# NON-PRECIOUS METAL-CATALYZED SUSTAINABLE SYNTHESIS OF C-C AND C-N BONDS

**Ph.D. THESIS**

*by*

**JAGADISH DAS**

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**INDIAN INSTITUTE OF TECHNOLOGY ROORKEE**
**ROORKEE - 247 667 (INDIA)**
**JUNE, 2019**

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**A THESIS**

***Submitted in partial fulfilment of the requirements for the award of the degree***

*of*

**DOCTOR OF PHILOSOPHY**

*in*

**CHEMISTRY**

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# INDIAN INSTITUTE OF TECHNOLOGY ROORKEE
# ROORKEE

## CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled **"NON-PRECIOUS METAL-CATALYZED SUSTAINABLE SYNTHESIS OF C-C AND C-N BONDS"** in partial fulfilment of the requirements for the award of the Degree of Doctor of Philosophy and submitted in the Department of Chemistry of the Indian Institute of Technology Roorkee, Roorkee is an authentic record of my own work carried out during a period from December, 2015 to June, 2019 under the supervision of Dr. Debasis Banerjee, Assistant Professor, Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee.

The matter presented in the thesis has not been submitted by me for the award of any other degree of this or any other Institution.

**Signature of the Candidate**

This is to certify that the above statement made by the candidate is correct to the best of my knowledge.

**Signature of the Supervisor**

The Ph.D. Viva-Voce Examination of **Mr. Jagadish Das**, Research Scholar, has been held on **06-09-2019.**

**Chairperson, SRC** **Signature of External Examiner**

This is to certify that the student has made all the corrections in the thesis.

**Signature of Supervisor** **Head of the Department**

Dated: _____

“DEDICATED

TO

MY FAMILY”

# ***ACKNOWLEDGEMENTS***

All the way through the journey of my PhD several peoples helped and motivated me in carrying out my research work smoothly and I take this opportunity to express my sincere gratitude and appreciation to all of them.

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Thanks to God for this journey…

***Jagadish Das***

# ***Abstract/Synopsis***

This thesis contains the research work carried out during the Ph.D. tenure and is entitled as "**Non-precious Metal-Catalyzed Sustainable Synthesis of C-C and C-N Bonds**". The thesis has been divided into the following five chapters:

**CHAPTER-1**: Transition-metal catalyzed synthesis of C-C and C-N bonds: A Concise Literature Survey.

**CHAPTER-2:** Nickel-catalyzed direct *N*-alkylation of amides with alcohols.

**CHAPTER-3:** Nickel-catalyzed $\alpha$-alkylation of ketones with alcohols.

**CHAPTER-4:** Nickel-catalyzed alkylation of methyl *N*-heteroaromatics with alcohols.

**CHAPTER-5: Section-A:** Nickel-catalyzed dehydrogenative alkylation of methyl *N*-heteroaromatics with alcohols.

**CHAPTER-5: Section-B:** Iron-catalyzed dehydrogenative alkylation of alkyl-substituted *N*-heteroaromatics with alcohols

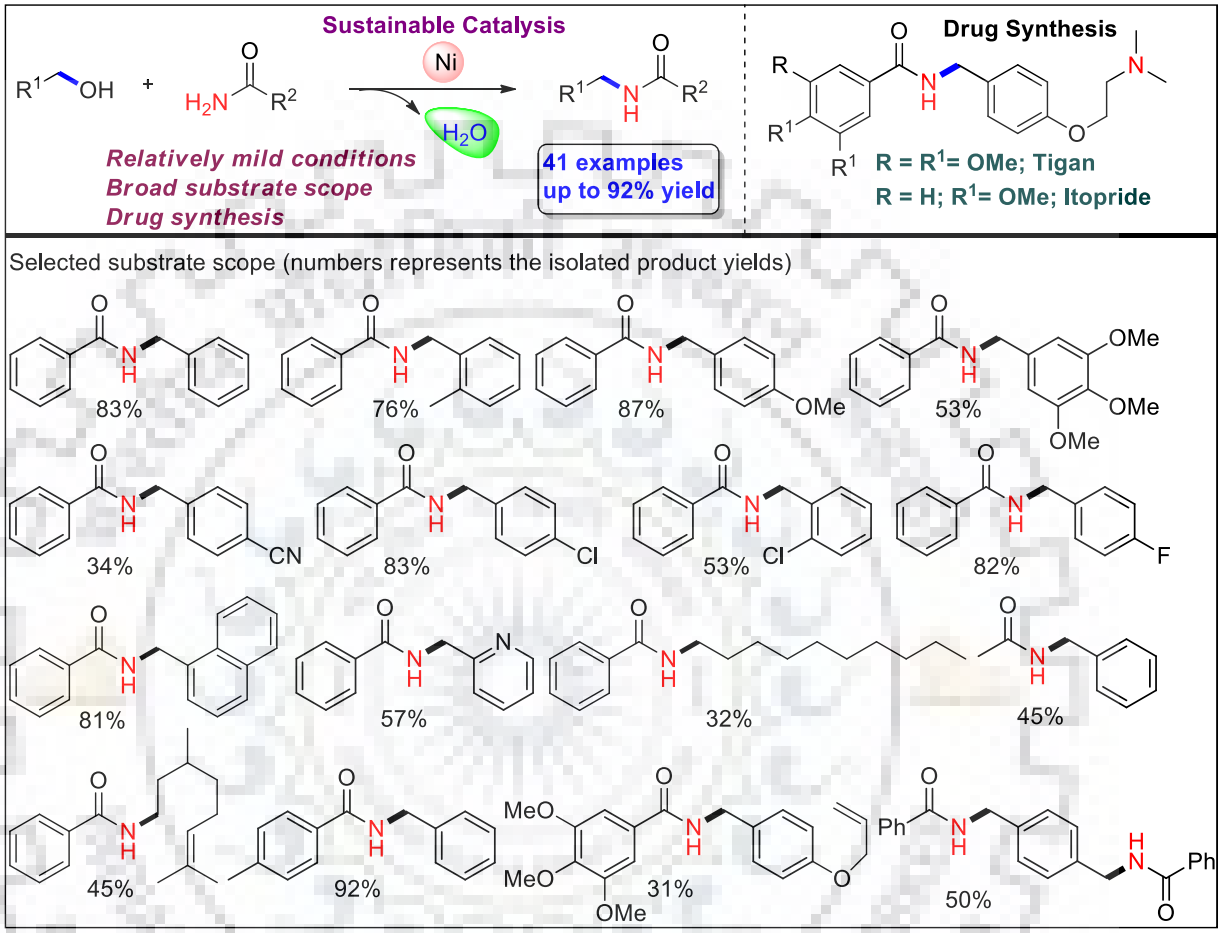
**CHAPTER-1**: **Transition-metal catalyzed synthesis of C-C and C-N bonds: A Concise Literature Survey**

This chapter deals with a brief literature survey about the transition metal catalyzed C-C and C-N bond forming reactions. Metal-catalyzed synthesis of C-C and C-N bonds are extremely important reactions widely used for the synthesis of pharmaceuticals, agrochemicals, bio-active natural products and in material chemistry at laboratory scale as well as in industrial bulk-scale processes. Classical methodologies involve for these process are generally associated with stoichiometric side waste. Again, often, metal catalyzed synthesis of C-C and C-N bonds were also known to use activated derivatives, such as, alkyl halides, esters and anhydrides as alkylating agents. In this direction, application of renewable alcohols would be more sustainable and environmentally benign process, releasing only water as by product. Till last decades, applications of toxic and expensive noble metal-catalysts, such as, Ru, Ir, Pd, Rh, etc. were known for such processes following borrowing hydrogen approach. Recently, there is a potential drive for the applications of earth-abundant and inexpensive metals, such as, Fe-, Co-, Mn- and Ni-for such applications with equal efficiency. This

chapter cover the applications of precious as well as non-precious metal-catalyzed synthesis of C-C and C-N bonds under hydrogen auto-transfer principle.

**CHAPTER-2: Nickel-catalyzed direct *N*-alkylation of amides with alcohols**

(Das, J.; Banerjee, D. *J. Org. Chem*. **2018**, *83*, 3378−3384)

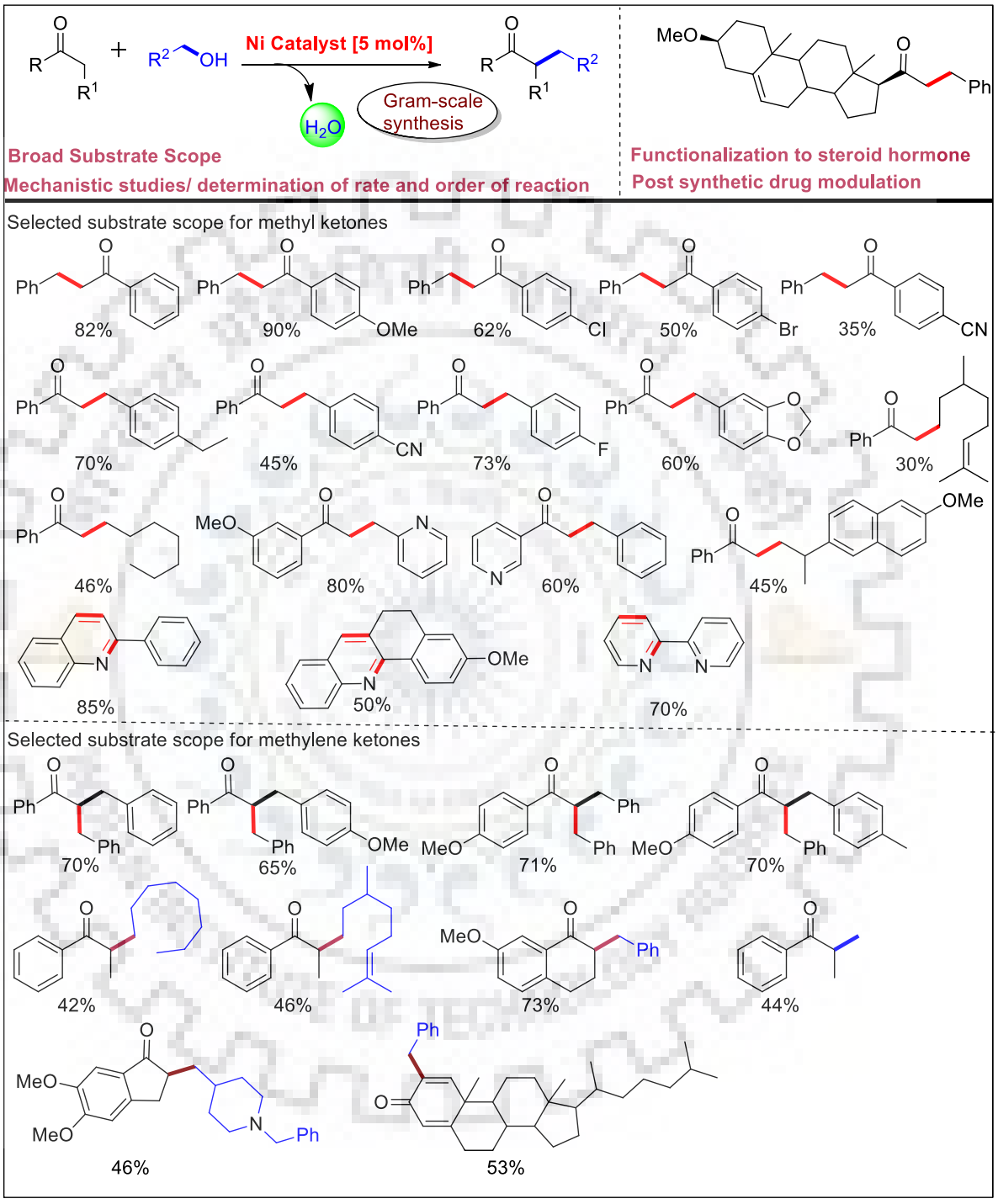



In the Chapter-2 we demonstrated the development of an operational simple, practical, and selective Ni-catalyzed synthesis of secondary amides. Application of renewable alcohols, earth-abundant and non-precious nickel catalyst facilitates the transformations, releasing water as byproduct. The catalytic system is tolerant to a variety of functional groups including nitrile, allylic ether, and alkene and could be extended to the synthesis of bisamide, antiemetic drug Tigan, and dopamine D2 receptor antagonist Itopride. Preliminary mechanistic studies revealed the participation of a benzylic C-H bond in the rate determining step.

**CHAPTER-3: Nickel-catalyzed *α*-alkylation of ketone enolates with alcohols**

(Das, J.; Vellakkaran, M.; Banerjee, D. *J. Org. Chem*. **2019**, *84*, 769-779)

(Das, J.; Singh, K.; Vellakkaran, M.; Banerjee, D. *Org. Lett*. **2018**, *20*, 5587−5591.)

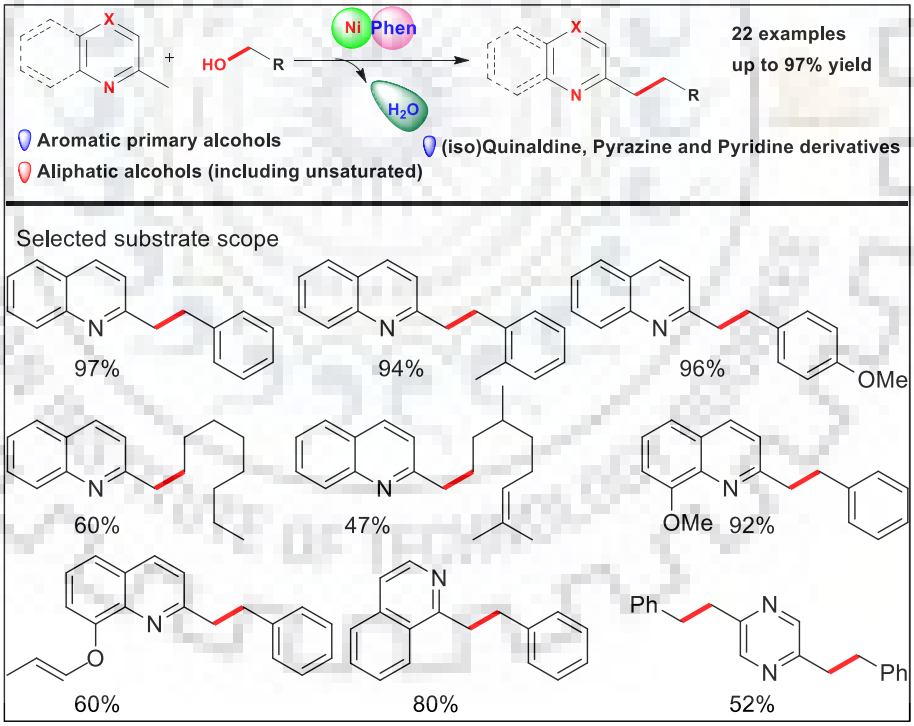



Herein, we have demonstrated an inexpensive and operational simple base-metal catalyzed protocol for selective mon-alkylation of methyl-ketones as well as methylene ketones with alcohols using borrowing hydrogen approach. This Ni-catalyzed dehydrogenative coupling of alcohol could be performed in gram scale and extended to a range of aryl, alkyl and

hetero-aryl derivatives (>40 examples) in up to 90% yield including green synthesis of *N*-heterocycles. For a synthetic application, functionalization of steroid hormone, unsaturated fatty acids and post synthetic modification of naproxen drug have shown. Also, this nickel-catalyzed reaction could be performed in gram scale and successfully applied in the synthesis of donepezil (Alzheimer's drug) and functionalization of steroid hormones and fatty acid derivatives. The methylation of ketones using methanol, and one-pot double alkylation to bis-hetero aryl ketones using two different alcohols with a single catalyst broadens the scope of the catalytic protocol. Detailed mechanistic studies involving isolation of a Ni intermediate, defined Ni-H species, intermediate Ni-alkoxy species and determination of rate and order of reaction as well as a series of deuterium labeling experiments were crucial for preliminary mechanistic studies for selective alkylation of ketones.

**CHAPTER-4: Nickel-catalyzed alkylation of methyl *N*-heteroaromatics with alcohols**

(Vellakkaran, M.;[#] Das, J.;[#] Bera, S.; Banerjee, D. *Chem. Commun*. **2018**, *54*, 12369; [#]-Equal authorship)

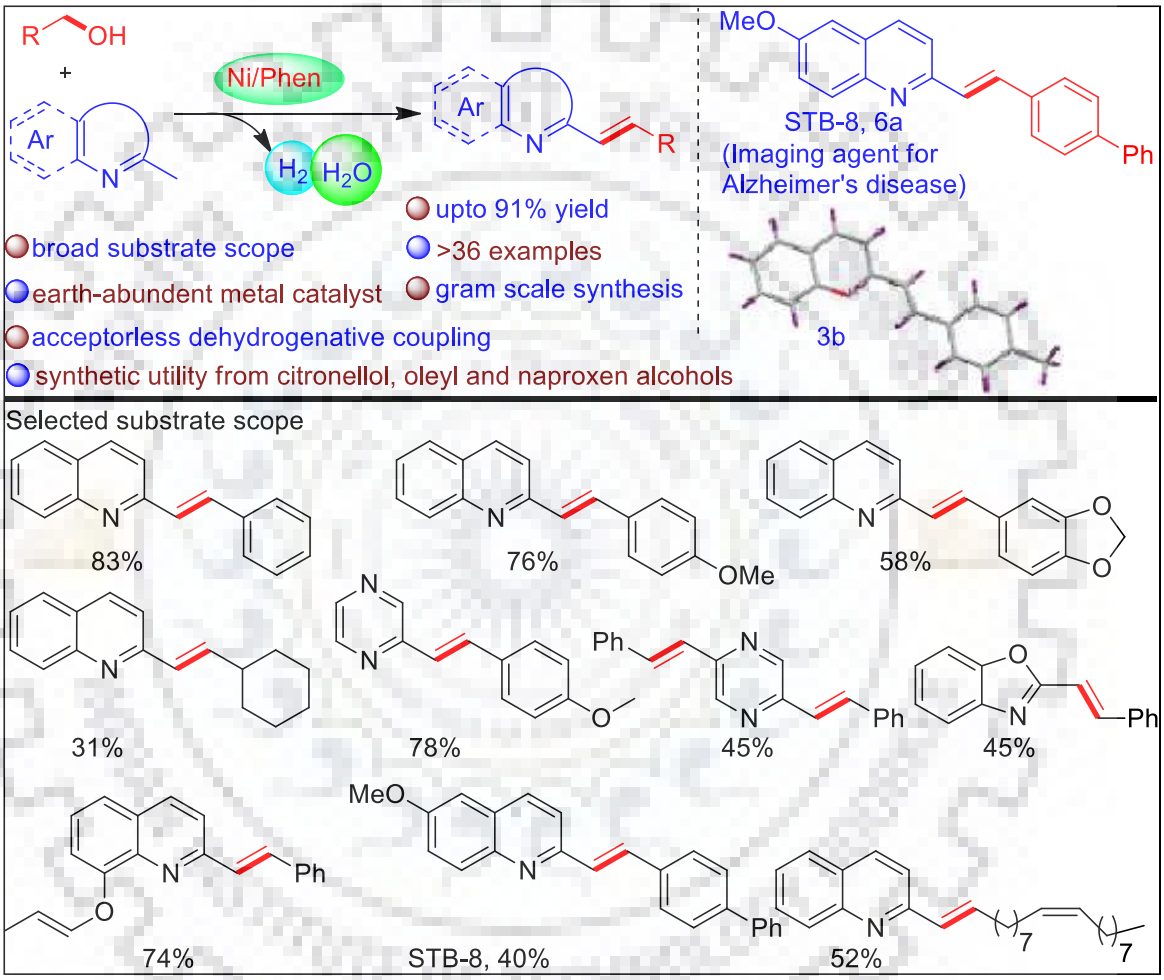



In this chapter, we have illustrated the first Ni-catalyzed functionalization of C($sp^3$)–H bonds in methyl *N*-heteroaromatics using primary alcohols. Easily available, inexpensive Ni-catalysts and 1,10-phenanthroline ligands enable long chain C2-alkylated *N*-heteroaromatics in up to quantitative yields. The catalytic system allows transformations in the presence of reducible functional moieties, such as allylic ethers and alkenes, including unsaturated

alcohols. Initial mechanistic studies strongly support the participation of a Ni–H species and the bi-functional nature of the Ni-catalyst. A series of deuterium labeling experiments revealed the involvement of H/D exchange during the progress of the reaction.

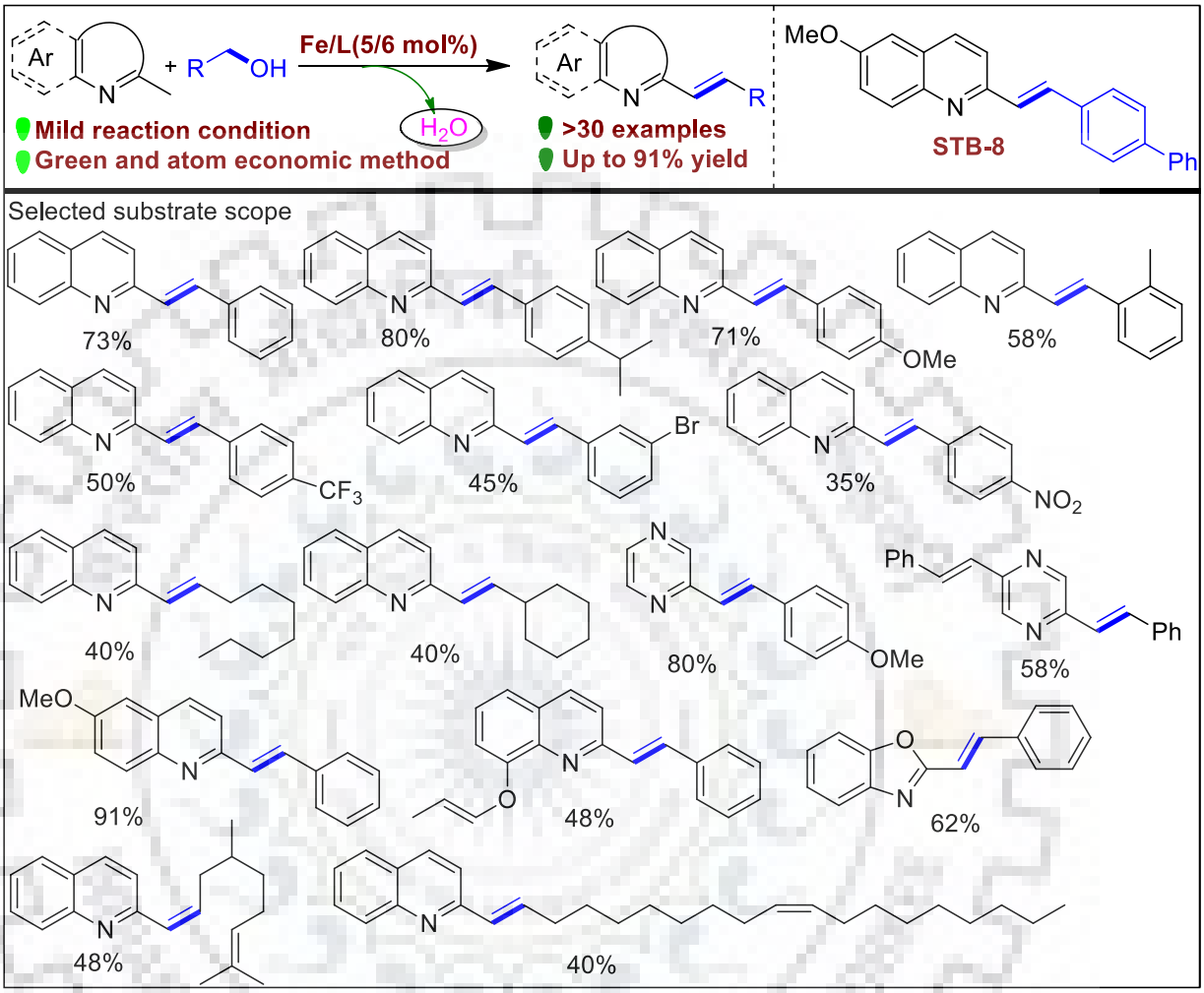
**CHAPTER-5: Section-A: Nickel-catalyzed dehydrogenative alkylation of methyl *N*-heteroaromatics with alcohols**

(Das, J.; Vellakkaran, M.; Banerjee, D. *Chem. Commun*. **2019**, 55, 7530-7533)




We have demonstrated catalytic α-olefination of 2-methylheteroarenes with primary alcohols *via* dehydrogenative coupling. A simple nickel catalyst system stabilized by readily available nitrogen ligand enables a series of interesting *E*-configured vinylarenes (X-ray crystal-structure analysis) in good to excellent yields with olefin/alkane selectivity of >20:1. Hydrogen and water are generated as byproducts and rendering the process environmentally benign.

**CHAPTER-5: Section-B: Iron-catalyzed dehydrogenative alkylation of alkyl-substituted *N*-heteroaromatics with alcohols** (Das, J.; Vellakkaran, M.; SK, M.; Banerjee, D. *Org. Lett*. **2019.** DOI: 10.1021/acs.orglett.9b02793).




This chapter describe the direct *α*-olefination of alkyl substituted *N*-heteroarenes with primary alcohols using an efficient Fe-catalyst ligated with nitrogen ligands. This dehydrogenated coupling involving alkyl *N*-heteroaromatics with a series of primary alcohols resulted a series of functionalized *E*-substituted olefins with very high olefin/alkane selectivity. A series of deuterium labeling experiments, kinetics studies and control-experiments provide evidences for the participation of the benzylic C-H/D bond of alcohols and C($sp^3$)-H/D bond of 2-alkylheteroarenes following dehydrogenative couplings.

# *Table of Contents*

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# *List of Abbreviations*

| | | |
|---|---|---|
| Ac | : | Acetyl |
| acac | : | Acetyl acetonate |
| Ar | : | Aryl or Aromatic |
| AgF | : | Silver(I) fluoride |
| Bn | : | Benzyl |
| Bpy | : | 2,2'-Bipyridine |
| Dbpy | : | 4,4′-Dimethyl-2,2′-dipyridyl |
| Brs | : | Broad singlet |
| *n*-Bu | : | *n*-Butyl |
| Cat | : | Catalyst |
| $CDCl_3$ | : | Deuterated chloroform |
| $CHCl_3$ | : | Chloroform |
| $CH_2Cl_2$ | : | Dichloromethane |
| $CH_3OH$ | : | Methanol |
| COD | : | 1,5-Cyclooctadiene |
| $CD_3OD$ | : | Methanol D4 |
| CN | : | Cyano |
| Cp | : | Cyclopentadiene |
| CPME | : | Cyclopentyl methyl ether |
| $Cs_2CO_3$ | : | Cesium carbonate |
| DCE | : | Dichloroethane |
| Dppe | : | 1,2-Bis(diphenylphosphino)ethane |
| Dppp | : | 1,3-Bis(diphenylphosphino)propane |
| Dppb | : | 1,4-Bis(diphenylphosphino)butane |
| Dpppentane | : | 1,5-Bis(diphenylphosphino)pentane |
| DPEphos | : | Bis(2-diphenylphosphinophenyl)ether |
| Dppf | : | Bis(diphenylphosphino)ferrocene |
| DPPBz | : | 1,2-Bis(diphenylphosphino)benzene |
| DMPhen | : | 2,9-Dimethyl-1,10-phenanthroline |
| DCM | : | Dichloromethane |
| dd | : | Doublet of doublets |
| ddd | : | Doublet of doublet of doublets |

| | | |
|---|---|---|
| DFT | : | Density functional theory |
| DMF | : | *N,N*-Dimethylformamide |
| DMA | : | Dimethylacetamide |
| DME | : | 1,2-Dimethoxyethane |
| DMSO | : | Dimethyl sulfoxide |
| dt | : | Doublet of triplets |
| equiv. | : | Equivalent |
| Et | : | Ethyl |
| $Et_2O$ | : | Diethyl ether |
| EtOH | : | Ethanol |
| $Et_3N$ | : | Triethyl amine |
| EtOAc | : | Ethyl acetate |
| EWG | : | Electron withdrawing group |
| FTIR | : | Fourier transform infrared |
| g | : | Gram |
| GC | : | Gas chromatography |
| GC-MS | : | Gas chromatography–mass spectrometry |
| h | : | Hour |
| $HBF_4$ | : | Tetrafluoroboric acid |
| HRMS | : | High Resolution Mass Spectrum |
| $H_2O$ | : | Water |
| Hz | : | Hertz |
| IR | : | Infrared |
| *J* | : | Coupling constant |
| KBr | : | Potassium bromide |
| KOH | : | Potassium hydroxide |
| $K_2CO_3$ | : | Potassium carbonate |
| KHMDS | : | Potassium bis(trimethylsilyl)amides |
| LiOH | : | Lithium hydroxide |
| M | : | Molar |
| m | : | Multiplet |
| mg | : | Millligram |
| MHz | : | Mega hertz |
| min | : | Minutes |

| | | |
|---|---|---|
| mL | : | Millilitre |
| mmol | : | Millimole |
| MeOH | : | Methanol |
| $MgSO_4$ | : | Magnesium Sulphate |
| $Me_3NO$ | : | Trimethylamine *N*-oxide |
| MS | : | Molecular sieves |
| $NaBH_4$ | : | Sodium borohydride |
| NaH | : | Sodium hydride |
| $NEt_3$ | : | Triethylamine |
| *n*-BuOH | : | n-Butanol |
| *n*-BuLi | : | *n*-Butyl lithium |
| $NO_2$ | : | Nitro |
| NaOH | : | Sodium hydroxide |
| $NH_4Cl$ | : | Ammonium chloride |
| NHC | : | N-heterocyclic carbene |
| $NH_3$ | : | Ammonia |
| $Na_2CO_3$ | : | Sodium carbonate |
| $Na_2SO_4$ | : | Sodium sulphate |
| $NaHCO_3$ | : | Sodium bicarbonate |
| NaOEt | : | Sodium ethoxide |
| $NaHBEt_3$ | : | Sodium triethylborohydride |
| $NiCl_2$ | : | Nickel(II) chloride |
| $NiBr_2$ | : | Nickel(II) bromide |
| $NiCl_2$.DME | : | Nickel(II) chloride, dimethoxyethane |
| $NiCl_2(COD)_2$ | : | Bis(1,5-cyclooctadiene)nickel(0) |
| $Ni(acac)_2$ | : | Nickel(II) acetylacetonate |
| NMR | : | Nuclear magnetic resonance |
| Nu | : | Nucleophile |
| Ph | : | Phenyl |
| $PCy_3$ | : | Tricyclohexylphosphine |
| Phen | : | 1,10-Phenanthroline |
| $P(CH_2CH_2PPh_2)_3$ | : | Tris[2-(diphenylphosphino)ethyl]phosphine |
| $P(2\text{-Fur})_3$ | : | Tri(2-furyl)phosphine |
| $PPh_3$ | : | Triphenylphosphine |

| | | |
|---|---|---|
| PhCl | : | Chlorobenzene |
| ppm | : | Parts per million |
| Py | : | Pyridine |
| PTA | : | *p*-tolylacetic acid |
| PTSA | : | *p*-Toluenesulfonic acid |
| q | : | Quartet |
| RT | : | Room temperature |
| s | : | Singlet |
| Sub | : | Substrate |
| t | : | Triplet |
| TBA | : | *tert*-butyl alcohol |
| TBHP | : | *tert*-butyl hydropeoxide |
| *t*-BuOK | : | Potassium tertiary butoxide |
| *t*-BuONa | : | Sodium tertiary butoxide |
| *t*-BuOH | : | *tert*-Butanol |
| THF | : | Tetrahydrofuran |
| TLC | : | Thin layer chromatography |
| TMS | : | Tetramethylsilane |
| TS | : | Transition state |
| Xantphos | : | 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene |

**LIST OF NOTATIONS**

| | | |
|---|---|---|
| $\alpha$ | : | Alpha |
| $\beta$ | : | Beta |
| $\gamma$ | : | Gamma |
| % | : | Percentage |
| *J* | : | Coupling constant |
| $\delta$ | : | Chemical shift |
| ºC | : | Degree centigrade |

# *List of Publications*

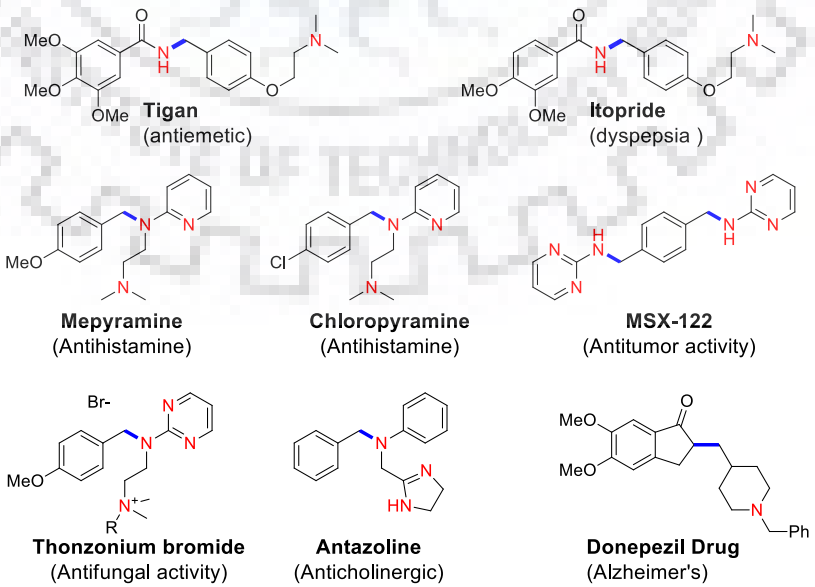
1. **Das, J**.; Banerjee, D. Nickel-Catalyzed Phosphine Free Direct *N*-Alkylation of Amides with Alcohols. *J. Org. Chem*. **2018**, *83*, 3378−3384.
2. **Das, J**.; Singh, K.; Vellakkaran, M.; Banerjee, D. Nickel-Catalyzed Hydrogen-Borrowing Strategy for α-Alkylation of Ketones with Alcohols: A New Route to Branched *gem*-Bis(alkyl) Ketones. *Org. Lett*. **2018**, *20*, 5587−5591.
3. Vellakkaran, M.;[#] **Das, J**.;[#] Bera, S.; Banerjee, D. Nickel-catalysed alkylation of C($sp^3$)–H bonds with alcohols: direct access to functionalised N-heteroaromatics. *Chem. Commun*. **2018**, *54*, 12369−12372; [#]-**Equal authorship**.
4. Kabadwal, L. M.; [#] **Das, J**.; [#] Banerjee, D. Mn(II)-catalysed alkylation of methylene ketones with alcohols: direct access to functionalized branched products. *Chem. Commun*., **2018**, 54, 14069−14072. [#]-**Equal authorship**.
5. **Das, J**.; Vellakkaran, M.; Banerjee, D. Nickel-Catalyzed Alkylation of Ketone Enolates: Synthesis of Monoselective Linear Ketones. *J. Org. Chem*. **2019**, *84*, 769−779.
6. **Das, J**.; Vellakkaran, M.; Banerjee, D. Nickel-catalysed direct α-olefination of alkyl substituted *N*-heteroarenes with alcohols *Chem. Commun*. **2019**, *55*, 7530−7533.
7. **Das, J**.; Vellakkaran, M.; SK, M.; Banerjee, D. Iron-Catalyzed Coupling of Methyl *N*-Heteroarenes with Primary Alcohols: Direct Access to *E*-Selective Olefins. *Org. Lett*. **2019.** DOI: 10.1021/acs.orglett.9b02793.

# Chapter-1: Transition-metal catalyzed synthesis of C-C and C-N bonds: A Concise Literature Survey.

This chapter deals with a brief literature survey about the transition metal catalyzed C-C and C-N bond forming reactions. Metal-catalyzed synthesis of C-C and C-N bonds are extremely important reactions widely used for the synthesis of pharmaceuticals, agrochemicals, bio-active natural products and in material chemistry at laboratory scale as well as in industrial bulk-scale processes. This chapter covers the applications of precious as well as non-precious metal-catalyzed synthesis of C-C and C-N bonds under hydrogen auto-transfer principle.

## [1.1] Introduction:

Recently there has been a significant interest to utilize the renewable resources and convert them to key chemicals of potential uses. Therefore, recent focus in chemical research is to develop environmentally benign and atom economic technologies for the synthesis of C-C and C-N bonds, which are widely used in pharmaceuticals, agrochemicals and in natural products (Scheme 1). In this context, transition metal-catalyzed borrowing hydrogen methodology emerged as an elegant alternative to classical approaches for their synthesis.[1] Classical methodologies mostly associated with drawbacks, such as, generation of stoichiometric waste, toxic byproducts and required strong and hazardous reagents. However, borrowing hydrogen (BH) strategy involving un-activated alcohols gaining potential interests in this direction. It is to be note that, alcohols are renewable feedstock and could be extracted from lignocellulosic biomass and possess significant challenges for the applications as coupling partner in C-C and C-N bond formation. Notably, use of alcohols as coupling partner, generates water as sole byproduct. However, from last decades, precious transition metal catalysts based on Pd, Pt, Rh, Ir and Ru are widely used for such transformations involving borrowing hydrogen strategy. But, having low natural abundance, high toxic and expensive nature of such metals limits their application. Therefore, current focus is to replace those expensive and toxic metal-catalysts with earth-abundant and inexpensive metal-catalysts (Fe, Ni, Mn, and Co etc.) with equal efficiency. In this chapter we briefly represents an overview of C-C and C-N bond formations based on earth-abundant metal catalysts.[2]

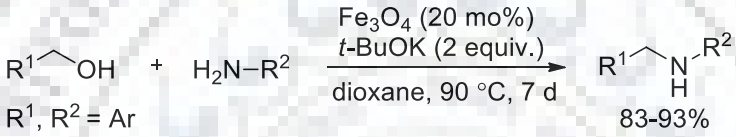



**Scheme 1:** Some pharmaceutically important molecules containing C-C and C-N bonds

In 1899, Marcel Guerbet pioneer the discovery for the synthesis of *β*-alkylated alcohols starting from primary alcohol through BH methodology.[3] In 1932, Winans and Adkins, reported the first *N*-alkylation of amines by alcohols based on heterogeneous nickel catalysts.[4] In recent years, there has been excellent progress in the area of C-C and C-N bond formation using non-noble metal catalysts and we will discuss in this chapter.

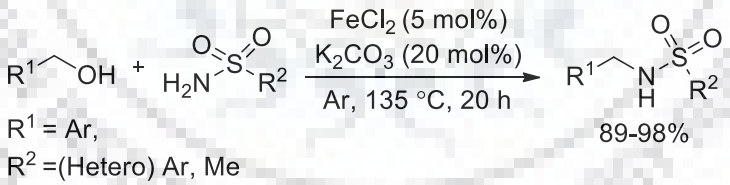
**[1.2] Fe-catalyzed formation of C-C and C-N bond using alcohols:**

Iron is the most earth abundant element in earth's crust and applications of Fe-based catalysts in BH methodology has potential interests. In 2009, Yus and coworkers employed commercially available $Fe_3O_4$ as catalyst for *N*-alkylation of aromatic amines by alcohols. This recyclable catalyst system is highly selective for aromatic amines as well as benzyl alcohols to achieve higher product yields (Scheme 2). [5]



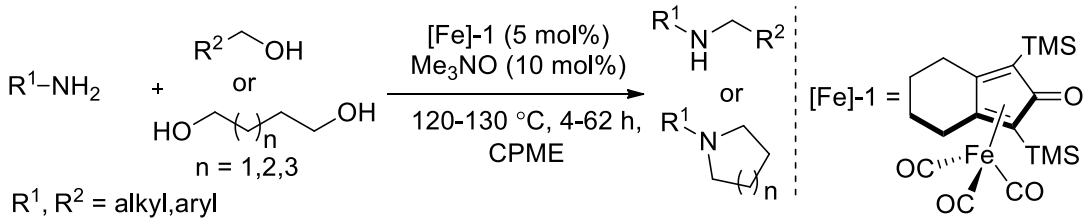

**Scheme 2:** Fe-based heterogeneous catalysts for *N*-alkylation of amines

In 2010, Shi and Deng and coworkers developed an efficient $FeCl_2$ catalyzed *N*-alkylation of sulfonamides with a series of benzyl and alkyl alcohols in excellent yields. The preliminary mechanistic studies involving deuterated benzyl alcohol evident the BH mechanism (Scheme 3).[6]

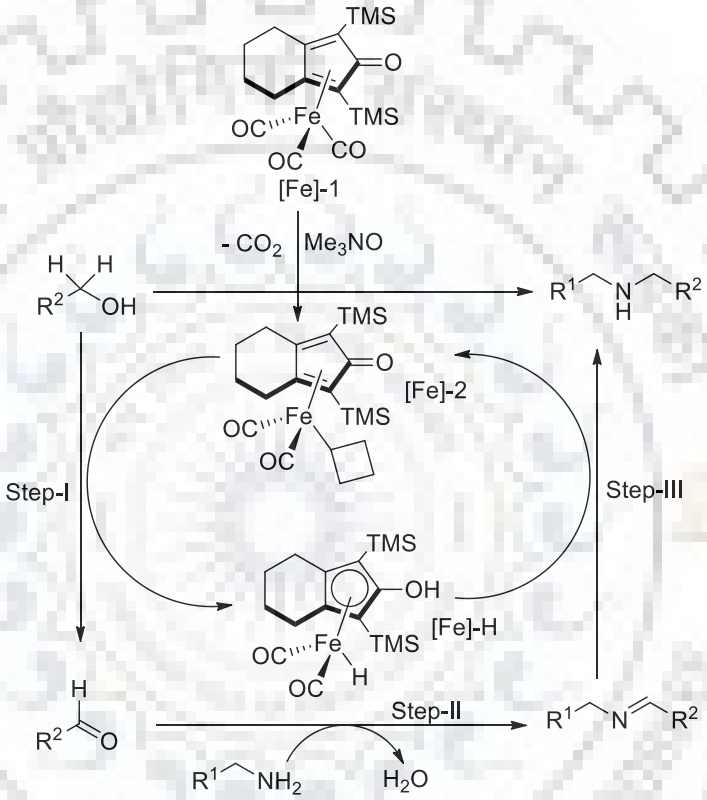



**Scheme 3:** Fe(II)-catalyzed alkylation of sulfonamides

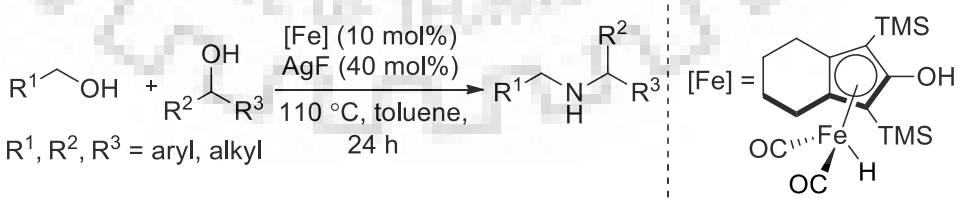
Thereafter, Feringa and Barta and coworkers developed a well-defined Knölker's iron complex for the first N-alkylation of amines with alcohols. Initial mechanistic studies were perform to establish the nature of the active Fe-catalyst and revealed the potential role of the catalyst for broad substrate scope (Scheme 4).[7] Thereafter, Zao and coworkers (2015), Wills and Co-workers, Kirchner and coworkers (2016) and others employed these Knölker's types iron-based complexes as well as $PN_3P$ ligated iron-based complexes for the amination of secondary alcohols, allylic alcohols and primary alcohols following hydrogen borrowing approaches (Schemes 5-8).[8-10]



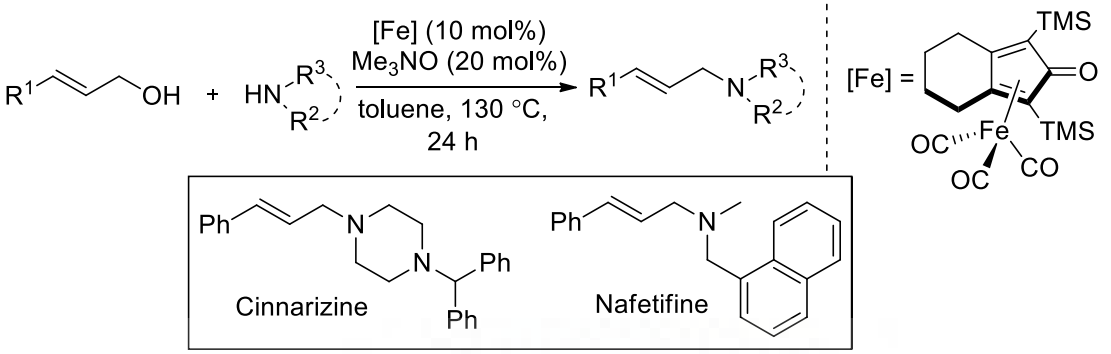

**Scheme 4:** *N*-alkylation of amines with alcohol



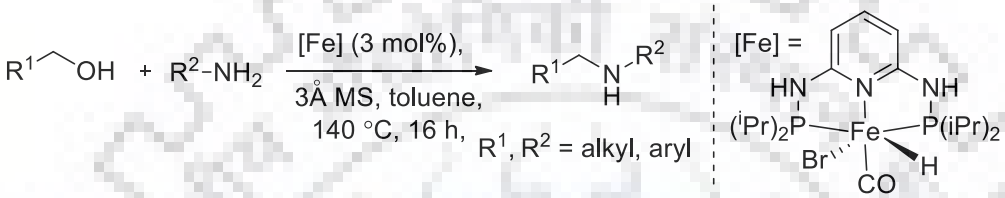

**Scheme 5:** Plausible mechanism for *N*-alkylation of amine with alcohol




**Scheme 6:** Amination using secondary alcohols

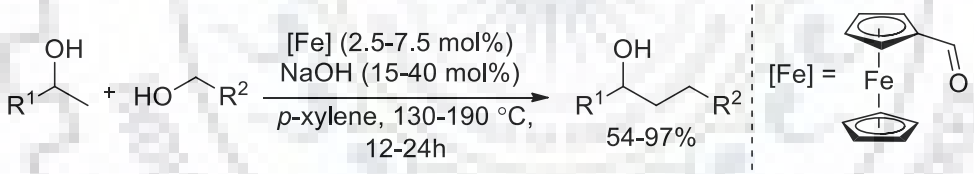



**Scheme 7:** Amination with allylic alcohols using Knölker type-complex



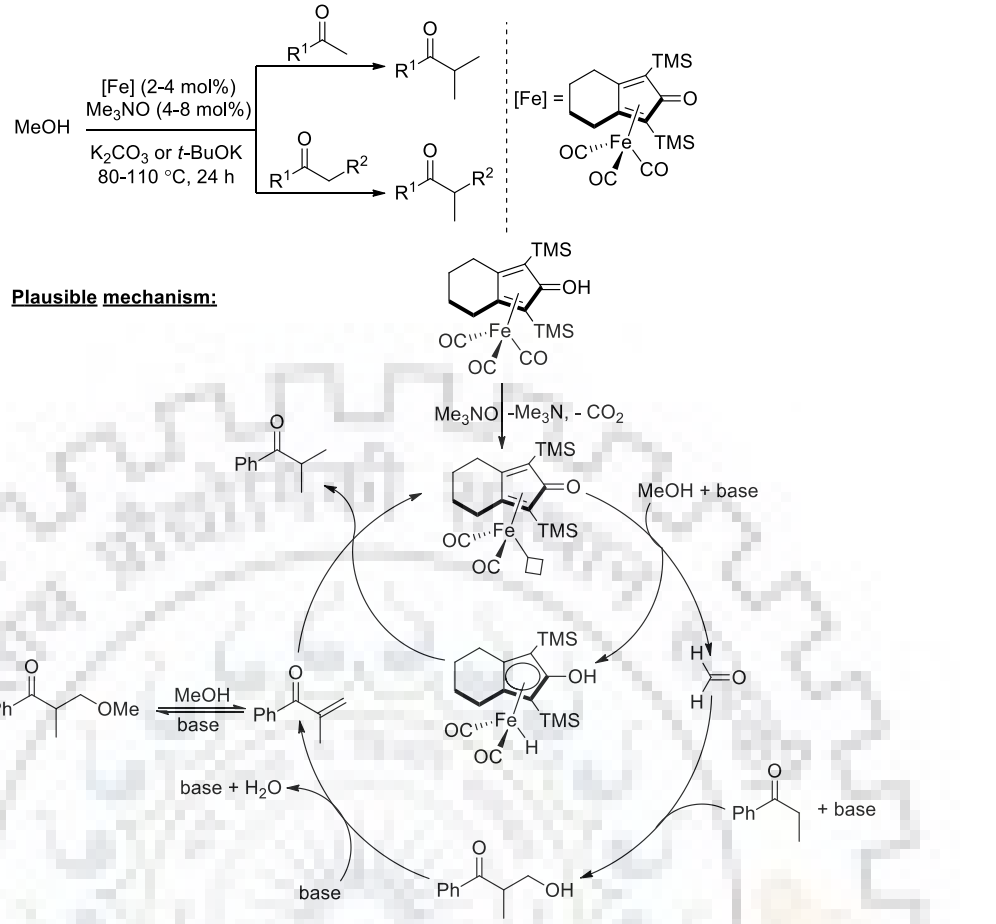

**Scheme 8:** Amination of alcohols using pincer complex

*β*-alkylation of secondary alcohols with primary alcohols has also been developed using inexpensive and commercially available ferrocene-carboxaldehyde as catalyst in combination with catalytic amount of NaOH base and resulted *β*-alkylated alcohol in up to 94% yields (Scheme 9).[9]



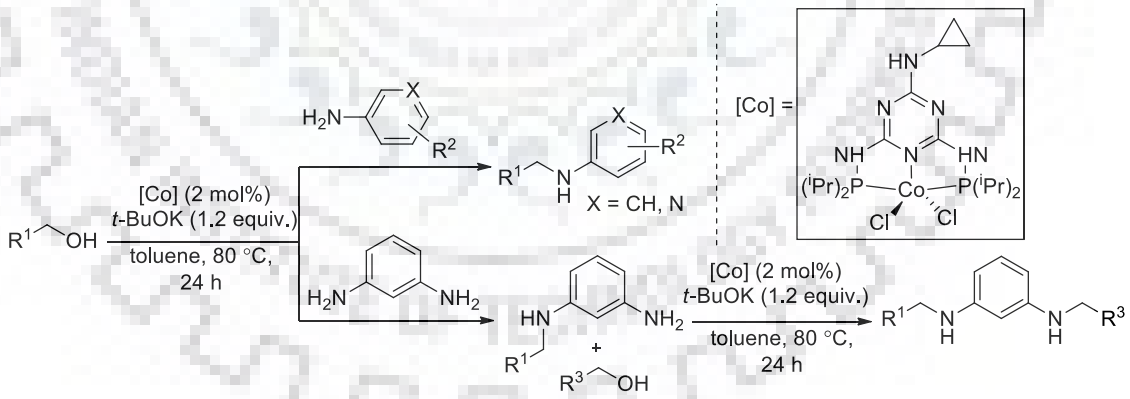

**Scheme 9:** Fe-catalyzed *β*-alkylation of secondary alcohols

Recently, Morrill and coworkers reported Fe-catalyzed methylation using methanol as a C1-source. Fe-catalyst could be synthesized in a multi-step process and the active catalyst generated in presence of an activator, trimethyl *N*-oxide. The catalytic conditions resulted mono- and di-methylation of a variety of ketones, C(3)-methylation of indoles and oxindole derivatives in high isolated yields. Mechanistic investigation support the participation of borrowing hydrogen mechanism (Scheme 10).[10]




**Scheme 10:** Knölker's Fe-complex-catalyzed mono and dimethylation with methanol

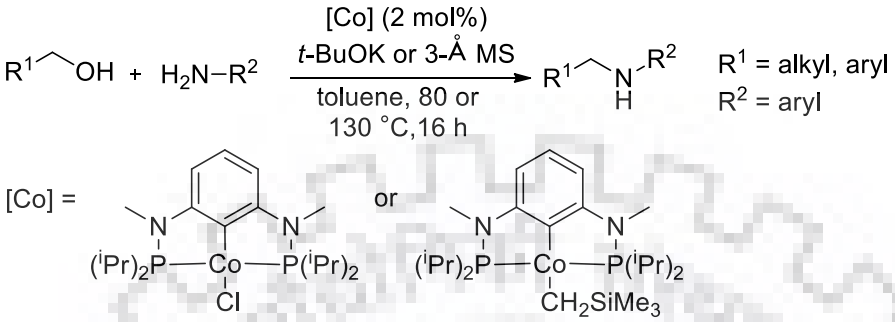
**[1.3] Co-catalyzed synthesis of C-C and C-N bonds:**




**Scheme 11:** Co(II)-catalyzed amination of alcohols

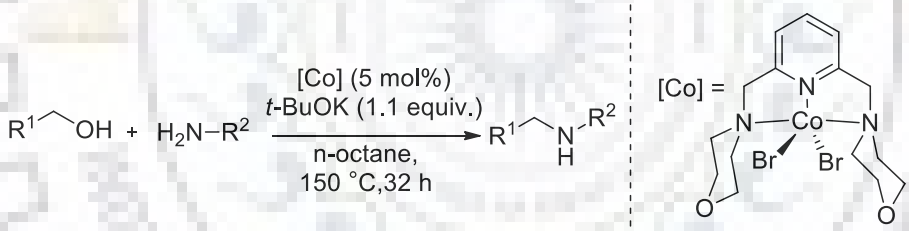
It was demonstrated that, cobalt complexes based on tridentate PNP, PCP or NNN ligands are highly active catalyst for the synthesis of C-C and C-N bonds. These air-stable complexes are easy to synthesize and can undergo self-activation in the presence of a base. In 2015, Kempe and co-workers developed a series of $PN_5P$ triazine-backbone-based ligands stabilized by Co complex for *N*-alkylation of aromatic amines with alcohols. A series of aliphatic and aromatic alcohols selectively yielded desired amines in up to 96%

yields (Scheme 11).[11] Similarly, Co(II)-complex stabilized by a 1,3-diaminobenzene scaffold was also known to catalyze the mono-*N*-alkylation of amines with alcohols. The catalytic system could be useful for a range of aliphatic and aromatic alcohols and aromatic amines having different functional groups (scheme 12).[12]

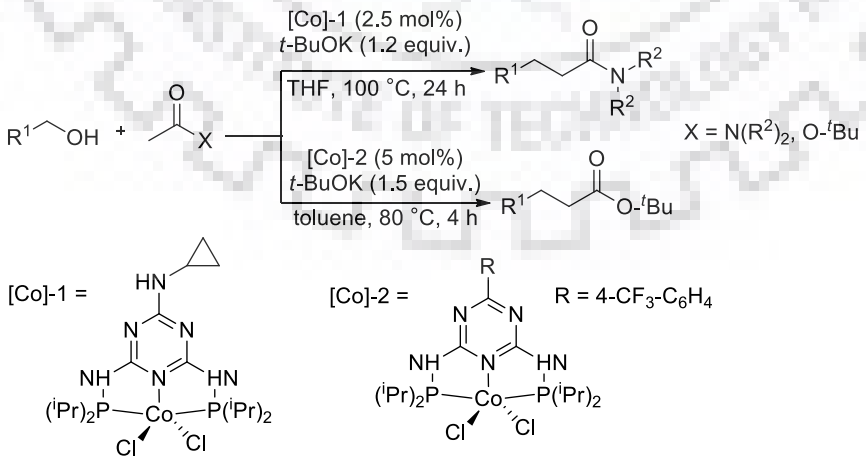



**Scheme 12:** Co(II)-PCP-catalyzed *N*-alkylation of aromatic amines with alcohols

In 2018, Balaraman and coworkers demonstrated a phosphine free Co(II)-NNN complex for the *N*-alkylation of amines using alcohols. The Co(II)-NNN complex was paramagnetic in nature and was efficient for a series of primary alcohols, including heterocyclic alcohols and functionalized anilines (scheme 13).[13]



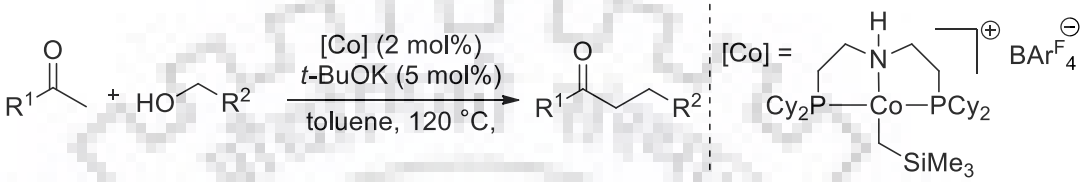

**Scheme 13:** Co(II)-NNN-catalyzed *N*-alkylation of aromatic amines with alcohols




**Scheme 14:** Co(II)-$PN_5P$-catalyzed *α*-alkylation of amides and esters with alcohols

In 2016, Kempe and coworkers developed the first Co(II)-$PN_5P$ complex-catalyzed *α*-alkylation of esters and amides with alcohols. The catalytic system could also be useful for alkylation of amides and gave up to 93% yield to the desired products. (Scheme 14).[14]

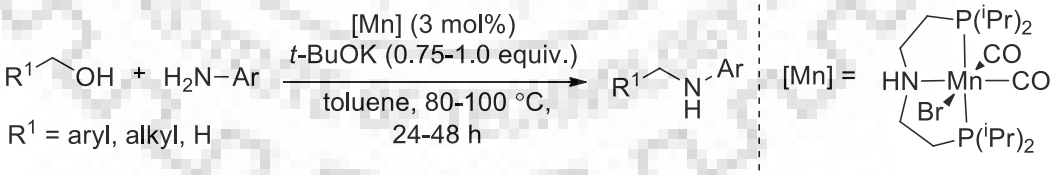
In the similar direction, Zhang and coworkers developed an ionic Co-PNP catalyst system for selective *α*-alkylation of ketones with primary alcohols. Furthermore, the catalytic system was applied to one-pot synthesis of *N*-heterocycles involving 2-aminobenzyl alcohol and acetophenone derivatives (scheme 15).[15]




**Scheme 15:** Co-PNP-catalyzed *α*-alkylation of ketones with primary alcohols

**[1.4] Mn-catalyzed formation of C-C and C-N bond using alcohols:**

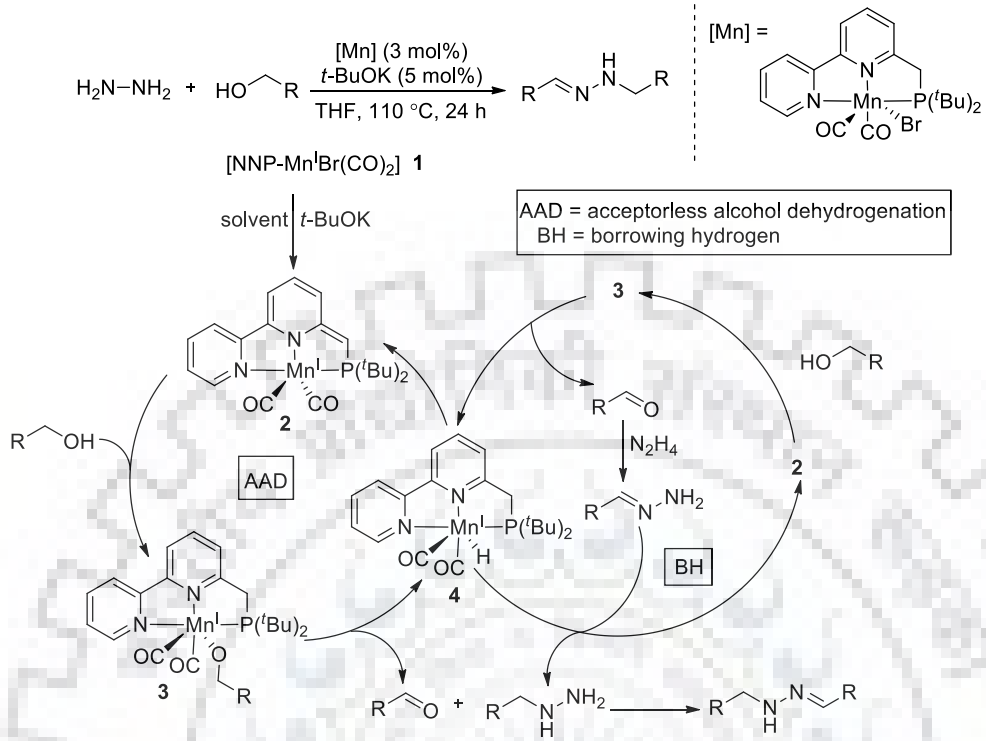
Mn is considered as the third most abundant elements, after Fe and Ti. Therefore, the application of Mn based complex in sustainable catalysis is in high demand and in the direction of C-C and C-N bond formation, Mn-catalyst is still underdeveloped. In this direction, pioneering work has been done by Beller and coworkers. They first reported an air stable [Mn(I)$(CO)_2$Br] complex stabilized by a tridentate PNP ligand for the *N*-alkylation of amines with alcohols under mild reaction conditions. The catalytic system is highly efficient for *N*-alkylation of aromatic amines with alcohols. A wide range of functional groups are tolerant under the optimized reaction conditions. Notably, *N*-methylation of various primary amines with methanol has been demonstrated (scheme 16).[16]




**Scheme 16:** Mn-PNP-catalyzed *N*-alkylation of amines with alcohols

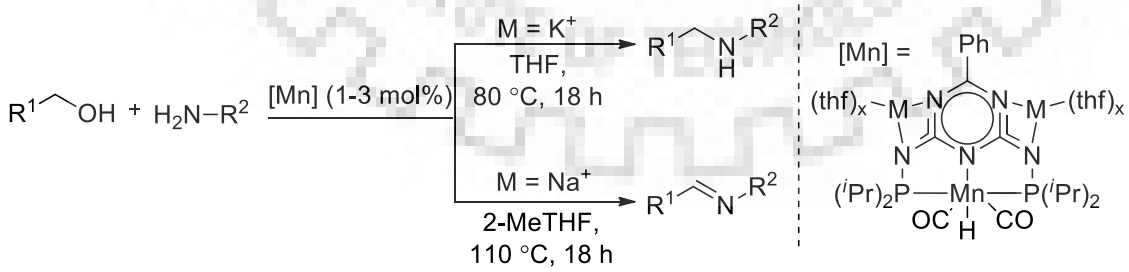
In 2018, Milstein and coworkers developed the pincer based [Mn$(CO)_2$Br]-complex stabilized by $^t$Bu-PNN ligand for one pot synthesis of *N*-substituted hydrazones. Mechanistic investigations revealed the participation of both BH and AAD (acceptorless alcohol dehydrogenation) mechanism in one-pot operation. For instance, the complex **2** is formed by base mediated deprotonation in the presence of *t*-BuOK from catalyst **1.** A metal-ligand cooperative mechanism was observed and metal-hydride complex **4** is generated.

Thereafter, coupling of aldehyde and hydrazone furnish the desired *N*-substituted hydrazine following subsequent steps (scheme 17).[17]




**Scheme 17:** Mn-PNN-catalyzed coupling of hydrazine with alcohols

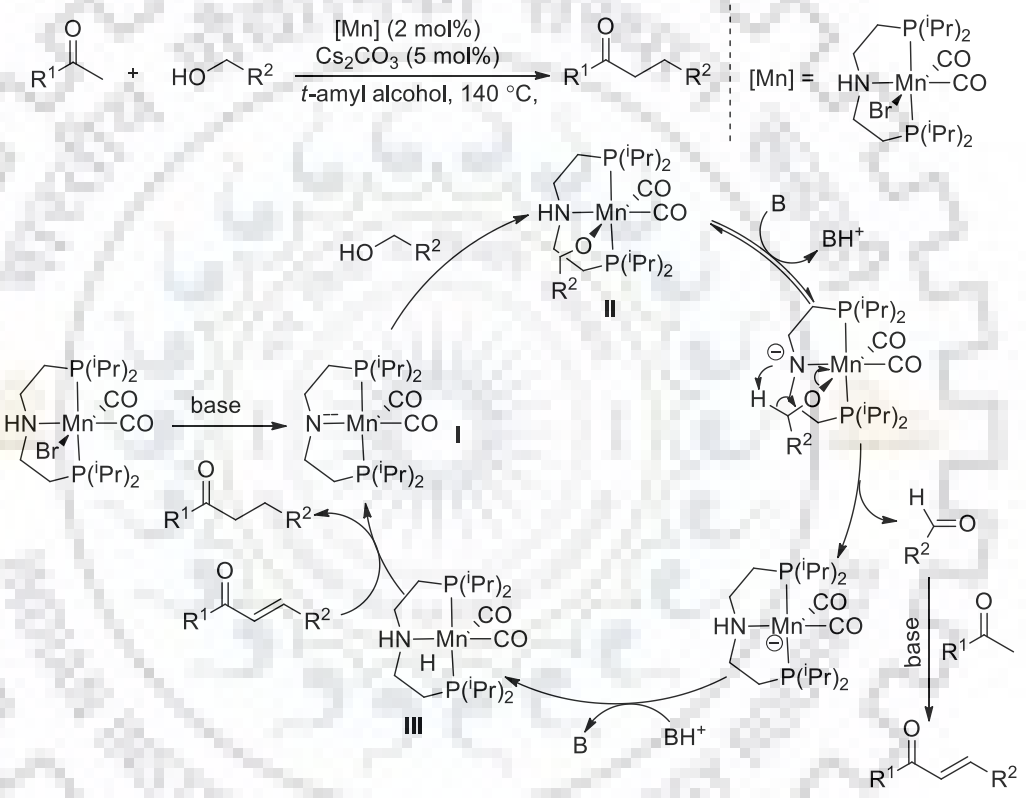
Kempe and coworkers introduced Mn-PNP catalyzed synthesis of *N*-alkylated amines or imines via BH or dehydrogenetive coupling mechanism. The reaction is switchable by base, as *t*-BuOK gives selectively *N*-alkylated amines by BH whereas *t*-BuONa gives the corresponding imines via dehydrogenative condensation with alcohols. Experimental findings prove that the Mn-hydride precatalyst undergoes double deprotonation with base to form the corresponding potassium or sodium manganate hydride responsible for catalyzes the reaction (scheme 18).[18]




**Scheme 18:** Mn-PNP-catalyzed synthesis of amines and imines

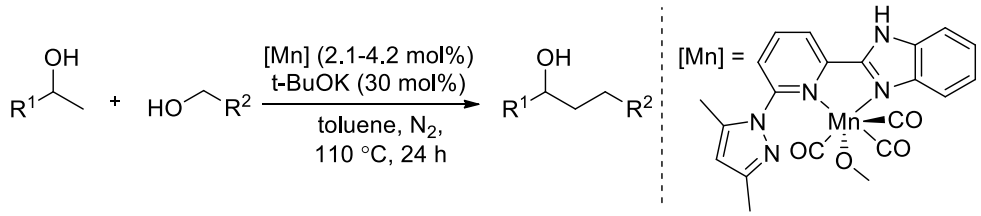
Again, in 2016, Beller and coworkers utilized the Mn-PNP pincer complex for the *α*-alkylation of ketones with primary alcohols (scheme 14). The reaction occured under mild conditions with only 5 mol% of $Cs_2CO_3$ in *t*-amyl alcohol. A wide range of alcohols and

ketones including pharmaceutically important 2-oxindole, estrone 3-methyl ether and testosterone were successfully transformed into corresponding alkylated ketones in excellent isolated yields. Preliminary mechanistic studies emphasized on NH-assisted outer sphere mechanism for *β*-hydride elimination. The active catalyst **I** is generated by de-hydro-bromination of Mn-pre-catalyst and forms strong complex with alcohol to give **II.** Complex **II** then converted to Mn-H **III,** following ligand-assisted outer sphere mechanism. Finally complex **III** hydrogenates the intermediate enone to deliver the desired product, and active catalyst **I** regenerates (scheme 19).[19]




**Scheme 19:** Mn-PNP-catalyzed α-alkylation of ketones with primary alcohols

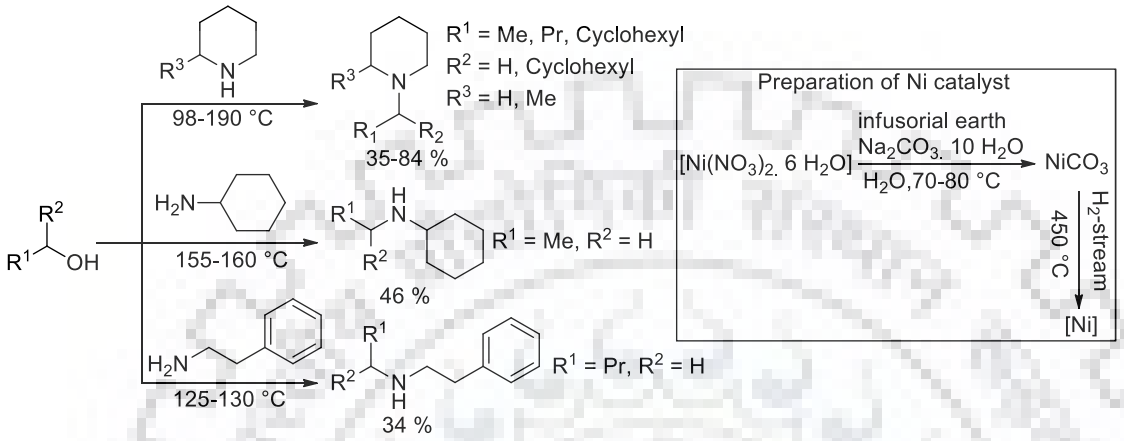
In 2018, Yu and coworkers introduced a Mn-complex, bearing pyridyl-supported pyrazolyl-imidazolyl ligand, for *β*-alkylation of secondary alcohols with primary alcohols. The catalytic system is efficient for the di-*β*-alkylation of cyclopentanol and *β*-alkylation of cholesterol derivatives (scheme 20).[20]




**Scheme 20:** Mn-catalyzed alkylation of secondary alcohols with primary alcohols

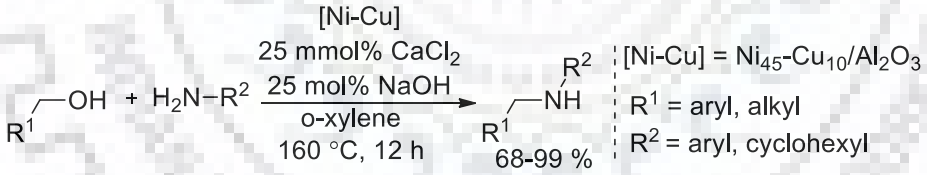
**[1.5] Ni-catalyzed formation of C-C and C-N bond using alcohols:**

In 1932, Winans and Adkins introduced the first nickel catalyzed borrowing hydrogen method for the *N*-alkylation of aliphatic amines with primary alcohols. The Ni-heterogeneous catalyst was prepared from nickel-nitrate in a stream of hydrogen at 450 °C (scheme 21).[4]



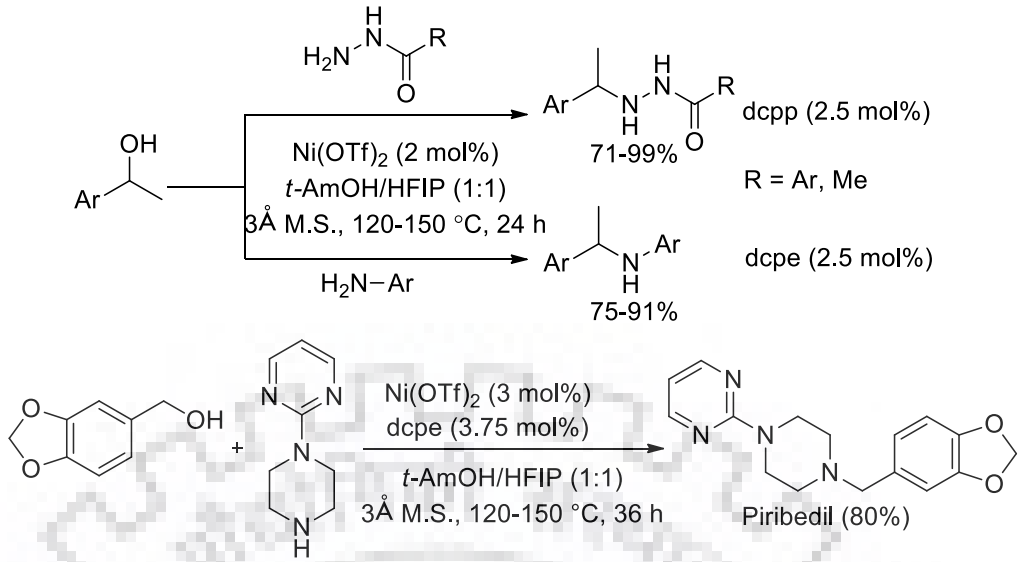

**Scheme 21:** *N*-alkylation of aliphatic amines with primary alcohols by Ni catalyst

Thereafter, in 2012, Li and coworkers prepared a $\gamma$-$Al_2O_3$ supported Ni-Cu bimetallic nanoparticle-catalyst for the *N*-alkylation of amines with alcohols. The catalyst system is highly active for the *N*-alkylation of amines with a series of alcohols and required catalytic amount or base or acids (scheme 22).[21]



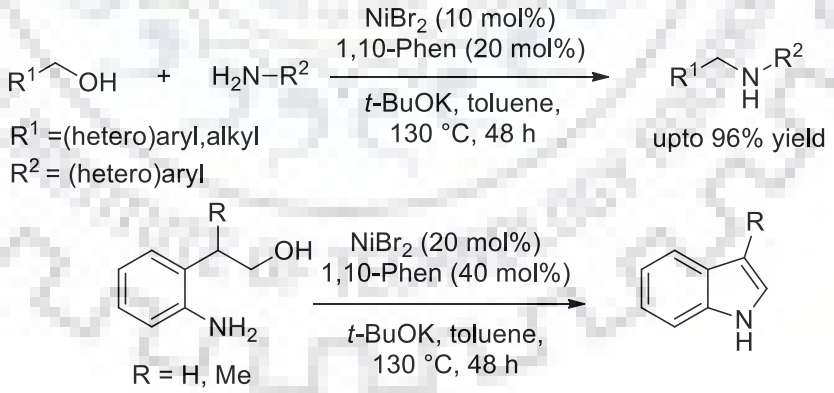

**Scheme 22:** Ni-Cu/$\gamma$-$Al_2O_3$ -catalyzed *N*-alkylation of amines with alcohols

In 2017, Tang and Zhou and coworkers reported a $Ni(OTf)_2$/P-ligands-based catalyst system for the *N*-alkylation of hydrazides and aryl amines with alcohols. The *N*-alkylation of hyrazides proceeds with a 2 mol% of catalyst, 2.5 mol% of ligand dcpp and 3Å molecular sieves in a 1:1 mixture of *tert*-amyl alcohol and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) to produce the *N*-alkylated hydrazides in good to high yields. The protocol was less efficient for *N*-alkylation of aryl amines. An application to Piribedil, an important drug for the treatment of Alzheimer's disease could also be isolated in 80% yield. The protocol could be useful for the synthesis of chiral amines derivatives (scheme 23).[22]




**Scheme 23:** $Ni(OTf)_2$ -catalyzed *N*-alkylation of hyrazides and amines with alcohols

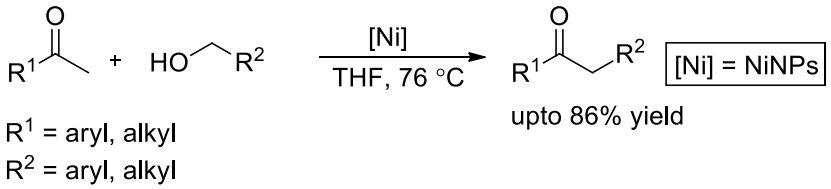
Our group has also developed an operationally simple and inexpensive homogeneous $NiBr_2$/Phen catalyst system for the selective *N*-alkylation of amines with alcohols. The catalytic protocol is tolerant to a series of of functional groups and aromatic and heteroaromatic amines were efficiently alkylated by aryl and alkyl alcohols in moderate to excellent isolated yields. The derivatization of vitamin E, (±)-α-tocopherol under the catalytic reaction condition is noteworthy. Preliminary mechanistic investigation with defined catalyst, Ni-hydride species and deuterium labeling experiments supports for hydrogen borrowing catalysis (scheme 24).[23]




**Scheme 24:** Ni-catalyzed *N*-alkylation of amines with primary alcohols

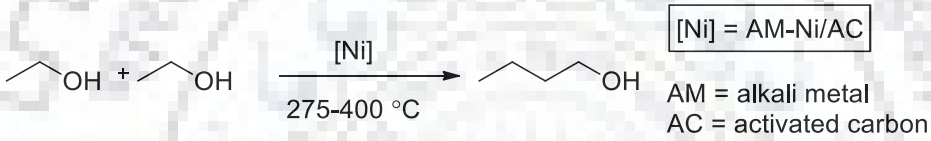
In the direction of C-C bond formation, Yus and coworkers developed a nickel nanoparticle system for the α-alkylation of methyl ketones with primary alcohols. Ni(0) nanoparticles could be synthesized from anhydrous $NiCl_2$ by reduction with lithium powder and a catalytic amount of DTBB (4,4-di-tert-butylbiphenyl) in THF at room temperature.

Stoichiometric amount of Ni-nanoparticles is required for alkylation to ketones using alcohols (scheme 25).[24]




**Scheme 25:** α-alkylation of ketones with alcohols catalyzed by Ni nanoparticles

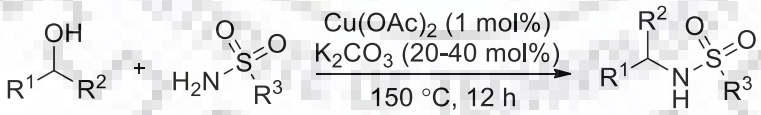
Recently, Onyestyák and co-workers, developed a heterogeneous nickel-catalyst having alkali metal salt and activated carbon support for the synthesis of butanol from ethanol. The reaction was carried out in a flow-microreactor at 450 °C and highest yield was obtained for butanol, while in case of long chain aliphatic alcohols, only lower yields were obtained (scheme 26).[25]



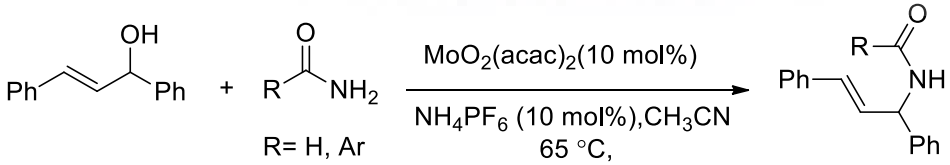

**Scheme 26:** Upgradation of ethanol using Ni catalyst

**[1.6] Other transition metal-catalyzed synthesis of C-C and C-N bonds:**

In 2009, Beller and Deng and coworkers reported the copper catalyst system for *N*-alkylation of sulfonamides with alcohols. A series of mechanistic studies involving deuterium labeling experiments, established the participation of BH mechanism and the dehydrogenation of alcohol to aldehyde is reported as the rate determining step (scheme 27).[26]



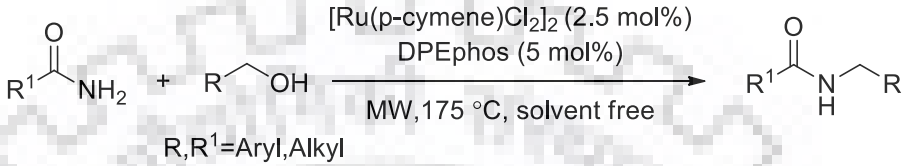

**Scheme 27:** Copper-catalyzed *N*-alkylation of suphonamides with alcohols




**Scheme 28:** Mo-catalyzed *N*-alkylation of amides with allylic alcohol

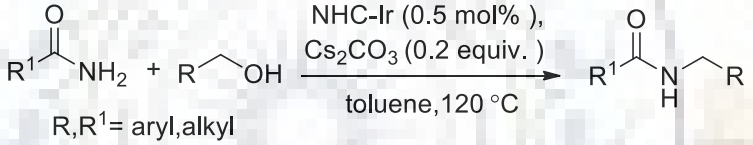
Zhu and co-workers demonstrated the direct nucleophilic substitution of allylic alcohols with nitrogen, oxygen and carbon nucleophiles using $MoO_2(acac)_2$ as a catalyst. The reaction proceeds through a carbenium ion intermediate (Scheme 28).[27]

Williams *et al*., reported an interesting process for the *N*-alkylation of amide using alcohols involving Ru-based catalyst. The reaction was performed using $[Ru(p\text{-cymene})Cl_2]_2$ in combination with DPEphos at 175 $^0$C under microwave conditions and resulted the corresponding alkylated amides in moderate to high isolated yield (Scheme 29).[28]



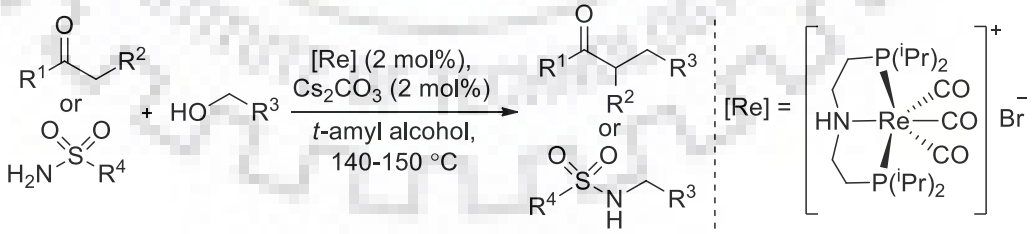

**Scheme 29:** Ru-catalyzed *N*-alkylation of amides with alcohols

In 2015, Andersson and coworkers developed a NHC-Ir catalyst for the N-monoalkylation of amides with alcohols. The NHC-Ir catalyst is highly active and resulted excellent product yields of the secondary amides (Scheme 30).[29]



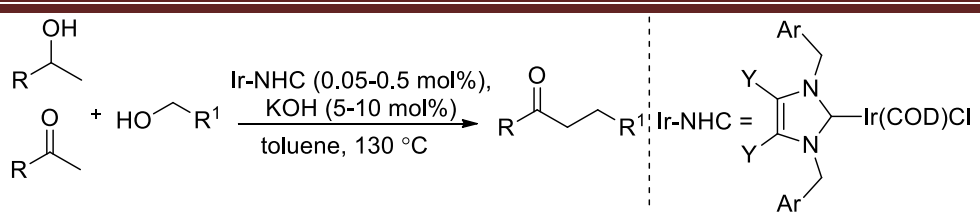

**Scheme 30:** NHC-Ir-catalyzed amidation of alcohols

In 2017, Beller and coworkers developed a Re-complex using PNP-ligand for the alkylation of ketones and sulfonamides with primary alcohols. Notably, 2 mol% catalyst with catalytic amount of base afford the corresponding alkylated ketones and sulphonamides in good to excellent yields (Scheme 31).[30]



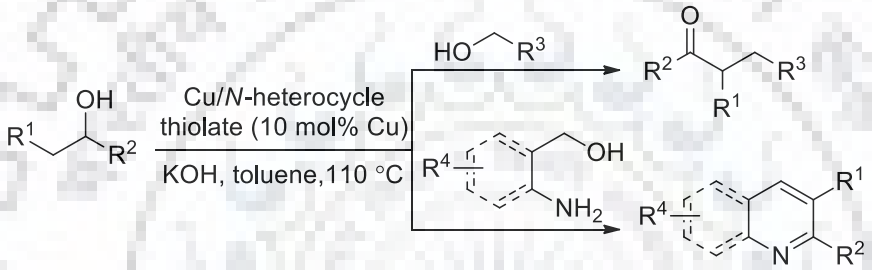

**Scheme 31:** Re-catalyzed alkylation of ketones and sulphonamides with alcohols

Another interesting, Ir-NHC complex is reported for the $\alpha$-alkylation of ketones with primary alcohols. The reaction required only 0.05-0.5 mol% catalyst and catalytic amount of KOH, gave $\alpha$-alkylated ketones in high yields (Scheme 32).[31]




**Scheme 32:** Ir-NHC-catalyzed synthesis of *α*-alkylated ketones

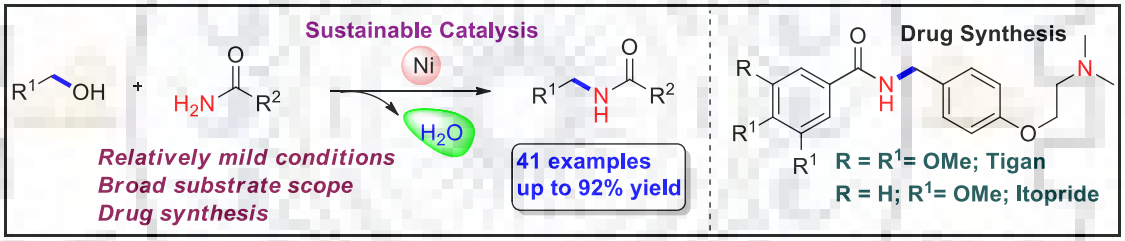
In 2018, Lang and coworkers developed a hexa-nuclear-Cu(I)-cluster bearing 4, 6-dimethyl-pyrimidine-2-thiolate as ligands for the synthesis of *α*-alkylated ketones. The catalytic protocol follows double de-hydrogenative-coupling of secondary and primary alcohols to *α*-alkylated ketones. Application to the synthesis of quinolines and pyridines highlighted the potential of the catalytic protocol (Scheme 33).[32]




**Scheme 33:** Cu-catalyzed synthesis of *α*-alkylated ketones and *N*-heterocycles

## Chapter-2: Nickel-catalyzed direct *N*-alkylation of amides with alcohols

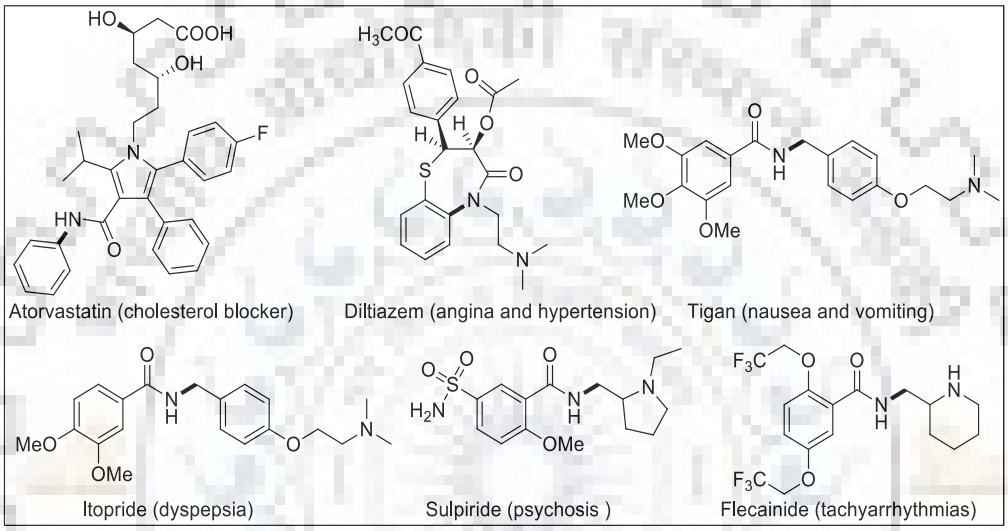
In the Chapter-2 we demonstrated the development of an operational simple, practical, and selective Ni-catalyzed synthesis of secondary amides. Application of renewable alcohols, earth-abundant and non-precious nickel catalyst facilitates the transformations, releasing water as byproduct. The catalytic system is tolerant to a variety of functional groups including nitrile, allylic ether, and alkene and could be extended to the synthesis of bisamide, antiemetic drug Tigan, and dopamine D2 receptor antagonist Itopride. Preliminary mechanistic studies revealed the participation of a benzylic C-H bond in the rate determining step.




*J. Org. Chem.* **2018**, *83*, 3378−33843

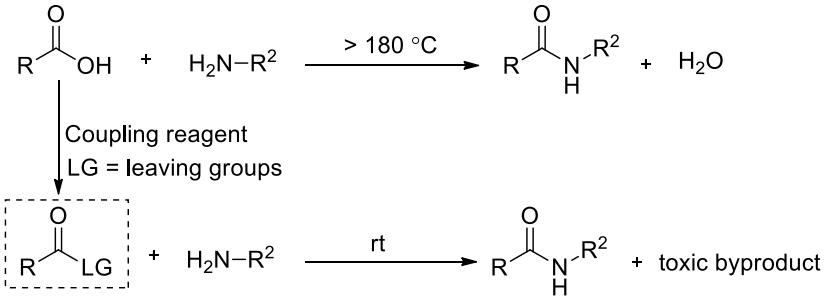
## [2.1] Introduction:

Amide bonds are omnipresent in living systems as peptide bond to pharmaceutically active natural products. The amide functionality is also versatile in frequently used materials such as nylon, artificial silks, hydrogels, supported catalysts and biocompatible matrices for cell growth.[1] In a survey in 2006, it was found that amide bond is present in 25% of all current marketed drugs.[2] This includes Atorvastatin (top selling drug which blocks production of cholesterol),[3] Diltiazem (calcium channel blocker),[4] Tigan (nausea and vomiting),[5] Itopride (dyspepsia),[6] etc. (Scheme 1).




**Scheme 1:** Some important drug molecules containing amide bond

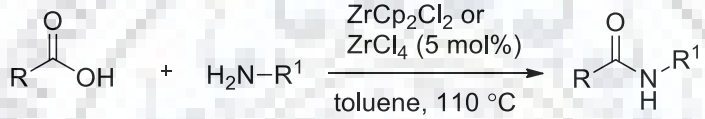
Owing to their high importance and demand, although several methods were developed for the synthesis of amide bonds, still a large number of pharmaceuticals synthesis has to rely on classical methodologies. Classical methodologies for the synthesis of amide bonds involves carboxylic acids or their derivatives with amines, which required high reaction temperature (>180 °C), limited functional group tolerance and generates stoichiometric waste (Scheme 2). Further, a few enzymatic methods were also available, but high isolation cost and substrate scope limits their applications in large scale synthesis.[7] Hence in 2007, American Chemical Society of Green Chemistry Institute recognized sustainable and atom-economic technology for amide synthesis, which minimize the waste generation.[8] Metal-catalysis could be the probable solution which not only minimize the expenses associated with previous methodologies but also environmentally benign and it provides an opportunity to use other coupling partner such as ester, aldehyde, alcohol, nitrile and oxime instead of carboxylic acid.




**Scheme 2:** Classical methods for the synthesis of amide

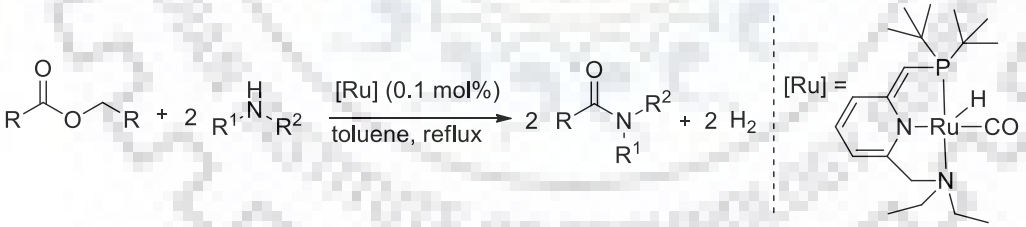
**[2.2] Brief literature review for transition metal-catalyzed amide bond formation:**

In this direction, Williams and coworkers utilized 5 mol% of $ZrCl_4$ or $ZrCp_2Cl_2$ to couple carboxylic acid with amine and the corresponding amide products were isolated in moderate to excellent yields using toluene as a solvent at 110 °C (Scheme 3).[9]




**Scheme 3:** Zr-catalyzed formation of amide from carboxylic acid and amine

In 2011, Milstein and coworkers developed a ruthenium-pincer PNN complex for the synthesis of amide directly from ester and amine with the liberation of hydrogen as byproduct. Both primary and secondary amines were transformed into corresponding amides in moderate to excellent isolated yields with high turnover number (up to 1000) (Scheme 4).[10]

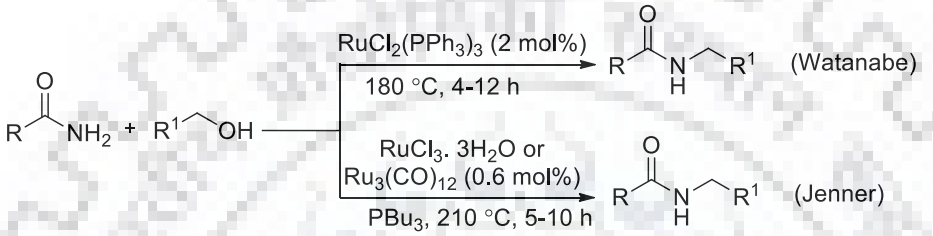



**Scheme 4:** Formation of amide from ester catalyzed by Ru-PNN complex

It is to be noted that, aldehydes, nitriles, oximes, acid chlorides and anhydrides could be utilized as coupling partner with amine for the synthesis of amide bond.[11] In addition, aryl and alkenyl halides were also employed for *N*-alkylation of amide as a suitable coupling partner.[12] But the use of alcohol as a coupling partner is preferable, due to its, highly abundant as well as inexpensive nature and generates only water as a byproduct. However, due to strong co-ordination properties of the hydroxyl group and poor leaving ability makes it inferior substrate class for such transformations and required harsh reaction conditions. Nevertheless, in terms of sustainability, metal-catalyzed borrowing hydrogen or hydrogen

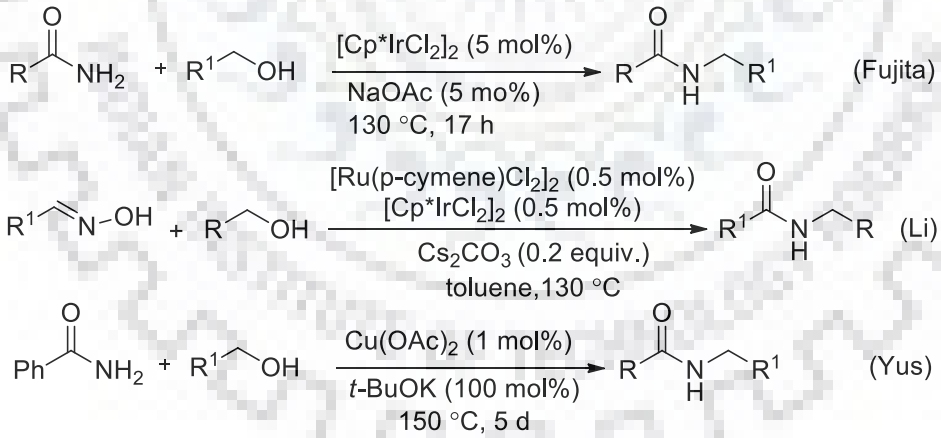
auto-transfer (BH/HA) approach renders an elegant technology for formal C-N bond forming reactions.[13] Over the past decades, *N*-alkylation of amines using alcohols *via* BH/HA strategy has been well studied.[13]

On the other hand, *N*-alkylation of primary amides are quite limited, because of poor nucleophilicity compare to amines and often required higher catalyst loadings or higher reaction temperature. In this direction, notable breakthrough by the group of Watanabe,[14] and Jenner,[15] for *N*-alkylation of amide using alcohols under ruthenium catalysis at 180 $^{o}$C-210 $^{o}$C is worth mentioning (Scheme 5).



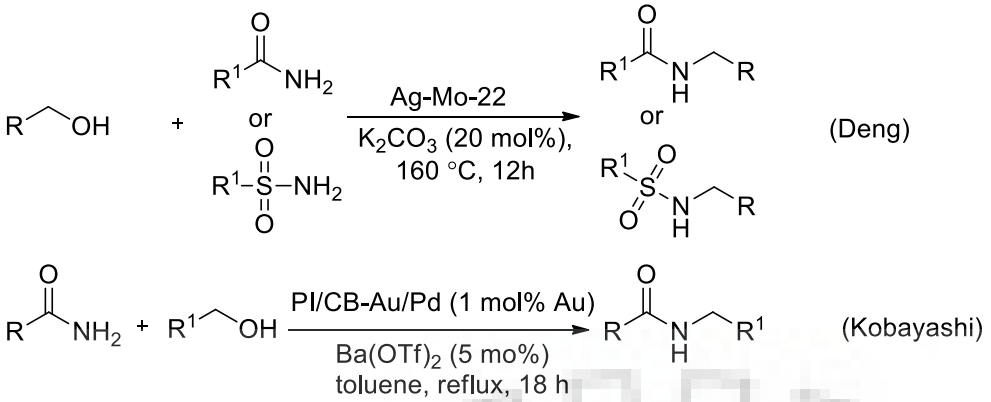

**Scheme 5:** Ru-catalyzed *N*-alkylation of amide

Later, significant contribution by Fujita, Yu and Xu, Trudell and Anderson (Ir-catalysts),[16] Williams (Ru-catalyst),[17] Li (Ru/Ir-dual catalyst),[18] and Yus (Cu-catalyst),[19] for amidation of alcohols are noteworthy (Scheme 6).




**Scheme 6:** Ru, Ir and Cu-catalyzed *N*-alkylation of amides with alcohols

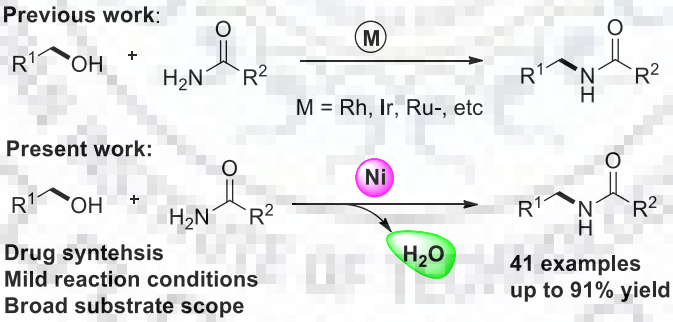
Further, Deng and co-workers as well as Kobayashi and co-workers, independently studied the application of Ag/Mo oxide and Au/Pd nanoparticle for amidation of alcohols using hydrogen transfer strategy (Scheme 7).[20]




**Scheme 7:** Au/Mo and Au/Pd catalyzed *N*-alkylation of amides with alcohols

**[2.3] Aim of Present Work:**

Direct *N*-alkylation of amides with alcohols for the synthesis of secondary amides using non-precious and earth-abundant transition metal-based catalysts is highly interesting and has not been explored much. Herein, in this chapter, we have uncovered the reactivity of nickel-catalysts for the selective synthesis of secondary amides from primary amide with alcohols. Application of renewable alcohols, earth-abundant and non-precious nickel catalyst enables the transformation, releasing water as by product. The catalytic system is tolerant to variety of functional groups including nitrile, allylic ether and alkene and could be extended to the synthesis of bis-amide, antiemetic drug Tigan and dopamine D2 receptor antagonist Itopride.




**Scheme 8**: Ni-catalyzed direct amidation of alcohols

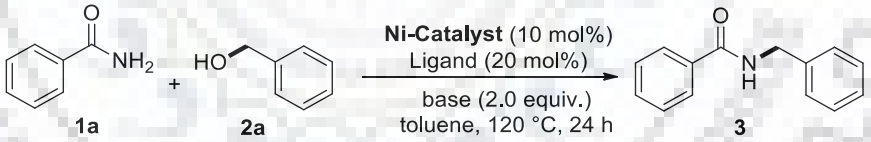
**[2.4] Results and discussion:**

With this aim, to explore the scope of earth-abundant base-metal catalysts, we became interested in the nickel-catalyzed amidation of alcohols with primary amide. The high natural abundance and inexpensive nature associated with nickel would serve an attractive sustainable alternative to palladium-catalysts. To the best of our knowledge, till date no nickel-catalyzed general methodology for amidation of primary alcohols have been

disclosed. Herein, for the first time we have developed a simple nickel catalyst system in combination with nitrogen ligands that enables the selective mono-alkylation of a variety of amides with primary alcohols. Notably, the optimized protocol could be applied in the presence of nitrile, allylic and alkene moieties as reducible functional groups. The key features of the methodology provide a general synthesis of bis-amide, and drug molecules Tigan and Itopride.

However, to explore the direct amidation of alcohols, initially we anticipated two key challenges: (i) the efficiency of the Ni-catalyst to obtain alcohol dehydrogenation and (ii) the ability of the *in situ* formed Ni-hydride species for imide hydrogenation. To realize this goal, five different nickel complexes having oxidation state of Ni(0) and Ni(II) were assayed for their efficiency to catalyze the model reaction of benzamide **1a** and benzyl alcohol **2a** (Table 1). Notably, we observed that, a combination of 10 mol% $NiBr_2$, 20 mol% 1,10-phenthroline **L1** and 0.5 mmol of $K_3PO_4$ at 120 °C in toluene resulted *N*-alkylated amide **3** with 75% selectivity in GC-MS analysis of the crude reaction mixture (Table 1). Further to improve the product yield, a variety of nitrogen-based ligands, **L2-L5** having variable electronic nature were employed and exhibited poor selectivity of **3**, whereas the phosphine-based ligands, **L6-L7** resulted in up to 45-65% conversion to product **3** (Table 2).

**Table 1**: Screening of catalysts [a]

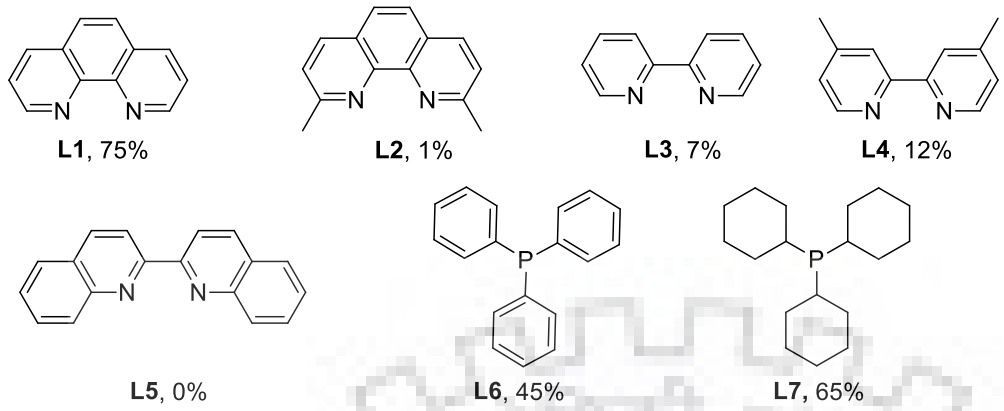



| Entry | **Ni-Catalyst** | **3**, GC-MS conversion (%) |
|---|---|---|
| 1 | $NiCl_2$ | 15 |
| **2** | **$NiBr_2$** | **75** |
| 3 | $Ni(acac)_2$ | 60 |
| 4 | $Ni(DME)Cl_2$ | 58 |
| 5 | $Ni(COD)_2$ | 7 |
| 6 | - | 0 |

Reaction conditions: [a] Benzyl alcohol **1a** (1.0 mmol), benzamide **2a** (0.25 mmol), **Ni-catalyst (10 mol%)**, Phen (20 mol%), $K_3PO_4$ (0.5 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 120 ºC oil bath, 24 h reaction time.

The product conversion suppressed significantly, when xylene and 1,4-dioxane were used as solvents instead of toluene (Table 3). Moreover, the application of polar solvents, such as, *N*,*N*-dimethylacetamide (DMA) and *N*,*N*-dimethyl-formamide (DMF) did not result any desired product (Table 3).

**Table 2**: Screening of ligands [a]




Reaction conditions: [a] Benzyl alcohol **1a** (1.0 mmol), benzamide **2a** (0.25 mmol), $NiBr_2$ (10 mol%), **ligand (20 mol%),** $K_3PO_4$ (0.5 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 120 ºC oil bath, 24 h reaction time.

**Table 3**: Screening of solvents [a]

| Entry | **Solvent** | **3,** GC-MS conversion (%) |
|---|---|---|
| **1** | **Toluene** | **75** |
| 2 | *p*-Xylene | 22 |
| 3 | Dioxane | 30 |
| 4 | DMA | 0 |
| 5 | DMF | 0 |

Reaction conditions: [a] Benzyl alcohol **1a** (1.0 mmol), benzamide **2a** (0.25 mmol), $NiBr_2$ (10 mol%), ligand **L1** (20 mol%), $K_3PO_4$ (0.5 mmol), **solvent (2.0 mL)**, Schlenk tube under nitrogen atmosphere, 120 ºC oil bath, 24 h reaction time.

**Table 4**: Screening of base [a]

| Entry | **Base** | NMR yield of **3** (%) |
|---|---|---|
| 1[b] | *t*-BuOK | 32 |
| 2[c] | *t*-BuONa | 60 |
| 3[c] | $Cs_2CO_3$ | 5 |
| 4[c] | $K_2CO_3$ | 65 |
| 5[c] | $Na_2CO_3$ | 15 |
| **6[c]** | **$K_3PO_4$** | **75** |

Reaction condition: [a] Benzyl alcohol **1a** (1.0 mmol), benzamide **2a** (0.25 mmol), $NiBr_2$ (10 mol%), Phen (20 mol%), **base (0.5 mmol)**, toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 120 ºC oil bath, 24 h reaction time. [b] GC-MS conversion, [c] NMR yield using diphenylmethane as internal standard.

The use of carbonate bases and alkali metal alkoxide such as sodium or potassium tertiary butoxide did not increase the product conversion further (Table 4). To our delight, under identical conditions we observed 83% isolated yield and >98% selectivity of **3** at 130 °C. Decreasing the base equivalency results in reduced product conversion (Table 5).

**Table 5**: Screening of base equivalents [a,b]

| Entry | **Base equiv. (X equiv.)** | NMR yield of **3** (%) |
|---|---|---|
| **1** | **$K_3PO_4$ (2.0)** | **>98(83)** |
| 2 | $K_3PO_4$ (1.5) | 74 |
| 3 | $K_3PO_4$ (1.0) | 49 |
| 4 | No Base | 0 |

Reaction condition: [a] Benzyl alcohol **1a** (1.0 mmol), benzamide **2a** (0.25 mmol), $NiBr_2$ (10 mol%), Phen (20 mol%), $K_3PO_4$ **(X equiv.)**, toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 130 ºC oil bath, 24 h reaction time. Isolated yield in bracket. [b] NMR yield using diphenylmethane as internal standard.

As expected, lower catalyst loading suppressed the product conversion and no *N*-alkylated product was observed in absence of catalyst (Table 6). Control experiments in absence of ligand and base resulted poor or no product conversions to **3** (Table 5).

**Table 6**: Screening of catalyst and ligand loading [a]

| Entry | **Catalyst loading** | **Ligand loading** | GC-MS conversion of **3** (%) |
|---|---|---|---|
| **1** | **$NiBr_2$ (10 mol%)** | **Phen (20 mol%)** | **>98** |
| 2 | $NiBr_2$ (5 mol%) | Phen (10 mol%) | 70 |
| 3 | $NiBr_2$ (2.5 mol%) | Phen (5 mol%) | 60 |
| 4 | - | - | 0 |

Reaction condition: [a] Benzyl alcohol **1a** (1.0mmol), benzamide **2a** (0.25 mmol), **$NiBr_2$ (X mol%), Phen (Y mol%)**, $K_3PO_4$ (0.5 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 130 ºC oil bath, 24 h reaction time.

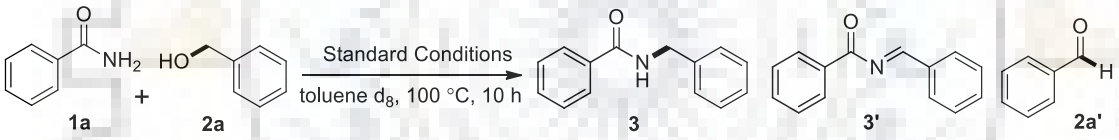
Alcohol equivalency also played a crucial role for this catalytic transformations and four equivalents of alcohols was found to be necessary to obtain excellent product yield and selectivity (Table 7).

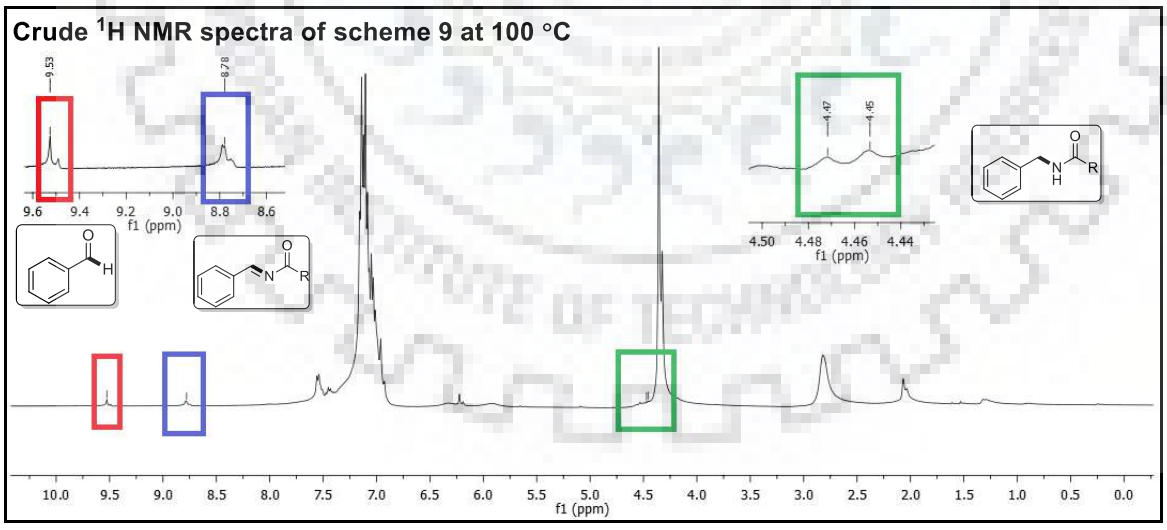
**Table 7**: Screening of alcohol equivalents [a,b]

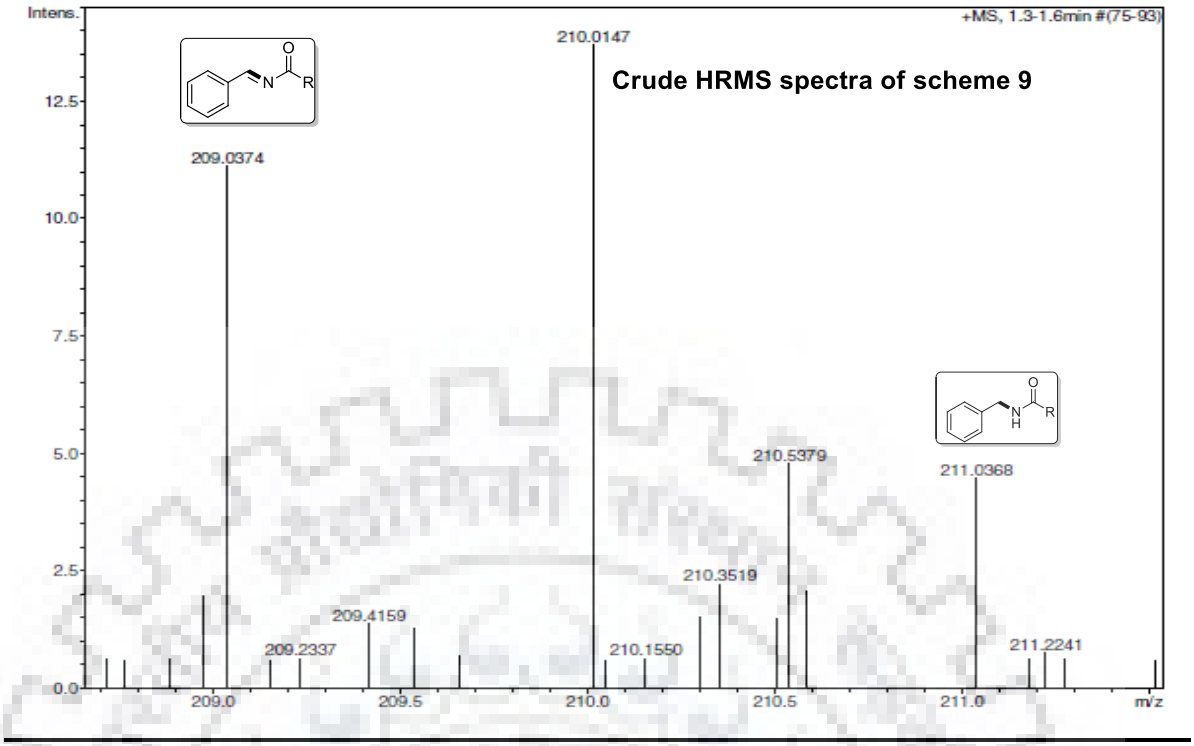
| Entry | **Benzyl alcohol (X equiv.)** | Time (h) | NMR yield of **3** (%) |
|---|---|---|---|
| **1** | **4** | **24** | **>98(83)** |
| 2 | 3 | 24 | 62 |
| 3 | 2 | 24 | 41 |
| 4 | 1 | 24 | 10 |

Reaction condition: [a] **Benzyl alcohol 1a (X mmol)**, benzamide **2a** (0.25 mmol), $NiBr_2$ (10 mol%), Phen **L1** (20 mol%), $K_3PO_4$ (0.5 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 130 ºC oil bath, 24 h reaction time. Isolated yield in parenthesis. [b] NMR yield using diphenylmethane as internal standard.

Further, under optimal conditions an *in situ* NMR studies were performed using toluene-$d_8$ at 100 °C and monitor the progress of the reaction. The product formation profile allows the detection of **1a**, benzaldehyde, imide and **3**, all possible reaction intermediates, which are in strong agreement of the hydrogen borrowing methodology under nickel catalysis (Scheme 9).



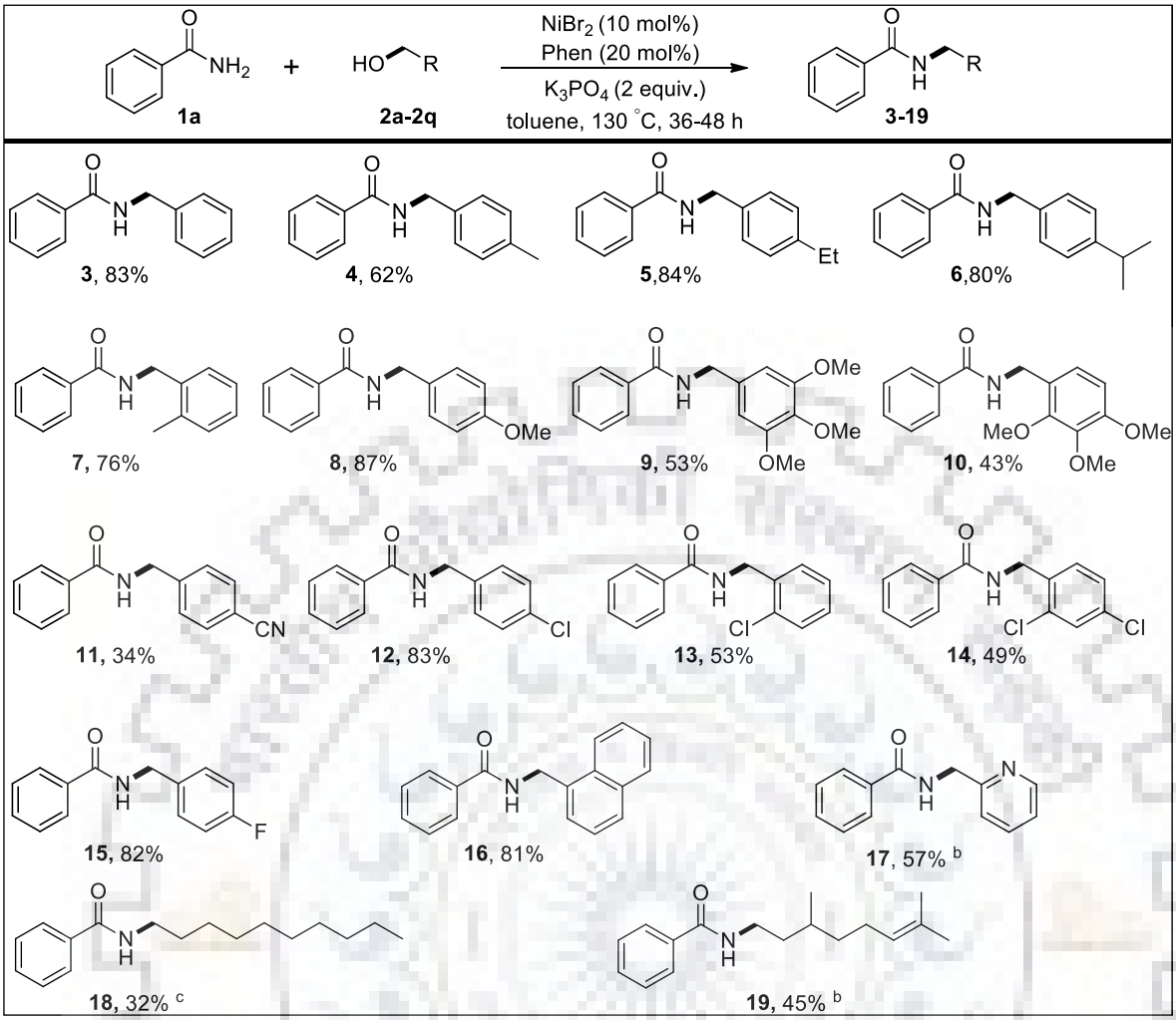






**Scheme 9:** Detection of probable intermediates by $^{1}$H-NMR experiment and HRMS analysis

Reaction conditions: Benzyl alcohol **1a** (0.2 mmol), benzamide **2a** (0.1mmol), $NiBr_2$ (0.025 mmol), Phen (0.05 mmol), $K_3PO_4$ (0.5 mmol), toluene $d_8$ (0.4 mL), NMR tube under nitrogen atmosphere, $^{1}$H NMR was recorded at 100 °C.

After having identified the optimized conditions, the scope and efficiency of the nickel-catalyzed amidation of alcohols were studied (Scheme 10). Electron donating substituents on benzyl alcohols are well tolerated and furnished 62-87% yield of *N*-alkylated amides (Scheme 10, **4-6** and **8**). Sterically hindered substrate such as 2-methyl benzyl alcohol, 2-chloro and 2,4-dichloro benzyl alcohols were efficiently transformed into the corresponding amides in up to 76% isolated yields (Scheme 10, **7**, **13**-**14**). It is to be noted that, lower product yields were obtained when benzyl alcohol having multiple electron donating substituent were used (Scheme 10, **9-10**). Further, 1-naphthalenemethanol, *p*-chloro and *p*-fluoro-benzyl alcohols furnished the desired products with excellent isolated yields, 81-83% and no de-halogenated product was observed (Scheme 10, **12, 15** and **16**). Gratifyingly, 2-pyridenemethanol, decanol and renewable terpenoid intermediate citronellol were also employed for the alkylation under optimized reaction conditions (Scheme 10, **17-19**). Notably, the chemo-selective transformation of unsaturated alcohol and nitrile group represents a rare instance, otherwise difficult under precious-metal catalysis (Scheme 10, **11** and **19**).

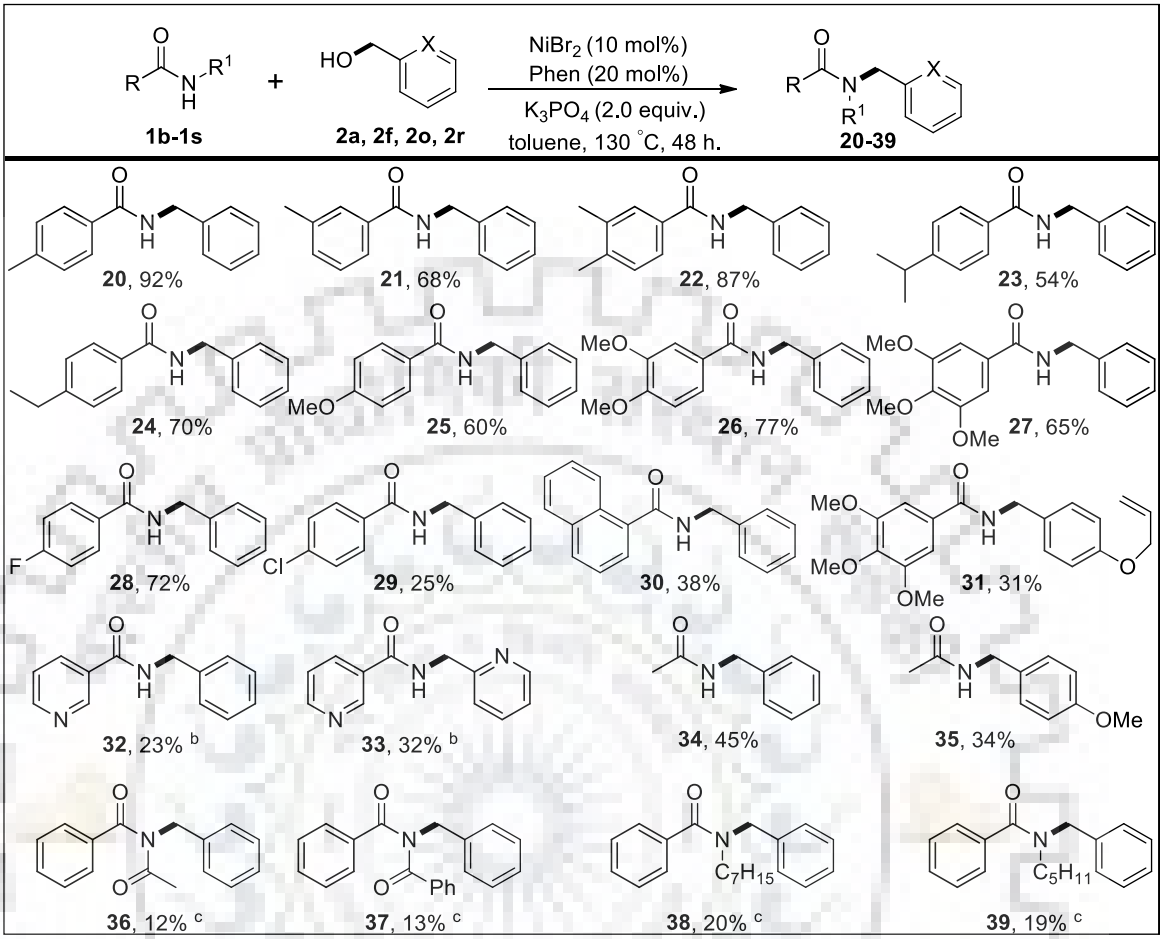



**Scheme 10:** Scope of primary alcohols [a]

Reaction conditions: [a] The reaction was carried out with **1a** (0.25 mmol), **2** (1.0 mmol), $NiBr_2$. (10 mol%), Phen (20 mol%), $K_3PO_4$ (0.5 mmol), 130 °C in toluene (2.0 mL).[b] *t*-BuONa (0.5 mmol) was used. [c] GC-MS yield.

Next, selective mono-alkylation of various benzamides were demonstrated using optimum catalytic conditions (Scheme 11). Benzamide derivatives bearing electron rich functionalities, such as, methyl, ethyl, isopropyl and methoxy groups were well tolerated and furnished the desired products in moderate to excellent isolated yields in up to 92% respectively (Scheme 11, **20-25**). Di-methoxy and tri-methoxy benzamides were also underwent the reaction smoothly and **26** and **27** were isolated in 65-77% yield respectively. It is to be noted that, electron poor *p*-fluorobenzamide resulted 72% yield of the *N*-alkylated amide whereas, chloro substituent was less reactive under the optimized conditions (Scheme 11, **28** and **29**). The catalytic protocol is tolerant to terminal double bond as well as ether moiety to afford the sterically hindered amide **31** (Scheme 11). Importantly, the scope of nicotinamide was also studied with benzyl alcohol as well as with 2-pyridenemethanol and

affords the corresponding pharmaceutically active nicotinamide derivatives in moderate yields (Scheme 11, **32-33**).



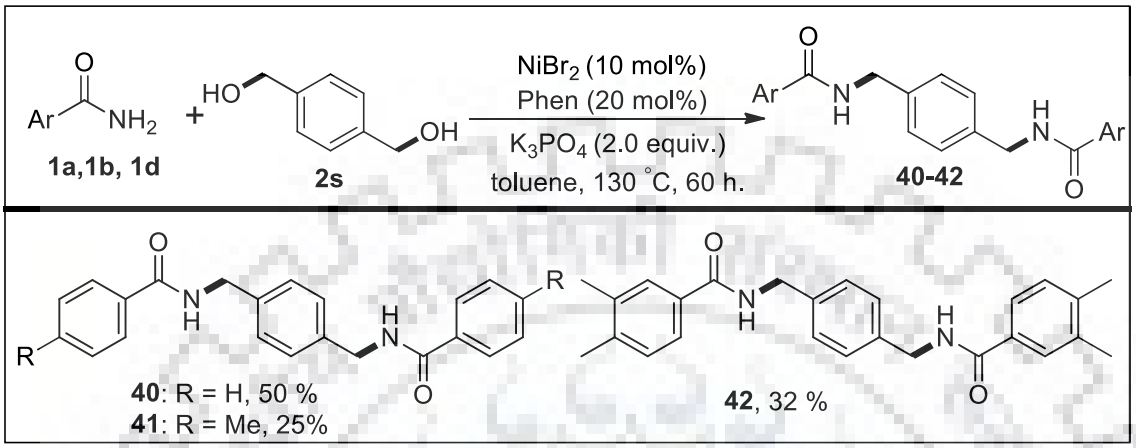

**Scheme 11:** Scope of amides [a]

Reaction conditions: [a] Unless specified, the reaction was carried out with **1a** (0.25 mmol), **2** (1.0 mmol), $NiBr_2$. (10 mol%), Phen (20 mol%), $K_3PO_4$ (0.5 mmol), 130 °C in toluene (2.0 mL).[b] *t*-BuONa (0.5 mmol) was used. [c] $^1$H-NMR yield using diphenylmethane as an internal standard.

Gratifyingly, more challenging, acetamide resulted the desired products in 34-45% yields respectively (Scheme 11, **34-35**). The catalytic protocol is highly selective for primary amides and the applications of secondary amide derivatives under the optimized conditions resulted poor product conversions (Scheme 11, **36-39**).

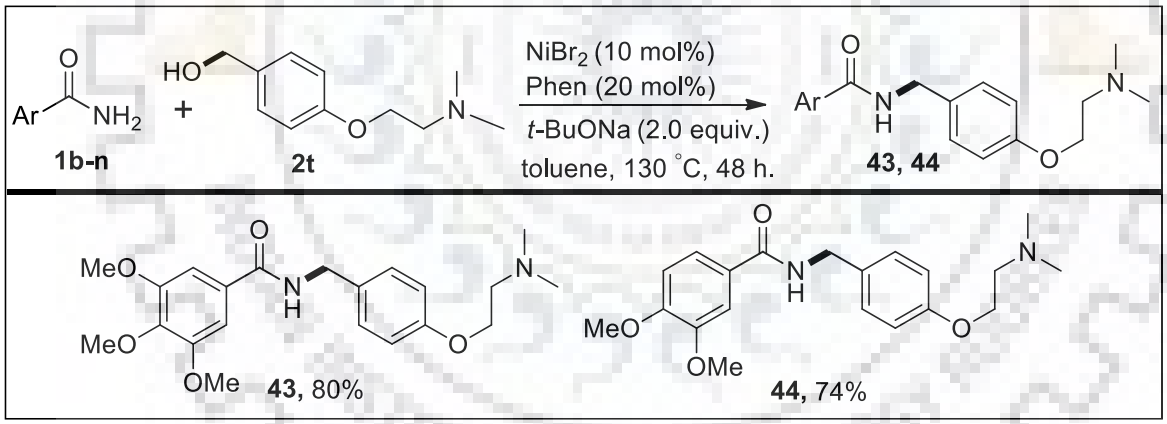
Having demonstrated the broad scope of the amidation protocol, we were interested to explore the application of 1,4-phenylenedimethanol with different benzamide derivatives. Notably, the resulted multi-functional amides **40**-**42** were obtained in 25-50% yield (Scheme 12). Further, to explore the synthetic potential of the catalytic protocol, an attempt was established in one step synthesis of antiemetic drug Tigan, as well as dopamine D2 receptor antagonist, Itopride. To our delight, the resulted drugs were obtained in good isolated yields

(Scheme 13, **43** and **44**). It is noteworthy to mention that, the catalytic protocol is tolerant to nitrogen heterocycles, allylic ethers, nitrile and alkene, including halides and alkoxy moieties. Unfortunately, under identical conditions, reducible functional moieties, such as, nitro, carboxylic acids, esters and alkynes were not successful.




**Scheme 12. Amidation with 1,4-phenylenedimethanol**

Reaction conditions: [a] Unless specified, the reaction was carried out with **1** (0.25 mmol), **2s** (1.0 mmol), $NiBr_2$. (10 mol%), Phen (20 mol%), $K_3PO_4$ (0.5 mmol), 130 °C in toluene (2.0 mL).



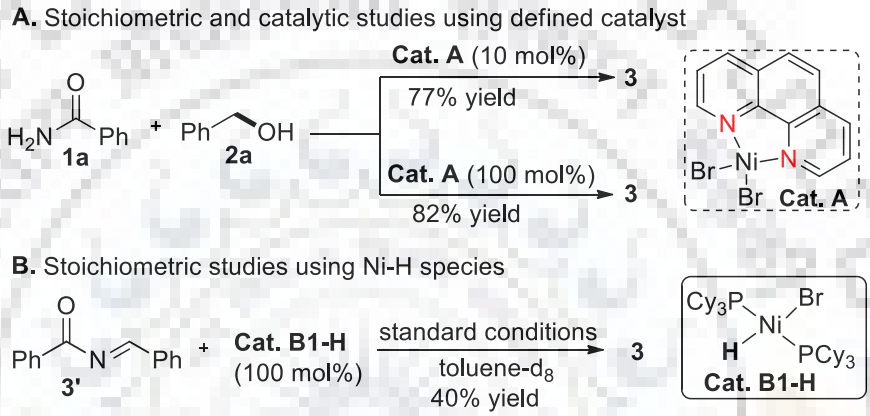

**Scheme 13: Synthetic applications**

Reaction conditions: [a] Unless specified, the reaction was carried out with **1** (0.25 mmol), **2t** (1.0 mmol), $NiBr_2$. (10 mol%), Phen (20 mol%), *t*-BuONa (0.5 mmol), 130 °C in toluene (2.0 mL).

**Kinetic and Mechanistic studies:**

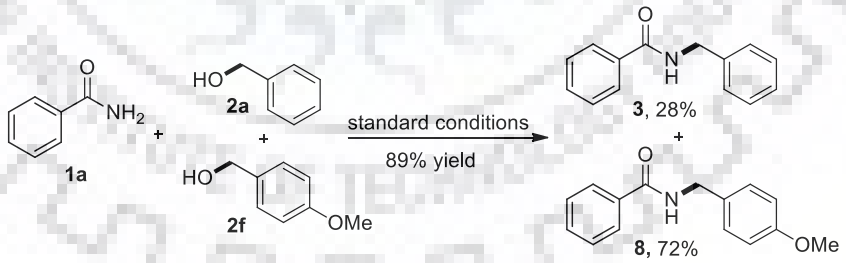
The excellent selectivity and broad substrate scope of this catalytic protocol encouraged us to gain more insight about the preliminary mechanistic investigation of the process. The *in situ* NMR-studies (Scheme 9) revealed that, the proposed amidation of alcohols composed of a multi-step BH/HA technique. Nevertheless, to confirm the participation of the putative Ni-intermediate species, the **Cat. A** was independently prepared, and used in catalytic as well as in stoichiometric equiv. in the model reaction.[21] The desired product **3** was obtained

in good isolated yields (Scheme 14A). In addition, an attempt to prepare the Ni-H species of **Cat. A** in combination with **2a** was not successful and we observed aldehyde formation using an *in situ* NMR studies at -75 °C. The experimental results evident that, the Ni-H species is highly unstable to identify even at low temperature. Gratifyingly, we choose tri-cyclohexyl phosphine **L7** (Table 2), the defined complex $\{(Cy)_3P\}_2NiBr_2$ and the Ni-hydride species $\{(Cy)_3P\}_2NiBrH$, **Cat.B1-H** were readily prepared. Next, the **Cat.B1-H** was employed in stoichiometric equiv. with imide **3'** under optimized conditions.[22] To our delight, **3** was obtained in 40% yield (Scheme 14B). These experimental findings evident the participation of Ni-H species.




**Scheme 14:** Mechanistic investigation using defined catalyst

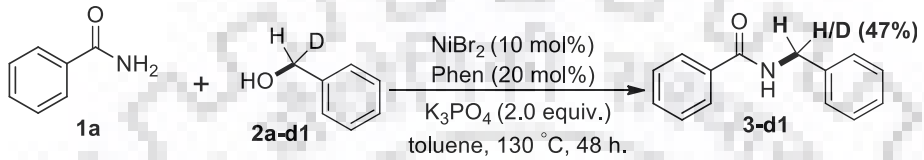
In addition, a competitive experiment between benzyl alcohol **2a** and 4-methoxy benzyl alcohol **2f** were performed and revealed that, for electron rich substituent amidation occurs at higher rates and a ratio of 1:2.6 of product **3** and **8** were observed (Scheme 15).



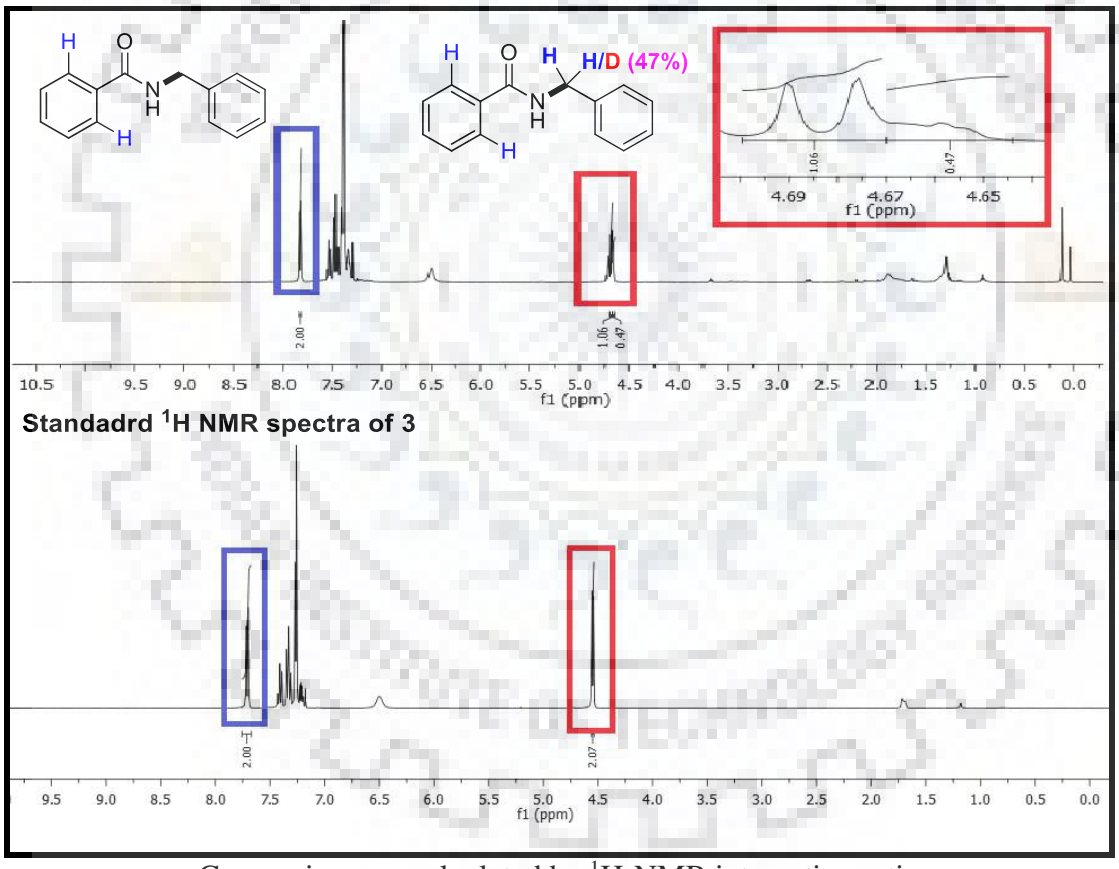

**Scheme 15:** Competitive reaction between **2a** and **2f** with benzamide **1a**

Further, amidation reaction of **1a** with **2a-d1** was studied and the product distribution analysis using $^1$H-NMR showed the selective formation of **3-d1** and **3** along with 47% deuterium incorporation at the benzylic position of **3-d1** (Scheme 16). Then benzamide **1a** was reacted with deuterated benzyl alcohol **2a-d2** under identical conditions and the product distribution was analyzed by $^1$H-NMR and HRMS. Both measurements showed the exclusive formation of **3-d2** (82%) and 18% of **3-d1** (Scheme 17). Notably, to gain more

insight about the kinetic isotope effect (KIE), an intermolecular competition reaction of **2a** and **2a-d2** with **1a** were studied under the standard catalytic conditions and the observed product ratio on the basis of $^1$H-NMR as well as HRMS analysis witnessed $k_{CHH}/k_{CDD}$ = 2.70. These deuterated experimental evidences are in strong agreement with the literature observation of D/H exchange and the micro-reversible transformation of BH/HA process (Scheme 18).[23] These experimental findings evident the involvement of the benzylic C-H bond cleavage in the rate determining step (Scheme 17, 18).[24]



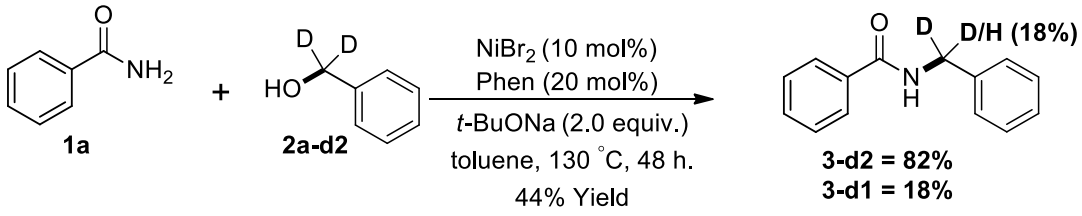

**Crude $^1$H NMR spectra of Scheme 16**

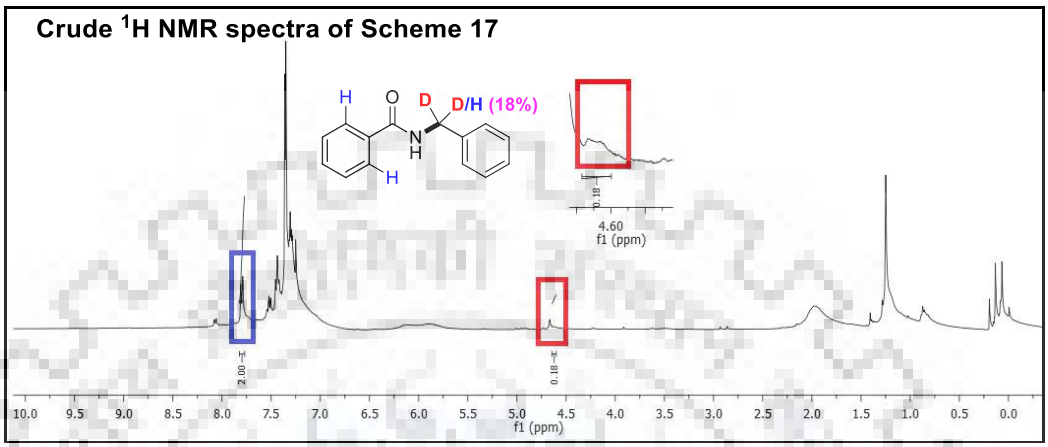


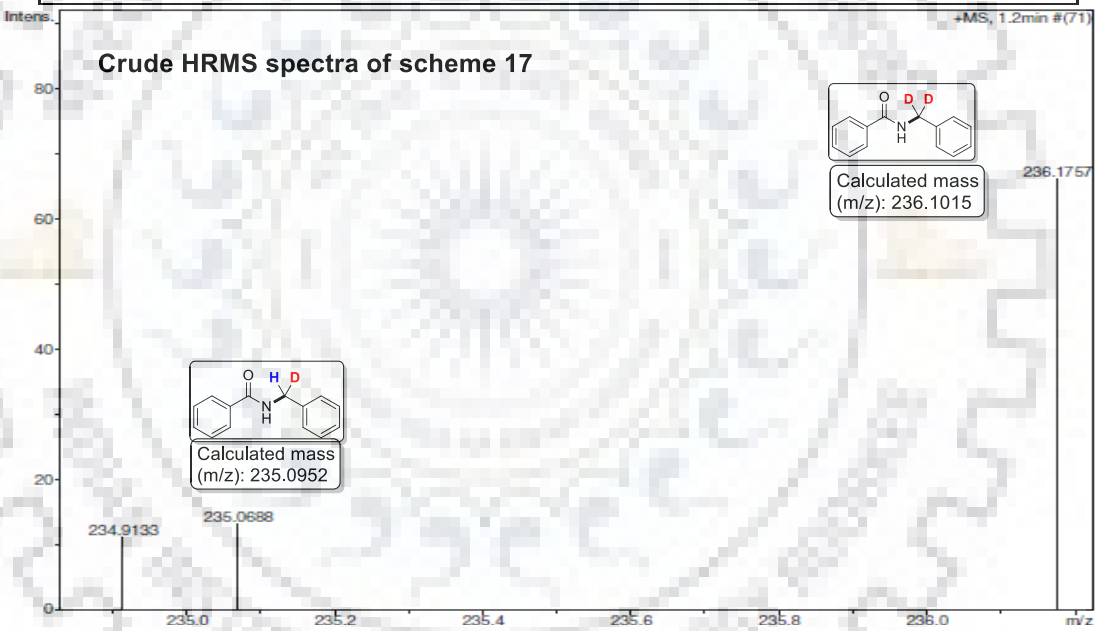

Conversion was calculated by $^1$H-NMR integration ratio

| | **3 + 3-d$_1$** | **3** | **3-d1** |
|---|---|---|---|
| Signal $\delta$ | 7.79 [*ortho*-H, (2H)] | 4.64 [benzyl-H (2H)] | 4.61 [benzyl-H (1H)] |
| Integral Value | 2.00 | 1.06/2.00 = 0.53 | 0.47 |
| Calculated ratio | - | 53% | 47% |

**Scheme 16:** Deuterium labeling experiment with benzyl alcohol **2a-d1**



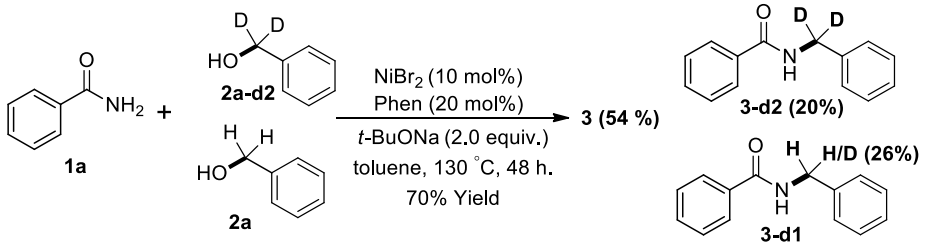



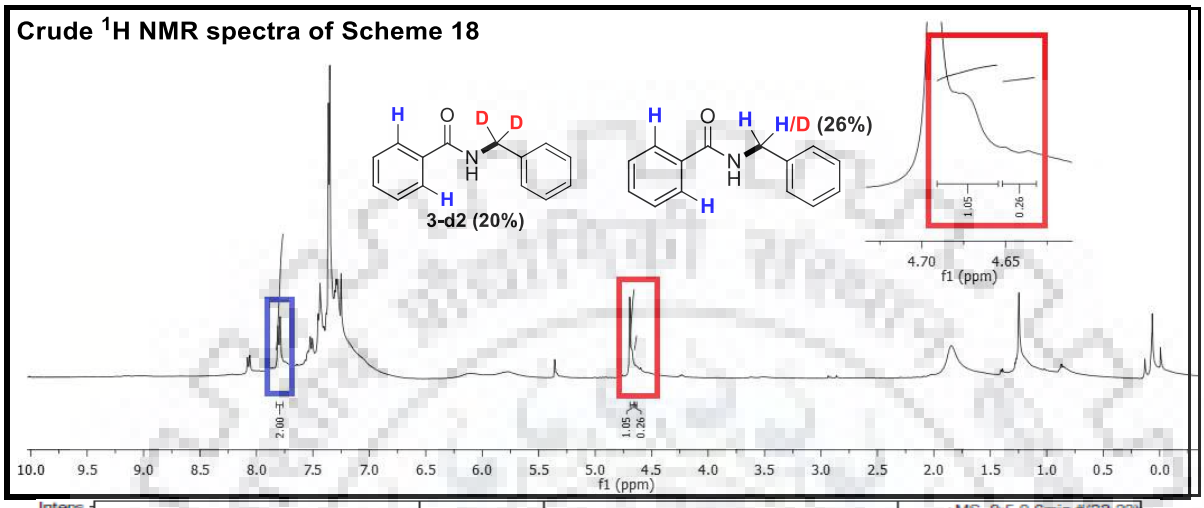



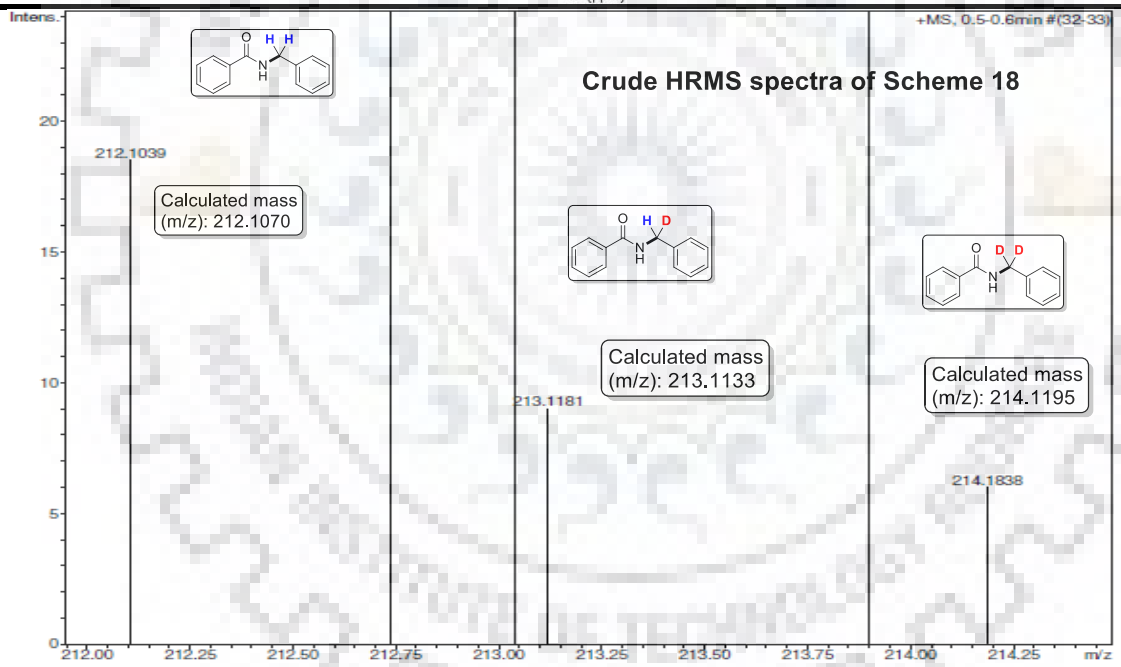

Conversion was calculated by $^1$H NMR integration and HRMS peak ratio

| | **3 + 3-*d*$_1$** | **3-*d*$_1$** | **3-*d*$_2$** |
|---|---|---|---|
| Signal $\delta$ | 7.79 [*ortho*-H, (2H)] | 4.65 [benzyl-H (1H)] | - |
| Integral Value | 2.00 | 0.18 | |
| Calculated ratio | | **18%** | **82%** |
| HRMS ratio | | **18%** | **82%** |

**Scheme 17:** Deuterium incorporation experiment with benzyl alcohol **2a-d2** and benzamide




Conversion was calculated by $^1$H NMR integration and HRMS peak ratio.

| | **3 + 3-$d_1$** | **3** | **3-$d_1$** | **3-$d_2$** |
|---|---|---|---|---|
| Signal $\delta$ | 7.79 [*ortho*-H, 2H)] | 4.66 [benzyl-H (2H)] | 4.65 [benzyl-H (1H)] | - |
| Integral Value | 2.00 | 1.06/2 = 0.53 | 0.26 | |
| Calculated ratio | | **53%** | **26%** | **21%** |
| HRMS ratio | | **54%** | **26%** | **20%** |
| KIE | | $K_{CHH}/K_{CDD}$ **= 2.70** | | |

**Scheme 18:** Competitive reaction between **2a** and **2a-d2** with benzamide **1a**

**[2.5] Conclusions:**

We have developed an efficient and selective direct amidation of renewable alcohols using earth-abundant and non-precious Ni-catalyst. The transformations could efficiently be performed in the presence of reducible functional moieties, such as, nitrile, allylic ether and alkenes. As a special highlight, we have demonstrated the synthesis of bis-amides, antiemetic drug Tigan **43**, and dopamine D2 receptor antagonist, Itopride **44**. Preliminary mechanistic investigation evident the participation of Ni-H species and established the bifunctional nature of the Ni-catalyst. The kinetic isotope effect (KIE) studies revealed the involvement of the benzylic C-H bond in the rate-determining step.

**[2.6] Experimental Section:**

**General Experimental Details:** All solvents and reagents were used, as received from the suppliers. TLC was performed on Merck Kiesel gel 60, $F_{254}$ plates with the layer thickness of 0.25 mm. Column chromatography was performed on silica gel (100-200 mesh) using a gradient of ethyl acetate and hexane as mobile phase. $^{1}$H NMR spectral data were collected at, 400 MHz(JEOL), and $^{13}$C NMR were recorded at 100 MHz. $^{1}$H NMR spectral data are given as chemical shifts in ppm followed by multiplicity (s- singlet; d- doublet; t- triplet; q- quartet; m- multiples), number of protons and coupling constants. $^{13}$C NMR chemical shifts are expressed in ppm. High-resolution mass spectra (HRMS) were obtained on a Brüker micro TOF-Q II mass spectrometer (ESI-MS). GC-MS were recorded using Perkin-Elmer Mass Spectrometer. Melting points were recorded using OptiMelt MPA100.

**General procedure for nickel-catalyzed amidation of alcohols:**

In a 20 mL oven dried Schlenk tube, amide **1** (0.25 mmol), base (0.5 mmol), Phen (20 mol%), $NiBr_2$ (10 mol%) and alcohols **2** (1.0 mmol) were added followed by toluene 2 mL under an atmosphere of $N_2$ and heated at 130 °C for 24-48 h. The reaction mixture was cooled to room temperature and 3.0 mL of ethyl acetate was added and concentrated *in vacuo.* The residue was purified by column chromatography using a gradient of hexane and ethyl acetate (eluent system) to afford the pure products.

**Synthesis and characterization of *N*-(4-ethylbenzyl)benzamide (5)**:

Following the general procedure the title compound **5** was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/ hexane (1:4), (0.050g, Yield: 84%); mp 101-102 °C. All the compounds were characterized by $^{1}$H-NMR, $^{13}$C-NMR,

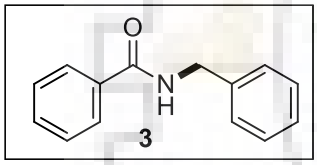
HRMS (ESI-TOF) and IR and the results are shown in spectral data. For an example, all the spectral data of compound 5 are explained here.

**$^1$H NMR**. the five aromatic region protons are well separated and appeared as d and t at 7.79 (d, *J* = 7.2 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H). The peak at 6.42 ppm which is a broad singlet belongs to –NH proton and the doublet at 4.62 (d, *J* = 5.6 Hz, 2H) belongs to two benzylic –$CH_2$ protons. The quartet peak at 2.65 (q, *J* = 7.6 Hz, 2H) and triplet peak at 1.24 (t, *J* = 7.6 Hz, 3H) belong to two –$CH_2$ and three –$CH_3$ protons of ethyl substituent group respectively (Fig. 2a).

**$^{13}$C NMR.** The peaks at 28.6, 15.8 ppm belong to –$CH_2$ and –$CH_3$ carbons respectively; and the peak at 44.0 ppm belongs to benzylic –$CH_2$ carbon. The peak at 167.4 ppm belongs to amide -CO carbon and the peaks at 143.9, 135.5, 134.5, 131.6, 128.7, 128.4, 128.1, 127.1 ppm belong to aromatic benzene ring carbons.

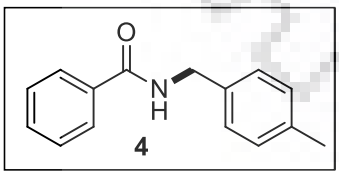
**Analytical data for all products:**

***N*-Benzylbenzamide (3)**[18a]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.044g, Yield: 83%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.79 (d, *J* = 6.9 Hz, 2H), 7.49 (t, *J* = 7.3Hz, 1H), 7.41 (t, *J* = 7.8Hz, 2H), 7.32-7.35 (m, 4H), 7.26-7.32 (m, 1H), 6.58 (br s, 1H), 4.63 (d, *J* = 5.5Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.5, 138.3, 134.5, 131.6, 128.9, 128.7, 128.0, 127.7, 127.1, 44.2.



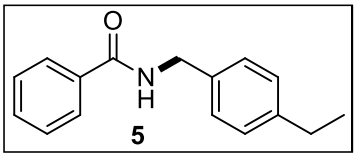
3

***N*-(4-Methylbenzyl)benzamide (4)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.035g, Yield: 62%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.70 (d, *J* = 6.7 Hz, 2H), 7.41 (t, *J* = 7.3Hz, 1H), 7.33 (t, *J* = 7.3Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 6.34 (br s, 1H), 4.52 (d, *J* = 5.5Hz, 2H), 2.27 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.4, 137.5, 135.2, 134.5, 131.6, 129.6, 128.7, 128.1, 127.0, 44.0, 21.2.



4

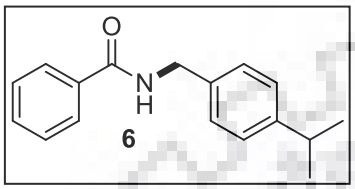
***N*-(4-Ethylbenzyl)benzamide (5)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.050g, Yield: 84%); mp 101-102 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.79 (d, *J* = 7.2 Hz, 2H), 7.50



5

(t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.42 (br s, 1H), 4.62 (d, *J* = 5.6 Hz, 2H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.4, 143.9, 135.5, 134.5, 131.6, 128.7, 128.4, 128.1, 127.1, 44.0, 28.6, 15.8. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{17}NONa$ 262.1202; Found 262.1209.

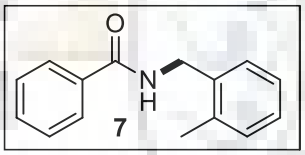
***N*-(4-Isopropylbenzyl)benzamide (6)**[18b]:The title compound was isolated as a white solid



6

using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.051g, Yield: 80%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.71 (d, *J* = 8.5 Hz, 2H), 7.42 (t, *J* = 7.3Hz, 1H), 7.35 (t, *J* = 7.6Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 6.31(br s, 1H), 4.54 (d, *J* = 5.5Hz, 2H), 2.89-2.78 (m, 1H), 1.17 (d, *J* = 6.7 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.4, 148.5, 135.5, 134.5, 131.6, 128.7, 128.2, 127.0, 126.9, 44.1, 33.9, 24.1. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}NONa$ 276.1359; Found 276.1353.

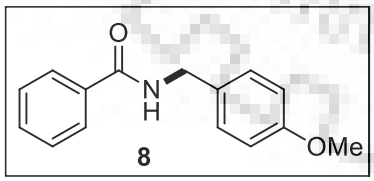
***N*-(2-Methylbenzyl)benzamide (7)**[19b]: The title compound was isolated as a white solid



7

using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.043g, Yield: 76%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.70 (d, *J* = 7.9 Hz, 2H), 7.41 (t, *J* = 7.0 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.22 (d, *J* = 6.7 Hz, 1H), 7.12 (q, *J* = 6.9 Hz, 3H), 6.22 (br, s, 1H), 4.55 (d, *J* = 5.5 Hz, 2H), 2.29 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.3, 136.7, 135.8, 134.4, 131.6, 130.7, 128.8, 128.7, 128.0, 127.0, 126.4, 42.5, 19.2.

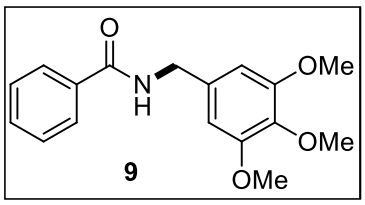
***N*-(4-Methoxybenzyl)benzamide (8)**[18b]: The title compound was isolated as a white solid



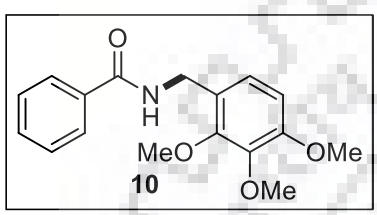
8

using silica-gel column chromatography eluting with ethyl acetate/hexane (1:3), (0.053g, Yield: 87%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.78 (d, *J* = 6.8 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.38 (br s, 1H), 4.57 (d, *J* = 6.4 Hz, 2H), 3.80 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.4, 159.2, 134.5, 131.6, 130.4, 129.4, 128.6, 127.1, 114.2, 55.4, 43.7.

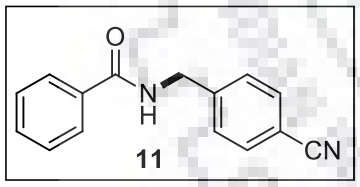
***N*-(3,4,5-Trimethoxybenzyl)benzamide (9)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (3:7), (0.040g, Yield: 53%); mp 110-111°C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.82 (d, $J$ = 7.3 Hz, 2H), 7.50 (t, $J$ = 7.3 Hz, 1H), 7.42 (t, $J$ = 7.3 Hz, 2H), 6.68 (br s, 1H), 6.55 (s, 2H), 4.55 (d, $J$ = 6.1 Hz, 2H), 3.82 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.5, 153.4, 137.3, 134.4, 134.1, 131.7, 128.7, 127.1, 105.0, 60.9, 56.2, 44.5. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{20}NO_4$ 302.1387; Found 302.1381.



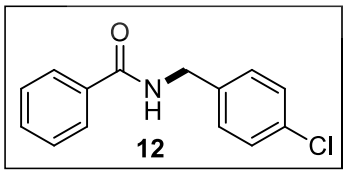

***N*-(2,3,4-Trimethoxybenzyl)benzamide (10)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (3:7), (0.032g, Yield: 43%); mp 108-109°C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.77 (d, $J$ = 7.3 Hz, 2H), 7.48 (t, $J$ = 7.3 Hz, 1H), 7.42 (t, $J$ = 7.3 Hz, 2H), 7.05 (d, $J$ = 8.5 Hz, 1H), 6.64 (d, $J$ = 8.5 Hz, 1H), 6.59 (br s, 1H), 4.58 (d, $J$ = 6.1 Hz, 2H), 3.96 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.1, 153.7, 152.1, 142.2, 134.7, 131.5, 128.6, 127.0, 124.3, 123.9, 107.3, 61.2, 60.9, 56.1, 39.8. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{20}NO_4$ 302.1387; Found 302.1383.



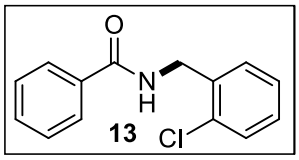

***N*-(4-Cyanobenzyl)benzamide (11)**[19a]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (1:3), (0.022g ,Yield: 37%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.81 (d, $J$ = 7.2 Hz, 2H), 7.63 (d, $J$ = 8.4 Hz, 2H), 7.54 (t, $J$ = 7.3 Hz, 1H), 7.44-7.47 (m, 4H), 6.60 (br s, 1H), 4.71 (d, $J$ = 6.1 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.7, 143.9, 133.9, 132.6, 132.1, 128.8, 128.3, 127.1, 118.8, 111.4, 43.6.



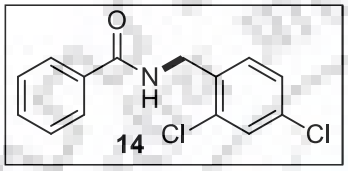

***N*-(4-Chlorobenzyl)benzamide (12)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.051g, Yield: 83%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.74 (d, $J$ = 6.9 Hz, 2H), 7.57 (d, $J$ = 8.2 Hz, 2H), 7.47 (t, $J$ = 7.3 Hz, 1H), 7.37-7.41 (m, 4H), 6.50 (br s, 1H), 4.65 (d, $J$ = 6.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.4, 143.9, 133.9, 132.6, 132.1, 128.8, 128.3, 127.1, 118.8, 43.6.



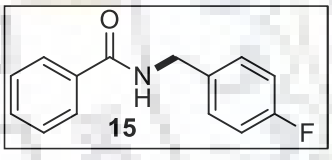
***N*-(2-Chlorobenzyl)benzamide (13)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.033g, Yield: 53%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.71 (d, $J$ = 8.4 Hz, 2H), 7.29-7.46 (m, 5H), 7.16-7.19(m, 2H), 6.57 (br s, 1H), 4.46 (d, $J$ = 6.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.4, 135.7, 134.3, 133.8, 131.7, 130.6, 129.7, 129.2, 128.7, 127.3, 127.1, 42.2. HRMS (ESI-TOF) m/z: [M+Na] $^+$ Calcd for $C_{14}H_{12}ClNONa$ 268.0500; Found 268.0490.



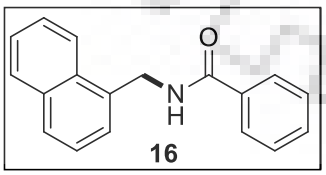

***N*-(2,4-Dichlorobenzyl)benzamide (14)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane(1:4), (0.034g, Yield: 49%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.76 (d, $J$ = 8.4 Hz, 2H), 7.50 (t, $J$ = 7.0 Hz, 1H), 7.36-7.44 (m, 4H), 7.21 (d, $J$ = 8.4 Hz, 1H), 6.72 (br s, 1H), 4.66 (d, $J$ = 5.6 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.6, 134.3, 134.0, 133.9, 133.7, 131.9, 131.2, 129.4, 128.7, 127.5, 127.1, 41.6.



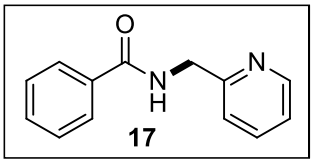

***N*-(4-Fluorobenzyl)benzamide (15)**[18e]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.047g, Yield: 82%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.71 (d, $J$ = 7.3 Hz, 2H), 7.42 (t, $J$ = 7.3 Hz, 1H), 7.33 (t, $J$ = 7.3 Hz, 2H), 7.21-7.24 (m, 2H), 6.93 (d, $J$ = 8.5, 2H), 6.53 (br s, 1H), 4.51 (d, $J$ = 5.5Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.5, 162.3(d, $J_{C\text{-}F}$ = 246.4 Hz), 134.3, 134.1 (d, $J_{C\text{-}F}$ = 2.9 Hz), 131.7, 129.6, 128.7, 127.1, 115.7 (d, $J_{C\text{-}F}$ = 22.1 Hz), 43.4.



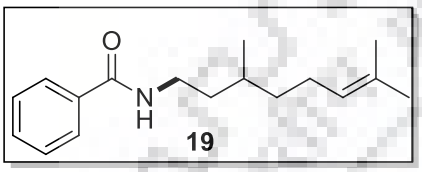

***N*-(Naphthalen-1-ylmethyl)benzamide (16)**[18b]:The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.053g, Yield: 81%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.95 (d, $J$ = 9.2 Hz, 1H), 7.77 (d, $J$ = 9.6 Hz, 1H), 7.71 (d, $J$ = 7.8 Hz, 1H), 7.63 (d, $J$ = 7.3 Hz, 2H), 7.35-7.43 (m, 3H), 7.28-7.37 (m, 2H), 7.23 (t, $J$ = 7.6 Hz, 2H), 6.47 (br s, 1H), 4.92 (d, $J$ = 5.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.3, 134.4, 134.0, 133.5, 131.6, 128.9, 128.8, 128.6, 127.1, 126.9, 126.8, 126.1, 125.5, 123.6, 42.4.



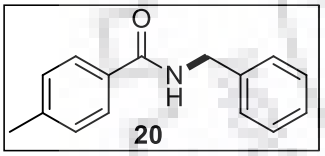
***N*-(Pyridin-2-ylmethyl)benzamide (17)**[18c]: The title compound was isolated as a yellow solid using silica-gel column chromatography eluting with ethyl acetate/hexane (2:3), (0.030g, Yield: 57%); $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ 8.49 (d, $J$ = 4.1 Hz, 1H), 7.81 (d, $J$ = 7.8 Hz, 2H), 7.59-7.63 (m, 2H), 7.35-7.45 (m, 2H), 7.26 (d, $J$ = 7.8 Hz, 1H), 7.13-7.19 (m, 1H), 4.69 (d, $J$ = 5.0 Hz, 2H), 2.29 (br s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.5, 156.3, 149.0, 137.0, 134.4, 131.6, 128.6, 127.2, 122.5, 122.3, 44.8; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{12}N_2ONa$ 235.0842; Found 235.0833.



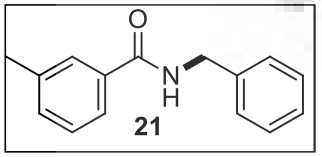

***N*-(3,7-dimethyloct-6-en-1-yl)benzamide (19)**[20e]: The title compound was isolated as a viscous liquid using silica-gel column chromatography eluting with ethyl acetate/hexane (3:7), (0.029g, Yield:45%); $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ 8.23 (d, $J$ = 7.3 Hz, 2H), 8.01 (s, 1H), 7.75 (d, $J$ = 1.8 Hz, 2H), 7.60 (q, $J$ = 4.3 Hz, 1H), 5.09 (t, $J$ = 7.0 Hz, 1H), 2.80-2.94 (m, 2H), 1.96-2.02 (m, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 1.38-1.44 (m, 1H), 1.24-1.29 (m, 4H), 0.99 (d, $J$ = 6.1 Hz, 3H); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{26}NO$ 260.2009; Found 260.2009.



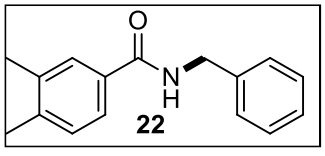

***N*-Benzyl-4-methylbenzamide (20)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.052g, Yield: 92%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.68 (d, $J$ = 8.0 Hz, 2H), 7.26-7.42 (m, 5H), 7.21 (d, $J$ = 7.6 Hz, 2H), 6.39 (s, 1H), 4.63 (d, $J$ = 5.5Hz, 2H), 2.38 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.4, 142.1, 138.4, 131.6, 129.3, 128.9, 128.0, 127.7, 127.0, 44.18, 21.5.




***N*-Benzyl-3-methylbenzamide (21)**[19d]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.038g, Yield: 68%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.62 (s, 1H), 7.55-7.57 (m, 1H), 7.28-7.36 (m, 7H), 6.44 (br s, 1H), 4.64 (d, $J$ = 5.2 Hz, 2H), 2.38 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.6, 138.6, 138.3, 134.5, 132.4, 128.9, 128.6, 128.0, 127.8, 127.7, 124.0, 44.2, 21.4.

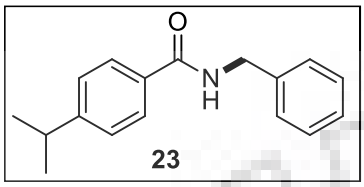



***N*-Benzyl-3,4-dimethylbenzamide (22)**[19c]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.052g, Yield: 87%); $^1$H NMR (400 MHz,



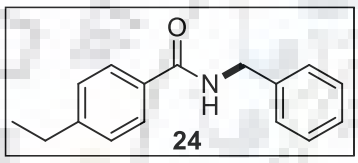
$CDCl_3$) $\delta$ 7.58 (s, 1H), 7.50 (d, $J$ = 8 Hz, 1H), 7.26-7.36 (m, 5H), 7.17 (d, $J$ = 8 Hz, 1H), 6.37 (br s, 1H), 4.64 (d, $J$ = 5.2 Hz, 2H), 2.29 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.5, 140.7, 138.5, 137.1, 131.9, 129.8, 128.9, 128.3, 128.0, 127.7, 124.4, 44.2, 19.9,19.8.

***N*-Benzyl-4-isopropylbenzamide (23)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.034g, Yield: 54%); mp 117-118°C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.73 (d, $J$ = 8.8 Hz, 2H), 7.30-7.35 (m, 5H), 7.28 (d, $J$ = 8.0 Hz, 2H), 6.41 (br s, 1H), 4.64 (d, $J$ = 6.0 Hz, 2H), 2.91-2.98 (m, 1H), 1.25 (d, $J$ = 6.8 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.4, 152.9, 138.4, 132.0, 128.9, 128.0, 127.6, 127.2, 126.8, 44.2, 34.2, 23.9. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}NONa$ 276.1359; Found 276.1356.



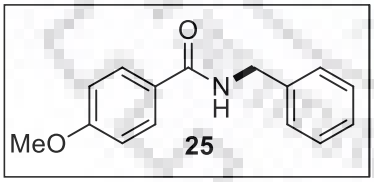
**23**

***N*-Benzyl-4-ethylbenzamide (24)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane(1:4), (0.042g, Yield: 70%); mp 112-113°C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.72 (d, $J$ = 8.4 Hz, 2H), 7.29-7.38 (m, 5H), 7.25 (d, $J$ = 8 Hz, 2H), 6.37 (br s, 1H), 4.65 (d, $J$ = 6.0 Hz, 2H), 2.69 (q, $J$ = 7.6 Hz, 2H), 1.24 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.4, 148.3, 138.4, 131.8, 128.9, 128.2, 128.0, 127.7, 127.1, 44.2, 28.9, 15.5. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{17}NONa$ 262.1202; Found 262.1223.



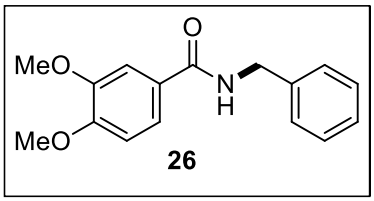
**24**

***N*-Benzyl-4-methoxybenzamide (25)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane(1:4), (0.036g, Yield: 60%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.76 (d, $J$ = 8.8 Hz, 2H), 7.27-7.35 (m, 5H), 6.90 (d, $J$ = 8.4 Hz, 2H), 6.46 (br s, 1H), 4.61 (d, $J$ = 5.2 Hz, 2H), 3.83 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.0, 162.3, 138.5, 128.9, 128.8, 128.0, 127.6, 126.7, 113.8, 55.5, 44.1.



**25**

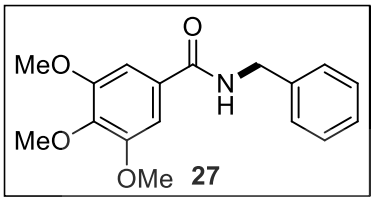
***N*-Benzyl-3,4-dimethoxybenzamide (26)**[21b]:The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (3:7), (0.052g, Yield: 77%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$7.46 (d, $J$ = 1.8 Hz, 1H), 7.25-7.33 (m, 6H), 6.81 (d, $J$ = 8.5 Hz, 1H), 6.67 (br s, 1H), 4.61 (d, $J$ =



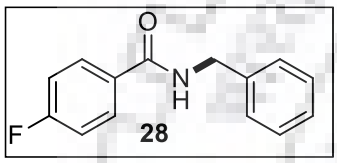
**26**

5.5 Hz, 2H), 3.88 (2s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.2, 151.8, 149.0, 138.5, 128.8, 127.9, 127.6, 127.0, 119.6, 110.7, 110.3, 56.1, 44.2.

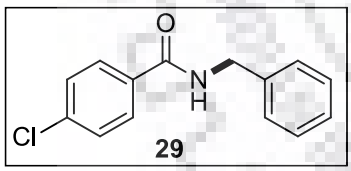
***N*-Benzyl-3,4,5-trimethoxybenzamide (27)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (2:3), (0.049g, Yield: 65%); mp 140-141°C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.28-7.37 (m, 5H), 7.02 (s, 2H), 6.41 (br s, 1H), 4.64 (d, $J$ = 5.6 Hz, 2H), 3.88-3.89 (m, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.1, 153.3, 141.1, 138.3, 129.9, 128.9, 128.0, 127.8, 104.5, 61.0, 56.4, 44.3. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}NO_4Na$ 324.1206; Found 324.1201.



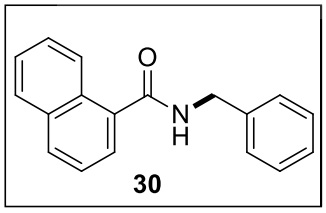

***N*-Benzyl-4-fluorobenzamide (28)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.041g, Yield: 72%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.78-7.81 (m, 2H), 7.26-7.39 (m, 5H), 7.08 (t, $J$ = 8.7 Hz, 2H), 6.56 (br s, 1H), 4.61 (d, $J$ = 5.5Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.5, 164.8 (d, $J_{C\text{-}F}$ = 253.0 Hz), 138.2, 130.6, 129.4 (d, $J_{C\text{-}F}$ = 8.6 Hz), 128.9, 128.0, 127.8, 115.7 (d, $J_{C\text{-}F}$ = 22.2 Hz), 44.3.



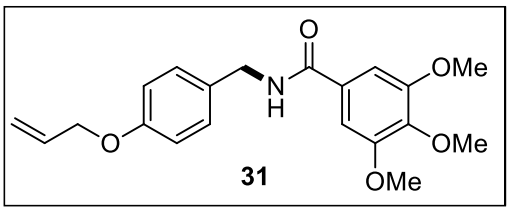

***N*-Benzyl-4-chlorobenzamide (29)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.015g, Yield: 25%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.73 (d, $J$ = 8.4 Hz, 2H), 7.40 (d, $J$ = 8.4 Hz, 2H), 7.30-7.37 (m, 5H), 6.36 (br s, 1H), 4.64 (d, $J$ = 5.2Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.3, 138.0, 137.9, 132.8, 129.0, 128.5, 128.1, 127.9, 127.0, 44.4.




***N*-Benzyl-1-naphthamide (30)**[18b]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (1:4), (0.026g, Yield: 40%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.34 (d, $J$ = 8.5 Hz, 1H), 7.85-7.91 (m, 3H), 7.60-7.62 (m, 1H), 7.52-7.58 (m, 2H), 7.29-7.45 (m, 5H), 6.30 (br s, 1H), 4.73 (d, $J$ = 5.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.5, 138.2, 134.4, 133.8, 130.8, 130.3, 128.9, 128.4, 128.0, 127.8, 127.3, 126.5, 125.5, 125.0, 124.8, 44.2.

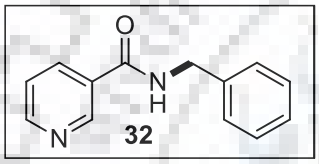


***N*-(4-(allyloxy)benzyl)-3,4,5-trimethoxybenzamide (31)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (2:3), (0.028g, Yield: 31%); mp 142-143°C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.26 (d, $J$ = 8.7 Hz, 2H), 7.02 (s, 2H), 6.89 (d, $J$ = 8.2 Hz, 2H), 6.48 (br s, 1H), 6.09-5.99 (m, 1H), 5.41 (dd, $J$ = 17.4, 1.4 Hz, 1H), 5.29 (dd, $J$ = 10.5, 1.4 Hz, 1H), 4.56-4.52 (m, 4H), 3.87 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.1, 158.2, 153.3, 141.0, 133.2, 130.5, 129.9, 115.3, 114.8, 104.7, 104.2, 68.9, 61.1, 56.4, 43.8. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{23}NO_5Na$ 380.1468; Found 380.1462.



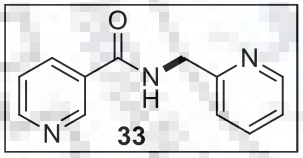
31

***N*-benzylnicotinamide (32)**[18c]: The title compound was isolated as a colorless liquidusing silica-gel column chromatography eluting with ethyl acetate/hexane (3:7), (0.008g, Yield: 23%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.98 (d, $J$ = 1.8 Hz, 1H), 8.71 (d, $J$ = 3.1 Hz, 1H), 8.14 (d, $J$ = 7.9 Hz, 1H), 7.32-7.40 (m, 6H), 6.58 (br s, 1H), 4.66 (d, $J$ = 6.1 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.5, 152.5, 147.9, 137.8, 135.4, 130.2, 129.0, 128.0, 127.8, 123.6, 44.4.



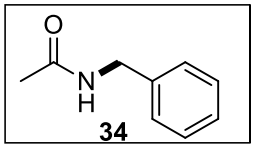
32

***N*-(pyridin-2-ylmethyl)nicotinamide (33)**[18d]: The title compound was isolated as a viscous yellow oil using silica-gel column chromatography eluting with ethyl acetate/hexane (7:3), (0.011g, Yield: 32%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.11 (d, $J$ = 1.8 Hz, 1H), 8.73 (dd, $J$ = 4.8, 1.6 Hz, 1H), 8.56 (d, $J$ = 4.9 Hz, 1H), 8.21 (dt, $J$ = 7.9, 1.8 Hz, 1H), 7.89 (s, 1H), 7.71 (td, $J$ = 7.6, 1.4 Hz, 1H), 7.40 (q, $J$ = 4.3 Hz, 1H), 7.35 (d, $J$ = 7.9 Hz, 1H), 7.23-7.26 (m, 1H), 4.77 (d, $J$ = 4.9 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.6, 155.7, 152.2, 149.1, 148.3, 137.1, 135.2, 130.1, 123.6, 122.8, 122.3, 44.7.



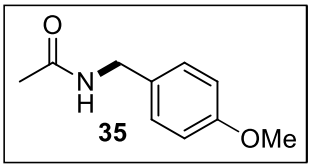
33

***N*-Benzylacetamide (34)**[19e]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (3:7), (0.017g, Yield: 45%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.48-7.52 (m, 2H), 7.37-7.34 (m, 3H), 5.88 (br s, 1H), 4.59 (d, $J$ = 5.5 Hz, 2H), 1.60 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.7, 138.2, 128.9, 127.9, 127.7, 43.9, 29.8.

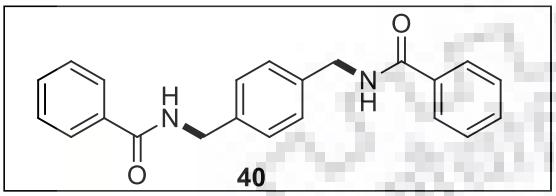


34

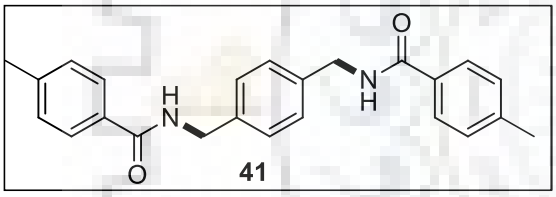
***N*-(4-methoxybenzyl)acetamide (35)**[21c]: The title compound was obtained as sticky solid using silica-gel column chromatography eluting with ethyl acetate/hexane (3:7), (0.015g, Yield: 34%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.18–6.87 (m, 4H), 6.42 (brs, 1H), 4.38 (d, $J$ = 5.60 Hz, 1H), 3.78 (s, 3H), 2.00 (s, 3H).



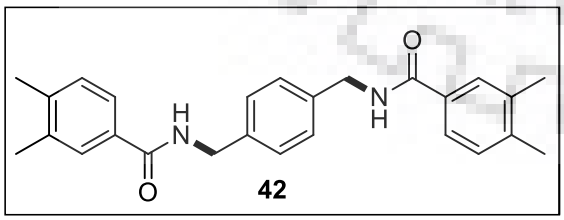

***N,N'*-(1,4-phenylenebis(methylene))dibenzamide (40)**[20d]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane(3:7), (0.022g, Yield: 50%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.80 (d, $J$ = 7.3 Hz, 4H), 7.51 (t, $J$ = 7.3 Hz, 2H), 7.42 (t, $J$ = 7.3 Hz, 4H), 7.33 (d, $J$ = 1.2 Hz, 4H), 6.29 (br s, 2H), 4.67 (d, $J$ = 4.3 Hz, 4H). HRMS (ESI-TOF) m/z: [M+Na] $^+$ Calcd for $C_{22}H_{20}N_2O_2Na$ 367.1417; Found 367.1409.



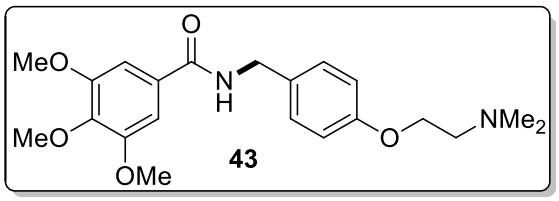

***N,N'*-(1,4-phenylenebis(methylene))bis(4-methylbenzamide) (41)**[20c]: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (3:7), (0.012g, Yield: 25%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.67 (d, $J$ = 7.9 Hz, 4H), 7.33 (d, $J$ = 7.9 Hz, 4H), 7.22 (d, $J$ = 7.9 Hz, 4H), 6.46 (br s, 2H), 4.60 (d, $J$ = 5.5 Hz, 4H), 2.39 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.9, 142.1, 137.8, 133.0, 130.1, 128.4, 127.0, 45.3, 22.7; HRMS (ESI-TOF) m/z: [M+Na] $^+$ Calcd for $C_{24}H_{24}N_2O_2Na$ 395.1730; Found 395.1764.




***N,N'*-(1,4-phenylenebis(methylene))bis(3,4-dimethylbenzamide) (42)**: The title compound was isolated as a white solid using silica-gel column chromatography eluting with ethyl acetate/hexane (3:7), (0.016g, Yield: 32%); mp 202-203 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.57 (s, 2H), 7.51-7.42 (m, 2H), 7.33 (s, 4H), 7.17 (d, $J$ = 7.9 Hz, 2H), 6.41 (br s, 2H), 4.62 (d, $J$ = 5.5 Hz, 4H), 2.29 (s, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.6, 140.8, 137.8, 137.1, 131.9, 129.8, 128.4, 128.4, 124.4, 43.8, 19.9,19.8. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{26}H_{28}N_2O_2Na$ 423.2043; Found 423.2042.

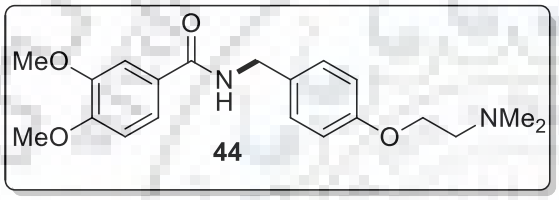


***N*-(4-(2-(dimethylamino)ethoxy)benzyl)-3,4,5-trimethoxybenzamide (43)**[20a]: The title compound was isolated as a pale yellow solid using silica-gel column chromatography eluting with methanol/ethyl acetate (1:9), (0.078g, Yield: 80%); $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.27(d, $J$ = 8.4 Hz, 2H), 7.03 (s, 2H), 6.88 (d, $J$ = 8.8 Hz, 2H), 6.55 (br s, 1H), 4.56 (d, $J$ = 5.6 Hz, 2H), 4.14 (t, $J$ = 5.6 Hz, 2H), 3.88 (s, 9H), 2.92-2.89 (m, 2H), 2.46 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.1, 158.0, 153.3, 141.0, 130.8, 129.9, 129.5, 114.8, 104.5, 65.2, 61.0, 57.6, 56.4, 45.1, 43.7. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{29}N_2O_5$ 389.2071; Found 389.2075.



**43**

***N*-(4-(2-(dimethylamino)ethoxy)benzyl)-3,4-dimethoxybenzamide (44)**[20b]: The title compound was isolated as a pale yellow solid using silica-gel column chromatography eluting with methanol/ethyl acetate (1:9), (0.066g, Yield: 74%); $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45 (d, $J$ = 1.8 Hz, 1H), 7.26-7.30 (m, 3H), 6.89 (d, $J$ = 8.5 Hz, 2H), 6.85 (d, $J$ = 8.5 Hz, 1H), 6.33 (br s, 1H), 4.57 (d, $J$ = 5.5 Hz, 2H), 4.15 (t, $J$ = 5.5 Hz, 2H), 3.91 (s, 6H), 2.91 (t, $J$ = 4.6 Hz, 2H), 2.46 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.0, 158.1, 151.5, 148.8, 131.0, 129.4, 127.4, 119.3, 114.8, 110.5, 110.1, 65.1, 57.7, 56.1, 45.1, 43.7. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{27}N_2O_4$ 359.1965; Found 359.1956.



**44**

## [2.7] Spectra of selected compounds:

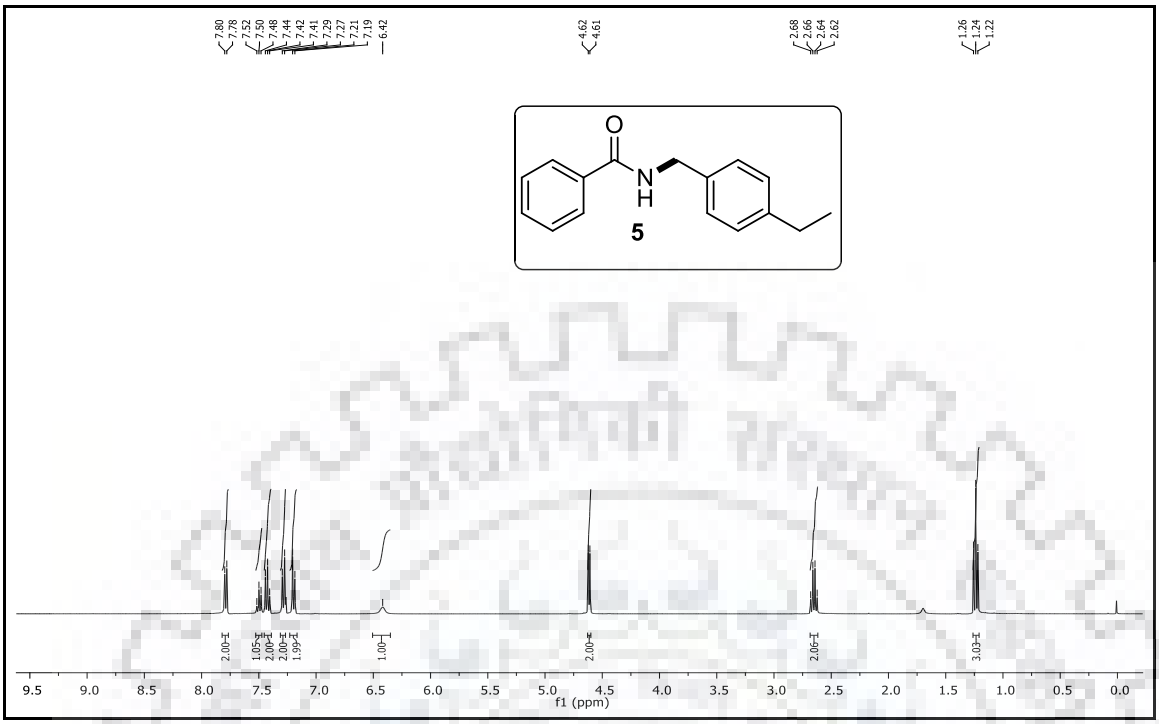



**Fig 1a:** $^{1}$H-NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **5**

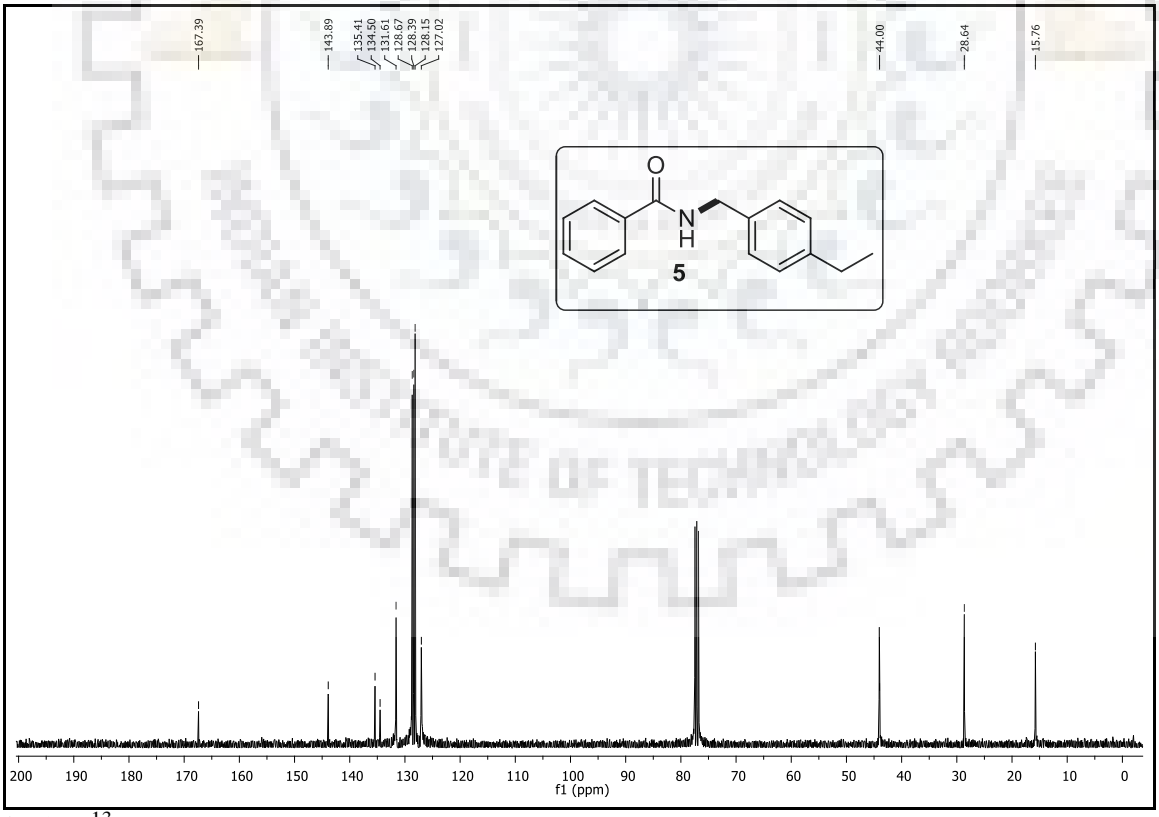



**Fig 1b:** $^{13}$C-NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **5**

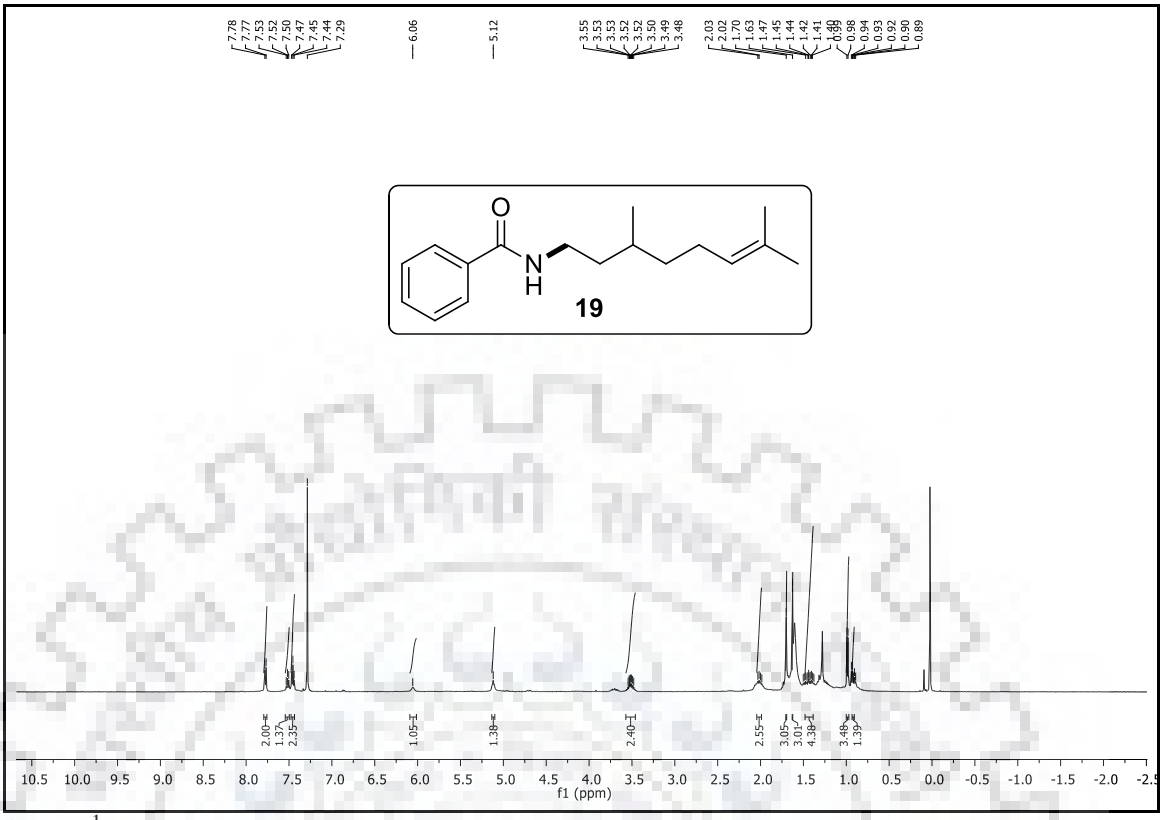



**Fig 2a:** $^{1}$H-NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **19**

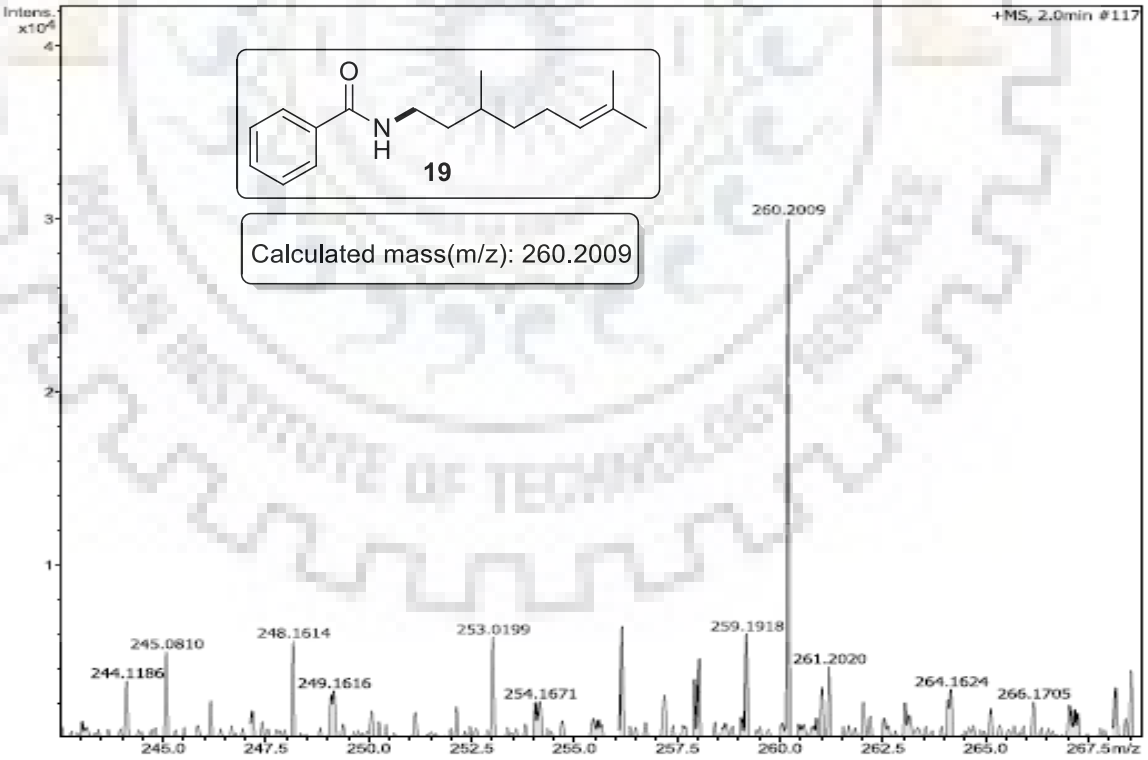



**Fig 2b:** HRMS Spectrum of Compound **19**

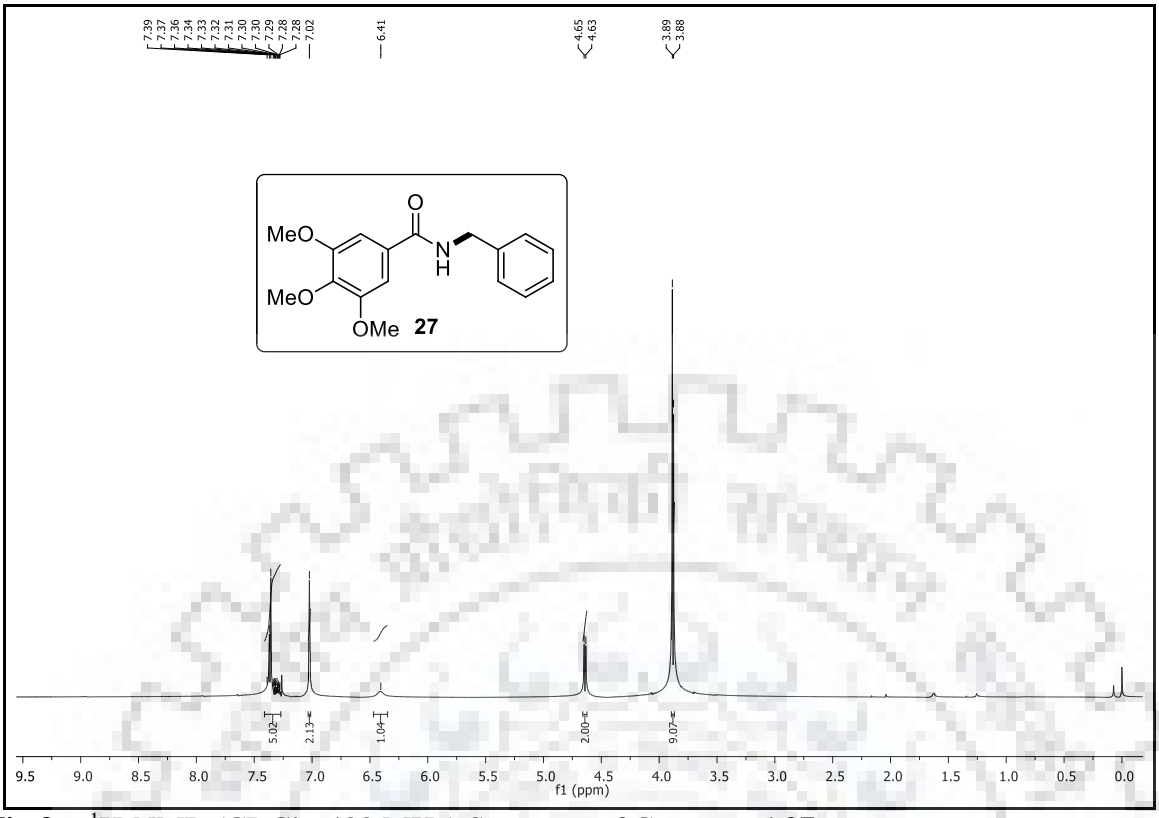



**Fig 3a:** $^{1}$H-NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **27**

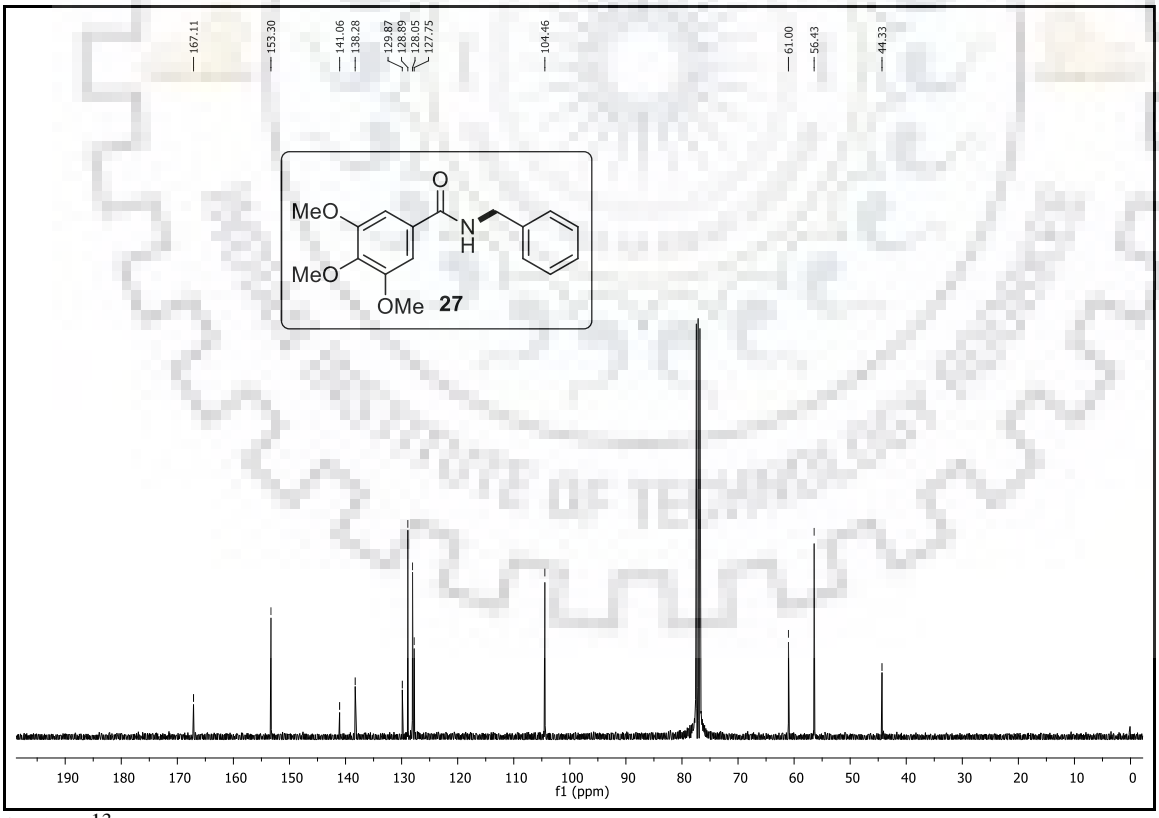



**Fig 3b:** $^{13}$C-NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **27**

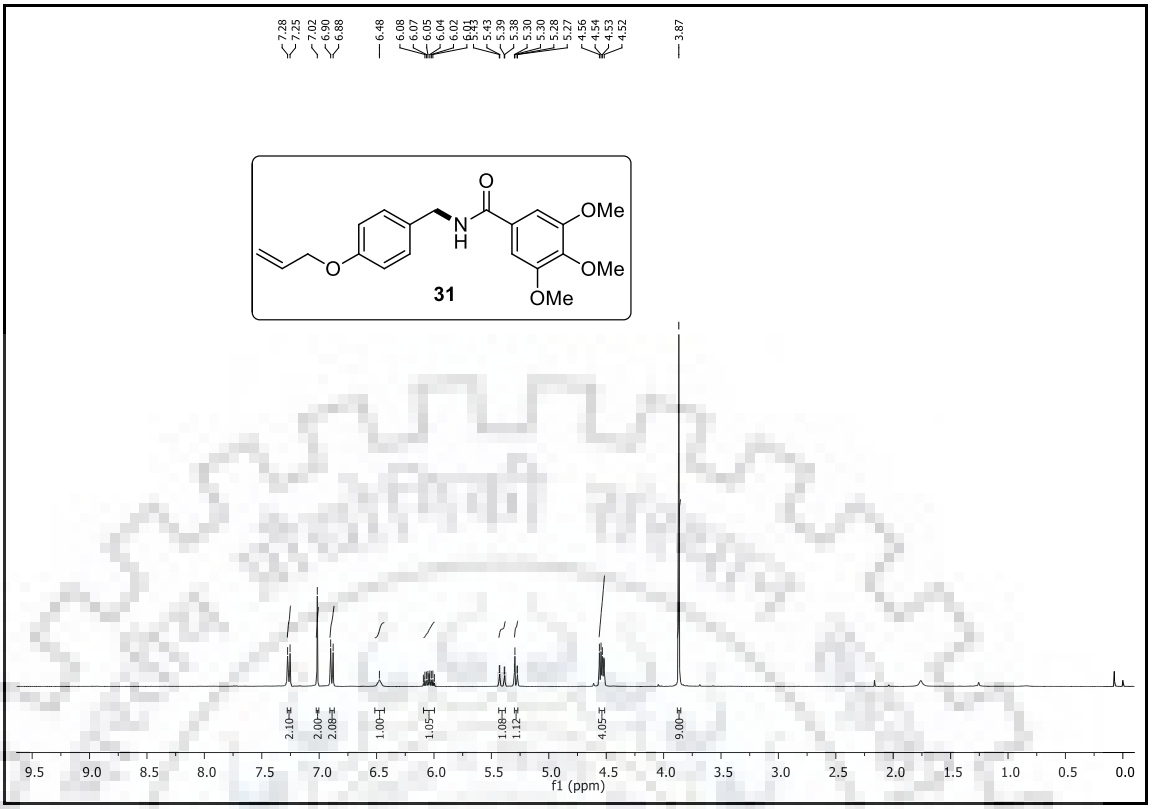



**Fig 4a:** $^{1}$H-NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **31**

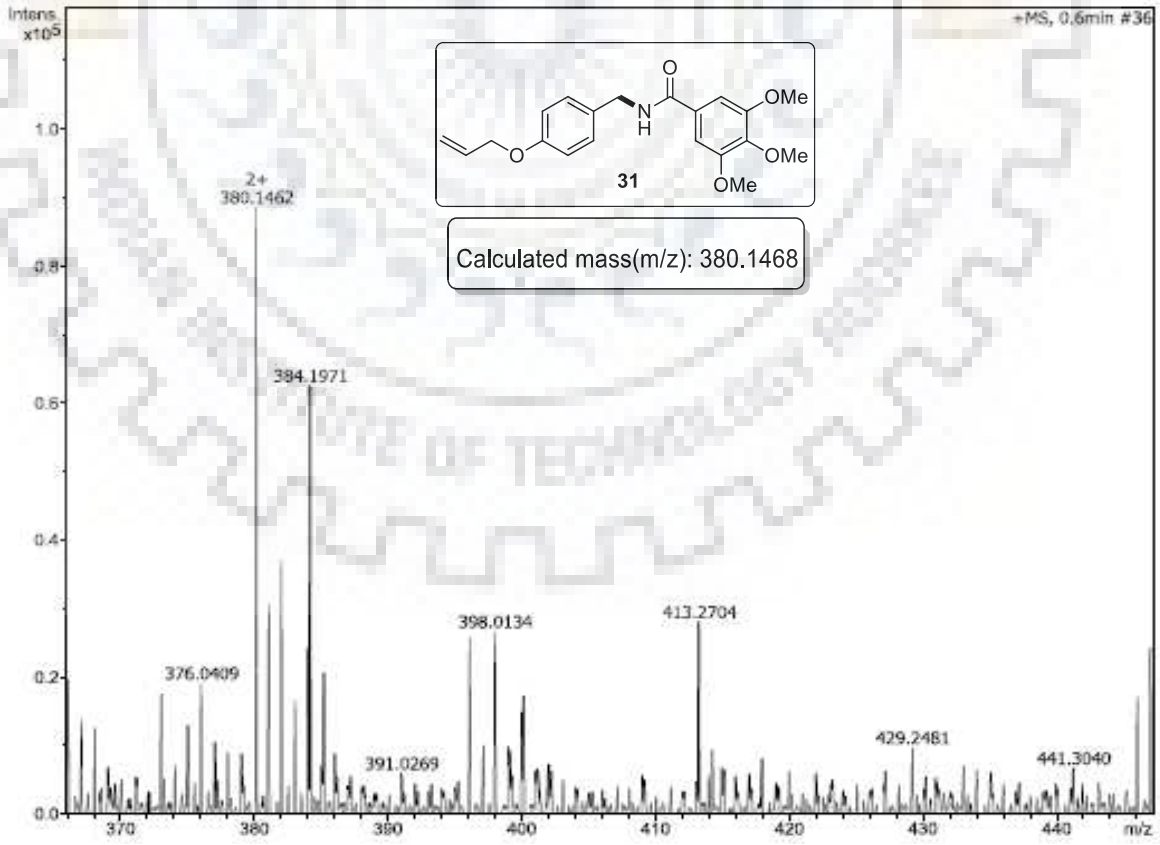



**Fig 4b:** HRMS Spectrum of Compound **31**

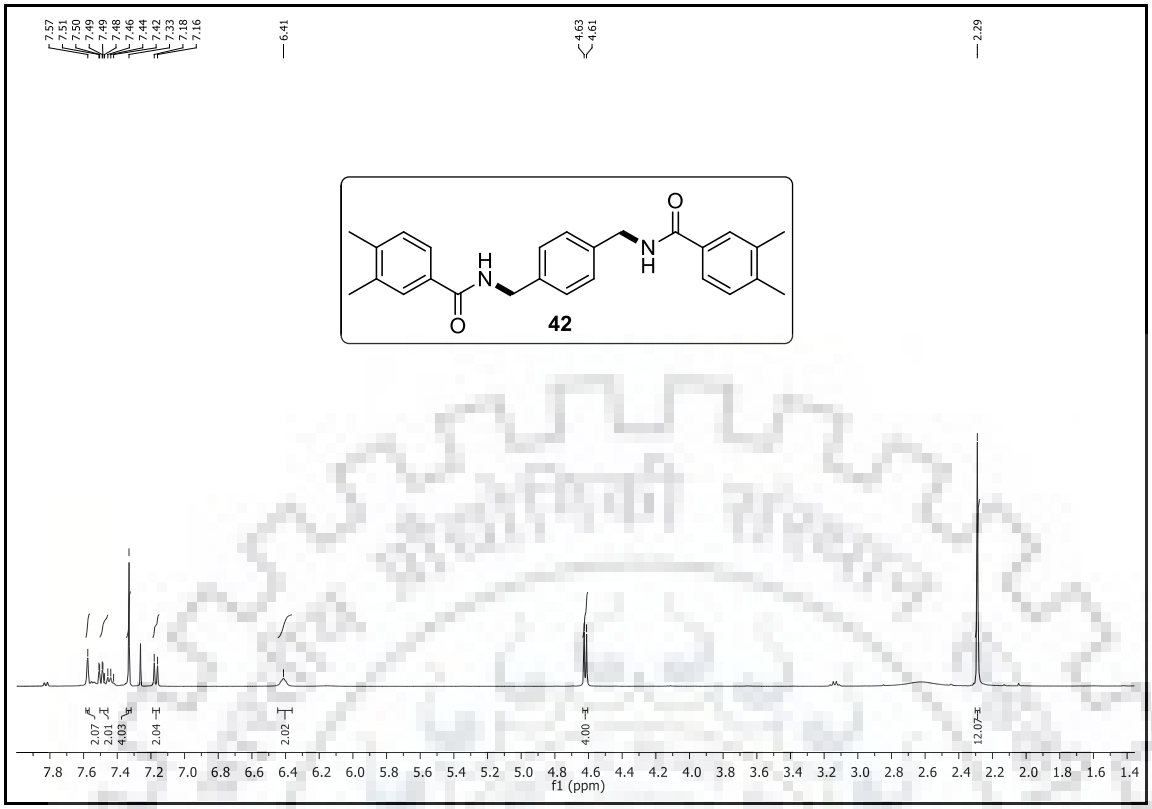



**Fig 5a:** $^{1}$H-NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **42**

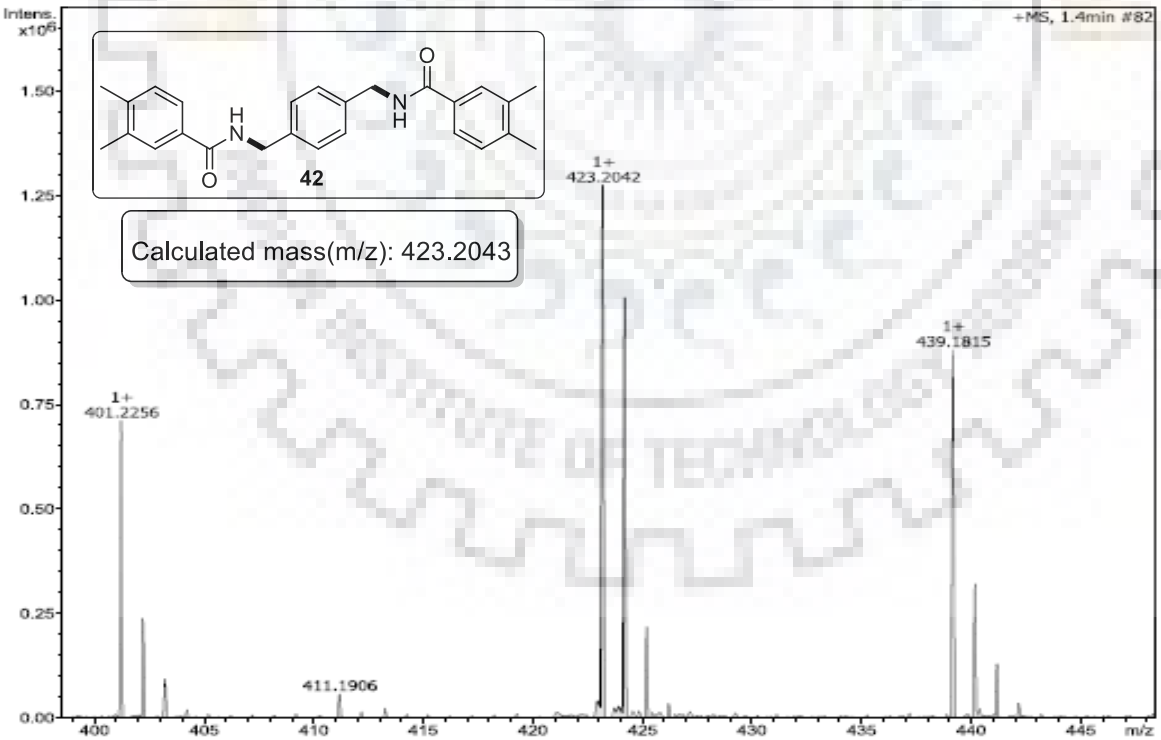
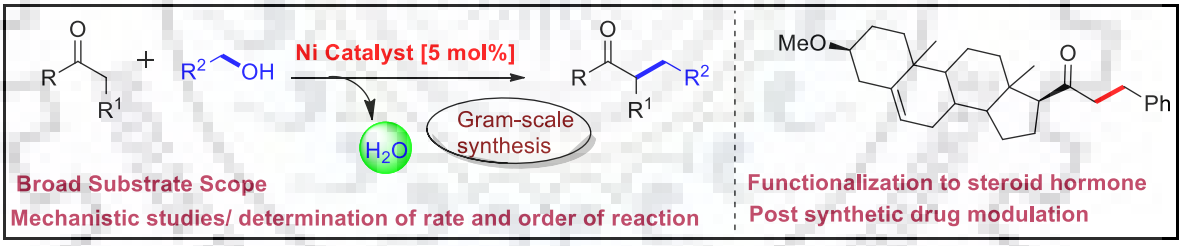



**Fig 5b:** HRMS Spectrum of Compound **42**

## Chapter-3: Nickel-catalyzed *α*-alkylation of ketone enolates with alcohols

Herein, we have demonstrated an inexpensive and operational simple base-metal catalyzed protocol for selective mon-alkylation of methyl-ketones as well as methylene ketones with alcohols using borrowing hydrogen approach. This Ni-catalyzed dehydrogenative coupling of alcohol could be performed in gram scale and extended to a range of aryl, alkyl and hetero-aryl derivatives (>40 examples) in up to 90% yield including green synthesis of N-heterocycles. For a synthetic application, functionalization of steroid hormone, unsaturated fatty acids and post synthetic modification of naproxen drug have shown. Also, this nickel-catalyzed reaction could be performed in gram scale and successfully applied in the synthesis of donepezil (Alzheimer's drug) and functionalization of steroid hormones and fatty acid derivatives. The methylation of ketones using methanol, and one-pot double alkylation to bis-hetero aryl ketones using two different alcohols with a single catalyst broadens the scope of the catalytic protocol.

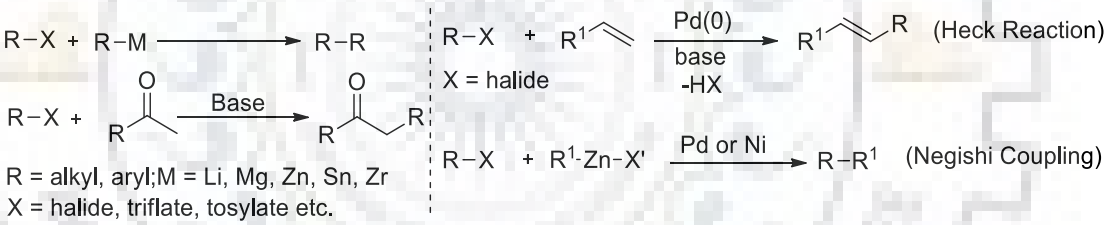



*J. Org. Chem.* **2019**, *84*, 769-779.
*Org. Lett.* **2018**, *20*, 5587−5591.

## [3.1] Introduction:

Transition-metal catalyzed hydrogen borrowing (HB) strategy has emerged as a potential tool and environmental benign green alternative for the construction of C-C and C-N bonds.[1] Notably, application of high natural abundant and inexpensive alcohols and versatility to a broad range of amine and C-nucleophiles enables the synthesis of valuable agrochemicals, pharmaceuticals and bioactive heterocycles.[2]

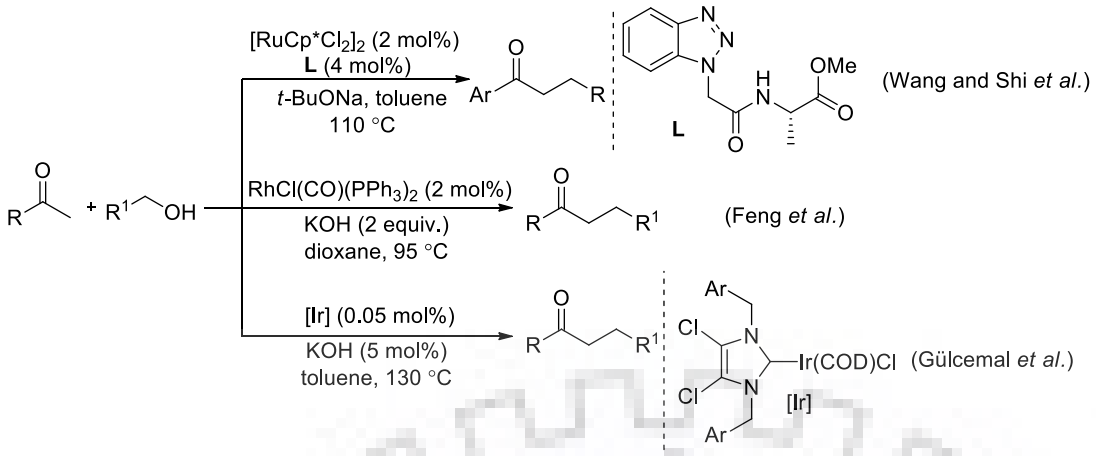
Furthermore, application of HB approach for α-alkylation of carbonyl compounds involving ketone enolates using unactivated alcohols represents the most important milestones to forge the new C-C bonds.[3] Construction of C-C bond is a fundamental process in organic synthesis and traditionally, hazardous alkyl or aryl halides, triflates, tosylates, mesylates with stoichiometric amount of strong bases are used for such methodologies and equivalent excess of waste are formed (Scheme 1). However, use of halides, triflates etc. and generation of salt waste are the key drawbacks (Scheme 1). Nevertheless, the main advantages of HB process is to avoid such stoichiometric salt waste as water is formed as the sole by-product makes this technology more sustainable and atom-economic.[1]




**Scheme 1:** Traditional methods for the synthesis of C-C bond

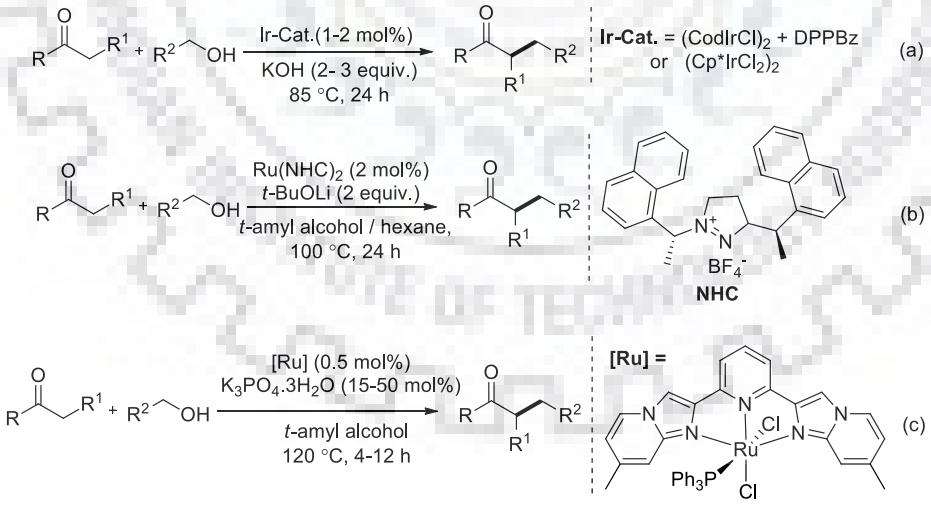
## [3.2] Brief literature survey of transition metal-catalyzed α-alkylation of ketone:

It is noteworthy to mention that, dehydrogenative coupling of alcohols for α-alkylation of carbonyl compounds, were generally performed with precious noble-metal catalysts, such as, Ru,[4] Rh,[5] Ir [6] and Pd-complexes (Scheme 2).[7] In spite of notable progress, potential application of renewable resources along with earth-abundant, inexpensive and non-precious transition metal catalysts for key chemical transformations is a long standing goal and crucial challenge in catalysis.[8] More recently, significant achievements for α-alkylation of carbonyl compounds with alcohols were realized using Fe,[9] Mn,[10] and Co-catalysts (discussed in Chapter 1).[11]




**Scheme 2:** Ru, Rh and Ir-catalyzed α-alkylation of ketones with alcohols

Importantly, alkylation of methylene ketones is only limited to precious metal-based catalysts. For instance, Donohoe and coworkers introduced the synthesis of *α*-branched ketones from *o*-di-substituted phenyl or cyclopropyl ketones with alcohols using an Ir-catalyzed system (Scheme 2A(a)). Later, Glorious and coworkers developed a Ru-NHC catalyst for the *α*-alkylation of methylene ketones which follows the borrowing hydrogen strategy (Scheme 2A(b)). Recently Shao and Zhu and coworkers and others employed a Ru-NNN pincer complex for the *α*-alkylation of both methyl and methylene ketones with alcohols as an alkylating agent (Scheme 2A(c)).

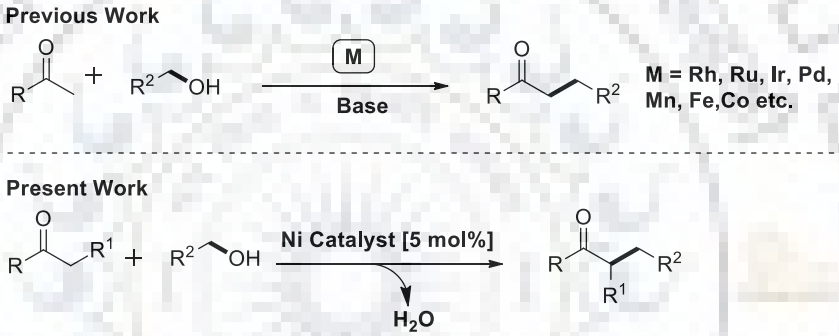



**Scheme 2A:** Ir and Ru-catalyzed *α*-alkylation of methylene ketones

Recently, Morril and coworkers employed more promising Knölker-type Fe precatalyst for such transformations (discussed in Chapter 1).[25a-e]

In this direction, nickel has economic benefits and would function as sustainable alternative to palladium.[12] Thus, still there is a need to develop more exciting and challenging methodologies using nickel. It is noteworthy to mention that, due to poor leaving ability and strong binding capacity of free hydroxyl group in alcohol, often un-activated alcohols behave as an inferior substrate class for such nickel-catalyzed transformations.[13a-d] Notably, Yus and co-workers studied the nickel nanoparticle mediated coupling of ketones using primary alcohols.[13e-f] In this direction, herein we demonstrated the homogeneous Ni-catalyzed alkylation of acetophenone derivatives to a range of α-alkylated long chain ketones with a variety of alcohol electrophiles. The catalytic protocol is highly selective to linear and branched α-alkylated ketones following hydrogen-borrowing strategy.[14]

**[3.3] Aim of Present Work:**




**Scheme 3:** Transition-metal-catalyzed ketone alkylation

Herein we demonstrated the homogeneous Ni-catalyzed alkylation of acetophenone derivatives to a range of α-alkylated long chain ketones with a variety of alcohol electrophiles. The catalytic protocol is highly selective to linear α-alkylated ketones following hydrogen-borrowing strategy.[14] Aryl, alkyl, and heteroaryl ketones as well as alcohols yielded the mono-selective ketones in up to 90% yield. The catalytic protocol was successfully applied in to a gram-scale synthesis. For a practical utility, applications of a steroid derivative, oleyl alcohol, and naproxen alcohol were employed. Preliminary catalytic investigations involving the isolation of a Ni intermediate and defined Ni–H species as well as a series of deuterium-labeling experiments were performed.

**[3.4] Results and discussion:**

**Optimization of the catalytic protocol for α-alkylation of carbonyl compounds**.

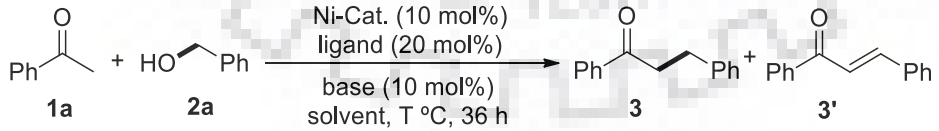
As part of our ongoing studies, recently we demonstrated the nickel-catalyzed protocols for amination and amidation of primary alcohols as well as tandem synthesis to *N*-heterocycles.[14a-c] At this point, we wondered, whether such Ni-catalyzed system would be

beneficial for α-alkylation of methyl ketones or acetophenone derivatives to linear products. Further, we envisioned that, relatively milder basic conditions might be useful for recent studies (Scheme 3). For instance, mild basic conditions not only allow higher selectivity to product, it will also prevent *in situ* bis-alkylation to higher order ketones.[14d] However, addition of excess alcohols often displayed reduced alcohol products.

Previously we demonstrated the nickel-catalyzed dehydrogenation of alcohol to aldehyde followed by generation of transient Ni-H species.[14] During this process, intermediate enone is formed. Next, selective hydrogenation of C=C bond of enone by nickel hydride facilitate to product. Notably, in later process, nitrogen ligands play a key role. It is noteworthy to mention that, to attain selective hydrogenation of C=C bond over C=O bond under nickel-catalysis is a crucial challenge.[15] To overcome the aforementioned issues, we hypothesized following key challenges for α-alkylation of ketones: (i) selective hydrogenation of C=C bond of enone using transient Ni-H species; (ii) selectivity of the catalytic protocol to reduce hydrogenation of C=O bond of product and enone and (iii) selective control in base-catalyzed self-condensation of ketones.[15] At this point, we realized that, a combination of suitable nickel-catalyst with nitrogen ligand is crucial for such mono-selective transformations.[16]

To achieve this goal, primarily we studied the catalytic α-alkylation of acetophenone **1a** with benzyl alcohol **2a** using five different nickel pre-catalysts. Gratifyingly, application of 10 mol% $NiBr_2$, 20 mol% 1,10-phenanthroline **L1** and catalytic (10 mol%) of $Cs_2CO_3$ afford the desired product **3** in 76 % isolated yield, when 1,4-dioxane was used as solvent in 140 °C (Table 1, entries 1-5). Under identical catalytic conditions, applications of a range of nitrogen and phosphine-based ligands, **L2**-**L8** with electronically different nature, did not improve the product yield further (Table 2).

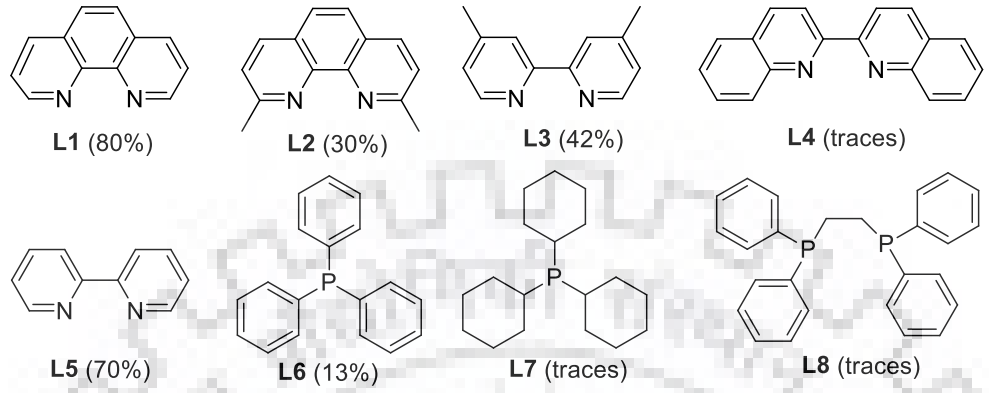
**Table 1**: Screening of catalysts [a]




| Entry | **Ni-Catalyst** | GC-MS Conversion **3** (%) | GC-MS Conversion **3'** (%) |
|---|---|---|---|
| **1** | **$NiBr_2$** | **80(76)[b]** | **7** |
| 2 | $NiCl_2$ | 29 | 2 |
| 3 | $Ni(acac)_2$ | 63 | 9 |
| 4 | $NiCl_2(DME)$ | 10 | 0 |
| 5 | $Ni(COD)_2$ | 22 | 4 |
| 6 | No Catalyst | 6 | 11 |

Reaction conditions: [a] Benzyl alcohol **2a** (0.375mmol), acetophenone **1a** (0.25 mmol), **Ni-catalyst (10 mol%)**, Phen (20 mol%), $Cs_2CO_3$ (10 mol%), 1,4-dioxane (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 ºC oil bath, 36 h reaction time. [b] Isolated yield (average of two run).

**Table 2.** Ligand screening for nickel-catalyzed mono-alkylation of **1a** with **2a**.[a,b]




Reaction conditions: [a] Unless specified, the reaction was carried out with **1a** (0.25mmol), **2a** (0.375 mmol), $NiBr_2$. (0.025mmol), ligand (0.05mmol), $Cs_2CO_3$ (0.025mmol) under $N_2$ atmosphere at 140 °C in 1,4-dioxane (2.0 mL) for 36 h. [b] Conversion was determined by GC-MS.

**Table 3**: Screening of solvents [a]

| Entry | **Solvent** | GC-MS Conversion **3** (%) | GC-MS Conversion **3'** (%) |
|---|---|---|---|
| 1 | Toluene | 5 | 1 |
| **2** | **1,4-Dioxane** | **80(76)**[b] | **7** |
| 3 | Pentanol | 24 | 15 |
| 4 | P-Xylene | 19 | 4 |
| 5 | DMF | 0 | 0 |

Reaction condition: [a] Benzyl alcohol **2a** (0.375 mmol), acetophenone **1a** (0.25 mmol), $NiBr_2$ (10 mol%), Phen (20 mol%), $Cs_2CO_3$ (10 mol%), **solvent (2.0 mL)**, Schlenk tube under nitrogen atmosphere, 140 ºC oil bath, 36 h reaction time. [b] Isolated yield (average of two run).

At this point, application of various polar solvents such as, *n*-propanol, *N*,*N*-dimethyl-formamide (DMF), as well as replacement of 1,4-dioxane with toluene and xylene were found inefficient for alkylation of acetophenone (Table 3). Next, influences of different organic and inorganic bases were performed and resulted poor or no product yield (Table 4). To our delight, we observed a slight increment of product yield, when a lower equivalent of alcohol was used (Table 5). Further reaction using 20 mol% of *t*-BuOK in place of 10 mol% of $Cs_2CO_3$ with lower catalyst loading resulted 82% isolated yield of **3** (Table 6). As expected, we did not observe any alkylation product in absence of catalyst and base whereas, control experiment in absence of ligand or variable amount of catalyst loading resulted albeit with moderate to poor product yield (Table 7). Notably, in some cases we detected 2-10% C=O bond reduced product of **3** and **3'** using GC-MS analysis of crude reaction mixture. Further lowering the reaction temperature had detrimental effect on product conversion and we observed only 6% conversion at 130 °C (Table 8).

**Table 4**: Screening of base [a]

| Entry | **Base** | GC-MS Conversion **3** (%) | GC-MS Conversion **3'** (%) |
|---|---|---|---|
| **1** | **$Cs_2CO_3$** | **80(76)** [b] | **7** |
| 2 | $K_3PO_4$ | 5 | 10 |
| 3 | $Na_2CO_3$ | <1 | 0 |
| 4 | $K_2CO_3$ | 6 | 4 |
| 5 | NaOAc | 0 | 0 |
| 6 | $Et_3N$ | 0 | 0 |
| 7 | Pyridine | 0 | 0 |
| 8 | No Base | 0 | 0 |

Reaction condition: [a] Benzyl alcohol **2a** (0.375mmol), acetophenone **1a** (0.25 mmol), $NiBr_2$ (10 mol%), Phen (20 mol%), **Base (10 mol%)**, 1,4-dioxane (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 ºC oil bath, 36 h reaction time. [b] Isolated yield (average of two run).

**Table 5**: Screening of alcohol equivalents [a]

| Entry | alcohol (X equiv.) | GC-MS Conversion **3** (%) | GC-MS Conversion **3'** (%) |
|---|---|---|---|
| 1 | 1.5 | 80(76)[b] | 7 |
| **2** | **1.25** | **85(80)**[b] | **10** |
| 3 | 1.1 | 81 | 5 |

Reaction condition: [a] **Benzyl alcohol (X equiv.)**, acetophenone (0.25 mmol), $NiBr_2$ (10 mol%), Phen (20 mol%), $Cs_2CO_3$ (10 mol%), 1,4-dioxane (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 ºC, 36 h reaction time. [b] Isolated yield (average of two run).

**Table 6**: Screening for base loading [a]

| Entry | Base | GC-MS Conversion 3 (%) | GC-MS Conversion **3'** (%) |
|---|---|---|---|
| 1 | *t*-BuOK (10 mol%) | 50 | 10 |
| 2 | *t*-BuOK (15 mol%) | 70 | 18 |
| 3 | *t*-BuOK (20 mol%) | 94(82)[c] | **1** |

Reaction condition: [a] Benzyl alcohol **2a** (0.3125mmol), acetophenone **1a** (0.25 mmol), $NiBr_2$ (5mol%), Phen (6mol%), **base (x mol%)**, toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 ºC oil bath, 36 h reaction time. [b] Isolated yield (average of two run).

**Table 7**: Screening of catalyst and ligand loading [a]

| Entry | Catalyst Loading | Ligand Loading | GC-MS Conversion **3** (%) | GC-MS Conversion **3'** (%) |
|---|---|---|---|---|
| 1 | $NiBr_2$ (10 mol% ) | Phen (20 mol%) | 85(80)[b] | 10 |
| 2 | $NiBr_2$ (7.5 mol%) | Phen (15 mol%) | 63 | 16 |
| 3 | $NiBr_2$ (5.0 mol%) | Phen (10 mol%) | 42 | 8 |
| 4 | $NiBr_2$ (2.5 mol%) | Phen (5 mol%) | 25 | 3 |

Reaction condition: [a] Benzyl alcohol **2a** (0.3125mmol), acetophenone **1a** (0.25 mmol), **$NiBr_2$ (x mol%), Phen (y mol%)**, $Cs_2CO_3$ (10 mol%), 1,4-dioxane (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 ºC oil bath, 36 h reaction time. [b] Isolated yield (average of two run).

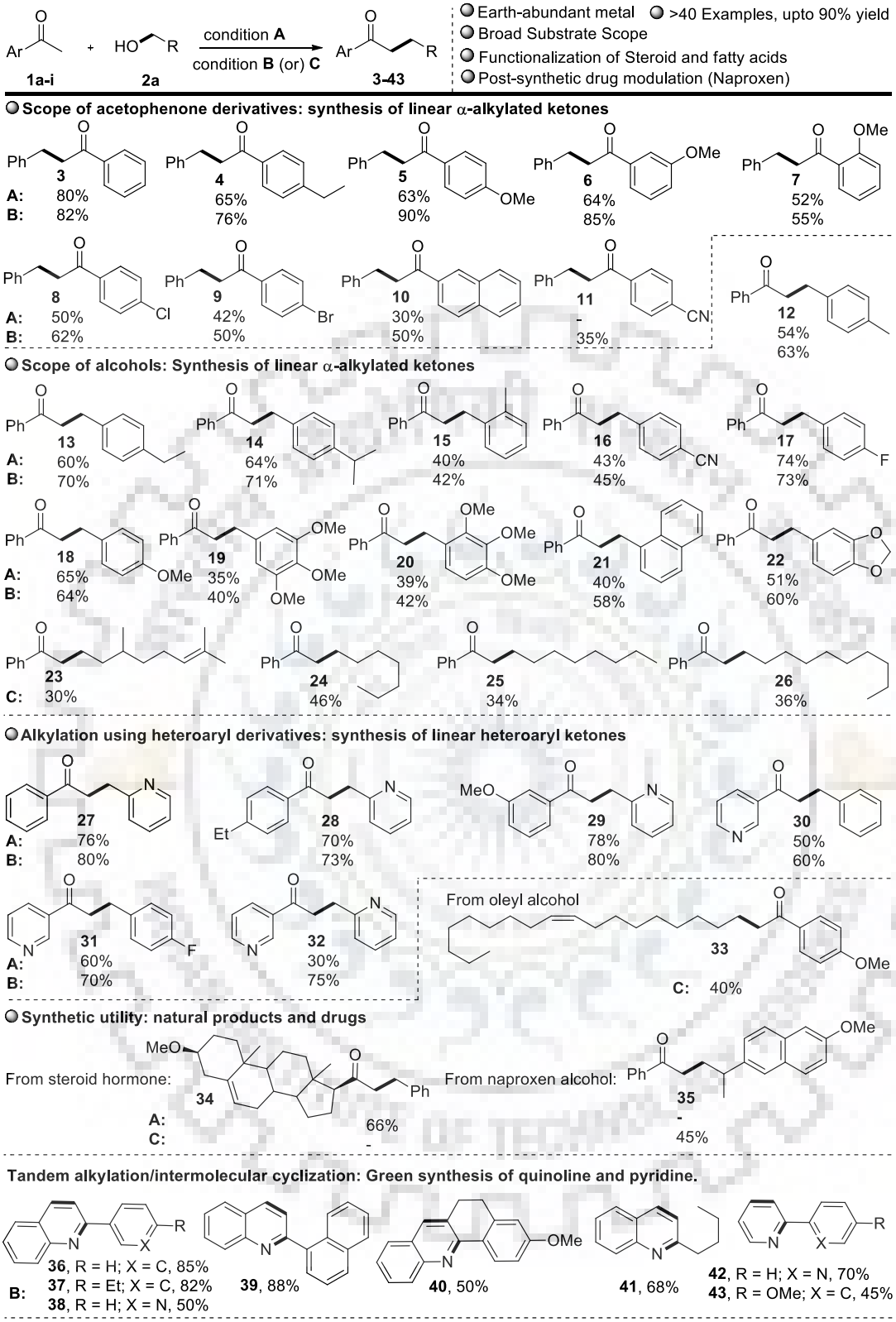
**Table 8**: Screening of temperature [a]

| Entry | **T (°C)** | GC-MS Conversion **3** (%) | GC-MS Conversion **3'** (%) |
|---|---|---|---|
| 1 | 120 | 0 | 0 |
| 2 | 130 | 6 | 0 |
| **3** | **140** | **80(76)**[b] | **7** |

Reaction condition: [a] Benzyl alcohol **2a** (0.375mmol), acetophenone **1a** (0.25 mmol), $NiBr_2$ (10 mol%), Phen (20 mol%), $Cs_2CO_3$ (10 mol%), 1,4-dioxane (2.0 mL), Schlenk tube under nitrogen atmosphere, **T ºC** oil bath for 36 h reaction time. [b] Isolated yield (average of two run).

**Mono-selective alkylation of acetophenone with benzyl alcohol**: After having optimized conditions in hand, we explored the scope and limitations of the catalytic protocol using electronically different various acetophenone derivatives with benzyl alcohols for selective mono-alkylation. To our delight, ethyl, methoxy, as well as halide substituents on the aryl ring of acetophenone are well tolerated and resulted α-alkylated acetophenone in up to 90% yield (**3-11**). Importantly, sterically hindered ortho-methoxy acetophenone efficiently converted into 55% yield of **7**. It is to be note that, under standard conditions 2-naphthylacetophenone affords linear mono-selective ketone **10** in moderate yield. Notably, the catalytic protocol is highly selective for methyl-ketone derivative and we did not observe any bis-alkylated ketone using GC-MS analysis of the crude reaction mixture (Scheme 4).

***α*-Alkylation of acetophenone with a range of benzyl and alkyl alcohols**: Having witnessed excellent catalytic activity of acetophenone derivatives with benzyl alcohol, further we studied the reactivity profile of various benzyl alcohols with a series of acetophenones (Scheme 4, **12-22**). Benzyl alcohols bearing electron rich functionalities including 2-methyl substituent at aryl ring, resulted corresponding mono-alkylated products **12-15** in 42-71% yield respectively. Advantageously, 4-fluoro and 4-nitrile substituted benzyl alcohols efficiently transformed into the desired products **16-17** in up to 74% yield. Notably, when using benzyl alcohols having multiple electron rich substituents, resulted a lower product yield due to strong electronic effect (Scheme 4, **18-20**). Gratifyingly, 1-naphthylmethanol as well as benzyl alcohol having oxygen heterocycles selectively converted into linear ketone derivatives **21-22**. Next, we explored the reactivity of more challenging long chain renewable alkyl alcohols with acetophenone (**23-26**, Scheme 4). It is noteworthy to mention that, renewable terpenoid intermediate citronellol efficiently converted to **23** under standard catalytic conditions. Notably, this is a rare instance of a chemo-selective transformation of an alkyl alcohol having internal double-bond using nickel, often quite challenging under precious-metal catalysis.[4-7]

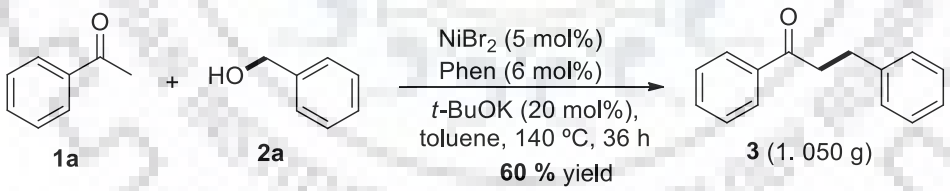



**Scheme 4:** Synthesis of linear α-alkylated ketones

**Reaction conditions A:** Unless specified otherwise, the reaction was carried out with **1** (0.25 mmol), **2** (0.3125 mmol), $NiBr_2$ (0.025 mmol), **L1** (0.050 mmol), and $Cs_2CO_3$ (0.025 mmol) in 1,4-dioxane (2.0 mL) under $N_2$ at 140 °C (oil bath) for 48 h. **Conditions B:** $NiBr_2$ (0.0125 mmol), **L1** (0.015 mmol), and *t*-BuOK (0.050 mmol) in toluene (2.0 mL) at 140 °C for 36 h. **Conditions C:** **2** (0.375 mmol), $NiBr_2$ (0.0125 mmol), **L1** (0.015 mmol), and *t*-BuOK (0.375 mmol) in toluene (2.0 mL) at 140 °C for 36 h.

**Alkylation using hetero aromatic ketones and alcohols**: Pleasingly, we analyzed the scope of hetero-aryl alcohols for alkylation with methyl ketones. Gratifyingly, 2-pyridinemethanol efficiently alkylated with acetophenone derivatives and resulted in up to 80% yield (Scheme 4, **27-29**). Notably, more challenging, 3-acetyl pyridine gave 60% yield of **30** with benzyl alcohol. Furthermore, 4-fluorophenyl benzyl alcohol and 2-pyridinemethanol afford pharmaceutically active ketones **31-32** in 70-75% yield, respectively. It is important to note that, the catalytic protocol is tolerant to the pyridine derivatives, otherwise known to poison the catalytic system.

**Synthetic applications**: Thereafter, we extend our nickel-catalyzed selective alkylation in the synthesis of complex natural products and drug molecules with impressive functional group compatibility (Scheme 2, **33-35**). For instance, alcohol derived from sensitive fatty acid, such as, oleic acid, alkylated with 4-methoxy acetophenone to **33** without significantly affecting the double bond and resulted reasonable product yield. Methyl ketone from steriod hormone efficiently alkylated with benzyl alcohol to **34**. Again, alkyl alcohol derived from drug, naproxen, transformed to the corresponding α-alkylated product in moderate yield (**35**). All these examples demonstrate the potential application of the present methodology and could be useful for selective and efficent post-synthetic drug functionalization using nickel catalyst. Further, we applied our optimized protocol for the synthesis of C-2 substituted quinolines and pyridines (using 2-amino benzyl alcohol and 3-amino-1-propanol as coupling partners) in up to 88% yields (Scheme 4, **36-43**).




**Scheme 5:** Practical utility: gram scale synthesis of **3**

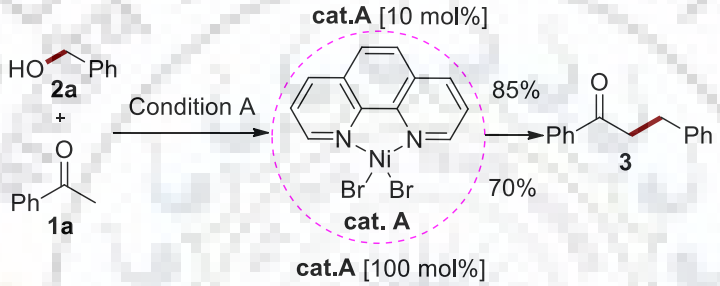
Reaction Conditions (Procedure B): **1a** (1.0 g, 8.33 mmol), **2a** (1.125 g, 10.42 mmol), $NiBr_2$ (91 mg, 5 mol%), phen (90 mg, 6 mol%), *t*-BuOK (187 mg, 7.46 mmol) and toluene (15.0 mL) in a 100 mL pressure tube under nitrogen atmosphere at 140 °C in oil bath for 36 h.

Notably, we observed impressive functional group tolerance for the present catalytic protocol. For instance, halides (Cl, Br, and F), alkyl, alkoxy and di-oxolone functionalities, as well as benzyl and the pyridine moiety used efficiently for alkylation reactions. Importantly, remarkable transformations in the presence of reducible functional groups, such as, nitrile, internal double bond in fatty acid alcohol, citronellol including steroid framework represents the synthetic potential of the optimized protocol. The alkylation

reaction could be performed in gram scale using acetophenone **1a** (1.0 g, 8.33 mmol) with benzyl alcohol **2a** and the desired product **3** (1.050 g) was obtained in 60% yield (Scheme 5).

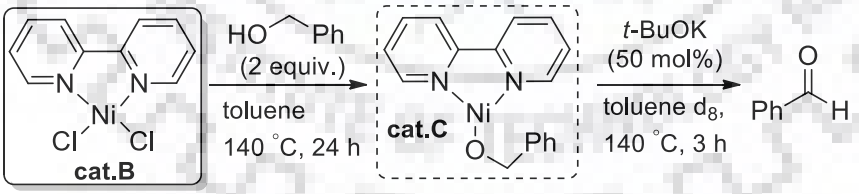
**Kinetic and mechanistic studies:**

Having observed excellent catalytic activity for α-alkylation of ketones with primary alcohols, we next focused to study the mechanistic investigation for the course of the reactions. In our earlier studies we observed that,[14] Ni-catalyzed alcohol dehydrogenation is a multi-step process following HB methodology (Scheme 9). We performed a series of control and mechanistic studies to understand the catalytic behaviour of the Ni-catalyst in case of alkylation of acetophenone derivatives.




**Scheme 6:** Catalytic and stoichiometric studies using defined **cat. A**

Hence, to understand the involvement of the Ni-intermediate species for alkylation reaction, we readily prepared **cat. A** using literature procedure,[18] and applied in the reaction of **1a** with **2a** under standard conditions. To our delight, when catalytic (10 mol%) as well as in stoichiometric equiv. (100 mol%) of **cat. A** were used, **3** was obtained in 70-85% yield (Scheme 6).




**Scheme 7:** Evidence for intermediate nickel-alkoxy species

During optimization studies we observed that, base plays a key role to obtain higher product yield.[14] We anticipated that, base facilitate the process for activation of nickel pre-catalysts *via* dehalogenation of $NiX_2$ and substitution with alcohol counterpart resulted alkoxy-nickel species.[14d,18] Next, the pre-formed alkoxy-nickel species undergoes β-hydride elimination in presence of a base and aldehyde is formed. Importantly, active nickel-hydride species generates during this process, facilitate enone reduction. Based on the above proposal, we

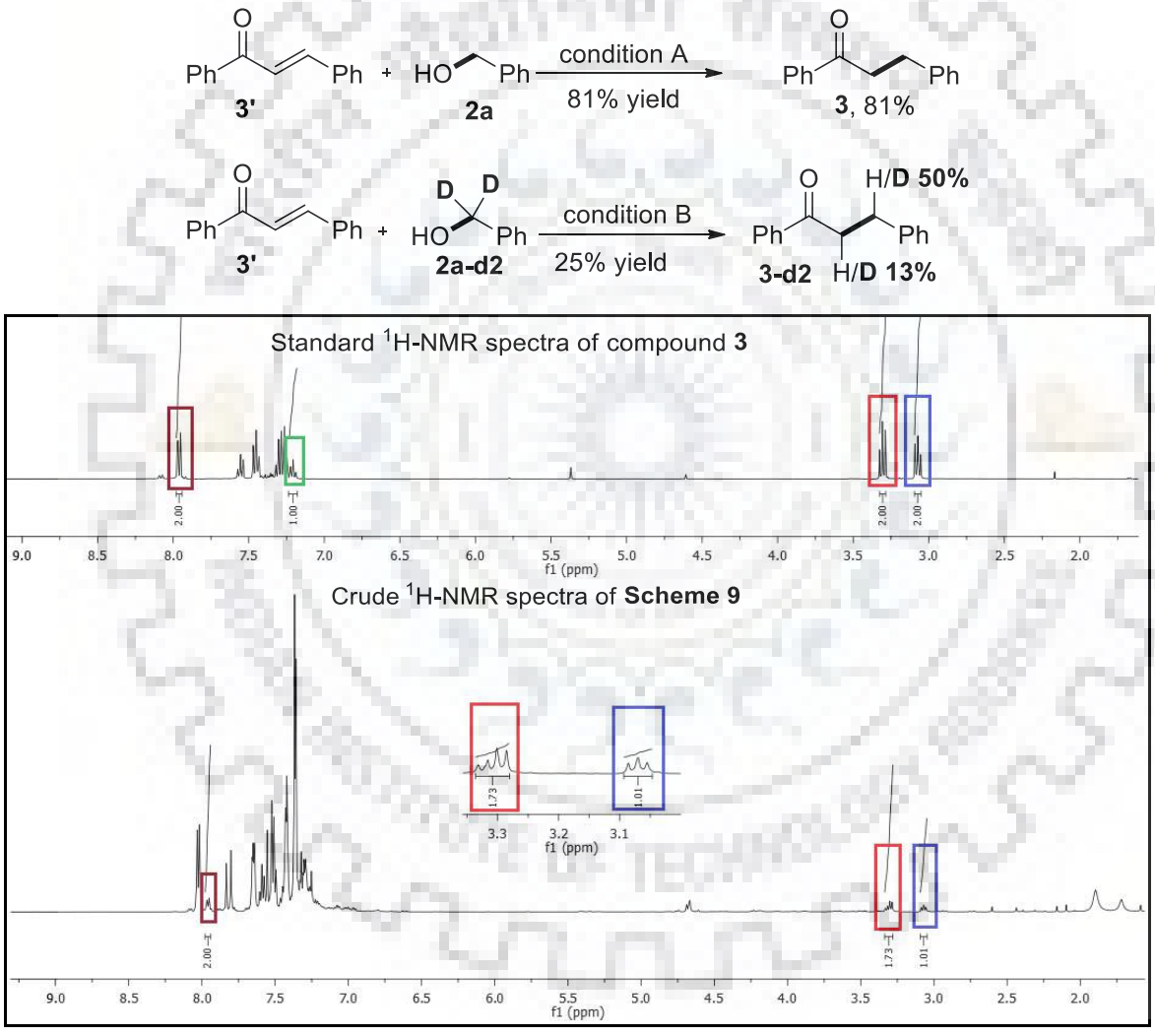
prepared the defined Ni-alkoxy species of **cat. B** and allowed to react under standard conditions using 50 mol% *t*-BuOK. The reaction was interrupted after three hours and detected benzaldehyde formation using GC-MS analyis of the crude reaction mixture (Scheme 7). These experiments proof the involvement of the nickel-alkoxy intermediate for alkylation process.[14d]


**Scheme 8:** Stoichiometric studies using define Ni-H catalyst

Further to strengthen our hypothesis, we made an attempt to prepare the Ni-H species of **cat. A**., unfortunately, after several attempt at variable temperature we failed to detect any Ni-H species even using an *in situ* NMR studies at -75 °C.[14] At this point we realized that ligand might be playing a crucial role to stabilize the *in situ* generated Ni-H species. Therefore, we choose highly electron rich phosphine ligand, tri-cyclohexyl phosphine, **L7** and prepared the defined Ni-H complex, $[(Cy)_3]_2PNiBrH$.[17] Further, stoichiometric reaction of $[(Cy)_3]_2PNiBrH$ with enone **3a'** using 20 mol% *t*-BuOK gave 38% yield of **3a** (Scheme 8). These experimental outcomes strongly support our hypothesis for the involvement of the nickel-alkoxy as well as Ni-H species for α-alkylation of methyl ketones using dehydrogenative coupling of alcohols under nickel catalysis.[14d]

Additionally, we performed detailed deuterium-labeling experiments for α-alkylation of methyl ketones. Initially, we prepared intermediate enone **3'**and reacted with **2a** and **2a-d2** under standard conditions. We observed 13% and 50% incorporation of deuterium in α-, and β-position of **3-d2** respectively (Scheme 9). Again, we studied the α-alkylation of **1a** using benzyl alcohol **2a-d2**, after a careful examination using $^1$H-NMR and GC-MS analysis; we observed almost equal distribution of deuterium atom in α-, and β-position of **3-d2** (Scheme 10). Crossover experiments using acetophenone **1a** with 1:1 mixture of **2a** and **2a-d2** under standard catalytic conditions also resulted product **3-d2** and detected deuterium incorporation at α, and β-position in almost equivalent ratio (Scheme 11). Next, when **1a-d3** reacted with benzyl alcohol **1a**, a variable D/H exchange-ratio in the product **3-d2** observed (Scheme 12). To our delight, catalytic experiment using **2a**-**d**, resulted deuterium incorporation at α, and β-position in equal distribution in product **3-d2** (Scheme 13).

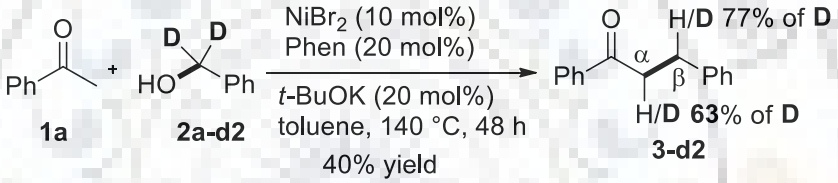
We believe that, results obtained using deuterated investigation for alkylation of methyl ketones are in strong agreement for involvement of hydrogen auto-transfer strategy and D/H exchange during the course of the reaction.[19a] Notably, alcohol was crucial for generic hydride source, involvement of alkoxy-nickel species as well as *in situ* generated nickel-hydride species was the key for catalytic α-alkylation of methylene ketones.[19] Finally, we also performed kinetic studies in two sets of experiments for the determination of rate laws (Scheme 14). Considering a steady state approximation for alcohols, first order kinetics with respect to **1a** was observed for α-alkylation of methyl ketones.

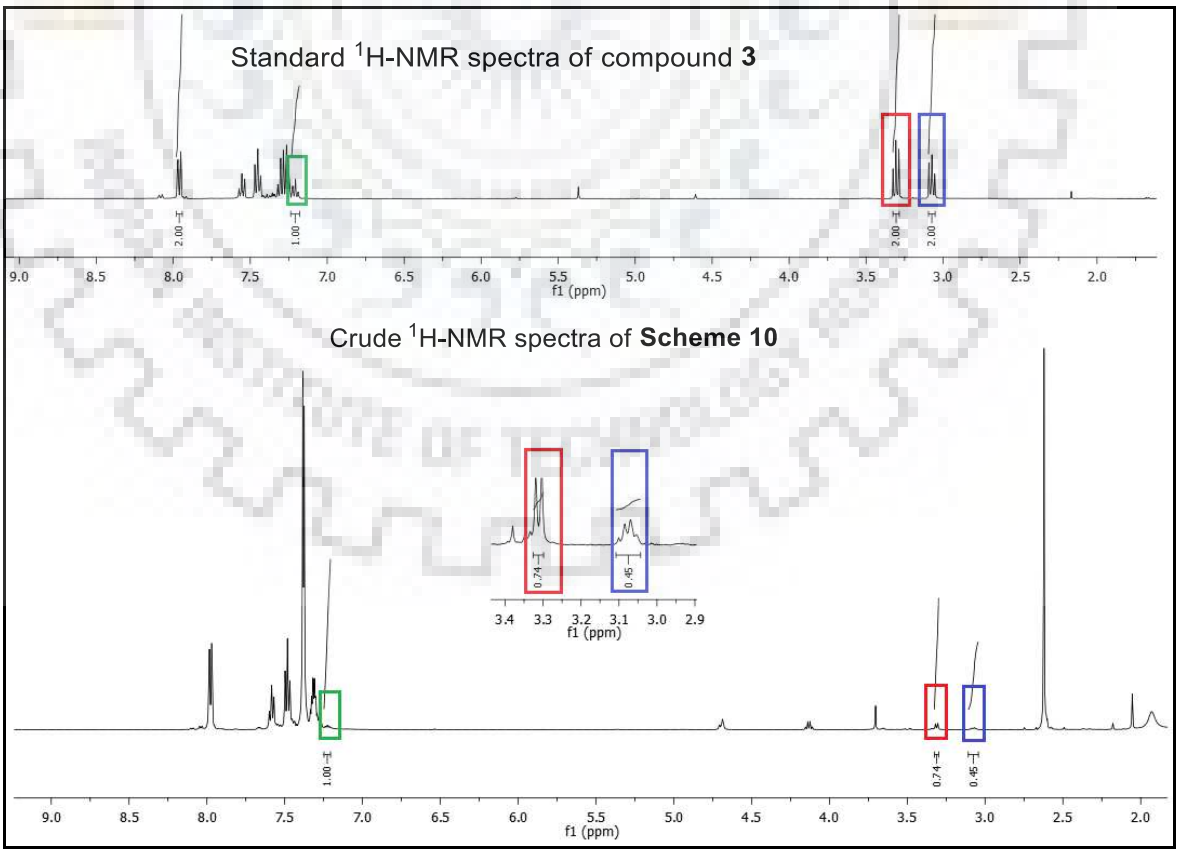


Conversion was calculated by $^{1}$H-NMR integration value

| | | Deuterium incorporation in **α position** | Deuterium incorporation in **β position** |
|---|---|---|---|
| Signal $\delta$ ppm | 7.96 [ortho-H,(2H)] | 3.31 (2H) | 3.07 (2H) |
| Integral Value | 2.0 | 1.73 | 1.01 |
| **Calculated ratio** | | {(2-1.73) / 2}×100 = 13% | {(2-1.01) / 2}×100 = 50% |

**Scheme 9:** Reduction of enone **3'** with benzyl alcohol **2a** and **2a-d2**

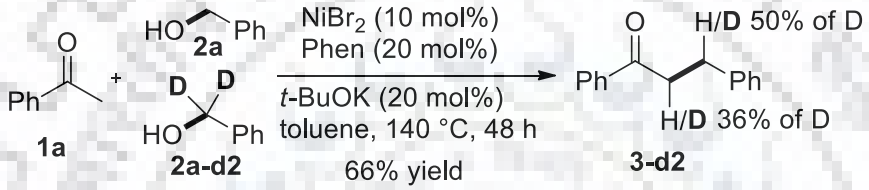


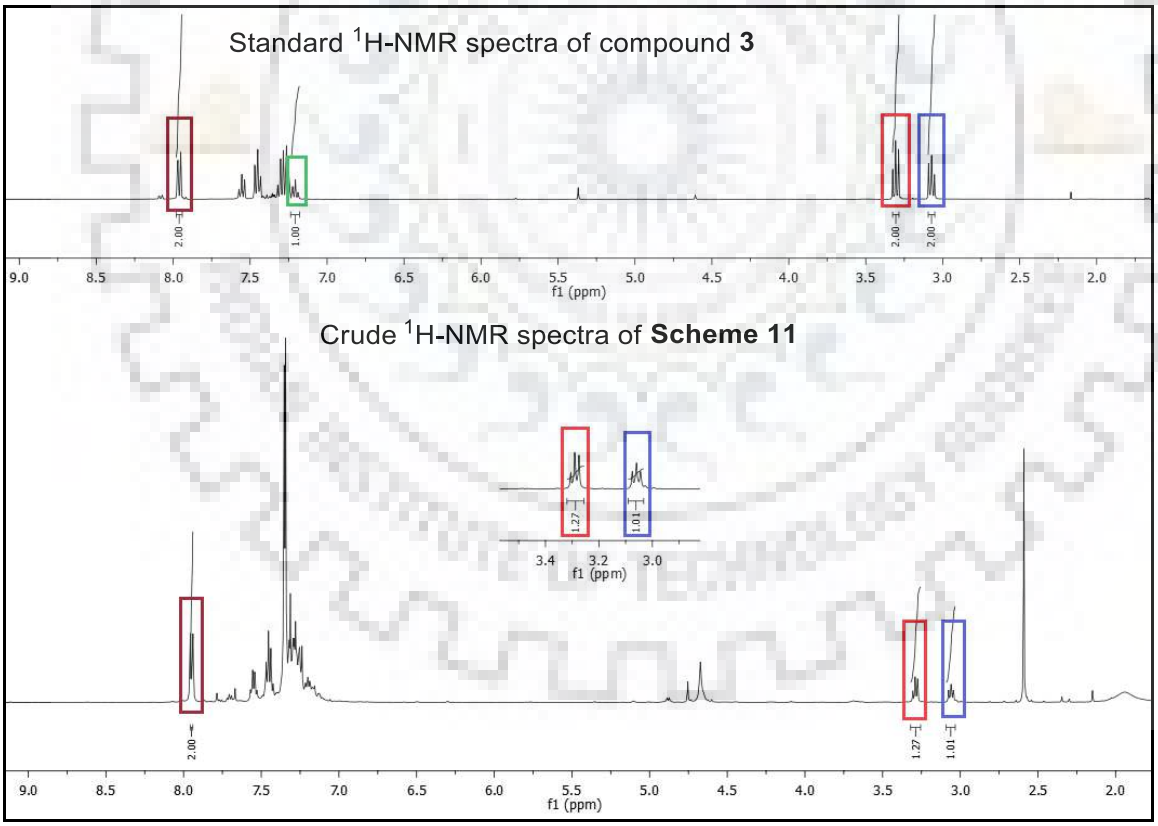



Conversion was calculated by $^1$H-NMR integration value

| | | Deuterium incorporation in **α** position | Deuterium incorporation in **β** position |
|---|---|---|---|
| Signal $\delta$ ppm | 7.21 [para-H,(1H)] | 3.31 (2H) | 3.07 (2H) |
| Integral Value | 1.0 | 0.74 | 0.46 |
| **Calculated ratio** | | {(2-0.74) / 2}×100 = **63%** | {(2-0.46) / 2}×100 = **77%** |

**Scheme 10:** Reaction of acetophenone **1a** with **2a-d2**

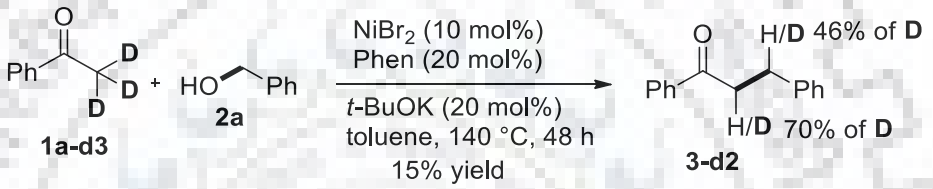


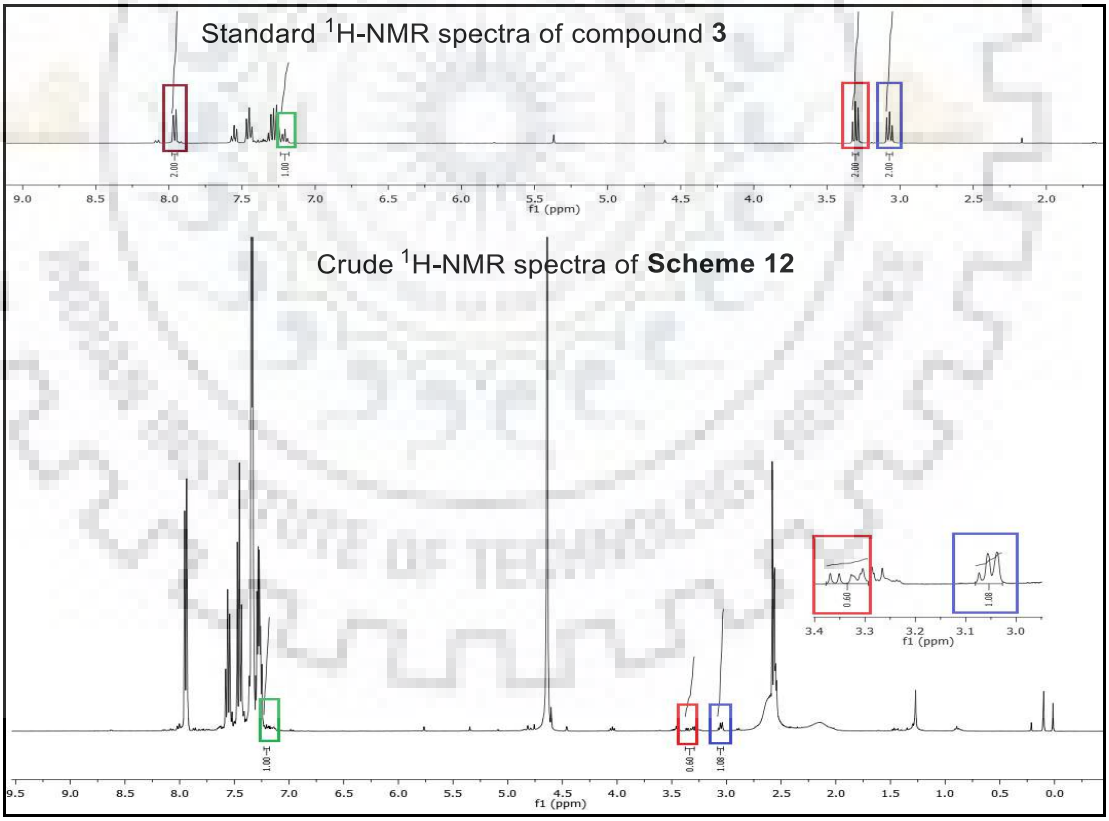



Conversion was calculated by $^{1}$H-NMR integration value

| | | Deuterium incorporation in **α position** | Deuterium incorporation in **β position** |
|---|---|---|---|
| Signal $\delta$ ppm | 7.96 [ortho-H,(2H)] | 3.31 (2H) | 3.07 (2H) |
| Integral Value | 2.0 | 1.27 | 1.01 |
| **Calculated ratio** | | {(2-1.27) / 2}×100 = **36%** | {(2-1.01) / 2}×100 = **50%** |

**Scheme 11:** Competitive reaction between **2a** and **2a-d2** with acetophenone **1a**

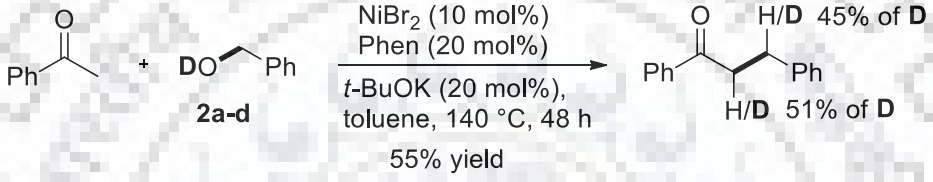


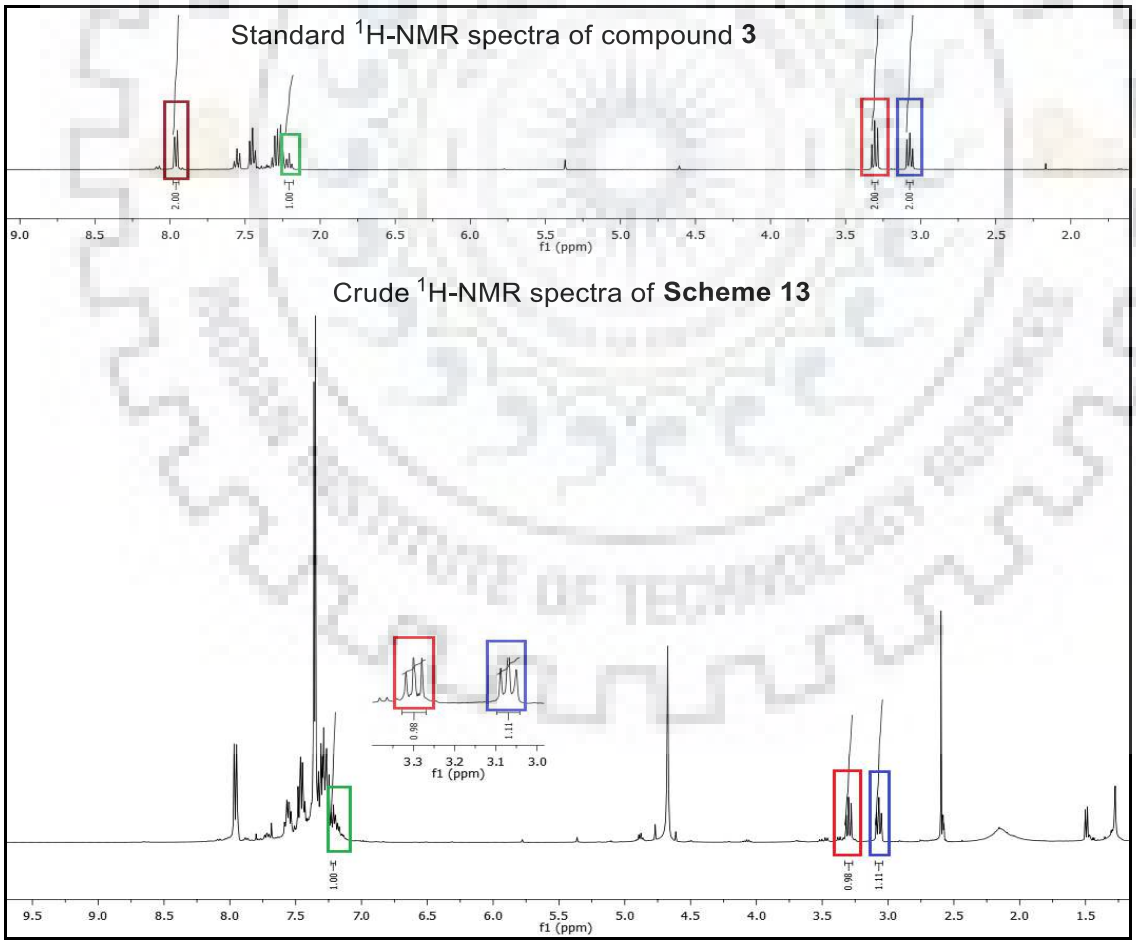



Conversion was calculated by $^{1}$H-NMR integration value

| | | Deuterium incorporation in **α position** | Deuterium incorporation in **β position** |
|---|---|---|---|
| Signal $\delta$ ppm | 7.21 [para-H,(1H)] | 3.31 (2H) | 3.07 (2H) |
| Integral Value | 1.0 | 0.40 | 1.08 |
| **Calculated ratio** | | {(2-0.60) / 2}×100 = **70%** | {(2-1.08) / 2}×100 = **46%** |

**Scheme 12:** Reaction of **1a-d3** with **2a-d2**



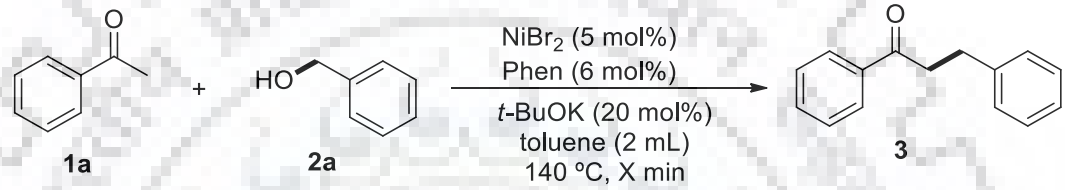



Conversion was calculated by $^{1}$H-NMR integration value

| | | Deuterium incorporation in **α position** | Deuterium incorporation in **β position** |
|---|---|---|---|
| Signal $\delta$ ppm | 7.21 [para-H,(1H)] | 3.31 (2H) | 3.07 (2H) |
| Integral Value | 1.0 | 0.98 | 1.11 |
| **Calculated ratio** | | {(2-0.98) / 2}×100 = **51%** | {(2-1.08) / 2}×100 = **45%** |

**Scheme 13:** Reaction of acetophenone with **2a-d**

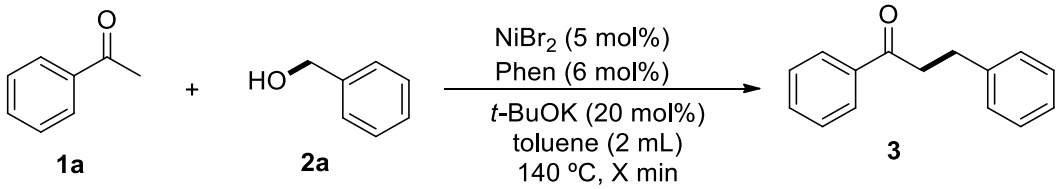
Run 1: Reaction was carried out in 2 mL of toluene and yield was calculated by GC




| No. | **1a** (mmol) | **2a** (mmol) | $NiBr_2$ (mmol) | Phen (mmol) | *t*-BuOK (mmol) | Toluene (mL) |
|---|---|---|---|---|---|---|
| Run 1 | 0.2 | 0.3 | 0.01 | 0.012 | 0.04 | 2.0 |

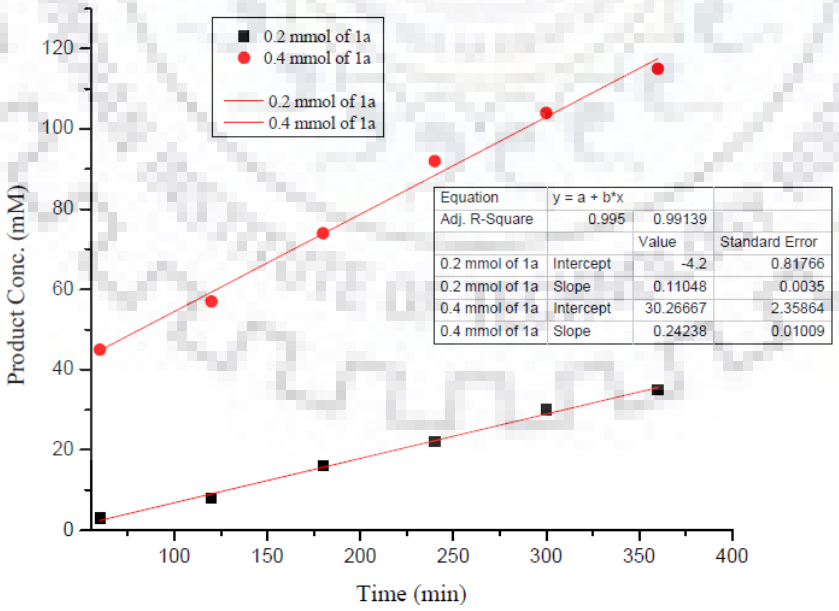
| Sl. No. | Time (min) | Concentration of **3** (mM) |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 60 | 3 |
| 3 | 120 | 8 |
| 4 | 180 | 16 |
| 5 | 240 | 22 |
| 6 | 300 | 30 |
| 7 | 360 | 35 |

Run 2: Reaction was carried out in 2 mL of toluene and yield was calculated by GC




| No. | **1a** (mmol) | **2a** (mmol) | $NiBr_2$ (mmol) | Phen (mmol) | *t*-BuOK (mmol) | toluene (mL) |
|---|---|---|---|---|---|---|
| Run 2 | 0.4 | 0.6 | 0.02 | 0.024 | 0.08 | 2.0 |

| Sl. No. | Time (min) | Concentration of **3** (mM) |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 60 | 45 |
| 3 | 120 | 57 |
| 4 | 180 | 74 |
| 5 | 240 | 92 |
| 6 | 300 | 104 |
| 7 | 360 | 115 |




Graphical representation for determination of rate and order of reaction

Considering steady state approximation for benzyl alcohol

From Run 1: Slope = k [1a] $^{x}$

0.11 = k [0.2] $^{x}$

From Run 2: Slope = k [1a] $^{x}$

0.24 = k [0.4] $^{x}$

0.24/0.11 = [0.4] $^{x}$ / [0.2] $^{x}$

2.18 = [2] $^{x}$

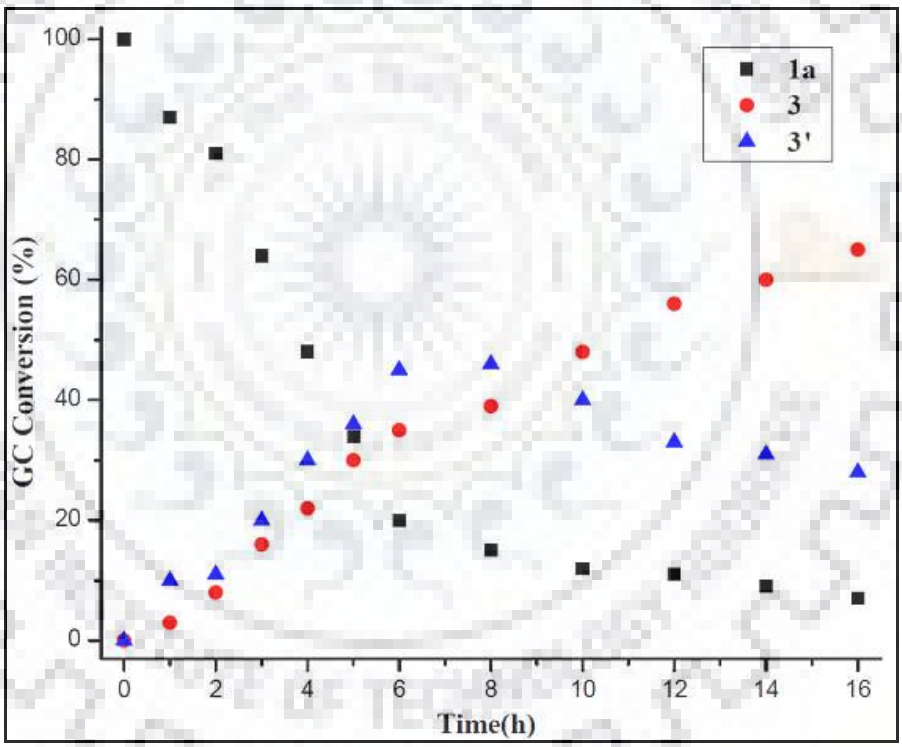
Log (2.18) = x. Log (2)

x = 0.338 / 0.301

= 1.1 ≈ 1

Rate = k [1a] $^{1}$

**Scheme 14:** Determination of rate and order of reaction




**Scheme 15:** Time-conversion-plot for the reaction of acetophenone (**1a**) with benzyl alcohol (**2a**)

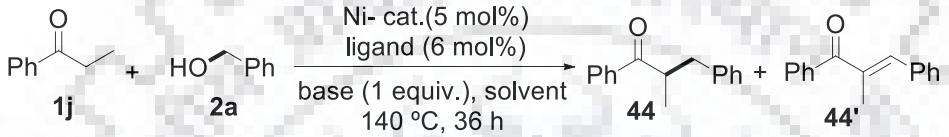
**Reaction conditions**: Acetophenone **1a** (0.20 mmol), benzyl alcohol **2a** (0.30 mmol), $NiBr_2$ (5.0 mol%), Phen (6.0 mol%), *t*-BuOK (0.04 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 °C oil bath.

### [3.5] Ni-catalyzed *α*-alkylation of methylene ketones:

Further, we explored the alkylation of methylene ketones with primary alcohols. Notably, under the optimized conditions of acetophnone derivatives, we observed albeit with lower

product yields. Therefore, we have performed initial optimization studies using Ni-catalyzed protocol involving propiophenone (**1j**) with benzyl alcohol (**2a**) as model substrate. Reactions with a variety of Ni-salts, ligands, solvents and bases were performed to furnish the *α*-branched ketone (**44**). Initially, different Ni(0) and Ni(II) salts were employed in presence of 1,10 phenanthroline as ligand and *t*-BuOK in toluene at 140 °C for 36 h. To our delight, in case of $NiBr_2$ we observed 86% conversion to product while others showed moderate reactivity (Table 9).

**Table 9**: Optimization of reaction condition [a]




| Entry | Catalyst | Ligand | Conv. (%) [b] | |
|---|---|---|---|---|
| | | | **44** | **44'** |
| 1 | $NiBr_2$ | 1,10-Phenanthroline | 86(78) | 10 |
| 2 | $NiCl_2$ | 1,10-Phenanthroline | 50 | 39 |
| 3 | $Ni(cod)_2$ | 1,10-Phenanthroline | 55 | 32 |
| 4 | $NiBr_2$ | Bpy | 50 | 30 |
| 5 | $NiBr_2$ | $PPh_3$ | 61 | 30 |
| 6 | $NiBr_2$ | $PCy_3$ | 57 | 24 |
| 7 [c] | $NiBr_2$ | 1,10-Phenanthroline | 18 | 10 |
| 8 [d] | $NiBr_2$ | 1,10-Phenanthroline | 5 | <1 |
| 9 [e] | $NiBr_2$ | 1,10-Phenanthroline | 70 | 20 |
| 10 [f] | $NiBr_2$ | 1,10-Phenanthroline | 50 | 40 |
| **11 [g]** | **$NiBr_2$** | **1,10-Phenanthroline** | **95(92)** | **1** |
| 12 [h] | $NiBr_2$ | 1,10-Phenanthroline | 0 | 0 |
| 13 | - | - | 10 | 35 |

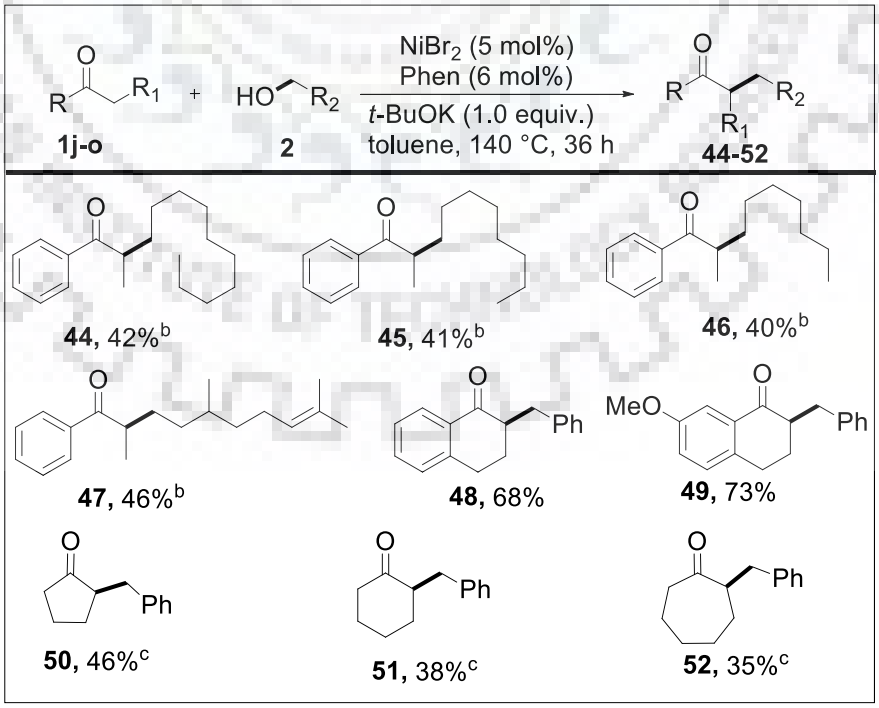
Reaction condition: [a] Unless specified otherwise, the reaction was carried out with **1j** (0.5 mmol), **2a** (0.625 mmol), Ni cat. (5 mol%), Ligand (6 mol%), and *t*-BuOK (1 equiv.) under an $N_2$ atmosphere at 140 °C (oil bath) in toluene (2.0 mL) for 36 h in a Schlenk tube. [b] Conversion was determined by GC-MS (isolated yield in parentheses, average yield of two runs). [c] DMA, [d] pentanol was used. [e] *t*-BuONa, [f] $Cs_2CO_3$ was used. [g] **2a** (0.75 mmol) was used. [h] No base was used.

In order to understand the electronic effects of ligands on the reactions, several electron rich nitrogen and phosphine-based ligands were tested but there was no increment in product conversion. It is noteworthy to mention that, in polar solvents such as DMF, DMA and pentanol the formation of the product decreases abruptly although moderate conversion was

observed in *p*-xylene and 1,4-dioxane (Table 9). Application of different carbonate, phosphate and tertiary butoxide bases also did not increase the product conversion further. Gratifyingly, the use of excess of alcohol (1.5 equiv.) increases the product conversion up to 95% with an isolated yield of 92%. Further, control experiments in absence of catalyst and base revealed their potential role for this transformation and we only observed poor or no product conversion respectively (Table 9).

**Alkylation using renewable alkyl alcohols**

We observed that, $NiBr_2$ (5 mol%), 1,10-phenanthroline (6 mol%), *t*-BuOK (1 equiv.), alcohol (1.5 equiv.) in toluene at 140 °C for 36 h is necessary for the higher product yields. After having the optimized condition, we explored the reactivity of more challenging primary alkyl alcohols and alkyl ketones (Scheme 16). For instance, readily abundant $C_7$-$C_{10}$ primary alcohols as well as renewable terpenoid intermediate citronellol efficiently converted to branched gem-di-alkyl substituted ketones **44**-**47**. Notably, this is a rare chemo-selective transformation of unsaturated alcohol under Ni-catalysis. Again, the reaction of tetralone derivatives (**1k**-**1l**) and cyclic alkyl ketones, such as, cyclopentanone, cyclohexanone as well as cycloheptanone, converted into α-benzyl cyclic ketones in up to 73% yield (Scheme 16, **48-52**). These examples showed the potential of the present catalytic protocol.



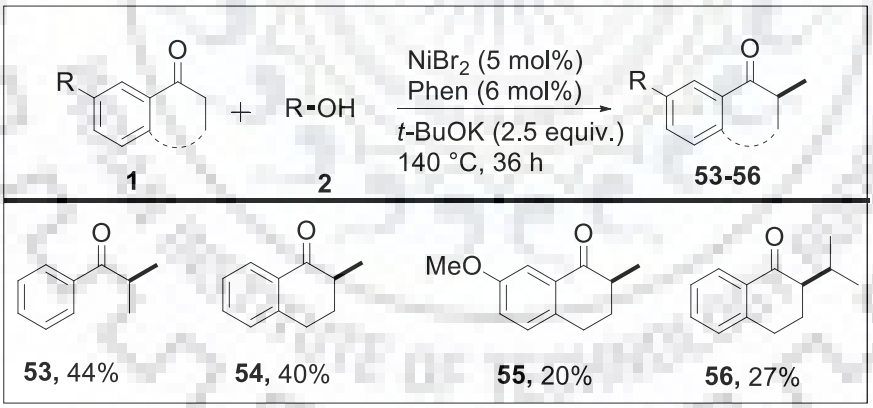

**Scheme 16**: Scope of alkyl alcohol: Synthesis of branched gem-bis(alkyl) ketones [a]

Reaction condition: [a] Unless otherwise specified, the reaction was carried out with **1** (0.25 mmol), **2** (0.375 mmol), $NiBr_2$ (0.0125 mmol), Phen (0.015 mmol), *t*-BuOK (0.25 mmol) in toluene (2.0 mL) at 140 °C for 36 h; [b] $NiBr_2$ (0.0187 mmol), Phen (0.0225 mmol), *t*-BuOK (0.5 mmol) was used; [c] *t*-BuOK (0.0625 mmol) was used, 24 h.

**C-alkylation using methanol:**

To demonstrate the general applicability of the catalytic protocol we utilize methanol as a $C_1$ source for α-methylation of ketones under standard catalytic conditions. Despite significant advancement acceptorless dehydrogenative coupling (ADC) of smaller alcohols is a challenging task in catalysis. High energy barrier for activation of smaller alcohols often limits its applications and till date use of precious noble metal-catalysts (Ir-, Rh-, and Ru- etc.) are known for such processes. Hence, still there is a need for sustainable and earth-abundant non-precious metal catalysts for such applications.

To our delight, when propiophenone and tetralone derivatives were employed under the optimized conditions using methanol, α-methylated ketones **53**-**56** were obtained in up to 44% yield (Scheme 17). Under identical conditions we also observed α-isopropyl tetralone **56** in moderate yield. To the best of our knowledge, this represents the first example of homogeneous nickel catalyzed process for methanol activation.



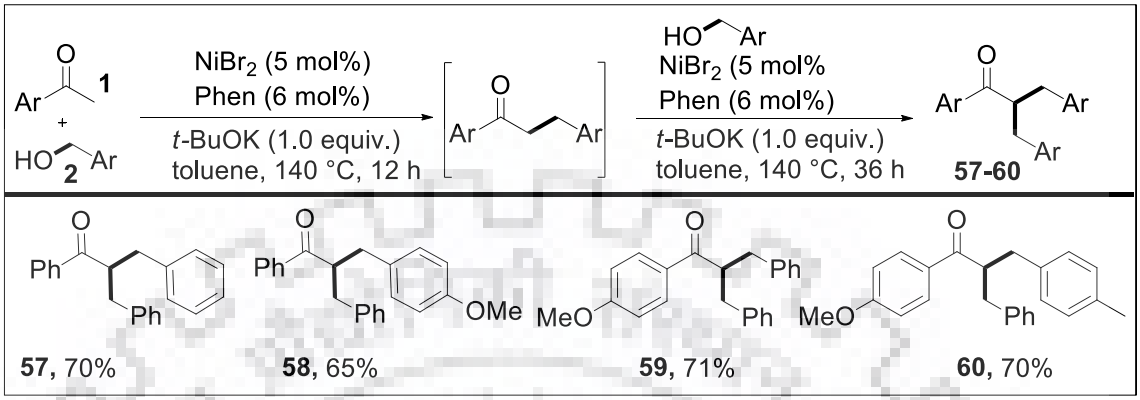

**Scheme 17:** Methanol as C1-source: Synthesis of branched α-methylated ketones [a]

Reaction condition: [a] Unless otherwise specified, the reaction was carried out with **1** (0.25 mmol), **2** (1.0 mL), $NiBr_2$ (0.0125 mmol), Phen (0.015 mmol), *t*-BuOK (0.625 mmol) at 140 °C for 36 h.

**Sequential one-pot double alkylation of acetophenone using a single catalyst:**

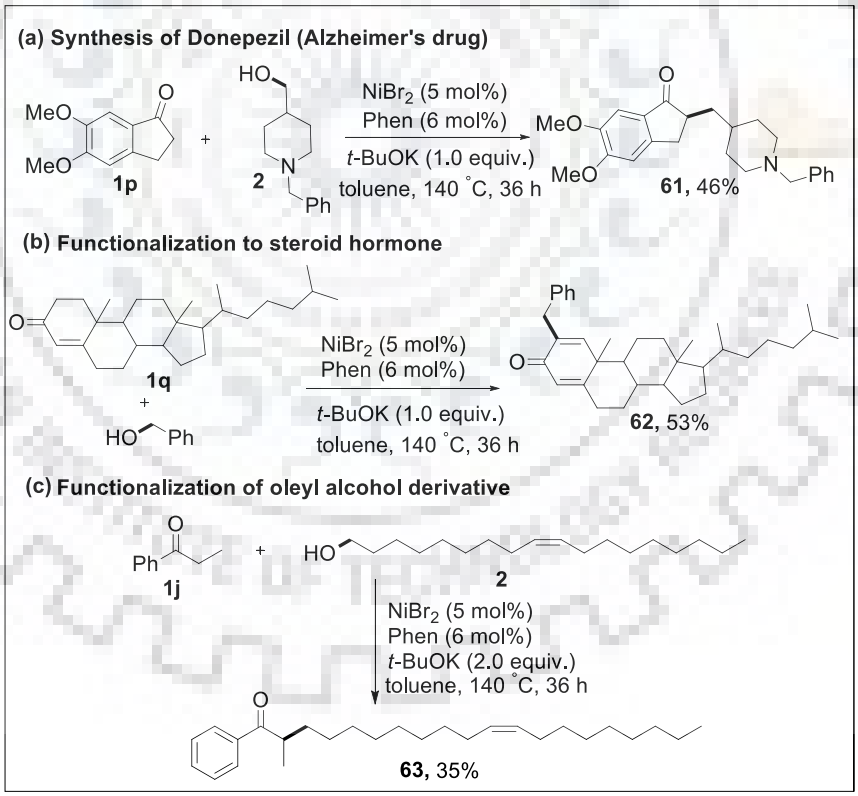
Further to exploit the synthetic potential of the catalytic process, we next studied the one-pot sequential double alkylation of α-methyl ketones using primary alcohols (Scheme 18). We choose acetophenone and 4-methoxyphenyl acetophenone and were subjected to one-pot sequential alkylation catalyzed by **$NiBr_2$/L1** using different primary alcohols. Notably,

in the first step we observed a selective mono-benzylation followed by a second addition of similar catalyst composition and different benzyl alcohols facilitate to one-pot hetero bis-alkylated ketones in 65-71% yield respectively (Scheme 18).




**Scheme 18:** Sequential one-pot double alkylation of acetophenone

**Synthetic application in drug synthesis and functionalization of steroid hormone:**



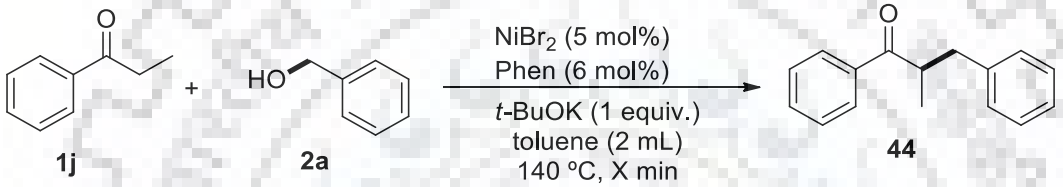

**Scheme 19**: Scope with steroid hormone, fatty acid derivative and synthesis of Alzheimer's drug

We also demonstrated the synthetic potential of the catalytic process in one step direct synthesis of donepezil **61** from commercially available starting materials (Scheme 19a). Donepezil is known as best-selling drug used for the treatment of Alzheimer's disease.[26]

Interestingly, application of 4-cholesten-3-one resulted α-benzylated product **62** in 53% yield without affecting the parent cholesten moiety (Scheme 19b). Next, fatty acid alcohol derived from oleic acid, having unsaturated double bond, efficiently alkylated with **1j** and resulted moderate yield of **63** without significantly affecting the double bond.

Finally, we explored our interests for the determination of rate and order of the reaction. To calculate the rate laws we performed kinetic studies using two sets of experiments (Scheme 20). Considering a steady state approximation for benzyl alcohol, first order kinetics with respect to **3** was observed for *α*-alkylation of methylene ketones.

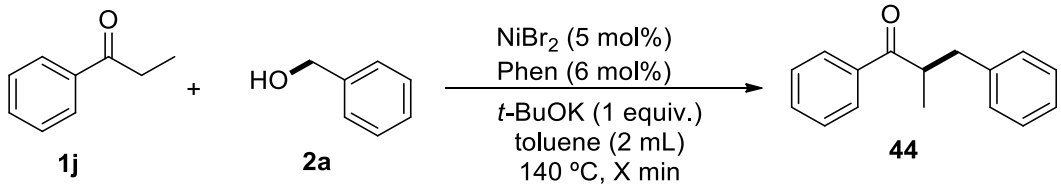
Run 1: Reaction was carried out in 2 mL of toluene and yield was calculated by GC




| No. | **1j** (mmol) | **2a** (mmol) | $NiBr_2$ (mmol) | Phen (mmol) | *t*-BuOK (mmol) | Toluene (mL) |
|---|---|---|---|---|---|---|
| Run 1 | 0.2 | 0.3 | 0.01 | 0.012 | 0.2 | 2.0 |

| Sl. No. | Time (min) | Concentration of **44** (mM) |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 30 | 8 |
| 3 | 60 | 10 |
| 4 | 90 | 13 |
| 5 | 120 | 16 |
| 6 | 150 | 18 |
| 7 | 180 | 21 |
| 8 | 210 | 22 |

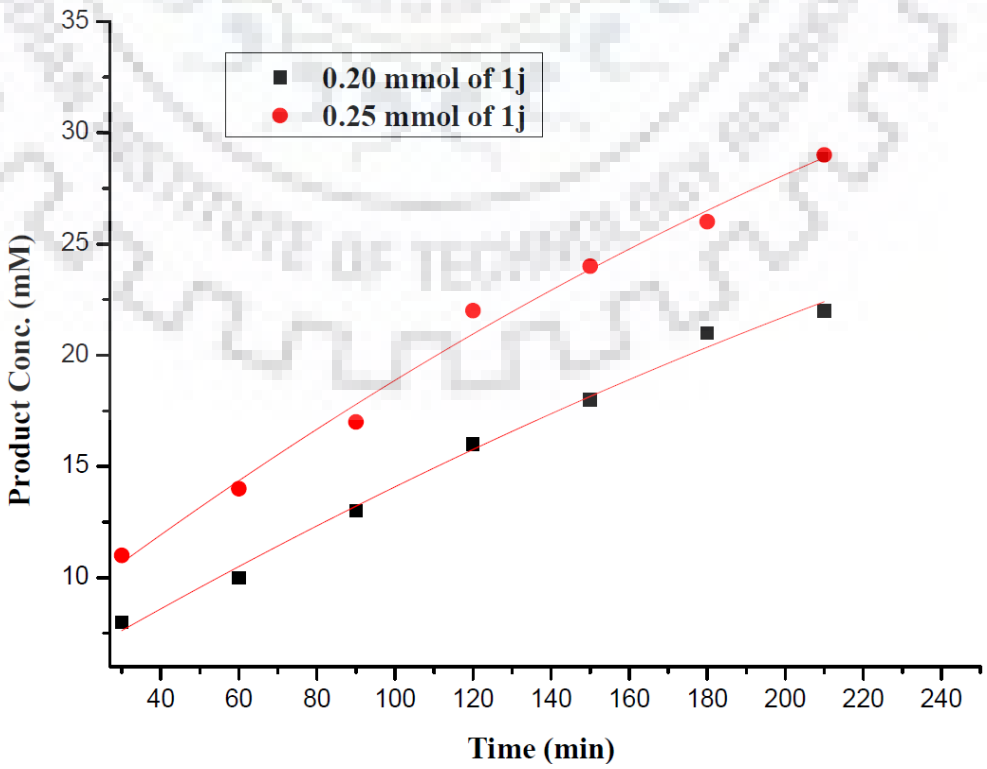
Run 2: Reaction was carried out in 2 mL of toluene and yield was calculated by GC




1j 2a 44

| No. | **1j** (mmol) | **2a** (mmol) | $NiBr_2$ (mmol) | Phen (mmol) | *t*-BuOK (mmol) | Toluene (mL) |
|---|---|---|---|---|---|---|
| Run 2 | 0.25 | 0.375 | 0.0125 | 0.015 | 0.25 | 2.0 |

| Sl. No. | Time (min) | Concentration of **44** (mM) |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 30 | 11 |
| 3 | 60 | 14 |
| 4 | 90 | 17 |
| 5 | 120 | 22 |
| 6 | 150 | 24 |
| 7 | 180 | 26 |
| 8 | 210 | 29 |

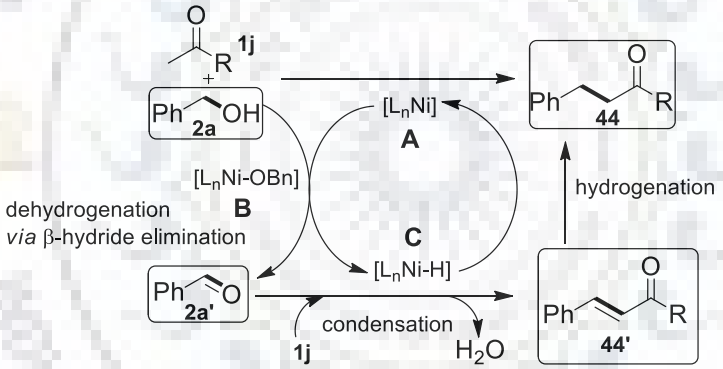


Graphical representation for determination of rate and order of reaction

Considering steady state approximation for benzyl alcohol

$$\text{From Run 1:} \quad \text{Slope} = k\,[1j]^{x}$$
$$0.082 = k\,[0.20]^{x}$$
$$\text{From Run 2:} \quad \text{Slope} = k\,[1j]^{x}$$
$$0.101 = k\,[0.25]^{x}$$
$$0.101 / 0.082 = [0.25]^{x} / [0.2]^{x}$$
$$1.23 = [1.25]^{x}$$
$$\text{Log}\,(1.23) = x.\ \text{Log}\,(1.25)$$
$$x = 0.0899 / 0.0969$$
$$= 0.93 \approx 1$$
$$\text{Rate} = k\,[1j]^{1}$$

**Scheme 20:** Determination of rate and order of reaction




**Scheme 21:** Plausible mechanistic cycle for *α*-alkylation of methyl ketones

Based on the above mechanistic studies we herein proposed a plausible mechanism for nickel-catalyzed *α*-alkylation of methyl ketones (Scheme 21). Initially, nitrogen ligated nickel-complex **A** transformed into the alkoxy-nickel species **B** *via* dehalogenation followed by substitution with benzyl alcohol. Base mediated β-hydride elimination of complex **B**, resulted the formation of transition Ni-H species **C** and benzaldehyde **2a'** is formed. Subsequently, a base-catalyzed condensation of benzaldehyde with acetophenone **1j** generates the intermediate enone **44'**, which, thereafter undergoes hydrogenation by Ni-H species selectively at C=C bond and deliver the product **44**. Overall, the process is sustainable, atom-economic and water is released as by product.

## [3.6] Conclusions:

In conclusions, we demonstrated an inexpensive and operational simple base-metal catalyzed protocol for selective mon-alkylation of methyl and methylene ketones with alcohols using borrowing hydrogen approach. This Ni-catalyzed dehydrogenative coupling of alcohol performed in gram scale and extended to a range of aryl, alkyl and hetero-aryl derivatives in up to 92% yield including green synthesis of *N*-heterocycles. For a synthetic application, functionalization of steroid hormone, unsaturated fatty acids and post synthetic modification of naproxen drug have shown. Detailed mechanistic studies involving isolation of a Ni-intermediate, defined Ni-H species, intermediate Ni-alkoxy species and determination of rate and order of reaction as well as a series of deuterium labeling experiments were crucial for preliminary mechanistic studies for selective alkylation of methyl and methylene ketones.

## [3.7] Experimental Section:

**General Experimental Details:** All solvents and reagents were used, as received from the suppliers. TLC was performed on Merck Kiesel gel 60, $F_{254}$ plates with the layer thickness of 0.25 mm. Column chromatography was performed on silica gel (100-200 mesh) using a gradient of ethyl acetate and hexane as mobile phase. $^{1}H$ NMR spectral data were collected at, 400 MHz (JEOL), 500 MHz (Bruker) and $^{13}C$ NMR were recorded at 100, 125 MHz. $^{1}H$ NMR spectral data are given as chemical shifts in ppm followed by multiplicity (s- singlet; d- doublet; t- triplet; q- quartet; m- multiplet), number of protons and coupling constants. $^{13}C$ NMR chemical shifts are expressed in ppm. HRMS (ESI) spectral data were collected using Agilent Q-TOF mass spectrometer. GC-MS were recorded using Agilent GC Mass Spectrometer. All the reactions were performed in a close system using Schlenk tube. All nickel salts were purchased from Sigma Aldrich. Nickel(II) bromide (Assay- 98%; CAS Number 13462-88-9; EC Number 236-665-0; Pack Size- No 217891-10G). Potassium *tert*-butoxide (Purity-98%, CAS No: 865-47-4, Catalog No- ASP2012) and Sodium *tert*-butoxide (Purity-97%, CAS No: 865-48-5, Catalog No- ASS2615) were purchased from Avra Synthesis Pvt. Ltd., India.

**General procedure for nickel-catalyzed alkylation of acetophenone with benzyl alcohols:**

**Procedure [A]:**

In a 15 mL oven dried Schlenk tube, **1** (0.25 mmol), $Cs_2CO_3$ (0.025 mmol), phen (20 mol%), $NiBr_2$ (10 mol%) and alcohols **2** (0.3125 mmol) were added followed by 1,4-dioxane 2.0 mL under an atmosphere of $N_2$ and the reaction mixture was heated at 140 °C for 36-48 h in close system. The reaction mixture was cooled to room temperature and 3.0 mL of ethyl acetate was added and concentrated *in vacuo.* The residue was purified by column chromatography using a gradient of hexane and ethyl acetate (eluent system) to afford the pure product.

**Procedure [B]:**

In a 15 mL oven dried Schlenk tube, **1** (0.25 mmol), *t*-BuOK (0.050 mmol), phen (6 mol%), $NiBr_2$ (5 mol%) and alcohols **2** (0.3125 mmol) were added followed by toluene 2.0 mL under an atmosphere of $N_2$ and the reaction mixture was heated at 140 °C for 36 h in closed system. The reaction mixture was cooled to room temperature and 3.0 mL of ethyl acetate was added and concentrated *in vacuo.* The residue was purified by column chromatography using a gradient of hexane and ethyl acetate (eluent system) to afford the pure product.

**Procedure [C]:**

In a 15 mL oven dried Schlenk tube, **1** (0.25 mmol), *t*-BuOK (0.375 mmol), phen (6 mol%), $NiBr_2$ (5 mol%) and alcohols **2** (0.375 mmol) were added followed by toluene 2.0 mL under an atmosphere of $N_2$ and the reaction mixture was heated at 140 °C for 36 h in close system. The reaction mixture was cooled to room temperature and 3.0 mL of ethyl acetate was added and concentrated *in vacuo.* The residue was purified by column chromatography using a gradient of hexane and ethyl acetate (eluent system) to afford the pure product.

**Synthesis of [$NiCl_2$(bpy)] complex (cat. B):** A solution of bpy (78 mg, 0.5 mmol) in EtOH (2 mL) was added to a solution of $NiCl_2$•$6H_2O$ (119 mg, 0.5 mmol) in EtOH (2 mL) at room temperature. After stirring for 6 h, a pale green precipitate formed and was filtered off, washed with EtOH (3×3 mL), and dried in *vacuo* to afford **cat. B** as a pale green solid 114 mg (80%) yield. Anal. Calcd for $C_{10}H_8Cl_2N_2Ni$: C, 42.03; H, 2.82; Cl, 24.81; N, 9.80; Found: C, 41.75; H, 2.76; N, 9.61.

**Synthesis of (cat. C): cat. B** (57 mg, 0.2 mmol) and benzyl alcohol (43.2 mg, 0.4 mmol) in toluene (2 mL) was heated at 140 °C under nitrogen atmosphere in a Schlenk tube, after 24h the precipitate was filtered off, washed with hexane (3×5 mL), and dried *in vacuo* to afford **cat. C** as a pale green solid 50 mg (78%) yield. Then in a Schlenk the **cat. C** (40 mg, 0.12 mmol), Acetophenone **1a** (21.6 mg, 0.18 mmol) and *t*-BuOK (14 mg, 0.12 mmol) in toluene $d_8$ (0.5mL) under nitrogen atmosphere was heated at 140 °C, after 3 h the reaction mixture was cooled to room temperature and the crude reaction mixture was analyzed by GC-MS which confirmed the formation of benzaldehyde (EI, m/z = 106.0).

**Gram scale reaction procedure**: Gram Scale reaction was performed using acetophenone **1a** (1.0 g, 8.33 mmol), benzyl alcohol **2a** (1.125 g, 10.42 mmol), $NiBr_2$ (91 mg, 5 mol%), Phen (90 mg, 6 mol%), *t*-BuOK (187 mg, 1.67 mmol), toluene (15.0 mL) in a 100 mL pressure tube under nitrogen atmosphere at 140 ºC in oil bath for 36 h. The reaction mixture was cooled to room temperature and 15.0 mL of ethyl acetate was added and concentrated in vacuo. The residue was purified by silica-gel column chromatography eluting with 1% ethyl acetate in hexane to afford the pure product **3** (1.050 g, 60% Yield).

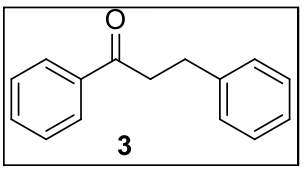
**Synthesis and Characterization of 1-(4-ethylphenyl)-3-(pyridin-2-yl)propan-1-one (28)**: Following the general procedure A and B, the title compound **28** was isolated as a yellow oil using silica-gel column chromatography eluting with 10% ethyl acetate in hexane. Yield (A: 70%, 42 mg; B: 73%, 43.5 mg). All the compounds were characterized by $^1$H-NMR, $^{13}$C-NMR, HRMS (ESI-TOF) and IR and the results are shown in spectral data. For an example, all the spectral data of compound **28** are explained here.

**$^1$H-NMR**. the five aromatic region protons are well separated and appeared as d, dd, ddd and m at 8.49 (dd, $J$ = 4.8, 0.6 Hz, 1H), 7.90 (d, $J$ = 8.2 Hz, 2H), 7.56 (ddd, $J$ = 7.7, 1.8, 0.9 Hz, 1H), 7.25 – 7.22 (m, 3H), 7.08 (dd, $J$ = 7.0, 5.4 Hz, 1H). The two triplet peaks at 3.46 (t, $J$ = 7.3 Hz, 2H), 3.21 (t, $J$ = 7.3 Hz, 2H) ppm belong to $–CH_2$ proton α and β to –C=O group respectively. The quartet peak at 2.67 (q, $J$ = 7.6 Hz, 2H) and triplet peak at 1.23 (t, $J$ = 7.6 Hz, 3H) belong to two $–CH_2$ and three $–CH_3$ protons of ethyl substituent group respectively (Figure 2a).

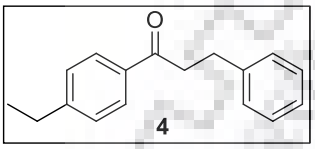
**$^{13}$C-NMR**. The peaks at 28.9, 15.3 ppm belong to $–CH_2$ and $–CH_3$ carbons respectively; and the peaks at 37.8 and 32.2 ppm belong to $–CH_2$ carbon α and β to -C=O group respectively. The peak at 199.0 ppm belongs to –C=O carbon and the peaks at 160.9, 150.0, 149.3, 136.4, 134.7, 128.4, 128.1, 123.4, 121.3 aromatic benzene ring carbons.

**Analytical data for all products:**

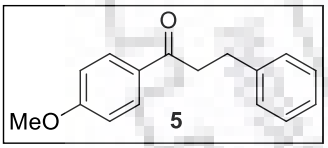
**1,3-diphenylpropan-1-one (3)**[10]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 80%, 42 mg; B: 82%, 43 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96 (d, $J$ = 8.1 Hz, 2H), 7.55 (t, $J$ = 7.4 Hz, 1H), 7.45 (t, $J$ = 7.6 Hz, 2H), 7.32-7.19 (m, 5H), 3.33-3.29 (m, 2H), 3.09 – 3.05 (m, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.3, 141.4, 136.9, 133.2, 128.7, 128.6, 128.5, 128.1, 126.2, 40.5, 30.2.



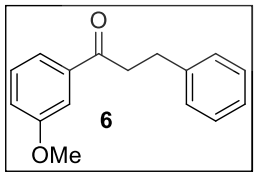

**1-(4-ethylphenyl)-3-phenylpropan-1-one (4)**[21c]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 65%, 39 mg; B: 76%, 45 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.89 (d, $J$ = 8.5 Hz, 2H), 7.32-7.24 (m, 6H), 7.20 (t, $J$ = 7.0 Hz, 1H), 3.28 (t, $J$ = 7.9 Hz, 2H), 3.06 (t, $J$ = 7.6 Hz, 2H), 2.70 (q, $J$ = 7.5 Hz, 2H), 1.25 (t, $J$ = 7.3 Hz, 3H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.0, 150.1, 141.5, 134.7, 128.6, 128.5, 128.4, 128.2, 126.2, 40.7, 30.3, 29.0, 15.3.



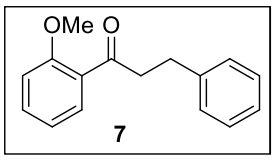

**1-(4-methoxyphenyl)-3-phenylpropan-1-one (5)**[21c]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. Yield (A: 63%, 38 mg; B: 90%, 54 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.94 (d, $J$ = 8.5 Hz, 2H), 7.32-7.20 (m, 5H), 6.92 (d, $J$ = 9.2 Hz, 2H), 3.86 (s, 3H), 3.25 (t, $J$ = 7.9 Hz, 2H), 3.06 (t, $J$ = 7.6 Hz, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 197.9, 163.5, 141.6, 130.4, 130.1, 128.6, 128.5, 126.2, 113.8, 55.6, 40.2, 30.4.



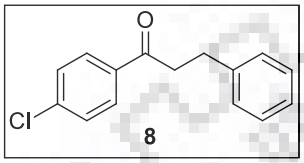

**1-(3-methoxyphenyl)-3-phenylpropan-1-one (6)**[21d]: Following the general procedure A and B, the title compound was isolated as a colorless oil using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. Yield (A: 64%, 38.5 mg; B: 85%, 51 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.53 (d, $J$ = 7.9 Hz, 1H), 7.48 (s, 1H), 7.37-7.19 (m, 6H), 7.11-7.08 (m, 1H), 3.84 (s, 3H), 3.29 (t, $J$ = 7.6 Hz, 2H), 3.06 (t, $J$ = 7.6 Hz, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.1, 159.9, 141.4, 138.3, 129.7, 128.6, 128.5, 126.2, 120.8, 119.7, 112.3, 55.5, 40.7, 30.3.



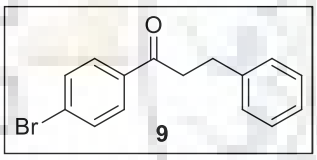
**1-(2-methoxyphenyl)-3-phenylpropan-1-one (7)**[21d]: Following the general procedure A and B, the title compound was isolated as a colorless oil using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. Yield (A: 52%, 31 mg; B: 55%, 33 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.69 (d, $J$ = 7.7 Hz, 1H), 7.43-7.48 (m, 1H), 7.16-7.31 (m, 5H), 6.95-7.02 (m, 2H), 3.88 (s, 3H), 3.30 (t, $J$ = 8.0 Hz, 2H), 3.02 (t, $J$ = 8.0 Hz, 2H).



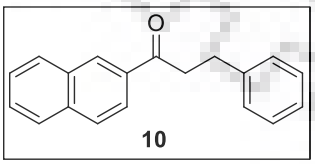

**1-(4-chlorophenyl)-3-phenylpropan-1-one (8)**[21c]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 50%, 30.5 mg; B: 62%, 38 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.89 (d, $J$ = 8.6 Hz, 2H), 7.42 (d, $J$ = 8.6 Hz, 2H), 7.30 (t, $J$ = 6.5 Hz, 2H), 7.28-7.21 (m, 3H), 3.29-3.25 (m, 2H), 3.08-3.04 (m, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 198.1, 141.1, 139.6, 135.3, 129.6, 129.0, 128.6, 128.5, 126.3, 40.5, 30.1.



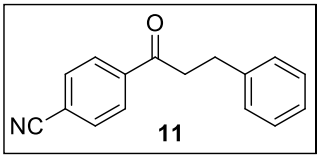

**1-(4-bromophenyl)-3-phenylpropan-1-one (9)**[21c]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 42%, 30 mg; B: 50%, 36 mg).$^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.84 (d, $J$ = 8.6 Hz, 2H), 7.62 (d, $J$ = 8.6 Hz, 2H), 7.33 (dd, $J$ = 9.3, 5.5 Hz, 2H), 7.26-7.17 (m, 3H), 3.31-3.27 (m, 2H), 3.11-3.06 (m, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.3, 141.4, 133.1, 132.0, 129.6, 128.7, 128.6, 128.5, 126.2, 40.5, 30.2.



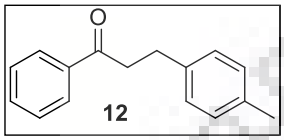

**1-(naphthalen-2-yl)-3-phenylpropan-1-one (10)**[21c]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 30%, 19.5 mg; B: 50%, 32.5 mg). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.49 (s, 1H), 8.06 (dd, $J$ = 8.6, 1.7 Hz, 1H), 7.96 (d, $J$ = 8.0 Hz, 1H), 7.93-7.90 (m, 2H), 7.64-7.61 (m, 1H), 7.59-7.56 (m, 1H), 7.37-7.32 (m, 4H), 7.25 (dd, $J$ = 9.0, 4.3 Hz, 1H), 3.49-3.46 (m, 2H), 3.18-3.15 (m, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.1, 141.4, 135.6, 134.2, 132.5, 129.7, 129.6, 128.6, 128.5, 127.8, 126.8, 126.2, 123.9, 40.4, 30.4.



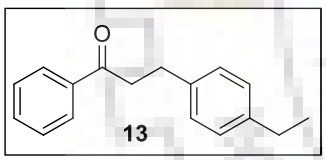
**4-(3-phenylpropanoyl)benzonitrile (11)**[22b]**:** Following the general procedure B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. (Yield 35%, 20.5 mg). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.01 (d, $J$ = 8.7 Hz, 2H), 7.74 (d, $J$ = 8.6 Hz, 2H), 7.31-7.28 (m, 2H), 7.23-7.21 (m, 3H), 3.30 (t, $J$ = 7.6 Hz, 2H), 3.07 (t, $J$ = 7.6 Hz, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 197.9, 140.9, 138.6, 132.6, 128.7, 128.5, 128.4, 126.4, 117.9, 116.5, 40.8, 29.9.



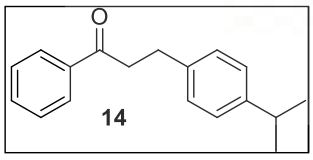

**1-phenyl-3-(*p*-tolyl)propan-1-one (12)**[20a]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 54%, 30 mg; B: 63%, 35 mg). $^1$H NMR (400 MHz, $CDCl_3$ ) $\delta$ 7.95 (d, $J$ = 8.0 Hz, 2H), 7.54 (t, $J$ = 8.0 Hz, 1H), 7.44 (t, $J$ = 6.8 Hz, 2H), 7.20-7.09 (m, 4H), 3.29-3.25 (m, 2H), 3.04-3.00 (m, 2H), 2.31 (s, 3H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.4, 138.3, 136.9, 135.7, 133.1, 129.3, 128.7, 128.4, 128.1, 40.7, 29.8, 21.1.



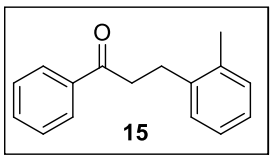

**3-(4-ethylphenyl)-1-phenylpropan-1-one (13)**[20b]: Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 60%, 36 mg; B: 70%, 41.5 mg).$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96 (d, $J$ = 8.1 Hz, 2H), 7.55 (t, $J$ = 7.4 Hz, 1H), 7.45 (t, $J$ = 7.6 Hz, 2H), 7.19-7.12 (m, 4H), 3.29 (t, $J$ = 7.8 Hz, 2H), 3.04 (t, $J$ = 7.8 Hz, 2H), 2.62 (q, $J$ = 7.6 Hz, 2H), 1.23 (t, $J$ = 7.6 Hz, 3H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.5, 142.2, 138.5, 136.9, 133.1, 129.8, 128.7, 128.5, 128.1, 40.7, 29.8, 28.5, 15.7.



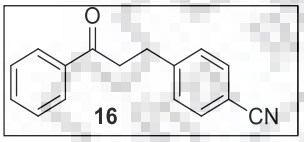

**3-(4-isopropylphenyl)-1-phenylpropan-1-one (14)**[20c]: Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 64%, 40 mg; B: 71%, 45 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96 (d, $J$ = 7.3 Hz, 2H), 7.55 (t, $J$ = 6.7 Hz, 1H), 7.45 (t, $J$ = 7.6 Hz, 2H), 7.15-7.20 (m, 4H), 3.30 (t, $J$ = 7.6 Hz, 2H), 3.04 (t, $J$ = 7.6 Hz, 2H), 2.90-2.85 (m, 1H), 1.24 (d, J = 6.7 Hz, 6H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$199.5, 146.8, 138.7, 136.9, 133.1, 128.7, 128.4, 128.1, 126.6, 40.6, 33.8, 29.8, 24.1.



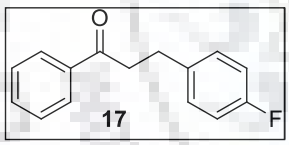
**1-phenyl-3-(o-tolyl)propan-1-one (15)**[11]: Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 40%, 22.5 mg; B: 42%, 23.5 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.97 (d, $J$ = 8.6 Hz, 2H), 7.56 (t, $J$ = 7.3 Hz, 1H), 7.45 (t, $J$ = 7.6 Hz, 2H), 7.23-7.12 (m, 4H), 3.25 (t, $J$ = 7.9 Hz, 2H), 3.05 (t, $J$ = 7.9 Hz, 2H), 2.35 (s, 3H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.5, 139.5, 136.9, 136.1, 133.2, 130.4, 128.7, 128.6, 128.1, 126.4, 126.3, 39.2, 27.6, 19.4.



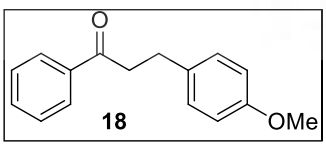

**4-(3-oxo-3-phenylpropyl)benzonitrile (16)**[22a]: Following the general procedure A and B, the title compound was isolated as a colorless solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. Yield (A: 43%, 25 mg; B: 45%, 26.5 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.95 (d, $J$ = 7.3 Hz, 2H), 7.57 (t, $J$ = 6.7 Hz, 3H), 7.46 (t, $J$ = 7.7 Hz, 2H), 7.37 (d, $J$ = 8.1 Hz, 2H), 3.33 (t, $J$ = 7.3 Hz, 2H), 3.14 (t, $J$ = 7.4 Hz, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 198.3, 147.1, 136.6, 133.4, 132.4, 129.4, 128.8, 128.1, 119.1, 110.2, 39.5, 30.1.



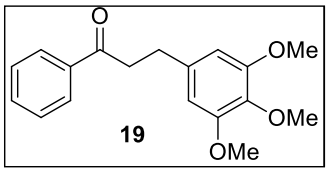

**3-(4-fluorophenyl)-1-phenylpropan-1-one (17)**[20d]: Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 74%, 42 mg; B: 73%, 41.5 mg).$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96-7.94 (m, 2H), 7.56 (t, $J$ = 7.6 Hz, 1H), 7.45 (t, $J$ = 7.6 Hz, 2H), 7.22-7.19 (m, 2H), 6.99-6.95 (m, 2H), 3.28 (t, $J$ = 7.6 Hz, 2H), 3.04 (t, $J$ = 7.6 Hz, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.1,161.5 (d, $J_{C\text{-}F}$= 243 Hz), 136.9, 136.8, 133.2, 129.9 (d, $J_{C\text{-}F}$= 9 Hz), 128.7, 128.1, 115.3(d, $J_{C\text{-}F}$= 19 Hz), 40.5, 29.3.



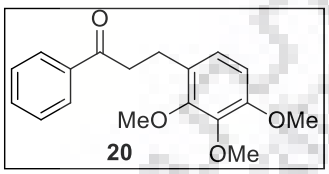

**3-(4-methoxyphenyl)-1-phenylpropan-1-one (18)**[20c]: Following the general procedure A and B, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. Yield (A: 65%, 39 mg; B: 64%, 38.5 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96 (d, $J$ = 7.3 Hz, 2H), 7.56 (t, $J$ = 7.6 Hz, 1H), 7.46 (t, $J$ = 7.6 Hz, 2H), 7.18 (d, $J$ = 8.5 Hz, 2H), 6.85 (d, $J$ = 8.5 Hz, 2H), 3.79 (s, 3H), 3.28 (t, $J$ = 7.6 Hz, 2H), 3.02 (t, $J$ = 7.6 Hz, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.5, 158.1, 137.0, 133.4, 133.1, 129.4, 128.7, 128.1, 114.0, 55.3, 40.8, 29.4.



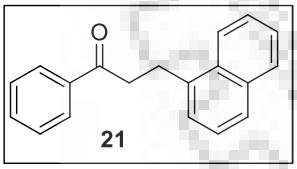
**1-phenyl-3-(3,4,5-trimethoxyphenyl)propan-1-one (19)**[21b]: Following the general procedure A and B, the title compound was isolated as a colorless oil using silica-gel column chromatography eluting with 15% ethyl acetate in hexane. Yield (A: 35%, 34 mg; B: 40%, 30 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96 (dd, $J$ = 8.7, 1.3 Hz, 2H), 7.56 (t, $J$ = 7.5 Hz, 1H), 7.46 (t, $J$ = 8.0 Hz, 2H), 6.47 (s, 2H), 3.84 (s, 6H), 3.82 (s, 3H), 3.32-3.28 (m, 2H), 3.04-3.00 (m, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.4, 153.3, 137.2, 136.9, 133.2, 128.7, 128.1, 105.4, 60.9, 56.2, 40.7, 30.7.



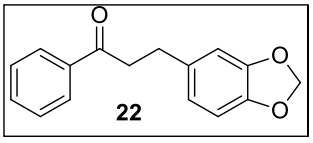

**1-phenyl-3-(2,3,4-trimethoxyphenyl)propan-1-one (20)**: Following the general procedure A and B, the title compound was isolated as a colorless oil using silica-gel column chromatography eluting with 15% ethyl acetate in hexane. Yield (A: 39%, 29 mg; B: 42%, 31.5). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.98 (d, $J$ = 7.3 Hz, 2H), 7.55 (t, $J$ = 7.3 Hz, 1H), 7.45 (t, $J$ = 7.6 Hz, 2H), 6.89 (d, $J$ = 8.5 Hz, 1H), 6.61 (d, $J$ = 8.5 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.25 (t, $J$ = 7.9 Hz, 2H), 2.98 (t, $J$ = 7.6 Hz, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.9, 152.5, 152.0, 142.4, 136.9, 133.1, 128.6, 128.2, 127.2, 124.1, 107.3, 60.9, 60.8, 56.1, 39.9, 25.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{21}O_4$ 301.1434; Found 301.1437.




**3-(naphthalen-1-yl)-1-phenylpropan-1-one (21)**[21c]: Following the general procedure A and B, the title compound was isolated as a colorless solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (A: 40%, 26 mg; B: 58%, 38 mg). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.09 (d, $J$ = 8.4 Hz, 1H), 7.99 (d, $J$ = 7.2 Hz, 2H), 7.91 (d, $J$ = 7.3 Hz, 1H), 7.79-7.77 (m, 1H), 7.60-7.50 (m, 2H), 7.49-7.44 (m, 4H), 7.32 (dd, $J$ = 11.6, 7.9 Hz, 1H), 3.59-3.56 (m, 2H), 3.48-3.45 (m, 2H); $^{13}$C{1H} NMR (125 MHz, $CDCl_3$) $\delta$ 199.3, 137.4, 136.9, 133.9, 133.1, 131.7, 128.9, 128.6, 128.1, 127.0, 126.2, 126.1, 125.7, 125.6, 123.5, 39.8, 27.2.

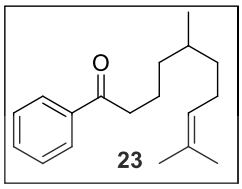



**3-(benzo[d][1,3]dioxol-5-yl)-1-phenylpropan-1-one (22)**[21a]: Following the general procedure A and B, the title compound was isolated as a colorless oil using silica-gel column chromatography eluting with 4% ethyl acetate in hexane. Yield (A: 51%, 32 mg; B: 60%, 38 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.87 (d, $J$ = 7.3 Hz, 2H), 7.48 (t, $J$ = 7.3 Hz, 1H), 7.37 (t, $J$ = 7.6 Hz, 2H), 6.66-6.60 (m, 3H), 5.84 (s, 2H), 3.18 (t, $J$ = 7.6 Hz, 2H), 2.91 (t, $J$

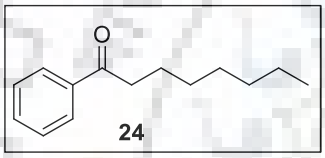


= 7.6 Hz, 2H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 199.3, 147.7, 145.9, 136.9, 135.2, 133.2, 128.7, 128.1, 121.3, 109.0, 108.4, 100.9, 40.7, 29.9.

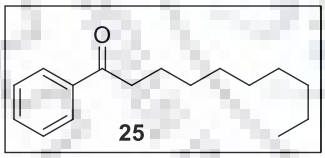
**5,9-dimethyl-1-phenyldec-8-en-1-one (23)**[23a]: Following the general procedure C, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 2% ethyl acetate in hexane. Yield (30%, 19.5 mg). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.96 (dd, $J$ = 8.3, 1.0 Hz, 2H), 7.59-7.54 (m, 1H), 7.46 (t, $J$ = 7.6 Hz, 2H), 5.09 (td, $J$ = 5.6, 4.2 Hz, 1H), 2.95 (t, $J$ = 7.4 Hz, 2H), 1.99-1.94 (m, 2H), 1.77 (dddd, $J$ = 10.6, 8.6, 6.0, 3.3 Hz, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.46-1.42 (m, 1H), 1.38-1.32 (m, 2H), 1.20-1.14 (m, 2H), 0.90 (d, $J$ = 6.3 Hz, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.7, 137.2, 132.9, 131.2, 128.6, 128.1, 124.9, 39.0, 37.1, 36.7, 32.4, 25.8, 25.6, 21.9, 19.6, 17.7.



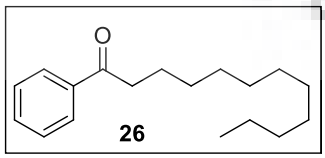

**1-phenylnonan-1-one (24)**[22c]: Following the general procedure C, the title compound was isolated as a colorless oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. (Yield: 46%, 25 mg). $^1H$ NMR (400 MHz) $\delta$ 7.96 (d, $J$ = 7.8 Hz, 2H), 7.55 (t, $J$ = 7.4 Hz, 1H), 7.45 (t, $J$ = 7.2 Hz, 2H), 2.96 (t, $J$ = 7.4 Hz, 2H), 1.77-1.70 (m, 2H), 1.35-1.25 (d, $J$ = 8.1 Hz, 10H), 0.88 (t, $J$ = 7.4 Hz, 3H); GC-MS (EI) m/z = 218.1.



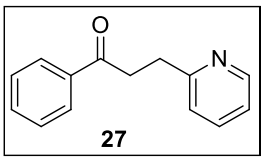

**1-phenyldecan-1-one (25)**[20c]: Following the general procedure C, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. (Yield: 34%, 20 mg). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.95 (d, $J$ = 7.4 Hz, 2H), 7.54 (t, $J$ = 7.3 Hz, 1H), 7.45 (t, $J$ = 7.9 Hz, 2H), 2.95 (t, $J$ = 7.4 Hz, 2H), 1.76-1.71 (m, 2H), 1.33-1.22 (m, 9H), 0.88- 0.85 (m, 6H); GC-MS (EI) m/z = 232.2.



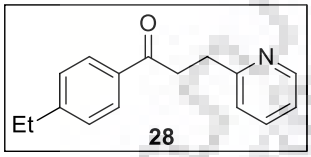

**1-phenyldodecan-1-one (26)**[22d]: Following the general procedure C, the title compound was isolated as a colorless oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. (Yield: 36%, 23.5 mg). $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.99 (d, $J$ = 7.1 Hz, 2H), 7.58 (t, $J$ = 6.1 Hz, 1H), 7.49 (t, $J$ = 7.9 Hz, 2H), 2.99 (t, $J$ = 7.4 Hz, 2H), 1.79 – 1.73 (m, 2H), 1.42-1.21 (m, 16H), 0.88 (t, $J$ = 7.1 Hz, 3H); GC-MS (EI) m/z = 260.2.



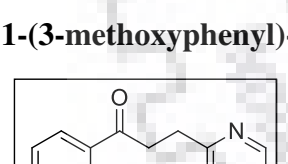
**1-phenyl-3-(pyridin-2-yl)propan-1-one (27)**[23b]: Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 10% ethyl acetate in hexane. Yield (A: 76%, 40 mg; B: 80%, 42 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.51 (d, $J$ = 4.6 Hz, 1H), 7.99 (d, $J$ = 7.1 Hz, 2H), 7.62-7.52 (m, 2H), 7.44 (t, $J$ = 7.6 Hz, 2H), 7.26 (d, $J$ = 7.9 Hz, 1H), 7.12-7.09 (m, 1H), 3.51 (t, $J$ = 7.2 Hz, 2H), 3.24 (t, $J$ = 7.3 Hz, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.4, 160.8, 149.4, 136.9, 136.4, 133.1, 128.6, 128.1, 123.5, 121.3, 37.9, 32.2.



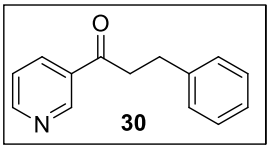

**1-(4-ethylphenyl)-3-(pyridin-2-yl)propan-1-one (28)**: Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 10% ethyl acetate in hexane. Yield (A: 70%, 42 mg; B: 73%, 43.5 mg). $^1$H NMR (400 MHz,$CDCl_3$ ) $\delta$ 8.49 (dd, $J$ = 4.8, 0.6 Hz, 1H), 7.90 (d, $J$ = 8.2 Hz, 2H), 7.56 (ddd, $J$ = 7.7, 1.8, 0.9 Hz, 1H), 7.25-7.22 (m, 3H), 7.08 (dd, $J$ = 7.0, 5.4 Hz, 1H), 3.46 (t, $J$ = 7.3 Hz, 2H), 3.21 (t, $J$ = 7.3 Hz, 2H), 2.67 (q, $J$ = 7.6 Hz, 2H), 1.23 (t, $J$ = 7.6 Hz, 3H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.0, 160.9, 150.0, 149.3, 136.4, 134.7, 128.4, 128.1, 123.4, 121.3, 37.8, 32.2, 28.9, 15.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{18}NO$ 240.1383; Found 240.1387.




**1-(3-methoxyphenyl)-3-(pyridin-2-yl)propan-1-one (29)**: Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 15% ethyl acetate in hexane. Yield (A: 78%, 47 mg; B: 80%, 48 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.51 (d, $J$ = 4.7 Hz, 1H), 7.61-7.57 (m, 2H), 7.52-7.51 (m, 1H), 7.35 (t, $J$ = 7.9 Hz, 1H), 7.25 (d, $J$ = 7.8 Hz, 1H), 7.12-7.08 (m, 2H), 3.84 (s, 3H), 3.50 (t, $J$ = 7.2 Hz, 2H), 3.23 (t, $J$ = 7.2 Hz, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.2, 160.8, 159.9, 149.3, 138.3, 136.4, 129.6, 123.4, 121.3, 120.9, 119.7, 112.3, 55.5, 37.9, 32.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{16}NO_2$ 242.1176; Found 242.1186.

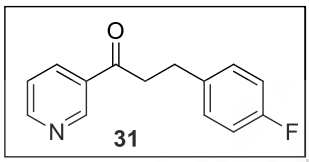



**3-phenyl-1-(pyridin-3-yl)propan-1-one (30)**[23c]: Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 10% ethyl acetate in hexane. Yield (A: 50%, 26.5 mg; B: 60%, 31.5 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.15 (s, 1H), 8.77 (s, 1H), 8.21 (d, $J$ = 8.0 Hz, 1H), 7.42-7.34 (m, 2H), 7.32-7.27



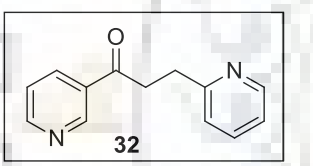
(m, 2H), 7.21 (ddd, *J* = 7.1, 4.8, 2.9 Hz, 2H), 3.33-3.28 (m, 2H), 3.08 (t, *J* = 7.6 Hz, 2H); $^{13}$C{1H} NMR (125 MHz, $CDCl_3$) $\delta$ 198.1, 153.5, 149.6, 140.8, 135.3, 128.6, 128.4, 126.3, 123.7, 115.0, 40.7, 29.8.

**3-(4-fluorophenyl)-1-(pyridin-3-yl)propan-1-one (31):** Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 10% ethyl acetate in hexane. Yield (A: 60%, 34 mg; B: 70%, 40 mg). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.16 (d, *J* = 1.5 Hz, 1H), 8.78 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.23-8.21 (m, 1H), 7.43-7.40 (m, 1H), 7.21 (dd, *J* = 8.5, 5.5 Hz, 2H), 6.98 (t, *J* = 8.7 Hz, 2H), 3.30 (t, *J* = 7.4 Hz, 2H), 3.07 (t, *J* = 7.5 Hz, 2H); $^{13}$C{1H} NMR (125 MHz, $CDCl_3$) $\delta$ 197.8, 161.5 (d, $J_{C\text{-}F}$= 240 Hz), 153.6, 149.6, 136.4, 135.3, 132.0, 129.9(d, $J_{C\text{-}F}$= 7.5 Hz), 123.7, 115.4(d, $J_{C\text{-}F}$= 21.3 Hz), 40.7, 28.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{13}FNO$ 230.0976; Found 230.0983.



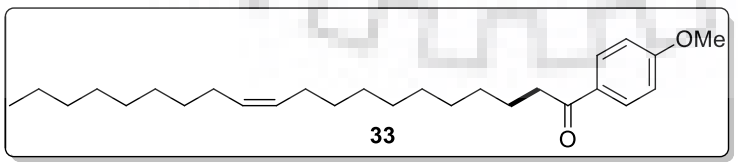
31

**3-(pyridin-2-yl)-1-(pyridin-3-yl)propan-1-one (32)**: Following the general procedure A and B, the title compound was isolated as a yellow oil using silica-gel column chromatography eluting with 25% ethyl acetate in hexane. Yield (A: 30%, 16 mg; B: 75%, 40 mg).$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.20 (d, *J* = 2.1 Hz, 1H), 8.75 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.49 (d, *J* = 4.6 Hz, 1H), 8.24 (ddd, *J* = 7.9, 3.8, 1.8 Hz, 1H), 7.59 (td, *J* = 7.7, 1.8 Hz, 1H), 7.39 (dd, *J* = 8.2, 4.8 Hz, 1H), 7.25 (d, *J* = 3.2 Hz, 1H), 7.10 (dd, *J* = 7.5, 4.9 Hz, 1H), 3.52 (t, *J* = 7.1 Hz, 2H), 3.25 (t, *J* = 7.1 Hz, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 198.4, 160.2, 153.5, 149.8, 149.3, 136.5, 135.4, 132.3, 123.6, 123.4, 121.4, 37.9, 31.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{13}N_2O$ 213.1022; Found 213.1029.



32

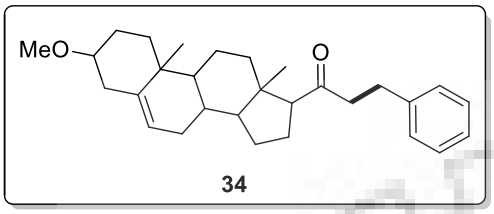
**(Z)-1-(4-methoxyphenyl)icos-11-en-1-one (33):** Following the general procedure C, the title product was obtained as a yellow oil using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. (Yield: 40%, 40 mg); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96-7.91 (m, 2H), 6.95-6.90 (m, 2H), 5.33 (t, *J* = 4.8 Hz, 2H), 3.86 (s, 3H), 2.89 (t, *J* = 8.0 Hz, 2H), 2.02-1.97 (m, 4H), 1.72-1.67 (m, 2H), 1.27-1.25 (m, 24H), 0.87 (t, *J* = 7.0 Hz, 3H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 199.3, 163.4, 130.4, 130.3, 130.00, 129.9, 113.7, 55.5, 38.4, 31.9, 29.85, 29.84,



33

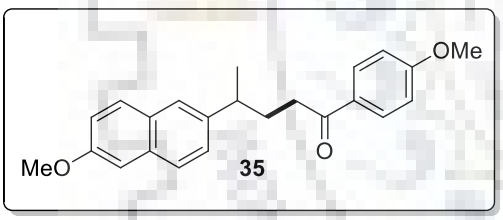
29.60, 29.59, 29.57, 29.52, 29.40, 29.37, 27.3, 24.7, 22.8, 14.2. Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07; Found: C, 80.65; H, 10.76.

**1-(3-methoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-3-phenylpropan-1-one (34)**: Following the general procedure A (50 mol% of $Cs_2CO_3$was used), the title product was obtained as a yellow oil using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. (Yield: 66%, 69 mg); $^1$H NMR (400 MHz, $CDCl_3$ ) $\delta$ 7.26 (dd, $J$ = 10.2, 4.6 Hz, 2H), 7.19-7.14 (m, 3H), 5.35-5.31 (m, 1H), 3.34 (s, 3H), 3.04 (tt, $J$ = 11.2, 4.4 Hz, 1H), 2.88 (t, $J$ = 7.6 Hz, 2H), 2.74-2.63 (m, 2H), 2.47 (t, $J$ = 8.9 Hz, 1H), 2.41-2.35 (m, 1H), 2.22-2.11 (m, 2H), 1.97-1.82 (m, 4H), 1.63-1.37 (m, 8H), 1.30-1.15 (m, 3H), 0.98-0.95 (m, 4H), 0.56 (s, 3H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 210.6, 141.6, 140.9, 128.5, 126.1, 121.4, 121.3, 80.4, 63.2, 60.7, 57.1, 55.7, 50.7, 50.1, 49.6, 47.3, 46.1, 44.4, 39.1, 38.7, 37.0, 31.9, 29.9, 28.1, 24.6, 23.0, 21.1, 19.4, 13.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{41}O_2$ 421.3101; Found 421.3108.



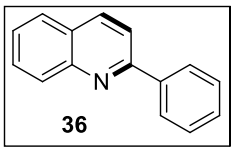
34

**4-(6-methoxynaphthalen-2-yl)-1-(4-methoxyphenyl)-pentan-1-one (35):** Following the general procedure C, the title product was obtained as a colorless solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. (Yield: 45%, 36 mg); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.72-7.65 (m, 4H), 7.57-7.51 (m, 2H), 7.31 (dd, $J$ = 8.3, 1.2 Hz, 1H), 7.15-7.11(m, 3H), 3.91 (s, 6H), 2.81-2.75 (m, 2H), 2.11 (dd, $J$ = 8.0, 0.9 Hz, 2H), 1.86-1.84 (m, 1H), 1.33-1.29 (m, 3H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 198.9, 157.2, 139.5, 135.4, 132.9, 129.6, 128.9, 127.6, 126.8, 125.5, 124.9, 123.7, 122.4, 118.7, 112.2, 105.8, 55.4, 28.9, 21.9, 15.7, 14.5. Anal. Calcd for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94; Found: C, 78.92; H, 6.27.



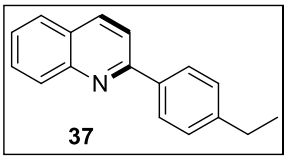
35

**2-phenylquinoline (36)**[14c]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title compound was isolated as a white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. (Yield: 85%, 43.5 mg). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.13-8.07 (m, 4H), 7.78 (d, $J$ = 8.6 Hz, 1H), 7.74-7.72 (m, 1H), 7.64 (ddd, $J$ = 8.4, 7.0, 1.4 Hz, 1H), 7.46-7.41 (m, 3H), 7.40-7.36 (m, 1H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 157.5, 148.4, 139.8, 136.9, 129.8, 129.4, 128.9, 127.7, 127.6, 127.3, 126.4, 119.1, 119.0.

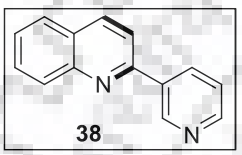


36

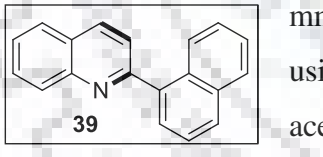
**2-(4-Ethylphenyl)quinoline (37)**[14c]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title product was obtained as a colorless solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. (Yield: 82%, 48 mg); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.17 (t, $J$ = 8.0 Hz, 2H), 8.09 (d, $J$ = 6.8 Hz, 2H), 7.85 (d, $J$ = 8.7 Hz, 1H), 7.81 (d, $J$ = 8.2 Hz, 1H), 7.71 (t, $J$ = 7.7 Hz, 1H), 7.50 (t, $J$ = 7.5 Hz, 1H), 7.36 (d, $J$ = 7.8 Hz, 2H), 2.73 (q, $J$ = 7.6 Hz, 2H), 1.29 (t, $J$ = 7.6 Hz, 3H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 157.5, 148.4, 145.8, 137.3, 136.7, 129.8, 129.7, 128.5, 127.6, 127.5, 127.2, 126.2, 119.0, 28.8, 15.7.



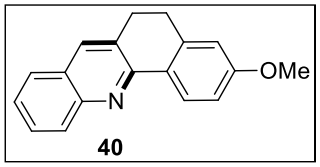

**2-(Pyridin-3-yl)quinoline (38)**[14c]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title product was obtained as a colorless solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. (Yield: 50%, 26 mg); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.34 (d, $J$ = 1.6 Hz, 1H), 8.69 (dd, $J$ = 4.8, 1.5 Hz, 1H), 8.53-8.48 (m, 1H), 8.26 (d, $J$ = 8.5 Hz, 1H), 8.17 (d, $J$ = 8.5 Hz, 1H), 7.86 (dd, $J$ = 12.8, 8.4 Hz, 2H), 7.75 (ddd, $J$ = 8.4, 6.9, 1.4 Hz, 1H), 7.55 (ddd, $J$ = 8.1, 6.9, 1.1 Hz, 1H), 7.45 (dd, $J$ = 7.3, 4.8 Hz, 1H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 154.7, 150.3, 148.9, 148.5, 137.3, 135.2, 135.1, 130.1, 129.8, 127.7, 127.5, 126.9, 123.8, 118.6.




**2-(Naphthalen-2-yl)quinoline (39)**[24a]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title product was obtained as a colorless solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. (Yield: 88%, 56 mg); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.65 (s, 1H), 8.41 (dd, $J$ = 8.6, 1.7 Hz, 1H), 8.27 (dd, $J$ = 12.5, 8.6 Hz, 2H), 8.05 (dd, $J$ = 15.8, 8.2 Hz, 3H), 7.93 (dd, $J$ = 5.9, 3.4 Hz, 1H), 7.88 (d, $J$ = 7.9 Hz, 1H), 7.79 (ddd, $J$ = 8.3, 6.9, 1.3 Hz, 1H), 7.57 (dd, $J$ = 6.4, 2.9 Hz, 3H); $^{13}$C{1H} NMR (125 MHz, $CDCl_3$) $\delta$ 157.2, 148.4, 136.9, 136.9, 133.9, 133.5, 129.8, 128.9, 128.6, 128.5, 127.8, 127.5, 127.3, 127.1, 126.8, 126.4, 119.2, 115.0.

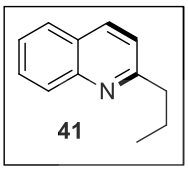



**2-methoxy-5,6-dihydrobenzo[c]acridine (40)**[14c]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title product was obtained as a colorless solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. (Yield: 50%, 32.5 mg); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.17-8.11 (m, 2H), 7.90 (s, 1H), 7.73 (d, $J$ = 8.1 Hz, 1H), 7.64 (dd, $J$ = 8.2, 7.1 Hz, 1H), 7.47 (dd, $J$ = 8.0, 7.0 Hz, 1H), 7.18

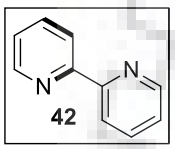


(d, *J* = 8.3 Hz, 1H), 6.94 (dd, *J* = 8.3, 2.8 Hz, 1H), 3.96 (s, 3H), 3.12-3.06 (m, 2H), 2.96-2.90 (m, 2H); $^{13}$C{1H} NMR (100 MHz, $CDCl_3$) $\delta$ 159.2, 153.4, 147.6, 135.8, 133.8, 131.9, 130.8, 129.5, 129.1, 128.7, 128.0, 127.0, 126.2, 117.0, 109.7, 55.7, 29.2, 27.6.

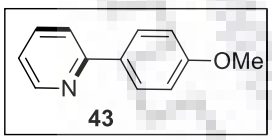
**2-propylquinoline (41)**[24]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title product was obtained as a pale yellow oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. (Yield: 68%, 29 mg); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.04 (t, *J* = 7.5 Hz, 2H), 7.76 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.47 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 7.31-7.24 (m, 1H), 2.97-2.91 (m, 2H), 1.88-1.80 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H), 1.32-1.29 (m, 3H); $^{13}$C{1H} NMR (125 MHz, $CDCl_3$) $\delta$ 157.6, 145.3, 136.9, 128.3, 126.9, 125.9, 121.8, 120.3, 115.0, 28.7, 15.5.



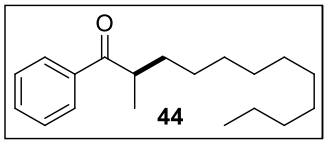

**2,2'-Bipyridine (42)**[14c]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title product was obtained as a colorless solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. (Yield: 70%, 27 mg); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.70 (d, *J* = 4.0 Hz, 2H), 8.41 (t, *J* = 6.5 Hz, 2H), 7.83 (td, *J* = 7.8, 1.8 Hz, 2H), 7.32 (ddd, *J* = 7.3, 4.7, 1.0 Hz, 2H); $^{13}$C{1H} NMR (125 MHz, $CDCl_3$) $\delta$ 156.2, 149.3, 136.9, 123.7, 121.1.



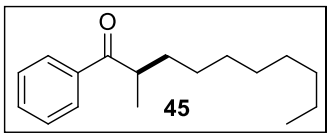

**2-(4-Methoxyphenyl)pyridine (43)**[14c]: Following the general procedure B, *t*-BuOK (0.125 mmol) was used, the title product was obatined as a colorless oil using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. (Yield: 45%, 21 mg); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.68 (d, *J* = 4.1 Hz, 1H), 8.00-7.95 (m, 2H), 7.73 (ddd, *J* = 20.6, 13.4, 4.9 Hz, 1H), 7.20 (ddd, *J* = 7.2, 4.8, 1.2 Hz, 1H), 7.03 (d, *J* = 8.9 Hz, 2H), 6.96 (d, *J* = 8.9 Hz, 1H), 3.89 (s, 3H); $^{13}$C{1H} NMR (125 MHz, $CDCl_3$) $\delta$ 160.5, 157.1, 149.5, 136.7, 132.0, 128.2, 121.4, 119.9, 114.1, 55.4.



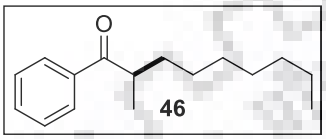

**2-Methyl-1-phenyldodecan-1-one (44):**[27] Following the general procedure the title product was obtained as a colourless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.88 (d, *J* = 7.3 Hz, 2H), 7.51-7.45 (m, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 3.43-3.35 (m, 1H), 1.82-1.62 (m, 1H), 1.42-1.27 (m, 1H), 1.21-1.17 (m, 16H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.80 (t, *J* = 7.0 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 204.68, 136.90, 132.83, 128.66, 128.35, 40.67, 33.83, 31.96, 30.03, 29.80, 29.65, 29.55, 29.37, 27.48, 22.74, 17.27, 14.17.



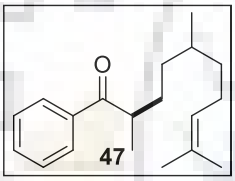
**2-methyl-1-phenyldecan-1-one (45):**[28] Following the general procedure, the title product was obtained as a colourless oil; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.98 (d, $J$ = 7.3 Hz, 2H), 7.59-7.57 (m, 1H), 7.50 (t, $J$ = 7.4 Hz, 2H), 3.51-3.45 (m, 1H), 1.85-1.78 (m, 1H), 1.48-1.42 (m, 1H),1.29-1.26 (m, 12H), 1.22 (d, $J$ = 6.7 Hz, 3H), 0.89 (t, $J$ = 6.4 Hz, 3H). GC-MS (EI) m/z = 246.2.



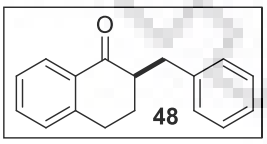

**2-methyl-1-phenylnonan-1-one (46):**[28] Following the general procedure, the title product was obtained as a colourless oil; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.98 (d, $J$ = 7.3 Hz, 2H), 7.61-7.57 (m, 1H), 7.49 (t, $J$ = 6.8 Hz, 2H), 3.49-3.47 (m, 1H), 1.87-1.77 (m, 1H), 1.51-1.40 (m, 1H), 1.27-1.21 (s, 10H), 1.22 (d, $J$ = 6.6 Hz, 3H), 0.88 (t, $J$ = 6.7 Hz, 3H). GC-MS (EI) m/z = 232.2.



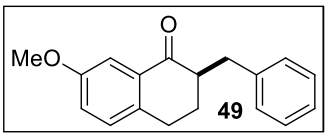

**2,5,9-Trimethyl-1-phenyldec-8-en-1-one (47):** Following the general procedure, the title product was obtained as a pale yellow oil;$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.94 (d, $J$ = 7.9 Hz, 2H), 7.54 (dd, $J$ = 8.2, 6.5 Hz, 1H), 7.45 (t, $J$ = 7.6 Hz, 2H), 5.05 (ddd, $J$ = 12.8, 5.8, 1.3 Hz, 1H), 3.41 (ddd, $J$ = 13.5, 6.7, 2.2 Hz, 1H), 1.97-1.74 (m, 3H), 1.65 (d, $J$ = 4.2 Hz, 3H), 1.57 (d, $J$ = 5.0 Hz, 2H), 1.47-1.24 (m, 5H), 1.18 (d, $J$ = 6.9 Hz, 3H), 1.15-1.08 (m, 2H), 0.84 (t, $J$ = 6.5 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 204.66, 133.34, 132.84, 131.16, 129.03, 128.66, 128.28, 40.93, 37.03, 36.85, 34.63, 32.57, 31.22, 25.51, 19.47, 17.24; Elemental Analysis: Calculated C, 83.77; H, 10.36; Found C, 83.39; H, 9.87.



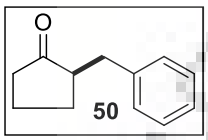

**2-Benzyl-3,4-dihydronaphthalen-1(2*H*)-one (48):**[29] Following the general procedure, the title product was obtained as a colourless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.07 (dd, $J$ = 7.9, 1.0 Hz, 1H), 7.45 (td, $J$ = 7.5, 1.4 Hz, 1H), 7.33-7.28 (m, 3H), 7.25-7.19 (m, 4H), 3.49 (dd, $J$ = 13.6, 3.9 Hz, 1H), 2.95-2.92 (m, 2H), 2.79-2.69 (m, 1H), 2.64 (dd, $J$ = 13.6, 9.6 Hz, 1H), 2.13-2.07 (m, 1H), 1.83-1.73 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.52, 144.13, 140.14, 133.37, 132.55, 129.36, 128.81, 128.50, 127.64, 126.72, 126.23, 49.55, 35.75, 28.71, 27.74.



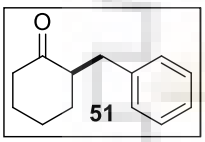
**2-Benzyl-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (49):**[30] Following the general procedure, the title product was obtained as a pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.54 (d, $J$ = 2.8 Hz, 1H), 7.32-7.28 (m, 2H), 7.25-7.19 (m, 3H), 7.12 (d, $J$ = 8.4 Hz, 1H), 7.04 (dd, $J$ = 8.4, 2.8 Hz, 1H), 3.83 (s, 3H), 3.47 (dd, $J$ = 13.4, 3.8 Hz, 1H), 2.88-2.86 (m, 2H), 2.69-2.61 (m, 2H), 2.10-2.06 (m, 1H), 1.81-1.72 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.49, 158.40, 140.13, 136.74, 133.30, 130.02, 129.35, 128.48, 126.22, 121.77, 109.52, 55.57, 49.37, 35.80, 27.98, 27.85.



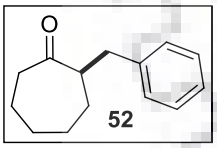

**2-Benzylcyclopentan-1-one (50):**[31] Following the general procedure, the title product was obtained as a colourless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.33-7.25 (m, 2H), 7.24-7.10 (m, 3H), 3.41 (dd, $J$ = 14.0, 3.8 Hz, 1H), 3.22 (t, $J$ = 7.4 Hz, 1H), 3.04-2.93 (m, 1H), 2.88-2.75 (m, 3H), 2.68-2.56 (m, 1H), 2.19-2.09 (m, 2H). GC-MS (EI) m/z = 174.2



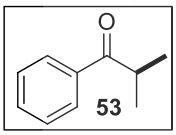

**2-Benzylcyclohexan-1-one (51):**[31] Following the general procedure, the title product was obtained as a colourless liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.30-7.24 (m, 2H), 7.22-7.12 (m, 3H), 2.82-2.72 (m, 1H), 2.66-2.25 (m, 4H), 1.94-1.59 (m, 2H), 1.48-1.17 (m, 4H). GC-MS (EI) m/z = 188.2



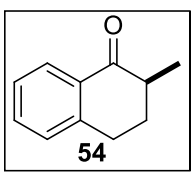

**2-Benzylcycloheptan-1-one (52):**[32] Following the general procedure, the title product was obtained as a colourless oil; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.44-7.35 (m, 2H), 7.34-7.23 (m, 3H), 3.17-2.70 (m, 3H), 2.66-2.25 (m, 2H), 1.93-1.64 (m, 4H), 1.53-1.28 (m, 4H). GC-MS (EI) m/z = 202.2



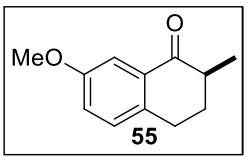

**2-Methyl-1-phenylpropan-1-one (53):**[33] Following the general procedure, the title product was obtained as a colourless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.93-7.89 (m, 2H), 7.58-7.50 (m, 1H), 7.47-7.39 (m, 2H), 3.79-3.62 (m, 1H), 1.19 (d, $J$ = 6.9 Hz, 6H). GC-MS (EI) m/z = 148.2



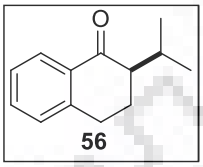

**2-Methyl-3,4-dihydronaphthalen-1(2*H*)-one (54):**[33] Following the general procedure, the title product was obtained as a colourless oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (dd, $J$ = 7.8, 1.2 Hz, 1H), 7.44 (td, $J$ = 7.5, 1.4 Hz, 1H), 7.29 (t, $J$ = 7.5 Hz, 1H), 7.22 (dd, $J$ = 8.4, 3.9 Hz, 1H), 3.04-2.94 (m, 2H), 2.62-2.53 (m, 1H), 2.22-2.14 (m, 1H), 1.99-1.82 (m, 1H), 1.26 (d, $J$ = 6.8 Hz, 3H). GC-MS (EI) m/z = 160.2



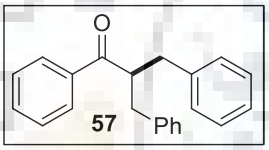
**7-Methoxy-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (55):**[34] Following the general procedure, the title product was obtained as a pale yellow oil;[1]H NMR (400 MHz, $CDCl_3$) $\delta$ 7.51 (d, $J$ = 2.8 Hz, 1H), 7.12 (dd, $J$ = 8.4, 4.9 Hz, 1H), 7.03 (dd, $J$ = 8.4, 2.8 Hz, 1H), 3.82 (s, 3H), 2.97-2.87 (m, 2H), 2.60-2.49 (m, 1H), 2.21-2.13 (m, 1H), 1.99-1.78 (m, 2H), 1.25 (d, $J$ = 6.8 Hz, 3H). GC-MS (EI) m/z = 190.2



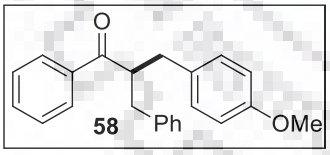

**2-Isopropyl-3,4-dihydronaphthalen-1(2*H*)-one (56):**[35] Following the general procedure, the title product was obtained as a colourless oil; [1]H NMR (500 MHz, $CDCl_3$) $\delta$ 8.06 (d, $J$ = 7.0 Hz, 1H), 7.53-7.44 (m, 1H), 7.35-7.31 (m, 1H), 7.26 (d, $J$ = 7.5 Hz, 1H), 3.13-2.87 (m, 2H), 2.86-2.71 (m, 1H), 2.40-2.25 (m, 1H), 2.17-2.03 (m, 1H), 1.99-1.77 (m, 1H), 1.06 (d, $J$ = 10.2 Hz, 3H), 0.90 (d, $J$ = 7.0 Hz, 3H). GC-MS (EI) m/z = 188.2



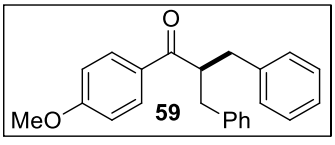

**2-benzyl-1,3-diphenylpropan-1-one (57):**[29] Following the general procedure, the title product was obtained as a colourless oil; [1]H NMR (400 MHz, $CDCl_3$) $\delta$ 7.72 (d, $J$ = 8.2 Hz, 2H), 7.45 (t, $J$ = 7.5 Hz, 1H), 7.34-7.30 (m, 2H), 7.22 (dd, $J$ = 15.4, 7.1 Hz, 4H), 7.19-7.11 (m, 6H), 4.05-3.98 (m, 1H), 3.13 (dd, $J$ = 14.2, 8.1 Hz, 2H), 2.80 (dd, $J$ = 14.1, 6.5 Hz, 2H). [13]C NMR (100 MHz, $CDCl_3$) $\delta$ 203.46, 139.59, 137.45, 132.88, 129.11, 128.53, 128.50, 128.19, 126.36, 50.57, 38.30.




**2-Benzyl-3-(4-methoxyphenyl)-1-phenylpropan-1-one (58):**[29] Following the general procedure, the title product was obtained as a colourless oil; [1]H NMR (400 MHz, $CDCl_3$) $\delta$ 7.71 (d, $J$ = 7.5 Hz, 2H), 7.45 (t, $J$ = 7.4 Hz, 1H), 7.32 (t, $J$ = 7.7 Hz, 2H), 7.21-7.18 (m, 2H), 7.13-7.10 (m, 3H), 7.04 (d, $J$ = 8.6 Hz, 2H), 6.74 (d, $J$ = 8.6 Hz, 2H), 4.00-3.93 (m, 1H), 3.73 (s, 3H), 3.12-3.03 (m, 2H), 2.80-2.71 (m, 2H). [13]C NMR (100 MHz, $CDCl_3$) $\delta$ 203.60, 158.11, 139.68, 137.50, 132.82, 131.60, 130.05, 129.08, 128.51, 128.46, 128.18, 126.29, 113.89, 55.29, 50.80, 38.21, 37.45.

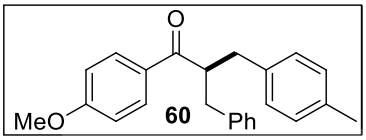



**2-Benzyl-1-(4-methoxyphenyl)-3-phenylpropan-1-one (59):**[36] Following the general procedure, the title product was obtained as a colourless oil; [1]H NMR (400 MHz, $CDCl_3$) $\delta$ 7.73 (d, $J$ = 9.2 Hz, 2H), 7.43-7.37 (m, 1H), 7.23-7.19 (m, 4H), 7.13 (d, $J$ = 7.7 Hz, 5H), 6.80 (d, $J$ = 9.1 Hz, 2H), 3.98-3.94 (m, 1H), 3.80 (s, 3H), 3.12 (dd, $J$ = 14.2, 8.1 Hz, 2H), 2.79 (dd, $J$ =

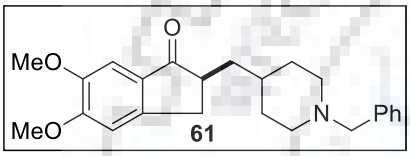


14.1, 6.5 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 201.76, 163.37, 139.79, 130.53, 130.45, 129.09, 128.46, 126.29, 113.70, 55.49, 50.06, 38.43.

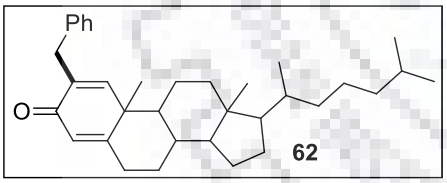
**2-Benzyl-1-(4-methoxyphenyl)-3-(*p*-tolyl)propan-1-one (60):**[36] Following the general procedure, the title product was obtained as a colourless liquid; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.73 (d, $J$ = 8.9 Hz, 2H), 7.26 – 7.17 (m, 3H), 7.13-7.10 (m, 3H), 7.01 (d, $J$ = 3.0 Hz, 3H), 6.80 (d, $J$ = 8.9 Hz, 2H), 3.98-3.89 (m, 1H), 3.80 (s, 3H), 3.10-3.04 (m, 2H), 2.79-2.72 (m, 2H), 2.25 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 201.79, 163.33, 139.88, 136.63, 135.71, 130.53, 130.45, 129.08, 128.95, 128.41, 127.69, 126.21, 113.69, 55.50, 50.09, 38.26, 37.95, 21.13.



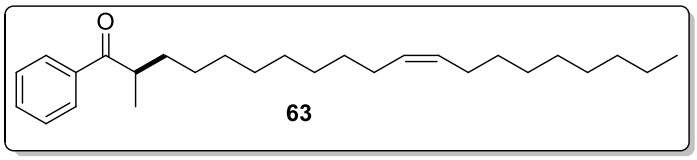

**2-((1-Benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (61):** [29] Following the general procedure, the title product was obtained as a yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35-7.26 (m, 5H), 7.15 (s, 1H), 6.84 (s, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.54 (s, 2H), 3.22 (dd, $J$ = 17.5, 8.2 Hz, 1H), 3.01-2.77 (m, 2H), 2.73-2.63 (m, 2H), 2.08-1.82 (m, 2H), 1.76-1.56 (m, 3H), 1.43-1.31 (m, 4H).




**2-Benzyl-10,13-dimethyl-17-(6-methylheptan-2-yl)-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one (62):** Following the general procedure, the title product was obtained as a yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.29-7.25 (m, 2H), 7.18 (t, $J$ = 6.6 Hz, 3H), 6.59 (s, 1H), 6.05 (s, 1H), 3.63 (s, 2H), 2.44-2.30 (m, 2H), 2.16 (s, 1H), 2.02-1.89 (m, 3H), 1.85-1.77 (m, 1H), 1.56-1.48 (m, 4H), 1.33-1.24 (m, 4H), 1.14-1.04 (m, 9H), 0.99-0.92 (m, 4H), 0.85 (dd, $J$ = 6.4, 4.6 Hz, 9H), 0.68 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 186.05, 168.97, 152.47, 139.69, 137.14, 129.23, 128.42, 126.09, 123.65, 56.15, 55.51, 52.76, 43.59, 42.72, 39.55, 36.15, 35.79, 35.56, 35.29, 32.70, 32.56, 28.22, 28.17, 28.08, 24.48, 23.88, 22.99, 22.88, 22.62, 18.78, 18.66, 12.03. HRMS (ESI): Calculated for $[C_{34}H_{49}O]^+$ 473.3778; Found 473.3775.



**2-methyl-1-phenylicos-11-en-1-one (63):** Following the general procedure, the title product was obtained as a pale yellow oil; $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.38-7.29 (m, 5H), 5.38 (t, $J$ = 3.7 Hz, 2H), 3.59-3.52 (m, 1H), 2.09-2.04 (m, 4H), 1.89-1.70 (m, 2H), 1.35-1.30 (m, 24H), 0.95-0.77 (m, 6H);$^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 206.05, 142.78, 128.84, 127.07, 126.32, 125.61, 125.27, 113.91, 39.10, 32.07, 31.15, 30.82, 29.88, 28.88, 28.70, 28.56, 28.44, 28.23, 26.14, 25.93, 21.60, 14.59, 13.02. Elemental Analysis: Calculated C, 84.31; H, 11.53; Found C, 85.01; H, 11.79.




63

**[3A.8] Spectra of Selected Compounds**:

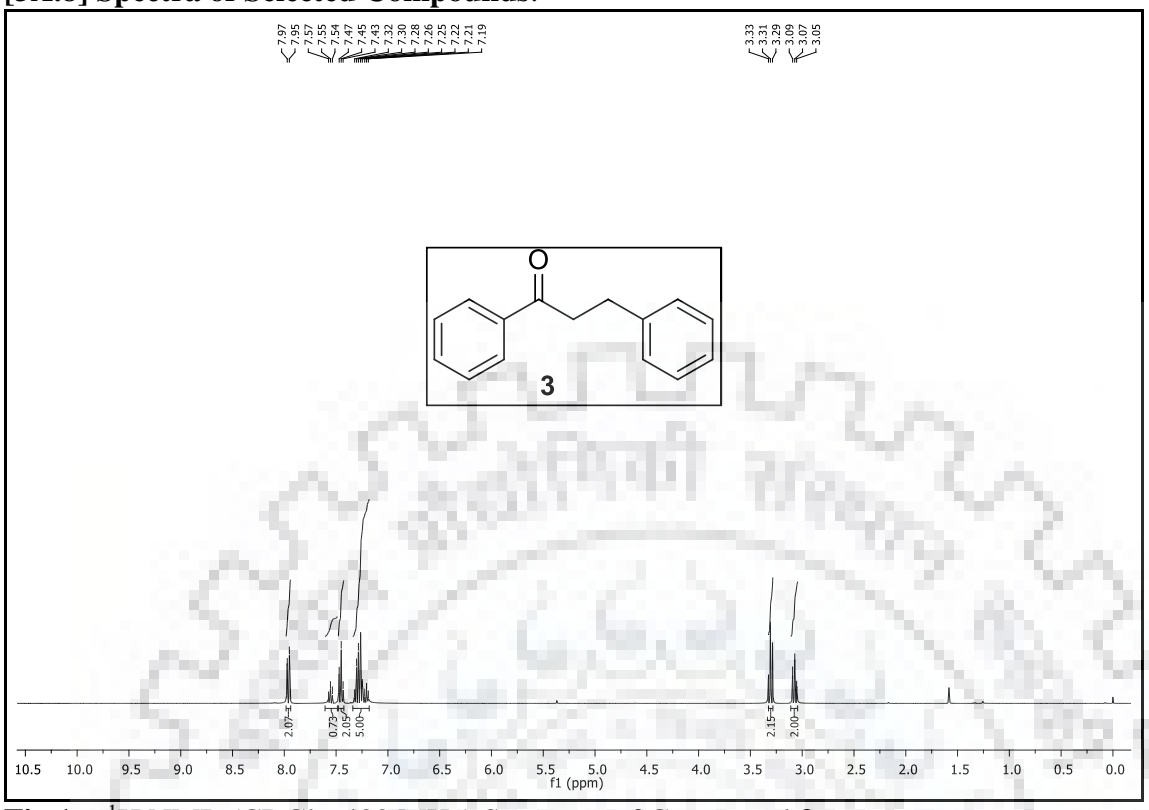



**Fig 1a:** $^{1}$H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **3**

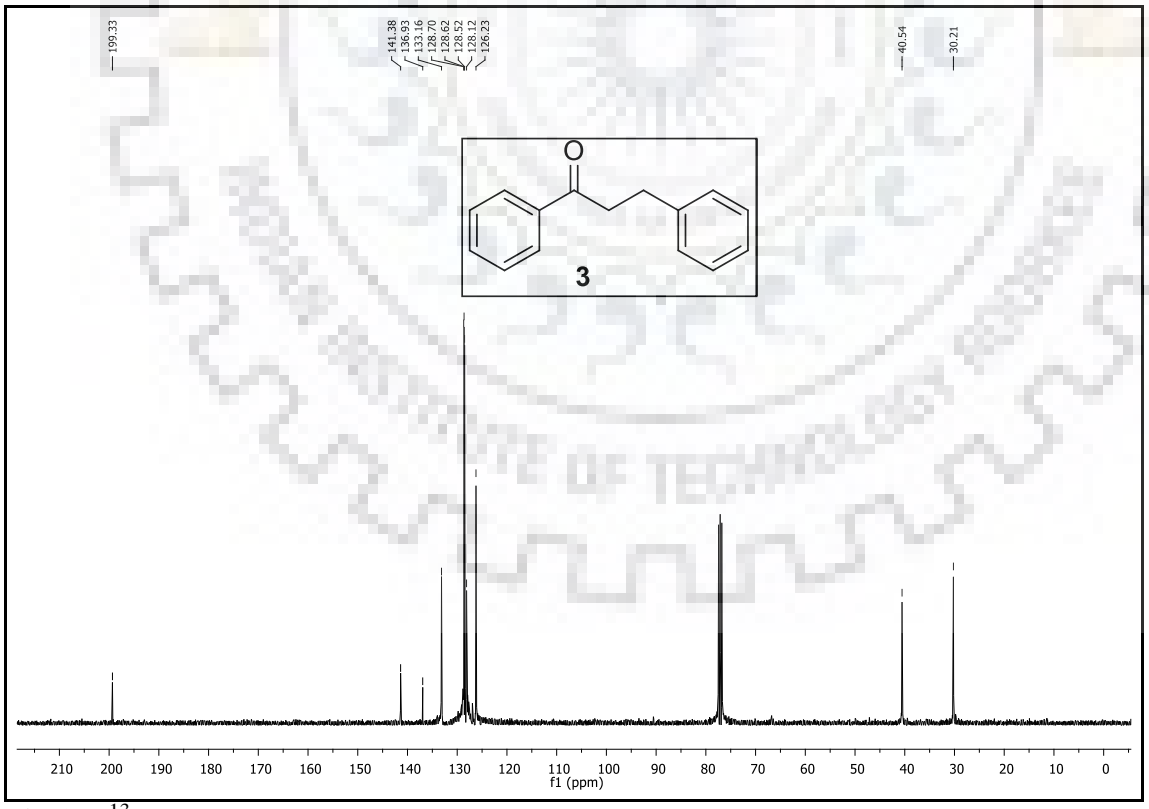



**Fig 1b:** $^{13}$C NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **3**

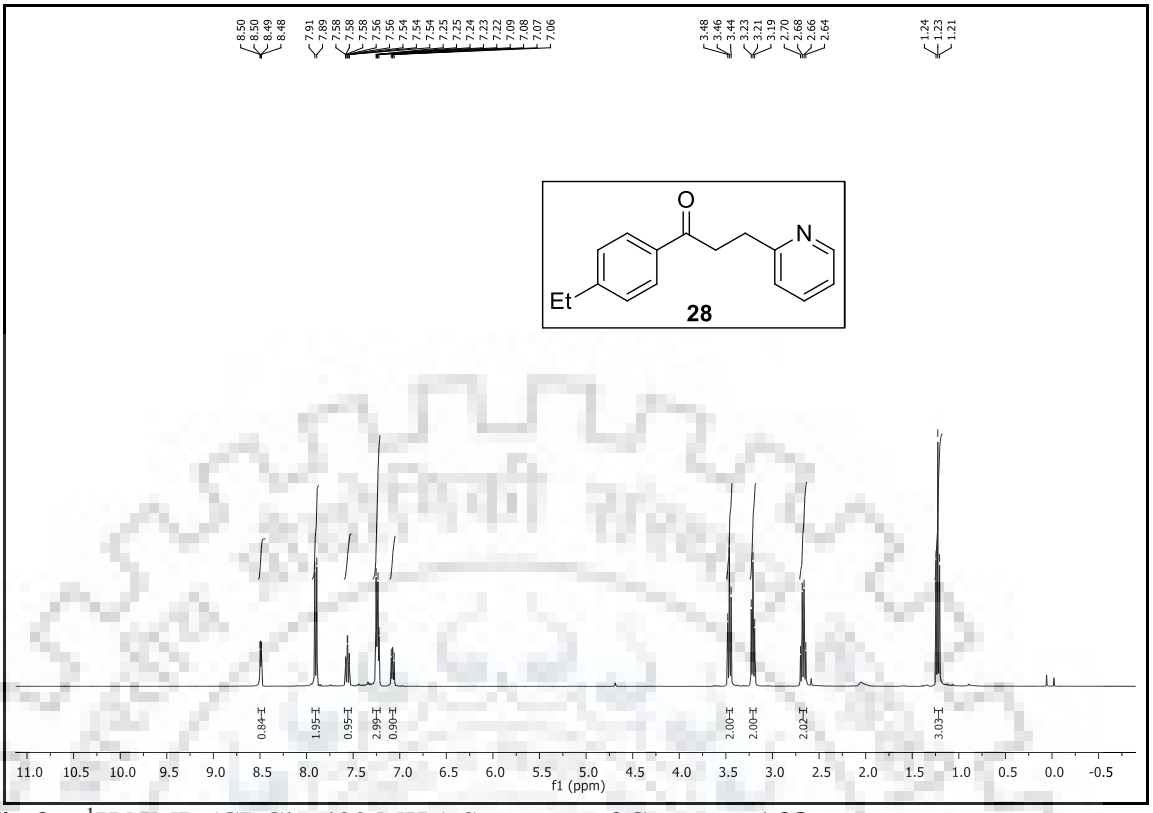



**Fig 2a:** $^{1}$H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **28**

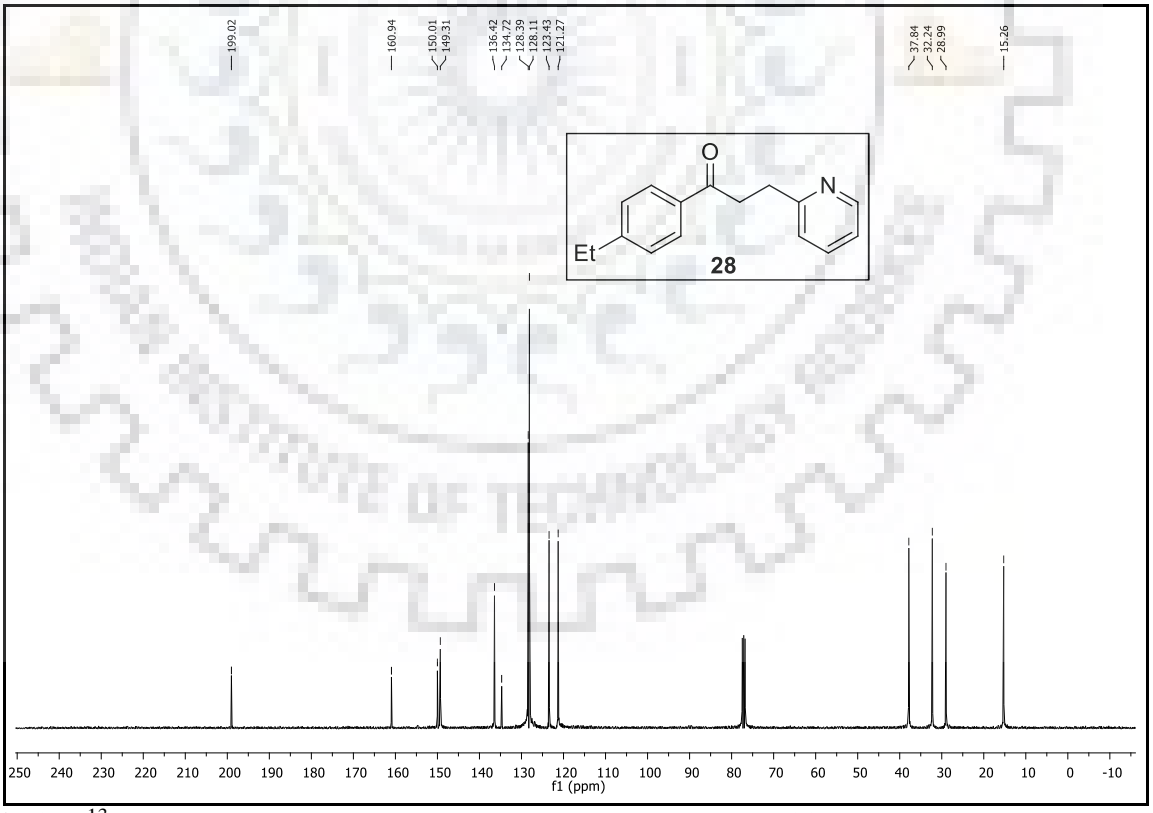



**Fig 2b:** $^{13}$C NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **28**

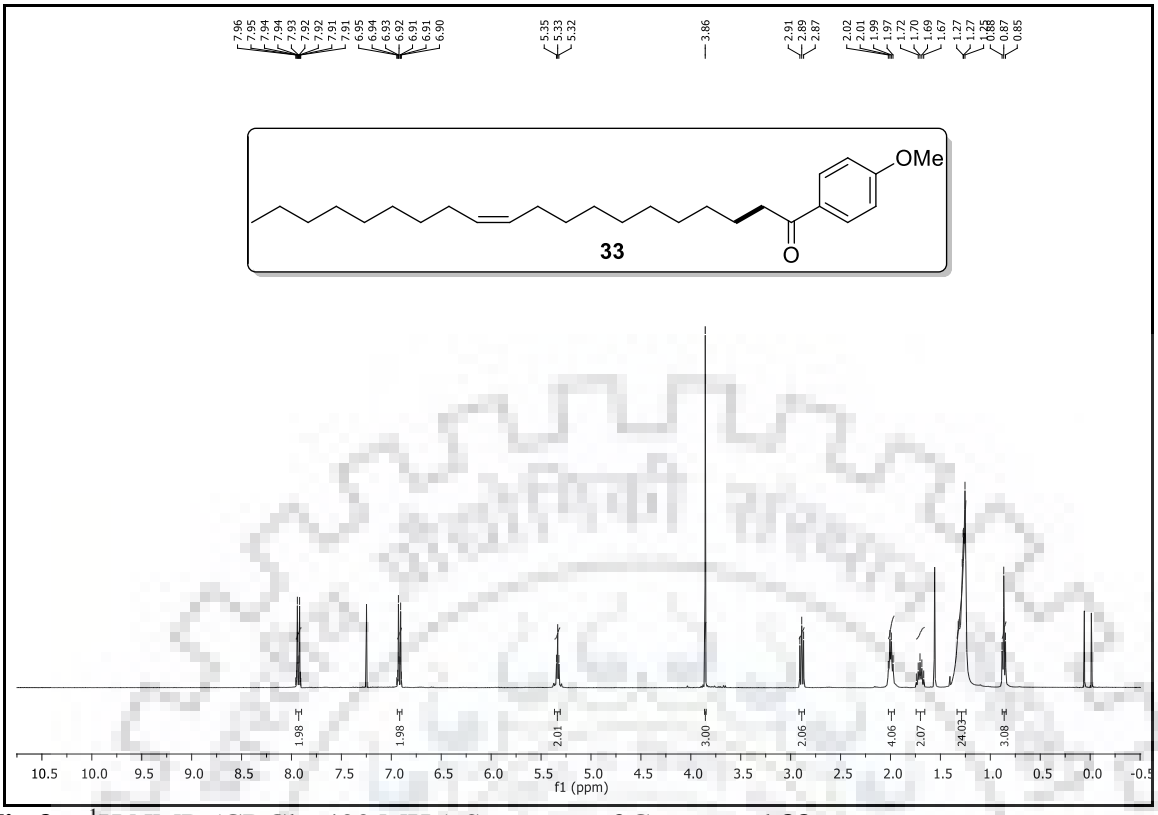



**Fig 3a:** $^{1}H$ NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **33**

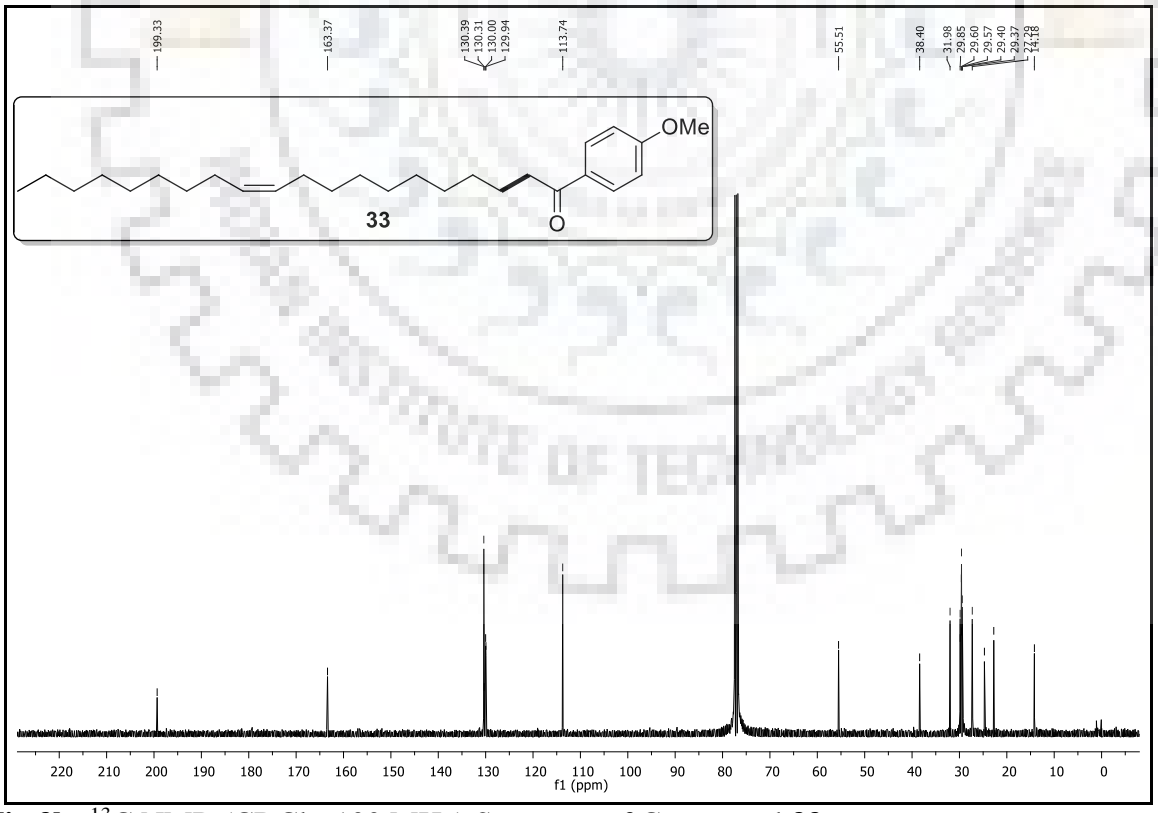



**Fig 3b:** $^{13}C$ NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **33**

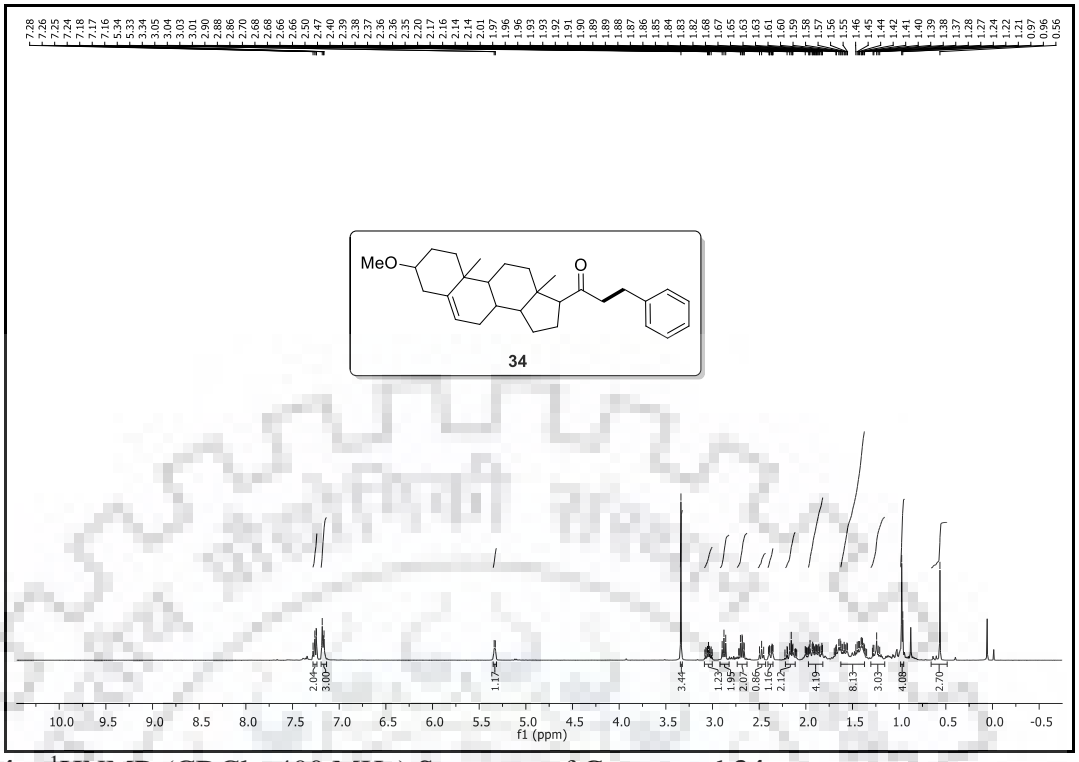



**Fig 4a:** $^{1}$HNMR ($CDCl_3$, 400 MHz) Spectrum of Compound **34**

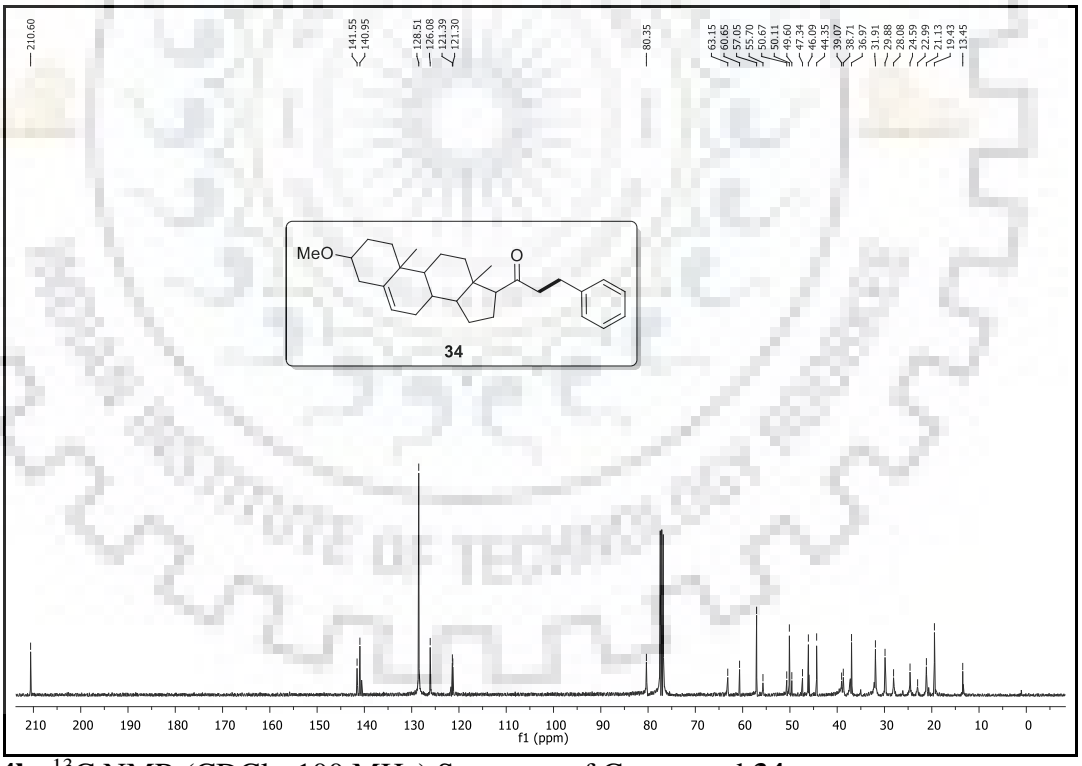



**Fig 4b:** $^{13}$C NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **34**

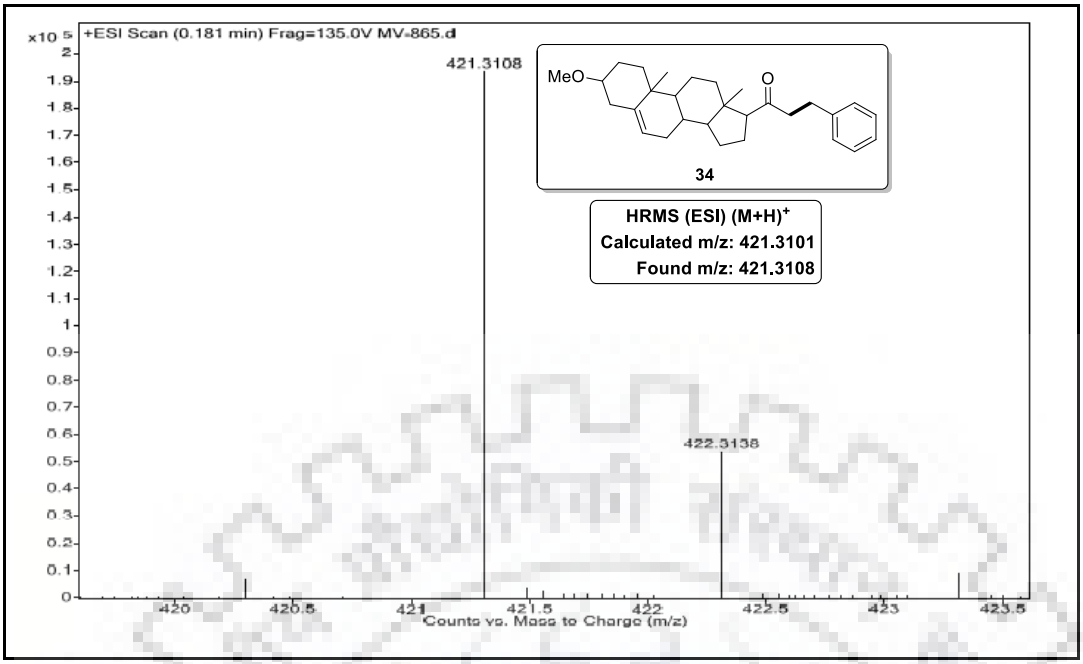
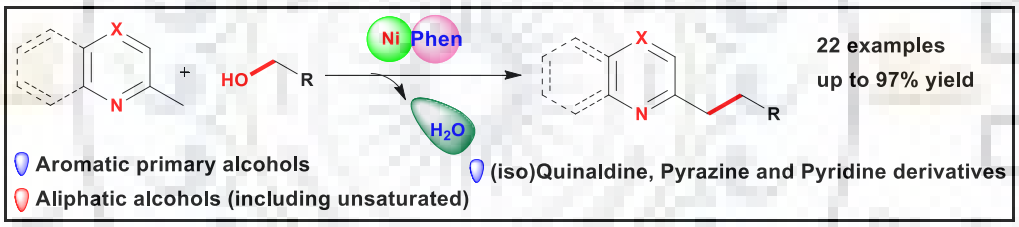



**Fig 4c:** HRMS spectra of compound **34**

## Chapter-4: Nickel-catalyzed alkylation of methyl *N*-heteroaromatics with alcohols

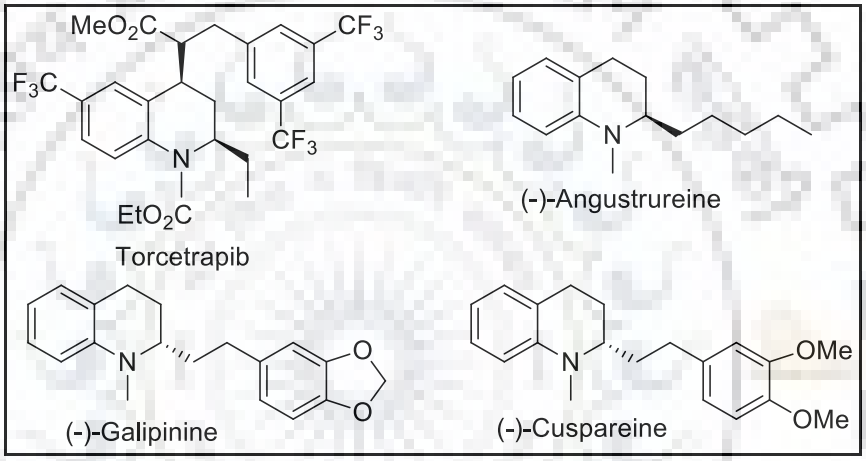
In this chapter, we have illustrated the first Ni-catalyzed functionalization of C(sp3)–H bonds in methyl *N*-heteroaromatics using primary alcohols. Easily available, inexpensive Ni-catalysts and 1,10-phenanthroline ligands enable long chain C2-alkylated *N*-heteroaromatics in up to quantitative yields. The catalytic system allows transformations in the presence of reducible functional moieties, such as allylic ethers and alkenes, including unsaturated alcohols. Initial mechanistic studies strongly support the participation of a Ni–H species and the bi-functional nature of the Ni-catalyst. A series of deuterium labeling experiments revealed the involvement of H/D exchange during the progress of the reaction.




*Chem. Commun.* **2018**, *54*, 12369

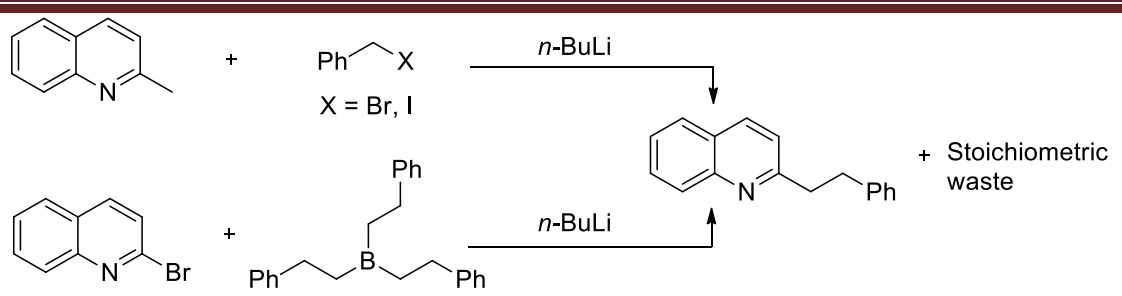
## [4.1] Introduction:

Transition metal-catalyzed alkylation of C($sp^3$)–H bonds for the construction of elongated carbon-chain products constitutes a fundamental challenge in organic synthesis. Due to high C($sp^3$)–H bond dissociation energy, an efficient and selective functionalization of alkyl chains often represents a key issue in catalysis. Therefore, since the last decade significant efforts have been made involving C–H bond activation using alkyl halides,[1] directing group assisted functionalization of C($sp^3$)–H bonds with olefins,[2] and reductive alkylation including nucleophilic substitutions and α-alkylation of ketone enolates and related studies have been documented.[3,4]




**Scheme 1:** Some important bioactive compounds containing *N*-heteroaromatics

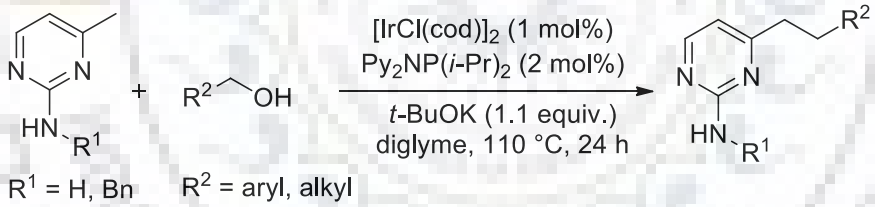
*N*-Heteroaromatics and their derivatives are important targets in medicine, pharmaceuticals, and material chemistry, and they are significantly used as intermediates for natural products and ligands in catalysis (Scheme 1).[5] However, the functionalization of the C($sp^3$)–H bonds in methylazaarenes provides direct access to chain-elongated *N*-heteroaromatics with valuable applications. However, such transformations are often limited by pre-functionalized alkyl halides, carbonates or esters and often require harsh reaction conditions involving the generation of stoichiometric equivalents of waste (Scheme 2).[6] Therefore, the development of environmentally benign, sustainable and atom-economical alkylation technologies for C($sp^3$)–H bonds in *N*-heteroaromatics is still a desired goal.[7–9e,f]




**Scheme 2:** Classical method for the alkylation of *N*-heteroaromatics

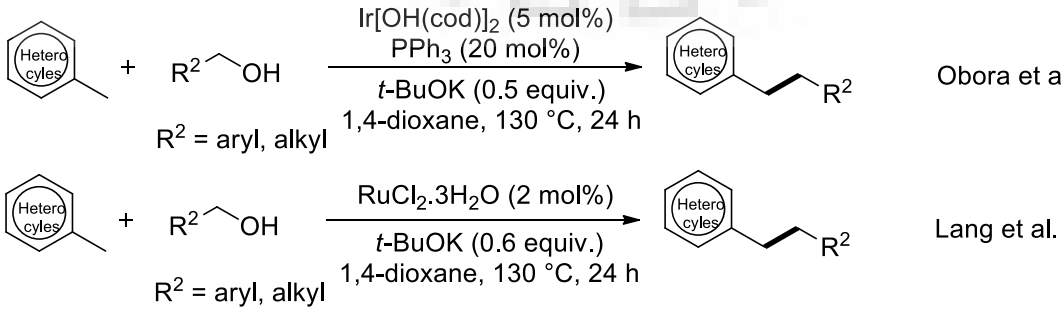
**[4.2] Brief literature survey for metal-catalyzed alkylation of methyl *N*-heteroaromatics:**

The direct application of highly abundant and renewable alcohols would be a promising alternative to the alkylation of methyl *N*-heteroarmoatics.[6b] Nevertheless, currently, a metal-catalyzed hydrogen borrowing (HB) approach has been identified as an elegant tool to construct C–X (X = C, N etc.) bonds.[8] In this direction, only a handful of examples are known and they are based on precious metal catalysts (Ir-, Ru-, and Pt-) for such C($sp^3$)-H bond functionalization of *N*-heteroaromatics using alcohol as a coupling partner. A notable breakthrough by Kempe,[9a] on well-defined Ir-catalyzed alkylation of *N*-heteroaromatics, is worth mentioning (Scheme 3).




**Scheme 3:** Ir-catalyzed alkylation of methyl *N*-heteroaromatics

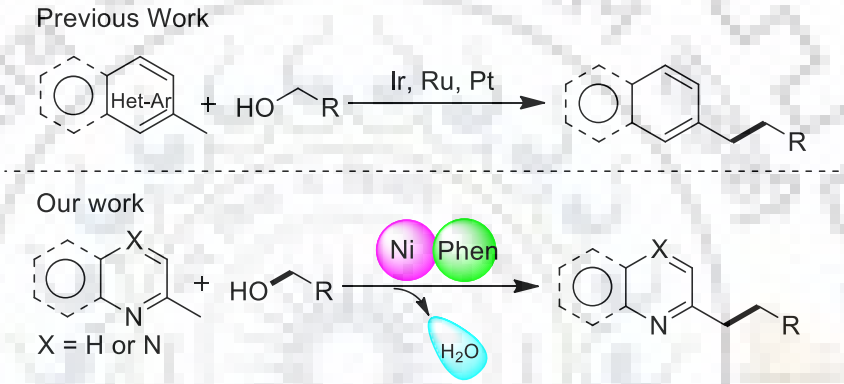
Later, Obora and co-workers also reported the functionalization of 2-methyl heteroarenes using Ir-catalysts.[9b] Recently, a Ru-catalyzed ligand-free alkylation and a Pt-supported heterogeneous catalysis has also been developed for the alkylation of methyl *N*-heteroaromatics using alcohols following the HB approach (Scheme 4).[9c,d]




**Scheme 4:** Ir and Ru-catalyzed alkylation of methyl *N*-heteroaromatics with alcohols

## [4.3] Aim of Present Work:

The recent trends in catalysis is to replace the precious and expensive metal catalysts with earth abundant and inexpensive metal-based catalysts for key catalytic conversions.[10a,b] Therefore, the development of a sustainable catalytic protocol involving renewable resources in combination with non-precious metal catalysts is in demand. Nevertheless, to the best of our knowledge, till date, no nickel-catalyzed protocol for coupling of primary alcohols with methyl-*N*-heteroaromatics is known.[11] Herein, we report the first example of an earth-abundant base-metal-catalyzed route for alkylation of C($sp^3$)-H bonds in *N*-heteroaromatics, such as, quinolines, pyridines and pyrazines (Scheme 5b).




**Scheme 5**: (a) Precious metal-catalyzed alkylation of methyl *N*-heteroaromatics; (b) Nickel-catalyzed coupling of alcohols with methyl *N*-heteroaromatics

## [4.4] Result and discussions:

To explore the direct functionalization of C($sp^3$)-H bonds into chain elongated methyl-*N*-heteroaromatics using alcohols, we realized the potential role of diversely available nitrogen ligands to forge a new C-C bond using nickel. Therefore, to optimize an efficient catalytic protocol, five different nickel pre-catalysts with oxidation states of Ni(0) and Ni(II) were examined using the model reaction of quinaldine **1a** and benzyl alcohol **2a** (Table 1). Gratifyingly, we observed a 70% isolated yield for the α-alkylated product **3** when a combination of 10 mol% $NiBr_2$, 20 mol% 1,10-phenanthroline **L1** in combination with 0.25 mmol of *t*-BuOK at 130 °C in toluene were used (Table 1, entry 2).

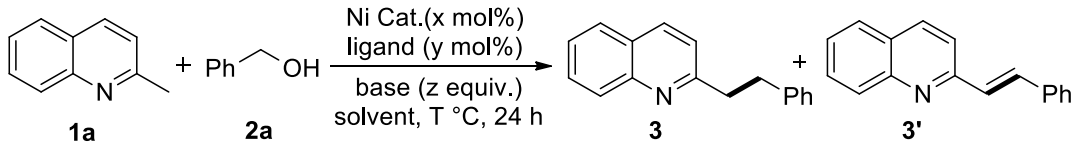
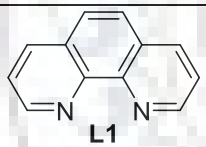
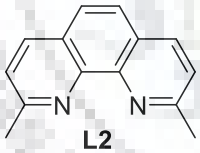
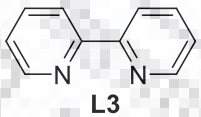
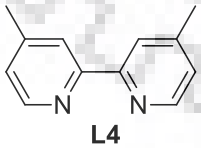
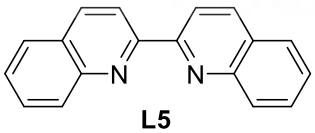



**Table 1**: Screening of catalyst [a]

| Entry | **Ni-Catalyst** | GC-MS Conversion **3** (%) | GC-MS Conversion **3'** (%) |
|---|---|---|---|
| 1 | $NiCl_2$ | 53 | 47 |
| **2** | **$NiBr_2$** | **73 (70%)** [b] | **25** |
| 3 | $Ni(acac)_2$ | 30 | 34 |
| 4 | $NiCl_2(DME)$ | 13 | 48 |
| 5 | $Ni(COD)_2$ | 8 | 22 |
| 6 | No Catalyst | 0 | 0 |

Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (0.50 mmol), **Ni-Cat. (10 mol%)**, Phen (20 mol%), *t*-BuOK (0.25 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 130 ºC oil bath, 24 h reaction time. [b] Isolated yield average of two run.

**Table 2**: Screening of ligand [a]

| Entry | **Ligand** | GC-MS Conversion **3** (%) | GC-MS Conversion **3'** (%) |
|---|---|---|---|
| 1 |  **L1** | **73 (70%)** [b] | **25** |
| 2 |  **L2** | 1 | 9 |
| 3 |  **L3** | 0 | 12 |
| 4 |  **L4** | 2 | 47 |
| 5 |  **L5** | 0 | 10 |
| 6 | No Ligand | 8 | 22 |

Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (0.50 mmol), $NiBr_2$ (10 mol%), **ligand (20 mol%)**, *t*-BuOK (0.25 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 130 ºC oil bath, 24 h reaction time. [b] Isolated yield average of two run.

Furthermore, the application of a variety of nitrogen-based ligands, **L2**–**L5** were found inefficient to form the product **3**, instead we observed 74% conversion into the α-olefinated product **3'** using GC-MS analysis (Table 2). This result demonstrates the significant role of ligands in achieving higher product yields. At this point we envisioned that ligands might be playing a crucial role in the hydrogenation of the α-olefinated product **3'**, present in inadequate amount in the reaction mixture. Therefore, we examined the role of additional ligands. To our delight, when using excess ligands, a quantitative yield of product **3** was observed with 99% selectivity (Table 6).

**Table 3**: Screening of base [a]

| Entry | **Base** | GC-MS Conversion **3** (%) | GC-MS Conversion **3'** (%) |
|---|---|---|---|
| **1** | ***t*-BuOK** | **73 (70%)** [b] | **25** |
| 2 | *t*-BuONa | 14 | 39 |
| 3 | $K_3PO_4$ | 0 | 18 |
| 4 | $Na_2CO_3$ | 2 | 12 |

Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (0.50 mmol), $NiBr_2$ (10 mol%), Phen (20 mol%), **base (0.25 mmol)**, toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 130 ºC oil bath, 24 h reaction time. [b] Isolated yield average of two run.

**Table 4**: Screening of solvent [a]

| Entry | **Solvent** | GC-MS Conversion **3** (%) | GC-MS Conversion **3'** (%) |
|---|---|---|---|
| **1** | **toluene** | **73 (70%)** [b] | **25** |
| 2 | *p*-xylene | 34 | 40 |
| 3 | 1,4-dioxane | 1 | 5 |
| 4 | DMA | 0 | 0 |
| 5 | *t*-amylalcohol | 0 | 1 |

Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (0.50 mmol), $NiBr_2$ (10 mol%), Phen (20 mol%), *t*-BuOK (0.25 mmol), **solvent (2.0 mL)**, Schlenk tube under nitrogen atmosphere, 130 ºC oil bath, 24 h reaction time. [b] Isolated yield average of two run.

The screening of different bases (Table 3), solvents (Table 4) and control experiments resulted in only moderate product yields. As expected, the product yield was suppressed significantly when a lower catalyst/ligand combination was employed (Table 6). Control experiments in the absence of a catalyst, ligand and base show their potential roles as individual catalytic components.

**Table 5**: Screening of base equivalents

| Entry | **Base Equivalent (X equiv.)** | GC-MS Conversion **3** (%) | GC-MS Conversion **3'** (%) |
|---|---|---|---|
| **1** | ***t*-BuOK (1.0 equiv.)** | **73 (70%)** [b] | **25** |
| 2 | *t*-BuOK (0.75 equiv.) | 12 | 35 |
| 3 | *t*-BuOK (0.50 equiv.) | 9 | 29 |
| 4 | *t*-BuOK (0.25 equiv.) | 0 | 1 |
| 5 | - | 0 | 0 |

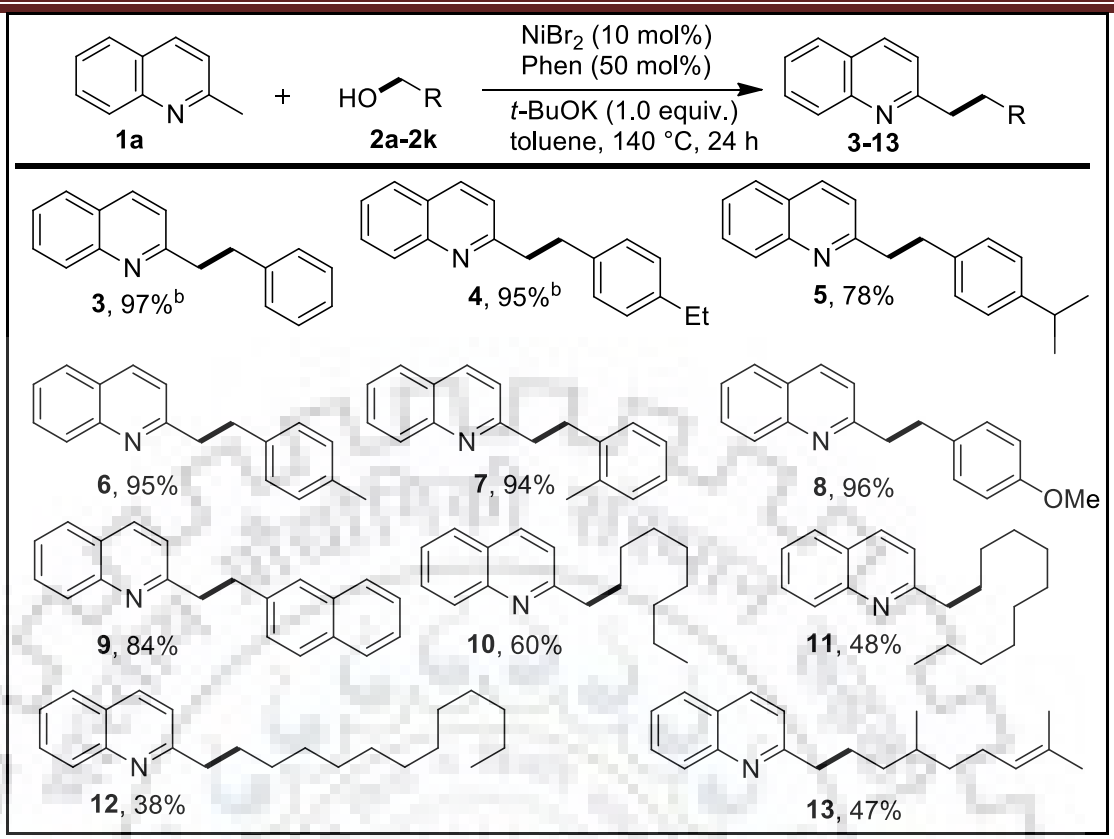
Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (0.50 mmol), $NiBr_2$ (10 mol%), Phen (20 mol%), *t*-BuOK (**X equiv.**), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 130 ºC oil bath, 24 h reaction time. [b] Isolated yield average of two run.

**Table 6**: Screening of catalyst and ligand loading [a]

| Entry | **Cat. (X mol%)** | **Ligand (Y mol%)** | GC-MS Conv. **3** (%) | GC-MS Conv. **3'** (%) |
|---|---|---|---|---|
| **1** | **$NiBr_2$ (10 mol%)** | **Phen (20 mol%)** | **73 (70%)** [b] | **25** |
| 2 | $NiBr_2$ (10 mol%) | Phen (30 mol%) | 27 | 58 |
| 3 | $NiBr_2$ (10 mol%) | Phen (40 mol%) | 65 | 34 |
| **4** | **$NiBr_2$ (10 mol%)** | **Phen (50 mol%)** | **100 (96%)** [b] | **0** |
| **5** | **$NiBr_2$ (10 mol%)** | **Phen (50 mol%)** | **100 (97%)** [b,c] | **0** |
| 6 | $NiBr_2$ (5.0 mol%) | Phen (25 mol%) | 13 | 18 |
| 7 | $NiBr_2$ (2.5 mol%) | Phen (12.5 mol%) | 8 | 36 |
| 8 | - | - | 0 | 0 |

Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (0.50 mmol), **$NiBr_2$ (X mol%), Phen (Y mol%)**, *t*-BuOK (0.25 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 130 ºC oil bath, 24 h reaction time. [b] Isolated yield average of two run. [c] 140 ºC, 24 h.

After having identified the optimum conditions, the nickel-catalyzed functionalization of the C($sp^3$)–H bond in 2-methylquinoline was performed using a series of electronically different benzyl alcohols (Scheme 6). Pleasingly, irrespective of the electronic nature, almost quantitative yields of the C2-alkylated *N*-heteroaromatic compounds **4-6** were obtained (Scheme 6). A quantitative product yield of **7** was achieved when sterically hindered 2-methylbenzylalcohol was used. To our delight, 4-methoxybenzyl alcohol and 1-naphthalenemethanol furnished the desired alkylated product with excellent isolated yields, 96% and 84% respectively (Scheme 6, **8** and **9**).

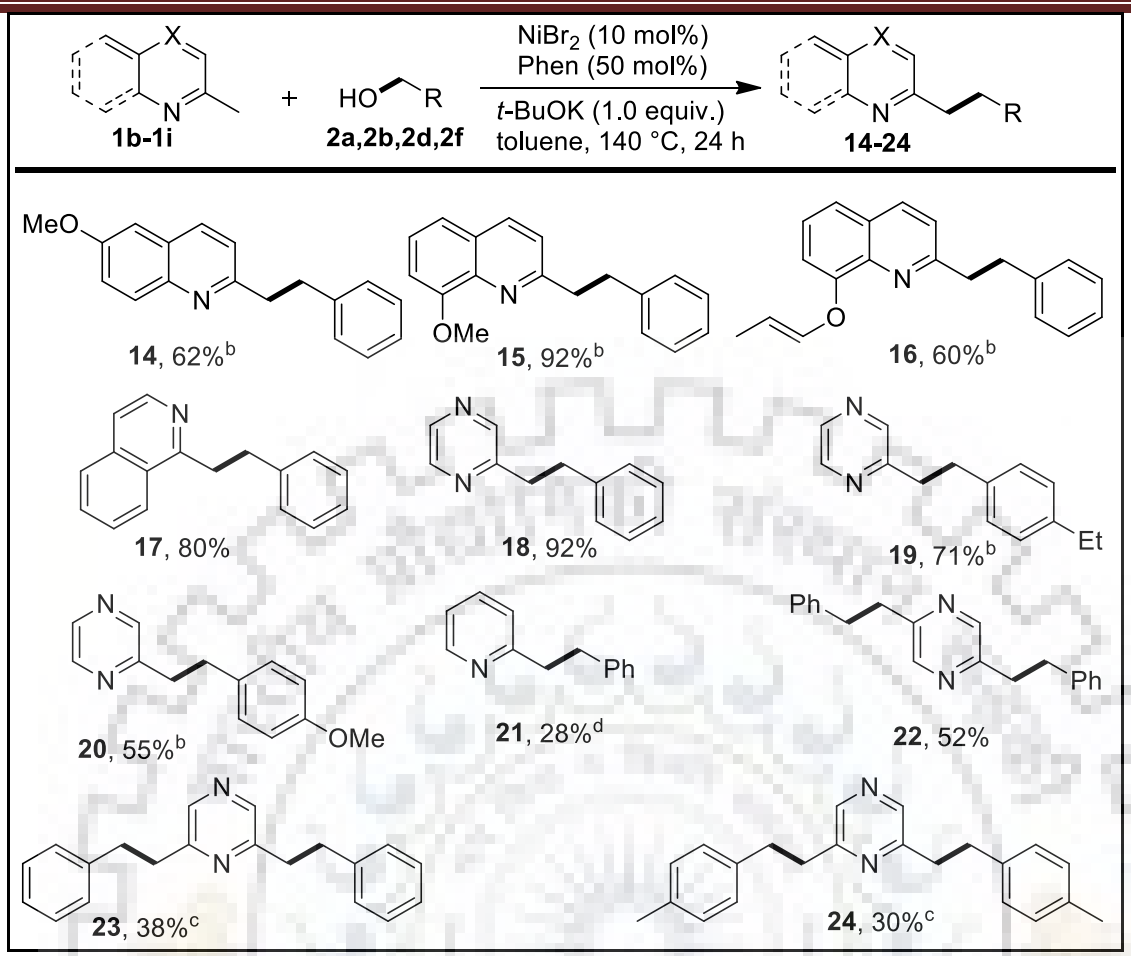



**Scheme 6**: Ni-Catalyzed α-alkylation of quinaldine with alcohols [a]

Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), alcohol **2** (0.50 mmol), $NiBr_2$ (10 mol%), Phen (50 mol%), *t*-BuOK (0.25 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 °C oil bath, 24 h reaction time. [b] 130 °C, 24 h.

Gratifyingly, more challenging long chain C8–C12 renewable alkyl alcohols efficiently participated in C($sp^3$)–H bond functionalization with **1a** under standard catalytic conditions and resulted in chain-elongated C2-alkylated *N*-heteroaromatics in up to 60% yield of **10-12**. To our delight, the renewable terpenoid intermediate, citronellol, could be employed for α-alkylation and it could afford 47% isolated yield of **13**. It is noteworthy to mention that this chemo-selective transformation of an unsaturated alcohol represents a rare instance under Ni-catalysis.[10,11] To our delight, we witnessed excellent reactivity profiles of various alkyl and benzyl alcohols using inexpensive nickel-catalysts.

Next, the functionalization of C($sp^3$)-H bonds in various methyl *N*-heteroaromatics using benzyl alcohols was demonstrated under standard conditions (Scheme 7). For instance, 2-methylquinoline substituted with methoxy or alkoxy groups at different positions of the aryl ring ($C_6$ or $C_8$ position) furnished the desired products **14-16** in up to 60–92% isolated yield (Scheme 7). Importantly, 1-methylisoquinoline also participated in the α-alkylation process and was efficiently transformed with an excellent product yield (Scheme 7, **17**).



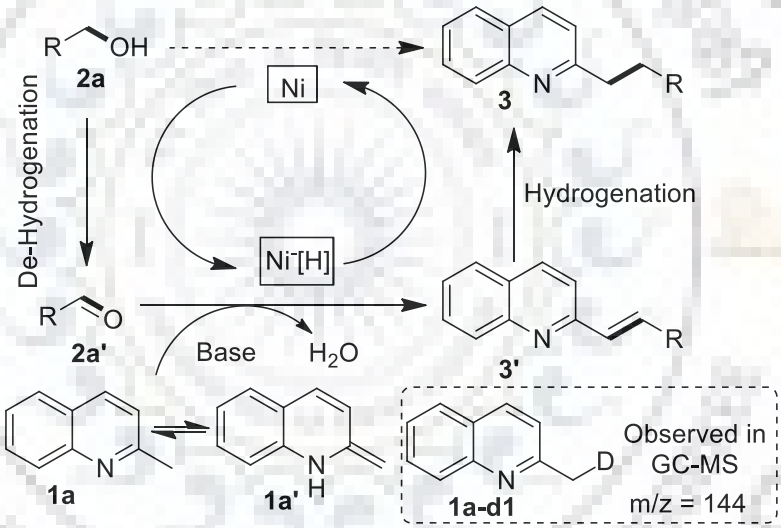

**Scheme 7**: Scope of quinaldine, pyridine and pyrazine derivatives [a]

Reaction conditions: [a] **1** (0.25 mmol), alcohol **2** (0.50 mmol), $NiBr_2$ (10 mol%), Phen (50 mol%), *t*-BuOK (0.25 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 °C oil bath, 24 h reaction time. [b] *t*-BuOK (0.375 mmol) was used. [c] **1** (0.25 mmol), alcohol **2** (1.0 mmol), $NiBr_2$ (20 mol%), Phen (100 mol%), *t*-BuOK (0.50 mmol) were used. [d] GC-MS conversion.

Furthermore, the scope of electronically different alcohols for alkylation was investigated using C2-alkylated pyrazines, and moderate to excellent isolated yields of **18-20** were obtained (Scheme 7). Notably, the reaction with 2-methylpyridine was sluggish under the optimized conditions and a diminished product yield of **21** was observed. The catalytic protocol could also be applied for the synthesis of symmetric pyrazine derivatives. Gratifyingly, when 2,5-dimethyl and 2,6-dimethyl pyrazines were employed with benzyl alcohols, moderate yields of the bis-alkylated pyrazines **22-24** were obtained. Interestingly, the catalytic protocol is tolerant to nitrogen heterocycles (pyridine, pyrazine, quinolines etc.), and allylic ethers, including alkene and alkoxy moieties. Remarkable transformations in the presence of reducible groups such as terminal alkenes demonstrate the synthetic potential of the established protocol.

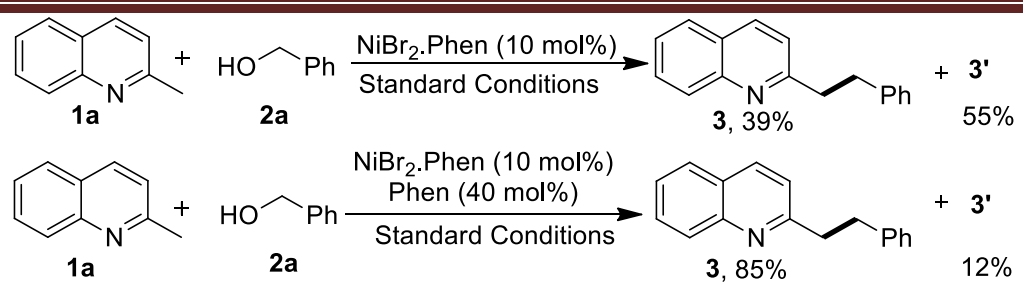
**Kinetic and Mechanistic studies:**

After having excellent reactivity for a diverse range of substrates we performed the preliminary mechanistic investigations for such C($sp^3$)-H bond functionalization of methyl *N*-heteroaromatics using Ni-catalyst. To date, no such mechanistic study has been reported for the α-alkylation of C2-alkylated *N*-heteroaromatics with primary alcohols. During the progress of the reaction we realized that such Ni-catalyzed α-alkylation consisting a multi-step process, such as the dehydrogenation of alcohol **2a** to aldehyde **2a'**, where a transient Ni–H species is generated (Scheme 8). Subsequently, base mediated isomerization of **1a** to **1a'** followed by the reaction with aldehyde **2a'** resulted in the α-olefinated product **3'**. At this point, hydrogenation of **3'** by a Ni-H species resulted the desired product **3**. However, we realized that nitrogen ligands play a key role in achieving the selective hydrogenation of **3'** (Scheme 8).

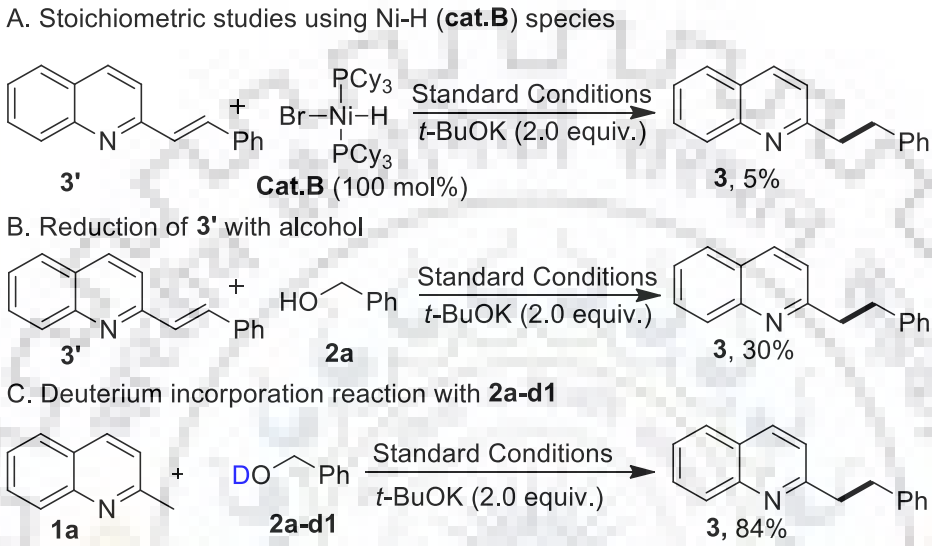



**Scheme 8**: Proposed mechanism for C2-alkylated *N*-heteroaromatics with alcohols

Furthermore, to confirm the participation of **1a'**, deuterium labeling experiments using **2a-d2** (92% D) were performed, and **1a-d1** was detected using GC-MS analysis of the crude reaction mixture (Scheme 10). Next, to understand the participation of the key Ni-intermediate species, $NiBr_2$-Phen was prepared,[12] and independently employed in a catalytic (10 mol%) amount in the model reaction. Under optimized conditions, **3** was obtained in 39% yield along with 55% conversion to **3'** (Scheme 9). However, when using 40 mol% **L1** with $NiBr_2$-Phen, 85% yield of **3** was obtained. These experimental results provide evidence for the role of excess ligands in the hydrogenation step (Scheme 9).



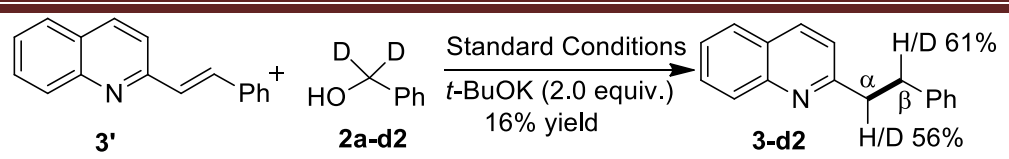

**Scheme 9**: Catalytic studies using $NiBr_2$.Phen defined catalyst

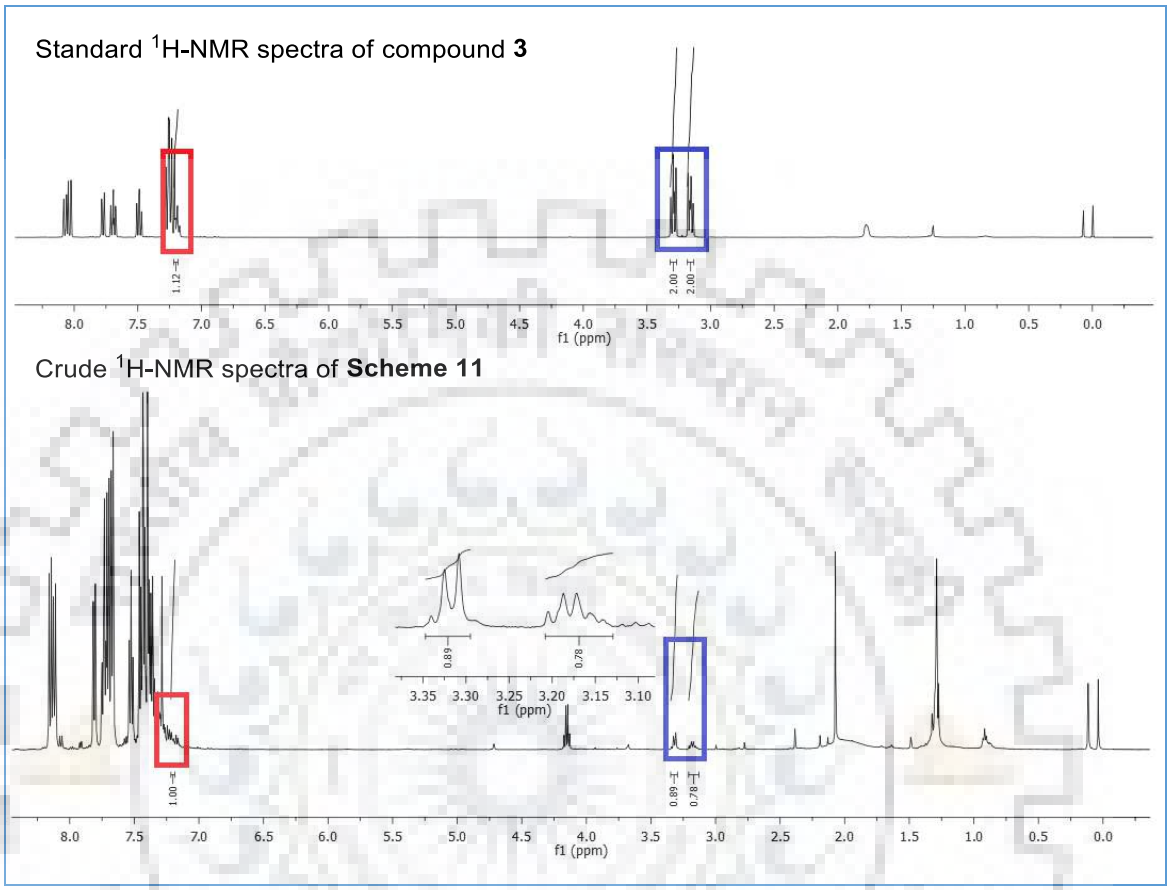



**Scheme 10**: Preliminary mechanistic investigation study

Additionally, we made an attempt to prepare the Ni-H species, $NiBr_2$-Phen, which was not successful.[13] At that point, when electron rich tri-cyclohexyl phosphine was used, the defined complex $[(Cy)_3P]_2NiBr_2$ and the Ni-hydride species $[(Cy)_3P]_2NiBrH$ were readily prepared,[12] and employed in stoichiometric equivalents with the α-olefinated product **3'** under standard conditions. Pleasingly, **3** was detected by GC-MS analysis of the crude reaction mixture (Scheme 10A). These experimental outcomes are in strong agreement with the participation of the Ni-H species for C($sp^3$)–H bond functionalization of methyl *N*-heteroaromatics.

Furthermore, we performed a series of deuterium-labeling experiments on the α-alkylation process. Initially, the α-olefinated product **3'** was employed with **2a** and **2a-d2** (92% D) under standard conditions, and the resulting **3** and **3-d2** products were obtained in moderate yields and exhibited 56% and 61% incorporation of deuterium in α-and β-positions in **3-d2** (Scheme 10B and 11).



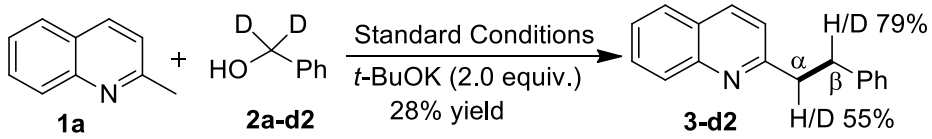



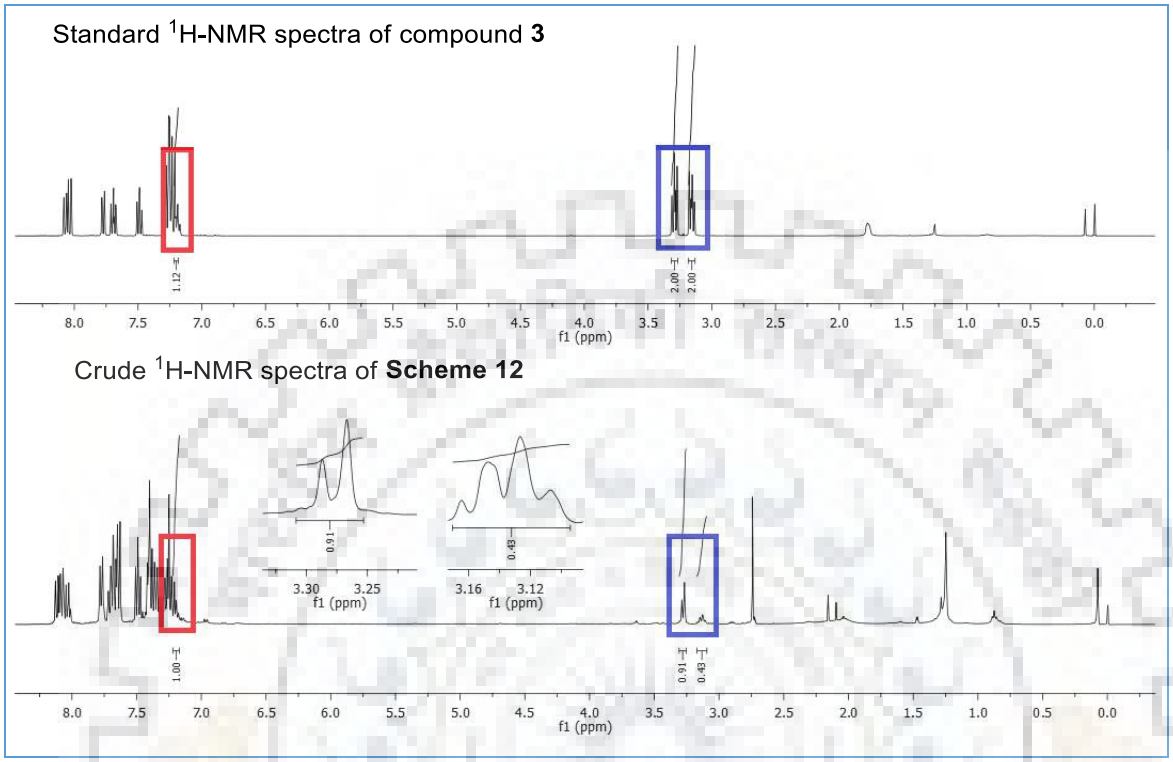

Conversion was calculated by $^1$H-NMR integration value

| | | Deuterium incorporation in **α** position | Deuterium incorporation in **β** position |
|---|---|---|---|
| Signal $\delta$ ppm | 7.21 (1H) | 3.29 (2H) | 3.15 (2H) |
| Integral Value | 1.0 | 0.89 | 0.78 |
| **Calculated ratio** | | {(2-0.89)/2}×100 = **56%** | {(2-0.78)/2}×100 = **61%** |

**Scheme 11**: Reduction of **3'** with deuterated benzyl alcohol (**2a-d2**)

Afterward, α-alkylation of **1a** with **2a-d2** (92% D) was performed, and $^1$H-NMR spectroscopy and GC-MS analysis detected the formation of **3-d2** along with deuterium incorporation at variable ratios in the α- and β- positions (Scheme 12). In addition, a crossover experiment using a 1:1 mixture of **2a** and **2a-d2** under the standard conditions afforded the formation of the H/D-scrambled product **3-d2** (Scheme 13).[14]



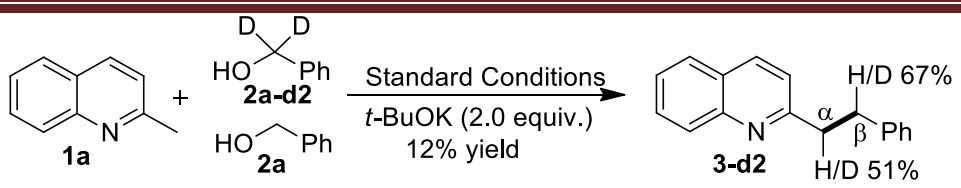



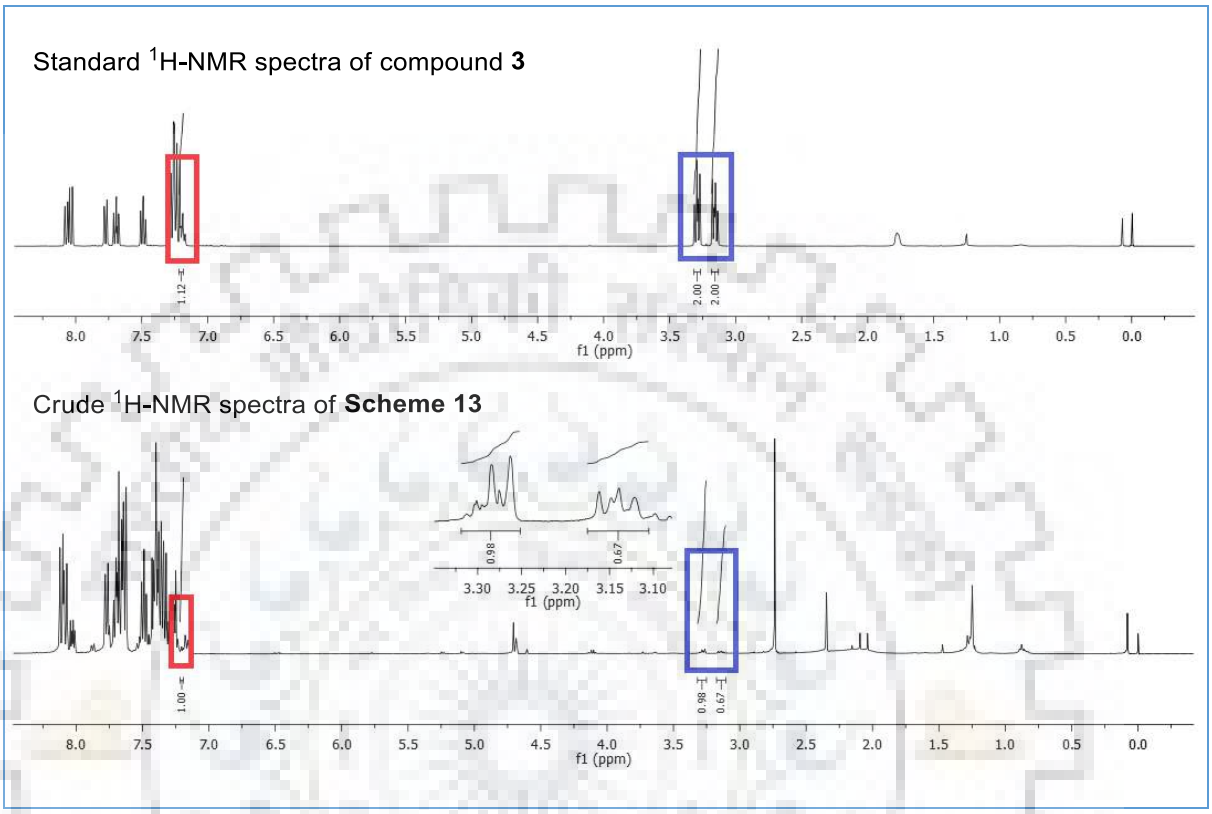

Conversion was calculated by $^{1}$H-NMR integration value

| | | Deuterium incorporation in **α** position | Deuterium incorporation in **β** position |
|---|---|---|---|
| Signal $\delta$ ppm | 7.21 (1H) | 3.29 (2H) | 3.15 (2H) |
| Integral Value | 1.0 | 0.91 | 0.43 |
| **Calculated ratio** | | {(2-0.91)/2}×100 = **55%** | {(2-0.43)/2}×100 = **79%** |

**Scheme 12**: Deuterium incorporation experiment quinaldine **1a** with **2a-d2**

These deuterium labeling experiments strongly support the micro-reversible transformation of the alkylation process under nickel-catalysis, and the formation of the H/D-scrambled products provides evidences for the participation of the hydrogen borrowing strategy.[12,14] Notably, when the reaction of **1a** was performed with benzyl alcohol **2a-d1**, we did not observe any deuterated labeling products and only **3** was obtained in 84% yield, suggesting that the hydrogen in the hydroxyl group does not participate in hydrogen shuffling involving the Ni–H species (Scheme 10C).

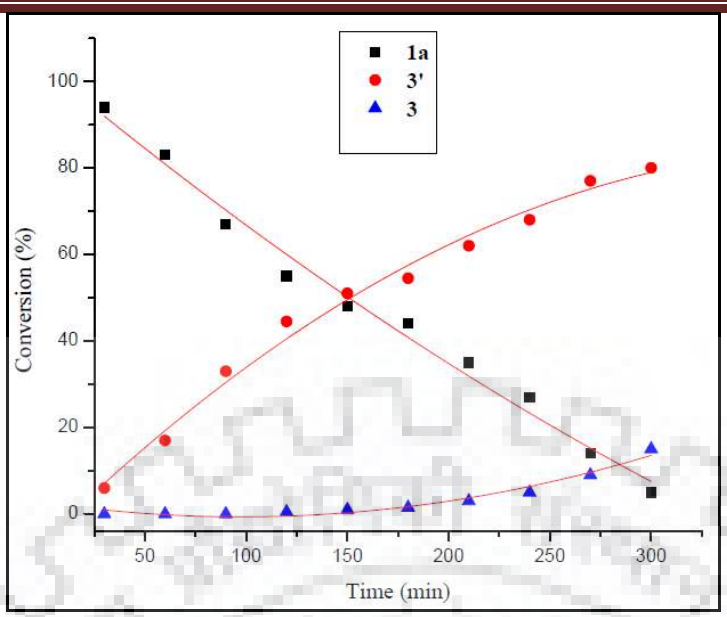



Conversion was calculated by $^{1}$H-NMR integration value

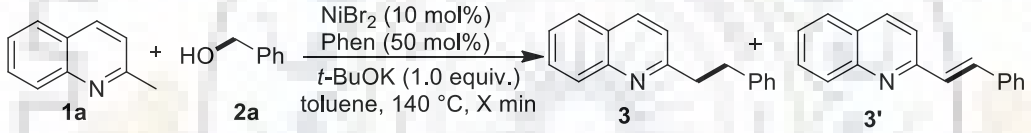
| | | Deuterium incorporation in **α** position | Deuterium incorporation in **β** position |
|---|---|---|---|
| Signal $\delta$ ppm | 7.21 (1H) | 3.29 (2H) | 3.15 (2H) |
| Integral Value | 1.0 | 0.98 | 0.67 |
| **Calculated ratio** | | {(2-0.98)/2}×100 = **51%** | {(2-0.67)/2}×100 = **67%** |

**Scheme 13**: Deuterium incorporation experiment with **1a** 1:1 mixture of **2a** and **2a-d2**




**Scheme 14:** Time-conversion-plot for the reaction of **1a** with **2a**

**Determination of rate and order of reaction:**




Run 1: Reaction was carried out in 2 mL of toluene and yield was calculated by GC

| No. | **1a** (mmol) | **2a** (mmol) | $NiBr_2$ (mmol) | Phen (mmol) | *t*-BuOK (mmol) | toluene (mL) |
|---|---|---|---|---|---|---|
| Run 1 | 0.2 | 0.4 | 0.02 | 0.1 | 0.2 | 2.0 |

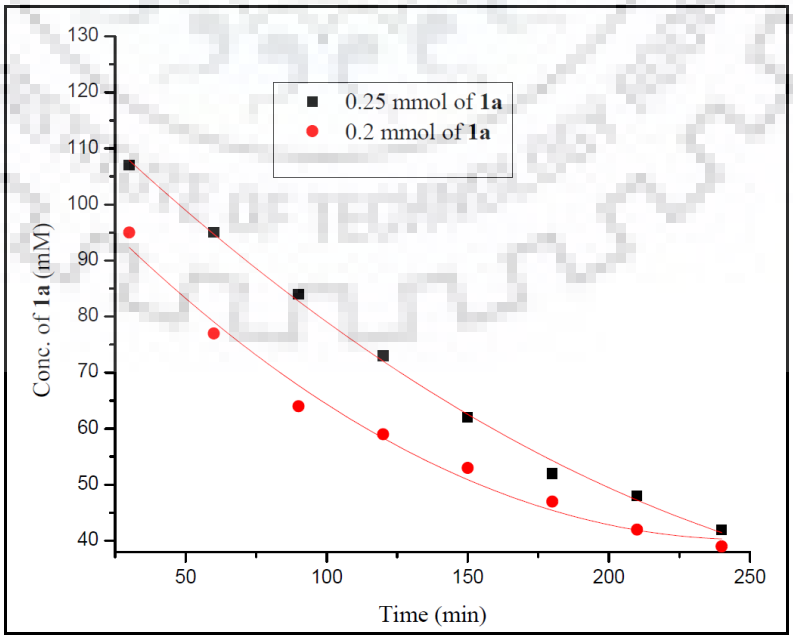
| Sl. No. | Time (min) | Concentration of **1a** (mM) |
|---|---|---|
| 1 | 30 | 95 |
| 2 | 60 | 77 |
| 3 | 90 | 64 |
| 4 | 120 | 59 |
| 5 | 150 | 53 |
| 6 | 180 | 47 |
| 7 | 210 | 42 |
| 8 | 240 | 39 |

Run 2: Reaction was carried out in 2 mL of toluene and yield was calculated by GC

| No. | **1a** (mmol) | **2a** (mmol) | $NiBr_2$ (mmol) | Phen (mmol) | *t*-BuOK (mmol) | toluene (mL) |
|---|---|---|---|---|---|---|
| Run 2 | 0.25 | 0.5 | 0.025 | 0.125 | 0.25 | 2.0 |

| Sl. No. | Time (min) | Concentration of **1a** (mM) |
|---|---|---|
| 1 | 30 | 107 |
| 2 | 60 | 95 |
| 3 | 90 | 84 |
| 4 | 120 | 73 |
| 5 | 150 | 62 |
| 6 | 180 | 52 |
| 7 | 210 | 48 |
| 8 | 240 | 42 |

Furthermore, we studied the progress of the alkylation reaction and monitored it over time using gas-chromatography. The reaction was interrupted after five hours and the reaction profile indicated the formation of intermediate **3'** occurred at a faster rate, whereas the hydrogenation to **3** was quite slow. These kinetic experiments revealed the crucial role of excess ligands and another equivalent of alcohol in achieving higher product yields. Finally, to determine the rate and order of the reaction, we performed two sets of kinetic studies. First order kinetics with respect to quinaldine **1a** was observed for the α-alkylation of *N*-heteroaromatics, considering a steady state approximation for benzyl alcohol (Scheme 15).




**Scheme 15:** Graphical representation for determination of rate and order of reaction

Considering steady state approximation for benzyl alcohol

From Run 1: Slope = k $[1a]^x$

$-0.248 = k\,[0.2]^x$

From Run 2: Slope = k $[1a]^x$

$-0.316 = k\,[0.25]^x$

$-0.316 / -0.248 = [0.25]^x / [0.2]^x$

$1.27 = [1.25]^x$

$\text{Log}(1.27) = x.\ \text{Log}(1.25)$

$x = 0.103 / 0.097$

$= 1.06 \approx 1$

$\text{Rate} = k\,[1a]^1$

**[4.5] Conclusions:**

In conclusion, we have reported the first Ni-catalyzed functionalization of C($sp^3$)-H bonds in methyl *N*-heteroaromatics using primary alcohols. Easily available, inexpensive Ni-catalysts and 1,10-phenanthroline ligand enables long chain C2-alkylated *N*-heteroaromatics in up to quantitative yields. The catalytic system allows transformations in the presence of reducible functional moieties, such as allylic ethers and alkenes, including unsaturated alcohols. Initial mechanistic studies strongly support the participation of the Ni–H species and the bifunctional nature of the Ni-catalyst. A series of deuterium labeling experiments revealed the involvement of H/D exchange during the progress of the reaction.

**[4.6] Experimental Section:**

**General Experimental Details:** All solvents and reagents were used, as received from the suppliers. TLC was performed on Merck Kiesel gel 60, $F_{254}$ plates with the layer thickness of 0.25 mm. Column chromatography was performed on silica gel (100-200 mesh) using a gradient of ethyl acetate and hexane as mobile phase. $^1$H NMR spectral data were collected at, 400 MHz (JEOL), 500 MHz (Bruker) and $^{13}$C NMR were recorded at 100 MHz. $^1$H NMR spectral data are given as chemical shifts in ppm followed by multiplicity (s- singlet; d- doublet; t- triplet; q- quartet; m- multiplet), number of protons and coupling constants. $^{13}$C NMR chemical shifts are expressed in ppm. Elemental analysis data were recorded in Vario Micro Cube. GC-MS were recorded using Agilent GC Mass Spectrometer. All the

reactions were performed in a close system using Schlenk tube. All nickel salts were purchased from Sigma Aldrich. Nickel(II) bromide (Assay- 98%; CAS Number 13462-88-9; EC Number 236-665-0; Pack Size- No 217891-10G). Potassium *tert*-butoxide was purchased from Avra Synthesis Pvt. Ltd., India. (Purity-98%, CAS No: 865-47-4, Catalog No- ASP2012).

**General procedure for Ni-catalyzed alkylation of methylquinolines with primary alcohols:**

**Procedure A:**

In a 15 mL oven dried Schlenk tube, **1** (0.25 mmol), *t*-BuOK (0.25 mmol), $NiBr_2$ (10 mol%), Phen (50 mol%), and alcohols **2** (0.50 mmol) were added followed by toluene 2.0 mL under an atmosphere of $N_2$ and the reaction mixture was heated at 140 °C for 24 h in close system. The reaction mixture was cooled to room temperature and 3.0 mL of ethyl acetate was added and concentrated *in vacuo*. The residue was purified by column chromatography using a gradient of hexane and ethyl acetate (eluent system) to afford the pure product.

**Procedure B:**

In a 15 mL oven dried Schlenk tube, **1** (0.25 mmol), *t*-BuOK (0.375 mmol), $NiBr_2$ (10 mol%), Phen (50 mol%), and alcohols **2** (0.50 mmol) were added followed by toluene 2.0 mL under an atmosphere of $N_2$ and the reaction mixture was heated at 140 °C for 24 h in close system. The reaction mixture was cooled to room temperature and 3.0 mL of ethyl acetate was added and concentrated *in vacuo*. The residue was purified by column chromatography using a gradient of hexane and ethyl acetate (eluent system) to afford the pure product.

**Procedure C:**

In a 15 mL oven dried Schlenk tube, **1** (0.25 mmol), *t*-BuOK (0.50 mmol), $NiBr_2$ (20 mol%), Phen (100 mol%), and alcohols **2** (1.0 mmol) were added followed by toluene 2.0 mL under an atmosphere of $N_2$ and the reaction mixture was heated at 140 °C for 24 h in close system. The reaction mixture was cooled to room temperature and 3.0 mL of ethyl acetate was added and concentrated *in vacuo*. The residue was purified by column chromatography using a gradient of hexane and ethyl acetate (eluent system) to afford the pure product.

**Procedure D:**

In a 15 mL oven dried Schlenk tube, **1** (0.25 mmol), *t*-BuOK (0.25 mmol), $NiBr_2$ (10 mol%), Phen (50 mol%), and alcohols **2** (0.50 mmol) were added followed by toluene 2.0 mL under an atmosphere of $N_2$ and the reaction mixture was heated at 130 °C for 24 h in close system. The reaction mixture was cooled to room temperature and 3.0 mL of ethyl acetate was added and concentrated *in vacuo*. The residue was purified by column chromatography using a gradient of hexane and ethyl acetate (eluent system) to afford the pure product.

**Synthesis and characterization of 2-(4-ethylphenethyl)quinoline (4)**:

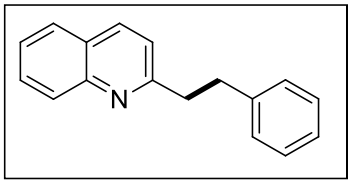
Following the general procedure D, the title compound **4** was isolated as light brown oil using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (95%, 62 mg). All the compounds were characterized by $^1$H-NMR, $^{13}$C-NMR, HRMS (ESI-TOF) and the results are shown in spectral data. For an example, all the spectral data of compound **4** are explained here.

**$^1$H NMR**. The seven aromatic region protons are well separated and appeared as d, dd, ddd and m at 8.06 (dd, *J* = 13.6, 8.5 Hz, 2H), 7.78 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.70 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.49 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H). The two multiplet peaks at 3.30-3.26 (m, 2H), 3.14-3.10 (m, 2H) ppm belong to $-CH_2$ proton β and ɣ to the nitrogen of quinaldine respectively. The quartet peak at 2.62 (q, *J* = 7.6 Hz, 2H) and triplet peak at 1.23 (t, *J* = 7.6 Hz, 3H) belong to two $-CH_2$ and three $-CH_3$ protons of ethyl substituent group respectively (Figure 2a).

**$^{13}$C NMR**. The peaks at 28.55, 15.74 ppm belong to $-CH_2$ and $-CH_3$ carbons respectively; and the peaks at 41.22 and 35.67 ppm belong to $-CH_2$ carbon β and ɣ to the nitrogen of quinaldine respectively. The peaks at 162.08, 148.06, 141.98, 138.80, 136.33, 129.49, 128.95, 128.53, 127.98, 127.62, 126.90, 125.87 and 121.67 belong to aromatic benzene ring carbons.

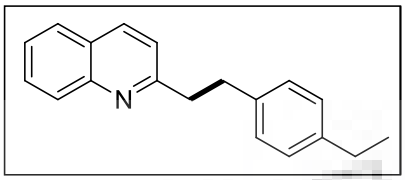
**Analytical data for all products:**

**2-Phenethylquinoline (3)**[9b]**:** Following the general procedure D the title compound was isolated as a light brown oil (Yield 97%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.08-8.02 (m, 2H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.69 (ddt, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.51-7.47 (m, 1H), 7.30-7.17

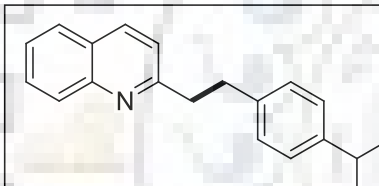


(m, 6H), 3.32-3.27 (m, 2H), 3.18-3.14 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.91, 148.08, 141.61, 136.30, 129.49, 128.96, 128.61, 128.48, 127.61, 126.90, 126.08, 125.88, 121.65, 41.07, 36.02.

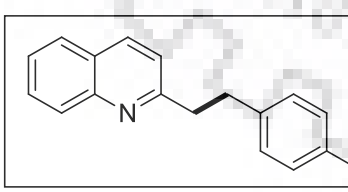
**2-(4-Ethylphenethyl)quinoline (4):** Following the general procedure D the title compound was isolated as a light brown oil (Yield 95%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (dd, $J$ = 13.6, 8.5 Hz, 2H), 7.78 (dd, $J$ = 8.1, 1.1 Hz, 1H), 7.70 (ddd, $J$ = 8.4, 6.9, 1.4 Hz, 1H), 7.49 (ddd, $J$ = 8.0, 6.9, 1.1 Hz, 1H), 7.25 (d, $J$ = 8.4 Hz, 1H), 7.18 (d, $J$ = 8.0 Hz, 2H), 7.12 (d, $J$ = 7.9 Hz, 2H), 3.30-3.26 (m, 2H), 3.14-3.10 (m, 2H), 2.62 (q, $J$ = 7.6 Hz, 2H), 1.23 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.08, 148.06, 141.98, 138.80, 136.33, 129.49, 128.95, 128.53, 127.98, 127.62, 126.90, 125.87, 121.67, 41.22, 35.67, 28.55, 15.74. Elemental Analysis: Calculated C, 87.31; H, 7.33; N, 5.36; Found C, 86.42; H, 7.27; N, 4.08.



**2-(4-Isopropylphenethyl)quinoline (5):** Following the general procedure A the title compound was isolated as a light brown oil (Yield 78%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.07 (dd, $J$ = 15.3, 8.4 Hz, 2H), 7.78 (dd, $J$ = 8.1, 1.1 Hz, 1H), 7.70 (ddd, $J$ = 8.4, 6.9, 1.5 Hz, 1H), 7.49 (ddd, $J$ = 8.1, 7.0, 1.1 Hz, 1H), 7.26 (d, $J$ = 8.4 Hz, 1H), 7.21-7.19 (m, 2H), 7.17- 7.15 (m, 2H), 3.31-3.27 (m, 2H), 3.15-3.11(m, 2H), 2.93-2.85 (m, 1H), 1.25 (d, $J$ = 6.9 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.11, 148.08, 146.63, 138.95, 136.33, 129.49, 128.97, 128.50, 127.63, 126.90, 126.55, 125.87, 121.66, 41.20, 35.66, 33.80, 24.17; Elemental Analysis: Calculated C, 87.23; H, 7.69; N, 5.09; Found C, 88.02; H, 7.19; N, 4.38.



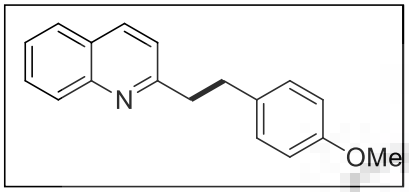
**2-(4-Methylphenethyl)quinoline (6)**[9b]**:** Following the general procedure A the title compound was isolated as a light brown oil (Yield 95%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (dd, $J$ = 12.3, 8.5 Hz, 2H), 7.77 (dd, $J$ = 8.1, 1.1 Hz, 1H), 7.69 (ddd, $J$ = 8.4, 6.9, 1.4 Hz, 1H), 7.49 (ddd, $J$ = 8.0, 7.0, 1.1 Hz, 1H), 7.25-7.22 (m, 1H), 7.15 (d, $J$ = 8.0 Hz, 2H), 7.09 (d, $J$ = 8.1 Hz, 2H), 3.29- 3.25 (m, 2H), 3.13-3.09 (m, 2H), 2.31 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.05, 148.06, 138.52, 136.34, 135.54, 129.49, 129.18, 128.94, 128.48, 128.02, 127.62, 126.89, 121.68, 41.22, 35.63, 21.13.



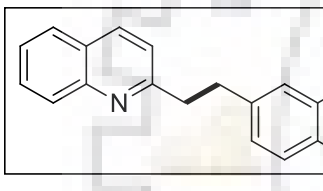
**2-(2-Methylphenethyl)quinoline (7)**[9b]**:** Following the general procedure A the title compound was isolated as a light brown oil (Yield 94%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (dd, $J$ = 13.9, 8.5 Hz, 2H),

7.78 (d, *J* = 8.1 Hz, 1H), 7.72-7.68 (m, 1H), 7.50 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.25-7.10 (m, 5H), 3.27-3.23 (m, 2H), 3.15- 3.11 (m, 2H), 2.34 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.08, 148.09, 139.77, 136.32, 136.12, 130.29, 129.50, 128.98, 128.95, 127.62, 126.89, 126.24, 126.12, 125.90, 121.61, 39.78, 33.35, 19.46.

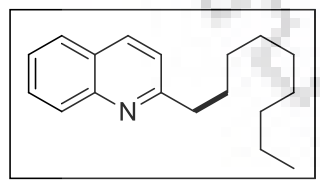
**2-(4-Methoxyphenethyl)quinoline (8)**[9b]**:** Following the general procedure A the title compound was isolated as a light brown oil (Yield 96%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.07-8.02 (m, 2H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.69 (ddt, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.48 (ddt, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.22 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 6.81 (dd, *J* = 8.7, 0.7 Hz, 2H), 3.77 (s, 3H), 3.27-3.23 (m, 2H), 3.10-3.06 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.03, 157.94, 148.04, 136.30, 133.65, 129.52, 129.48, 128.91, 127.63, 126.87, 125.85, 121.72, 113.86, 55.33, 41.38, 31.05.




**2-(2-(Naphthalen-2-yl)ethyl)quinoline (9)**[9d]**:** Following the general procedure A the title compound was isolated as a light brown oil (Yield 84%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.18 (d, *J* = 8.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.06-8.02 (m, 1H), 7.89-7.85 (m, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.75-7.69 (m, 2H), 7.55-7.52 (m, 3H), 7.39-7.32 (m, 2H), 7.19 (dd, *J* = 12.8, 10.3 Hz, 1H), 3.64 -3.60 (m, 2H), 3.44-3.40 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.05, 148.08, 137.61, 136.39, 135.19, 133.36, 131.88, 129.57, 128.92, 127.67, 126.94, 126.24, 126.04, 125.95, 125.68, 125.62, 124.90, 123.85, 121.74, 40.16, 33.16.



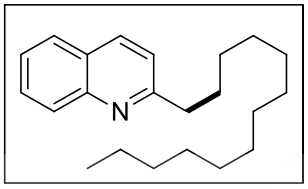

**2-Nonylquinoline (10)**[9b]**:** Following the general procedure A the title compound was isolated as a pale yellow oil (Yield 60%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.66 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.00-7.97 (m, 1H), 7.27-7.25 (m, 2H), 7.14 (d, *J* = 8.2 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 2.90 (t, *J* = 6.4 Hz, 2H), 1.44-1.40 (m, 2H), 1.30-1.25 (m, 12H), 0.85 (t, *J* = 8 Hz, 3H); GC-MS (EI) m/z = 255.1.



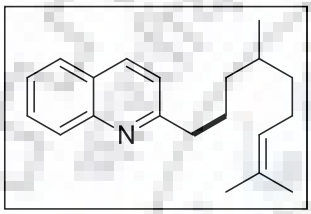

**2-Undecylquinoline (11)**[15]**:** Following the general procedure A the title compound was isolated as a pale yellow oil (Yield 48%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.66 (dd, *J* = 4.2, 1.7 Hz, 1H), 7.99 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.29-7.25 (m, 2H), 7.14 (d, *J* = 8.2 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 2.90 (t, *J* = 6.4 Hz, 2H), 1.46-1.40 (m, 2H), 1.32-1.25 (m, 16H), 0.85 (t, *J* = 8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.30, 147.04, 140.75,

135.99, 130.72, 129.15, 127.44, 120.63, 113.19, 40.60, 31.99, 30.99, 30.16, 26.97, 22.77, 14.22.

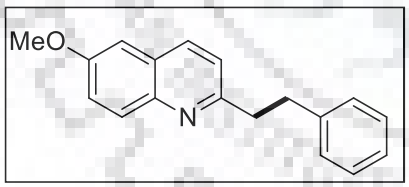
**2-Dodecylquinoline (12)**[9b]**:** Following the general procedure A the title compound was isolated as a pale yellow oil (Yield 38%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.66 (dd, $J$ = 4.2, 1.7 Hz, 1H), 7.99 (dd, $J$ = 8.3, 1.7 Hz, 1H), 7.30-7.25 (m, 2H), 7.14 (d, $J$ = 8.2 Hz, 1H), 6.96 (d, $J$ = 8.2 Hz, 1H), 2.91 (t, $J$ = 6.4 Hz, 2H), 1.46-1.41 (m, 2H), 1.27-1.24 (m, 20H), 0.85 (t, $J$ = 8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.80, 147.02, 140.74, 136.00, 130.88, 129.16, 127.44, 120.63, 113.18, 40.60, 32.02, 30.99, 30.17, 29.75, 29.46, 26.97, 22.79, 14.23.



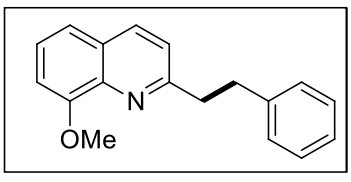
**2-(4,8-Dimethylnon-7-en-1-yl)quinoline (13):** Following the general procedure A the title compound was isolated as a pale yellow oil (Yield 47%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.70 (dd, $J$ = 4.1, 1.4 Hz, 1H), 8.03 (dd, $J$ = 8.2, 1.4 Hz, 1H), 7.33-7.29 (m, 2H), 7.18 (d, $J$ = 8.2 Hz, 1H), 7.00 (d, $J$ = 8.2 Hz, 1H), 5.95 (t, $J$ = 6.8 Hz, 1H), 3.57-3.54 (m, 2H), 2.95 (t, $J$ = 6.3 Hz, 2H), 2.20 (s, 3H), 2.09 (dd, $J$ = 11.6, 6.0 Hz, 2H), 1.71-1.61 (m, 5H), 1.28 (s, 3H), 0.90 (dd, $J$ = 11.6, 5.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 146.94, 140.70, 137.53, 135.85, 129.05, 127.38, 121.24, 120.52, 116.57, 113.10, 41.28, 31.92, 30.88, 29.69, 29.35, 27.04, 22.68, 21.84, 14.09. Elemental Analysis: Calculated C, 85.35; H, 9.67; N, 4.98; Found C, 84.16; H, 9.91; N, 5.19.



**6-Methoxy-2-phenethylquinoline (14)**[9d]**:** Following the general procedure B the title compound was isolated as a light brown oil (Yield 62%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.95 (t, $J$ = 9.0 Hz, 2H), 7.34 (dd, $J$ = 9.1, 2.9 Hz, 1H), 7.29-7.16 (m, 6H), 7.04 (d, $J$ = 2.8 Hz, 1H), 3.91 (s, 3H), 3.26-3.22 (m, 2H), 3.14-3.10 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 157.64, 155.68, 142.44, 140.03, 133.41, 128.66, 126.90, 126.75, 126.05, 124.32, 120.27, 120.16, 103.64, 53.89, 39.07, 34.40.

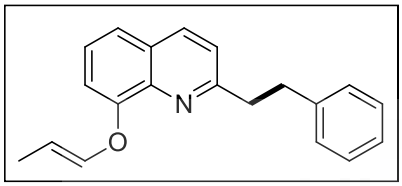


**8-Methoxy-2-phenethylquinoline (15)**[9e]**:** Following the general procedure B the title compound was isolated as a light brown oil (Yield 92%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01 (d, $J$ = 8.4 Hz, 1H), 7.44-7.38 (m, 1H), 7.35 (dd, $J$ = 8.1, 0.9 Hz, 1H), 7.33-7.23 (m, 5H), 7.19 (ddd, $J$ = 8.5, 5.1, 2.0 Hz, 1H), 7.04 (d, $J$ = 7.5 Hz, 1H),

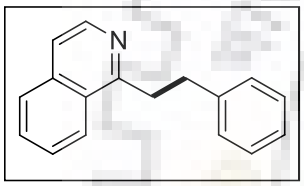


4.08 (s, 3H), 3.38-3.34 (m, 2H), 3.17-3.13 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 157.65, 151.79, 138.32, 136.57, 132.86, 125.22, 125.08, 124.67, 122.65, 118.66, 116.20, 111.69, 104.54, 52.84, 37.68, 32.76.

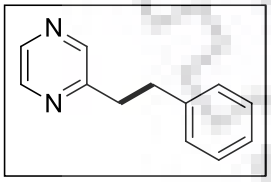
**8-(Allyloxy)-2-phenethylquinoline (16):** Following the general procedure B the title compound was isolated as a pale yellow oil (Yield 60%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01 (d, $J$ = 8.5 Hz, 1H), 7.45-7.34 (m, 3H), 7.28-7.25 (m, 2H), 7.22-7.10 (m, 2H), 7.09-7.04 (m, 2H), 6.57-6.54 (m, 1H), 5.11-5.04 (m, 1H), 3.38-3.34 (m, 2H), 3.20-3.17 (m, 2H), 1.87-1.83 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.30, 153.13, 141.83, 141.44, 139.84, 136.16, 129.49, 128.70, 128.45, 128.16, 126.01, 121.40, 112.72, 111.30, 109.68, 40.88, 35.70, 9.94; Elemental Analysis: Calculated C, 83.01; H, 6.62; N, 4.84; Found C, 82.36; H, 6.11; N, 4.08.



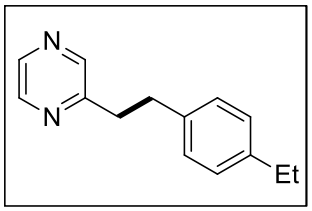

**1-Phenethylisoquinoline (17)**[16]**:** Following the general procedure A the title compound was isolated as a light brown oil (Yield 80%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.48 (d, $J$ = 5.7 Hz, 1H), 8.15 (d, $J$ = 8.5 Hz, 1H), 7.82 (d, $J$ = 8.2 Hz, 1H), 7.66 (ddd, $J$ = 8.2, 6.9, 1.1 Hz, 1H), 7.58 (ddd, $J$ = 8.2, 6.9, 1.3 Hz, 1H), 7.53 (d, $J$ = 5.7 Hz, 1H), 7.32 (d, $J$ = 4.3 Hz, 4H), 7.25-7.20 (m, 1H), 3.63-3.58 (m, 2H), 3.23-3.18 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.95, 139.89, 134.18, 127.72, 126.40, 126.38, 125.35, 125.00, 124.88, 123.97, 122.98, 117.32, 35.13, 33.38.



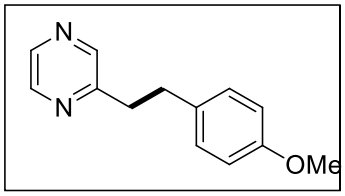

**2-Phenethylpyrazine (18)**[17]**:** Following the general procedure A the title compound was isolated as a light brown oil (Yield 92%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.50 (dd, $J$ = 2.5, 1.6 Hz, 1H), 8.38 (d, $J$ = 2.6 Hz, 1H), 8.34 (d, $J$ = 1.5 Hz, 1H), 7.29-7.23 (m, 2H), 7.21-7.14 (m, 3H), 3.14-3.03 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.83, 144.83, 144.75, 144.25, 144.16, 142.48, 142.39, 140.83, 128.54, 126.36, 37.32, 35.47.



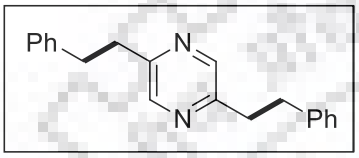

**2-(4-Ethylphenethyl)pyrazine (19)**[17]**:** Following the general procedure B the title compound was isolated as a light brown oil (Yield 71%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.57 (s, 1H), 8.42 (d, $J$ = 15.6 Hz, 2H), 7.46-7.43 (m, 2H), 7.13-7.10 (m, 2H), 3.14-3.11 (m, 2H), 3.05-3.01 (m, 2H), 2.60 (q, $J$ = 7.6 Hz, 2H), 1.21 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.65, 144.81, 144.20, 142.28, 140.97, 137.90, 130.33, 128.43, 37.40, 35.15, 28.52, 15.72.



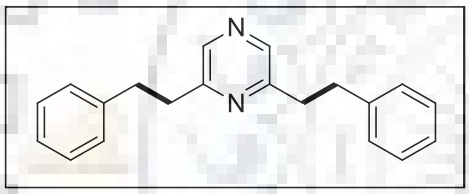
**2-(4-Methoxyphenethyl)pyrazine (20)**[9a]**:** Following the general procedure B the title compound was isolated as a light brown oil (Yield 55%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.55-8.52 (m, 1H), 8.42 (d, $J$ = 2.4 Hz, 1H), 8.37 (d, $J$ = 1.0 Hz, 1H), 7.10 (d, $J$ = 8.5 Hz, 2H), 6.84 (d, $J$ = 8.6 Hz, 2H), 3.80 (s, 3H), 3.13-3.10 (m, 2H), 3.05-3.02 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.06, 156.93, 144.81, 144.19, 142.36, 132.83, 129.44, 113.95, 55.33, 37.64, 34.67.



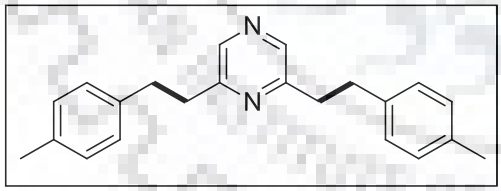

**2,5-Diphenethylpyrazine (22)**[9a]**:** Following the general procedure A the title compound was isolated as a colorless solid (Yield 52%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.34 (s, 2H), 7.33-7.29 (m, 4H), 7.21 (dd, $J$ = 11.3, 7.2 Hz, 6H), 3.19-3.14 (m, 4H), 3.13-3.08 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.66, 142.86, 140.91, 128.61, 128.53, 126.31, 37.11, 35.61.




**2,6-Diphenethylpyrazine (23):** Following the general procedure C the title compound was isolated as a colorless oil (Yield 38%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.14 (s, 2H), 7.27 (dd, $J$ = 11.1, 3.9 Hz, 4H), 7.18 (dd, $J$ = 12.7, 7.2 Hz, 6H), 3.13-3.03 (m, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.67, 141.77, 140.94, 128.46, 128.44, 126.15, 37.09, 35.44. Elemental Analysis: Calculated C, 83.30; H, 6.99; N, 9.71; Found C, 82.79; H, 6.57; N, 9.01.




**2,6-bis(4-Methylphenethyl)pyrazine (24):** Following the general procedure C the title compound was isolated as a colorless oil (Yield 30%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.13 (s, 2H), 7.07-7.04 (m, 8H), 3.10-3.06 (m, 4H), 3.03-2.99 (m, 4H), 2.30 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.76, 141.76, 137.86, 135.59, 129.12, 128.34, 37.27, 35.06, 21.00. Elemental Analysis: Calculated C, 83.50; H, 7.64; N, 8.85; Found C, 84.18; H, 6.95; N, 7.98.



**[4.8] Spectra of selected compounds**:

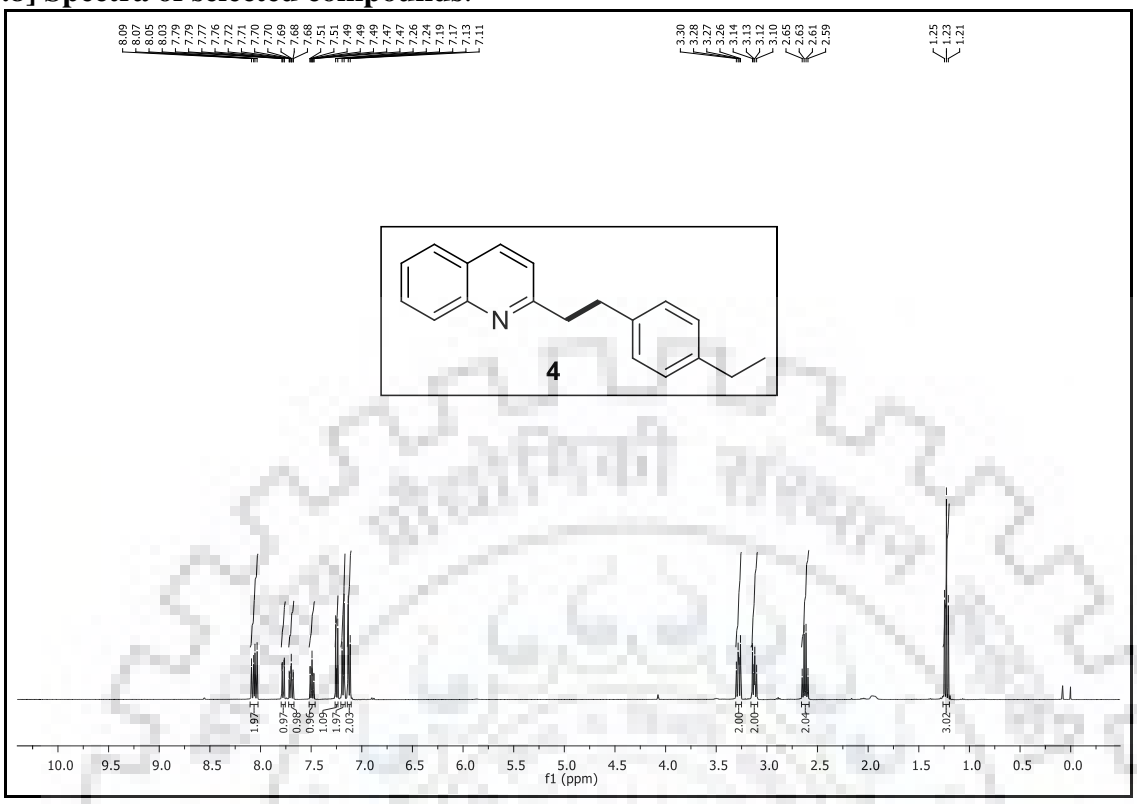



**Fig 1a:** $^{1}H$ NMR ($CDCl_3$, 400 MHz) spectrum of compound **4**

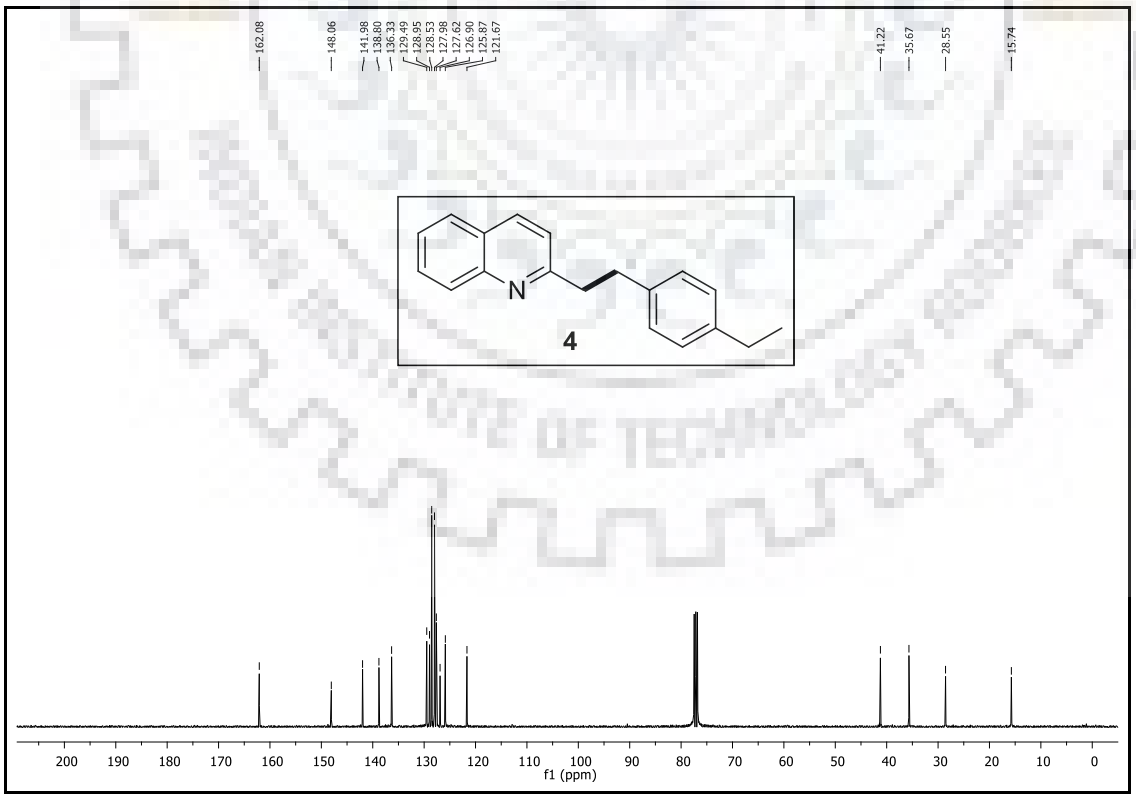



**Fig 1b:** $^{13}C$ NMR ($CDCl_3$, 100 MHz) spectrum of compound **4**

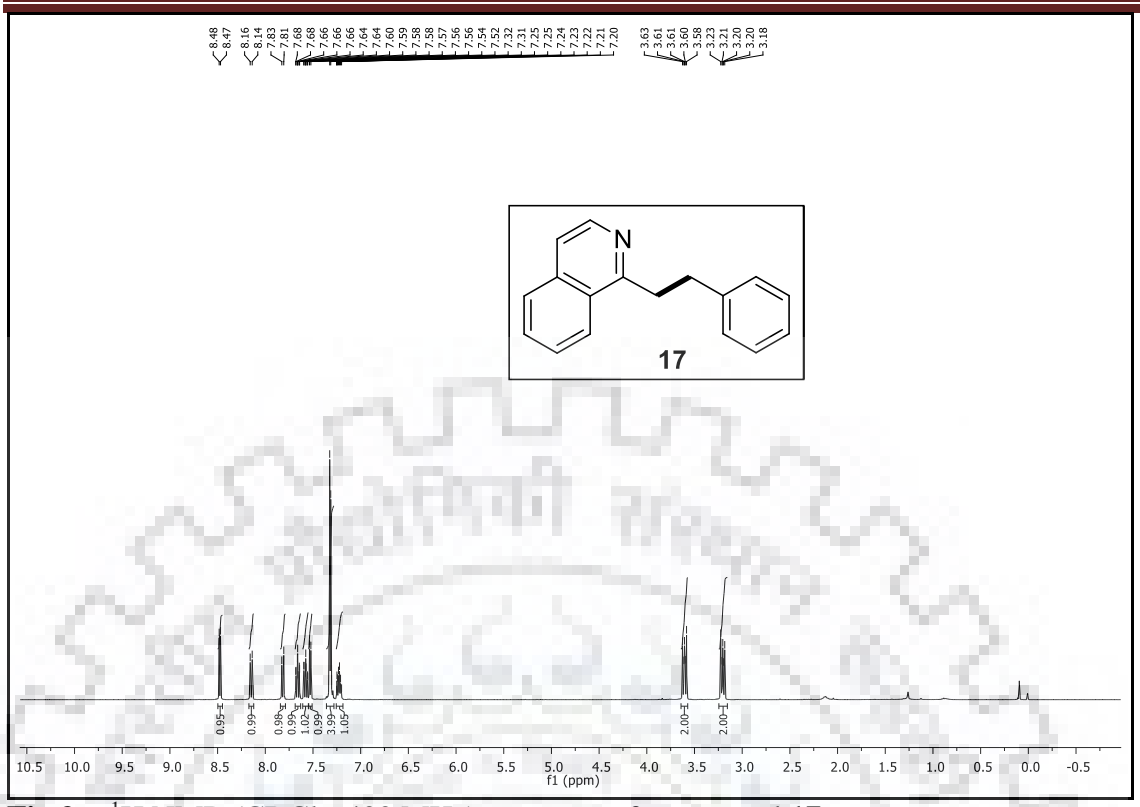



**Fig 2a:** $^{1}$H NMR ($CDCl_3$, 400 MHz) spectrum of compound **17**

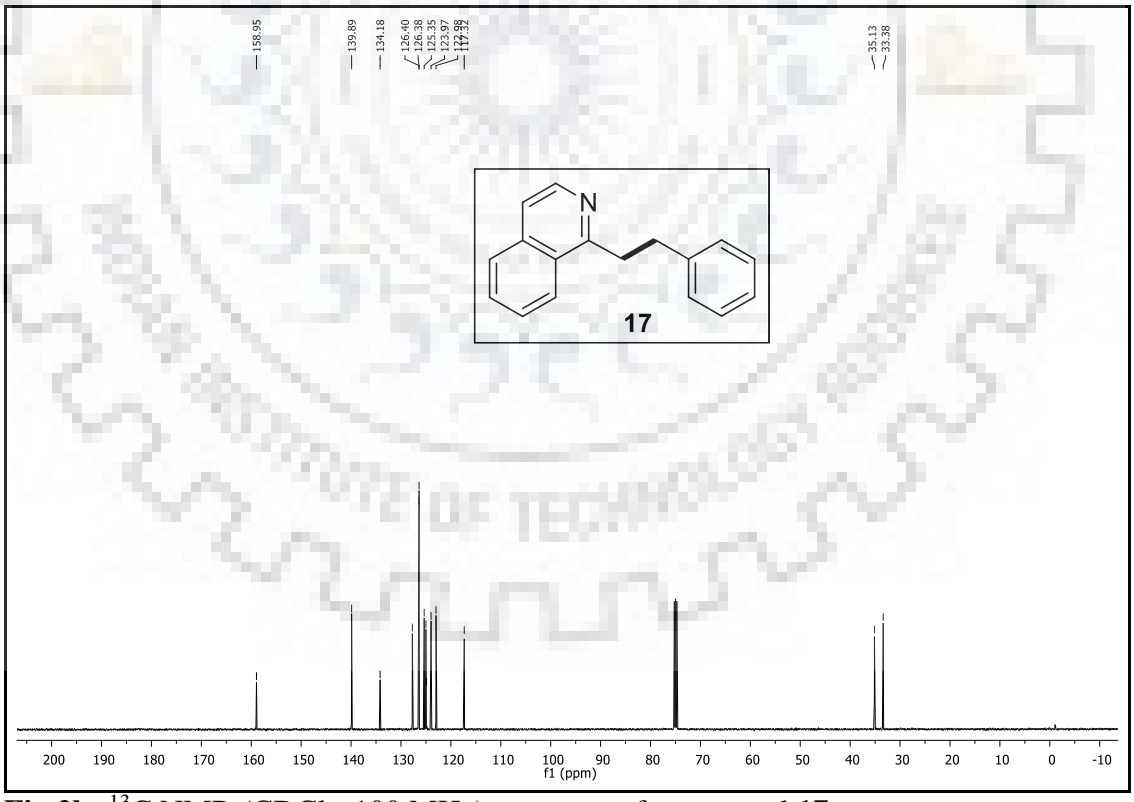



**Fig 2b:** $^{13}$C NMR ($CDCl_3$, 100 MHz) spectrum of compound **17**

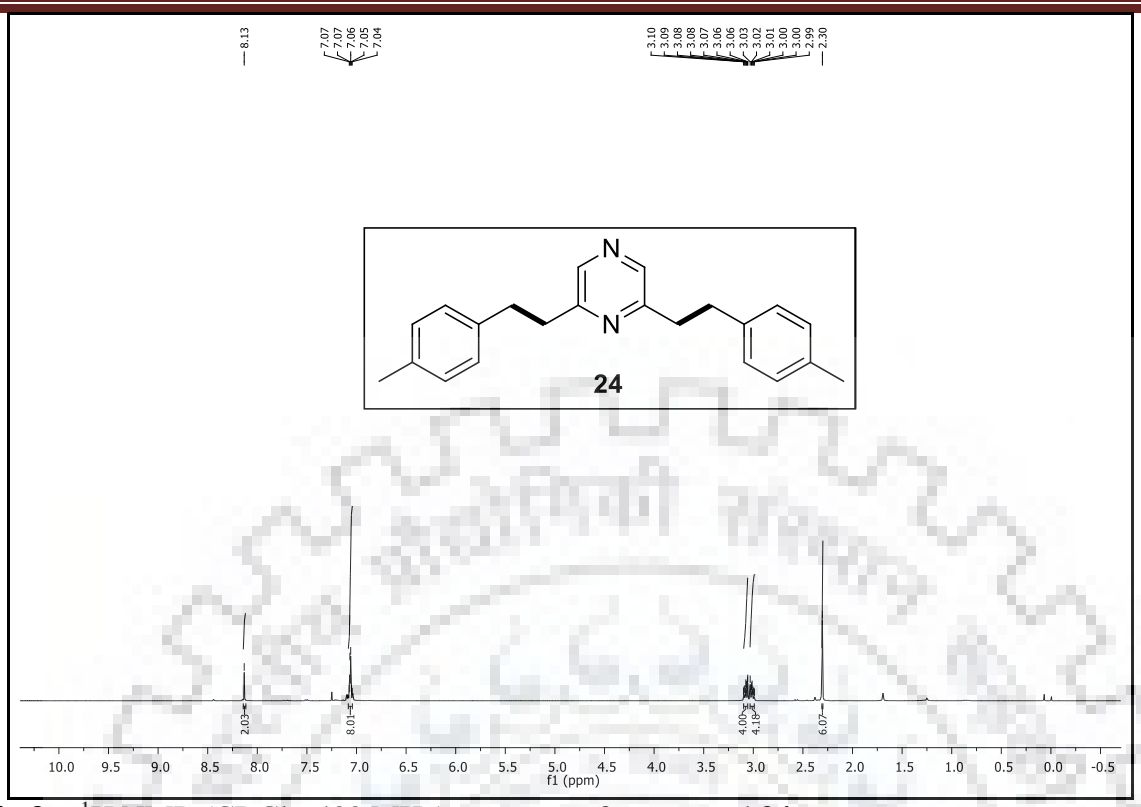



**Fig 3a:** $^{1}$H NMR ($CDCl_3$, 400 MHz) spectrum of compound **24**

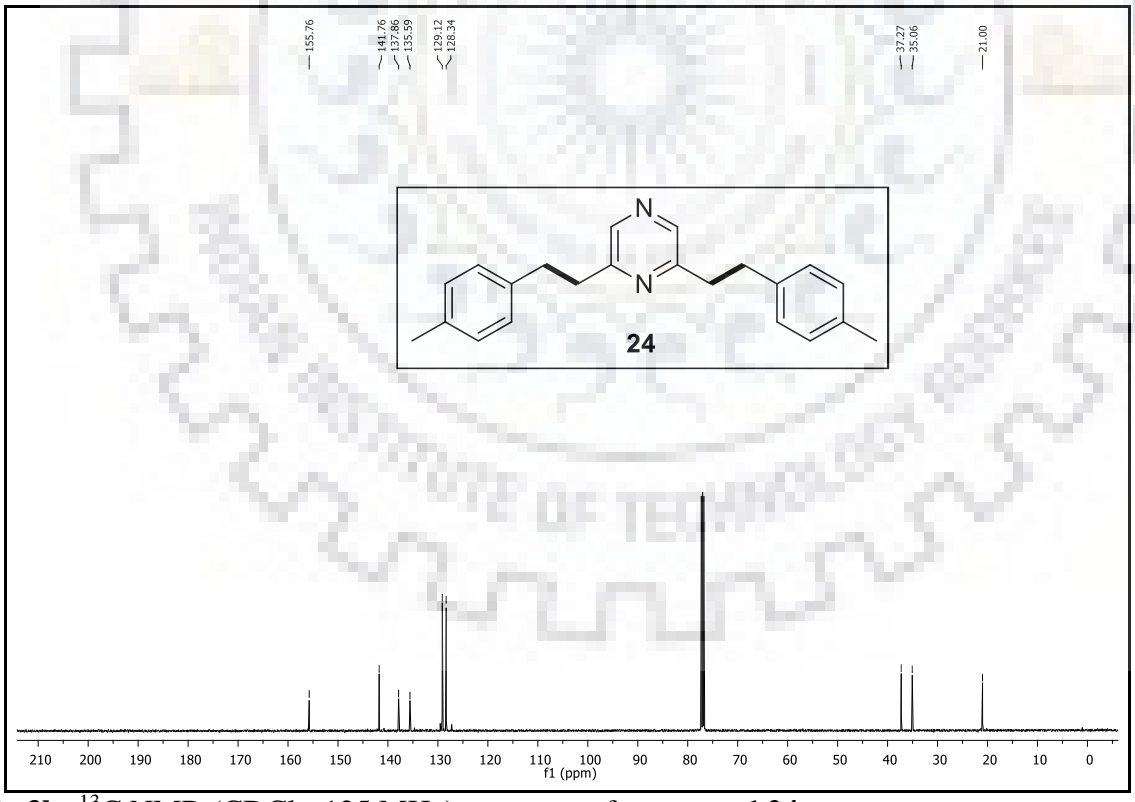
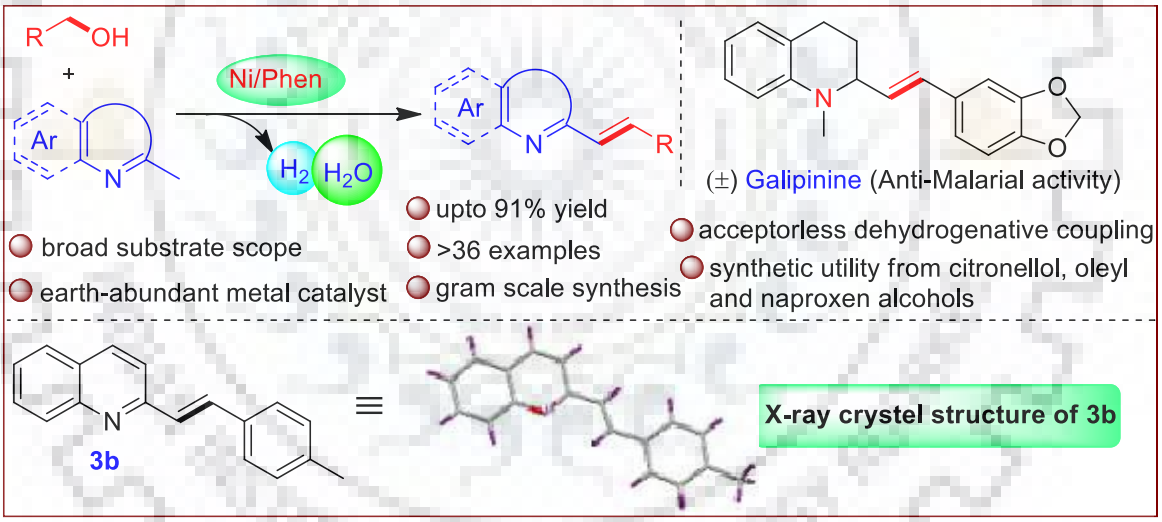



**Fig 3b:** $^{13}$C NMR ($CDCl_3$, 125 MHz) spectrum of compound **24**

## Chapter-5: Section-A: Nickel-catalyzed dehydrogenative alkylation of methyl *N*-heteroaromatics with alcohols

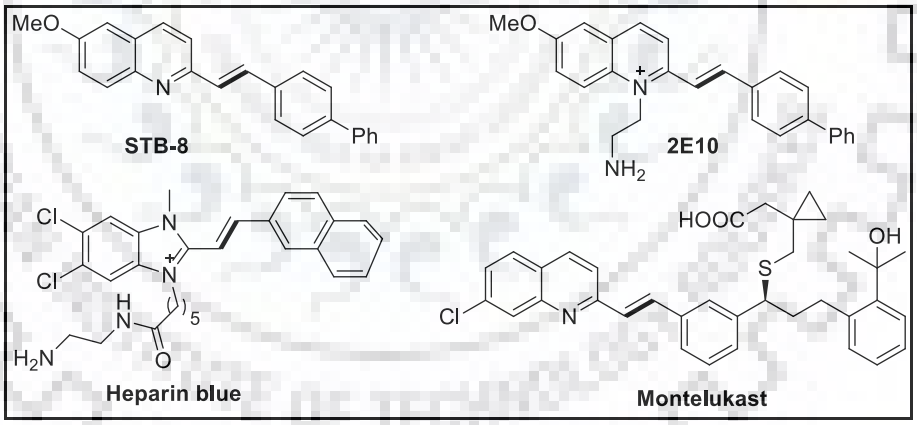
We have demonstrated catalytic α-olefination of 2-methylheteroarenes with primary alcohols *via* dehydrogenative coupling. A simple nickel catalyst system stabilized by readily available nitrogen ligand enables a series of interesting *E*-configured vinylarenes (X-ray crystal-structure analysis) in good to excellent yields with olefin/alkane selectivity of >20:1. Hydrogen and water are generated as byproducts and rendering the process environmentally benign.




*Chem. Commun.* **2019**, 55, 7530-7533

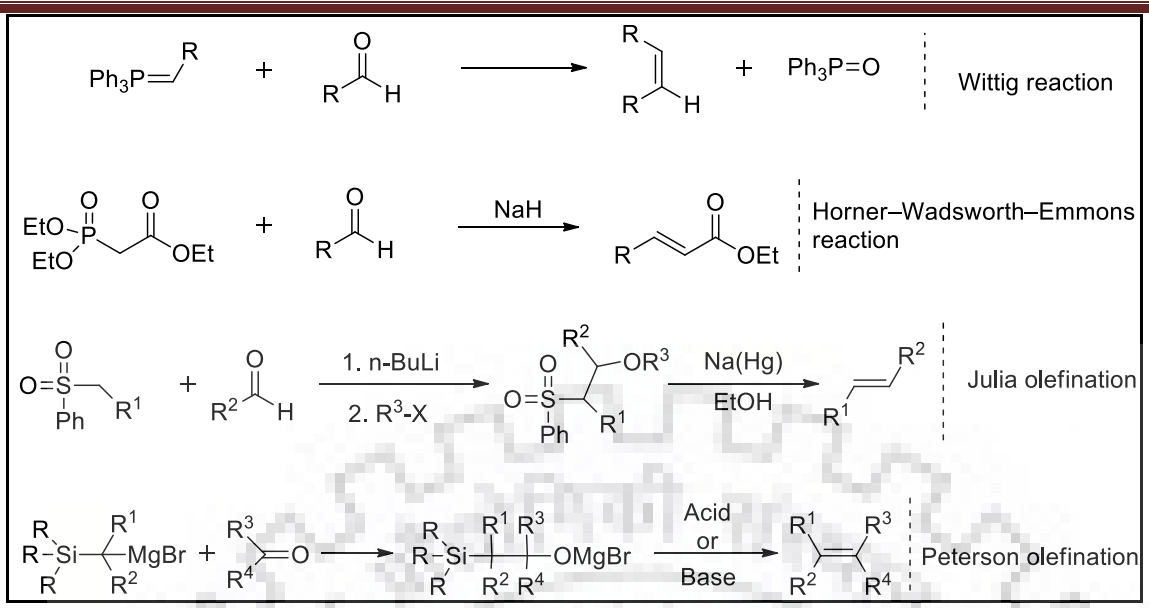
## [5A.1] Introduction:

Olefins, in particular stereo-selective conjugated *N*-heteroarenes are extensively used as intermediates for the synthesis of bulk and specialty chemicals, pharmaceuticals, agrochemicals and displayed important biological activities.[1-4] Moreover, conjugated styryl derivatives find applications as organic light emitting diodes, conducting polymers and in material chemistry (Scheme 1).[5] Designing methods for *E*-selective synthesis of di-substituted olefins is a difficult task and poses new challenges for several reasons.[1] There are a number of classical approaches for the synthesis of stereo-selective alkenes, but most of these suffers from key shortfalls: (i) association of appropriate carbonyl functionality to control the stereo-chemical outcomes; (ii) strong basic or acidic reaction conditions; (iii) lengthy sequences; (iv) generation of stoichiometric waste and (v) often selection of appropriate leaving groups (Wittig reactions, Horner-Wadsworth-Emmons reaction, Julia olefination, Peterson olefination etc.) are crucial to obtain the desired stereo-selective olefins (Scheme 2).[2] Additionally, precious-metal catalyzed Suzuki or Heck couplings and olefin metathesis continues to be efficient technologies for the synthesis of styryl derivatives as well.[3]




**Scheme 1:** Some important bioactive molecules containing olefinated heteroarenes

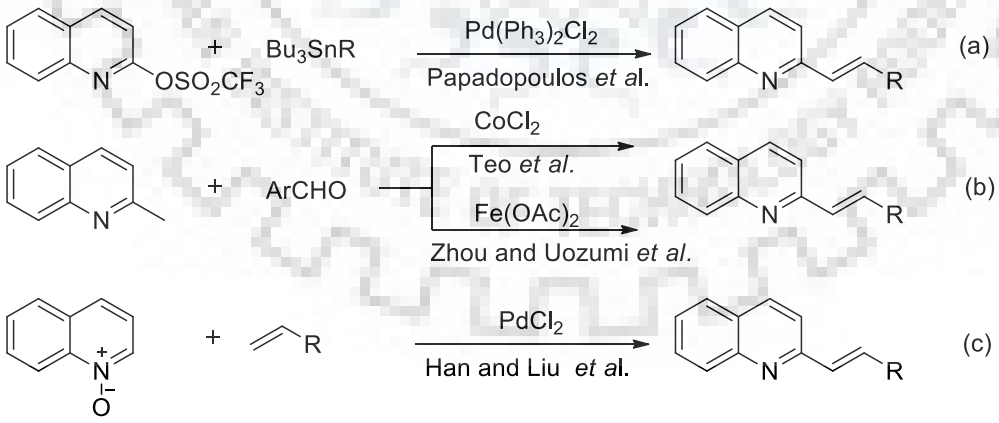
Since last few decades, rare noble metals enabled and shaped the catalytic technologies with myriad applications using acceptorless dehydrogenative couplings (ADCs) of alcohols.[6] However, use of earth abundant and inexpensive metal-catalysts (Fe, Mn, Ni and Co) for such applications and to explore new reactivities are highly desirable.[7] Arguably, significant progress has been achieved using non-noble metal-complexes in various (de)hydrogenative coupling reactions.[8]




**Scheme 2:** Classical methodologies for the synthesis of olefins

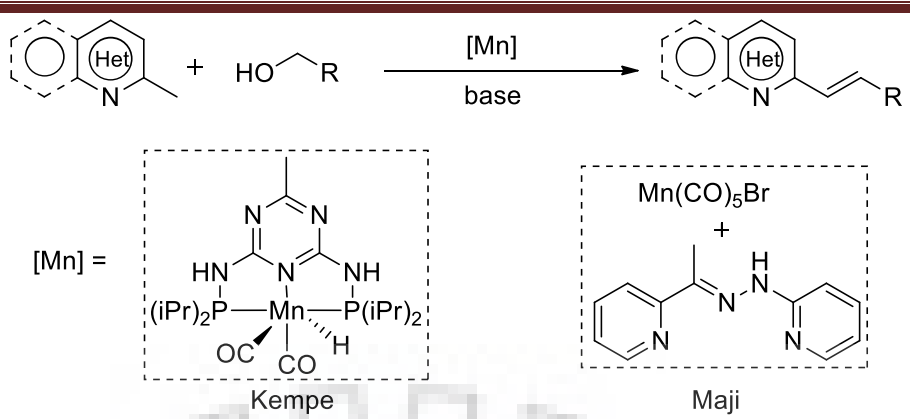
**[5A.2] Brief literature survey for metal-catalyzed olefination of methyl *N*-heteroaromatics:**

In 1989, Papadopoulos reported the synthesis of olefinated heteroarenes *via* coupling of heteroaromatic triflates with organostannanes in presence of palladium catalyst (Scheme 3a).[17a] Later on, Teo (Co-catalyst),[17b] Zhou and Uozumi (Fe-catalyst)[17c] also developed a direct route for the synthesis of styryl derivatives from aldehydes (Scheme 3b). In 2016, Han and Liu demonstrated the palladium-catalyzed coupling of activated quinoline *N*-oxide with olefins (Scheme 3c).[17d]




**Scheme 3:** Metal-catalyzed synthesis of olefins

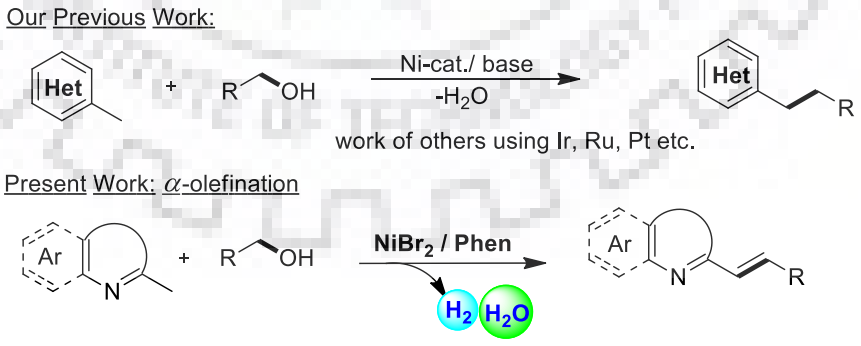
Recently, earth-abundant manganese-catalyzed olefination of methyl *N*-heteroarenes with readily available alcohols with excellent *E*-stereoselectivity was reported (Scheme 4).[14]




**Scheme 4:** Mn-catalyzed olefination of methyl *N*-heteroarenes

**[5A.3] Aim of the Present Work:**

Indeed, among others, nickel offers attractive sustainable alternative to precious metals for ADC reactions. Till date, nickel complexes have been successfully used for various C-C and C-N bond formations.[9] We reported *N*-alkylation of amines and amides with alcohols using a simple nickel-catalyst *via* hydrogen borrowing strategy.[10] Subsequently, others have also reported nickel-catalyzed coupling of alcohols for various sustainable transformations.[11] Recently, we demonstrated unprecedented nickel catalyst system for synthesis of *N*-heterocycles and α,α-di-substituted branched ketones using renewable alcohols.[12] Very recently, we have also developed alcohols based alkylation of weak C-H bonds in methyl substituted *N*-heteroarenes to chain elongated $C_2$-alkylated *N*-heteroarenes;[13] and become interested for the nickel-catalyzed dehydrogenative alkylation or *α*-olefination of alkyl substituted *N*-heteroarenes with alcohols (Scheme 5).




**Scheme 5:** Ni-catalyzed alkylation and *α*-olefination using alcohols

**[5A.4] Results and discussion:**

Considering the challenges, we wondered whether a simple nickel catalyst in combination with commercially available inexpensive nitrogen ligands could be beneficial to achieve

higher selectivity for such α-olefination of alkyl substituted *N*-heteroarenes with alcohols. Therefore, we systematically investigated the reactions between 2-methylquinoline **1a** with benzylalcohol **2a** to (*E*)-2-styrylquinoline **3**. Primarily, five different Ni-pre-catalysts having variable oxidation states were employed and resulted in up to 65% conversion to **3** (Table 1).

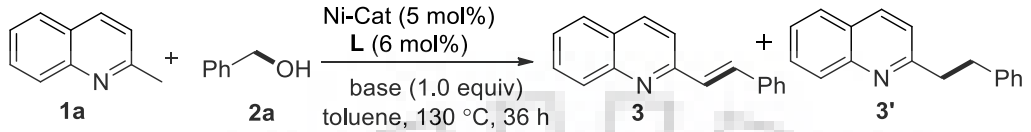


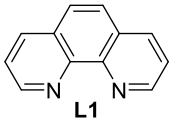
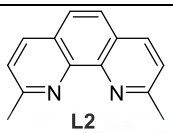
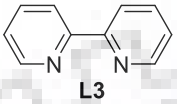
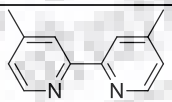
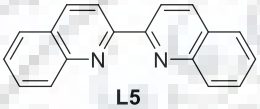
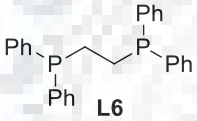
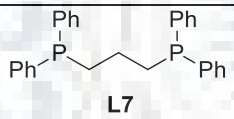
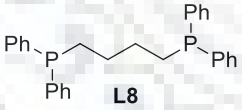
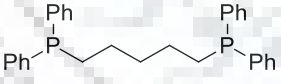
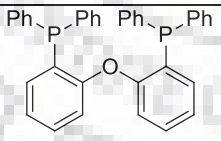
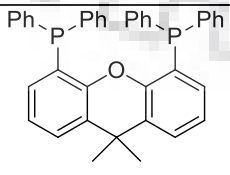
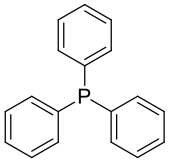

**Table 1**: Screening of catalyst [a]

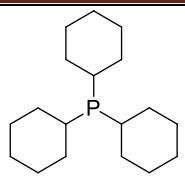
| Entry | **Ni-Catalyst** | GC-MS Conversion **3** (%) | Ratio (**3 / 3'**) |
|---|---|---|---|
| 1 | $NiCl_2$ | 49 | 1.5 : 1 |
| **2** | **$NiBr_2$** | **65** | **13 : 1** |
| 2 | $Ni(acac)_2$ | 21 | 1.3 : 1 |
| 3 | $NiCl_2(DME)$ | 49 | 5.4 : 1 |
| 4 | $Ni(COD)_2$ | 21 | 3.5 : 1 |

Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (0.50 mmol), **Ni-Cat. (5.0 mol%)**, Phen (6.0 mol%), *t*-BuOK (0.25 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 130 ºC oil bath, 36 h reaction time.

Thereafter, applications of various nitrogen and phosphorous-based ligands, **L2-L13** proof inefficient for the olefination process (Table 2). Systematic evaluation for the influence of different bases and solvents were also performed for this transformation and KOH proved quite promising in combination with toluene as solvent (Table 3 and 4). A Ni-catalyst stabilized by 1,10-phenanthroline **L1** resulted 83% yield of **3** with olefin/alkane selectivity of >20:1 (Table 1-6). Notably, control experiments in absence of ligand and nickel catalyst resulted albeit with poor product yield; whereas, in absence of base no α-olefination product was obtained. Further lowering the base and alcohol equivalency results in only moderate product conversion (Table 5 and 7). To our delight, NMR analysis identified as the *E*-selective desired product. GC-MS analysis of the crude reaction mixture detected trace amount of alkylated product **3′**, whereas we did not observe any *Z*-selective olefin.

**Table 2**: Screening of ligands [a]

| Entry | **Ligand** | GC-MS Conversion **3** (%) | Ratio (**3/3'**) |
|---|---|---|---|
| 1 |  **L1** | **65** | **13 : 1** |
| 2 |  **L2** | 15 | 7.5 : 1 |
| 3 |  **L3** | 15 | - |
| 4 |  **L4** | 43 | - |
| 5 |  **L5** | 10 | - |
| 6 |  **L6** | 12 | - |
| 7 |  **L7** | 30 | 15 : 1 |
| 8 |  **L8** | 28 | - |
| 9 |  **L9** | 34 | 17 : 1 |
| 10 |  **L10** | 17 | 8.5 : 1 |
| 11 |  **L11** | 15 | 15 : 1 |
| 12 [b] |  **L12** | 7 | 7 : 1 |

| | | | |
|---|---|---|---|
| 13 [b] |  L13 | 20 | 4 : 1 |
| 14 | No Ligand | 22 | 2.8 : 1 |

Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (0.50 mmol), $NiBr_2$ (5.0 mol%), **Ligand (6.0 mol%)**, *t*-BuOK (0.25 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 130 ºC oil bath, 36 h reaction time. [b] 10 mol% of Ligand was used.

**Table 3**: Screening of solvents [a]

| Entry | **Solvent** | GC-MS Conversion **3** (%) | Ratio (**3 / 3'**) |
|---|---|---|---|
| **1** | **Toluene** | **65** | **13 : 1** |
| 2 | *p*-Xylene | 40 | 1.2 : 1 |
| 3 | 1,4-Dioxane | 5 | 5 : 1 |
| 4 | *n*-BuOH | 10 | 10 : 1 |
| 5 | *t*-Amylalcohol | 11 | 11 : 1 |

Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (0.50 mmol), $NiBr_2$ (5.0 mol%), Phen (6.0 mol%), *t*-BuOK (0.25 mmol), **solvent (2.0 mL)**, Schlenk tube under nitrogen atmosphere, 130 ºC oil bath, 36 h reaction time.

**Table 4**: Screening of base [a]

| Entry | **Base** | GC-MS Conversion **3** (%) | Ratio (**3 / 3'**) |
|---|---|---|---|
| **1** | ***t*-BuOK** | **65** | **13 : 1** |
| 2 | *t*-BuONa | 62 | 15 : 1 |
| 3 | $Cs_2CO_3$ | 1 | 1 : 1 |
| 4 | $Na_2CO_3$ | 6 | 3 : 1 |
| 5 | NaOH | 70 | 17 : 1 |
| **6** | **KOH** | **81 (78)** [b] | **5.7 : 1** |

Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (0.50 mmol), $NiBr_2$ (5.0 mol%), Phen (6.0 mol%), **base (0.25 mmol)**, toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 130 ºC oil bath, 36 h reaction time. [b] Isolated yield (average of two run).

**Table 5**: Screening of base equivalents [a]

| Entry | **Base Equivalent (X equiv.)** | GC-MS Conversion **3** (%) | Ratio (**3 / 3'**) |
|---|---|---|---|
| **1** | **KOH (1.0 equiv.)** | **81 (78)** [b] | **5.7 : 1** |
| 2 | KOH (0.75 equiv.) | 65 | 7.2 : 1 |
| 3 | KOH (0.50 equiv.) | 41 | - |
| 4 | - | 0 | - |

Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (0.50 mmol), $NiBr_2$ (5.0 mol%), Phen (6.0 mol%), KOH (**X equiv.**), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 130 ºC oil bath, 36 h reaction time. [b] Isolated yield (average of two run).

**Table 6**: Screening of catalyst and ligand loading [a]

| Entry | Cat. (X mol%) | Ligand (Y mol%) | GC-MS Conversion 3 (%) | Ratio (**3 / 3'**) |
|---|---|---|---|---|
| 1 | $NiBr_2$ (5.0) | Phen (6.0) | 81 (78) [b] | 5.7 : 1 |
| 2 | $NiBr_2$ (2.5) | Phen (3.0) | 76 (74) [b] | >20 : 1 |
| 3 | $NiBr_2$ (5.0) | Phen (6.0) | 85 (83) [b,c] | >20 : 1 |
| 4 | - | - | 20 | - |

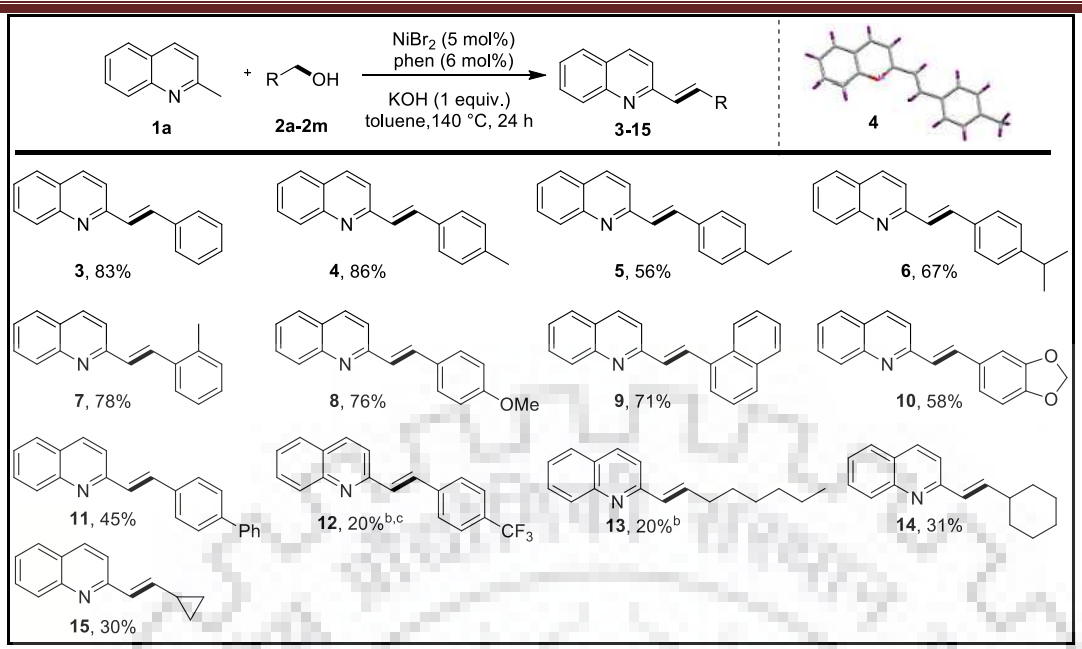
Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (0.50 mmol), **$NiBr_2$ (X mol%), Phen (Y mol%)**, KOH (0.25 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 130 ºC oil bath, 36 h reaction time. [b] Isolated yield average of two run. [c] 140 ºC, 24 h reaction time.

**Table 7**: Screening of alcohol equivalents [a]

| Entry | Benzyl Alcohol Equivalent (X equiv.) | GC-MS Conversion **3** (%) | Ratio (**3 / 3'**) |
|---|---|---|---|
| 1 | 2.0 equiv. | 85 (83) [b] | >20 : 1 |
| 2 | 1.5 equiv. | 65 | - |
| 3 | 1.0 equiv. | 40 | - |

Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (x mmol), $NiBr_2$ (5.0 mol%), Phen (6.0 mol%), KOH (1.0 equiv.), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 ºC oil bath, 24 h reaction time. [b] Isolated yield average of two run.

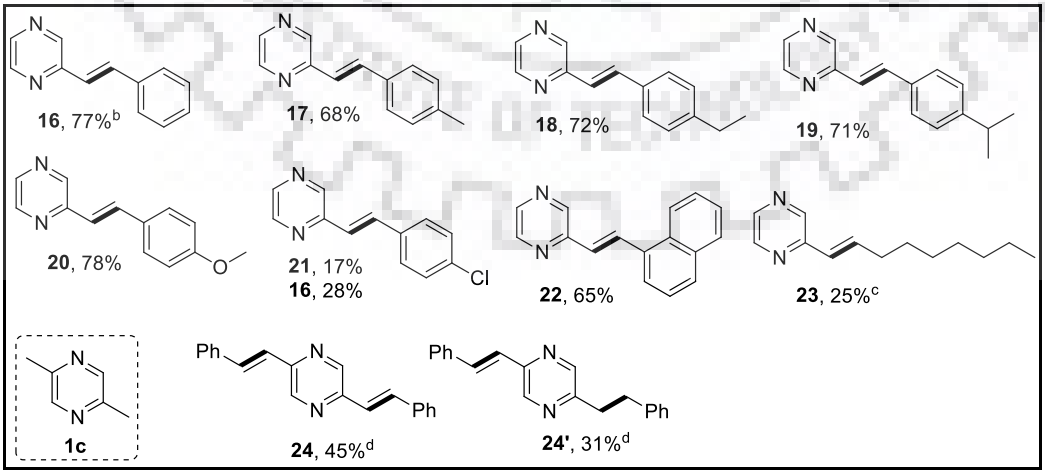
After having the optimal conditions, a range of primary alcohols were employed for *E*-selective 2-vinylquinoline derivatives (Scheme 6). To our delight, X-ray crystal-structure analysis of **4** provides evidence for the formation of thermodynamically more stable *E*-isomer.[15] Notably, in some cases we observed (<5%) of C=C hydrogenated products and no *Z*-selective olefins were observed (Scheme 6). A variety of electronic and sterically different benzyl alcohols were subjected to *E*-configured 2-styrylquinolines **4-12** in up to 86% isolated yields (Scheme 6). For instance, benzylalcohol bearing *o*-methyl and *p*-methoxy moiety efficiently participated for the olefination process and resulted 76-78% yield of **7-8** respectivelly. Gratifyingly, 1-naphthylmethanol and biphenyl methanol proceeded efficiently to give the desired products **9** and **11** in acceptable yields. Pleasingly, electronically poor 1,3-dioxolone and trifluoromethyl groups could be tolerated under the standard catalytic conditions. Next, the scope of more challenging primary alkyl alcohols were found sluggish. When using cyclohexyl methanol (**2l**) and cyclopropyl methanol (**2m**), desired *E*-selective olefins **14** and **15** were obtained in 30-31% yields (Scheme 6). A gram scale reaction could be performed under this procedure and 75% yield of **3** was obtained, highlighting the synthetic potential of the catralytic protocol.




**Scheme 6**: Scope of primary alcohols [a]

Reaction conditions: [a] quinaldine **1a** (0.25 mmol), alcohols **2** (0.50 mmol), $NiBr_2$ (5.0 mol%), Phen (6.0 mol%), KOH (0.25 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 °C, closed system, 24 h.

Thereafter, the scope of the dehydrogenative process was further demonstrated using 2-methylpyrazine **1b** with a series of primary alcohols to access a variety of *E*-vinylpyrazines **16**-**20** and **22** in up to 78% yields (Scheme 7). However, reaction of **2n** with **1b** was sluggish and **21** was obtained along with the de-halogenated product **16.** Further, *n*-octanol was found less reactive under the optimized conditions and resulted to **23**. Notably, when using 2,5-dimethyl pyrazine as coupling partner with benzyl alcohol, selective bis-olefination product **24** was obtained in 45% isolated yield along with mono-alkylated product **24'** in moderate yield (Scheme 7).

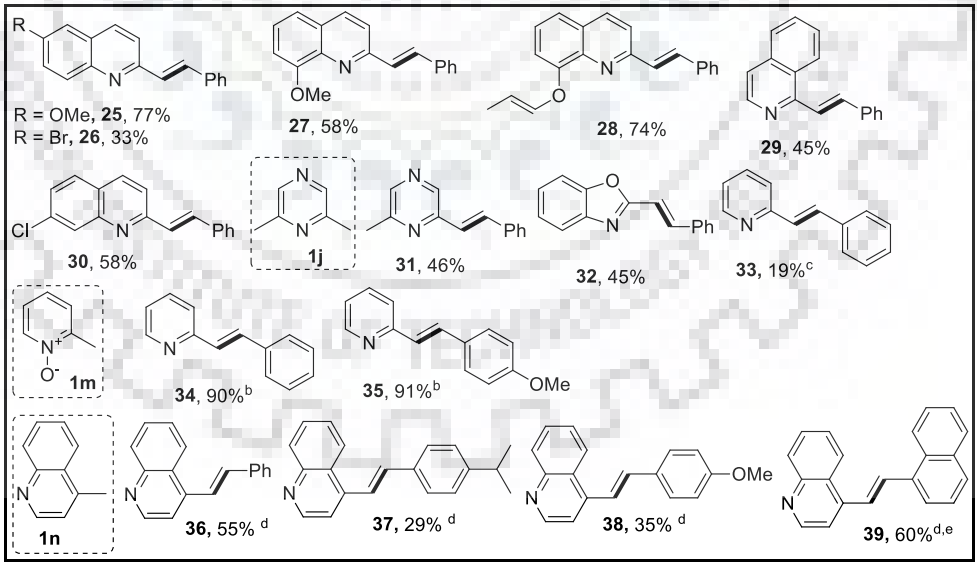



**Scheme 7**: Scope of methylpyrazine with primary alcohols [a]

**Reaction conditions**: [a] Methyl heteroarenes **1** (0.25 mmol), alcohols **2** (0.50 mmol), $NiBr_2$ (5.0 mol%), Phen (6.0 mol%), KOH (0.25 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 °C, closed

system, 36 h. [b] 24 h reaction time. [c] $NiBr_2$ (10 mol%), Phen (12 mol%) and KOH (0.50 mmol) were used. [d] benzyl alcohol **2a** (1.0 mmol), $NiBr_2$ (10 mol%), Phen (12 mol%) and KOH (0.50 mmol) were used.

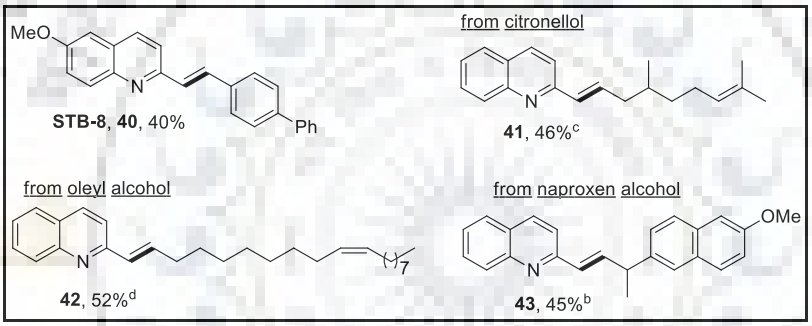
Again, we extended the scope of the olefination reactions using various 2-methylheteroarenes. For instance, 6-methoxy substituted 2-methylquinoline **1d** efficiently transformed into the desired product in 77% yield to **25** (Scheme 8). Whereas, 6-bromo-2-methylquinoline **1e** was less reactive and resulted moderate yield of **26**. 2-methylquinoline bearing 8-methoxy or alkoxy functionality (**1f-1g**) smoothly converted to *E*-vinylquinoline **27-28** in up to 58-74% yield respectively. Notably, sterically hindered 1-methylisoquinoline **1h** and 2-methylbenzoxazole **1k** were evaluated under the present reaction conditions and provides interesting *E*-olefinated products **29** and **32** in 45% yield (Scheme 8). Interestingly, 6-chloro-2-methylquinoline **1i** afford the *E*-vinylquinoline **30** without affecting the chloro-substituent. When 2,6-dimethyl pyrazine **1j** subjected to olefination reaction, mono-selective product **31** was obtained in moderate yield. Under identical conditions 2-methylpicoline **1l** was less reactive with benzyl alcohol. However, 2-methylpicoline-*N*-oxide **1m** efficiently converted to the interesting deoxygenated vinylarenes **34** and **35** in excellent yields. Further, 4-methylquinoline **1n** was employed with **2a**, *p*-isopropyl and *p*-methoxy substituted benzyl alcohol **2d** and **2f** and the desired *E*-vinylquinolines **36-38** were obtained in up to 55% yield (Scheme 8). Gratifyingly, sterically hindered 1-naphthylmethanol **2g** furnished the desired vinyl-quinolines **39** in 60% yield.




**Scheme 8**: Scope of methyl heteroarenes with primary alcohols [a]

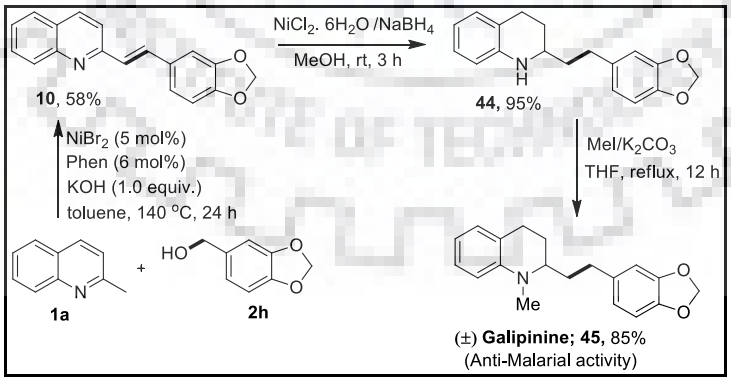
Reaction conditions: [a] Methyl heteroarenes **1** (0.25 mmol), alcohols **2** (0.50 mmol), $NiBr_2$ (5.0 mol%), Phen (6.0 mol%), KOH (0.25 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 °C, closed system, 24 h. [b] Pyridine-*N*-oxide (**1m**) was used. [c] GC-MS conversion. [d] toluene (1mL) was used. [e] $NiBr_2$ (10 mol%), Phen (12 mol%) and KOH (0.50 mmol) were used.

Next, we explored our interests for selective synthesis of complex natural products and drug molecules having *E*-olefinated functionalities. For instance, when 6-methoxy-2-methylquinoline **1d** subjected to standard conditions with biphenyl-4-methanol **2i**, *E*-olefinated product **STB-8**, extensively used as an imaging agent for Alzheimer's disease β-amyloid plaques, was obtained in moderate yield.[4] Thereafter, citronellol **2p**, a natural terpenoid intermediate, as well as oleyl alcohol **2q**, derived from fatty acids, chemoselectively transformed to the *E*-olefinated products **41-42** in up to 52% yield (Scheme 9). It is to be noted that, these examples provide evidences for the rare chemo-selective conversion of unsaturated alcohol without affecting the internal double bonds under Ni-catalysis.[8] Interestingly, alkyl alcohol **2q**, derived from drug naproxen, reacted with **1a** to the desired product **43** in acceptable yield (Scheme 9). These examples established the potential applications of the present protocol.




**Scheme 9**: Synthetic utility [a]

Reaction conditions: [a] Methyl heteroarenes **1** (0.25 mmol), alcohols **2** (0.50 mmol), $NiBr_2$ (5.0 mol%), Phen (6.0 mol%), KOH (0.25 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 °C, closed system, 24 h. [b] $NiBr_2$ (10 mol%), Phen (12 mol%) and KOH (0.50 mmol) were used. [c] KOH (0.3125 mmol) was used. [d] $NiBr_2$ (10 mol%), Phen (12 mol%) were used.

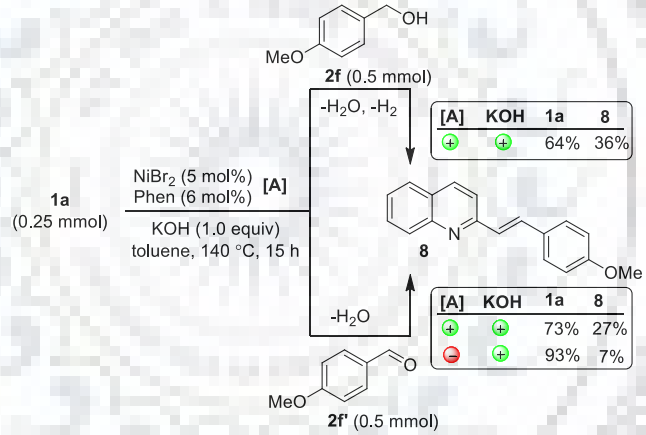



**Scheme 10**: Synthesis of drug (±) Galipinine **45**

Encouraged by these present studies, herein we developed a formal straightforward synthetic route of the alkaloid (±)- galipinine from *E*-vinylquinoline **10**.[13] Nickel-catalyzed

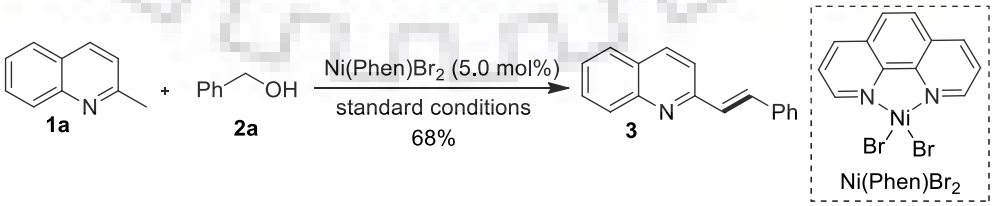
hydrogenation followed by *N*-methylation gave the desired natural product **45**, commonly utilized for multiple biological activities (Scheme 10).

Next, we explored our interests towards the reaction mechanism for the olefination process. Therefore, a series of experiments were performed using **1a** with 4-methoxy benzaldehyde as well as 4-methoxy benzyl alcohol **2f** in presence and absence of nickel catalyst for 15 h (Scheme 11). When 4-methoxy benzaldehyde subjected to olefination with **1a** under standard conditions using nickel, resulted **8** in 27% yield. However, under identical conditions in absence of nickel, **8** was obtained in 7% yield. Interestingly, under optimized conditions, similar reaction using 4-methoxy benzylalcohol **2f** gave rise to five times increment of the product **8**. These experimental outcomes are in agreement with the participation of nickel catalyst for alcohol dehydrogenation as well as crucial for C-C bond forming condensation process.[14] Nevertheless, either in absence of catalyst and KOH or in absence of KOH, 4-methoxy benzaldehyde did not result any desired product (Scheme 11).



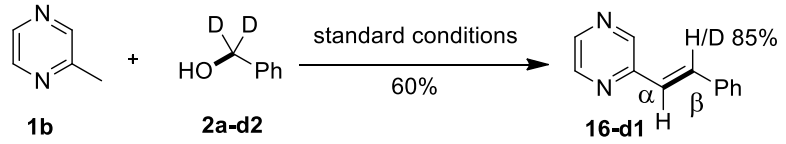

**Scheme 11:** Control experiments for α-olefination

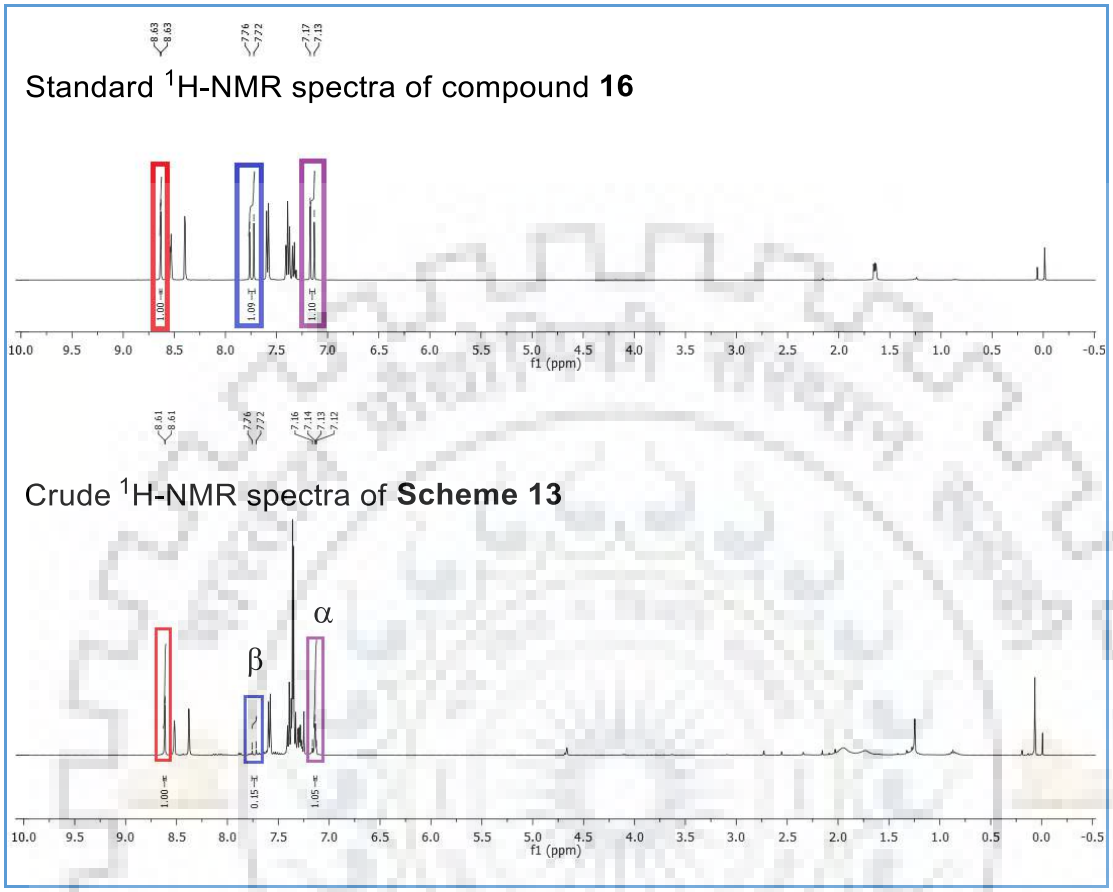
Further, to understand the nature of the active nickel-catalyst, Ni(Phen)$Br_2$ was prepared and employed for catalytic olefination reaction.[10,12] Pleasingly, **3** was obtained in good isolated yield (Scheme 12).




**Scheme 12:** Catalytic studies using defined nickel catalyst

Further, to analyze the involvement of the benzylic C-H bond a series of deuterium labeling experiments were performed. *α*-olefination of **1b** with **2a-d2** (92% D) resulted 62% yield to **16-d1** and exhibited 85% deuterium incorporation at the β-position (Scheme 13).



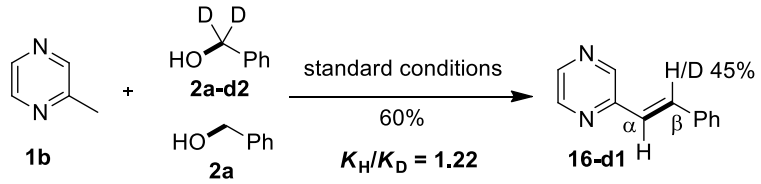



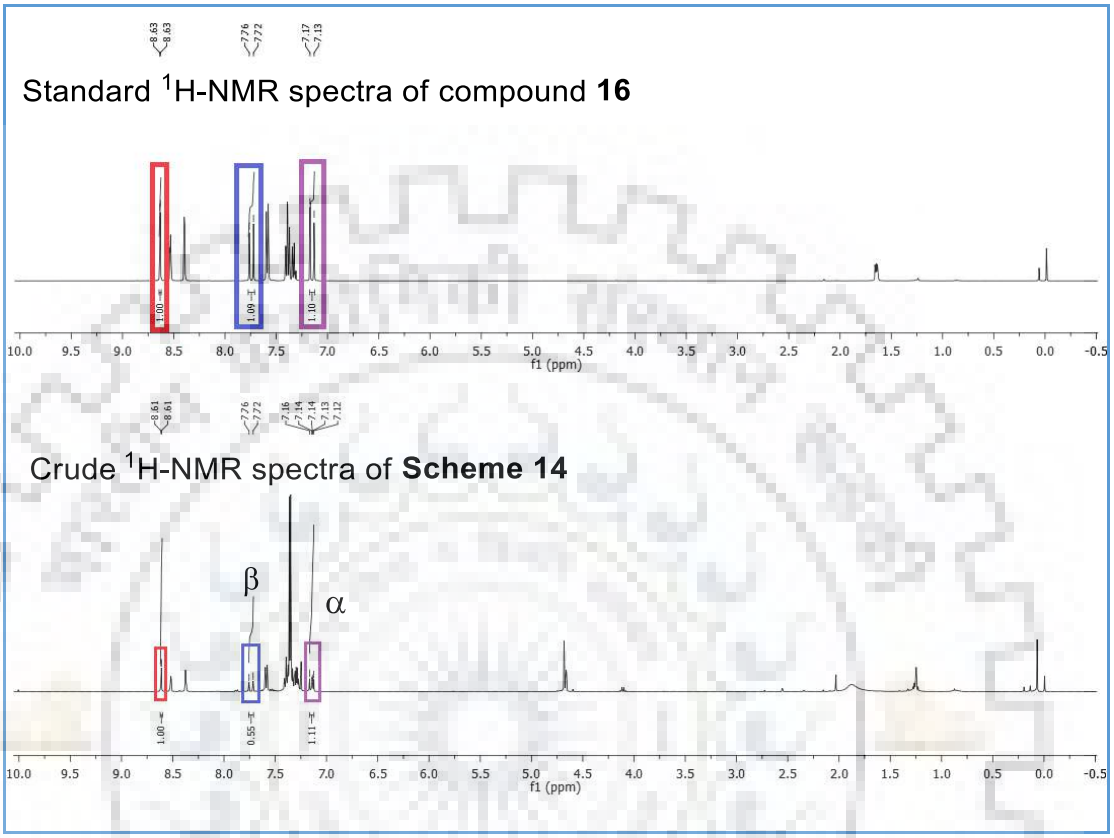

Conversion was calculated by $^1$H-NMR integration value

| | | Deuterium incorporation in β position | Deuterium incorporation in α position |
|---|---|---|---|
| Signal $\delta$ ppm | 8.63 (1H) | 7.74 (1H) | 7.15 (1H) |
| Integral Value | 1.0 | 0.15 | 1.05 |
| **Calculated ratio** | | {(1-0.15)/1}×100 = **85%** | {(1-1)/1}×100 = **0%** |

**Scheme 13:** Deuterium labeling experiment 2-methylpyrazine **1b** with **2a-d2**

Next, a cross-over experiment was performed using 1:1 mixture of **2a** and **2a-d2** with **1b** using standard conditions presented in Scheme 14. Importantly, **16-d1** was obtained in moderate yield and we observed a kinetic isotope effect $k_H/k_D$ = 1.22 (Scheme14). In addition, α-olefination of **1a** with **2a-d1** did not result any deuterated product (Scheme 15). Additionally, when **1a-d3** was reacted with **2a**, **3-d1** was obtained in moderate yield and exhibited 65% deuterium incorporation at the α-position (Scheme 16). These deuterium labeling experiments provide evidences for the involvement of the benzylic C-H bond of **2a** as well as C(sp$^3$)-H bond of 2-alkylheteroarenes for the olefination process.[16]

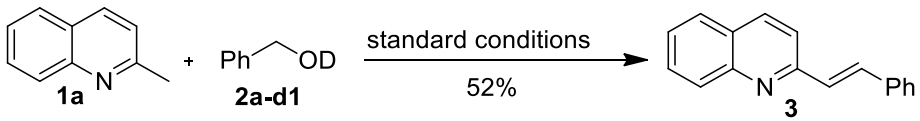


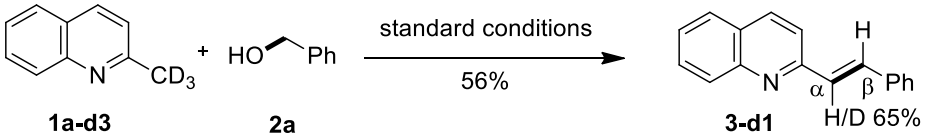

Conversion was calculated by $^1$H-NMR integration value

| | | Deuterium incorporation in β position | Deuterium incorporation in α position |
|---|---|---|---|
| Signal $\delta$ ppm | 8.63 (1H) | 7.74 (1H) | 7.15 (1H) |
| Integral Value | 1.0 | 0.55 | 1.11 |
| **Calculated ratio** | | {(1-0.55)/1}×100 = **45%** | {(1-1)/1}×100 = **0%** |

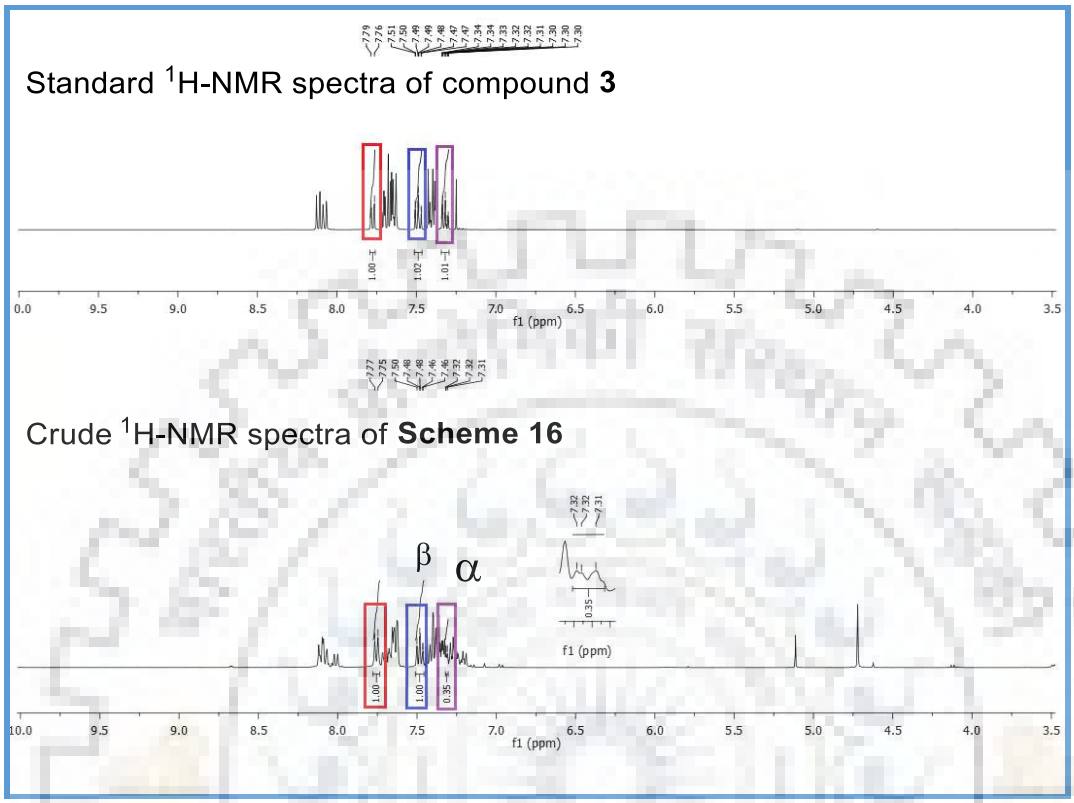
**Scheme 14:** Cross-over experiment **1b** with **2a** and **2a-d2**




**Scheme 15:** Deuterium labeling experiment **1a** with **2a-d1**




**1a-d3** **2a** **3-d1**

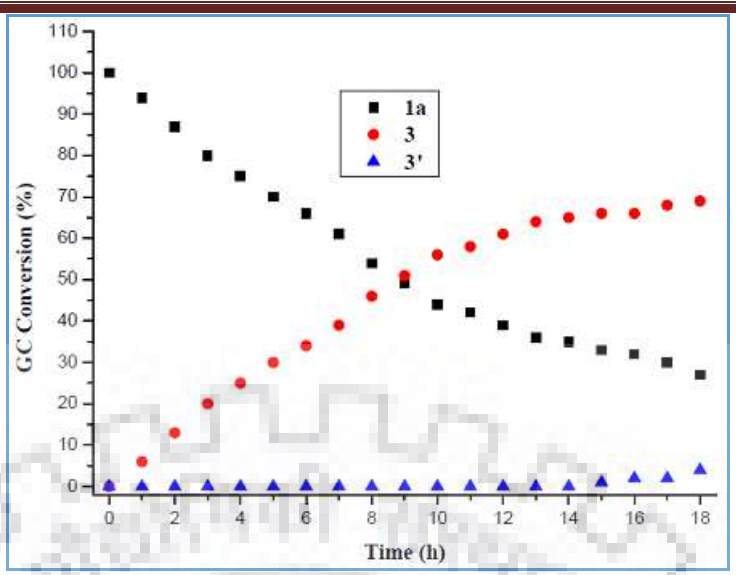



Conversion was calculated by $^1$H-NMR integration value

| | | Deuterium incorporation in β position | Deuterium incorporation in α position |
|---|---|---|---|
| Signal $\delta$ ppm | 7.76 (1H) | 7.49 (1H) | 7.32 (1H) |
| Integral Value | 1.0 | 1.0 | 0.35 |
| **Calculated ratio** | | {(1-1)/1}×100 = **0%** | {(1-0.35)/1}×100 = **65%** |

**Scheme 16:** Deuterium incorporation experiment of **1a-d3** and **2a**

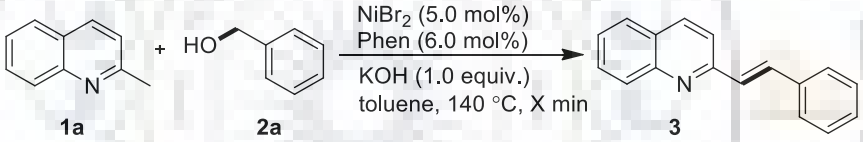
A time conversion plot for α-olefination of **1a** with **2a** was monitored using GC for 18 h and indicated that longer reaction time might have diminished the selectivity of **3** (Scheme 17). We have also studied the rate and order of the olefination process and observed second order kinetics (Scheme 18).




**Scheme 17:** Time-conversion-plot for the reaction of **1a** with **2a**

Reaction conditions: Quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (0.50 mmol), $NiBr_2$ (5.0 mol%), Phen (6.0 mol%), KOH (0.25 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 °C oil bath.

**Scheme 18:** Determination of rate and order of reaction




Run 1: Reaction was carried out in 2 mL of toluene and yield was calculated by GC

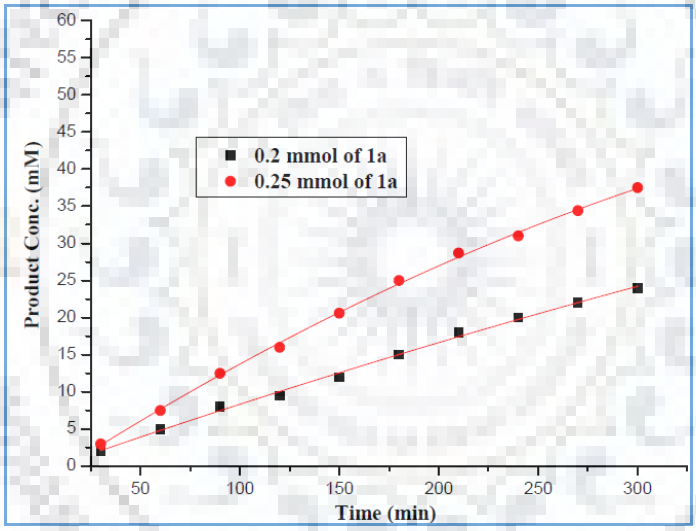
| No. | **1a** (mmol) | **2a** (mmol) | $NiBr_2$ (mmol) | Phen (mmol) | KOH (mmol) | toluene (mL) |
|---|---|---|---|---|---|---|
| Run 1 | 0.2 | 0.4 | 0.01 | 0.012 | 0.2 | 2.0 |

| Sl. No. | Time (min) | Concentration of **3** (mM) |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 30 | 2 |
| 3 | 60 | 5 |
| 4 | 90 | 8 |
| 5 | 120 | 9.5 |
| 6 | 150 | 12 |
| 7 | 180 | 15 |
| 8 | 210 | 18 |
| 9 | 240 | 20 |
| 10 | 270 | 22 |
| 11 | 300 | 24 |

Run 2: Reaction was carried out in 2 mL of toluene and yield was calculated by GC

| No. | **1a** (mmol) | **2a** (mmol) | $NiBr_2$ (mmol) | Phen (mmol) | KOH (mmol) | toluene (mL) |
|---|---|---|---|---|---|---|
| Run 2 | 0.25 | 0.5 | 0.0125 | 0.015 | 0.25 | 2.0 |

| Sl. No. | Time (min) | Concentration of **3** (mM) |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 30 | 3 |
| 3 | 60 | 7.5 |
| 4 | 90 | 12.5 |
| 5 | 120 | 16 |
| 6 | 150 | 20.6 |
| 7 | 180 | 25 |
| 8 | 210 | 28.7 |
| 9 | 240 | 31 |
| 10 | 270 | 34.4 |
| 11 | 300 | 37.5 |




Graphical representation for determination of rate and order of reaction

Considering steady state approximation for benzyl alcohol

From Run 1: Slope = k $[1a]^x$

$0.082 = k\,[0.20]^x$

From Run 2: Slope = k $[1a]^x$

$0.129 = k\,[0.25]^x$

$0.129/0.082 = [0.25]^x / [0.2]^x$

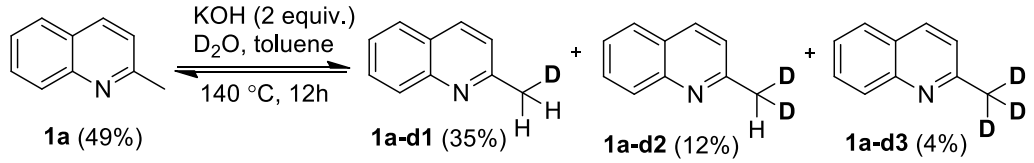
$1.57 = [1.25]^x$

$\text{Log}\,(1.57) = x.\ \text{Log}\,(1.25)$

$x = 0.195 / 0.0969$

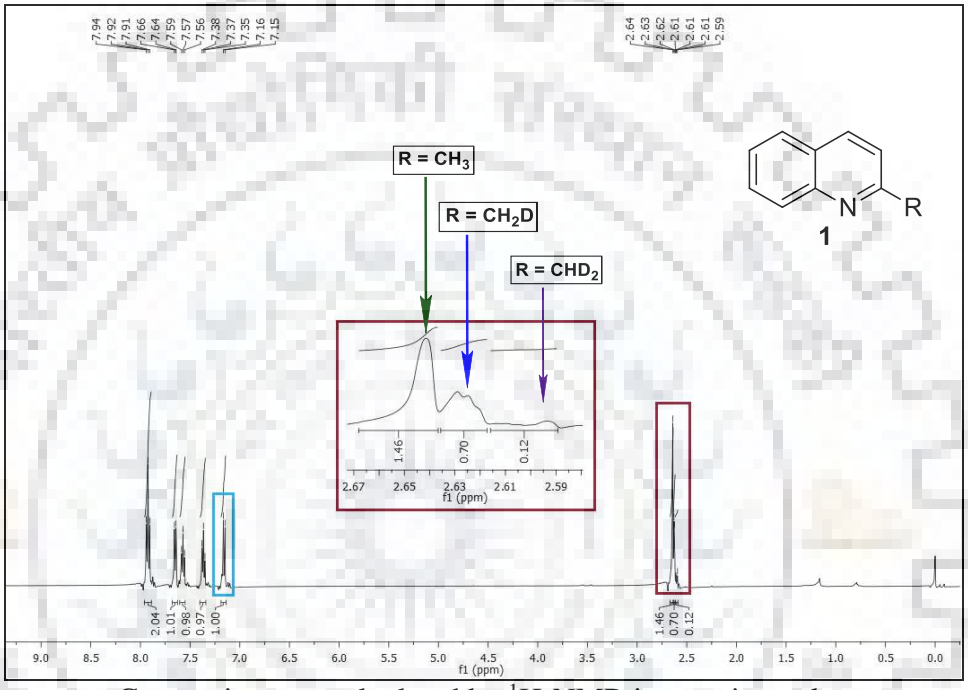
$= 2.01 \approx 2$

Rate = k $[1a]^2$




**Scheme 19**: Evidence for the enamine intermediate formation

Reaction conditions: Quinaldine **1a** (0.25 mmol), $D_2O$ (0.2 mL), KOH (0.5 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 °C oil bath, 12 h.

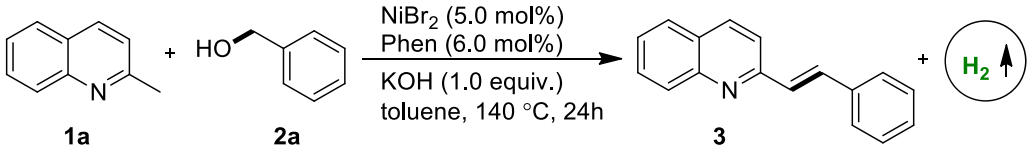



Conversion was calculated by $^1$H-NMR integration value

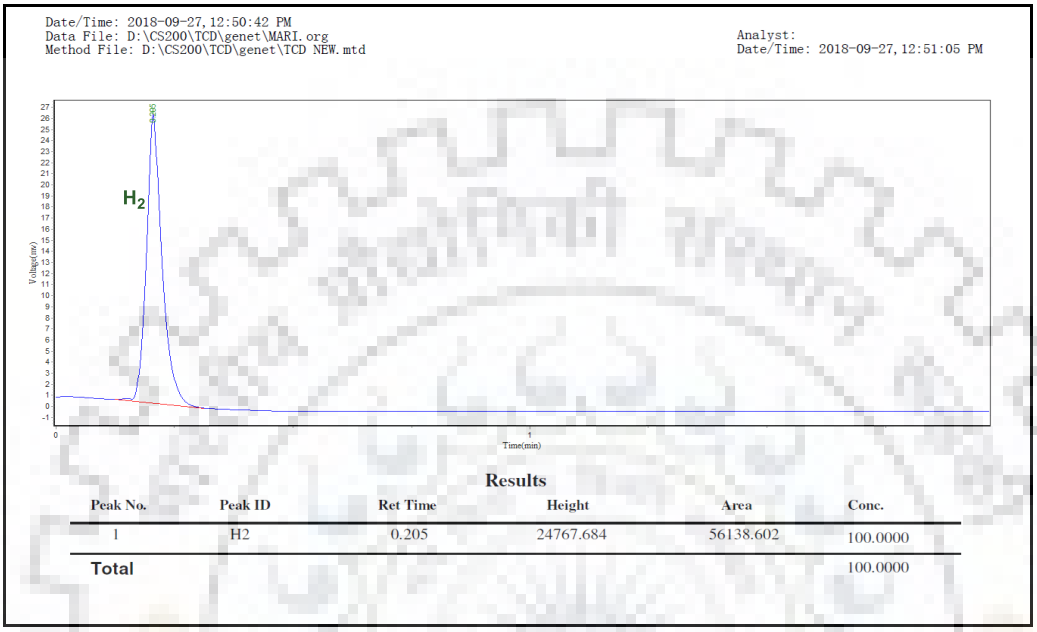
| | | 1a | 1a-d1 | 1a-d2 | 1a-d3 |
|---|---|---|---|---|---|
| Signal $\delta$ ppm | 7.15 (1H) | 2.64 (3H) | 2.62 (2H) | 2.59-2.61 (1H) | |
| Integral Value | 1.0 | 1.46 | 0.70 | 0.12 | |
| Calculated ratio | | (1.46 / 3)×100 = **49%** | (0.70 / 2)×100 = **35%** | (0.12 / 1)×100 = **12%** | 100-(49+35+12) = **4%** |

Finally, the evolution of hydrogen gas detection and quantitative determination were performed during olefination process (Schemes 20 and Scheme 21).

**Scheme 20:** Detection of $H_2$ gas liberation



In a 100 mL oven dried Ace Pressure tube, quinaldine **1a** (3.0 mmol), $NiBr_2$ (5 mol%), Phen (6 mol%), benzyl alcohol **2a** (6.0 mmol) and KOH (3.0 mmol), were added followed by toluene 10.0 mL under an atmosphere of $N_2$ and the reaction mixture was sealed with septum and heated at 140 °C for 24 h. After completion of reaction $H_2$ gas was detected by Centurion Scientific Gas Chromatograph (CS-5700$^+$) through TCD Detector.




**Results**

| Peak No. | Peak ID | Ret Time | Height | Area | Conc. |
|---|---|---|---|---|---|
| 1 | H2 | 0.205 | 24767.684 | 56138.602 | 100.0000 |
| **Total** | | | | | 100.0000 |

**Scheme 21**: Quantitative determination of hydrogen gas produced in the reaction

In a 10 mL oven dried Schlenk tube, quinaldine **1a** (0.5 mmol), $NiBr_2$ (5 mol%), Phen (6 mol%), benzyl alcohol **2a** (1.0 mmol) and KOH (0.5 mmol), were added followed by toluene 4.0 mL and connected to the gas burette as shown in below figure. Then the reaction mixture was heated at 140 °C until the production of hydrogen gas ceased. The procedure was repeated three times to get concordant reading.

Total volume of water displaced, V = 0.0176 L

Vapor pressure of water at 298K, $P_{H2O}$ = 23.7695 Torr

Atmospheric pressure at 298K, $P_{atm}$ = 758.3124 Torr

Pressure of $H_2$ gas, $P_{H2} = P_{atm} - P_{H2O}$ = (758.3124 - 23.7695) Torr = 734.5429 Torr

$P_{H2} * V = nH_2 * R * T$

$nH_2 = P_{H2} * V / R * T$

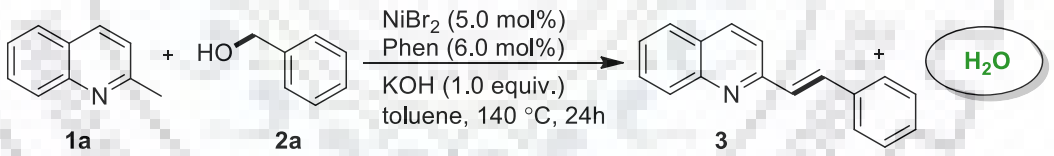
$= 734.5429 \text{ Torr} * 0.0176 \text{ L} / 62.3635 \text{ L Torr K}^{-1} \text{ mol}^{-1} * 298\text{K}$

$= 0.000696$ mol

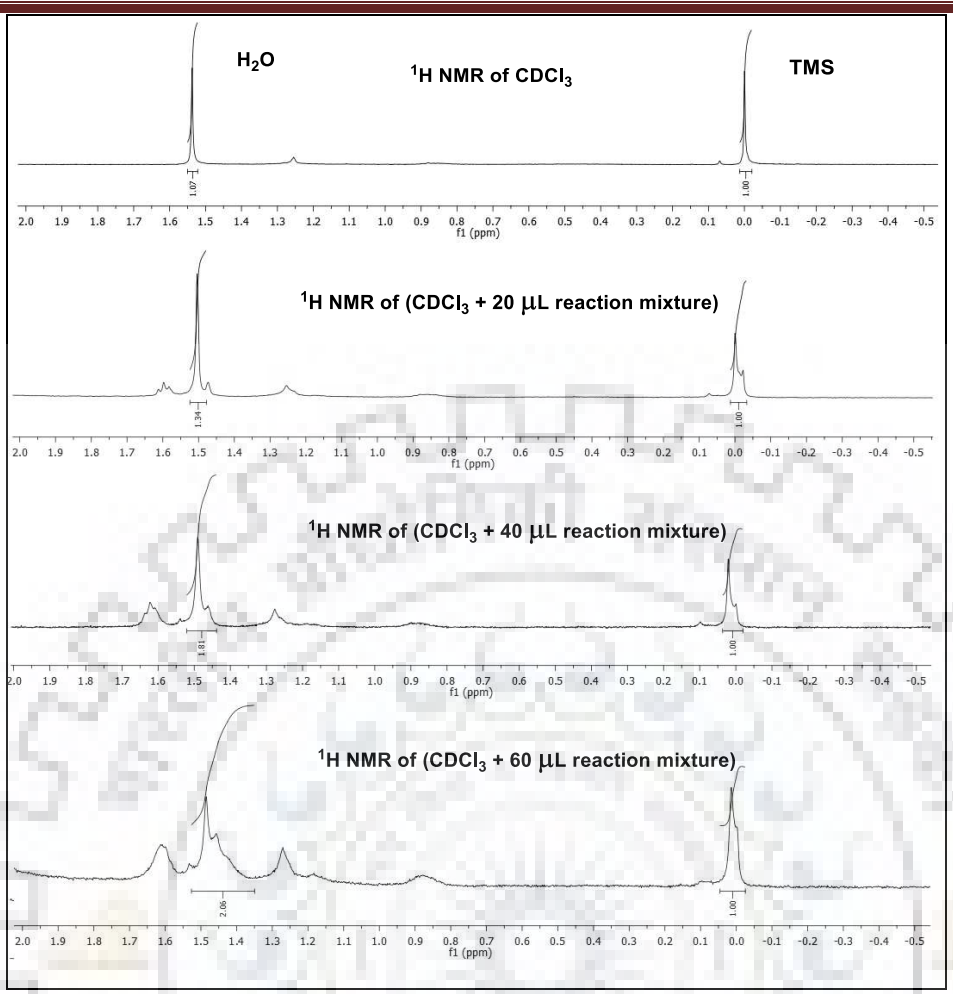
$\approx 0.70$ mmol

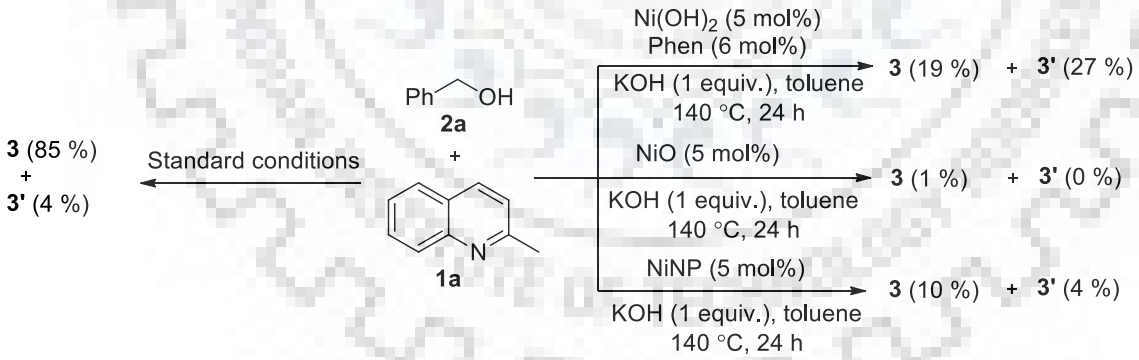
An in situ 1H-NMR studies were performed to detect the generation of water during the reaction (Scheme 22). Additionally, to exclude the involvement of the heterogeneous nickel-catalysts, we performed a series of experiments including mercury test, which strongly support the homogeneous nature of the present catalytic system (Schemes 23 and 24).

**Scheme 22**: Detection of water in reaction mixture by $^1$H-NMR



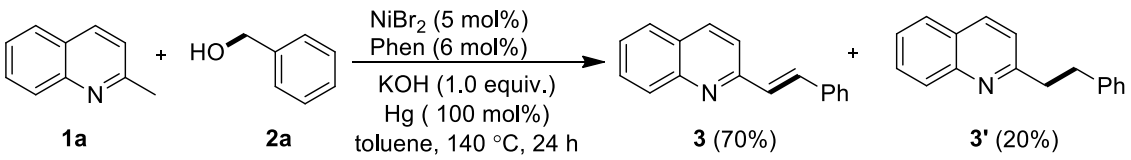

In a 15 mL oven dried Schlenk tube, quinaldine **1a** (0.25 mmol), $NiBr_2$ (5 mol%), Phen (6 mol%), benzyl alcohol **2a** (0.50 mmol) and KOH (0.25 mmol), were added followed by toluene (dry) 2.0 mL under an atmosphere of $N_2$ and the reaction mixture was heated at 140 °C for 24 h in a closed system. Then the reaction mixture was cooled to room temperature. Initially $^1$H NMR of $CDCl_3$ was measured and 1:1 ratio of $H_2O$ and TMS was found. Afterwards 20 µL of reaction mixture was added to the nmr tube and $^1$H NMR was measured which shows increment in the ratio of $H_2O$. Further addition of reaction mixture shows enhancement in the ratio of $H_2O$ which proves that water was produced in the reaction.




**Scheme S23**: Test for homogeneity experiments

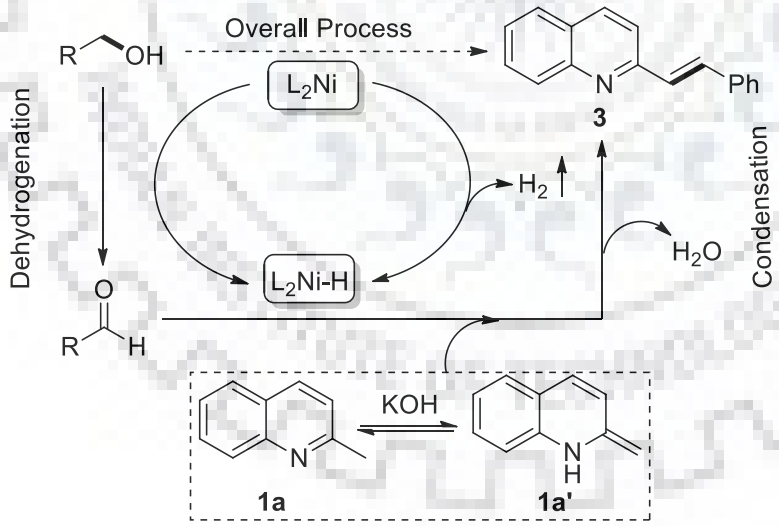
Reaction conditions: Quinaldine **1a** (0.25 mmol), benzyl alcohol **2a** (0.50 mmol), Ni-Cat. (5.0 mol%), Phen (6.0 mol%), KOH (0.25 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 °C oil bath, 24 h.




**Scheme S24:** Test for catalyst poisoning experiment

In a 15 mL oven dried Schlenk tube, quinaldine **1a** (0.25 mmol), $NiBr_2$ (5 mol%), Phen (6 mol%), benzyl alcohol **2a** (0.50 mmol) and KOH (0.25 mmol), were added followed by toluene 2.0 mL. Then Hg (50 mg, 100 mol%) was added to the mixture and flushed with $N_2$ four times, the reaction mixture was heated at 140 °C for 24 h in close system. The reaction mixture was cooled to room temperature and 3.0 mL of ethyl acetate was added and analyzed by GC-MS. Product **3** (70%) and reduced product **3'** (20%) was observed in GC-MS analysis of crude reaction mixture which eliminates the probability of a heterogeneous reaction.

Regarding mechanism, we believe that an enamine intermediate **1a**' involves in the olefination process and a base mediated equilibrium exist with **1a** (Scheme 25). Control experiments in absence of base did not result any **3**, indicated that, KOH plays a crucial role for de-aromatization of **1a** to **1a**'. To confirm the participation of enamine intermediate, **1a** was employed with $D_2O$ in KOH and deuterium incorporation at **1a** provides evidence for the participation of enamine intermediate (Scheme 19). Considering these experimental findings, we postulated that, condensation of aldehyde, generated in situ by nickel-catalyzed dehydrogenation of alcohol, with enamine **1a**' transformed to the desired *E*-configured olefins. Notably, during this process water and hydrogen generated as sole by products, rendering the overall process sustainable (Scheme 25).




**Scheme S25: Plausible mechanistic cycle**

**Figure 1:** Crystallographic data for compound **4**

| | | | |
|---|---|---|---|
| Identification code: | UPS3491DB_MVB110_0m_a | | |
| CCDC | 1871614 | | |
| Bond precision: | C-C = 0.0076 A | | Wavelength = 0.71073 |
| Cell: | a = 5.9624(3) | b = 8.0092(4) | c = 28.9234(16) |
| | alpha = 90 | beta = 90 | gamma = 90 |
| Temperature: | 296 K | | |

| | Calculated | Reported |
|---|---|---|
| Volume | 1381.21(12) | 1381.21(12) |
| Space group | P 21 21 21 | P 21 21 21 |
| Hall group: | P 2ac 2ab | P 2ac 2ab |
| Moiety formula | $C_{18}$ $H_{15}$ N | |
| Sum formula | $C_{18}$ $H_{15}$ N | $C_{18}$ $H_{15}$ N |
| Mr | 245.31 | 245.31 |
| Dx, g cm-3 | 1.180 | 1.180 |
| Z | 4 | 4 |
| Mu (mm-1) | 0.068 | 0.068 |
| F000 | 520.0 | 520.0 |
| F000' | 520.18 | |
| h,k,l max | 7,10,38 | 7,10,38 |
| Nref | 3436[2018] | 3417 |
| Tmin,Tmax | 0.985, 0.985 | 0.985,0.985 |
| Tmin' | 0.985 | |

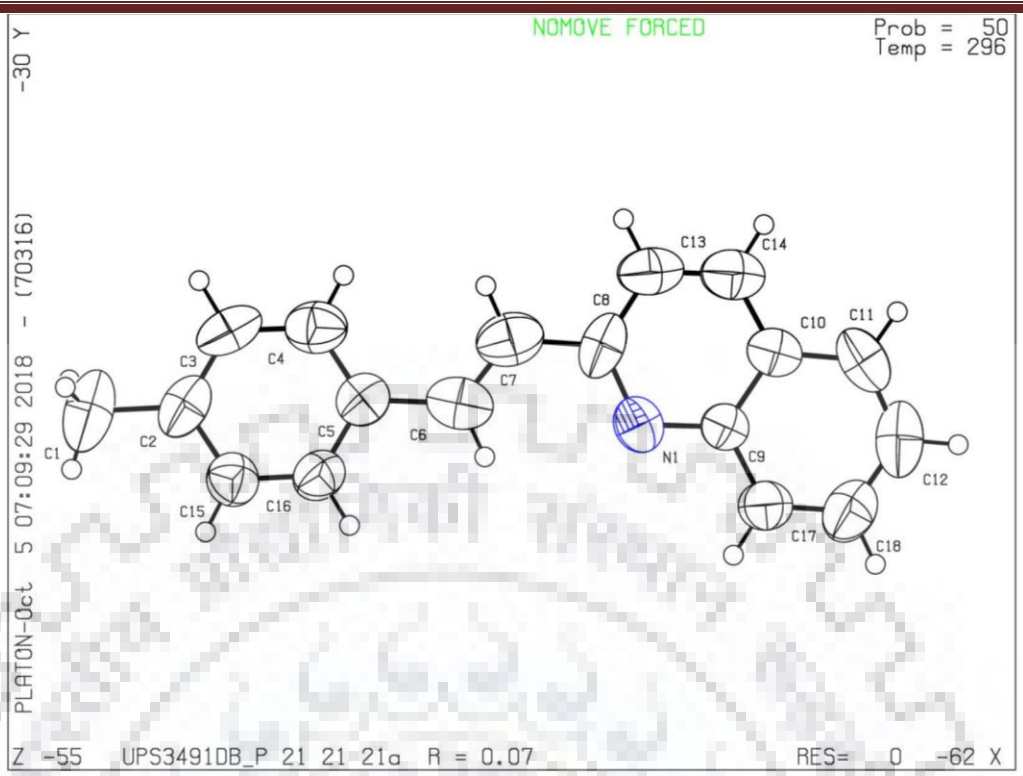
Correction method = # Reported T Limits: Tmin = 0.985 Tmax = 0.985

AbsCorr = MULTI-SCAN

Data completeness = 1.69/0.99 Theta (max) = 28.315

R (reflections) = 0.0684 (1657) wR2 (reflections) = 0.2304 (3417)

S = 0.955 Npar = 173




Platon-ellipsoid plot for compound **4**

**[5A.5] Conclusions:**

In conclusion, we have demonstrated an unprecedented nickel-catalyzed highly selective synthesis of *E*-configured olefins using a range of 2-methylheteroarenes with primary alcohols. A simple nickel catalyst stabilized by inexpensive nitrogen ligand give rise to various interesting *E*-vinylarenes in up to 91% yield. For a practical utility, gram scale synthesis could be performed. A series of deuterium labeling experiments, kinetic studies as well as control experiments support the participation of enamine intermediate for the condensation process under nickel catalysis.

**[5A.6] Experimental Section:**

**General Experimental Details:** All solvents and reagents were used, as received from the suppliers. TLC was performed on Merck Kiesel gel 60, $F_{254}$ plates with the layer thickness of 0.25 mm. Column chromatography was performed on silica gel (100-200 mesh) using a gradient of ethyl acetate and hexane as mobile phase. $^{1}H$ NMR spectral data were collected at, 400 MHz (JEOL), 500 MHz (Bruker) and $^{13}C$ NMR were recorded at 100 MHz. $^{1}H$ NMR spectral data are given as chemical shifts in ppm followed by multiplicity (s- singlet; d- doublet; t- triplet; q- quartet; m- multiplet), number of protons and coupling constants. $^{13}C$ NMR chemical shifts are expressed in ppm. Elemental analysis data were recorded in

Vario Micro Cube. GC-MS were recorded using Agilent GC Mass Spectrometer. All the reactions were performed in a close system using Schlenk tube. All nickel salts were purchased from Sigma Aldrich. Nickel (II) bromide (Assay-98%; CAS Number 13462-88-9; EC Number 236-665-0; Pack Size-No 217891-10G).

**General procedure for Ni-catalyzed alkylation of methylquinolines with primary alcohols:**

In a 15 mL oven dried Schlenk tube,methylazaarenes **1** (0.25 mmol), $NiBr_2$ (5 mol%), Phen (6 mol%), alcohols **2** (0.50 mmol) and KOH (0.25 mmol), were added followed by toluene (2.0 mL) under an atmosphere of $N_2$ and the reaction mixture was heated at 140 °C for 24 h in close system. The reaction mixture was cooled to room temperature and 3.0 mL of ethyl acetate was added and concentrated *in vacuo*. The residue was purified by column chromatography using a gradient of hexane and ethyl acetate (eluent system) to afford the pure product.

**Synthesis and characterization of 8-((*E*)-prop-1-en-1-yloxy)-2-((*E*)-styryl)quinoline (28)**:

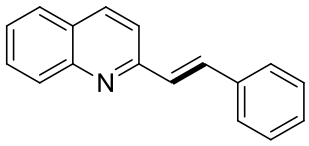
Following the general procedure, the title compound **28** was isolated as a white solid using silica-gel column chromatography eluting with 5% ethyl acetate in hexane. Yield (74%, 62 mg). All the compounds were characterized by $^1$H-NMR, $^{13}$C-NMR, HRMS (ESI-TOF) and IR and the results are shown in spectral data. For an example, all the spectral data of compound **28** are explained here.

**$^1$H NMR**. the seven aromatic region protons are well separated and appeared as d, dd and m at 8.12 (d, *J* = 8.6 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.71 – 7.64 (m, 3H), 7.56 (d, *J* = 16.4 Hz, 1H), 7.48-7.42 (m, 4H), 7.35 (dd, *J* = 10.5, 4.1 Hz, 1H), 7.23 (dd, *J* = 7.5, 1.3 Hz, 1H). The doublet of quartet and multiplet peaks at 6.61 (dq, *J* = 5.7, 1.6 Hz, 1H) and 5.17-5.12 (m, 1H) ppm belong to –CH proton α and β to the oxygen of quinaldine respectively. The doublet of doublet peak at 1.91 (dd, *J* = 6.9, 1.7 Hz, 3H) belongs to three $–CH_3$ protons of vinyl group (Figure 2a).

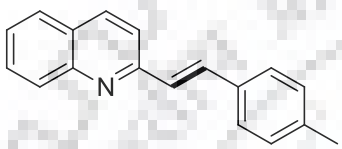
**$^{13}$C NMR**. The peak at 9.87 ppm belongs to $–CH_3$ carbon of vinyl group; and the peaks at 112.95 and 109.55 ppm belong to –CH carbon α and β to the oxygen of quinaldine respectively. The peaks at 134.25 and 129.66 ppm belong to two carbons of olefin moiety. The peaks at 155.47, 153.32, 141.43, 140.18, 136.65, 136.20, 128.79, 128.67, 128.55, 127.32, 126.09, 121.29 and 119.45 ppm belong to aromatic benzene ring carbons.

**Analytical data for all products:**

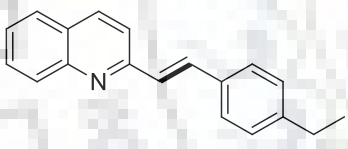
**(*E*)-2-Styrylquinoline (3)**[14a]: Following the general procedure, the title compound was isolated as a white solid (48 mg, Yield: 83%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.10 (dd, $J$ = 16.4, 8.6 Hz, 2H), 7.78 (dd, $J$ = 8.1, 1.1 Hz, 1H), 7.71 (dd, $J$ = 6.5, 2.0 Hz, 1H), 7.65 (ddd, $J$ = 8.0, 7.3, 3.0 Hz, 4H), 7.49 (ddd, $J$ = 8.1, 6.9, 1.1 Hz, 1H), 7.43-7.38 (m, 3H), 7.34-7.30 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.09, 148.36, 136.61, 136.43, 134.52, 129.83, 129.30, 129.12, 128.88, 128.72, 127.58, 127.44, 127.35, 126.26, 119.35.



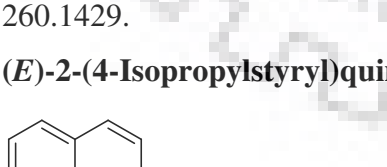
**(*E*)-2-(4-Methylstyryl)quinoline (4)**[14a]: Following the general procedure, the title compound was isolated as a white solid (53 mg, Yield: 86%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.08 (dd, $J$ = 16.0, 8.5 Hz, 2H), 7.77 (d, $J$ = 8.2 Hz, 1H), 7.68 (ddd, $J$ = 23.1, 11.5, 4.1 Hz, 3H), 7.54 (d, $J$ = 8.1 Hz, 2H), 7.48 (ddd, $J$ = 8.0, 7.0, 1.1 Hz, 1H), 7.36 (d, $J$ = 16.3 Hz, 1H), 7.20 (d, $J$ = 7.9 Hz, 2H), 2.37 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.30, 148.31, 138.88, 136.42, 134.53, 133.80, 129.83, 129.64, 129.19, 128.09, 127.60, 127.37, 127.31, 126.17, 119.28, 21.49.



**(*E*)-2-(4-Ethylstyryl)quinoline (5)**: Following the general procedure, the title compound was isolated as a white solid (36 mg, Yield: 56%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.09 (dd, $J$ = 15.3, 8.6 Hz, 2H), 7.77 (d, $J$ = 8.1 Hz, 1H), 7.72-7.63 (m, 3H), 7.56 (dd, $J$ = 8.2, 2.0 Hz, 2H), 7.50-7.46 (m, 1H), 7.37 (dd, $J$ = 16.3, 2.3 Hz, 1H), 7.23 (dd, $J$ = 8.1, 1.8 Hz, 2H), 2.70-2.64 (m, 2H), 1.26 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.22, 147.25, 144.09, 135.25, 133.42, 132.99, 128.68, 128.13, 127.32, 127.09, 126.47, 126.28, 126.27, 125.03, 118.16, 27.71, 14.41. HRMS (ESI): Calculated for $[C_{19}H_{18}N]^+$ 260.1434; Found 260.1429.



**(*E*)-2-(4-Isopropylstyryl)quinoline (6)**: Following the general procedure, the title compound was isolated as a white solid (46 mg, Yield: 67%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.09 (dd, $J$ = 17.8, 8.5 Hz, 2H), 7.77 (dd, $J$ = 8.1, 1.2 Hz, 1H), 7.71-7.63 (m, 3H), 7.57 (d, $J$ = 8.2 Hz, 2H), 7.48 (ddd, $J$ = 8.0, 6.9, 1.2 Hz, 1H), 7.37 (d, $J$ = 16.4 Hz, 1H), 7.26 (d, $J$ = 8.8 Hz, 2H), 2.93 (dt, $J$ = 13.9, 6.9 Hz, 1H), 1.27 (d, $J$ = 6.9 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.26, 149.73, 148.30, 136.28, 134.44,



134.18, 129.71, 129.17, 128.18, 127.51, 127.34, 127.31, 126.93, 126.07, 119.18, 34.02, 23.90. HRMS (ESI): Calculated for $[C_{20}H_{20}N]^+$ 274.1590; Found 274.1582.

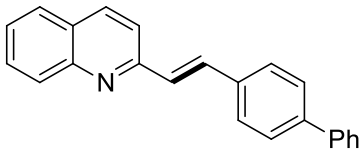
**(*E*)-2-(2-Methylstyryl)quinoline (7)**[14b]: Following the general procedure, the title compound was isolated as a colorless oil (48 mg, Yield: 78%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.10 (dd, $J$ = 13.8, 8.6 Hz, 2H), 7.93 (d, $J$ = 16.2 Hz, 1H), 7.79-7.76 (m, 1H), 7.75-7.66 (m, 3H), 7.49 (ddd, $J$ = 8.1, 7.0, 1.1 Hz, 1H), 7.32 (d, $J$ = 16.2 Hz, 1H), 7.27-7.20 (m, 3H), 2.52 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.30, 148.32, 136.69, 136.47, 135.56, 132.18, 130.69, 130.26, 129.86, 129.31, 128.60, 127.61, 127.43, 126.44, 126.28, 125.89, 119.41, 20.16.

**(*E*)-2-(4-Methoxystyryl)quinoline (8)**[14a]: Following the general procedure, the title compound was isolated as a white solid (49.5 mg, Yield: 76%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.07 (t, $J$ = 9.4 Hz, 2H), 7.76 (dd, $J$ = 8.1, 1.2 Hz, 1H), 7.71-7.64 (m, 2H), 7.62 (d, $J$ = 4.0 Hz, 1H), 7.60-7.56 (m, 2H), 7.47 (ddd, $J$ = 8.1, 7.0, 1.1 Hz, 1H), 7.28 (d, $J$ = 16.3 Hz, 1H), 6.95-6.91 (m, 2H), 3.84 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.18, 156.43, 148.33, 136.38, 134.14, 129.81, 129.34, 129.13, 128.77, 127.60, 127.29, 126.87, 126.03, 119.21, 114.30, 55.45.

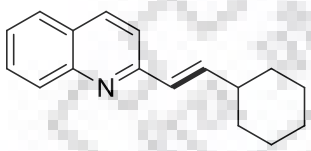
**(*E*)-2-(2-(Naphthalen-1-yl)vinyl)quinoline (9)**[14b]: Following the general procedure, the title compound was isolated as a yellow oil (50 mg, Yield: 71%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.52 (d, $J$ = 16.0 Hz, 1H), 8.34 (d, $J$ = 8.4 Hz, 1H), 8.14 (dd, $J$ = 12.5, 8.5 Hz, 2H), 7.91-7.85 (m, 3H), 7.80 (d, $J$ = 8.0 Hz, 1H), 7.76-7.70 (m, 2H), 7.60-7.45 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.13, 148.38, 136.57, 134.12, 133.84, 131.83, 131.57, 131.46, 129.92, 129.39, 129.09, 128.80, 127.65, 127.52, 126.46, 126.36, 126.08, 125.84, 124.31, 123.85, 119.67.

**(*E*)-2-(2-(Benzo[d][1,3]dioxol-5-yl)vinyl)quinoline (10)**[14a]: Following the general procedure, the title compound was isolated as a white solid (40 mg, Yield: 58%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.14 (d, $J$ = 8.6 Hz, 1H), 8.09 (d, $J$ = 8.5 Hz, 1H), 7.80 (d, $J$ = 7.9 Hz, 1H), 7.75-7.71 (m, 1H), 7.65 (t, $J$ = 12.3 Hz, 2H), 7.53-7.49 (m, 1H), 7.29 (s, 1H), 7.22 (d, $J$ = 1.5 Hz, 1H), 7.11 (dd, $J$ = 8.0, 1.4 Hz, 1H), 6.87 (d, $J$ = 8.0 Hz, 1H), 6.03 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.12, 148.29, 136.30, 134.15, 131.10, 129.72, 129.13, 127.49, 127.27, 127.25, 126.03, 122.81, 119.26, 115.00, 108.53, 106.06, 101.30.

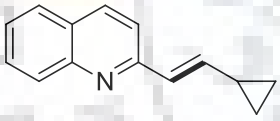
**(*E*)-2-(2-([1,1'-Biphenyl]-4-yl)vinyl)quinoline (11)**[14b]: Following the general procedure, the title compound was isolated as a white solid (34.5 mg, Yield: 45%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.13 (d, $J$ = 8.6 Hz, 1H), 8.08 (d, $J$ = 8.4 Hz, 1H), 7.78 (d, $J$ = 8.1 Hz, 1H), 7.75-7.68 (m, 5H), 7.66-7.62 (m, 3H), 7.60-7.56 (m, 1H), 7.48-7.42 (m, 4H), 7.36 (ddd, $J$ = 8.2, 4.6, 1.8 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.01, 148.32, 141.37, 140.53, 136.37, 135.58, 133.97, 129.78, 129.23, 129.02, 128.85, 128.82, 127.74, 127.52, 127.48, 127.15, 126.99, 126.20, 119.34.



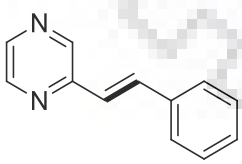
**(*E*)-2-(2-Cyclohexylvinyl)quinoline (14)**[14a]: Following the general procedure, the title compound was isolated as a pale-yellow oil (18 mg, Yield: 31%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (dd, $J$ = 13.4, 8.6 Hz, 2H), 7.73 (d, $J$ = 8.1 Hz, 1H), 7.68-7.62 (m, 1H), 7.53 (d, $J$ = 8.6 Hz, 1H), 7.44 (dd, $J$ = 11.0, 4.1 Hz, 1H), 6.76 (dd, $J$ = 16.1, 6.4 Hz, 1H), 6.66 (d, $J$ = 16.3 Hz, 1H), 2.30-2.19 (m, 1H), 1.93-1.66 (m, 6H), 1.36-1.23 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.88, 148.16, 143.48, 136.20, 129.57, 129.18, 128.74, 127.50, 127.21, 125.88, 118.80, 41.23, 32.63, 26.23, 26.10.



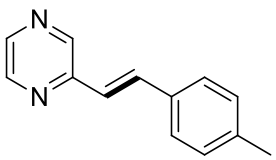
**(*E*)-2-(2-Cyclopropylvinyl)quinoline (15)**[14a]: Following the general procedure, the title compound was isolated as a pale-yellow oil (14.5 mg, Yield: 30%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01 (dd, $J$ = 16.4, 8.5 Hz, 2H), 7.72 (d, $J$ = 8.0 Hz, 1H), 7.64 (ddd, $J$ = 8.4, 6.9, 1.3 Hz, 1H), 7.46-7.40 (m, 2H), 6.76 (d, $J$ = 15.7 Hz, 1H), 6.37 (dd, $J$ = 15.7, 9.3 Hz, 1H), 1.75-1.65 (m, 1H), 0.94-0.89 (m, 2H), 0.70-0.63 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.28, 151.74, 148.20, 142.15, 136.23, 129.57, 129.10, 128.32, 127.49, 125.72, 118.93, 15.00, 8.13.



**(*E*)-2-Styrylpyrazine (16)**[14a]: Following the general procedure, the title compound was isolated as a white solid (35 mg, Yield: 77%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.63 (d, $J$ = 1.4 Hz, 1H), 8.54-8.53 (m, 1H), 8.39 (d, $J$ = 2.5 Hz, 1H), 7.74 (d, $J$ = 16.1 Hz, 1H), 7.59 (d, $J$ = 7.4 Hz, 2H), 7.41-7.37 (m, 2H), 7.34-7.31 (m, 1H), 7.15 (d, $J$ = 16.1 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 151.33, 144.45, 143.89, 142.86, 136.08, 135.27, 129.11, 128.95, 127.43, 124.06.

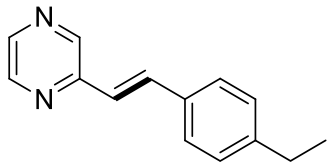


**(*E*)-2-(4-Methylstyryl)pyrazine (17)**[14a]: Following the general procedure, the title compound was isolated as a white solid (33.3 mg, Yield: 68%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.61 (d, $J$ = 1.4 Hz, 1H), 8.52-8.51 (m, 1H), 8.37 (d, $J$ = 2.5 Hz, 1H), 7.71 (d, $J$ = 16.1 Hz, 1H), 7.48 (d, $J$ = 8.1 Hz, 2H), 7.19 (d, $J$ = 8.0 Hz, 2H), 7.10 (d, $J$ = 16.1 Hz, 1H), 2.37 (s, 3H); $^{13}$C NMR

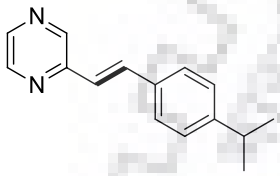


(100 MHz, $CDCl_3$) $\delta$ 151.57, 144.38, 143.76, 142.60, 139.27, 135.23, 133.36, 129.67, 127.37, 123.09, 21.48.

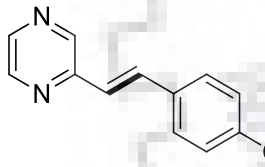
**(*E*)-2-(4-Ethylstyryl)pyrazine (18)**: Following the general procedure, the title compound was isolated as a white solid (38 mg, Yield: 72%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.62 (d, $J$ = 1.4 Hz, 1H), 8.52-8.51 (m, 1H), 8.37 (d, $J$ = 2.5 Hz, 1H), 7.72 (d, $J$ = 16.1 Hz, 1H), 7.51 (d, $J$ = 8.1 Hz, 2H), 7.22 (d, $J$ = 8.1 Hz, 2H), 7.10 (d, $J$ = 16.1 Hz, 1H), 2.66 (q, $J$ = 7.6 Hz, 2H), 1.24 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 151.59, 145.62, 144.41, 143.73, 142.63, 135.27, 133.61, 128.42, 127.44, 123.12, 28.83, 15.50. HRMS (ESI): Calculated for $[C_{14}H_{15}N_2]^+$ 211.1230; Found 211.1233.



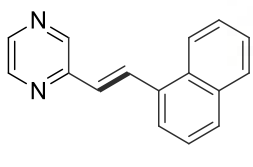
**(*E*)-2-(4-Isopropylstyryl)pyrazine (19)**[14a]: Following the general procedure, the title compound was isolated as a white solid (40 mg, Yield: 71%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.62 (d, $J$ = 1.5 Hz, 1H), 8.52 (dd, $J$ = 2.4, 1.6 Hz, 1H), 8.38 (d, $J$ = 2.5 Hz, 1H), 7.72 (d, $J$ = 16.1 Hz, 1H), 7.53-7.51 (m, 2H), 7.26-7.24(m, 2H), 7.11 (d, $J$ = 16.1 Hz, 1H), 2.92 (dt, $J$ = 13.8, 6.9 Hz, 1H), 1.26 (d, $J$ = 7.0 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 151.57, 150.25, 144.40, 143.79, 142.61, 135.22, 133.72, 127.48, 127.06, 123.15, 34.11, 23.97.



**(*E*)-2-(4-Methoxystyryl)pyrazine (20)**[18]: Following the general procedure, the title compound was isolated as a white solid (41.3 mg, Yield: 78%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.60 (d, $J$ = 1.7 Hz, 1H), 8.51 (d, $J$ = 3.8 Hz, 1H), 8.36 (d, $J$ = 2.5 Hz, 1H), 7.69 (dd, $J$ = 16.0, 2.4 Hz, 1H), 7.55-7.52 (m, 2H), 7.05-6.98 (m, 1H), 6.93-6.91 (m, 2H), 3.83 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.45, 151.73, 144.34, 143.65, 142.36, 134.85, 128.91, 128.85, 121.86, 114.38, 55.45.



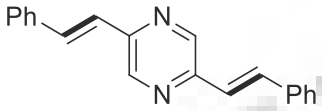
**(*E*)-2-(2-(Naphthalen-1-yl)vinyl)pyrazine (22)**[19]: Following the general procedure, the title compound was isolated as a white solid (38 mg, Yield: 65%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.55 (d, $J$ = 5.2 Hz, 1H), 8.49 (d, $J$ = 3.7 Hz, 1H), 8.29 (d, $J$ = 8.2 Hz, 1H), 8.09 (d, $J$ = 7.3 Hz, 1H), 7.87 (d, $J$ = 7.7 Hz, 2H), 7.79 (d, $J$ = 7.8 Hz, 2H), 7.58-7.52 (m, 3H), 7.15 (d, $J$ = 15.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 151.41, 144.47, 143.78, 142.72, 136.51, 133.86, 132.41, 131.32, 128.76, 128.56, 126.40, 125.96, 125.51, 125.35, 124.27, 123.79.



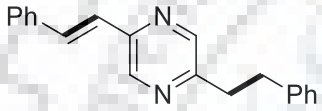
**(*E*)-2-(Non-1-en-1-yl)pyrazine (23)**: Following the general procedure, the title compound was isolated as a white solid (13 mg, Yield: 25%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.50 (d, $J$ = 1.4 Hz, 1H), 8.46-8.45 (m, 1H), 8.34 (d, $J$ = 2.5

Hz, 1H), 6.87 (dt, *J* = 15.7, 7.0 Hz, 1H), 6.47 (dt, *J* = 15.8, 1.4 Hz, 1H), 2.28 (ddd, *J* = 14.8, 7.3, 1.5 Hz, 2H), 1.53-1.46 (m, 2H), 1.37-1.27 (m, 8H), 0.86 (d, *J* = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 150.90, 144.05, 142.86, 142.22, 139.15, 126.27, 33.02, 31.77, 29.19, 29.13, 28.75, 22.64, 14.10. HRMS (ESI): Calculated for $[C_{13}H_{21}N_2]^+$ 205.1699; Found 205.1696.

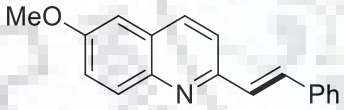
**2,5-Di((*E*)-styryl)pyrazine (24)**[20]: Following the general procedure, the title compound was isolated as a white solid (32 mg, Yield: 45%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.59 (s, 2H), 7.73 (d, *J* = 16.1 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 4H), 7.39 (d, *J* = 7.2 Hz, 3H), 7.33 (d, *J* = 7.2 Hz, 2H), 7.18 (d, *J* = 16.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.98, 149.17, 143.39, 136.33, 134.45, 128.94, 127.37, 124.15.



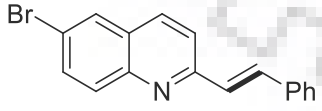

**(*E*)-2-Phenethyl-5-styrylpyrazine (24')**[14a]: Following the general procedure, the title compound was isolated as a white solid (22 mg, Yield: 31%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.57 (s, 1H), 8.30 (s, 1H), 7.67 (d, *J* = 16.1 Hz, 1H), 7.58 (d, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.33-7.26 (m, 3H), 7.23 – 7.12 (m, 4H), 3.14-3.04 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.57, 148.71, 143.94, 142.77, 140.84, 136.27, 134.07, 128.82, 128.75, 128.52, 128.45, 127.20, 126.23, 124.10, 37.02, 35.48.



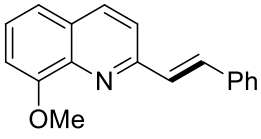

**(*E*)-6-Methoxy-2-styrylquinoline (25)**[14a]: Following the general procedure, the title compound was isolated as a white solid (50 mg, Yield: 77%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.99 (dd, *J* = 17.6, 8.9 Hz, 2H), 7.64-7.58 (m, 4H), 7.40-7.28 (m, 5H), 7.05 (d, *J* = 2.8 Hz, 1H), 3.92 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 157.72, 153.80, 144.34, 136.76, 135.21, 133.30, 130.71, 129.13, 128.87, 128.50, 128.38, 127.22, 122.44, 119.65, 105.31, 55.65.




**(*E*)-6-bromo-2-styrylquinoline (26)**[22]: Following the general procedure, the title compound was isolated as a white solid (25.5 mg, Yield: 33%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (d, *J* = 8.6 Hz, 1H), 7.95-7.91 (m, 2H), 7.75 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.72-7.61 (m, 4H), 7.43-7.30 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.43, 146.92, 136.39, 135.43, 135.10, 133.28, 130.95, 129.66, 129.18, 128.94, 128.59, 128.47, 127.42, 120.31, 120.00.

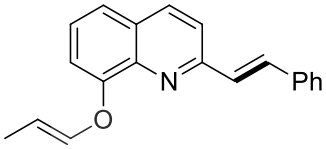



**(*E*)-8-Methoxy-2-styrylquinoline (27)**[16c]: Following the general procedure, the title compound was isolated as a white solid (38 mg, Yield: 58%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.07 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.64-7.61 (m, 2H), 7.56 (d, *J* = 11.0 Hz, 2H), 7.41-7.33 (m,

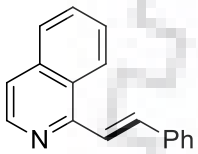


5H), 7.04 (d, *J* = 7.4 Hz, 1H), 4.09 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.23, 155.18, 140.10, 136.66, 136.39, 134.06, 129.77, 128.89, 128.62, 128.49, 128.46, 127.33, 126.48, 119.53, 119.27, 108.02, 56.20.

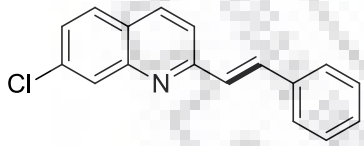
**8-((*E*)-Prop-1-en-1-yloxy)-2-((*E*)-styryl)quinoline (28)**: Following the general procedure, the title compound was isolated as a white solid (53 mg, Yield: 74%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.12 (d, *J* = 8.6 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.71-7.64 (m, 3H), 7.56 (d, *J* = 16.4 Hz, 1H), 7.48-7.42 (m, 4H), 7.35 (dd, *J* = 10.5, 4.1 Hz, 1H), 7.23 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.61 (dq, *J* = 5.7, 1.6 Hz, 1H), 5.17 – 5.12 (m, 1H), 1.91 (dd, *J* = 6.9, 1.7 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.47, 153.32, 141.43, 140.18, 136.65, 136.20, 134.25, 129.66, 128.79, 128.67, 128.55, 127.32, 126.09, 121.29, 119.45, 112.95, 109.55, 9.87. Elemental Analysis calculated: C, 83.59; H, 5.96; Found: C, 83.13; H, 6.07.



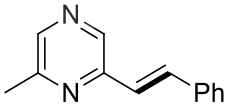

**(*E*)-1-Styrylisoquinoline (29)**[14b]: Following the general procedure, the title compound was isolated as a white solid (26 mg, Yield: 45%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.56 (d, *J* = 5.6 Hz, 1H), 8.37 (d, *J* = 8.5 Hz, 1H), 8.00 (t, *J* = 8.9 Hz, 2H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.71-7.60 (m, 4H), 7.56 (d, *J* = 5.6 Hz, 1H), 7.43-7.39 (m, 2H), 7.35-7.31 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.62, 142.55, 136.98, 136.82, 135.91, 130.03, 128.88, 128.73, 127.55, 127.43, 127.31, 126.84, 124.56, 122.89, 120.10.



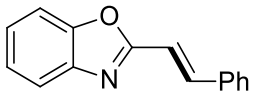

***(E)*-7-Chloro-2-styrylquinoline (30)**[23]: Following the general procedure, the title compound was isolated as a yellow solid (39 mg, Yield: 58%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.61 (s, 1H), 7.56 (dd, *J* = 7.9, 2.8 Hz, 3H), 7.34 (dd, *J* = 15.2, 7.2 Hz, 3H), 7.27 (t, *J* = 3.7 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.89, 147.65, 135.30, 135.09, 134.51, 134.15, 127.81, 127.64, 127.46, 127.38, 127.18, 126.33, 126.06, 124.64, 118.61.



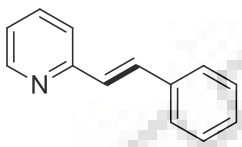

**(*E*)-2-Methyl-6-styrylpyrazine (31)**[14b]: Following the general procedure, the title compound was isolated as a white solid (22.5 mg, Yield: 46%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.44 (s, 1H), 8.28 (s, 1H), 7.71 (d, *J* = 16.1 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 16.1 Hz, 1H), 2.58 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 153.43, 150.16, 142.66, 140.60, 136.27, 134.73, 128.91, 128.90, 127.36, 124.49, 21.84.



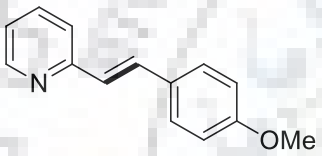
**(*E*)-2-Styrylbenzo[*d*]oxazole (32)**[14b]: Following the general procedure, the title compound was isolated as a white solid (25 mg, Yield: 45%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.80 (dd, $J$ = 16.3, 11.9 Hz, 1H), 7.75-7.66 (m, 1H), 7.63-7.59 (m, 2H), 7.56-7.51 (m, 1H), 7.41 (dd, $J$ = 11.5, 4.0 Hz, 2H), 7.37-7.25 (m, 3H), 7.09 (dd, $J$ = 16.4, 11.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.90, 150.51, 142.27, 139.57, 135.24, 129.87, 129.07, 127.65, 125.31, 124.61, 119.97, 114.05, 110.42.



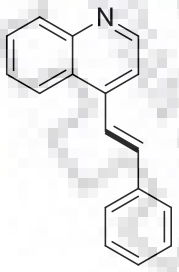

**(*E*)-2-Styrylpyridine (34)**[14a]: Following the general procedure, the title compound was isolated as a white solid (41 mg, Yield: 90%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.61-8.59 (m, 1H), 7.66-7.64 (m, 1H), 7.63-7.61 (m, 1H), 7.59-7.56 (m, 2H), 7.38-7.35 (m, 3H), 7.29 (ddd, $J$ = 7.2, 3.7, 1.2 Hz, 1H), 7.18 (s, 1H), 7.12 (ddd, $J$ = 4.8, 2.4, 1.2 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.71, 149.76, 136.74, 136.63, 132.82, 128.82, 128.43, 128.04, 127.20, 122.18, 122.15.



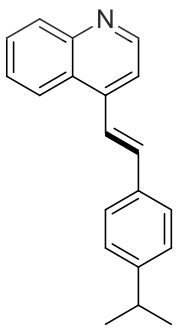

**(*E*)-2-(4-Methoxystyryl)pyridine (35)**[21]: Following the general procedure, the title compound was isolated as a white solid (48 mg, Yield: 91%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.58-8.56 (m, 1H), 7.64-7.55 (m, 2H), 7.53-7.49 (m, 2H), 7.33 (d, $J$ = 7.9 Hz, 1H), 7.09 (ddd, $J$ = 7.3, 4.8, 1.0 Hz, 1H), 7.03 (d, $J$ = 16.1 Hz, 1H), 6.91-6.88 (m, 2H), 3.81 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.93, 156.01, 149.67, 136.62, 132.35, 129.48, 128.53, 125.86, 121.90, 121.79, 114.26, 55.42.



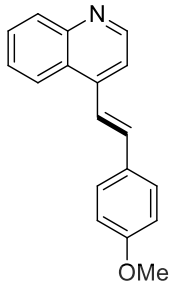

**(*E*)-4-Styrylquinoline (36)**[14a]: Following the general procedure, the title compound was isolated as a yellow oil (32 mg, Yield: 55%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.93 (d, $J$ = 4.4 Hz, 1H), 8.24 (d, $J$ = 8.4 Hz, 1H), 8.17 (d, $J$ = 8.4 Hz, 1H), 7.84 (d, $J$ = 16.1 Hz, 1H), 7.76 (t, $J$ = 7.5 Hz, 1H), 7.68-7.60 (m, 4H), 7.46 (t, $J$ = 7.3 Hz, 2H), 7.38 (t, $J$ = 12.9 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 150.23, 148.75, 142.97, 136.61, 135.16, 130.17, 129.31, 128.91, 128.80, 127.13, 126.51, 126.45, 123.49, 122.96, 117.10.



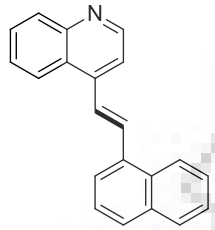

***(E)*-4-(4-Isopropylstyryl)quinoline (37)**[24]: Following the general procedure, the title compound was isolated as a yellow oil (20 mg, Yield: 29%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.88 (d, $J$ = 4.6 Hz, 1H), 8.21 (dd, $J$ = 8.5, 0.9 Hz, 1H), 8.12 (dd, $J$ = 8.5, 0.6 Hz, 1H), 7.74 (ddd, $J$ = 12.5, 10.8, 8.5 Hz, 2H), 7.57 (ddd, $J$ = 8.2, 3.3, 1.7 Hz, 4H), 7.30 (dd, $J$ = 13.9, 12.1 Hz, 3H), 2.95 (dq, $J$ = 13.8, 6.9 Hz, 1H), 1.28 (d, $J$ = 6.9 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 150.30, 150.04, 148.78, 143.25, 135.18, 135.16, 134.31, 130.19, 129.37, 127.27, 127.09, 126.53, 123.58, 122.02, 117.02, 34.10, 23.99. GC-MS (EI) m/z = 273.1



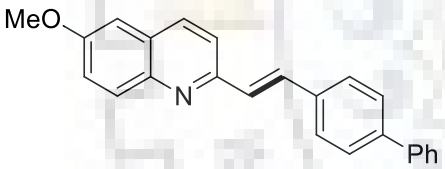
***(E)*-4-(4-Methoxystyryl)quinoline (38)**[24]: Following the general procedure, the title compound was isolated as a yellow oil (23 mg, Yield: 35%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.87 (d, $J$ = 4.6 Hz, 1H), 8.21 (dd, $J$ = 8.5, 0.9 Hz, 1H), 8.12 (dd, $J$ = 8.5, 0.6 Hz, 1H), 7.74-7.64 (m, 2H), 7.59-7.55 (m, 4H), 7.29 (d, $J$ = 16.1 Hz, 1H), 6.95 (d, $J$ = 8.8 Hz, 2H), 3.85 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.31, 150.23, 148.73, 143.39, 134.78, 130.10, 129.46, 129.36, 128.62, 126.51, 126.47, 123.57, 120.56, 116.80, 114.43, 55.48.



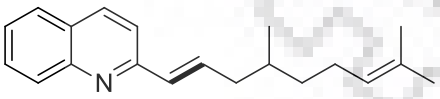

***(E)*-4-(2-(Naphthalen-1-yl)vinyl)quinoline (39)**[22]: Following the general procedure, the title compound was isolated as a yellow solid (42 mg, Yield: 60%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.87 (d, $J$ = 4.6 Hz, 1H), 8.15 (t, $J$ = 8.2 Hz, 2H), 8.06 (dd, $J$ = 20.3, 12.2 Hz, 2H), 7.84-7.75 (m, 4H), 7.67 (ddd, $J$ = 8.3, 6.8, 1.4 Hz, 1H), 7.62 (d, $J$ = 4.5 Hz, 1H), 7.53-7.46 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 150.38, 148.83, 143.24, 134.38, 133.84, 132.52, 131.47, 130.24, 129.48, 129.26, 128.86, 126.71, 126.65, 126.55, 126.21, 125.75, 124.49, 123.67, 123.65, 117.47. GC-MS (EI) m/z = 281.1.




**(E)-2-(2-([1,1'-Biphenyl]-4-yl)vinyl)-6-methoxyquinoline (40)**[14a]: Following the general procedure, the title compound was isolated as a white solid (34 mg, Yield: 40%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.00 (dd, $J$ = 16.5, 8.9 Hz, 2H), 7.64 (ddd, $J$ = 6.6, 5.5, 2.6 Hz, 8H), 7.49-7.41 (m, 3H), 7.36 (ddd, $J$ = 7.6, 5.3, 3.9 Hz, 2H), 7.06 (d, $J$ = 2.8 Hz, 1H), 3.93 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.63, 152.68, 143.27, 140.06, 139.52, 134.71, 134.10, 131.70, 129.61, 128.01, 127.81, 127.29, 126.55, 126.44, 126.41, 125.94, 121.34, 118.60, 104.23, 54.54.




**(E)-2-(4,8-Dimethylnona-1,7-dien-1-yl)quinoline (41)**[14b]: Following the general procedure, the title compound was isolated as a colorless oil (32 mg, Yield: 46%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (dd, $J$ = 15.0, 8.5 Hz, 2H), 7.74 (dd, $J$ = 8.1, 1.1 Hz, 1H), 7.66 (ddd, $J$ = 8.4, 6.9, 1.5 Hz, 1H), 7.53 (d, $J$ = 8.6 Hz, 1H), 7.45 (ddd, $J$ = 8.0, 7.0, 1.1 Hz, 1H), 6.77 (ddd, $J$ = 36.6, 21.8, 11.5 Hz, 2H), 5.10 (dddd, $J$ = 7.1, 5.7, 2.7, 1.4 Hz, 1H), 2.36-2.31 (m, 1H), 2.16 (ddd, $J$ = 11.0, 8.1, 4.0 Hz, 1H), 2.15-1.97 (m, 2H), 1.71 – 1.68 (m, 1H), 1.67 (d, $J$ = 1.0 Hz, 3H), 1.60 (s, 3H), 1.49-1.38 (m, 1H), 1.23 (dddd, $J$ = 13.7, 9.3, 7.0, 5.0 Hz, 1H), 0.96 (d, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.52, 148.13, 136.75, 136.25, 132.37, 131.41, 129.63, 129.17, 127.51, 127.23, 125.94, 124.76, 118.75, 40.72, 36.91, 32.78, 25.84, 25.71, 19.72, 17.78.



**2-((1*E*,10*Z*)-Nonadeca-1,10-dien-1-yl)quinoline (42)**: Following the general procedure, the title compound was isolated as a colorless oil (51 mg, Yield: 52%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (dd, $J$ = 13.4, 8.5 Hz, 2H), 7.75 (t, $J$ = 8.8 Hz, 1H), 7.66 (ddd, $J$ = 8.3, 5.3, 1.2 Hz, 1H), 7.51 (d, $J$ = 8.6 Hz, 1H), 7.45 (t, $J$ = 7.2 Hz, 1H), 6.81 (dt, $J$ = 15.8, 6.6 Hz, 1H), 6.70 (d, $J$ = 16.0 Hz, 1H), 5.34 (dd, $J$ = 9.5, 4.7 Hz, 2H), 2.32 (p, $J$ = 7.3 Hz, 2H), 2.00 (d, $J$ = 2.9 Hz, 4H), 1.54 (dt, $J$ = 14.9, 7.3 Hz, 2H), 1.28 (dd, $J$ = 14.9, 9.8 Hz, 20H), 0.86 (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.62, 148.17, 138.12, 136.20, 131.11, 130.04, 129.90, 129.57, 129.20, 127.47, 127.22, 125.88, 118.77, 33.13, 31.97, 29.85, 29.83, 29.59, 29.48, 29.40, 29.38, 29.34, 29.30, 28.98, 27.30, 27.28, 22.75, 14.17. Elemental Analysis calculated: C, 85.87; H, 10.55; Found: C, 85.52; H, 10.27.

**(*E*)-2-(3-(6-Methoxynaphthalen-2-yl)but-1-en-1-yl)quinoline (43)**: Following the general procedure, the title compound was isolated as a pale blue oil (38 mg, Yield: 45%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.40 (d, $J$ = 6.2 Hz, 1H), 8.00 (d, $J$ = 8.5 Hz, 2H), 7.85 (d, $J$ = 8.8 Hz, 2H), 7.76 (d, $J$ = 8.6 Hz, 1H), 7.68 (dd, $J$ = 17.9, 9.8 Hz, 1H), 7.36-7.25 (m, 4H), 7.16 (dd, $J$ = 26.9, 13.1 Hz, 3H), 3.94 (s, 3H), 3.93-3.89 (m, 1H), 2.69 (d, $J$ = 1.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.01, 159.78, 137.30, 132.65, 131.13, 130.08, 129.18, 127.84, 127.11, 124.69, 119.78, 119.75, 115.00, 105.77, 55.44, 29.71, 26.56. Elemental Analysis calculated: C, 84.92; H, 6.22; Found: C, 84.47; H, 5.97.

**Procedure for the synthesis of 2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-1,2,3,4-tetrahydroquinoline (44)**[25]: Compound **3h** (0.073 mmol) and $NiCl_2.6H_2O$ (0.0146 mmol) were taken in a 50 mL RB and dissolved in 3 mL of methanol. Then $NaBH_4$ (0.3 mmol) was added in portion at 0 °C and stirred for 30 min at RT. After completion of the reaction methanol was evaporated and black ppt. was dissolved in 10% HCl, the acidic solution was basified by adding conc. ammonium hydroxide solution and then extracted with ether. The extract was dried over MgSO4, evaporated and purified by column chromatography to yield the desired product as yellow oil (19.5 mg, 95% yield).

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.96 (t, $J$ = 7.4 Hz, 2H), 6.72 (dd, $J$ = 14.1, 4.7 Hz, 2H), 6.66-6.58 (m, 2H), 6.46 (d, $J$ = 7.6 Hz, 1H), 5.92 (s, 2H), 3.74 (s, 1H), 3.28 (dtd, $J$ = 9.4, 6.3, 3.0 Hz, 1H), 2.77 (tdd, $J$ = 16.2, 11.0, 4.9 Hz, 2H), 2.68-2.63 (m, 2H), 2.01-1.95 (m, 1H), 1.78 (ddd, $J$ = 8.7, 8.1, 3.3 Hz, 2H), 1.70-1.61 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$

147.76, 145.80, 144.52, 135.72, 129.35, 126.83, 121.43, 121.11, 117.20, 114.27, 108.87, 108.32, 100.90, 51.07, 38.54, 31.96, 28.04, 26.29.

**Procedure for the synthesis of 2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (45)**[25]: In a 25 mL RB compound **3ha** ( 0.0391 mmol), $K_2CO_3$ (0.06 mmol), MeI (0.235 mmol) and THF (3 mL) were taken, sealed and refluxed for 20h. The reaction mixture was cooled to rt, then $H_2O$ (3 mL) was added and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ then concentrated *in vacuo*. Purification afforded the desired products **3hb** (10 mg, 85% yield).

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.96 (dd, $J$ = 36.2, 7.2 Hz, 2H), 6.64 (t, $J$ = 9.2 Hz, 2H), 6.52 (dd, $J$ = 32.1, 19.1 Hz, 3H), 5.85 (s, 2H), 3.21 (t, $J$ = 8.1 Hz, 1H), 2.84 (s, 3H), 2.76 (dd, $J$ = 17.5, 10.1 Hz, 1H), 2.65-2.54 (m, 2H), 2.44 (dd, $J$ = 19.4, 10.3 Hz, 1H), 2.27 (dd, $J$ = 15.7, 8.1 Hz, 1H), 1.90-1.83 (m, 2H), 1.63 (dd, $J$ = 12.0, 7.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 147.35, 145.33, 144.97, 135.96, 127.94, 127.20, 121.31, 120.86, 115.71, 110.26, 107.84, 107.68, 100.94, 58.50, 38.07, 33.25, 31.17, 24.56, 23.05.

**[5A.8] Spectra of Selected Compounds**:

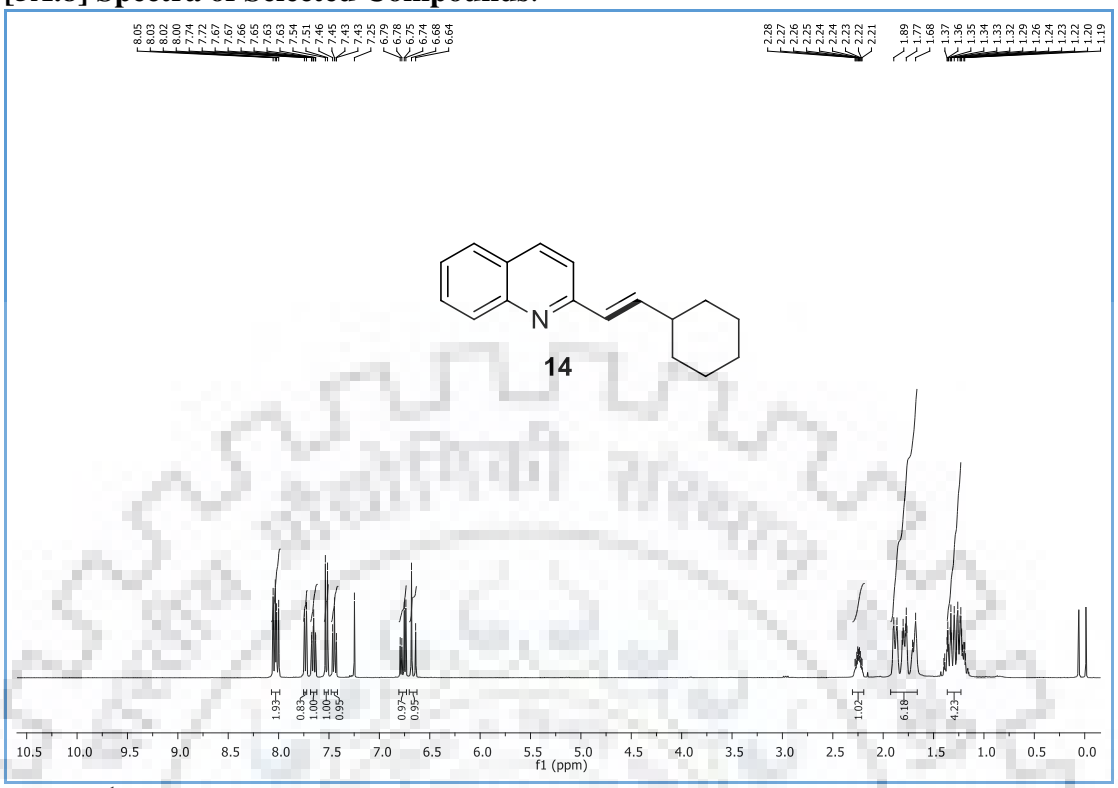



**Fig 2a:** $^{1}$H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **14**

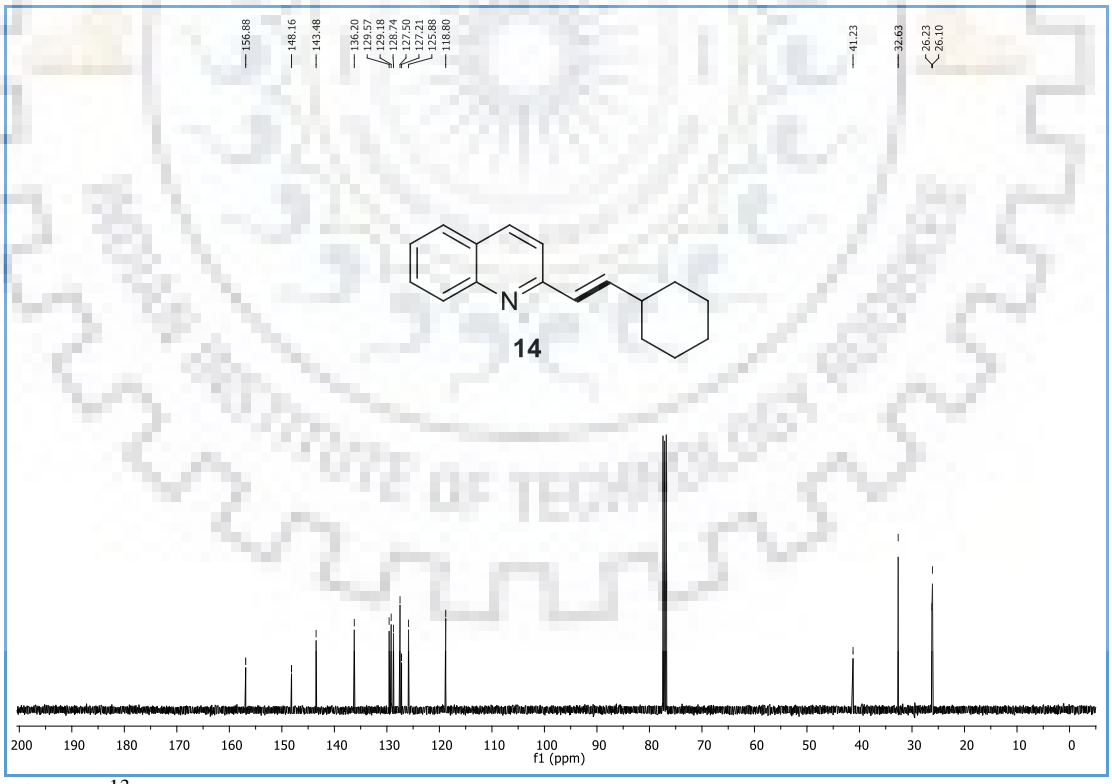



**Fig 2b:** $^{13}$C NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **14**

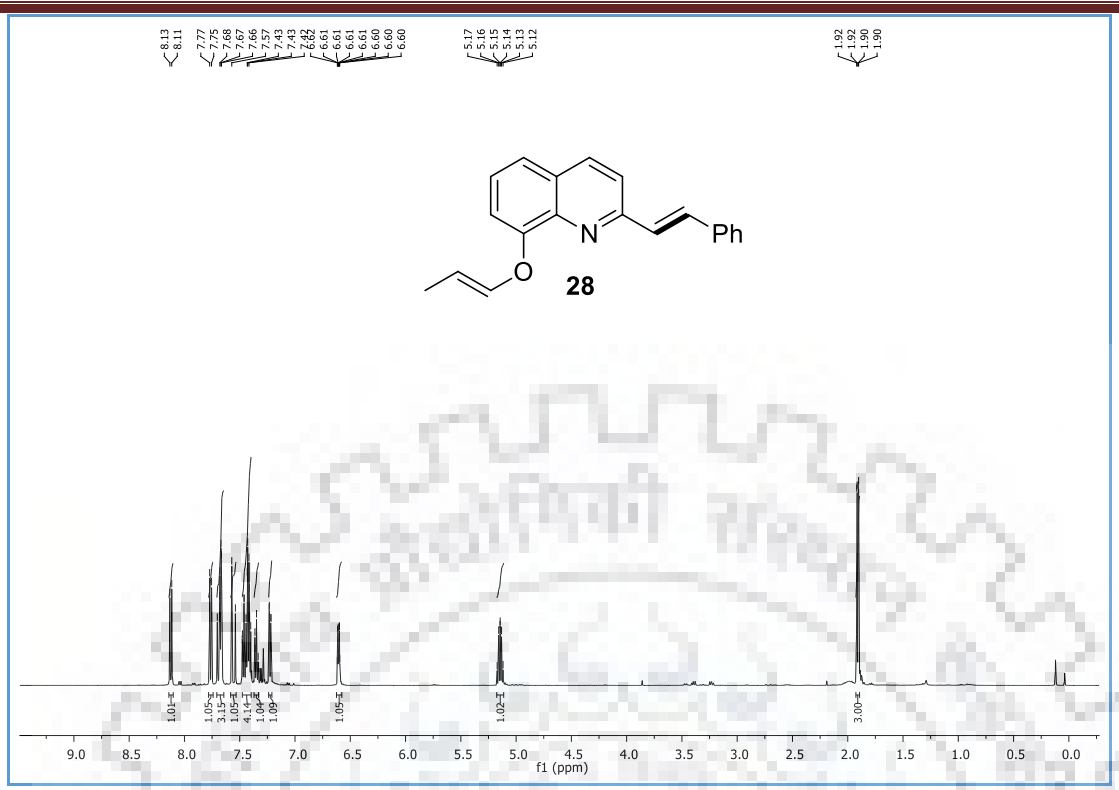



**Fig 3a:** $^{1}$H NMR ($CDCl_3$, 500 MHz) Spectrum of Compound **28**

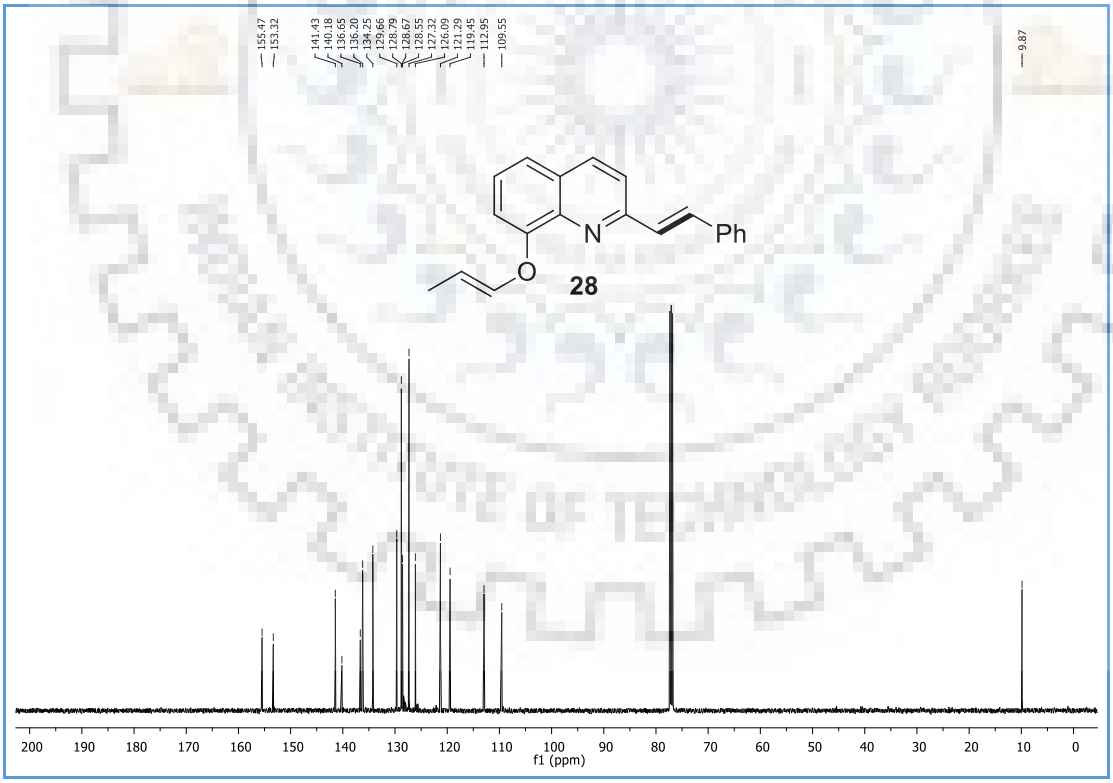



**Fig 3b:** $^{13}$C NMR ($CDCl_3$, 125 MHz) Spectrum of Compound **28**

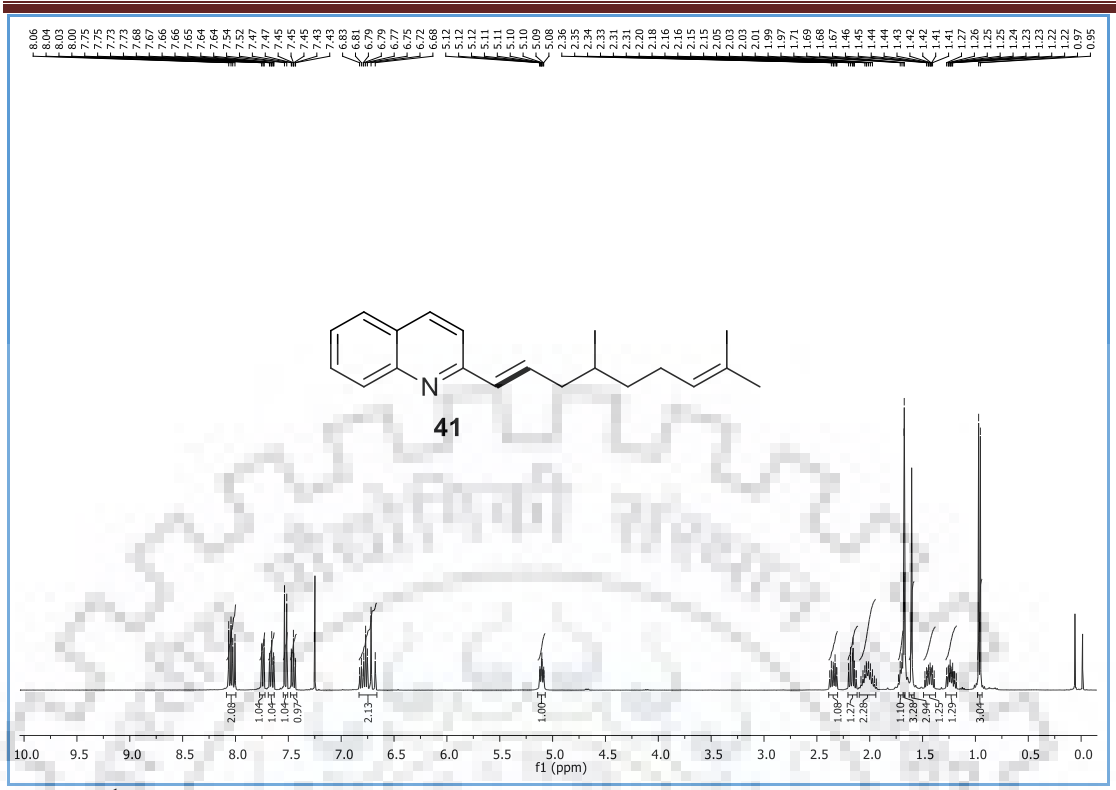



**Fig 4a:** $^{1}$H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **41**

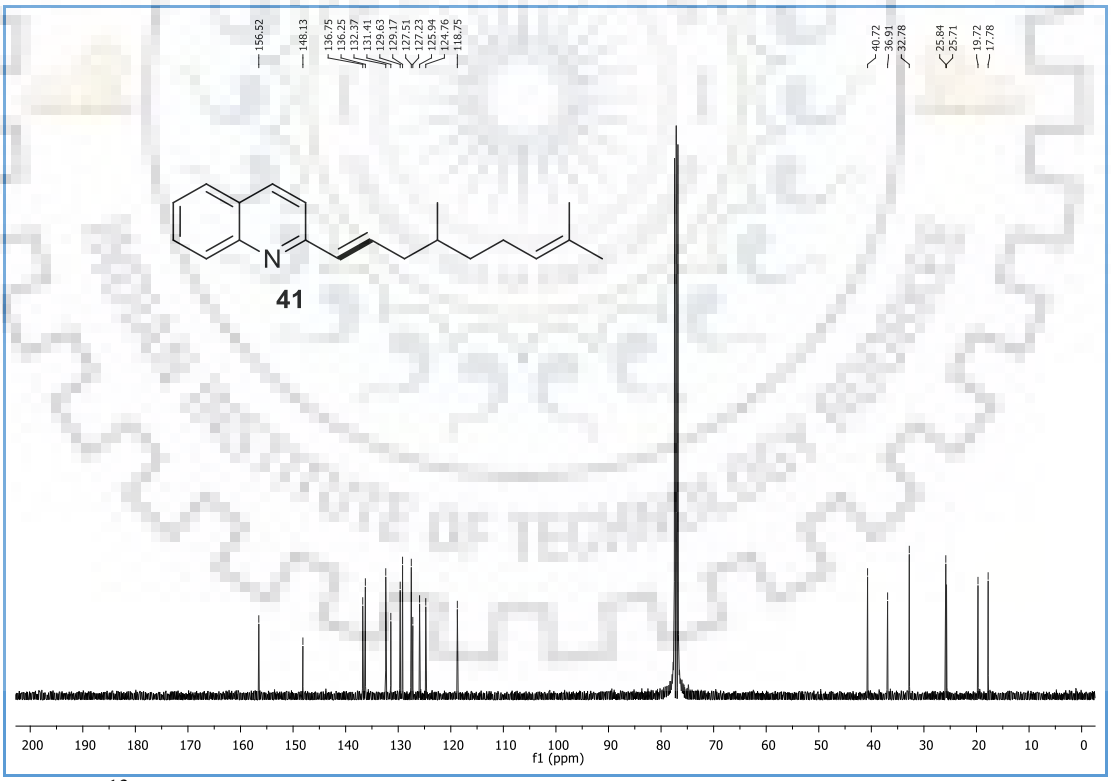
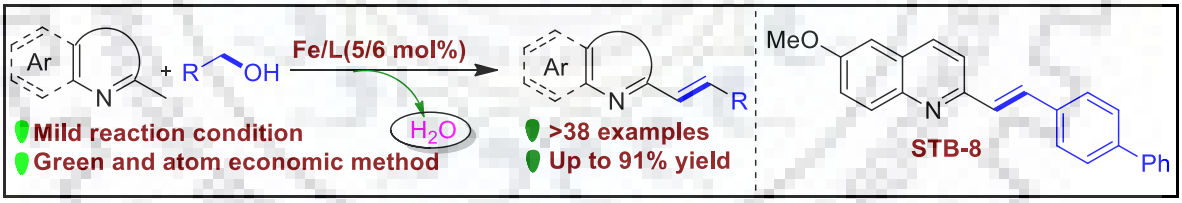



**Fig 4b:** $^{13}$C NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **41**

## Chapter-5: Section-B: Iron-catalyzed dehydrogenative alkylation of alkyl-substituted *N*-heteroaromatics with alcohols

This chapter describe the direct $\alpha$-olefination of alkyl substituted *N*-heteroarenes with primary alcohols using an efficient Fe-catalyst ligated with nitrogen ligands. This dehydrogenated coupling involving alkyl *N*-heteroaromatics with a series of primary alcohols resulted a series of functionalized *E*-substituted olefins with very high olefin/alkane selectivity. A series of deuterium labeling experiments, kinetics studies and control-experiments provide evidences for the participation of the benzylic C-H/D bond of alcohols and C($sp^3$)-H/D bond of 2-alkylheteroarenes following dehydrogenative couplings.



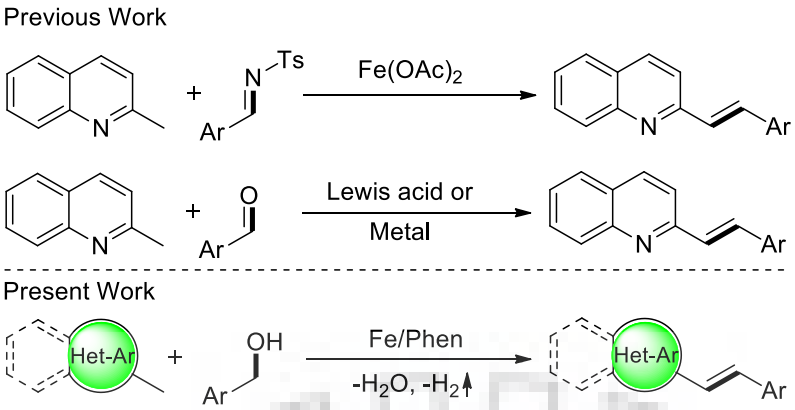

*Org. Lett.* **2019.** DOI: 10.1021/acs.orglett.9b02793

## [5B.1] Introduction:

Transition metal-catalyzed C($sp^3$)-H bond functionalization is an expedient transformation for the construction of C-C bond in synthetic organic chemistry.[1] Functionalization of an alkyl group directly attached to heteroaromatic ring remains limited. The direct C($sp^3$)-H bond activation of alkylazaarenes provides valuable access to *E*-olefins substituted heteroaromatic rings which, are ubiquitous structural motifs found in many bioactive natural products, agrochemicals, pharmaceuticals, and as important precursors used in the synthesis of numerous heterocycles.[2] These structures were originally synthesized by the condensation of 2-methylazaarenes and aldehydes using stoichiometric amounts of strong acids or bases.[3] Currently, there are several methods including classical approaches for the synthesis of stereo-selective alkenes. Generally, the leaving group have been conventionally exploited for the synthesis of stereo-selective olefin derivatives, such as, Wittig reactions, Horner-Wadsworth-Emmons reaction, Julia olefination, Peterson olefination etc.[4] Furthermore, precious-metal-catalyzed Heck or Suzuki couplings and olefin metathesis are also efficient methods for the synthesis of styryl derivatives.[5] Notably, most of these methods suffers from: (i) generation of stoichiometric waste (ii) strong basic or acidic reaction conditions (iii) multi-step sequences (iv) harsh reaction conditions and (v) poor *E*/*Z* selectivity.[4-5] Recently, direct C($sp^3$)-H bond functionalization of 2-alkylazaarenes catalyzed by iron metal with the electrophilic reagents, such as, *N*-sulfonyl aldimines,[6] Brønsted acids or Lewis acids,[7] as well as palladium-based metals,[8] has been extensively used to synthesize substituted azaarene derivatives and has been discussed in the Chapter 5A.

## [5B.2] Aim of Present Work:

Since last few decades, acceptorless dehydrogenative couplings (ADCs) of alcohols have extensively been used for the synthesis of unsaturated compounds. However, the replacement of expensive and precious metal catalysts with non-precious earth abundant metal catalysts (Fe, Mn, Ni and Co) for such key catalytic conversions gained more attention for sustainable technologies.[9] However, to the best of our knowledge, no iron-catalyzed olefination of primary alcohols with methyl-*N*-heteroaromatics is known. Herein, we report the first Fe-catalyzed example for *E*-olefination of C($sp^3$)–H bonds in alkylazaarenes, such as quinolines, pyridines and pyrazines (Scheme 1).




**Scheme 1:** Iron-catalyzed direct α-olefination of alkyl *N*-Heteroaromatics with primary alcohols

**[5B.3] Results and discussion:**

At the outset of the investigation, the reaction of 2-methylquinoline (**1a**) with 4-methoxy benzyl alcohol (**2a**) was chosen as a model substrate for optimization studies. Iron (II) acetate (5 mol%) and 1,10-phenanthroline **L1** (6 mol%) in the presence of *t*-BuOK (1.0 equiv.) as a base, resulted 80% isolated yield of **3** along with trace amount of undesired alkylated product **3'** (Table 1). No improvements in product yields were observed with iron catalyst having oxidation state of (0, or III) (Table 1).

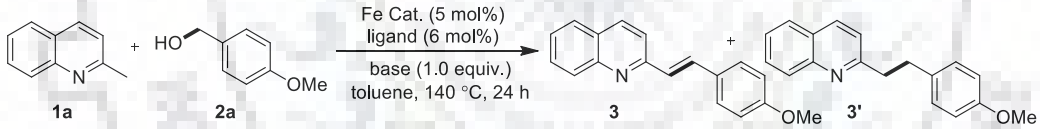



**Table 1**: Screening of catalyst [a]

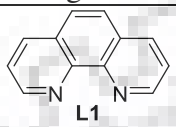
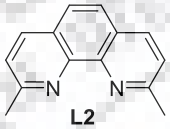
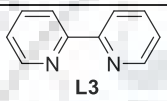
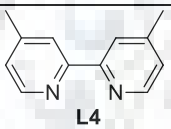
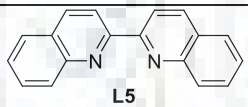
| Entry | Fe-Catalyst | GC-MS Conversion, **3** (%) | GC-MS Conversion, **3'** (%) |
|---|---|---|---|
| **1** | **$Fe(OAc)_2$** | **82 (80)** | **8** |
| 2 | $Fe(acac)_3$ | 29 | 5 |
| 3 [b] | $Fe_2(CO)_9$ | 69 | 19 |
| 4 [c] | $Fe(OAc)_2$ | 43 | 6 |
| 5 | - | 20 | 0 |

Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), 4-Methoxy Benzyl alcohol **2a** (0.50 mmol), **Fe Cat. (5 mol%)**, Phen (6 mol%), *t*-BuOK (0.25 mmol), toluene (1.0 mL), Schlenk tube under nitrogen atmosphere, 140 ºC oil bath, 24 h reaction time. [b] $Fe_2(CO)_9$ (2.5 mol%), Phen (3 mol%) were used. [c] $Fe(OAc)_2$ (2.5 mol%), Phen (3 mol%) were used.

Further, screening of nitrogen-based ligands **L2-L5** were found inefficient (Table 2). Furthermore, screening of other solvents, such as *p*-xylene, 1,4-Dioxane, DMA and *t*-amyl alcohol, proven less effective (Table 3). Next, we examined the effect of a variety of bases and no increment in the product yield was observed (Table 4). When, catalyst loading was reduced to 2.5 mol% with 3 mol% ligand, we observed albeit with moderate product yield

(Table 1). Control experiments in absence of ligand and iron catalyst resulted in 20% yield, whereas, in absence of base no α-olefination product was obtained. To our delight, GC-MS analysis of the crude reaction mixture detected trace amount of alkylated product **3′**. Notably, NMR analysis identified the *E*-selective desired product, whereas, we did not notice any *Z*-selective olefin under standard reaction conditions.

**Table 2**: Screening of ligands [a]

| Entry | Ligand | GC-MS Conversion **3** (%) | GC-MS Conversion **3'** (%) |
|---|---|---|---|
| 1 |  L1 | **82 (80)** [b] | **8** |
| 2 |  L2 | 59 | 39 |
| 3 |  L3 | 56 | 22 |
| 4 |  L4 | 12 | 2 |
| 5 |  L5 | 41 | 8 |
| 6 | No Ligand | 21 | <5 |

Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), 4-methoxy benzyl alcohol **2a** (0.50 mmol), $Fe(OAc)_2$ (5.0 mol%), **Ligand (6.0 mol%)**, *t*-BuOK (0.25 mmol), toluene (1.0 mL), Schlenk tube under nitrogen atmosphere, 140 ºC oil bath, 24 h reaction time. [b] Isolated yield.

**Table 3**: Screening of solvents [a]

| Entry | Solvent | GC-MS Conversion, **3** (%) | GC-MS Conversion, **3'** (%) |
|---|---|---|---|
| **1** | **Toluene** | **82 (80)** [b] | **8** |
| 2 | *p*-Xylene | 33 | 1 |
| 3 | 1,4-Dioxane | 29 | 66 |
| 4 | DMA | 1 | 0 |
| 5 | *t*-Amylalcohol | 44 | 16 |

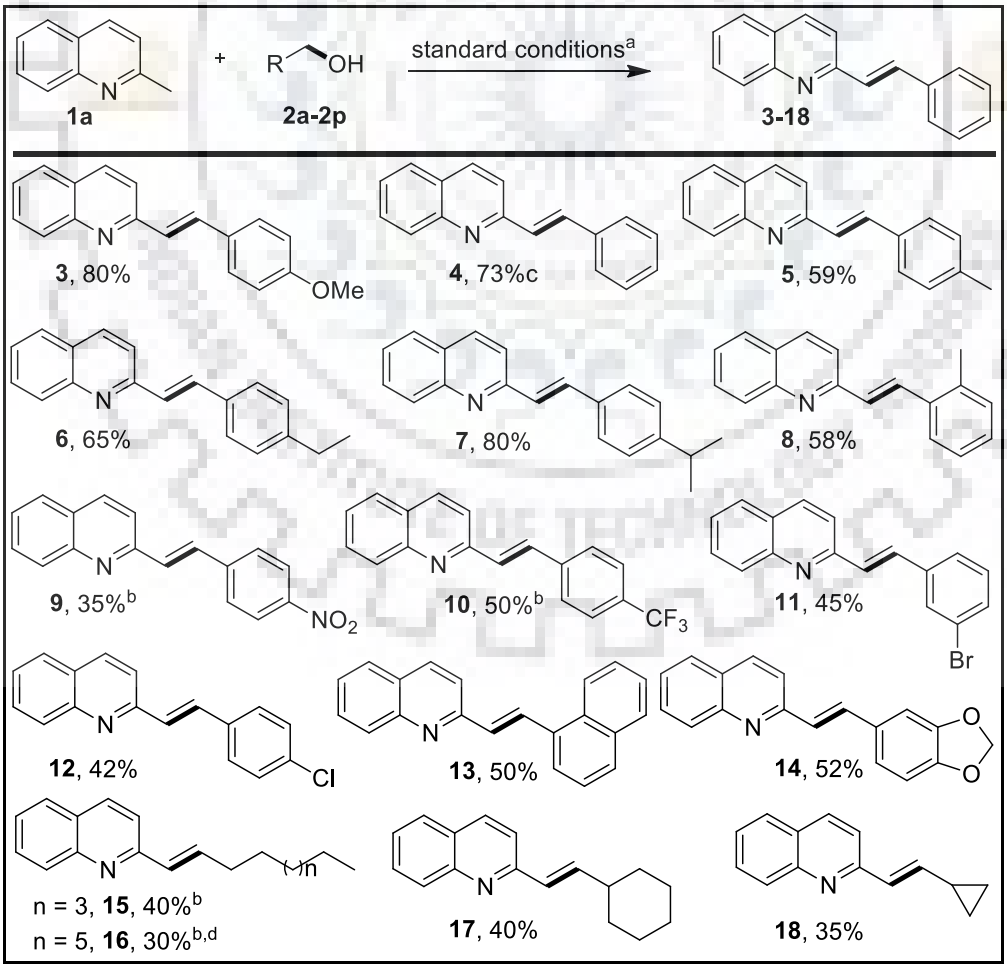
Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), 4-Methoxy Benzyl alcohol **2a** (0.50 mmol), $Fe(OAc)_2$ (5 mol%), Phen (6 mol%), *t*-BuOK (0.25 mmol), **solvent** (1.0 mL), Schlenk tube under nitrogen atmosphere, 140 ºC oil bath, 24 h reaction time.

**Table 4**: Screening of base [a]

| Entry | Base | GC-MS Conversion **3** (%) | GC-MS Conversion **3'** (%) |
|---|---|---|---|
| **1** | ***t*-BuOK** | **82 (80)** [b] | **8** |
| 2 | *t*-BuONa | 47 | 9 |
| 4 | $K_2CO_3$ | 1 | 0 |
| 5 | NaOH | 66 | 11 |
| 6 | KOH | 26 | 6 |
| 7 | - | 0 | 0 |

Reaction conditions: [a] Quinaldine **1a** (0.25 mmol), 4-methoxy benzyl alcohol **2a** (0.50 mmol), $Fe(OAc)_2$ (5.0 mol%), Phen (6.0 mol%), **base (0.25 mmol)**, toluene (1.0 mL), Schlenk tube under nitrogen atmosphere, 140 ºC oil bath, 24 h reaction time. [b] Isolated yield.

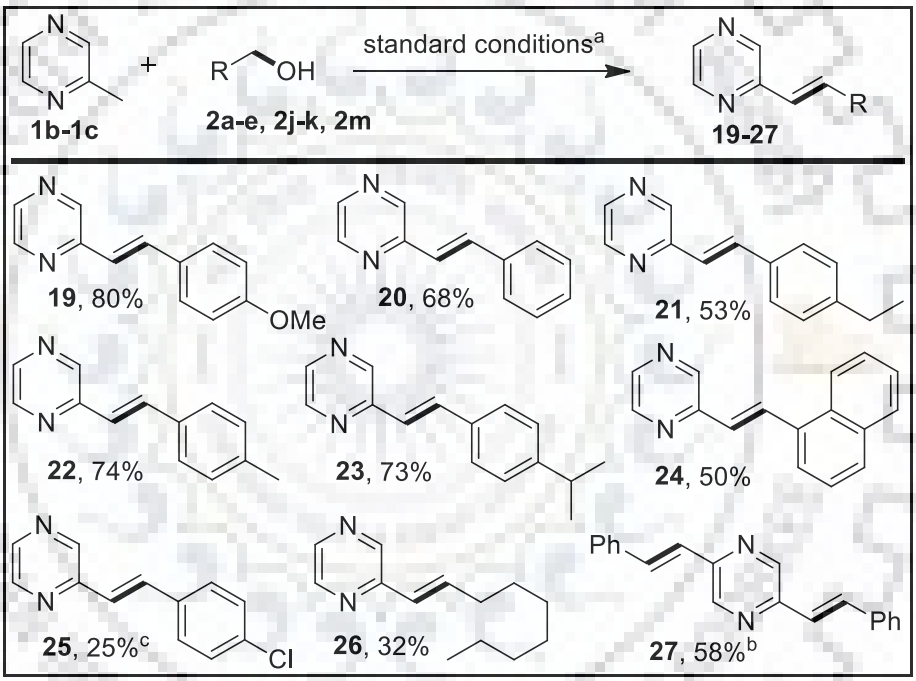
With the optimized reaction conditions of Table 1, we then investigated the impact of electronic and steric modulation of both methylazaarenes and alcohol derivatives on the reaction outcomes. Initially, the 2-methylquinoline **1a** reacted with electronically rich benzyl alcohol derivatives to give the corresponding products in good to moderate yields (Scheme 2, **3-7**). The satisfactory yield was observed even with sterically hindered 2-methyl benzyl alcohol (**8**). Importantly, electronically deficient 4-nitrobenzyl alcohol and 4-$CF_3$-benzyl alcohol resulted the desired products in moderate to good isolated yields (Scheme 2, **9-10**). The 2-alkylazaareenes, bearing halogen groups, were also obtained in good yields (**11-12**). Gratifyingly, 1-naphthylmethanol as well as benzyl alcohol having oxygen heterocycles smoothly reacted to obtain the corresponding products in acceptable yields (**13-14**). Importantly, alkyl alcohols such as, octanol, decanol, 1-cyclopropyl methanol and 1-cyclohexylmethanol also reacted smoothly to give the desired products **15-18**.




**Scheme 2**: Scope the 2-methylquinoline with alcohols [a]

Reaction conditions: [a] Unless specified, the reaction was carried out with quinaldine **1a** (0.25 mmol), alcohols **2** (0.50 mmol), $Fe(OAc)_2$ (5.0 mol%), Phen (6.0 mol%), *t*-BuOK (0.25 mmol), toluene (1.0 mL), Schlenk tube under nitrogen atmosphere, 140 ºC oil bath, 24 h reaction time. [b] 1,4-dioxane was used. [c] *t*-BuOK (0.125 mmol) was used. [d] GC-MS conversion.

Further, the scopes and limitations of several different methylazaarene derivatives were investigated (Schemes 3–5). 2-methylpyrazine was reacted efficiently with benzyl alcohols having electron-donating functionalities (Scheme 3, **19-23**). Again, halogen substituted benzyl alcohol delivered the corresponding product in moderate yield (**25**). 1-naphthyl methanol and octanol gave the desired products **24** and **26** in 32-50% yield respectivelly. Remarkably, the 2,5-dimethyl pyrazine was reacted with benzylalcohol, to give selective bis-*E*-olefination product **27** in 58% yield.

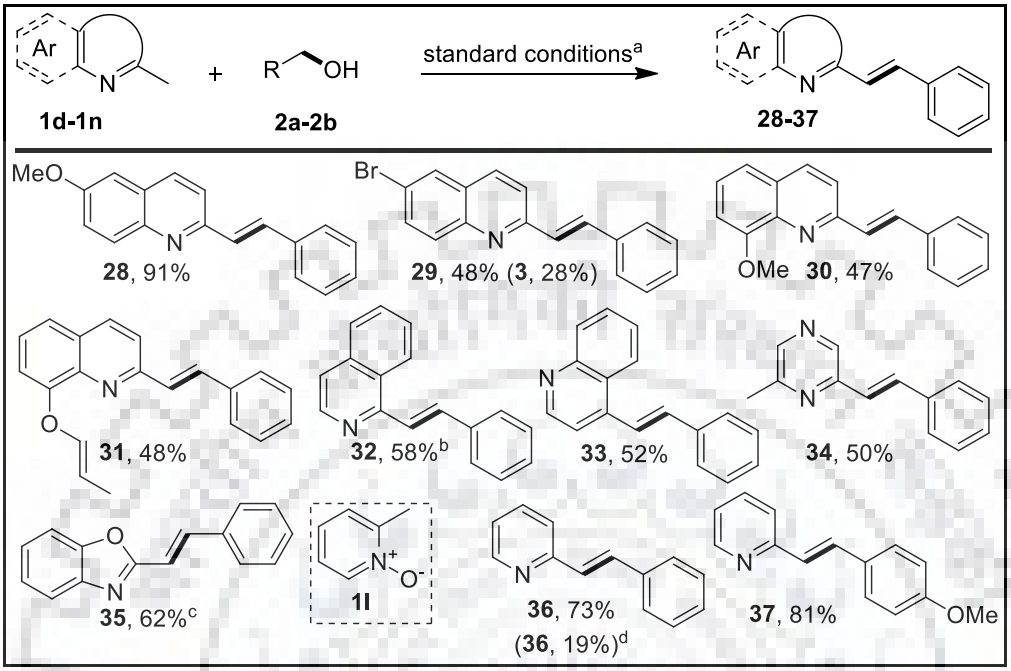



**Scheme 3:** Scope of methylpyrazine with alcohols [a]

Reaction conditions: [a] Unless specified, the reaction was carried out with **1** (0.25 mmol), alcohols **2** (0.50 mmol), $Fe(OAc)_2$ (5.0 mol%), Phen (6.0 mol%), *t*-BuOK (0.25 mmol), toluene (1.0 mL), Schlenk tube under nitrogen atmosphere, 140 ºC oil bath, 24 h reaction time. [b] Alcohol **2b** (1.0 mmol), $Fe(OAc)_2$ (10.0 mol%), Phen (12.0 mol%), *t*-BuOK (0.50 mmol) were used. [c] GC-MS conversion.

Further to determine the efficiency and feasibility of this method, substituted 2-methyl quinolines were chosen as the substrates (Scheme 4). Methoxy and ether substituted 2-methyl quinolines were readily converted to the desired products in good to excellent yields (**28**, **30-31**). To our delight, 6-bromo-2-methyl quinoline also participated in the reaction to give the desired product (**29**) in 48% yield along with the dehalogenated product (**3**) in 28% yield. Notably, 1-methylisoquinoline, 4-methylquinoline, 2,6-dimethyl pyrazine and 2-methylbenzoxazole were efficiently transformed to **32-35**. However, 2-methyl pyridine *N*-

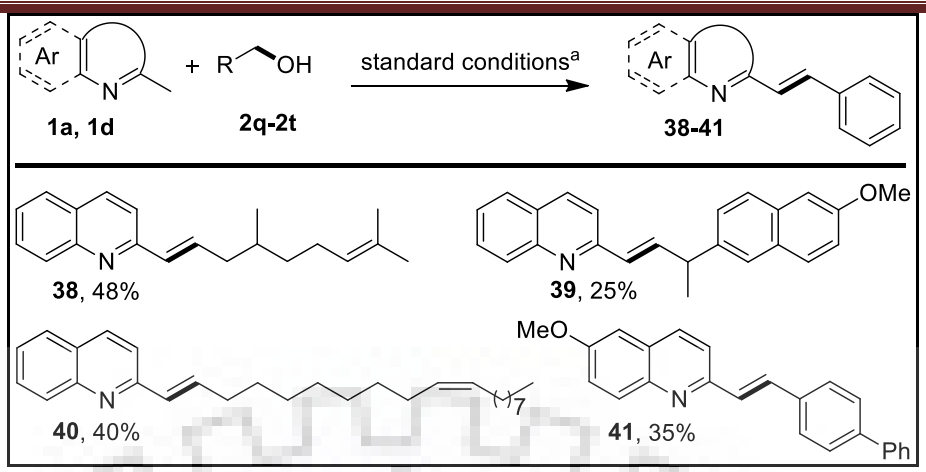
oxide was reacted efficiently, to obtain the corresponding products **36-37** in excellent yields; whereas in case of 2-methyl pyridine only 19% product yield was observed in GC-MS analysis.




**Scheme 4**: Scope of methylazaarenes with alcohols [a]

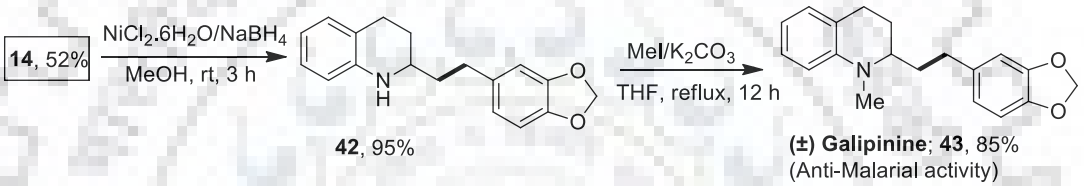
Reaction conditions: [a] Unless specified, the reaction was carried out with **1** (0.25 mmol), alcohols **2** (0.50 mmol), $Fe(OAc)_2$ (5.0 mol%), Phen (6.0 mol%), *t*-BuOK (0.25 mmol), toluene (1.0 mL), Schlenk tube under nitrogen atmosphere, 140 ºC oil bath, 24 h reaction time. [b] 12 h reaction time. [c] 1,4-dioxane was used. [d] 2-methyl pyridine (**1m**) was used.

Further, we explored our interest for selective drug derivatization such as, Naproxen used as nonsteroidal anti-inflammatory drug. The corresponding naproxen alcohol was reacted with 2-methylquinoline to obtain the respective *E*-olefinated product (Scheme 5, **38**) in 25% yield. Afterward, dihydrogeraniol, a natural acyclic monoterpenoid, as well as oleyl alcohol an unsaturated fatty alcohol, chemoselectively converted to the *E*-olefinated products **39-40** in acceptable yields. Agreeably, 6-methoxy-2-methylquinoline was reacted with biphenyl-4-methanol to give the *E*-olefinated product **41** (STB-8) in 35% yield, widely used as an imaging agent for Alzheimer's disease β-amyloid plaques. Furthermore, the present protocol was examined for gram scale synthesis of *E*-olefinated product and resulted 72% yield. In addition, we have synthesized the (±) Galipinine (**43**), in two step synthesis from **14**. This is used as an anti-malarial activity drug (Scheme 6). These examples confirmed the potential applications of the present methods.




**Scheme 5:** Synthetic applications [a]

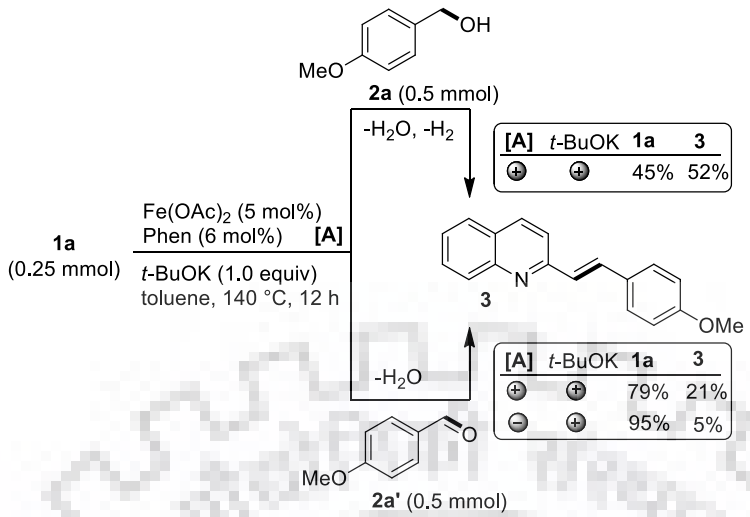
Reaction conditions: [a] Unless specified, the reaction was carried out with quinaldine **1** (0.25 mmol), alcohols **2** (0.50 mmol), $Fe(OAc)_2$ (5.0 mol%), Phen (6.0 mol%), *t*-BuOK (0.25 mmol), 1,4-dioxane (1.0 mL), Schlenk tube under nitrogen atmosphere, 140 ºC oil bath, 24 h reaction time.



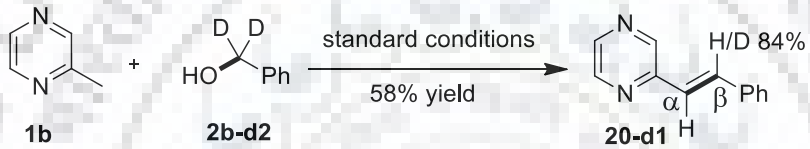

**Scheme 6:** Synthesis of Galipinine

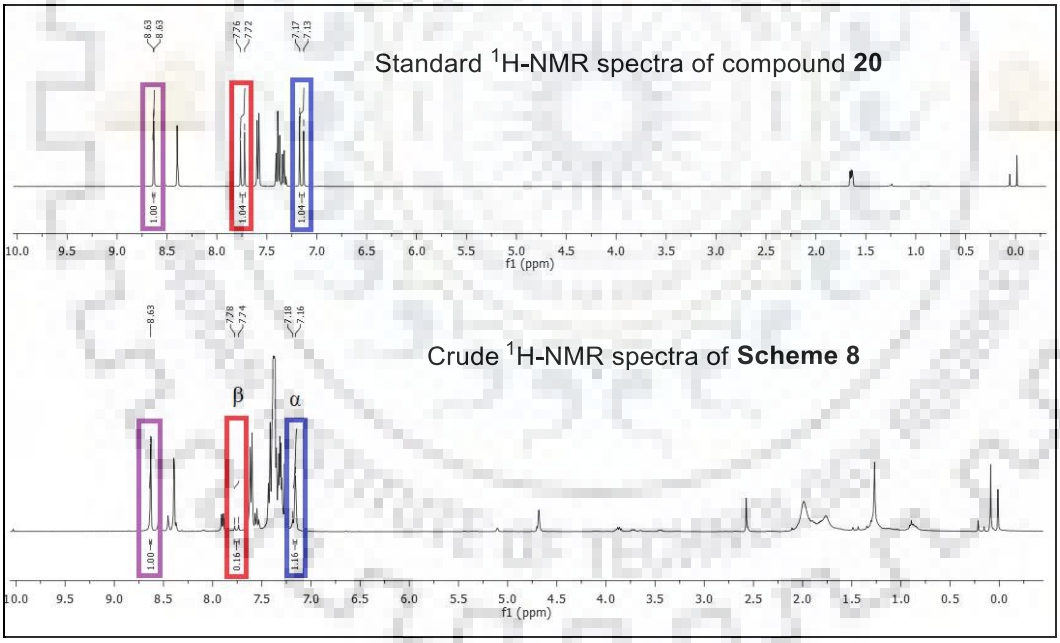
Thereafter, we study a series of control experiments using **1a** with 4-methoxy benzaldehyde **2a**' as well as 4-methoxybenzyl alcohol **2a** in presence and absence of iron catalyst for 12 h (Scheme 7). Notably, the key condensation reaction between **1a** with 4-methoxy benzaldehyde **2a** was carried out in the presence and absence of $Fe(OAc)_2$/**L1** system to investigate its high catalytic activity. Nevertheless, in absence of iron catalyst, **3** was obtained in 5% yield. Interestingly, the $Fe(OAc)_2$/**L1** catalyst system exhibited fourfold increment of higher reactivity than catalyst free conditions. However, either in absence of catalyst and base or in absence of base, 4-methoxy benzaldehyde did not result any desired product. Nevertheless, when, the 4-methoxybenzyl alcohol **2a** was treated with **1a** under standard conditions, gave the 52% yield of **3**. These experimental outcomes clearly indicating the participation of iron catalyst for alcohol dehydrogenation as well as crucial for C-C bond forming steps.[12]

Further, to understand the mechanistic aspects of the reactions, a series of deuterium labeling experiments were performed. The $\alpha$-olefination of **1b** with **2b-d2** (92% D) delivered 58% yield of **20-d1** and 84% deuterium incorporation was observed at the β-position (Scheme 8).




**Scheme 7:** Control experiments



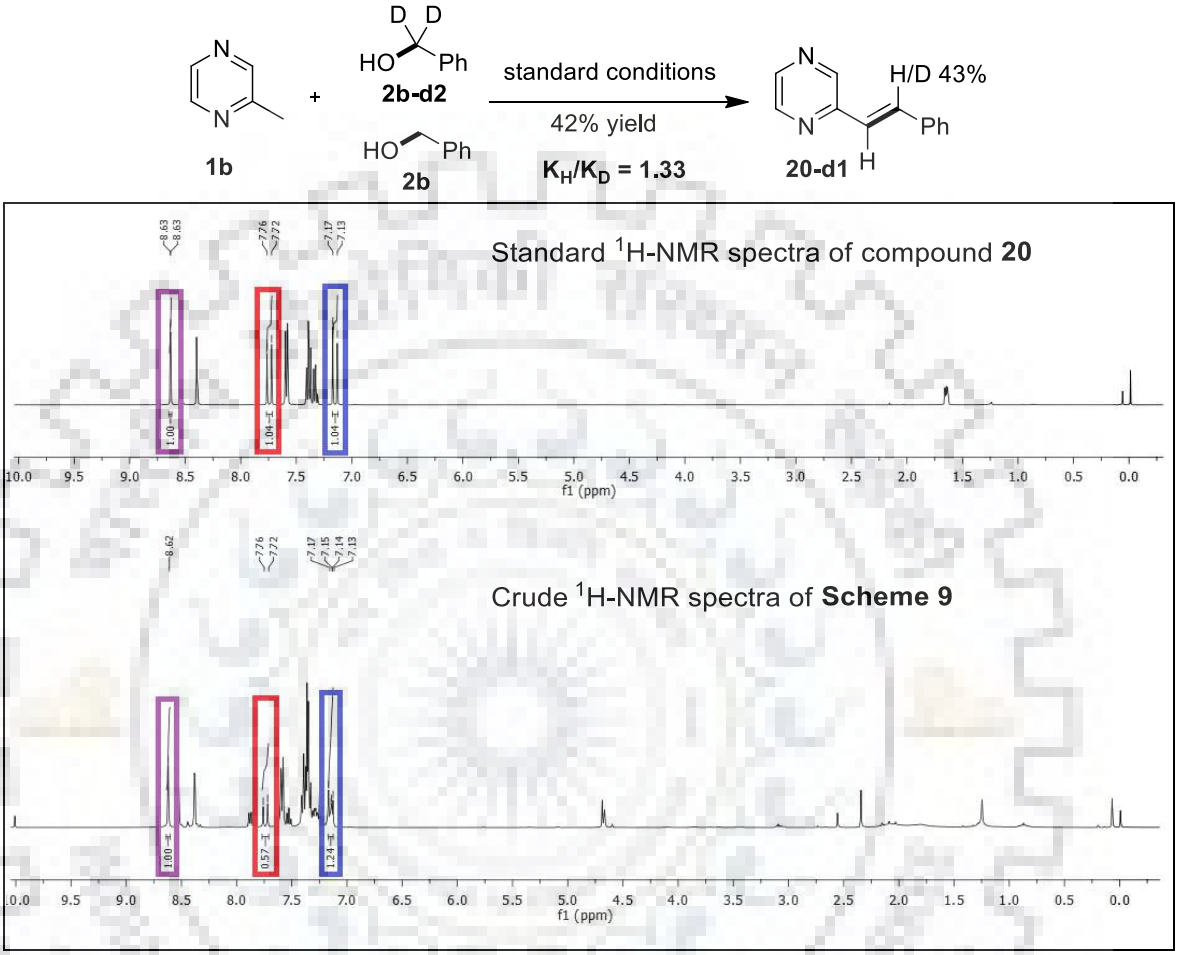




Conversion was calculated by $^1$H-NMR integration value

| | | Deuterium incorporation in **β** position | Deuterium incorporation in **α** position |
|---|---|---|---|
| Signal $\delta$ ppm | 8.63 (1H) | 7.74 (1H) | 7.15 (1H) |
| Integral Value | 1.0 | 0.16 | 1.16 |
| **Calculated ratio** | | {(1-0.16) / 1} × 100 = **84%** | {(1-1) / 1} × 100 = **0%** |

**Scheme 8:** Deuterium labeling experiment **1b** with **2b-d2**

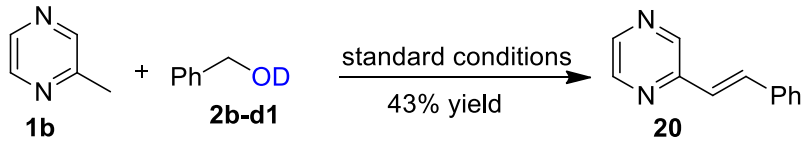
Next, a cross-over experiment was performed using 1:1 mixture of **2b** and **2b-d2** with **1b** using standard conditions. Notably, **20-d1** was obtained in moderate yield and a kinetic isotope effect $k_H/k_D$ = 1.33 was observed (Scheme 9).



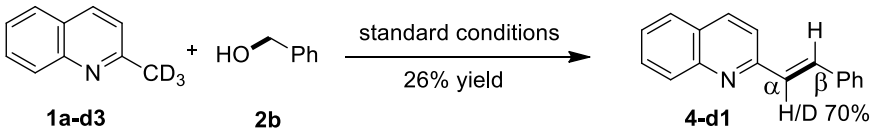

Conversion was calculated by $^1$H-NMR integration value

| | | Deuterium incorporation in **β** position | Deuterium incorporation in **α** position |
|---|---|---|---|
| Signal $\delta$ ppm | 8.63 (1H) | 7.74 (1H) | 7.15 (1H) |
| Integral Value | 1.0 | 0.57 | 1.24 |
| **Calculated ratio** | | {(1-0.55) / 1} × 100 = **43%** | {(1-1) / 1} × 100 = **0%** |

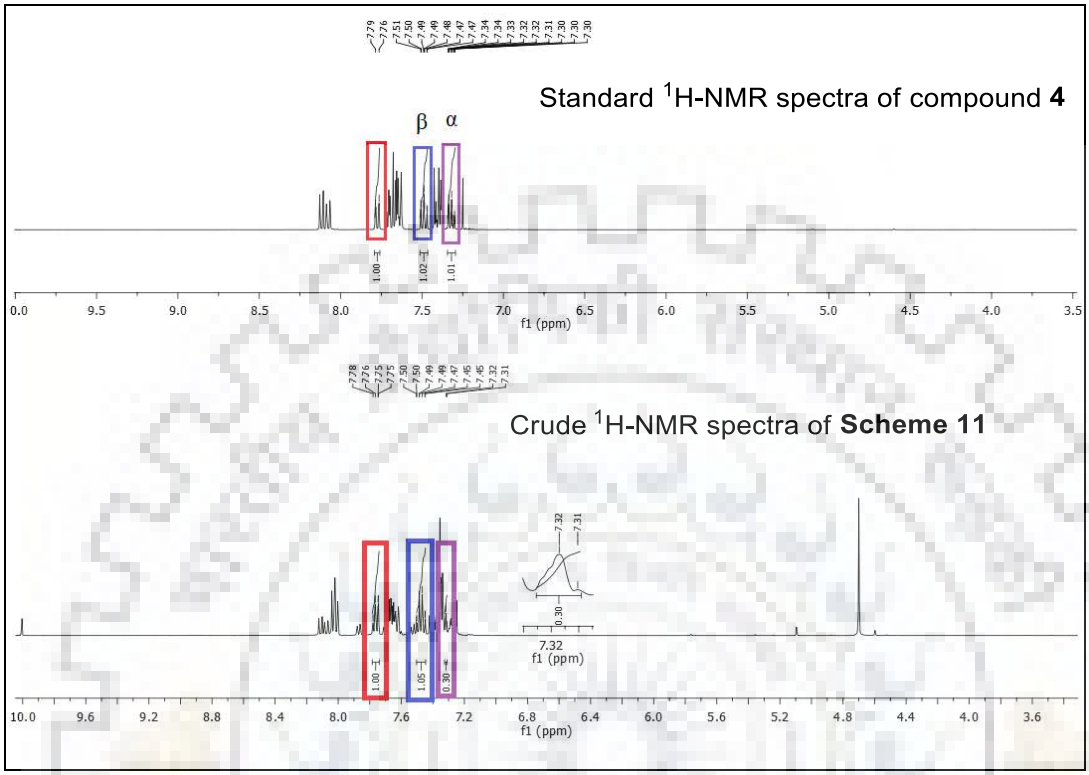
**Scheme 9:** Cross-over experiment with **2b** and **2b-d2**




**Scheme 10:** Deuterium labeling experiment **1b** with **2b-d1**




1a-d3 2b 4-d1




Conversion was calculated by $^1$H-NMR integration value

| | | Deuterium incorporation in **β** position | Deuterium incorporation in **α** position |
|---|---|---|---|
| Signal $\delta$ ppm | 7.76 (1H) | 7.49 (1H) | 7.32 (1H) |
| Integral Value | 1.0 | 1.05 | 0.30 |
| **Calculated ratio** | | {(1-1) / 1} × 100 = **0%** | {(1-0.30) / 1} × 100 = 70% |

**Scheme 11:** Deuterium incorporation experiment with **1a-d3** and **2b**

Furthermore, in case of $\alpha$-olefination of **1a** with **2b-d1**, no deuterated product was observed (Scheme 10). Moreover, when **1a-d3** was treated with **2b**, the deuterium incorporated product **4-d1** was obtained in 26% yield and showed 70% deuterium incorporation at the $\alpha$-position (Scheme 11). These deuterium labeling experiments gives the evidences for the participation of the benzylic C-H/D bond of **2b** as well as C($sp^3$)-H/D bond of 2-alkylazaarenes for the *E*-olefinations.[13]

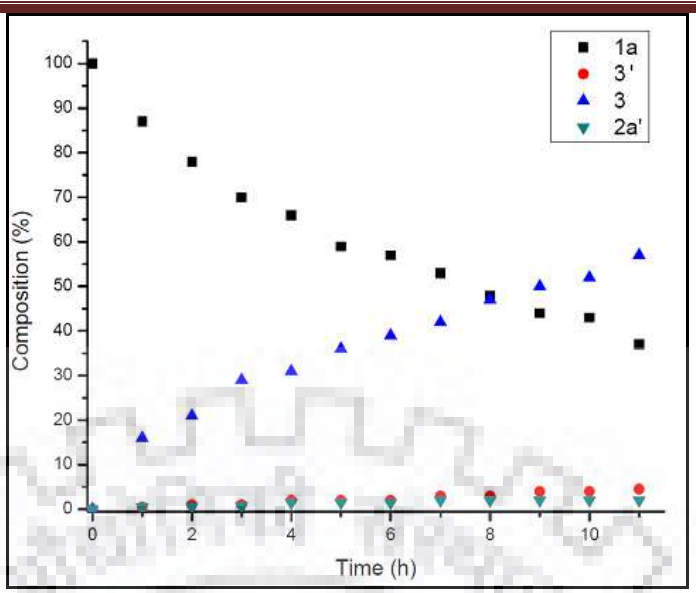



**Fig 1:** Time-conversion-plot for the 2-methylquinoline (**1a**) with benzyl alcohol (**2b**)

Reaction conditions: Quinaldine **1a** (0.25 mmol), benzyl alcohol **2b** (0.50 mmol), $Fe(OAc)_2$ (5.0 mol%), Phen (6.0 mol%), *t*-BuOK (0.25 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 °C oil bath.

A time-course conversion plot was depicted in Figure 1. The $\alpha$-olefination of **1a** with **2a** was examined using GC for 11 h. Continuous formation of aldehyde showed the involvement of dehydrogenation steps. We have also determined the evolution of hydrogen gas during olefination process and was detected using gas chromatography using thermal TCD analysis. We have determined the quantity of the evolution of hydrogen gas in 0.63 mmol (Scheme 12).

In a 10 mL oven dried Schlenk tube, quinaldine **1a** (0.5 mmol), ($Fe(OAc)_2$ (5 mol%), Phen (6 mol%), benzyl alcohol **2b** (1.0 mmol) and *t*-BuOK (0.5 mmol), were added followed by toluene 4.0 mL and connected to the gas burette as shown in figure. Then the reaction mixture was heated at 140 °C until the production of hydrogen gas ceased. The procedure was repeated three times to get concordant reading.

Total volume of water displaced, V = 0.0158 L

Vapor pressure of water at 298K, $P_{(H2O)}$ = 23.7695 Torr

Atmospheric pressure at 298K, $P_{atm}$ = 758.3124 Torr

Pressure of $H_2$ gas, $P_{H2} = P_{atm} - P_{H2O}$ = (758.3124 - 23.7695) Torr = 734.5429 Torr

$P_{H2} * V = nH_2 * R * T$

$nH_2 = P_{H2} * V / R * T$

= 734.5429 Torr * 0.0158 L / 62.3635 L Torr $K^{-1}$ $mol^{-1}$ * 298K

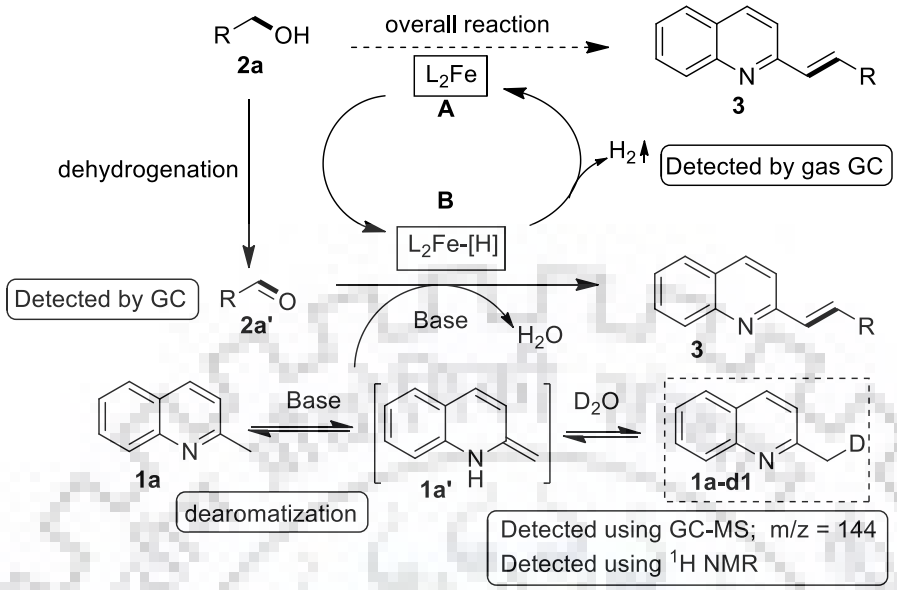
= 0.000625 mol

≈ 0.63 mmol

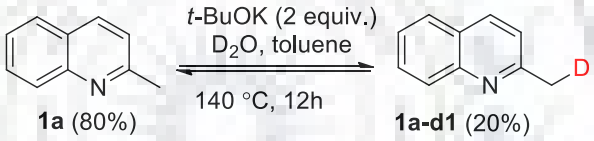
**Scheme 12**: Quantitative determination of hydrogen gas produced in the reaction

After observing the excellent reactivity, a plausible reaction mechanism is postulated in Scheme 13.[12] Initially, the dehydrogenation of benzyl alcohol **2a** to benzaldehyde **2a'** was happened and iron hydride (**B**) is formed. We believe that an enamine intermediate **1a'** is participated in the olefination process. Indeed, in absence of base, no dehydrogenative product **3** was observed, indicated that, *t*-BuOK plays a crucial role for (de)aromatization of 2-methylquinoline **1a** to 1**a'** (Scheme 13). The participation of enamine intermediate **1a'** was confirmed by the reaction between **1a** with **2b-d2** under standard conditions and **1a-d1** was detected in the GC-MS analysis. Furthermore, 2-methylquinoline **1a** was treated with $D_2O$ in the presence of *t*-BuOK at 140 °C, and deuterated quinaldine **1a-d1** is formed in 20% yield. This process confirm that a base mediated equilibrium exists with **1a** to **1a'** (Scheme 14). Again, base-metal mediated condensation of aldehyde with enamine **1a'**

transformed to the anticipated *E*-olefinated product **3** with the elimination of water and hydrogen as sole by products.

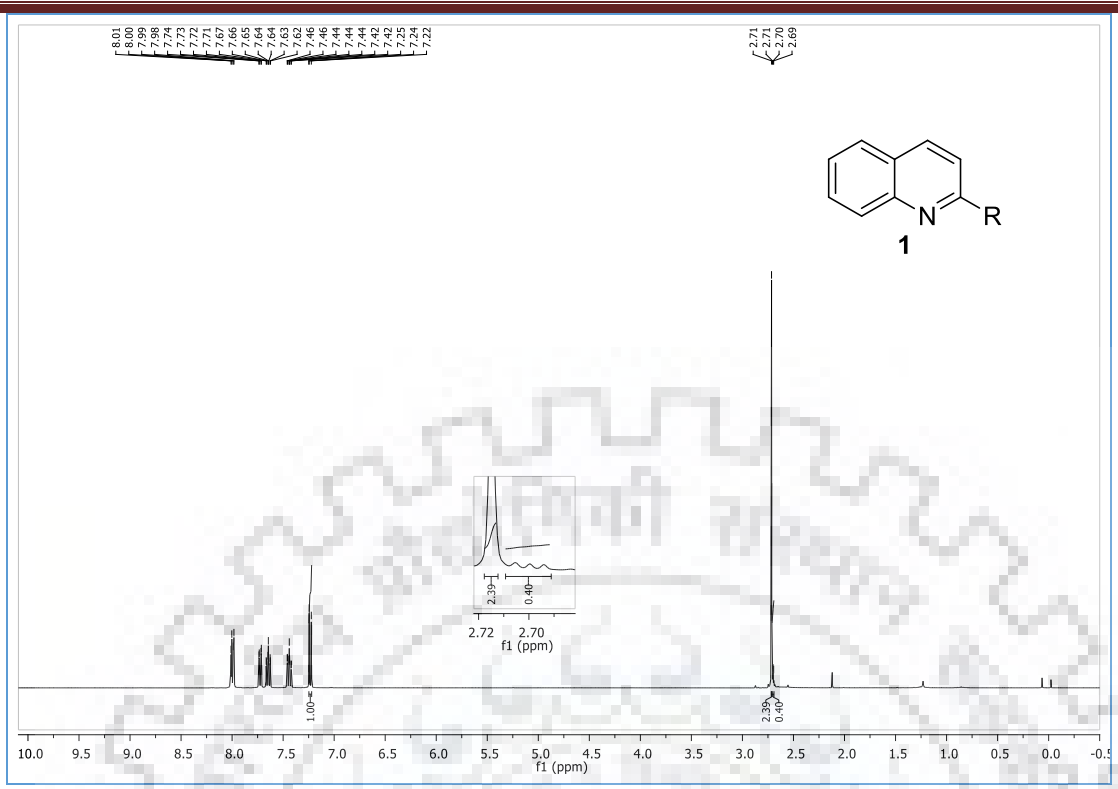



**Scheme 13:** Plausible catalytic cycle for *α*-olefination




**Scheme 14**: Evidence for the enamine intermediate

Reaction conditions: Quinaldine **1a** (0.25 mmol), $D_2O$ (0.2 mL), *t*-BuOK (0.5 mmol), toluene (1.0 mL), Ace Pressure tube under nitrogen atmosphere, 140 °C oil bath, 12 h.




Conversion was calculated by $^{1}$H-NMR integration value

| | | **1a** | **1a-d1** |
|---|---|---|---|
| Signal $\delta$ ppm | 7.23 (1H) | 2.71 (3H) | 2.70 (2H) |
| Integral Value | 1.0 | 2.39 | 0.40 |
| **Calculated ratio** | | (2.39 / 3)×100 **= 80%** | (0.40 / 2)×100 **= 20%** |

**[5B.4] Conclusions**:

In conclusions, we have developed an efficient iron-catalyzed direct $\alpha$-olefination of alkyl substituted *N*-heteroaromatics with primary alcohols via dehydrogenative coupling. This Fe-catalyzed dehydrogenative coupling of an alcohol with alkyl substituted quinolines, pyridines and pyrazines were explored well and extended to a range of aryl, alkyl, and heteroaryl alcohol derivatives (>38 examples) in up to 91% yield. For a synthetic application, functionalization of acyclic monoterpenoid, unsaturated fatty alcohol, and post-synthetic drug modification of naproxen also explored. The deuterium labeling experiments confirm the participation of the benzylic C-H/D bond as well as C($sp^3$)-H/D bond of 2-alkylazaarenes for the olefination process.

**[5B.5] Experimental Section:**

**General experimental details:** All solvents and reagents were used, as received from the suppliers. TLC was performed on Merck Kiesel gel 60, $F_{254}$ plates with the layer thickness of 0.25 mm. Column chromatography was performed on silica gel (100-200 mesh) using a gradient of ethyl acetate and hexane as mobile phase. $^1$H NMR spectral data were collected at, 400 MHz (JEOL), 500 MHz (Bruker) and $^{13}$C NMR were recorded at 100 MHz. $^1$H NMR spectral data are given as chemical shifts in ppm followed by multiplicity (s- singlet; d- doublet; t- triplet; q- quartet; m- multiplet), number of protons and coupling constants. $^{13}$C NMR chemical shifts are expressed in ppm. Elemental analysis data were recorded in Vario Micro Cube. GC-MS were recorded using Agilent GC Mass Spectrometer. All the reactions were performed in a close system using Schlenk tube. All Iron salts and nitrogen ligands were purchased from Sigma Aldrich or Alfa Aesar. Potassium *tert*-butoxide was purchased from Avra Synthesis Pvt. Ltd., India. (Purity-98%, CAS No: 865-47-4, Catalog No- ASP2012).

**General procedure for iron-catalyzed alkenylation of methylquinolines with primary alcohols:**

**Procedure**: In a 15 mL oven dried Ace pressure tube, **1** (0.25 mmol), $Fe(OAc)_2$ (5 mol%), Phen (6 mol%), alcohols **2** (0.50 mmol) and *t*-BuOK (0.25 mmol), were added followed by toluene 1.0 mL under an atmosphere of $N_2$ and the reaction mixture was heated at 140 °C for 24 h in close system. The reaction mixture was cooled to room temperature and 3.0 mLof ethyl acetate was added and concentrated *in vacuo.* The residue was purified by column chromatography using a gradient of hexane and ethyl acetate (eluent system) to afford the pure product.

**Synthesis and Characterization of (*E*)-2-(4-Ethylstyryl)quinoline (6)**:

Following the general procedure, the title compound **6** was isolated as white solid using silica-gel column chromatography eluting with 1% ethyl acetate in hexane. Yield (65%, 42 mg). All the compounds were characterized by $^1$H-NMR, $^{13}$C-NMR, HRMS (ESI-TOF) and IR and the results are shown in spectral data. For an example, all the spectral data of compound **6** are explained here.

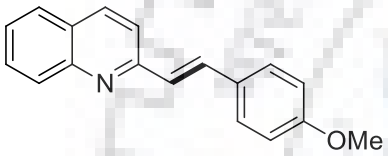
**$^1$H NMR**. the seven aromatic region protons are well separated and appeared as d, dd and m at 8.09 (dd, $J$ = 15.3, 8.6 Hz, 2H), 7.77 (d, $J$ = 8.1 Hz, 1H), 7.72-7.63 (m, 3H), 7.56 (dd,

*J* = 8.2, 2.0 Hz, 2H), 7.50-7.46 (m, 1H), 7.37 (dd, *J* = 16.3, 2.3 Hz, 1H), 7.23 (dd, *J* = 8.1, 1.8 Hz, 2H) ppm. The multiplet peak at 2.70-2.64 (m, 2H) and triplet peak at 1.26 (t, *J* = 7.6 Hz, 3H) belong to two -$CH_2$ and three -$CH_3$ protons of ethyl substituent group respectively (Figure 2a).

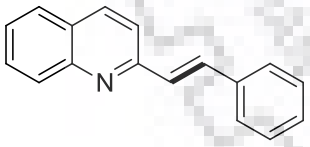
**$^{13}$C NMR**. The peaks at 27.71, 14.41 ppm belong to -$CH_2$ and -$CH_3$ carbons respectively; and the peaks at 133.42 and 132.99 ppm belong to –CH carbon β and ɣ to the nitrogen of quinaldine respectively. The peaks at 155.22, 147.25, 144.09, 135.25, 128.68, 128.13, 127.32, 127.09, 126.47, 126.28, 126.27, 125.03 and 118.16 ppm belong to aromatic benzene ring carbons.

**Analytical data for all products:**

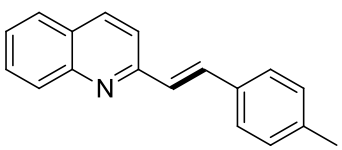
**(*E*)-2-(4-Methoxystyryl)quinoline (3)**[12a]: Following the general procedure, the title compound was isolated as a white solid (Yield: 80%). $^1$H NMR (400 MHz, $CDCl_3$) *δ* 8.07 (t, *J* = 9.4 Hz, 2H), 7.76 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.71-7.64 (m, 2H), 7.62 (d, *J* = 4.0 Hz, 1H), 7.60-7.56 (m, 2H), 7.47 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.28 (d, *J* = 16.3 Hz, 1H), 6.95-6.91 (m, 2H), 3.84 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) *δ* 160.18, 156.43, 148.33, 136.38, 134.14, 129.81, 129.34, 129.13, 128.77, 127.60, 127.29, 126.87, 126.03, 119.21, 114.30, 55.45.




**(*E*)-2-Styrylquinoline (4)**[12a]: Following the general procedure, the title compound was isolated as a white solid (Yield: 73%). $^1$H NMR (400 MHz, $CDCl_3$) *δ* 8.10 (dd, *J* = 16.4, 8.6 Hz, 2H), 7.78 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.71 (dd, *J* = 6.5, 2.0 Hz, 1H), 7.65 (ddd, *J* = 8.0, 7.3, 3.0 Hz, 4H), 7.49 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.43-7.38 (m, 3H), 7.34-7.30 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) *δ* 156.09, 148.36, 136.61, 136.43, 134.52, 129.83, 129.30, 129.12, 128.88, 128.72, 127.58, 127.44, 127.35, 126.26, 119.35.

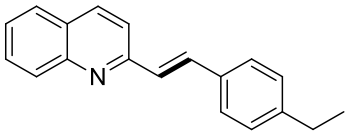



**(*E*)-2-(4-Methylstyryl)quinoline (5)**[12a]: Following the general procedure, the title compound was isolated as a white solid (Yield: 59%). $^1$H NMR (400 MHz, $CDCl_3$) *δ* 8.08 (dd, *J* = 16.0, 8.5 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.68 (ddd, *J* = 23.1, 11.5, 4.1 Hz, 3H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.48 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.36 (d, *J* = 16.3 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 2H), 2.37 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) *δ* 156.30, 148.31,

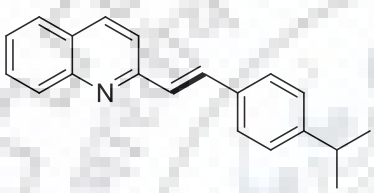


138.88, 136.42, 134.53, 133.80, 129.83, 129.64, 129.19, 128.09, 127.60, 127.37, 127.31, 126.17, 119.28, 21.49.

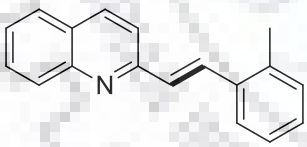
**(*E*)-2-(4-Ethylstyryl)quinoline (6)**: Following the general procedure, the title compound was isolated as a white solid (Yield: 65%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.09 (dd, $J$ = 15.3, 8.6 Hz, 2H), 7.77 (d, $J$ = 8.1 Hz, 1H), 7.72-7.63 (m, 3H), 7.56 (dd, $J$ = 8.2, 2.0 Hz, 2H), 7.50-7.46 (m, 1H), 7.37 (dd, $J$ = 16.3, 2.3 Hz, 1H), 7.23 (dd, $J$ = 8.1, 1.8 Hz, 2H), 2.70-2.64 (m, 2H), 1.26 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.22, 147.25, 144.09, 135.25, 133.42, 132.99, 128.68, 128.13, 127.32, 127.09, 126.47, 126.28, 126.27, 125.03, 118.16, 27.71, 14.41. HRMS (ESI): Calculated for $[C_{19}H_{18}N]^+$ 260.1434; Found 260.1429.



**(*E*)-2-(4-Isopropylstyryl)quinoline (7)**: Following the general procedure, the title compound was isolated as a white solid (Yield: 80%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.09 (dd, $J$ = 17.8, 8.5 Hz, 2H), 7.77 (dd, $J$ = 8.1, 1.2 Hz, 1H), 7.71-7.63 (m, 3H), 7.57 (d, $J$ = 8.2 Hz, 2H), 7.48 (ddd, $J$ = 8.0, 6.9, 1.2 Hz, 1H), 7.37 (d, $J$ = 16.4 Hz, 1H), 7.26 (d, $J$ = 8.8 Hz, 2H), 2.93 (dt, $J$ = 13.9, 6.9 Hz, 1H), 1.27 (d, $J$ = 6.9 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.26, 149.73, 148.30, 136.28, 134.44, 134.18, 129.71, 129.17, 128.18, 127.51, 127.34, 127.31, 126.93, 126.07, 119.18, 34.02, 23.90. HRMS (ESI): Calculated for $[C_{20}H_{20}N]^+$ 274.1590; Found 274.1582.



**(*E*)-2-(2-Methylstyryl)quinoline (8)**[12b]: Following the general procedure, the title compound was isolated as a colourless oil (Yield: 58%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.10 (dd, $J$ = 13.8, 8.6 Hz, 2H), 7.93 (d, $J$ = 16.2 Hz, 1H), 7.79-7.76 (m, 1H), 7.75-7.66 (m, 3H), 7.49 (ddd, $J$ = 8.1, 7.0, 1.1 Hz, 1H), 7.32 (d, $J$ = 16.2 Hz, 1H), 7.27-7.20 (m, 3H), 2.52 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.30, 148.32, 136.69, 136.47, 135.56, 132.18, 130.69, 130.26, 129.86, 129.31, 128.60, 127.61, 127.43, 126.44, 126.28, 125.89, 119.41, 20.16.



**(*E*)-2-(4-Nitrostyryl)quinoline (9)**[17]: Following the general procedure, the title compound was isolated as a pale yellow solid (Yield: 35%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.27 (d, $J$ = 7.9 Hz, 2H), 8.19 (d, $J$ = 8.4 Hz, 1H), 8.11 (d, $J$ = 8.4 Hz, 1H), 7.85-7.73 (m, 5H), 7.68 (d, $J$ = 8.3 Hz, 1H), 7.54 (dd, $J$ = 15.1, 7.1 Hz, 2H); $^{13}$C NMR (10 MHz, $CDCl_3$) $\delta$ 154.75, 150.79, 148.39, 143.07, 136.83, 133.27, 131.77, 130.68, 130.16, 129.50, 127.76, 127.67, 126.91, 124.29, 119.86.

**(*E*)-2-(4-(Trifluoromethyl)styryl)quinoline (10)**[17]: Following the general procedure, the title compound was isolated as a colourless solid (Yield: 50%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.15 (d, $J$ = 8.6 Hz, 1H), 8.08 (d, $J$ = 8.4 Hz, 1H), 7.80 (dd, $J$ = 8.1, 1.1 Hz, 1H), 7.74-7.68 (m, 4H), 7.65 (t, $J$ = 8.4 Hz, 3H), 7.52 (ddd, $J$ = 8.1, 6.9, 1.1 Hz, 1H), 7.46 (d, $J$ = 16.3 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.29, 148.34, 140.06, 136.66, 132.75, 131.42, 130.40, 130.02, 129.39, 127.63, 127.62, 127.40, 126.62, 125.84 (q, $J$ = 3.8 Hz), 125.55, 119.58.

**(*E*)-2-(3-Bromostyryl)quinoline (11)**[17]: Following the general procedure, the title compound was isolated as a colourless solid (Yield: 45%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.09 (dd, $J$ = 15.3, 8.5 Hz, 2H), 7.79-7.75 (m, 2H), 7.70 (ddd, $J$ = 8.4, 6.9, 1.4 Hz, 1H), 7.63-7.57 (m, 2H), 7.54-7.46 (m, 2H), 7.44-7.41 (m, 1H), 7.36 (d, $J$ = 16.3 Hz, 1H), 7.24 (dd, $J$ = 9.4, 6.3 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.42, 148.31, 138.75, 136.59, 132.76, 131.45, 130.39, 130.10, 129.97, 129.35, 127.64, 127.53, 126.50, 125.94, 123.06, 119.53.

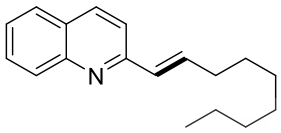
**(*E*)-2-(4-Chlorostyryl)quinoline (12)**[17]: Following the general procedure, the title compound was isolated as a colourless solid (Yield: 42%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.15-8.04 (m, 2H), 7.78 (d, $J$ = 8.1 Hz, 1H), 7.73-7.61 (m, 4H), 7.57-7.55 (m, 1H), 7.53-7.47 (m, 1H), 7.43-7.32 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 155.69, 148.35, 136.54, 135.14, 134.38, 129.93, 129.60, 129.31, 129.10, 128.89, 128.48, 127.61, 127.35, 126.40, 119.45.

**(*E*)-2-(2-(Naphthalen-1-yl)vinyl)quinoline (13)**[12b]: Following the general procedure, the title compound was isolated as a yellow oil (Yield: 50%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.52 (d, $J$ = 16.0 Hz, 1H), 8.34 (d, $J$ = 8.4 Hz, 1H), 8.14 (dd, $J$ = 12.5, 8.5 Hz, 2H), 7.91-7.85 (m, 3H), 7.80 (d, $J$ = 8.0 Hz, 1H), 7.76-7.70 (m, 2H), 7.60-7.45 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.13, 148.38, 136.57, 134.12, 133.84, 131.83, 131.57, 131.46, 129.92, 129.39, 129.09, 128.80, 127.65, 127.52, 126.46, 126.36, 126.08, 125.84, 124.31, 123.85, 119.67.

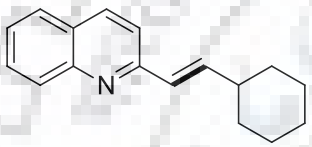
**(*E*)-2-(2-(Benzo[*d*][1,3]dioxol-5-yl)vinyl)quinoline (14)**[12a]: Following the general procedure, the title compound was isolated as a white solid (Yield: 52%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.14 (d, $J$ = 8.6 Hz, 1H), 8.09 (d, $J$ = 8.5 Hz, 1H), 7.80 (d, $J$ = 7.9 Hz, 1H), 7.75-7.71 (m, 1H), 7.65 (t, $J$ = 12.3 Hz, 2H), 7.53-7.49 (m, 1H), 7.29 (s, 1H), 7.22 (d, $J$ =

1.5 Hz, 1H), 7.11 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.03 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.12, 148.29, 136.30, 134.15, 131.10, 129.72, 129.13, 127.49, 127.27, 127.25, 126.03, 122.81, 119.26, 115.00, 108.53, 106.06, 101.30.

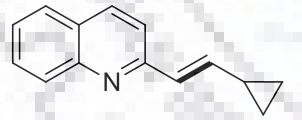
**(*E*)-2-(Non-1-en-1-yl)quinoline (15)**[20]: Following the general procedure, the title compound was isolated as a pale yellow oil (Yield: 40%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06-8.00 (m, 2H), 7.75 (t, *J* = 8.7 Hz, 1H), 7.69-7.64 (m, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.48-7.43 (m, 1H), 6.82 (dt, *J* = 15.9, 6.7 Hz, 1H), 6.70 (d, *J* = 15.9 Hz, 1H), 2.32 (td, *J* = 7.8, 1.1 Hz, 2H), 1.32-1.23 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.64, 138.20, 136.23, 131.09, 129.59, 129.19, 127.50, 127.21, 125.89, 125.70, 118.78, 33.16, 31.90, 29.35, 29.27, 29.00, 22.76, 14.19.



**(*E*)-2-(2-Cyclohexylvinyl)quinoline (17)**[12a]**:** Following the general procedure, the title compound was isolated as a pale yellow oil (Yield: 40%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (dd, *J* = 13.4, 8.6 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.68-7.62 (m, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.44 (dd, *J* = 11.0, 4.1 Hz, 1H), 6.76 (dd, *J* = 16.1, 6.4 Hz, 1H), 6.66 (d, *J* = 16.3 Hz, 1H), 2.30-2.19 (m, 1H), 1.93-1.66 (m, 6H), 1.36-1.23 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.88, 148.16, 143.48, 136.20, 129.57, 129.18, 128.74, 127.50, 127.21, 125.88, 118.80, 41.23, 32.63, 26.23, 26.10.

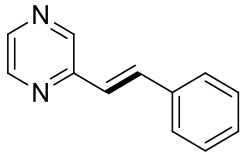


**(*E*)-2-(2-Cyclopropylvinyl)quinoline (18)**[12a]**:** Following the general procedure, the title compound was isolated as a pale-yellow oil (Yield: 35%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01 (dd, *J* = 16.4, 8.5 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.64 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.46-7.40 (m, 2H), 6.76 (d, *J* = 15.7 Hz, 1H), 6.37 (dd, *J* = 15.7, 9.3 Hz, 1H), 1.75-1.65 (m, 1H), 0.94-0.89 (m, 2H), 0.70-0.63 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.28, 151.74, 148.20, 142.15, 136.23, 129.57, 129.10, 128.32, 127.49, 125.72, 118.93, 15.00, 8.13.

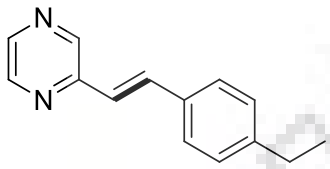


**(*E*)-2-(4-Methoxystyryl)pyrazine (19)**[14]: Following the general procedure, the title compound was isolated as a white solid (Yield: 80%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.60 (d, *J* = 1.7 Hz, 1H), 8.51 (d, *J* = 3.8 Hz, 1H), 8.36 (d, *J* = 2.5 Hz, 1H), 7.69 (dd, *J* = 16.0, 2.4 Hz, 1H), 7.55-7.52 (m, 2H), 7.05-6.98 (m, 1H), 6.93-6.91 (m, 2H), 3.83 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.45, 151.73, 144.34, 143.65, 142.36, 134.85, 128.91, 128.85, 121.86, 114.38, 55.45.

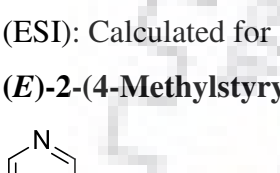
**(*E*)-2-Styrylpyrazine (20)**[12a]: Following the general procedure, the title compound was isolated as a white solid (Yield: 68%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.63 (d, $J$ = 1.4 Hz, 1H), 8.54-8.53 (m, 1H), 8.39 (d, $J$ = 2.5 Hz, 1H), 7.74 (d, $J$ = 16.1 Hz, 1H), 7.59 (d, $J$ = 7.4 Hz, 2H), 7.41-7.37 (m, 2H), 7.34-7.31 (m, 1H), 7.15 (d, $J$ = 16.1 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 151.33, 144.45, 143.89, 142.86, 136.08, 135.27, 129.11, 128.95, 127.43, 124.06.



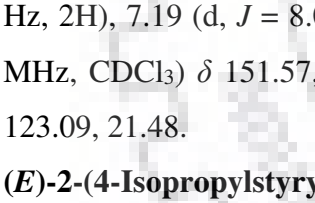
**(*E*)-2-(4-Ethylstyryl)pyrazine (21)**: Following the general procedure, the title compound was isolated as a white solid (Yield: 53%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.62 (d, $J$ = 1.4 Hz, 1H), 8.52-8.51 (m, 1H), 8.37 (d, $J$ = 2.5 Hz, 1H), 7.72 (d, $J$ = 16.1 Hz, 1H), 7.51 (d, $J$ = 8.1 Hz, 2H), 7.22 (d, $J$ = 8.1 Hz, 2H), 7.10 (d, $J$ = 16.1 Hz, 1H), 2.66 (q, $J$ = 7.6 Hz, 2H), 1.24 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 151.59, 145.62, 144.41, 143.73, 142.63, 135.27, 133.61, 128.42, 127.44, 123.12, 28.83, 15.50. HRMS (ESI): Calculated for $[C_{14}H_{15}N_2]^+$ 211.1230; Found 211.1233.



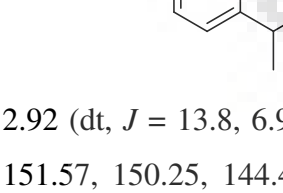
**(*E*)-2-(4-Methylstyryl)pyrazine (22)**[12a]: Following the general procedure, the title compound was isolated as a white solid (Yield: 74%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.61 (d, $J$ = 1.4 Hz, 1H), 8.52-8.51 (m, 1H), 8.37 (d, $J$ = 2.5 Hz, 1H), 7.71 (d, $J$ = 16.1 Hz, 1H), 7.48 (d, $J$ = 8.1 Hz, 2H), 7.19 (d, $J$ = 8.0 Hz, 2H), 7.10 (d, $J$ = 16.1 Hz, 1H), 2.37 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 151.57, 144.38, 143.76, 142.60, 139.27, 135.23, 133.36, 129.67, 127.37, 123.09, 21.48.



**(*E*)-2-(4-Isopropylstyryl)pyrazine (23)**[12a]: Following the general procedure, the title compound was isolated as a white solid (Yield: 73%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.62 (d, $J$ = 1.5 Hz, 1H), 8.52 (dd, $J$ = 2.4, 1.6 Hz, 1H), 8.38 (d, $J$ = 2.5 Hz, 1H), 7.72 (d, $J$ = 16.1 Hz, 1H), 7.53-7.51 (m, 2H), 7.26-7.24(m, 2H), 7.11 (d, $J$ = 16.1 Hz, 1H), 2.92 (dt, $J$ = 13.8, 6.9 Hz, 1H), 1.26 (d, $J$ = 7.0 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 151.57, 150.25, 144.40, 143.79, 142.61, 135.22, 133.72, 127.48, 127.06, 123.15, 34.11, 23.97.

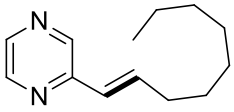


**(*E*)-2-(2-(Naphthalen-1-yl)vinyl)pyrazine (24)**[15]: Following the general procedure, the title compound was isolated as a white solid (Yield: 50%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.55 (d, $J$ = 5.2 Hz, 1H), 8.49 (d, $J$ = 3.7 Hz, 1H), 8.29 (d, $J$ = 8.2 Hz, 1H), 8.09 (d, $J$ = 7.3 Hz, 1H), 7.87 (d, $J$ = 7.7 Hz, 2H), 7.79 (d, $J$ = 7.8 Hz, 2H), 7.58-7.52 (m, 3H), 7.15 (d, $J$ = 15.8 Hz, 1H); $^{13}$C



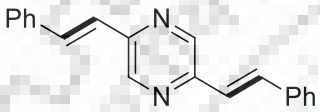
NMR (100 MHz, $CDCl_3$) $\delta$ 151.41, 144.47, 143.78, 142.72, 136.51, 133.86, 132.41, 131.32, 128.76, 128.56, 126.40, 125.96, 125.51, 125.35, 124.27, 123.79.

**(*E*)-2-(Non-1-en-1-yl)pyrazine (26)**: Following the general procedure, the title compound



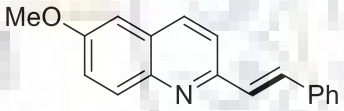
was isolated as a white solid (Yield: 32%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.50 (d, $J$ = 1.4 Hz, 1H), 8.46-8.45 (m, 1H), 8.34 (d, $J$ = 2.5 Hz, 1H), 6.87 (dt, $J$ = 15.7, 7.0 Hz, 1H), 6.47 (dt, $J$ = 15.8, 1.4 Hz, 1H), 2.28 (ddd, $J$ = 14.8, 7.3, 1.5 Hz, 2H), 1.53-1.46 (m, 2H), 1.37-1.27 (m, 8H), 0.86 (d, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 150.90, 144.05, 142.86, 142.22, 139.15, 126.27, 33.02, 31.77, 29.19, 29.13, 28.75, 22.64, 14.10. HRMS (ESI): Calculated for $[C_{13}H_{21}N_2]^+$ 205.1699; Found 205.1696.

**2,5-Di((*E*)-styryl)pyrazine (27)**[16]: Following the general procedure, the title compound

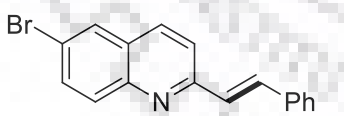


was isolated as a white solid (Yield: 58%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.59 (s, 2H), 7.73 (d, $J$ = 16.1 Hz, 2H), 7.60 (d, $J$ = 8.5 Hz, 4H), 7.39 (d, $J$ = 7.2 Hz, 3H), 7.33 (d, $J$ = 7.2 Hz, 2H), 7.18 (d, $J$ = 16.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.98, 149.17, 143.39, 136.33, 134.45, 128.94, 127.37, 124.15.

**(*E*)-6-Methoxy-2-styrylquinoline (28)**[12a]: Following the general procedure, the title compound was isolated as a white solid (Yield: 91%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.99 (dd, $J$ = 17.6, 8.9 Hz, 2H), 7.64-7.58 (m, 4H), 7.40-7.28 (m, 5H), 7.05 (d, $J$ = 2.8 Hz, 1H), 3.92 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 157.72, 153.80, 144.34, 136.76, 135.21, 133.30, 130.71, 129.13, 128.87, 128.50, 128.38, 127.22, 122.44, 119.65, 105.31, 55.65.



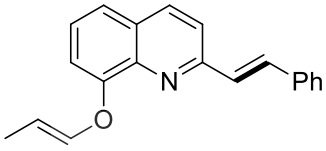
**(*E*)-6-bromo-2-styrylquinoline (29)**[19]: Following the general procedure, the title compound was isolated as a white solid (Yield: 48%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (d, $J$ = 8.6 Hz, 1H), 7.95-7.91 (m, 2H), 7.75 (dd, $J$ = 9.0, 2.2 Hz, 1H), 7.72-7.61 (m, 4H), 7.43-7.30 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.43, 146.92, 136.39, 135.43, 135.10, 133.28, 130.95, 129.66, 129.18, 128.94, 128.59, 128.47, 127.42, 120.31, 120.00.



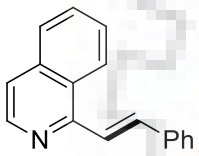
**(*E*)-8-Methoxy-2-styrylquinoline (30)**[17]: Following the general procedure, the title compound was isolated as a white solid (Yield: 47%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.07 (d, $J$ = 8.5 Hz, 1H), 7.74 (d, $J$ = 8.6 Hz, 1H), 7.64-7.61 (m, 2H), 7.56 (d, $J$ = 11.0 Hz, 2H), 7.41-7.33 (m, 5H),

7.04 (d, *J* = 7.4 Hz, 1H), 4.09 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.23, 155.18, 140.10, 136.66, 136.39, 134.06, 129.77, 128.89, 128.62, 128.49, 128.46, 127.33, 126.48, 119.53, 119.27, 108.02, 56.20.

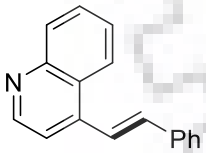
**8-((*E*)-Prop-1-en-1-yloxy)-2-((*E*)-styryl)quinoline (31)**: Following the general procedure, the title compound was isolated as a white solid (Yield: 48%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.12 (d, *J* = 8.6 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.71-7.64 (m, 3H), 7.56 (d, *J* = 16.4 Hz, 1H), 7.48-7.42 (m, 4H), 7.35 (dd, *J* = 10.5, 4.1 Hz, 1H), 7.23 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.61 (dq, *J* = 5.7, 1.6 Hz, 1H), 5.17-5.12 (m, 1H), 1.91 (dd, *J* = 6.9, 1.7 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.47, 153.32, 141.43, 140.18, 136.65, 136.20, 134.25, 129.66, 128.79, 128.67, 128.55, 127.32, 126.09, 121.29, 119.45, 112.95, 109.55, 9.87. Elemental Analysis calculated: C, 83.59; H, 5.96; Found: C, 83.13; H, 6.07.



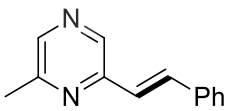

**(*E*)-1-Styrylisoquinoline (32)**[12b]: Following the general procedure, the title compound was isolated as a white solid (Yield: 58%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.56 (d, *J* = 5.6 Hz, 1H), 8.37 (d, *J* = 8.5 Hz, 1H), 8.00 (t, *J* = 8.9 Hz, 2H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.71-7.60 (m, 4H), 7.56 (d, *J* = 5.6 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.35-7.31 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.62, 142.55, 136.98, 136.82, 135.91, 130.03, 128.88, 128.73, 127.55, 127.43, 127.31, 126.84, 124.56, 122.89, 120.10.




**(*E*)-4-Styrylquinoline (33)**[19]: Following the general procedure, the title compound was isolated as a white solid (Yield: 52%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.93 (d, *J* = 4.4 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 16.1 Hz, 1H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.68 – 7.60 (m, 4H), 7.46 (t, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 12.9 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 150.23, 148.75, 142.97, 136.61, 135.16, 130.17, 129.31, 128.91, 128.80, 127.13, 126.51, 126.45, 123.49, 122.96, 117.10.




**(*E*)-2-Methyl-6-styrylpyrazine (34)**[12b]: Following the general procedure, the title compound was isolated as a white solid (Yield: 50%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.44 (s, 1H), 8.28 (s, 1H), 7.71 (d, *J* = 16.1 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 16.1 Hz, 1H), 2.58 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 153.43, 150.16, 142.66, 140.60, 136.27, 134.73, 128.91, 128.90, 127.36, 124.49, 21.84.



**(*E*)-2-Styrylbenzo[*d*]oxazole (35)**[12b]: Following the general procedure, the title compound was isolated as a white solid (Yield: 62%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.80 (dd, $J$ = 16.3, 11.9 Hz, 1H), 7.75-7.66 (m, 1H), 7.63-7.59 (m, 2H), 7.56-7.51 (m, 1H), 7.41 (dd, $J$ = 11.5, 4.0 Hz, 2H), 7.37-7.25 (m, 3H), 7.09 (dd, $J$ = 16.4, 11.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 162.90, 150.51, 142.27, 139.57, 135.24, 129.87, 129.07, 127.65, 125.31, 124.61, 119.97, 114.05, 110.42.

**(*E*)-2-Styrylpyridine (36)**[12a]: Following the general procedure, the title compound was isolated as a white solid (Yield: 73%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.61-8.59 (m, 1H), 7.66-7.64 (m, 1H), 7.63-7.61 (m, 1H), 7.59-7.56 (m, 2H), 7.38-7.35 (m, 3H), 7.29 (ddd, $J$ = 7.2, 3.7, 1.2 Hz, 1H), 7.18 (s, 1H), 7.12 (ddd, $J$ = 4.8, 2.4, 1.2 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.71, 149.76, 136.74, 136.63, 132.82, 128.82, 128.43, 128.04, 127.20, 122.18, 122.15.

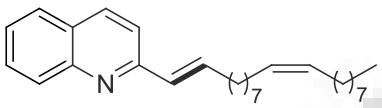
**(*E*)-2-(4-Methoxystyryl)pyridine (37)**[18]: Following the general procedure, the title compound was isolated as a white solid (Yield: 81%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.58-8.56 (m, 1H), 7.64-7.55 (m, 2H), 7.53-7.49 (m, 2H), 7.33 (d, $J$ = 7.9 Hz, 1H), 7.09 (ddd, $J$ = 7.3, 4.8, 1.0 Hz, 1H), 7.03 (d, $J$ = 16.1 Hz, 1H), 6.91-6.88 (m, 2H), 3.81 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.93, 156.01, 149.67, 136.62, 132.35, 129.48, 128.53, 125.86, 121.90, 121.79, 114.26, 55.42.

**(*E*)-2-(4,8-Dimethylnona-1,7-dien-1-yl)quinoline (38)**[12b]: Following the general procedure, the title compound was isolated as a colorless oil (Yield: 48%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (dd, $J$ = 15.0, 8.5 Hz, 2H), 7.74 (dd, $J$ = 8.1, 1.1 Hz, 1H), 7.66 (ddd, $J$ = 8.4, 6.9, 1.5 Hz, 1H), 7.53 (d, $J$ = 8.6 Hz, 1H), 7.45 (ddd, $J$ = 8.0, 7.0, 1.1 Hz, 1H), 6.77 (ddd, $J$ = 36.6, 21.8, 11.5 Hz, 2H), 5.10 (dddd, $J$ = 7.1, 5.7, 2.7, 1.4 Hz, 1H), 2.36-2.31 (m, 1H), 2.16 (ddd, $J$ = 11.0, 8.1, 4.0 Hz, 1H), 2.15-1.97 (m, 2H), 1.71-1.68 (m, 1H), 1.67 (d, $J$ = 1.0 Hz, 3H), 1.60 (s, 3H), 1.49-1.38 (m, 1H), 1.23 (dddd, $J$ = 13.7, 9.3, 7.0, 5.0 Hz, 1H), 0.96 (d, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.52, 148.13, 136.75, 136.25, 132.37, 131.41, 129.63, 129.17, 127.51, 127.23, 125.94, 124.76, 118.75, 40.72, 36.91, 32.78, 25.84, 25.71, 19.72, 17.78.

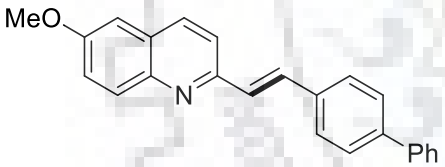
**(*E*)-2-(3-(6-Methoxynaphthalen-2-yl)but-1-en-1-yl)quinoline (39)**: Following the general procedure, the title compound was isolated as a pale blue oil (Yield: 25%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.40 (d, $J$ = 6.2 Hz, 1H), 8.00 (d, $J$

= 8.5 Hz, 2H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.68 (dd, *J* = 17.9, 9.8 Hz, 1H), 7.36-7.25 (m, 4H), 7.16 (dd, *J* = 26.9, 13.1 Hz, 3H), 3.94 (s, 3H), 3.93-3.89 (m, 1H), 2.69 (d, *J* = 1.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.01, 159.78, 137.30, 132.65, 131.13, 130.08, 129.18, 127.84, 127.11, 124.69, 119.78, 119.75, 115.00, 105.77, 55.44, 29.71, 26.56. Elemental Analysis calculated: C, 84.92; H, 6.22; Found: C, 84.47; H, 5.97.

**2-((1*E*,10*Z*)-Nonadeca-1,10-dien-1-yl)quinoline (40)**: Following the general procedure, the title compound was isolated as a colorless oil (Yield: 40%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (dd, *J* = 13.4, 8.5 Hz, 2H), 7.75 (t, *J* = 8.8 Hz, 1H), 7.66 (ddd, *J* = 8.3, 5.3, 1.2 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 1H), 6.81 (dt, *J* = 15.8, 6.6 Hz, 1H), 6.70 (d, *J* = 16.0 Hz, 1H), 5.34 (dd, *J* = 9.5, 4.7 Hz, 2H), 2.32 (p, *J* = 7.3 Hz, 2H), 2.00 (d, *J* = 2.9 Hz, 4H), 1.54 (dt, *J* = 14.9, 7.3 Hz, 2H), 1.28 (dd, *J* = 14.9, 9.8 Hz, 20H), 0.86 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.62, 148.17, 138.12, 136.20, 131.11, 130.04, 129.90, 129.57, 129.20, 127.47, 127.22, 125.88, 118.77, 33.13, 31.97, 29.85, 29.83, 29.59, 29.48, 29.40, 29.38, 29.34, 29.30, 28.98, 27.30, 27.28, 22.75, 14.17. Elemental Analysis calculated: C, 85.87; H, 10.55; Found: C, 85.52; H, 10.27.




**(*E*)-2-(2-([1,1'-Biphenyl]-4-yl)vinyl)-6-methoxyquinoline (41)**[12a]: Following the general procedure, the title compound was isolated as a white solid (Yield: 35%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.00 (dd, *J* = 16.5, 8.9 Hz, 2H), 7.64 (ddd, *J* = 6.6, 5.5, 2.6 Hz, 8H), 7.49-7.41 (m, 3H), 7.36 (ddd, *J* = 7.6, 5.3, 3.9 Hz, 2H), 7.06 (d, *J* = 2.8 Hz, 1H), 3.93 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 156.63, 152.68, 143.27, 140.06, 139.52, 134.71, 134.10, 131.70, 129.61, 128.01, 127.81, 127.29, 126.55, 126.44, 126.41, 125.94, 121.34, 118.60, 104.23, 54.54.



**[5B.7] Spectra of Selected Compounds**:

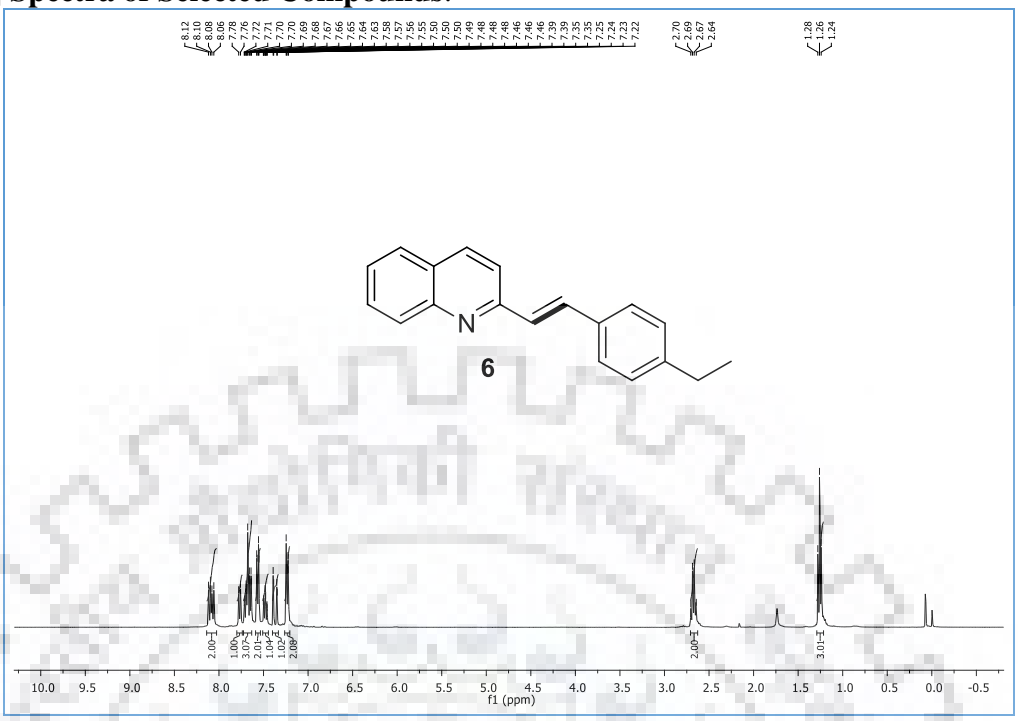



**Fig 2a:** $^{1}$H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **6**

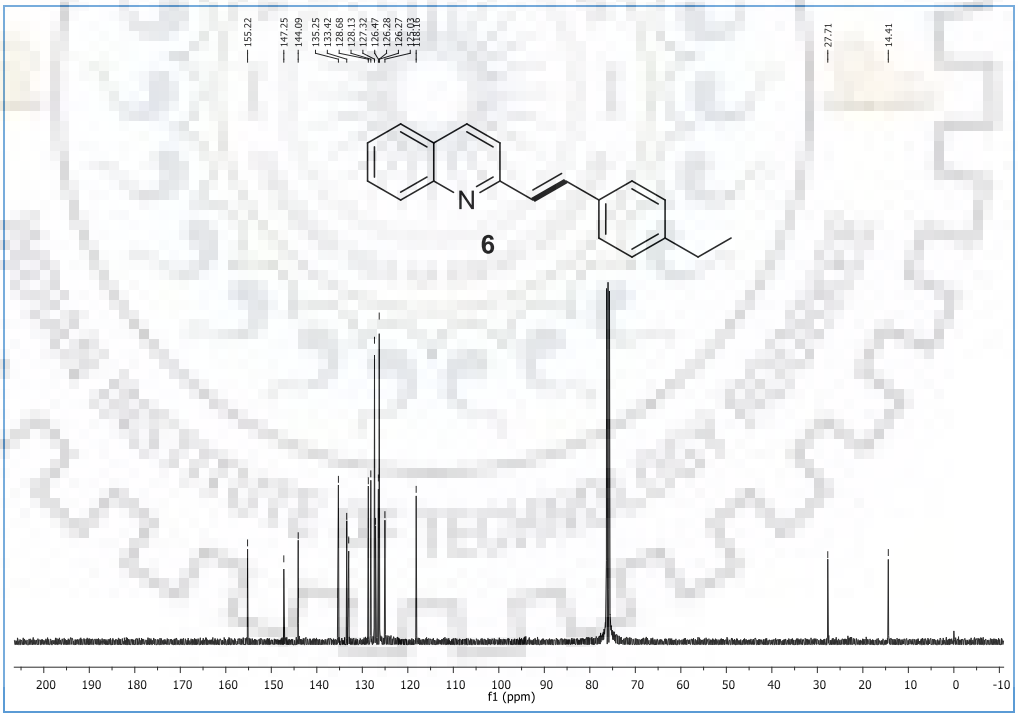



**Fig 2b:** $^{13}$C NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **6**

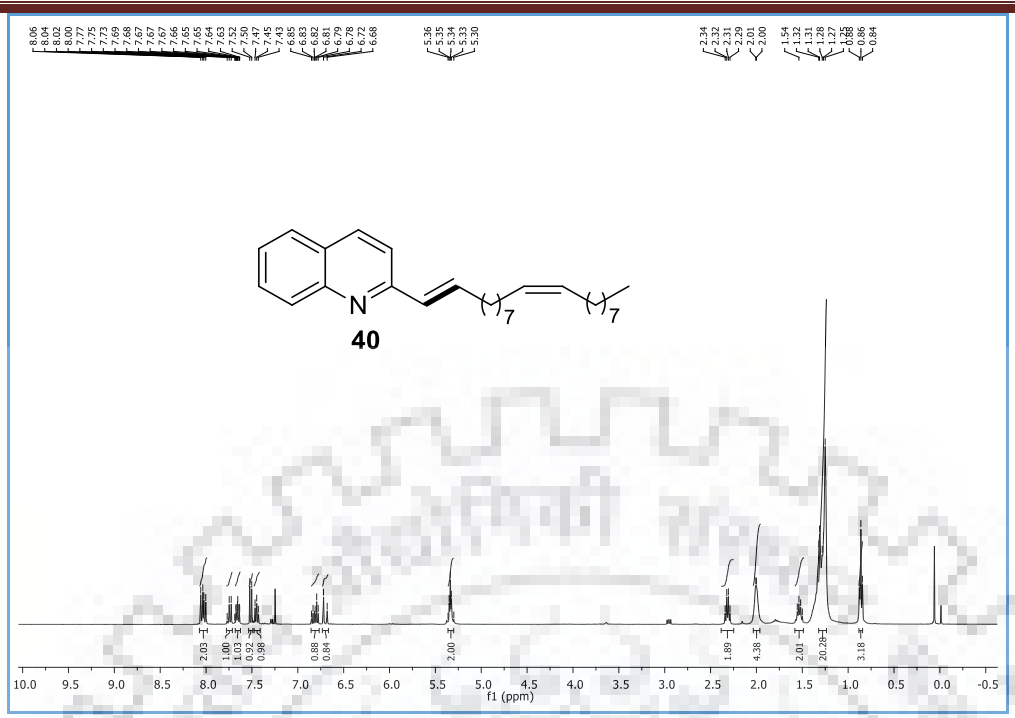



**Fig 3a:** $^{1}$H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **40**

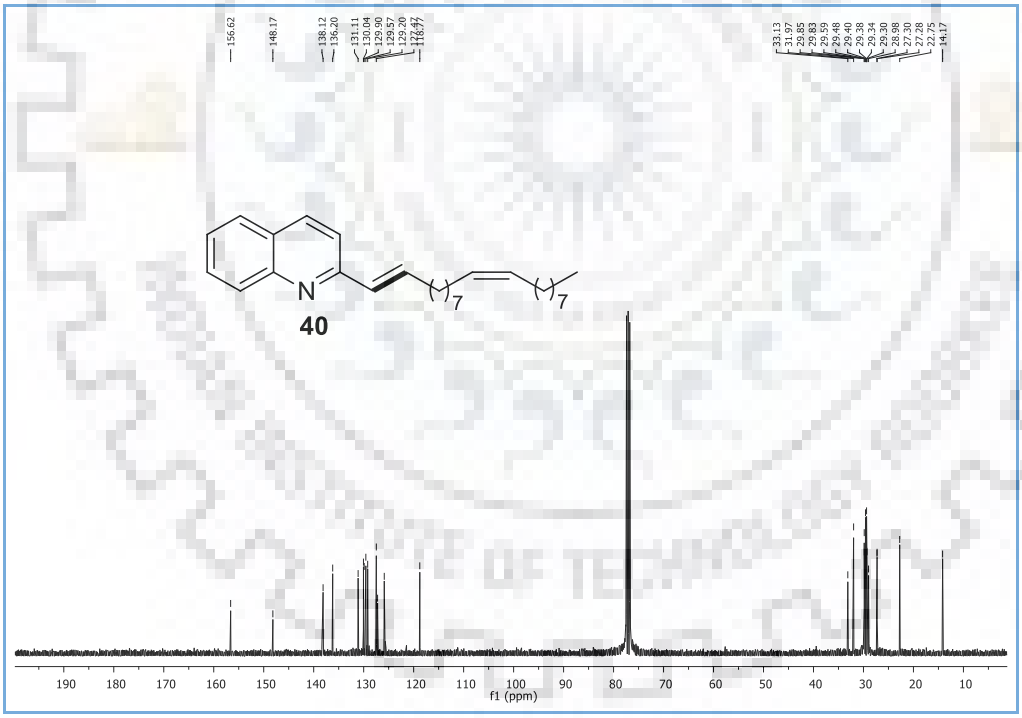



**Fig 3b:** $^{13}$C NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **40**

## Chapter 6: References

**[6.1] Chapter 1**: Metal-Catalyzed Sustainable Synthesis of C-C and C-N Bonds: A Brief Literature Summary

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**[6.2] Chapter 2:** Nickel-catalyzed direct *N*-alkylation of amides with alcohols

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**[6.6] Chapter 5 Section B:** Iron-catalyzed dehydrogenetive alkylation of alkyl-substituted heteroaromatics

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# Nickel-Catalyzed Phosphine Free Direct N-Alkylation of Amides with Alcohols

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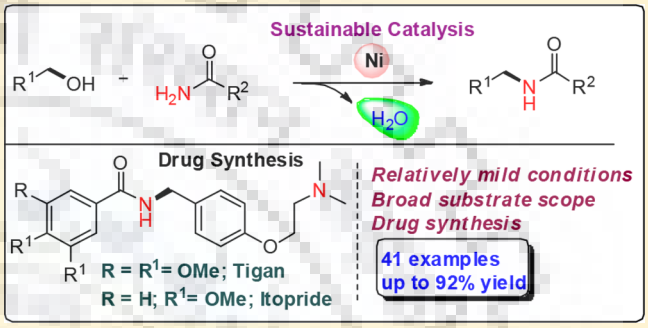
Supporting Information

**ABSTRACT:** Herein, we developed an operational simple, practical, and selective Ni-catalyzed synthesis of secondary amides. Application of renewable alcohols, earth-abundant and nonprecious nickel catalyst facilitates the transformations, releasing water as byproduct. The catalytic system is tolerant to a variety of functional groups including nitrile, allylic ether, and alkene and could be extended to the synthesis of bis-amide, antiemetic drug Tigan, and dopamine D2 receptor antagonist Itopride. Preliminary mechanistic studies revealed the participation of a benzylic C−H bond in the rate-determining step.




Transition-metal-catalyzed efficient and selective synthesis of an amide C−N bond represents a key challenge and most commonly used in chemical transformations in the synthesis of pharmaceuticals, peptides, and in natural products (Figure 1).[1] In this direction, sustainable and atom-economic

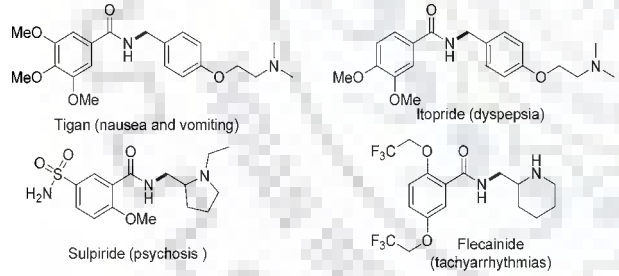


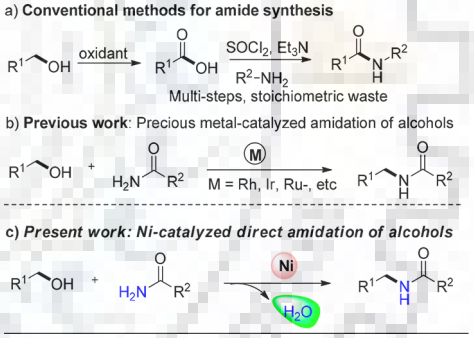

**Figure 1.** Selected examples of important pharmaceuticals with amide functionalities.

technology for amide synthesis, which minimizes the waste generation, is recognized by the ACS Pharmaceutical Roundtable as one of the important areas where significant method development is most desirable.[2]

Traditionally, laboratory scale synthesis of amides relies on the condensation of carboxylic acids or their derivatives (such as acid chlorides, anhydrides, and esters) with amines.[3] In addition, aryl and alkenyl halides were also employed for N-alkylation of amide.[4] Unfortunately, in spite of broader applications, these methodologies inevitably generate a stoichiometric equivalent of waste and involves multi-step synthesis (Scheme 1a).[5]

Notably, the direct application of an alcohol would represent a promising alternative to the above processes.[5d] Alcohols are highly abundant renewable feedstocks, low cost, nontoxic, and easy to handle. However, strong binding and poor leaving

**Scheme 1. Approaches for Synthesis of Amides**[a]




[a](a) Conventional methods for amide synthesis; (b) precious metal-catalyzed N-alkylation of amides with alcohols; (c) nickel-catalyzed amidation of alcohols.

ability of the hydroxyl group makes it an inferior substrate class for such transformations and required harsh reaction conditions. Nevertheless, in terms of sustainability, metal-catalyzed borrowing hydrogen or hydrogen autotransfer (BH/HA) approach renders an elegant technology for formal C−N bond forming reactions.[6] This catalytic method involves a tandem dehydrogenation of alcohol to an electrophilic aldehyde, followed by condensation with an amide. Advantageously, the newly formed C═N bond gets hydrogenated by metal-hydride to the N-alkylated amide and water is formed as sole byproduct. Over the past decades, the BH/HA strategy for N-alkylation of amines using alcohols has been well documented (Scheme 1b).[6]

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# Nickel-Catalyzed Alkylation of Ketone Enolates: Synthesis of Monoselective Linear Ketones

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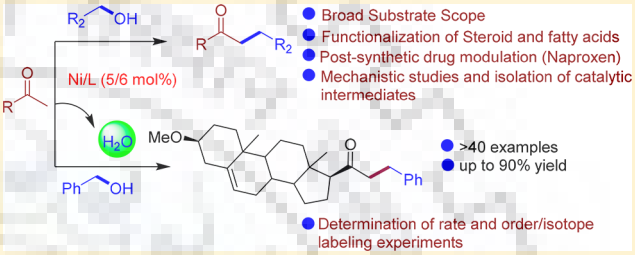
Supporting Information

**ABSTRACT:** Herein we have developed a Ni-catalyzed protocol for the synthesis of linear ketones. Aryl, alkyl, and heteroaryl ketones as well as alcohols yielded the monoselective ketones in up to 90% yield. The catalytic protocol was successfully applied in to a gram-scale synthesis. For a practical utility, applications of a steroid derivative, oleyl alcohol, and naproxen alcohol were employed. Preliminary catalytic investigations involving the isolation of a Ni intermediate and defined Ni−H species as well as a series of deuterium-labeling experiments were performed.

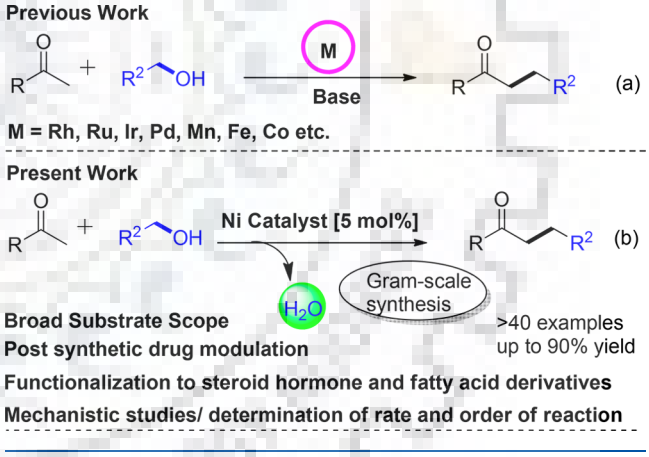



## INTRODUCTION

Utilization of high natural abundant and inexpensive alcohols and the versatility of a broad range of amine and C-nucleophiles enable the synthesis of valuable agrochemicals, pharmaceuticals, and bioactive heterocycles involving a hydrogen autotransfer strategy.[1,2] Furthermore, α-alkylation of carbonyl compounds involving ketone enolates using unactivated alcohols represents the most important milestones to forge the new C−C bonds.[3]

Traditionally, hazardous alkyl halides and a stoichiometric amount of strong bases are used for such methodologies, and an equivalent excess of waste is formed. However, the main advantage of a hydrogen-borrowing process is to avoid such stoichiometric salt waste as water is formed as the sole byproduct, making this technology more sustainable and atom-economic.[1] Importantly, catalytic upgradation of alcohols to energy efficient biofuels has been developed using the Guerbet process. These self-coupling alcohols could be performed using bifunctional Ir or Ru catalysts.[4a,b] In this context, it is noteworthy to mention that (de)hydrogenative coupling of alcohols for α-alkylation of carbonyl compounds was generally performed with precious noble-metal catalysts, such as, Ru,[4c−f] Rh,[5] Ir,[6] and Pd complexes (Scheme 1a).[7] In spite of notable progress, the potential application of renewable resources along with earth-abundant, inexpensive, and nonprecious transition-metal catalysts for key chemical transformations is a long-standing goal and crucial challenge in catalysis.[8] More recently, significant achievements for α-alkylation of carbonyl compounds with alcohols were realized using Fe,[9] Mn,[10] and Co catalysts.[11] However, the use of fancy pincer ligands based on a pyridinyl, diethylamine, or triazinyl framework is required to achieve a higher efficiency.[9−11] Further, application of these highly expensive ligands and their multistep synthesis often is a major concern in comparison to base-metal catalysts.

**Scheme 1. Transition-Metal-Catalyzed Ketone Alkylation**




In this direction, nickel has economic benefits and would function as a sustainable alternative to palladium.[12] Thus, still, there is a need to develop more exciting and challenging methodologies using nickel. However, due to the poor leaving ability and strong binding capacity of free hydroxyl group in alcohol, often unactivated alcohols behave as an inferior substrate class for such nickel-catalyzed transformations.[13a−d] Notably, Yus and co-workers studied the nickel nanoparticle-mediated coupling of ketones using primary alcohols.[13e,f] In this direction, herein, we demonstrated the homogeneous Ni-catalyzed alkylation of acetophenone derivatives to a range of α-alkylated long chain ketones with a variety of primary alcohols. The catalytic protocol is highly selective to linear α-alkylated ketones following a hydrogen-borrowing strategy.[3,14]

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# Nickel-Catalyzed Hydrogen-Borrowing Strategy for α-Alkylation of Ketones with Alcohols: A New Route to Branched *gem*-Bis(alkyl) Ketones

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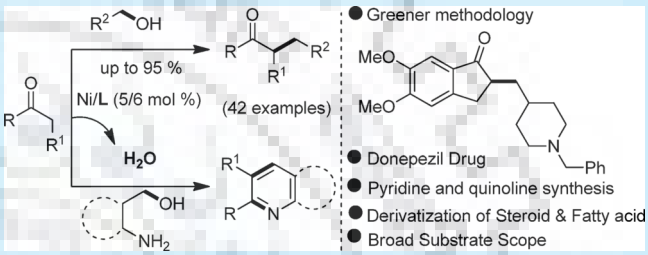
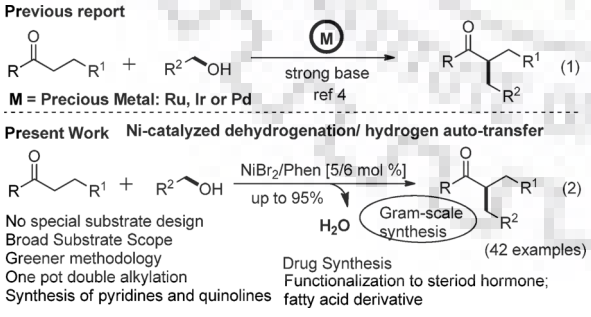
Supporting Information

**ABSTRACT:** The α-alkylation of ketones using an earth-abundant and nonprecious $NiBr_2$/**L1** system is reported. This nickel-catalyzed reaction could be performed in gram scale and successfully applied in the synthesis of donepezil (Alzheimer's drug) and functionalization of steroid hormones and fatty acid derivatives. Synthesis of N-heterocycles, methylation of ketones, and one-pot double alkylation to bis-hetero aryl ketones using two different alcohols with a single catalyst broadens the scope of the catalytic protocol. Preliminary mechanistic studies using defined Ni-H species and deuterium-labeling experiments established the participation of the borrowing-hydrogen strategy.




The transition-metal-catalyzed hydrogen borrowing strategy for α-alkylation of ketone enolates using renewable alcohols is a green and sustainable strategy for construction of C−C bonds that avoids the use of presynthesized alkyl halides and gives water as the only byproduct.[1,2] However, such α-alkylation of ketones is often limited to monoalkylation, pertaining to the linear products.[3] In contrast, synthesis of α,α-disubstituted branched products is more challenging and relatively underdeveloped (Scheme 1).

**Scheme 1. Metal-Catalyzed Synthesis of Disubstituted Ketones**




Branched *gem*-bis(alkyl) ketones are privileged structural motifs extensively used as intermediates in organic synthesis.[3a] Surprisingly, only a handful examples are known for such geminal disubstituted ketones (Scheme 1, eq 1).[3] Notably, until now, application of homogeneous Ir[4a−e] and Ru catalysts[4f] and heterogeneous Pd,[4g−i] Ni,[3a,b] and Ag/Mo catalysts,[4j] has been known for α,α-disubstituted ketones using primary alcohols. Nevertheless, applications of renewable resources in combination with rare noble metal catalysts is highly desirable for key catalytic transformations.[5a−c] In this direction, use of earth-abundant nonprecious base metals, such as Fe, Mn, Ni, and Co, would be a more sustainable and attractive alternative.[5a] Unfortunately, such processes are only known to catalyze the monoalkylation of acetophenone derivatives and have never been demonstrated in the synthesis of geminal α,α-disubstituted ketones.[3g,h] Nevertheless, the use of renewable alcohols represents an alternative powerful and straightforward strategy with high atom and step economy (Scheme 1, eq 2).[2,6a,b] Unfortunately, poor leaving group character and strong coordination ability of the hydroxyl group limits its applications for nickel-catalyzed transformations.[7]

To date, to the best of our knowledge, nickel-catalyzed alkylation of ketones with primary alcohols in the synthesis of α,α-disubstituted branched products have not been developed.[3b,c] More specifically, this represents the first example of an earth-abundant nonprecious base-metal-catalyzed practical route to branched *gem*-bis(alkyl) ketones. The key to success is the application of diversely available nitrogen ligands for nickel to forge the C−C coupling. This strategy provides new methods for the facile synthesis of branched *gem*-bis(alkyl) ketones, substituted pyridines, and quinolines with broad substrate scope.

Recently, we established an efficient nickel-catalyzed system for amination and amidation of primary alcohols as well as intermolecular cyclization to N-heterocycles.[8] Our mechanistic studies revealed that nickel catalysts facilitate the dehydrogenation of alcohol to aldehyde and form Ni−H intermediates

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# Nickel-catalysed alkylation of C(sp$^3$)–H bonds with alcohols: direct access to functionalised N-heteroaromatics†

Mari Vellakkaran,‡ Jagadish Das,‡ Sourajit Bera and Debasis Banerjee *

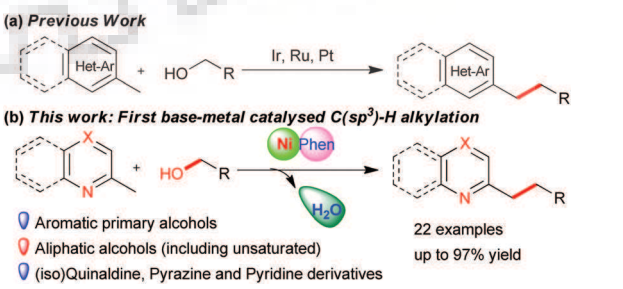
**The first base-metal catalysed coupling of primary alcohols with methyl-N-heteroaromatics is reported. The use of an earth abundant and nonprecious $NiBr_2$/L1 system enables access to a series of C(sp$^3$)-alkylated N-heteroaromatics. Mechanistic studies have established the participation of a hydrogen-borrowing strategy for α-alkylation.**

Transition metal-catalysed alkylation of C(sp$^3$)–H bonds for the construction of elongated carbon-chain products constitutes a fundamental challenge in organic synthesis. Due to a high C(sp$^3$)–H bond dissociation energy, an efficient and selective functionalisation of alkyl chains often represents a key issue in catalysis. Therefore, since the last decade significant efforts have been made involving C–H bond activation using alkyl halides,[1] directing group assisted functionalisation of C(sp$^3$)–H bonds with olefins,[2] and reductive alkylation including nucleophilic substitutions and α-alkylation of ketone enolates and related studies have been documented.[3,4]

N-Heteroaromatics and their derivatives are important targets in medicine, pharmaceuticals, and material chemistry, and they are significantly used as intermediates for natural products and ligands in catalysis.[5] Therefore, the functionalisation of the C(sp$^3$)–H bonds in methylazaarenes provides direct access to chain-elongated N-heteroaromatics with valuable applications. However, such transformations are often limited by pre-functionalised alkyl halides, carbonates or esters and often require harsh reaction conditions involving the generation of stoichiometric equivalents of waste.[6] Therefore, the development of environmentally benign, sustainable and atom-economical alkylation technology for C(sp$^3$)–H bonds in N-heteroaromatics is still a desired goal.[7–9e,f]

Notably, the direct application of highly abundant and renewable alcohols would be a promising alternative to the above process.[6b] Nevertheless, currently, a metal-catalysed hydrogen borrowing (HB) approach has been identified as an elegant tool to construct C–X (X = C, N *etc.*) bonds.[8] In this direction, only a handful of examples are known and they are based on precious metal catalysts (Ir-, Ru-, and Pt) for such C(sp$^3$)–H bond functionalisation in N-heteroaromatics using alcohol as a coupling partner. A notable breakthrough by Kempe,[9a] on well-defined Ir-catalysed alkylation of N-heteroaromatics, is worth mentioning. Later, Obora and co-workers reported the functionalisation of 2-methyl heteroarenes using Ir-catalysts.[9b] Recently, an Ru-catalysed ligand-free alkylation method as well as a Pt-supported heterogeneous catalysis method has also been developed for the alkylation of methyl N-heteroaromatics using alcohols following the HB approach (Scheme 1a).[9c,d]

However, recent trends in catalysis are to replace precious and expensive metal catalysts with earth abundant and rare noble metal catalysts for such key catalytic conversions.[10a,b] Therefore, the development of a sustainable catalytic protocol involving renewable resources in combination with non-precious metal catalysts is in demand. For instance, recently, the Mn-catalysed α-olefination of N-heteroaromatics using alcohols has been reported.[10c,d] Nevertheless, to the best of our knowledge, to date, no nickel catalysed protocol for coupling primary alcohols with




Scheme 1 (a) Precious metal-catalysed alkylation of methyl N-heteroaromatics; (b) nickel-catalysed coupling of alcohols with methyl N-heteroaromatics.

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# Nickel-catalysed direct α-olefination of alkyl substituted N-heteroarenes with alcohols†

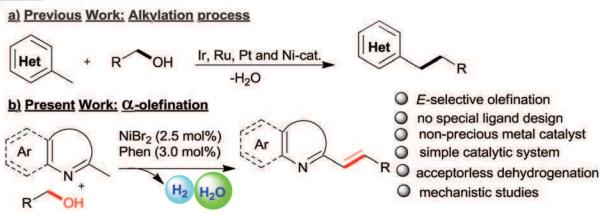
Jagadish Das, Mari Vellakkaran and Debasis Banerjee *

**Catalytic α-olefination of alkylheteroarenes with primary alcohols *via* dehydrogenative coupling is presented. A simple nickel catalyst system stabilised by readily available nitrogen ligands enables a series of interesting *E*-configured vinylarenes (confirmed by X-ray crystal-structure analysis) to be synthesised in good to excellent yields with olefin/alkane selectivity of >20 : 1. Hydrogen and water are generated as byproducts and quantitative determination of $H_2$ was performed.**

Designing methods for *E*-selective synthesis of di-substituted olefins is a difficult task and poses new challenges for several reasons.[1] Though a number of classical approaches for the synthesis of stereo-selective alkenes are known, most of these suffer from key shortfalls: (i) association of appropriate carbonyl functionality to control the stereo-chemical outcomes; (ii) strong basic or acidic reaction conditions; (iii) lengthy sequences; (iv) generation of stoichiometric waste and (v) often selection of appropriate leaving groups (Wittig reactions, Horner–Wadsworth–Emmons reaction, Julia olefination, Peterson olefination *etc.*) is crucial to obtain the desired olefins.[2] Additionally, precious-metal catalysed Suzuki or Heck couplings and olefin metathesis continue to be efficient technologies for the synthesis of styryl derivatives.[3] Olefins, in particular *E*-selective conjugated N-heteroarenes, are extensively used as intermediates for the synthesis of bulk and specialty chemicals, pharmaceuticals, agrochemicals, organic light emitting diodes, conducting polymers and in material chemistry and display important biological activities.[4] Therefore, the synthesis of highly *E*-selective olefins conjugated with N-heteroarenes is a demanding goal and represents a new challenge.[2]

In this context, acceptorless dehydrogenative couplings (ADCs) of renewable alcohols with alkyl N-heteroarenes for the synthesis of *E*-selective olefins would be an efficient technology, as it generates water and dihydrogen as valuable side products. Notably, often ADCs of alcohols are limited with precious metal-catalysts (Scheme 1a).[5a–c] However, the use of earth abundant and inexpensive metal-catalysts (Fe, Mn, Ni and Co) for such applications and to explore new reactivities is highly desirable for more attractive and elegant sustainable technologies.[5d,6] Arguably, significant progress has been achieved using non-noble metal-complexes in various (de)hydrogenative coupling reactions.[7] Indeed, among others, nickel offers an attractive sustainable alternative to precious metals for such applications. To date, nickel complexes have been successfully used for various C–C and C–N bond formations.[8] In this direction, we have reported nickel-catalysed coupling of alcohols for various sustainable transformations.[9] Very recently, we have also developed alkylation of C–H bonds in methyl substituted N-heteroarenes to chain elongated $C_2$-alkylated N-hetero-arenes;[10] and become interested in nickel catalyzed dehydrogenative alkylation or α-olefination of alkyl substituted N-heteroarenes with alcohols (Scheme 1). However, 10 mol% Ni–salt and 50 mol% ligand were essential to achieve these alkylations. We observed that application of excess ligands was key for the successful reduction of the intermediate C=C bond to the desired alkylated products. These excess ligands facilitate the formation of the desired Ni–H species required for the hydrogenation of the C=C bond. Furthermore, only a limited substrate scope was explored for the alkylation process.

Nevertheless, recently Mn-catalysed olefination of alkyl N-heteroarenes with alcohols was reported using pincer-based catalysts.[11a,b] Notably, these manganese-complexes were stabilized by triazinyl-core $PN_3P$ ligands or NNN pincer ligands to attain higher catalytic efficiency. Importantly, the multi-step synthesis




Scheme 1 (a) Metal-catalysed alkylation of 2-methyl N-heteroaromatics with alcohols; (b) nickel-catalysed coupling of alcohols with methyl N-heteroaromatics.

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# Iron-Catalyzed Coupling of Methyl *N*-Heteroarenes with Primary Alcohols: Direct Access to *E*-Selective Olefins

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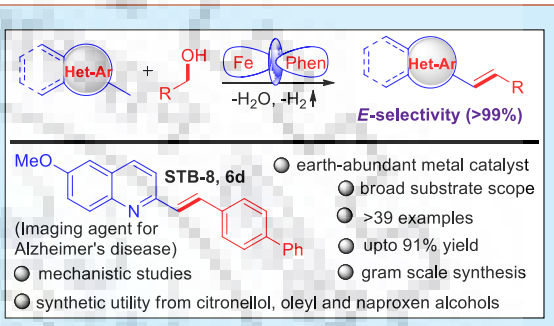
Supporting Information

**ABSTRACT:** An efficient Fe-catalyzed system is reported for direct α-olefination of methyl-substituted *N*-heteroarenes with primary alcohols. The catalytic dehydrogenative coupling enables a series of functionalized *E*-olefinated *N*-heteroaromatics with excellent selectivity (>99%). Initial mechanistic studies including deuterium-labeling experiments provide evidence for the participation of the benzylic C−H/D bond of alcohols.




Transition-metal-catalyzed functionalization of methylazaarenes with suitable nucleophiles provides access to valuable *E*-olefins having heteroaromatic cores. These *E*-selective conjugated heteroarenes are ubiquitous structural motifs found in many bioactive natural products, agrochemicals, and pharmaceuticals.[1,2] Notably, several classical approaches for the synthesis of regioselective alkenes are Wittig reaction, Horner−Wadsworth−Emmons reaction, Julia olefination, Peterson olefination, etc.,[3] involving a suitable leaving group. Furthermore, Heck or Suzuki couplings and olefin metathesis are well-established approaches for their synthesis (Scheme 1a).[4] Again, condensation of methylazaarenes with aldehydes using stoichiometric amounts of strong acids or bases were also used for such conjugated olefins.[5] Nevertheless, often such processes suffer from (i) generation of stoichiometric waste, (ii) harsh reaction conditions, (iii) multistep sequences, (iv) and poor *E*/*Z* selectivity.[3,4] In this direction, a recent report for the functionalization of alkylazaarenes using Fe catalyst involving activated *N*-sulfonylaldimines has been developed (Scheme 1b).[6] Applications of Lewis acids,[7] or Pd catalysts,[8] were also used for such azaarene derivatives.

In the past decades, dehydrogenative coupling of alcohols were extensively used for the synthesis of unsaturated compounds. In this context, replacement of expensive and precious metal catalysts by nonprecious earth abundant metals (Fe, Mn, Ni, and Co) would be more attractive for such key catalytic conversions.[9] In this direction, recently we developed a couple of nickel-catalyzed novel protocols for the synthesis of secondary amines, amides, including interesting *N*-heterocycles.[10] Most recently, we and others have also developed the alkylation of methyl substituted *N*-heteroarenes with alcohols.[11a−h,12] Recent studies for α-olefination of alkylazaarenes with primary alcohols has been developed using manganese pincer catalysts.[12a,b] Notably, such pincer complexes employed expensive ligands systems based on $PN_5P$ or NNN core and required multistep synthesis (Scheme 1c).

Therefore, storing, handling, and expensive nature of these ligands are key issues in comparison to base−metal catalysts.[12a,b] More recently, we have also demonstrated the Ni-catalyzed synthesis of *E*-selective olefins involving methyl substituted *N*-heteroarenes with alcohols (Scheme 1c).[12c] We observed diminished reactivity for electron poor functionalities, halides substituted alcohols (Cl or Br) and even with alkyl alcohols.[12c] Therefore, there is still a need to develop a general and chemoselective catalytic protocol for the synthesis of functionalized *E*-olefins.

Notably, iron is the most earth-abundant metal, inexpensive and less toxic. Iron is capable of existing in variable oxidation states and is an integral part of living systems. Therefore, utilization of iron catalysts for key organic transformations is attracting increased interest.[13] However, to the best of our knowledge, to date, no iron-catalyzed olefination of methyl *N*-heteroaromatics with primary alcohols is known.

Herein, we report the first Fe-catalyzed route for *E*-olefination of a series of methylazaarenes with alcohols (Scheme 1d). The catalytic protocol is tolerant of a series of electron-poor functional groups, halides, and linear as well as cyclic alkyl alcohols that established the novelty of the present protocol.

Initially, we examined the reaction between 2-methylquinoline (**1a**) with 4-methoxybenzyl alcohol (**2a**) as the model substrates of our choice. When Fe(II) acetate (5 mol %) and 1,10-phenanthroline **L1** (6 mol %) were used with *t*-BuOK (1.0 equiv) as a base, 80% isolated yield of **3a** was obtained along with a trace amount of undesired alkylated product **3a′**

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