mmol) and 1-(6-bromohexyl)indoline (**2y**; 0.17 g, 0.60 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3ay** (0.057 g, 48%) as a light yellow liquid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.30 (dd, *J* = 5.0, 1.1 Hz, 1H, Ar–H), 7.63 (d, *J* = 7.9 Hz, 1H, Ar–H), 7.48-7.44 (m, 1H, Ar–H), 7.30 (d, *J* = 8.1 Hz, 1H, Ar–H), 7.19 (t, *J* = 8.0 Hz, 1H, Ar–H), 7.12-7.07 (m, 2H, Ar–H), 7.04-6.95 (m, 3H, Ar–H), 6.78-6.75 (m, 1H, Ar–H), 6.62 (d, *J* = 8.4 Hz, 1H, Ar–H), 6.47 (d, *J* = 3.0 Hz, 1H, Ar–H), 4.29 (t, *J* = 7.8 Hz, 2H, $CH_2$), 4.03 (t, *J* = 7.1 Hz, 2H, $CH_2$), 3.04 (t, *J* = 7.8 Hz, 2H, $CH_2$), 2.39 (t, *J* = 7.5 Hz, 2H, $CH_2$), 1.77-1.70 (m, 2H, $CH_2$), 1.53-1.46 (m, 2H, $CH_2$), 1.19-1.17 (m, 4H, $CH_2$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 158.6 ($C_q$), 148.1 (CH), 143.8 ($C_q$), 137.0 (CH), 136.1 ($C_q$), 135.0 ($C_q$), 130.8 ($C_q$), 128.7 ($C_q$), 128.2 (CH), 125.9 (CH), 123.6 (CH), 122.6 (CH), 121.4 (CH), 121.1 (CH), 119.3 (CH), 115.7 (CH), 111.4 (CH), 109.5 (CH), 100.9 (CH), 55.2 ($CH_2$), 46.5 ($CH_2$), 33.0 ($CH_2$), 30.2 ($CH_2$), 30.1 ($CH_2$), 29.0 (2C, $CH_2$), 26.8 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{27}H_{29}N_3$ + $H^+$ $[M + H]^+$ 396.2434; Found 396.2438.

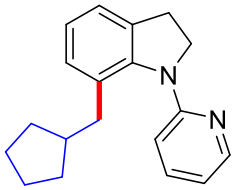


**9-(4-(1-(Pyridin-2-yl)indolin-7-yl)butyl)-9*H*-carbazole (3az):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.059 g, 0.30 mmol) and 9-(4-bromobutyl)-9*H*-carbazole (**2z**; 0.195 g, 0.60 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3az** (0.039 g, 31%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.21 (dd, $J$ = 5.0, 1.3 Hz, 1H, Ar–H), 8.07 (d, $J$ = 7.8 Hz, 2H, Ar–H), 7.42-7.33 (m, 3H, Ar–H), 7.24-7.17 (m, 4H, Ar–H), 7.07 (d, $J$ = 6.8 Hz, 1H, Ar–H), 6.98-6.91 (m, 2H, Ar–H), 6.70-6.67 (m, 1H, Ar–H), 6.50 (d, $J$ = 8.4 Hz, 1H, Ar–H), 4.19 (t, $J$ = 7.9 Hz, 2H, $CH_2$), 4.13 (t, $J$ = 6.9 Hz, 2H, $CH_2$), 3.01 (t, $J$ = 7.9 Hz, 2H, $CH_2$), 2.45 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.72-1.55 (m, 4H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 158.6 ($C_q$), 148.1 (CH), 143.9 ($C_q$), 140.5 (2C, $C_q$), 137.1 (CH), 134.9 ($C_q$), 129.9 ($C_q$), 128.2 (CH), 125.7 (2C, CH), 123.5 (CH), 122.9 (2C, $C_q$), 122.7 (CH), 120.4 (2C, CH), 118.8 (2C, CH), 115.8 (CH), 111.5 (CH), 108.8 (2C, CH), 55.1 ($CH_2$), 42.8 ($CH_2$), 32.8 ($CH_2$), 30.0 ($CH_2$), 28.6 ($CH_2$), 26.4 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{29}H_{27}N_3$ + $H^+$ $[M + H]^+$ 418.2278; Found 418.2283.

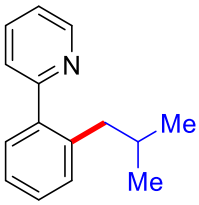


**1-Octyl-9-(pyridin-2-yl)-9*H*-carbazole (3ba).** The representative procedure **A** was followed, using 9-(pyridin-2-yl)-9*H*-carbazole (**3b**; 0.050 g, 0.204 mmol), 1-bromooctane (**2a**; 0.077 g, 0.40 mmol), Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yield **3ba** (0.046 g, 63%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.12 (d, $J$ = 7.7 Hz, 2H, Ar–H), 7.84-7.75 (m, 3H, Ar–H), 7.43-7.23 (m, 5H, Ar–H), 7.13 (d, $J$ = 7.5 Hz, 1H, Ar–H), 2.89 (t, $J$ = 7.4 Hz, 2H, $CH_2$), 1.88-1.81 (m, 2H, $CH_2$), 1.37-1.27 (m, 10H, $CH_2$), 0.87 (t, $J$ = 6.6 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 163.2 ($C_q$), 151.4 ($C_q$), 139.9 (2C, $C_q$), 138.7 (CH), 126.2 (2C, CH), 124.3 (2C, $C_q$), 120.9

(2C, CH), 120.4 (CH), 120.3 (2C, CH), 116.2 (CH), 111.5 (2C, CH), 38.4 ($CH_2$), 32.1 ($CH_2$), 29.9 ($CH_2$), 29.7 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 22.9 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{25}H_{28}N_2 + H^+$ $[M + H]^+$ 357.2325; Found 357.2328.

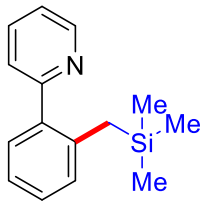



**7-(Cyclopentylmethyl)-1-(pyridin-2-yl)indoline (3aC):** The representative procedure **A** was followed, using 1-(pyridin-2-yl)indoline (**1a**; 0.040 g, 0.204 mmol) and 6-bromohex-1-ene (**2C**; 0.065 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3aC** (0.017 g, 30%) as a light yellow liquid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.30 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H, Ar–H), 7.49-7.45 (m, 1H, Ar–H), 7.11 (d, *J* = 7.1 Hz, 1H, Ar–H), 7.06 (d, *J* = 7.6 Hz, 1H, Ar–H), 6.96 (vt, *J* = 7.4 Hz, 1H, Ar–H), 6.78-6.75 (m, 1H, Ar–H), 6.62 (d, *J* = 8.4 Hz, 1H, Ar–H), 4.30 (t, *J* = 7.8 Hz, 2H, $CH_2$), 3.02 (t, *J* = 7.8 Hz, 2H, $CH_2$), 2.42 (d, *J* = 7.4 Hz, 2H, $CH_2$), 2.09-2.02 (m, 1H, CH), 1.57-1.39 (m, 6H, $CH_2$), 1.03-0.94 (m, 2H, $CH_2$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 158.6 ($C_q$), 148.3 (CH), 144.1 ($C_q$), 137.0 (CH), 135.1 ($C_q$), 130.9 ($C_q$), 128.7 (CH), 123.5 (CH), 122.5 (CH), 115.5 (CH), 111.3 (CH), 55.1 ($CH_2$), 40.1 (CH), 39.3 ($CH_2$), 32.7 (2C, $CH_2$), 30.1 ($CH_2$), 25.1 (2C, $CH_2$). HRMS (ESI): *m/z* Calcd for $C_{19}H_{22}N_2 + H^+$ $[M + H]^+$ 279.1853; Found 279.1853.

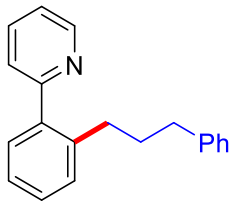



**2-(2-Isobutylphenyl)pyridine (5an):** The representative procedure **B** was followed using 2-phenylpyridine (**4a**; 0.045 g, 0.30 mmol) and 1-bromo-2-methylpropane (**2n**; 0.082 g, 0.60 mmol). After purification by column chromatography on silica gel (petroleum ether/EtOAc 20:1) **5an** (0.056 g, 88%) was obtained as a colorless oil. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.68 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H, Ar–H), 7.71 (td, *J* = 7.8, 1.9 Hz, 1H, Ar–H), 7.36 (dt, *J* = 7.8, 1.0 Hz, 1H, Ar–H), 7.34-7.20 (m, 5H, Ar–H), 2.62 (d, *J* = 7.2 Hz, 2H, $CH_2$), 1.65-1.55 (m, 1H, CH), 0.72 (d, *J* = 6.6 Hz, 6H, $CH_3$). $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 160.7 ($C_q$), 149.2 (CH), 140.8 ($C_q$), 139.7 ($C_q$), 136.2 (CH), 130.7 (CH), 130.0 (CH), 128.1 (CH),

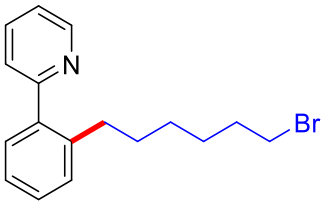
125.9 (CH), 124.4 (CH), 121.7 (CH), 42.1 ($CH_2$), 29.9 (CH), 22.5 (2C, $CH_3$).



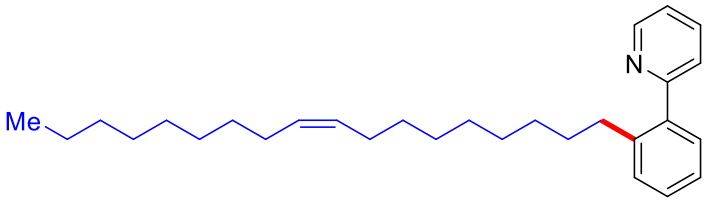

**2-(2-((Trimethylsilyl)methyl)phenyl)pyridine (5ap):** The representative procedure **B** was followed using 2-phenylpyridine (**4a**; 0.045 g, 0.30 mmol) and (bromomethyl)trimethylsilane (**2p**; 0.10 g, 0.60 mmol). After purification by column chromatography on silica gel (petroleum ether/EtOAc 20:1) **5ap** (0.034 g, 47%) was obtained as a colorless oil. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.68 (ddd, $J$ = 4.9, 1.9, 0.9 Hz, 1H, Ar–H), 7.72 (td, $J$ = 7.9, 1.9 Hz, 1H, Ar–H), 7.41 (dt, $J$ = 7.9, 1.0 Hz, 1H, Ar–H), 7.32 (dd, $J$ = 7.6, 1.4 Hz, 1H, Ar–H), 7.27−7.21 (m, 2H, Ar–H), 7.18 (td, $J$ = 7.4, 1.4 Hz, 1H, Ar–H ), 7.12 (dd, $J$ = 7.6, 1.0 Hz, 1H, Ar–H), 2.45 (s, 2H, $CH_2$), –0.21 (s, 9H, $CH_3$). $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 161.0 ($C_q$), 149.1 (CH), 139.0 (2C, $C_q$), 136.3 (CH), 130.3 (CH), 130.1 (CH), 128.2 (CH), 124.7 (CH), 124.4 (CH), 121.6 (CH), 23.6 ($CH_2$), –1.3 (3C, $CH_3$). HRMS (ESI): *m/z* Calcd for $C_{15}H_{19}NSi + H^+$ $[M + H]^+$ 242.1360; Found 242.1360.



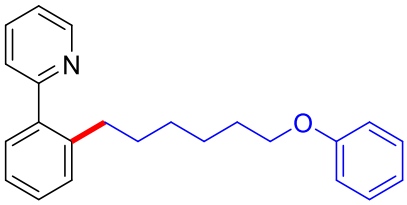

**2-(2-(3-Phenylpropyl)phenyl)pyridine (5aq) :** The representative procedure **B** was followed using 2-phenylpyridine (**4a**; 0.045 g, 0.30 mmol) and (3-bromopropyl)benzene (**2q**; 0.12 g, 0.60 mmol). After purification by column chromatography on silica gel (petroleum ether/EtOAc 20:1) **5aq** (0.067 g, 82%) was obtained as a colorless oil. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.63 (dd, $J$ = 4.9, 0.9 Hz, 1H, Ar–H), 7.66 (td, $J$ = 7.8, 1.9 Hz, 1H, Ar–H), 7.35-7.04 (m, 11H, Ar–H), 2.75 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 2.51 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.83-1.75 (m, 2H, $CH_2$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 160.2 ($C_q$), 149.2 (CH), 142.3 ($C_q$), 140.4 ($C_q$), 140.3 ($C_q$), 136.2 (CH), 129.9 (CH), 129.8 (CH), 128.4 (3C, CH), 128.2 (2C, CH), 126.0 (CH), 125.6 (CH), 124.1 (CH), 121.7 (CH), 35.7 ($CH_2$), 32.8 ($CH_2$), 32.7 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{20}H_{19}N + H$ $[M + H]^+$ 274.1590; Found 274.1589.



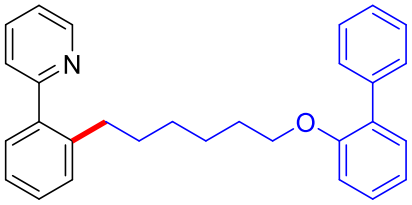

**2-(2-(6-Bromohexyl)phenyl)pyridine (5ar):** The representative procedure **B** was followed using 2-phenylpyridine (**4a**; 0.045 g, 0.30 mmol) and 1,6-dibromohexane (**2r**; 0.15 g, 0.60 mmol). After purification by column chromatography on silica gel (petroleum ether/EtOAc 20:1) **5ar** (0.020 g, 21%) was obtained as a colorless oil. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.61 (d, $J$ = 4.4 Hz, 1H, Ar–H), 7.76 (td, $J$ = 7.8, 1.8 Hz, 1H, Ar–H), 7.31 (d, $J$ = 7.8 Hz, 1H, Ar–H), 7.27-7.18 (m, 5H, Ar–H), 3.26 (t, $J$ = 6.9 Hz, 2H, $CH_2$), 2.63 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.71-1.64 (m, 2H, $CH_2$), 1.42-1.35 (m, 2H, $CH_2$), 1.25-1.12 (m, 4H, $CH_2$). $^{13}$C-NMR (100 MHz, $CDCl_3$): $\delta$ = 160.5 ($C_q$), 149.3 (CH), 140.6 ($C_q$), 140.5 ($C_q$), 136.3 (CH), 129.9 (2C, CH), 128.5 (CH), 126.0 (CH), 124.3 (CH), 121.8 (CH), 34.1 ($CH_2$), 32.9 ($CH_2$), 32.8 ($CH_2$), 31.1 ($CH_2$), 28.6 ($CH_2$), 27.9 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{17}H_{20}NBr + H^+$ $[M + H]^+$ 318.0852, 320.0831; Found 318.0860, 320.0818.




**(*Z*)-2-(2-(Octadec-9-en-1-yl)phenyl)pyridine (5at):** The representative procedure **B** was followed using 2-phenylpyridine (**4a**; 0.031 g, 0.20 mmol) and (*Z*)-1-bromooctadec-9-ene (**2t**; 0.13 g, 0.40 mmol). After purification by column chromatography on silica gel (petroleum ether/EtOAc 20:1) **5at** (0.039 g, 48%) was obtained as a colorless oil. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.67 (ddd, $J$ = 4.9, 1.8, 0.9 Hz, 1H, Ar–H), 7.73 (td, $J$ = 7.8, 1.9 Hz, 1H, Ar–H), 7.37 (d, $J$ = 7.9 Hz, 1H, Ar–H), 7.34-7.22 (m, 5H, Ar–H), 5.38-5.29 (m, 2H, CH), 2.69 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 2.02-1.96 (m, 4H, $CH_2$), 1. 45-1.40 (m, 2H, $CH_2$), 1.29-1.16 (m, 22H, $CH_2$), 0.87 (t, $J$ = 6.6 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 160.5 ($C_q$), 149.3 (CH), 140.9 ($C_q$), 140.5 ($C_q$), 136.2 (CH), 130.1 (CH), 130.0 (CH), 129.9 (2C, CH), 128.4 (CH), 125.9 (CH), 124.3 (CH), 121.7 (CH), 33.1 ($CH_2$), 32.1 ($CH_2$), 31.4 ($CH_2$), 30.0 ($CH_2$), 29.9 ($CH_2$), 29.7 ($CH_2$), 29.6 ($CH_2$), 29.5 (4C, $CH_2$), 29.4 (2C, $CH_2$), 27.4 ($CH_2$), 22.9 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{29}H_{43}N + H^+$ $[M + H]^+$ 406.3468; Found 406.3464.

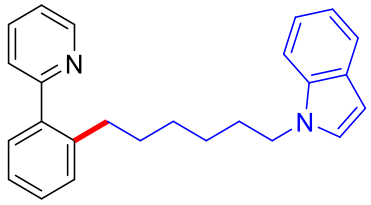


**2-(2-(6-Phenoxyhexyl)phenyl)pyridine (5au):** The representative procedure **B** was followed using 2-phenylpyridine (**4a**; 0.31 g, 0.20 mmol) and (6-phenoxyhexyl)benzene (**2u**; 0.10 g, 0.40 mmol). After purification by column chromatography on silica gel (petroleum ether/EtOAc 20:1) **5au** (0.045 g, 68%) was obtained as a colorless oil. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.67 (d, $J$ = 4.8, Hz, 1H, Ar–H), 7.72 (td, $J$ = 7.8, 1.8 Hz, 1H, Ar–H), 7.37 (d, $J$ = 7.8 Hz, 1H, Ar–H), 7.34-7.20 (m, 7H, Ar–H), 6.92 (t, $J$ = 7.4 Hz, 1H, Ar–H), 6.86 (d, $J$ = 8.3, Hz, 2H, Ar–H), 3.87 (t, $J$ = 6.5 Hz, 2H, $CH_2$), 2.71 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.70-1.63 (m, 2H, $CH_2$) 1.52-1.44 (m, 2H, $CH_2$), 1.37-1.23 (m, 4H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 160.5 ($C_q$), 169.3 ($C_q$), 149.3 (CH), 140.8 ($C_q$), 140.5 ($C_q$), 136.3 (CH), 129.9 (2C, CH), 129.6 (2C, CH), 128.5 (CH), 126.0 (CH), 124.3 (CH), 121.8 (CH), 120.6 (CH), 114.6 (2C, CH), 67.9 ($CH_2$), 33.0 ($CH_2$), 31.3 ($CH_2$), 29.3 (2C, $CH_2$), 25.8 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{23}H_{25}NO + H^+$ $[M + H]^+$ 332.2009; Found 332.2012.

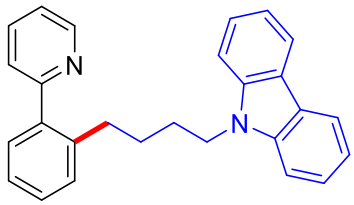


**2-(2-(6-([1,1'-Biphenyl]-2-yloxy)hexyl)phenyl)pyridine (5av):** The representative procedure **B** was followed using 2-phenylpyridine (**4a**; 0.031 g, 0.20 mmol) and (3-2-((6-bromohexyl)oxy)-1,1'-biphenyl (**2v**; 0.13 g, 0.40 mmol). After purification by column chromatography on silica gel (petroleum ether/EtOAc 20:1) **5av** (0.060 g, 74%) was obtained as a colorless oil. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.63 (ddd, $J$ = 4.9, 1.6, 0.9 Hz, 1H, Ar–H), 7.66 (td, $J$ = 7.7, 1.9 Hz, 1H, Ar–H), 7.52-7.50 (m, 2H, Ar–H), 7.36-7.24 (m, 10H, Ar–H), 7.19-7.15 (m, 1H, Ar–H), 6.99 (td, $J$ = 7.5, 1.0 Hz, 1H, Ar–H), 6.92 (d, $J$ = 8.3 Hz, 1H, Ar–H), 3.86 (t, $J$ = 6.4 Hz, 2H, $CH_2$), 2.67 (t, $J$ = 7.9 Hz, 2H, $CH_2$), 1.62-1.55 (m, 2H, $CH_2$), 1.46-1.38 (m, 2H, $CH_2$), 1.27-1.15 (m, 4H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 160.4 ($C_q$), 156.1 ($C_q$), 149.2 (CH), 140.7 ($C_q$), 140.4 ($C_q$), 138.7 ($C_q$), 136.2 (CH), 131.0 ($C_q$), 130.9 (CH), 130.0 (2C, CH), 129.7 (2C, CH), 128.6 (CH), 128.4 (CH), 127.9 (2C, CH), 126.8 (CH), 125.9 (CH), 124.2 (CH), 121.7 (CH), 120.8 (CH), 112.6 (CH), 68.4 ($CH_2$), 32.9

($CH_2$), 31.2 ($CH_2$), 29.1 ($CH_2$), 29.0 ($CH_2$), 25.7 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{29}H_{29}NO + H^+$ $[M + H]^+$ 408.2322; Found 408.2327.

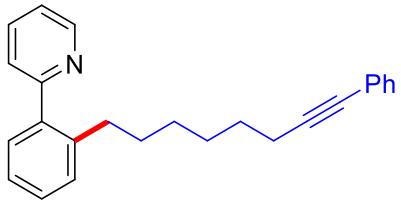


**1-(6-(2-(Pyridin-2-yl)phenyl)hexyl)-1*H*-indole (5ay):** The representative procedure **B** was followed using 2-phenylpyridine (**4a**; 0.031 g, 0.20 mmol) and 1-(6-bromohexyl)-1*H*-indole (**2y**; 0.11 g, 0.40 mmol). After purification by column chromatography on silica gel (petroleum ether/EtOAc 20:1) **5ay** (0.046 g, 65%) was obtained as a colorless oil. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.63 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H, Ar–H), 7.67 (td, *J* = 7.8, 1.9 Hz, 1H, Ar–H), 7.62 (dt, *J* = 7.9, 0.9 Hz, 1H, Ar–H), 7.34-7.16 (m, 8H, Ar–H), 7.10-7.06 (m, 1H, Ar–H), 7.02 (d, *J* = 3.1 Hz, 1H, Ar–H), 6.46 (dd, *J* = 3.1, 0.8 Hz, 1H, Ar–H), 4.01 (t, *J* = 7.1 Hz, 2H, $CH_2$), 2.67 (t, *J* = 7.8 Hz, 2H, $CH_2$), 1.74-1.67 (m, 2H, $CH_2$), 1.46-1.38 (m, 2H, $CH_2$), 1.21-1.16 (m, 4H, $CH_2$). $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 160.4 ($C_q$), 149.2 (CH), 140.6 ($C_q$), 140.4 ($C_q$), 136.3 (CH), 136.0 ($C_q$), 129.9 (CH), 129.8 (CH), 128.7 ($C_q$), 128.4 (CH), 127.9 (CH), 126.0 (CH), 124.2 (CH), 121.8 (CH), 121.4 (CH), 121.0 (CH), 119.3 (CH), 109.5 (CH), 100.9 (CH), 46.4 ($CH_2$), 32.9 ($CH_2$), 31.2 ($CH_2$), 30.1 ($CH_2$), 29.0 ($CH_2$), 26.7 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{25}H_{27}N_2O + H^+$ $[M + H]^+$ 355.2169; Found 355.2172.

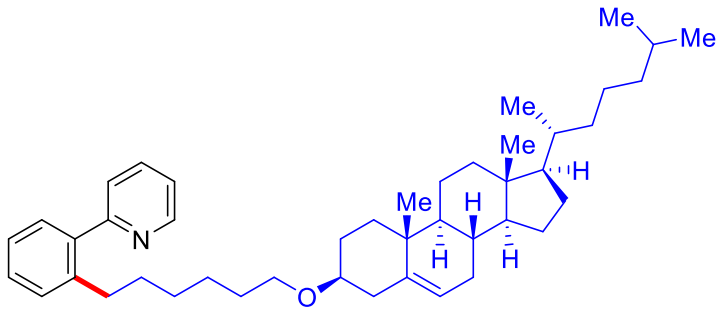


**9-(4-(2-(Pyridin-2-yl)phenyl)butyl)-9*H*-carbazole (5az):** The representative procedure **B** was followed using 2-phenylpyridine (**4a**; 0.031 g, 0.20 mmol) and 9-(4-bromobutyl)-9*H*-carbazole (**2z**; 0.13 g, 0.40 mmol). After purification by column chromatography on silica gel (petroleum ether/EtOAc 20:1) **5az** (0.042 g, 56%) was obtained as a colorless oil. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.60 (ddd, *J* = 4.9, 1.6, 0.9 Hz, 1H, Ar–H), 8.07 (dt, *J* = 7.7, 1.1 Hz, 2H, Ar–H), 7.60 (td, *J* = 7.8, 1.9 Hz, 1H, Ar–H), 7.41 (td, *J* = 7.1, 1.1 Hz, 2H, Ar–H), 7.31-7.13 (m, 10H, Ar–H), 4.15 (t, *J* = 7.1 Hz, 2H, $CH_2$), 2.75 (t, *J* = 7.8 Hz, 2H, $CH_2$), 1.79-1.72

(m, 2H, $CH_2$), 1.54-1.48 (m, 2H, $CH_2$). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): $\delta$ = 160.3 ($C_q$), 149.1 (CH), 140.5 (2C, $C_q$), 140.4 ($C_q$), 140.0 ($C_q$), 136.4 (CH), 130.0 (CH), 129.9 (CH), 128.5 (CH), 126.2 (CH), 125.7 (2C, CH), 124.1 (CH), 122.9 (2C, $C_q$), 121.8 (CH), 120.4 (2C, CH), 118.8 (2C, CH), 108.8 (2C, CH), 42.9 ($CH_2$), 32.9 ($CH_2$), 28.8 ($CH_2$), 28.6 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{27}H_{24}N_2 + H^+$ $[M + H]^+$ 377.2012; Found 377.2013.

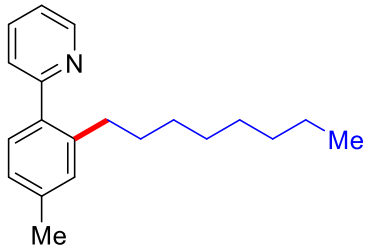



**2-(2-(8-Phenyloct-7-yn-1-yl)phenyl)pyridine (5aA):** The representative procedure **B** was followed using 2-phenylpyridine (**4a**; 0.031 g, 0.20 mmol) and (8-bromooct-1-yn-1-yl)benzene (**2A**; 0.11 g, 0.40 mmol). After purification by column chromatography on silica gel (petroleum ether/EtOAc 20:1) **5aA** (0.016 g, 24%) was obtained as a colorless oil. $^1H$-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.68 (d, *J* = 4.4 Hz, 1H, Ar–H), 7.63 (td, *J* = 7.8, 1.8 Hz, 1H, Ar–H), 7.38-7.25 (m, 11H, Ar–H), 2.71 (t, *J* = 7.9 Hz, 2H, $CH_2$), 2.32 (t, *J* = 7.1 Hz, 2H, $CH_2$), 1.36-1.22 (m, 4H, $CH_2$), 1.21-1.16 (m, 4H, $CH_2$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 160.5 ($C_q$), 149.3 (CH), 140.8 ($C_q$), 140.5 ($C_q$), 136.3 (2C, CH), 131.7 (2C, CH), 129.9 (CH), 129.9 ($C_q$) 128.5 (CH), 128.4 (2C, CH), 127.7 (CH), 126.0 (CH), 124.3 (CH), 121.8 (CH), 90.6 ($C_q$), 80.7 ($C_q$), 33.0 ($CH_2$), 31.3 ($CH_2$), 29.1 ($CH_2$), 28.7 (2C, $CH_2$), 19.5 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{25}H_{25}N + [M + H]^+$ 340.2060; Found 340.2064.

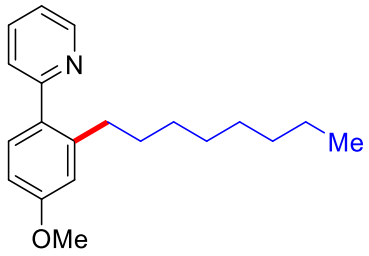



**2-(2-(6-(((3S,8S,9S,10R,13R,14S,17R)-10,13-Dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)hexyl)phenyl)pyridine (5aB):** The representative procedure **B** was followed using 2-phenylpyridine (**4a**; 0.031 g, 0.20 mmol) and (3S,8S,9S,10R,13R,14S,17R)-3-((6-bromohexyl)oxy)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)

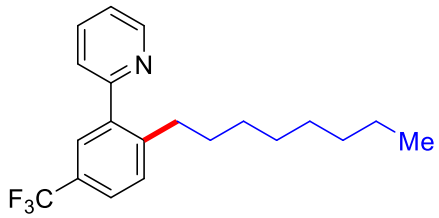
2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthrene (**2B**; 0.22 g, 0.40 mmol). After purification by column chromatography on silica gel (petroleum ether/EtOAc 20:1) **5aB** (0.059 g, 47%) was obtained as a colorless oil. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.68 (ddd, *J* = 4.9, 1.6, 0.9 Hz, 1H, Ar–H), 7.74 (td, *J* = 7.6, 1.8 Hz, 1H, Ar–H), 7.38 (d, *J* = 7.9 Hz, 1H, Ar–H), 7.34-7.23 (m, 5H, Ar–H), ), 5.34 (d, *J* = 5.3 Hz, 1H, CH), 3.38 (t, *J* = 6.8 Hz, 2H, $CH_2$), 3.13-3.06 (m, 1H, CH), 2.70 (t, *J* = 7.9 Hz, 2H, $CH_2$), 2.36-2.31 (m, 1H, CH), 2.20-1.14 (m, 1H, CH), 2.05-1.95 (m, 2H, $CH_2$) 1.88-1.79 (m, 4H, $CH_2$), 1.62-1.05 (m, 25H, $CH_2$), 1.00 (s, 6H, $CH_3$), 0.92 (d, *J* = 6.6 Hz, 3H, $CH_3$), 0.87 (d, *J* = 6.6 Hz, 6H, $CH_3$), 0.68 (s, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 160.5, 149.3, 141.3, 140.8, 140.5, 136.3, 129.9, 129.8, 128.4, 125.9, 124.3, 121.8, 121.6, 79.1, 68.2, 57.0, 56.3, 50.4, 42.5, 40.0, 39.7, 39.4, 37.5, 37.1, 36.4, 36.0, 68.2, 33.0, 32.1, 31.4, 30.2, 29.4, 28.7, 28.4, 28.2, 26.0, 24.5, 24.0, 23.0, 22.7, 21.2, 19.6, 18.9, 12.0.




**2-(4-Methyl-2-octylphenyl)pyridine (5ba):** The representative procedure **B** was followed using 2-(*p*-tolyl)pyridine (**4b**; 0.034 g, 0.2 mmol) and 1-bromooctane (**2a**; 0.077 g, 0.40 mmol). After purification by column chromatography on silica gel (petroleum ether/EtOAc 20:1) **5ba** (0.031 g, 55%) was obtained as a colorless oil. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.67 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H, Ar–H), 7.71 (td, *J* = 7.7, 1.9 Hz, 1H, Ar–H), 7.49 (dt, *J* = 7.9, 1.0 Hz, 1H, Ar–H), 7.25-7.20 (m, 2H, Ar–H), 7.11-7.06 (m, 2H, Ar–H), 2.67 (t, *J* = 7.9 Hz, 2H, $CH_2$), 2.38 (s, 3H, $CH_3$), 1.47-1.40 (m, 2H, $CH_2$), 1.28-1.17 (m, 10H, $CH_2$), 0.86 (t, *J* = 6.9 Hz, 3H, $CH_3$). $^{13}$C-NMR (125 MHz, $CDCl_3$): $\delta$ = 160.6 ($C_q$), 149.2 (CH), 140.8 ($C_q$), 138.1 ($C_q$), 137.7 ($C_q$), 136.2 (CH), 130.6 (CH), 129.9 (CH), 126.6 (CH), 124.3 (CH), 121.5 (CH), 33.1 ($CH_2$), 32.0 ($CH_2$), 31.5 ($CH_2$), 29.7 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 22.8 ($CH_2$), 21.4 ($CH_3$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{20}H_{27}N + H^+$ $[M + H]^+$ 282.2216; Found 282.2215.



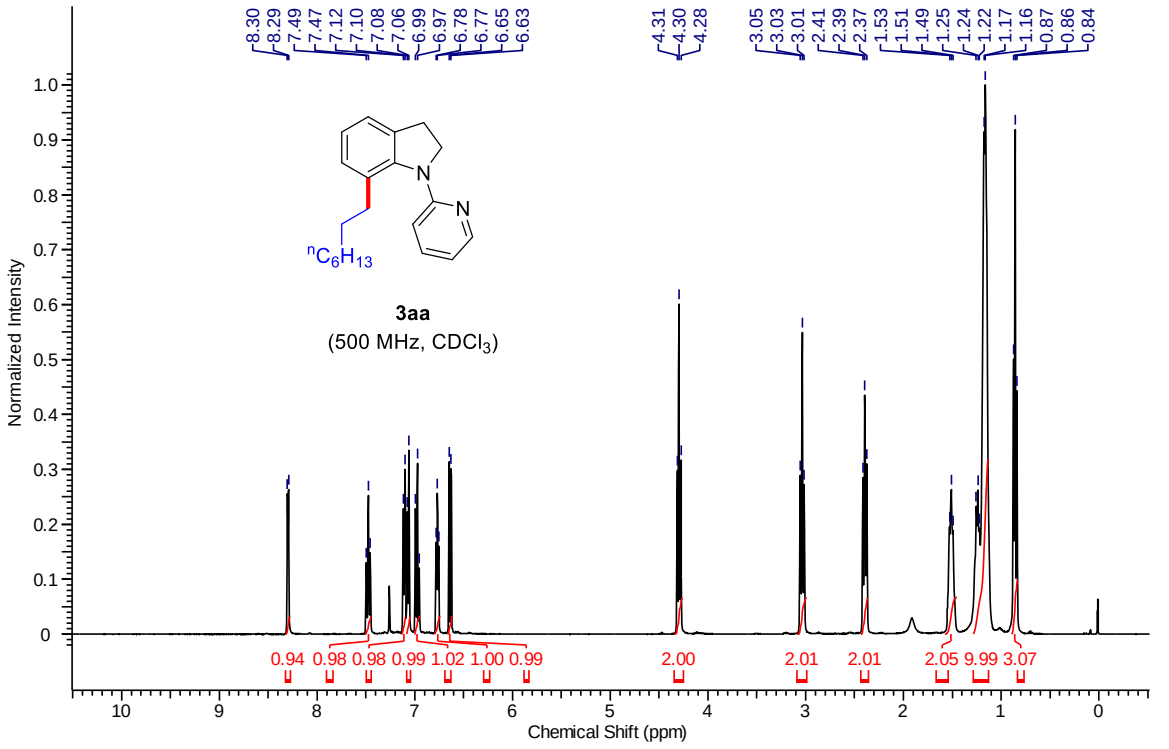

**2-(4-Methoxy-2-octylphenyl)pyridine (5ca) :** The representative procedure **B** was followed using 2-(4-methoxyphenyl)pyridine (**4c**; 0.037 g, 0.2 mmol) and 1-bromooctane (**2a**; 0.077 g, 0.40 mmol). After purification by column chromatography on silica gel (petroleum ether/EtOAc 20:1) **5ca** (0.038 g, 64%) was obtained as a colorless oil. $^{1}$H-NMR (400 MHz, $CDCl_3$): δ = 8.67 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H, Ar–H), 7.72 (d, *J* = 7.8 Hz, 1H, Ar–H), 7.29 (d, *J* = 8.4 Hz, 1H, Ar–H), 7.23-7.19 (m, 2H, Ar–H), 6.85-6.79 (m, 2H, Ar–H), 3.84 (s, 3H, $CH_3$), 2.70 (t, *J* = 7.8 Hz, 2H, $CH_2$), 1.48-1.42 (m, 2H, $CH_2$), 1.27-1.17 (m, 10H, $CH_2$), 0.88 (t, *J* = 6.9 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): *δ* = 160.3 ($C_q$), 159.7 ($C_q$), 149.2 (CH), 142.7 ($C_q$), 136.2 (CH), 133.4 ($C_q$), 131.2 (CH), 124.3 (CH), 121.4 (CH), 115.4 (CH), 111.1 (CH), 55.4 ($CH_3$), 33.3 ($CH_2$), 32.0 ($CH_2$), 31.4 ($CH_2$), 29.6 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{20}H_{27}NO + H^+$ $[M + H]^+$ 298.2165; Found 298.2163.

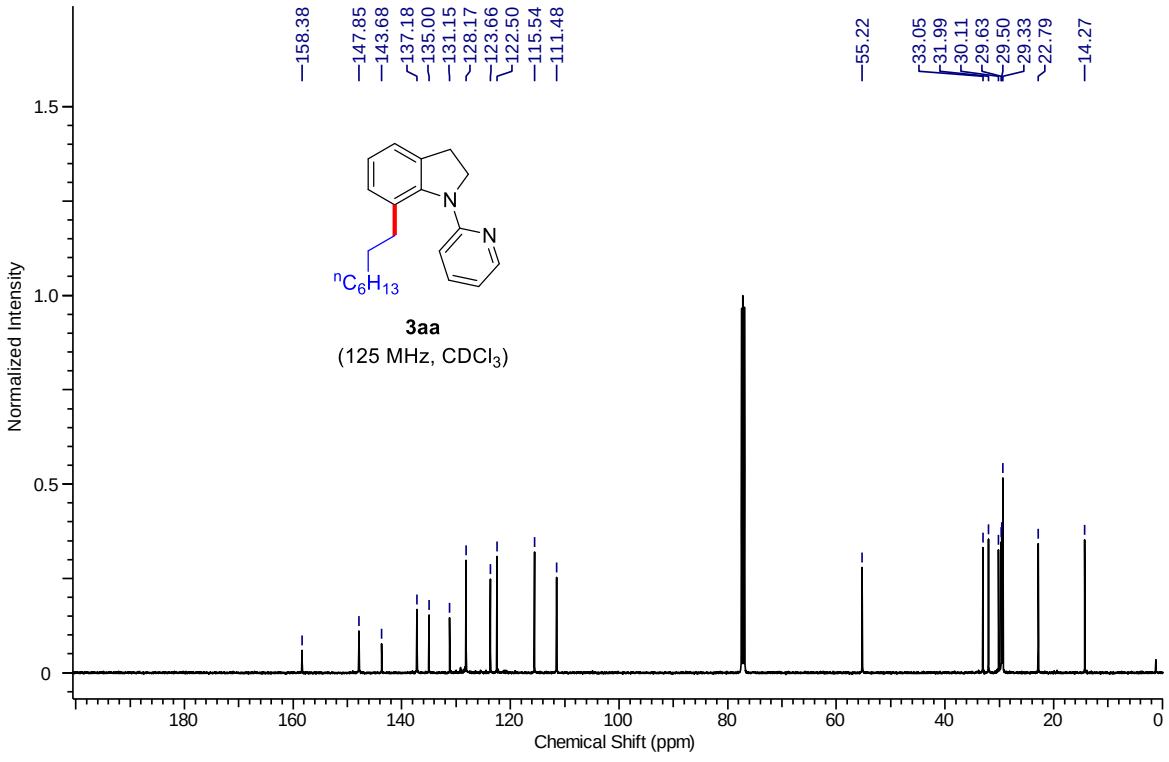


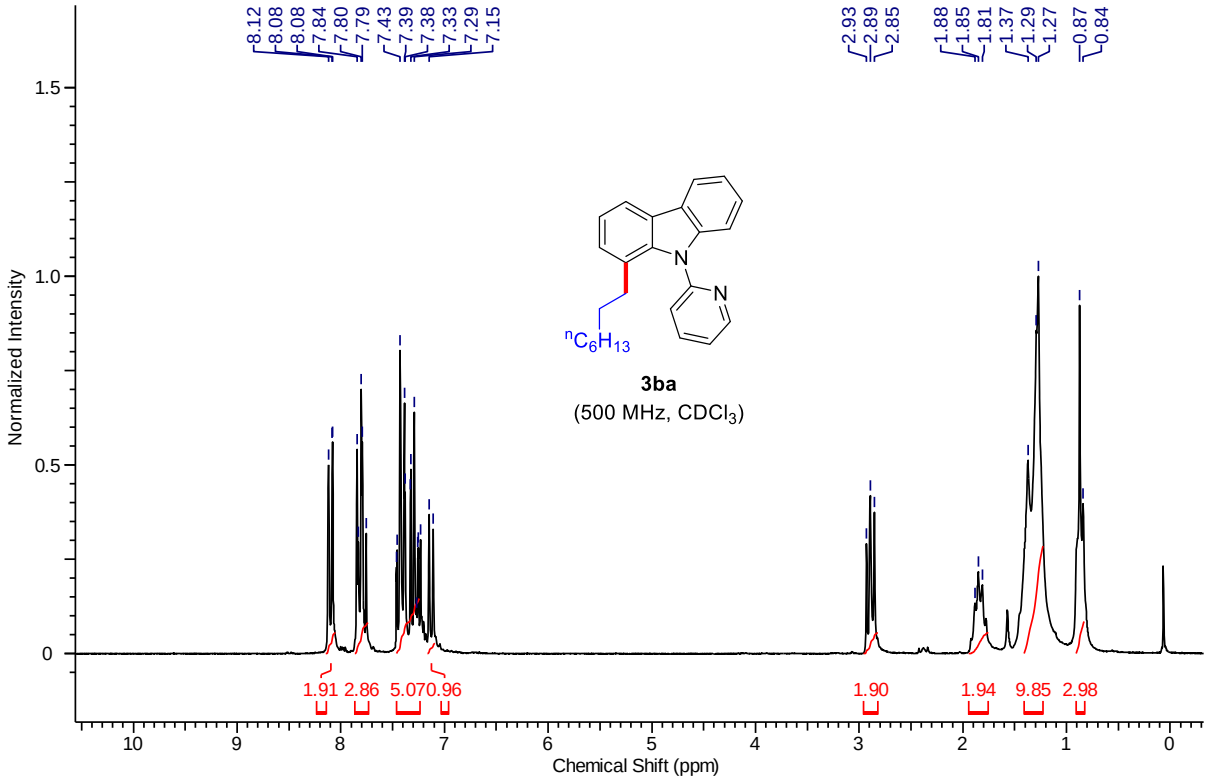

**2-(2-Octyl-5-(trifluoromethyl)phenyl)pyridine (5da):** The representative procedure **B** was followed using 2-(3-(trifluoromethyl)phenyl)pyridine (**4d**; 0.11 g, 0.50 mmol) and 1-bromooctane (**2a**; 0.19 g, 1.0 mmol). After purification by column chromatography on silica gel (petroleum ether/EtOAc 20:1) **5da** (0.035 g, 21%) was obtained as a colorless oil. $^{1}$H-NMR (400 MHz, $CDCl_3$): *δ* = 8.84 (d, *J* = 4.6 Hz, 1H, Ar–H), 7.91 (t, *J* = 7.8 Hz, 1H, Ar–H), 7.70 (s, 1H, Ar–H), 7.67 (d, J = 8.3 Hz, 1H, Ar–H), 7.53 (t, *J* = 8.4 Hz, 2H, Ar–H), 7.44-7.39 (m, 1H, Ar–H), 2.87 (t, *J* = 7.6 Hz, 2H, $CH_2$), 1.60-1.57 (m, 2H, $CH_2$), 1.39-1.30 (m, 10H, $CH_2$), 0.99 (t, *J* = 6.9 Hz, 3H, $CH_3$). $^{13}$C-NMR (100 MHz, $CDCl_3$): *δ* = 159.0 ($C_q$), 149.5 (CH), 145.2 ($C_q$), 141.0 ($C_q$), 136.6 (CH), 130.4 (CH), 128.4 (q, $^{2}J_{C–F}$ = 32.8 Hz, $C_q$), 126.8 (q, $^{3}J_{C–F}$ = 3.8 Hz, CH), 125.1 (q, $^{3}J_{C–F}$ = 3.8 Hz, CH), 124.2 (CH), 123.1 (q, $^{1}J_{C–F}$ = 271.6 Hz, $CF_3$), 122.4 (CH), 33.1 ($CH_2$), 32.0 ($CH_2$), 31.1 ($CH_2$), 29.5 ($CH_2$), 29.3 ($CH_2$), 29.2 ($CH_2$),

22.8 ($CH_2$), 14.2 ($CH_3$). $^{19}$F-NMR (376 MHz, $CDCl_3$): $\delta$ = -62.3 (s). HRMS (ESI): *m/z* Calcd for $C_{20}H_{24}NF_3$ + $H^+$ $[M + H]^+$ 336.1934; Found 336.1929.

### 3.4.5 $^1$H and $^{13}$C{$^1$H} NMR Spectra of Selected Alkylated Products

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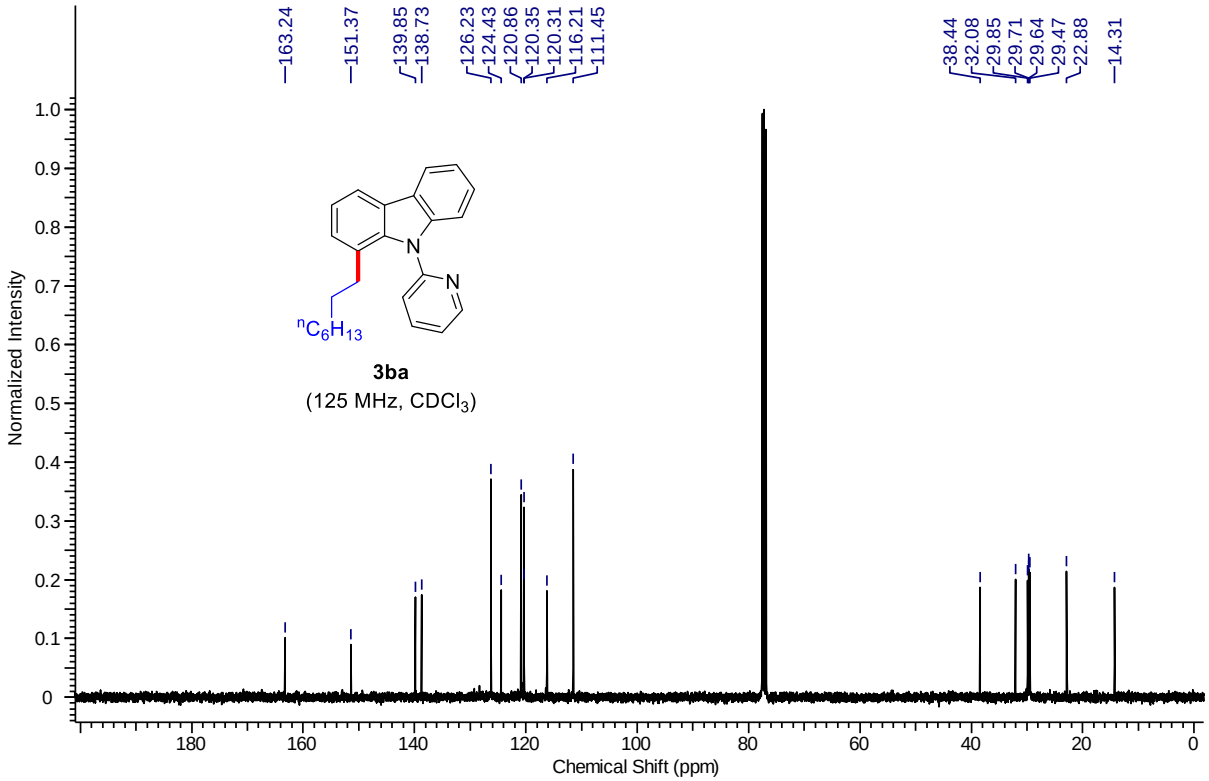
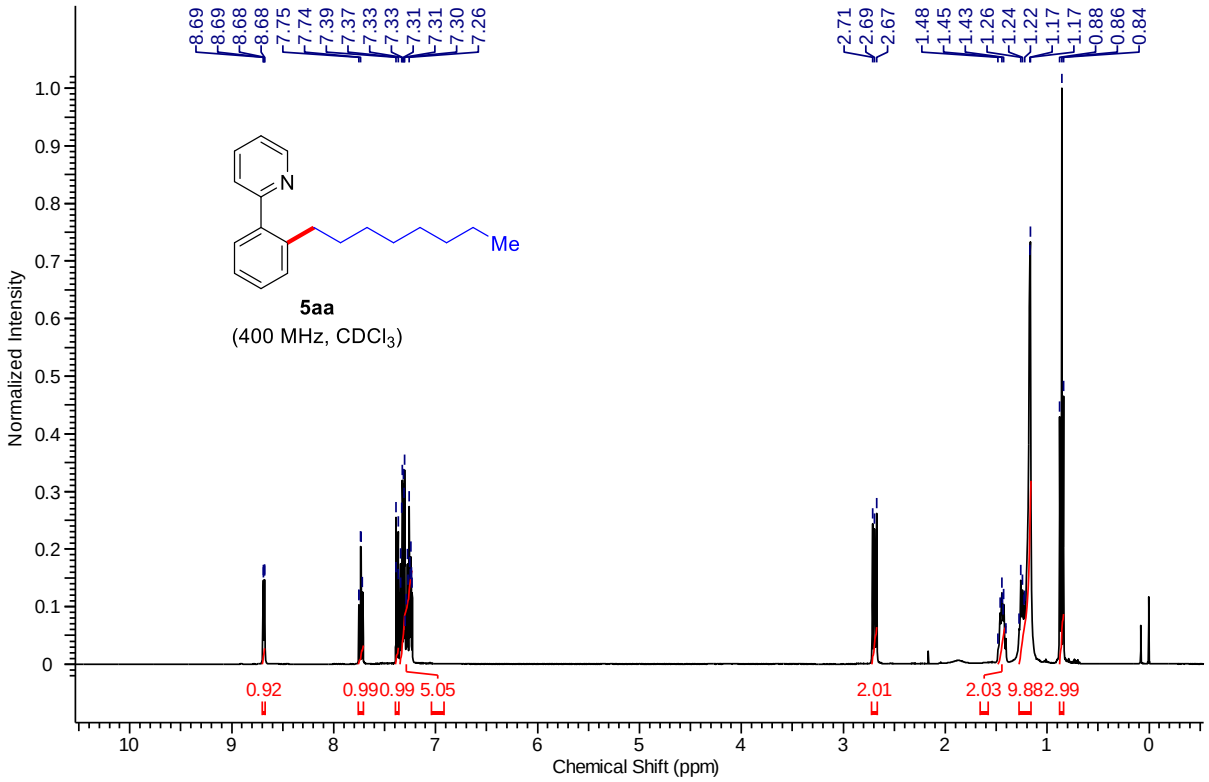
8.08
7.84
7.80
7.79
7.43
7.39
7.38
7.33
7.29
7.15
2.93
2.89
2.85
1.88
1.85
1.81
1.37
1.29
1.27
0.87
0.84
Normalized Intensity
1.91 2.86 5.07 0.96
1.90
1.94 9.85 2.98
Chemical Shift (ppm)
3ba
(500 MHz, CDCl3)


163.24
151.37
139.85
138.73
126.23
124.43
120.86
120.35
120.31
116.21
111.45
38.44
32.08
29.85
29.71
29.64
29.47
22.88
14.31
Normalized Intensity
Chemical Shift (ppm)
3ba
(125 MHz, CDCl3)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8.69
8.68
8.68
7.75
7.74
7.39
7.37
7.33
7.33
7.31
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7.26
2.71
2.69
2.67
1.48
1.45
1.43
1.26
1.24
1.22
1.17
1.17
0.88
0.86
0.84
N
Me
5aa
(400 MHz, CDCl3)
Normalized Intensity
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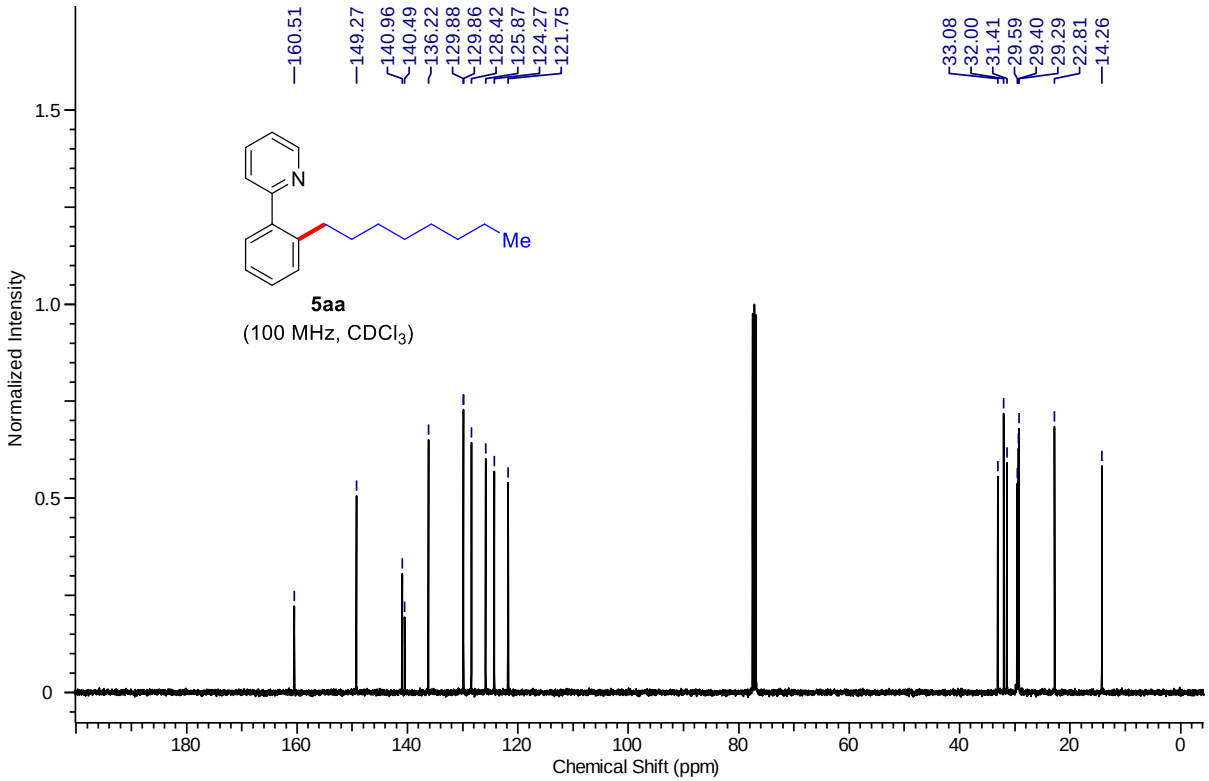
0.99
5.05
2.01
2.03
9.88
2.99
Chemical Shift (ppm)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140.49
136.22
129.88
129.86
128.42
125.87
124.27
121.75
33.08
32.00
31.41
29.59
29.40
29.29
22.81
14.26
N
Me
5aa
(100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)

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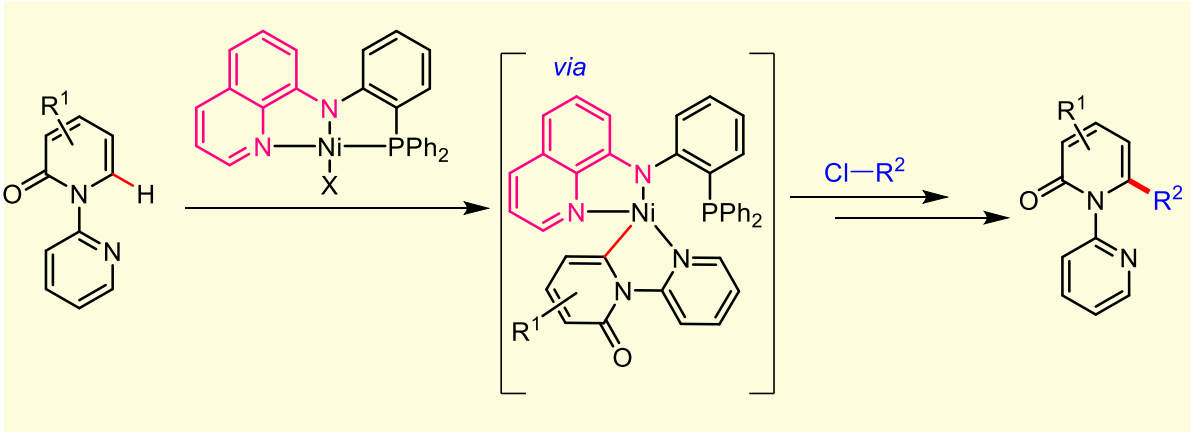
# Chapter 4

# Regioselective C(6)–H Alkylation of 2-Pyridones with Unactivated Alkyl Chlorides Using a Well-defined Ni(II)-Catalyst



## 4.1 INTRODUCTION

Six-membered nitrogen-containing heterocycles, 2-pyridone and its derivatives are prevalent in various drug molecules, pharmaceuticals, and agrochemicals.[1-4] In addition, they play crucial roles in many biologically active molecules and synthetic compounds, as exemplified by well-known substances like ciclopirox, milrinone, A58365A, and sophoramine (Figure. 4.1).[5] Consequently, synthetic chemists have been increasingly interested in developing efficient and selective functionalization approaches for 2-pyridones over the past few decades. Traditionally, 2-pyridones have been functionalized through traditional cross-coupling reactions using prefunctionalized substrates like halogenated 2-pyridones.[6-10] The selective direct functionalization of C–H bonds poses a significant challenge within the framework of the 2-pyridone ring, largely related to the presence of four reactive C($sp^2$)–H bonds.[11-16] Nevertheless, different research groups have devised methods for selectively functionalizing C–H bonds in 2-pyridones by exploiting their electronic characteristics, employing directing groups, and steric effects of the catalyst. Recently, numerous groups demonstrated C–H activation of 2-pyridones with mono-chelation assistance, predominantly utilizing late transition metals, while exploration with 3d transition metals has been less extensive.[17-21] Particularly, regioselective C($sp^2$)–H bond arylation and alkenylation of 2-pyridones have been synthesized by different groups. However, achieving the regioselective alkylation of 2-pyridones is particularly challenging using unactivated alkyl halides as coupling partners due to the challenge in the oxidative addition of these halides to the metal center.[22] Additionally, alkyl halides containing $\beta$-hydrogens tend to underlying $\beta$-hydride elimination reactions as unwanted side products. In 2020, Patrick group reported C($sp^2$)–H bond alkylation of 2-pyridones, utilizing acid anhydrides as coupling partners with rhodium catalyst.[5] Notably, various groups have developed C($sp^2$)–H bond alkylation of 2-pyridones with mono chelation assistance using 3d transition metals such as Mn, Ni, and Co as catalysts. These methodologies employed diverse coupling partners, including diazomalonates,[23] alkyl trifluoroborates,[24] 3-bromo-2,2-difluoropropene,[25] alkenes,[26] methyleneoxetonones,[27] $\alpha$-carbonyl sulfoxonium ylides,[28] 2-carboxy allylic alcohols,[29] and both enones and aldehydes,[30] at the C6 position of 2-pyridones. However, regioselective alkylation of 2-pyridones with unactivated alkyl halides has not been reported to date.

Nickel catalysts are attractive due to their abundance, cost-effectiveness, and low toxicity. They exhibit unique catalytic activity stemming from their variable oxidation states.[31] In addition, nickel complexes are found widespread use in various organic transformations.[32,33] However, the C–H bond alkylation using nickel catalysts has been less explored. In 2012, Hiyama established an approach for the alkylation of 2-pyridone with an alkene coupling partner using a nickel/Lewis acid cooperative catalyst.[34] Another significant advancement was demonstrated in 2017 by Miura, who achieved alkylation of 2-pyridone at C6 position with nickel catalyst using activated alkenes as coupling partners (Scheme 4.1).[35] However, the existing methodologies are limited to activated alkenes and typically require highly air-sensitive Ni(0) catalysts and main group organometallic reagents as additives. Notably, the C6 alkylation of 2-pyridone with unactivated alkyl halides as coupling partners has not been reported, likely due to the presence of *β*-hydrogen and the strong bond strength between carbon and halide. To address this challenge, we have designed a quinoline-based (NNP)NiX complex that is air-stable and easy to handle. Interestingly, Ni pincer complexes have shown outstanding thermal and catalytic activity, providing an ideal electronic environment for the nickel center. This facilitates the C6 alkylation of 2-pyridone with both primary and secondary alkyl halides.

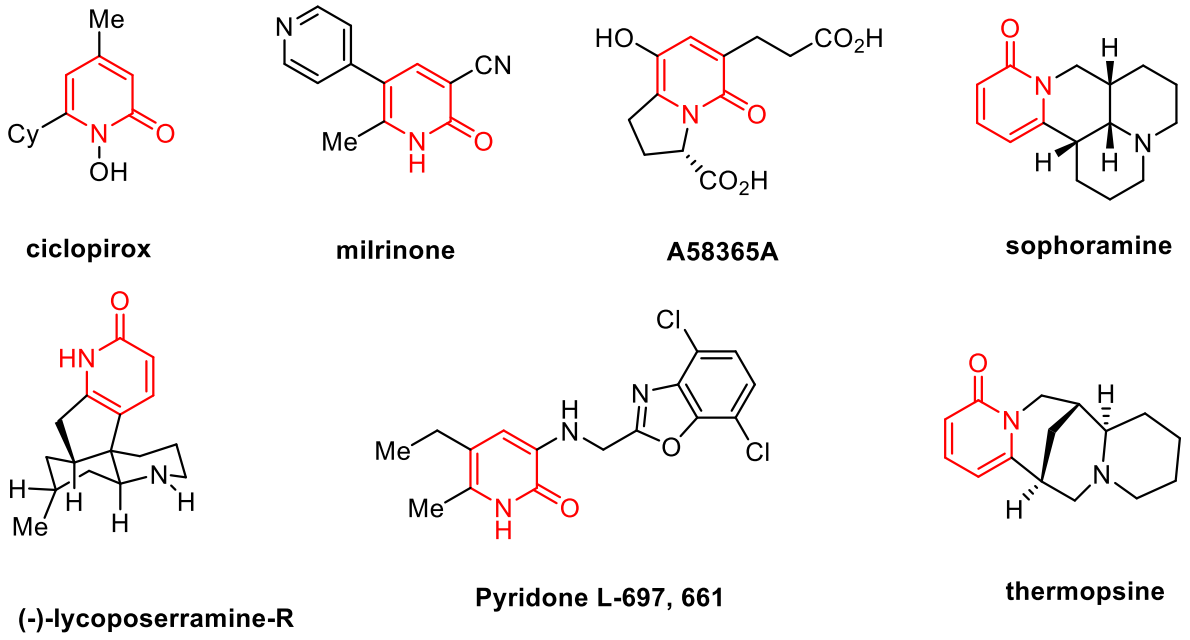
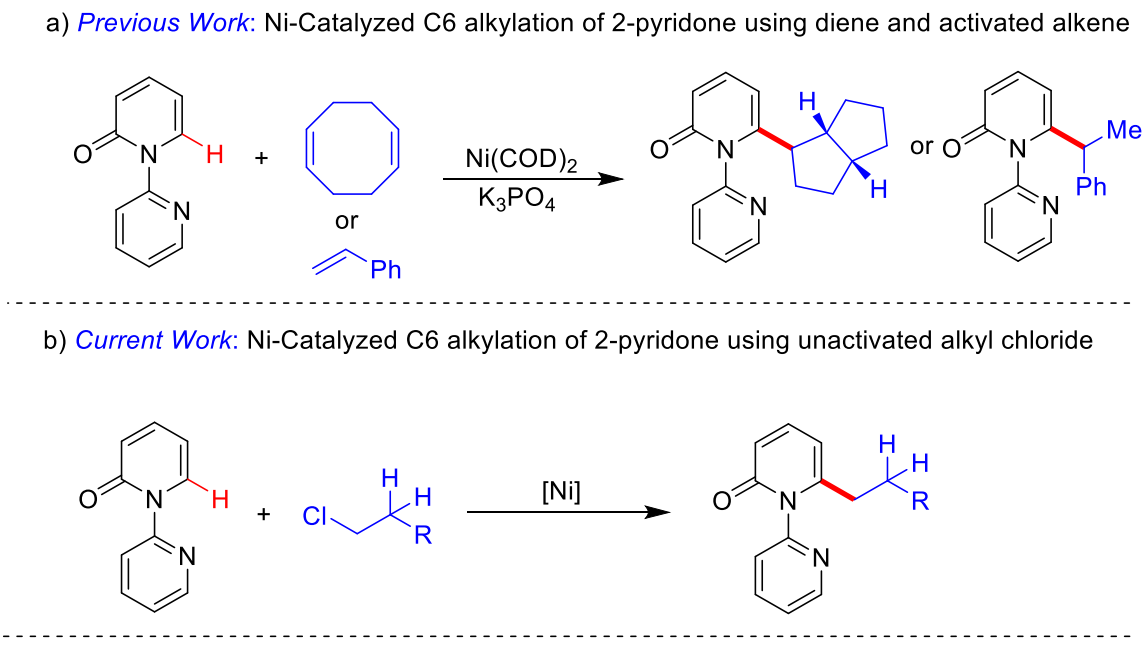



**Figure 4.1** Bioactive molecules containing 2-pyridone scaffold.

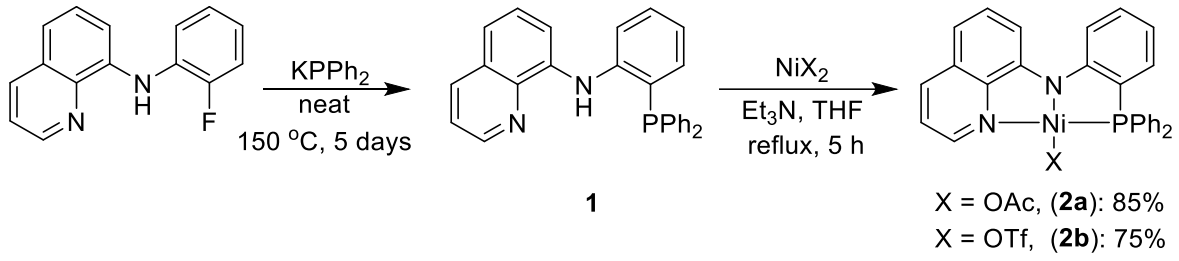



**Scheme 4.1** Selective C6 alkylation of 2-pyridones

## 4.2 RESULTS AND DISCUSSION

### 4.2.1 Synthesis and Characterization of Ligand Precursor and Ni Complexes

The *N*-(2-(diphenylphosphaneyl)phenyl)quinolin-8-amine ligand (**1**) was synthesized from *N*-(2-fluorophenyl)quinolin-8-amine[36] with $KPPh_2$ in neat condition for 5 days in 76% yield. The ligand (**1**) reacted with $NiX_2$ (X = OAc, OTf) in the presence of $Et_3N$ in THF, providing 85% yield of complex **2a** and 75% of **2b**, respectively. The nickel complexes were analyzed by $^{1}H$ NMR and $^{13}C$ NMR. The molecular structure of **2a** was confirm by X-ray diffraction study (Scheme 4.2).



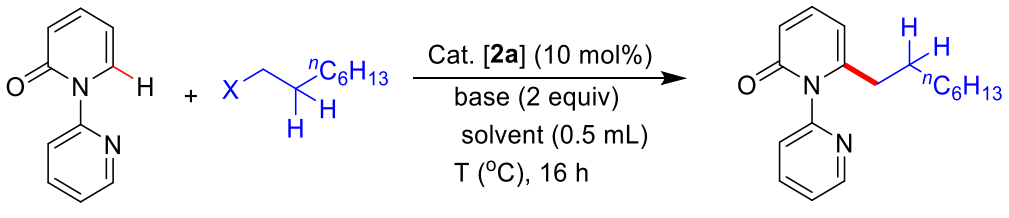

**Scheme 4.2** Synthesis of $^{Q}NNP^{Ph2}$ ligand and $^{Q}NNP^{Ph2}NiX$

### 4.2.2 Reaction Optimization

We started optimizing the reaction parameters for the C6 alkylation of 2-pyridone (**3a**) *via* mono-chelated assistance, using 1-chlorooctane (**4a**) as the coupling partner, and Ni catalyst (Cat. **2a**) at 140 °C in toluene (Table 4.1). We have observed a low yield of alkylated

product **5aa** when using 1-iodooctane and 1-bromooctane as the coupling partners, possibly due to the formation of unwanted side products (entry 1 and 2). Remarkably, the more challenging and demanding coupling partner, such as 1-chlorooctane reacted smoothly with **3a**, resulting in a 74% yield of the desired alkylated product **5aa** (entry 3). Subsequently, we tested catalyst **2b** (entry 4), which resulted in a slightly lower yield of **5aa**. Thereafter, we utilized a variety of bases, including NaO$^t$Bu, KO$^t$Bu, $Li_2CO_3$, $Na_2CO_3$, and $K_2CO_3$ (entries 5-9), with LiO$^t$Bu proving to be the most effective base for this transformation. Among the nonpolar solvents tested, toluene was determined to be the optimal solvent for this transformation (entries 10-17). Additionally, we observed the decomposition of the starting compound in polar solvents (entry 18). The yield of **5aa** decreased slightly when the reaction was performed lower temperatures (entry 19), but interestingly, the yield of **5aa** improved to 96% with a longer reaction time of 24 hours (entry 20). Further, lowering the reaction temperature to110 $^oC$ and the employment of catalyst **2a** (5 mol%) produced a low yield of alkylated product **5aa** (entry 21 and 22). Additionally, $Ni(OAc)_2$ was tested with different nitrogen and phosphorus-based ligands, resulting in only trace amounts of alkylated product **5aa** (entries 23-28). Installation of phenyl at the *N*-centre of 2-pyridone prevented the formation of the alkylated product, highlighting the crucial role of the nitrogen center in this transformation. The C6 alkylated product was not observed without the employment of catalyst **2a** (entry 29).

**Table 4.1**. Optimization of Reaction Condition for C6 Alkylation of 2-Pyridone[a]




**3a** **4a** **5aa**

| Entry | X | [Ni] Cat. | Base | Solvent | T ($^o$C) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | I | **2a** | LiO$^t$Bu | toluene | 140 | 20 |
| 2 | Br | **2a** | LiO$^t$Bu | toluene | 140 | 50 |
| 3 | Cl | **2a** | LiO$^t$Bu | toluene | 140 | 74 |
| 4 | Cl | **2b** | LiO$^t$Bu | toluene | 140 | 70 |
| 5 | Cl | **2a** | NaO$^t$Bu | toluene | 140 | 42 |
| 6 | Cl | **2a** | KO$^t$Bu | toluene | 140 | NR |

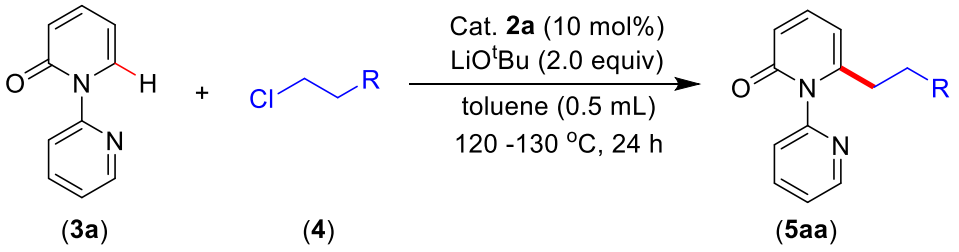
| | | | | | | |
|---|---|---|---|---|---|---|
| 7 | Cl | **2a** | $Li_2CO_3$ | toluene | 140 | NR |
| 8 | Cl | **2a** | $Na_2CO_3$ | toluene | 140 | NR |
| 9 | Cl | **2a** | $K_2CO_3$ | toluene | 140 | NR |
| 10 | Cl | **2a** | LiO$^t$Bu | *o*-xylene | 140 | 30 |
| 11 | Cl | **2a** | LiO$^t$Bu | *m*-xylene | 140 | 50 |
| 12 | Cl | **2a** | LiO$^t$Bu | *p*-xylene | 140 | 67 |
| 13 | Cl | **2a** | LiO$^t$Bu | *p*-cymene | 120 | 50 |
| 14 | Cl | **2a** | LiO$^t$Bu | cumene | 140 | trace |
| 15 | Cl | **2a** | LiO$^t$Bu | mesitylene | 140 | 34 |
| 16 | Cl | **2a** | LiO$^t$Bu | $^t$Bu-benzene | 140 | 72 |
| 17 | Cl | **2a** | LiO$^t$Bu | dioxane | 140 | 62 |
| 18 | Cl | **2a** | LiO$^t$Bu | Cl-benzene | 140 | NR |
| 19 | Cl | **2a** | LiO$^t$Bu | toluene | 120 | 68 |
| **20**[c] | Cl | **2a** | LiO$^t$Bu | **toluene** | **120** | **96 (93)** |
| 21[c] | Cl | **2a** | LiO$^t$Bu | toluene | 110 | 40 |
| 22[c,d] | Cl | **2a** | LiO$^t$Bu | toluene | 120 | 50 |
| 23[c] | Cl | Ni(OAc)$_2$/phen | LiO$^t$Bu | toluene | 120 | trace |
| 24[c] | Cl | Ni(OAc)$_2$/bpy | LiO$^t$Bu | toluene | 120 | trace |
| 25[c] | Cl | Ni(OAc)$_2$/$PPh_3$ | LiO$^t$Bu | toluene | 120 | 23 |
| 26[c] | Cl | Ni(OAc)$_2$/dppf | LiO$^t$Bu | toluene | 120 | trace |
| 27[c] | Cl | Ni(OAc)$_2$/dppe | LiO$^t$Bu | toluene | 120 | 34 |
| 28[c] | Cl | Ni(OAc)$_2$/xantphos | LiO$^t$Bu | toluene | 120 | 17 |
| 29[c] | Cl | -- | LiO$^t$Bu | toluene | 120 | NR |

[a]Reaction Conditions: **3a** (0.034 g, 0.2 mmol), **4a** (0.059 g, 0.40 mmol), [Ni] Cat. (0.02 mmol, 10 mol%), LiO$^t$Bu (0.032 g, 0.40 mmol), solvent (0.5 mL). [b]NMR yield using dibromomethane as an internal standard; isolated yield is given in parentheses. [c]Reaction is performed by 24 h. [d]5.0 mol% of [Ni] Cat. was used. NR = No Reaction

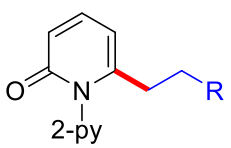
### 4.2.3 Substrate Scope Using Primary Alkyl Chlorides

After optimizing the reaction parameters for the C6 alkylation of 2-pyridone with mono-chelated assistance using the air-stable catalyst **2a**, we investigated the reaction's scope with various simple and functionalized alkyl chlorides (Scheme 4.3). Initially, linear alkyl chlorides with various carbon chain lengths were reacted with substrate **3a** to yield the desired C6 alkylated products (**5aa-5ae**) in moderate to excellent yields. We observed lower

yields with long-chain alkyl chlorides compared to short-chain ones, likely due to the lower solubility of long-chain saturated hydrocarbons. Particularly, we achieved a good yield of **5af** with $\gamma$-substituted branching alkyl chloride. Alkyl chlorides containing a phenyl ring reacted with **3a** to provide **5ag** and **5af** with excellent yields. Notably, alkyl chlorides bearing phenyl ether and phenyl thioether smoothly coupled with **3a** to afford corresponding **5ai-5aw** products in good yields. Unfortunately, base-sensitive functionalized alkyl chlorides such as acetyl, ester, and nitrile could not be coupled with **3a**. Additionally, 1,6-dichlorohexane efficiently reacted at one C–Cl position to give a moderate yield of **5ax**. In addition, oleyl chloride, derived from an unsaturated fatty alcohol, could be coupled with **3a** with a moderate yield of 60%. Important functionalities such as heterocycles containing pyrrolyl, indolyl, and carbazolyl derived alkyl chlorides are moderately coupled with **3a** to afford **5az**, **5aA**, and **5aB**. Notably, the 2-pyridone reacted smoothly with biologically relevant compounds like pterostilbene, nonyl phenol, sesamol-derived alkyl chlorides, providing optimal yields of the alkylated products (**5aC**-**5aE**). In addition, pharmacologically significant polycyclic compounds like estrone, vitamin E, stigmasterol, cholesterol and diosgenin-derived alkyl chlorides were suitable with the optimized reaction conditions, providing good yield of C6 alkylated product (**5aF**-**5aJ**).




(**3a**) (**4**) (**5aa**)



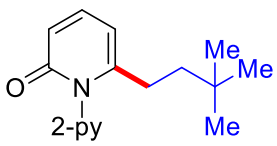
R = $^n$C$_6$H$_{13}$ (**5aa**): 93%

R = $^n$C$_4$H$_9$ (**5ab**): 90%

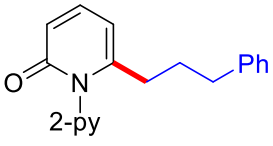
R = $^n$C$_8$H$_{17}$ (**5ac**): 85%

R = $^n$C$_{12}$H$_{25}$ (**5ad**): 75%

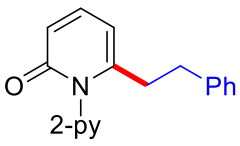
R = $^n$C$_{20}$H$_{41}$ (**5ae**): 73%



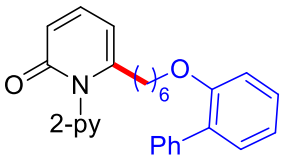
(**5af**): 63%



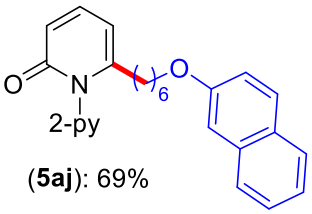
(**5ag**): 93%



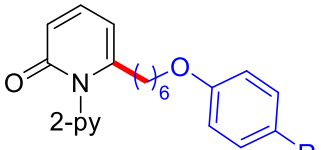
(**5ah**): 68%



(**5ai**): 67%



(**5aj**): 69%

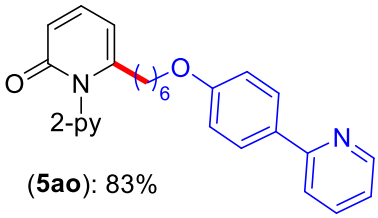


R = H, (**5ak**): 67%

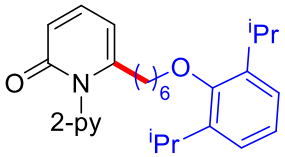
R = OMe, (**5al**): 67%

R = F, (**5am**): 70%

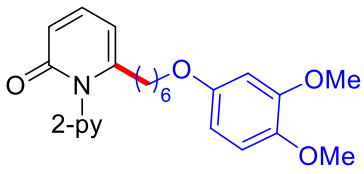
R = Ph, (**5an**): 79%



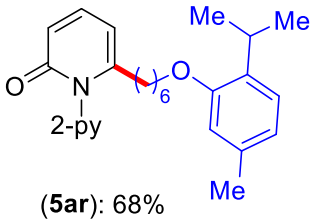
(**5ao**): 83%



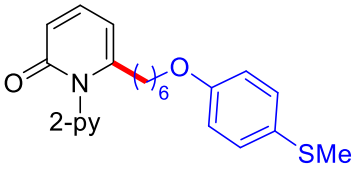
(**5ap**): 73%



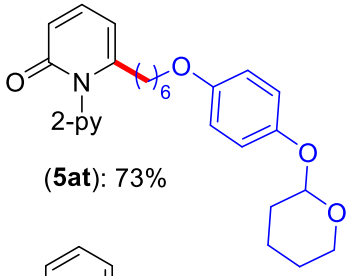
(**5aq**): 64%



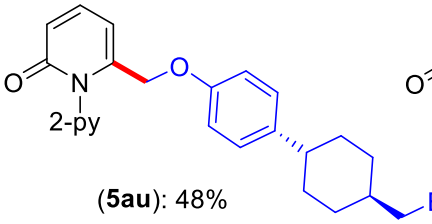
(**5ar**): 68%



(**5as**): 82%



(**5at**): 73%



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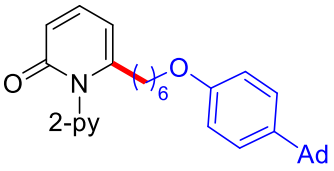
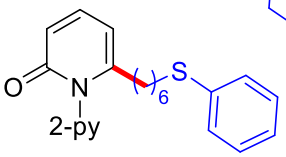
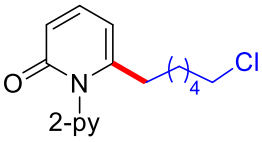


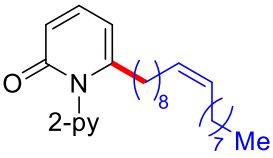
(**5av**): 69%



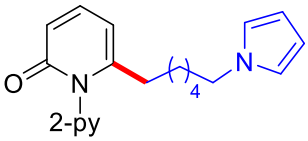
(**5aw**): 78%



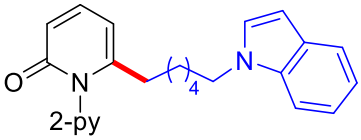
(**5ax**): 62%



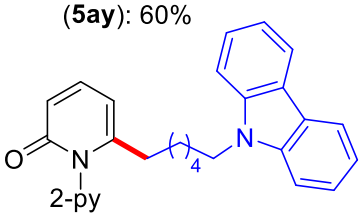
(**5ay**): 60%



(**5az**): 39%

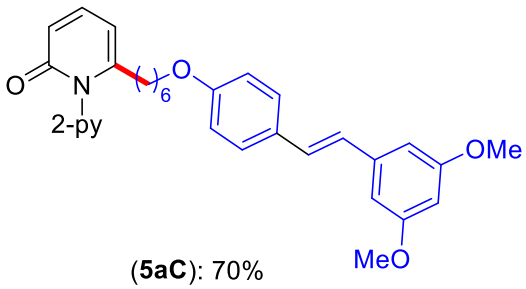


(**5aA**): 66%



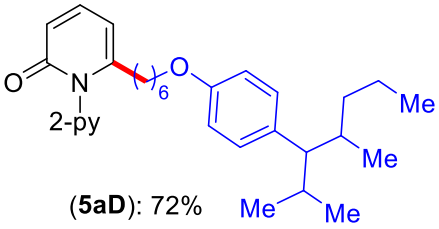
(**5aB**): 71%

Biologically relevent compounds



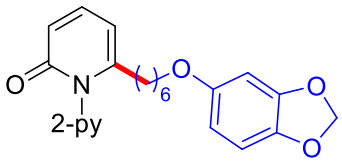
(**5aC**): 70%

*from Pterostilbene (antioxidant)*



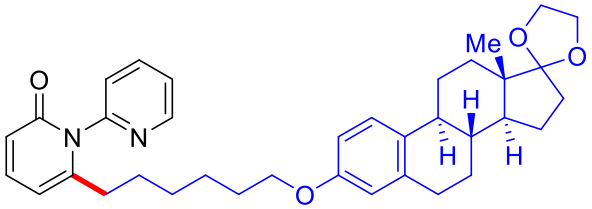
(**5aD**): 72%

*from nonylphenol,*
*(used as surfactants/lubricant additives)*

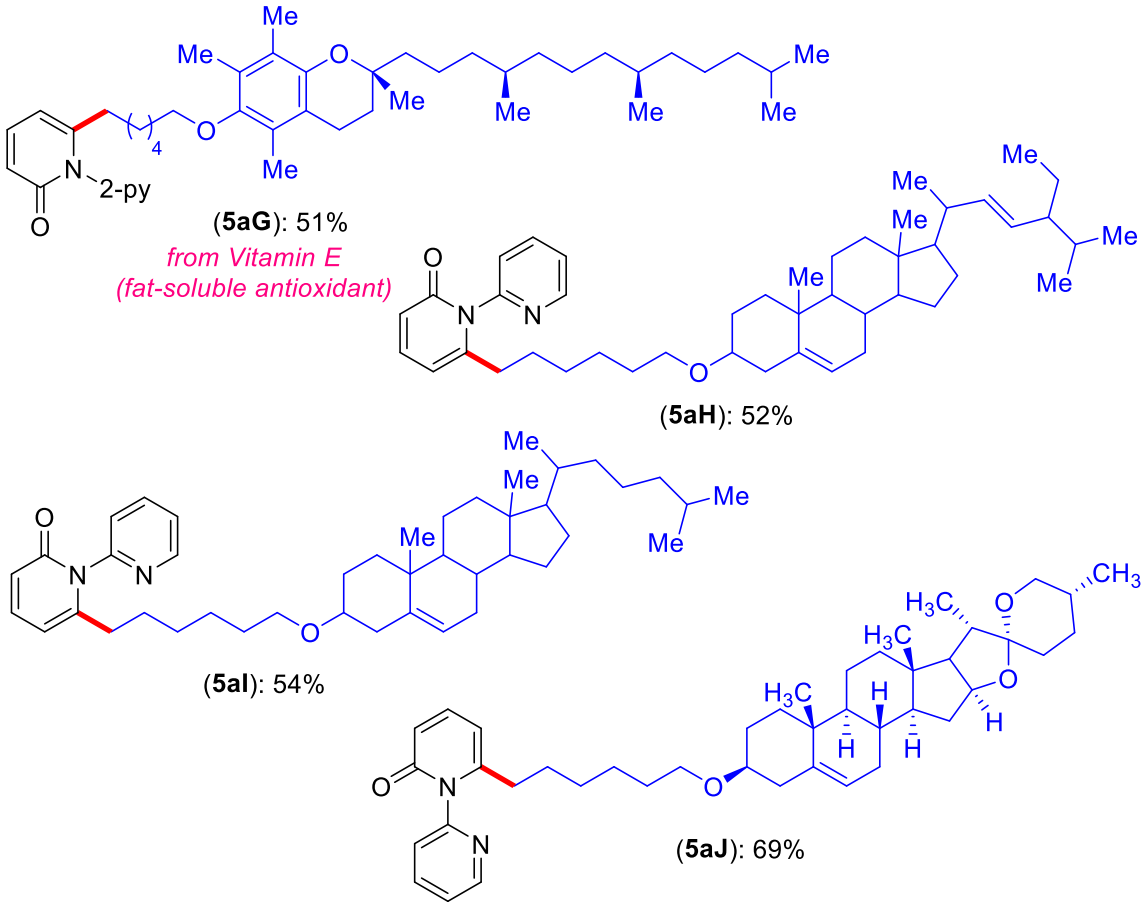


(**5aE**): 70%

*from Sesamol (antidepressant)*



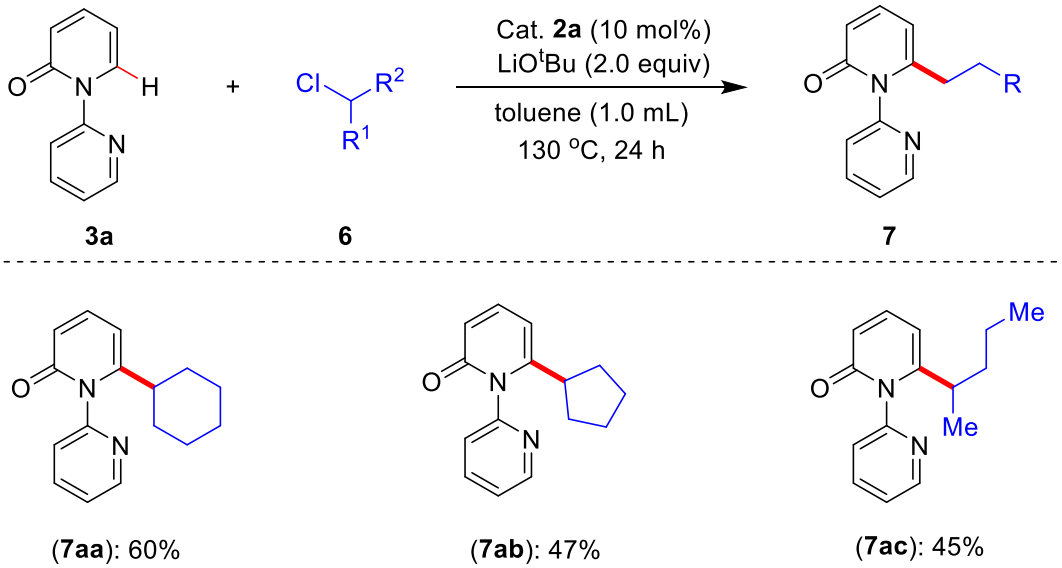
(**5aF**): 60%




**Scheme 4.3** Nickel-catalyzed C6 alkylation of 2-pyridone using primary alkyl chlorides.

### 4.2.4 Substrate Scope Using Secondary Alkyl Chlorides

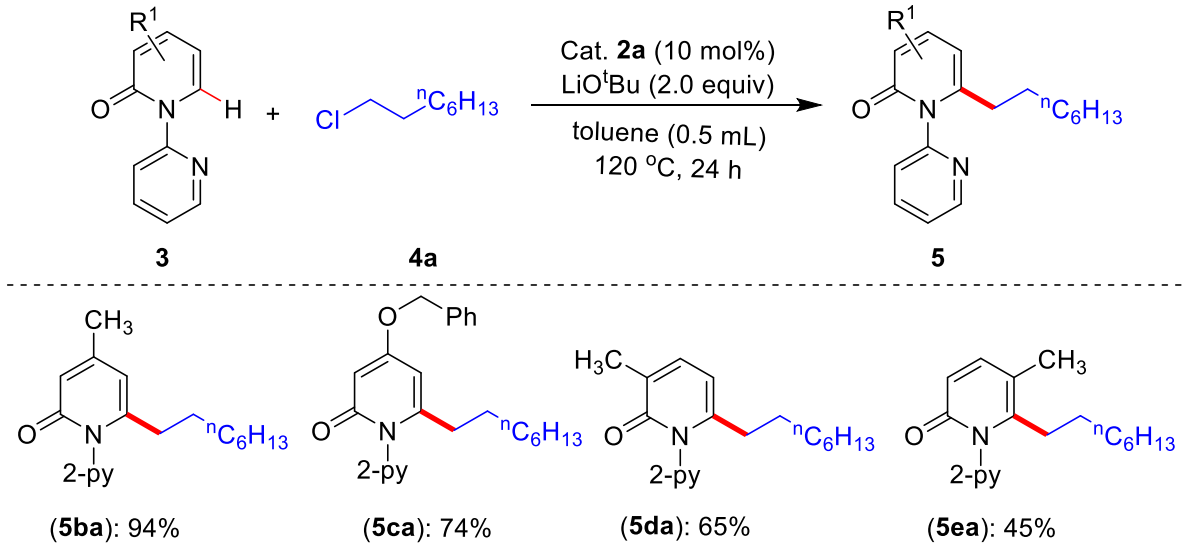
The optimized protocol were applied to the C6 alkylation of 2-pyridone using more challenging secondary alkyl chloride as a coupling partner with catalyst **2a** at 130 °C in toluene (Scheme 4.4). Interestingly, 2-pyridone reacted smoothly with cyclic alkyl chlorides such as cyclohexyl chloride and cyclopentyl chloride, providing satisfactory yields of **7aa** and **7ab**. Additionally, acyclic 2-chloropentane was coupled with **3a** to give a moderate yield of the desired alkylated product **7ac**. However, tertiary alkyl chloride failed to participate in the alkylation.

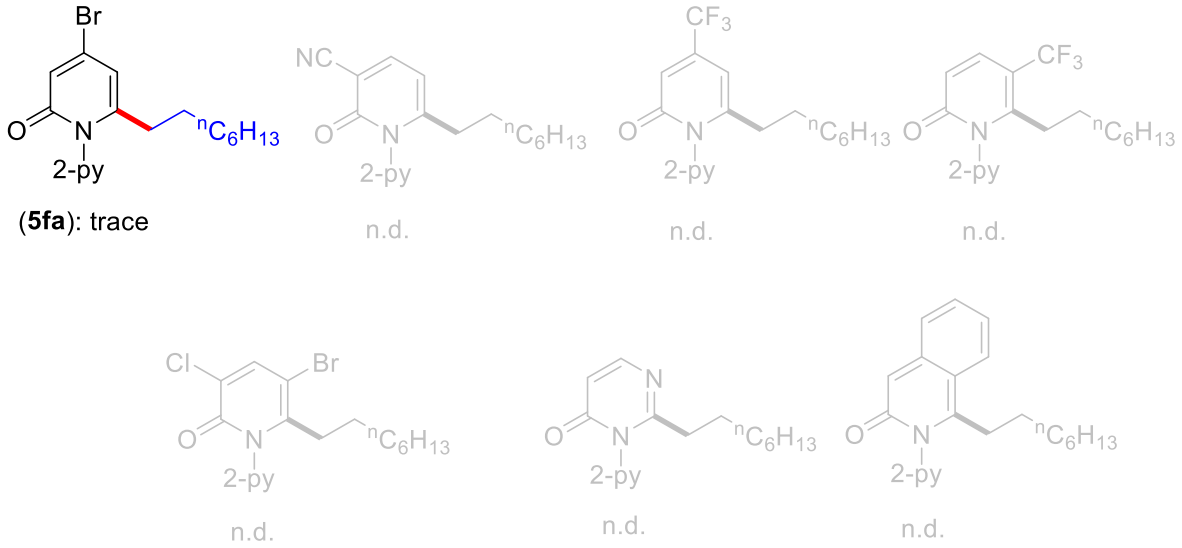



**Scheme 4.4** Nickel-catalyzed C6 alkylation of 2-pyridone using secondary alkyl chlorides.

### 4.2.5 Substrate Scope of 2-Pyridone Derivatives

We also examined the scope of different substituents, such as methyl and benzyl ether, on 2-pyridone, which gave good yields with 1-chlorooctane (Scheme 4.5). Unfortunately, we observed only trace amounts of alkylated products in the case of bromo-substituted 2-pyridone. On the other hand, an electron-withdrawing group such as –CN, –$CF_3$ as well as dihalide substituted 2-pyridone decomposed under the optimized reaction conditions. Unfortunately, pyrimidinone and isoquinolinone do not undergo coupling reaction with 1-chlorooctane.

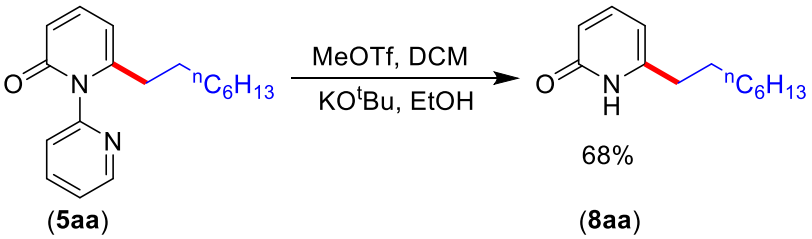





**Scheme 4.5** Nickel-catalyzed C6 alkylation of 2-pyridone derivatives using primary octyl chloride.

### 4.2.6 Scale-up and Deprotection of the Directing Group

We conducted a scale-up reaction using **3a** (4.90 mmol) with 1-chlorooctane, yielding 68% of the alkylated product **5aa**, demonstrating the practical utility of the reaction. Additionally, deprotection of 6-octyl-2*H*-[1,2'-bipyridin]-2-one was performed with MeOTf and KO$^t$Bu to provide 68% of the deprotected alkylated product of **8aa** (Scheme 4.6).

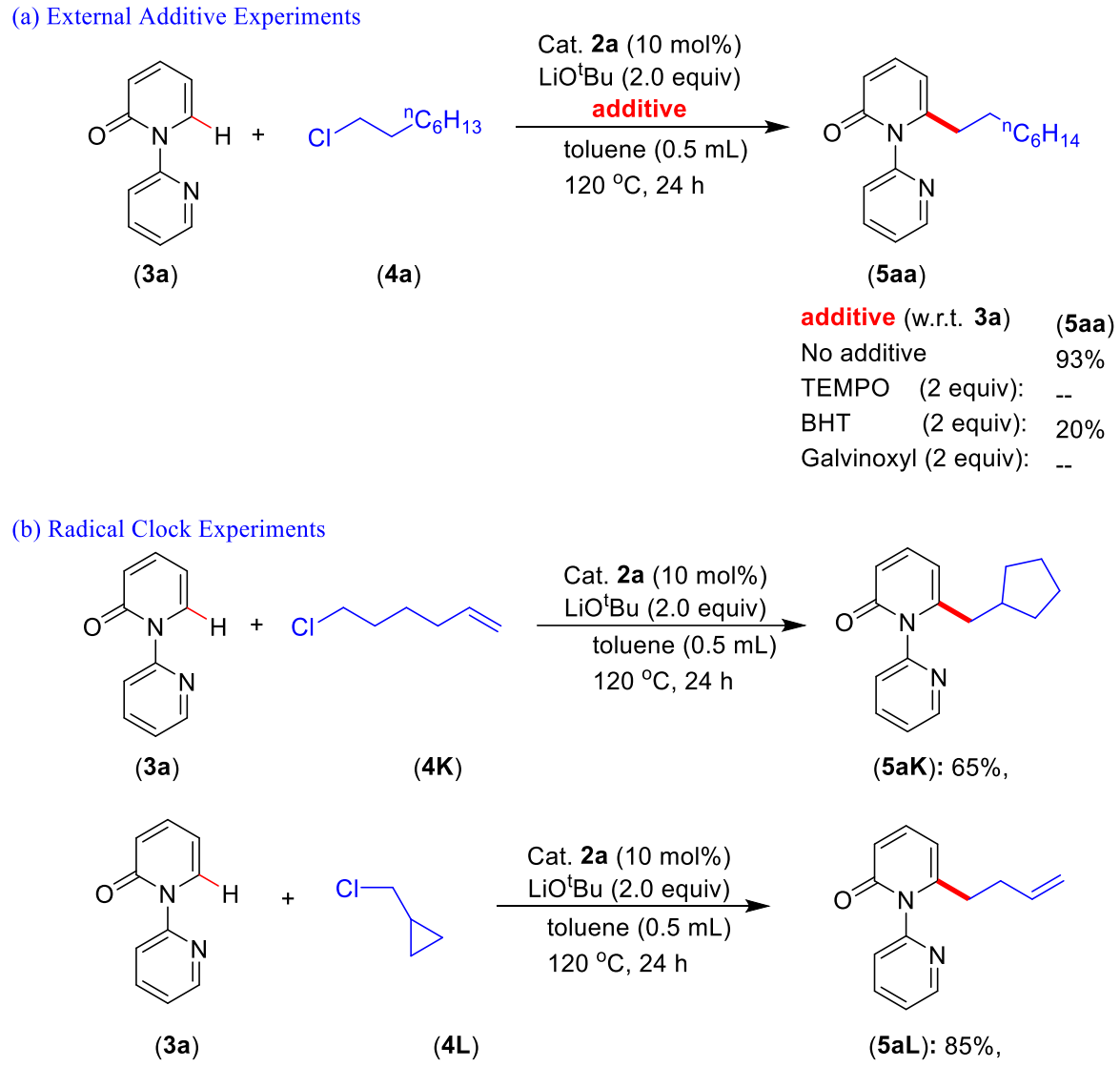



**Scheme 4.6** Removal of directing group.

### 4.2.7 Mechanistic Aspects

A preliminary mechanistic study was conducted to elucidate the working mode of Ni-catalyzed alkylation of 2-pyridone. Radical scavengers such as TEMPO and galvinoxyl were used as additives in the standard alkylation reaction, where the alkylated product **5aa** was not observed. However, when a radical inhibitor such as BHT was added, 20% of the alkylated product **5aa** was observed (Scheme 4.7a). Additionally, 2-pyridone reacted with 6-chlorohex-1-ene (**4K**) and (chloromethyl)cyclopropane (**4L**) to give 65% of 6-(cyclopentylmethyl)-2*H*-[1,2'-bipyridin]-2-one (**5aK**) and 85% of 6-(but-3-en-1-yl)-2*H*-[1,2'-bipyridin]-2-one (**5aL**)

*via* a cyclization and decyclization radical pathway (Scheme 4.7b). This observation suggests the involvement of an alkyl radical.




**Scheme 4.7** External additive and radical clock Experiments

### 4.2.8 Probable Catalytic Cycle

Based on our mechanistic analysis and literature reports,[37,38] we have hypothesized a tentative plausible catalytic cycle (Figure 4.2). The cycle begins with catalyst **2a** reacting with **3a** in the presence of LiO$^t$Bu to form a nickelacycle intermediate **A**. This nickel species is believed to facilitate the formation of an alkyl radical, which then undergoes a radical rebound causing the formation of intermediate species **C**. Subsequently, reductive elimination delivered **5aa** resulting in the reactivation of the active catalyst **2a** in the presence lithium acetate.

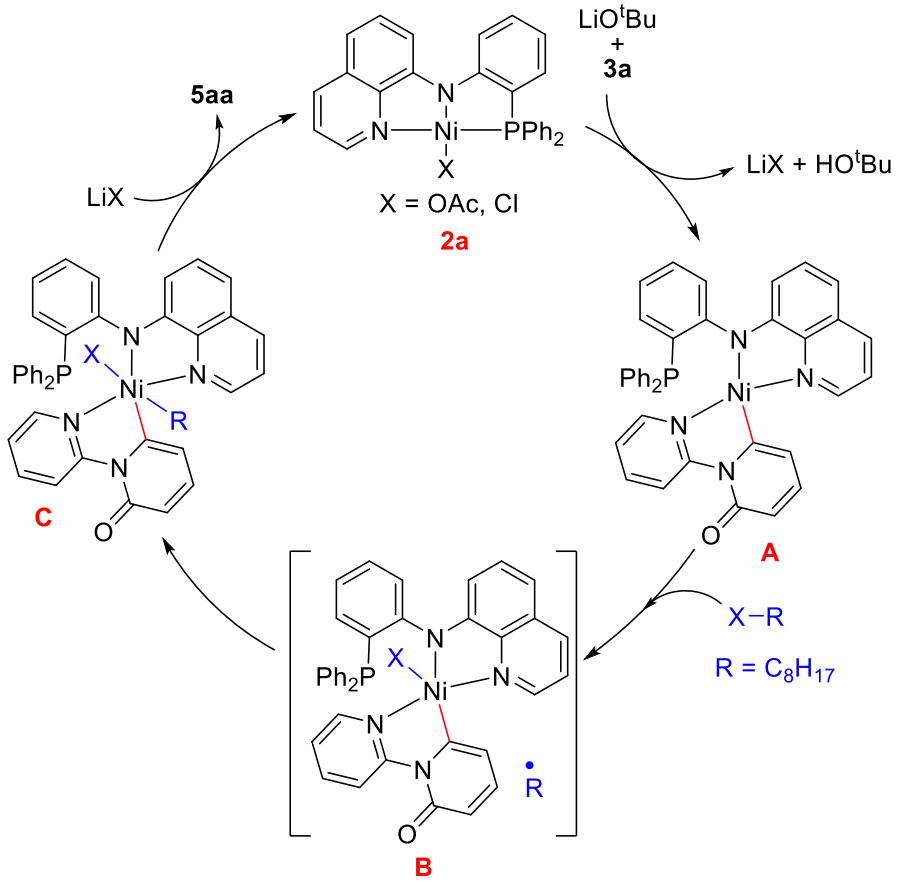



**Figure 4.2** Plausible catalytic cycle for C6 alkylation of 2-pyridone using nickel catalyst.

## 4.3 CONCLUSION

In conclusion, we have devised a nickel-catalyzed C6 alkylation of 2-pyridone using a more challenging unactivated alkyl chlorides as coupling partners. The use of quinoline-based nickel pincer complex is crucial for achieving this transformation. This method offers a wide substrate scope and tolerant of different functional groups. Alkyl halides containing thioether, ether, indolyl, pyrrolyl, and carbazolyl groups, as well as polycyclic-steroid moieties, perform well under the optimized conditions. Furthermore, secondary alkyl chlorides can also be coupled with 2-pyridones to provide good yields. Additionally, we have investigated the mechanistic aspects of the reaction which suggested the SET pathway for the reaction.

## 4.4 EXPERIMENTAL SECTION

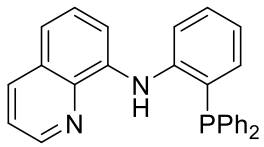
### 4.4.1 General Information

All the manipulations were conducted under an argon atmosphere either in a glove box or using standard Schlenk techniques in pre-dried glassware. The catalytic reactions were performed in flame-dried reaction vessels with a Teflon screw cap. Solvents were dried over

Na/benzophenone or $CaH_2$ and distilled prior to use. Liquid reagents were flushed with argon prior to use. The alkyl chlorides **4i-4w**,[39-43] **4z-4B**,[44,43] **4C-4J**[40,43] were prepared according to the previously described procedures. All other chemicals were obtained from commercial sources and were used without further purification. High-resolution mass spectrometry (HRMS) mass spectra were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. NMR: ($^1$H and $^{13}$C) spectra were recorded at 400 or 500 MHz ($^1$H), 100 or 125 MHz $^{13}$C, DEPT (distortionless enhancement by polarization transfer), respectively in $CDCl_3$ solutions, if not otherwise specified; chemical shifts ($\delta$) are given in ppm. The $^1$H and $^{13}$C NMR spectra are referenced to residual solvent signals ($CDCl_3$: $\delta$ H = 7.26 ppm, $\delta$ C = 77.2 ppm).

### 4.4.2 Synthesis of Ligand and Ni-complexes

To a Schlenk tube, *N*-(2-fluorophenyl)quinolin-8-amine (0.1 g, 0.42 mmol) and $KPPh_2$ (1.26 mL, 0.5 M in THF), was added under an argon atmosphere. The resulting reaction mixture was heated at 150 $^o$C for 5 days. At ambient temperature, the reaction mixture was diluted with EtOAc (20 mL). After evaporation of solvents in *vacuo*, the crude product was purified by column chromatography on neutral alumina (petroleum ether/EtOAc: 100/1) to yield **1** (0.13 g, 77%) as a yellow solid.

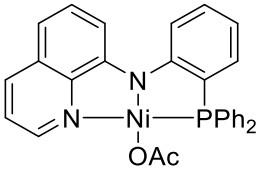



$^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.62 (dd, *J* = 4.1, 1.6 Hz, 1H, Ar–H), 8.49 (br. s, 1H, NH), 8.03 (dd, *J* = 8.3, 1.6 Hz, 1H, Ar–H), 7.72 (dd, *J* = 8.0, 4.6 Hz, 1H, Ar–H), 7.46-7.41 (m, 4H, Ar–H), 7.39-7.31 (m, 10H, Ar–H), 7.16 (dd, *J* = 7.8, 1.5 Hz, 1H, Ar–H), 7.05-6.96 (m, 2H, Ar–H). $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.1 ($C_q$), 147.5 (CH), 145.0 ($C_q$), 144.8 ($C_q$), 140.4 ($C_q$), 139.0 ($C_q$), 136.0 ($C_q$), 135.9 (CH), 134.4 (2C, CH), 134.2 (2C, CH), 130.0 ($C_q$), 129.7 (CH), 129.0 (2C, CH), 128.8 ($C_q$), 128.7 (4C, CH), 127.1 (CH), 123.0 (CH), 121.6 (CH), 120.5 (2C, CH), 116.7 (CH), 108.1 (CH). $^{31}$P-NMR: –17.1.

#### Synthesis and Characterization of ($^{Q}$NNP$^{Ph2}$)NiX

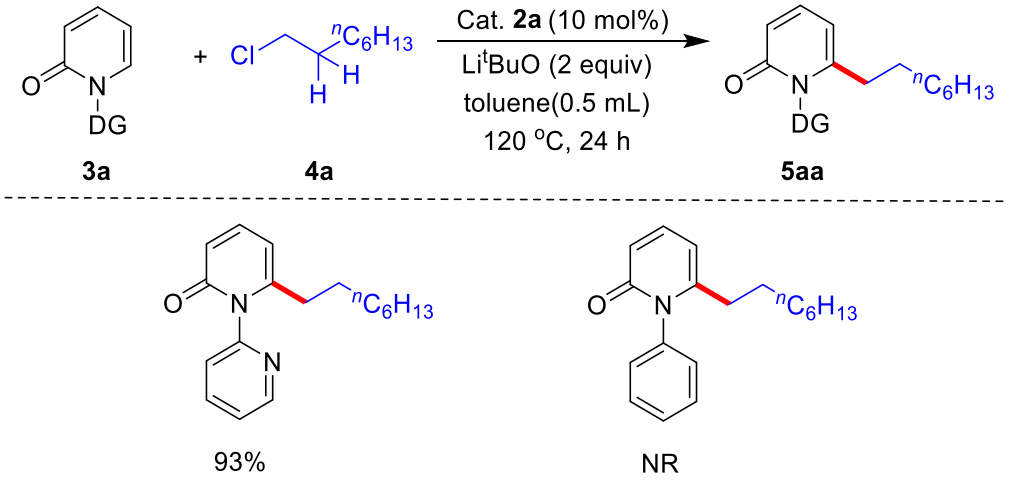
To an oven dried Schlenk flask was charged with ($^{Q}$NNP$^{Ph2}$)-H (0.1 g, 0.742 mmol) and $Ni(OAc)_2$ (0.15 g, 0.890 mmol) and THF (20 mL) was added into it. To the resultant reaction mixture, $Et_3N$ (0.09 g, 0.890 mmol) was added and the reaction mixture was stirred at 70 $^o$C for 5 h in a preheated oil bath. The reaction mixture was cooled to room temperature and all

the volatiles were evaporated. The product was then extracted with toluene (10 mL X 2), and then concentrated to 5 mL. Addition of hexane (10 mL) afforded a brown precipitate, which was filtered, washed with additional hexane and dried under vacuum. Yield: 0.33 g, 85%.




$^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.22-8.19 (m, 1H, Ar–H), 7.99-7.94 (m, 5H, Ar–H), 7.69 (dd, $J$ = 8.5, 5.3 Hz, 1H, Ar–H), 7.53 (dd, $J$ = 7.6, 4.3 Hz, 3H, Ar–H), 7.48-7.44 (m, 4H, Ar–H), 7.37 (dd, $J$ = 8.2, 4.9 Hz, 1H, Ar–H), 7.30 (t, $J$ = 8.0 Hz,, 1H, Ar–H), 7.20-7.16 (m, 1H, Ar–H), 7.11-7.06 (m, 1H, Ar–H), 6.95 (d, $J$ = 8.0 Hz, 1H, Ar–H), 6.58 (t, $J$ = 7.3 Hz, 1H, Ar–H), 1.74 (br s, 3H, $CH_3$). $^{31}$P-NMR: 21.3.

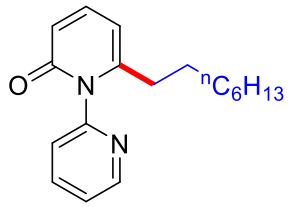
### 4.4.3 Effect of *N*-Substituents of 2-Pyridone on Alkylation




### 4.4.4 Representative Procedure for Alkylation

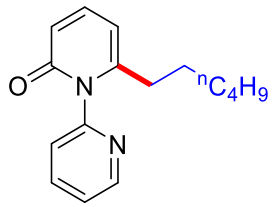
**Synthesis of 6-Octyl-2*H*-[1,2'-bipyridin]-2-one (5aa):** To a flame-dried screw-cap tube equipped with magnetic stir bar were introduced 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol), 1-chlorooctane (**4a**; 0.059 g, 0.40 mmol), Cat.**2a** (0.010 g, 0.02 mmol, 10.0 mol%) and Li$O^t$Bu (0.032 g, 0.40 mmol) inside the glove box. To the above mixture in the tube was added toluene (0.5 mL). The resultant reaction mixture in the tube was immersed in a preheated oil bath at 120 $^{o}$C and stirred for 24 h. At ambient temperature, the reaction mixture was quenched with distilled $H_2O$ (10.0 mL) and the crude product was extracted with EtOAc (15 mL x 3). The combined organic extract was dried over $Na_2SO_4$ and the volatiles were evaporated *in vacuo*. The remaining residue was purified by column chromatography on

neutral alumina (petroleum ether/EtOAc: 1/2) to yield **5aa** (0.053 g, 93%) as a white solid.

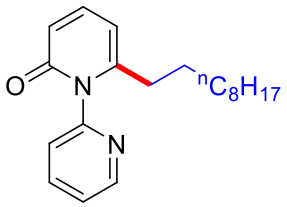



$^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.18 (dd, $J$ = 4.9, 1.8 Hz, 1H, Ar–H), 7.87 (td, $J$ = 7.8, 1.9 Hz, 1H, Ar–H), 7.40-7.36 (m, 1H, Ar–H), 7.34-7.30 (m, 2H, Ar–H), 6.49 (d, $J$ = 9.3 Hz, 1H, Ar–H), 6.08 (d, $J$ = 7.0 Hz, 1H, Ar–H), 2.18 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 1.38 (s, 2H, $CH_2$), 1.25-1.20 (m, 2H, $CH_2$), 1.15-1.11 (m, 8H, $CH_2$), 0.83 (t, $J$ = 7.0 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.0 (CO), 151.9 ($C_q$), 150.2 ($C_q$), 149.9 (CH), 140.3 (CH), 138.6 (CH), 124.2 (CH), 124.1 (CH), 118.6 (CH), 105.1 (CH), 33.1 ($CH_2$) 31.8 ($CH_2$), 29.1 (3C, $CH_2$), 27.9 ($CH_2$), 22.7 ($CH_2$), 14.2 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{18}H_{24}ON_2$ + $H^+$ $[M + H]^+$ 285.1961; Found 285.1953.

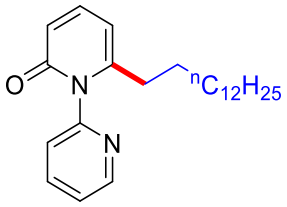
### 4.4.5 Characterization Data for Alkylation



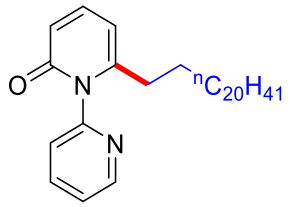

**6-Hexyl-2*H*-[1,2'-bipyridin]-2-one (5ab):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and 1-chlorohexane (**4b**; 0.048 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ab** (0.046 g, 90%) as a white solid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.67 (dd, $J$ = 4.8, 1.0 Hz, 1H, Ar–H), 7.90 (td, $J$ = 7.6, 1.9 Hz, 1H, Ar–H), 7.42-7.39 (m, 1H, Ar–H), 7.36-7.32 (m, 2H, Ar–H), 6.51 (d, $J$ = 9.1 Hz, 1H, Ar–H), 6.10 (d, $J$ = 6.9 Hz, 1H, Ar–H), 2.19 (t, $J$ = 7.0 Hz, 2H, $CH_2$), 1.40 (s, 2H, $CH_2$), 1.22-1.09 (m, 6H, $CH_2$), 0.81 (t, $J$ = 6.9 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.4 (CO), 152.0 ($C_q$), 150.2 ($C_q$), 150.0 (CH), 140.3 (CH), 138.6 (CH), 124.2 (2C, CH), 118.7 (CH), 105.2 (CH), 33.1 ($CH_2$) 33.4 ($CH_2$), 28.9 ($CH_2$), 27.9 ($CH_2$), 22.5 ($CH_2$), 14.1 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{16}H_{20}ON_2$ + $H^+$ $[M + H]^+$ 257.1648; Found 257.1648.



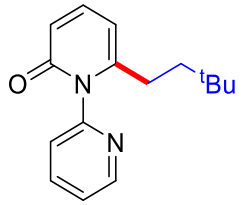

**6-Decyl-2*H*-[1,2'-bipyridin]-2-one (5ac):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and 1-chlorodecane (**4c**; 0.071 g, 0.4 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ac** (0.053 g, 85%) as a white solid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.65 (dd, $J$ = 4.9, 1.1 Hz, 1H, Ar–H), 7.88 (td, $J$ = 7.8, 1.9 Hz, 1H, Ar–H), 7.40-7.37 (m, 1H, Ar–H), 7.35-7.31 (m, 2H, Ar–H), 6.50 (d, $J$ = 9.3 Hz, 1H, Ar–H), 6.09 (d, $J$ = 6.9 Hz, 1H, Ar–H), 2.18 (t, $J$ = 7.4 Hz, 2H, $CH_2$), 1.39 (s, 2H, $CH_2$), 1.29-1.11 (m, 14H, $CH_2$), 0.86 (t, $J$ = 6.8 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 152.0 ($C_q$), 150.2 ($C_q$), 149.9 (CH), 140.3 (CH), 138.6 (CH), 124.2 (CH), 124.1 (CH), 118.6 (CH), 105.1 (CH), 33.1 ($CH_2$) 32.0 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.2 (2C, $CH_2$), 27.9 ($CH_2$), 22.8 ($CH_2$), 14.2 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{20}H_{28}ON_2$ + $H^+$ $[M + H]^+$ 313.2274; Found 313.2229.



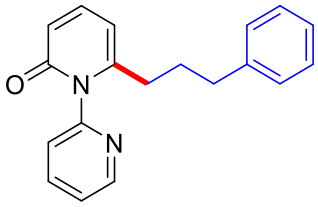

**6-Tetradecyl-2*H*-[1,2'-bipyridin]-2-one (5ad):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and 1-chlorotetradecane (**4d**; 0.093 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ad** (0.055 g, 75%) as a white solid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.66 (dd, $J$ = 4.9, 1.1 Hz, 1H, Ar–H), 7.89 (td, $J$ = 7.6, 1.9 Hz, 1H, Ar–H), 7.41-7.38 (m, 1H, Ar–H), 7.36-7.32 (m, 2H, Ar–H), 6.50 (d, $J$ = 9.0 Hz, 1H, Ar–H), 6.10 (d, $J$ = 6.8 Hz, 1H, Ar–H), 2.19 (t, $J$ = 7.3 Hz, 2H, $CH_2$), 1.39 (s, 2H, $CH_2$), 1.31-1.12 (m, 22H, $CH_2$), 0.87 (t, $J$ = 6.6 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 152.0 ($C_q$), 150.2 ($C_q$), 150.0 (CH), 140.3 (CH), 138.6 (CH), 124.2 (CH), 124.1 (CH), 118.6 (CH), 105.1 (CH), 33.1 ($CH_2$) 32.1 ($CH_2$), 29.8 (4C, $CH_2$), 29.7 ($CH_2$), 29.5 (2C, $CH_2$), 29.2 (2C, $CH_2$), 28.0 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{24}H_{36}ON_2$ + $H^+$ $[M + H]^+$ 369.2900; Found 369.2895.



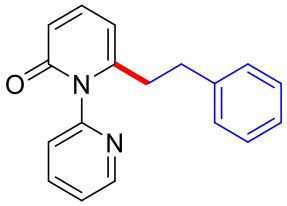

**6-Docosyl-2*H*-[1,2'-bipyridin]-2-one (5ae):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and 1-chlorodocasane (**4e**; 0.140 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ae** (0.070 g, 73%) as a white solid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.66 (dd, $J$ = 4.9, 1.8 Hz, 1H, Ar–H), 7.89 (td, $J$ = 7.8, 1.9 Hz, 1H, Ar–H), 7.41-7.38 (m, 1H, Ar–H), 7.36-7.32 (m, 2H, Ar–H), 6.51 (d, $J$ = 9.3 Hz, 1H, Ar–H), 6.10 (d, $J$ = 6.9 Hz, 1H, Ar–H), 2.19 (t, $J$ = 7.1 Hz, 2H, $CH_2$), 1.38 (s, 2H, $CH_2$), 1.29-1.18 (m, 38H, $CH_2$), 0.87 (t, $J$ = 6.6 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 152.0 ($C_q$), 150.2 ($C_q$), 150.0 (CH), 140.3 (CH), 138.6 (CH), 124.2 (CH), 124.1 (CH), 118.6 (CH), 105.1 (CH), 33.1 ($CH_2$) 32.1 ($CH_2$), 29.8 (12C, $CH_2$), 29.7 ($CH_2$), 29.5 (2C, $CH_2$), 29.2 (2C, $CH_2$), 28.0 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$).



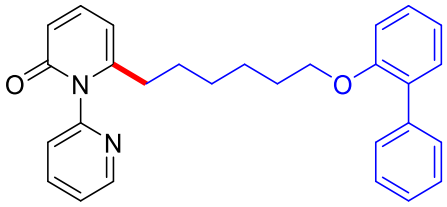

**6-(3,3-Dimethylbutyl)-2*H*-[1,2'-bipyridin]-2-one (5af):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and 1-chloro-3,3-dimethylbutane (**4f**; 0.048 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5af** (0.032 g, 63%) as a white solid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.67 (dd, $J$ = 4.9, 1.1 Hz, 1H, Ar–H), 7.90 (td, $J$ = 7.8, 1.9 Hz, 1H, Ar–H), 7.42-7.40 (m, 1H, Ar–H), 7.38-7.31 (m, 2H, Ar–H), 6.50 (d, $J$ = 8.6 Hz, 1H, Ar–H), 6.10 (d, $J$ = 6.8 Hz, 1H, Ar–H), 2.23-2.16 (m, 2H, $CH_2$), 1.39 (s, 2H, $CH_2$), 0.65 (s, 9H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 151.9 ($C_q$), 150.9 ($C_q$), 149.9 (CH), 140.4 (CH), 138.6 (CH), 124.4 (CH), 124.2 (CH), 118.6 (CH), 105.4 (CH), 42.9 ($CH_2$) 30.2 ($C_q$), 28.9 (3C, $CH_3$), 28.3 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{16}H_{20}ON_2$ + $H^+$ $[M + H]^+$ 257.1648; Found 257.1647.



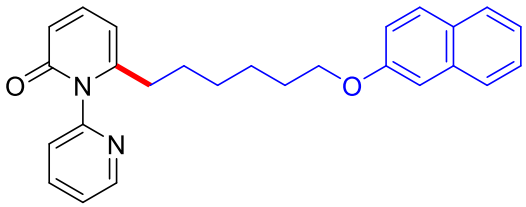
**6-(3-Phenylpropyl)-2*H*-[1,2'-bipyridin]-2-one (5ag):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and (3-chloropropyl)benzene (**4g**; 0.062 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ag** (0.054 g, 93%) as a white solid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.60 (ddd, $J$ = 4.8, 1.8, 0.63 Hz, 1H, Ar–H), 7.84 (td, $J$ = 7.6, 1.9 Hz, 1H, Ar–H), 7.38-7.28 (m, 3H, Ar–H), 7.24-7.13 (m, 3H, Ar–H), 7.00-6.98 (m, 2H, Ar–H), 6.52 (d, $J$ = 9.1 Hz, 1H, Ar–H), 6.11 (d, $J$ = 6.9 Hz, 1H, Ar–H), 2.46 (t, $J$ = 7.4 Hz, 2H, $CH_2$), 2.23 (t, $J$ = 7.9 Hz, 2H, $CH_2$), 1.75 (s, 2H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.0 (CO), 151.7 ($C_q$), 149.9 (CH), 149.7 ($C_q$), 141.1 ($C_q$), 140.3 (CH), 138.6 (CH), 128.5 (2C, CH), 128.4 (2C, CH), 126.1 (CH), 124.1 (2C, CH), 118.8 (CH), 105.3 (CH), 35.3 ($CH_2$), 32.6 ($CH_2$), 29.7 ($CH_2$).



**6-Phenethyl-*2H*-[1,2'-bipyridin]-2-one (5ah):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and (2-chloroethyl)benzene (**4h**; 0.056 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ah** (0.038 g, 69%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.69 (ddd, $J$ = 4.8, 1.9, 0.75 Hz, 1H, Ar–H), 7.89 (td, $J$ = 7.8, 1.9 Hz, 1H, Ar–H), 7.44-7.40 (m, 1H, Ar–H), 7.37-7.31 (m, 2H, Ar–H), 7.23-7.16 (m, 3H, Ar–H), 6.93-6.91 (m, 2H, Ar–H), 6.52 (d, $J$ = 9.3 Hz, 1H, Ar–H), 6.10 (d, $J$ = 6.8 Hz, 1H, Ar–H), 2.75 (s, 2H, $CH_2$), 2.52 (t, $J$ = 8.0 Hz, 2H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.0 (CO), 151.9 ($C_q$), 150.0 (CH), 149.0 ($C_q$), 140.3 (CH), 140.2 ($C_q$), 138.8 (CH), 128.7 (2C, CH), 128.3 (2C, CH), 126.5 (CH), 124.3 (2C, CH), 119.1 (CH), 105.6 (CH), 35.1 ($CH_2$), 34.7 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{18}H_{16}ON_2 + H^+$ $[M + H]^+$ 277.1335; Found 277.1292.

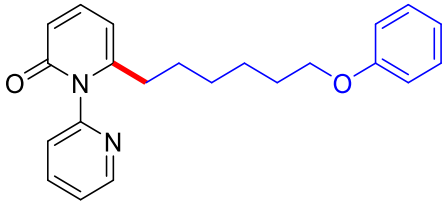


**6-(6-([1,1'-Biphenyl]-2-yloxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5ai):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and 2-((6-chlorohexyl)oxy)-1,1'-biphenyl (**4i**; 0.12 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ai** (0.057 g, 67%) as a white solid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.63 (dd, $J$ = 4.8, 1.1 Hz, 1H, Ar–H), 7.84 (td, $J$ = 7.8, 1.9 Hz, 1H, Ar–H), 7.53-7.50 (m, 2H, Ar–H), 7.39-7.28 (m, 8H, Ar–H), 7.04-7.00 (m, 1H, Ar–H), 6.94 (d, $J$ = 8.3 Hz, 1H, Ar–H), 6.54 (d, $J$ = 9.1 Hz, 1H, Ar–H), 6.08 (d, $J$ = 6.8 Hz, 1H, Ar–H), 3.88 (t, $J$ = 6.3 Hz, 2H, $CH_2$), 2.17 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.63-1.56 (m, 2 H, $CH_2$), 1.37 (br. s, 2H, $CH_2$), 1.27-1.20 (m, 2H, $CH_2$), 1.17-1.08 (m, 2H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 156.0 ($C_q$), 151.8 ($C_q$), 150.0 (2C, $C_q$), 149.9 (CH), 140.4 (CH), 138.7 (CH), 138.7 ($C_q$), 131.0 (CH), 129.7 (2C, CH), 128.7 (CH), 127.9 (2C, CH), 126.8 (CH), 124.2 (CH), 124.1 (CH), 121.0 (CH), 118.6 (CH), 112.6 (CH), 105.3 (CH), 68.2 ($CH_2$), 32.9 ($CH_2$), 28.9 ($CH_2$), 28.7 ($CH_2$), 27.8 ($CH_2$), 25.6 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{28}H_{28}O_2N_2 + H^+$ $[M + H]^+$ 425.2224; Found 425.2227.

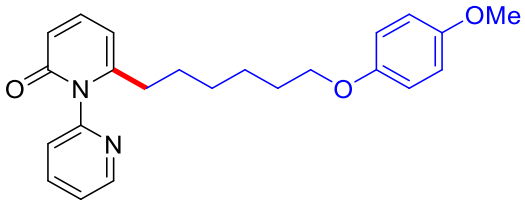


**6-(6-(Naphthalen-2-yloxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5aj):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and 2-((6-chlorohexyl)oxy)naphthalene (**4j**; 0.11 g, 0.40 mmol) Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5aj** (0.055 g, 69%) as a white solid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.68 (ddd, $J$ = 4.9, 1.9, 0.75 Hz, 1H, Ar–H), 7.87 (td, $J$ = 7.7, 1.9 Hz, 1H, Ar–H), 7.77-7.70 (m, 3H, Ar–H), 7.43 (td, $J$ = 7.0, 1.1 Hz, 1H, Ar–H), 7.38-7.31 (m, 4H, Ar–H), 7.13-7.09 (m, 2H, Ar–H), 6.53 (d, $J$ = 9.1 Hz, 1H, Ar–H), 6.11 (d, $J$ = 6.8 Hz, 1H, Ar–H), 4.01 (t, $J$ = 6.4 Hz, 2H, $CH_2$), 2.23 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.78-1.71 (m, 2H, $CH_2$), 1.47 (br, s, 2H, $CH_2$), 1.39-1.33 (m, 2H, $CH_2$), 1.26-1.23 (m, 2H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 157.1 ($C_q$), 151.9 ($C_q$), 150.0 (CH), 150.0 ($C_q$), 140.3 (CH), 138.7 (CH), 134.7 ($C_q$), 129.5 (CH), 129.0 ($C_q$), 127.8 (CH),

126.8 (CH), 126.5 (CH), 124.2 (CH), 124.2 (CH), 123.7 (CH), 119.0 (CH), 118.7 (CH), 106.7 (CH), 105.2 (CH), 67.8 ($CH_2$), 33.0 ($CH_2$), 29.1 ($CH_2$), 28.9 ($CH_2$), 27.9 ($CH_2$), 25.8 ($CH_2$).

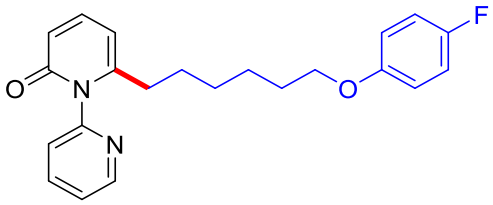


**6-(6-phenoxyhexyl)-2H-[1,2'-bipyridin]-2-one (5ak):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and ((6-chlorohexyl)oxy)benzene (**4k**; 0.085 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ak** (0.047 g, 67%) as a white solid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.66 (ddd, $J$ = 4.9, 1.8, 0.75 Hz, 1H, Ar–H), 7.88 (td, $J$ = 7.6, 1.9 Hz, 1H, Ar–H), 7.39-7.32 (m, 3H, Ar–H), 7.29-7.25 (m, 2H, Ar–H), 6.95-6.91 (m, 1H, Ar–H), 6.86 (dd, $J$ = 7.8, 0.9 Hz, 2H, Ar–H), 6.52 (d, $J$ = 7.8 Hz, 1H, Ar–H), 6.10 (d, $J$ = 6.9 Hz, 1H, Ar–H), 3.88 (t, $J$ = 6.4 Hz, 2H, $CH_2$), 2.22 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.71-1.64 (m, 2H, $CH_2$), 1.45 (br. s, 2H, $CH_2$), 1.34-1.29 (m, 2H, $CH_2$), 1.26-1.20 (m, 2H, $CH_2$). $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 159.1 ($C_q$), 152.0 ($C_q$), 150.0 (CH), 150.0 ($C_q$), 140.3 (CH), 138.7 (CH), 129.6 (2C, CH), 124.2 (2C, CH), 120.7 (CH), 118.7 (CH), 114.6 (2C, CH), 105.2 (CH), 67.7 ($CH_2$), 33.0 ($CH_2$), 29.1 ($CH_2$), 28.9 ($CH_2$), 27.9 ($CH_2$), 25.7 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{22}H_{24}O_2N_2 + H^+$ $[M + H]^+$ 349.1911; Found 349.1911.

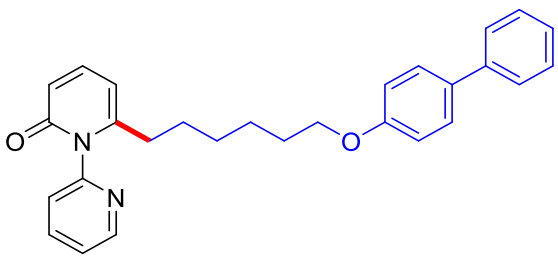


**6-(6-(4-Methoxyphenoxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5al):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and 1-((6-chlorohexyl)oxy)-4-methoxybenzene (**4l**; 0.097 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5al** (0.051 g, 67%) as a light yellow liquid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.66 (dd, $J$ = 4.9, 1.0 Hz, 1H, Ar–H), 7.88 (td, $J$ = 7.8, 1.8 Hz, 1H, Ar–H), 7.39-7.32 (m, 3H, Ar–H), 6.83-6.78 (m, 4H, Ar–H), 6.52 (d, $J$ = 9.1 Hz, 1H, Ar–H), 6.10 (d, $J$ = 6.9 Hz, 1H, Ar–H), 3.83 (t, $J$ = 6.4 Hz, 2H, $CH_2$), 3.76 (s, 3H, $CH_3$), 2.21 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.68-1.61 (m, 2H, $CH_2$), 1.44 (br. s, 2H,

$CH_2$), 1.33-1.29 (m, 2H, $CH_2$), 1.25-1.19 (m, 2H, $CH_2$). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 153.9 ($C_q$), 153.3 (2C, $C_q$), 151.9 ($C_q$), 150.0 (CH), 140.3 (CH), 138.7 (CH), 124.2 (2C, CH), 118.7 (CH), 115.5 (2C, CH), 114.8 (2C, CH), 105.2 (CH), 68.5 ($CH_2$), 55.9 ($CH_3$), 33.0 ($CH_2$), 29.2 ($CH_2$), 28.9 ($CH_2$), 27.9 ($CH_2$), 25.7 ($CH_2$).

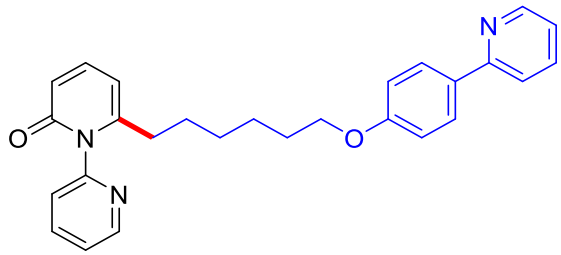



**6-(6-(4-Fluorophenoxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5am):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) 1-((6-chlorohexyl)oxy)-4-fluorobenzene (**4m**; 0.092 g, 0.40 mmol) and the reaction mixture was stirred at 130 °C. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **4am** (0.051 g, 70%) as a white solid. $^1H$-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.67-8.65 (m, 1H, Ar–H), 7.89 (td, $J$ = 7.7, 1.9 Hz, 1H, Ar–H), 7.40-7.32 (m, 3H, Ar–H), 6.97-6.93 (m, 2H, Ar–H), 6.80-6.77 (m, 2H, Ar–H), 6.52 (d, $J$ = 9.3 Hz, 1H, Ar–H), 6.10 (d, $J$ = 6.8 Hz, 1H, Ar–H), 3.83 (t, $J$ = 6.4 Hz, 2H, $CH_2$), 2.22 (t, $J$ = 7.7 Hz, 2H, $CH_2$), 1.69-1.62 (m, 2H, $CH_2$), 1.45 (br. s, 2H, $CH_2$), 1.35-1.28 (m, 2H, $CH_2$), 1.25-1.19 (m, 2H, $CH_2$). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.1(CO), 157.3 (d, $^1J_{C\text{-}F}$ = 238.0 Hz, $C_q$), 155.3 (d, $^4J_{C\text{-}F}$ = 2.3 Hz, $C_q$), 152.0 ($C_q$), 150.0 ($C_q$), 149.9 (CH), 140.3 (CH), 138.7 (CH), 124.2 (2C, CH), 118.8 (CH), 116.0 (d, $^2J_{C\text{-}F}$ = 22.9 Hz, 2C, CH), 115.6 (d, $^3J_{C\text{-}F}$ = 7.6 Hz, 2C, CH), 105.2 (CH), 68.5 ($CH_2$), 33.0 ($CH_2$), 29.2 ($CH_2$), 28.9 ($CH_2$), 27.9 ($CH_2$), 25.7 ($CH_2$). $^{19}F$-NMR (377 MHz, $CDCl_3$): $\delta$ = –124.4 (s). HRMS (ESI): *m/z* Calcd for $C_{22}H_{23}O_2N_2F + H^+$ $[M + H]^+$ 367.1816; Found 367.1821.

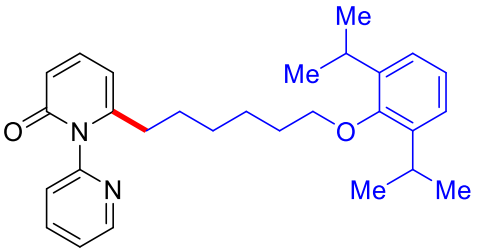



**6-(6-([1,1'-Biphenyl]-4-yloxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5an):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 00.034 g, 0.20 mmol) and 4-((6-chlorohexyl)oxy)-1,1'-biphenyl (**4n**; 0.12 g, 0.40 mmol) and the reaction mixture was

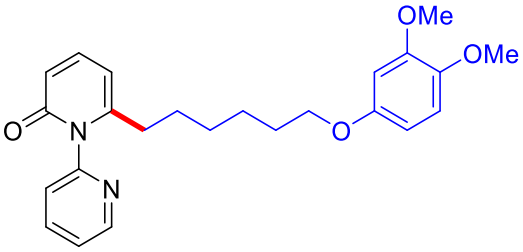
stirred at 130 °C. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5an** (0.067 g, 79%) as a white solid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.66 (dd, *J* = 4.9, 1.1 Hz, 1H, Ar–H), 7.89 (td, *J* = 7.8, 2.0 Hz, 1H, Ar–H), 7.56-7.50 (m, 4H, Ar–H), 7.43-7.28 (m, 6H, Ar–H), 6.94 (d, *J* = 8.8 Hz, 2H, Ar–H), 6.53 (d, *J* = 9.0 Hz, 1H, Ar–H), 6.11 (d, *J* = 6.9 Hz, 1H, Ar–H), 3.93 (t, *J* = 6.4 Hz, 2H, $CH_2$), 2.23 (t, *J* = 7.8 Hz, 2H, $CH_2$), 1.72-1.67 (m, 2H, $CH_2$), 1.47 (br. s, 2H, $CH_2$), 1.37-1.31 (m, 2H, $CH_2$), 1.27-1.22 (m, 2H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 158.8 ($C_q$), 152.0 ($C_q$), 150.0 (CH), 150.0 ($C_q$), 141.0 ($C_q$), 140.3 (CH), 138.7 (CH), 133.9 ($C_q$), 128.9 (2C, CH), 128.3 (2C, CH), 126.9 (2C, CH), 126.8 (CH), 124.2 (2C, CH), 118.8 (CH), 114.9 (2C, CH), 105.2 (CH), 67.9 ($CH_2$), 33.1 ($CH_2$), 29.2 ($CH_2$), 28.9 ($CH_2$), 27.9 ($CH_2$), 25.8 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{28}H_{28}O_2N_2$ + $H^+$ $[M + H]^+$ 425.2224; Found 425.2232.




**6-(6-(4-(Pyridin-2-yl)phenoxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5ao):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) 2-(4-((6-chlorohexyl)oxy)phenyl)pyridine (**4o**; 0.12 g, 0.40 mmol) and the reaction mixture was stirred at 130 °C. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ao** (0.071 g, 83%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.65-8.62 (m, 2H, Ar–H), 7.94-7.91 (m, 2H, Ar–H), 7.87 (td, *J* = 7.8, 1.9 Hz, 1H, Ar–H), 7.71-7.63 (m, 2H, Ar–H), 7.38-7.31 (m, 3H, Ar–H), 7.15 (ddd, *J* = 7.1, 4.8, 1.31 Hz, 1H, Ar–H), 6.96-6.92 (m, 2H, Ar–H), 6.51 (d, *J* = 8.5 Hz, 1H, Ar–H), 6.09 (d, *J* = 6.8 Hz, 1H, Ar–H), 3.93 (t, *J* = 6.4 Hz, 2H, $CH_2$), 2.21 (t, *J* = 7.7 Hz, 2H, $CH_2$), 1.72-1.65 (m, 2H, $CH_2$), 1.45 (br. s, 2H, $CH_2$), 1.36-1.29 (m, 2H, $CH_2$), 1.25-1.19 (m, 2H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.0 (CO), 160.0 ($C_q$), 157.2 ($C_q$), 151.9 ($C_q$), 149.9 (CH), 149.9 ($C_q$), 149.6 (CH), 140.3 (CH), 138.6 (CH), 136.8 (CH), 132.0 ($C_q$), 128.2 (3C, CH), 124.1 (CH), 121.5 (CH), 119.9 (CH), 118.7 (CH), 114.7 (2C, CH), 105.1 (CH), 67.8 ($CH_2$), 33.0 ($CH_2$), 29.0 ($CH_2$), 28.8 ($CH_2$), 27.8 ($CH_2$), 25.7 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{27}H_{27}O_2N_3$ + $H^+$ $[M + H]^+$ 426.2176; Found 426.2177.

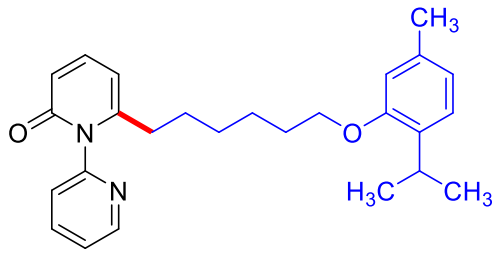



**6-(6-(2,6-Diisopropylphenoxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5ap):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and 2-((6-chlorohexyl)oxy)-1,3-diisopropylbenzene (**4p**; 0.12 g, 0.40 mmol) and the reaction mixture was stirred at 130 $^{o}$C. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ap** (0.063 g, 73%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.66 (ddd, $J$ = 4.9, 1.9, 0.75 Hz, 1H, Ar–H), 7.90 (td, $J$ = 7.7, 1.9 Hz, 1H, Ar–H), 7.42-7.34 (m, 3H, Ar–H), 7.09-7.08 (m, 3H, Ar–H), 6.53 (d, $J$ = 9.0 Hz, 1H, Ar–H), 6.13 (d, $J$ = 6.9 Hz, 1H, Ar–H), 3.66 (t, $J$ = 6.5 Hz, 2H, $CH_2$), 3.29-3.22 (m, 2H, $CH_2$), 2.24 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.76-1.69 (m, 2H, $CH_2$), 1.49 (br. s, 2H, $CH_2$), 1.43-1.35 (m, 2H, $CH_2$), 1.29-1.25 (m, 2H, CH), 1.22 (s, 6H, $CH_3$), 1.20 (s, 6H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 153.5 ($C_q$), 152.0 ($C_q$), 150.0 (2C, CH), 141.9 (3C, $C_q$), 140.3 (CH), 138.7 (CH), 124.6 (CH), 124.2 (2C, CH), 124.1 (CH), 118.7 (CH), 105.1 (CH), 74.7 ($CH_2$), 33.1 ($CH_2$), 30.3 ($CH_2$), 29.2 ($CH_2$), 28.0 ($CH_2$), 26.5 (2C, CH), 25.9 ($CH_2$), 24.2 (4C, $CH_3$). HRMS (ESI): *m/z* Calcd for $C_{28}H_{36}O_2N_2 + H^+$ $[M + H]^+$ 433.2850; Found 433.2785.

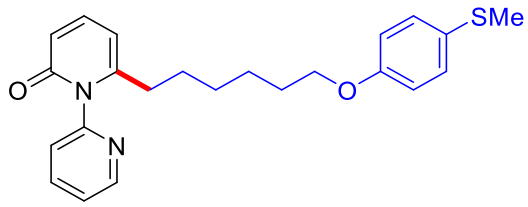



**6-(6-(3,4-Dimethoxyphenoxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5aq):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) 4-((6-chlorohexyl)oxy)-1,2-dimethoxybenzene (**4q**; 0.11 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5aq** (0.052 g, 64%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.65 (dd, $J$ = 4.9, 1.6 Hz, 1H, Ar–H), 7.88 (td, $J$ = 7.8, 1.9 Hz, 1H, Ar–H), 7.40-7.32 (m, 3H, Ar–H), 6.76 (d, $J$ = 8.8 Hz, 1H, Ar–H), 6.51 (d, $J$ = 9.0 Hz, 1H, Ar–H), 6.48 (d, $J$ = 2.8 Hz, 1H, Ar–H), 6.35 (dd, $J$ = 8.7, 2.8 Hz, 1H, Ar–H), 6.10 (d, $J$ = 6.9 Hz, 1H, Ar–H), 3.85-3.81 (m, 2H, $CH_2$, 6H, $CH_3$), 2.22 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 1.69-1.62 (m, 2H, $CH_2$), 1.45 (br. s, 2H, $CH_2$), 1.34-1.28 (m, 2H,

$CH_2$), 1.25 -1.19 (m, 2H, $CH_2$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 153.8 ($C_q$), 151.9 ($C_q$), 150.0 ($C_q$), 150.0 (CH), 149.9 ($C_q$), 143.6 ($C_q$), 140.3 (CH), 138.7 (CH), 124.2 (2C, CH), 118.7 (CH), 112.0 (CH), 105.2 (CH), 103.8 (CH), 101.0 (CH), 68.3 ($CH_2$), 56.6 ($CH_3$), 56.0 ($CH_3$), 33.0 ($CH_2$), 29.2 ($CH_2$), 28.9 ($CH_2$), 27.9 ($CH_2$), 25.8 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{24}H_{28}O_4N_2 + H^+$ $[M + H]^+$ 409.2122; Found 409.2122.

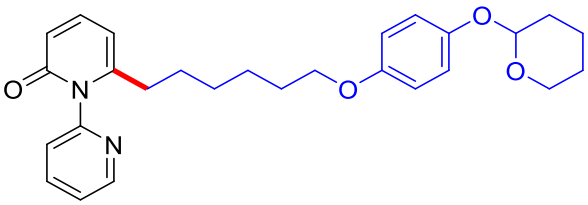



**6-(6-(2-Isopropyl-5-methylphenoxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5ar):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and 2-((6-chlorohexyl)oxy)-1-isopropyl-4-methylbenzene (**4r**; 0.11 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ar** (0.055 g, 68%) as a white solid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.66 (ddd, *J* = 4.9, 1.8, 0.75 Hz, 1H, Ar–H), 7.88 (td, *J* = 7.8, 1.9 Hz, 1H, Ar–H), 7.40-7.33 (m, 3H, Ar–H), 7.08 (d, *J* = 7.8 Hz, 1H, Ar–H), 6.73 (d, *J* = 7.3 Hz, 1H, Ar–H), 6.62 (s, 1H, Ar–H), 6.53 (d, *J* = 8.5 Hz, 1H, Ar–H), 6.11 (d, *J* = 6.9 Hz, 1H, Ar–H), 3.88 (t, *J* = 6.3 Hz, 2H, $CH_2$), 3.27-3.21 (m, 1H, CH), 2.31 (s, 3H, $CH_3$), 2.23 (t, *J* = 7.7 Hz, 2H, $CH_2$), 1.73-1.67 (m, 2H, $CH_2$), 1.46 (br. s, 2H, $CH_2$), 1.40-1.32 (m, 2H, $CH_2$), 1.27-1.23 (m, 2H, $CH_2$), 1.19 (s, 3H, $CH_3$), 1.17 (s, 3H, $CH_3$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 156.2 ($C_q$), 151.9 ($C_q$), 150.0 ($C_q$, CH), 140.3 (CH), 138.7 (CH), 136.4 ($C_q$), 134.1 ($C_q$), 126.0 (CH), 124.2 (CH), 124.2 (CH), 121.1 (CH), 118.7 (CH), 112.2 (CH), 105.2 (CH), 67.6 ($CH_2$), 33.1 ($CH_2$), 29.3 ($CH_2$), 28.9 ($CH_2$), 27.9 ($CH_2$), 26.8 ($CH_3$), 25.9 ($CH_2$), 22.9 (2C, $CH_3$), 21.5 (CH). HRMS (ESI): *m/z* Calcd for $C_{26}H_{32}O_2N_2 + H^+$ $[M + H]^+$ 405.2537; Found 405.2544.

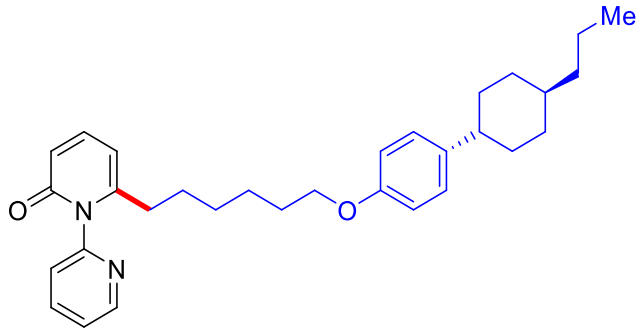



**6-(6-(4-(Methylthio)phenoxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5as):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 00.034 g, 0.20 mmol) and (4-((6-chlorohexyl)oxy)phenyl)(methyl)sulfane (**4s**; 0.10 g, 0.40 mmol) and the reaction mixture

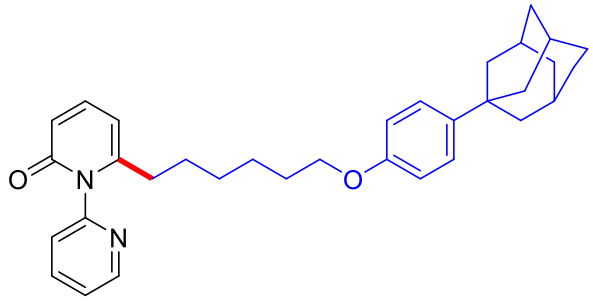
was stirred at 130 °C. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5as** (0.065 g, 82%) as a white solid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.66 (ddd, *J* = 4.9, 1.8, 0.63 Hz, 1H, Ar–H), 7.88 (td, *J* = 7.8, 1.9 Hz, 1H, Ar–H), 7.40-7.32 (m, 3H, Ar–H), 7.26-7.23 (m, 2H, Ar–H), 6.80 (d, *J* = 8.9 Hz, 2H, Ar–H), 6.52 (d, *J* = 9.3 Hz, 1H, Ar–H), 6.10 (d, *J* = 6.8 Hz, 1H, Ar–H), 3.85 (t, *J* = 6.4 Hz, 2H, $CH_2$), 2.43 (s, 3H, $CH_3$), 2.21 (t, *J* = 7.7 Hz, 2H, $CH_2$), 1.68-1.62 (m, 2H, $CH_2$), 1.45-1.40 (m, 2H, $CH_2$), 1.33-1.29 (m, 2H, $CH_2$), 1.25-1.21 (m, 2H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.0 (CO), 157.8 ($C_q$), 151.9 ($C_q$), 150.0 (CH), 149.9 ($C_q$), 140.3 (CH), 138.7 (CH), 130.3 (2C, CH), 128.8 ($C_q$), 124.2 (2C, CH), 118.7 (CH), 115.3 (2C, CH), 105.2 (CH), 67.9 ($CH_2$), 33.0 ($CH_2$), 29.1 ($CH_2$), 28.9 ($CH_2$), 27.9 ($CH_2$), 25.7 ($CH_2$), 18.2 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{23}H_{26}O_2N_2S$ + $H^+$ $[M + H]^+$ 395.1788; Found 395.1791.




**6-(6-(4-((Tetrahydro-2*H*-pyran-2-yl)oxy)phenoxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5at):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and 2-(4-((6-chlorohexyl)oxy)phenoxy)tetrahydro-2*H*-pyran (**4t**; 0.13 g, 0.40 mmol) and the reaction mixture was stirred at 130 °C. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5at** (0.066 g, 73%) as a white solid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.65 (dd, *J* = 4.9, 1.1 Hz, 1H, Ar–H), 7.88 (td, *J* = 7.8, 1.9 Hz, 1H, Ar–H), 7.39-7.31 (m, 3H, Ar–H), 6.99-6.95 (m, 2H, Ar–H), 6.79-6.75 (m, 2H, Ar–H), 6.51 (d, *J* = 8.8 Hz, 1H, Ar–H), 6.10 (d, *J* = 6.9 Hz, 1H, Ar–H), 5.28 (t, *J* = 3.3 Hz, 1H, CH), 3.93 (ddd, *J* = 11.5, 8.9, 3.1 Hz, 1H, CH), 3.82 (t, *J* = 6.4 Hz, 2H, $CH_2$), 3.60-3.55 (m, 1H, CH), 2.21 (t, *J* = 7.7 Hz, 2H, $CH_2$), 2.04-1.96 (m, 1H, CH), 1.87-1.82 (m, 1H, CH, 2H, $CH_2$), 1.67-1.60 (4H, $CH_2$), 1.44 (br. s, 2H, $CH_2$), 1.34-1.28 (m, 2H, $CH_2$), 1.25-1.18 (m, 2H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.0 (CO), 154.1(2C, $C_q$), 151.9 ($C_q$), 151.2 ($C_q$), 150.0 (CH), 140.3 (CH), 138.7 (CH), 124.2 (2C, CH), 118.7 (2C, CH), 117.9 (CH), 115.3 (2C, CH), 105.2 (CH), 97.5 (CH), 68.3 ($CH_2$), 62.2 ($CH_2$), 33.0 ($CH_2$), 30.6 ($CH_2$), 29.2 ($CH_2$), 28.9 ($CH_2$), 27.9 ($CH_2$), 25.7 ($CH_2$), 25.4 ($CH_2$), 19.1 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{27}H_{32}O_4N_2$ + $H^+$ $[M + H]^+$ 449.2435; Found 449.2431.

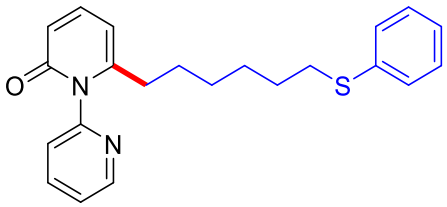



**6-(6-(4-((1*s*,4*r*)-4-Propylcyclohexyl)phenoxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5au):** The representative procedure was followed, using using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) 1-((6-chlorohexyl)oxy)-4-((1*s*,4*r*)-4-propylcyclohexyl)benzene (**4u**; 0.13 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5au** (0.045 g, 48%) as a white solid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.66-8.64 (m, 1H, Ar–H), 7.88 (td, *J* = 7.7, 1.9 Hz, 1 H, Ar–H), 7.39 (ddd, *J* = 5.8, 4.9, 0.88 Hz, 1H, Ar–H), 7.37-7.32 (m, 2H, Ar–H), 7.09 (d, *J* = 8.6 Hz, 2H, Ar–H), 6.78 (d, *J* = 8.6 Hz, 2H, Ar–H), 6.52 (d, *J* = 8.9 Hz, 1H, Ar–H), 6.10 (d, *J* = 6.9 Hz, 1H, Ar–H), 3.85 (t, *J* = 6.4 Hz, 2H, $CH_2$), 2.43-2.37 (m, 1H, CH), 2.22 (t, *J* = 7.6 Hz, 2H, $CH_2$), 1.86-1.84 (m, 4H, $CH_2$), 1.69-1.62 (m, 2H, $CH_2$), 1.46-1.17 (m, 1H, CH, 12H, $CH_2$), 1.08-0.99 (m, 2H, $CH_2$), 0.90 (t, *J* = 7.3 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 157.3 ($C_q$), 152.0 ($C_q$), 150.0 (CH), 150.0 ($C_q$), 140.3 (CH), 140.2 ($C_q$), 138.7 (CH), 127.8 (2C, CH), 124.2 (2C, CH), 118.8 (CH), 114.4 (2C, CH), 105.2 (CH), 67.8 ($CH_2$), 43.9 (CH), 39.9 ($CH_2$), 37.2 (CH), 34.8 (2C, $CH_2$), 33.8 (2C, $CH_2$), 33.0 ($CH_2$), 29.2 ($CH_2$), 28.9 ($CH_2$), 27.9 ($CH_2$), 25.8 ($CH_2$), 20.2 ($CH_2$), 14.6 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{31}H_{40}O_2N_2$ + $H^+$ $[M + H]^+$ 473.3163; Found 473.3174.

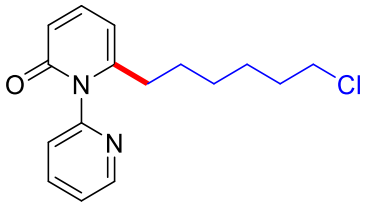



**6-(6-(4-((3*r*,5*r*,7*r*)-Adamantan-1-yl)phenoxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5av):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) (3*r*,5*r*,7*r*)-1-(4-((6-chlorohexyl)oxy)phenyl)adamantane (**4v**; 0.14 g, 0.40 mmol) and the reaction mixture was stirred at 130 °C. Purification by column chromatography on neutral

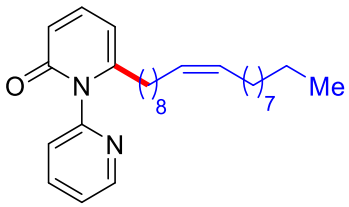
alumina (petroleum ether/EtOAc: 1/2) yielded **5av** (0.067 g, 69%) as a white solid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.65 (dd, $J$ = 4.8, 1.1 Hz, 1H, Ar–H), 7.87 (td, $J$ = 7.7, 1.8 Hz, 1H, Ar–H), 7.38- 7.31 (m, 3H, Ar–H), 7.27-7.25 (m, 2H, Ar–H), 6.81 (d, $J$ = 8.8 Hz, 2H, Ar–H), 6.51 (d, $J$ = 9.1 Hz, 1H, Ar–H), 6.09 (d, $J$ = 6.9 Hz, 1H, Ar–H), 3.86 (t, $J$ = 6.4 Hz, 2H, $CH_2$), 2.22 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 2.08 (s, 3H, CH), 1.88 (s, 6H, $CH_2$), 1.80-1.72 (m, 6H, $CH_2$), 1.69-1.62 (m, 2H, $CH_2$), 1.44 (br. s, 2H, $CH_2$), 1.35-1.21 (m, 4H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.0 (CO), 156.9 ($C_q$), 151.9 ($C_q$), 150.0 (CH, $C_q$), 143.8 ($C_q$), 140.3 (CH), 138.7 (CH), 125.9 (2C, CH), 124.2 (2C, CH), 118.7 (CH), 114.1 (2C, CH), 105.2 (CH), 67.7 ($CH_2$), 43.5 (4C, $CH_2$), 36.9 (2C, $CH_2$), 35.7 ($C_q$), 33.0 ($CH_2$), 29.2 ($CH_2$), 29.1 (3C, CH), 28.9 ($CH_2$), 27.9 ($CH_2$), 25.7 ($CH_2$).



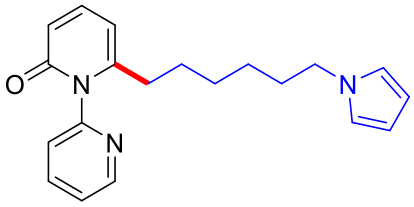

**6-(6-(Phenylthio)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5aw):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and (6-chlorohexyl)(phenyl)sulfane (**4w**; 0.091 g, 0.40 mmol) and the reaction mixture was stirred at 130 $^{o}$C. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5aw** (0.057 g, 78%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.66 (ddd, $J$ = 4.9, 1.8, 0.75 Hz, 1H, Ar–H), 7.88 (td, $J$ = 7.8, 2.0 Hz, 1H, Ar–H), 7.41-7.37 (m, 1H, Ar–H), 7.36-7.32 (m, 2H, Ar–H), 7.28-7.26 (m, 4H, Ar–H), 7.18-7.14 (m, 1H, Ar–H), 6.52 (d, $J$ = 9.0 Hz, 1H, Ar–H), 6.08 (d, $J$ = 6.9 Hz, 1H, Ar–H), 2.84 (t, $J$ = 7.3 Hz, 2H, $CH_2$), 2.19 (t, $J$ = 7.8 Hz, 2H, $CH_2$), 1.58-1.50 (m, 2H, $CH_2$), 1.41 (br. s, 2H, $CH_2$), 1.32-1.24 (m, 2H, $CH_2$), 1.19-1.13 (m, 2H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 152.0 ($C_q$), 150.0 (CH), 149.9 ($C_q$), 140.3 (CH), 138.7 (CH), 136.9 ($C_q$), 129.1 (2C, CH), 129.0 (2C, CH), 126.0 (CH), 124.2 (CH), 124.2 (CH), 118.8 (CH), 105.2 (CH), 33.6 ($CH_2$), 33.0 ($CH_2$), 28.9 ($CH_2$), 28.7 ($CH_2$), 28.3 ($CH_2$), 27.8 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{22}H_{24}ON_2S + H^+$ $[M + H]^+$ 365.1682; Found 365.1691.



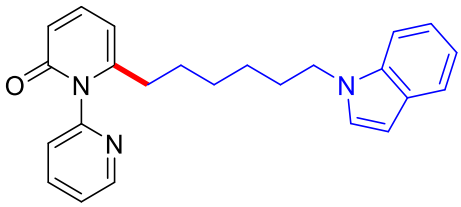

**6-(6-Chlorohexyl)-2*H*-[1,2'-bipyridin]-2-one (5ax):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and 1,6-dichlorohexane (**5x**; 0.062 g, 0.40 mmol) and the reaction mixture was stirred at 130 °C. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ax** (0.036 g, 62%) as a brown solid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.66 (ddd, *J* = 4.9, 1.8, 0.75 Hz, 1H, Ar–H), 7.90 (td, *J* = 7.8, 2.0 Hz, 1H, Ar–H), 7.42-7.39 (m, 1H, Ar–H), 7.36-7.32 (m, 2H, Ar–H), 6.51 (d, *J* = 9.1 Hz, 1H, Ar–H), 6.09 (d, *J* = 6.3 Hz, 1H, Ar–H), 3.45 (t, *J* = 6.6 Hz, 2H, $CH_2$), 2.21 (t, *J* = 7.8 Hz, 2H, $CH_2$), 1.69-1.62 (m, 2H, $CH_2$), 1.43 (br. s, 2H, $CH_2$), 1.30-1.25 (m, 2H, $CH_2$), 1.20-1.15 (m, 2H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.0 (CO), 151.9 ($C_q$), 150.0 (CH), 149.8 ($C_q$), 140.3 (CH), 138.7 (CH), 124.2 (2C, CH), 118.8 (CH), 105.2 (CH), 45.0 ($CH_2$), 33.0 ($CH_2$), 32.4 ($CH_2$), 28.4 ($CH_2$), 27.8 ($CH_2$), 26.5 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{16}H_{19}ON_2Cl + H^+$ $[M + H]^+$ 291.1259; Found 291.1261.




**(*Z*)-6-(Octadec-9-en-1-yl)-2*H*-[1,2'-bipyridin]-2-one (5ay):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and (*Z*)-1-chlorooctadec-9-ene (**4y**; 0.11 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ay** (0.051 g, 60%) as a light brown solid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.66 (dd, *J* = 4.8, 1.0 Hz, 1H, Ar–H), 7.89 (td, *J* = 7.8, 1.9 Hz, 1H, Ar–H), 7.42-7.38 (m, 1H, Ar–H), 7.36-7.32 (m, 2H, Ar–H), 6.52 (d, *J* = 9.1 Hz, 1H, Ar–H), 6.10 (d, *J* = 6.9 Hz, 1H, Ar–H), 5.38-5.28 (m, 2H, CH), 2.19 (t, *J* = 6.6 Hz, 2H, $CH_2$), 2.00-1.96 (m, 4H, $CH_2$), 1.39 (s, 2H, $CH_2$), 1.26-1.13 (m, 22H, $CH_2$), 0.87 (t, *J* = 6.5 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 152.0 ($C_q$), 150.2 ($C_q$), 150.0 (CH), 140.3 (CH), 138.6 (CH), 130.2 (CH), 129.9 (CH), 124.2 (CH), 124.1 (CH), 118.7 (CH), 105.1 (CH), 33.1 ($CH_2$), 32.1 ($CH_2$), 29.9 (2C, $CH_2$), 29.8 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 29.2 (2C, $CH_2$), 28.0 ($CH_2$), 27.4 ($CH_2$), 27.3 ($CH_2$), 22.9 ($CH_2$), 14.3 ($CH_3$).

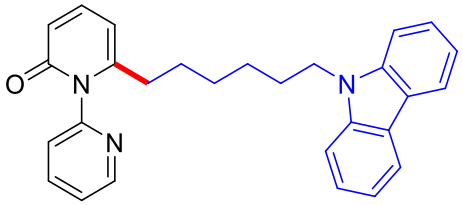


**6-(6-(1*H*-Pyrrol-1-yl)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5az):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) 1-(6-chlorohexyl)-1*H*-pyrrole (**4z**; 0.074 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5az** (0.025 g, 39%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.65 (dd, $J$ = 4.8, 1.3Hz, 1H, Ar–H), 7.89 (td, $J$ = 7.7, 1.9 Hz, 1H, Ar–H), 7.41-7.38 (dd, $J$ = 4.9, 7.4 Hz, 1H, Ar–H), 7.34-7.32 (m, 2H, Ar–H), 6.59 (t, $J$ = 2.0 Hz, 2H, Ar–H), 6.52 (d, $J$ = 9.1 Hz, 1H, Ar–H), 6.12 (t, $J$ = 2.1 Hz, 2H, Ar–H), 6.08 (d, $J$ = 6.9 Hz, 1H, Ar–H), 3.80 (t, $J$ = 7.0 Hz, 2H, $CH_2$), 2.18 (t, $J$ = 7.7 Hz, 2H, $CH_2$ ), 1.6-1.62 (m, 2H, $CH_2$), 1.40 (br. s, 2H, $CH_2$), 1.21-1.09 (m, 4H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.0 (CO), 151.9 ($C_q$), 150.0 (CH), 149.8 ($C_q$), 140.3 (CH), 138.7 (CH), 124.2 (2C, CH), 120.5 (2C, CH), 118.8 (CH), 108.0 (2C, CH), 105.1 (CH), 49.5 ($CH_2$), 33.0 ($CH_2$), 31.4 ($CH_2$), 28.7 ($CH_2$), 27.8 ($CH_2$), 26.4 ($CH_2$).

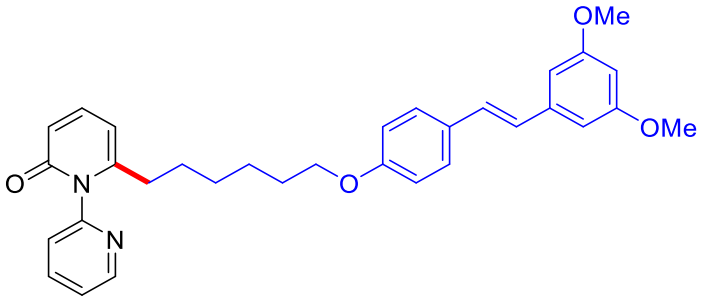


**6-(6-(1*H*-Indol-1-yl)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5aA):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) 1-(6-chlorohexyl)-1*H*-indole (**4A**; 0.094 g, 0.40 mmol) and the reaction mixture was stirred at 130 $^{o}$C. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5aA** (0.049 g, 66%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.62 (dd, $J$ = 4.8, 1.3 Hz, 1H, Ar–H), 7.84 (td, $J$ = 7.7, 1.9 Hz, 1H, Ar–H), 7.64 (d, $J$ = 7.9 Hz, 1H, Ar–H), 7.36-7.29 (m, 4H, Ar–H), 7.22-7.18 (m, 1H, Ar–H), 7.12-7.09 (m, 1H, Ar–H), 7.04 (d, $J$ = 3.1 Hz, 1H, Ar–H), 6.52 (d, $J$ = 9.1 Hz, 1H, Ar–H), 6.48 (d, $J$ = 3.0 Hz, 1H, Ar–H), 6.04 (d, $J$ = 6.9 Hz, 1H, Ar–H), 4.05 (t, $J$ = 6.9 Hz, 2H, $CH_2$), 2.16 (t, $J$ = 7.7 Hz, 2H, $CH_2$), 1.77-170 (m, 2H, $CH_2$), 1.38 (br. s, 2H, $CH_2$), 1.20-1.15 (m, 4H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.0 (CO), 151.8 ($C_q$), 149.9 (CH), 149.8 ($C_q$), 140.3 (CH), 138.6 (CH), 136.0 ($C_q$), 128.7 ($C_q$), 127.8 (CH), 124.1 (2C, CH), 121.5 (CH), 121.1 (CH), 119.3 (CH), 118.7 (CH), 109.4 (CH), 105.1 (CH), 101.1 (CH), 46.3 ($CH_2$), 32.9 ($CH_2$), 30.1 ($CH_2$), 28.8

($CH_2$), 27.8 ($CH_2$), 26.6 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{24}H_{25}ON_3$ + $H^+$ $[M + H]^+$ 372.2070; Found 372.2073.

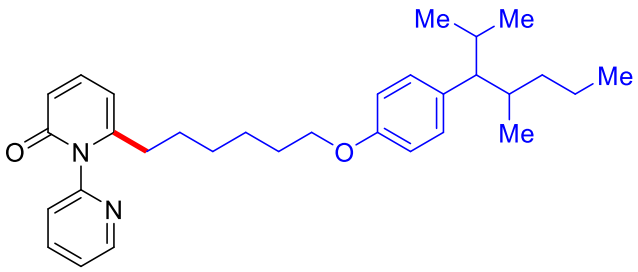


**6-(6-(9*H*-Carbazol-9-yl)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5aB):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and 9-(6-chlorohexyl)-9*H*-carbazole (**4B**; 0.11 g, 0.40 mmol) and the reaction mixture was stirred at 130 °C. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5aB** (0.06 g, 71%) as a light yellow liquid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.59 (dd, *J* = 4.8, 1.1 Hz, 1H, Ar–H), 8.11 (d, *J* = 7.8 Hz, 2H, Ar–H), 7.80 (td, *J* = 7.8, 1.9 Hz, 1H, Ar–H), 7.48-7.44 (m, 2H, Ar–H), 7.36-7.28 (m, 5H, Ar–H), 7.24-7.22 (m, 2H, Ar–H), 6.51 (d, *J* = 9.1 Hz, 1H, Ar–H), 6.02 (d, *J* = 6.9 Hz, 1H, Ar–H), 4.25 (t, *J* = 7.0 Hz, 2H, $CH_2$), 2.14 (t, *J* = 7.6 Hz, 2H, $CH_2$), 1.82-1.75 (m, 2H, $CH_2$), 1.36 (s, 2H, $CH_2$), 1.24-1.15 (m, 4H, $CH_2$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 151.9 ($C_q$), 149.9 (CH), 149.8 ($C_q$), 140.5 (2C, $C_q$), 140.3 (CH), 138.6 (CH), 125.8 (2C, CH), 124.2 (2C, CH), 123.0 (2C, $C_q$), 120.5 (2C, CH), 119.0 (2C, CH), 118.8 (CH), 108.7 (2C, CH), 105.2 (CH), 43.0 ($CH_2$), 33.0 ($CH_2$), 29.0 ($CH_2$), 28.9 ($CH_2$), 27.8 ($CH_2$), 26.9 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{28}H_{27}ON_3$ + $H^+$ $[M + H]^+$ 422.2227; Found 422.2232.



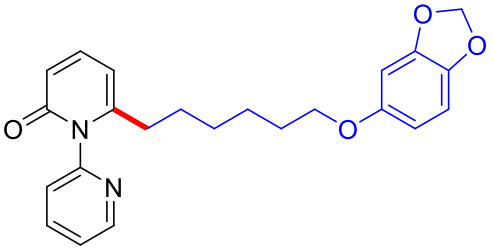

**(*E*)-6-(6-(4-(3,5-Dimethoxystyryl)phenoxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5aC):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) (*E*)-1-(4-((6-chlorohexyl)oxy)styryl)-3,5-dimethoxybenzene (**4C**; 0.15 g, 0.40 mmol) and the reaction mixture was stirred at 130 °C. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5aC** (0.071 g, 70%) as a white solid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.66-8.65 (m, 1H, Ar–H), 7.88 (td, *J* = 7.7, 1.9 Hz, 1H, Ar–

H), 7.43 (d, *J* = 8.6 Hz, 2H, Ar–H), 7.40-7.32 (m, 3H, Ar–H), 7.03 (d, *J* = 16.3 Hz, 1H, Ar–H), 6.92-6.84 (m, 3H, Ar–H), 6.65 (d, *J* = 2.3 Hz, 2H, Ar–H), 6.52 (d, *J* = 9.1 Hz, 1H, Ar–H), 6.37 (t, *J* = 2.2 Hz, 1H, Ar–H), 6.10 (d, *J* = 6.8 Hz, 1H, Ar–H), 3.90 (t, *J* = 6.4 Hz, 2H, $CH_2$), 3.82 (s, 6H , $CH_3$), 2.22 (t, *J* = 7.6 Hz, 2H, $CH_2$), 1.71-1.65 (m, 2H, $CH_2$), 1.46 (br. s, 2H , $CH_2$), 1.35-1.29 (m, 2H, $CH_2$), 1.25-1.22 (m, 2H, $CH_2$). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.0 (CO), 161.1 (2C, $C_q$), 159.0 ($C_q$), 151.9 ($C_q$), 150.0 (CH), 149.9 (CH), 140.3 (CH), 139.8 ($C_q$), 138.7 (CH), 129.9 ($C_q$), 128.8 (CH), 127.9 (2C, CH), 126.6 (CH), 124.2 (CH), 124.2 ($C_q$), 118.7 (CH), 114.8 (2C, CH), 105.1 (CH), 104.4 (2C, CH), 99.7 (CH), 67.8 ($CH_2$), 55.5 (2C, $CH_3$), 33.0 ($CH_2$), 29.1 ($CH_2$), 28.9 ($CH_2$), 27.8 ($CH_2$), 25.7 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{32}H_{34}O_4N_2 + H^+$ $[M + H]^+$ 511.2591; Found 511.2601.

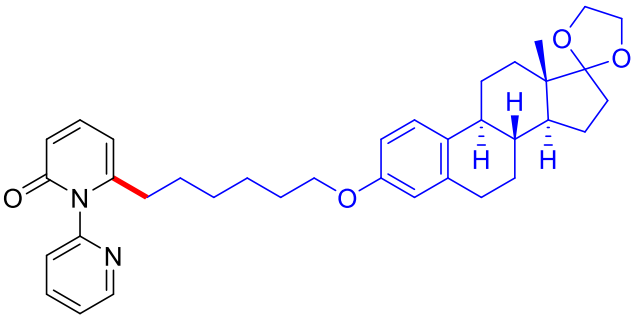



**6-(6-(4-(2,4-Dimethylheptan-3-yl)phenoxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5aD):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) 1-((6-chlorohexyl)oxy)-4-(2,4-dimethylheptan-3-yl)benzene (**4D**; 0.14 g, 0.40 mmol) and the reaction mixture was stirred at 130 $^oC$. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5aD** (0.068 g, 72%) as a light yellow liquid. $^1H$-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.65 (dd, *J* = 4.9, 1.1 Hz, 1H, Ar–H), 7.88 (td, *J* = 7.7, 1.9 Hz, 1H, Ar–H), 7.39-7.32 (m, 3H, Ar–H), 7.24-7.13 (m, 2H, Ar–H), 6.80-6.77 (m, 2H, Ar–H), 6.52 (d, *J* = 8.6 Hz, 1H, Ar–H), 6.10 (d, *J* = 6.9 Hz, 1H, Ar–H), 3.86 (t, *J* = 6.3 Hz, 2H, $CH_2$), 2.22 (t, *J* = 7.6 Hz, 2H, $CH_2$), 1.68-1.43 (m, 6H, $CH_2$), 1.42-1.29 (m, 1H, CH, 2H, $CH_2$), 1.29-1.23 (m, 3H, $CH_3$, 1H, CH), 1.22- 1.15 (m, 1H, CH, 2H, $CH_2$), 1.15-1.01 (m, 2H, $CH_2$), 0.90-0.48 (m, 9H, $CH_3$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.1, 156.8-156.6 (m), 151.9, 150.0, 140.3, 138.7, 128.1-126.9 (m), 124.1, 124.2, 118.7, 113.9-113.6 (m), 105.2, 67.6, 33.4, 29.2, 28.9, 27.9, 25.8. and multiple peaks for nonylphenol backbone. HRMS (ESI): *m/z* Calcd for $C_{31}H_{42}O_2N_2 + H^+$ $[M + H]^+$ 475.3319; Found 475.3318.

*Note: Due to the nonylphenol backbone (which is mixture of several isomers), the $^{13}C$-NMR for nonylphenol moiety show multiple peaks. Thus, we have provided only major peaks in $^{13}C$ NMR.*

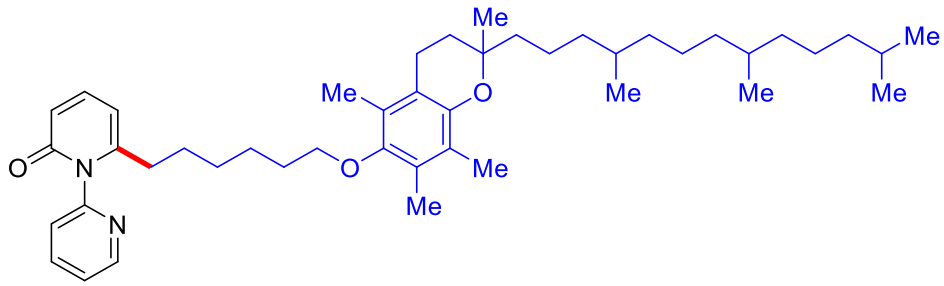


**6-(6-(Benzo[*d*][1,3]dioxol-5-yloxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5aE):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and 5-((6-chlorohexyl)oxy)benzo[*d*][1,3]dioxole (**4E**; 0.10 g, 0.40 mmol) Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5aE** (0.055 g, 70%) as a white solid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.66 (dd, *J* = 4.9, 1.1 Hz, 1H, Ar–H), 7.89 (td, *J* = 7.8, 2.0 Hz, 1H, Ar–H), 7.40-7.32 (m, 3H, Ar–H), 6.68 (d, *J* = 8.5 Hz, 1H, Ar–H), 6.51 (d, *J* = 9.1 Hz, 1H, Ar–H), 6.45 (d, *J* = 2.5 Hz, 1H, Ar–H), 6.28 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar–H), 6.10 (d, *J* = 7.0 Hz, 1H, Ar–H), 5.90 (s, 2H, $CH_2$), 3.80 (t, *J* = 6.4 Hz, 2H, $CH_2$), 2.21 (t, *J* = 7.5 Hz, 2H, $CH_2$), 1.67-1.60 (m, 2H, $CH_2$), 1.44 (s, 2H, $CH_2$), 1.31-1.20 (m, 4H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 154.7 ($C_q$), 151.9 ($C_q$), 150.0 (CH), 149.9 ($C_q$), 148.4 ($C_q$), 141.7 ($C_q$), 140.3 (CH), 138.7 (CH), 124.2 (2C, CH), 118.7 (CH), 108.1 (CH), 105.8 (CH), 105.2 (CH), 101.3 ($CH_2$), 98.1 ($CH_2$), 68.8 ($CH_2$), 33.3 ($CH_2$), 29.1 ($CH_2$), 28.9 ($CH_2$), 27.9 ($CH_2$), 25.7 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{23}H_{24}O_4N2 + H^+$ $[M + H]^+$ 393.1809; Found 393.1810.

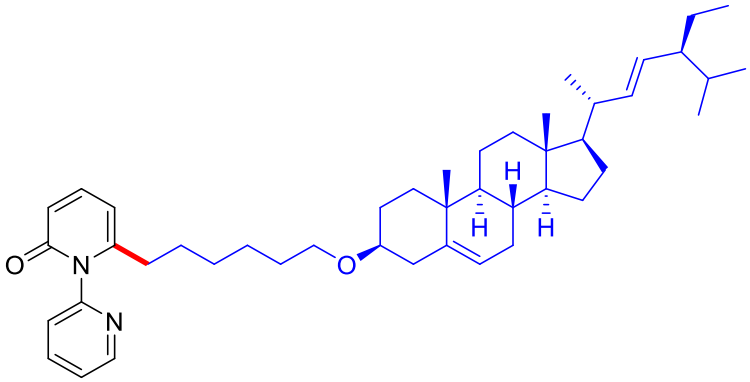


**6-(6-(((8*R*,9*S*,13*S*,14*S*)-13-Methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolan]-3-yl)oxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5aF):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) (8*R*,9*S*,13*S*,14*S*)-3-((6-chlorohexyl)oxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolane] (**4F**; 0.173 g, 0.40 mmol) and the reaction mixture was stirred at 130 $^{o}$C. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2)

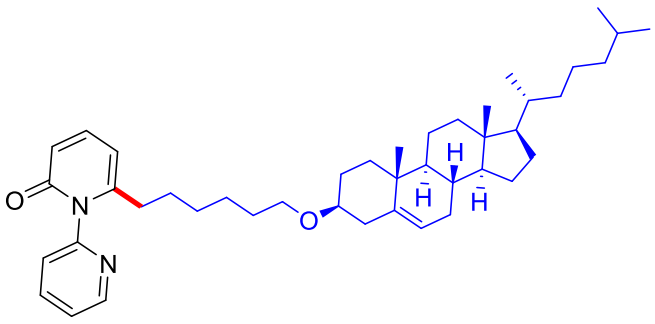
yielded **5aF** (0.068 g, 60%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.66 (dd, $J$ = 4.9, 1.3 Hz, 1H, Ar–H), 7.89 (td, $J$ = 7.7, 1.9 Hz, 1H, Ar–H), 7.40-7.32 (m, 3H, Ar–H), 7.19 (d, $J$ = 8.6 Hz, 1H, Ar–H), 6.66 (dd, $J$ = 8.6, 2.6 Hz, 1H, Ar–H), 6.58 (d, $J$ = 2.5 Hz, 1H, Ar–H), 6.52 (d, $J$ = 9.1 Hz, 1H, Ar–H), 6.10 (d, $J$ = 6.9 Hz, 1H, Ar–H), 3.97-3.93 (m, 4H), 3.85 (t, $J$ = 6.4 Hz, 2H), 2.85-2.82 (m, 2H), 2.33-2.29 (m, 1H), 2.25-2.17 (m, 3H), 2.06-1.99 (m, 1H), 1.91-1.73 (m, 4H), 1.68-1.59 (m, 3H), 1.56-1.29 (m, 7 H), 1.31-1.19 (m, 4H), 0.88 (s, 3H). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.0, 157.0, 151.9, 150.0, 140.3, 138.7, 138.1, 132.8, 126.4, 124.2, 124.2, 119.6, 118.7, 114.5, 112.1, 105.1, 67.7, 65.4, 64.7, 49.5, 46.3, 43.8, 39.2, 34.4, 33.0, 30.9, 30.0, 29.2, 28.9, 27.9, 27.1, 26.3, 25.7, 22.5, 14.5. HRMS (ESI): *m/z* Calcd for $C_{36}H_{44}O_4N_2$ + $H^+$ $[M + H]^+$ 569.3374; Found 569.3376.



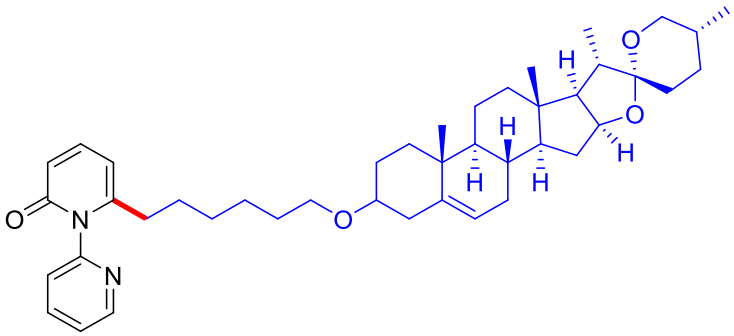

**6-(6-((2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl)oxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5aG):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) 6-((6-chlorohexyl)oxy)-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chromane (**4G**; 0.22 g, 0.40 mmol) and the reaction mixture was stirred at 130 $^{o}$C. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5aG** (0.070 g, 51%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.67-8.66 (m, 1H, Ar–H), 7.89 (td, $J$ = 7.7, 1.6 Hz, 1H, Ar–H), 7.41-7.33 (m, 3H, Ar–H), 6.52 (d, $J$ = 9.3 Hz, 1H, Ar–H), 6.12 (d, $J$ = 6.9 Hz, 1H, Ar–H), 3.56 (t, $J$ = 6.4 Hz, 2H, $CH_2$), 2.56 (t, $J$ = 6.7 Hz, 2H, $CH_2$), 2.23 (t, $J$ = 7.3 Hz, 2H, $CH_2$), 2.13 (s, 3H, $CH_3$), 2.08 (s, 6H, $CH_3$), 1.81-1.74 (m, 2H, $CH_2$), 1.70-1.66 (m, 2H, $CH_2$), 1.56-1.43 (m, 6H, $CH_2$), 1.41-1.32 (m, 6H, $CH_2$, 1H, CH), 1.28-1.22 (m, 8H, $CH_2$, 1H, CH, 3H, $CH_3$), 1.16-1.05 (m, 1H, CH, 4H, $CH_2$), 0.87- 0.84 (m, 12H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.0, 151.9, 150.0, 149.9, 148.3, 147.8, 140.3, 138.6, 127.8, 125.8, 124.2, 124.1, 122.9, 118.7, 117.6, 105.1, 74.9, 72.9, 40.2, 39.5, 37.7, 37.6, 37.5, 37.4, 37.4, 33.0, 32.9, 32.9, 32.8, 31.4, 30.2, 29.2, 28.1, 28.0, 26.0, 24.9, 24.5, 22.8, 21.2, 20.8, 19.9, 19.8, 19.7, 12.8, 12.0, 11.9.



**6-(6-(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-((2*R*,5*S*,*E*)-5-Ethyl-6-methylhept-3-en-2-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5aH):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) (3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-((6-chlorohexyl)oxy)-17-((2*R*,5*S*,*E*)-5-ethyl-6-methylhept-3-en-2-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthrene (**4H**; 0.13 g, 0.30 mmol) and the reaction mixture was stirred at 130 °C. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5aH** (0.070 g, 52%) as a light yellow liquid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.66-8.65 (m, 1H, Ar–H), 7.89 (td, *J* = 7.7, 1.8 Hz, 1H, Ar–H), 7.39 (dd, *J* = 6.9, 5.1Hz, 1H, Ar–H), 7.36-7.32 (m, 2H, Ar–H), 6.51 (d, *J* = 9.1 Hz, 1H, Ar–H), 6.09 (d, *J* = 6.9 Hz, 1H, Ar–H), 5.32 (d, *J* = 5.0 Hz, 1H), 5.14 (dd, *J* = 15.1, 8.5 Hz, 1H), 5.01 (dd, *J* = 15.1, 8.6 Hz, 1H), 3.37 (t, *J* = 6.6 Hz, 2H), 3.10-3.05 (m, 1H), 2.31 (dd, *J* = 12.9, 3.3 Hz, 1H), 2.19-2.12 (m, 3H), 2.00-1.95 (m, 2H), 1.84 (d, *J* = 10.5 Hz, 2H), 1.72-1.65 (m, 1H), 1.55-1.40 (m, 12H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.17-1.09 (m, 8H), 1.07-0.99 (m, 9H), 0.84-0.78 (m, 9H), 0.69 (s, 3H). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.1, 152.0, 150.1, 150.0, 141.2, 140.3, 138.6, 138.5, 129.4, 124.2, 124.1, 121.6, 118.7, 105.1, 79.1, 68.0, 60.5, 57.0, 56.1, 51.4, 50.4, 42.4, 40.6, 39.8, 39.4, 37.4, 37.1, 33.1, 32.1, 32.1, 32.0, 30.1, 29.1, 28.6, 27.9, 26.0, 25.6, 24.5, 21.4, 21.2, 21.2, 19.5, 19.1, 14.4, 12.4, 12.2.

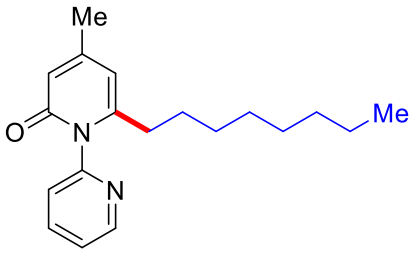


**6-(6-(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)oxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one** (**5aI**): The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) 6-chlorohex-1-e(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-3-((6-chlorohexyl)oxy)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H* cyclopenta[a]phenanthrene (**4I**; 0.20 g, 0.40 mmol) and the reaction mixture was stirred at 130 °C. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5aI** (0.069 g, 54%) as a light yellow liquid. $^{1}$H-NMR (400 MHz, CDCl3): δ = 8.66-8.65 (m, 1H, Ar–H), 7.89 (td, J = 7.7, 1.9 Hz, 1H, Ar–H), 7.39 (ddd, J = 7.5, 4.9, 0.9, Hz, 1H, Ar–H), 7.36-7.32 (m, 2H, Ar–H), 6.51 (d, J = 9.0 Hz, 1H, Ar–H), 6.09 (d, J = 6.8 Hz, 1H, Ar–H), 5.33-5.32 (m, 1H), 3.37 (t, J = 6.7 Hz, 2H), 3.12-3.05 (m, 1H), 2.34-2.29 (m, 1H), 2.21-2.12 (m, 3H), 2.02-1.94 (m, 3H), 1.85-1.79 (m, 3H), 1.60-1.40 (m, 12H), 1.32-1.07 (m, 14H), 0.99 (s, 4H), 0.91 (d, J = 6.5 Hz, 4H), 0.86 (dd, J = 6.6, 1.7 Hz, 6H), 0.67 (s, 3H). $^{13}$C{1H}-NMR (100 MHz, CDCl3): δ = 164.1, 152.0, 150.1, 150.0, 141.2, 140.3, 138.7, 124.2, 124.1, 121.6, 118.7, 105.1, 79.1, 68.0, 56.9, 56.3, 50.4, 42.5, 39.9, 39.7, 39.4, 37.4, 37.1, 36.4, 35.9, 33.1, 32.1, 32.1, 30.1, 29.1, 28.6, 28.4, 28.2, 27.9, 26.0, 24.4, 24.0, 23.0, 22.7, 21.2, 19.5, 18.9, 12.0.

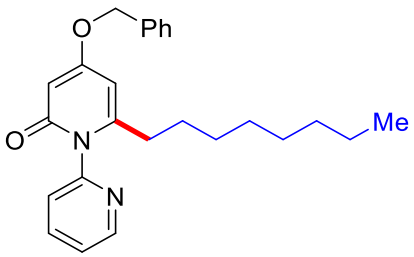



**6-(6-(((5'*R*,6*aR*,6*bS*,8*aS*,8*bR*,9*S*,10*R*,11*aS*,12*aS*,12*bS*)-5',6*a*,8*a*,9-Tetramethyl-1,3,3',4,4',5,5',6,6*a*,6*b*,6',7,8,8*a*,8b,9,11*a*,12,12*a*,12*b*-icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-b]furan-10,2'-pyran]-4-yl)oxy)hexyl)-2*H*-[1,2'-bipyridin]-2-one (5aJ):** The representative procedure was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) (5'*R*,6*aR*,6*bS*,8*aS*,8*bR*,9*S*,10*R*,11*aS*,12*aS*,12*bS*)-4-((6-chlorohexyl)oxy)-5',6*a*,8*a*,9-tetramethyl 1,3,3',4,4',5,5',6,6*a*,6*b*,6',7,8,8*a*,8b,*9*,11*a*,12,12*a*,12*b* icosahydrospiro[naphtho[2',1':4,5]indeno[2,1-*b*]furan-10,2'-pyran] (**4J**; 0.22 g, 0.40 mmol) and the reaction mixture was stirred at 130 °C. Purification by column chromatography on

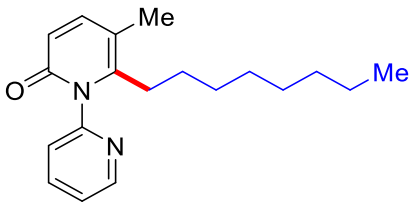
neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5aJ** (0.092 g, 69%) as a white s as a light yellow liquid olid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.64 (dd, $J$ = 4.9, 1.1 Hz, 1H, Ar–H), 7.88 (td, $J$ = 7.7, 1.9 Hz, 1H, Ar–H), 7.38 (ddd, $J$ = 7.5, 4.9, 0.8 Hz, 1H, Ar–H), 7.34-7.30 (m, 2H, Ar–H), 6.49 (d, $J$ = 9.0 Hz, 1H, Ar–H), 6.08 (d, $J$ = 6.9 Hz, 1H, Ar–H), 5.32-5.31 (m, 1H), 4.39 (q, $J$ = 7.5 Hz, 1H), 3.47-3.43 (m, 1H), 3.38-3.33 (m, 3H), 3.09-3.03 (m, 1H), 2.33-2.29 (m, 1H), 2.20-2.14 (m, 3H), 2.02-1.93 (m, 2H), 1.87-1.81 (m, 3H), 1.77-1.68 (m, 2H), 1.66-1.55 (m, 6H), 1.53-1.39 (m, 9H), 1.31-1.22 (m, 2H), 1.19-1.15 (m, 4H), 0.99 (s, 4H), 0.95 (d, $J$ = 6.9 Hz, 4H), 0.77 (t, $J$ = 3.1 Hz, 6H). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.0, 151.9, 150.0, 149.9, 141.2, 140.3, 138.6, 124.2, 124.1, 121.3, 118.6, 109.4, 105.1, 80.9, 79.0, 67.9, 67.0, 62.2, 56.7, 50.2, 41.7, 40.4, 39.9, 39.3, 37.4, 37.2, 33.0, 32.2, 32.0, 31.6, 31.5, 30.4, 30.0, 29.0, 28.9, 28.6, 27.9, 25.9, 21.0, 19.5, 17.3, 16.4, 14.7.




**4-methyl-6-octyl-2*H*-[1,2'-bipyridin]-2-one (5ba):** The representative procedure was followed, using 4-methyl-2*H*-[1,2'-bipyridin]-2-one (**3b**; 0.037 g, 0.2 mmol) 1-chlorooctane (**4a**; 0.059 g, 0.4 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ba** (0.056 g, 94%) as a white solid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.65 (dd, $J$ = 4.9, 1.1 Hz, 1H, Ar–H), 7.88 (td, $J$ = 7.8, 1.9 Hz, 1H, Ar–H), 7.40-7.37 (m, 1H, Ar–H), 7.34 (d, $J$ = 7.9 Hz, 1H, Ar–H), 6.36 (s, 1H, Ar–H), 5.99 (s, 1H, Ar–H), 2.23-2.16 (m, 2H, $CH_2$, 3H, $CH_3$), 1.39 (br. s., 2H, $CH_2$), 1.27-1.12 (m, 10H, $CH_2$), 0.86 (t, $J$ = 7.1 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 152.1($C_q$), 151.8 ($C_q$), 149.7 (CH), 148.7 ($C_q$), 138.5 (CH), 124.3 (CH), 124.0 (CH), 116.8 (CH), 108.1 (CH), 32.9 ($CH_2$), 31.8 ($CH_2$), 29.1 (2C, $CH_2$), 29.0 ($CH_2$), 27.9 ($CH_2$), 22.6 ($CH_2$), 21.6 ($CH_3$), 14.1($CH_3$).



**4-(Benzyloxy)-6-octyl-2*H*-[1,2'-bipyridin]-2-one (5ca):** The representative procedure was followed, using 4-(benzyloxy)-2*H*-[1,2'-bipyridin]-2-one (**3c**; 0.056 g, 0.20 mmol) 1-chlorooctane (**4a**; 0.059 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ca** (0.058 g, 74%) as a white solid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.65-8.63 (m, 1H, Ar–H), 7.87 (td, *J* = 7.7, 1.9Hz, 1H, Ar–H), 7.43-7.32 (m, 8H, Ar–H), 5.98-5.92 (m, 2H, Ar–H), 5.02 (s, 2H, $CH_2$), 2.16-2.14 (m, 2H, $CH_2$), 1.40-1.39 (m, 2H, $CH_2$), 1.25-1.13 (m, 10H, $CH_2$), 0.85 (t, *J* = 7.1 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 167.6 (CO), 165.6 (Cq), 151.9 (Cq), 150.0 (Cq), 149.9 (CH), 138.5 (CH), 135.6 (Cq), 128.9(2C, CH), 128.6(CH), 127.9 (3C, CH), 124.6 (CH), 124.0 (CH), 100.3 (CH), 96.1 (CH), 70.3 ($CH_2$), 32.9 ($CH_2$), 31.9 ($CH_2$), 29.2 ($CH_2$), 29.1 (2C, $CH_2$), 27.6 ($CH_2$), 22.7 ($CH_2$), 14.2 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{25}H_{30}O_2N_2 + H^+$ $[M + H]^+$ 391.2380; Found 391.2379.




**5-Methyl-6-octyl-2*H*-[1,2'-bipyridin]-2-one (5ea):** The representative procedure was followed, using 5-methyl-2*H*-[1,2'-bipyridin]-2-one (**3e**; 0.055 g, 0.3 mmol) 1-chlorooctane (**4a**; 0.089 g, 0.60 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5ea** (0.040 g, 45%) as a white solid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.64 (dd, *J* = 4.9, 1.1 Hz, 1H, Ar–H), 7.87 (td, *J* = 7.7, 1.9 Hz, 1H, Ar–H), 7.38 (ddd, *J* = 7.5, 4.9, 0.9 Hz, 1H, Ar–H), 7.32 (d, *J* = 7.9 Hz, 1H, Ar–H), 7.21 (dd, *J* = 7.0. 0.9 Hz, 1H, Ar–H), 6.02 (d, *J* = 7.0 Hz, 1H, Ar–H), 2.17-2.15 (m, 2H, $CH_2$), 2.11 (s, 3H, $CH_3$), 1.38 (br. s, 2H, $CH_2$), 1.24-1.12 (m, 10H, $CH_2$), 0.84 (t, *J* = 7.1 Hz, 3H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.3 (CO), 152.4 ($C_q$), 149.9 (CH), 147.0 ($C_q$), 138.4 (CH), 137.5 (CH), 127.3 ($C_q$), 124.3 (CH), 123.9 (CH), 104.7 (CH), 32.9 ($CH_2$), 31.9 ($CH_2$), 29.2 (3C, $CH_2$), 28.0 ($CH_2$), 22.7 ($CH_2$), 16.9 ($CH_3$), 14.2 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{19}H_{26}ON_2 + H^+$ $[M + H]^+$ 299.2118; Found 299.2119.

### 4.4.6 Procedure for Removal of the Directing Group

**Removal of DG from 2-Pyridone (Synthesis of 8aa):** In an oven dried round bottom flask, 6-octyl-2*H*-[1,2'-bipyridin]-2-one (**5aa**: 0.10 g, 0.402 mmol) was introduced and

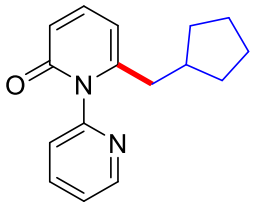
$CH_2Cl_2$ (6 mL) was added into it. Methyl trifluoromethanesulfonate (MeOTf; 0.13 g, 0.080 mmol) was added drop wise *via* a syringe to the reaction mixture and the resultant mixture was stirred at room temperature under argon atmosphere for 20 h. The reaction mixture was cooled to ambient temperature and the solvent was evaporated under vacuum. The crude product was dissolved in dry $Et_2O$ (3 mL) and KO$^t$Bu (0.14 g, 1.21 mmol) and EtOH (0.8 mL) was added and the reaction mixture was stirred for 4 h at room temperature. At ambient temperature, the volatiles were evaporated under reduced pressure, and the crude product was extracted with DCM (30 mL x 3). The combined organic extract was washed with 1N HCL, dried over $Na_2SO_4$ and the volatiles were evaporated in *vacuo*. The remaining residue was purified by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) to yield **8aa** (0.57 g, 68) as a light yellow liquid.

### 4.4.7 External Additive Experiments

**Procedure for TEMPO/galvinoxyl/BHT Added Experiment:** To a flame dried screw-capped tube equipped with magnetic stir bar was introduced *2H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol), 1-chlorooctane (**4a**; 0.059 g, 0.4 mmol), Cat. **2a** (0.010 g, 0.02 mmol, 10 mol %) and Li$^t$BuO (0.032 g, 0.4 mmol) and TEMPO (0.063 g, 0.40 mmol) [or galvinoxyl (0.16 g, 0.40 mmol) or BHT (0.088 g, 0.4 mmol]. To the reaction mixture toluene (1.0 mL) was added and stirred at 120 $^o$C in a pre-heated oil bath for 24 h. At ambient temperature, the reaction mixture was quenched with distilled $H_2O$ (10 mL) and *n*-dodecane (0.02 mL, 0.088 mmol; internal standard) was added. An aliquot of the sample was subjected to the GC analysis. The formation of coupled product (**5aa**) was not observed in the presence of TEMPO or galvinoxyl, whereas 20% of coupled product **5aa** was formed in the presence of BHT.

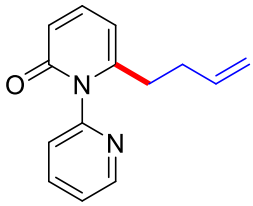
### 4.4.8 Radical Clock Experiments

**Procedure: Synthesis of 6-(Cyclopentylmethyl)-2*H*-[1,2'-bipyridin]-2-one (5aK).** The representative procedure of alkylation was followed, using 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and 6-chlorohex-1-ene (**4K**; 0.047 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5aK** (0.032 g, 65%) as a light yellow liquid.



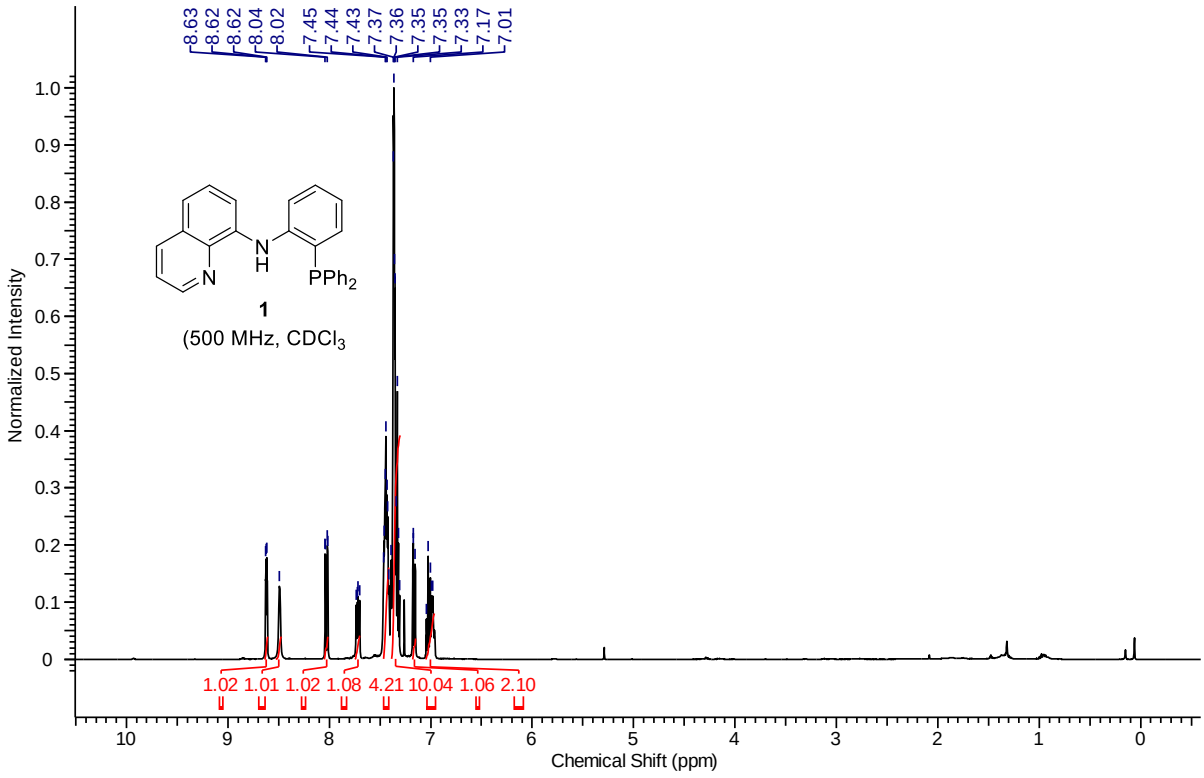
$^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.66-8.64 (m, 1H, Ar–H), 7.88 (td, *J* = 7.7, 1.9Hz, 1H, Ar–H), 7.39 (ddd, *J* = 1.0, 4.9, 7.5 Hz, 1H, Ar–H), 7.36-7.32 (m, 2H, Ar–H), 6.51 (d, *J* = 9.1 Hz, 1H, Ar–H), 6.12 (d, *J* = 6.9 Hz, 1H, Ar–H), 2.22 (d, *J* = 7.3 Hz, 2H, $CH_2$), 1.91-1.84 (m, 1H, CH), 1.65-1.57 (m, 2H, $CH_2$), 1.54-1.42 (m, 4H, $CH_2$), 1.00 (br. s, 2H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 164.1 (CO), 152.0 ($C_q$), 149.9 (CH), 149.6 ($C_q$), 140.3 (CH), 138.6 (CH), 124.3 (CH), 124.1 (CH), 118.6 (CH), 105.9 (CH), 39.3 (2C, $CH_2$), 38.0 (CH), 25.0 (3C, $CH_2$). HRMS (ESI): *m/z* Calcd for $C_{16}H_{18}ON_2$ + $H^+$ $[M + H]^+$ 255.1492; Found 255.1464.

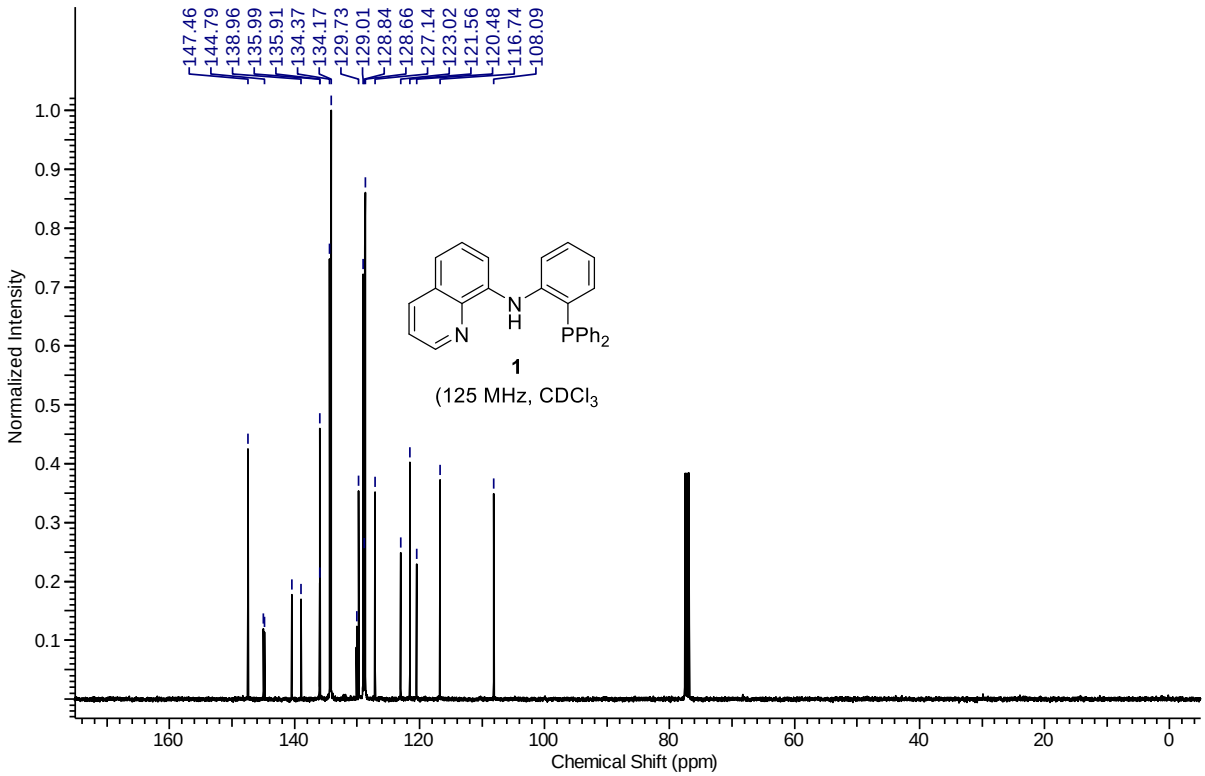
**Procedure: 6-(But-3-en-1-yl)-2*H*-[1,2'-bipyridin]-2-one (5aL):** The representative procedure was followed, 2*H*-[1,2'-bipyridin]-2-one (**3a**; 0.034 g, 0.20 mmol) and (chloromethyl)cyclopropane (**4L**; 0.036 g, 0.4 mmol) Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **5aL** (0.036 g, 80%) as colorless liquid.



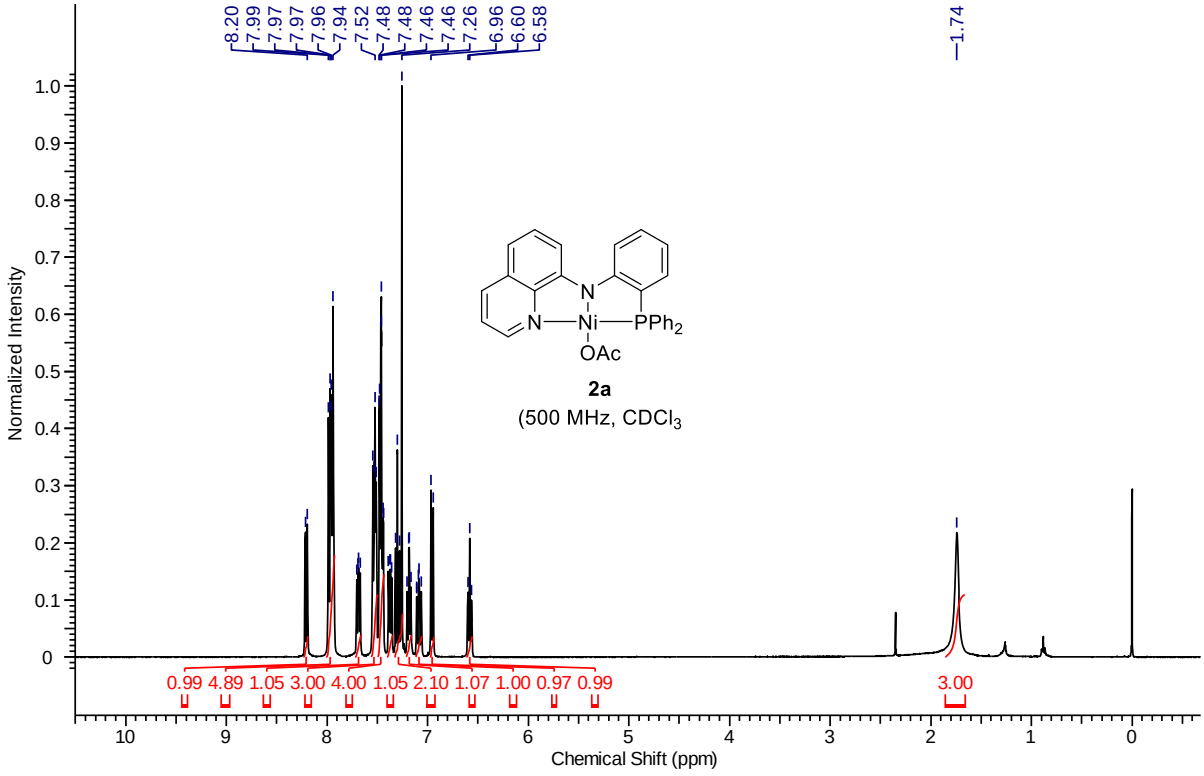
$^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.66-8.65 (m, 1H, Ar–H), 7.89 (td, J = 7.7, 1.9 Hz, 1H, Ar–H), 7.40 (ddd, J = 7.5, 4.9, 0.9, Hz, 1H, Ar–H), 7.36-7.32 (m, 2H, Ar–H), 6.52 (d, J = 9.3 Hz, 1H, Ar–H), 6.11 (d, J = 6.9 Hz, 1H, Ar–H), 5.66-5.56 (m, 1H, CH), 4.92-4.87 (m, 2H, $CH_2$), 2.30-2.17 (m, 4H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 164.0 (CO), 151.8 ($C_q$), 150.0 (CH), 149.0 ($C_q$), 140.2 (CH), 138.7 (CH), 136.4 (CH), 124.2 (2C, CH), 118.9 (CH), 116.0 ($CH_2$), 105.3 (CH), 32.5 ($CH_2$), 31.8 ($CH_2$). HRMS (ESI): *m/z* Calcd for $C_{14}H_{14}ON_2$ + $H^+$ $[M + H]^+$ 227.1179; Found 227.1180.

## 4.4.9 $^{1}H$ and $^{13}C\{^{1}H\}$ NMR Spectra of $^{Q}NNNP^{Ph2}$ Ligand

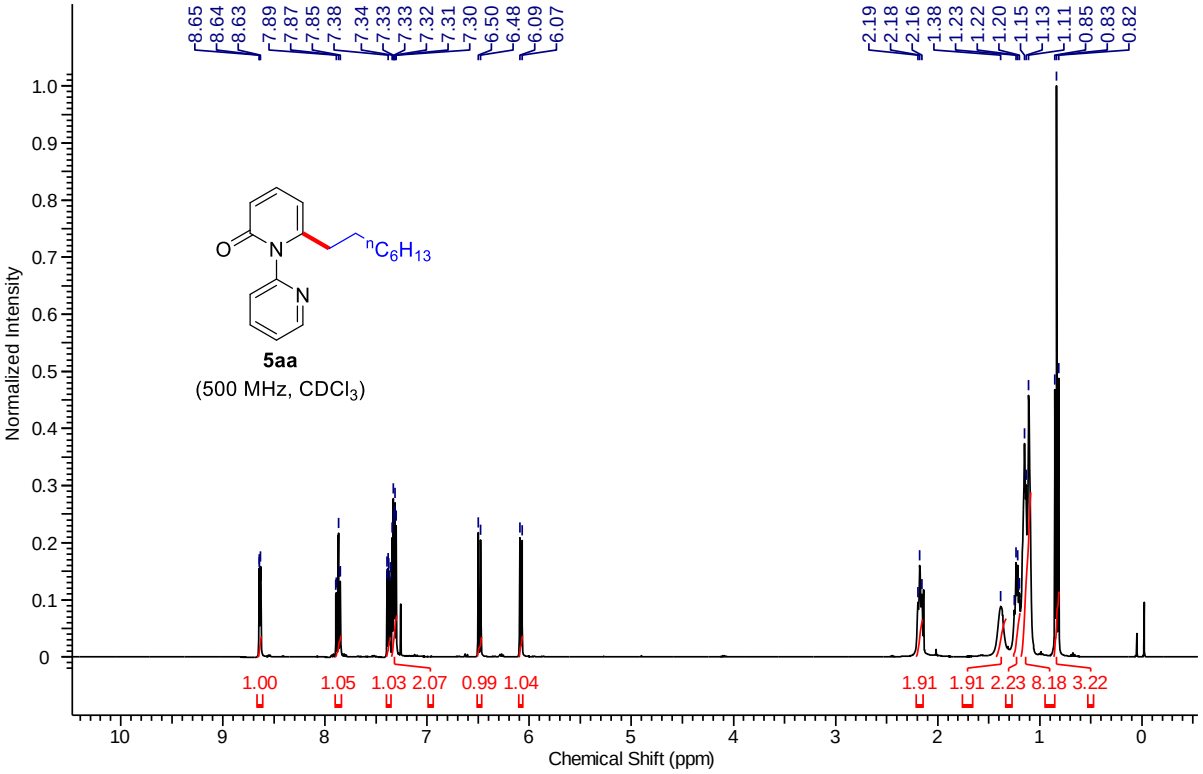


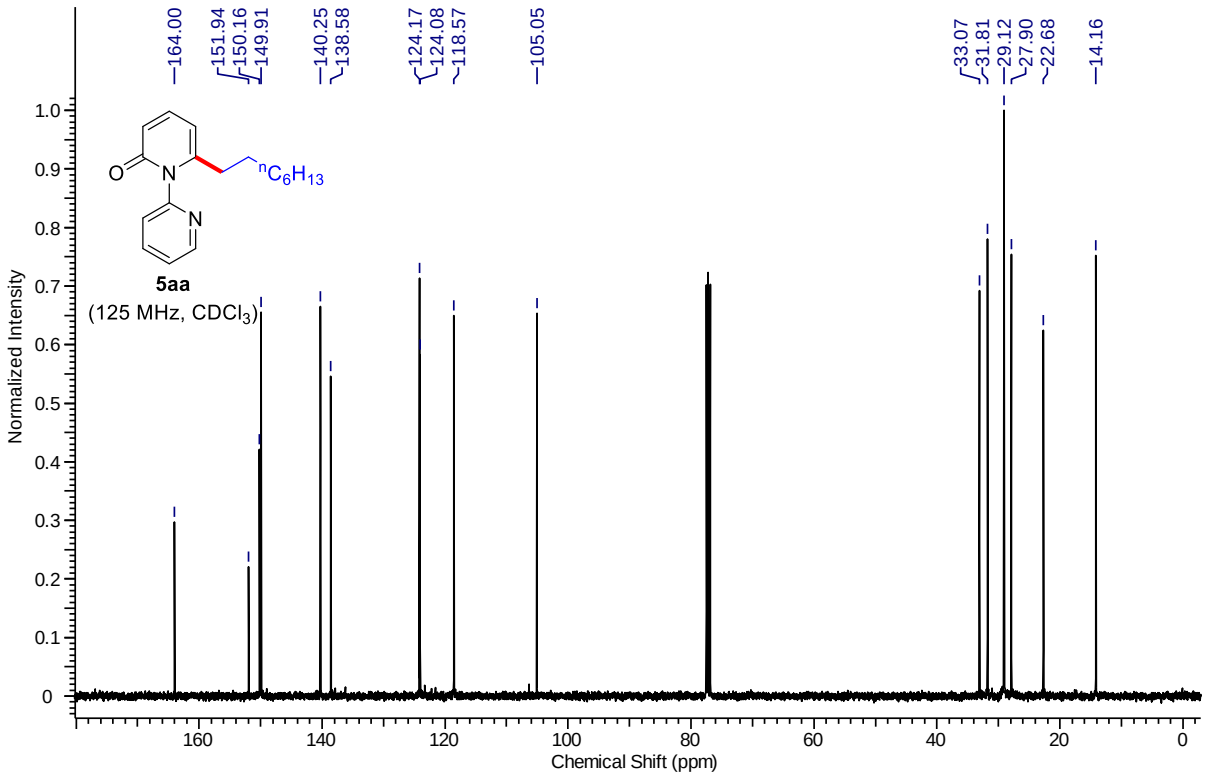



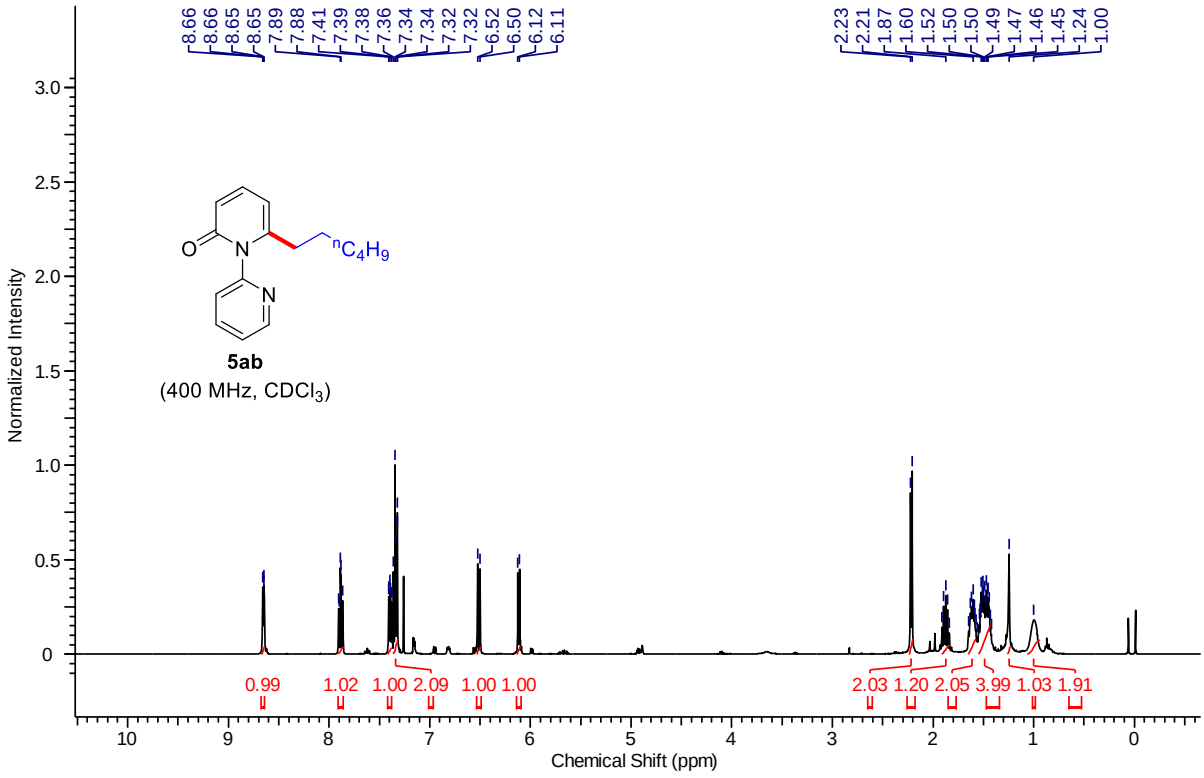
## 4.4.10 $^{1}$H NMR Spectra of ($^{Q}$NNP$^{Ph2}$)NiOAc

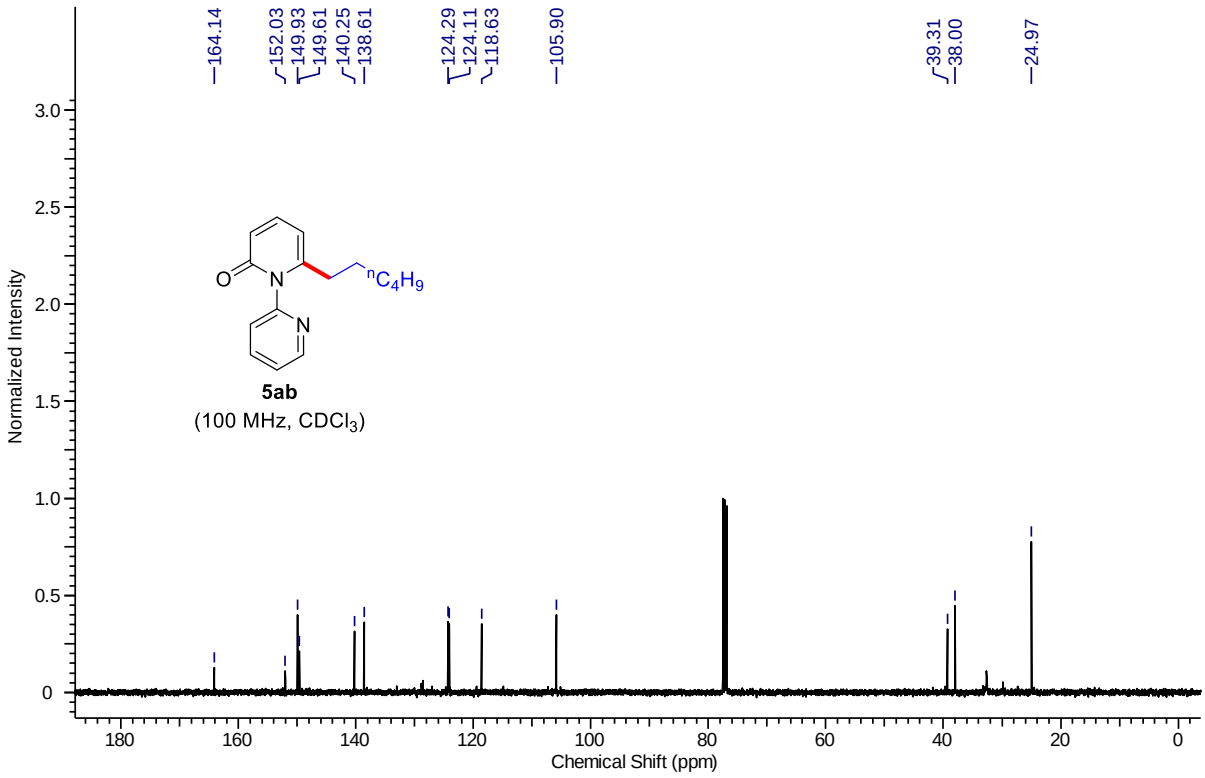


## 4.4.11 $^{1}H$ and $^{13}C\{^{1}H\}$ NMR Spectra of Selected Alkylated Products




8.66
8.66
8.65
8.65
7.89
7.88
7.41
7.39
7.38
7.36
7.34
7.34
7.32
7.32
6.52
6.50
6.12
6.11
2.23
2.21
1.87
1.60
1.52
1.50
1.50
1.49
1.47
1.46
1.45
1.24
1.00
O
N
N
nC4H9
5ab
(400 MHz, CDCl3)
Normalized Intensity
0.99
1.02
1.00
2.09
1.00
1.00
2.03
1.20
2.05
3.99
1.03
1.91
Chemical Shift (ppm)


164.14
152.03
149.93
149.61
140.25
138.61
124.29
124.11
118.63
105.90
39.31
38.00
24.97
O
N
N
nC4H9
5ab
(100 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)

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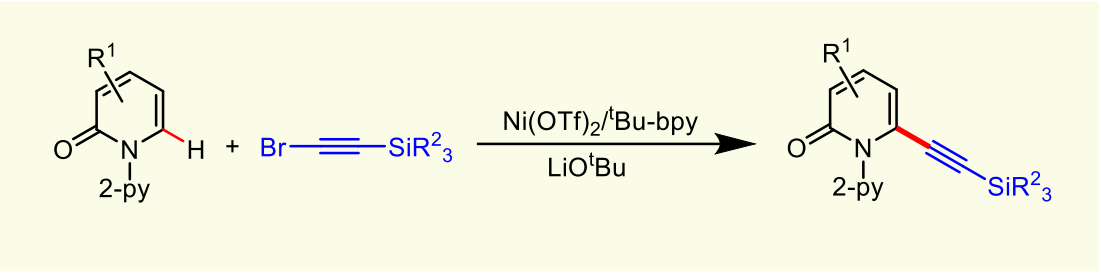
# Chapter 5

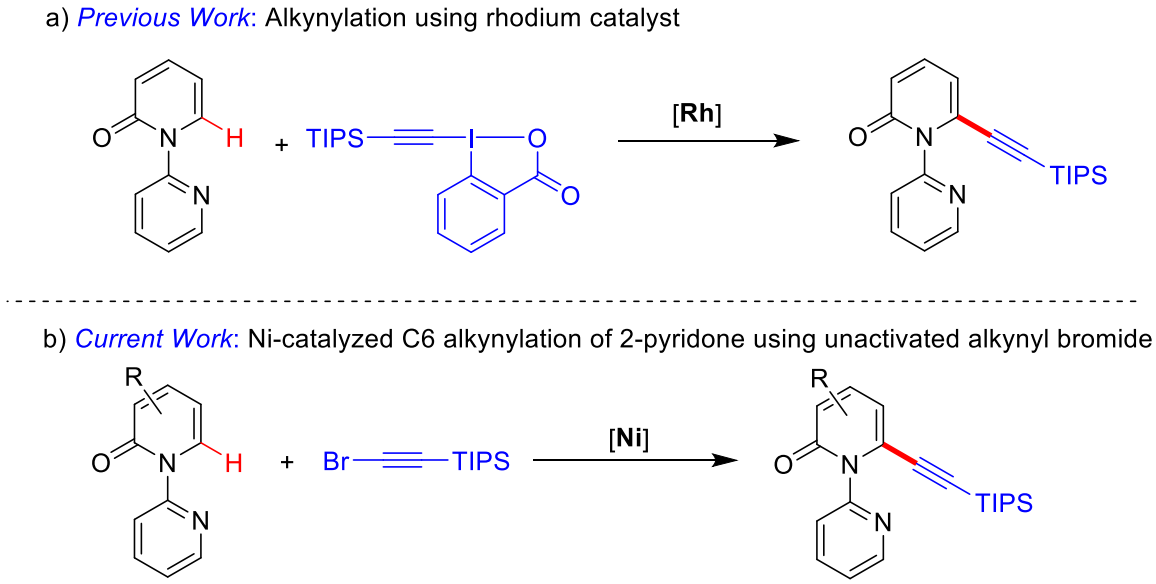
# Nickel-Catalyzed C6 Selective Alkynylation of 2-Pyridones Using Unactivated Alkynyl Bromides



## 5.1 INTRODUCTION

For many years, researchers have been interested in the direct modification of nitrogen-containing heteroarenes due to their importance in pharmaceuticals, natural products, biologically active molecules and agrochemicals.[1-7] A significant part of study involves using transition metal catalysts to activate C–H bonds in heteroarenes directly, enabling direct alkylation, arylation, and alkenylation reactions, which are valuable tools in organic synthesis.[8-12] Among these, the alkynylation reactions is particularly important due to their utility both as intermediates in organic synthesis and for late-stage functionalization.[13-15] In recent decades, the development of alkynylation reactions has been disclosed by the Sonogashira cross-coupling reaction.[16-18] However, a major drawback of this methodology is the use of halogenated substrates. To address this limitation, various groups have developed direct alkynylation of (hetero)arenes using transition metal-catalyst as an alternative method. This approach typically employed 4d and 5d transition metals as a catalysts.[19,20] However, these elements are costly, less abundance, and more toxic in nature. The current attention in developing alkynylation reactions using 3d transition metals stems from their advantageous features and low cost. This focus highlights the potential of 3d metals as a promising alternative in these reactions. In 2017, Punji *et. al.* disclosed a Ni-catalyzed azoles alkynylation using alkynyl bromides as coupling partners.[21] They also demonstrated the regioselective alkynylation of indole using nickel/phenanthroline catalyst system.[22] These advancements were significant in expanding the scope of transition metal-catalyzed alkynylation reactions to include 3d transition metals. On a related note, the nitrogen-containing 2-pyridone is a prevalent motif in various natural and bioactive compounds.[23-25]. The regioselective alkylation, alkenylation, and arylation of 2-pyridones methods employing late transition metals are well explored.[26] However, selective C–H bond alkynylation of 2-pyridones remains rare. In 2016, the Li group disclosed a Rh-catalyzed C6 alkynylation of 2-pyridone using hypervalent iodine alkyne as a coupling partner.[27] While this method demonstrated the feasibility of C–H bond alkynylation, it required a 4d transition metal and an activated alkyne, limiting its practicality. Additionally, this methodology has not been explored using cost effective 3d transition metals.

In this chapter, we disclose a cost-effective nickel-catalyzed protocol for the alkynylation of 2-pyridone using unactivated alkynyl bromides as a coupling partner (Scheme 5.1).




**Scheme 5.1** Selective C6 alkynylation of 2-pyridones

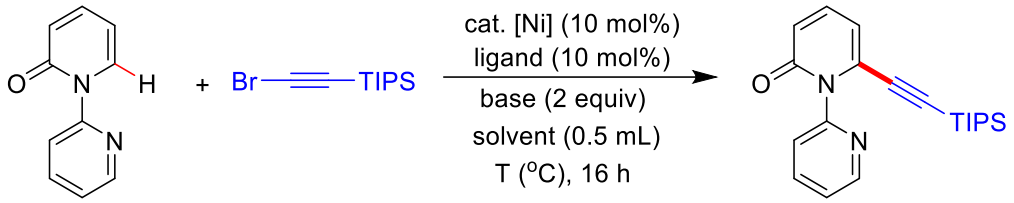
## 5.2 RESULTS AND DISCUSSION

### 5.2.1 Reaction Optimization

We began by optimizing the alkynylation reaction using 2*H*-[1,2'-bipyridin]-2-one as the model substrate (**1a**), alkynyl bromide as the coupling partner, LiO$^t$Bu as the base, and nickel as the catalyst in toluene solvent (Table 5.1). Various nickel precursors, including $Ni(OAc)_2$, $NiCl_2$, $NiBr_2$, $Ni(DME)Cl_2$, $Ni(DME)Br_2$, $NiBr_2$·diglyme, $Ni(Cp)_2$, $NiCl_2(PPh_3)_2$, and $NiBr_2(THF)_2$, provided low yields or trace amounts of the alkynylated product **3aa** (entries 1-10). Among these, $Ni(OTf)_2$ was identified as the most efficient catalyst for the reaction. We also explored a range of nitrogen-based ligands such as bpy, phen, and neocuproine, discovering that the more electron-rich ligand 4,4′-di-*tert*-butyl-2,2′-dipyridyl was efficient for the transformation delivering **3aa** in 75% yield (entries 11-14). In contrast, the presence of several phosphine-based ligands, including $PPh_3$, xantphos, dppe, and dppbz provided trace amount of the desired alkynylated product (entries 15-18). Successful alkynylation reactions were achieved using strong bases like LiO$^t$Bu, NaO$^t$Bu, and KO$^t$Bu, while weak bases like $Li_2CO_3$, $Na_2CO_3$, and $K_2CO_3$ resulted in trace amounts of **3aa**, indicating their inability to activate the C–H bond of 2-pyridone (entries 19-24). Furthermore, we investigated the reaction in various solvents such as *o*-xylene, *m*-xylene, *p*-xylene, *p*-cymene, mesitylene, $^t$Bu-benzene, and 1,4-dioxane. Among these, toluene and $^t$Bu-benzene emerged as the most effective solvents for this transformation (entries 25-31). Notably, we did not observe the desired alkynylated product **3aa** in polar solvents. Interestingly, the yield of **3aa** improved up to 85% when the reaction was performed at 130 $^o$C. (entry 32). However, lower yield was obtained at 120 °C or

with the reduced catalyst loading (entry 33 and 34). The alkynylation failed in the absence of nickel catalyst (entry 35). Notably, the desired product **3aa** was not observed without a directing group, highlighting the essential role of the nitrogen center for this transformation.

Table 5.1 Optimization of Reaction Condition for C6 Alkynylation of 2-Pyridone[a]




(**1a**) (**2a**) (**3aa**)

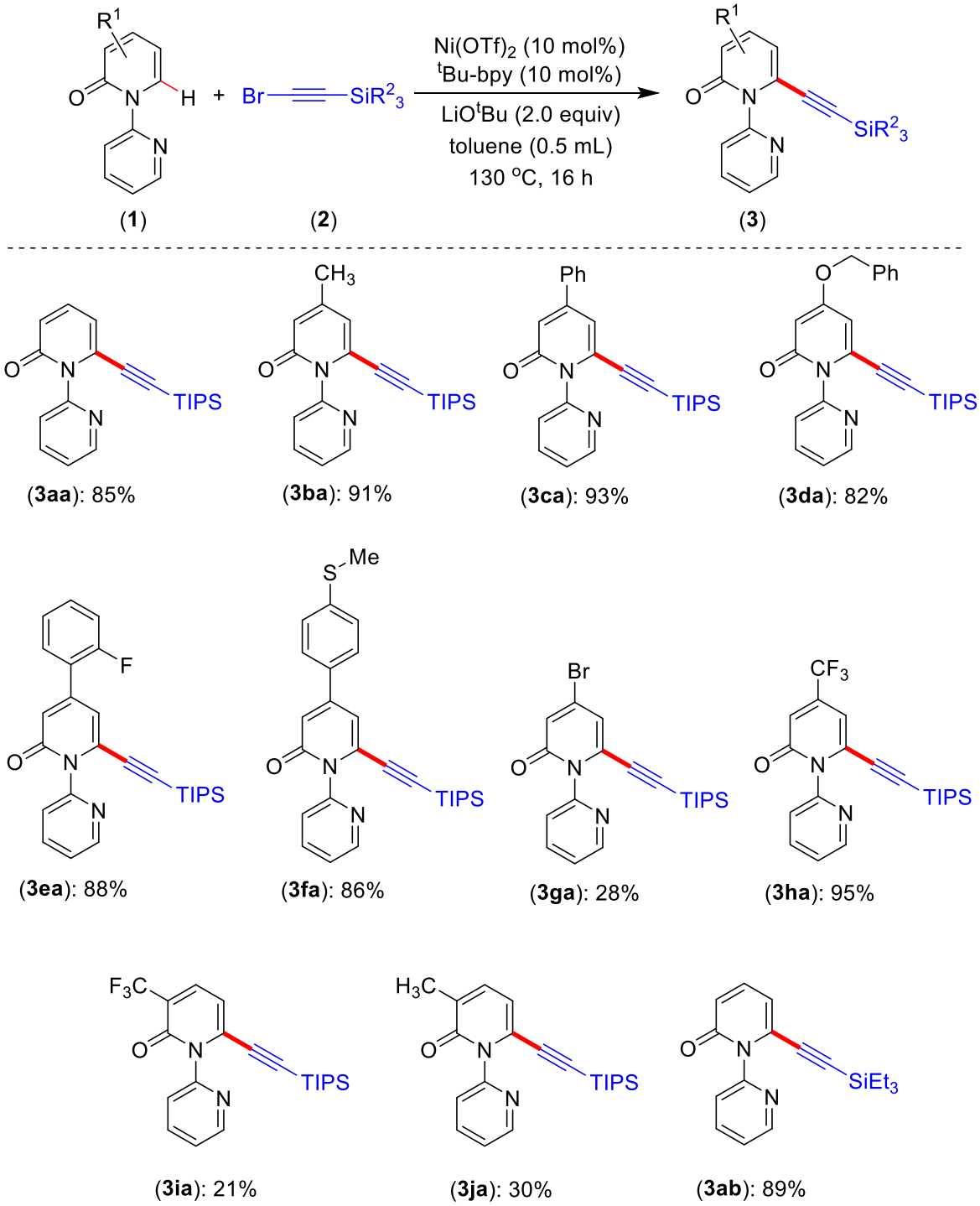
| Entry | Cat [Ni] | Ligand | Base | Solvent | T (°C) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | $Ni(OAc)_2$ | -- | $LiO^tBu$ | toluene | 140 | trace |
| 2 | $NiCl_2$ | -- | $LiO^tBu$ | toluene | 140 | trace |
| 3 | $NiBr_2$ | -- | $LiO^tBu$ | toluene | 140 | trace |
| 4 | $Ni(OTf)_2$ | -- | $LiO^tBu$ | toluene | 140 | 40 |
| 5 | $Ni(DME)Cl_2$ | -- | $LiO^tBu$ | toluene | 140 | 10 |
| 6 | $Ni(DME)Br_2$ | -- | $LiO^tBu$ | toluene | 140 | 15 |
| 7 | $NiCl_2$.diglyme | -- | $LiO^tBu$ | toluene | 140 | 20 |
| 8 | $Ni(Cp)_2$ | -- | $LiO^tBu$ | toluene | 140 | trace |
| 9 | $NiCl_2(PPh_3)_2$ | -- | $LiO^tBu$ | toluene | 140 | trace |
| 10 | $NiBr_2(thf)_2$ | -- | $LiO^tBu$ | toluene | 140 | 30 |
| 11 | $Ni(OTf)_2$ | bpy | $LiO^tBu$ | toluene | 140 | 70 |
| 12 | $Ni(OTf)_2$ | phen | $LiO^tBu$ | toluene | 140 | 68 |
| 13 | $Ni(OTf)_2$ | neocuprione | $LiO^tBu$ | toluene | 140 | 30 |
| 14 | $Ni(OTf)_2$ | $^t$Bu-bpy | $LiO^tBu$ | toluene | 140 | 75 |
| 15 | $Ni(OTf)_2$ | $PPh_3$ | $LiO^tBu$ | toluene | 140 | trace |
| 16 | $Ni(OTf)_2$ | xantphos | $LiO^tBu$ | toluene | 140 | trace |
| 17 | $Ni(OTf)_2$ | dppe | $LiO^tBu$ | toluene | 140 | trace |
| 18 | $Ni(OTf)_2$ | dppbz | $LiO^tBu$ | toluene | 140 | trace |
| 19 | $Ni(OTf)_2$ | $^t$Bu-bpy | $NaO^tBu$ | toluene | 140 | 66 |
| 20 | $Ni(OTf)_2$ | $^t$Bu-bpy | $KO^tBu$ | toluene | 140 | 60 |
| 21 | $Ni(OTf)_2$ | $^t$Bu-bpy | LiOMe | toluene | 140 | 40 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 22 | $Ni(OTf)_2$ | $^t$Bu-bpy | $Li_2CO_3$ | toluene | 140 | trace |
| 23 | $Ni(OTf)_2$ | $^t$Bu-bpy | $Na_2CO_3$ | toluene | 140 | trace |
| 24 | $Ni(OTf)_2$ | $^t$Bu-bpy | $K_2CO_3$ | toluene | 140 | trace |
| 25 | $Ni(OTf)_2$ | $^t$Bu-bpy | Li$O^t$Bu | *o*-xylene | 140 | 45 |
| 26 | $Ni(OTf)_2$ | $^t$Bu-bpy | Li$O^t$Bu | *m*-xylene | 140 | 40 |
| 27 | $Ni(OTf)_2$ | $^t$Bu-bpy | Li$O^t$Bu | *p*-xylene | 140 | 43 |
| 28 | $Ni(OTf)_2$ | $^t$Bu-bpy | Li$O^t$Bu | *p*-cymene | 140 | 17 |
| 29 | $Ni(OTf)_2$ | $^t$Bu-bpy | Li$O^t$Bu | mesitylene | 140 | 46 |
| 30 | $Ni(OTf)_2$ | $^t$Bu-bpy | Li$O^t$Bu | $^t$Bu-benzene | 140 | 74 |
| 31 | $Ni(OTf)_2$ | $^t$Bu-bpy | Li$O^t$Bu | 1,4-dioxane | 140 | NR |
| **32** | **$Ni(OTf)_2$** | **$^t$Bu-bpy** | **Li$O^t$Bu** | **toluene** | **130** | **90 (85)** |
| 33 | $Ni(OTf)_2$ | $^t$Bu-bpy | Li$O^t$Bu | toluene | 120 | 78 |
| 34[c] | $Ni(OTf)_2$ | $^t$Bu-bpy | Li$O^t$Bu | toluene | 130 | 50 |
| 35 | -- | $^t$Bu-bpy | Li$O^t$Bu | toluene | 130 | NR |

[a]Reaction Conditions: **1a** (0.034 g, 0.2 mmol), **2a** (0.10 g, 0.40 mmol), [Ni] Cat. (0.02 mmol, 10 mol%), Li$O^t$Bu (0.032 g, 0.40 mmol), solvent (0.5 mL). [b]NMR yield using $CH_2Br_2$ as an internal standard; isolated yield is given in parentheses. [c]5.0 mol% of [Ni] Cat. was used. NR = No Reaction

### 5.2.2 Substrate Scope of 2-Pyridone Derivatives

After attaining the Optimized reaction parameters, we investigated the substrate scope and limitations of this coupling reaction (Scheme 5.2). The unsubstituted 2-pyridone exhibited good reactivity with (bromoethynyl)triisopropylsilane, giving the C6-selectively alkynylated product **3aa** in 85% yield. We found that 4-substituted 2-pyridones, such as methyl, phenyl and its derivatives such as benzyloxy, 2-fluoro benzene and 4-thiomethyl benzene reacted with alkynyl bromide to provide alkynylated products in excellent yields (**3ba**-**3fa**). However, when bromo was present at the 4-position on the 2-pyridone, the yield was lower due to self-coupling of the 4-bromo 2-pyridone (**3ga**). Notably, the 2-pyridone with electron-deficient group at the 4-position smoothly reacted with the alkynyl bromide, providing **3ha** in excellent yield. In contrast, $-CH_3$ and $-CF_3$ substituted 2-pyridones at the C-3 position provided lower yields likely due to electronic effects whereas 5-methyl 2-pyridones with **2a** produced only trace amount of the product **3ja**. Additionally, the reaction of 2-pyridone with (bromoethynyl)triethylsilane obtained the desired product **3ab** in good yield.

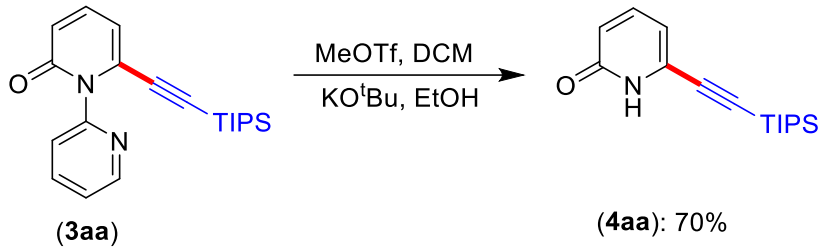



**Scheme 5.2** Nickel-catalyzed C6 alkynylation of 2-pyridone using unactivated alkynyl bromide.

### 5.2.3 Scale-up and Deprotection of the Directing Group

In a scale-up reaction, we utilized **1a** (4.90 mmol) with(bromoethynyl)triisopropylsilane, providing 70% of the alkynylated product **3aa**, showcasing the practical utility of the reaction.

Furthermore, deprotection of the 2-pyridinyl group resulted in a good yield of the deprotected alkynylated 2-pyridone. Specifically, 6-((triisopropylsilyl)ethynyl)-2*H*-[1,2'-bipyridin]-2-one reacted with MeOTf and KO$^t$Bu to afford the product **4aa** in 70% yield (Scheme 5.3).

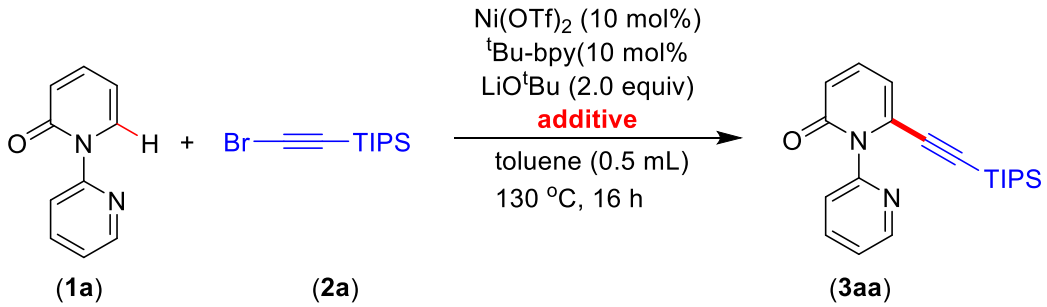



(**3aa**) (**4aa**): 70%

**Scheme 5.3** Removal of directing group.

### 5.2.4 Mechanistic Aspects

**External Additive Experiments**: In order to know the catalytic pathway and catalyst mechanism, various additive and controlled studies were conducted. The use of TEMPO, a radical scavenger, did not hamper the reaction and delivered 3aa in 74% with no significant decrease compared to the same reaction without the additive. However, when radical inhibitors such as BHT and 1,1-diphenylethylene were added, 25% and 85% of the alkynylated product **3aa** were observed (Scheme 5.4). As the reaction was completely not quenched, we believe that the alkynyl radical is not forming during the reaction.




(**1a**) (**2a**) (**3aa**)

| additive (w.r.t. **1a**) | | (**3aa**) |
|---|---|---|
| No additive | | 84% |
| TEMPO | (2 equiv): | 74% |
| 1,1-diphenylethylene | (2 equiv): | 85% |
| BHT | (2 equiv): | 25% |

**Scheme 5.4** External additive experiment

### 5.2.5 Plausible Catalytic Cycle

The tentative mechanistic cycle for the Ni-catalyzed alkynylation of 2-pyridone is begun by the generation of a reactive catalyst **A** through the reaction between $Ni(OTf)_2$ and $^{t}$Bu-bpy (Figure 5.1). This catalyst **A** then reacts with a molecule of 2-pyridone to form an intermediate **B**. Next, the intermediate **B** undergoes a crucial step where it reacts with an alkynyl bromide through an oxidative additive pathway. This reaction initiates the formation of an alkynylated intermediate **C,** resulting in reductive elimination to deliver the desired alkynylation product **3aa** and the regeneration of the active catalyst **A**.

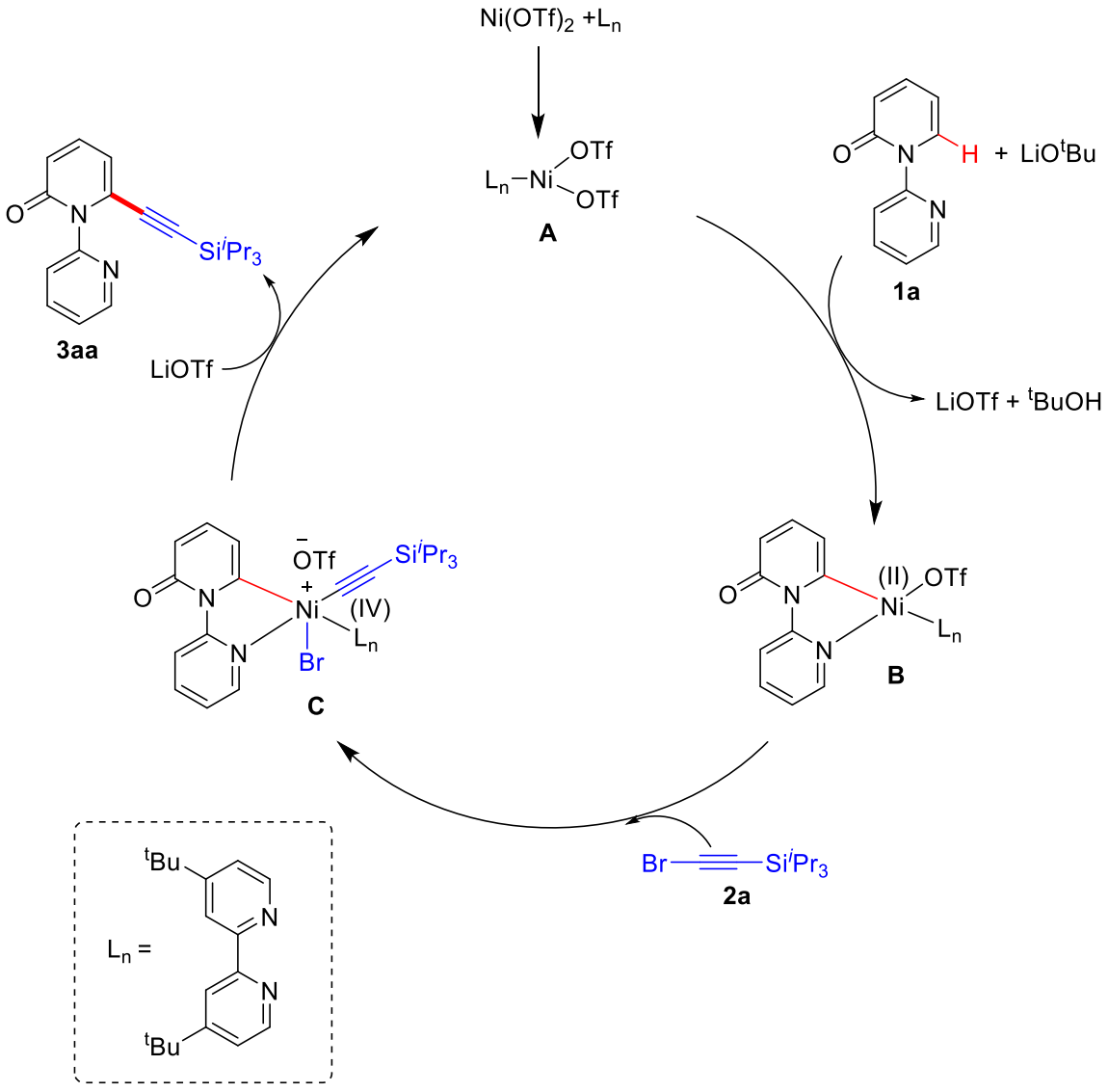



**Figure 5.1** Plausible catalytic cycle for C6 alkynylation of 2-pyridone.

## 5.3 CONCLUSION

In conclusion, we introduced a novel approach for the nickel-catalyzed C6 alkynylation of 2-pyridone, utilizing an unactivated alkynyl bromide as a coupling partner. This method requires the combination of $Ni(OTf)_2$/$^t$Bu-bpy to achieve the selective C6 alkynylation of 2-pyridone. Various functional groups such as methyl, benzyloxy, –Br, $–CF_3$, and phenyl on the 2-pyridone scaffold are smoothly coupled with the alkynyl bromide with good to excellent yields. Scale-up of the reaction demonstrated the practical utility Additionally, the external additive experiment indicates that a carbon radical is not a part of the reaction mechanism. Based on the literature and our finding a tentative reaction mechanism is proposed the proceed via Ni(II)/Ni(IV) pathway.

## 5.4 EXPERIMENTAL SECTION

### 5.4.1 General Information

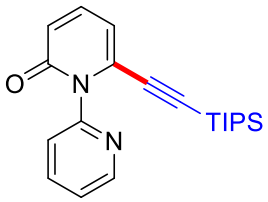
All the manipulations were conducted under an argon atmosphere either in a glove box or using standard Schlenk techniques in pre-dried glassware. The catalytic reactions were performed in flame-dried reaction vessels with a Teflon screw cap. Solvents were dried over Na/benzophenone or $CaH_2$ and distilled prior to use. Liquid reagents were flushed with argon prior to use. The 2-pyridone derivatives **1a-1j**[28,29] were prepared according to the previously described procedures. All other chemicals were obtained from commercial sources and were used without further purification. High-resolution mass spectrometry (HRMS) mass spectra were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. NMR: ($^1$H and $^{13}$C) spectra were recorded at 400 or 500 MHz ($^1$H), 100 or 125 MHz $^{13}$C, DEPT (distortionless enhancement by polarization transfer)}, respectively in $CDCl_3$ solutions, if not otherwise specified; chemical shifts ($\delta$) are given in ppm. The $^1$H and $^{13}$C{$^1$H} NMR spectra are referenced to residual solvent signals ($CDCl_3$: $\delta$ H = 7.26 ppm, $\delta$ C = 77.2 ppm).

### 5.4.2 Representative Procedure for Alkynylation

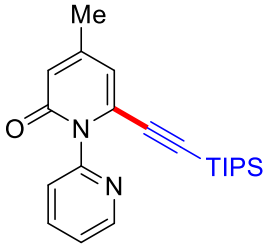
**Synthesis of 6-((Triisopropylsilyl)ethynyl)-2*H*-[1,2'-bipyridin]-2-one (3ba):** To a flame-dried screw-cap tube equipped with magnetic stir bar were introduced 2*H*-[1,2'-bipyridin]-2-one (**1a**; 0.034 g, 0.20 mmol), (bromoethynyl)triisopropylsilane (**2a**; 0.10 g, 0.40 mmol), $Ni(OTf)_2$ (0.0071 g, 0.02 mmol, 10.0 mol%), 4,4′-di-t*ert*-butyl-2,2′-dipyridyl (0.0054 g, 0.02 mmol, 10.0 mol%) and Li$^t$BuO (0.032 g, 0.40 mmol) inside the glove box. To the above mixture in the tube was added toluene (0.5 mL). The resultant reaction mixture in the tube was immersed in a preheated oil bath at 130 $^o$C and stirred for 16 h. At ambient temperature, the

reaction mixture was quenched with distilled $H_2O$ (10.0 mL) and the crude product was extracted with EtOAc (15 mL x 3). The combined organic extract was dried over $Na_2SO_4$ and the volatiles were evaporated *in vacuo*. The remaining residue was purified by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/1) to yield **3aa** (0.060 g, 85%) as a light yellow solid.

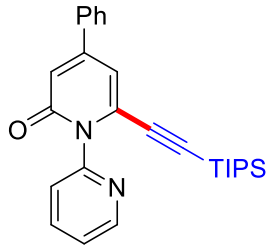
### 5.4.3 Characterization Data for Alkynylation



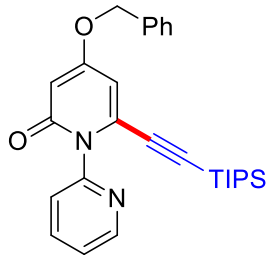

$^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.64-8.57 (m, 1H, Ar–H), 7.87-7.78 (m, 1H, Ar–H), 7.38-7.28 (m, 3H, Ar–H), 6.64 (td, $J$ = 9.4, 1.0 Hz, 1H, Ar–H), 6.52 (td, $J$ = 6.9, 0.9 Hz, 1H, Ar–H), 0.91-0.83 (m, 3H, CH, 18H, $CH_3$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 162.4 (CO), 152.2 ($C_q$), 149.8 (CH), 139.4 (CH), 138.4 (CH), 130.7 ($C_q$), 124.1 (CH), 123.5 (CH), 122.7 (CH), 112.5 (CH), 101.9 ($C_q$), 98.3 ($C_q$), 18.4 (6C, $CH_3$), 10.9 (3C, CH).



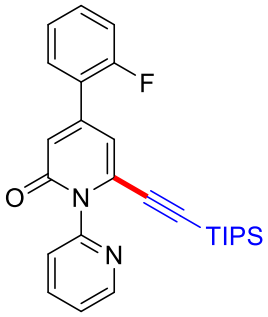

**4-Methyl-6-((triisopropylsilyl)ethynyl)-2*H*-[1,2'-bipyridin]-2-one (3ba):** The representative procedure was followed, using 4-methyl-2*H*-[1,2'-bipyridin]-2-one (**1b**; 0.074 g, 0.40 mmol) and (bromoethynyl)triisopropylsilane (**2a**; 0.20 g, 0.80 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/1) yielded **3ba** (0.134 g, 91%) as a light yellow solid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.62 (dd, $J$ = 4.8, 1.1 Hz, 1H, Ar–H), 7.84 (td, $J$ = 7.8, 1.9 Hz, 1H, Ar–H), 7.38-7.34 (m, 2H, Ar–H), 6.47 (s, 1H, Ar–H), 6.42 (d, $J$ = 1.5 Hz, 1H, Ar–H), 2.20 (s, 3H, $CH_3$), 0.89 (s, 3H, CH, 18H , $CH_3$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 162.4 (CO), 152.1 ($C_q$), 151.0 ($C_q$), 149.7 (CH), 138.3 (CH), 129.5 ($C_q$), 124.0 (CH), 123.7 (CH), 121.0 (CH), 115.1 (CH), 101.1 ($C_q$), 98.4 ($C_q$), 21.2 ($CH_3$), 18.4 (6C, $CH_3$), 10.9 (3C, CH).



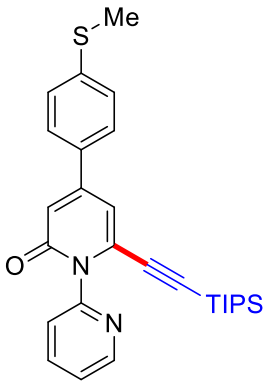

**4-phenyl-6-((triisopropylsilyl)ethynyl)-2*H*-[1,2'-bipyridin]-2-one (3ca):** The representative procedure was followed, using 4-phenyl-2*H*-[1,2'-bipyridin]-2-one (**1b**; 0.050 g, 0.20 mmol) and (bromoethynyl)triisopropylsilane (**2a**; 0.10 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/1) yielded **3ca** (0.0.080 g, 93%) as a light yellow solid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.62 (d, $J$ = 4.4 Hz, 1H, Ar–H), 7.86-7.82 (m, 1H, Ar–H), 7.58-7.56 (m, 2H, Ar–H), 7.45-7.40 (m, 4H, Ar–H), 7.35-7.33 (m, 1H, Ar–H), 6.85 (s, 1H, Ar–H), 6.80 (s, 1H, Ar–H), 0.88 (s, 3H, CH, 18H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 162.7 (CO), 152.1 ($C_q$), 151.8 ($C_q$), 149.8 (CH), 138.4 (CH), 136.9 ($C_q$), 130.4 ($C_q$), 129.7 (CH), 129.1 (2C, CH), 126.7 (2C, CH), 124.2 (CH), 123.6 (CH), 118.8 (CH), 112.4 (CH), 101.7 ($C_q$), 98.5 ($C_q$), 18.4 (6C, $CH_3$), 10.9 (3C, CH).




**4-(Benzyloxy)-6-((triisopropylsilyl)ethynyl)-2*H*-[1,2'-bipyridin]-2-one (3da):** The representative procedure was followed, using 4-(benzyloxy)-2*H*-[1,2'-bipyridin]-2-one (**1d**; 0.056 g, 0.2 mmol) and (bromoethynyl)triisopropylsilane (**2a**; 0.10 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/1) yielded **3da** (0.075 g, 82%) as a light yellow solid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.62 (dd, $J$ = 1.0, 4.8 Hz, 1H, Ar–H), 7.86-7.81 (m, 1H, Ar–H), 7.40-7.33 (m, 7H, Ar–H), 6.38 (d, $J$ = 2.5 Hz, 1H, Ar–H), 6.07 (d, $J$ = 2.5 Hz, 1H, Ar–H), 5.03 (s, 2H, $CH_2$), 0.89-0.84 (m, 3H, CH, 18H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 166.7 (CO), 164.0 ($C_q$), 152.1 ($C_q$), 149.8 (CH), 138.4 (CH), 135.2 ($C_q$), 130.6 ($C_q$), 128.9 (2C, CH), 128.6 (CH), 127.8 (2C, CH), 124.1 (CH), 124.0 (CH), 108.0 (CH), 101.6 ($C_q$), 99.9 (CH), 98.2 ($C_q$), 70.5 ($CH_2$), 18.5 (6C, $CH_3$), 11.0 (3C, CH). HRMS (ESI): *m/z* Calcd for $C_{28}H_{34}N_2O_2Si + H^+$ $[M + H]^+$ 459.2462; Found 459.2470.

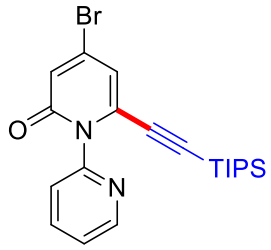



**4-(2-fluorophenyl)-6-((triisopropylsilyl)ethynyl)-2*H*-[1,2'-bipyridin]-2-one (3ea):** The representative procedure was followed, using 4-(2-fluorophenyl)-2*H*-[1,2'-bipyridin]-2-one (**1d**; 0.053 g, 0.2 mmol) and (bromoethynyl)triisopropylsilane (**2a**; 0.10 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/1) yielded **3ea** (0.079 g, 88%) as a light yellow solid. $^{1}$H-NMR (500 MHz, $CDCl_3$): $\delta$ = 8.65-8.63 (m, 1H, Ar–H), 7.89-7.84 (m, 1H, Ar–H), 7.46-7.35 (m, 4H, Ar–H), 7.24-7.13 (m, 2H, Ar–H), 6.83 (s, 1H, Ar–H), 6.77 (t, $J$ = 1.8 Hz, 1H, Ar–H), 0.88 (s, 3H, CH, 18H, $CH_3$). $^{13}$C{$^{1}$H}-NMR (125 MHz, $CDCl_3$): $\delta$ = 162.5 (CO), 160.0 (d, $^{1}J_{C\text{-}F}$ = 251.0 Hz, $C_q$), 152.1 ($C_q$), 149.9 (CH), 147.3 ($C_q$), 138.5 (CH), 131.2 (d, $^{3}J_{C\text{-}F}$ = 8.4 Hz, CH), 130.2 (d, $^{2}J_{C\text{-}F}$ = 28.2 Hz, $C_q$), 129.9 (d, $^{4}J_{C\text{-}F}$ = 3.1 Hz, CH), 125.4 (d, $^{3}J_{C\text{-}F}$ = 13.0 Hz, $C_q$), 124.8 (d, $^{4}J_{C\text{-}F}$ = 3.8 Hz, CH), 124.3 (CH), 123.7 (CH), 121.7 (d, $^{4}J_{C\text{-}F}$ = 3.8 Hz, CH), 116.5 (d, $^{2}J_{C\text{-}F}$ = 22.1 Hz, CH), 113.9 (d, $^{4}J_{C\text{-}F}$ = 3.1 Hz, CH), 102.0 ($C_q$), 98.5 ($C_q$), 18.5 (6C, $CH_3$), 11.0 (3C, CH).

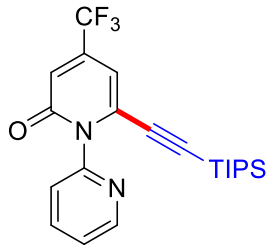



**4-(4-(Methylthio)phenyl)-6-((triisopropylsilyl)ethynyl)-2*H*-[1,2'-bipyridin]-2-one (3fa):** The representative procedure was followed, using 4-(4-(methylthio)phenyl)-2*H*-[1,2'-bipyridin]-2-one (**1f**; 0.058 g, 0.2 mmol) and (bromoethynyl)triisopropylsilane (**2a**; 0.10 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/1) yielded **3fa** (0.082 g, 86%) as a light yellow solid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.64 (dd, $J$ = 4.7, 1.3 Hz, 1H, Ar–H), 7.86 (td, $J$ = 7.7, 1.8 Hz, 1H, Ar–H), 7.53 (d, $J$ = 8.4 Hz, 2H, Ar–H), 7.42 (d, $J$ = 7.9 Hz, 1H, Ar–H), 7.37 (dd, $J$ = 7.4, 4.9 Hz, 1H, Ar–H), 7.31 (d, $J$ = 8.5 Hz, 2H, Ar–H), 6.85 (d, $J$ = 1.8 Hz, 1H, Ar–H), 6.80 (d, $J$ = 1.8 Hz, 1H,

Ar–H), 2.51 (s, 3H, $CH_3$), 0.90-0.88 (s, 3H, CH, 18H, $CH_3$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 162.8 (CO), 152.2 ($C_q$), 151.1 ($C_q$), 149.9 (CH), 141.5 ($C_q$), 138.5 (CH), 133.3 ($C_q$), 130.6 ($C_q$), 127.2 (2C, CH), 126.5 (2C, CH), 124.3 (CH), 123.8 (CH), 118.2 (CH), 112.2 (CH), 101.8 ($C_q$), 98.7 ($C_q$), 18.5 (6C, $CH_3$), 15.4 ($CH_3$), 11.0 (3C, CH).

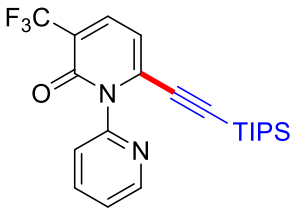



**4-Bromo-6-((triisopropylsilyl)ethynyl)-2*H*-[1,2'-bipyridin]-2-one (3ga):** The representative procedure was followed, using 4-bromo-2*H*-[1,2'-bipyridin]-2-one (**1g**; 0.050 g, 0.2 mmol) and (bromoethynyl)triisopropylsilane (**2a**; 0.10 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **3ga** (0.060 g, 85%) as a light yellow solid. $^1H$-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.63 (dd, $J$ = 4.8, 1.1 Hz, 1H, Ar–H), 7.86 (td, $J$ = 7.8, 1.9 Hz, 1H, Ar–H), 7.39-7.35 (m, 2H, Ar–H), 6.93 (d, $J$ = 1.9 Hz, 1H, Ar–H), 6.69 (d, $J$ = 1.9 Hz, 1H, Ar–H), 0.90-0.89 (m, 3H, CH, 18H, $CH_3$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 161.2 (CO), 151.6 ($C_q$), 150.1 (CH), 138.7 (CH), 135.7 ($C_q$), 130.9 ($C_q$), 124.7 (CH), 124.6 (CH), 123.7 (CH), 116.4 (CH), 104.2 ($C_q$), 97.2 ($C_q$), 18.5 (6C, $CH_3$), 11.0 (3C, CH). HRMS (ESI): *m/z* Calcd for $C_{21}H_{27}N_2OBrSi + H^+$ $[M + H]^+$ 433.1128; Found 433.1114.

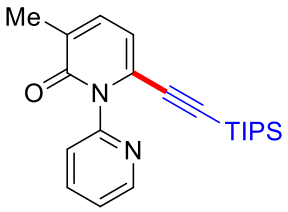



**4-(trifluoromethyl)-6-((triisopropylsilyl)ethynyl)-2*H*-[1,2'-bipyridin]-2-one (3ha):** The representative procedure was followed, using 4-(trifluoromethyl)-2*H*-[1,2'-bipyridin]-2-one (**1g**; 0.048 g, 0.2 mmol) and (bromoethynyl)triisopropylsilane (**2a**; 0.10 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **3ha** (0.080 g, 95%) as a light yellow solid. $^1H$-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.63 (dd, $J$ = 4.8, 1.1 Hz, 1H, Ar–H), 7.86 (td, $J$ = 7.8, 1.9 Hz, 1H, Ar–H), 7.39-7.35 (m, 2H, Ar–H), 6.93 (d, $J$ = 1.9 Hz, 1H, Ar–H), 6.69 (d, $J$ = 1.9 Hz, 1H, Ar–H), 0.90-0.89 (m, 3H, CH, 18H, $CH_3$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): $\delta$ = 161.5, 151.5, 150.1, 141.7 (q, $J$ = 34.3 Hz), 138.8,

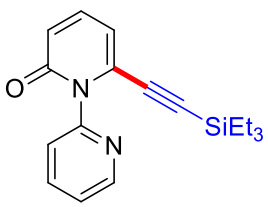
132.7, 124.7, 123.4, 122.0 (q, *J* = 274.6 Hz), 120.0 (q, *J* = 3.8 Hz), 107.4 (q, *J* = 2.3 Hz), 104.6, 97.55, 18.5, 11.0.




**3-(Trifluoromethyl)-6-((triisopropylsilyl)ethynyl)-2*H*-[1,2'-bipyridin]-2-one (3ia):** The representative procedure was followed, using 3-(trifluoromethyl)-2*H*-[1,2'-bipyridin]-2-one (**1i**; 0.048 g, 0.2 mmol) and (bromoethynyl)triisopropylsilane (**2a**; 0.10 g, 0.4 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **3ia** (0.018 g, 21%) as a light yellow solid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.65-8.63 (m, 1H, Ar–H), 7.90-7.86 (m, 1H, Ar–H), 7.75 (d, *J* = 7.4 Hz, 1H, Ar–H), 7.42-7.38 (m, 2H, Ar–H), 6.58 (d, *J* = 7.3 Hz, 1H, Ar–H), 0.90-0.88 (m, 3H, CH, 18H, $CH_3$). HRMS (ESI): *m/z* Calcd for $C_{22}H_{27}ON_2F_3Si + H^+$ $[M + H]^+$ 421.1918; Found 421.1918.




**3-Methyl-6-((triisopropylsilyl)ethynyl)-2*H*-[1,2'-bipyridin]-2-one (3ja):** The representative procedure was followed, using 3-methyl-2*H*-[1,2'-bipyridin]-2-one (**1j**; 0.037 g, 0.2 mmol) and (bromoethynyl)triisopropylsilane (**2a**; 0.10 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/1) yielded **3ja** (0.022 g, 30%) as a light yellow solid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.62 (dd, *J* = 4.9, 1.1 Hz, 1H, Ar–H), 7.86-7.82 (m, 1H, Ar–H), 7.39-7.33 (m, 2H, Ar–H), 7.21 (dd, *J* = 7.1, 1.1, Hz, 1H, Ar–H), 6.50 (d, *J* = 7.0 Hz, 1H, Ar–H), 2.17 (s, 3H, $CH_3$), 0.99-0.83 (m, 3H, CH, 18H, $CH_3$). HRMS (ESI): *m/z* Calcd for $C_{22}H_{30}ON_2Si + H^+$ $[M + H]^+$ 367.2200; Found 367.2212.




**6-((Triethylsilyl)ethynyl)-2*H*-[1,2'-bipyridin]-2-one (3ab):** The representative procedure

was followed, using 2*H*-[1,2'-bipyridin]-2-one (**1a**; 0.034 g, 0.2 mmol) and (bromoethynyl)triethylsilane (**2b**; 0.09 g, 0.40 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) yielded **3ab** (0.055g, 89%) as a light yellow solid. $^{1}$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 8.62 (dd, $J$ = 5.4, 1.8 Hz, 1H, Ar–H), 7.84-7.82 (m, 1H, Ar–H), 7.38-7.35 (m, 2H, Ar–H), 7.31 (dd, $J$ = 9.4, 6.9 Hz, 1H, Ar–H), 6.65 (d, $J$ = 9.3 Hz, 1H, Ar–H), 6.51 (d, $J$ = 7.8 Hz, 1H, Ar–H), 0.79-0.75 (m, 9H, $CH_3$), 0.42-0.36 (m, 6H, $CH_2$). $^{13}$C{$^{1}$H}-NMR (100 MHz, $CDCl_3$): $\delta$ = 162.5 (CO), 152.3 ($C_q$), 149.7 (CH), 139.5 (CH), 138.4 (CH), 130.7 ($C_q$), 124.2 (CH), 123.6 (CH), 122.9 (CH), 112.3 (CH), 102.9 ($C_q$), 97.6 ($C_q$), 7.3 (3C, $CH_3$), 3.9 (3C, $CH_2$).

### 5.4.4 Procedure for Removal of the Directing Group

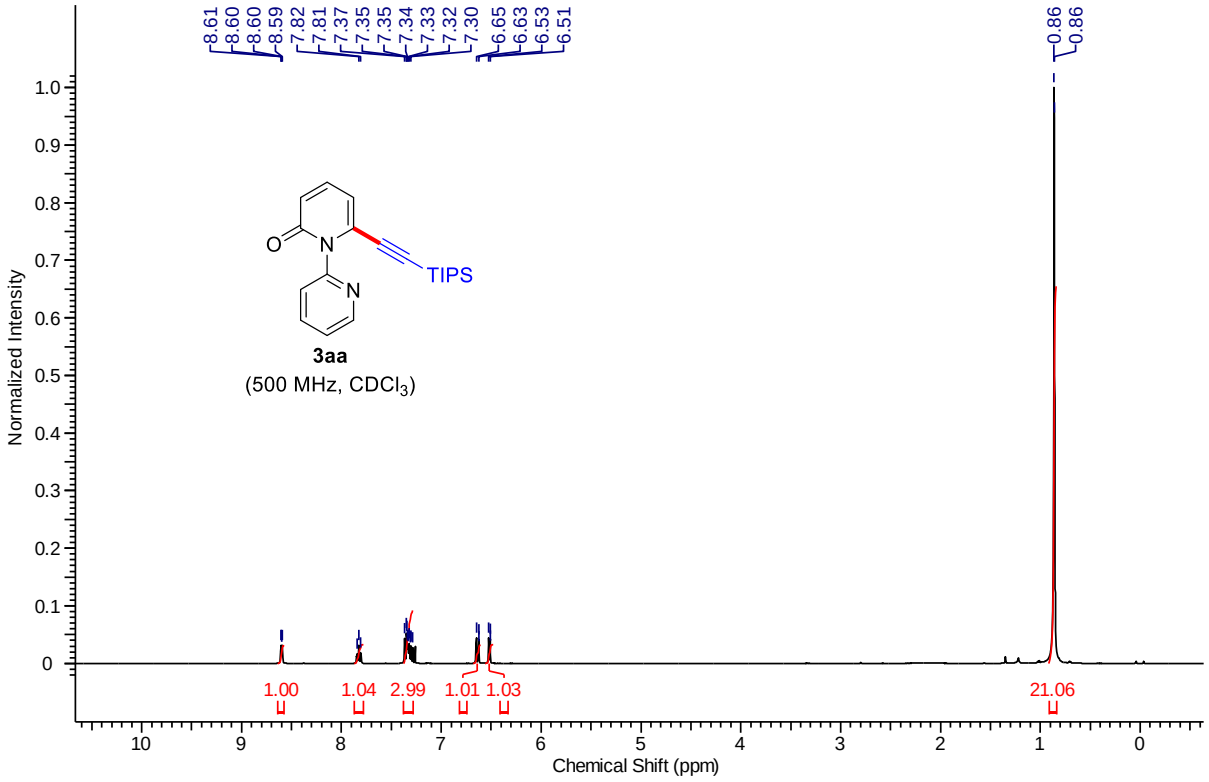
**Removal of DG from 2-Pyridone (Synthesis of 4aa):** In an oven dried round bottom flask, 6-((triisopropylsilyl)ethynyl)-2*H*-[1,2'-bipyridin]-2-one (**3aa**: 0.10 g, 0.284 mmol) was introduced and $CH_2Cl_2$ (6 mL) was added into it. Methyl trifluoromethanesulfonate (MeOTf; 0.093 g, 0.568 mmol) was added drop wise *via* a syringe to the reaction mixture and the resultant mixture was stirred at room temperature under argon atmosphere for 20 h. The reaction mixture was cooled to ambient temperature and the solvent was evaporated under vacuum. The crude product was dissolved in dry $Et_2O$ (3 mL) and KO$^{t}$Bu (0.096 g, 0.852 mmol) and EtOH (0.8 mL) was added and the reaction mixture was stirred for 4 h at room temperature. At ambient temperature, the volatiles were evaporated under reduced pressure, and the crude product was extracted with DCM (30 mL x 3). The combined organic extract was washed with 1N HCL, dried over $Na_2SO_4$ and the volatiles were evaporated in *vacuo*. The remaining residue was purified by column chromatography on neutral alumina (petroleum ether/EtOAc: 1/2) to yield **4aa** (0.55 g, 70) as a light yellow liquid.

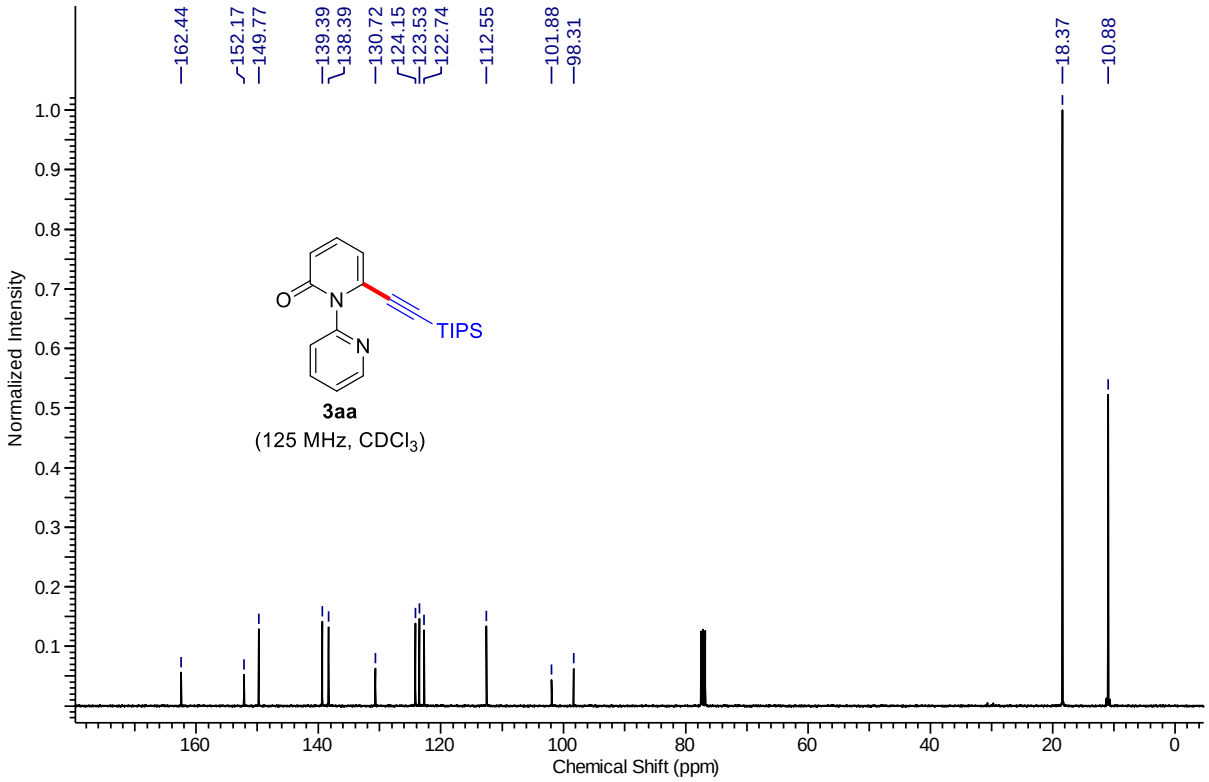
### 5.4.5 External Additive Experiments

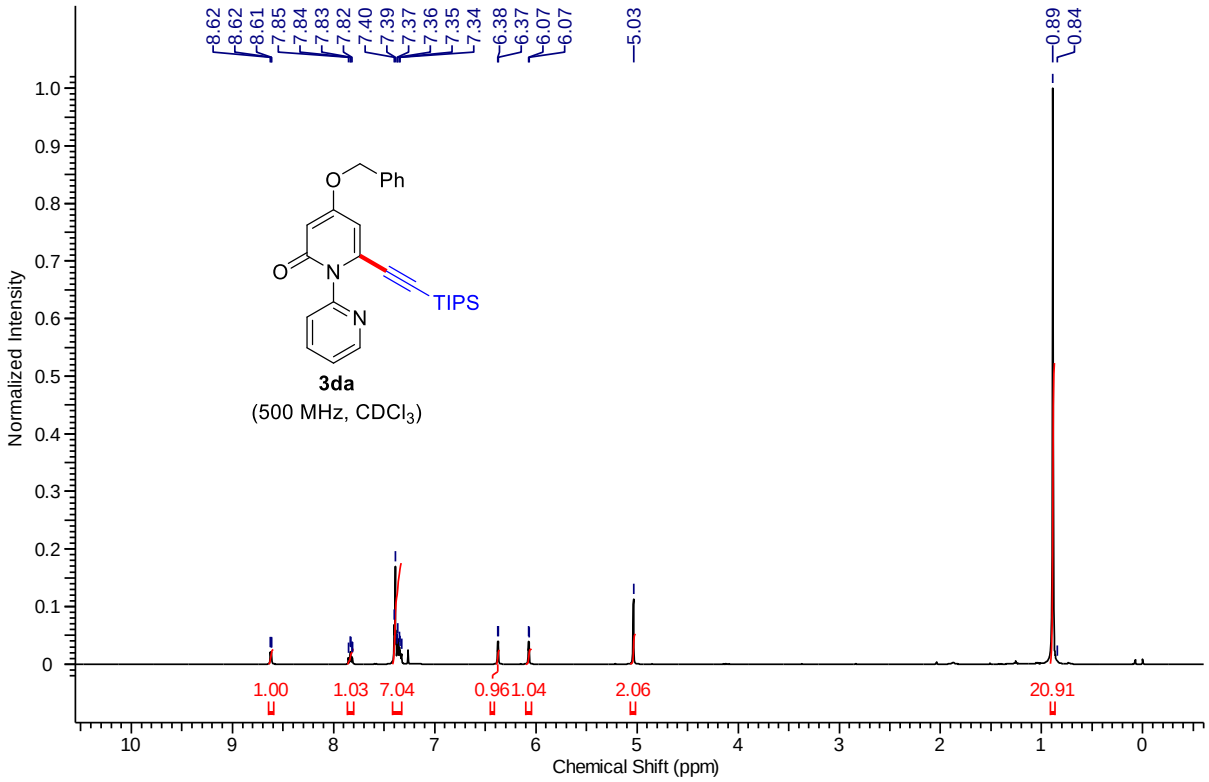
**Procedure for TEMPO/1,1-diphenylethylene/BHT Added Experiment:** To a flame dried screw-capped tube equipped with magnetic stir bar was introduced *2H*-[1,2'-bipyridin]-2-one (**1a**; 0.034 g, 0.20 mmol), (bromoethynyl)triisopropylsilane (**2a**; 0.010 g, 0.4 mmol), $Ni(OTf)_2$ (0.0071 g, 0.02 mmol, 10 mol %), $^{t}$Bu-bpy (0.0054 g, 0.02 mmol, 10 mol%) and Li$^{t}$BuO (0.032 g, 0.4 mmol) and TEMPO (0.063 g, 0.40 mmol) [or 1,1-diphenylethylene (0.072 g, 0.40 mmol) or BHT (0.088 g, 0.4 mmol]. To the reaction mixture toluene (1.0 mL) was added and stirred at 130 $^{o}$C in a pre-heated oil bath for 16 h. At ambient temperature, the reaction mixture was quenched with distilled $H_2O$ (10 mL) and *n*-dodecane (0.02 mL, 0.088

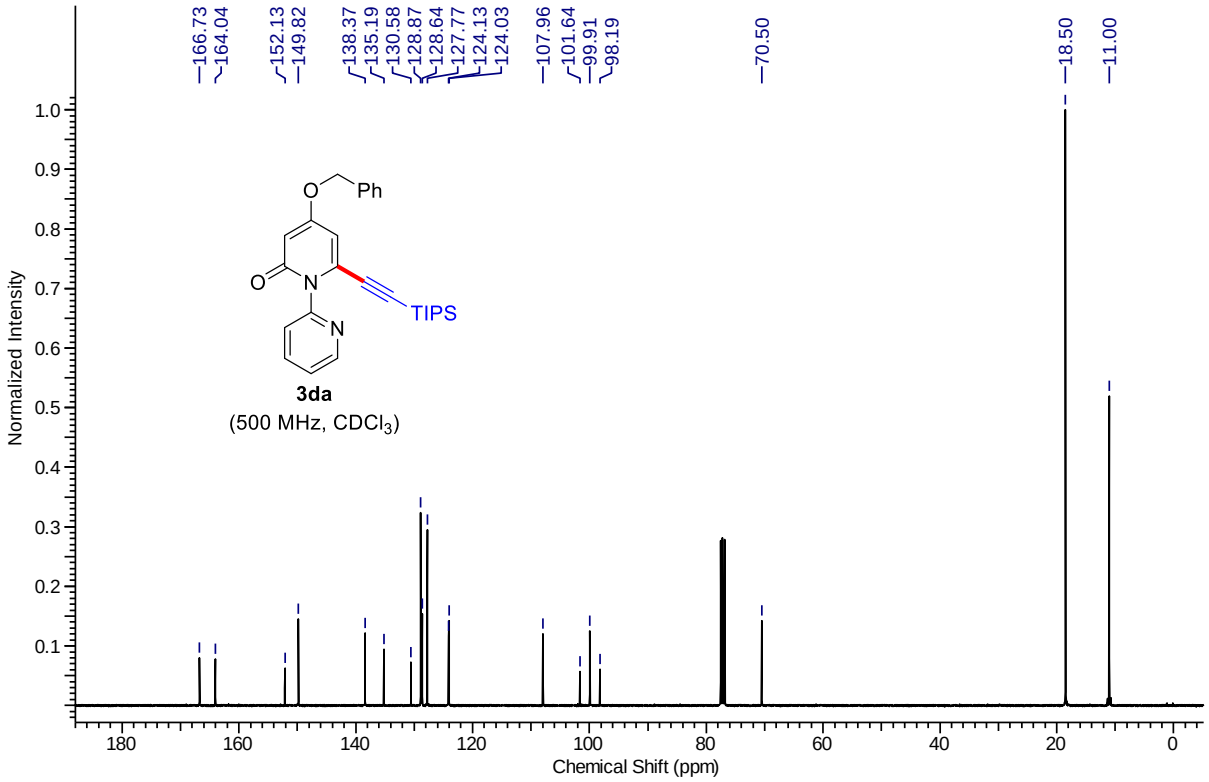
mmol; internal standard) was added. An aliquot of the sample was subjected to the GC analysis. The formation of coupled product (**3aa)** was observed 71% and 85% in the presence of TEMPO or 1,1-diphenylethylene whereas 25% of coupled product **3aa** was formed in the presence of BHT.

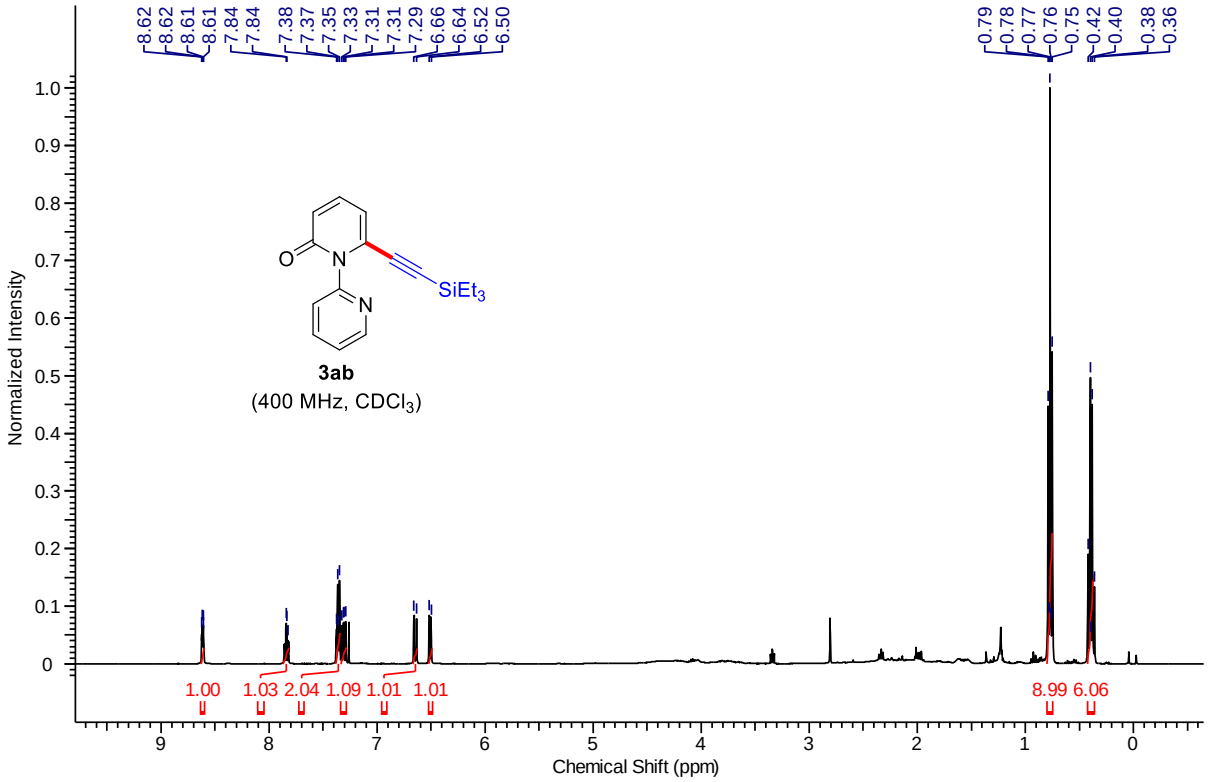
## 5.4.6 $^{1}H$ and $^{13}C\{^{1}H\}$ NMR Spectra of Selected Alkynylated Products

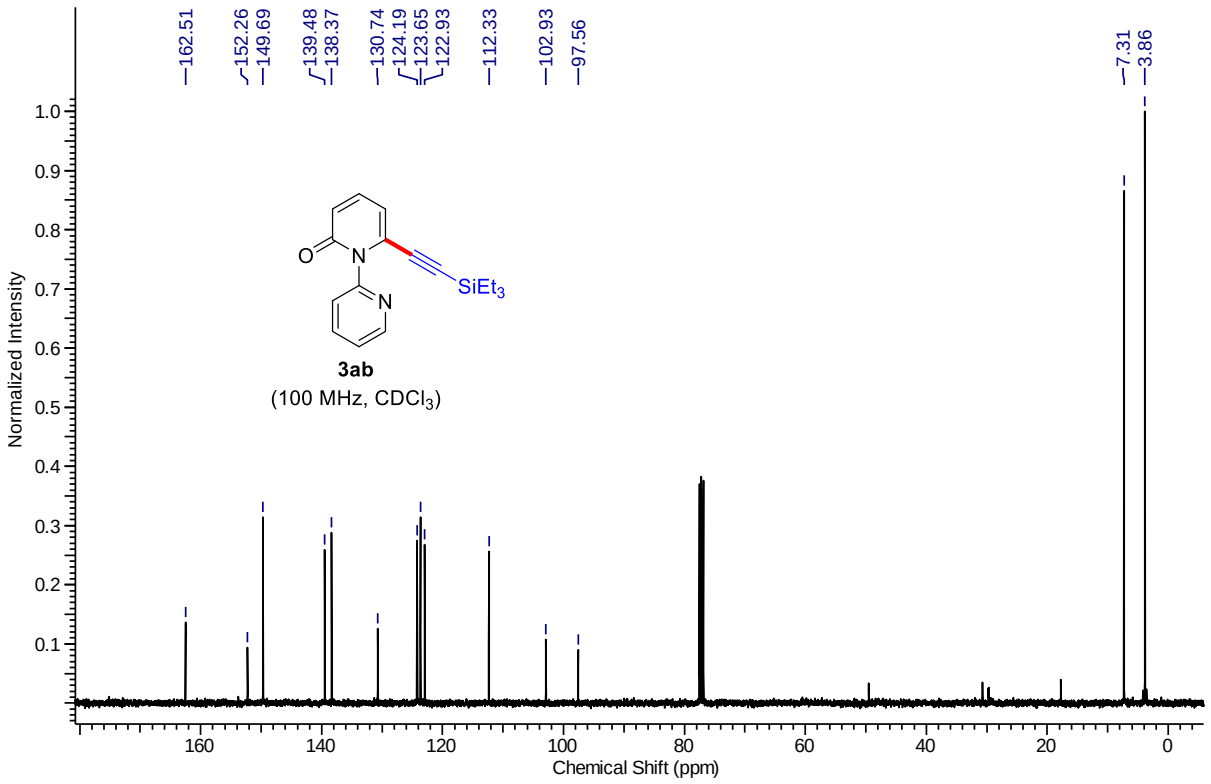



8.62
8.62
8.61
7.85
7.84
7.83
7.82
7.40
7.39
7.37
7.36
7.35
7.34
6.38
6.37
6.07
6.07
5.03
0.89
0.84
Ph
O
N
O
N
TIPS
3da
(500 MHz, CDCl3)
Normalized Intensity
1.00
1.03
7.04
0.96
1.04
2.06
20.91
Chemical Shift (ppm)


166.73
164.04
152.13
149.82
138.37
135.19
130.58
128.87
128.64
127.77
124.13
124.03
107.96
101.64
99.91
98.19
70.50
18.50
11.00
Ph
O
N
O
N
TIPS
3da
(500 MHz, CDCl3)
Normalized Intensity
Chemical Shift (ppm)


8.62
8.62
8.61
8.61
7.84
7.84
7.38
7.37
7.35
7.33
7.31
7.31
7.29
6.66
6.64
6.52
6.50
0.79
0.78
0.77
0.76
0.75
0.42
0.40
0.38
0.36
Normalized Intensity
1.00
1.03
2.04
1.09
1.01
1.01
8.99
6.06
Chemical Shift (ppm)
SiEt3
3ab
(400 MHz, CDCl3)


162.51
152.26
149.69
139.48
138.37
130.74
124.19
123.65
122.93
112.33
102.93
97.56
7.31
3.86
Normalized Intensity
Chemical Shift (ppm)
SiEt3
3ab
(100 MHz, CDCl3)

## 5.5 REFERENCES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# Chapter 6

# Summary and Outlook

## 6.1 SUMMARY

The alkylation of C−H bonds in (hetero)arenes has become a valuable tool in organic chemistry, allowing for the modification of important compounds with enhanced properties, such as lipophilicity and metabolic stability. Traditionally, this process has relied on activated coupling partners, often catalyzed by 4d and 5d transition metals. However, these methods frequently suffer from limited substrate scopes, multistep synthetic sequences, and the formation of undesired products. To address these challenges, my thesis focuses on developing methods for the alkylation and alkynylation of (hetero)arenes using unactivated and demanding coupling partners. We have also replaced strong bases, such as Grignard reagents, with more user-friendly inorganic bases. Furthermore, all functionalization reactions are catalyzed by earth-abundant and inexpensive 3d transition metals.

In that context, **Chapter 1** provides an in-depth literature review on the C−H alkylation and alkynylation of (hetero)arenes. This chapter highlights the alkylation and alkynylation of (hetero)arenes using 3d transition metals.

**Chapter 2:** we have developed an efficient copper-catalyzed method for the regioselective coupling of unactivated alkyl chlorides with the *ortho* C–H bond of phenol derivatives. The employment of inexpensive, abundant, and non-toxic copper catalysts and widely available unactivated alkyl chlorides for the reaction make this protocol highly viable. The reaction is compatible with a variety of simple and functionalized alkyl chlorides as well as with a range of phenol derivatives. The use of LiHMDS base played a critical role in the success of alkylation by generating a Cu-amido complex during the reaction. Detailed mechanistic investigation of the alkylation allowed us to draw a catalytic path that follows the rate-limiting 2e oxidative addition of alkyl chloride. Controlled experiments, kinetic analyses, and EPR studies revealed the participation of a Cu(I) active species, therefore supporting a Cu(I)/Cu(III) pathway. We trust that the simplicity and uniqueness of the demonstrated sustainable copper-catalyzed protocol would contribute significantly to the investigation and development of many other such processes.

**Chapter 3:** we have disclosed a ligand-free and cost-effective Mn-catalyzed chemo- and regioselective method for the C($sp^2$)–H bond alkylation of indolines and 2-phenyl pyridines. This protocol provided a wide range of alkylated products using numerous unactivated alkyl bromides, and tolerated a range of functionalities including alkenyl, alkynyl, silyl, ethers, and heteroaromatics. The alkyl-bearing fatty alcohol and cholesterol were compatible in the reaction. Notably, this alkylation proceeded either via a five-membered or a six-membered

metallacycle leading to the desired products. The use of LiHMDS base is very crucial, as it can produce an active Mn-amido species for the reaction. A preliminary mechanistic study suggests that the alkylation reaction proceeds through a single electron transfer (SET) process involving the rate-limiting C–H bond metalation of indoline.

**Chapter 4:** The 2-pyridone is one of the most important heteroaromatic rings found in natural products, bioactive molecules and pharmaceutical agents. Interestingly, the alkylated 2-pyridones are directly found in several classes of drugs and bioactive molecules such as ciclopirox, milrinone and camptothecin. Notably, the alkylation of 2-pyridones is mostly explored by using 4d and 5d transition metals as a catalyst, whereas it is not precedented by 3d transition metals. In this chapter. we discussed the synthesizing of quinoline-based (NNP)Ni(II)X complexes for C–H alkylation of 2-pyridones with unactivated alkyl chlorides . We have synthesized quinoline-based NNP ligand and its complexes. Notable features of this protocol include wide substrate scope and outstanding tolerance for diverse functional groups.

**Chapter 5**: The alkynylated 2-pyridones play a crucial role in many pharmaceutically active compounds and natural products. The alkynylation of 2-pyridone is not precedented with unactivated alkynyl halide as a coupling partner. However, a rhodium-catalyzed C-6 alkynylation of 2-pyridone is reported with activated alkyne as a coupling partner. In this chapter, we established Ni(II)-catalyzed C-6 selective alkynylation of 2-pyridones using alkynyl bromide as a coupling partner. The combination of $Ni(OTf)_2$ with an electron-rich $^{t}$Bu-bpy ligand was found to be an excellent catalyst system for the alkynylation reaction. We have demonstrated substantial substrate scope and investigated detailed reaction mechanisms.

## 6.2 OUTLOOK

Significant progress has been made in recent decades toward functionalizing various (hetero)arenes, with base metal catalysts receiving considerable attention for such reactions. However, many reactions still require extreme conditions, such as high temperatures, strong bases, and long reaction times, limiting their efficiency and sustainability. More environmentally benign approaches are therefore essential. Additionally, the development of base metal-catalyzed asymmetric C–H bond functionalization for the synthesis of chiral heterocycles remains a significant challenge in organic chemistry. There is a pressing need to develop methodologies for enantioselective C–H bond functionalizations. Furthermore, the use of directing groups is mostly limited to pyridine, pyrimidine, and 8-aminoquinoline, highlighting the need to replace them with simpler and more transient directing groups.

# ABSTRACT

**Name of the Student:** Suryadev Kumar Verma **Registration No. :** 10CC18A26053

**Faculty of Study:** Chemical Science **Year of Submission:** 2024

**AcSIR academic centre/CSIR Lab:** CSIR-NCL

**Name of the Supervisor(s):** Dr. Benudhar Punji

**Title of the thesis:** " Manganese, Nickel and Copper-Catalyzed C−H Bond Alkylation and Alkynylation of (Hetero)arenes "

The alkylation and alkynylation of C–H bonds in (hetero)arenes have emerged as powerful tools with applications in material sciences, pharmaceutical industries, and the synthesis of natural products. However, selective C($sp^2$)–H functionalization of (hetero)arenes is frequently limited to traditional methods or restricted to the use of 4d and 5d transition metals and sensitive reagents. **Chapter 1** of this thesis shows a detailed literature survey on the C–H bond alkylation and alkynylation of (hetero)arenes using 3d transition metals, aiming to provide insights into the development of more efficient and sustainable methodologies for these transformations. **Chapter 2** describes an efficient and cost-effective copper-catalyzed protocol for coupling unactivated alkyl chlorides with the C–H bond of phenol derivatives via 2-pyridinyl-chelation assistance. The reaction shows a high level of regioselectivity, leading to an exclusive *ortho* alkylation and providing a broad scope with the endurance of numerous functionalities. Detailed mechanistic investigations suggest that the alkylation occurs through a two-electron oxidative addition of alkyl chloride to an active Cu(I) species. **Chapter 3** discusses the selective C($sp^2$)–H bond alkylation of indolines, carbazoles and (2-pyridinyl)arenes with unactivated alkyl bromides is achieved using $MnBr_2$ catalyst in the absence of an external ligand. This protocol stands out for its ability to accommodate a wide range of substrates and its high tolerance for diverse functional groups. Mechanistic studies highlight a single electron transfer (SET) pathway for the alkylation involving 1e oxidative addition of alkyl bromide and a rate-limiting metalation. **Chapter 4** focuses on the synthesis of quinoline-based ($^{Q}$NNPP$^{Ph2}$)Ni(II)OAc complex for the C–H alkylation of 2-pyridones using unactivated alkyl chlorides. Key highlights of this protocol include its broad substrate scope and excellent tolerance for diverse functional groups and **Chapter 5** describes the development of a Ni(II)-catalyzed C-6 selective alkynylation of 2-pyridones using alkynyl bromide as a coupling partner. The study showcases a wide substrate scope and includes a detailed investigation of the reaction mechanism.

# List of Thesis-Related Publications

1. **Verma, S. K.**; Punji, B., Copper-catalyzed regioselective C−H alkylation of phenol derivatives with unactivated alkyl chlorides: Manifesting a Cu(I)/Cu(III) pathway. *J. Catal.* **2024**, *430*, 115351.

2. **Verma, S. K.**; Punji, B., Manganese-Catalyzed C($sp^2$)−H Alkylation of Indolines and Arenes with Unactivated Alkyl Bromides. *Chem. Asian J.* **2022**, *17*, e202200103.

3. **Verma, S. K.**; Punji, B., Regioselective C(6)–H Alkylation of 2-Pyridones with Unactivated Alkyl Chlorides Using a Well-defined Ni(II)-Catalyst. (*Manuscript under preparation*)

4. **Verma, S. K.**; Punji, B., Nickel-Catalyzed Regioselective C6 Alkynylation of 2-Pyridones Using Unactivated Alkynyl Bromide. (*Manuscript under preparation*)

# Other Publications

1. Jagtap, R. A., **Verma**, **S.K.**, and Punji, B., $MnBr_2$-Catalyzed Direct and Site-Selective Alkylation of Indoles and Benzo[*h*]quinoline, *Org. Lett.* **2020**, *22*, 4643 – 4647.

2. Mallick, S.; Mukhi, P.; Kumari, P.; Mahato, K. R.; **Verma, S. K.**; Das, D., Synthesis, Characterization and Catalytic Application of Starch Supported Cuprous Iodide Nanoparticles. *Catal. Lett.* **2019,** *149*, 3501-3507.

# LIST OF NATIONAL/INTERNATIONAL CONFERENCES

1. **Suryadev K. Verma**; Punji, B. "Synthesis of Quinoline-Based (NNP)Ni(II) Complexes: A Robust Catalyst System for C−H Alkylation of 2-Pyridones" *Poster Presentation in International Conference on Emerging Trends in Catalysis and Synthesis (ETCS-2024*) at Department of Chemistry, Indian Institute of Technology Kharagpur.

2. **Suryadev K. Verma**; Punji, B. "Copper-Catalyzed *ortho*-Selective C–H Bond Alkylation of Phenols using Unactivated Alkyl Chlorides" *Poster Presentation in International Conference on Modern Trends in Inorganic Chemistry (MTIC XIX-2023*) at Department of Chemistry, Banaras Hindu University, Varanasi.

3. **Suryadev K. Verma**; Punji, B. "Copper-Catalyzed *ortho*-Selective C–H Bond Alkylation of Phenols using Unactivated Alkyl Chlorides" *Poster Presentation in NCL-RF Annual Student Conference 2022* at CSIR-National Chemical Laboratory, Pune.

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Research article

# Copper-catalyzed regioselective C−H alkylation of phenol derivatives with unactivated alkyl chlorides: Manifesting a Cu(I)/Cu(III) pathway

Suryadev K. Verma [a,b], Benudhar Punji [a,b,*]

[a] Organometallic Synthesis and Catalysis Lab, Organic Chemistry Division, CSIR–National Chemical Laboratory (CSIR–NCL), Dr. Homi Bhabha Road, Pune - 411 008, India

[b] Academy of Scientific and Innovative Research (AcSIR), Ghaziabad- 201 002, India

A B S T R A C T

The use of unactivated alkyl chlorides in regioselective C−H alkylation is a highly challenging process with diverse applications of alkylation strategy in drug discovery and agrochemistry. In this work, we report an efficient and cost-effective copper-catalyzed protocol for the coupling of unactivated alkyl chlorides with the C−H bond of phenol derivatives via 2-pyridinyl chelation assistance. The reaction shows a high level of regioselectivity, leading to an exclusive *ortho* alkylation and providing a broad scope with the endurance of numerous functionalities such as silyl, ether, thioether, pyrrolyl, indolyl, carbazolyl groups, including alkyl bearing fatty alcohol, nonylphenol, and vitamin E. Detailed mechanistic investigations suggest that the alkylation occurs through a two-electron oxidative addition of alkyl chloride to an active Cu(I) species. Deuterium labeling and kinetics experiments indicate a facile and reversible C−H bond activation process. Overall, the alkylation follows a Cu(I)/Cu(III) pathway involving chelation-assisted smooth C−H metalation and rate-limiting C−Cl oxidative addition of alkyl chloride.

## 1. Introduction

Phenols are distinctive structural motifs substantially found in a range of pharmaceuticals, agrochemicals, natural products, and dyes [1–6]. Additionally, they are commonly used as basic starting material in various cross-coupling reactions for synthesizing diverse functional molecules [7,8]. Thus, efficient and cost-effective functionalization of phenolic derivatives, particularly by step-economical C–H bond activation [9], has attracted significant attention. The C–H functionalization of phenol and phenolic derivatives has been substantially demonstrated during the past two decades [10–12]. Several of these functionalizations include chemo and regioselective arylation, alkenylation, halogenation, acetoxylation, and nitration of phenols; however, a more challenging alkylation protocol is limited. Amongst the alkylation, diazoesters, alcohols, and alkenes are used as alkylating sources, and the reactions are mostly established with expensive and deleterious 4d and 5d transition metal catalysts (Scheme 1a) [13–21]. However, the employment of challenging alkyl halides as coupling partners in phenols alkylation under base-metal catalysis is rare [22–24]; though few reports are known using simple and activated diazoesters (Scheme 1b) [25].

In particular, the C–H bond alkylation of aromatics using unactivated alkyl halides bearing $\beta$–hydrogen is limited and highly challenging due to various reasons, including difficulty in oxidative addition of alkyl halides and undesired side products resulting from $\beta$-hydride elimination [26,27]. Additionally, the use of inexpensive and low-reactive alkyl chlorides in the C–H alkylation of phenols is unknown. Therefore, implementing the alkyl chlorides in the C–H alkylation of phenols using cost-effective 3d metal catalysts [28–31], particularly copper [32–41], would be highly beneficial for the sustainable development of the protocol.

In view of the natural abundance, cost-effectiveness, and low toxicity of copper, copper complexes are widely used as catalysts in various organic transformations. The pioneering work of Ullman and Goldberg demonstrated both C–C and C–heteroatom bond formations using copper catalysts [42]. In recent years, copper-catalyzed C–H functionalization of arenes and heteroarenes has been reported by various groups [43–49]. Unfortunately, the C–H functionalization of phenols by the copper catalyst is very scarce [50]. In a significant development, Zhang and Liu reported the *ortho*-alkylation of phenol with activated α-aryl-α-diazoester under copper catalysis (Scheme 1b) [51]. Notably, this protocol is limited to activated α-aryl-substituted diazoesters, and O-substituted phenolic compounds failed to participate in the reaction. To our knowledge, the *ortho*-alkylation of phenol derivatives using unactivated and demanding alkyl halides is unknown. As a part of our research activity on sustainable 3d metal-catalyzed C−H functionalization [52–55], herein, we report the first general protocol for the efficient coupling of unactivated alkyl chlorides with the *ortho* C−H bond of phenol derivatives using an inexpensive and abundant Cu(II)-catalyst (Scheme 1c).

* Corresponding author.
*E-mail address:* b.punji@ncl.res.in (B. Punji).

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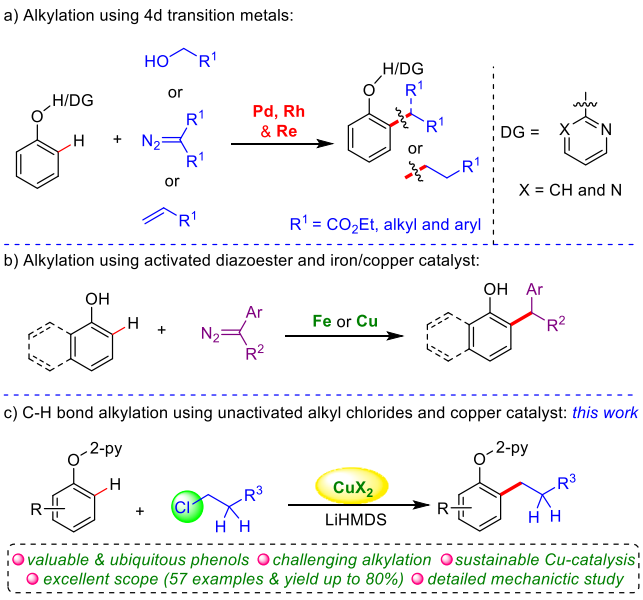


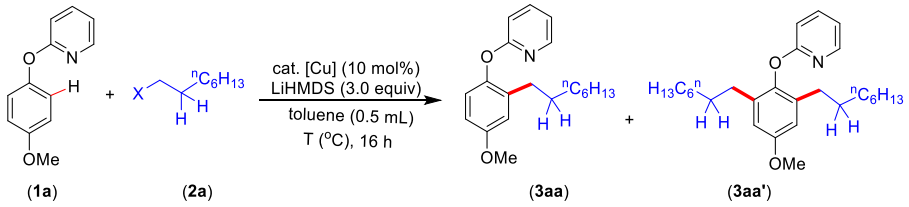

**Scheme 1.** Approaches for *ortho*-alkylation of phenol derivatives.

## 2. Results and discussion

### 2.1. Reaction optimization

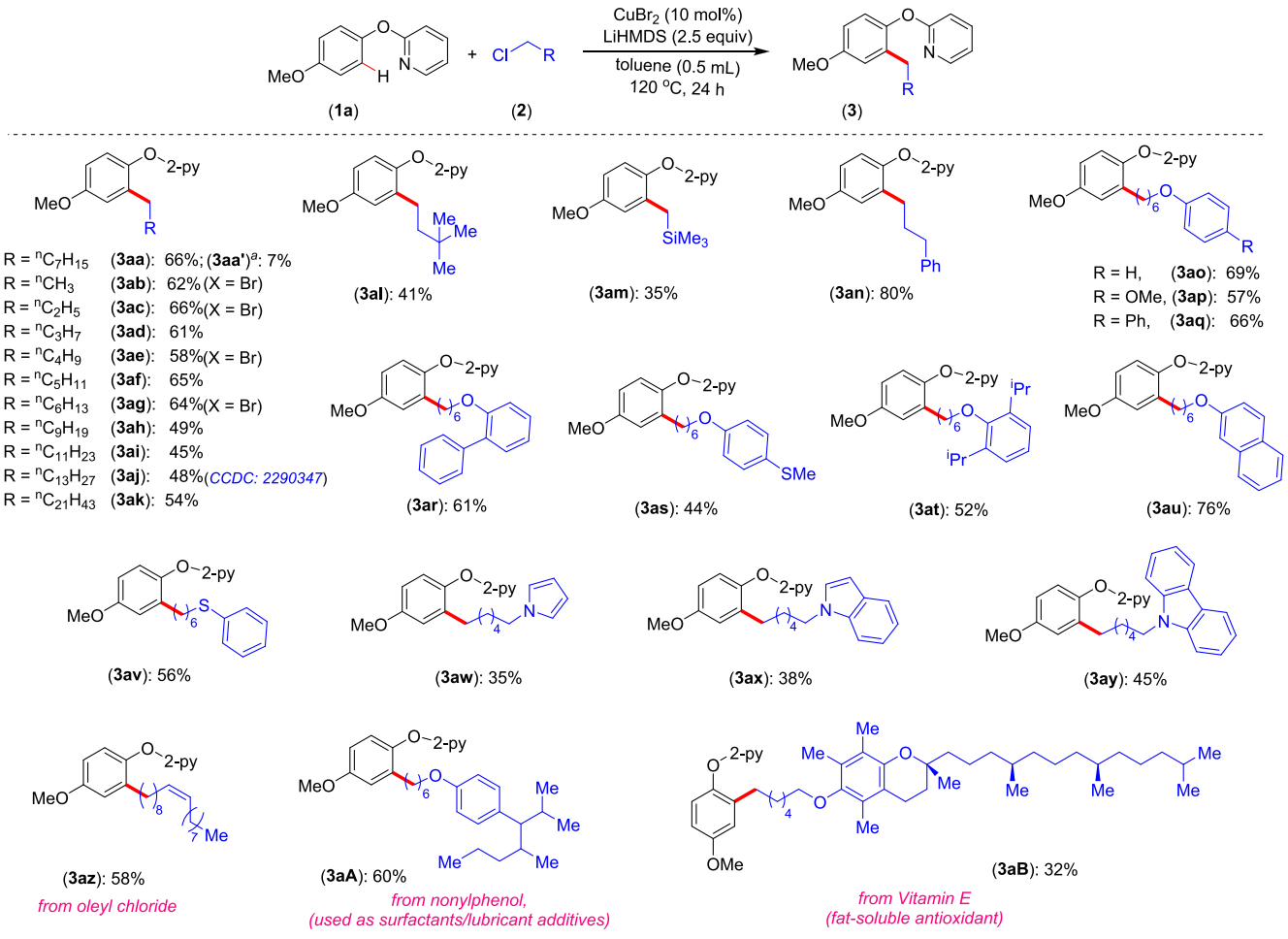
We initiated the optimization of reaction parameters for the Cu-catalyzed *ortho*-alkylation of phenol derivatives using 2-(4-methoxyphenoxy)pyridine (**1a**) as a model substrate with octyl halide in the form of coupling partner and lithium bis(trimethylsilyl)amide (LiHMDS) as a base in toluene at 140 °C under argon atmosphere. Using 1-iodooctane or 1-bromooctane as the coupling partners provided the desired product **3aa** in 31 % and 50 %, respectively. Notably, in these cases, a significant quantity of unwanted side products was observed upon the reaction of 1-bromooctane or 1-iodooctane with LiHMDS (Table 1, entries 1 and 2). Interestingly, using the more challenging coupling partner, 1-chlorooctane, substantially reduced the side product and delivered product **3aa** in 58 % yield (entry 3). Among the various Cu(II) metal precursors screened (entries 4–7), the use of $CuBr_2$ as a catalyst provided marginally better yield for the mono-alkylated product **3aa** (61 %), and the *ortho*-dialkylated product obtained in 15 %. The Cu(I) salts like CuCl, CuBr, and CuI were also effective catalysts, providing **3aa** in 51–60 % yield (entries 8–10). The employment of ancillary nitrogen and phosphorus-based ligands such as bpy, phen, $PPh_3$, dppe, dppf, and xantphos, along with the $CuBr_2$ catalyst, did not show a positive effect on the alkylation process (Table S1 in the Supporting Information). In fact, the overall yield of alkylation was reduced in the presence of external ligands, probably due to the undesired extra stability of copper intermediate or difficulty in the approach of 2-pyridinylphenoxy (**1a**) towards the ligated copper complex. The attempted alkylation in the presence of mild inorganic bases, such as LiO$^t$Bu, NaO$^t$Bu, KO$^t$Bu, $Na_2CO_3$, or $K_2CO_3$, did not occur (Table S1 in SI). The LiHMDS was the only practical base for the reaction, which could be due to the effective formation of active Cu-amido species. In addition to the toluene, the alkylation successfully occurred in various non-polar solvents such as *ortho*-xylene, *meta*-xylene, *para*-xylene, *para*-cymene, and $^t$Bu-benzene, even though the obtained yields were on the lower side (Table S1 in SI). The alkylation was competitive even with 2.5 equiv each of 1-chlorooctane and LiHMDS (entry 11); however, the yield of **3aa** was slightly reduced by further lowering the amount of 1-chlorooctane and LiHMDS. Notably, the alkylation also proceeded smoothly at 120 °C, providing **3aa** in 62 % yield (entry 12). Interestingly, the

**Table 1**
Optimization of the reaction parameters.[a]

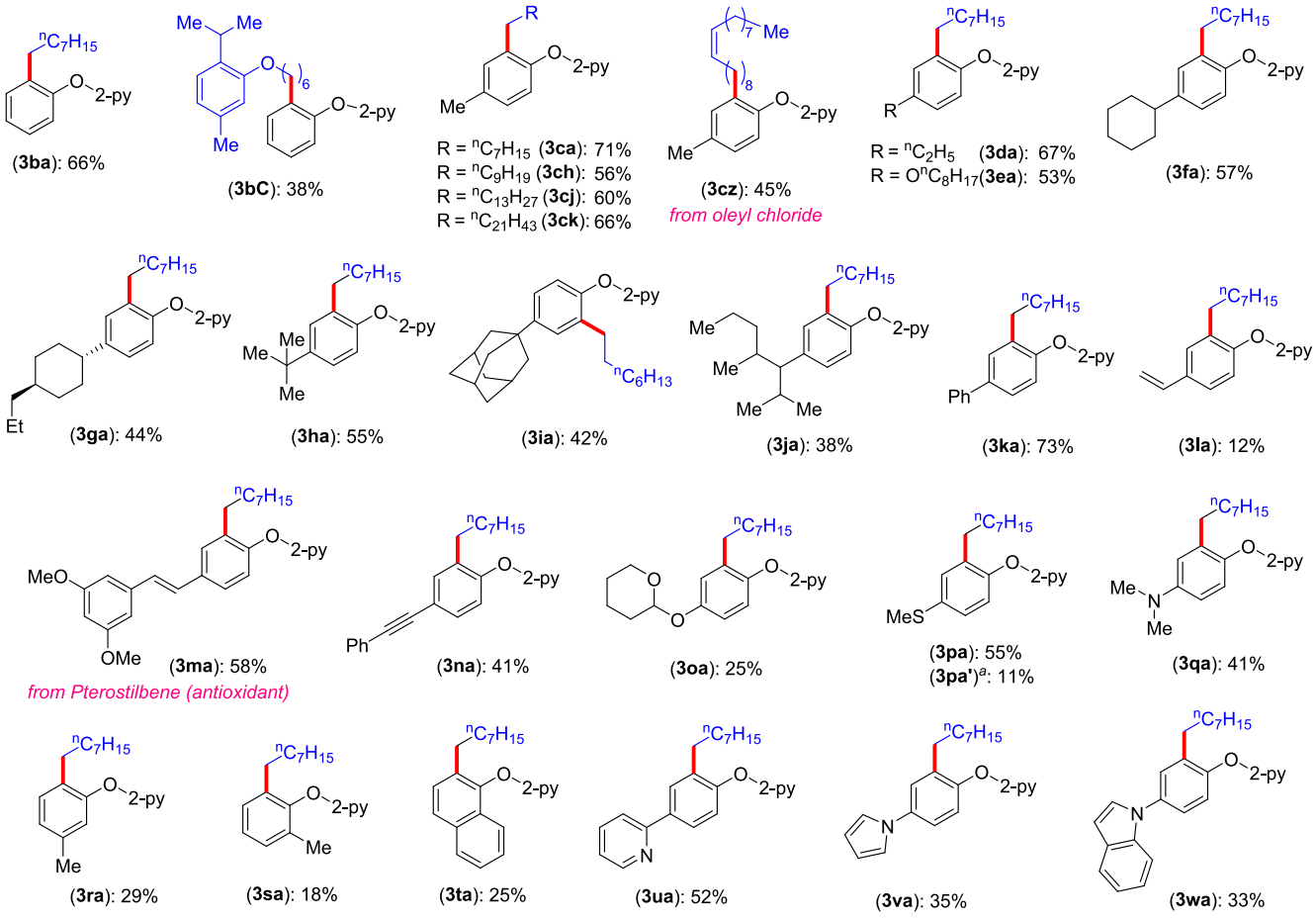



| entry | X | [Cu] | T (°C) | **3aa** (%)[b] | **3aa'** (%)[b] |
|---|---|---|---|---|---|
| 1 | I | $CuCl_2$ | 140 | 31 | – |
| 2 | Br | $CuCl_2$ | 140 | 50 | – |
| 3 | Cl | $CuCl_2$ | 140 | 58 | 15 |
| 4 | Cl | $CuBr_2$ | 140 | 61 | 20 |
| 5 | Cl | $Cu(OAc)_2$ | 140 | 30 | trace |
| 6 | Cl | $Cu(OTf)_2$ | 140 | trace | – |
| 7 | Cl | $Cu(acac)_2$ | 140 | 37 | 10 |
| 8 | Cl | CuCl | 140 | 55 | 9 |
| 9 | Cl | CuBr | 140 | 60 | 27 |
| 10 | Cl | CuI | 140 | 51 | 11 |
| 11[c] | Cl | $CuBr_2$ | 140 | 60 | 20 |
| 12[c] | Cl | $CuBr_2$ | 120 | 62 | 10 |
| **13**[c, d] | **Cl** | **$CuBr_2$** | **120** | **70 (66)** | **11 (7)** |
| 14[c,d,e] | Cl | $CuBr_2$ | 120 | 43 | 4 |
| 15[c,d] | Cl | – | 120 | NR | – |

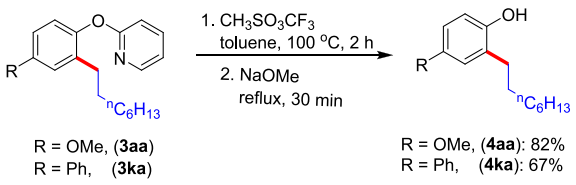
[a] Reaction conditions: **1a** (0.040 g, 0.204 mmol), **2a** (0.089 g, 0.60 mmol), [Cu] precursor (0.02 mmol, 10 mol%), LiHMDS (0.10 g, 0.60 mmol), solvent (0.5 mL) under argon atmosphere.
[b] GC yield using n-dodecane as an internal standard; isolated yield is given in parentheses.
[c] Employing 2.5 equiv of LiHMDS and 2.5 equiv of **2a**.
[d] Reaction performed for 24 h.
[e] 5.0 mol% of $CuBr_2$ was used. NR = No reaction




**Scheme 2.** Substrates scope using various alkyl chlorides. Reaction conditions: **1a** (0.040 g, 0.204 mmol), compound **2** (0.50 mmol), $CuBr_2$ (0.0045 g, 0.02 mmol, 10 mol%), LiHMDS (0.084 g, 0.5 mmol), toluene (0.5 mL). [a]2,2-dialkylated product.




**Scheme 3.** Scope using substituted phenol derivatives. Reaction conditions: **1** (0.204 mmol), 1-chlorooctane **2a** (0.074 g, 0.5 mmol), $CuBr_2$ (0.0045 g, 0.02 mmol, 10 mol%), LiHMDS (0.084 g, 0.5 mmol), toluene (0.5 mL). [a]2,2-dialkylated product.




**Scheme 4.** Deprotection of 2-pyridinyl directing group.

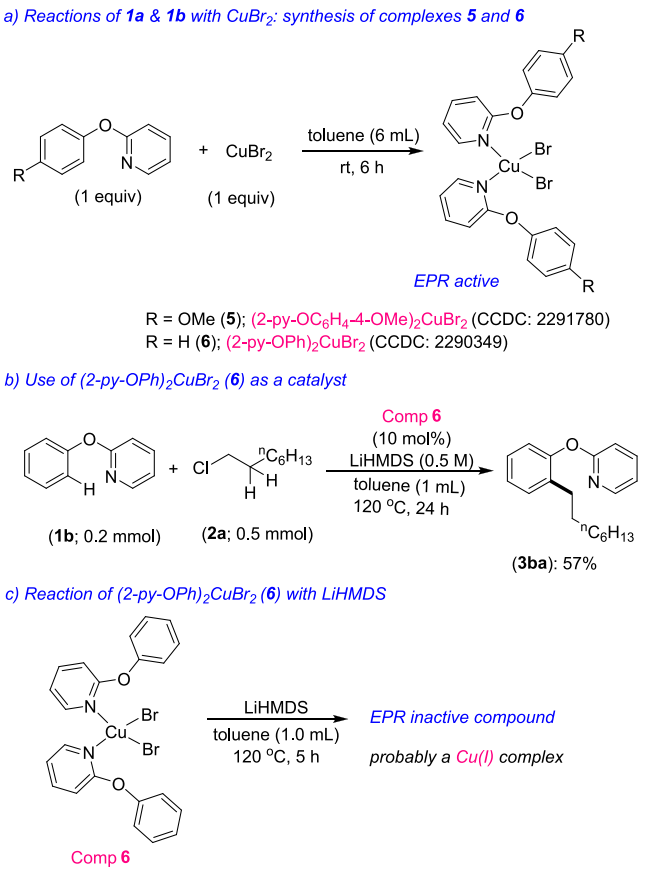
product yield was improved by performing the reaction at 120 °C for 24 h and afforded **3aa** in 66 % yield (entry 13). Further lowering the catalyst loading or reaction temperature led to a decrease in the yield of the alkylation product (entry 14 and Table S1 in SI). The alkylation reaction did not occur without a $CuBr_2$ catalyst (entry 15).

In addition to the 2-pyridinyl as a directing group for the alkylation of 2-(4-methoxyphenoxy)pyridine, other possibilities were investigated (see, sec 4 in the Supporting Information). The use of 2-pyrimidinyl as a directing functionality led to the complete decomposition of the starting compound, 2-(4-methoxyphenoxy)pyrimidine. A substrate without a coordinating atom, such as 1-methoxy-4-phenoxybenzene, did not participate in the alkylation. Similarly, a weak coordination directing functionality like –C(O)$^t$Bu in the substrate 4-methoxyphenyl pivalates was unsuitable for the desired alkylation. All these findings suggest that robust directing nitrogen functionality is essential for the regioselective copper-catalyzed *ortho*-alkylation of phenol derivatives.

### 2.2. Reaction scope

After having optimized reaction parameters for the *ortho*-alkylation of phenoxy-2-pyridine using an inexpensive copper catalyst, we explored the generality of the reaction protocol with various functionalized and unactivated alkyl chlorides (Scheme 2). Initially, the linear alkyl chlorides with different carbon chain lengths were reacted with substrate **1a** to give desired *ortho*-alkylated products **3aa-3ak** in moderate to good yields. In general, the short-chain alkyl chlorides provided slightly higher yields than the long-chain derivatives, probably due to the better solubility of short-chain saturated alkyl partners. The branched $\gamma$-substituted alkyl chloride reacted with low efficacy to afford mono-alkylated product **3al** in 41 %. Similarly, a synthetically important functionality, the silyl group-containing alkylated compound **3am** could be obtained in low yield. The phenyl ring bearing alkyl chloride reacted with **1a** to provide **3an** in 80 % yield. Notably, phenyl ether and phenyl thioether-containing alkyl chlorides were smoothly coupled with **1a** to afford corresponding products **3ao-3av** in good yields. Important heteroarene functionalities, such as pyrrolyl, indolyl, and carbazolyl-containing alkyl chlorides, reacted moderately with **1a** to afford **3aw**, **3ax**, and **3ay**, respectively. Unfortunately, the alkyl chlorides bearing base-sensitive functionalities, such as acetyl, ester, and nitrile, could not be coupled with **1a**. The oleyl chloride, derived from an unsaturated fatty alcohol, could be coupled with a moderate yield (58 %) of **3az**. Interestingly, biologically relevant compounds like nonylphenol (**2A**) and vitamin-E derived (**2B**) alkyl chlorides were compatible with the optimized protocol and provided corresponding coupled products in 60 % and 32 % yields, respectively. The starting precursors remained unreacted wherever the product yields were low. Unfortunately, the secondary alkyl chlorides failed to participate in the reaction. In particular, most primary alkyl chlorides reacted smoothly and provided exclusively mono-alkylated products. The traces of the 2,2′-dialkylated products were obtained in some cases. Nevertheless, the use of diverse, cost-effective, and challenging alkyl chlorides in the regioselective C−H alkylation is notable. Moreover, the copper, being inexpensive and environment friendly, makes the overall alkylation process highly user-friendly.

We examined the scope and limitations of diverse 2-phenoxypyridine derivatives for the alkylation strategy (Scheme 3). The unsubstituted 2-




**Scheme 5.** Synthesis of (2-aryloxy-pyridine)$_2CuBr_2$ complexes and control experiments.

phenoxypyridine showed good reactivity with 1-chlorooctane and provided the *ortho* mono-alkylated product **3ba** in 66 % yield. Moreover, a thymol-derived alkyl chloride coupled with the 2-phenoxypyridine affords 38 % of **3bC**. The 4-methylphenoxypyridine (**1c**) reacted smoothly with various linear alkyl chlorides to provide desired *ortho*-alkylated products **3ca**, **3ch**, **3cj**, and **3ck** in good yields. The oleyl chloride reacted with low efficacy to afford a vital compound **3cz** in a 45 % yield. The ethyl, octyloxy cyclohexyl, cyclohexyl propyl, *tert*-butyl, adamantyl, nonyl, and phenyl-substitutions at the *para* position of the phenol ring were compatible and delivered expected mono-alkylated products **3da-3 ka**. Surprisingly, an alkenyl-substituted phenol gave the alkylated product **3la** in a meager yield, most likely due to the self-polymerization of starting alkenyl phenol. Interestingly, the pterostilbene (**1 m**), phenylacetylene substituted phenol (**1n**), and 4-((tetrahydro-2*H*-pyran-2-yl)oxy)phenol (**1o**) could also deliver the desired alkylated products in low to moderate yields. Moreover, the thiomethyl and *N*,*N*-dimethylamino-substituted 2-phenoxypyridine underwent efficient alkylation to provide a reasonable yield of desired products **3pa** and **3qa**. On the other hand, the *ortho*/*meta*-substituted 2-phenoxypyridine ring afforded a low yield of alkylated products **3ra** and **3sa**, probably due to steric factors. A 2-(naphthalen-1-yloxy)pyridine was also compatible with the alkylation strategy, giving a 24 % yield of alkylated product **3ta**. Furthermore, the 2-phenoxypyridines substituted with heteroarenes such as pyridinyl (**1u**), pyrrolyl (**1v**), and indolinyl (**1w**) at the *para* position participated in the alkylation process with moderate activity. Notably, substrate **1u** delivered alkylation at the *ortho* position to 2-pyO (**3ua**), and a 2-py directed alkylation at the ortho to pyridine was not observed. Unfortunately, the phenols bearing electron-withdrawing as well as halide functionalities could not undergo alkylation with alkyl chloride under the optimized conditions.

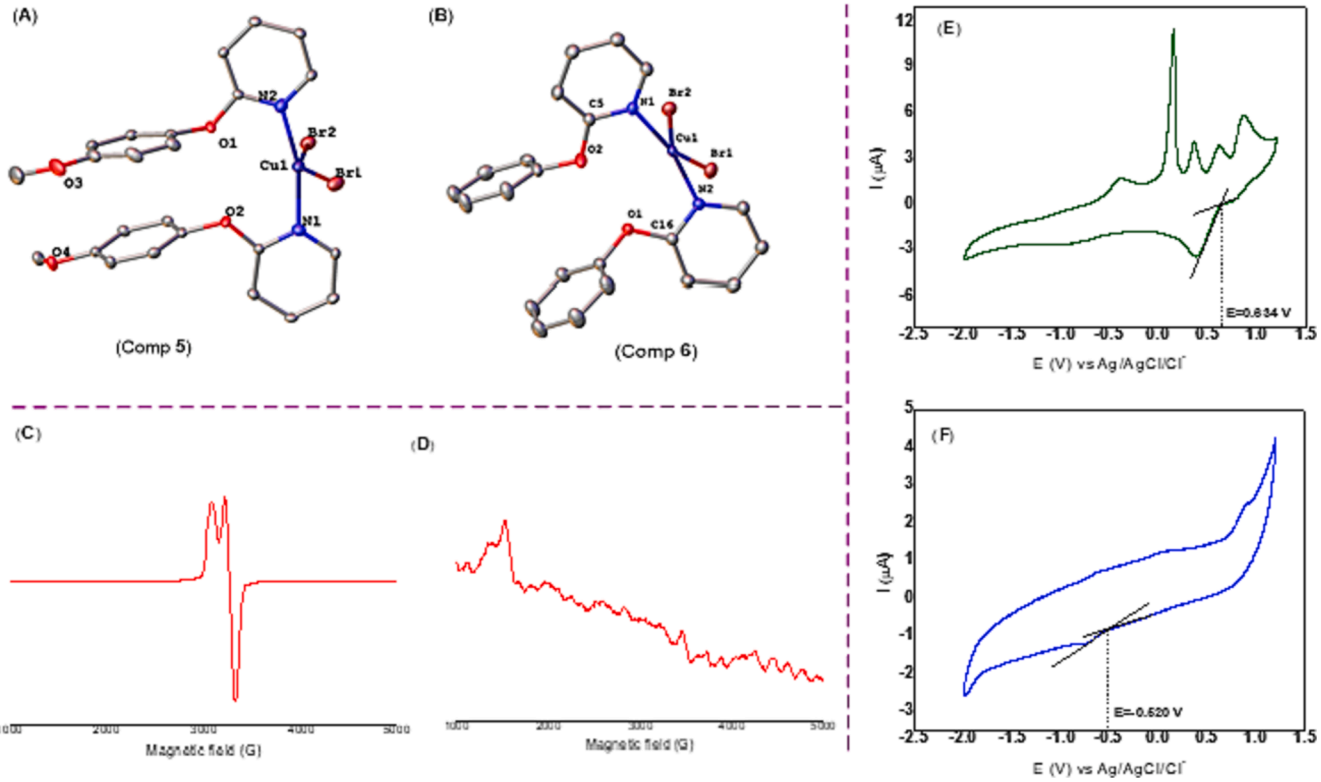



**Fig. 1.** (A) Thermal ellipsoid plot of (2-py-$OC_6H_4$-4-OMe)$_2CuBr_2$ (**5**), (B) Thermal ellipsoid plot of (2-py-OPh)$_2CuBr_2$ (**6**), (C) EPR spectrum of the complex (2-py-OPh)$_2CuBr_2$ (**6**) with the g anisotropy value (g = 2.063), (D) EPR spectrum of (2-py-OPh)$_2CuBr_2$ (**6**) + LiHMDS, (E) Cyclic voltammogram of 1.0 mM (2-py-O-$C_6H_4$-4-OMe)$_2CuBr_2$ (**5**), (F) Cyclic voltammogram of 1.0 mM LiHMDS.

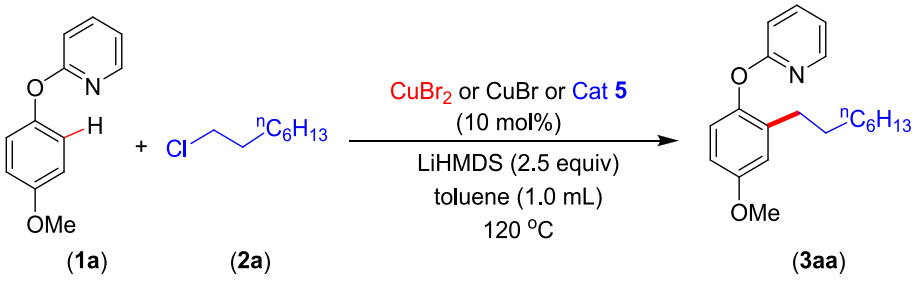
### 2.3. Scale-up and deprotection of the directing group

A gram-scale alkylation of 2-(4-methoxyphenoxy)pyridine (**1a**; 4.97 mmol) with 1-chlorooctane provided 0.89 g (57 %) of product **3aa** under the optimal condition, which highlights the usefulness of the reaction for probable practical use. It is important to note that the 2-pyridinyl group can be readily deprotected to deliver *ortho*-alkylated phenol derivatives in good yields (Scheme 4). Thus, the treatments of **3aa** and **3 ka** with MeOTf/NaOMe provided **4aa** and **4 ka**. The synthesis of such *ortho*-alkylated phenol is challenging to access by other traditional functionalization methods.

### 2.4. Mechanistic aspects

The reaction mechanism was investigated to identify the active Cu-catalytic species and to understand the pathway of the *ortho*-alkylation of phenol. The treatments of compounds **1a** and **1b** with $CuBr_2$ afforded complex (2-py-$OC_6H_4$-4-OMe)$_2CuBr_2$ (**5**) and (2-py-OPh)$_2CuBr_2$ (**6**), respectively (Scheme 5a), which were structurally characterized by the X-ray diffraction study (Fig. 1A and 1B). The complex **6** serves as the catalyst for the alkylation to produce a quantitative yield of **3ba** (Scheme 5b). The EPR analysis of complex **6** shows a peak with g-factor 2.06, suggesting unpaired spin residing in an orbital with significant metal character ($d^9$ system) (Fig. 1C) [56]. Interestingly, treatment of (2-py-OPh)$_2CuBr_2$ (**6**) with LiHMDS resulted in a species that is EPR silent (Scheme 5c, Fig. 1D). Similarly, the EPR measurement of the incomplete catalytic reaction mixture ($CuBr_2$, **1a**, **2a**, and LiHMDS) suggested the absence of an odd-electron species. These findings indicate that the Cu(II) species transformed to Cu(I) intermediate ($d^{10}$ system, EPR silent) in the presence of LiHMDS, which is assumed to be an active catalytic species. Notably, the formation of a di-copper(II) species, wherein two Cu(II) centers antiferromagnetically coupled (could be EPR silent), cannot be ruled out. However, the superior reaction rate with Cu(I) than with the Cu(II) catalyst, and the absence of a 1e- radical species during the reaction (discussed vide infra) do not validate a Cu (II)/Cu(III) pathway. In the cyclic voltammetry analysis, the $E^0$ values for complex **5**, complex **6**, $CuBr_2$, and LiHMDS are found to be 0.634 V (Fig. 1E), 0.601 V, 0.648 V and −0.520 V (Fig. 1F), respectively (For details, see Fig S7 in SI)0.16 As the $E^0$ value of LiHMDS is lower compared to Cu(II) complexes, the electron transfer is feasible from LiHMDS to Cu(II) complexes in generating active Cu(I) complex [57]. To further support these findings, the independent reaction rate was determined using $CuBr_2$ and CuBr as catalysts, wherein the reaction rate with Cu(I)Br was slightly higher (Fig. 2 and Table S3 in SI). The EPR analysis of the reaction mixture also suggested the absence of a probable carbon-centric radical (alkyl radical). Further, radical clock experiments were performed to understand the reactivity pattern of alkyl chloride (Scheme 6a). Thus, the reactions of **1a** with 6-chlorohex-1-ene and (chloromethyl)cyclopropane in the presence of Cu-catalyst under standard conditions provided direct coupled products, **4aD** and **4aE**, respectively. The absence of radical cyclization or radical-induced ring opening supports the non-involvement of an alkyl radical species. Therefore, we assume a plausible two-electron oxidative addition of alkyl chloride to an active Cu(I) species.

Next, we focussed our objectives on the pathway of C−H bond cleavage. The independent rate measurement of alkylation of **1a** and **1a**-$d_4$ with **2a** provided the KIE value of 1.11 (Scheme 6b and Fig S5), indicating that the C−H bond metalation of 2-(4-methoxyphenoxy) pyridine is unlikely the rate-limiting step [58]. Furthermore, a substantial H/D exchange between the **1a**-$d_4$ and **1b** at the *ortho* position of 2-phenoxypyridine was observed (Scheme 6c), suggesting the reversible nature of the C−H bond cleavage followed by metalation with copper. The reaction of **1a** with LiHMDS followed by quenching with $D_2O$ does not show deuterium incorporation at the *ortho*-position of **1a**. This observation ruled out the simple $SN^2$-type reaction involving **1a** and LiHMDS.



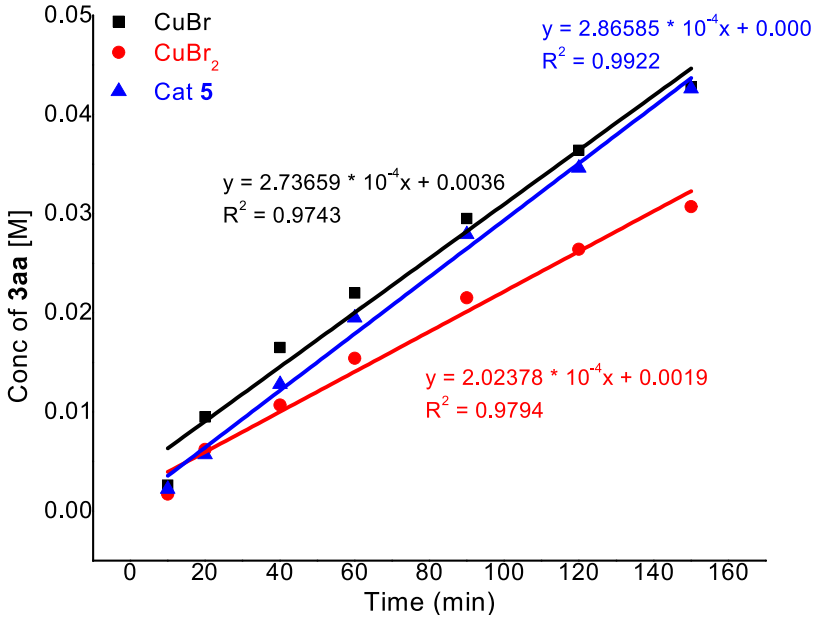
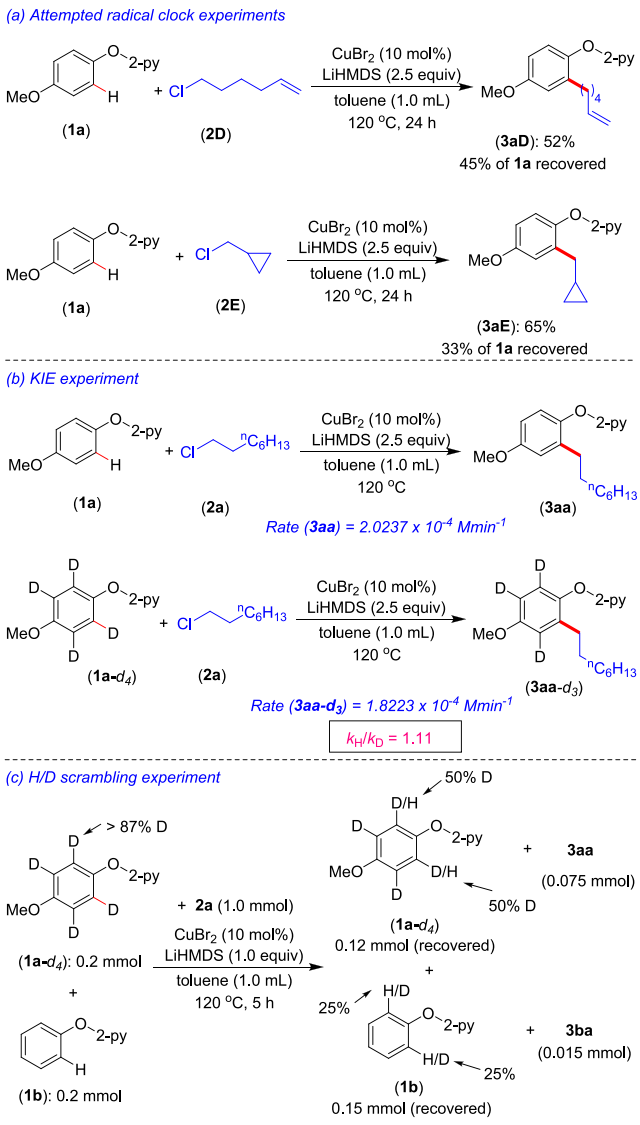




**Fig. 2.** Time-dependent formation of **3aa** using catalysts $CuBr_2$, CuBr and (2-py-$OC_6H_4$-4-OMe)$_2CuBr_2$ (Cat **5**).




**Scheme 6.** Radical clock and deuterium labeling experiments.

We have determined the rate order of alkylation reaction with various reaction components to obtain additional mechanistic information. The reaction is approximately first-order dependent on substrate **1a** (Fig S1), whereas it is fractional order dependent on alkyl chloride (**2a**) and catalyst $CuBr_2$ (Fig S2 and Fig S4). The first-rate order with **1a** suggests the diverse approach of **1a** interaction with $CuBr_2$ (mono-ligated and bis-ligated). The fractional rate order with catalyst $CuBr_2$ is reasonable as the copper species is involved in multiple steps. However, the fractional rate order on alkyl chloride is attributed to the probable involvement of C−Cl bond activation in the rate-limiting step. Notably, the alkylation reaction is negative rate order on the concentration of LiHMDS (Fig S3), due to the excessive side reaction of LiHMDS with alkyl chloride with the increased concentration of base LiHMDS. Further, the independent rate determination of the alkylation reaction using 1-chlorooctane and 1-bromooctane as coupling partners was 2.19 x $10^{-4}$ $Mmin^{-1}$ and 5.18 x $10^{-4}$ $Mmin^{-1}$, respectively (Fig. 3). During the alkylation process, the slow reaction of 1-chlorooctane over the 1-bromooctane supports the assumed rate-limiting oxidative cleavage of the C−Cl bond in alkyl chloride.

### 2.5. Catalytic cycle

We have drawn a tentative catalytic cycle based on our mechanistic findings and literature precedents (Fig. 4) [38,41,59,60]. The 2-py-OAr will first coordinate to Cu(II) species to form $(2\text{-py-OAr})_2Cu(II)X_2$, which will reduce to amido species, $(2\text{-py-OAr})_2Cu(I)X$ [X = halide or N$(SiMe_3)_2$] (**A**) in the presence of LiHMDS [61,62]. The Cu(II) might reduce to Cu(I) via the comproportionation reaction between completely reduced Cu(0) and Cu(II). The Cu(II) complexes were isolated and structurally characterized, and controlled studies and EPR analysis support the formation of Cu(I) species **A**. The absence of a radical intermediate tentatively rules out the Cu(II)/Cu(III) 1e- oxidation pathway [63,64]. The coordinated 2-py-OAr (**1**) then undergoes facile and reversible *ortho* C−H cleavage to deliver metallacycle intermediate **B** [65]. The deuterium labeling study supported the reversibility of this step, and the formation of intermediate **B** was established by MALDI-TOF analysis. The low-valent and electron-rich Cu(I) species **B** would facilitate the oxidative addition of alkyl chloride in the rate-limiting step to produce Cu(III) intermediate **C**. The radical clock experiments and EPR analysis ruled out a one-electron radical path and strongly support the 2e oxidative addition of alkyl chloride. Moreover, the controlled experiments and kinetic analysis endorsed the oxidative addition as the rate-limiting step. Upon reductive elimination of product **3** from Cu(III) species **C**, the active catalyst **A** will be regenerated in the presence of incoming substrate **1**.

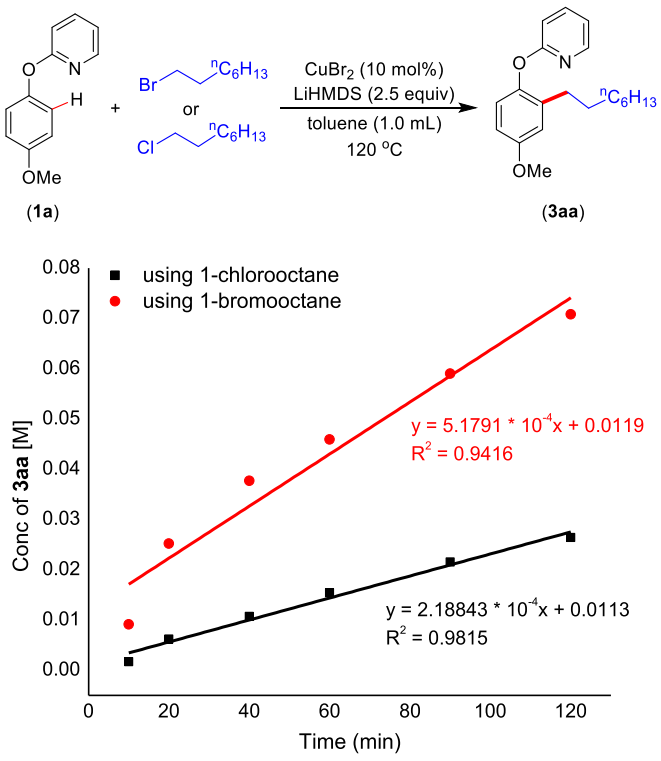



**Fig. 3.** Time-dependent formation of **3aa** using 1-chlorooctane and 1-bromooctane.

## 3. Conclusions

In summary, we have developed an efficient copper-catalyzed method for the regioselective coupling of unactivated alkyl chlorides with the *ortho* C−H bond of phenol derivatives. The employment of inexpensive, abundant, and non-toxic copper catalysts and widely available unactivated alkyl chlorides make this alkylation protocol highly viable. The reaction is compatible with a variety of simple and functionalized alkyl chlorides as well as with a range of phenol derivatives. The use of LiHMDS base played a critical role in the success of alkylation by generating a Cu-amido complex during the reaction. Detailed mechanistic investigation of the alkylation allowed us to draw a

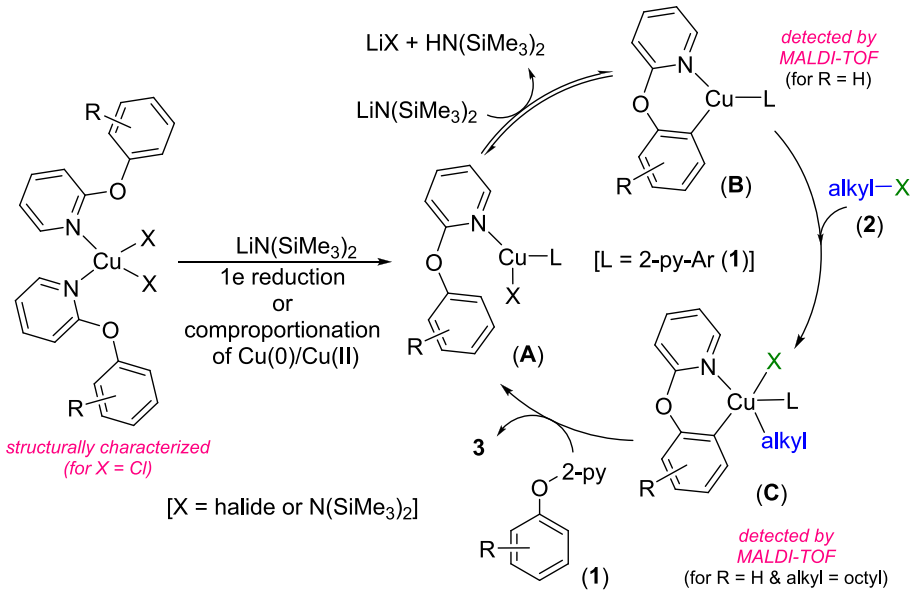



**Fig. 4.** Plausible pathway for the Cu-catalyzed alkylation.

catalytic path that follows the rate-limiting 2e oxidative addition of alkyl chloride. Controlled experiments, kinetic analyses, and EPR studies revealed the participation of a Cu(I) active species, therefore supporting a Cu(I)/Cu(III) pathway. We trust that the simplicity and uniqueness of the demonstrated sustainable copper-catalyzed protocol would contribute significantly to the investigation and development of many other such processes.

## CRediT authorship contribution statement

**Suryadev K. Verma:** Conceptualization, Data curation, Formal analysis, Methodology. **Benudhar Punji:** Conceptualization, Funding acquisition, Writing – original draft, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcat.2024.115351.

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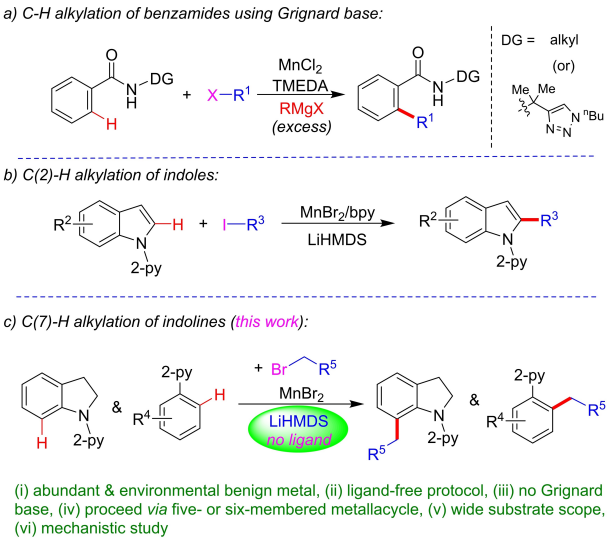
# Manganese-Catalyzed C(sp$^2$)–H Alkylation of Indolines and Arenes with Unactivated Alkyl Bromides

Suryadev K. Verma[a, b] and Benudhar Punji*[a, b]

**Abstract:** Selective C(sp$^2$)–H bond alkylation of indoline, carbazole and (2-pyridinyl)arenes with unactivated alkyl bromides is achieved using $MnBr_2$ catalyst in the absence of an external ligand. The alkylation uses a simple LiHMDS base and avoids the necessity of Grignard reagent, unlike other Mn-catalyzed C–H functionalization. This reaction proceeded either through a five- or a less-favored six-membered metallacycle, and tolerated diverse functionalities, including alkenyl, alkynyl, silyl, aryl ether, pyrrolyl, indolyl, carbazolyl and alkyl bearing fatty alcohol and polycyclic-steroid moieties. Alkylation follows a single electron transfer (SET) pathway involving 1e oxidative addition of alkyl bromide and a rate-limiting C–H metalation.

## Introduction

Manganese complexes as catalysts are highly appealing in building molecular architecture through C–C bond formation,[1] considering the ease of availability, inexpensiveness and distinct characteristic of Mn-metal. In recent years, molecular construction *via* the ubiquitous C–H bond activation and functionalization has given special consideration.[2] Therefore, the relatively challenging C–H transformation by employing the 3$^{rd}$ most abundant transition metal, manganese, would be extremely beneficial. Notably, the manganese catalysts in C–H functionalization is under-utilized compared to other metal catalysts,[3] though it has a huge potential in environmentally benign and sustainable molecular synthesis.[4] The groups of Kuninobu and Takai,[5] Wang,[6] Ackermann,[7] Glorius,[8] and others[9] have independently established the Mn-catalysis in C–H functionalization, wherein an expensive Mn(I) {*i.e.*, $MnBr(CO)_5$} is used, and the coupling partners are mostly restricted to unsaturated species bearing polar multiple bonds. Particularly, Mn-catalysis in the coupling of C–H bonds with organic halides employing an easily available $Mn(II)X_2$ salt is limited. Ackermann established the C–H alkylation of benzamides with alkyl halides using $MnCl_2$/TMEDA, where an excess of Grignard reagent is utilized that might limit the practical synthesis (Scheme 1a).[10] Therefore, developing Mn-catalyzed C–H functionalization methodologies with organic halides using a simple inorganic base is highly attractive. In that direction, recently, we demonstrated the C(2)–H alkylation of indoles with alkyl iodides using a user-friendly LiHMDS, without the Grignard reagent (Scheme 1b).[11]




**Scheme 1.** Mn(II)-catalyzed C–H alkylation strategies.

Selective C–H alkylation of heteroarenes, particularly that of indoles and indolines, is significant considering their biological and pharmacological importance.[12] In particular, most functionalization in indoles is directed towards the pyrrole-ring (C2 and C3),[13] whereas C(7)–H functionalization of benzene-ring in indole/indoline is relatively scant.[14] Very recently, we have shown the C(7)–H alkylation of indolines using a $Fe(OTf)_2$/xantphos catalyst.[15] Though limited reports are established for the C(7)–H functionalization of indoles and indolines, the earth-abundant manganese has never been explored for the benzenoid-ring C–H functionalization. Thus, a simple and user-friendly approach for the C(7)–H alkylation of indolines, without employing a phosphine ligand or Grignard reagent, under low-cost Mn(II) catalysis would be extremely profitable. With this assumption and a step towards sustainable synthesis, herein, we disclosed the ligandless $MnBr_2$-catalyzed C-7 alkylation of indolines and related arenes with unactivated alkyl bromides employing a LiHMDS base (Scheme 1c).

[a] *S. K. Verma, Prof. Dr. B. Punji*
*Organometallic Synthesis and Catalysis Group, Organic Chemistry Division, CSIR-National Chemical Laboratory (CSIR–NCL)*
*Dr. Homi Bhabha Road, Pune 411 008 (India)*
*E-mail: b.punji@ncl.res.in*

[b] *S. K. Verma, Prof. Dr. B. Punji*
*Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201 002 (India)*

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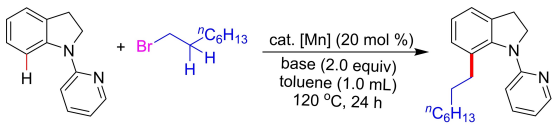
## Results and Discussion

**Reaction optimization**. The demonstrated Mn-catalyzed C-2 alkylation of indoles with alkyl iodides proceeds through a favorable five-membered metallacycle (Scheme 1b);[11] whereas the C-7 alkylation of indoline (**1 a**) would occur *via* a less favored six-membered metallacycle intermediate (Scheme 1c). In searching for a more facile and straightforward Mn-catalyst for the C-7 alkylation of indoline, we initiated the reaction of **1 a** with different 1-octyl halides using 10 mol% of $MnBr_2$ at 120 °C (Table 1 and Table S1 in the SI). Among the coupling partners, the use of 1-octyl bromide provided a 52% yield of **3 aa** (Table 1, entry 1), whereas 1-octyl chloride afforded 22% and the 1-octyl iodide gave **3 aa** in 45% yield, with a substantial side reaction of LiHMDS with 1-octyl iodide (see Table S1 in SI). Using the 1-octyl bromide and $MnBr_2$ catalyst, the employment of nitrogen- or phosphine-based ligands, bpy, phen, xantphos, dppm and dppf did not help overall reaction performance that could be due to the undesired stabilization of Mn-species (entries 2–6 and Table S1, in SI). Interestingly, with an increase in the $MnBr_2$ loading to 20 mol%, the reaction provided **3 aa** in 70% yield with a significant reduction in undesired reaction (entry 7). The inspection of other Mn(II) or Mn(I) precursors like $MnCl_2$, $Mn(OAc)_2$ and $Mn(CO)_5Br$ as catalysts afforded a slightly low yield of **3 aa** (entries 8–10). The inorganic bases such as $LiO^tBu$, $NaO^tBu$, $KO^tBu$ and $Li_2CO_3$ were ineffective, whereas a significant decomposition of **1 a** was observed in the presence of NaHMDS (Table S1 in SI). We assume that the employment of LiHMDS generates an active Mn-amido species that initiates the alkylation, thus, the use Grignard base is not necessary like other Mn-catalyzed C–H functionalization.[10] As the LiHMDS is needed to activate $MnX_2$ catalyst, and involves in the C–H activation process, more than a stoichiometric amount of base was used. The alkylation in *ortho*-xylene, *para*-xylene, *meta*-xylene or $^t$Bu-benzene provided a moderate yield of **3 aa** (entries 12–15). The alkylation proceeded efficiently at 120 °C; however, further lowering in reaction temperature (100 °C) or reaction time led to a low yield. The employment of $MnBr_2$ catalyst was essential, without which the alkylation did not occur (entry 16). The screening of various *N*-substitutions (directing group) suggests that the 2-pyridinyl is an ideal group. In contrast, the indoline having *N*-2-pyrimidinyl or *N*-pivaloyl decomposes under the reaction conditions, and the *N*-Me-indoline did not participate in the reaction (Sec 3 of SI).

**Table 1.** Optimization of reaction parameters.[a]

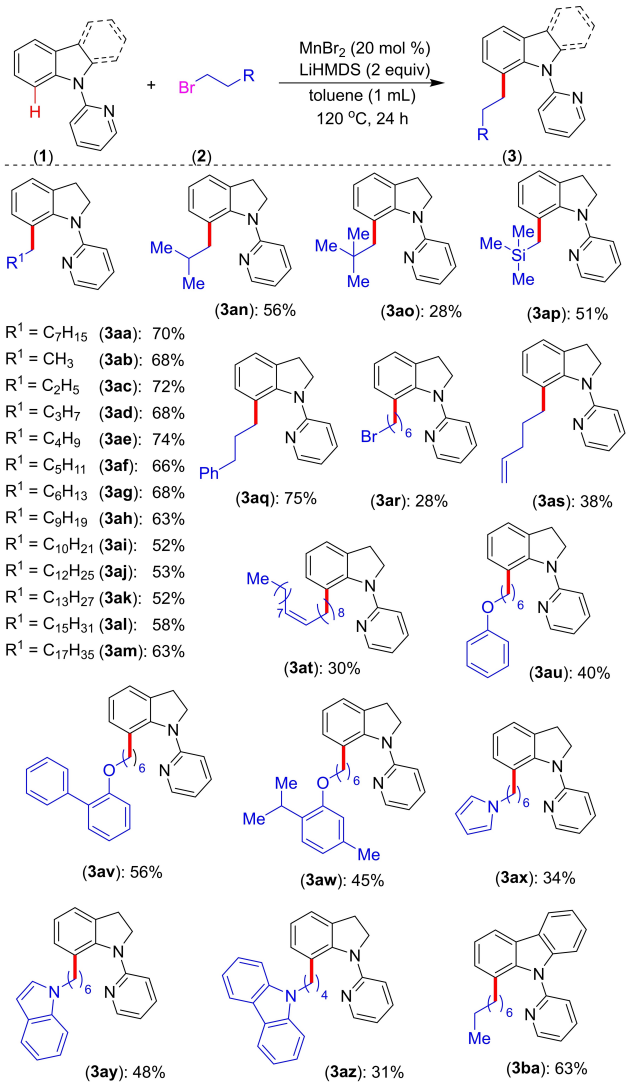



1a 2a 3aa

| entry | [Mn] | base | solvent | **3 aa** [%][b] |
|---|---|---|---|---|
| 1 | $MnBr_2$ | LiHMDS | toluene | 52 |
| 2 | $MnBr_2$/bpy | LiHMDS | toluene | 32 |
| 3 | $MnBr_2$/phen | LiHMDS | toluene | 29 |
| 4 | $MnBr_2$/xantphos | LiHMDS | toluene | 14 |
| 5 | $MnBr_2$/dppm | LiHMDS | toluene | 24 |
| 6 | $MnBr_2$/dppf | LiHMDS | toluene | 15 |
| 7 | $MnBr_2$ | LiHMDS | toluene | 72 (70) |
| 8 | $MnCl_2$ | LiHMDS | toluene | 60 |
| 9 | $Mn(OAc)_2$ | LiHMDS | toluene | 52 |
| 10 | $MnBr(CO)_5$ | LiHMDS | toluene | 18 |
| 11 | $MnBr_2$ | $LiO^tBu$ | toluene | trace |
| 12 | $MnBr_2$ | LiHMDS | *o*-xylene | 53 |
| 13 | $MnBr_2$ | LiHMDS | *m*-xylene | 44 |
| 14 | $MnBr_2$ | LiHMDS | *p*-xylene | 45 |
| 15 | $MnBr_2$ | LiHMDS | $^{tBu}$benzene | 61 |
| 16 | – | LiHMDS | toluene | NR |

[a] Conditions: **1 a** (0.040 g, 0.204 mmol), **2 a** (0.40 mmol), base (0.40 mmol). Entries 1–6: 10 mol% $MnBr_2$. Entries 7–15: 20 mol% $MnBr_2$. [b] GC yield using *n*-dodecane as internal standard; isolated yield is given in parentheses. NR = No reaction.

**Scope for alkylation**. After a comprehensive screening of reaction parameters, the ligand-free $MnBr_2$-catalyzed protocol was applied to coupling various unactivated primary alkyl bromides with C(7)–H of indoline (Scheme 2). The linear alkyl bromides with varying chain lengths were efficiently coupled with **1 a** to give C-7 alkylated compounds **3 aa**–**3 am** in moderate to good yields. Generally, short-chain length alkyl



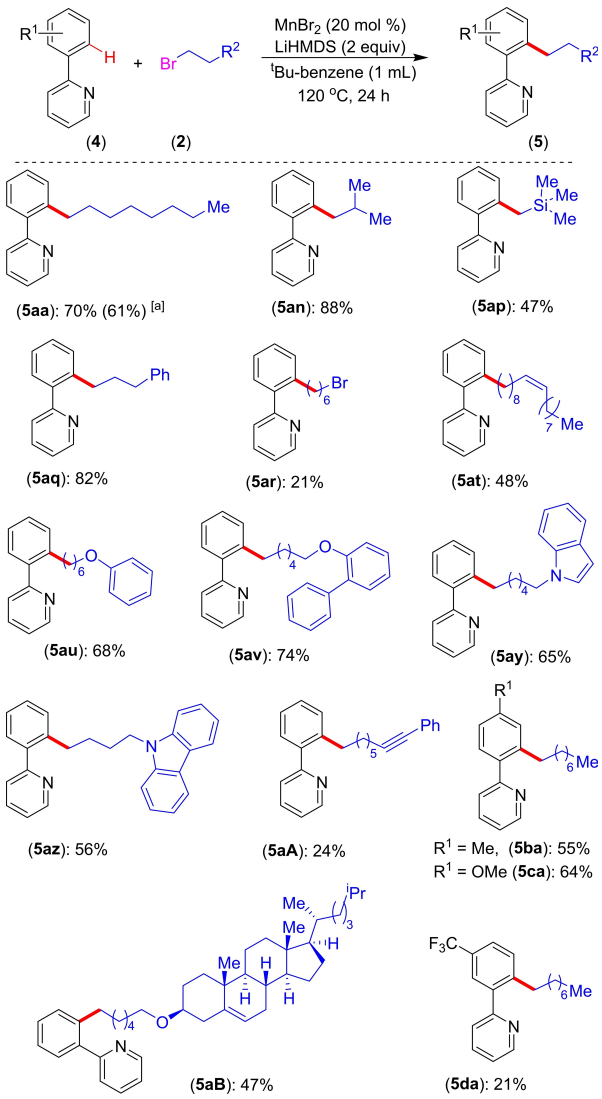

**Scheme 2.** C-7 alkylation of indoline. Conditions: **1** (0.20 mmol), **2** (0.40 mmol), LiHMDS (0.067 g, 0.40 mmol), $MnBr_2$ (0.0086 g, 0.04 mmol).

bromides were more productive than the long-chain alkyl bromides, which could be due to the better solubility of the former. The isobutyl bromide reacted actively to provide **3 an** in 56% yield, whereas the sterically demanding neopentyl bromide reacted at a low pace to give **3 ao**. In particular, silyl- and aryl-substituted alkyl bromides were smoothly reacted with 2-pyridinyl indoline to provide **3 ap** and **3 aq**. The 1,6-dibromohexane as a coupling partner selectively reacted to give mono-bromo alkylated **3 ar**, albeit in low yield. Internal as well as terminal alkenyl functionalities were well tolerated to provide **3 as** and **3 at**. Important functionalities, such as phenyl ether (**3 au**, **3 av**), thymol (**3 aw**), and heteroarenes like pyrrolyl (**3 ax**), indolyl (**3 ay**) and carbazolyl (**3 az**) were well tolerated. Unfortunately, the alkyl halides containing base-sensitive functionalities such as acetyl, ester and nitrile as well as bulky secondary and tertiary alkyl could not participate in the reaction. Similarly, the electrophile-containing sulfur atom failed to react, attributed to the catalyst poisoning due to a sulfur moiety. Notably, the 2-pyridinyl carbazole reacted with 1-octyl bromide to afford selective mono-alkylated **3 ba** in 63% yield, even though two C($sp^2$)–H bonds were susceptible for the alkylation. Unfortunately, the attempted C-7 alkylation of 2-methyl-*N*-pyridinyl indole did not occur, which is expected to proceed *via* a similar six-membered metallacycle.

The alkylation protocol was extended to the C–H coupling of (2-pyridinyl)arenes with various alkyl bromides in *tert*-butylbenzene (Scheme 3). The linear and branched alkyl bromides are efficiently coupled to deliver **5 aa**, **5 an**, **5 ap**, **5 aq** in good yields. The synthetically useful bromo, alkenyl and alkynyl functionalities were tolerated (**5 ar**, **5 at**, **5 aA**). Notably, the phenyl ethers and heteroarene-substituted alkyl bromides conveniently coupled with 2-phenyl pyridine and afforded good yields (**5 au**, **5 av**, **5 ay**, **5 az**), which were less effective with the 2-pyridinyl indoline. Cholesterol-derived alkyl bromide reacted moderately with 2-phenyl pyridine affording a satisfactory yield of **5 aB**. In addition, the substituted 2-pyridinyl arenes underwent alkylation and gave a moderate yield of **5 ba**–**5 ca**. Strikingly, selective mono-alkylation was observed in all the (2-pyridinyl)arenes, and the dialkylation was not detected.

The scaling-up of the Mn-catalyzed alkylation of indoline was demonstrated by reacting 0.7 g of **1 a** with 1-bromooctane, wherein **3 aa** was isolated in 62% yield. Though the yield obtained was slightly on the low side than the small-scale reaction, the survey highlights the usefulness of the reaction.

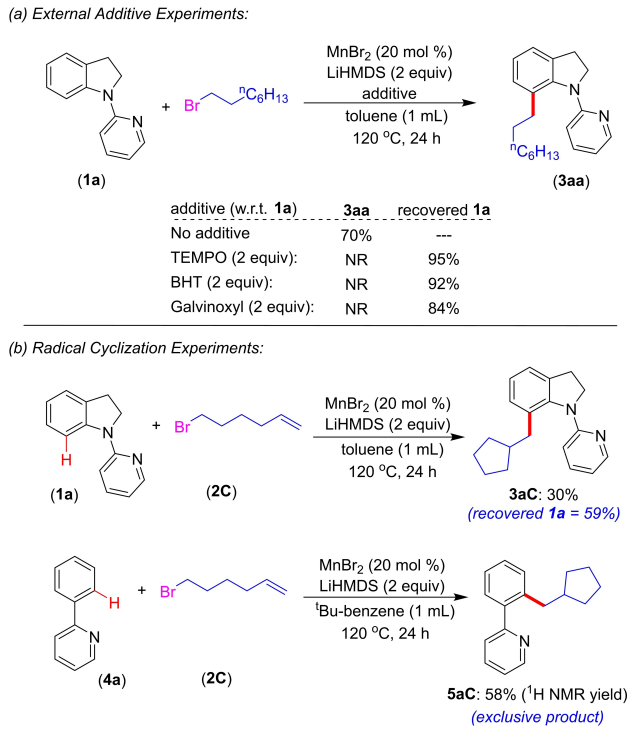
**Mechanistic study**. The alkylation in the presence of mercury (500 equiv. w.r.t. Mn) afforded a reduced yield of **3 aa** (48%), suggesting the involvement of a homogeneous active catalytic species though a partial formation of heterogeneous species cannot be ruled out. The attempted alkylation of **1 a** was completely quenched in the presence of radical scavengers, TEMPO, galvinoxyl or BHT, wherein the compound **1 a** was recovered in 95%, 84% and 92%, respectively (Scheme 4a). These findings highlighted the involvement of a radical species during the alkylation.[11,16] Furthermore, the exclusive rearranged/cyclized products **3 aC** and **5 aC** were obtained in the reaction of 6-brormohex-1-ene with **1 a** and **4 a**, respectively (Scheme 4b). All this experimental evidence suggested the




**Scheme 3.** Alkylation of (2-pyridinyl)arenes. Conditions: **4** (0.20 mmol), **2** (0.40 mmol), LiHMDS (0.067 g, 0.40 mmol), $MnBr_2$ (0.0086 g, 0.04 mmol).[a] Using toluene.

participation of an alkyl radical intermediate during the alkylation.[11,13c–d]

The kinetic analysis of alkylation indicates the absence of an induction period (Figure 1), which supports the direct involvement of Mn(II) active species. Independent rate measurements for the alkylation of **1 a** and **1 a**-[7-D] with **2 a** showed a substantial isotope effect (KIE = 4.0), suggesting the probable involvement of a rate-limiting C–H activation.[17] Moreover, the treatment of indoline **1 a** with LiHMDS under standard reaction conditions followed by quenching with $CD_3OD$ or $D_2O$, did not incorporate deuterium at the C7 position of **1 a**. This finding clearly indicates that the LiHMDS does not act on substrate directly in the absence of Mn. The reaction rates with the different catalyst concentrations suggest a positive rate-order (Figure 2), highlighting the involvement of catalyst in multiple ways during the alkylation.




**Scheme 4.** Mechanistic experiments.

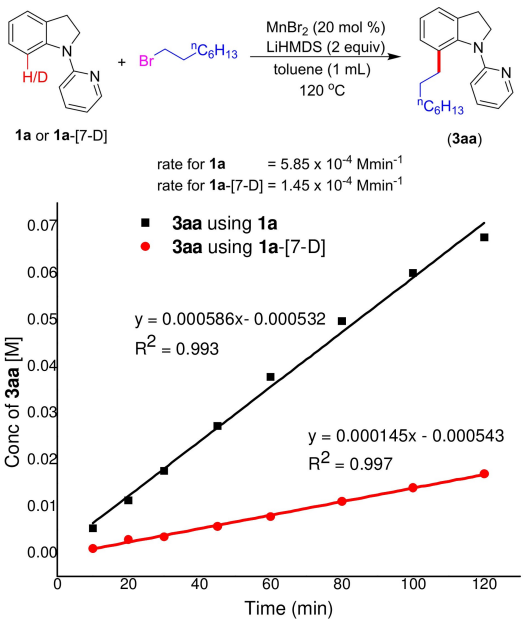



**Figure 1.** Time-dependent formation of **3aa** using substrates **1a** and **1a**-[7-D].

Based on our study and precedents,[10a,11] two tentative catalytic cycles were proposed (Path I and Path II; Figure 3). The reaction would start by $MnBr_2$ or Mn(II)-amido species that reacts with C(7)–H of **1a** in the rate-limiting step to form intermediate **A**. The Mn-intermediate triggers the halide atom transfer (HAT) of **2**, leading to species **B** and alkyl radical (Path I). Controlled and radical clock studies have proved the involve-

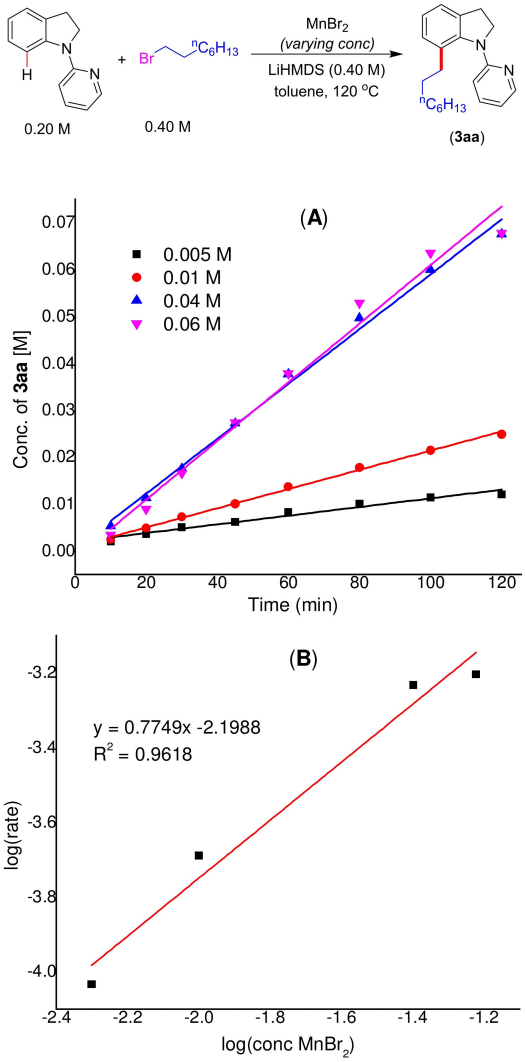



**Figure 2.** (A) Time-dependent formation of **3aa** at different initial concentrations of $MnBr_2$, (B) Plot of log(rate) *versus* log(conc $MnBr_2$).

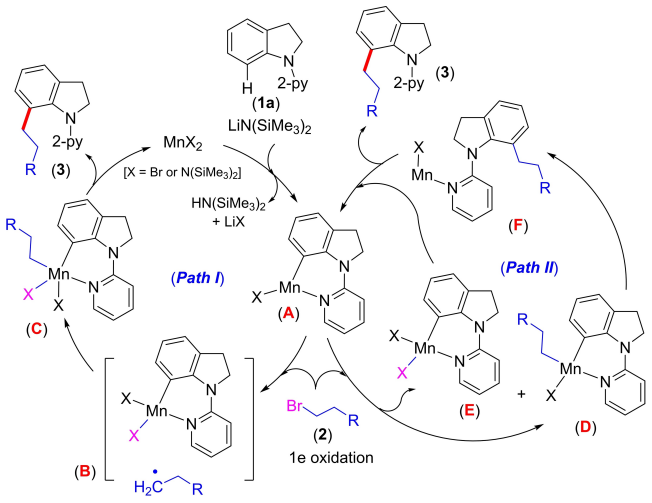



**Figure 3.** Plausible catalytic cycles.

ment of alkyl radicals. Radical recombination followed by the reductive elimination from **C** would result in the formation of **3**. Alternately, two molecules of intermediate **A** can participate in homolytic cleavage of the C–Br bond in **2** to generate Mn(III) intermediates **D** and **E** (Path II). Considering the positive fractional rate order of alkylation on catalyst concentrations, this pathway seems more feasible. The reductive elimination of **3** would generate the product (or substrate) coordinated Mn(I) complex **F**. Upon releasing **3**; the Mn(I) can undergo comproportionation with **E** to form active species **A** and $MnX_2$, both of which can re-enter the catalytic cycle.

## Conclusion

In summary, we have disclosed a ligand-free and cost-effective Mn(II)-catalyzed chemo- and regioselective method for the C($sp^2$)–H bond alkylation of indolines and (2-pyridinyl)arenes. This protocol provided a wide range of alkylated products containing alkenyl, alkynyl, silyl, ethers and heteroaromatic functionalities, including fatty alcohol and cholesterol. Alkylation proceeded either *via* a five-membered or a six-membered metallacycle leading to the desired products. The use of a LiHMDS base is very crucial, as it can produce an active Mn-amido species. A preliminary mechanistic study suggests that the alkylation proceeds through a single electron transfer (SET) process involving the rate-limiting C–H bond metalation of indoline.

## Experimental Section

### Representative procedure A: synthesis of 7-octyl-1-(pyridin-2-yl)indoline (3 aa)

To a flame-dried screw-cap tube equipped with magnetic stir bar were introduced 1-(pyridin-2-yl)indoline (**1 a**; 0.040 g, 0.204 mmol), 1-bromooctane (**2 a**; 0.077 g, 0.40 mmol), $MnBr_2$ (0.0086 g, 0.04 mmol, 20.0 mol%), and LiHMDS (0.067 g, 0.40 mmol) inside the glove box. To the above mixture in the tube was added toluene (1.0 mL). The resultant reaction mixture in the tube was immersed in a preheated oil bath at 120 °C and stirred for 24 h. At ambient temperature, the reaction mixture was quenched with distilled $H_2O$ (10.0 mL) and the crude product was extracted with EtOAc (15 mL × 3). The combined organic extract was dried over $Na_2SO_4$ and the volatiles were evaporated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) to yield **3 aa** (0.044 g, 70%) as a light yellow liquid. $^1$H-NMR (500 MHz, $CDCl_3$): $\delta = 8.30$ (d, $J = 4.9$ Hz, 1H, Ar–H), 7.47 (t, $J = 7.9$ Hz, 1H, Ar–H), 7.11 (d, $J = 7.1$ Hz, 1H, Ar–H), 7.07 (d, $J = 7.6$ Hz, 1H, Ar–H), 6.97 (vt, $J = 7.4$ Hz, 1H, Ar–H), 6.77 (vt, $J = 5.5$ Hz, 1H, Ar–H), 6.64 (d, $J = 8.4$ Hz, 1H, Ar–H), 4.30 (t, $J = 7.8$ Hz, 2H, $CH_2$), 3.03 (t, $J = 7.8$ Hz, 2H, $CH_2$), 2.39 (t, $J = 7.5$ Hz, 2H, $CH_2$), 1.53-1.49 (m, 2H, $CH_2$), 1.25–1.16 (m, 10H, $CH_2$), 0.86 (t, $J = 6.8$ Hz, 3H, $CH_3$). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): $\delta = 158.4$ ($C_q$), 147.9 (CH), 143.7 ($C_q$), 137.2 (CH), 135.0 ($C_q$), 131.2 ($C_q$), 128.2 (CH), 123.7 (CH), 122.5 (CH), 115.5 (CH), 111.5 (CH), 55.2 ($CH_2$), 33.1 ($CH_2$), 32.0 ($CH_2$), 30.1 ($CH_2$), 29.6 ($CH_2$), 29.5 ($CH_2$), 29.3 (2 C, $CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{21}H_{28}N_2 + H^+$ $[M+H]^+$ 309.2325; Found 309.2325.

### Representative procedure B: synthesis of 2-(2-octylphenyl)pyridine (5 aa)

To a flame-dried screw-cap tube equipped with magnetic stir bar were introduced 2-phenylpyridine (**4 a**; 0.030 g, 0.20 mmol), 1-bromooctane (**2 a**; 0.077 g, 0.40 mmol), $MnBr_2$ (0.0086 g, 0.04 mmol, 20.0 mol%), and LiHMDS (0.067 g, 0.40 mmol) inside the glove box. To the above mixture in the tube was added *tert*-butyl benzene (1.0 mL). The resultant reaction mixture in the tube was immersed in a preheated oil bath at 120 °C and stirred for 24 h. At ambient temperature, the reaction mixture was quenched with distilled $H_2O$ (10.0 mL) and the crude product was extracted with EtOAc (15 mL × 3). The combined organic extract was dried over $Na_2SO_4$ and the volatiles were evaporated *in vacuo*. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) to yield **5 aa** (0.038 g, 70%) as a light yellow liquid. $^1$H-NMR (400 MHz, $CDCl_3$): $\delta = 8.69$ (ddd, $J = 4.9$, 1.9, 0.9 Hz, 1H, Ar–H), 7.74 (td, $J = 7.8$, 1.9 Hz, 1H, Ar–H), 7.38 (dt, $J = 7.9$, 1.0 Hz, 1H, Ar–H), 7.35–7.23 (m, 5H, Ar–H), 2.69 (t, $J = 7.9$ Hz, 2H, $CH_2$), 1.48–1.41 (m, 2H, $CH_2$), 1.27–1.17 (m, 10H, $CH_2$), 0.86 (t, $J = 7.1$ Hz, 3H, $CH_3$). $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): $\delta = 160.5$ ($C_q$), 149.3 (CH), 141,0 ($C_q$), 140.5 ($C_q$), 136.2 (CH), 129.9 (2C, CH), 128.4 (CH), 125.9 (CH), 124.3 (CH), 121.8 (CH), 33.1 ($CH_2$), 32.0 ($CH_2$), 31.4 ($CH_2$), 29.6 ($CH_2$), 29.4 ($CH_2$), 29.3 ($CH_2$), 22.8 ($CH_2$), 14.3 ($CH_3$). HRMS (ESI): *m/z* Calcd for $C_{19}H_{25}N + H^+$ $[M+H]^+$ 268.2060; Found 268.2056.

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## Conflict of Interest

*The authors declare no conflict of interest.*

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** alkylation · C–H activation · indoline · ligand-free · manganese

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