NICKEL-CATALYZED SUSTAINABLE ORGANIC TRANSFORMATIONS: DIRECT ACCESS TO AMINES, PYRROLES, PYRIDINES, QUINOLINES AND GEM-BIS-SUBSTITUTED KETONES

Ph.D. THESIS

by

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ROORKEE - 247 667 (INDIA)
NOVEMBER, 2018

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A THESIS

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

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CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled **"NICKEL-CATALYZED SUSTAINABLE ORGANIC TRANSFORMATIONS: DIRECT ACCESS TO AMINES, PYRROLES, PYRIDINES, QUINOLINES AND GEM-BIS-SUBSTITUTED KETONES"** 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 is an authentic record of my own work carried out during a period from July, 2015 to November, 2018 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.

Khushboo Singh (KHUSHBOO SINGH)

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

Debasis Banerjee.

(Debasis Banerjee)
Supervisor

The Ph.D. Viva-Voce examination of **Khushboo Singh**, Research Scholar, has been held on 05/04/2019.

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

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“DEDICATED

TO

MY FAMILY”

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Thanks to God for this journey…

Khushboo Singh

Abstract/Synopsis

The work carried out in the research tenure has been accumulated in the form of a thesis entitled as "**NICKEL-CATALYZED SUSTAINABLE ORGANIC TRANSFORMATIONS: DIRECT ACCESS TO AMINES, PYRROLES, PYRIDINES, QUINOLINES AND GEM-BIS-SUBSTITUTED KETONES**". The thesis has been divided into four chapters, as follows:

CHAPTER-1: Metal-Catalyzed Sustainable Synthesis of C-C and C-N Bonds: A Brief Literature Summary

CHAPTER-2: Ni-Catalyzed Direct N-Alkylation of Anilines with Alcohols.

CHAPTER-3: **SECTION-A**: Nickel-Catalyzed Intermolecular Cyclization for the Synthesis of Five and Six Membered N-heterocycles.

CHAPTER-3: **SECTION-B**: Nickel-Catalyzed Synthesis of Pyrroles from Unsaturated Diols and Amines.

CHAPTER-4: Nickel-Catalyzed Synthesis of *gem*-Bis-Alkylkated Ketones.

Chapter-1: Metal catalyzed sustainable synthesis of C-C and C-N Bonds: A brief literature Summary

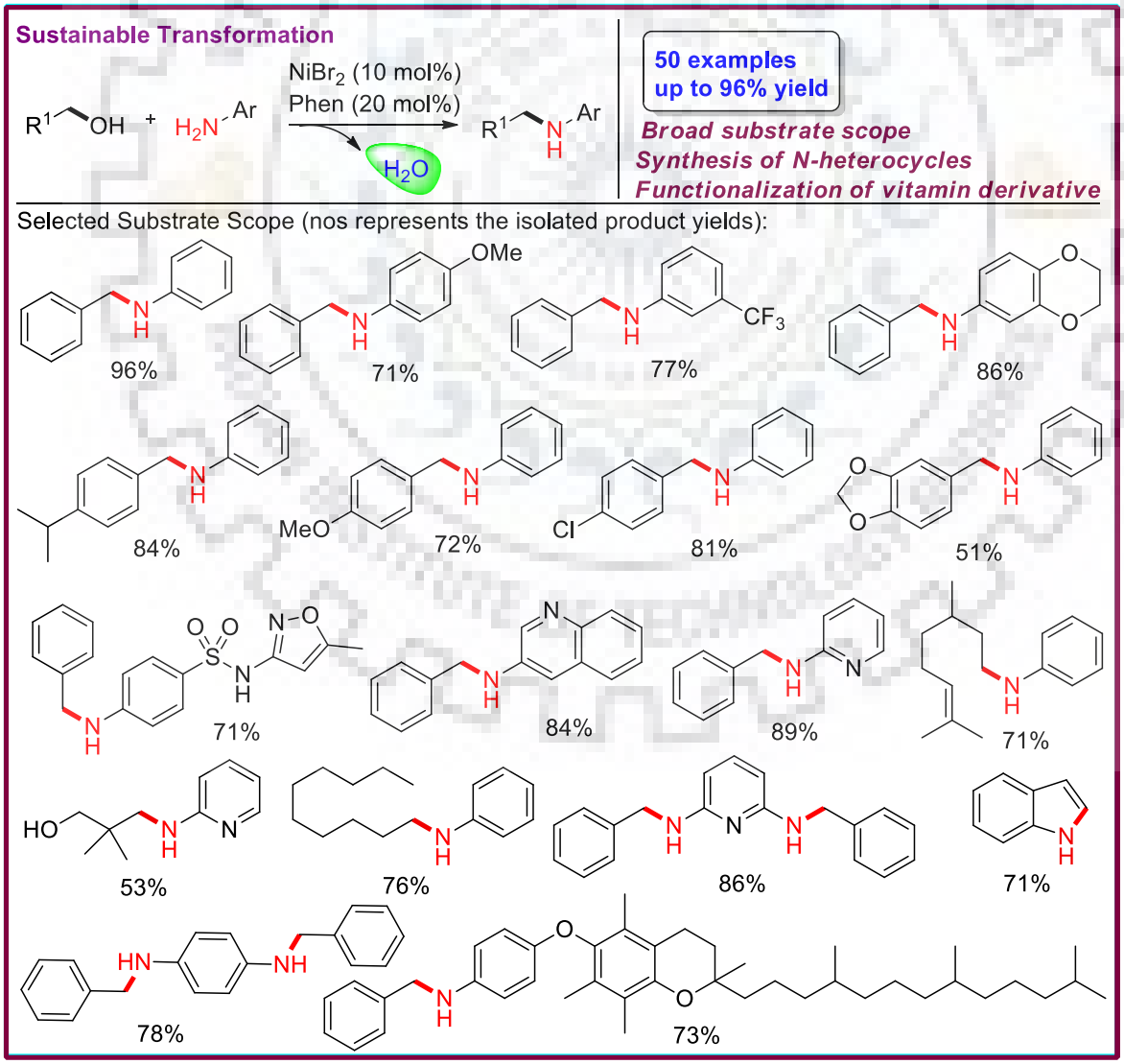
This chapter deals with the brief literature summary for transition metal catalyzed activation and functionalization of small molecules. Recent studies have attracted great attention towards sustainable development of new catalytic protocols for C-C and C-N bonds. This simple and straightforward method can be applied for the synthesis of bioactive natural product, drug molecules, agrochemicals and important pharmaceuticals. Thus, homogeneous catalysis using more abundant and inexpensive first row transition metals has become a widespread research theme. In this direction, cobalt, iron, nickel and manganese catalysis are mainly desirable because of their earth abundant, readily available, inexpensive and non-toxic nature.

The constructions of C-C and C-N bonds are the most important tasks in organic synthesis. Classical methods for these bond formations occur through electrophilic alkylation of an alkyl halide or pseudo-halide, reductive alkylation and amination of aryl halide. However, these conventional methods suffer with drawbacks such as pre-functionalization of starting materials, use of hazardous reagents and stoichiometric amount of waste production. In modern organic chemistry, chemists are concerned about the more efficient synthetic methodology which mainly involves environmental benign processes and thereby

contributing to atom economy. This strategy generates only water as a byproduct and avoids the use of multi-step production of dangerous alkylating agents. Compared to other synthetic methodologies for the synthesis of C-C and C-N bond, these transformation is highly attractive because often alcohols are readily available starting materials and most of them are available in a large scale from renewable sources. Further, application of hydrogen borrowing methodology using alcohols in combination with non-noble metal-catalysts are prime goal here described in the present thesis.

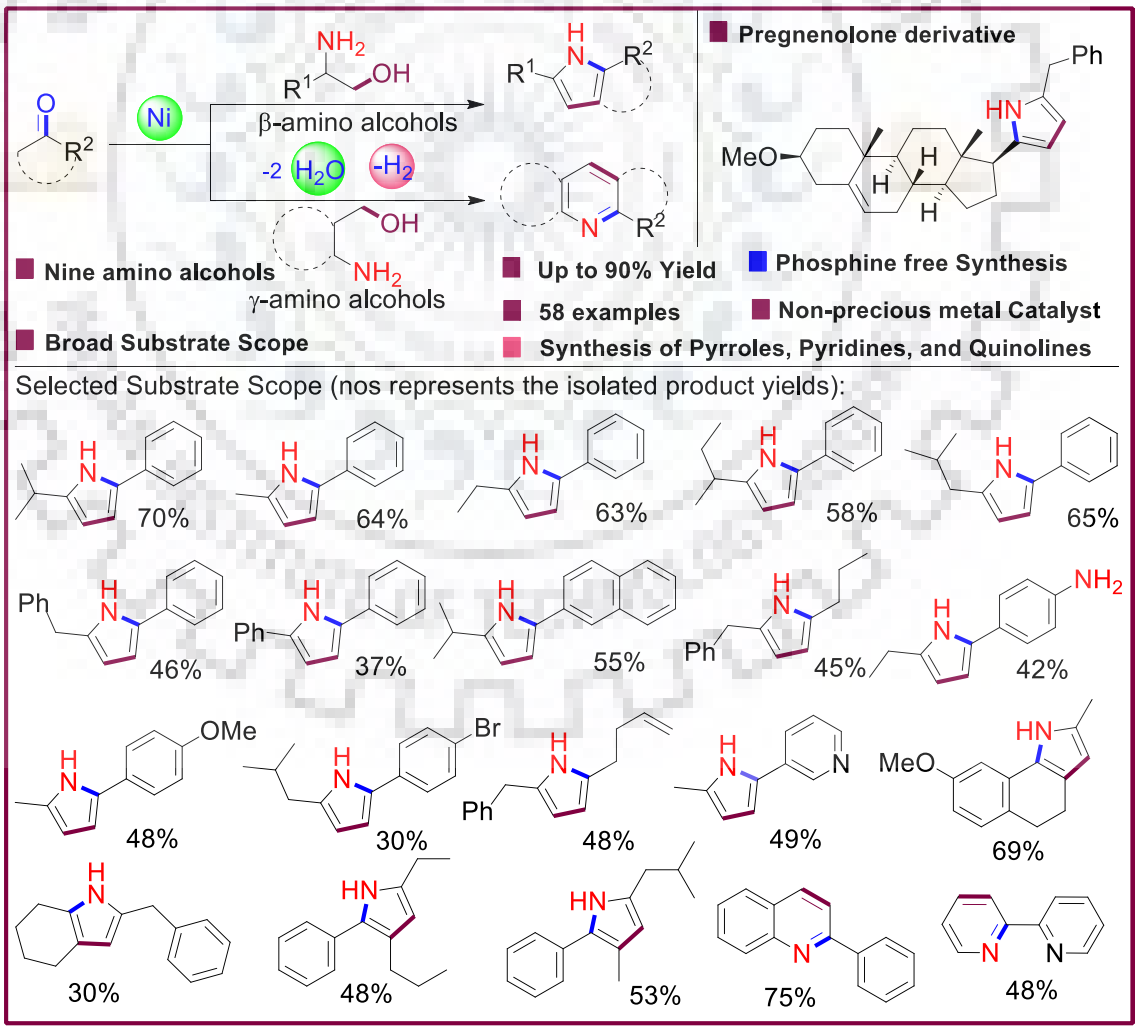
Chapter-2: Ni-catalyzed direct *N*-alkylation of anilines with alcohols (*ACS Catal*. **2017**, *7*, 8152-8158).

This chapter of thesis describe the development of a general and inexpensive nickel-nitrogen ligated system for selective alkylation of alcohols with amines to secondary amines derivatives.



More specifically, herein, we developed an efficient and selective nickel catalyzed mono-alkylation of a series of primary alcohols with aryl and hetero(aryl) amines together with diols and amino alcohol derivatives. Notably, the catalytic protocol consisting of earth abundant and non-precious $NiBr_2$/1,10-phenanthroline system enable the transformations in presence of hydroxyl, alkenes, nitrile and nitro-functionalities. As a special highlight, we have demonstrated the alkylation of di-aniline, intramolecular cyclization to N-heterocycles, and functionalization of complex vitamin E, (±) α-tocopherol derivative. Preliminary mechanistic studies including synthesis of defined Ni-catalysts, defined Ni-H species and a series of deuterium labeling experiments revealed the participation of benzylic C-H bond in the rate determining step.

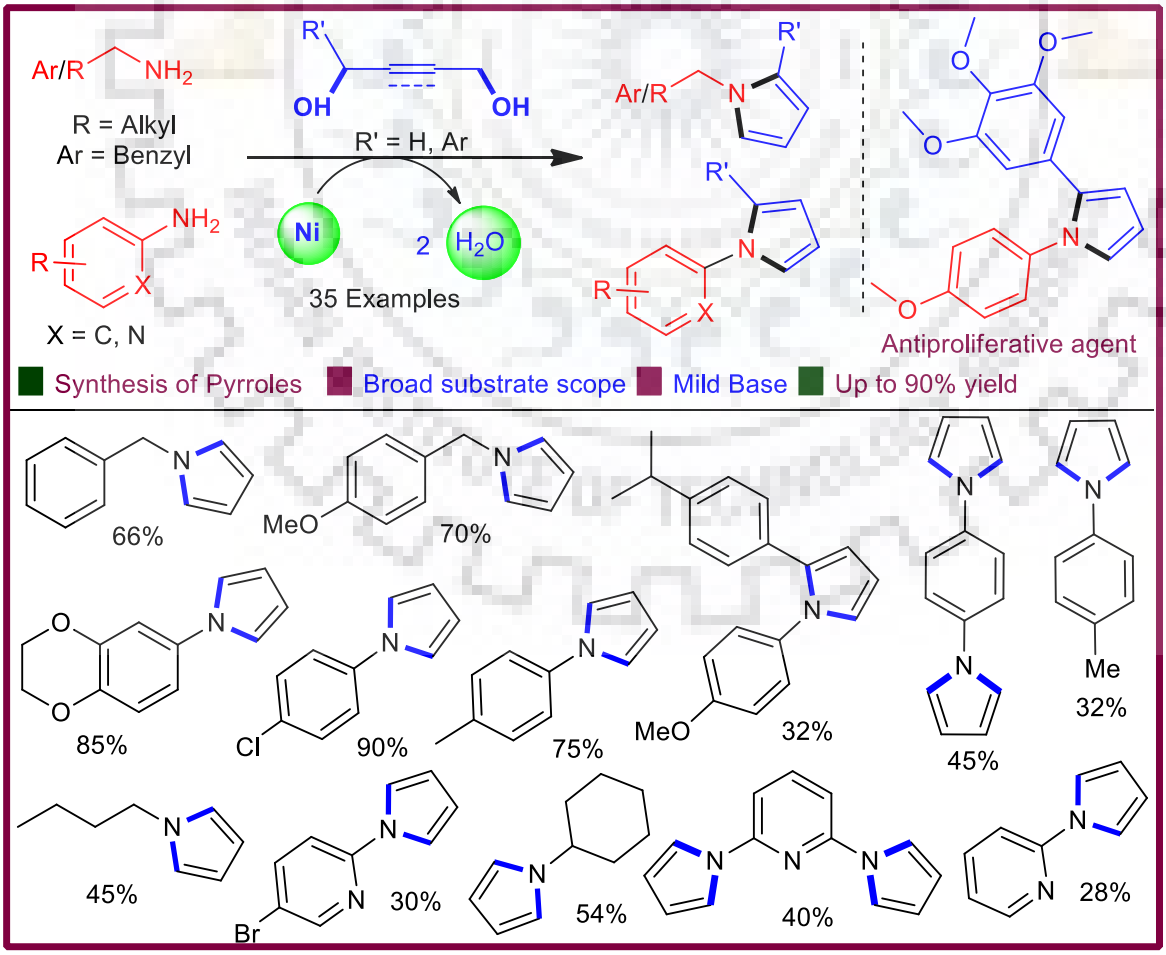
Chapter-3 Section-A: Nickel-catalyzed intermolecular cyclisation for the synthesis of five and six membered N-heterocycles (*Green Chem.* **2018**, *20*, 2250-2256).



The prime objective of this chapter is to develop a general and efficient nickel-catalyzed system for the synthesis of five and six-member N-heterocycles. Owing to the great demand for synthesis of N-heterocycles, development of new reactions that utilize renewable resources and convert them into key chemicals using non-precious base metal-catalysts is highly desirable.

Here we demonstrated a sustainable Ni-catalyzed dehydrogenative approach for pyrroles, pyridines and quinolines synthesis employing β- and γ-amino alcohols with ketones via C-N and C-C bond formations in a tandem fashion. A variety of aryl, hetero-aryl and alkyl ketones having free amine, halides, alkyl, alkoxy, alkenes, activated benzyl and pyridine moiety converted into synthetically interesting 2,3 and 2,3,5 substituted bicyclic as well as tricyclic N-heterocycles in up to 90% yields. As a special highlights, we demonstrated an interesting pyrrole derivative employing intermolecular cyclisation of steroid hormone with phenylalaninol.

Chapter-3 Section-B: Nickel-catalyzed synthesis of pyrroles from unsaturated diols and amines (*J. Org. Chem.*, **2018**, *83*,15406-15414).

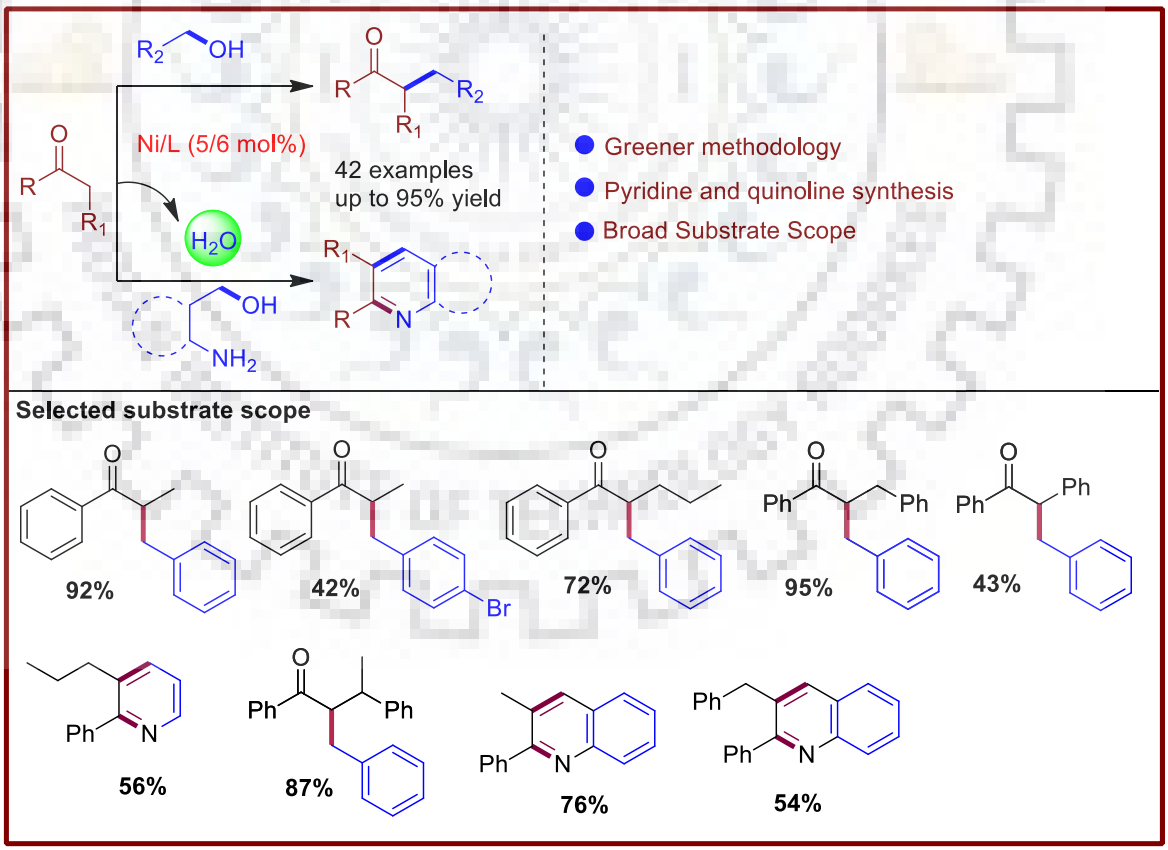


The main objective of this study is to develop an operational simple and inexpensive catalytic system that utilize renewable resources and convert them into key chemicals using base metal-catalysts is highly desirable. Herein, we reported the Ni-catalyzed dehydrogenative strategy for pyrroles formations using butene-1,4-diols and butyne-1,4-diols with a series of aryl, alkyl and hetero-aryl amines. The catalytic protocol is tolerant to free alcohol, halides, alkyl, alkoxy, oxygen heterocycles, activated benzyl and pyridines moieties and resulted in up to 90% yield. Initial mechanistic studies using defined Ni-catalyst, isolation of intermediate species as well as deuterium labeling experiments were performed to establish the hydrogen-borrowing strategy for pyrrole synthesis.

Chapter-4: Nickel-catalyzed synthesis of gem-bis-alkylkated ketones

(*Org. Lett*. **2018**, *20*, 5587-5591).

The work presented in this Chapter has recently been published in Org. Lett. **2018**, 20, 5587-5591. This work has been contributed equally by another author. Therefore, in this chapter we will only discuss those part of the work mainly contributed by me.



In this section we report the α-alkylation of methylene ketones using an earth-abundant and non-precious $NiBr_2$/N-ligand system that enables the transformations to a range of branched

gem-bis(alkyl) ketones using renewable primary alcohols. This nickel catalyzed system could be performed in gram scale and successfully applied in the synthesis of donepezil (Alzheimer's drug), functionalization of steroid hormone, and fatty acid derivatives. Green synthesis to N-heterocycles, α-methylation of ketones using methanol and one pot double alkylation to bis-hetero aryl ketones using two different alcohols with a single catalyst broaden the scope of the catalytic protocol. A detailed mechanistic studies involving isolation of defined Ni-intermediate species, Ni-H species, Ni-alkoxy complex, determination of rate and order of the reaction, competition reactions of electronically different alcohols and a series of deuterium labelling experiments established the participation of borrowing-hydrogen strategy for nickel-catalyzed α-alkylation of methylene ketones with alcohols.

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List of Abbreviations

Ac	:	Acetyl
acac	:	Acetyl acetonate
Ar	:	Aryl or Aromatic
AgF	:	Silver(I) fluoride
Al_2O_3	:	Aluminium oxide
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
COT	:	1,3,5,7-Cyclooctatetraene
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
m	:	Meta

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
o	:	Ortho
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
p	:	Para
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

α	:	Alpha
β	:	Beta
γ	:	Gamma
%	:	Percentage
J	:	Coupling constant
δ	:	Chemical shift
ºC	:	Degree centigrade

List of Publications

1. Vellakkaran, M.[‡]; **Singh, K.**[‡]; Banerjee, D. An Efficient and Selective Nickel-catalyzed Direct *N*-alkylation of Anilines with Alcohols. *ACS Catal.* **2017**, *7*, 8152−8158. [‡]These authors contributed equally to this work.
2. **Singh, K.**; Vellakkaran, M.; Banerjee, D. A nitrogen-ligated nickel-catalyst enables selective intermolecular cyclisation of β- and γ-amino alcohols with ketones: access to five and six membered *N*-heterocycles. *Green Chem*. **2018**, *20*, 2250−2256.
3. **Singh, K.**; Kabadwal, L. M.; Bera, S.; Alanthadka, A.; Banerjee, D. Nickel-Catalyzed Synthesis of N-substituted Pyrroles using Diols with Aryl and Alkyl Amines. *J. Org. Chem*. **2018**, *83*, 15406-15414.
4. 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. [‡]These authors contributed equally to this work.

Chapter-1: Metal catalyzed sustainable synthesis of C-C and C-N Bonds.

Transition metal catalyzed activation and functionalization of small molecules has attracted great attention towards sustainable development of new catalytic protocols for C-C and C-N bonds. This simple and straightforward method can be applied for the synthesis of bioactive natural product, drug molecules, agrochemicals and important pharmaceuticals. Thus, homogeneous catalysis using more abundant and inexpensive first row transition metals has become a widespread research theme. In this direction, cobalt, iron, nickel and manganese catalysis are mainly desirable because of their earth abundant, non-toxic nature, readily available, and inexpensive.

Chapter 1: Metal-Catalyzed Sustainable Synthesis of C-C and C-N Bonds: A Brief Literature Summary

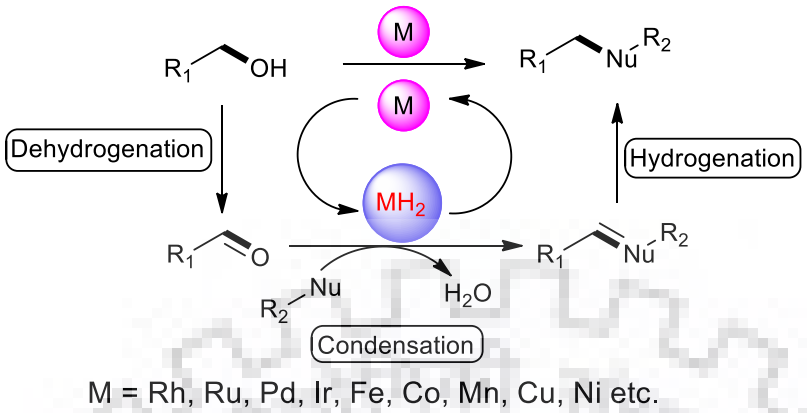
[1.1] Introduction:

Transition metal-catalyzed sustainable transformations for the constructions of new C-C and C-N bonds has emerged as a new tool in organic synthesis and catalysis. These processes facilitate to the formation of numerous pharmaceutically important compounds and natural products of important biological activities. Classical methods for their synthesis required multi-step process involving substitutions of an alkyl halide or pseudo-halide as well as reductive alkylation and amination of aryl halide. These conventional methods not only lower down the value of synthesis, often associated with expensive starting materials, application of hazardous reagents and overall generates stoichiometric amount of waste production. The major concern in present days is to develop efficient synthetic methodologies which not only minimize the waste production, streamline the organic synthesis and should be environmental benign and atom economic. [1]

In this direction, an efficient, step-economic as well as environmentally benign process would be the application of renewable alcohols as one of the important coupling partner. Operationally simple, highly abundant and inexpensive alcohols could be available from biomass derivatives or fermentation processes. Further, use of alcohols for such transformations only generates water as sole by product and rendering these processes sustainable. Another major concern in the catalytic research is to replace the precious noble metal catalysts, such as, Pd-, Rh, Ru-, Ir etc. by highly abundant non-noble metal catalysts (Fe, Co, Mn- and Ni). Highly expensive, toxic nature and limited availability of these noble-metal catalysts sometimes key issues for industrial bulk scale productions of speciality chemicals. On the other hand, there is of great interests to explore the reactivity profile for these non-precious metal catalysts, such as, Fe-, Co-, Mn- and Ni-based complexes to develop new reactions with similar efficiency as of precious metal catalysts.

Notably, such transformations using alcohols generally follows borrowing hydrogen or hydrogen auto transfer strategy. Initially dehydrogenation of an alcohol to aldehyde or ketone is occurred by the transition metal catalyst and metal hydride is formed. Next, condensation of an amine or ketone to the corresponding carbonyl compound resulted imine or enone intermediate. At this stage, hydrogenation of intermediate enone or imine by metal-hydride furnished the desired amines or substituted ketones. This strategy resulted the formation of new C-C and C-N bond and generates only water as the sole byproduct and avoids the use of

multi-step synthesis. Herein, we have depicted a general scheme for hydrogen borrowing process in Scheme 1. [1,2]



Scheme 1: General concept for hydrogen borrowing methodology

This chapter of the present thesis deals with such sustainable processes using hydrogen borrowing methodology for the constructions of new C-C and C-N bonds using alcohols as one of the coupling partner. Herein, we will briefly discuss few literatures reported key sustainable transformations using transition metal catalysts.

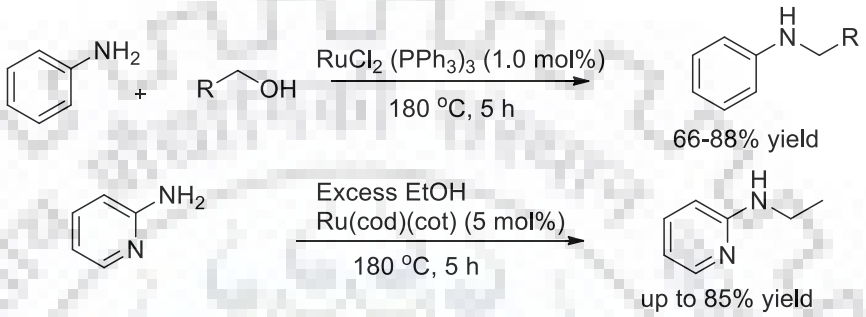
[1.2] Transition metal-catalyzed alkylation of amines and ketones using alcohols

[1.2.1] *N*-Alkylation of amines based on precious metals:

Amines are one of the most important functional compounds in organic chemistry and ubiquitous in various biologically active natural products, agrochemicals, pharmaceuticals as well as in drugs. Amines are extensively used as ligands in catalysis, material chemistry and as intermediates for various organic transformations. Classical methods for their synthesis includes Hofmann alkylation,[3] Buchwald-Hartwig amination,[4] Ullman reactions,[5] hydroamination,[6] hydroamino methylation,[7] reduction of nitrile,[8] and nitro-compounds,[9] as well as reductive amination,[10] have been well documented. The main drawback associated with these classical methodologies are used for multi-step synthesis, hazardous reagents, high temperature and pressure and generates stoichiometric amount of salt-waste. More specially, application of these methods for bulk scale synthesis are quite expensive.

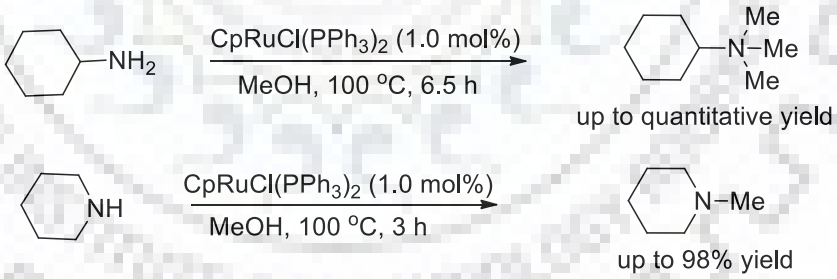
To overcome such limitations, applications of new reactions involving renewable resources, such as earth abundant renewable alcohols in combination with transition metals are in great

demand. These processes not only reduced the lengthy synthetic steps also avoids the production of stoichiometric waste generation, thereby streamline the synthetic procedure. In this direction pioneering studies by the group of Grigg and Watanabe independently demonstrated the synthesis of secondary amines using primary amines in combination with renewable alcohols catalyzed by Ru-complexes (Scheme 2). These amination of alcohols efficiently resulted the formation of various secondary as well as tertiary amines following hydrogen borrowing methodology.[11,12]



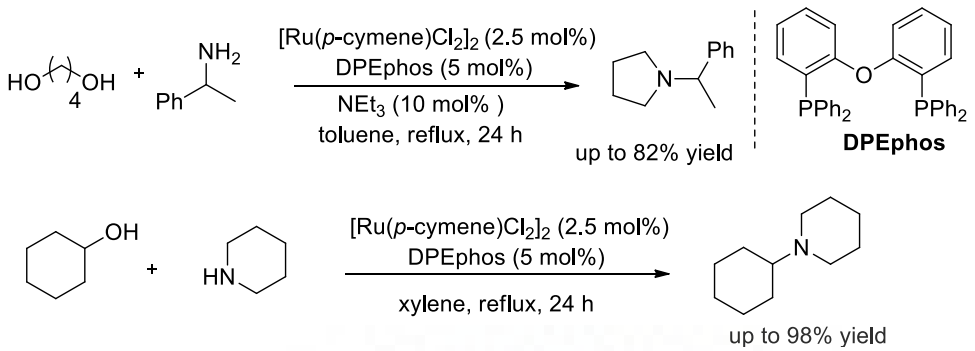
Scheme 2: Ru-catalyzed *N*-alkylation of amines

Thereafter, Zotto *et. al.* reported the methylation of primary and secondary amines with methanol using a Ru-based phosphine complex. The catalytic protocol is highly efficient for the construction of aliphatic tertiary amines as well as methylation of aromatic, cyclohexylamine and piperidine in up to quantitative yield (Scheme 3).[13]



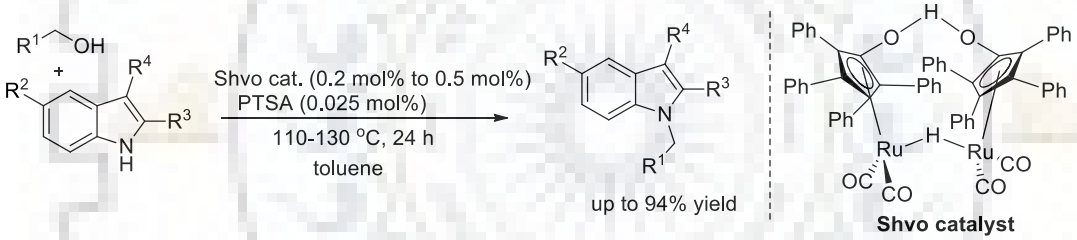
Scheme 3: Ru-Catalyzed *N*-methylation of primary and secondary amines

Williams and co-workers also reported [Ru(*p*-cymene)Cl_2]$_2$ as precatalyst in combination with dppf or DPEphos ligand for successful alkylation of primary and secondary amines with alcohols.[14] The catalytic protocol was further extended to the synthesis of tertiary amines using various secondary alcohols including cyclohexanol as well as diols and resulted good to excellent product yields (Scheme 4).[15]



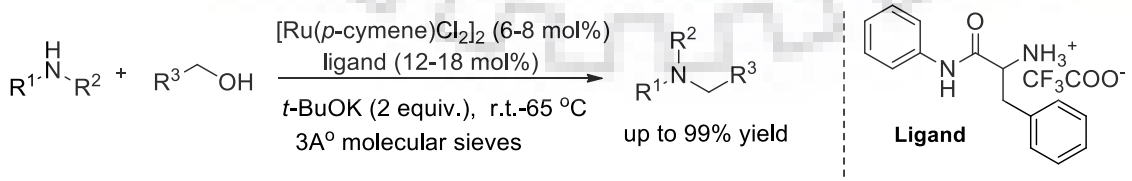
Scheme 4: *N*-alkylation of primary and secondary amines using Ru-based catalyst

In a similar direction, Beller and co-workers demonstrated *N*-alkylation of indoles with alcohols using 0.5 mol% of Shvo-catalyst activated by acid additives. It was proposed that, in the presence of Shvo-catalyst dehydrogenation of alcohol to aldehyde followed by intramolecular isomerisation, transfer hydrogenation as well as condensation resulted *N*-alkylated indole in up to 94% yield (Scheme 5).[16]



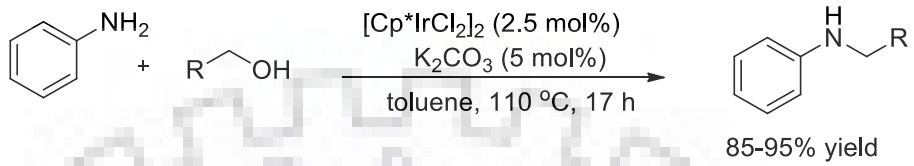
Scheme 5: *N*-alkylation of indoles with alcohols

Recent studies by Moasser and co-workers using a combination of Ru-based precatalyst in combination with amino amide ligand for *N*-alkylation of amines with alcohols is noteworthy. Alcohol was used as solvent and the reaction could be performed at room temperature with good to excellent product yield of secondary amines.[17]



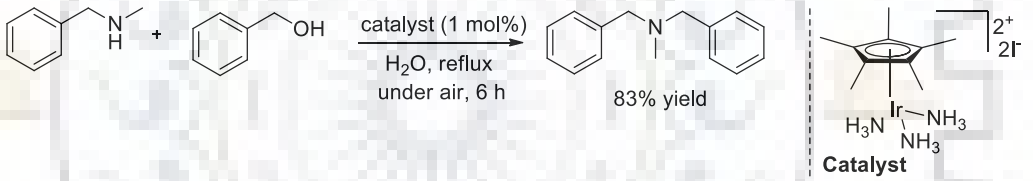
Scheme 6: Ru-catalyzed synthesis of secondary amines

Apart from Ru-based complexes, Ir-complexes were also identified as active catalyst composition for interesting C-C and C-N bond forming reactions. For instance, Fujita and co-workers studied the *N*-alkylation of amines with more challenging alkyl alcohols. Commercially available Ir-catalyst was also highly efficient for a series of electronically different benzyl and other primary and secondary alcohol derivatives (Scheme 7).[18]



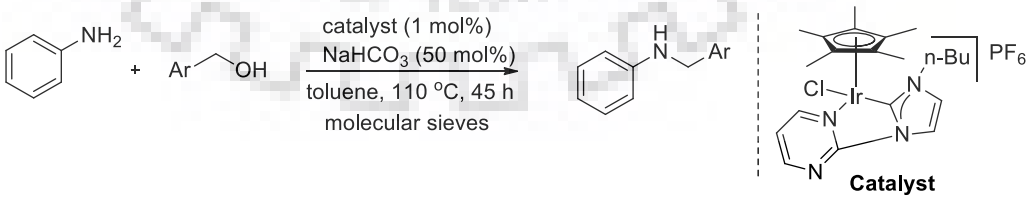
Scheme 7: Iridium catalyzed *N*-alkylation of alcohols

In 2011, they have designed a more efficient water soluble di-cationic Ir-catalyst using $[IrCp^*I_2]_2$ with aqueous ammonia in presence of methanol. The catalyst was employed for the synthesis of secondary and tertiary amines and quite efficient towards primary and secondary alcohols as well secondary amines (Scheme 8).[19]



Scheme 8: Amination of alcohols using water soluble Ir-catalyst

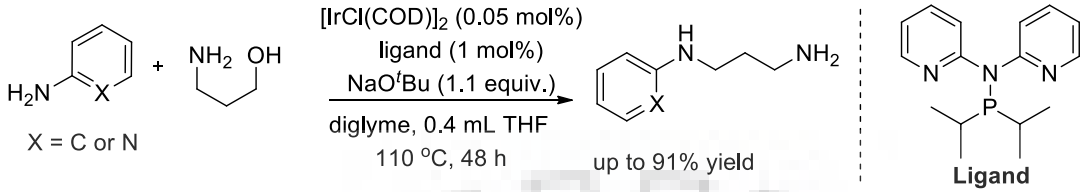
N-heterocyclic carbene (NHC) ligand were also found highly efficient for the amination of alcohols. For instance, Crabtree *et. al.* has developed an Iridium/NHC catalyst combination along with 50 mol% milder base to activate the catalyst and resulted good to excellent yield of the secondary amines (Scheme 9). [20]



Scheme 9: *N*-alkylation of amines using Ir-NHC catalyst

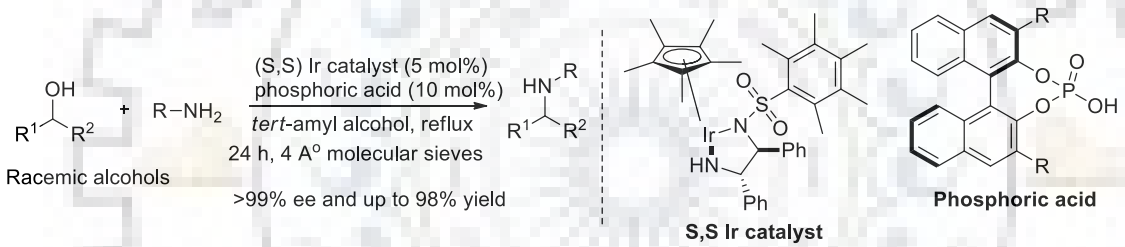
Kempe and co-workers established an *in situ* generated iridium catalyst system in combination with PNN-ligand for selective *N*-alkylation of anilines and amino pyridines with

primary alcohols. The catalytic system could be extended to various aliphatic amines, diols as well as amino alcohol derivatives and only a small amount 0.05 mol% catalyst is required for efficient transformations (Scheme 10).[21-23]



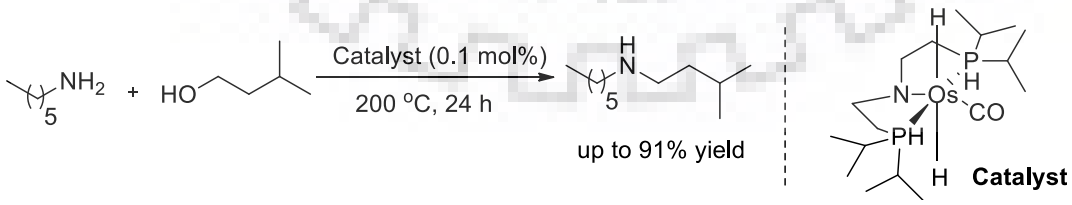
Scheme 10: Ir-catalyzed *N*-alkylation with aliphatic alcohols

Recently, first enantioselective version of catalytic amination has been developed by Zang *et. al.* using Ir-based chiral (*S*,*S*)-sulphonamide ligands in combination with chiral phosphoric acid. A series of chiral secondary amines as well as heterocycles were obtained in up to 99% yield and >99% ee (Scheme 11).[24]



Scheme 11: Enantioselective amination using chiral Ir-catalyst

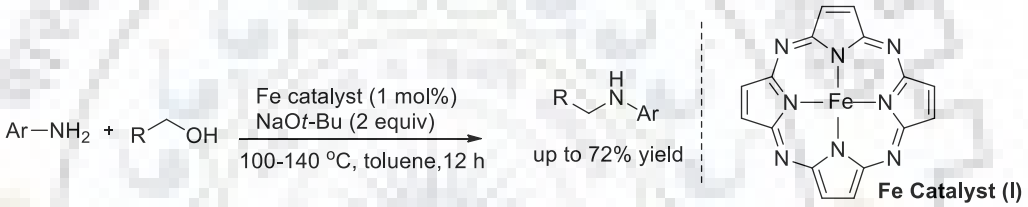
In 2011, Gusev *et. al.* developed a general Os-pincer based catalyst system for amination of primary alkyl alcohols with alkyl amines. Though, a low catalyst loading is efficient enough to achieve higher product yields, but, 200 °C reaction temperature limits its application and functional group performance (Scheme 12).[25]



Scheme 12: Os-pincer based catalyzed *N*-alkylation of amines with alcohols

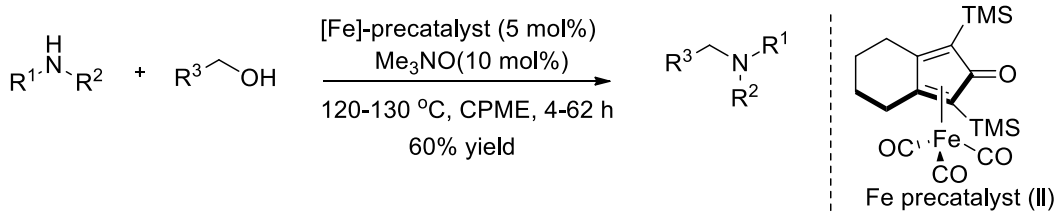
[1.2.2] *N*-alkylation of amines based on earth abundant non-precious metals:

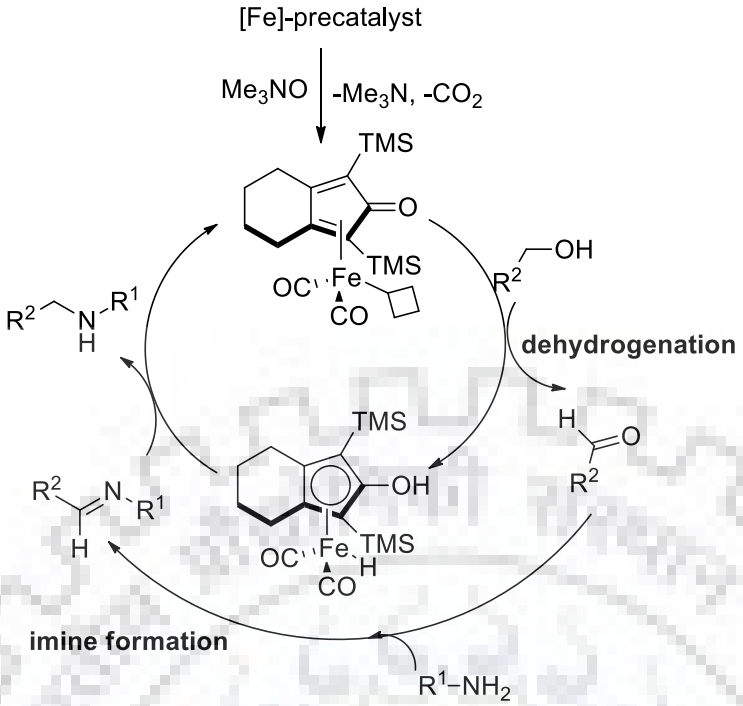
With the increasing demand for the development of more sustainable and environmental benign catalysis technologies for the synthesis of C-C and C-N bonds, recently there is a potential drive for the utilization of non-precious and earth abundant transition metals such as, Mn, Fe, Co, and Ni for key catalytic processes. More specifically, use of these earth abundant metals in combination with renewable resources are key attraction for the bulk scale industrial applications. In this section we will briefly discussed about some important organic transformations for *N*-alkylation of amines using borrowing hydrogen methodologies. For instance, in 2013 Singh and co-workers developed a suitable Fe(ll)-phthalocyanine based catalyst for *N*-alkylation of various hetro-aryl amines with benzyl alcohols and extended to the synthesis of a series of bio-active N-heterocycles. The catalytic protocol was also applied to linear unactivated amyl alcohol in up to 20% product yield (Scheme 13).[26]



Scheme 13: Fe-catalyzed intermolecular cyclization/*N*-alkyaltion of heteroaryl amines

Later on, Feringa and Barta successfully design a new cyclopentadienone based defined iron carbonyl precatalyst for the *N*-alkylation of amines with alcohols using cyclopentyl methyl ether (CPME) as green solvent. The key highlight includes, excellent product yield of secondary amines, *N*-aryl piperazine and direct synthesis of drug piribedil; used as dopamine antagonist for the treatment of Parkinson's disease (Scheme 14).[27a] Subsequently, they have extended the applications of the Fe-based catalyst for more challenging *N*-alkylation of benzyl amines with benzylic alcohol derivatives.[27b] A more significant, application of such Fe-catalyst has been demonstrated for selective *N*-alkylation of unprotected amino-acids with long chain alcohols for the synthesis of biologically important amino acid derivatives.[27c]

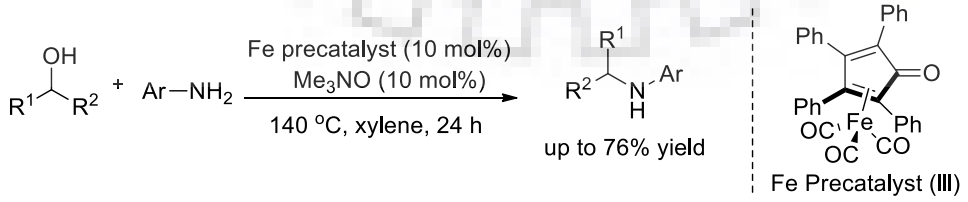




Scheme 14: Fe-catalyzed *N*-alkylation of secondary amines with benzyl alcohols

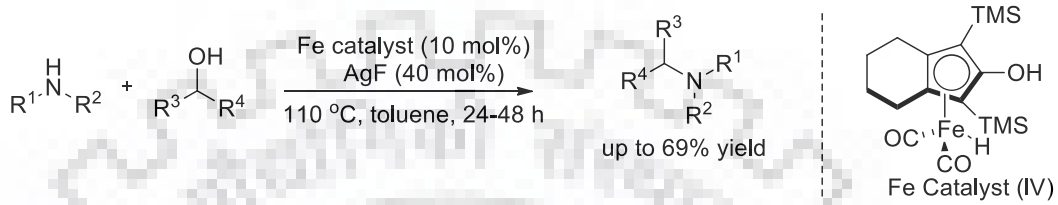
A plausible mechanism has been described for Fe-catalyzed borrowing hydrogen process for the synthesis of C-N bonds. As evident, initially active Fe-species is generated from Fe-precatalyst, which dehydrogenate the alcohol to corresponding aldehyde and transition Fe-H is formed. Next, condensation of aldehyde with amine gave imine intermediate and *in situ* hydrogen shuffling from metal hydride resulted the desired amine. During these process, again active catalyst has been generated and continue the catalytic cycles (Scheme 14).

Another report by Wills and co-workers demonstrated the *N*-alkylation of primary and secondary amines with secondary alcohols using Fe-catalyst. They have modified the Fe-catalyst used by Barta and co-workers and employed tetraphenylcyclopentdienone iron-carbonyl precatalyst for the N-alkylation of alcohols (Scheme 15).[28]



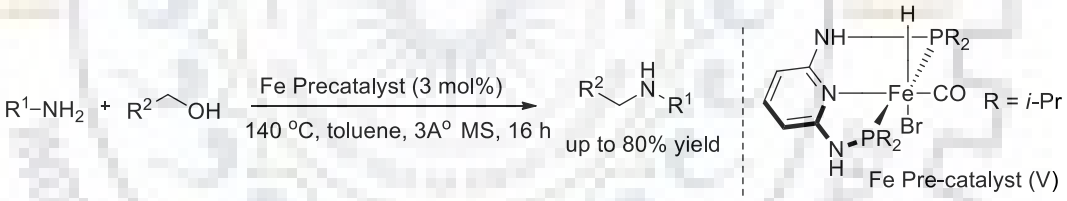
Scheme 15: Fe-catalyzed *N*-alkylation of amines with secondary alcohols

Zhao and *et. al.* has also developed the *N*-alkylation of amines with secondary alcohols. Application of Fe-catalyst in combination with Lewis acid additive furnished the corresponding secondary amines with moderate yield. Unfortunately, no *N*-alkylation was occurred when primary aliphatic alcohols, benzylic alcohols as well as diols were used. It was observed that AgF facilitates the formation of imine intermediate as well as catalyzed the imine hydrogenation (Scheme 16).[29]



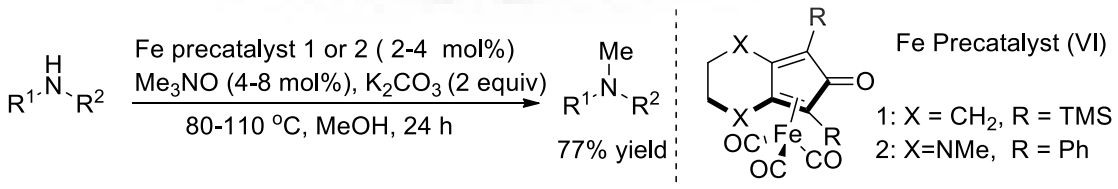
Scheme 16: Fe-catalyzed *N*-alkylation of secondary amines with secondary alcohols

Very recently Kirchner and co-workers established a new class of Fe(II) pincer precatalyst for the *N*-alkylation of amines using alcohols. It was observed that, molecular sieves plays a crucial role to promote imine formation as well as facilitate for removal of water, thereby furnishing the higher product yield (Scheme 17).[30]



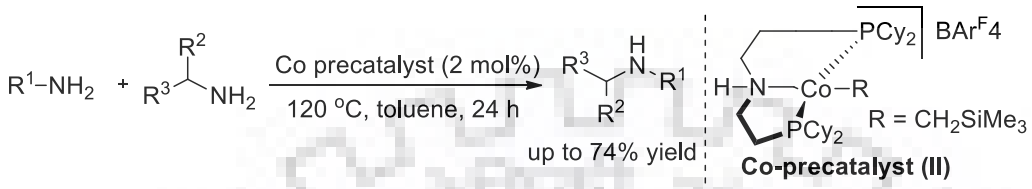
Scheme 17: Fe (II)-pincer catalyzed *N*-alkylation of amines

In 2018, Morrill and co-workers disclosed the iron-catalyzed *N*-methylation of amines using methanol through hydrogen borrowing approach. Methanol was used as solvent in presence of K_2CO_3 and furnished the desired *N*-methylation of cyclic as well as acyclic secondary amines with good product yield (Scheme 18).[31]



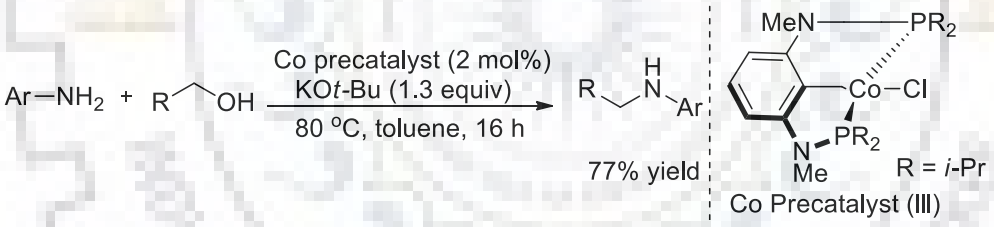
Scheme 18: Fe-catalyzed *N*-methylation of cyclic and acyclic amines

Apart from Fe-based catalysts, homogeneous Co-complexes were also reported for amination processes. In 2016, Zheng and co-workers employed phosphine based Co-complexes (II) for the synthesis of secondary amines. Application of two different primary amines in presence of cobalt resulted a series of important secondary amine derivatives releasing ammonia as side product (Scheme 19).[32]



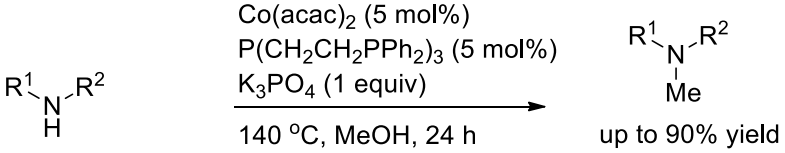
Scheme 19: Co-catalyzed amination with two different primary amines

Kirchner and co-workers has described the application of Co(II)-PCP pincer complexes for N-alkylation of various aromatic amines with a series of primary and secondary alcohols. Importantly, used of challenging alkyl alcohols, such as, ethanol, n-butanol, citronellol as well as cinnamyl alcohols as alkylating agent make this process highly important (Scheme 20).[33]



Scheme 20: Co-catalyzed *N*-alkylation of aryl amines with aliphatic alcohols

Very recently Liu and co-workers established a Co-based phosphine catalyst system for the methylation of amines using methanol. A variety of primary aryl amines and secondary amines undergoes selective mono *N*-methylation in presence of milder base. Preliminary catalytic and mechanistic studies established the participation of Co-H species following hydrogen borrowing methodology (Scheme 21).[34]

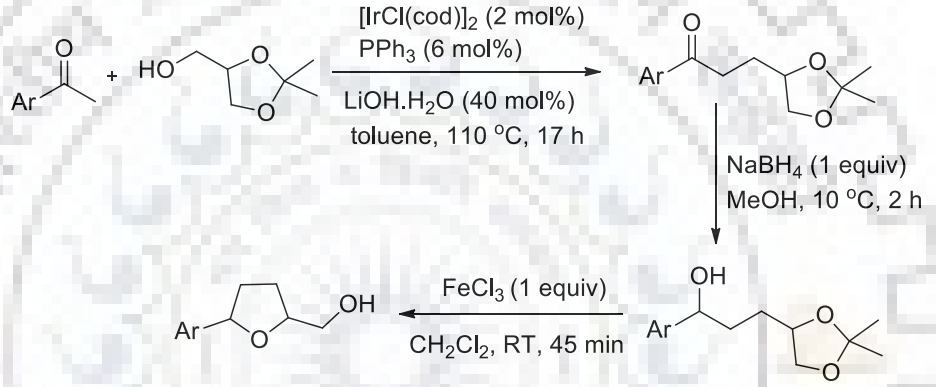


Scheme 21: Co-catalyzed *N*-methylation of primary and secondary amines

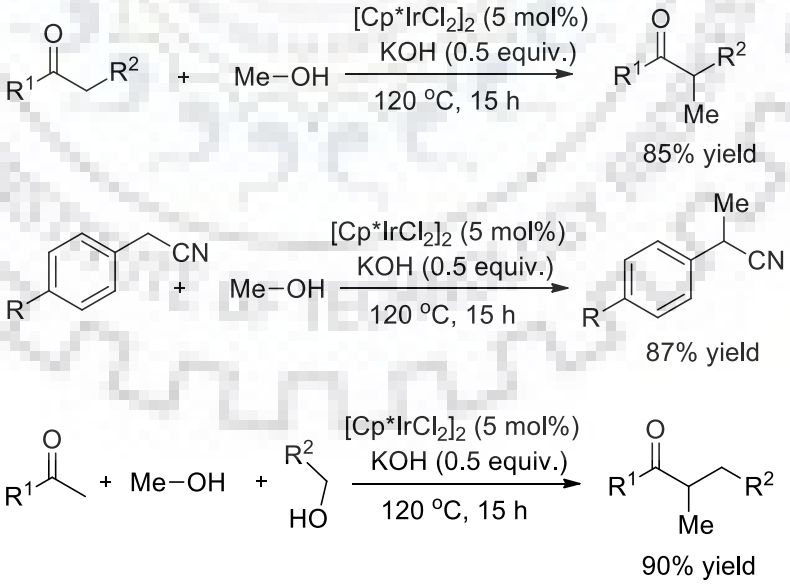
[1.2.3] *C*-alkylation of ketones based on precious metals:

Efficient synthesis of new C-C bonds using transition metal catalysts has attracted great attention. More specifically, catalytic processes utilized renewable resources in combination with non-precious metals are of great interest to organic chemists in academia as well as in industry. One efficient technology in this direction is the α-alkylation of ketone enolates with alcohols as alkylating agents, this process not only relieved water as byproducts avoids the use of stoichiometric waste, thereby rendering sustainable.[35-37]

Since last decades, several new methodologies were developed by the group of Shim, Cho, as well as Crabtree *et. al*. using Ru-catalysts for alkylation of ketone with primary alcohol,[38-40] as well as alkylation of ketone and β-alkylation of secondary alcohols were also reported.



Scheme 22: Synthesis of 2,5 di-substituted tetrahydrofuran following via *C*-alkylation

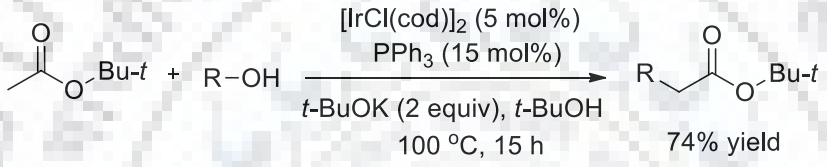


Scheme 23: Ir-catalyzed selective mono-methylation of ketone with methanol

Further, Phapale *et. al.* reported the synthesis of 2,5-disubstituted tetrahydrofuran using *α*-alkylation of substituted ketone with solketal using $IrCl(cod)_2$ catalyst and PPh_3 as ligand. Thereafter, following reduction as well as iron-mediated cyclization resulted the desired product (Scheme 22).[41]

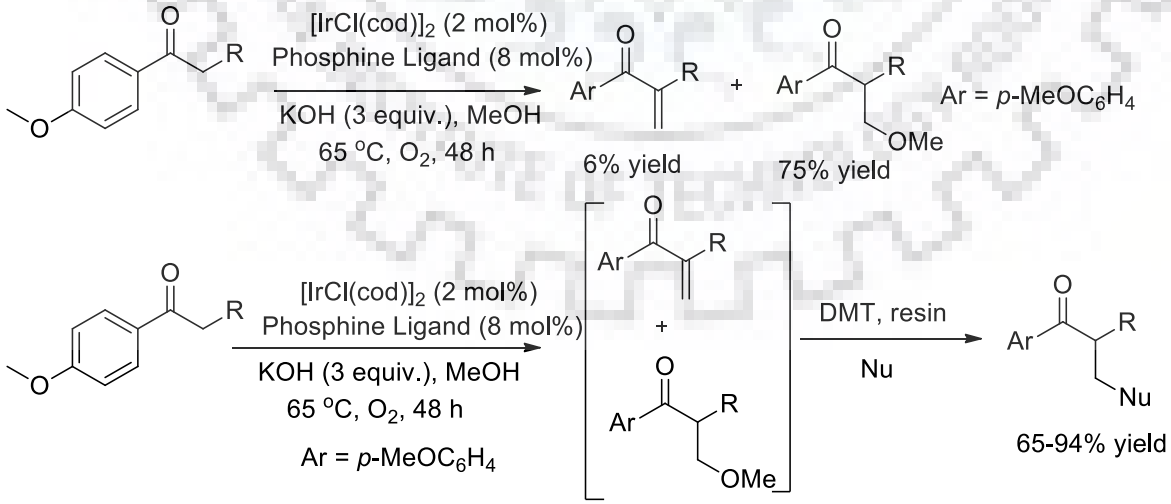
Obora and Ogawa have reported the iridium-catalyzed selective dimethylation and *α*-methylation of ketones or acetonitrile derivatives using methanol. The catalytic system could be applied successfully in a three components cross alkylation of methyl ketone using methanol and primary alcohols (Scheme 23).[42]

Ishii *et. al*. studies the Ir-catalyzed *α*-alkylation of tert-butyl acetate with primary alcohols and diols. The catalytic protocol have extended in the synthesis of ethylene brassylate in bulk scale as a synthetic perfume (Scheme 24).[43]



Scheme 24: Ir-catalyzed selective *α*-alkylation of esters with alcohols and diols

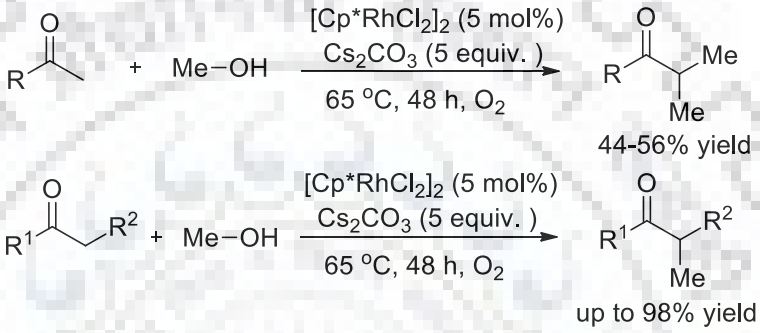
Donohoe and co-workers have reported Ir-catalyzed interrupted hydrogen borrowing methodology for methylation of ketone at milder conditions. The application of phosphine ligand plays a key role to control the selectivity. Subsequent addition of pro-nucleophile to the reaction mixture allowed a one-pot methylation-conjugate addition technology (Scheme 25).[44]



Scheme 25: Ir-catalyzed methylation of enolate ketone

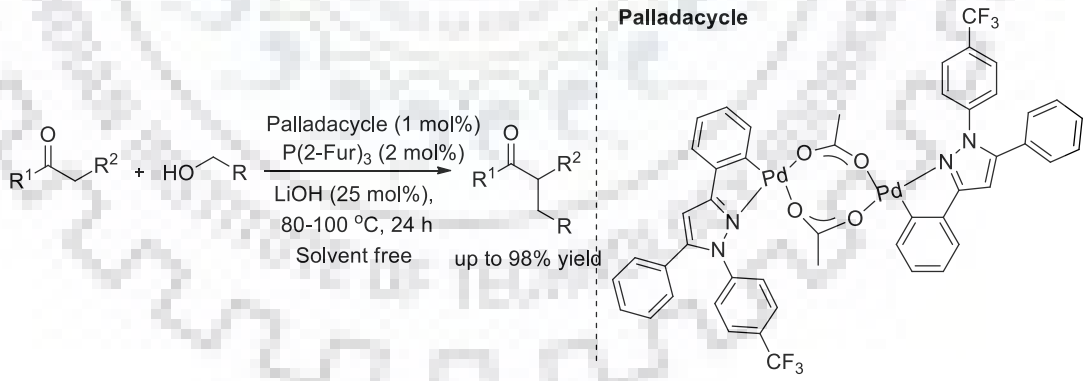
Apart from these, several other process for ketone alkylation using alcohols based on Ir-, or Ru-catalysts have been developed in recent days. For instance, some important examples are, Ir-NHC catalyst,[45] $RuHCl(CO)(PPh_3)_3$ in presence of 1,10-phenanthroline,[46] Ru-bis(diphenylphosphanyl)methane catalyst,[47] as well as others[48-49] are well established this field.

Donohoe and co-workers described the methylation of aliphatic and aromatic ketone using methanol in combination with Rh-based catalyst. The reaction could be performed using oxygen and plays a key role to achieve higher product yield of methylation (Scheme 26).[50]



Scheme 26: Rh-catalyzed methylation of ketones

Palladacycle based catalyst were also utilized for alkylation reactions and resulted *α*-*α* di-substituted branched ketone with excellent yields (Scheme 27).[51]

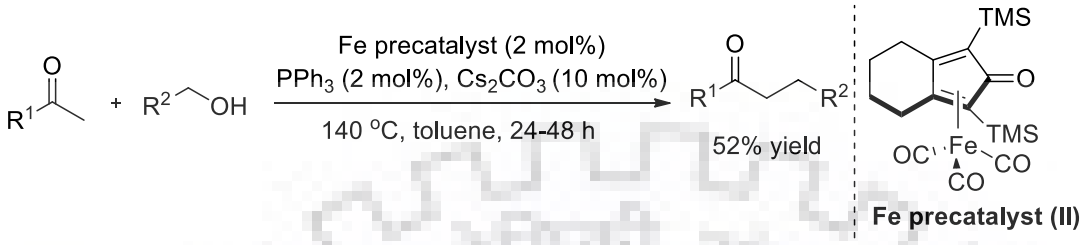


Scheme 27: Pd-catalyzed alkylation of ketones using primary alcohols

[1.2.4] *C*-alkylation based on non-precious metals

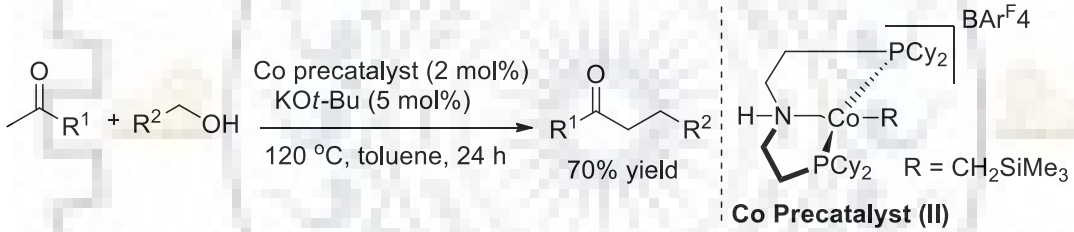
C-alkylation using earth abundant metal, Fe, Co, and Mn has been developed using borrowing hydrogen methodology. For instance, Darcel et al. described the (cyclopentadienone) iron carbonyl pre-catalyst in presence of PPh_3 for *α*-alkyaltion of

ketones with various alcohols. A series of ketone as well as benzylic and aliphatic primary alcohols, could participate to α-alkylated ketones (Scheme 28).[52] Thereafter, another report by Renaud *et. al*. using iron-complex bearing electron rich cyclopentadienone ligand is noteworthy.[53]



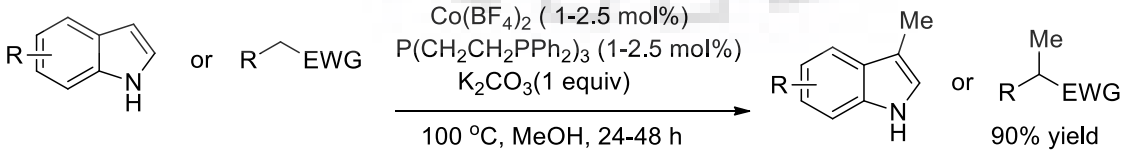
Scheme 28: Fe-catalyzed *α*-alkylation of ketones with alcohols

Zhang and co-workers demonstrated the *α*-alkylation of ketone with primary alcohols using an ionic Co-PNP complex in up to 98% yields. This method was also successfully applied in the greener synthesis for N-heterocycles (Scheme 29).[54]



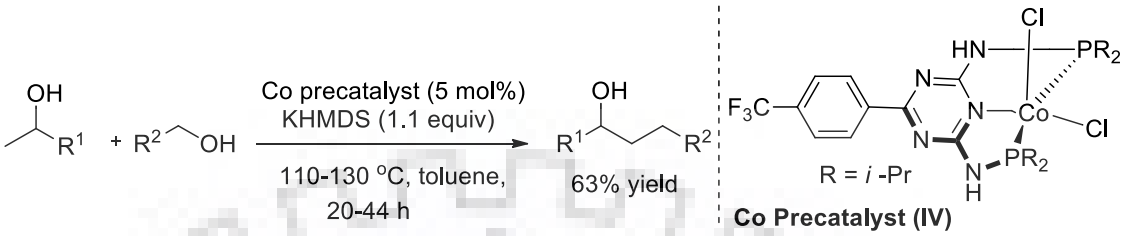
Scheme 29: Co-catalyzed *α*-alkylation of ketones

Liu and workers established the $Co(BF_4)_2.6H_2O$ in combination with tetradentate phosphine ligand system for *C*-methylation of ketone, acetonitrile and indoles. The catalytic cycle initiated by base and resulted transition Co-methoxy complex, which further undergoes β-hydride elimination to form a Co-hydride species. The *in situ* generated enone intermediate undergoes reduction by the Co-H to the desired products (Scheme 30).[55]



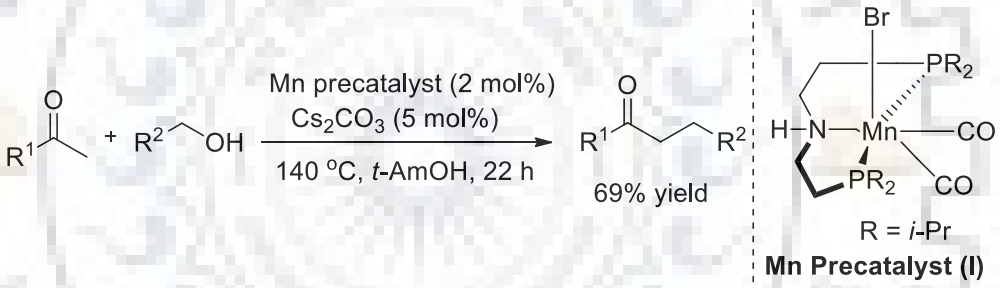
Scheme 30: Co-catalyzed methylation of ketones, indoles and acetonitriles

Kempe and co-workers developed a new class of Co-PNP pincer catalyst for coupling between secondary alcohols with primary alcohols. The modified Guerbet condensation required KHMDS as base and resulted a series of secondary alcohols in high yields (Scheme 37).[56]



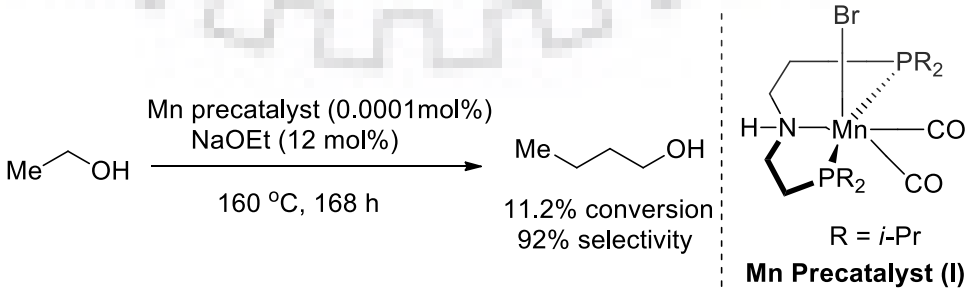
Scheme 31: Co-catalyzed alkylation of secondary alcohols with primary alcohols

In 2016, Beller *et al.* also reported the C-alkylation of ketones with a series of primary alcohols using Mn(I)-PNP pincer catalyst. The reaction could be initiated by a mild base and unfortunately in case of aliphatic ketone resulted poor product yields. (Scheme 32).[57]



Scheme 32: Mn-catalyzed *C*-alkylation of ketones and oxindoles

Another interesting report by Liu and co-workers for the upgrading of ethanol to butanol using Mn-catalyst is noteworthy. A low catalyst loading of Mn(I)-PNP pincer catalyst resulted 1-butanol in up to 11.2% conversion and 92% selectivity. Notably, the catalytic protocol have TON (114120) and TOF (3078 h^{-1}) (Scheme 33).[58]

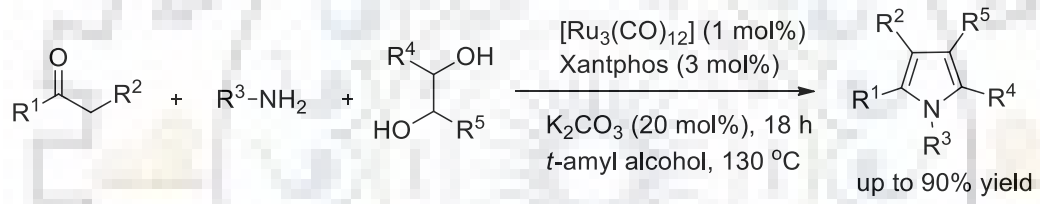


Scheme 33: Mn-catalyzed ethanol upgrading in to 1-butanol

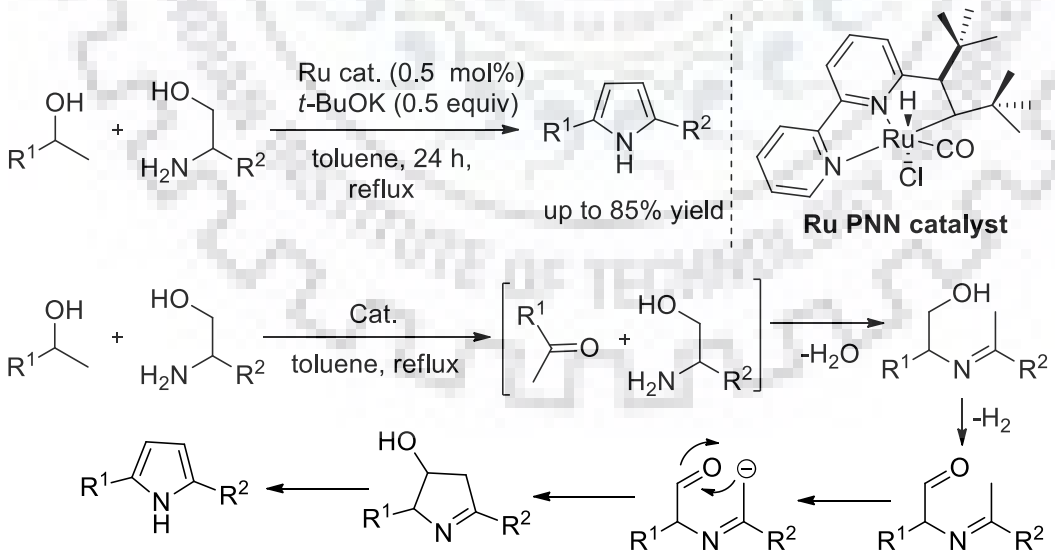
[1.2.5] Synthesis of *N*-heterocycles

The application of hydrogen transfer methodology for the construction of *N*-heterocycles molecule involving a tandem N-H/C-H coupling in one pot operation is noteworthy.[59] Heteroarenes, such as, pyrrole, pyridine, quinolines as well as benzimidazoles are important class of compounds with wide applications as antibacterial, antitumor and antifungal properties. Pyrrole and their derivatives used in molecular optics, as conducting polymers, in solar cells and in batteries and as sensors.[60-61]. Classical methods for their synthesis associated with multi-step synthesis, pre-functionalization of substrate, and generates salt wastes. In this respect, a more general and sustainable synthesis of pyrroles would be more attractive.

Towards this, Beller and co-workers described the three component synthesis of pyrrole using ruthenium catalyst for a variety of di-, tri-, tetra- and penta-substituted pyrroles involving ketones, vicinol diols and primary amines or ammonia (Scheme 34).[62]



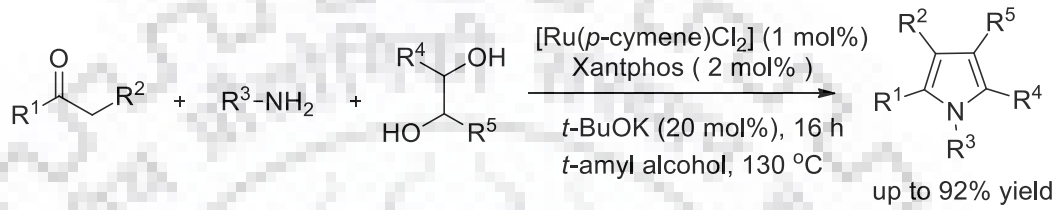
Scheme 34: Ru-catalyzed one-pot three component synthesis of pyrroles



Scheme 35: Ru-PNN pincer catalyzed synthesis of pyrroles with probable mechanism

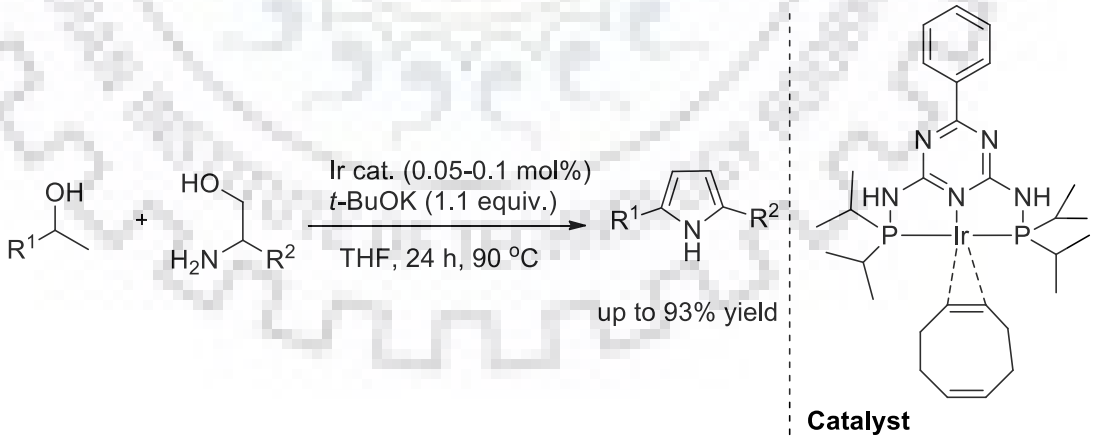
Milstien *et. al*. have studied a more general and straight forward atom-economical technology using ruthenium-pincer catalyst for the synthesis of pyrroles based on dehydrogenative coupling of β-amino alcohols and secondary alcohols with good yields (Scheme 35).[63] Metal catalyzed double dehydrogenation of alcohols followed by base catalyzed condensation with amines resulted the pyrroles in one pot operation.

Another process by Beller co-workers reported the synthesis of substituted pyrroles involving $[Ru(p\text{-cymene})Cl_2]_2$ catalyst and Xantphos as a ligand (Scheme 36).[64]



Scheme 36: Ru-catalyzed synthesis of pyrroles

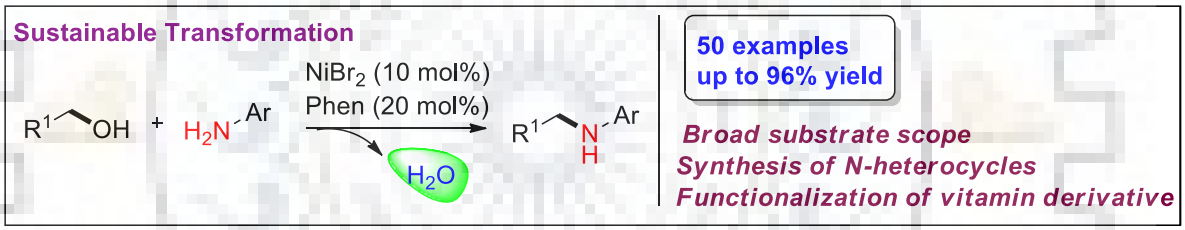
More recently, Kempe *et. al*. demonstrated a series of defined Iridium-pincer complexes for pyrrole synthesis using secondary alcohol and amino alcohols. An *in situ* dehydrogenation of alcohols followed by base catalyzed condensation resulted the formation of one pot C-C and C-N bonds and pyrroles. This catalytic protocol has excellent tolerance to a variety of functional groups, such as, olefins, chlorides, bromides, organometallic moieties, amines and hydroxyl groups for the pyrrole synthesis (Scheme 37).[65]



Scheme 37: Synthesis of 2,5-disubstituted pyrrole using Ir-pincer catalyst

Chapter-2: Metal catalyzed sustainable synthesis of C-C and C-N Bonds

Herein, we developed an efficient and selective nickel catalyzed mono-alkylation of various primary alcohols with aryl and hetero(aryl) amines together with diols and amino alcohol derivatives. Notably, the catalytic protocol consisting of earth abundant and non-precious $NiBr_2$/**L2** system enable the transformations in presence of hydroxyl, alkenes, nitrile and nitro-functionalities. As a special highlight, we have demonstrated the alkylation of di-aniline, intramolecular cyclization to N-heterocycles, and functionalization of complex vitamin E, (±) α-tocopherol derivative. Preliminary mechanistic studies, revealed the participation of benzylic C-H bond in the rate determining step.



ACS Catal. **2017**, *7*, 8152−8158

Chapter 2: Ni-Catalyzed Direct *N*-Alkylation of Anilines with Alcohols

[2.1] Introduction:

Amines are most valuable compounds for the chemical industry as intermediate products in the preparation of dyes, polymers, as well as for the synthesis of new pharmaceuticals and food additives. Amines are also useful for the chemical transformations, ubiquitous in biologically active natural products and extensively used in pharmaceuticals (Figure 1), agrochemicals, ligands for catalysis and in material chemistry. There are many powerful classical processes and catalytic protocols for the synthesis of amines. Notably, the vibrant catalytic protocols reported in this area is evident the significant potential for C-N bond forming reactions. The great demand for new reactions that fully or partially uses the renewable resources in combination with earth abundant non-precious metals are highly desirable. In Chapter 1, we have already discussed about transition-metal based *N*-alkylation of amines following hydrogen borrowing strategy. Herein we will briefly discuss about few selective non-precious metal catalyzed C-N bond formation reactions.

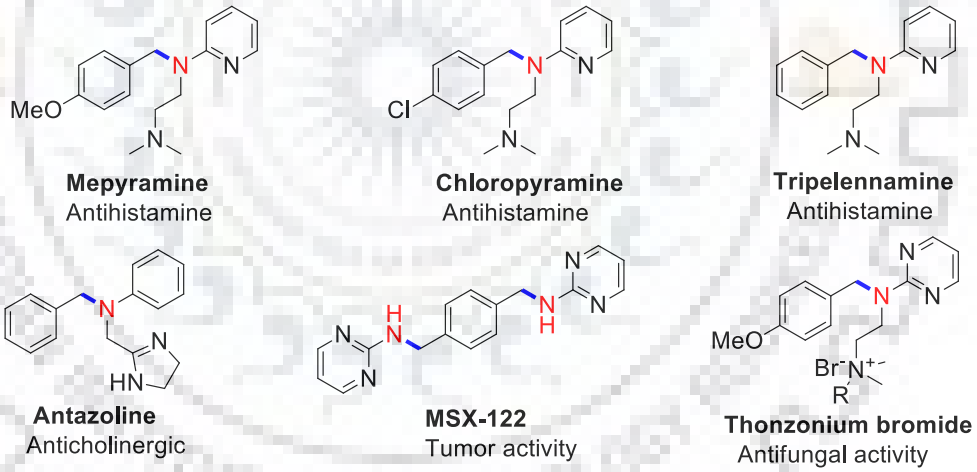
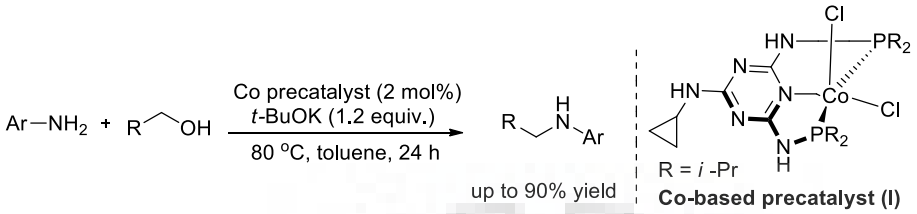


Figure 1: Selected examples of important pharmaceuticals with alkylated amine functionalities

[2.2] Relevant literature work:

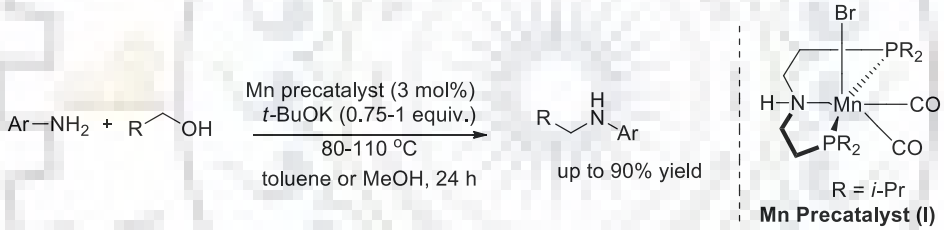
Notable contribution by the group of Barta, Wills, Kirchner and others have been discussed already in Chapter 1 for the amination reactions. A detailed discussion have also been documented for the recent development using well defined iron, cobalt as well as other non-precious metal catalysts.[1-5] Apart from these herein we have discussed some more recent examples for C-N bond forming process. For instance, in 2015, Kempe and co-workers reported a series of new Co-PNP pincer complexes for *N*-alkylation of aromatic amines using

alcohols employing *t*-BuOK as base. A variety of aryl and heteroaryl amines could participated with high product selectivity and desired secondary amines were obtained in good to excellent product yield (Scheme 1).[2]



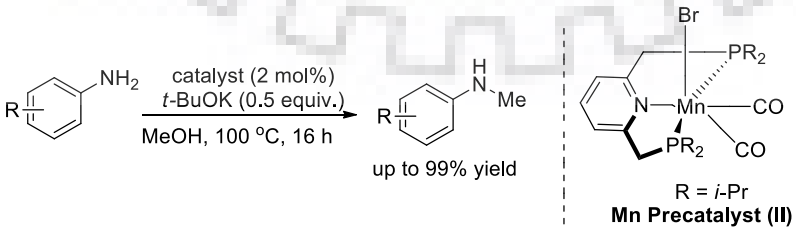
Scheme 1: Co-pincer complex catalyzed *N*-alkylation of aryl amines

Apart from Co, Mn is the third most earth abundant element after earth crust. In 2016 Beller *et al*. reported the first homogeneous manganese-catalyzed *N*-alkylation of amines via borrowing hydrogen methodology. Application of Mn(I) PNP pincer pre-catalyst with *t*-BuOK as base, a series of aryl and hetero-aryl amines efficiently transformed to secondary amines. The same protocol could be utilized for challenging *N*-methylation of amines using methanol (Scheme 2).[3]



Scheme 2: Mn-catalyzed synthesis of secondary amines

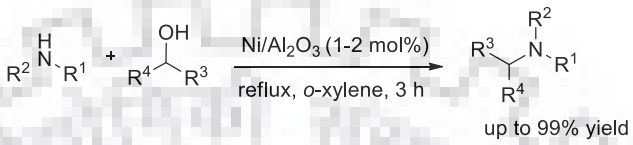
In 2017, Beller and co-workers has developed another novel second generation lutidine based Mn-pincer complex for selective *N*-methylation of amines using methanol as alkylating agents. These complexes were allowed for methylations under milder conditions with improved yields (Scheme 3).[4]



Scheme 3: Mn-catalyzed *N*-methylation of aryl amines

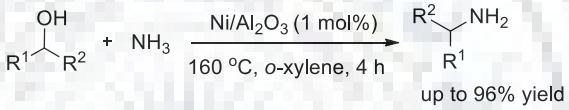
Apart from homogeneous catalysts, application of heterogeneous catalysts for sustainable organic transformations is an important goal. For instance, Raney nickel was well explored in

this directions for C-N bond formations. Often stoichiometric amount of catalyst is required for the *N*-alkylation of amines using alcohols. Further, limited substrate scope, less selectivity, low TON and high temp. and pressure are associated drawbacks for such processes. Towards this, recent studies by Shimizu and co-workers using Ni/Al_2O_3 heterogeneous catalyst for the *N*-alkylation of amines is noteworthy. A variety of secondary amines were obtained with higher activity and higher TON value for the *N*-alkylation. The catalyst could be recyclable to several cycles without losing any catalytic activities (Scheme 4).[5]



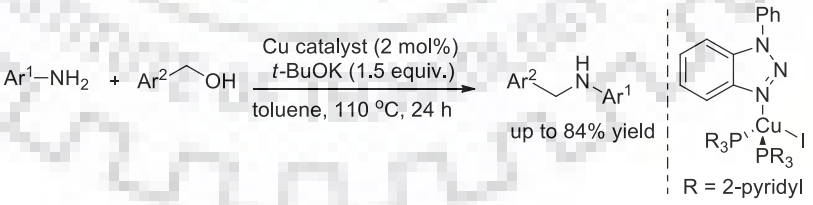
Scheme 4: Heterogeneous Ni-catalyzed *N*-alkylation of amines

Thereafter, they have extended the catalytic performance for the synthesis of primary amines using secondary alcohols with ammonia (Scheme 5).[6]



Scheme 5: Ni-catalyzed synthesis of primary amines

Triazole-phosphine-copper complex was also utilized as efficient catalyst for the synthesis of amines. Wang and co-workers reported the application of such copper complex for the *N*-alkylation of electron rich aryl amines using benzylic alcohols as the alkylating agent. Catalytic and mechanistic studies supported the participation of Cu-H species following hydrogen borrowing process (Scheme 6).[7]



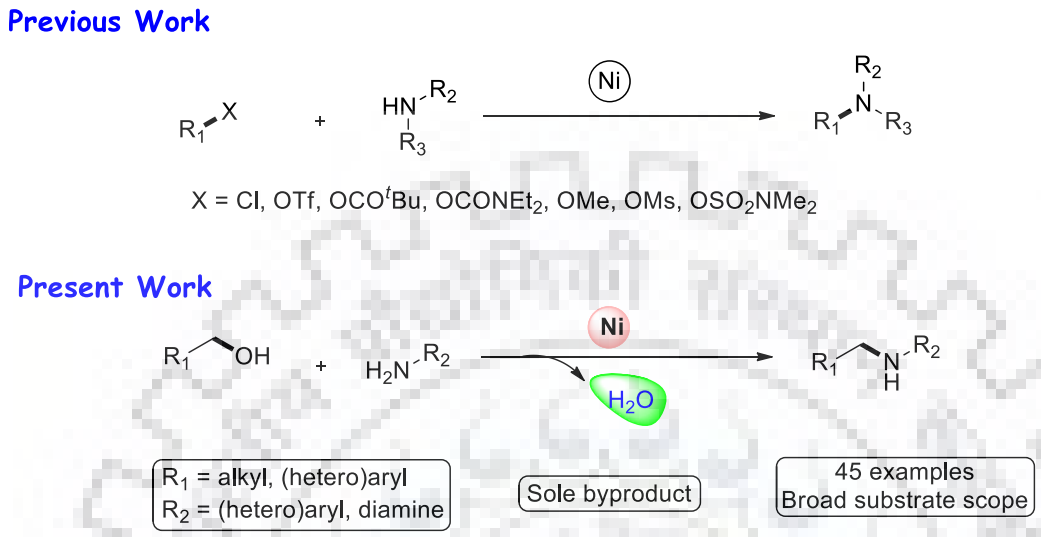
Scheme 6: Cu-catalyzed *N*-alkylation of amines

[2.3] Aim of Present work:

In this chapter we have disclosed an efficient Ni-catalyst system which enable the amination of primary alcohols with variety of anilines and afford diversely substituted functionalized secondary amine derivatives. The key features of the optimized protocol includes selective mono-alkylation of variety of alcohols, diols, amino-alcohols with anilines. Notably,

intramolecular cyclization to *N*-heterocycles and functionalization of complex vitamin derivative are of special interest.

[2.4] Results and discussion:



Scheme 7: Ni-catalyzed *N*-alkylation of amines

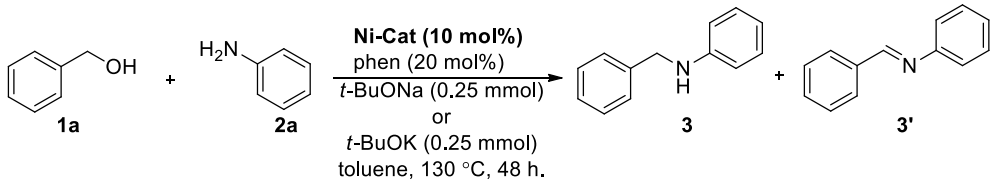
To date, the application of nickel catalysts is often limited with activated benzylic and phenolic substrates, such as, carbonates, carbamates, ethers and esters as electrophilic coupling partners (Scheme 7). Substantially poor leaving ability and strong co-ordination properties of hydroxyl group, make it inferior substrate class towards nickel-catalyzed transformations. However, to the best of our knowledge till date, the application of homogeneous nickel catalysts for amination of benzyl and alkyl alcohols has remain elusive.

Herein, we have disclosed an efficient Ni-catalyst system which enable the amination of primary alcohols with variety of anilines and afford diversely substituted functionalized secondary amine derivatives. The key challenge in direct amination of alcohols using Ni-catalyst is to attain alcohol dehydrogenation and the ability of the *in situ* formed Ni-hydride species for imine hydrogenation. Therefore, we reasoned that, it could possible to explore the bifunctional nature of homogeneous Ni-catalyst for direct C-N bond formation.

To achieve this goal, we initiated our studies with five different nickel precatalysts having oxidation state of Ni(0) and Ni(II) with aniline **2a** and benzyl alcohol **1a** as model reaction of our choice. Notably, a combination of 10 mol% $NiBr_2$, 20 mol% 1,10-phenanthroline **L2** and 0.25 mmol of *t*-BuOK at 130 °C in toluene resulted the formation of *N*-benzyl aniline **3** with 99% selectivity in GC-MS analysis of the crude reaction mixture (Table 1, entries 6-10).

Optimization studies for nickel-catalyzed *N*-alkylation of amines with benzyl alcohols

Table 1: Screening of catalyst [a]



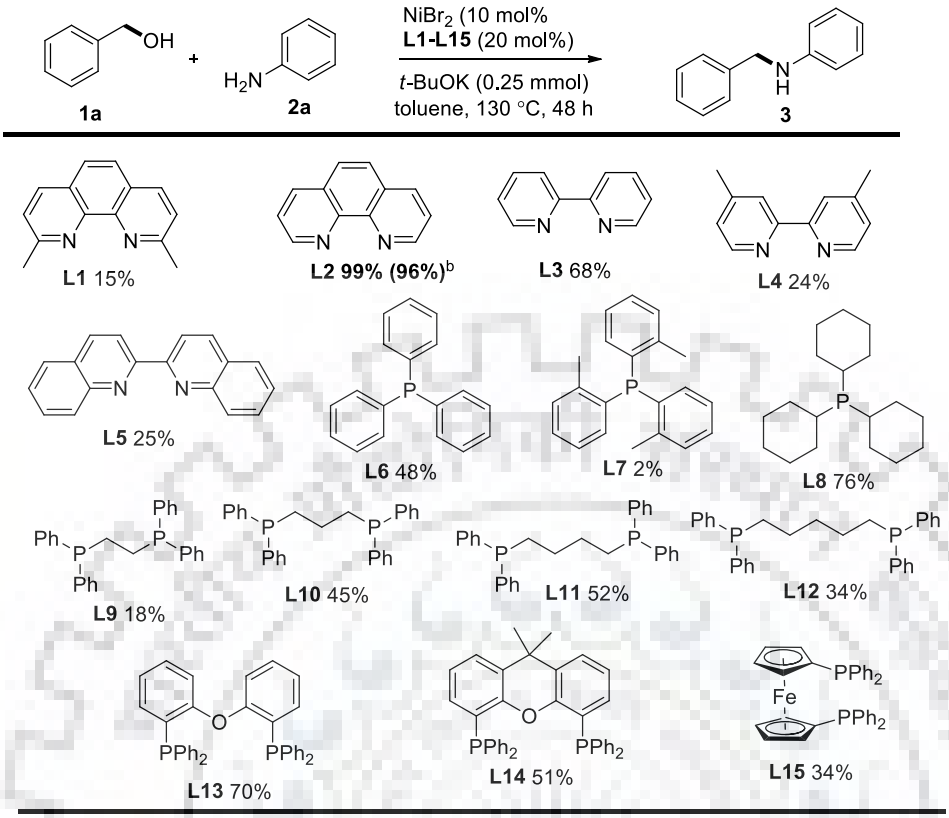
Entry	Ni-catalyst	Base	GC-MS Conversion (%)	
			3	**3'**
1.	$NiBr_2$	*t*-BuONa	10	58
2.	$NiCl_2$	*t*-BuONa	1	48
3.	$NiCl_2$.DME	*t*-BuONa	0	31
4.	$Ni(acac)_2$	*t*-BuONa	0	41
5.	$Ni(COD)_2$	*t*-BuONa	0	39
6.	**$NiBr_2$**	***t*-BuOK**	**99(96)[b]**	**0**
7.	$NiCl_2$	*t*-BuOK	87	13
8.	$NiCl_2$.DME	*t*-BuOK	35	55
9.	$Ni(acac)_2$	*t*-BuOK	81	19
10.	$Ni(COD)_2$	*t*-BuOK	83	17
[c]11.	$NiBr_2$	*t*-BuOK	49	40

[a] Reaction condition: Benzyl alcohol (1.0 mmol), aniline (0.25 mmol), Ni-catalyst (0.025 mmol), phen (0.05 mmol), *t*-BuONa or *t*-BuOK (0.25 mmol), toluene (2.0 mL), 130 ºC oil bath, 48 h reaction time. [b] Isolated yield. [c] Reaction was at 120 ºC for 36 h.

Under identical conditions, a variety of nitrogen and phosphine ligands **L1** and **L3**-**L15** with variable electronic and steric nature were tested and 15-76% **3** was obtained along with corresponding imine (21-73%) (Table 2).

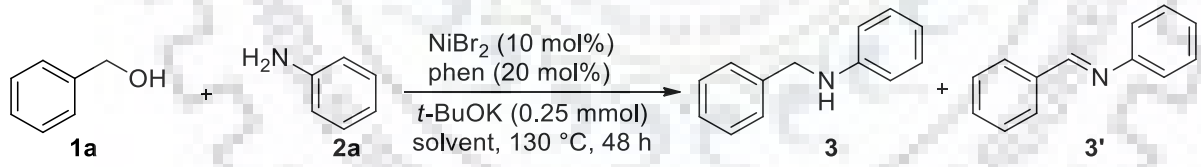
We anticipated that, generation of inadequate amount of nickel-hydride species is the key issue for insufficient imine reduction. However, under identical conditions, the use of various polar solvents, such as, *i*-PrOH, *n*-BuOH, EtOH, *N*,*N*-dimethylacetamide (DMA), *N*,*N*-dimethylformamide (DMF), as well as replacement of toluene with xylene and 1,4-dioxane further did not improve any product yield and we observed fast deactivation of the catalytic system (Table 3).

Table 2: Screening of ligands [a]



[a] Reaction condition: Benzyl alcohol (1.0 mmol), aniline (0.25 mmol), $NiBr_2$ (0.025 mmol), ligand (0.05 mmol), *t*-BuOK (0.25 mmol), toluene (2.0 mL), 130 °C oil bath, 48 h reaction time. [b] Isolated yield.

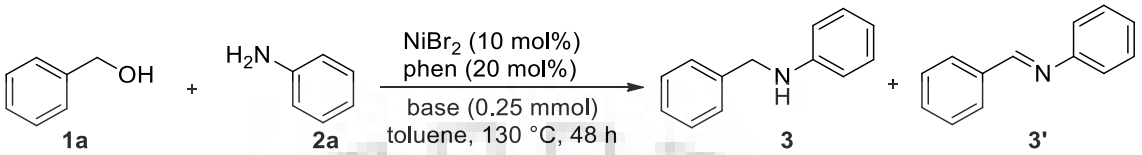
Table 3: Screening of solvents [a]



Entry	Solvents	Base	GC-MS Conversion (%)	
			3a	**3a'**
1.	**Toluene**	***t*-BuOK**	**99(96)** [b]	**0**
2.	Xylene	*t*-BuOK	10	84
3.	1, 4-Dioxane	*t*-BuOK	21	5
4.	*n*-BuOH	*t*-BuOK	0	18
5.	*i*-PrOH [c]	*t*-BuONa	0	0
6	EtOH [c]	*t*-BuONa	0	0
7.	DMA	*t*-BuONa	0	0
8.	DMF	*t*-BuONa	0	0

[a] Reaction condition: Benzyl alcohol (1.0 mmol), aniline (0.25 mmol), $NiBr_2$ (0.025 mmol), phen (0.05 mmol), *t*-BuOK (0.25 mmol), solvent (2.0 mL), 130 °C oil bath, 48 h reaction time. [b] Isolated yield. [c] Reaction temperature 100 °C.

Table 4: Screening of base [a]



1a 2a 3 3'

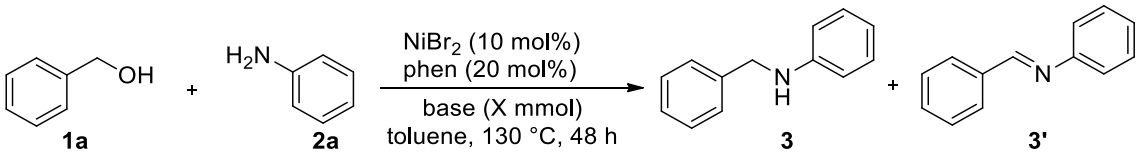
Entry	Base	GC-MS Conversion (%)	
		3	**3'**
1.	*t*-BuONa	10	58
2.	***t*-BuOK**	**99(96)** [b]	**0**
3.	K_2CO_3	2	17
4.	Na_2CO_3	0	0
5.	K_3PO_4	1	67
6.	Cs_2CO_3	0	41
7.	Pyridine	0	0
8.	Et_3N	0	0

[a] Reaction condition: Benzyl alcohol (1.0 mmol), aniline (0.25 mmol), $NiBr_2$ (0.025 mmol), phen (0.05 mmol), base (0.25 mmol), toluene (2.0 mL), 130 °C oil bath, 48 h reaction time. [b] Isolated yield.

In addition, the influence of different organic and inorganic bases, such as, *t*-BuONa, K_2CO_3, Na_2CO_3, K_3PO_4, Cs_2CO_3, pyridine and triethylamine were found inefficient for the alkylation of aniline (Table 4).

As expected, product conversion suppressed significantly when a lower equivalent of base was used (Table 5, entries 1-5).

Table 5: Screening of base equivalent [a,b]



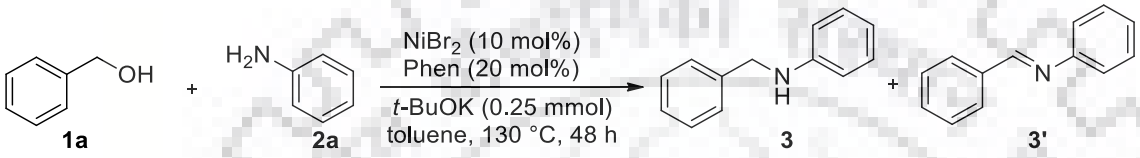
1a 2a 3 3'

Entry	Base equivalents	GC-MS Conversion (%)	
		3	**3'**

1.	*t*-BuOK (0.25 mmol)	85 [c]	15
2.	***t*-BuOK (0.25 mmol)**	**99(96) [b]**	**0**
3.	*t*-BuOK (0.1875 mmol)	65	35
4.	*t*-BuOK (0.125 mmol)	40	60
5.	No base	0	0

[a] Reaction condition: Benzyl alcohol (1.0 mmol), aniline (0.25 mmol), $NiBr_2$ (0.025 mmol), phen (0.05 mmol), *t*-BuOK (X mmol), toluene (2.0 mL), 130 °C oil bath, 48 h reaction time. [b] Isolated yield. [c] Reaction time 36 h.

Table 6: Screening of alcohol equivalents [a]

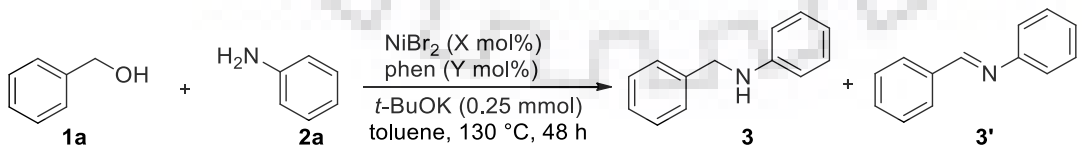


Entry	Alcohol equivalents	GC-MS Conversion	
		3	**3'**
1.	Benzyl alcohol (1.0 mmol)	99 (96)[b] %	0 %
2.	Benzyl alcohol (0.75 mmol)	76 %	8 %
3.	Benzyl alcohol (0.5 mmol)	59 %	11 %
4.	Benzyl alcohol (0.25 mmol)	29 %	5 %

[a] Reaction condition: Benzyl alcohol (X mmol), aniline (0.25 mmol), $NiBr_2$ (0.025 mmol), phen (0.05 mmol), *t*-BuOK (0.25 mmol), toluene (2.0 mL), 130 °C oil bath, 48 h reaction time. [b] Isolated yield.

Further, control reactions, using variable amount of benzyl alcohol proved to be inefficient to achieve higher product conversions and it was observed that, 1.0 mmol benzyl alcohol is minimum to get the excellent product yield (Table 6).

Table 7: Screening of catalyst/ligand loading [a]



Entry	Catalyst loading	Ligand Loading	GC-MS Conversion (%)	
			3	**3'**
1.	$NiBr_2$ (10 mol%)	Phen (20 mol%)	99 (96)[b]	0
2.	$NiBr_2$ (7.5 mol%)	Phen (15 mol%)	82	2
3.	$NiBr_2$ (5.0 mol%)	Phen (10 mol%)	79	5

4.	$NiBr_2$ (2.5 mol%)	Phen (5.0 mol%)	70	26
5.	-	-	0	0

[a] Reaction condition: Benzyl alcohol (1.0 mmol), aniline (0.25 mmol), $NiBr_2$ (0.025-0.00625 mmol), phen (0.05-0.0125 mmol), *t*-BuOK (0.25 mmol), toluene (2.0 mL), 130 °C oil bath, 48 h reaction time. [b] Isolated yield.

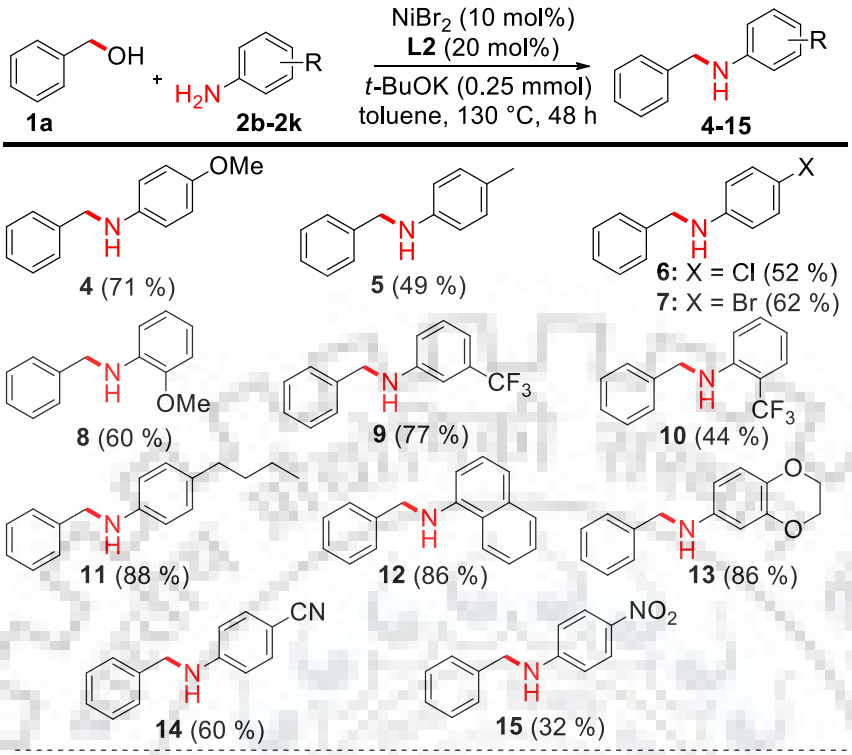
Notably, catalyst to ligand ratio also very crucial for this amination process. Any changes in the catalyst and ligand loading, we observed albeit will lower product conversion. Importantly, we did not observe any product in absence of catalyst and ligand (Table 7 entry 5). To our delight, a combination of 10 mol% $NiBr_2$, 20 mol% 1,10-phenanthroline **L2** and 0.25 mmol of *t*-BuOK at 130 °C in toluene resulted N-benzyl aniline **3** with 99% product selectivity and 96% isolated yield.

***N*-alkylation of aniline derivatives with benzyl alcohol**. Further, to demonstrate the general applicability of the optimized novel catalytic system, a variety of substituted aniline derivatives were tested for the selective mono-alkylation using benzyl alcohol **1a** (Table 8). We observed that, methoxy, methyl, *n*-butyl as well as halide substituents on the aryl ring of aniline are well tolerated and furnished 49-88% yield of selective mono-alkylated anilines irrespective of their electronic properties (Table 3, entries **4-7** and **11**). It is to be noted that, sterically hindered *o*-methoxy and *o*-trifluoromethyl aniline transformed efficiently into the desired secondary amines (Table 8, entries **8** and **10**). Importantly, pharmaceutically active, trifluoro-methyl and 1,4-dioxalone substituted aniline resulted corresponding product with excellent isolated yield, 77-86% respectively (Table 8, **9** and 1**3**).

To our delight, aniline substituted with reducible functionalities are well tolerated and furnished 32-60% yield of **14** and **15** (Table 8). Under identical conditions the application of aniline derivatives having ester, amide, carbonyl, epoxide as well as alkyne functionalities were not successful (Table 15). The catalytic protocol is highly selective for mono-alkylation, however, we did not observe any desired product in case of secondary amine derivatives.

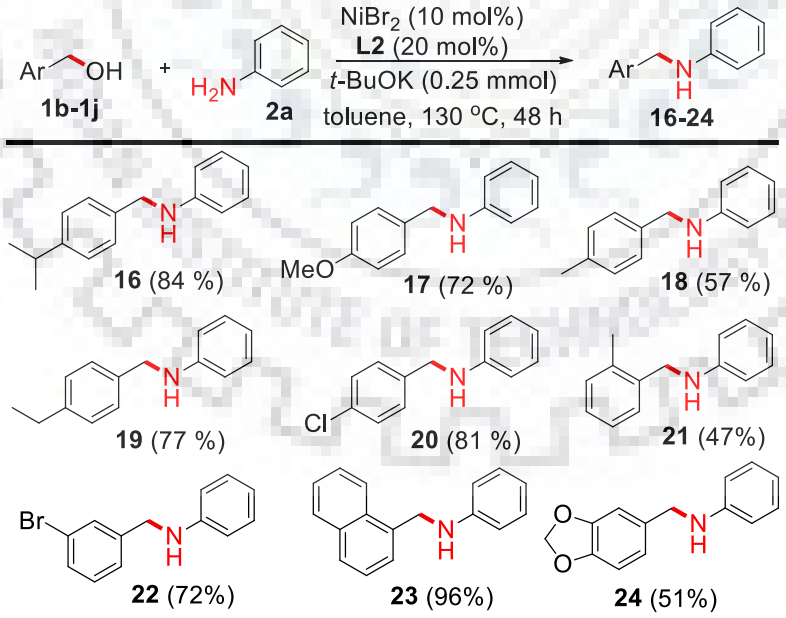
Inspired by the excellent catalytic activity of anilines with benzyl alcohol, next we studied the reactivity profile and scope of various benzyl alcohols with aniline (Table 9). Benzyl alcohols bearing electron rich and electron withdrawing functionalities as well as fused ring system and oxygen heterocycle at aryl ring, efficiently transformed to the corresponding mono-alkylated aniline in 57-96% isolated yield (Table 9, **16**-**20** and **22-24**). Advantageously, sterically hindered *o*-methyl substituted benzyl alcohol furnished *N*-alkylated amine **21** in 47% yield.

Table 8: Scope of amines: Synthesis of *N*-benzyl aryl amine derivatives



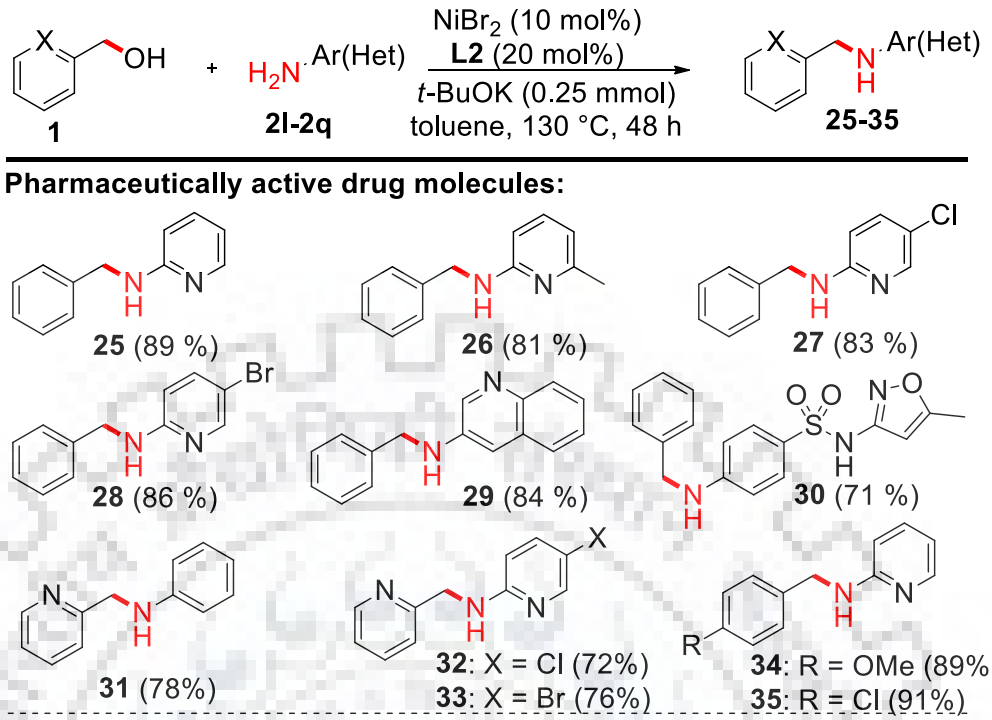
Reaction conditions: Unless specified, the reaction was carried out with **1a** (1.0 mmol), **2** (0.25 mmol), $NiBr_2$ (0.025 mmol), **L2** (0.05 mmol), *t*-BuOK (0.25 mmol), 130 °C in toluene (2.0 mL) for 48 h.

Table 9: *N*-alkylation of aniline with various benzyl alcohols



Reaction conditions: Unless specified, the reaction was carried out with **1** (1.0 mmol), **2** (0.25 mmol), $NiBr_2$ (0.025 mmol), **L2** (0.05 mmol), *t*-BuOK (0.25 mmol), 130 °C in toluene (2.0 mL) for 48 h.

Table 10: Scope of hetero-aromatic amines/alcohols



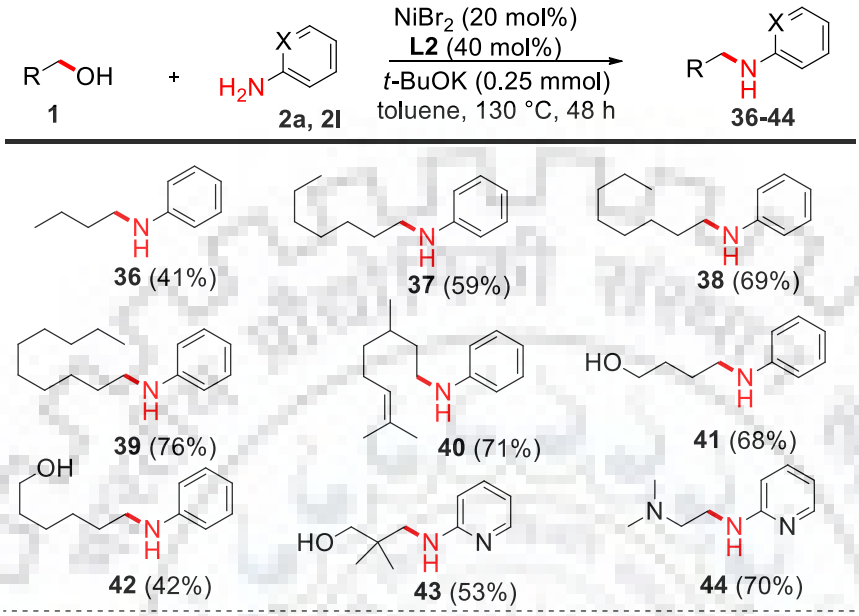
Reaction conditions: Unless specified, the reaction was carried out with 1 (1.0 mmol), 2 (0.25 mmol), $NiBr_2$ (0.025 mmol), **L2** (0.05 mmol), *t*-BuOK (0.25 mmol), 130 °C in toluene (2.0 mL) for 48 h.

***N*-alkylation using hetero aromatic amines and alcohols.** Gratifyingly, the application of substituted amino pyridines, quinoline and sulfonamide derivative alkylated efficiently with excellent chemo-selectivity (Table 10, **25-30**). Notably, alkylation of 2-pyridinemethanol with aniline and halide substituted 2-aminopyridine delivered pharmaceutically active product **31-33** in 72-78% yield, respectively. It is noteworthy to mention that, the catalytic protocol is highly chemo-selective and successfully transformed 2-aminopyridine into the intermediate of bio-active drug, mepyramine **34** and chloropyramine **35**, extensively used in antihistamine activity.

Next we explored the reactivity of more challenging alkyl alcohols with aniline and 2-amino pyridine (Table 11). For instance, butanol, heptanol, octanol as well as decanol efficiently converted to mono-substituted aniline derivative **36-39** in 41-76% isolated yield. It is to be noted that, renewable terpenoid intermediate citronellol readily alkylated to **40** under optimized reaction conditions. Importantly, this is a rare example of chemo-selective transformation of unsaturated alcohol under Ni-catalyzed protocol, otherwise impossible under noble-metal catalysis. Remarkable activity of functionalized alcohols, such as, 2,2-dimethyl-1,3-propanediol, butane-1,4-diol, hexane-1,6-diol as well as *N*,*N*-dimethyl ethanol selectively

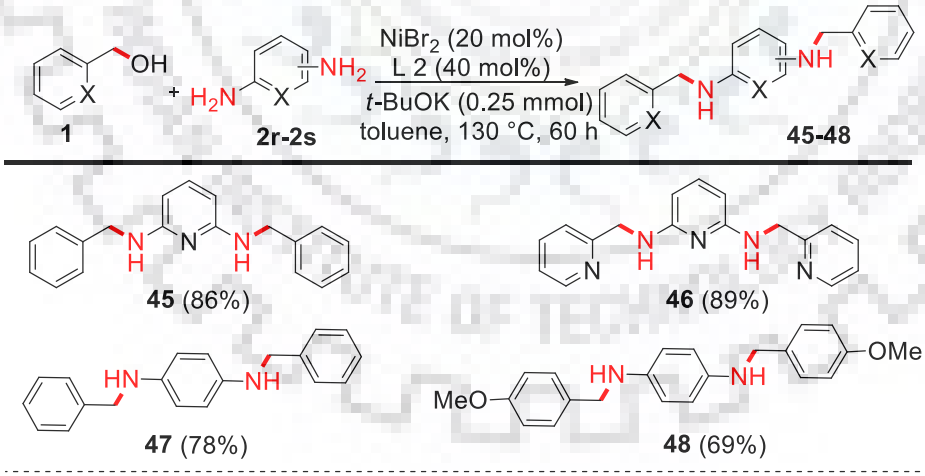
furnished valuable amino-alcohols **41**-**43** and **44** in 42-70% yield (Table 11). Unfortunately, under identical conditions application of methanol did not result any desired product.

Table 11: Scope of aliphatic alcohols



Reaction conditions: Unless specified, the reaction was carried out with **1** (1.25 mmol), **2** (0.25 mmol), $NiBr_2$ (0.05 mmol), **L2** (0.1 mmol), *t*-BuOK (0.25 mmol), 130 °C in toluene (2.0 mL) for 48 h.

Table 12: Alkylation of diamines

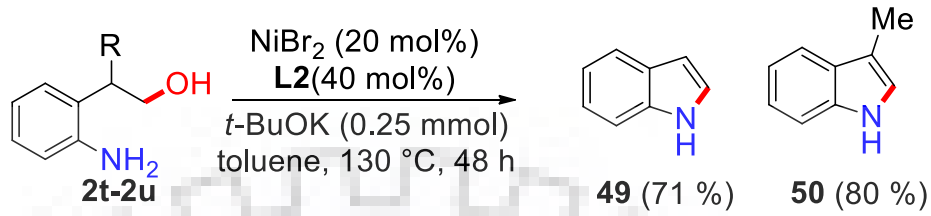


Reaction conditions: Unless specified, the reaction was carried out with **1** (2.0 mmol), **2** (0.25 mmol), $NiBr_2$ (0.05 mmol), **L2** (0.1 mmol), *t*-BuOK (0.50 mmol), 130 °C in toluene (2.0 mL) for 60 h.

Alkylation of diamines. Next, we were interested to explore the activity of pyridine-2,6-diamine and phenyl-1,4-diamine with aryl as well as hetero-aryl alcohols. To our delight,

multi-functional amines **45**-**48** are obtained in up to 89% yield and are important structural motif used as ligands in catalysis and in material chemistry applications.

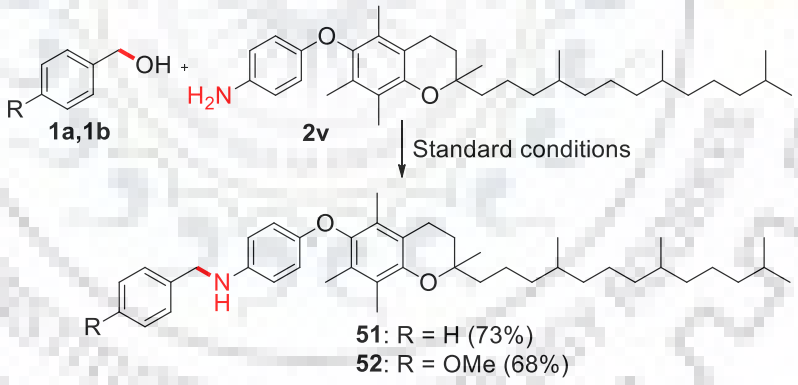
Table 13: Intramolecular cyclization to indole



Reaction conditions: Unless specified, the reaction was carried out with **2** (0.3 mmol), $NiBr_2$ (0.06 mmol), **L2** (0.12 mmol), *t*-BuOK (0.25 mmol), 130 °C in toluene (2.0 mL) for 48 h.

Synthesis of *N*-heterocycle. To establish the synthetic potential of the catalytic process, an attempt for intramolecular cyclization of substituted 2-(2-aminophenyl)-ethanol derivatives were performed. We were pleased to witness an alternative synthesis of indole derivatives via a tandem borrowing hydrogen/intramolecular cyclization (Table 13).

Table 14: Functionalization of complex vitamin E derivative

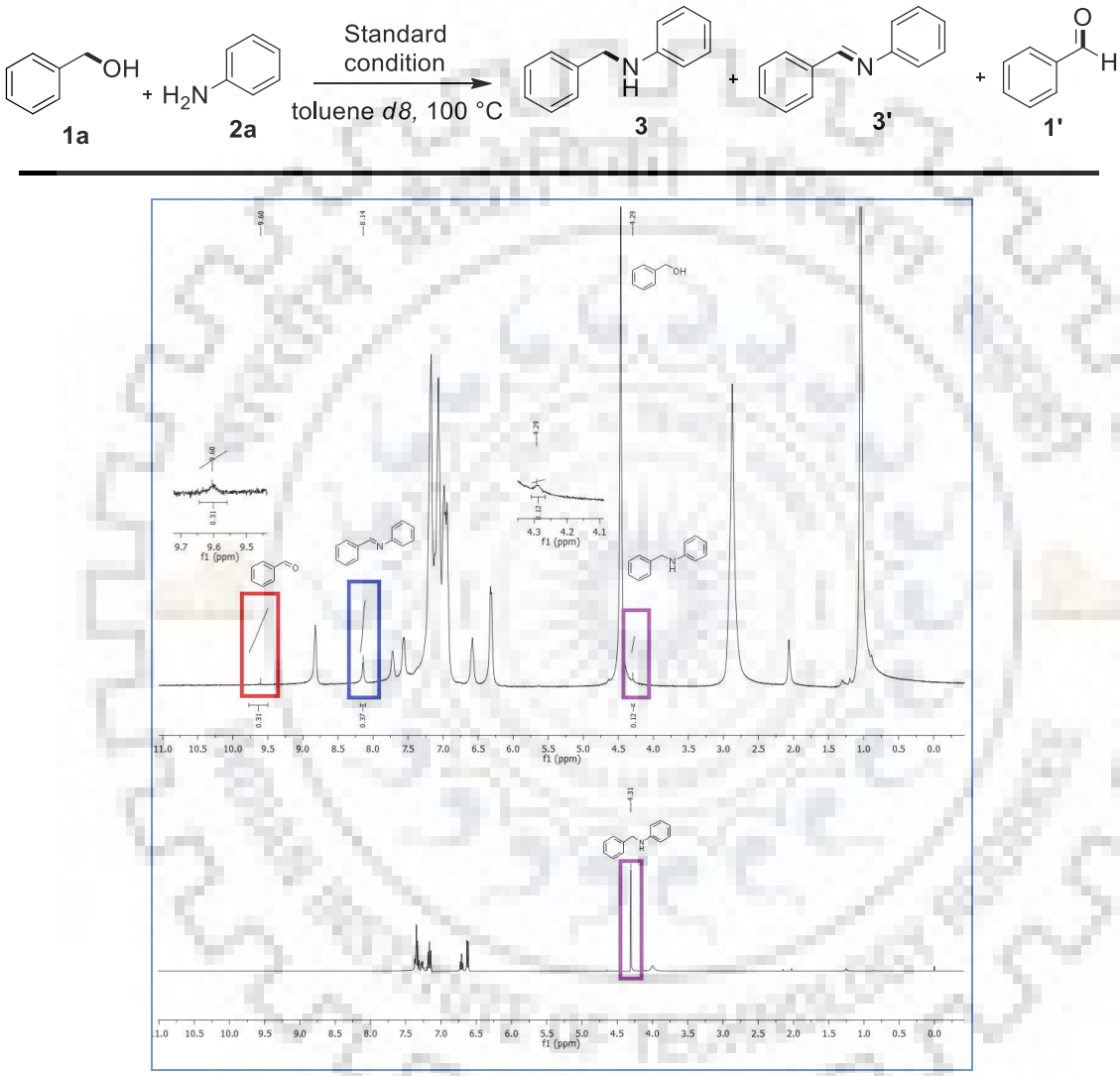


Reaction conditions: Unless specified, the reaction was carried out with **1** (1.0 mmol), **2** (0.25 mmol), $NiBr_2$ (0.025 mmol), L 2 (0.05 mmol), *t*-BuOK (0.25 mmol), 130 °C in toluene (2.0 mL) for 60 h.

Next, the synthetic application of the catalytic protocol again demonstrated using vitamin E, (±) α-tocopherol derivative of 4-bromoaniline **2v** with benzyl alcohols. Gratifyingly, 68-73% yield of secondary amine **51** and **52** were obtained without affecting the parent tocopherol moiety.

Notably, the catalytic system is tolerant to extensive functional groups, such as, halides, hydroxyl, trifluoro-methyl, 1,4-dioaxlone, di-methylamino, pyridine, quinolone and

sulphonamide derivatives including tocopherol moiety. Gratifyingly, the transformation proceeds in the presence of reducible functionalities, including alkenes, nitrile and nitro substituent revealed the synthetic potential of the catalytic protocol. Unfortunately under standard conditions aniline having functional groups such as, amide, alkyne, ester, acetophenone and cyclopropane did not result any desired product.

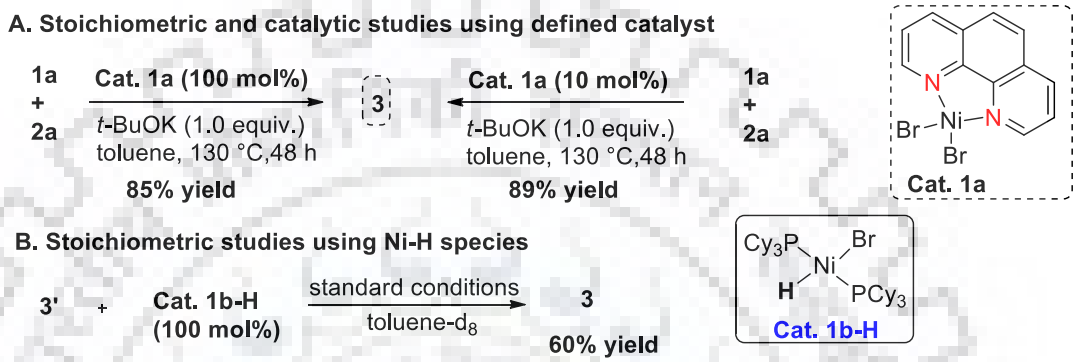


Scheme 8: In situ NMR studies and mechanistic investigation

Reaction conditions: [a] Benzyl alcohol (0.2 mmol), aniline (0.1 mmol), $NiBr_2$ (0.025 mmol), phen (0.05 mmol), *t*-BuOK (0.25 mmol), toluene d_8 (0.4 mL), NMR tube under nitrogen atmosphere, ^1H NMR was recorded at 100 °C.

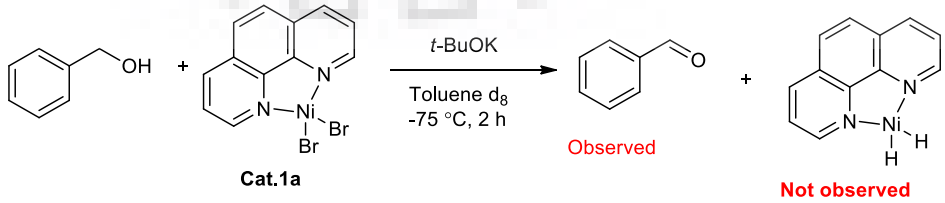
Kinetic and mechanistic studies. After having established the excellent catalytic activity of the homogeneous nickel catalysts for amination of alcohols, we studied the preliminary mechanistic investigation of the process. To the best of our knowledge, till date no systematic mechanism is known for Ni-catalyzed C-N bond formation using alcohol as electrophilic

coupling partner. Notably, we revealed that, the proposed Ni-catalyzed amination of alcohol composed of a formal multi-step process, mainly, borrowing hydrogen methodology, as described in formal in situ NMR-studies (Scheme 8). Further to confirm the putative Ni-intermediate species, the **Cat.1a** was readily prepared, and employed in catalytic as well as in stoichiometric equiv. in the reaction of **1a** with **2a** under optimized conditions and resulted **3** in good yields (Scheme 9).



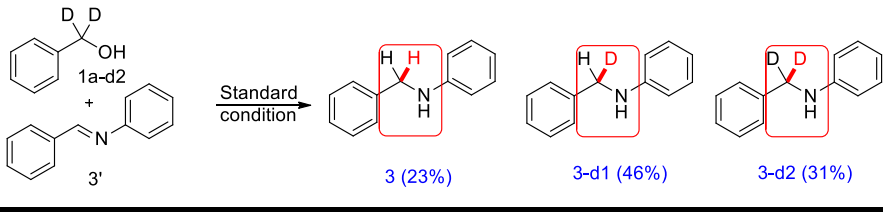
Scheme 9: Control experiment and mechanistic investigation

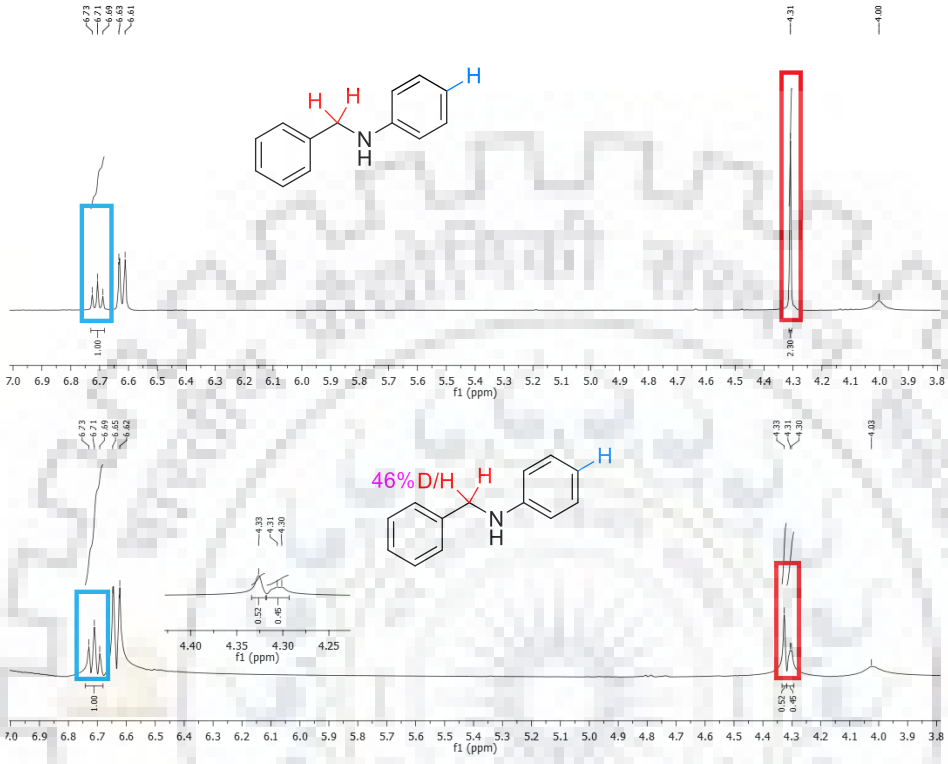
Additionally, in order to prepare the Ni-hydride species of **Cat.1a** was not successful after several attempt using different hydride donor at variable temperature.[8] The experimental results suggest that, the nickel hydride species is too unstable to detect even in an *in situ* NMR studies at -75 °C (Scheme 10). Further, an attempt to prepare the stable Ni-hydride species using electron rich phosphine ligand we choose tri-cyclohexyl phosphine, **L8** of our choice (Table 2). The defined complex, $(Cy_3)_2PNiBr_2$ and the Ni-hydride species $(Cy_3)_2PNiBrH$, **Cat.1b-H** were readily prepared according to the reported procedure, [9] and **Cat.1b-H** allowed to react with the imine **3'** in stoichiometric equiv. under standard catalytic conditions. The desired product **3** was obtained in 60% yield (Scheme 9B). This experimental finding is in strong agreement for the participation of Ni-H species and Ni-catalyzed hydrogen auto-transfer strategy.

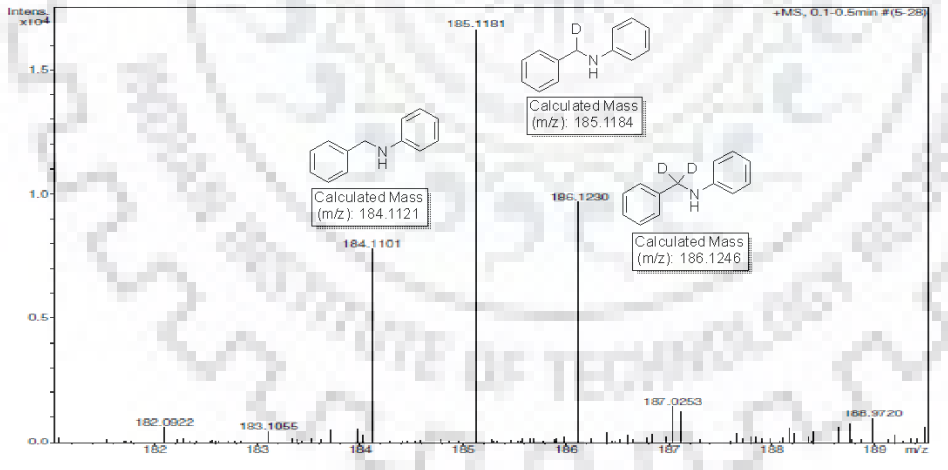


Scheme 10: Metal hydride trapping method *via* ^{1}H NMR

Reaction conditions**:** [a] Benzyl alcohol (0.2 mmol), $NiBr_2$.Phen complex (0.02 mmol), *t*-BuOK (0.2 mmol), Toluene d_8 (0.4 mL), in NMR tube under nitrogen atmosphere, ^{1}H NMR was recorded at -75 °C.





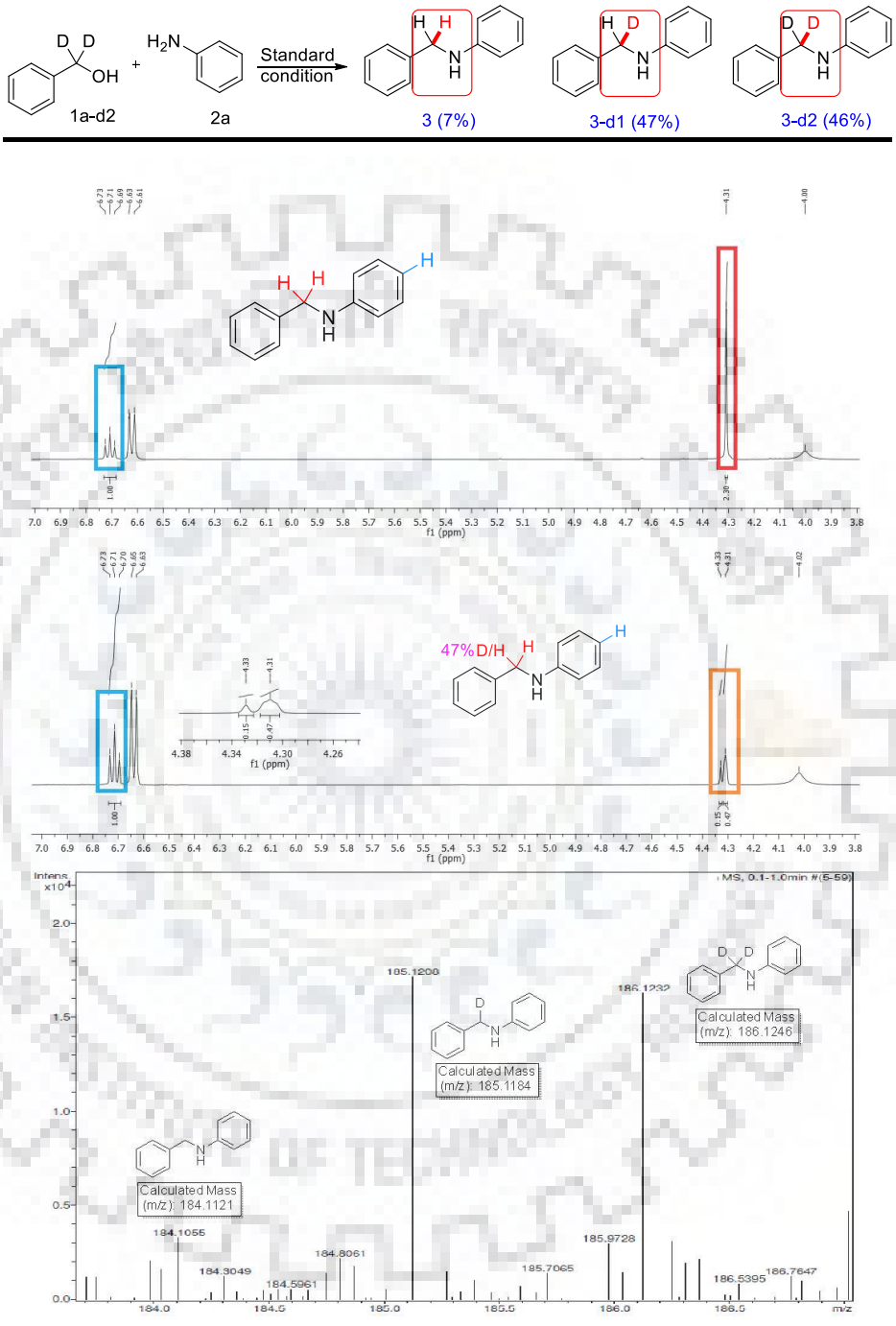


Conversion was calculated by ^{1}H NMR integration and HRMS peak ratio.

	3 + 3-d_1	3	3-d_1	3-d_2
Signal δ	6.65 [*para*-H, (1H)]	4.32[benzyl-H (2H)]	4.33 [benzyl-H (1H)]	-
Integral value	1.00	0.52/2.30 = 0.23	0.46	
Calculated ratio		**23%**	**46%**	**31%**

HRMS ratio		**23%**	**47%**	**30%**

Scheme 11: Deuterium incorporation and reduction of imine with alcohols

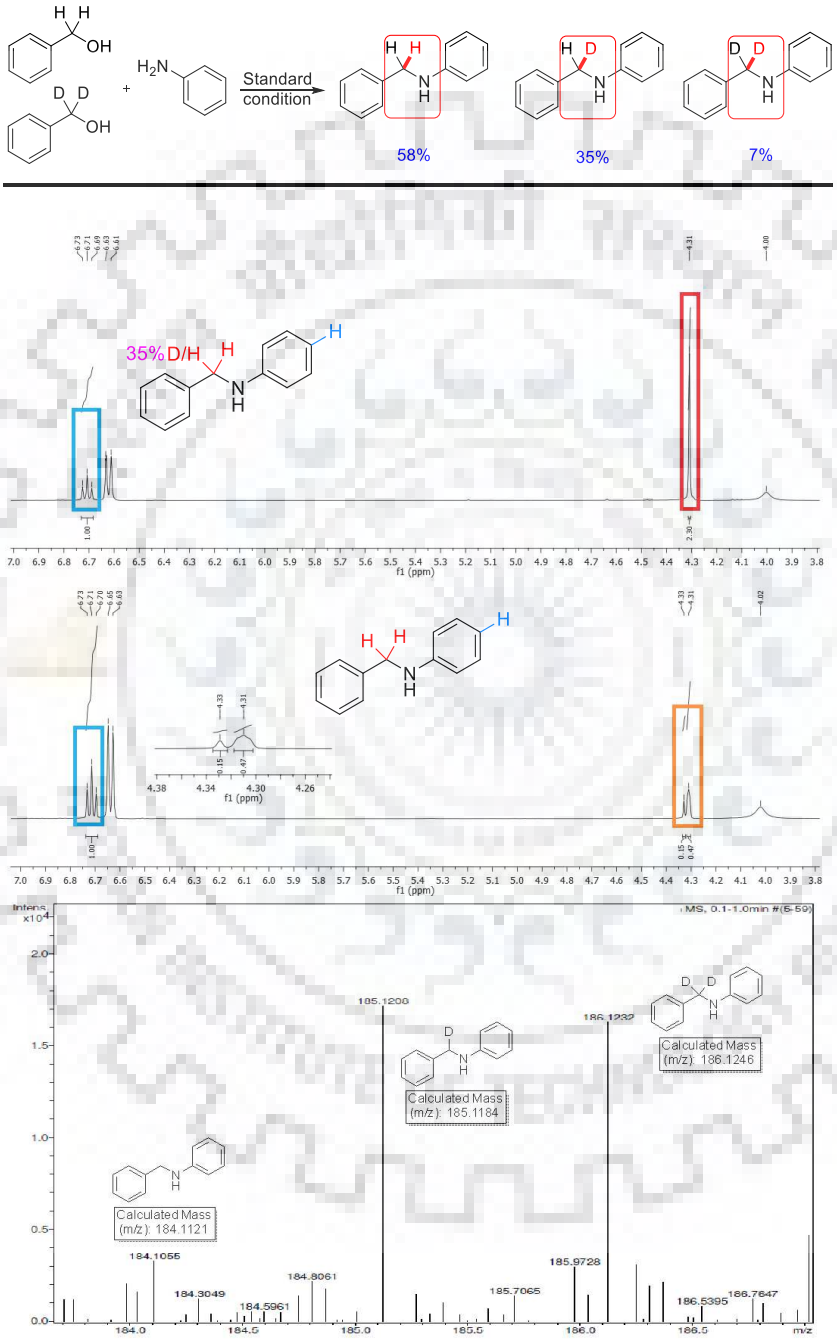


Conversion was calculated by ^{1}H NMR integration and HRMS peak ratio.

	3 + 3-d_1	3	3-d_1	3-d_2
Signal δ	6.65 [*para*-H, (1H)]	4.32 [benzyl-H (2H)]	4.33 [benzyl-H (1H)]	-
Integral Value	1.00	0.15/2.30 = 0.07	0.47	

Calculated ratio		**7 %**	**47 %**	**46 %**
HRMS ratio		**8 %**	**47 %**	**45 %**

Scheme 12: Amination with deuterated benzyl alcohol



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

	3a + 3a-d_1	3a	3a-d_1	3a-d_2
Signal δ	6.65 [*para*-H,	4.32 [benzyl-H	4.33 [benzyl-H	-

	(1H)]	(2H)]	(1H)]	
Integral Value	1.00	1.34/2.30 = 0.58	0.35	
Calculated ratio		**58 %**	**35 %**	**7 %**
HRMS ratio		**58 %**	**35 %**	**7 %**
KIE			k_{CHH}/k_{CHD} = *1.66*	

Scheme 13: Competetive and parallel experiments

Further, in order to prove the nickel hydride species as the active catalytic intermediate and the alcohol as a generic hydride source, the imine **3'** was allowed to react with **1a-d2** under standard reaction conditions. The product distribution analysis using ^{1}H-NMR as well as HRMS revealed the selective transformation of *N*-benzylaniline **3-d1** along with **3** and **3-d2** and exhibited 46% incorporation of deuterium at the benzylic position of **3-d1** (Scheme 11). Gratifyingly, a small amount of deuterated benzaldehyde was also detected by GC-MS analysis of the reaction mixture. All these deuterated experiments (Schemes 12-13), provide evidences and are in agreement with the literature observation of D/H exchange and the micro-reversible transformation of the catalytic process (Schemes 11-13). Notably, the hydride on nickel species originated from the benzylic proton of the alcohol during dehydrogenation to benzaldehyde.

Further, kinetic isotope effect (KIE) studies were performed to gain more insight into the reaction mechanism for the *N*-alkylation of alcohols. The intermolecular competition reaction of **1a** and **1a-d2** with **2a** were studied under the standard catalytic conditions and the observed product ratio gave k_{CHH}/k_{CDH} = 1.66; on the basis of ^{1}H-NMR as well as HRMS analysis. The experimental findings revealed the participation of the benzylic C-H bond cleavage in the rate determining step.

[2.5] Conclusions:

In conclusion in this chapter, we have developed the nickel-catalyzed direct application of various primary alcohols including diols and amino alcohols for selective N-alkylation of anilines. The catalytic protocol is tolerant to extensive functional groups and enable the catalytic transformations in presence of hydroxyl, alkenes, nitrile, nitro and tri-fluoromethyl functionalities in up to 96% yield. As a special highlight, we have demonstrated the synthetic potential of this protocol in the intramolecular cyclization to indoles, alkylation of di-aniline

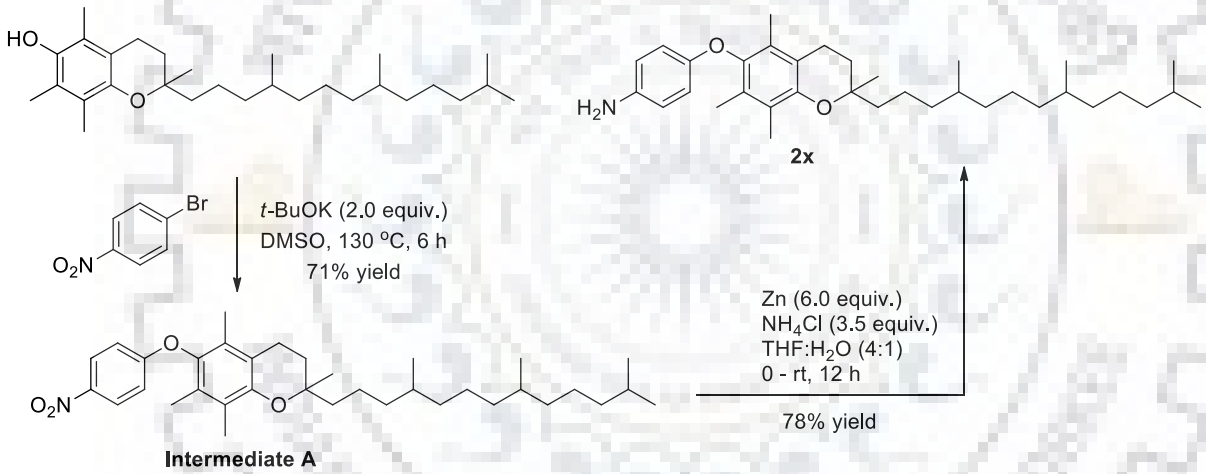
and functionalization of complex vitamin E derivative. Initial mechanistic studies revealed the involvement of the benzylic C-H bond in the rate determining step. Further, mechanistic studies for the Ni-catalyzed amination reactions are ongoing in our laboratory.

[2.6] Experimental details:

[2.6.1] General procedure for the synthesis of alcohols:

Sodium borohydride (1.5 equiv.) was added portion wise over 10 min to a solution of the corresponding aldehydes (5.0 mol) in THF (30 mL) at 0 °C. After 15 min the reaction was allowed to warm to rt and stirred for additional 4-12 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with Et_2O. The organic phase was washed with brine, dried over Na_2SO_4 and the solvent was subsequently removed to provide the product.

[2.6.2] Preparation of tocopherol derived amine (2x):



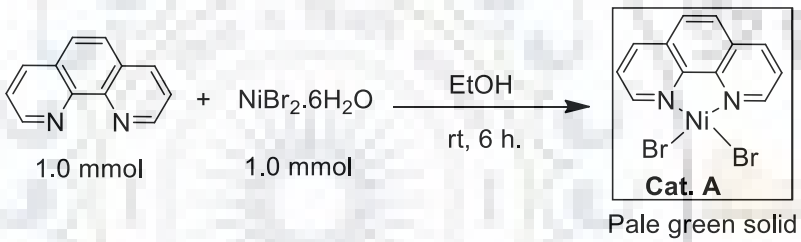
Procedure:

Step-1: In a 10 mL oven dried Schlenk tube, 4-nitroaniline (404 mg, 2.0 mmol, 2.0 equiv.), *t*-BuOK (2.0 equiv.), (±) *α*-tocopherol (430 mg, 1.0 mmol, 1.0 equiv.) and DMSO 5 mL were taken under an atmosphere of N_2. The reaction mixture was heated at 130 °C for 6 h and cooled to room temperature, and was partitioned between ethyl acetate (25.0 mL) and water (25.0 mL) in a separatory funnel. The organic layer was washed with water, and brine, dried over anhydrous Na_2SO_4 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 (intermediate A) as pale yellow oil (392 mg, 71% yield).

Step-2: In a 25 mL oven dried RB flask, intermediate A (392 mg, 0.71 mmol, 1.0 equiv.), Zn (6.0 equiv.) and 10 mL THF:H_2O (4:1) were taken. The reaction was cooled to 0°C, then solid NH_4Cl (3.5 equiv.) was added slowly over 10 min. Thereafter it was brought to room

temperature and stirred for 12 h. After completion of reaction monitored by TLC, the reaction mixture was partitioned between ethyl acetate (30.0 mL) and water (30.0 mL) in a separatory funnel. The organic layer was washed with water, and brine, dried over anhydrous Na_2SO_4 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 **2x** as pale yellow oil (289 mg, 78% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 – 6.51 (m, 4H), 3.30 (bs, 2H), 2.59 (t, J = 6.8 Hz, 2H), 2.10 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.80 (dq, J = 19.7, 6.7 Hz, 2H), 1.63 – 1.48 (m, 4H), 1.45 – 1.33 (m, 4H), 1.30 – 1.21 (m, 10H), 1.16 – 1.03 (m, 6H), 0.85 (dd, J = 9.0, 5.5 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 148.6, 143.9, 139.9, 128.5, 126.6, 123.2, 117.8, 116.5, 115.4, 75.0, 39.5, 37.7, 37.6, 37.5, 37.4, 32.9, 32.8, 28.1, 24.9, 24.5, 23.9, 22.8, 22.7, 21.1, 20.7, 19.8, 19.8, 19.7, 13.0, 12.1, 11.9; HRMS (ESI): Calculated for $[C_{35}H_{56}NO_2]^+$ 522.4306; Found 522.4295.

[2.6.3] Synthesis of [$NiBr_2$(1,10-phen)] complex:

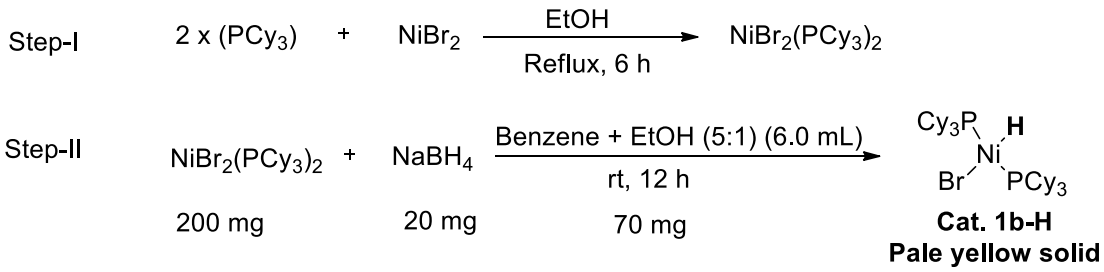


A solution of 1,10-phenanthroline (124 mg, 0.69 mmol) in EtOH (2 mL) was added to a solution of $NiBr_2$•$6H_2O$ (152 mg, 0.69 mmol) in EtOH (2 mL) at rt. After stirring for 6 h, a pale green precipitate formed and was filtered off, washed with EtOH (3×3 mL), and dried *in vacuo* to afford **Cat.A** as a pale green solid.[8]

*Characterization of **Cat.A**:* Chemical Formula: $C_{12}H_8Br_2N_2Ni$; Elemental Analysis calculated (%): C, 36.15; H, 2.02; Br, 40.08; N, 7.03; Ni, 14.72; Found (%): C, 35.57; H, 2.66; N, 6.91.

[2.6.4] Preparation of Cat.1b-H: The catalyst was prepared following literature reported procedure. The Ni-H species, **Cat.1b-H** was obtained as pale yellow solid and the solid decomposes very fast in solvent. Characterization data were in agreement with the literature reported data.[9]

Characterization of **Cat. 1b-H**: IR: Ni-H 1950 cm.$^{-1}$; M.P.- (150-151) ^{o}C (decompose).



[2.6.5] General Procedure for Ni-catalyzed amination reactions with alcohols:

Procedure A:

In a 10 mL oven dried Schlenk tube amines (0.25 mmol), *t*-BuOK (0.25 mmol), 1,10-phenanthroline (0.05 mmol), $NiBr_2$ (0.025 mmol) and alcohols (1.0 mmol) were added followed by 2 mL of toluene under N_2 atmosphere and the reaction mixture was heated at 130 $^{\circ}$C for 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 products.

Procedure B: Alkyl alcohols.

In a 10 mL oven dried Schlenk tube amines (0.25 mmol), *t*-BuOK (0.25 mmol), 1,10-phenanthroline (0.1mmol), $NiBr_2$ (0.05 mmol) and alcohols (1.25 mmol) were added followed by 2 mL of toluene under N_2 atmosphere and the reaction mixture was heated at 130 $^{\circ}$C for 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 products.

Procedure C: Bis-alkylation.

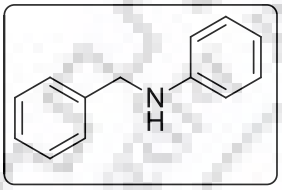
In a 10 mL oven dried Schlenk tube amines (0.25 mmol), *t*-BuOK (0.50 mmol), 1,10-phenanthroline (0.1 mmol), $NiBr_2$ (0.05 mmol) and alcohols (2.0 mmol) were added followed by 2 mL of toluene under N_2 atmosphere and the reaction mixture was heated at 130 $^{\circ}$C for 60 h in close system. The reaction mixture was cooled to room temperature and 5.0 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.

Procedure D: Cyclization

In a 10 mL oven dried Schlenk tube amino alcohols (0.30 mmol), *t*-BuOK (0.25 mmol), 1,10-phenanthroline (0.12 mmol), $NiBr_2$ (0.06 mmol) were added followed by 2 mL of toluene under N_2 atmosphere and the reaction mixture was heated at 130 °C for 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 products.

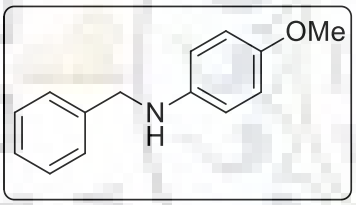
[2.6.6] Analytical data for all the products:

***N*-Benzylaniline (3)** [10]:



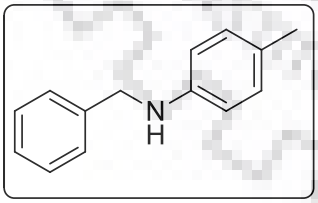
Following the general procedure A, the title product was obtained as a colourless oil (96% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 4H), 7.29 – 7.23 (m, 1H), 7.19 – 7.13 (m, 2H), 6.70 (t, J = 7.3 Hz, 1H), 6.62 (d, J = 7.6 Hz, 2H), 4.30 (s, 2H), 4.00 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 139.4, 129.2, 128.6, 127.4, 127.2, 117.5, 112.8, 48.2.

***N*-Benzyl-4-methoxyaniline (4)** [10]:



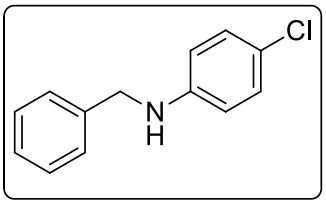
Following the general procedure A, the title product was obtained as a colourless oil (71% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 4H), 7.29 – 7.23 (m, 1H), 6.77 (d, J = 8.9 Hz, 2H), 6.60 (d, J = 8.8 Hz, 2H), 4.27 (s, 2H), 3.73 (s, 3H), 3.30 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 142.5, 139.8, 128.7, 127.7, 127.3, 115.0, 114.2, 55.9, 49.4.

***N*-Benzyl-4-methylaniline (5)** [13]:



Following the general procedure A, the title product was obtained as a colourless oil (49% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 4H), 7.28 (dd, J = 14.9, 8.1 Hz, 1H), 7.01 (d, J = 8.5 Hz, 2H), 6.59 (d, J = 8.3 Hz, 2H), 4.33 (s, 2H), 3.87 (s, br, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 139.6, 129.6, 128.5, 127.4, 127.1, 126.6, 112.9, 48.5, 20.3.

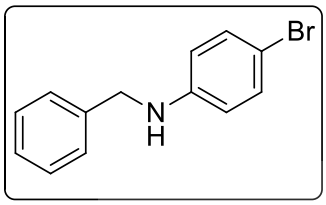
***N*-Benzyl-4-chloroaniline (6)** [10]:



Following the general procedure A, the title product was obtained as a colourless oil (52% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, 4H), 7.31 (tdd, J = 6.4, 4.2, 2.0 Hz, 1H), 7.21 (dd, J = 8.6, 7.4 Hz, 1H), 7.14 (d, J = 8.9 Hz, 1H), 6.67 (dd, J = 8.6, 1.1

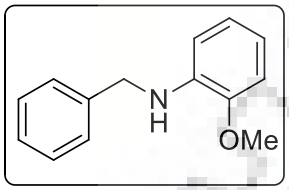
Hz, 1H), 6.56 (d, *J* = 8.9 Hz, 1H), 4.33 (d, *J* = 14.6 Hz, 2H), 4.06 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 139.1, 129.4, 129.2, 127.6, 127.5, 114.1, 113.0, 48.4.

***N*-Benzyl-4-bromoaniline (7)** [13]:



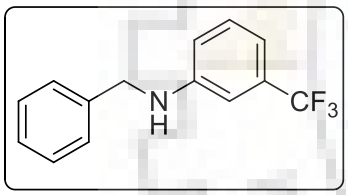
Following the general procedure A, the title product was obtained as a colourless oil (62% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 4.4 Hz, 4H), 7.32 – 7.28 (m, 1H), 7.27 – 7.22 (m, 2H), 6.50 (d, *J* = 8.9 Hz, 2H), 4.30 (s, 2H), 4.08 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 139.0, 132.1, 132.0, 128.8, 127.4, 114.5, 109.2, 48.3.

***N*-Benzyl-2-methoxyaniline (8)** [10]:



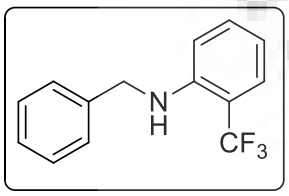
Following the general procedure A, the title product was obtained as a colourless oil (60% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 4H), 7.29 – 7.24 (m, 1H), 6.81 (ddd, *J* = 14.8, 7.8, 1.4 Hz, 2H), 6.69 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.60 (dd, *J* = 7.8, 1.5 Hz, 1H), 4.63 (s, br, 1H), 4.35 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 139.7, 138.2, 128.7, 127.6, 127.2, 121.4, 116.7, 110.2, 109.5, 55.5, 48.1.

***N*-Benzyl-3-(trifluoromethyl)aniline (9)** [3]:



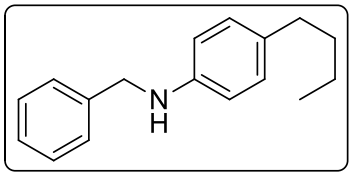
Following the general procedure A, the title product was obtained as a colourless oil (77% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.36 (m, 4H), 7.33 – 7.29 (m, 1H), 7.25 (t, *J* = 7.9 Hz, 1H), 6.97 – 6.94 (m, 1H), 6.86 (s, 1H), 6.75 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.35 (s, 2H), 4.22 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 138.7, 131.6 (q, J_{CF}= 31.7 Hz), 129.8, 128.9, 127.6, 115.8, 115.8, 114.1, 114.0, 109.2, 109.1, 48.2.

***N*-Benzyl-2-(trifluoromethyl)aniline (10)**



Following the general procedure A, the title product was obtained as a colourless oil (44% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 4.4 Hz, 4H), 7.35 – 7.30 (m, 2H), 6.74 (dd, *J* = 17.9, 8.0 Hz, 2H), 4.85 (s, br, 1H), 4.44 (d, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 138.5, 133.2, 128.9, 128.9, 127.5, 127.2, 126.7, 124.0, 116.3, 113.6 (q, J_{CF} = 29.4 Hz), 112.3, 47.7. HRMS (ESI): Calculated for $[C_{14}H_{13}F_3N]^+$ 252.0995; Found 252.1225.

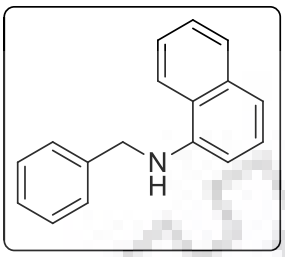
***N*-Benzyl-4-butylaniline (11)** [15]:



Following the general procedure A, the title product was obtained as a colourless oil (88% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 4H), 7.28 (t, *J* = 11.2 Hz, 1H), 7.01 (d,

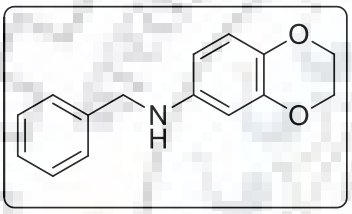
J = 8.2 Hz, 2H), 6.60 (d, *J* = 8.0 Hz, 2H), 4.32 (s, 2H), 3.95 (s, br, 1H), 2.56 – 2.46 (m, 2H), 1.62 – 1.50 (m, 2H), 1.36 (dd, *J* = 14.9, 7.4 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 139.8, 132.2, 129.2, 128.7, 127.7, 127.3, 113.0, 48.8, 34.8, 34.1, 22.5, 14.1.

***N*-Benzylnaphthalen-1-amine (12)** [13]:



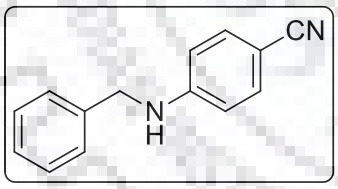
Following the general procedure A, the title product was obtained as a colourless oil (86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.63 (m, 2H), 7.37 – 7.12 (m, 9H), 6.51 (d, *J* = 7.4 Hz, 1H), 4.52 (s, br, 1H), 4.36 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 139.2, 134.4, 128.9, 128.8, 127.9, 127.6, 126.8, 125.9, 124.9, 123.5, 120.1, 117.8, 104.9, 48.7.

***N*-Benzyl-2,3-dihydrobenzo[*b*][1,4]dioxin-6-amine (13)** [3]:



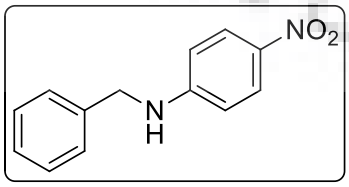
Following the general procedure A, the title product was obtained as a colourless oil (86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 4H), 7.28 (dt, *J* = 9.5, 4.2 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.21 (dd, *J* = 5.7, 2.7 Hz, 1H), 6.18 (d, *J* = 2.7 Hz, 1H), 4.25 (s, 2H), 4.23 – 4.20 (m, 2H), 4.19 – 4.16 (m, 2H), 3.67 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 143.4, 139.7, 135.8, 128.7, 127.7, 127.3, 117.8, 106.9, 101.7, 64.8, 64.3, 49.1.

4-(benzylamino)benzonitrile (14) [11]:



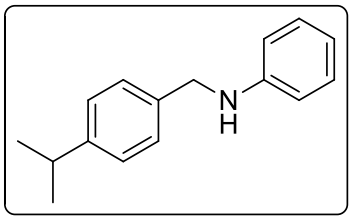
Following the general procedure A, the title product was obtained as a light yellow oil (60% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 7H), 6.58 (d, *J* = 9.1 Hz, 2H), 4.69 (br s, 1H), 4.36 (d, *J* = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.24, 137.93, 133.49, 128.96, 127.78, 127.40, 120.51, 112.51, 99.09, 47.41.

***N*-benzyl-4-nitroaniline** (**15**) [12]:



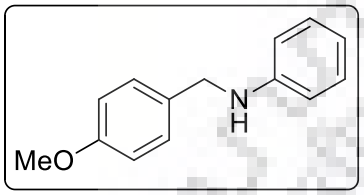
Following the general procedure A, the title product was obtained as a pale yellow oil (32% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 2H), 7.39 – 7.27 (m, 5H), 6.58 (d, *J* = 8.8 Hz, 2H), 4.57 (br s, 1H), 4.36 (d, *J* = 5.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.23, 137.79, 133.82, 128.97, 127.82, 127.41, 120.38, 112.49, 47.54.

***N*-(4-Isopropylbenzyl)aniline (16)** [19]:



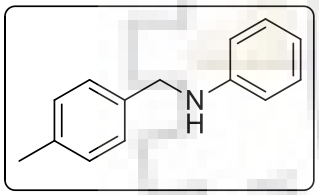
Following the general procedure A, the title product was obtained as a colourless oil (84% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.1 Hz, 2H), 7.28 – 7.19 (m, 4H), 6.79 – 6.75 (m, 1H), 6.68 (dd, J = 8.5, 0.9 Hz, 2H), 4.32 (s, 2H), 4.00 (s, br, 1H), 3.01 – 2.90 (m, 1H), 1.30 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 148.1, 136.9, 129.4, 127.8, 126.9, 117.6, 112.9, 48.2, 34.0, 24.2.

***N*-(4-Methoxybenzyl)aniline (17)** [10]:



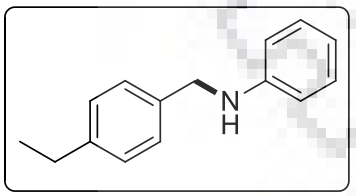
Following the general procedure A, the title product was obtained as a colourless oil (72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.9 Hz, 2H), 7.17 (dd, J = 8.7, 7.5 Hz, 2H), 6.93 – 6.81 (m, 2H), 6.77 – 6.67 (m, 1H), 6.63 (dd, J = 8.8, 1.0 Hz, 2H), 4.24 (s, 2H), 3.97 (s, br, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 148.3, 131.5, 129.4, 128.9, 117.6, 114.1, 112.9, 55.4, 47.9.

***N*-(4-Methylbenzyl)aniline (18)** [10]:



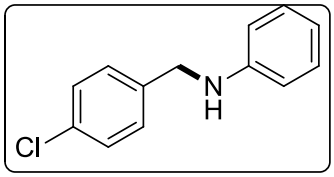
Following the general procedure A, the title product was obtained as a colourless oil (57% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, J = 6.9 Hz, 2H), 7.22 – 7.15 (m, 4H), 6.77 – 6.70 (m, 1H), 6.69 – 6.61 (m, 2H), 4.29 (s, 2H), 4.00 (s, br, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 137.0, 136.4, 129.4, 129.4, 127.6, 117.6, 112.9, 48.2, 21.2.

***N*-(4-Ethylbenzyl)aniline (19)** [20]:



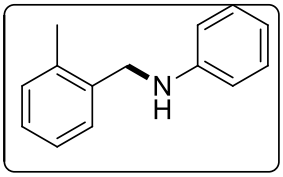
Following the general procedure A, the title product was obtained as a colourless oil (77% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.0 Hz, 2H), 7.23 – 7.14 (m, 4H), 6.78 – 6.69 (m, 1H), 6.66 (dd, J = 8.4, 0.8 Hz, 2H), 4.30 (s, 2H), 4.03 (s, br, 1H), 2.66 (q, J = 7.6 Hz, 2H), 1.25 (td, J = 7.6, 0.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 143.4, 136.7, 129.4, 128.2, 127.7, 117.6, 112.9, 48.2, 28.6, 15.8.

***N*-(4-Chlorobenzyl)aniline (20)** [13]:



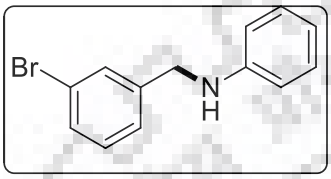
Following the general procedure A, the title product was obtained as a colourless oil (81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 1H), 7.32 (s, 3H), 7.22 – 7.17 (m, 2H), 6.80 – 6.73 (m, 1H), 6.65 – 6.60 (m, 2H), 4.32 (s, 2H), 4.06 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 138.1, 133.0, 129.4, 128.8, 127.6, 117.9, 113.0, 47.7.

***N*-(2-Methylbenzyl)aniline (21)** [15]:



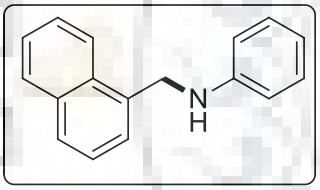
Following the general procedure A, the title product was obtained as a colourless oil (47% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 6.8 Hz, 1H), 7.24 – 7.15 (m, 5H), 6.74 (t, J = 4.2 Hz, 1H), 6.69 – 6.61 (m, 2H), 4.28 (s, 2H), 3.85 (s, br, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 137.1, 136.5, 130.5, 129.4, 128.4, 127.5, 126.3, 117.6, 112.8, 46.5, 19.0.

***N*-(3-Bromobenzyl)aniline (22)** [22]:



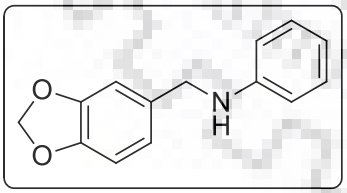
Following the general procedure A, the title product was obtained as a colourless oil (72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 1.5 Hz, 1H), 7.31 (dd, J = 4.0, 2.8 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.14 – 7.06 (m, 3H), 6.68 – 6.61 (m, 1H), 6.51 (dd, J = 8.6, 1.0 Hz, 2H), 4.21 (s, 2H), 3.98 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 142.1, 130.5, 130.4, 130.3, 129.4, 126.0, 122.9, 118.0, 113.0, 47.8.

***N*-(Naphthalen-1-ylmethyl)aniline (23)** [21]:



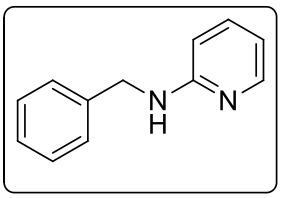
Following the general procedure A, the title product was obtained as a colourless oil (96% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 5.1, 4.0 Hz, 1H), 7.84 – 7.76 (m, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.43 (dt, J = 6.3, 3.4 Hz, 3H), 7.37 – 7.31 (m, 1H), 7.18 – 7.05 (m, 2H), 6.73 – 6.63 (m, 1H), 6.64 – 6.55 (m, 2H), 4.64 (s, 2H), 3.90 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 134.4, 134.0, 131.6, 129.4, 128.9, 128.3, 126.4, 126.2, 126.0, 125.6, 123.7, 117.7, 112.8, 46.5.

***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)aniline (24)** [3]:



Following the general procedure A, the title product was obtained as a colourless oil (51% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, J = 8.5, 7.4 Hz, 2H), 6.87 – 6.81 (m, 2H), 6.77 (d, J = 7.9 Hz, 1H), 6.73 – 6.70 (m, 1H), 6.65 – 6.60 (m, 2H), 5.94 (s, 2H), 4.23 (s, 2H), 3.98 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 148.0, 146.8, 133.4, 129.4, 120.7, 117.7, 112.9, 108.2, 108.1, 101.1, 48.2.

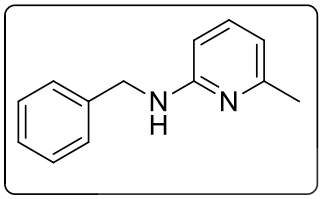
***N*-Benzylpyridin-2-amine (25)** [3]:



Following the general procedure A, the title product was obtained as a colourless solid (89% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 3.1 Hz, 1H), 7.43 – 7.30 (m, 5H), 7.29 – 7.24 (m, 1H), 6.57 (ddd, J = 7.0, 5.1, 0.6 Hz, 1H), 6.36 (d, J = 8.4 Hz, 1H), 5.07 (s, br, 1H), 4.49

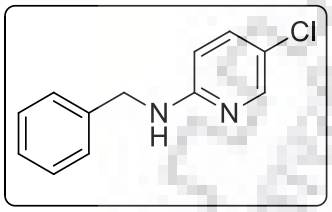
(d, J = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 148.2, 139.3, 137.6, 128.7, 127.5, 127.3, 113.2, 106.9, 46.4.

***N*-Benzyl-6-methylpyridin-2-amine (26)** [14]:



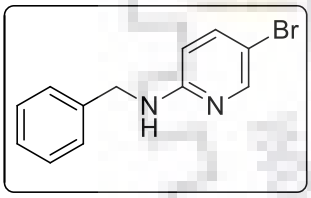
Following the general procedure A, the title product was obtained as a colourless solid (81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.22 (m, 6H), 6.46 (d, J = 7.3 Hz, 1H), 6.16 (d, J = 8.3 Hz, 1H), 4.97 (s, br, 1H), 4.45 (d, J = 5.9 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 157.1, 139.3, 138.1, 128.7, 127.4, 127.3, 112.6, 103.0, 46.6, 24.4.

***N*-Benzyl-5-chloropyridin-2-amine (27)** [17]:



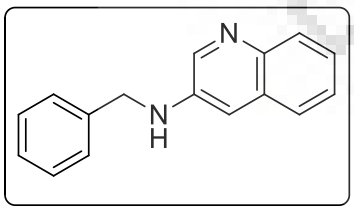
Following the general procedure A, the title product was obtained as a colourless solid (83% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 2.6, 0.5 Hz, 1H), 7.35 – 7.32 (m, 5H), 7.27 (ddd, J = 12.4, 5.0, 3.5 Hz, 1H), 6.31 (dd, J = 8.9, 0.6 Hz, 1H), 5.05 (s, br, 1H), 4.47 (d, J = 5.8 Hz, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 146.6, 138.8, 137.4, 137.3, 128.8, 127.5, 120.0, 107.7, 46.5.

***N*-Benzyl-5-bromopyridin-2-amine (28)** [16]:



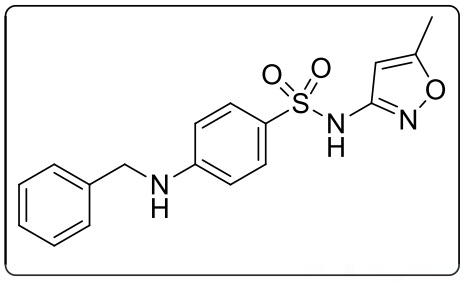
Following the general procedure A, the title product was obtained as a colourless solid (86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (ddd, J = 5.0, 1.8, 0.8 Hz, 1H), 7.39 – 7.34 (m, 4H), 7.29 – 7.26 (m, 1H), 6.60 – 6.56 (m, 1H), 6.35 (d, J = 8.4 Hz, 1H), 4.96 (s, br, 1H), 4.47 (d, J = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 148.1, 139.2, 137.7, 128.6, 127.5, 127.1, 113.2, 106.8, 46.4.

***N*-Benzylquinolin-3-amine (29)** [18]:



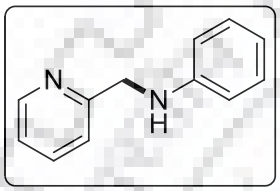
Following the general procedure A, the title product was obtained as a colourless solid (84% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 2.8 Hz, 1H), 7.94 (dd, J = 6.0, 3.5 Hz, 1H), 7.57 (dd, J = 6.1, 3.5 Hz, 1H), 7.44 – 7.26 (m, 7H), 7.01 (d, J = 2.8 Hz, 1H), 4.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 142.2, 141.5, 138.3, 129.5, 129.1, 128.9, 127.7, 127.6, 127.0, 126.1, 125.1, 110.5, 48.0.

4-(Benzylamino)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (30)



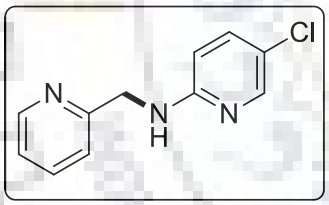
Following the general procedure A, the title product was obtained as a colourless solid (71% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 7.0 Hz, 2H), 7.29 – 7.18 (m, 3H), 6.56 (d, J = 8.7 Hz, 2H), 6.33 (s, 1H), 4.88 (s, 2H), 4.21 (s, br, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 159.9, 151.5, 136.2, 129.4, 129.4, 128.3, 127.6, 126.0, 114.1, 98.5, 51.7, 12.7; HRMS (ESI): Calculated for $[C_{17}H_{17}N_3NaO_3S]^+$ 366.0883; Found 366.0899.

***N*-(Pyridin-2-ylmethyl)aniline (31)** [15]:



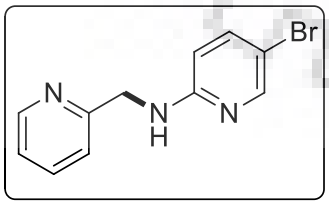
Following the general procedure A, the title product was obtained as a colourless solid (78% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 7.62 (td, J = 7.7, 1.8 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.21 – 7.14 (m, 3H), 6.74 – 6.65 (m, 3H), 4.77 (s, br, 1H), 4.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 149.3, 148.0, 136.7, 129.3, 122.2, 121.7, 117.7, 113.1, 49.4.

4-Chloro-*N*-(pyridin-2-ylmethyl)aniline (32)



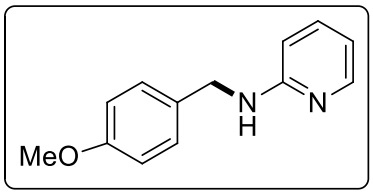
Following the general procedure A, the title product was obtained as a colourless solid (72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 – 8.51 (m, 1H), 8.04 (d, J = 2.4 Hz, 1H), 7.73 – 7.57 (m, 1H), 7.42 – 7.24 (m, 3H), 7.20 – 7.13 (m, 1H), 6.46 – 6.37 (m, 1H), 5.71 (s, br, 1H), 4.61 (d, J = 5.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 149.1, 146.4, 137.2, 136.8, 122.3, 121.9, 120.0, 108.8, 47.2; HRMS (ESI): Calculated for $[C_{11}H_{10}ClN_3Na]^+$ 242.0455; Found 242.1051.

4-Bromo-*N*-(pyridin-2-ylmethyl)aniline (33)



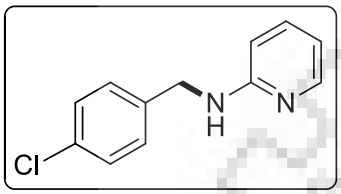
Following the general procedure A, the title product was obtained as a colourless solid (76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 – 8.55 (m, 1H), 8.11 – 8.08 (m, 1H), 7.68 – 7.61 (m, 1H), 7.42 – 7.35 (m, 1H), 7.25 – 7.17 (m, 3H), 6.52 (dd, J = 8.5, 0.5 Hz, 1H), 5.73 (s, br, 1H), 4.70 (d, J = 5.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 157.9, 149.0, 139.0, 136.6, 123.1, 121.9, 121.6, 95.6, 47.5; HRMS (ESI): Calculated for $[C_{11}H_{10}BrN_3Na]^+$ 285.9950; Found 286.1088.

***N*-(4-Methoxybenzyl)pyridin-2-amine (34)** [23]:



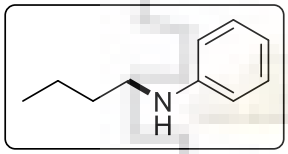
Following the general procedure A, the title product was obtained as a colourless solid (89% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.03 (m, 1H), 7.48 – 7.35 (m, 1H), 7.35 – 7.10 (m, 2H), 7.00 – 6.75 (m, 2H), 6.57 (ddd, J = 7.3, 5.1, 1.1 Hz, 1H), 6.46 – 6.29 (m, 1H), 4.79 (s, br, 1H), 4.42 (d, J = 5.9 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 158.7, 148.3, 137.5, 131.2, 128.8, 114.1, 113.2, 106.9, 55.4, 45.9.

***N*-(4-Chlorobenzyl)pyridin-2-amine (35)** [23]:



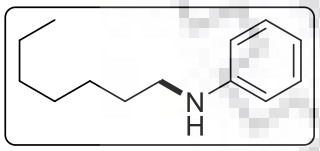
Following the general procedure A, the title product was obtained as a colourless solid (91% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.04 (m, 1H), 7.42 – 7.35 (m, 1H), 7.29 – 7.26 (m, 4H), 6.58 (dd, J = 7.2, 5.1 Hz, 1H), 6.35 – 6.31 (m, 1H), 4.98 (s, br, 1H), 4.46 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 148.3, 137.7, 133.2, 128.8, 128.7, 127.5, 113.5, 107.0, 45.6.

***N*-Butylaniline (36)** [14]:



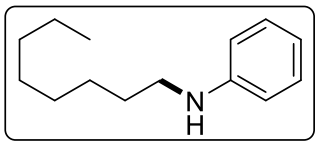
Following the general procedure B, the title product was obtained as a colourless oil (41% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.14 (m, 2H), 6.70 – 6.66 (m, 1H), 6.62 – 6.58 (m, 2H), 3.61 (s, br, 1H), 3.13 – 3.08 (m, 2H), 1.60 (tt, J = 7.5, 6.1 Hz, 2H), 1.48 – 1.38 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 129.3, 117.2, 112.8, 43.8, 31.7, 20.4, 14.0.

***N*-Heptylaniline (37)** [10]:



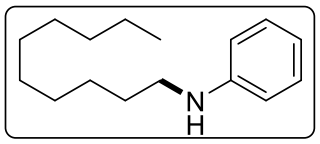
Following the general procedure B, the title product was obtained as a colourless oil (59% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, J = 8.5, 7.4 Hz, 2H), 6.67 (t, J = 7.3 Hz, 1H), 6.59 (dd, J = 8.5, 0.9 Hz, 2H), 3.63 (s, br, 1H), 3.09 (t, J = 7.1 Hz, 2H), 1.63 – 1.59 (m, 2H), 1.40 – 1.31 (m, 8H), 0.87 – 0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 129.2, 117.1, 112.8, 44.1, 31.9, 29.8, 29.7, 27.1, 22.7, 14.2.

***N*-Octylaniline (38)** [13]:



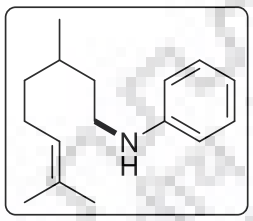
Following the general procedure B, the title product was obtained as a colourless oil (69% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, J = 8.4, 7.4 Hz, 2H), 6.68 (t, J = 7.3 Hz, 1H), 6.60 (d, J = 7.7 Hz, 2H), 3.53 (s, br, 1H), 3.09 (t, J = 7.1 Hz, 2H), 1.64 – 1.58 (m, 2H), 1.37 – 1.28 (m, 10H), 0.89 (d, J = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 129.4, 117.1, 112.8, 44.1, 31.9, 29.7, 29.5, 29.4, 27.3, 22.8, 14.2.

***N*-Decylaniline (39)** [19]:



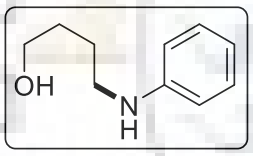
Following the general procedure B, the title product was obtained as a colourless oil (76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, J = 7.9 Hz, 2H), 6.72 – 6.66 (m, 1H), 6.60 (dd, J = 7.7, 0.9 Hz, 2H), 3.60 (s, br, 1H), 3.10 (t, J = 7.1 Hz, 2H), 1.66 – 1.57 (m, 2H), 1.42 – 1.26 (m, 14H), 0.89 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 129.4, 117.2, 112.8, 44.1, 29.7, 29.7, 29.6, 29.4, 27.3, 22.8, 14.2.

***N*-(3,7-dimethyloct-6-en-1-yl)aniline (40)** [24]:



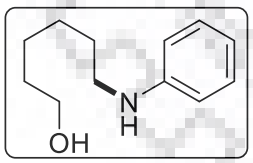
Following the general procedure B, the title product was obtained as a colourless oil (71% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, J = 8.5, 7.4 Hz, 2H), 6.69 (t, J = 7.3 Hz, 1H), 6.60 (dd, J = 8.6, 1.0 Hz, 2H), 5.14 – 5.05 (m, 1H), 3.19 – 3.04 (m, 2H), 2.08 – 1.93 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.59 – 1.52 (m, 1H), 1.49 – 1.32 (m, 3H), 1.29 – 1.16 (m, 2H), 0.94 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 131.4, 129.4, 124.7, 117.8, 112.8, 42.0, 37.2, 36.8, 25.9, 25.8, 25.7, 25.6, 19.7.

4-(Phenylamino)butan-1-ol (41) [25]:



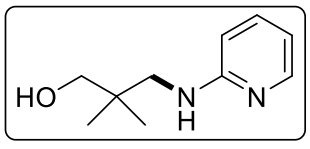
Following the general procedure B, the title product was obtained as a colourless oil (68% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, J = 8.8, 7.4 Hz, 2H), 6.69 (t, J = 7.4 Hz, 1H), 6.61 (dd, J = 8.8, 1.1 Hz, 2H), 3.68 (t, J = 6.1 Hz, 2H), 3.15 (t, J = 6.9 Hz, 2H), 1.73 – 1.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 129.4, 117.5, 113.0, 62.7, 44.0, 30.5, 26.2.

6-(Phenylamino)hexan-1-ol (42) [26]:



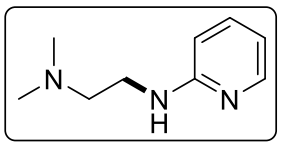
Following the general procedure B, the title product was obtained as a colourless oil (42% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.13 (m, 2H), 6.67 (t, J = 7.3 Hz, 1H), 6.59 (dd, J = 8.6, 1.0 Hz, 2H), 3.66 – 3.64 (m, 2H), 3.14 – 3.06 (m, 2H), 1.65 – 1.61 (m, 4H), 1.44 – 1.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 129.3, 117.2, 112.8, 62.9, 44.0, 32.7, 28.7, 27.1, 25.5.

2,2-Dimethyl-3-(pyridin-2-ylamino)propan-1-ol (43)



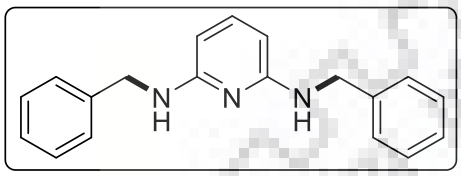
Following the general procedure B, the title product was obtained as a colourless solid (53% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 5.0 Hz, 1H), 7.36 – 7.29 (m, 1H), 6.50 (dd, J = 6.5, 5.7 Hz, 1H), 6.38 (d, J = 8.4 Hz, 1H), 5.89 (s, br, 1H), 4.66 (s, br, 1H), 3.21 (d, J = 6.9 Hz, 2H), 3.14 (s, 2H), 0.89 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 147.1, 137.6, 112.6, 109.3, 67.5, 48.7, 37.4, 22.9; HRMS (ESI): Calculated for $[C_{10}H_{17}N_2O]^+$ 181.1335; Found 181.1337.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(pyridin-2-yl)ethane-1,2-diamine (44)** [27]:



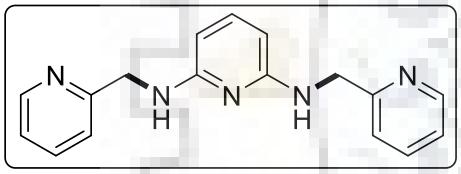
Following the general procedure B, the title product was obtained as a pale brown solid (70% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (ddd, J = 4.3, 2.6, 1.7 Hz, 1H), 8.27 – 8.18 (m, 1H), 7.83 – 7.70 (m, 1H), 7.67 – 7.56 (m, 1H), 5.61 (s, br, 1H), 4.20 – 4.13 (m, 2H), 2.65 – 2.59 (m, 2H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 136.0, 128.7, 126.6, 123.1, 57.5, 45.3, 31.3.

***N*^{2},*N*^{6}-Dibenzylpyridine-2,6-diamine (45)** [14,28]:



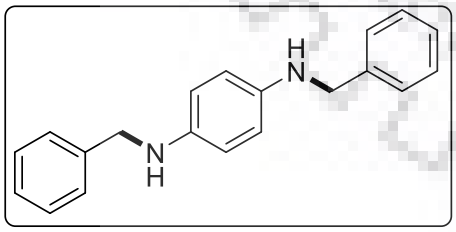
Following the general procedure C, the title product was obtained as a colourless solid (86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (q, J = 8.1 Hz, 8H), 7.29 – 7.18 (m, 3H), 5.74 (dd, J = 7.9, 1.0 Hz, 2H), 4.70 (s, br, 2H), 4.45 (d, J = 5.9 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 139.8, 139.3, 128.6, 127.6, 127.2, 95.2, 46.4; HRMS (ESI): Calculated for $[C_{19}H_{20}N_3]^+$ 290.1652; Found 290.1643.

***N*^{2},*N*^{6}-Bis(pyridin-2-ylmethyl)pyridine-2,6-diamine (46)**



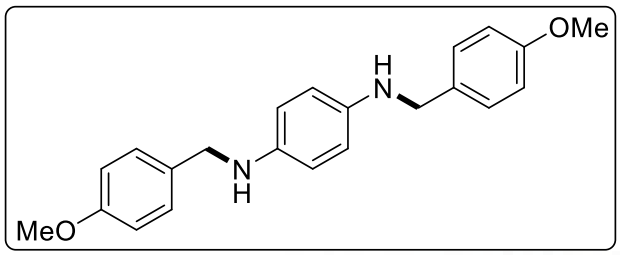
Following the general procedure C, the title product was obtained as a pale yellow solid (89% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 – 8.48 (m, 2H), 7.56 (td, J = 7.7, 1.8 Hz, 2H), 7.28 (d, J = 7.8 Hz, 2H), 7.17 – 7.08 (m, 3H), 5.74 (d, J = 7.9 Hz, 2H), 5.34 (s, br, 2H), 4.55 (d, J = 5.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 157.8, 149.2, 139.0, 136.6, 122.1, 121.7, 95.7, 47.5; HRMS (ESI): Calculated for $[C_{17}H_{18}N_5]^+$ 292.1557; Found 292.1542.

***N*^{1},*N*^{4}-Dibenzylbenzene-1,4-diamine(47)** [14,28]:



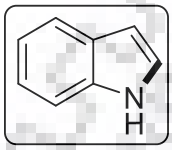
Following the general procedure C, the title product was obtained as a pale yellow solid (78% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dt, J = 12.8, 7.4 Hz, 8H), 7.31 – 7.24 (m, 2H), 6.58 (s, 4H), 4.27 (s, 4H), 3.63 (s, br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 140.0, 128.7, 127.7, 127.2, 127.2, 114.8, 49.7; HRMS (ESI): Calculated for $[C_{20}H_{21}N_2]^+$ 289.1699; Found 289.1747.

***N*^{1},*N*^{4}-Bis(4-methoxybenzyl)benzene-1,4-diamine (48)** [28]:



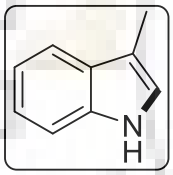
Following the general procedure C, the title product was obtained as a pale yellow solid (69% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.5 Hz, 4H), 6.87 (d, J = 8.6 Hz, 4H), 6.57 (s, 4H), 4.18 (s, 4H), 3.80 (s, 6H), 3.45 (s, br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 140.8, 131.9, 129.1, 129.0, 114.9, 114.0, 55.4, 49.2; HRMS (ESI): Calculated for $[C_{22}H_{24}N_2O_2]^+$ 349.1911; Found 349.1937.

1*H*-Indole (49) [21]:



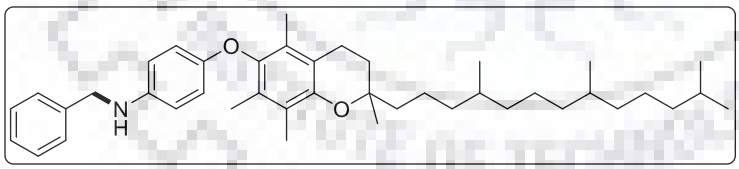
Following the general procedure D, the title product was obtained as a colourless solid (71% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, br, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.21 – 7.16 (m, 1H), 7.14 – 7.06 (m, 2H), 6.53 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 128.0, 124.4, 122.1, 120.9, 120.0, 111.3, 102.7.

3-Methyl-1*H*-indole (50) [29]:



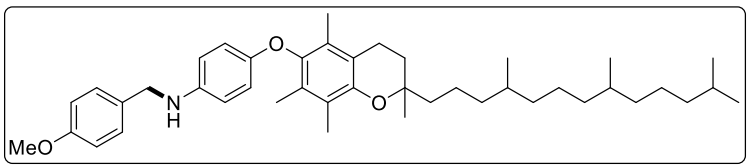
Following the general procedure D, the title product was obtained as a colourless solid (80% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, br, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.17 (dd, J = 11.1, 4.0 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 6.96 (d, J = 0.4 Hz, 1H), 2.33 (s, 3H).

***N*-Benzyl-4-((2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl)oxy)aniline (51)**



Following the general procedure A, the title product was obtained as a pale yellow oil (73% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dt, J = 15.0, 7.3 Hz, 4H), 7.30 – 7.24 (m, 1H), 6.57 (dd, J = 22.0, 9.0 Hz, 4H), 4.25 (s, 2H), 3.74 (s, br, 1H), 2.59 (t, J = 6.7 Hz, 2H), 2.11 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.87 – 1.75 (m, 2H), 1.66 – 1.48 (m, 4H), 1.47 – 1.36 (m, 4H), 1.32 – 1.23 (m, 10H), 1.18 – 1.04 (m, 6H), 0.86 (dd, J = 9.2, 5.3 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 148.5, 144.0, 142.4, 139.7, 128.7, 128.5, 127.8, 126.6, 123.2, 117.8, 115.4, 114.3, 114.2, 75.0, 49.5, 39.5, 37.6, 37.5, 37.4, 37.4, 37.4, 32.9, 32.8, 32.4, 28.1, 24.9, 24.5, 24.0, 22.8, 22.7, 19.9, 19.8, 19.7, 13.0, 12.1, 11.9; HRMS (ESI): Calculated for $[C_{42}H_{62}NO_2]^+$ 612.4775; Found 612.4804.

_N_-(4-Methoxybenzyl)-4-((2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl)oxy)aniline (52)



Following the general procedure A, the title product was obtained as a pale yellow oil (68% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H), 6.86 (d, J = 8.6 Hz, 2H), 6.56 (dd, J = 21.3, 9.0 Hz, 4H), 4.17 (s, 2H), 3.79 (s, 3H), 2.59 (t, J = 6.8 Hz, 2H), 2.10 (s, 3H), 2.01 (s, 3H), 1.97 (s, 3H), 1.87 – 1.73 (m, 2H), 1.62 – 1.47 (m, 4H), 1.42 – 1.32 (m, 4H), 1.29 – 1.22 (m, 10H), 1.17 – 1.03 (m, 6H), 0.85 (t, J = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 151.5, 148.5, 144.0, 131.7, 129.1, 129.0, 128.5, 126.6, 123.1, 117.8, 115.4, 114.2, 114.1, 75.0, 55.4, 48.9, 40.1, 39.5, 37.6, 37.5, 37.4, 32.9, 32.8, 31.4, 28.1, 24.9, 24.5, 23.9, 22.8, 22.7, 20.7, 19.9, 19.8, 19.7, 13.0, 12.1, 11.9; HRMS (ESI): Calculated for $[C_{43}H_{64}NO_3]^+$ 642.4881; Found 642.4846.

[2.7] Spectra of selected compounds

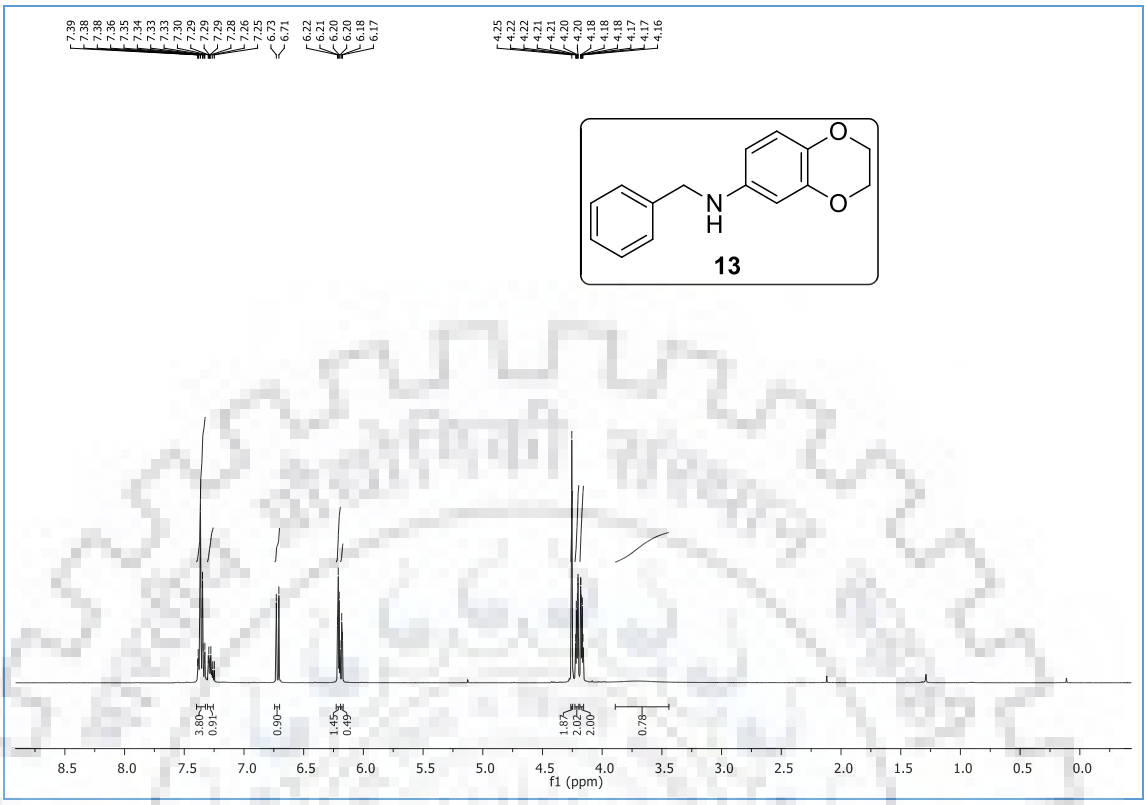


Figure 2a: ^{1}H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound 1**3**

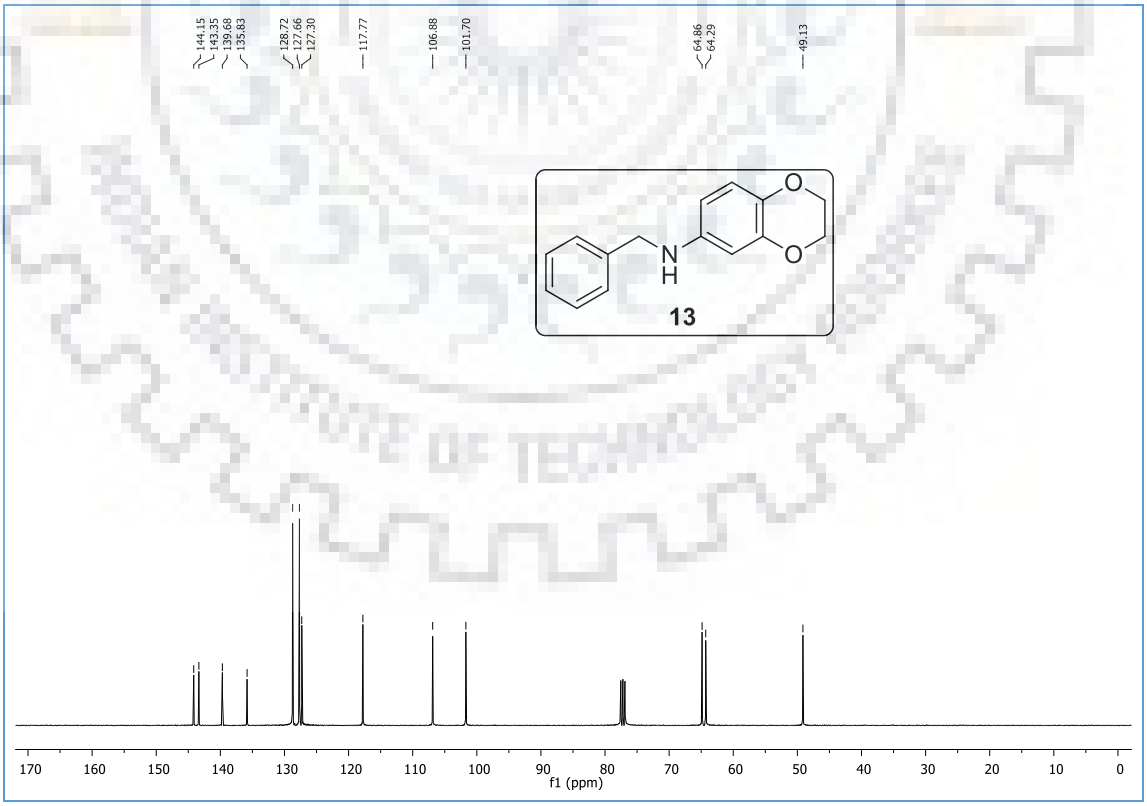


Figure 2b: ^{13}C NMR ($CDCl_3$, 100 MHz) Spectrum of Compound 1**3**

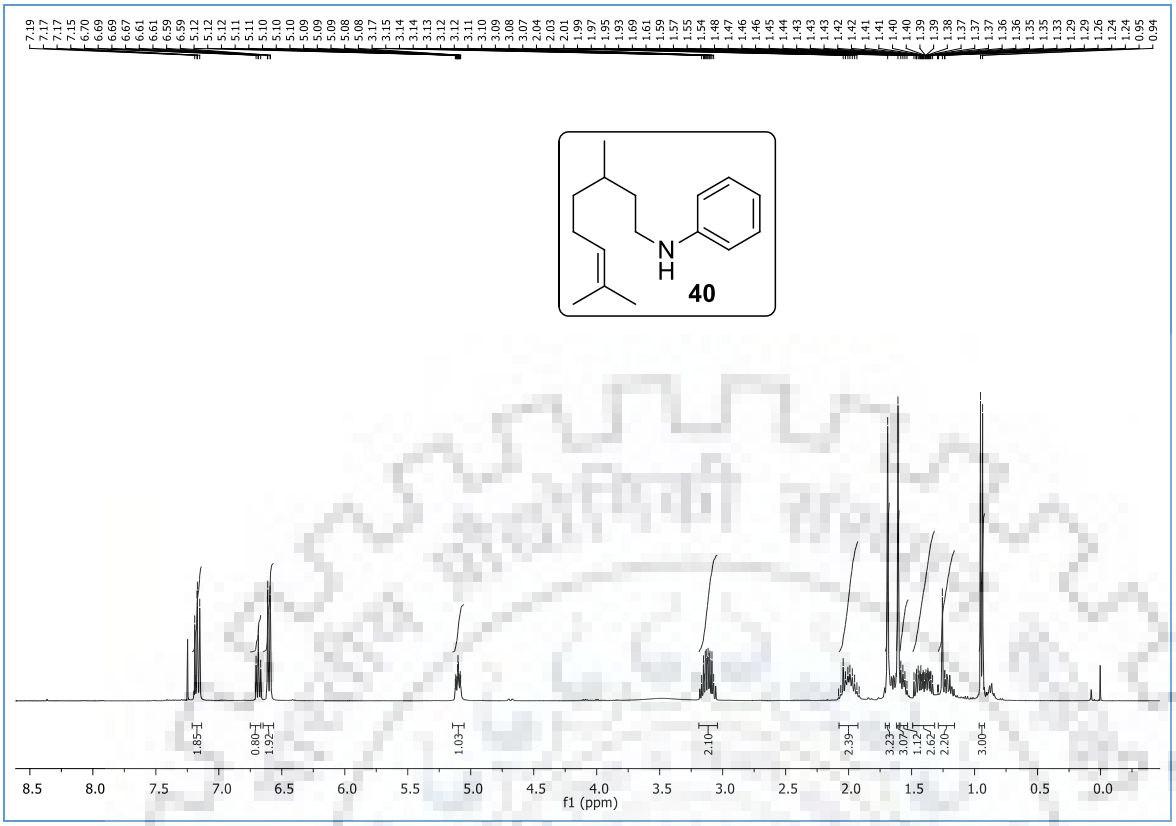


Figure 3a: ^{1}H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **40**

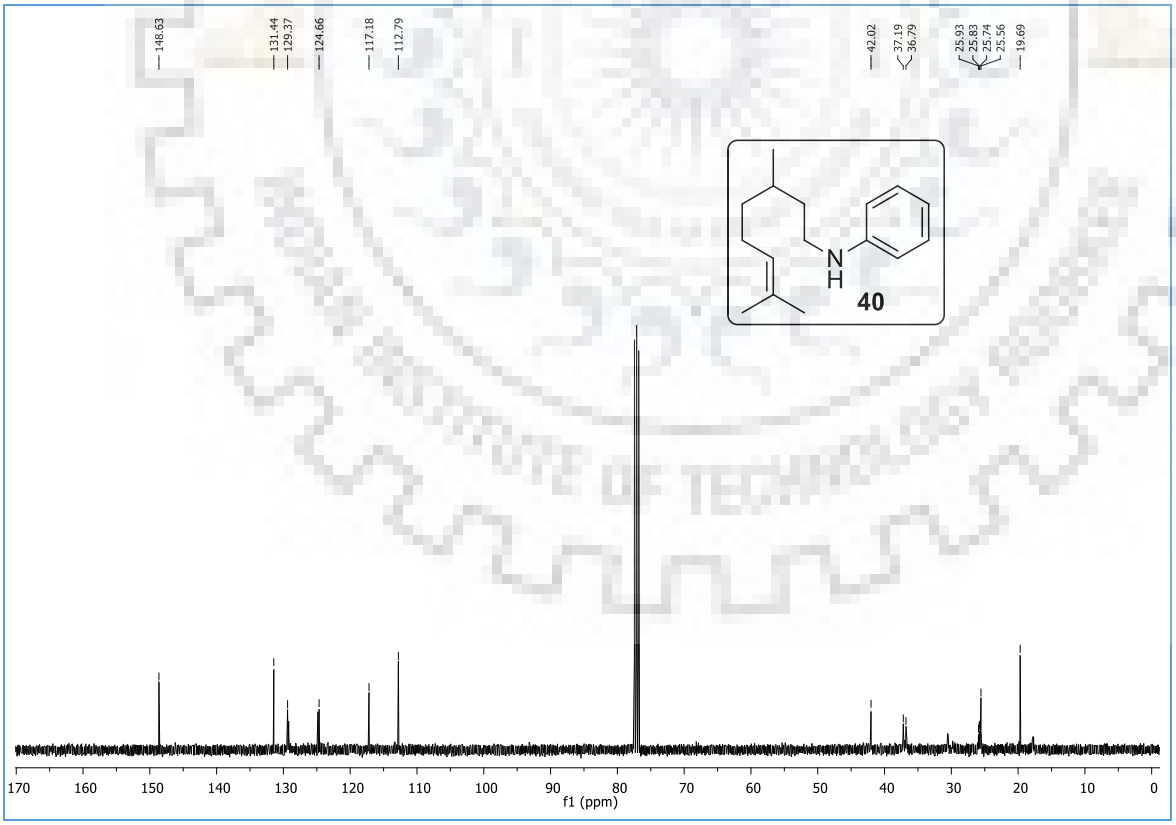


Figure 3b: ^{13}C NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **40**

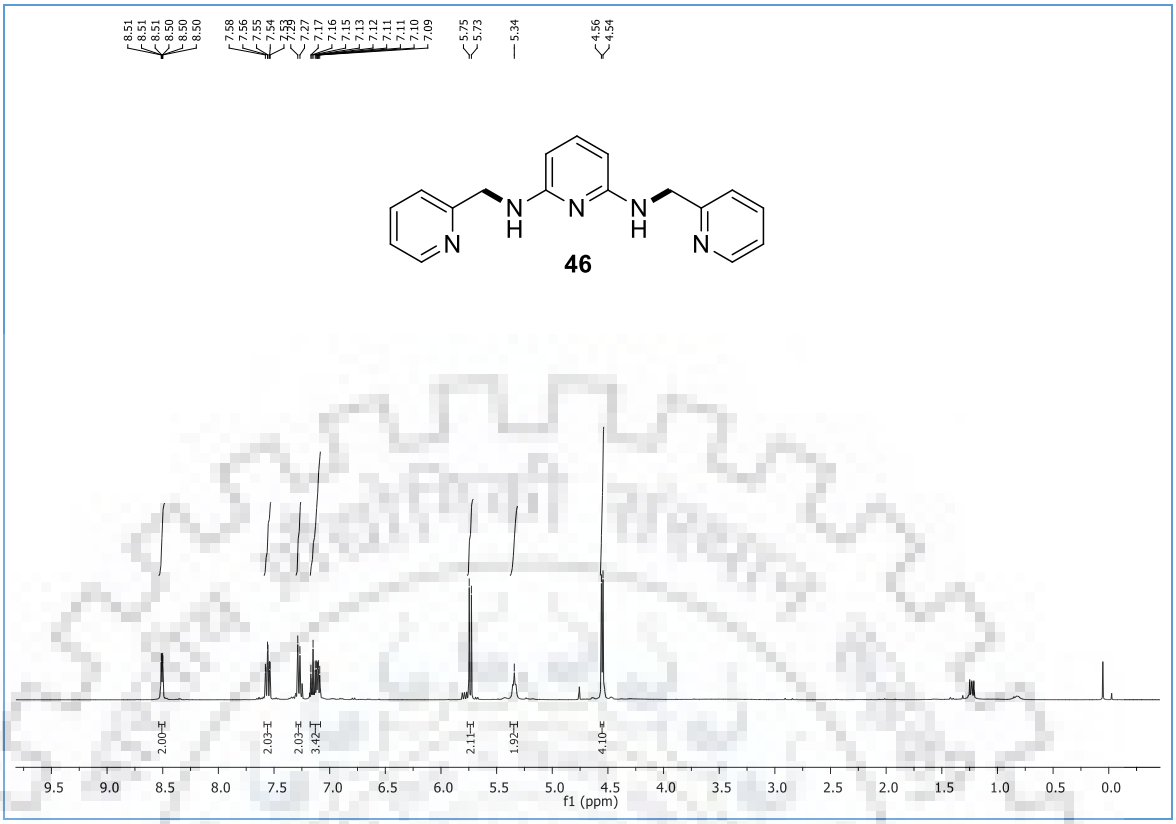


Figure 4a: ^{1}H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **40**

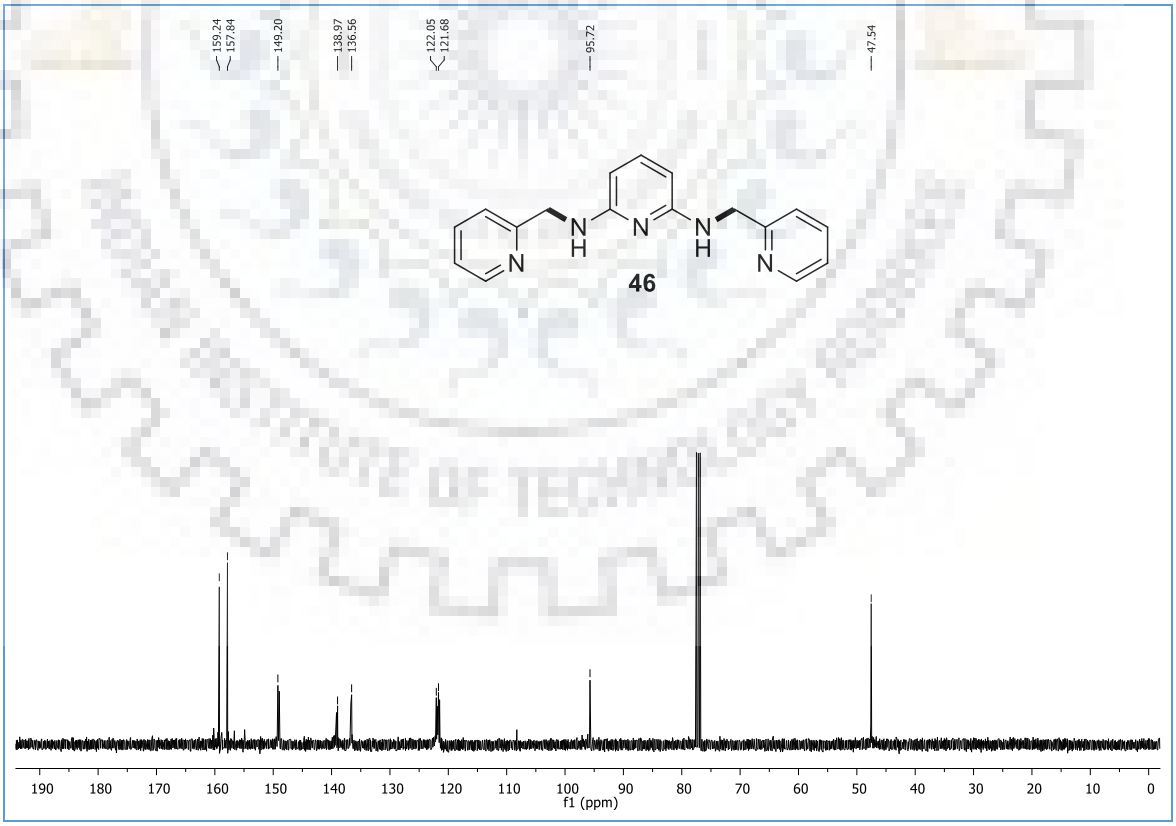


Figure 4b: ^{13}C NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **46**

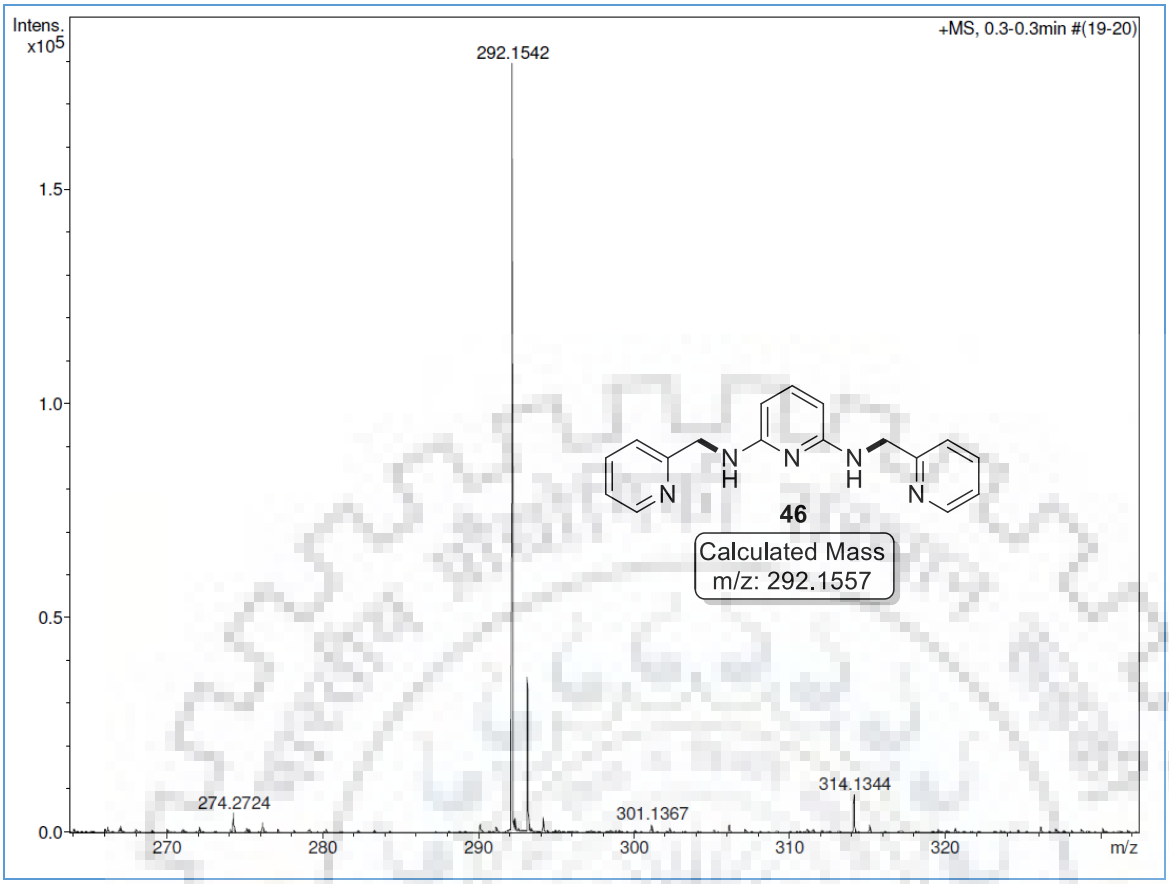


Figure 4c: HRMS (ESI) Spectrum of Compound **40**

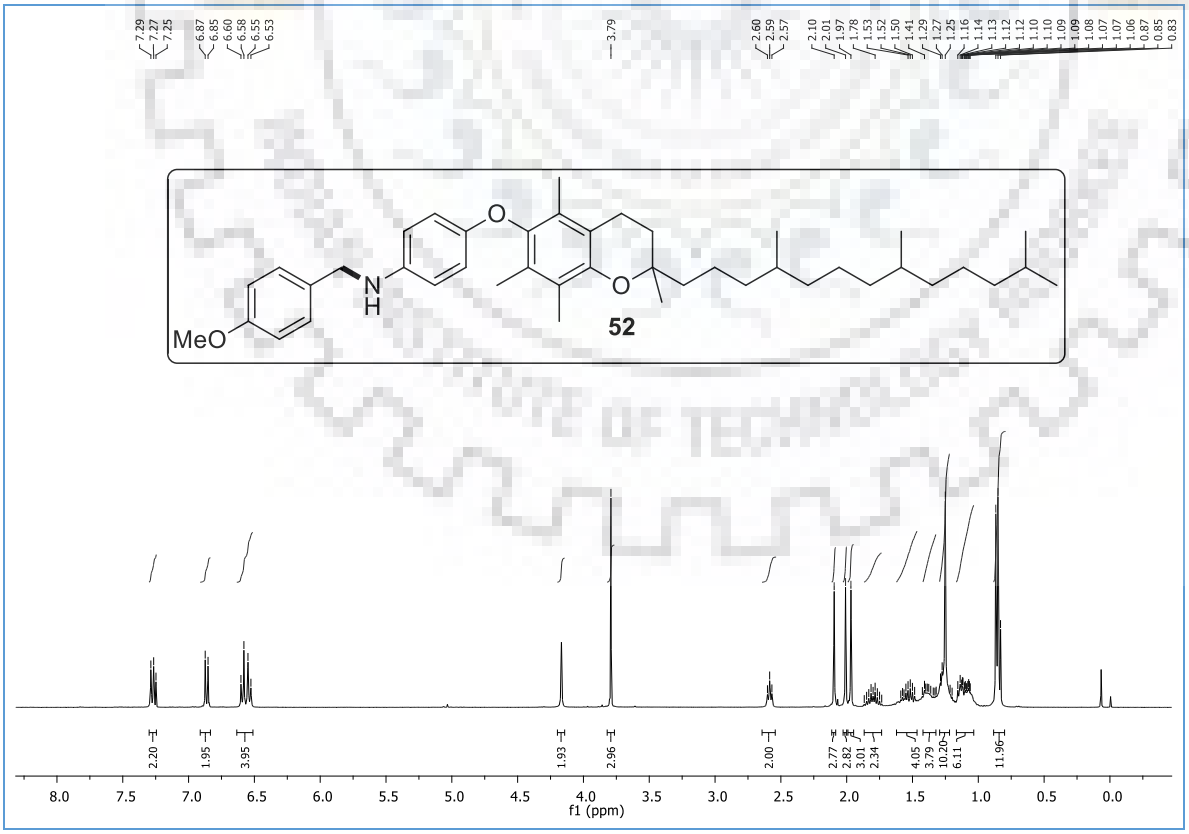


Figure 5a: ^{1}H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **52**

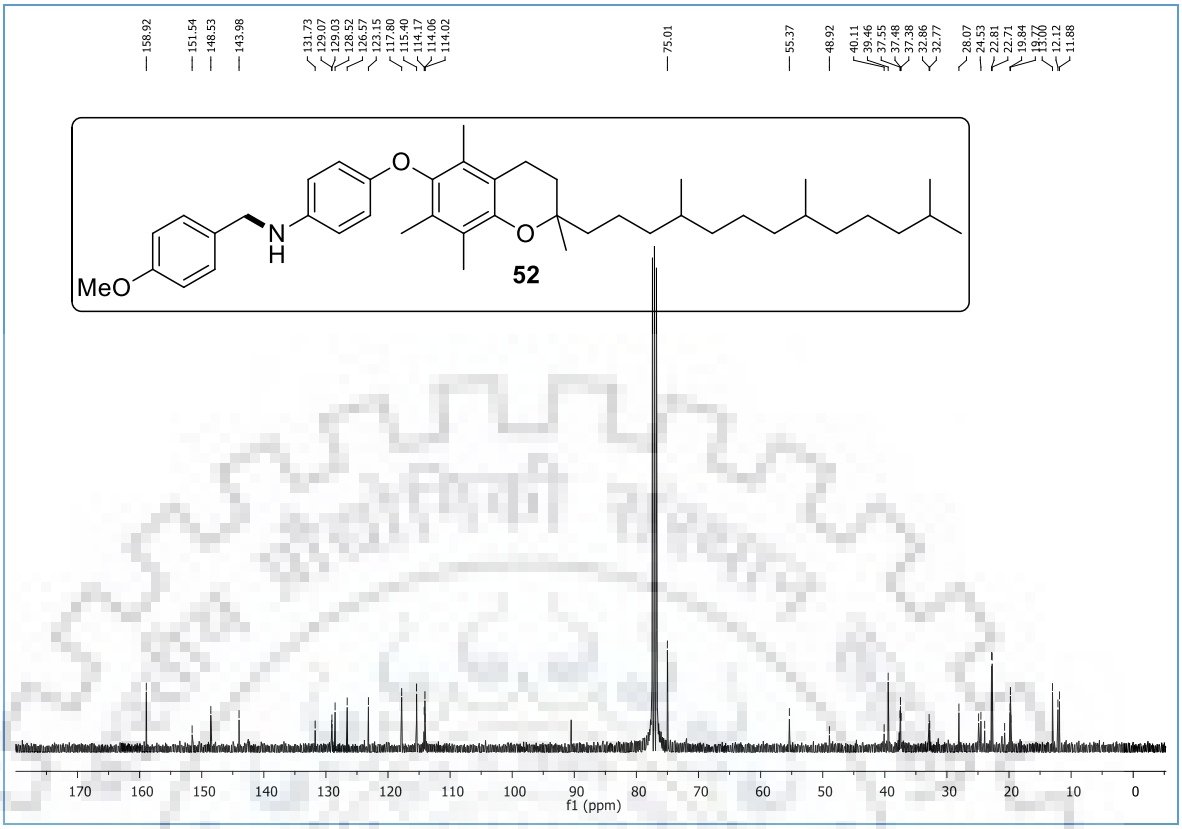


Figure 5b: ^{13}C NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **52**

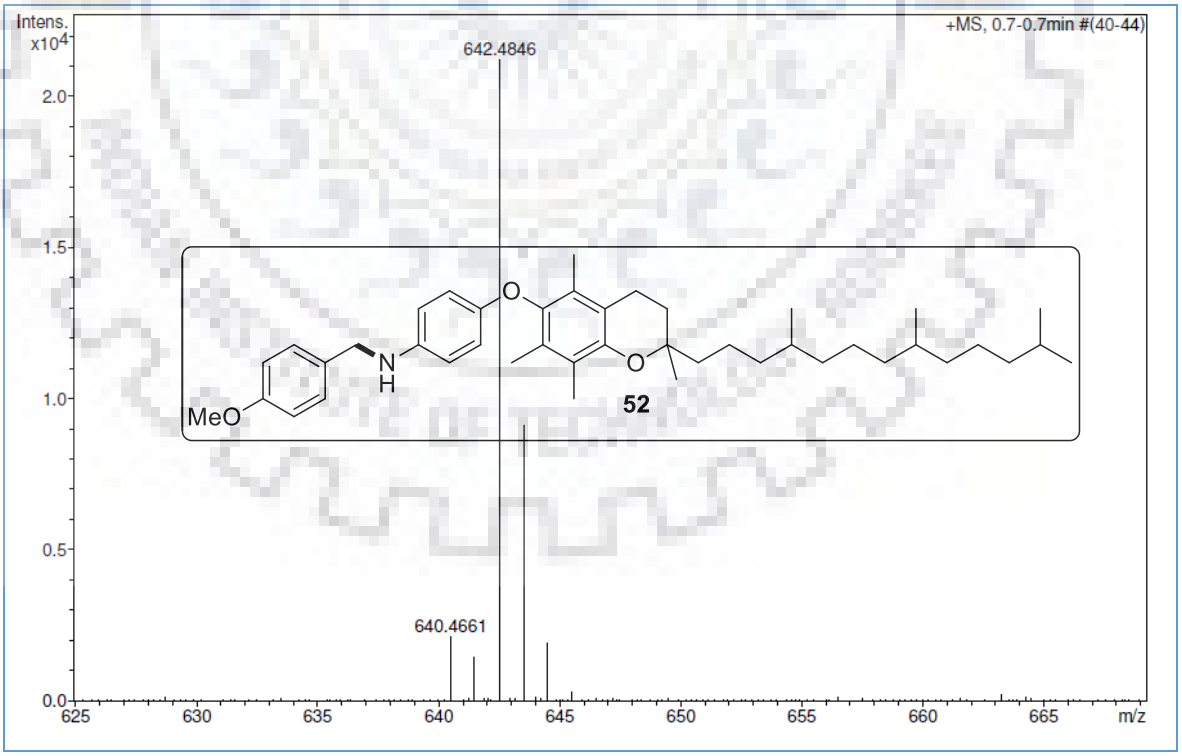
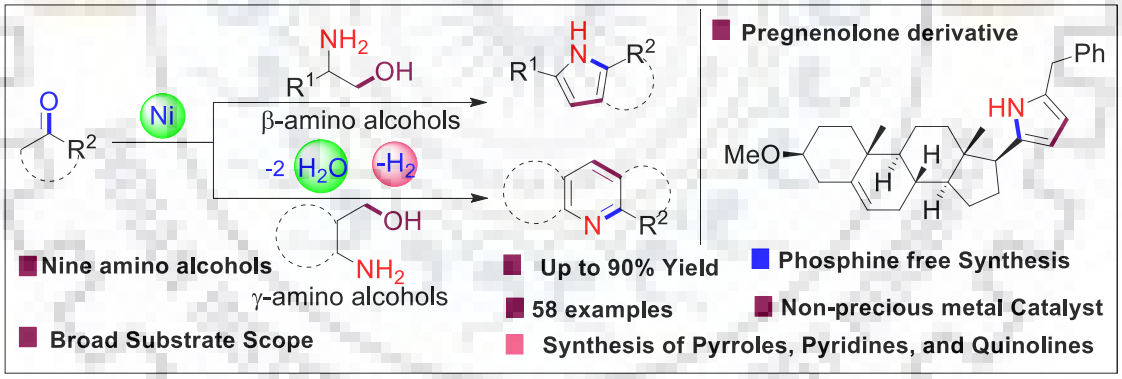


Figure 5c: HRMS Spectrum of Compound **52**

Chapter-3: Section-A: Nickel-catalyzed intermolecular cyclisation for the synthesis of five and six membered N-heterocycles

Owing to the great demand for synthesis of N-heterocycles, development of new reactions that utilize renewable resources and convert them into key chemicals using non-precious base metal-catalysts is highly desirable. Here we disclosed a sustainable Ni-catalyzed dehydrogenative approach for pyrroles, pyridines and quinolines synthesis employing β- and γ-amino alcohols with ketones via C-N and C-C bond formations in a tandem fashion. A variety of aryl, hetero-aryl and alkyl ketones having free amine, halides, alkyl, alkoxy, alkenes, activated benzyl and pyridine moiety converted into synthetically interesting 2,3 and 2,3,5 substituted bicyclic as well as tricyclic N-heterocycles in up to 90% yields. As a special highlights, we demonstrated an interesting pyrrole derivative employing intermolecular cyclisation of steroid hormone with phenylalaninol.



Green Chem. **2018**, *20*, 2250–2256

Chapter 3 Section A: Ni-Catalyzed Intermolecular Cyclization for the Synthesis of Five and Six Membered *N*-Heterocycles

[3A.1] Introduction:

Pyrroles and their derivatives are valuable intermediates in the synthesis of bioactive natural products, functional materials and as ligands in catalysis. Poly-pyrroles have significant applications as conducting polymers in batteries, solar cell devices and in material chemistry and extensively used in pharmaceuticals (Figure 1).[1] Well established classical methodologies for pyrrole synthesis are Knorr, Paal–Knorr and Hantzsch reactions and have been developed for the synthesis of functionalized pyrroles. Although these protocols are very efficient but most of them suffers from several problems, such as poor substrate availability, stoichiometric waste generation and multi-step transformations are key issues.[2] Unfortunately, synthesis of pyrroles from easily available biomass derived sustainable feedstocks is a challenging task and are rarely explored. Notably, substantial importance of pyrrole derivatives and great demand for aromatic heterocycles that utilised fully or partially renewable resources are highly desirable.[2,3] Importantly, such dehydrogenative transformations of alcohols often limited to the construction of C-C and C-N bonds *via* hydrogen auto-transfer approach.[4] However, application of hydrogen transfer methodology for the construction of aromatic *N*-heterocycles employing N-H/C-H coupling in a tandem fashion is scarcely reported. However, in recent years significant progress has been made for pyrrole synthesis employing acceptorless dehydrogenative couplings (ADCs) of alcohols using precious and non-precious metals based on homogeneous as well as heterogeneous catalyst.

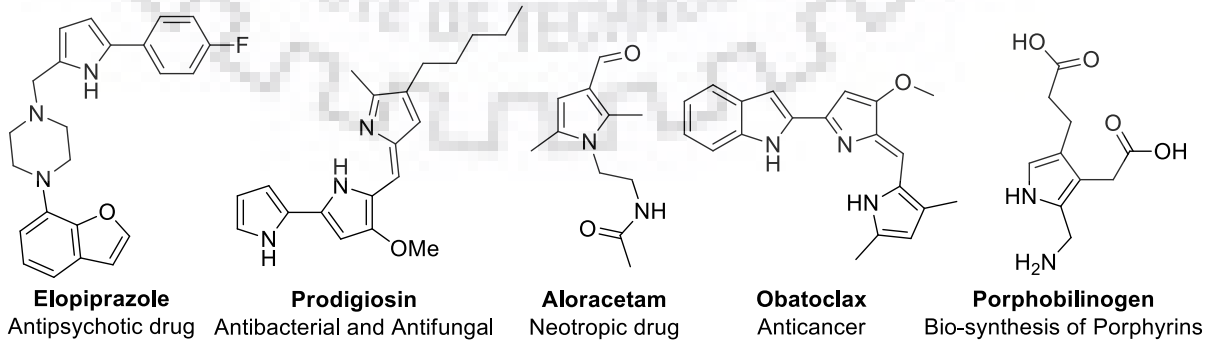
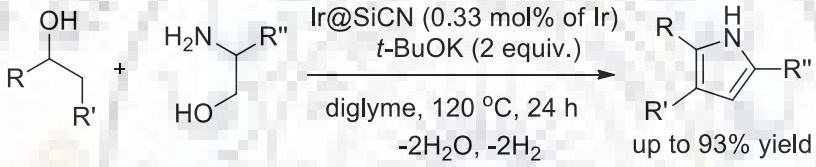


Figure 1: Selected examples of important pharmaceuticals having pyrrole moiety

Present chapter deals with the development of sustainable processes for the synthesis of pyrroles using non-precious metal-catalysts. Further, herein, we have also discussed a brief literature overview for the pyrrole synthesis demonstrated recently using non-precious metal catalysts in combination with renewable alcohols. A more detailed discussions of pyrrole synthesis have already been presented in Chapter 1.

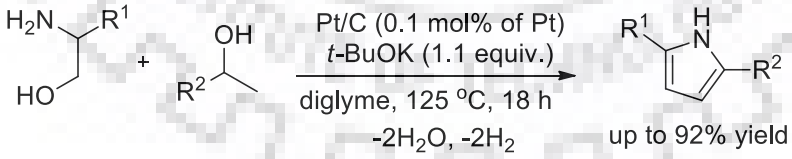
Brief literature survey for pyrrole synthesis:

Herein we are going to discuss a few selective metal-catalyzed processes for pyrrole synthesis after Chapter 1. For instance, a recent report by Kempe and co-workers using Ir-based nano-composite as heterogeneous catalyst has been developed for the synthesis of a series of substituted pyrroles. Intermolecular cyclization of secondary alcohols and 1,2-diamino alcohols using SiCN supported recyclable heterogeneous catalysts resulted in up to 93% yield of pyrroles under mild condition (Scheme 1).[5]



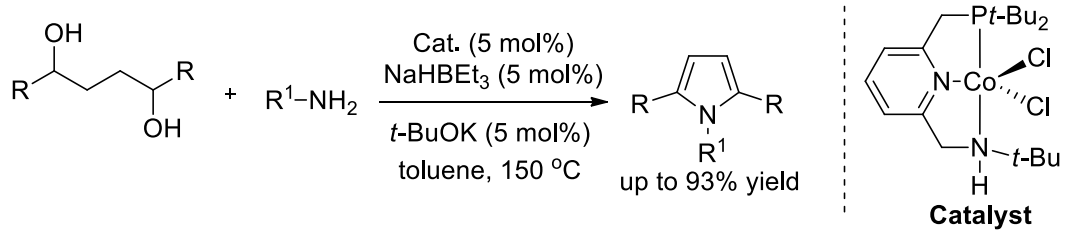
Scheme 1: Synthesis of pyrroles using Ir-based heterogeneous catalyst

In 2016, Shimizu et. al. demonstrated the heterogeneous Pt/C catalyzed direct synthesis of 2,5-disubstituted pyrroles using 1,2-aminoalcohols and secondary alcohols. Intermolecular cyclization as well as acceptorless dehydrogenation couplings of alcohols furnished the desired pyrroles in up to 92% yield with excellent catalytic turn over number (Scheme 2).[6]



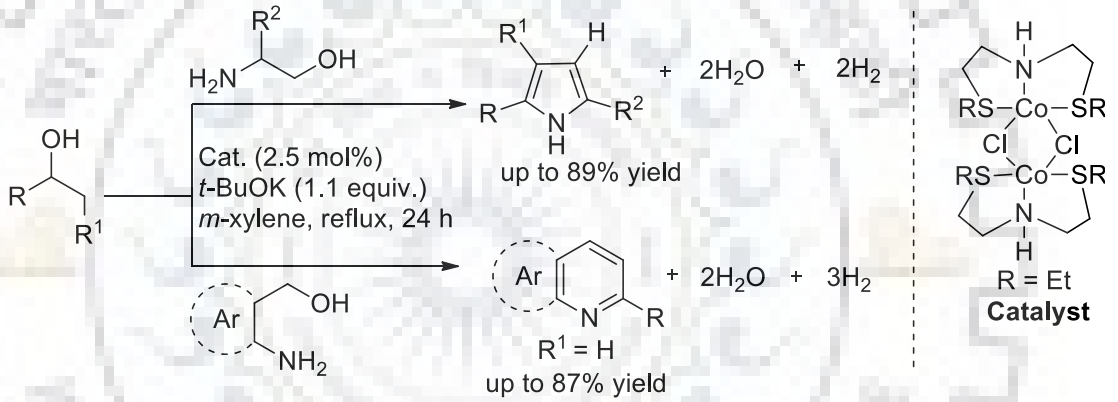
Scheme 2: Pt/C-catalyzed synthesis of pyrroles

The first non-precious Co-based pincer catalyst was developed by Milstein and co-workers for the synthesis of pyrroles following dehydrogenative coupling of diols and amines. The established catalytic protocol employed to a wide range of primary alkyl amines, benzyl amines as well as aniline derivatives in combination with primary and secondary diols (Scheme 3).[7]



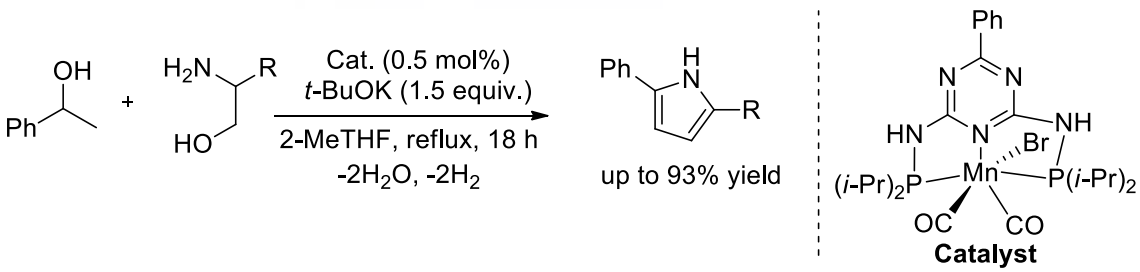
Scheme 3: Synthesis of pyrroles using cobalt-pincer catalyst

Recently, Balaraman and co-workers reported the intermolecular cyclization of unprotected amino-alcohols with secondary alcohols for the synthesis of pyrroles, pyridines, quinolines and pyrazine using a novel molecular defined ligand free SNS-cobalt(II) catalyst. These acceptorless dehydrogenative coupling generates hydrogen gas and water as the sole by-product rendering the process sustainable (Scheme 4).[8]



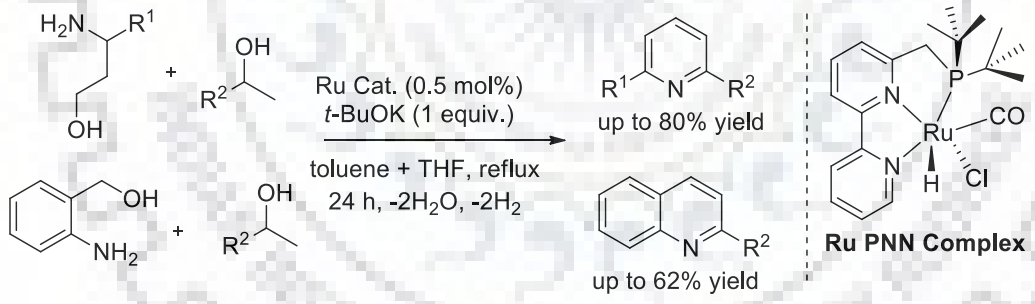
Scheme 4: Synthesis of *N*-heterocycles using SNS Cobalt(II)-catalyst

Very recently, Kempe group independently demonstrated the synthesis of highly efficient Mn-based NNP-pincer ligands and explored their catalytic efficiency for the pyrrole synthesis using secondary alcohols and amino alcohols under mild conditions. Low catalyst loading with broad scope as well as excellent functional group tolerance are the key highlights and resulted up to 93% yield of *N*-heterocycles (Scheme 5).[9]



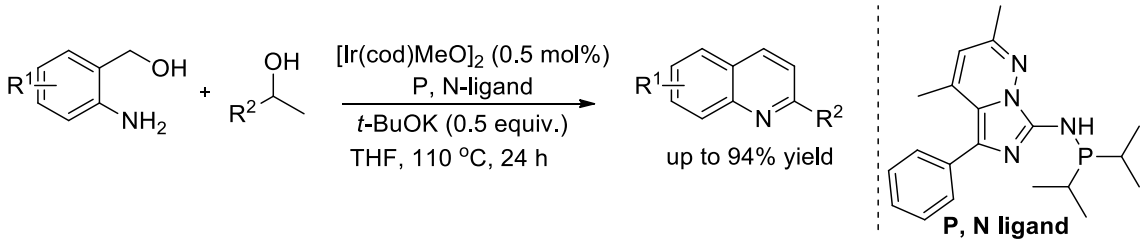
Scheme 5: Synthesis of pyrroles using Mn-pincer catalyst

Apart from the synthesis of pyrroles other members of *N*-heterocycles class, such as, quinolines and pyridines derivatives are also highly important because of their wide range of applications in pharmaceutical industries and in drug development. These *N*-heterocycles motifs show potential biological activities, such as, anti-inflammatory, anti-malarial, neuro-protection, and anti-parkinson and so on. Well established classical processes for their synthesis are; Skraup, Combes, Doebner-von Miller, Conrad-Limpach and Pfitzinger quinoline synthesis are well documented in literature.[10] However, often limited with harsh reaction conditions, low chemo-selectivity, multi-step synthesis and low product yields demands a more sustainable and higher yielding process. In this direction, recently there are potential drives in catalysis for the synthesis of quinolines following a more sustainable version of Friedlander annulation. Application of acceptorless dehydrogenative coupling of alcohols and amino alcohols could be a potential alternative for the intermolecular cyclization of C-C and C-N for *N*-heterocycles is highly demanding. In this direction, Milstein and co-workers described the synthesis of pyridines and quinolines *via* acceptorless dehydrogenative coupling of γ-amino alcohols with secondary alcohols. The application of bipyridyl-based ruthenium complex resulted the formation of six-membered *N*-heterocycles in moderate yields (Scheme 6).[11]



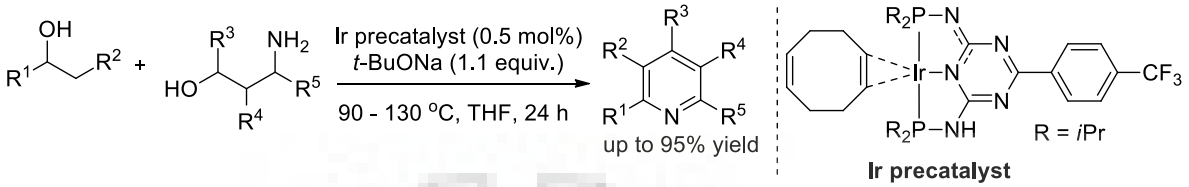
Scheme 6: Synthesis of pyridines and quinolines using Ru-PNN complex

Thereafter, they have established an Ir-catalyzed system for the synthesis of 2-substituted quinolines using 2-aminobenzyl alcohol with primary as well as secondary alcohol derivatives (Scheme 7).[12]



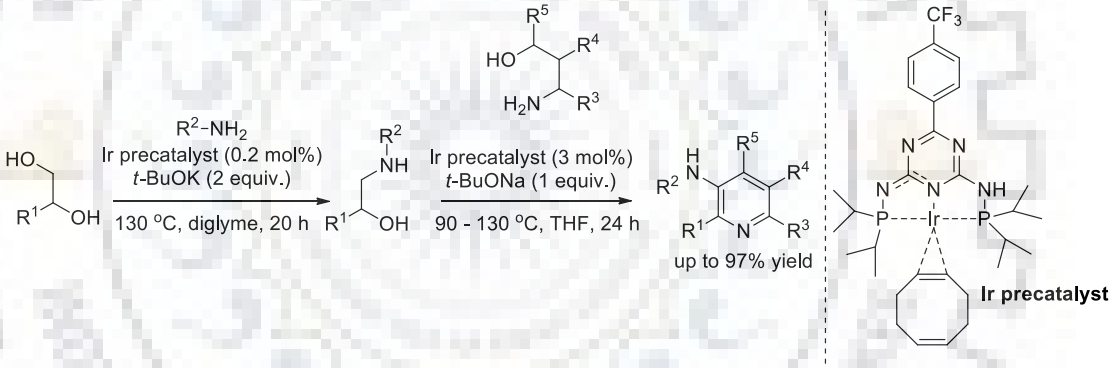
Scheme 7: Synthesis of quinolines using Ir-based complex

In an another report, they have also demonstrated the catalytic efficiency of newly developed Ir-based NNP-pincer catalyst for the synthesis of 2,4/2,5/2,6- as well as 3,5-disubstituted pyridines with excellent isolated yields (Scheme 8).[13]



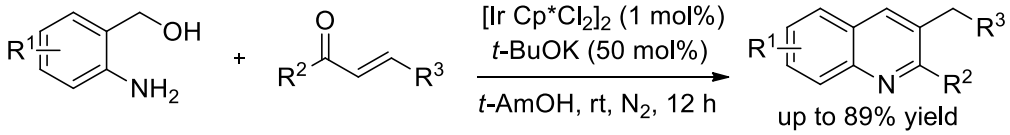
Scheme 8: Synthesis of pyridines using Ir-based precatalyst

Next, they have extended this Ir-NNP pincer catalyst system for multi-component synthesis of 3-amino pyridines. In the first step, amination of diols resulted the formation of β-amino alcohols, followed by intermolecular condensation and dehydrogenation with γ-amino alcohols furnished the desired 3-amino pyridines (Scheme 9).[14]



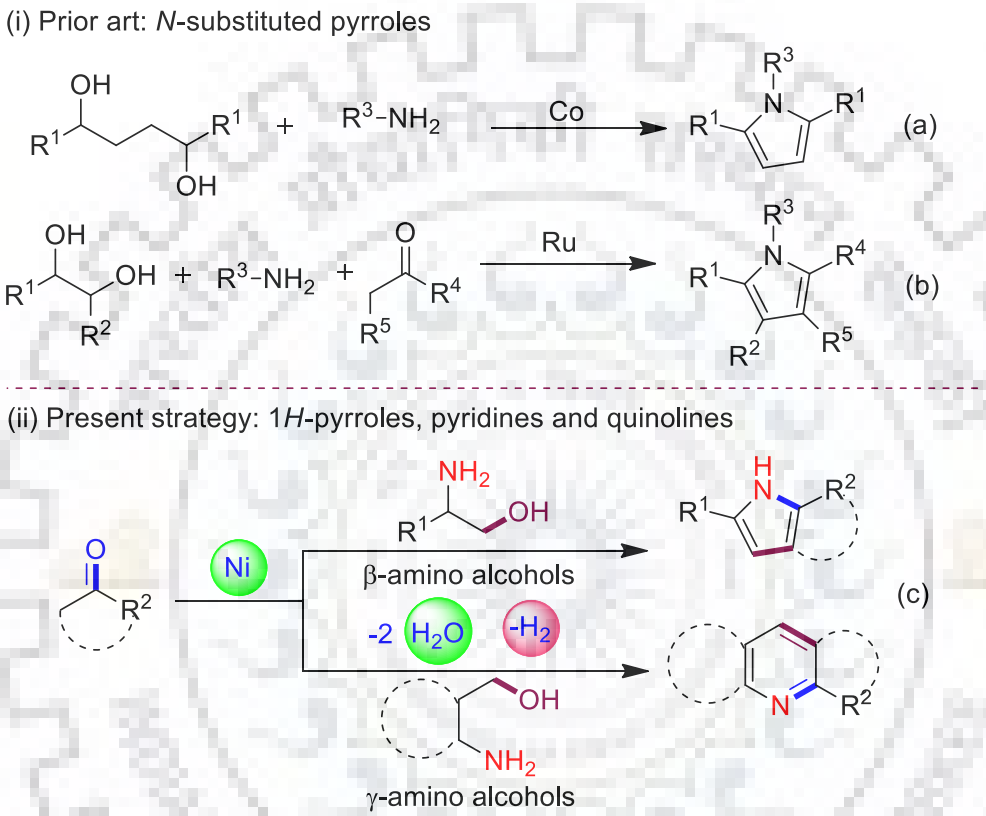
Scheme 9: Synthesis of 3-amino pyridines using Ir-precatalyst

Very recently, Ling and co-workers demonstrated a new Ir-catalyzed method for the synthesis of substituted quinolines using a combination of easily available enones with 2-aminobenzyl alcohols. Mechanistic investigation proved that, the catalytic process involves the hydrogen-transfer coupling and enables an efficient atom economic system with broad substrate scope under relatively mild conditions (Scheme 10).[15]



Scheme 10: Synthesis of quinolines using Ir-catalyst

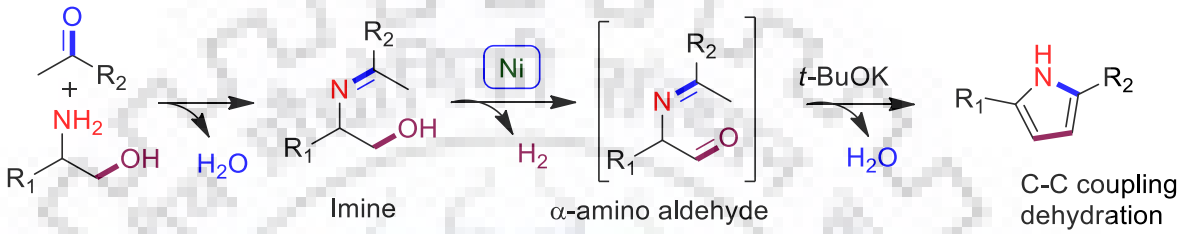
Herein, we have developed a sustainable and inexpensive Ni-catalyzed protocol for the construction of pyrroles from readily available β-amino alcohols with ketones as well as synthesis of pyridines and quinolines from intermolecular cyclization of γ-amino alcohols with ketones to avoid the use of hazardous alkylating agents. [4] Till date, nickel-catalyzed pyrrole synthesis only limited with activated substrates, such as, annulation of azides with alkynes/allenes or aryl aldehydes as well as enone alkyne reductive coupling.[16]



Scheme 11: (i) Metal-catalyzed dehydrogenative coupling for pyrrole synthesis (ii) Nickel-catalyzed sustainable synthesis of pyrroles, pyridines and quinolines

In general, strong binding and poor leaving ability of hydroxyl group limits its application towards nickel-catalyzed transformations.[17] To overcome these limitations, recently, for the first time we established an efficient Ni-catalyzed protocol for selective alkylation of amines and intra-molecular cyclization to indole derivatives using 2-(2-aminophenyl)ethanol. [18] The catalytic system is tolerant to hydroxyl and amino group. Thus, inspired by this promising results, we realised that unprotected aliphatic amino alcohols could be used to construct the *N*-heterocycles. Therefore, we explored nickel-catalyzed direct pyrrole synthesis starting from readily abundant β-amino alcohols with ketones (Scheme 11, c).

Based on our previous observations for the acceptorless dehydrogenation of alcohols to aldehydes using nickel catalysts, we anticipated that, α-amino aldehyde could be formed *in situ* from β-amino alcohol by nickel-catalyst, followed by sequential dehydration, alkylation and base-catalyzed condensation lead to the construction of substituted pyrroles in one pot operation (Scheme 12). To our delight, herein we established the first base metal-catalyzed reaction of β-amino alcohols with ketones to substituted pyrroles in a tandem fashion *via* C-C and C-N bond formations.



Scheme 12: Proposed mechanism for Ni-catalyzed tandem synthesis of pyrroles through intermolecular C-C and C-N bond formation

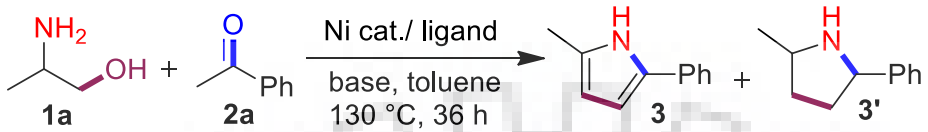
[3A.2] Results and discussion:

Notably, it was observed that, β-amino alcohol is highly prone to undergoes self-condensation to substituted pyrazine and resulted lower product yield of pyrroles. Hence, still there is a need for more selective and improve catalytic protocol. Nevertheless, to explore the possibilities for pyrrole synthesis under nickel catalysis, initially we envisioned following key challenges: (i) selective control to reduced product **3'**, (ii) minimize the self-condensation of β-amino alcohol **1a** to 2,5-dimethyl-pyrazine and (iii) catalytic selectivity to control the base-catalyzed self-condensation of ketones.

To achieve this goal, primarily we investigated the model reaction between 2-aminopropane-1-ol **1a** and acetophenone **2a** using five different nickel precatalyst having oxidation states of Ni(0) and Ni(II) (Table 1, entries 1-5). However, a combination of $NiCl_2$/**L1** resulted only 30% selectivity of **3** along with reduced product **3'** (Table 1, entry 1). Next, influence of various steric and electronically different phosphine and nitrogen ligands **L2-L11** were tested (Table 2). Among these, bipyridine (bpy) ligand was proved to be efficient ligand for the pyrrole synthesis. However, best results were obtained with 10 mol% $NiCl_2$, 12 mol% bipyridine **L7**, 1 equiv. of *t*-BuOK and toluene as efficient solvent (Table 1, entry 6). Further we have studied the influence of different bases, such as, *t*-BuONa, *t*-BuOK, K_2CO_3,

Na_2CO_3, K_3PO_4 and Cs_2CO_3 as indicated in Table 3 (entries 1-6). However, only *t*-BuOK resulted 64% isolated yield of **3**, while, in case of *t*-BuONa we only observed 50% product conversion.

Table 1: Optimization studies for nickel-catalyzed pyrrole synthesis [a, b]

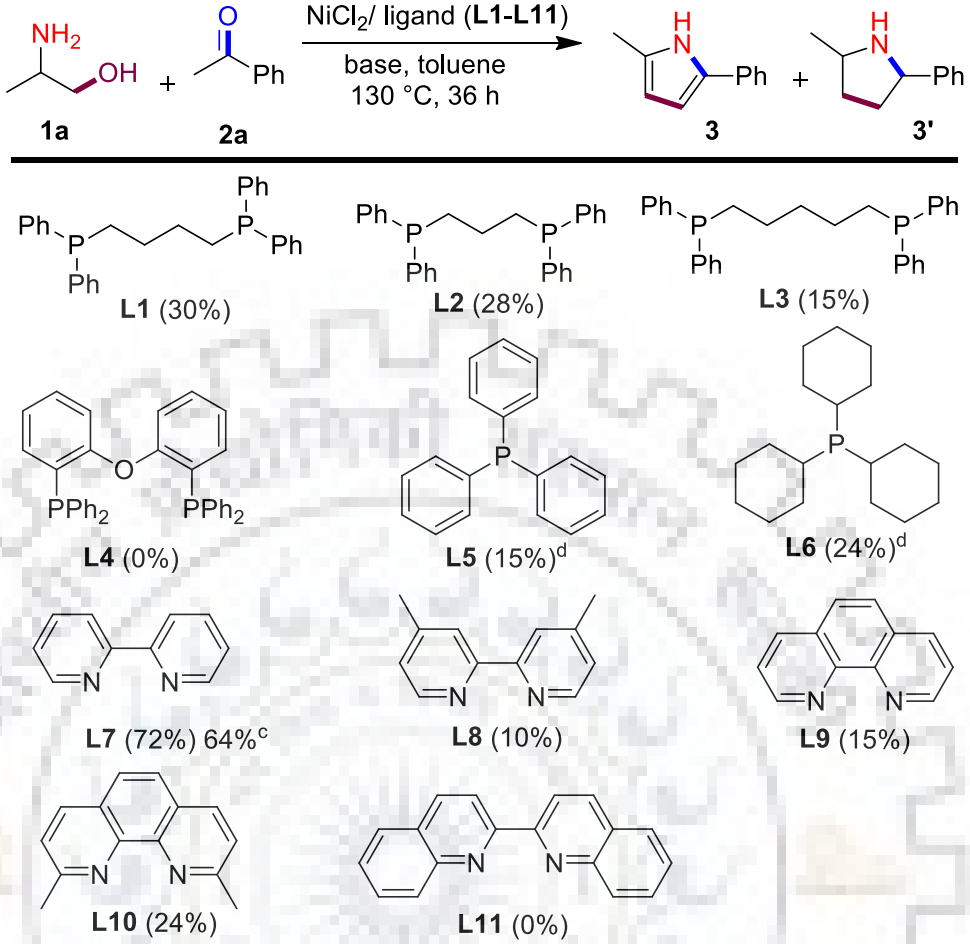


Entry	Catalyst	Ligand	Conv. (%)	
			3	**3'**
1	$NiCl_2$	**L1**	30	8
2	$NiBr_2$	**L1**	12	13
3	$Ni(acac)_2$	**L1**	18	9
4	$Ni(cod)_2$	**L1**	17	12
5	$NiCl_2$.DME	**L1**	25	0
6	**$NiCl_2$**	**L7**	**72(64)**	**0**
7[c]	$NiCl_2$	**L7**	50	0
8[d]	$NiCl_2$	**L7**	41	0
9[e]	$NiCl_2$	**L7**	29	0
10[f]	$NiCl_2$	**L7**	54	0
11[g]	$NiCl_2$	**L7**	42	0
12[h]	$NiCl_2$	**L7**	0	0
13[i]	-	-	5	0
14[j]	$NiCl_2$	**L7**	49	0
15[k]	$NiCl_2$	**L7**	36	0

[a] Unless specified, the reaction was carried out with **1a** (0.5 mmol), **2a** (1.0 mmol), Ni cat. (0.05 mmol), **L** (0.06 mmol), and *t*-BuOK (0.5 mmol) under an N_2 atmosphere at 130 °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] *t*-BuONa (0.5 mmol) was used. [d] 0.375 mmol of base was used. [e] 0.25 mmol of base was used. [f] $NiCl_2$ (0.0375 mmol) and **L7** (0.045 mmol) were used. [g] $NiCl_2$ (0.025 mmol) and **L7** (0.03 mmol) were used. [h] No base was used. [i] No catalyst was used. [j] Reaction was performed at 120 °C. [k] Reaction was performed at 110 °C.

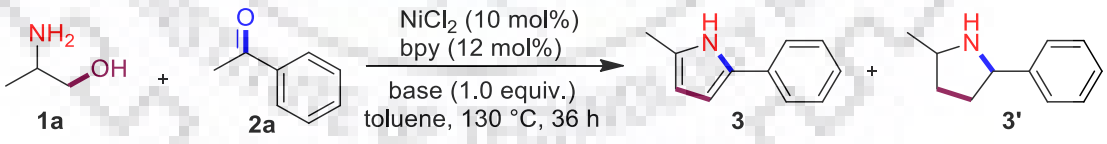
As expected, screening of different non-polar as well as polar solvents, such as, toluene, xylene, dioxane, DMA and DMF further did not improve the product yield and toluene was observed as the best solvent for pyrrole synthesis (Table 4, entries 1-5).

Table 2: Ligand screening for nickel-catalyzed pyrrole synthesis [a, b]



[a] Unless specified, the reaction was carried out with **1a** (0.5 mmol), **2a** (1.0 mmol), $NiCl_2$ (10 mol%), ligand (12 mol%), base (1.0 equiv.) under N_2 atmosphere at 130 °C in toluene (2.0 mL) for 36 h. [b] Conversion of **3** was determined by GC-MS. [c] Isolated yield. [d] Ligand (20 mol%) was used.

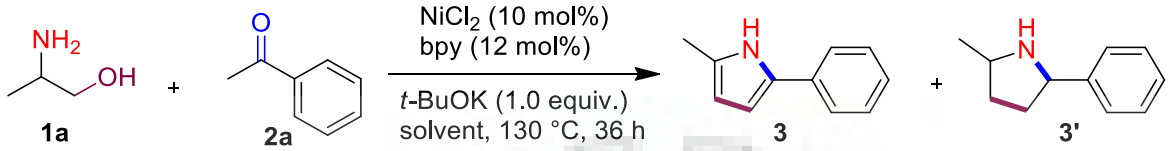
Table 3: Screening of Base [a]



Entry	Base	GC-MS Conversion (%)	
		3	**3'**
1.	*t*-BuONa	50	0
2.	*t*-BuOK	72 (64) [b]	0
3.	K_2CO_3	0	0
4.	Na_2CO_3	0	0
5.	K_3PO_4	0	0
6.	Cs_2CO_3	0	0

Reaction condition*:* [a] DL-Alaninol **1a** (0.5 mmol), acetophenone **2a** (1.0 mmol), $NiCl_2$ (10 mol%), bpy (12 mol%), base (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 130 °C in oil bath, 36 h reaction time. [b] Isolated yield.

Table 4: Screening of solvents [a]



Entry	Solvents	GC-MS Conversion (%)	
		3	**3'**
1.	Toluene	72 (64) [b]	0
2.	Xylene	31	3
3.	Dioxane	39	8
4.	DMA	14	10
5.	DMF	9	10

Reaction condition: [a] DL-Alaninol **1a** (0.5 mmol), acetophenone **2a** (1.0 mmol), $NiCl_2$ (10 mol%), bpy (12 mol%), *t*-BuOK (0.5 mmol), solvent (2.0 mL), Schlenk tube under N_2 atmosphere, 130 °C in oil bath, 36 h reaction time. [b] Isolated yield.

Table 5: Screening of base equivalents [a]

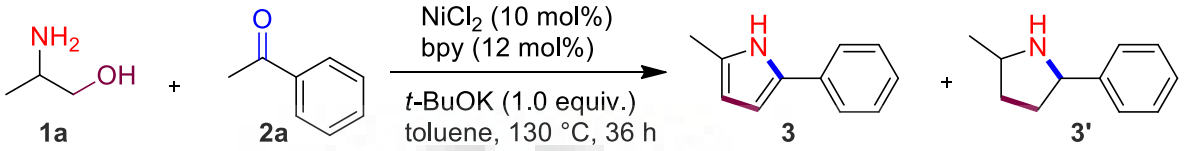
Entry	Base equivalents	GC-MS Conversion (%)	
		3	**3'**
1.	*t*-BuOK (1.0 equiv.)	72 (64) [b]	0
2.	*t*-BuOK (0.75 equiv.)	41	0
3.	*t*-BuOK (0.50 equiv.)	29	0
4.	-	0	0

Reaction condition: [a] DL-Alaninol (0.5 mmol), acetophenone (1.0 mmol), $NiCl_2$ (10 mol%), bpy (12 mol%), *t*-BuOK (X equiv.), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 130 °C in oil bath, 36 h reaction time. [b] Isolated yield.

Thereafter, we have tested the pyrrole synthesis using variable amount of *t*-BuOK, however, one equivalent of *t*-BuOK was optimum to achieve maximum product yield (Table 5, entries 1-3). Similarly, control experiment without base did not furnish any product, revealed its potential role (Table 5, entry 4). Next, it is important to note that, as the reaction proceeds in presence of base, we believe that, base could facilitate the self-coupling of acetophenone derivatives. To our delight, we did not observe any self-coupling of β-amino alcohol using

GC-MS analysis of the crude reaction mixture. Gratifyingly, the best result obtained when, two equivalent of acetophenone was used with β-amino alcohol (Table 6, entry 1).

Table 6: Screening of alcohol and ketone equivalents [a]



Entry	1a	2a	GC-MS Conversion (%)	
	X mmol	Y mmol	**3**	**3'**
1.	0.5	1.0	72 (64) [b]	0
2.	0.5	0.5	46	8
3.	0.75	0.5	17	43
4.	1.0	0.5	14	55

Reaction condition: [a] DL-Alaninol **1a** (X mmol), acetophenone **2a** (Y mmol), $NiCl_2$ (10 mol%), bpy (12 mol%), *t*-BuOK (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 130 °C in oil bath, 36 h reaction time. [b] Isolated yield.

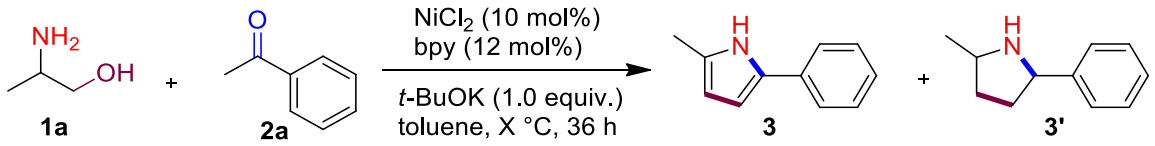
Table 7: Screening of catalyst/ligand loading [a]

Entry	Catalyst loading	Ligand Loading	GC-MS Conversion (%)	
			3	**3'**
1.	$NiCl_2$ (10 mol%)	bpy (12 mol%)	72 (64) [b]	0
2.	$NiCl_2$ (7.5 mol%)	bpy (9 mol%)	54	0
3.	$NiCl_2$ (5.0 mol%)	bpy (6 mol%)	42	0
4.	-	-	5	0

Reaction condition: [a] DL-Alaninol **1a** (0.5 mmol), acetophenone **2a** (1.0 mmol), $NiCl_2$ (X mol%), bpy (Y mol%), *t*-BuOK (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 130 °C in oil bath, 36 h reaction time. [b] Isolated yield.

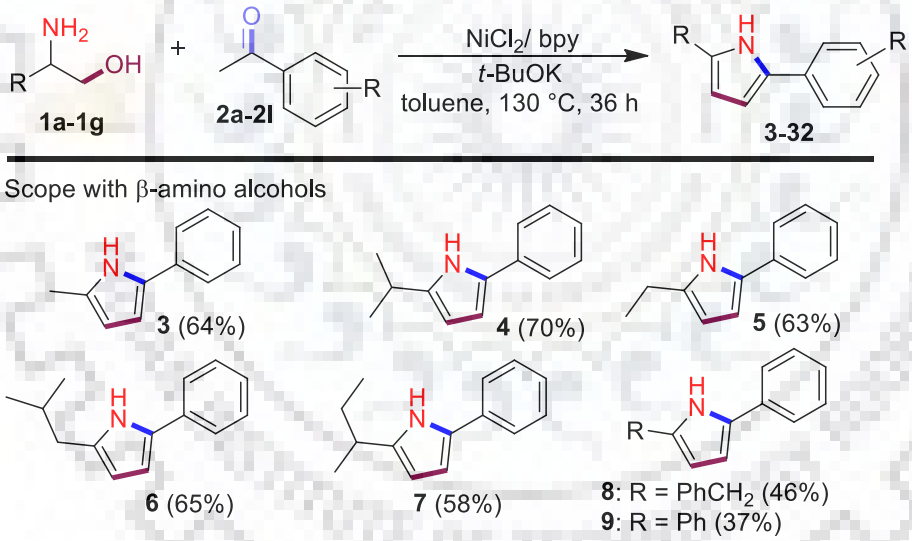
Control experiments as well as variations of ligands and catalyst loading greatly influence the pyrrole synthesis as observed in Table 7 (entries 1-4). In absence of catalyst and suitable ligand only 5% product was observed. (Table 7, entry 4). Similarly, lowering of reaction temperature also influence the product conversions and furnished albeit lower product yield under identical conditions (Table 8, entries 1-5).

Table 8: Screening of temperature [a]



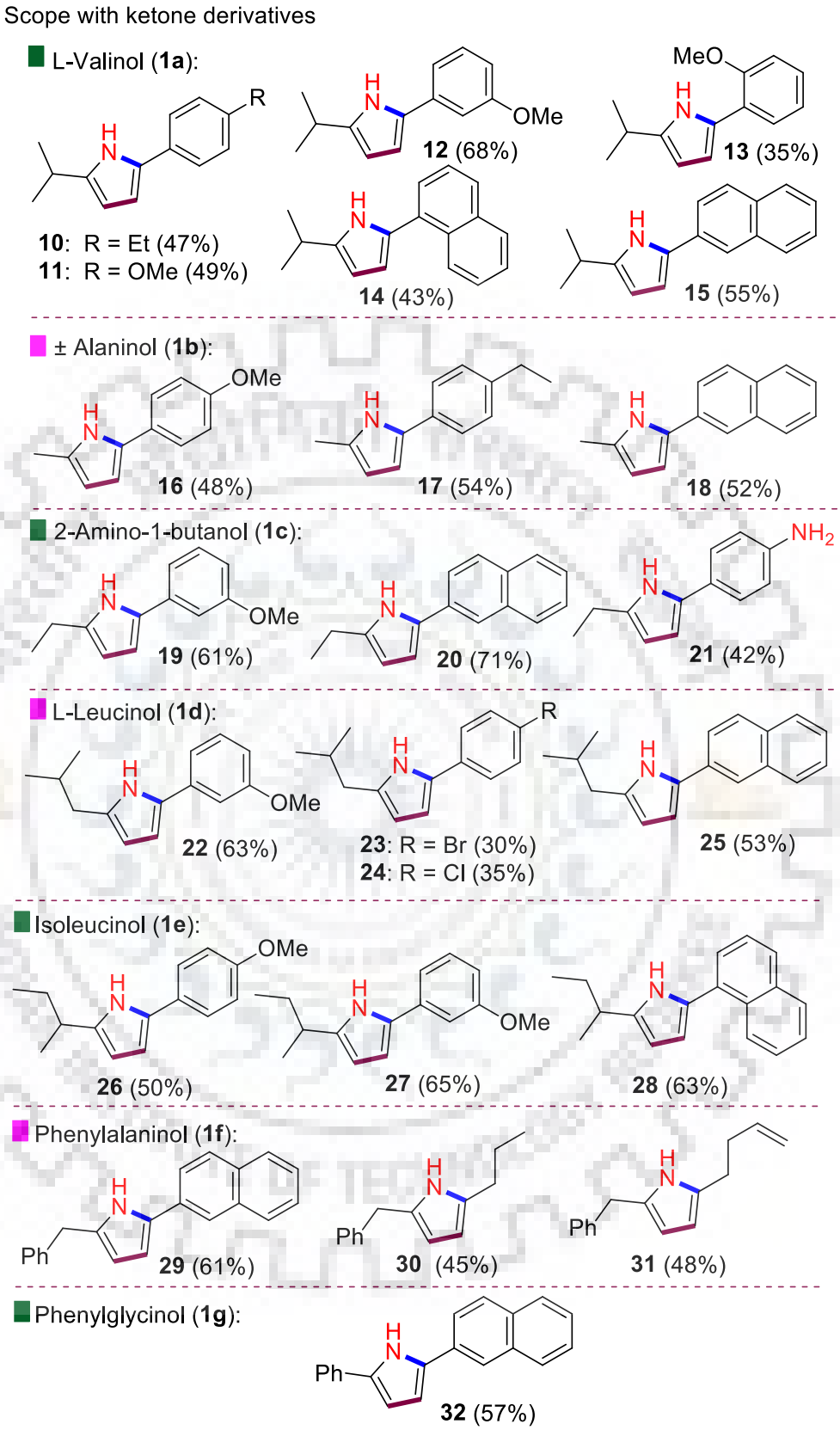
Entry	Temperature (X °C)	GC-MS Conversion (%)	
		3	**3'**
1.	130 °C	72 (64) [b]	0
2.	120 °C	49	0
3.	110 °C	36	0
4.	100 °C	25	0
5.	80 °C	1	0

Reaction condition: [a] DL-Alaninol **1a** (0.5 mmol), acetophenone **2a** (1.0 mmol), $NiCl_2$ (10 mol%), bpy (12 mol%), *t*-BuOK (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, X °C oil bath, 36 h reaction time. [b] Isolated yield.



Scheme 13: Synthesis of 2,5-disubstituted pyrroles. Reaction conditions: Unless specified, the reaction was carried out with amino alcohol **1** (0.5 mmol), ketone **2** (1.0 mmol), $NiCl_2$ (0.05 mmol), bpy (0.06 mmol), *t*-BuOK (0.5 mmol), 130 °C in toluene (2.0 mL) for 36 h.

Access to 2,5-disubstituted *N*-heterocycles: After having optimized conditions in hand we studied the substrate scope and limitations of the catalytic protocol using seven different amino alcohols substituted with alkyl and aryl groups. The reaction of acetophenone with less reactive methyl, ethyl, *iso*-propyl, *sec*-butyl as well as *iso*-butyl substituted β-amino alcohols furnished the desired products in up to 70% isolated yields (Scheme 13, **3-7**). Gratifyingly,

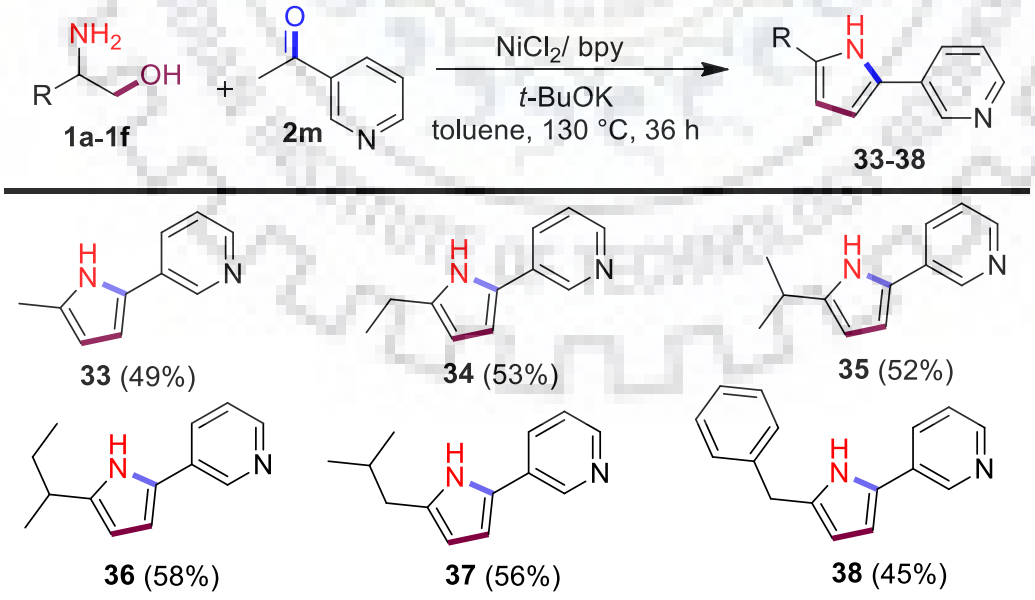


Scheme 14: Synthesis of 2,5-disubstituted pyrroles. *Reaction conditions:* Unless specified, the reaction was carried out with amino alcohol **1** (0.5 mmol), ketone **2** (1.0 mmol), $NiCl_2$ (0.05 mmol), bpy (0.06 mmol), *t*-BuOK (0.5 mmol), 130 °C in toluene (2.0 mL) for 36 h.

under identical conditions, phenylalaninol and phenylglycinol transformed into 2,5-diaryl substituted pyrroles (Scheme 13, **8** and **9**).

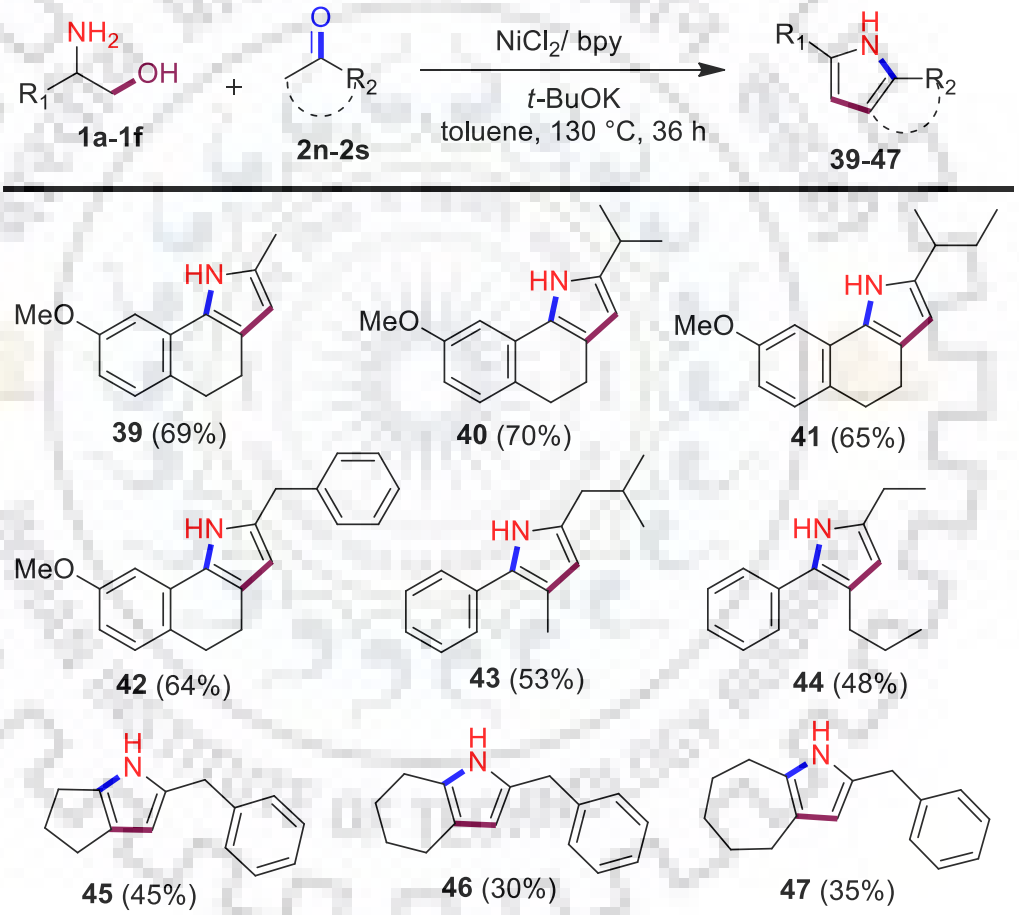
Pyrroles synthesis using ketone derivatives: Further, to demonstrate the general applicability, a variety of acetophenone derivatives substituted with ethyl or methoxy groups including 1-acetyl and 2-acetyl naphthalene were examined with different β-amino alcohols and a series of interesting 2,5-disubstituted pyrroles were obtained in up to 71% isolated yields (Scheme 14, **10-32**). It is to be noted that, sterically hindered *o*-methoxy and halide substituted 4-Cl, 4-Br acetophenone smoothly converted into the desired pyrroles in moderate yields (Scheme 14, **13** and **23-24**). Advantageously, aliphatic ketones containing long chain as well as terminal double bond efficiently transformed into the corresponding pyrroles **30-31** (Scheme 14).

Synthesis of *N*-heterocyclic 2,5-disubstituted pyrroles: Next, more challenging 3-acetylpyridine **2m** was used as substrate and yielded pharmaceutically active 3-(1*H*-pyrrol-2yl) pyridines **33-38** in 45-58% yields. Gratifyingly, irrespective of their electronic properties, methyl, ethyl, *iso*-propyl, *sec*-butyl, *iso*-butyl and benzyl substituted β-amino alcohols are well tolerated (Scheme 15). Importantly, this represents a rare example of selective transformation of di-substituted *N*-heterocyclic pyrrole derivatives using nickel, otherwise previously not reported with other metal-catalysts.



Scheme 15: Synthesis of *N*-heterocyclic 2,5-disubstituted pyrroles. Reaction conditions: Unless specified, the reaction was carried out with amino alcohol **1** (0.5 mmol), ketone **2** (1.0 mmol), $NiCl_2$ (0.05 mmol), bpy (0.06 mmol), *t*-BuOK (0.75 mmol), 130 °C in toluene (2.0 mL) for 36 h.

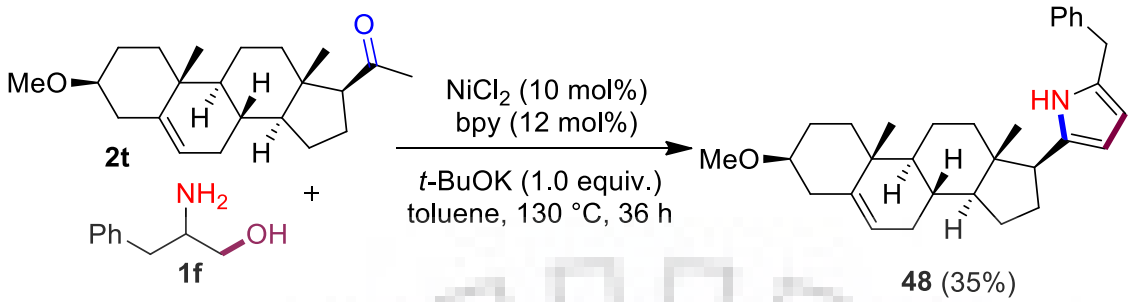
Synthesis of 2,3,5-trisubstituted bi-and tricyclic pyrroles: Inspired by this excellent catalytic activity, further we explored the synthesis of 2,3,5-trisubstituted bicyclic pyrroles. It is noteworthy to mention that, the application of 7-methoxy-tetralone with β-amino alcohols furnished the desired tri-substituted pyrroles in good isolated yields, 63-70% respectively (Scheme 16, **39-42**). Again, we studied the reactivity of more challenging acyclic and cyclic ketones. Intermolecular cyclization of propiophenone and valerophenone resulted into 2,3,5-trisubstituted pyrroles (Scheme 16, **43-44**). Nevertheless, the reaction of alkyl cyclic ketones, such as, cyclopentanone, cyclohexanone as well as cycloheptanone, converted into various annulated tri-substituted bicyclic products (Scheme 16, **45-47**). These examples established the potential application of the present catalytic protocol.



Scheme 16: Synthesis of 2,3,5-tri-substituted bi-cyclic and tri-cyclic pyrroles. Reaction conditions: Unless specified, the reaction was carried out with amino alcohol **1** (0.5 mmol), ketone **2** (1.0 mmol), $NiCl_2$ (0.05 mmol), bpy (0.06 mmol), *t*-BuOK (0.5 mmol), 130 °C in toluene (2.0 mL) for 36 h.

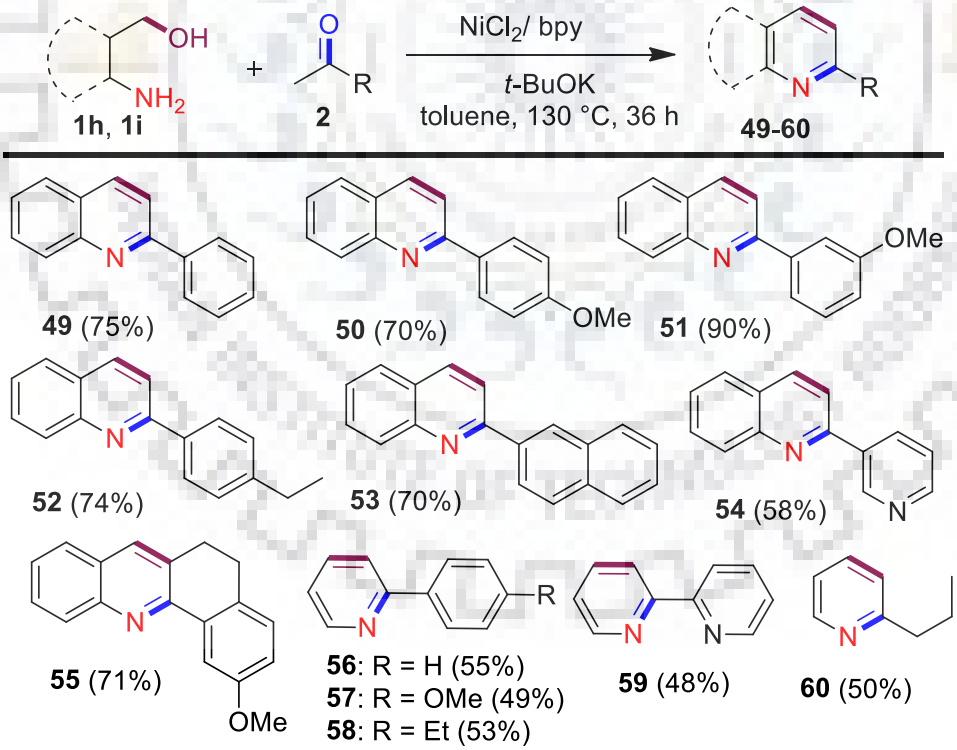
Intermolecular cyclization using steroid hormone: Next, to establish the versatility of the intermolecular cyclization, we studied the catalytic pyrrole synthesis using more interesting steroid hormone. Indeed, 3-methyl ether of 5-pregnen-3-β-ol-20-one (pregnenolone) was

efficiently converted into the desired 2,5-disubstituted pyrrole **48** using phenylalaninol without affecting the parent steroid framework (Scheme 17).



Scheme 17: Synthetic utility: pyrrole synthesis using steroid hormone. *Reaction conditions:* Unless specified, the reaction was carried out with amino alcohol **1** (0.2 mmol), ketone **2** (0.25 mmol), $NiCl_2$ (0.02 mmol), bpy (0.024 mmol), *t*-BuOK (0.2 mmol), 130 °C in toluene (2.0 mL) for 36 h.

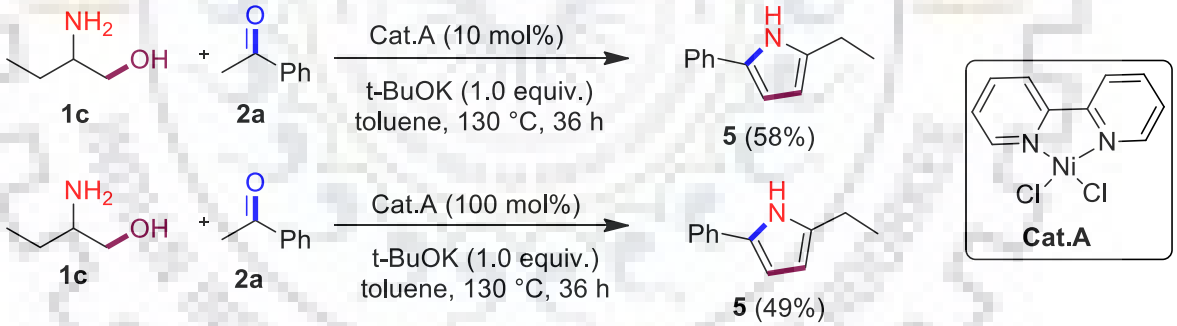
Intermolecular cyclization using γ-amino alcohols: After having demonstrated the excellent catalytic activity of β-amino alcohols for pyrrole synthesis, finally the generality of our nickel-catalyzed protocol was further evaluated using γ-amino alcohols as coupling partner to access, six-member *N*-heterocycles, pyridine and quinoline derivatives.



Scheme 18 Intermolecular cyclization for C-2 substituted quinoline and pyridine derivatives. Reaction conditions: Unless specified, the reaction was carried out with amino alcohol **1** (0.5 mmol), ketone **2** (1.0 mmol), $NiCl_2$ (0.05 mmol), bpy (0.06 mmol), *t*-BuOK (0.5 mmol), 130 °C in toluene (2.0 mL) for 36 h.

Because of the significant importance and interesting bioactivity, a general and versatile method for the synthesis of pyridine and quinoline is highly desirable. Gratifyingly, using our optimized protocol, applications of 2-amino benzyl alcohol with electronically different acetophenones furnished C-2 substituted quinolines **49-54** in up to 90% yields (Scheme 18). Additionally, when 3-amino-1-propanol was used as coupling partner, C-2 substituted pyridines **56-58** were obtained in 49-55% yield respectively (Scheme 18). Notably, 2-acetyl pyridine efficiently transformed into the ligand bipyridine **59**. Furthermore, application of more challenging 7-methoxytetralone and 2-pentanone yielded desired 2,3-disubstituted quinoline as well as 2-^{n}propyl pyridine **55** and **60** in 50-71% product (Scheme 18). To our delight, we are pleased to witness an alternative synthesis of pyridine and quinoline derivatives under nickel catalysis *via* a tandem intermolecular cyclization.

It is noteworthy to mention that, the catalytic protocol is tolerant to primary amine, halides, alkyl and alkoxy groups, including benzyl and pyridine derivatives. Gratifyingly, remarkable transformations in the presence of reducible functionalities, such as, terminal alkene, as well as steroid framework revealing the synthetic potential of the catalytic system. Unfortunately, application of 1-phenyl butane-1,3-dione and 4-Phenylbut-3-yn-2-one under standard catalytic conditions did not result any desired product.

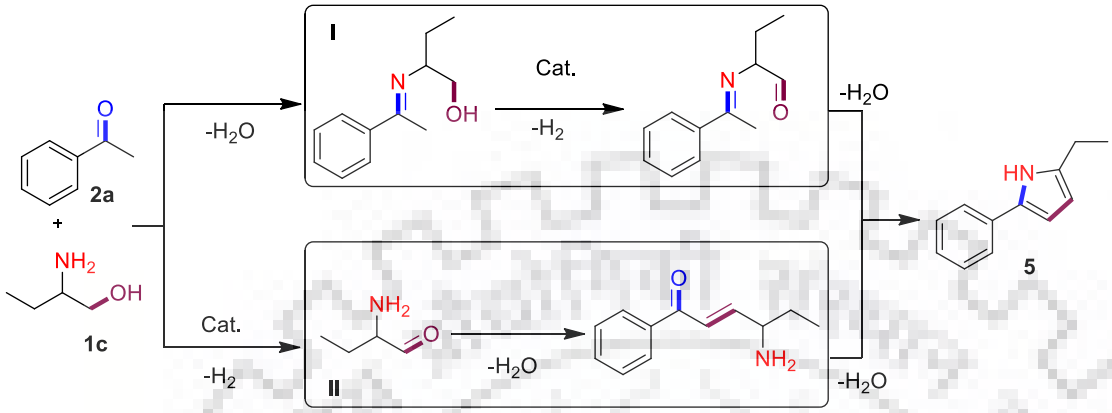


Scheme 19: Stoichiometric and catalytic studies using **Cat.A**

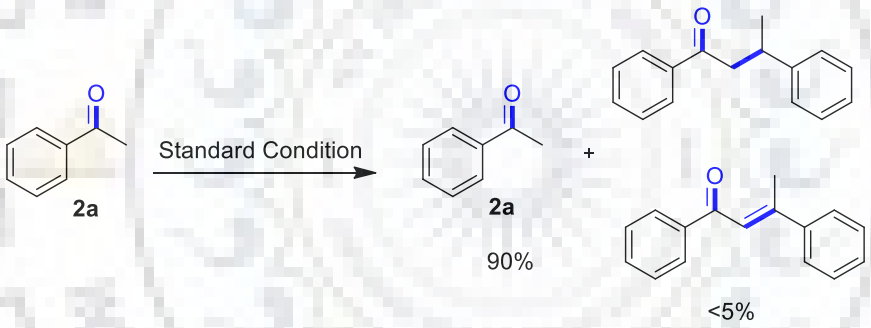
To understand the initial mechanism and the nature of the putative Ni-intermediate species, **Cat.A** was prepared, isolated separately and employed in catalytic as well as in stoichiometric equiv. for intermolecular pyrrole synthesis (Scheme 19). Using 10 mol% and 100 mol% of **Cat.A** in the reaction of **1c** with **2a** under standard conditions yielded 58% and 49% of **5**, comparable to the result obtained under optimized conditions (**5**, Scheme 13).

Reactions which confirm Pathway I: Nevertheless, mechanistically we anticipated that, Ni-catalyzed pyrrole synthesis composed of a formal multi-step processes: (i) condensation of ketone with β- amino alcohol to an imine intermediate and (ii) Ni-catalyzed *in situ*

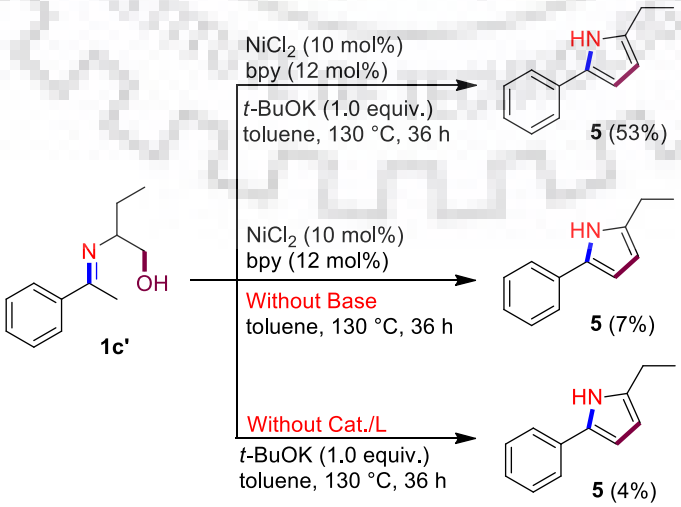
dehydrogenation to α-amino aldehyde followed by sequential intramolecular C-C coupling and dehydration results thermodynamically favorable substituted pyrroles (Scheme 12, Scheme 20).



Scheme 20: Possible reaction pathways



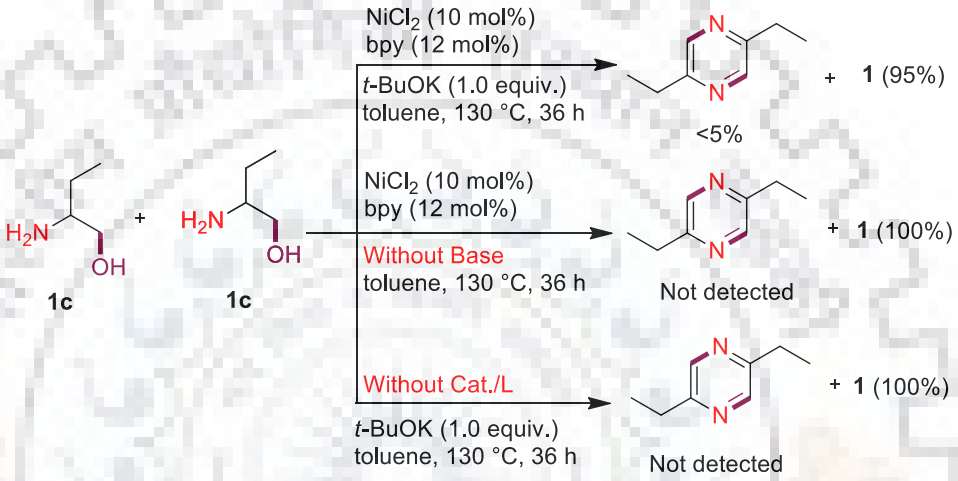
Scheme 21: Control experiment using acetophenone



Scheme 22: Control experiments using of 2-(1-phenylethylideneamino)butan-1-ol **1c'**

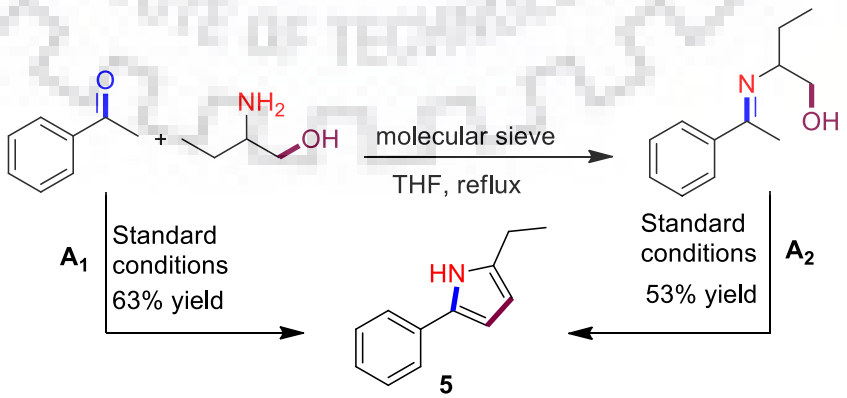
To test this hypothesis, when using acetophenone under standard catalytic conditions we only observed <5% of aldol condensation product and starting material was recovered (Scheme 21).

Further, under standard conditions application of intermediate 2-(1-phenylethylideneamino)butan-1-ol **1c'** is converted to 2-ethyl-5-phenyl-1*H*-pyrrole in 53% yield (Scheme 22). If no catalyst or base was used under standard conditions, we observed only 4-7% of product conversion and unreacted imine was recovered. These experiments evident the potential role of catalyst and base for intramolecular cyclization to pyrrole.



Scheme 23: Control experiments using 2-amino-1-butanol

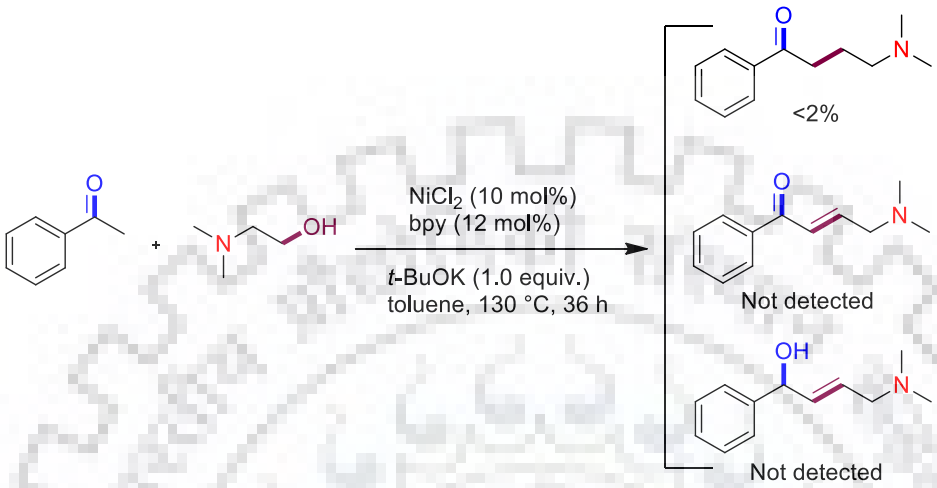
Again, we performed few control experiments for de-hydrogenation and condensation reaction of 2-amino-1-butanol. Unfortunately, we observed that homo-coupling of 2-amino-1-butanol to 2,5-diethylpyrazine is very slow under the standard reaction conditions. In absence of catalyst or base following standard conditions, we did not observe any product conversion (Scheme 23).



Scheme 24: Possible reaction pathways

Under standard catalytic conditions, the reaction of ketone and amino alcohol (path **A1**), or the reaction of preformed Schiff base (path **A2**), resulted similar efficiency as shown in Scheme 24.

Reactions which contradict Pathway II:



Scheme 25: Control experiments using acetophenone with substituted amino alcohols

Further, to exclude the possibilities for reaction pathways II, we preformed catalytic experiments between acetophenone and the *N*-protected amino alcohol using standard catalytic conditions and we observed only <2% of the α-alkylation product (Scheme 25). This experiment indicated that the α-alkylation is very slow and unlikely be first step during pyrrole synthesis (pathway II, Scheme 20).

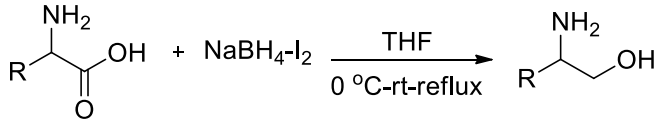
[3A.3] Conclusions

In conclusion, we have demonstrated Ni-catalyzed sustainable dehydrogenative coupling of β- and γ-amino alcohols with ketones to access five and six-member *N*-heterocycles. This is the first example of such base metal-catalyzed pyrrole synthesis using amino acid derived alcohols. Catalytic protocol is highly regio-selective, a variety of aryl and alkyl ketones including nine amino alcohols having free amine, halides, alkyl, alkoxy, alkenes, activated benzyl and pyridines smoothly transformed into 2,3 and 2,3,5 substituted bicyclic as well as tricyclic pyrroles, quinolines and pyridine derivatives in up to 90% yields. As a highlights, we demonstrated an interesting pyrrole derivative employing intermolecular cyclization of steroid hormone with phenylalaninol.

[3A.4] Experimental details

[3A.4.1] General procedure for the synthesis of starting materials:

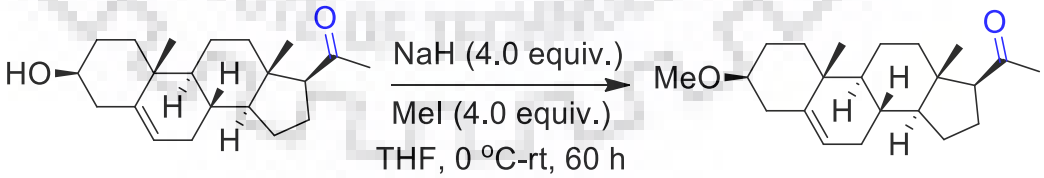
Synthesis of amino alcohols from amino acids:



In a 100 mL oven dried RB flask, amino acids (10.0 mmol) and $NaBH_4$ (2.4 equiv.) in 30 mL of dry THF were taken. The reaction mixture was kept in an ice bath with constant stirring. After 10 min, I_2 (equimolar with amino acid) in 5 mL of THF was added drop wise over a period of 30 min to maintain the temperature below 5 °C, resulting in vigorous evolution of H_2. After addition of I_2 was completed and gas evolution had ceased, then the reaction mixture kept at 70 °C for 16 h in reflux. After completion of reaction, methanol was added carefully until the mixture became clear to exhaust excess $NaBH_4$. The THF was removed by rotary evaporator, then 20 % of 30 mL KOH solution was added slowly and stirred for 2-3 hours. After completion of reaction, the slurry was partitioned between DCM (25.0 mL) and aqueous layer in a separatory funnel. The organic layer was washed with brine and dried over anhydrous Na_2SO_4 (s) 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.

Starting materials were prepared as general procedure. [2-Amino-3-methylbutan-1-ol, 2-Amino-3-methylpentan-1-ol, 2-Amino-2-phenylethanol, 2-Amino-3-phenylpropan-1-ol]. 2-Aminopropan-1-ol, 2-Aminobutan-1-ol, and 2-amino-4-methylpentan-1-ol were purchased from Avra synthesis and /or Alfa Aesar.

Synthesis of steroid ketone:

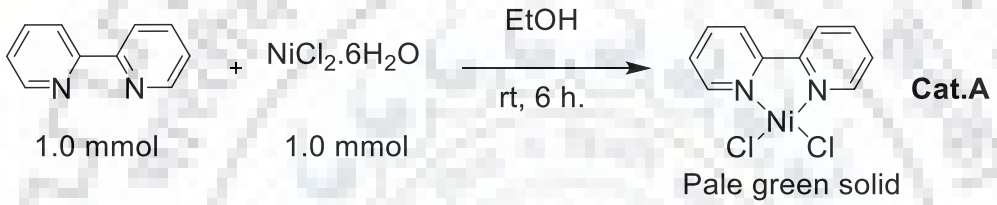


In a 50 mL oven dried RB flask, 5-pregnen-3β-ol-20-one (633 mg, 2.0 mmol), NaH (4.0 equiv.) in THF 10 mL were taken under an atmosphere of N_2 at 0 °C and stirred for 1 h. Then MeI (4.0 equiv.) was added to the reaction mixture at 0 °C and continued reaction at rt for 60 h. The reaction mixture was quenched with NH_4Cl solution and was partitioned between ethyl acetate (25.0 mL) and water (25.0 mL) in a separatory funnel. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4 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 as colourless solid (430 mg, 65% yield). NMR Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35-5.31 (m, 1H), 3.33 (d, J = 0.8 Hz, 3H), 3.09-2.99 (m, 1H), 2.51 (t, J = 8.9 Hz, 1H), 2.37 (ddd, J = 13.1, 4.6, 2.1 Hz, 1H), 2.16 (ddd, J = 12.9, 10.3, 7.8 Hz, 2H), 2.10 (s, 3H), 2.06-1.82 (m, 4H), 1.69-1.36 (m, 8H), 1.26-1.01 (m, 3H), 1.01-0.95 (m, 4H), 0.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.70, 140.93, 121.37, 80.30, 63.78, 56.99, 55.72, 50.09, 44.09, 38.91, 38.70, 37.24, 36.96, 31.91, 31.87, 31.66, 28.04, 24.56, 22.86, 21.15, 19.44, 13.31.

Preliminary catalytic and mechanistic studies:

Preparation: Synthesis of [$NiCl_2$(bpy)] complex:



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 rt, 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 pale green solid 114 mg (80%) yield.

Elemental Analysis calculated: C, 42.03; H, 2.82; Cl, 24.81; N, 9.80; Ni, 20.54; Found: C, 41.75; H, 2.76; N, 9.61.

[3A.4.2] General procedure for synthesis of pyrroles, quinolines and pyridines from amino alcohols.

Procedure A:

In a 15 mL oven dried Schlenk tube amino alcohols (0.5 mmol), *t*-BuOK (0.5 mmol), $NiCl_2$ (0.05 mmol), bpy (0.06 mmol) and ketones (1.0 mmol) were added followed by toluene 2.0 mL under an atmosphere of N_2 and after sealing the Schlenk tube the reaction mixture was heated at 130 $^{\circ}$C for 36 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.

Procedure B:

In a 15 mL oven dried Schlenk tube, amino alcohols (0.5 mmol), *t*-BuOK (0.75 mmol), $NiCl_2$ (0.05 mmol), bpy (0.06 mmol) and ketones (1.0 mmol) were added followed by toluene 2.0 under an atmosphere of N_2 and after sealing the Schlenk tube the reaction mixture was heated at 130 °C for 36 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.

Procedure C:

In a 15 mL oven dried Schlenk tube, amino alcohol (0.2 mmol), *t*-BuOK (0.2 mmol), $NiCl_2$ (0.02 mmol), bpy (0.024 mmol), ketone (0.25 mmol) were added followed by toluene 1.5 mL under an atmosphere of N_2 and after sealing the Schlenk tube the reaction mixture was heated at 130 °C for 36 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 product.

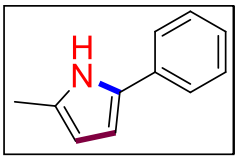
[3A.4.3] Synthesis and Characterization of 2-Ethyl-5-phenyl-1*H*-pyrrole (5):

Following the general procedure A, (section 3A.4.2), the title product **5** was obtained as a colorless oil (63% yield). All the compounds were characterized by ^{1}H NMR, ^{13}C NMR, ESI, HRMS 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 four aromatic region protons well separated and appeared as dd, td, td and dd at 8.12 (br s, 1H), 7.46-7.42 (m, 2H), 7.36-7.31 (m, 2H), 7.16 (t, J = 7.3 Hz, 1H), 6.42 (t, J = 3.0 Hz, 1H), 5.99 (t, J = 3.0 Hz, 1H), 2.69 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H).

The protons at 1.29 are triplet belongs to $–CH_3$ and 2.69 ppm are quartet belong to $–CH_2$ group. The two protons at 5.99 and 6.42 ppm belong to pyrrole ring (Figure **2a**). ^{13}C NMR: the peaks at 21.09, 13.68 ppm belong to $–CH_3$ and $–CH_2$ carbons, and the peak at 106.32, 106.10 belongs to pyrrole ring and 135.71, 133.10, 130.68, 128.89, 125.75, 123.49 ppm all belongs to carbons of benzene ring moiety (Figure **2b**).

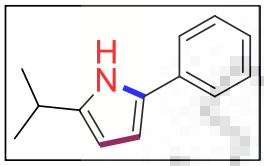
[3A.4.4] Analytical data for all compounds:

2-Methyl-5-phenyl-1*H*-pyrrole (3) [20]**:**



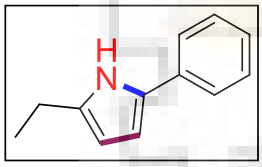
Following the general procedure A, the title product was obtained as a colourless oil (64% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.43 (dd, J = 8.2, 1.1 Hz, 2H), 7.36 – 7.32 (m, 2H), 7.19 – 7.13 (m, 1H), 6.40 (t, J = 3.0 Hz, 1H), 5.96 (t, J = 2.5 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.05, 130.88, 128.91, 128.60, 125.74, 123.44, 108.03, 106.27, 29.82.

2-Isopropyl-5-phenyl-1*H*-pyrrole (4) [20]**:**



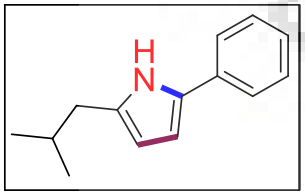
Following the general procedure A, the title product was obtained as a colourless solid (70% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.44 (dd, J = 8.2, 0.8 Hz, 2H), 7.33 (t, J = 7.7 Hz, 2H), 7.16 (t, J = 7.4 Hz, 1H), 6.41 (t, J = 3.1 Hz, 1H), 5.98 (t, J = 3.0 Hz, 1H), 2.97 (dt, J = 13.8, 6.9 Hz, 1H), 1.30 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.90, 133.18, 131.00, 128.94, 125.82, 123.56, 106.47, 105.93, 27.29, 22.76.

2-Ethyl-5-phenyl-1*H*-pyrrole (5) [20]**:**



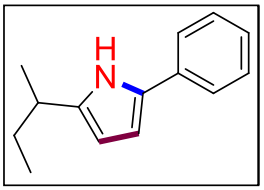
Following the general procedure A, the title product was obtained as a colourless oil (63% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.46 – 7.42 (m, 2H), 7.36 – 7.31 (m, 2H), 7.16 (t, J = 7.3 Hz, 1H), 6.42 (t, J = 3.0 Hz, 1H), 5.99 (t, J = 3.0 Hz, 1H), 2.69 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.71, 133.10, 130.68, 128.89, 125.75, 123.49, 106.32, 106.10, 21.09, 13.68.

2-Isobutyl-5-phenyl-1*H*-pyrrole (6) [20]**:**



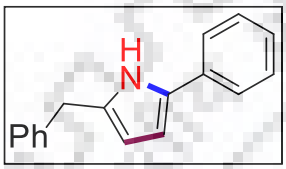
Following the general procedure A, the title product was obtained as a colourless solid (65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.46 – 7.42 (m, 2H), 7.35 (dd, J = 10.6, 5.0 Hz, 2H), 7.20 – 7.13 (m, 1H), 6.44 (t, J = 3.0 Hz, 1H), 5.98 (t, J = 3.0 Hz, 1H), 2.51 (d, J = 7.1 Hz, 2H), 1.90 (dp, J = 13.5, 6.7 Hz, 1H), 0.98 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.35, 133.09, 130.54, 128.92, 125.70, 123.42, 108.10, 106.15, 37.48, 29.40, 22.59.

2-(*sec*-Butyl)-5-phenyl-1*H*-pyrrole (7) [20]**:**



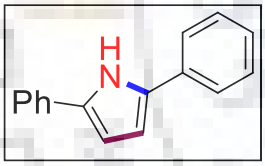
Following the general procedure A, the title product was obtained as a colourless oil (58% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.46 (d, J = 7.7 Hz, 2H), 7.35 (t, J = 7.7 Hz, 2H), 7.17 (t, J = 7.3 Hz, 1H), 6.45 (t, J = 2.9 Hz, 1H), 6.00 (t, J = 2.7 Hz, 1H), 2.79 – 2.69 (m, 1H), 1.66 (tdd, J = 20.7, 13.7, 7.1 Hz, 2H), 1.31 (d, J = 7.0 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.30, 133.13, 130.35, 128.91, 125.72, 123.46, 105.93, 105.75, 34.52, 30.36, 20.19, 11.97.

2-Benzyl-5-phenyl-1*H*-pyrrole (8) [20]**:**



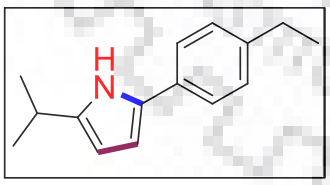
Following the general procedure A, the title product was obtained as a colourless solid (46% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.41 – 7.37 (m, 2H), 7.36 – 7.29 (m, 4H), 7.28 – 7.23 (m, 3H), 7.16 (t, J = 7.3 Hz, 1H), 6.45 (t, J = 3.0 Hz, 1H), 6.06 (t, J = 3.0 Hz, 1H), 4.03 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.38, 132.92, 132.10, 131.61, 128.89, 128.80, 128.76, 126.65, 125.92, 123.56, 108.72, 106.21, 34.35.

2,5-Diphenyl-1*H*-pyrrole (9) [20]**:**



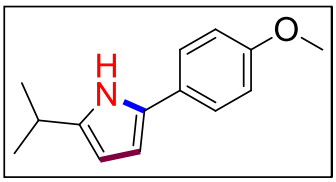
Following the general procedure A, the title product was obtained as a colourless solid (37% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (br s, 1H), 7.56 – 7.51 (m, 4H), 7.42 – 7.36 (m, 4H), 7.23 (dd, J = 10.7, 4.3 Hz, 2H), 6.59 (d, J = 2.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.21, 132.57, 129.05, 126.48, 123.88, 108.01.

2-(4-Ethylphenyl)-5-isopropyl-1*H*-pyrrole (10):



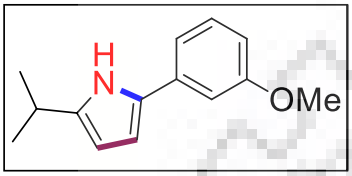
Following the general procedure A, the title product was obtained as a pale brown oil (47% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.37 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 6.39 – 6.35 (m, 1H), 5.98 (t, J = 3.4 Hz, 1H), 3.03 – 2.92 (m, 1H), 2.65 (q, J = 7.6 Hz, 2H), 1.31 (d, J = 6.9 Hz, 6H), 1.25 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.89, 140.00, 130.79, 130.70, 128.38, 123.68, 105.32, 104.84, 28.60, 27.31, 22.80, 15.68; HRMS (ESI): Calculated for $[C_{15}H_{19}N]^+$ 213.1512; Found 213.1534.

2-Isopropyl-5-(4-methoxyphenyl)-1*H*-pyrrole (11) [24]**:**



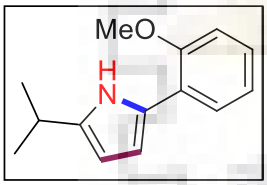
Following the general procedure A, the title product was obtained as a white solid (49% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.37 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.29 (t, J = 3.0 Hz, 1H), 5.96 (t, J = 2.8 Hz, 1H), 3.81 (s, 3H), 3.01 – 2.88 (m, 1H), 1.30 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.00, 139.70, 130.59, 126.32, 125.03, 124.96, 114.31, 104.77, 55.45, 27.38, 22.79.

2-Isopropyl-5-(3-methoxyphenyl)-1*H*-pyrrole (12) [21b]**:**



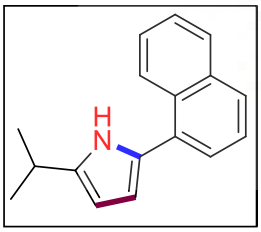
Following the general procedure A, the title product was obtained as a pale brown oil (68% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.24 – 7.21 (m, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.98 – 6.95 (m, 1H), 6.73 – 6.70 (m, 1H), 6.40 (t, J = 3.4 Hz, 1H), 5.97 (t, J = 3.4 Hz, 1H), 3.83 (s, 3H), 2.96 (dt, J = 13.8, 6.8 Hz, 1H), 1.29 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.14, 140.51, 134.58, 130.44, 129.95, 116.19, 111.13, 109.52, 106.24, 105.06, 55.40, 27.33, 22.79.

2-Isopropyl-5-(2-methoxyphenyl)-1*H*-pyrrole (13):



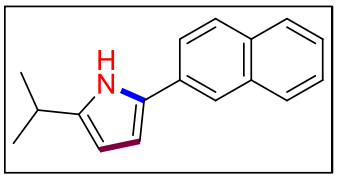
Following the general procedure A, the title product was obtained as a pale brown oil (35% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (br s, 1H), 7.61 (dd, J = 7.7, 1.6 Hz, 1H), 7.14 – 7.07 (m, 1H), 6.95 (ddd, J = 10.7, 5.9, 2.1 Hz, 2H), 6.52 – 6.48 (m, 1H), 5.97 (t, J = 3.5 Hz, 1H), 3.95 (s, 3H), 3.03 – 2.93 (m, 1H), 1.30 (d, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.45, 139.13, 128.02, 126.20, 126.09, 121.49, 111.75, 106.13, 103.81, 55.79, 27.23, 22.61; HRMS (ESI): Calculated for $[C_{14}H_{17}NONa]^+$ 238.1202; Found 238.1204.

2-Isopropyl-5-(naphthalen-1-yl)-1*H*-pyrrole (14) [24]**:**



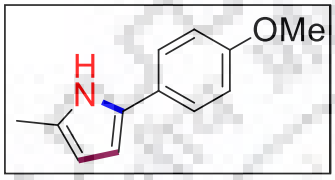
Following the general procedure A, the title product was obtained as a colourless solid (43% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (br s, 1H), 7.81 – 7.76 (m, 4H), 7.64 (dd, J = 8.5, 1.8 Hz, 1H), 7.47 – 7.36 (m, 2H), 6.54 (t, J = 3.1 Hz, 1H), 6.03 (t, J = 3.0 Hz, 1H), 3.07 – 2.95 (m, 1H), 1.34 (d, J = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.83, 133.88, 131.90, 130.46, 128.48, 127.73, 127.55, 126.38, 125.11, 123.16, 120.21, 106.65, 105.25, 27.32, 22.71.

2-Isopropyl-5-(naphthalen-2-yl)-1*H*-pyrrole (15) [21b]**:**



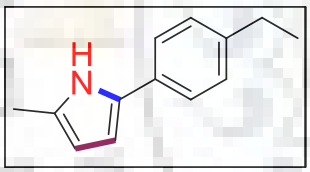
Following the general procedure A, the title product was obtained as a colourless solid (55% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dt, J = 7.3, 3.3 Hz, 1H), 8.14 (br s, 1H), 7.92 – 7.83 (m, 1H), 7.77 (dd, J = 7.0, 3.2 Hz, 1H), 7.49 (dt, J = 7.2, 4.0 Hz, 4H), 6.43 – 6.39 (m, 1H), 6.12 – 6.07 (m, 1H), 3.10 – 2.96 (m, 1H), 1.35 (d, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.93, 134.19, 131.93, 131.37, 128.99, 128.48, 127.15, 126.29, 125.96, 125.93, 125.72, 125.55, 109.43, 104.42, 27.27, 22.76.

2-(4-Methoxyphenyl)-5-methyl-1*H*-pyrrole (16) [21a]**:**



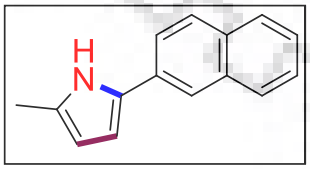
Following the general procedure A, the title product was obtained as a pale brown oil (48% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.35 (d, J = 9.1 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 6.30 – 6.24 (m, 1H), 5.95 – 5.88 (m, 1H), 3.81 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.97, 130.90, 128.39, 126.26, 124.88, 114.35, 107.69, 105.09, 55.38, 13.30.

2-(4-Ethylphenyl)-5-methyl-1*H*-pyrrole (17):



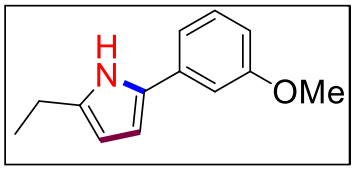
Following the general procedure A, the title product was obtained as a light brown oil (54% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.2 Hz, 2H), 6.34 (t, J = 3.0 Hz, 1H), 5.93 (t, J = 3.3 Hz, 1H), 2.63 (q, J = 7.6 Hz, 2H), 2.32 (s, 3H), 1.23 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.84, 131.06, 130.59, 128.66, 128.37, 123.52, 107.82, 105.70, 28.56, 15.62, 13.27; HRMS (ESI): Calculated for $[C_{13}H_{16}N]^+$ 185.1199; Found 185.1206.

2-Methyl-5-(naphthalen-2-yl)-1*H*-pyrrole (18) [21a]**:**



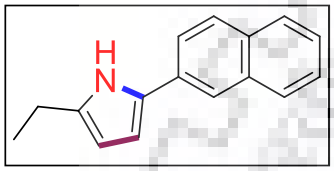
Following the general procedure A, the title product was obtained as a colourless solid (52% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 7.81 – 7.76 (m, 4H), 7.62 (dd, J = 8.6, 1.7 Hz, 1H), 7.46 – 7.35 (m, 2H), 6.52 (t, J = 3.0 Hz, 1H), 6.00 (t, J = 5.8 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.88, 131.88, 130.79, 130.35, 129.55, 128.48, 127.72, 127.55, 126.38, 125.11, 123.06, 120.13, 108.20, 106.99, 13.27.

2-Ethyl-5-(3-methoxyphenyl)-1*H*-pyrrole (19):



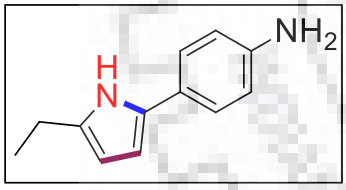
Following the general procedure A, the title product was obtained as a pale brown oil (61% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 7.7 Hz, 1H), 6.99 – 6.95 (m, 1H), 6.72 (dd, J = 8.2, 2.5 Hz, 1H), 6.41 (t, J = 3.0 Hz, 1H), 5.98 (t, J = 2.9 Hz, 1H), 3.83 (s, 3H), 2.68 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.11, 135.77, 134.49, 130.53, 129.91, 116.10, 111.09, 109.39, 106.36, 106.31, 55.32, 21.09, 13.68; HRMS (ESI): Calculated for $[C_{13}H_{16}NO]^+$ 202.1226; Found 202.1219.

2-Ethyl-5-(naphthalen-2-yl)-1*H*-pyrrole (20) [21a]**:**



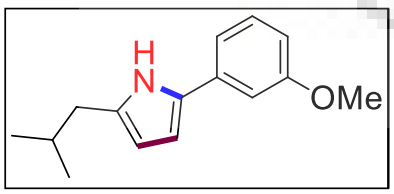
Following the general procedure A, the title product was obtained as a colourless solid (71% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (br s, 1H), 7.83 – 7.76 (m, 4H), 7.64 (dd, J = 8.6, 1.8 Hz, 1H), 7.48 – 7.36 (m, 2H), 6.55 (t, J = 3.1 Hz, 1H), 6.04 (t, J = 3.0 Hz, 1H), 2.73 (q, J = 7.6 Hz, 2H), 1.33 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.21, 133.96, 131.97, 130.68, 130.48, 128.56, 127.81, 127.63, 126.46, 125.19, 123.20, 120.25, 106.90, 106.57, 21.16, 13.69.

4-(5-Ethyl-1*H*-pyrrol-2-yl)aniline (21) [24]**:**



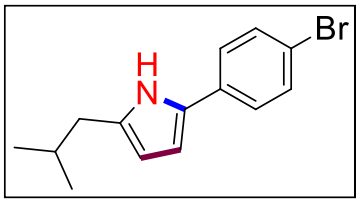
Following the general procedure A, the title product was obtained as a brown oil (42% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (br s, 1H), 7.29 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.5 Hz, 2H), 6.28 (t, J = 3.0 Hz, 1H), 5.97 (t, J = 2.9 Hz, 1H), 3.66 (s, 2H), 2.69 (q, J = 7.5 Hz, 2H), 1.30 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.51, 134.49, 130.88, 124.92, 124.30, 115.63, 105.77, 104.08, 26.03, 21.00.

2-Isobutyl-5-(3-methoxyphenyl)-1*H*-pyrrole (22) [21b]**:**



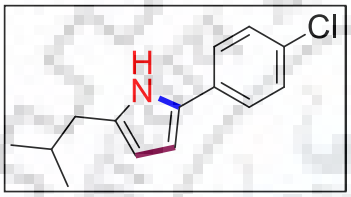
Following the general procedure A, the title product was obtained as a pale brown oil (63% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.16 – 7.09 (m, 1H), 7.08 – 7.03 (m, 1H), 7.01 – 6.99 (m, 1H), 6.75 (dd, J = 8.2, 1.9 Hz, 1H), 6.45 (t, J = 3.0 Hz, 1H), 5.99 (t, J = 2.9 Hz, 1H), 3.87 (s, 3H), 2.53 (d, J = 7.1 Hz, 2H), 1.92 (dp, J = 13.5, 6.8 Hz, 1H), 0.99 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.04, 136.70, 134.41, 130.30, 129.85, 115.93, 110.98, 109.23, 106.40, 106.29, 55.28, 37.39, 29.31, 22.49.

2-(4-Bromophenyl)-5-isobutyl-1*H*-pyrrole (23):



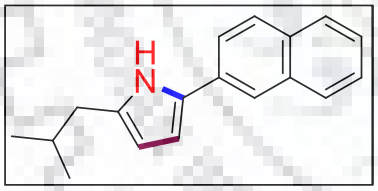
Following the general procedure A, the title product was obtained as a colourless oil (30% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.43 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H), 6.42 – 6.38 (m, 1H), 5.95 (t, J = 3.0 Hz, 1H), 2.48 (d, J = 7.1 Hz, 2H), 1.94 – 1.82 (m, 1H), 0.95 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.90, 131.92, 128.90, 124.83, 123.38, 118.99, 108.35, 106.74, 37.43, 29.34, 22.56; HRMS (ESI): Calculated for $[C_{14}H_{17}NBr]^+$ 278.0539; Found 278.0546.

2-(4-Chlorophenyl)-5-isobutyl-1*H*-pyrrole (24):



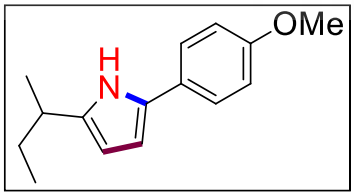
Following the general procedure A, the title product was obtained as a colourless oil (35% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 6.39 (t, J = 3.1 Hz, 1H), 5.95 (t, J = 3.0 Hz, 1H), 2.49 (d, J = 7.1 Hz, 2H), 1.94 – 1.82 (m, 1H), 0.95 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.79, 131.59, 131.09, 129.00, 128.31, 124.52, 108.30, 106.68, 37.44, 29.33, 22.54; HRMS (ESI): Calculated for $[C_{14}H_{17}NCl]^+$ 234.1044; Found 234.1041.

2-Isobutyl-5-(naphthalen-2-yl)-1*H*-pyrrole (25) [24]**:**



Following the general procedure A, the title product was obtained as a colourless solid (53% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (br s, 1H), 7.79 (dd, J = 10.7, 6.5 Hz, 4H), 7.67 – 7.60 (m, 1H), 7.49 – 7.35 (m, 2H), 6.58 – 6.53 (m, 1H), 6.05 – 6.00 (m, 1H), 2.55 (d, J = 7.5 Hz, 2H), 2.00 – 1.88 (m, 1H), 1.00 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.97, 133.85, 131.93, 130.55, 130.50, 128.55, 127.80, 127.60, 126.47, 125.16, 123.17, 120.14, 108.32, 106.96, 37.54, 29.39, 22.60.

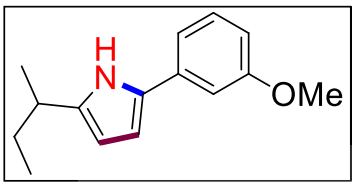
2-(*sec*-Butyl)-5-(4-methoxyphenyl)-1*H*-pyrrole (26):



Following the general procedure A, the title product was obtained as a pale brown oil (50% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.37 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.30 (t, J = 3.0 Hz, 1H), 5.95 (t, J = 3.0 Hz, 1H), 3.82 (s, 3H), 2.77 – 2.66 (m, 1H), 1.72 – 1.57 (m, 2H), 1.28 (d, J = 7.0 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.89, 138.50, 130.31, 126.31, 124.84, 114.30,

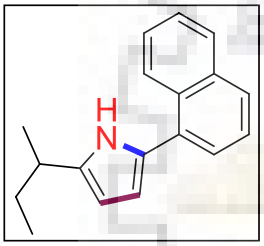
105.38, 104.68, 55.34, 34.42, 30.28, 20.10, 11.87; HRMS (ESI): Calculated for $[C_{15}H_{19}NONa]^+$ 252.1359; Found 252.1363.

2-(*sec*-Butyl)-5-(3-methoxyphenyl)-1*H*-pyrrole (27):



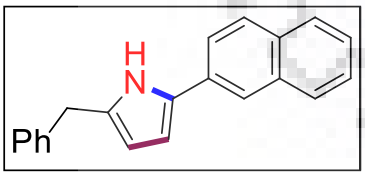
Following the general procedure A, the title product was obtained as a light brown oil (65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.02 (ddd, J = 7.7, 1.5, 0.9 Hz, 1H), 6.98 – 6.95 (m, 1H), 6.71 (ddd, J = 8.2, 2.5, 0.6 Hz, 1H), 6.43 – 6.38 (m, 1H), 5.96 (t, J = 2.9 Hz, 1H), 3.83 (s, 3H), 2.75 – 2.66 (m, 1H), 1.71 – 1.56 (m, 2H), 1.28 (d, J = 7.0 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.12, 139.33, 134.56, 130.19, 129.90, 116.07, 110.98, 109.44, 106.22, 105.71, 55.35, 34.50, 30.31, 20.14, 11.90; HRMS (ESI): Calculated for $[C_{15}H_{19}NONa]^+$ 252.1359; Found 252.1351.

2-(*sec*-Butyl)-5-(naphthalen-1-yl)-1*H*-pyrrole (28):



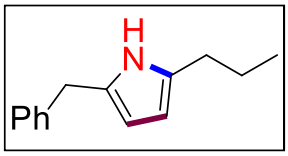
Following the general procedure A, the title product was obtained as a colourless solid (63% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 – 8.34 (m, 1H), 8.12 (br s, 1H), 7.88 (dd, J = 6.1, 3.4 Hz, 1H), 7.78 (dd, J = 6.0, 3.4 Hz, 1H), 7.53 – 7.47 (m, 4H), 6.44 (t, J = 3.0 Hz, 1H), 6.10 (t, J = 3.0 Hz, 1H), 2.84 – 2.73 (m, 1H), 1.79 – 1.58 (m, 2H), 1.34 (d, J = 7.0 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.82, 134.19, 131.98, 131.36, 128.79, 128.48, 127.09, 126.27, 125.94, 125.70, 125.55, 109.44, 105.08, 34.43, 30.43, 20.11, 12.00; HRMS (ESI): Calculated for $[C_{18}H_{20}N]^+$ 250.1590; Found 250.1598.

2-Benzyl-5-(naphthalen-2-yl)-1*H*-pyrrole (29):



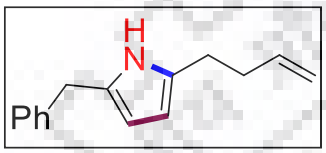
Following the general procedure A, the title product was obtained as a colourless solid (61% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (br s, 1H), 7.81 (dd, J = 13.1, 5.7 Hz, 3H), 7.76 (s, 1H), 7.64 (dd, J = 8.5, 1.7 Hz, 1H), 7.49 (d, J = 6.8 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.39 (t, J = 7.4 Hz, 2H), 7.34 – 7.30 (m, 3H), 6.61 (t, J = 3.0 Hz, 1H), 6.14 (t, J = 2.9 Hz, 1H), 4.10 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.28, 133.81, 132.52, 131.94, 131.56, 130.19, 128.76, 128.73, 128.52, 127.74, 127.59, 126.63, 126.43, 125.22, 123.09, 120.39, 108.95, 106.89, 34.34; HRMS (ESI): Calculated for $[C_{21}H_{18}N]^+$ 284.1434; Found 284.1442.

2-Benzyl-5-propyl-1*H*-pyrrole (30):



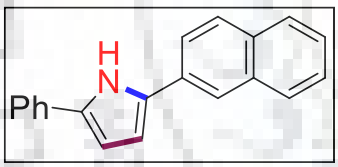
Following the general procedure A, the title product was obtained as a colourless oil (45% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (br s, 1H), 7.32 – 7.26 (m, 2H), 7.21 (t, J = 6.7 Hz, 3H), 5.85 (t, J = 2.9 Hz, 1H), 5.79 (t, J = 2.9 Hz, 1H), 3.93 (s, 2H), 2.50 – 2.45 (m, 2H), 1.59 (dt, J = 15.0, 7.4 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.93, 132.27, 129.00, 128.73, 128.62, 126.38, 106.45, 104.86, 34.28, 29.97, 22.99, 14.00; HRMS (ESI): Calculated for $[C_{14}H_{17}NNa]^+$ 222.1253; Found 222.1261.

2-Benzyl-5-(but-3-en-1-yl)-1*H*-pyrrole (31) [26]**:**



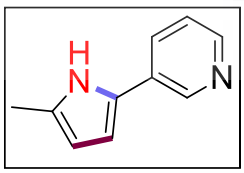
Following the general procedure A, the title product was obtained as a pale brown oil (48% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (br s, 1H), 7.32 (t, J = 7.4 Hz, 2H), 7.26 – 7.22 (m, 3H), 5.90 – 5.76 (m, 1H), 5.60 (dd, J = 16.0, 6.5 Hz, 1H), 5.51 – 5.34 (m, 1H), 5.08 – 4.93 (m, 2H), 3.96 (s, 2H), 2.64 – 2.58 (m, 2H), 2.36 (q, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.36, 138.86, 130.59, 129.75, 129.26, 129.23, 126.33, 115.00, 106.00, 105.04, 34.94, 34.44, 28.13.

2-(Naphthalen-2-yl)-5-phenyl-1*H*-pyrrole (32) [21a]**:**



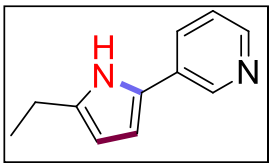
Following the general procedure A, the title product was obtained as a colourless solid (57% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (br s, 1H), 7.94 (s, 1H), 7.76 (d, J = 6.20 Hz, 1H), 7.56 (d, J = 8.5, 2H), 7.50 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 6.19 Hz, 2H), 7.38 (d, J = 6.6 Hz, 4H), 7.19 (t, J = 5.0 Hz, 1H), 6.66 (t, J = 3.1 Hz, 1H), 6.56 (t, J = 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.48, 132.81, 132.20, 128.96, 128.13, 127.82, 127.74, 127.34, 127.14, 126.65, 125.42, 125.16, 124.62, 123.50, 123.12, 120.67, 107.77, 107.29.

3-(5-Methyl-1*H*-pyrrol-2-yl)pyridine (33):



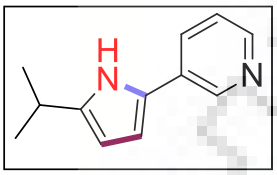
Following the general procedure B, the title product was obtained as a pale yellow solid (49% yield); ^{1}H NMR (400 MHz, $CDCl3$) δ 8.72 (d, J = 2.0 Hz, 1H), 8.42 (s, 1H), 8.37 (dd, J = 4.8, 1.5 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.26 – 7.22 (m, 1H), 6.46 (t, J = 3.0 Hz, 1H), 5.98 (t, J= 2.5 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.43, 144.75, 130.39, 128.99, 127.31, 123.64, 115.00, 108.44, 107.67, 13.14; HRMS (ESI): Calculated for $[C_{10}H_{10}N_2Na]^+$ 181.0736; Found 181.0738.

3-(5-Ethyl-1*H*-pyrrol-2-yl)pyridine (34):



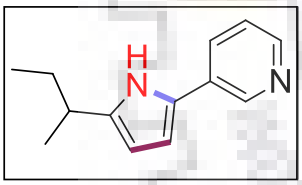
Following the general procedure B, the title product was obtained as a pale brown solid (53% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 1.8 Hz, 1H), 8.48 (s, 1H), 8.37 (dd, J = 4.8, 1.3 Hz, 1H), 7.74 – 7.67 (m, 1H), 7.26 – 7.23 (m, 1H), 6.47 (t, J = 3.1 Hz, 1H), 6.01 (t, J = 3.0 Hz, 1H), 2.74 – 2.63 (m, 2H), 1.29 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.52, 144.88, 137.08, 130.50, 129.08, 127.22, 123.72, 107.51, 106.77, 21.08, 13.67; HRMS (ESI): Calculated for $[C_{11}H_{13}N_2]^+$ 173.1073; Found 173.1076.

3-(5-Isopropyl-1*H*-pyrrol-2-yl)pyridine (35):



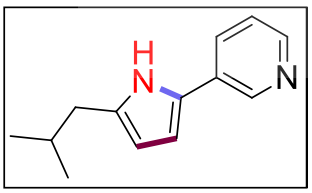
Following the general procedure B, the title product was obtained as a pale brown solid (52% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 2.3 Hz, 1H), 8.47 (s, 1H), 8.37 (dd, J = 4.8, 1.5 Hz, 1H), 7.73 – 7.68 (m, 1H), 7.27 – 7.22 (m, 1H), 6.49 – 6.45 (m, 1H), 6.01 (t, J = 3.0 Hz, 1H), 3.03 – 2.92 (m, 1H), 1.30 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.51, 144.97, 141.82, 130.60, 129.14, 127.10, 123.73, 107.36, 105.48, 27.37, 22.75; HRMS (ESI): Calculated for $[C_{12}H_{14}N_2]^+$ 186.1151; Found 186.1116.

3-(5-(*sec*-Butyl)-1*H*-pyrrol-2-yl)pyridine (36):



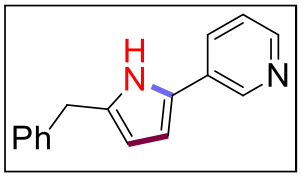
Following the general procedure B, the title product was obtained as a colourless solid (58% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 1.7 Hz, 1H), 8.37 (dd, J = 4.8, 1.5 Hz, 1H), 8.31 (s, 1H), 7.73 – 7.67 (m, 1H), 7.25 – 7.21 (m, 1H), 6.51 – 6.46 (m, 1H), 6.00 (t, J = 3.0 Hz, 1H), 2.77 – 2.68 (m, 1H), 1.68 – 1.58 (m, 2H), 1.28 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.57, 144.90, 140.65, 130.47, 129.08, 126.91, 123.70, 107.37, 106.18, 34.54, 30.29, 20.16, 11.91; HRMS (ESI): Calculated for $[C_{13}H_{17}N_2]^+$ 201.1386; Found 201.1338.

3-(5-Isobutyl-1*H*-pyrrol-2-yl)pyridine (37):



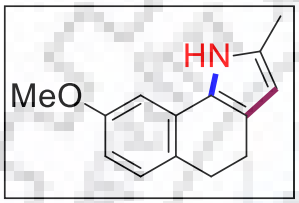
Following the general procedure B, the title product was obtained as a pale yellow solid (56% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 2.1 Hz, 1H), 8.42 (s, 1H), 8.36 (dd, J = 4.8, 1.5 Hz, 1H), 7.73 – 7.67 (m, 1H), 7.26 – 7.21 (m, 1H), 6.48 (t, J = 3.1 Hz, 1H), 5.99 (t, J = 3.0 Hz, 1H), 2.51 (d, J = 7.1 Hz, 2H), 1.95 – 1.83 (m, 1H), 0.95 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.49, 144.89, 134.68, 130.42, 129.08, 127.11, 123.71, 108.50, 107.56, 37.41, 29.32, 22.52; HRMS (ESI): Calculated for $[C_{13}H_{17}N_2]^+$ 201.1386; Found 201.1354.

3-(5-Benzyl-1*H*-pyrrol-2-yl)pyridine (38):



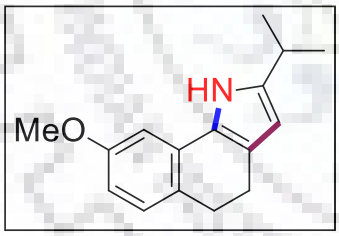
Following the general procedure B, the title product was obtained as a colourless solid (45% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (ddd, J = 3.2, 2.4, 1.0 Hz, 1H), 8.44 – 8.35 (m, 1H), 8.33 (dd, J = 2.7, 1.8 Hz, 1H), 7.68 – 7.61 (m, 1H), 7.7734 – 7.28 (m, 2H), 7.25 – 7.18 (m, 4H), 6.51 – 6.46 (m, 1H), 6.10 – 6.04 (m, 1H), 4.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.79, 145.03, 139.06, 133.44, 130.55, 128.86, 128.83, 128.73, 128.16, 126.74, 123.68, 109.09, 107.56, 34.29; HRMS (ESI): Calculated for $[C_{16}H_{15}N_2]^+$ 235.1230; Found 235.1247.

8-Methoxy-2-methyl-4,5-dihydro-1*H*-benzo[*g*]indole (39):



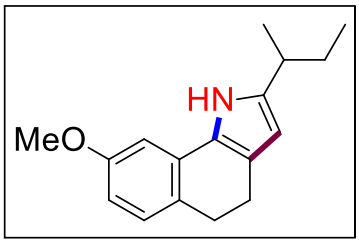
Following the general procedure A, the title product was obtained as a pale brown oil (69% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.09 (d, J = 8.2 Hz, 1H), 6.67 (d, J = 2.5 Hz, 1H), 6.57 (dd, J = 8.2, 2.5 Hz, 1H), 5.81 (d, J = 1.4 Hz, 1H), 3.81 (s, 3H), 2.84 (t, J = 7.6 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.58, 130.54, 128.95, 126.85, 126.54, 121.54, 108.88, 106.46, 106.43, 104.45, 55.44, 29.33, 22.24, 13.41; HRMS (ESI): Calculated for $[C_{14}H_{16}NO]^+$ 214.1226; Found 214.1243.

2-Isopropyl-8-methoxy-4,5-dihydro-1*H*-benzo[*g*]indole (40):



Following the general procedure A, the title product was obtained as a pale brown oil (70% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.06 (d, J = 8.1 Hz, 1H), 6.66 (d, J = 2.5 Hz, 1H), 6.54 (dd, J = 8.2, 2.6 Hz, 1H), 5.83 (d, J = 2.4 Hz, 1H), 3.81 (s, 3H), 2.83 (t, J = 7.6 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H), 2.17 – 2.01 (m, 1H), 1.29 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.56, 140.24, 130.51, 128.92, 126.87, 126.21, 121.00, 108.86, 104.42, 103.44, 55.46, 29.27, 27.46, 22.78, 22.24; HRMS (ESI): Calculated for $[C_{16}H_{20}NO]^+$ 242.1539; Found 242.1548.

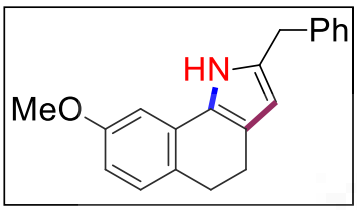
2-(*sec*-Butyl)-8-methoxy-4,5-dihydro-1*H*-benzo[*g*]indole (41):



Following the general procedure A, the title product was obtained as a pale brown oil (65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.53 (dd, J = 8.2, 2.5 Hz, 1H), 5.81 (d, J = 2.3 Hz, 1H), 3.80 (s, 3H), 2.83 (t, J = 7.6 Hz, 2H), 2.72 – 2.62 (m, 3H), 1.70 – 1.57 (m, 2H), 1.27 (d, J = 7.0 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz,

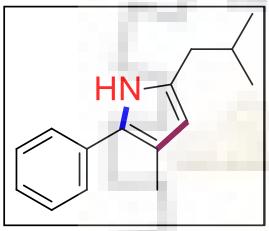
$CDCl_3$) δ 158.51, 139.07, 130.50, 128.84, 126.75, 125.95, 120.99, 108.73, 104.31, 104.05, 55.38, 34.60, 30.29, 29.18, 22.20, 20.11, 11.90: HRMS (ESI): Calculated for $[C_{17}H_{22}NO]^+$ 256.1696; Found 256.1634.

2-Benzyl-8-methoxy-4,5-dihydro-1*H*-benzo[*g*]indole (42):



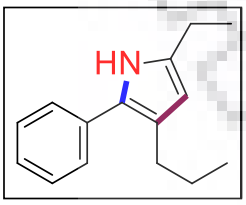
Following the general procedure A, the title product was obtained as a pale brown oil (64% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.36 – 7.28 (m, 2H), 7.28 – 7.23 (m, 3H), 7.06 (d, J = 8.1 Hz, 1H), 6.59 – 6.52 (m, 2H), 5.87 (d, J = 2.1 Hz, 1H), 4.00 (s, 2H), 3.77 (s, 3H), 2.83 (t, J = 7.6 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.17, 139.45, 131.84, 128.95, 128.80, 128.76, 126.88, 126.64, 121.25, 109.81, 109.06, 107.05, 107.02, 104.54, 55.41, 34.48, 29.21, 22.17; HRMS (ESI): Calculated for $[C_{20}H_{19}NONa]^+$ 312.1359; Found 312.1327.

5-Isobutyl-3-methyl-2-phenyl-1*H*-pyrrole (43) [22]**:**



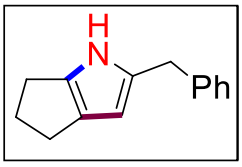
Following the general procedure A, the title product was obtained as a pale brown oil (53% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.41 – 7.34 (m, 4H), 7.21 – 7.16 (m, 1H), 5.83 (d, J = 2.8 Hz, 1H), 2.45 (d, J = 7.0 Hz, 2H), 2.24 (s, 3H), 1.92 – 1.80 (m, 1H), 0.96 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.06, 131.74, 128.72, 126.49, 125.90, 125.43, 116.38, 110.40, 37.35, 29.34, 22.63, 12.72.

5-Ethyl-2-phenyl-3-propyl-1*H*-pyrrole (44) [25]**:**



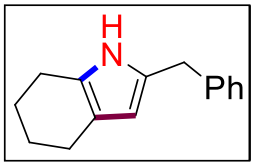
Following the general procedure A, the title product was obtained as a pale brown oil (48% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.43 – 7.35 (m, 4H), 7.25 – 7.17 (m, 1H), 5.92 (d, J = 2.7 Hz, 1H), 2.72 – 2.63 (m, 2H), 2.63 – 2.56 (m, 2H), 1.70 – 1.62 (m, 2H), 1.29 (t, J = 7.6 Hz, 3H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.16, 134.13, 128.40, 126.53, 126.47, 125.51, 121.60, 106.83, 28.91, 24.40, 20.91, 14.37, 13.55.

2-Benzyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole (45) [23]**:**



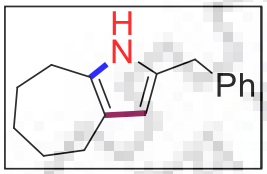
Following the general procedure A, the title product was obtained as a pale brown oil (45% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.33 – 7.18 (m, 5H), 5.70 (s, 1H), 3.92 (s, 2H), 2.79 – 2.67 (m, 4H), 2.34 – 2.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.43, 135.83, 134.59, 128.72, 126.38, 126.32, 102.35, 35.37, 29.43, 26.98, 25.03.

2-Benzyl-4,5,6,7-tetrahydro-1*H*-indole (46) [23]**:**



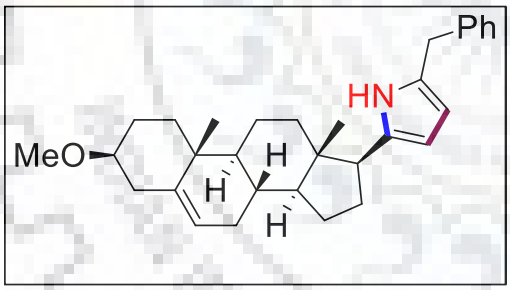
Following the general procedure A, the title product was obtained as a pale brown oil (30% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.19 (m, 6H), 5.69 (s, 1H), 3.90 (s, J = 7.3 Hz, 2H), 2.53 – 2.36 (m, 4H), 2.05 – 1.99 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.14, 128.88, 128.61, 128.09, 126.37, 126.26, 116.93, 105.78, 34.41, 23.90, 22.92, 22.75, 22.56.

2-Benzyl-1,4,5,6,7,8-hexahydrocyclohepta[*b*]pyrrole (47) [23]**:**



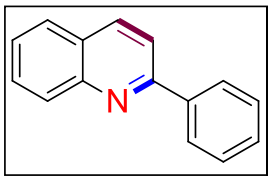
Following the general procedure A, the title product was obtained as a pale brown oil (35% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.33 – 7.17 (m, 5H), 5.67 (d, J = 3.0 Hz, 1H), 3.86 (s, J = 7.4 Hz, 2H), 2.54 – 2.48 (m, 4H), 1.82 – 1.77 (m, 2H), 1.68 – 1.64 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.36, 129.89, 128.81, 128.76, 126.41, 126.34, 121.52, 108.60, 34.30, 32.91, 30.96, 29.53, 28.24, 28.13.

2-Benzyl-5-((3*S*,8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-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)-1*H*-pyrrole (48):



Following the general procedure C, the title product was obtained as a pale yellow oil (35% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.33 (dd, J = 10.2, 4.6 Hz, 2H), 7.23 (dd, J = 15.3, 7.7 Hz, 3H), 5.90 (t, J = 2.8 Hz, 1H), 5.87 (t, J = 2.9 Hz, 1H), 5.40 – 5.37 (m, 1H), 3.97 (s, 2H), 3.38 (s, 3H), 3.09 (ddd, J = 11.3, 6.8, 4.6 Hz, 1H), 2.55 (t, J = 9.8 Hz, 1H), 2.44 – 2.40 (m, 1H), 2.22 – 2.15 (m, 2H), 2.04 – 1.94 (m, 3H), 1.92 – 1.87 (m, 2H), 1.76 – 1.70 (m, 2H), 1.61 – 1.56 (m, 2H), 1.47 (ddd, J = 12.4, 9.7, 4.8 Hz, 3H), 1.31 – 1.27 (m, 1H), 1.26 – 1.21 (m, 1H), 1.14 – 1.07 (m, 2H), 1.02 (s, 3H), 0.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.95, 139.94, 132.28, 128.80, 128.55, 128.51, 126.27, 121.42, 106.23, 105.39, 80.31, 55.84, 55.61, 50.41, 50.15, 43.58, 38.70, 37.98, 37.23, 37.00, 34.17, 32.32, 31.89, 28.00, 26.26, 24.27, 20.92, 19.42, 12.97; HRMS (ESI): Calculated for $[C_{31}H_{42}NO]^+$ 444.3261; Found 444.3160.

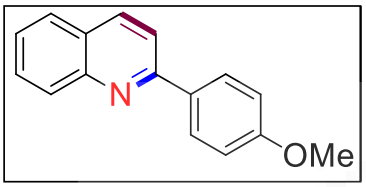
2-Phenylquinoline (49) [24]**:**



Following the general procedure A, the title product was obtained as a colourless solid (75% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 8.6 Hz, 1H), 8.22 – 8.18 (m, 3H), 7.91 (d, J = 8.6 Hz, 1H), 7.86 (d,

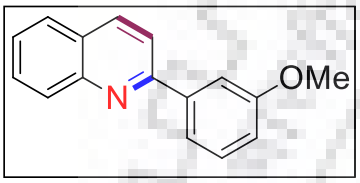
J = 7.9 Hz, 1H), 7.76 (t, *J* = 4.9 Hz, 1H), 7.58 – 7.54 (m, 3H), 7.50 (t, *J* = 2.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.41, 148.31, 139.72, 136.75, 129.69, 129.34, 129.33, 128.87, 127.66, 127.49, 127.20, 126.31, 119.07.

2-(4-Methoxyphenyl)quinoline (50) [27]**:**



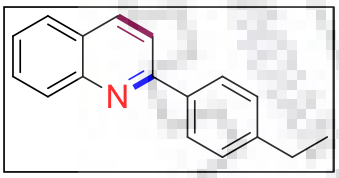
Following the general procedure A, the title product was obtained as a colourless solid (70% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.11 (m, 4H), 7.81 (dd, *J* = 13.1, 8.4 Hz, 2H), 7.70 (t, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.89, 157.00, 148.37, 136.71, 132.35, 129.64, 128.96, 127.51, 126.99, 125.97, 118.64, 114.26, 55.48.

2-(3-Methoxyphenyl)quinoline (51) [24]**:**



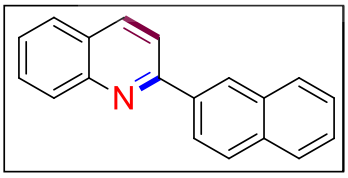
Following the general procedure A, the title product was obtained as a colourless oil (90% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (t, *J* = 8.5 Hz, 2H), 7.87 (dd, *J* = 18.2, 8.3 Hz, 2H), 7.81 (s, 1H), 7.75 (dd, *J* = 14.8, 7.9 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.05 (dd, *J* = 8.1, 2.3 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.16, 157.17, 148.24, 141.19, 136.70, 129.69, 127.49, 127.29, 126.36, 120.04, 119.16, 119.11, 115.40, 112.76, 112.70, 55.48.

2-(4-Ethylphenyl)quinoline (52) [27]**:**



Following the general procedure A, the title product was obtained as a colourless solid (74% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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 NMR (100 MHz, $CDCl_3$) δ 157.50, 148.41, 145.83, 137.26, 136.73, 129.77, 129.65, 128.45, 127.64, 127.53, 127.19, 126.15, 119.00, 28.82, 15.66.

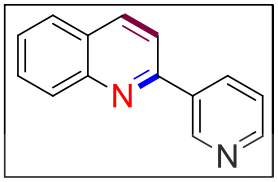
2-(Naphthalen-2-yl)quinoline (53) [27]**:**



Following the general procedure A, the title product was obtained as a colourless solid (70% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 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 NMR (125 MHz, $CDCl_3$) δ 157.20, 148.39, 136.99, 136.91, 133.88,

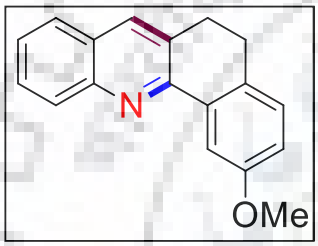
133.52, 129.78, 128.86, 128.62, 128.46, 127.76, 127.54, 127.25, 127.13, 126.75, 126.37, 119.19, 115.00.

2-(Pyridin-3-yl)quinoline (54) [28]**:**



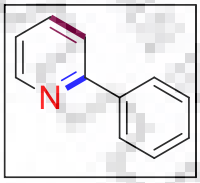
Following the general procedure A, the title product was obtained as a colourless solid (58% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, J = 1.6 Hz, 1H), 8.69 (dd, J = 4.8, 1.5 Hz, 1H), 8.53 – 8.48 (m, 1H), 8.26 (d, J = 8.5 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.86 (dd, J = 12.8, 8.4 Hz, 2H), 7.75 (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 NMR (100 MHz, $CDCl_3$) δ 154.72, 150.29, 148.90, 148.45, 137.29, 135.23, 135.07, 130.10, 129.83, 127.65, 127.46, 126.89, 123.76, 118.62.

2-Methoxy-5,6-dihydrobenzo[*c*]acridine (55):



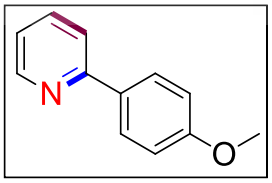
Following the general procedure A, the title product was obtained as a colourless solid (71% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.11 (t, 2H), 7.90 (s, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.64 (dd, J = 8.2, 7.1 Hz, 1H), 7.47 (dd, J = 8.0, 7.0 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 6.94 (dd, J = 8.3, 2.8 Hz, 1H), 3.96 (s, 3H), 3.12 – 3.06 (m, 2H), 2.96 – 2.90 (m, 2H): ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.16, 153.37, 147.63, 135.76, 133.80, 131.96, 130.77, 129.50, 129.09, 128.71, 128.00, 127.00, 126.18, 117.03, 109.73, 55.67, 29.19, 27.64; HRMS (ESI): Calculated for $[C_{18}H_{16}NO]^+$ 262.1226; Found 262.1219.

2-phenylpyridine (56) [24]**:**



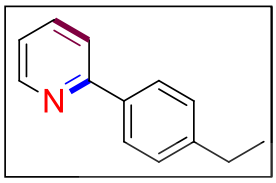
Following the general procedure A, the title product was obtained as a colourless oil (55% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, J = 4.5 Hz, 1H), 8.04 (dd, J = 6.1, 1.4 Hz, 2H), 7.77 (t, J = 8.6 Hz, 2H), 7.54 – 7.47 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.51, 145.19, 139.43, 136.79, 128.81, 128.54, 126.94, 122.13, 120.62.

2-(4-Methoxyphenyl)pyridine (57) [24]**:**



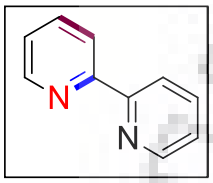
Following the general procedure A, the title product was obtained as a colourless oil (49% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 4.1 Hz, 1H), 8.00 – 7.95 (m, 2H), 7.73 (ddd, J = 20.6, 13.4, 4.9 Hz, 1H), 7.20 (ddd, J = 7.2, 4.8, 1.2 Hz, 1H), 7.03 (d, J = 8.9 Hz, 2H), 6.96 (d, J = 8.9 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.45, 157.14, 149.50, 136.71, 132.03, 128.18, 121.43, 119.85, 114.12, 55.36.

2-(4-Ethylphenyl)pyridine (58) [29]**:**



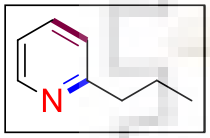
Following the general procedure A, the title product was obtained as a colourless oil (53% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 4.6 Hz, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.79 – 7.72 (m, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.31 – 7.14 (m, 4H), 2.67 (dd, J = 15.6, 7.8 Hz, 2H), 1.32 – 1.29 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.55, 145.30, 136.87, 128.31, 126.86, 125.93, 121.79, 120.32, 115.00, 28.66, 15.53.

2,2'-Bipyridine (59) [30]**:**



Following the general procedure A, the title product was obtained as a colourless solid (48% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 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 NMR (125 MHz, $CDCl_3$) δ 156.17, 149.33, 136.97, 123.74, 121.12.

2-Propylpyridine (60) [31]**:**



Following the general procedure A, the title product was obtained as a colourless oil (50% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, J = 4.1 Hz, 1H), 7.60 (td, J = 7.7, 1.8 Hz, 1H), 7.16 (d, J = 7.8 Hz, 1H), 7.11 (dd, J = 6.9, 5.4 Hz, 1H), 2.81 – 2.77 (m, 2H), 1.81 – 1.72 (m, 2H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.30, 149.17, 136.19, 122.75, 120.88, 40.40, 23.13, 13.84.

[3A.5] Spectra of selected compounds:

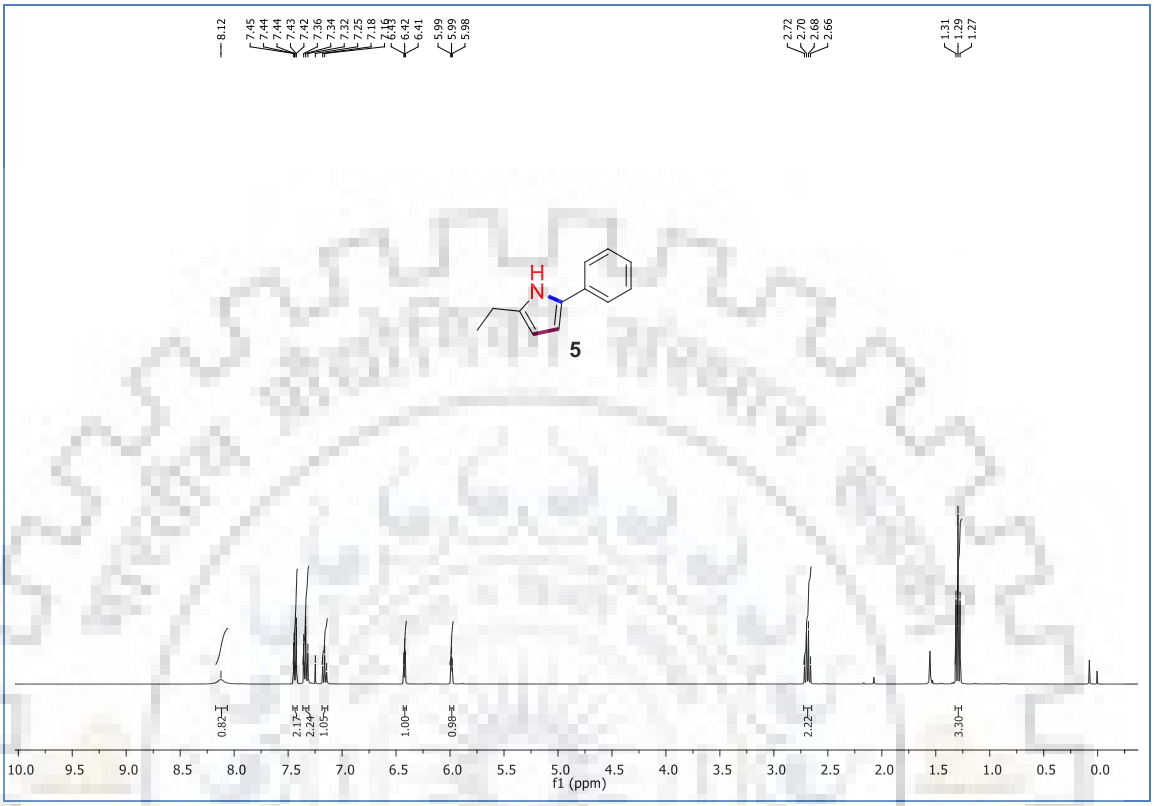


Figure 2a: ^{1}H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **5**

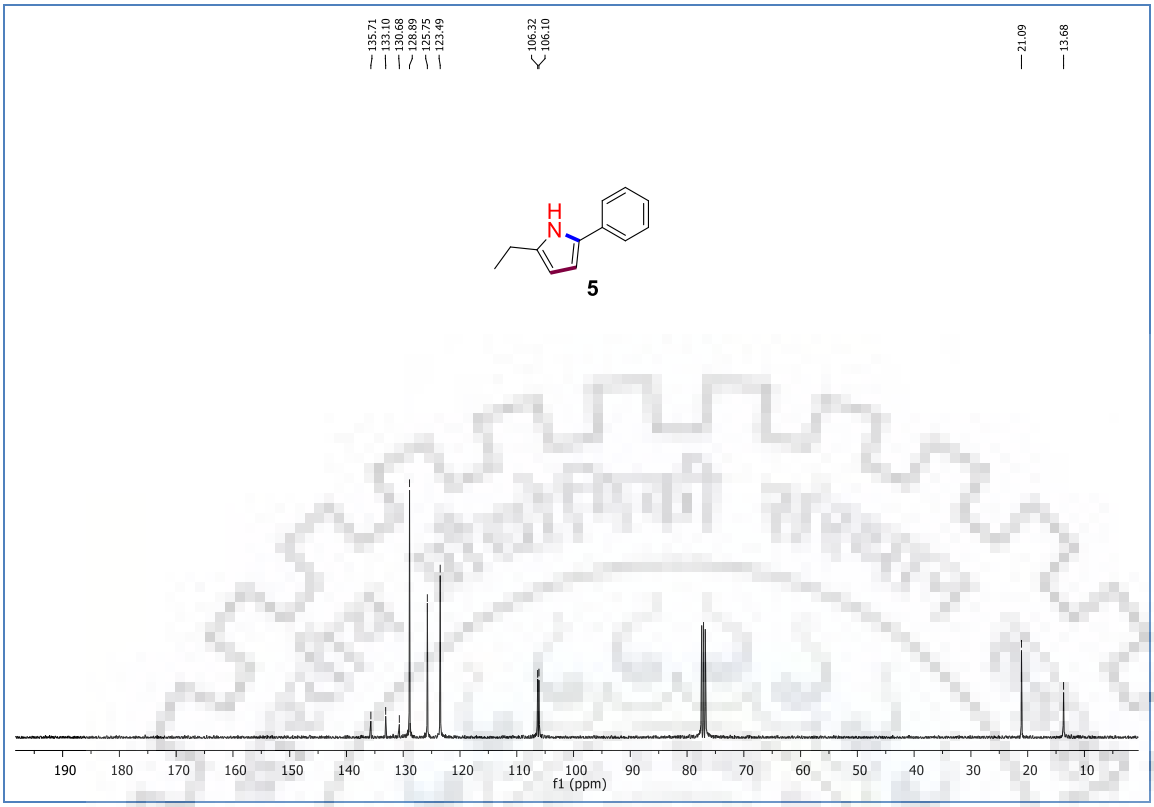


Figure 2b: ^{13}C NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **5**

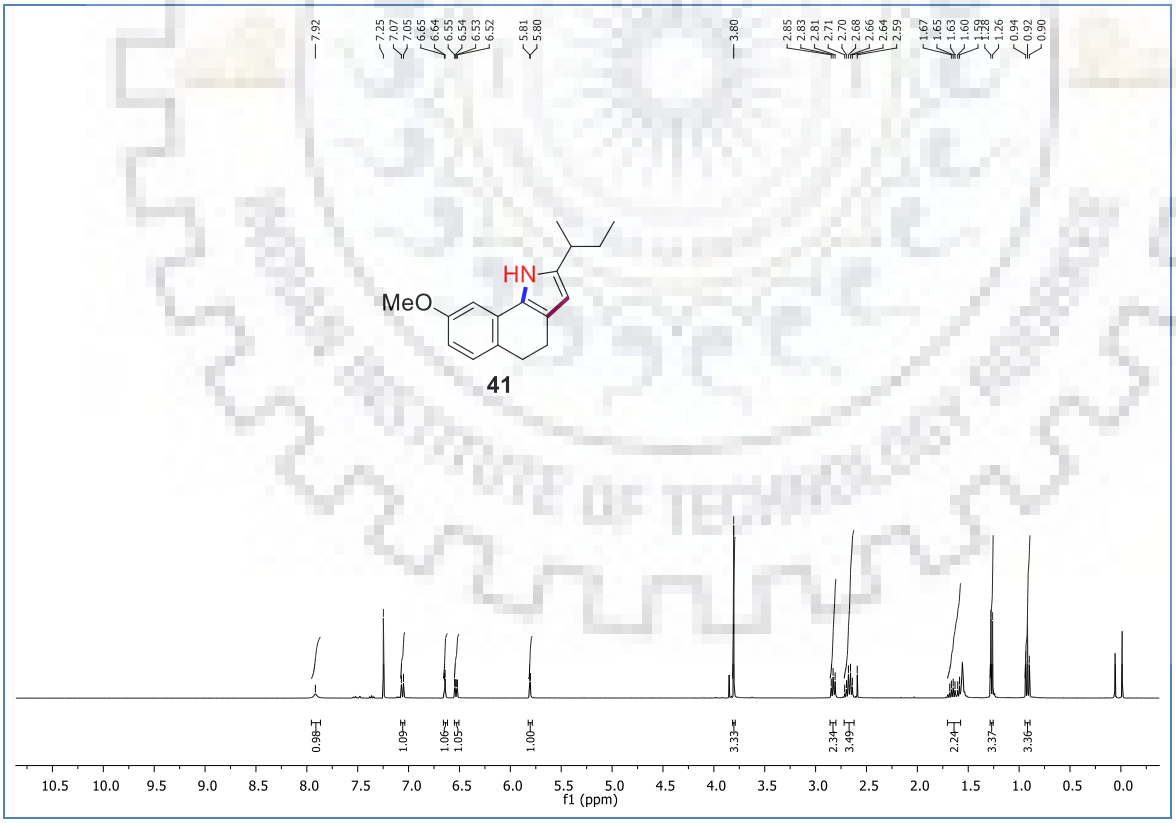


Figure 3a: ^{1}H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **41**

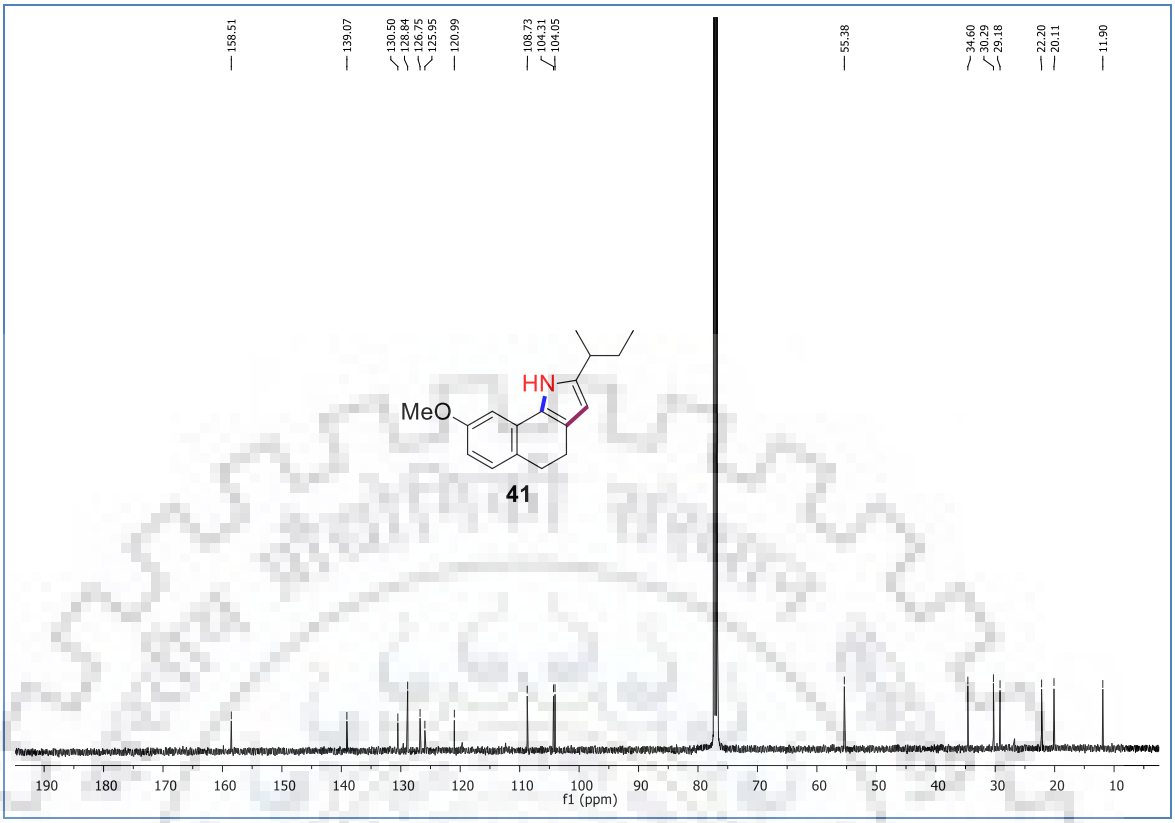


Figure 3b: ^{13}C NMR ($CDCl_3$, 125 MHz) Spectrum of Compound **41**

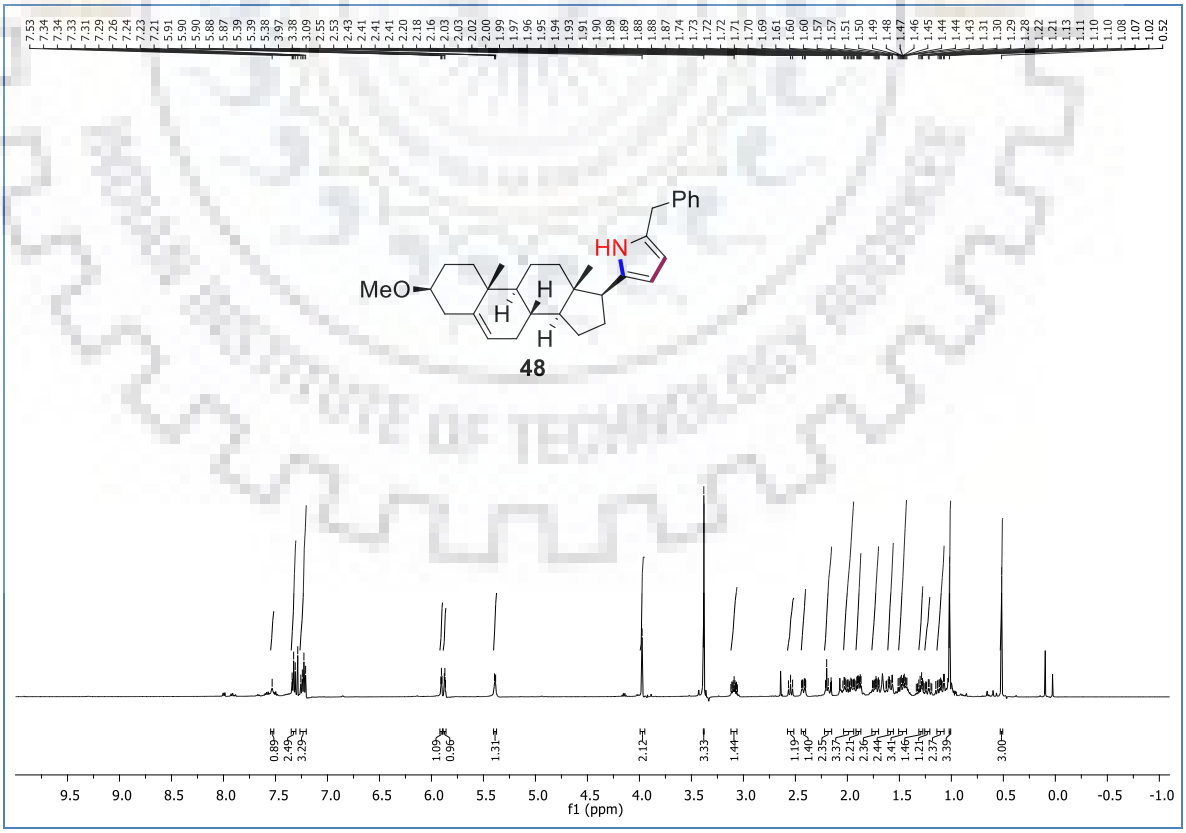


Figure 4a: ^{1}H NMR ($CDCl_3$, 500 MHz) Spectrum of Compound **48**

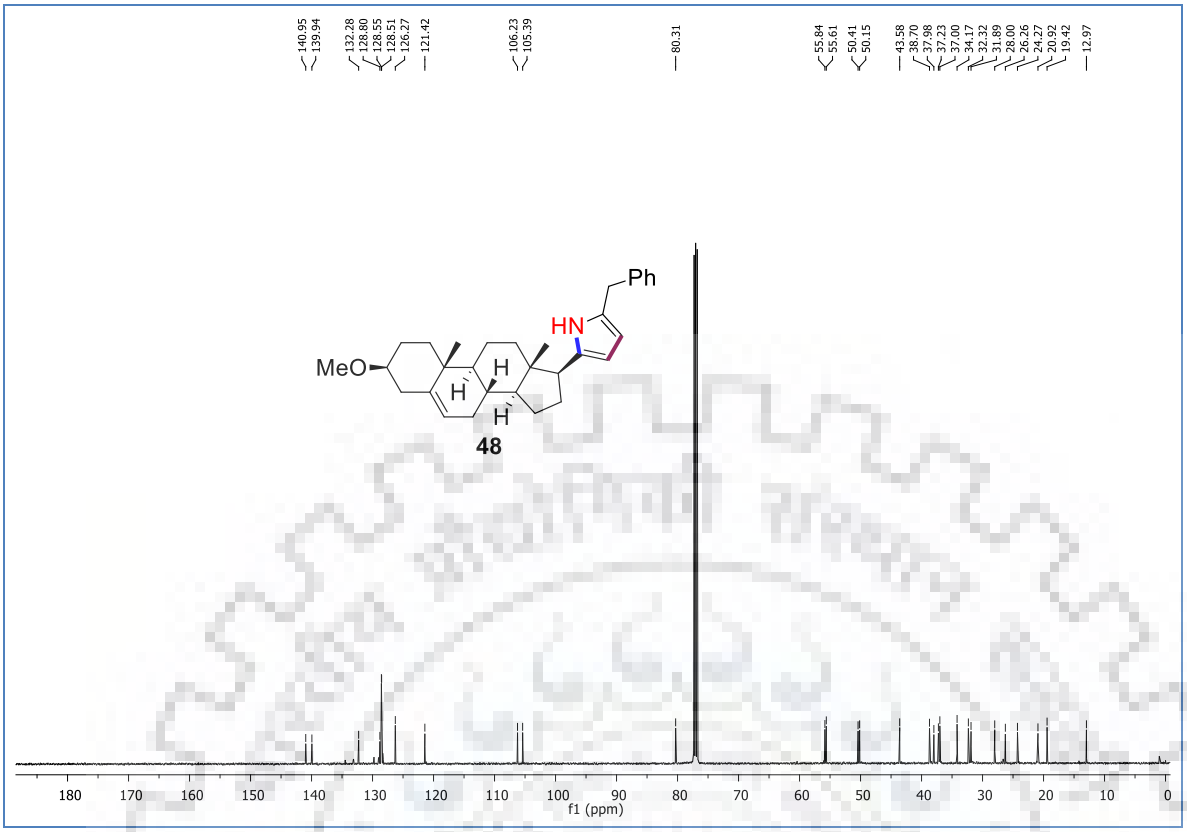


Figure 4b: ^{13}C NMR ($CDCl_3$, 125 MHz) Spectrum of Compound **48**

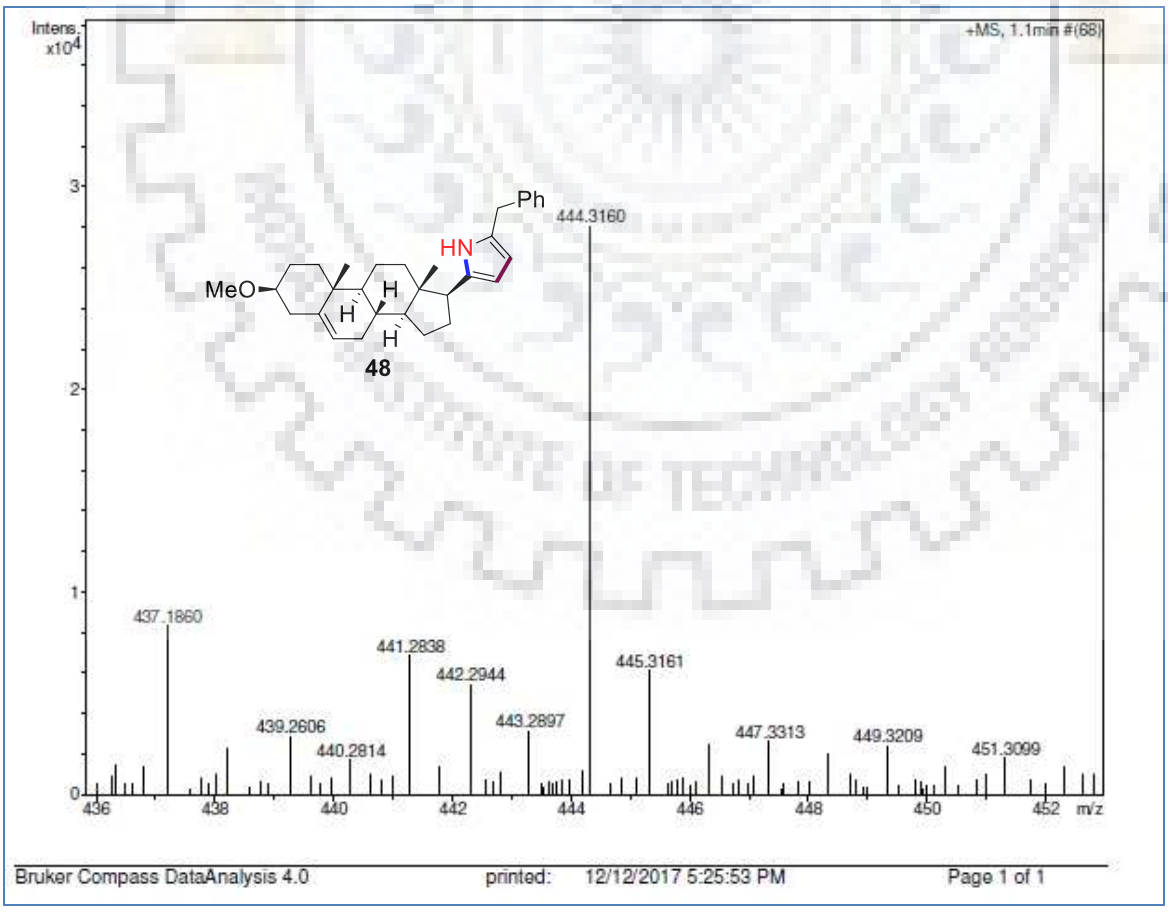


Figure 4c: HRMS (ESI) Spectrum of Compound **48**

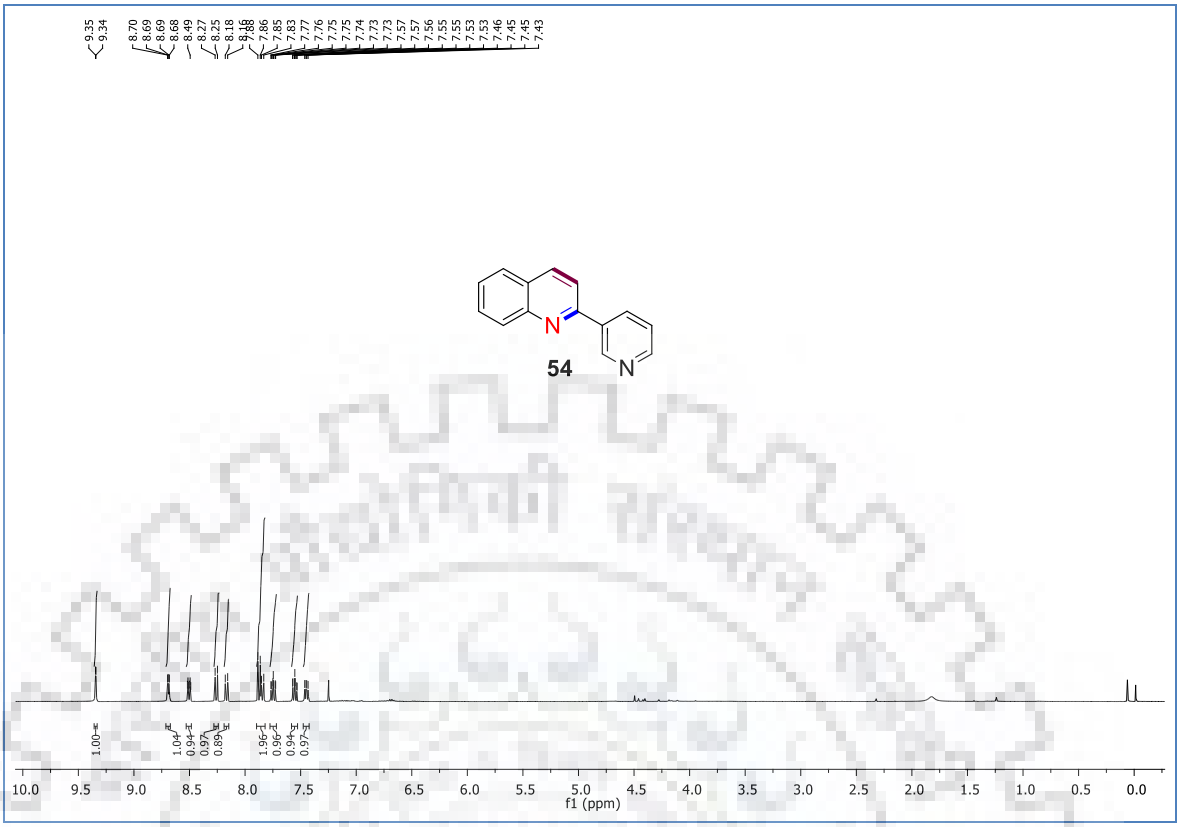


Figure 5a: ^{1}H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **54**

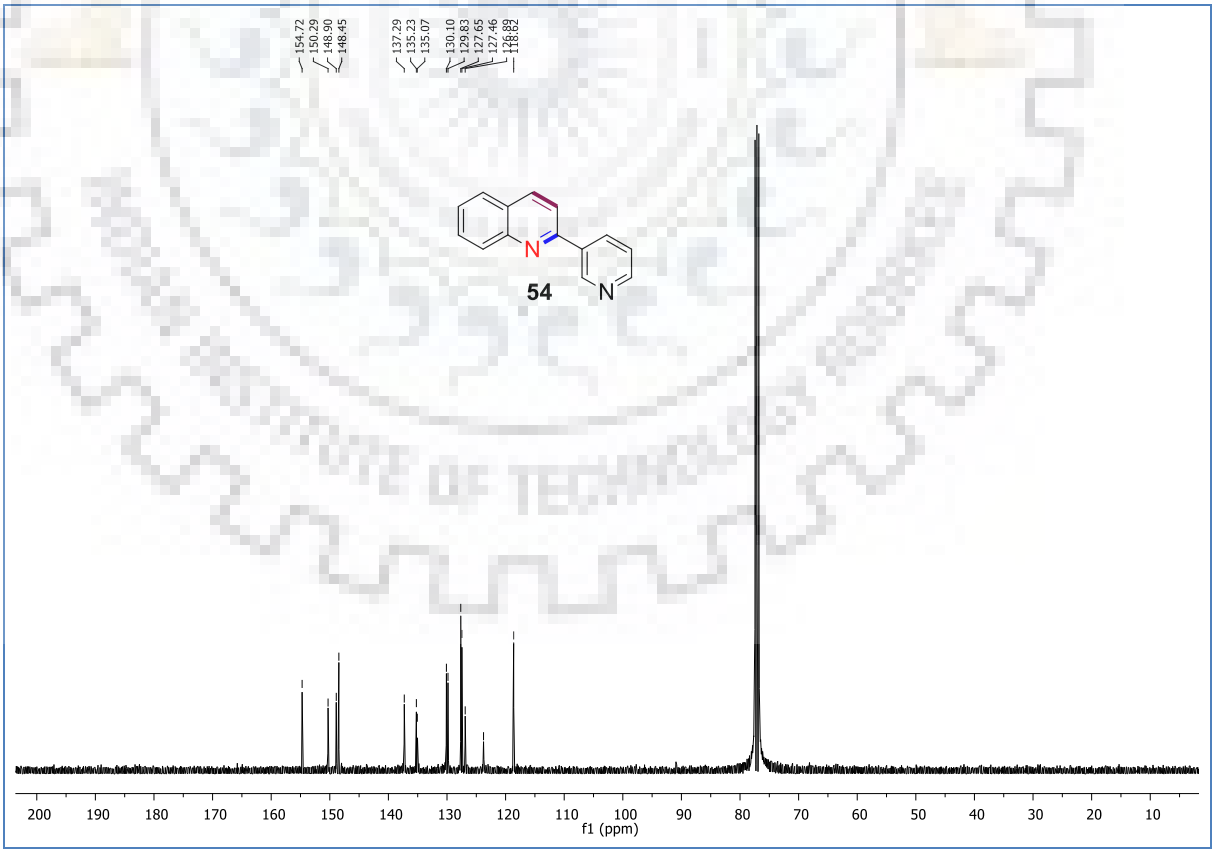
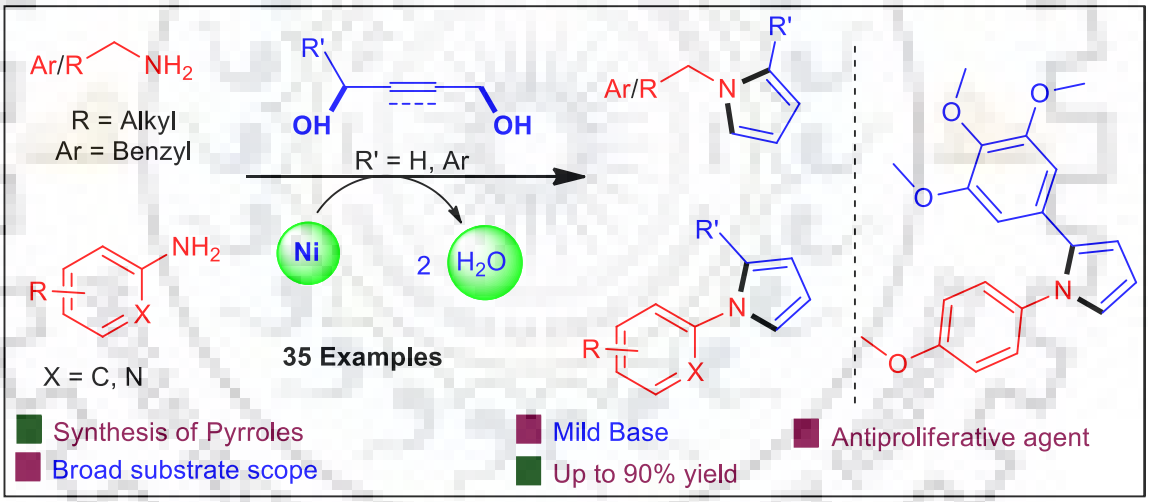


Figure 5b: ^{13}C NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **54**

Chapter-3: Section-B: Nickel-catalyzed synthesis of pyrroles from unsaturated diols and amines

The development of operational simple and inexpensive catalytic system that utilize renewable resources and convert them into key chemicals using base metal-catalysts is highly desirable. Herein, we reported the Ni-catalyzed dehydrogenative strategy for pyrroles formations using butene-1,4-diols and butyne-1,4-diols with a series of aryl, alkyl and hetero-aryl amines. The catalytic protocol is tolerant to free alcohol, halides, alkyl, alkoxy, oxygen heterocycles, activated benzyl and pyridines moieties and resulted in up to 90% yield. Initial mechanistic studies were performed to establish the hydrogen-borrowing strategy for pyrrole synthesis.



J. Org. Chem., **2018**, *83*, 15406-15414

Chapter 3 Section B: Nickel-Catalyzed Sustainable Synthesis of Pyrroles from Unsaturated Diols and Primary Amines

[3B.1] Introduction

Pyrroles are omnipresent in natural products, drugs, functional materials and are used as intermediate in the synthesis of bioactive molecules and as ligands in catalysis (Figure 1).[1] Poly-pyrroles have extensively used in material chemistry, batteries, and in solar cells.[2] Classical methodologies, as well as others multi-step transformations are well known for pyrroles synthesis, unfortunately, harsh reaction conditions, special substrate design including generation of stoichiometric waste are key limitations.[3]

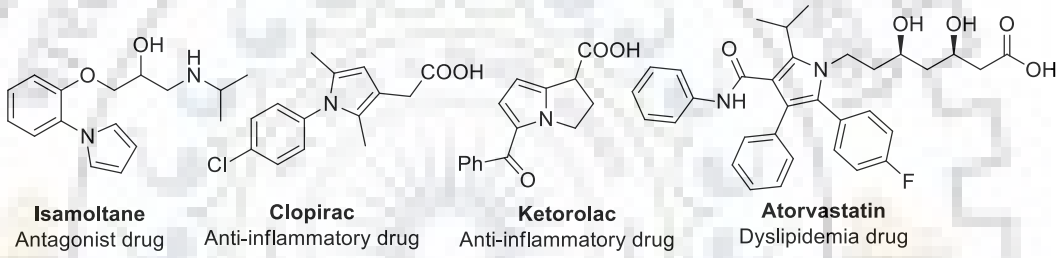


Figure 1: Selected examples of important pharmaceuticals having *N*-substituted pyrroles functionalities

The application of renewable resources to establish sustainable, atom-economic and environmentally benign technology for the production of bulk and special chemicals is a challenging goal in chemical research.[4] More specifically, utilization of most abundant and inexpensive alcohols, derived from lignocellulose biomass or fermentation process, is an attractive and potential green alternative to the existing metal-catalyzed transformations.[5] Notably, such catalytic (de)hydrogenative transformations follows hydrogen borrowing technology and generates water as sole by product and are in high demand in organic synthesis.[6] Therefore, such process could be more attractive if selectively used for pyrrole synthesis in a tandem fashion in one pot operation.[1]

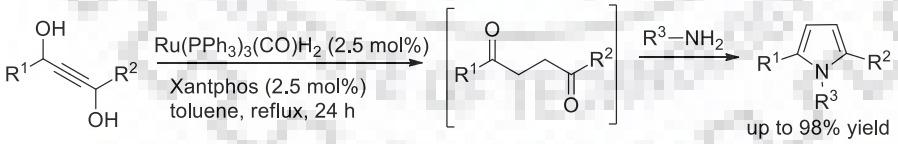
As a result, the recent surge is to develop more vibrant and potential sustainable technology, that utilize abundantly available renewable resources and significantly extend the scope of existing methodologies.[4-5,7] Though, acceptorless dehydrogenation of alcohols

widely used for pyrrole synthesis, often associated with several limitations and have already been briefly discussed in chapter 3A. Further, unsaturated version of diols, such as, *cis*-butene-1,4-diol or butyne-1,4-diol could be used for construction of pyrroles with suitable amines.

The aim of this chapter is to discuss the nickel-catalyzed sustainable pyrrole synthesis using *cis*-butene-1,4-diol or butyne-1,4-diol with suitable amines. Preliminary mechanistic and catalytic studies were also performed to establish the intermolecular cyclization as well as nickel-catalyzed dehydrogenation for pyrrole synthesis. A brief literature report has been presented for the same using various transition metal-catalyzed processes.

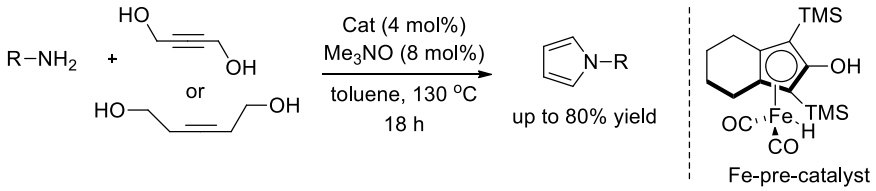
Relevant Literature:

Recently there is a trend to replace the precious noble-metal catalysts by inexpensive non-precious and earth abundant metals. Herein, briefly we will discuss some important examples for pyrrole synthesis using precious as well non-precious metal-catalysts *via* dehydrogenative coupling of alcohols. In Chapter 3A, we have highlighted the important catalytic technologies for pyrrole synthesis using β-amino alcohols in combination with ketones or diols. Still there exist another alternative sustainable strategy for the synthesis of pyrroles using *cis*-butene-1,4-diols or butyne-1,4-diols with primary amines. For instance, in 2007, Williams and co-workers reported a general synthesis of 1,2,5 tri-substituted pyrroles using a variety of 1,4-alkyne diols and anilines in presence of commercially available Ru-catalyst and Xantphos as a ligand (Scheme 1).[8] Thereafter, they have performed extended studies using similar catalytic combination for the synthesis of pyrroles, furans and pyrazines.[9]



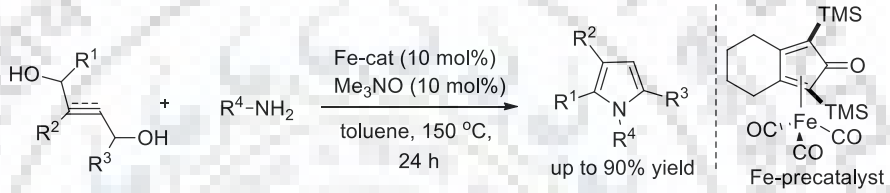
Scheme 1: Synthesis of substituted pyrroles using Ru-catalyst

In this direction, first non-precious metal-catalyzed synthesis of pyrroles was developed by Barta and co-workers using a molecular defined Fe-catalyst. The catalytic protocol establishes the synthesis of a variety of substituted pyrroles using butyne-1,4-diols and *cis*-butene-1,4-diols with anilines, benzyl amines as well as aliphatic amines in moderate to excellent yields. (Scheme 2).[10]



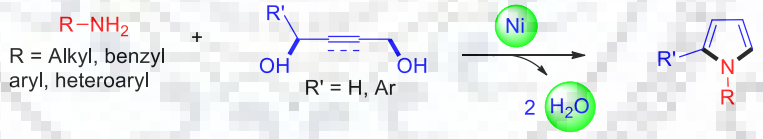
Scheme 2: Fe-catalyzed synthesis of *N*-substituted pyrroles

At the same time, Sundararaju and co-workers also demonstrated the synthesis of C-2/C-3 and C-2/C-4 substituted pyrroles using a similar Fe-catalyst. They have utilized a variety of substituted *cis*-, or *trans*-butene-1,4- diols as well as butyne-1,4-diols and the desired products were obtained in up to 90% yields (Scheme 3).[11]



Scheme 3: Fe-catalyzed synthesis of substituted pyrroles

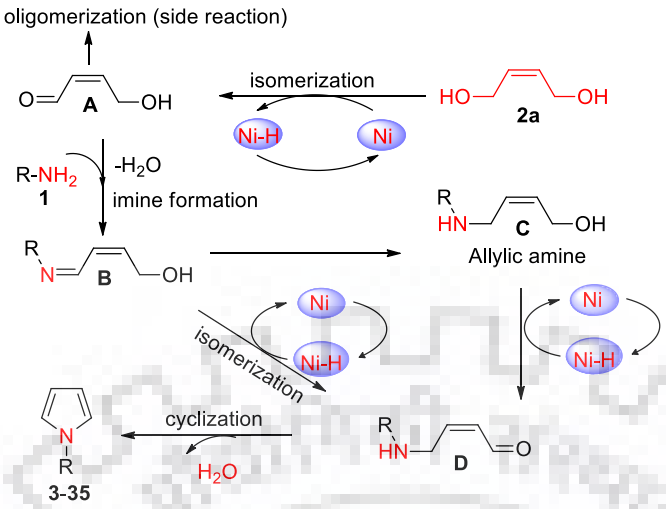
In this present chapter, we will discuss our nickel-catalyzed sustainable process for the synthesis of a vareity of pyrroles using unsaturated 1,4-diols in combination with aryl, alkyl as well as benzyl amines (Scheme 4).



Scheme 4: Nickel-catalyzed sustainable synthesis of pyrroles

[3B.2] Results and Discussion:

In general, it was observed that, free hydroxyl group in unprotected alcohol has very strong binding affinity with Ni-catalyst and resist its further transformations. Having witnessed our Ni-catalyzed intermolecular cyclization of amino alcohols with ketones to interesting *N*-heterocycles (Chapter 3A), we further extended our studies for direct pyrrole synthesis using *cis*-butene-1,4-diol with primary amines (Scheme 5).



Scheme 5: Proposed mechanism for Ni-catalyzed intermolecular cyclization to pyrroles

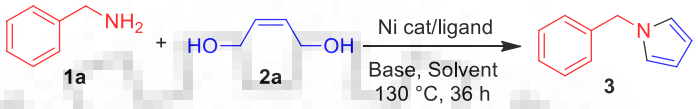
In our continuous efforts for Ni-catalyzed acceptorless dehydrogenation of alcohols, we hypothesized that, initial dehydrogenation of *cis*-butene-1,4-diol **2a** followed by condensation with primary amine **1** resulted the formation of allylic amine intermediate **C**. Thereafter, a second dehydrogenation of alcohol **C** to intermediate **D**, followed by intermolecular cyclization and dehydration lead to the construction of substituted pyrroles **3-35** in one pot operation (Scheme 5). To the best of our knowledge, this represents the first report for Ni-catalyzed intermolecular cyclization of various *cis*-butene-1,4-diol and butyne-1,4-diol with a range of primary amines to substituted pyrroles in a tandem fashion.

Optimization of the catalytic protocol for Ni-catalyzed synthesis of pyrroles.

For optimization of the efficient catalytic system initially we investigated the efficacy of four different nickel precatalysts with bipyridine (bpy) **L1** as ligand of our choice using benzyl amine **1a** and *cis*-butene-1,4-diol **2a** as model reaction (Table 1, entries 1-4). Gratifyingly, only 32% selectivity to pyrrole was obtained using a combination of $NiCl_2$/**L1** (Table 1, entry 2). Further, an increment of *cis*-butene-1,4-diol **2a** significantly increase the product conversion to 75% with 55% isolated yield of **3** (Table 1, entry 5). However, when the reaction was performed using milder base, such as, Na_2CO_3 almost quantitative conversion to product **3** was obtained (Table 1, entry 6). Further, control experiments revealed their potential role as individual catalytic component to achieve higher product conversions. For instance, in absence of base, ligand and catalyst only poor product conversions were observed

(Table 1, entries 9-12). Notably, a combination of 5 mol% $NiCl_2$, 6 mol% bpy **L1**, 1 equivalent of Na_2CO_3 and toluene, as the best solvent, 66% isolated yield of **3** was obtained (Table 1, entry 6).

Table 1: Catalytic screening for Ni-catalyzed synthesis of pyrrole from **1a** with **2a**. [a]

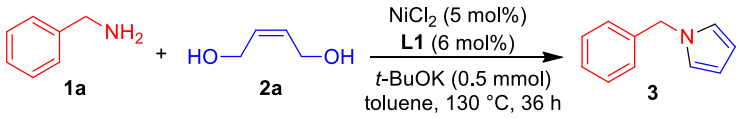


Entry	catalyst	Ligand	Base	**3** Conv. (%) [b,c]
1	$NiBr_2$	**L1**	*t*-BuOK	22
2	$NiCl_2$	**L1**	*t*-BuOK	32
3	$Ni(acac)_2$	**L1**	*t*-BuOK	5
4	$NiCl_2$.DME	**L1**	*t*-BuOK	18
5	$NiCl_2$	**L1**	*t*-BuOK	75(55)
6	$NiCl_2$	**L1**	Na_2CO_3	92(66)
7[d]	$NiCl_2$	**L1**	Na_2CO_3	62
8[e]	$NiCl_2$	**L1**	Na_2CO_3	55
9	$NiCl_2$	**L1**	-	9
10	-	**L1**	Na_2CO_3	13
11	$NiCl_2$	-	Na_2CO_3	35
12	-	-	Na_2CO_3	7

[a] Unless specified (entries 1-4), the reaction was carried out with benzyl amine **1a** (0.5 mmol), *cis*-2-butene-1,4-diol **2a** (1.0 mmol), Ni-cat. (0.05 mmol), **L** (0.06 mmol), and *t*-BuOK (0.5 mmol) under an N_2 atmosphere at 130 °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] Entries 5-12, **2a** (2.0 mmol) was used. [d] 120 °C was used. [e] 110 °C was used.

To understand the potential role of the other catalytic components we have performed optimization studies using alcohols, amines, solvents as well as ligands and catalyst loading. When using 1:1 ratio of benzyl amine and *cis*-butene-1,4-diol, we observed only 35% conversions to the product **3**. As reported in literature, *cis*-butene-1,4-diol highly prone to undergo oligomerizations and we observed poor product formation (Scheme 5 and Table 2, entry 1). Thereafter an increment of the amount of alcohols we observed 75% conversions to product **3** with 55% isolated yield (Table 2, entries 2-3).

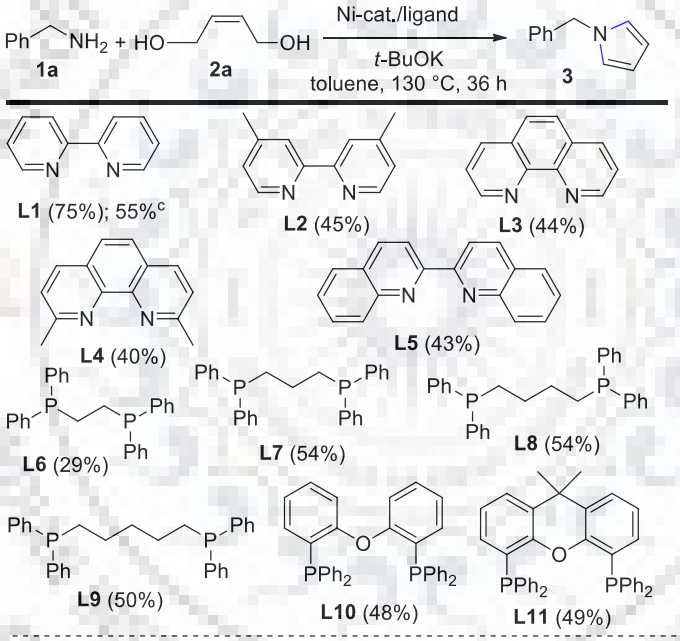
Table 2: Screening of alcohol equivalents [a]



Entry	2a (X mmol)	GC-MS conversion of 3 (%)
1	1	32
2	1.5	55
3	2	75(55)[b]

[a] Reaction conditions: Benzyl amine **1a** (0.5 mmol), *cis*-2-butene-1,4-diol **2a** (**X** mmol), $NiCl_2$ (5 mol%), **L1** (6 mol%), *t*-BuOK (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 130 °C oil bath, 36 h reaction time. [b] Isolated yield.

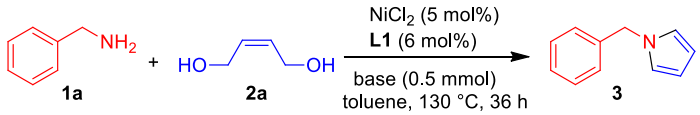
Table 3: Ligand screening for Ni-catalyzed pyrrole synthesis [a]



[a] Unless specified, the reaction was carried out with benzyl amine **1a** (0.5 mmol), *cis*-2-butene-1,4-diol **2a** (1.0 mmol), $NiCl_2$ (5 mol%), ligand (6 mol%), *t*-BuOK (1.0 equiv.) under N_2 atmosphere at 130 °C in toluene (2.0 mL) for 36 h. [b] Conversion of **3** was determined by GC-MS. [c] Isolated yield.

Next, we started screening of a series of nitrogen and phosphorus ligands **L2-L11** with variable electronic and steric nature and did not influence much on the product selectivity and resulted only 29-54% conversion to product (Table 3). Further, screening of different bases, such as, *t*-BuONa, K_2CO_3, K_3PO_4, and Cs_2CO_3 under identical condition proof inefficient. While milder base Na_2CO_3 showed higher selectivity to product and resulted in up to 92% yield (Table 4).

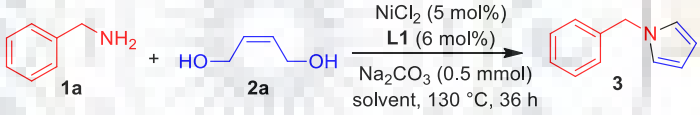
Table 4: Screening of base [a]



Entry	Base	GC-MS conversion of 3 (%)
1	*t*-BuONa	24
2	*t*-BuOK	75 (55)[b]
3	K_2CO_3	20
4	Na_2CO_3	92 (66)[b]
5	K_3PO_4	22
6	Cs_2CO_3	35
7	-	9

[a] Reaction conditions: Benzyl amine **1a** (0.5 mmol), *cis*-2-butene-1,4-diol **2a** (2.0 mmol), $NiCl_2$ (5 mol%), **L1** (6 mol%), **base** (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 130 °C oil bath, 36 h reaction time. [b] Isolated yield.

Table 5: Screening of solvents [a]

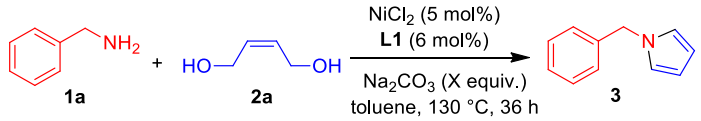


Entry	Solvent	GC-MS conversion of **3** (%)
1	Toluene	92 (66)[b]
2	Xylene	5
3	1,4-Dioxane	7
4	DMA	1
5	DMF	35
6	THF	52
7	*t*-Amyl alcohol	4

[a] Reaction conditions: Benzyl amine **1a** (0.5 mmol), *cis*-2-butene-1,4-diol **2a** (2.0 mmol), $NiCl_2$ (5 mol%), **L1** (6 mol%), Na_2CO_3 (0.5 mmol), **solvent** (2.0 mL), Schlenk tube under N_2 atmosphere, 130 °C oil bath, 36 h reaction time. [b] Isolated yield.

Further, when toluene get replaced by different non-polar and polar solvents, such as, xylene, 1-4-dioxane, *N*,*N*-dimethyl formamide, *N*-*N*-dimethyl acetamide, tetrahydrofuran as well as *t*-amyl-alcohol, resulted moderate to poor product yields (Table 5, entries 1-7). Base also plays a crucial role in the pyrrole synthesis and control experiments using variable amount of base did not improve the product yield further (Table 6, entries 1-4).

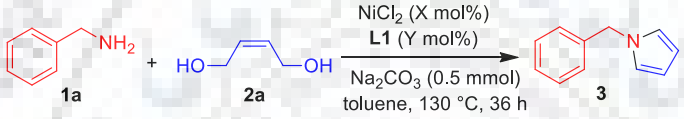
Table 6: Screening of base equivalents [a]



Entry	Na_2CO_3 equivalents	GC-MS conversion of **3** (%)
1	1.0	92(66)[b]
2	0.75	62
3	0.50	50
4	0.25	40

[a] Reaction conditions: Benzyl amine **1a** (0.5 mmol), *cis*-2-butene-1,4-diol **2a** (2.0 mmol), $NiCl_2$ (5 mol%), **L1** (6 mol%), Na_2CO_3 (**X** equiv.), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 130 °C oil bath, 36 h reaction time. [b] Isolated yield.

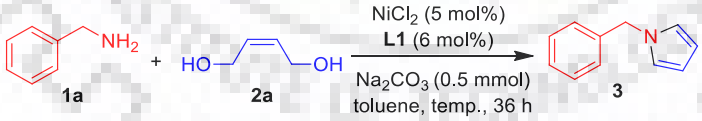
Table 7: Screening of catalyst/ligand loading [a]



Entry	$NiCl_2$ (X mol %)	bpy (Y mol%)	GC-MS conversion of 3 (%)
1	5	6	92 (66)[b]
2	2.5	3	36
3	1.0	1.2	25
5	-	-	7

[a] Reaction conditions: Benzyl amine **1a** (0.5 mmol), *cis*-2-butene-1,4-diol **2a** (2.0 mmol), $NiCl_2$ (**X** mol%), **L1** (**Y** mol%), Na_2CO_3 (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 130 °C oil bath, 36 h reaction time. [b] Isolated yield.

Table 8: Screening of temperature [a]

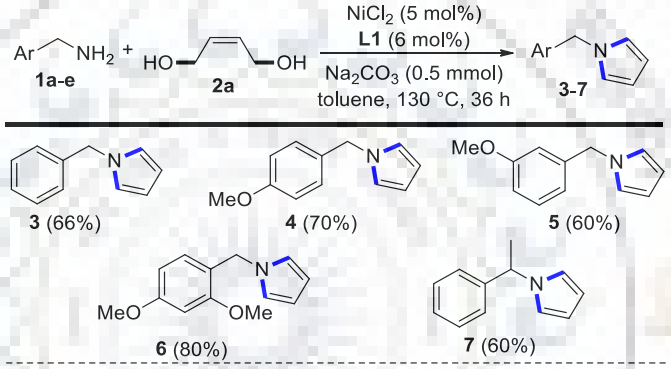


Entry	**Temp. (°C)**	**GC-MS conversion of 3 (%)**
1	130	92 (66) [b]
2	120	62
3	110	55

[a] Reaction conditions: Benzyl amine **1a** (0.5 mmol), cis-2-butene-1,4-diol **2a** (2.0 mmol), $NiCl_2$ (5 mol%), **L1** (6 mol%), Na_2CO_3 (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 110-130 °C oil bath, 36 h reaction time. [b] Isolated yield.

Ligands also playing a crucial role in controlling the product selectivity. For instance, any changes of catalyst and ligand loading drastically reduced the product yield. However, application of 5 mol% of catalyst in combination with 6 mol% of ligand furnished maximum selectivity with 66% isolated yield (Table 7, entries 1-4). Nevertheless, control experiment in absence of catalyst and ligand resulted albeit with poor product yield (Table 7, entry 5). It is noteworthy to mention that, lowering of reaction temperature also reduced the catalytic efficiency and resulted 55-62% product conversion in comparison to optimized conditions (Table 8, entries 1-3).

Table 9: Scope of benzyl amines [a]



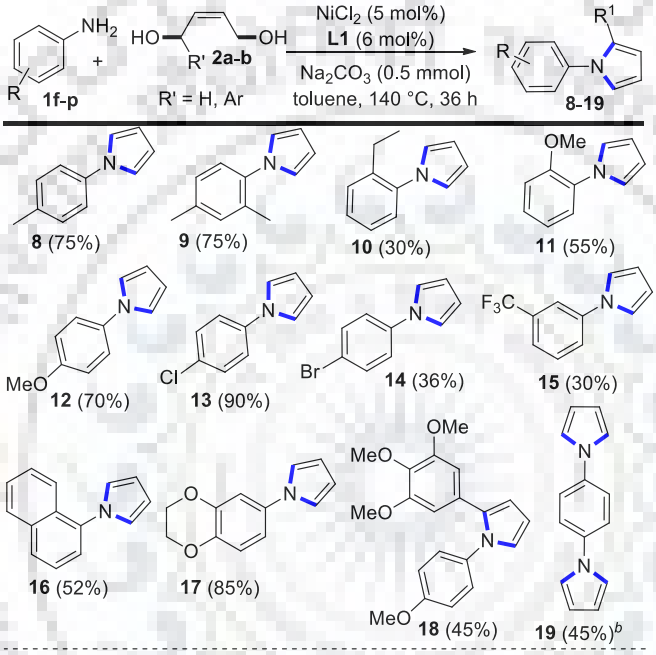
[a] Reaction conditions: **1** (0.5 mmol), *cis*-2-butene-1,4-diol **2a** (2.0 mmol), $NiCl_2$ (5 mol%), **L1** (6 mol%), Na_2CO_3 (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 130 °C oil bath, 36 h reaction time. Isolated yield in parenthesis.

After having optimized conditions in hand, we explored the scope and limitations of the catalytic protocol using electronically different various benzyl amines with *cis*-butene-1,4-diol (Table 9). For instance, *p*- and *m*-methoxy benzyl amines resulted desired pyrroles in 60-70% yields (**4** and **5**). However, when 2,4-dimethoxy benzyl amine was used as coupling partner, 80% yield of pyrrole **6** was obtained. To our delight, α-methyl benzyl amine also efficiently transformed into the desired pyrrole in 60% yield (Table 9, **7**).

Thereafter, we studied the pyrrole synthesis using a series of electronically different anilines with *cis*-butene-1,4-diols. For instance, anilines substituted with methyl or methoxy groups resulted a series of interesting pyrroles in up to 75% yields (Table 10, **8-9**, and **11-12**). Sterically hindered *o*-ethyl aniline as well as *p*-bromo and *m*-trifluoromethyl anilines resulted

only poor product yield (Table 10, **10**, **14-15**). Excellent yield of pyrrole was obtained with *p*-chloro (**13**) and 1,4-dioxolone anilines (**17**). Pleasingly, 1-naphthyl aniline resulted respective pyrrole in 52% yield (**16**). To our delight, C-2 substituted pyrrole was obtained when 3,4,5-trimethoxy phenyl substituted *cis*-butene-1,4-diols was used as coupling partner (Table 10, **18**).

Table 10: Scope of anilines and alcohols [a]



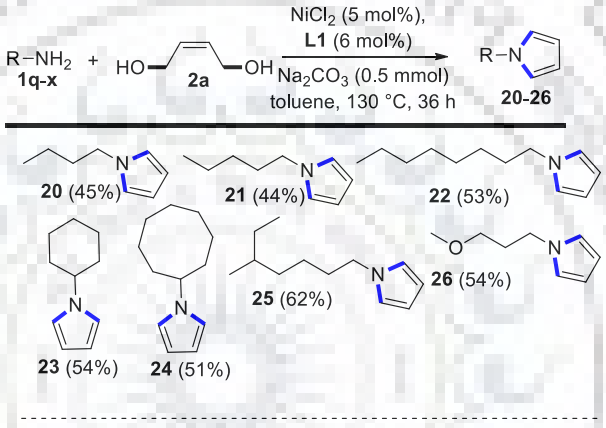
[a] Reaction conditions: **1** (0.5 mmol), **2** (2.0 mmol), $NiCl_2$ (5 mol%), **L1** (6 mol%), Na_2CO_3 (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 140 °C oil bath, 36 h reaction time. [b] **2a** (4.0 mmol), $NiCl_2$ (10 mol%), **L1** (12 mol%), Na_2CO_3 (1.0 mmol) was used. Isolated yield was reported.

Next, we studied the reactivity profile of more challenging acyclic and cyclic alkyl amines with *cis*-butene-1,4-diol as coupling partner for pyrrole synthesis (Table 11). Gratifyingly, alkyl amines, such as, butyl, pentyl, octyl and 3-methylheptyl amines as well as cyclohexyl and cyclooctyl amines resulted in up to 62% yield of pyrroles (Table 11, **20-25**). Additionally, substituted γ-amino alcohol could efficiently use for pyrrole synthesis and resulted 54% yield of pyrrole (Table 11, **26**).

Subsequently, we employed more exciting 2-aminopyridines for catalytic pyrrole synthesis using our optimized protocol (Table 12). In general pyridines are often known to poison the

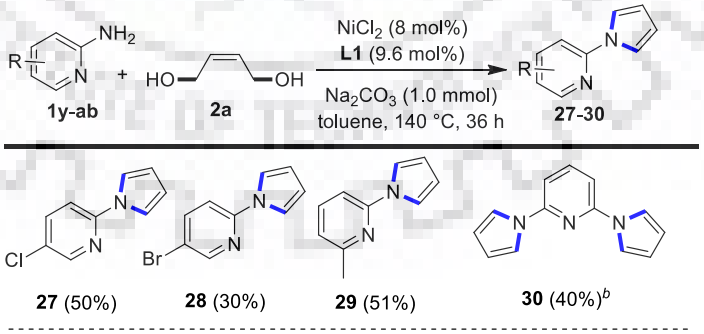
catalysts, hence diminished the reactivity. Notably, we observed moderate to fair reactivity with chloro, bromo as well as methyl-substituted 2-aminopyridines and resulted pharmaceutically active *N*-heterocyclic pyrrole derivatives in up to 51% yield (Table 12, **27-29**). Additionally, we extended the catalytic protocol in the synthesis of symmetrical *bis*-pyrroles. Importantly, *cis*-butene-1,4-diol **2a** was utilized as coupling partner with 1,4-diamino benzene as well as 2,6-di-amino pyridine, and respective *bis*-pyrroles were obtained in reasonable yields (Table 10, **19** and Table 12, **30**).

Table 11: Synthesis of pyrroles from alkyl amines [a]



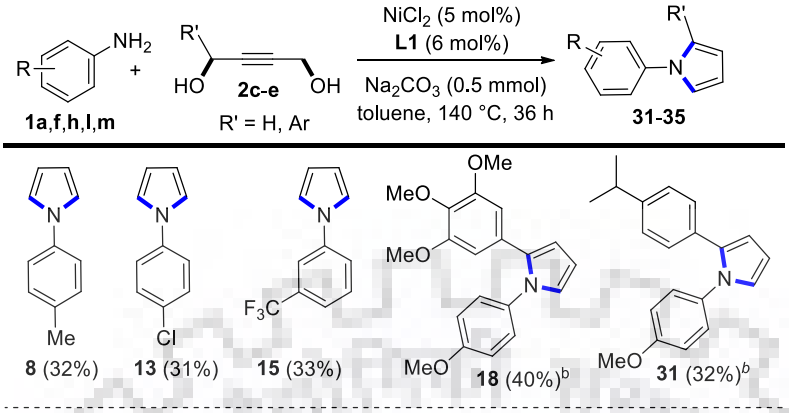
[a] Reaction conditions: **1** (0.5 mmol), *cis*-2-butene-1,4-diol **2a** (2.0 mmol), $NiCl_2$ (5 mol%), **L1** (6 mol%), Na_2CO_3 (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 130 °C oil bath, 36 h reaction time. Isolated yield was reported.

Table 12: Synthesis of pyrroles from 2-aminopyridines [a]



[a] Reaction conditions: **1** (0.5 mmol), *cis*-2-butene-1,4-diol **2a** (2.0 mmol), $NiCl_2$ (8 mol%), **L1** (9.6 mol%), Na_2CO_3 (1.0 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 140 °C oil bath, 36 h reaction time. Isolated yield in parenthesis. [b] **2a** (4.0 mmol), $NiCl_2$ (10 mol%), **L1** (12 mol%), was used.

Table 13: Synthesis of pyrroles from butyne-1,4-diols [a]

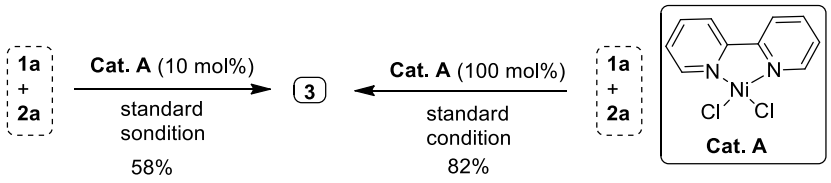


[a] Reaction conditions: **1** (0.5 mmol), butyne-1,4-diol **2** (2.0 mmol), $NiCl_2$ (5 mol%), **L1** (6 mol%), Na_2CO_3 (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 140 °C oil bath, 36 h reaction time. [b] Na_2CO_3 (1.0 mmol). Isolated yield was reported.

Having established the excellent catalytic activity with *cis*-butene-1,4-diols, the generality of our nickel-catalyzed protocol was further evaluated using butyne-1,4-diols as coupling partner for pyrrole synthesis (Table 13). For instance, application of electronically, different anilines with butyne-1,4-diols, **2c**-**2e** resulted respective pyrroles in moderate yields (Table 13). We are pleased to witness an alternative synthesis of pyrroles using nickel-catalysts *via* intermolecular cyclization.

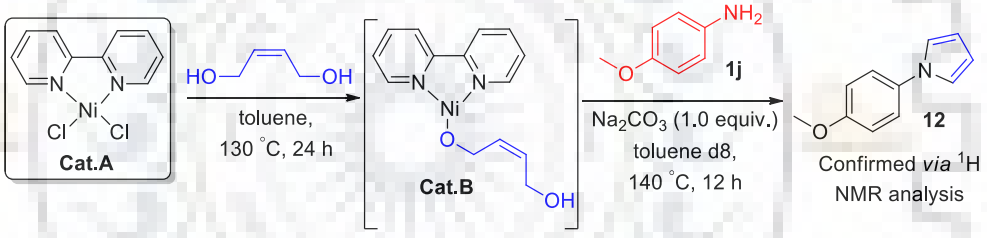
Notably, the catalytic protocol is tolerant to primary alcohol, halides, alkyl, alkoxy, trifluoro-methyl and oxygen heterocycles, including benzyl and pyridine derivatives. Gratifyingly, remarkable transformations in the presence of alkyl amines and 2-amino pyridines evident the synthetic potential of the newly established catalytic system.

Catalytic and mechanistic studies: After witnessed the excellent catalytic activities, we wanted to establish the reaction pathways for pyrrole synthesis and to understand the nature of the putative Ni-intermediate species. Therefore, **Cat. A** was readily prepared using literature procedure [12] and was independently employed in catalytic (10 mol%) as well as in stoichiometric equiv. (100 mol%) for intermolecular pyrrole synthesis in the reaction of **1a** with **2a** under standard conditions. To our delight, we observed 58% and 82% conversion to product **3** (Scheme 6).

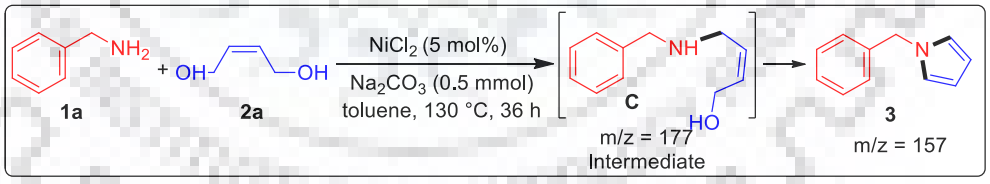


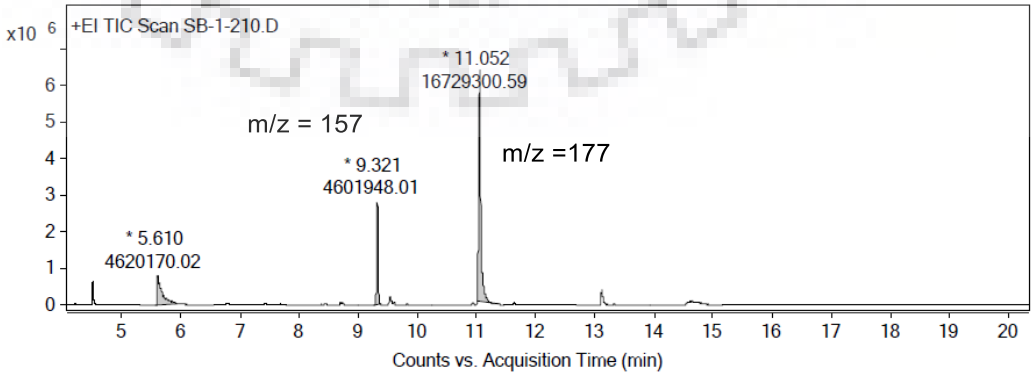
Scheme 6: Stoichiometric and catalytic studies using **Cat.A**

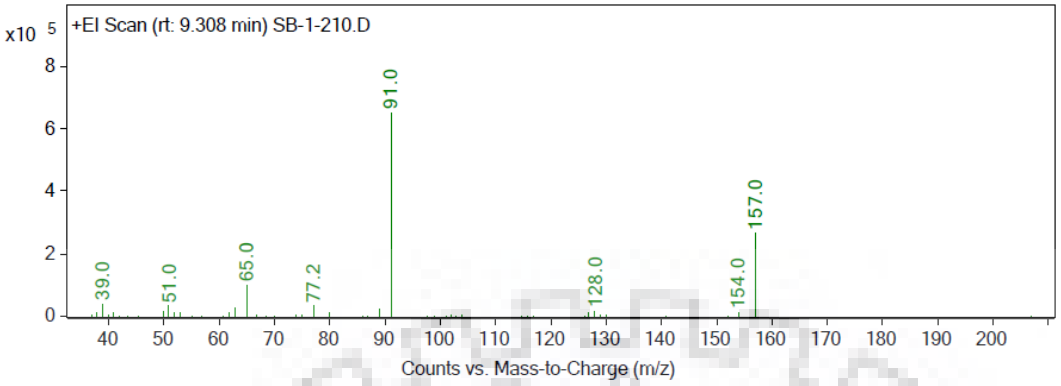
Thereafter, for the confirmation of participation of Ni-alkoxy species, we made an attempt for *in situ* preparation of Ni-alkoxy species of **Cat.A** (Scheme 7). Initially, **2a** was allowed to react with **Cat.A** under reflux condition for 24 h and the solid residue was allowed to react with aniline **1j** under standard conditions using toluene-d8 at 140 °C. The reaction was interrupted after twelve hours and ^{1}H-NMR analyis of the crude reaction mixture detected the formation of pyrrole **12**. These experiments are in agreement for the involvement of the intermediate Ni-alkoxy species for pyrrole synthesis.



Scheme 7: Confirmation of pyrrole synthesis *via* Ni-O species



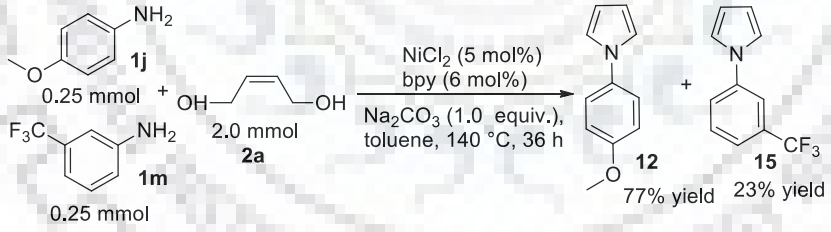




Scheme 8: Detection of intermediate species for pyrrole synthesis using GC-MS

For the confirmation of intermediate species **C** (Scheme 8), we used model reaction of **1a** with **2a** under standard conditions and was monitored using GC-MS. Gratifyingly, we detected intermediate species **C** as well as pyrrole **3** using GC-MS analysis.

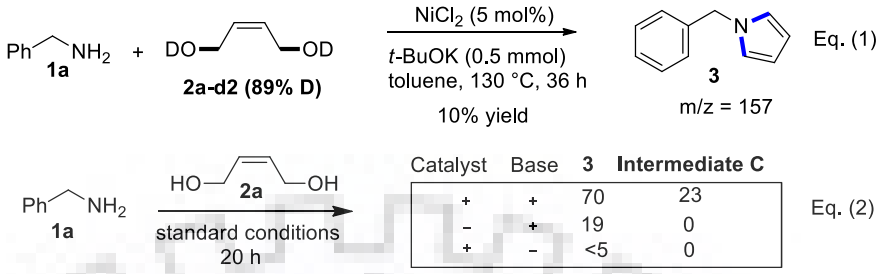
Further, a competitive experiment was performed using a 1:1 mixture of anilines **1j** and **1m** with alcohol **2a** under standard catalytic conditions. We observed the formation of pyrroles **12** and **15** at a ratio of 3:1 (Scheme 9). These experiments evident that, pyrrole formation occurred at higher rates for electron-rich aniline.



Scheme 9: Comparative experiments using electronically different anilines

However, using **1a** with **2a-d2** (89% D) under optimized conditions, we did not observe any deuterium incorporation in pyrrole and detected **3** in 10% yield using ^{1}H-NMR and GC-MS analysis (Scheme 10, eq. 1). Additionally, control experiments in absence of base and catalyst were performed and interrupted after 20 hours. GC-MS analysis of the crude reaction mixture revealed their potential role as individual component to achieve higher catalytic selectivity to **3** (Scheme 10, eq. 2). Notably, we detected intermediate **C** and these reactions evident the

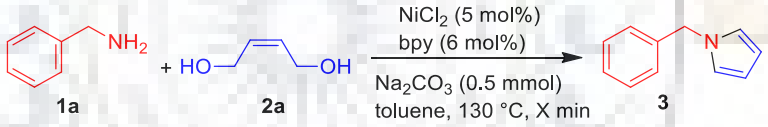
potential role of base and catalyst in the intermolecular cyclization involving C-C and C-N bond formation to pyrroles.



Scheme 10: Deuterium labeling and control experiment

Finally, we studied the rate and order of the pyrrole formation. To determine the rate laws, we performed kinetic studies using two sets of experiments with 0.5 mmol and 0.6 mmol of benzyl amine using our model reaction condition. We observed that along with time, product concentration also started to increase. Considering a steady state approximation for *cis*-butene-1,4-diol **2a**, first order kinetics with respect to **3** was observed for pyrrole formation.

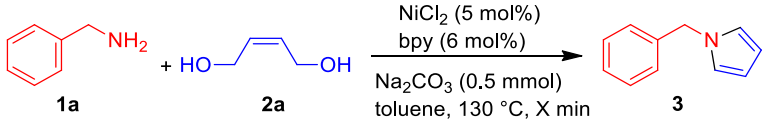
Run 1: Reaction was carried out in 2 mL of toluene and yield was calculated by GC



No.	**1a** (mmol)	**2a** (mmol)	$NiCl_2$ (mmol)	bpy (mmol)	Na_2CO_3 (mmol)	Toluene (mL)
Run 1	0.5	2	0.025	0.03	0.5	2.0

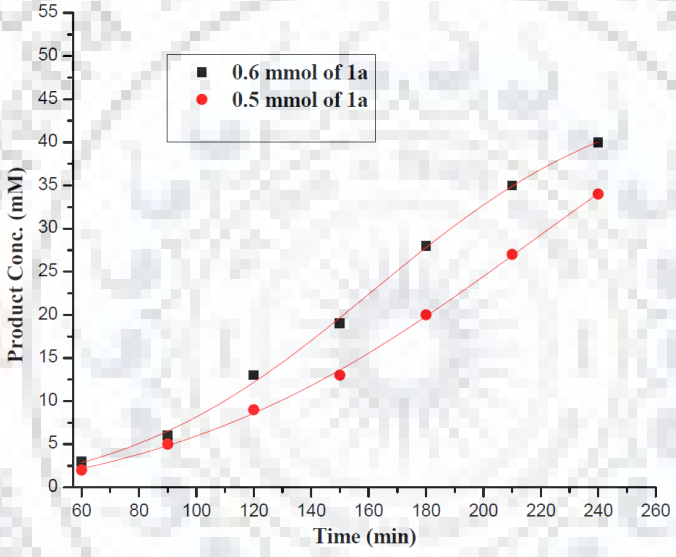
Sl. No.	Time (min)	Concentration of **3** (mM)
1	0	0
2	60	2
3	90	5
4	120	9
5	150	13
6	180	20
7	210	27
8	240	34

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



No.	**1a** (mmol)	**2a** (mmol)	$NiCl_2$ (mmol)	bpy (mmol)	Na_2CO_3 (mmol)	Toluene (mL)
Run 2	0.6	2.4	0.03	0.036	0.6	2.0

Sl. No.	Time (min)	Concentration of **3** (mM)
1	0	0
2	60	3
3	90	6
4	120	13
5	150	19
6	180	28
7	210	35
8	240	40



Graphical representation for determination of rate and order of reaction

Considering steady state approximation for *cis*-2-butene-1,4-diol

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

0.17978 = k [0.50] ^{x}

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

0.21905 = k [0.60] ^{x}

0.21905 /0.17978 = [0.60] ^{x}/ [0.50] ^{x}

1.2184 = [1.2] ^{x}

Log (1.2184) = x. Log (1.2)

x = 0.08579 / 0.07918

= 1.08 ≈ 1

Rate = k [1a] ^{1}

Scheme 11: Determination of rate and order for pyrrole formation

[3B.3] Conclusions

In conclusion, we established a straightforward and sustainable Ni-catalyzed dehydrogenative coupling for pyrrole synthesis using *cis*-butene-1,4-diols and butyne-1,4-diols with a series of aryl, alkyl and heteroaryl amines. Catalytic protocol is tolerant to amino alcohols, halides, alkyl, alkoxy and oxygen heterocycles as well as activated benzyl and pyridines. Initial mechanistic studies using defined intermediate Ni-species, competitive experiments between two electronically different anilines as well as rate and order of reactions were found to be crucial for elementary steps for nickel-catalyzed pyrrole formations using hydrogen-borrowing strategy.

[3B.4] Experimental details

[3B.4.1] General procedure for nickel-catalyzed synthesis of pyrroles:

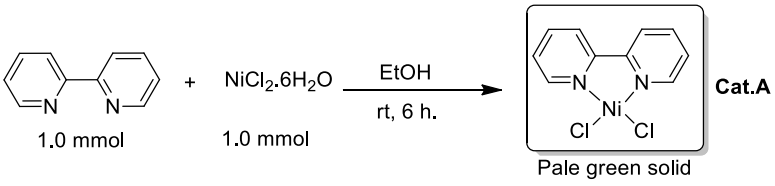
Procedure [A]:

In a 15 mL oven dried Schlenk tube, amines (0.50 mmol), Na_2CO_3 (0.50 mmol), bpy (6 mol%), $NiCl_2$ (5 mol%) and diol (2.0 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 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 [B]:

In a 15 mL oven dried Schlenk tube, amines (0.50 mmol), Na_2CO_3 (0.50 mmol), bpy (6 mol%), $NiCl_2$ (5 mol%) and diol (2.0 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 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.

Preparation of Cat.A:



A solution of bpy (100 mg, 0.64 mmol) in EtOH (2 mL) was added to a solution of $NiCl_2$•$6H_2O$ (152 mg, 0.64 mmol) in EtOH (2 mL) at rt. 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.A** as a pale green solid 175 mg (96%) yield. [12] Elemental Analysis calculated: C, 42.03; H, 2.82; Cl, 24.81; N, 9.80; Ni, 20.54; Found: C, 41.75; H, 2.76; N, 9.61.

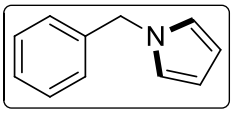
Synthesis of Cat. B: Cat.A (57 mg, 0.2 mmol) and *cis*-2-butene-1,4 diol (35 mg, 0.4 mmol) in toluene (2 mL) was heated at 130 °C under N_2 atmosphere in a Schlenk tube, after 24 h the precipitate was filtered off, washed with hexane (3×5 mL), and dried *in vacuo* to afford **Cat. B** as a pale green solid 50 mg (83%) yield. Then in a Schlenk tube the **Cat. B** (20 mg, 0.06 mmol), *p*-anisidine (8 mg, 0.06mmol) and Na_2CO_3 (7 mg, 0.06 mmol) in toluene d8 (0.4 mL) under N_2 atmosphere was heated at 140 °C, after 12 h the reaction mixture was cooled to room temperature and the crude reaction mixture was analyzed by ^{1}H NMR which confirms the formation of pyrrole.

[3B.4.2] Synthesis and Characterization of 1-Benzyl-1*H*-pyrrole (3):

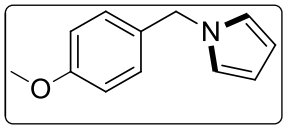
Following the general procedure A, (section 3B.4.1), the title product **3** was obtained as a colourless oil (66% yield). All the compounds were characterized by ^{1}H NMR, ^{13}C NMR, ESI, HRMS and the results are shown in spectral data. For example, all the spectra of compound **3** are explained here. ^{1}H NMR: the four aromatic region protons well separated and appeared as dd, td, td and dd at 7.27 – 7.17 (m, 3H), 7.06 – 7.01 (m, 2H), 6.62 (t, J = 2.1 Hz, 2H), 6.12 (t, J = 2.1 Hz, 2H), 4.99 (s, 2H). The protons at 4.99 are singlet belongs to –CH_2 and 6.62, 6.62 ppm are triplet belong to pyrrole ring –CH group. (Fig: **2a**). ^{13}C NMR: the peaks at 53.43 ppm belong to –CH_2 carbons, and the peak at 108.60, 121.27 belongs to pyrrole ring and 138.29, 128.83, 127.74, 127.10 ppm all belongs to carbons of benzene ring moiety (Fig: **2b**).

[3B.4.3] Analytical Data:

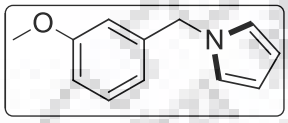
1-Benzyl-1*H*-pyrrole (3) [10]: Following the general procedure A, the title compound was isolated as a colourless oil (Yield: 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.17 (m, 3H), 7.06 – 7.01 (m, 2H), 6.62 (t, J = 2.1 Hz, 2H), 6.12 (t, J = 2.1 Hz, 2H), 4.99 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.29, 128.83, 127.74, 127.10, 121.27, 108.60, 53.43.



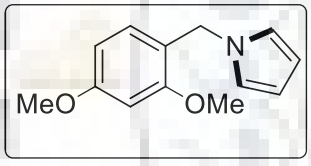
1-(4-methoxybenzyl)-1*H*-pyrrole (4) [13]: Following the general procedure A, the title compound was isolated as a colourless oil (Yield: 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.67 (t, J = 2.1 Hz, 2H), 6.19 – 6.14 (m, 2H), 5.00 (s, 2H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.21, 130.22, 128.57, 121.02, 114.16, 108.44, 55.38, 52.90.



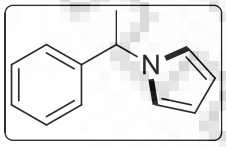
1-(3-methoxybenzyl)-1*H*-pyrrole (5) [13]: Following the general procedure A, the title compound was isolated as a colourless oil (Yield: 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.72 (dd, J = 6.2, 4.2 Hz, 4H), 6.25 – 6.17 (m, 2H), 5.05 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.01, 139.85, 129.78, 121.21, 119.30, 112.99, 112.78, 108.56, 55.21, 53.29.



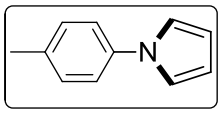
1-(2,4-dimethoxybenzyl)-1*H*-pyrrole (6) [14]: Following the general procedure A, the title compound was isolated as a colourless oil (Yield: 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, J = 8.3 Hz, 1H), 6.70 (t, J = 2.1 Hz, 2H), 6.44 (d, J = 2.4 Hz, 1H), 6.40 (dd, J = 8.3, 2.4 Hz, 1H), 6.14 (t, J = 2.1 Hz, 2H), 4.99 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.29, 155.52, 127.04, 118.72, 116.91, 105.55, 101.86, 96.16, 53.03, 53.02, 45.52.



1-(1-phenylethyl)-1*H*-pyrrole (7) [15]: Following the general procedure A, the title compound was isolated as a colourless oil (Yield: 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.27 – 7.24 (m, 1H), 7.09 (dd, J = 7.8, 1.0 Hz, 2H), 6.76 (t, J = 2.1 Hz, 2H), 6.19 (t, J = 2.1 Hz, 2H), 5.28 (q, J = 7.1 Hz, 1H), 1.83 (d, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.57, 128.64, 127.44, 125.86, 119.51, 108.03, 58.12, 22.11.

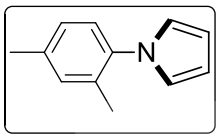


1-(*p*-tolyl)-1*H*-pyrrole (8) [10]: Following the general procedure B, the title compound was isolated as a white solid (Yield: 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 7.4 Hz, 2H), 7.25 (d, J = 7.6 Hz, 2H), 7.09 (s, 2H), 6.37 (s, 2H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.52, 135.37, 130.03,

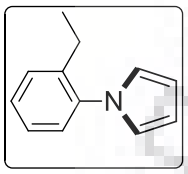


120.55, 119.39, 110.06, 20.83.

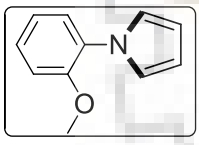
1-(2,4-dimethylphenyl)-1*H*-pyrrole (9) [16]: Following the general procedure B, the title compound was isolated as a white solid (Yield: 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.08 (m, 2H), 7.05 (d, J = 7.9 Hz, 1H), 6.76 (dd, J = 2.5, 1.6 Hz, 2H), 6.30 (dd, J = 2.5, 1.6 Hz, 2H), 2.36 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.33, 133.44, 129.75, 127.74, 123.21, 122.61, 118.28, 104.65, 17.08, 13.79.



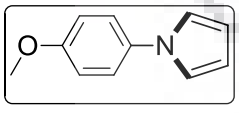
1-(2-ethylphenyl)-1*H*-pyrrole (10) [17]: Following the general procedure B, the title compound was isolated as a white solid (Yield: 30%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.28 (d, J = 5.1 Hz, 2H), 6.78 (s, 2H), 6.31 (s, 2H), 2.51 (q, J = 7.4 Hz, 2H), 1.10 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.24, 140.11, 129.33, 127.89, 127.11, 126.38, 122.38, 108.61, 24.12, 15.15.



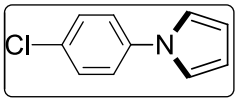
1-(2-methoxyphenyl)-1*H*-pyrrole (11) [18]: Following the general procedure B, the title compound was isolated as a white solid (Yield: 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.16 (m, 2H), 6.96 – 6.87 (m, 4H), 6.23 (dd, J = 2.5, 1.7 Hz, 2H), 3.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.85, 130.40, 127.59, 125.89, 122.20, 121.04, 112.44, 108.90, 55.92.



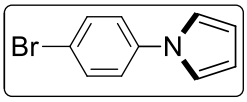
1-(4-methoxyphenyl)-1*H*-pyrrole (12) [10]: Following the general procedure B, the title compound was isolated as a white solid (Yield: 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 2H), 7.02 (td, J = 2.3, 0.7 Hz, 2H), 6.98 – 6.93 (m, 2H), 6.34 (td, J = 2.2, 0.7 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.86, 134.71, 122.36, 119.87, 114.82, 110.04, 55.73.



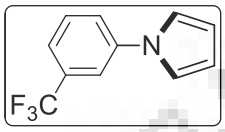
1-(4-chlorophenyl)-1*H*-pyrrole (13) [10]: Following the general procedure B, the title compound was isolated as a white solid (Yield: 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.08-7.04 (m, 2H), 6.35 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.34, 131.06, 129.63, 121.63, 119.28, 110.82.



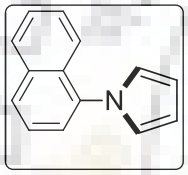
1-(4-bromophenyl)-1*H*-pyrrole (14) [10]: Following the general procedure B, the title compound was isolated as a white solid (Yield: 36%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.52 (m, 2H), 7.28 (d, J = 2.1 Hz, 2H), 7.07 – 7.04 (m, 2H), 6.37 – 6.35 (m, 2H).



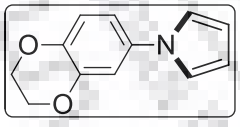
1-(3-(trifluoromethyl)phenyl)-1*H*-pyrrole (15) [19]: Following the general procedure B, the title compound was isolated as a white solid (Yield: 30%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.53 – 7.38 (m, 3H), 7.11 (t, J = 2.1 Hz, 2H), 6.38 (t, J = 2.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.17, 130.30, 125.13, 123.51 (d, J = 1.0 Hz), 122.42, 122.21(q, J=3.0 Hz), 119.30, 117.25 (q, J = 3.9 Hz), 111.38.



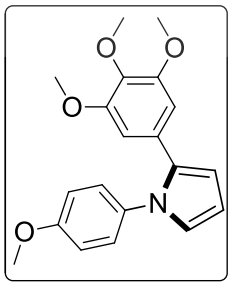
1-(naphthalene-1-yl)-1*H*-pyrrole (16) [20]: Following the general procedure B, the title compound was isolated as a white solid (Yield: 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 18.2, 7.9 Hz, 2H), 7.75 (d, J = 8.3 Hz, 1H), 7.54 – 7.43 (m, 4H), 6.99 (t, J = 2.1 Hz, 2H), 6.41 (t, J = 2.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.25, 134.28, 129.93, 128.11, 127.88, 126.96, 126.56, 125.30, 123.30, 123.23, 109.06.



1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1*H*-pyrrole (17) [21]: Following the general procedure B, the title compound was isolated as a white solid (Yield: 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (t, J = 2.2 Hz, 2H), 6.92 (d, J = 2.6 Hz, 1H), 6.89 – 6.85 (m, 2H), 6.31 (t, J = 2.2 Hz, 2H), 4.31 – 4.26 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.91, 141.68, 119.59, 117.76, 115.00, 113.90, 110.14, 109.89, 64.51, 64.29.

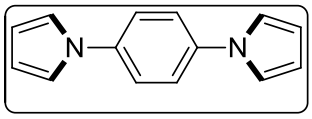


1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-1*H*-pyrrole (18) [22]: Following the general procedure B, the title compound was isolated as a white solid (Yield: 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.09 (m, 2H), 6.88 – 6.83 (m, 3H), 6.40 (dd, J = 3.6, 1.8 Hz, 1H), 6.33 – 6.31 (m, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.62 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.42, 152.78, 152.37, 136.57, 133.95, 133.81, 132.22, 128.57, 114.13,

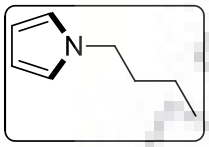


105.64, 105.57, 103.36, 63.56, 55.95, 55.92, 55.85.

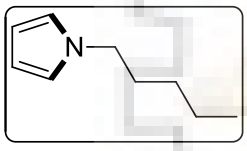
1,4-di(1*H*-pyrrol-1-yl)benzene (19) [23]: Following the general procedure B, the title compound was isolated as a white solid (Yield: 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.18 (m, 4H), 7.02 – 7.01 (m, 4H), 6.38 – 6.35 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.35, 112.43, 110.25, 105.90, 101.54.



1-butyl-1*H*-pyrrole (20) [25]: Following the general procedure B, the title compound was isolated as a colourless oil (Yield: 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (t, J = 1.7 Hz, 2H), 6.06 (t, J = 1.7 Hz, 2H), 3.80 (t, J = 7.2 Hz, 2H), 1.67 (dt, J = 14.9, 7.4 Hz, 2H), 1.26 – 1.20 (m, 2H), 0.86 (dt, J = 7.4, 3.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.54, 107.82, 49.40, 33.68, 20.01, 13.71.

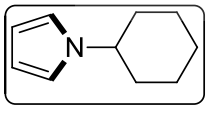


1-pentyl-1*H*-pyrrole (21) [26]: Following the general procedure B, the title compound was isolated as a colourless oil (Yield: 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (s, 2H), 6.06 (s, 2H), 3.78 (t, J = 7.2 Hz, 2H), 1.69 (dt, J = 14.7, 7.3 Hz, 2H), 1.29 – 1.17 (m, 4H), 0.82 (dd, J = 8.2, 6.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 121.01, 108.30, 50.18, 31.83, 29.48, 22.85, 14.50.



1-heptyl-1*H*-pyrrole (22) [27]: Following the general procedure B, the title compound was isolated as a colourless oil (Yield: 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (t, J = 2.1 Hz, 2H), 6.12 (t, J= 2.1 Hz, 2H), 3.87 – 3.83 (m, 2H), 1.79 – 1.71 (m, 2H), 1.30 – 1.25 (m, 8H), 0.89 – 0.85 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.45, 107.74, 49.64, 31.70, 31.57, 28.87, 26.74, 22.57, 14.03.

1-cyclohexyl-1*H*-pyrrole (23) [10]: Following the general procedure B, the title compound was isolated as a colourless oil (Yield: 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (t, J = 2.1 Hz, 2H), 6.13 (t, J = 2.1 Hz, 2H), 3.84 – 3.76 (m, 1H), 2.10 (dd, J = 13.2, 1.9 Hz, 2H), 1.92 – 1.83 (m, 2H), 1.76 – 1.68 (m, 1H), 1.62 (ddd, J = 24.6, 12.4, 3.2 Hz, 2H), 1.45 – 1.33 (m, 2H), 1.28 – 1.19 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.05, 103.99, 55.31, 31.33, 22.38, 22.16.



1-cyclooctyl-1*H*-pyrrole (24): Following the general procedure B, the title compound was isolated as a colourless oil (Yield: 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (dd, J = 3.8, 1.9 Hz, 2H), 6.16 (dd, J = 3.9, 1.9 Hz, 2H), 4.12 (dq, J = 13.4, 4.4 Hz, 1H), 2.03 (dt, J = 12.0, 6.3 Hz, 4H), 1.82 (dd, J = 6.0, 2.1 Hz, 2H), 1.72 – 1.53 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 119.17, 107.92, 60.50, 34.96, 27.50, 26.42, 25.11. HRMS (ESI-TOF) m/z: $[M+H]^+$Calcd for $C_{12}H_{19}N$ 178.1517; Found 178.1585.

1-(5-methylheptyl)-1*H*-pyrrole (25): Following the general procedure B, the title compound was isolated as a colourless oil (Yield: 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (t, J = 2.1 Hz, 2H), 6.12 (t, J = 2.0 Hz, 2H), 3.76 (dd, J = 7.0, 3.7 Hz, 2H), 1.69 (dt, J = 12.4, 6.3 Hz, 1H), 1.31 – 1.22 (m, 8H), 0.88 (td, J = 6.9, 3.7 Hz, 6H).^{13}C NMR (125 MHz, $CDCl_3$) δ 120.28, 106.87, 52.43, 40.58, 29.82, 27.90, 23.08, 22.21, 13.26, 9.86. HRMS (ESI-TOF) m/z: $[M+H]^+$Calcd for $C_{12}H_{21}N$ 180.1674; Found 180.1739.

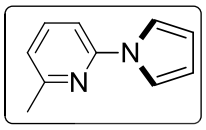
1-(3-methoxypropyl)-1*H*-pyrrole (26) [28]: Following the general procedure B, the title compound was isolated as a colourless oil (Yield: 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 – 6.62 (t, J = 3.1 Hz, 2H), 6.14 – 6.11 (t, J = 3.2 Hz, 2H), 3.99 (td, J = 6.9, 1.7 Hz, 2H), 3.34 – 3.28 (m, 5H), 2.04 – 1.93 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 121.25, 108.55, 69.74, 59.27, 46.79, 32.23.

5-chloro-2-(1*H*-pyrrol-1-yl)pyridine (27) [29]: Following the general procedure B, the title compound was isolated as a colourless oil (Yield: 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, J = 2.7, 0.8 Hz, 1H), 7.78 – 7.63 (m, 1H), 7.45 (dd, J = 3.3, 1.5 Hz, 2H), 7.28 – 7.22 (m, 1H), 6.35 (dd, J = 3.3, 1.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.75, 147.42, 138.25, 127.70, 118.23, 112.10, 111.82.

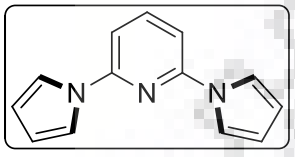
5-chloro-2-(1*H*-pyrrol-1-yl)pyridine (28) [30]: Following the general procedure B, the title compound was isolated as a colourless oil (Yield: 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 2.4 Hz, 1H), 7.82 (dd, J = 8.8, 2.4 Hz, 1H), 7.45 (t, J = 2.3 Hz, 2H), 7.20 (s, 1H), 6.37 – 6.34 (m, 2H). ^{13}C NMR

(125 MHz, $CDCl_3$) δ 150.13, 149.66, 140.98, 118.19, 115.63, 112.61, 111.86.

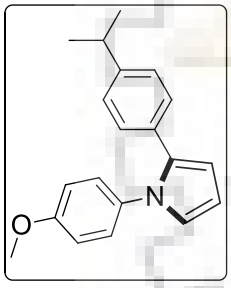
2-methyl-6-(1*H*-pyrrol-1-yl)pyridine (29) [31]: Following the general procedure B, the title compound was isolated as a colourless solid (Yield: 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.57 (m, 1H), 7.52 – 7.49 (m, 2H), 7.10 (d, J = 8.2 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.36 – 6.31 (m, 2H), 2.53 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.22, 151.03, 138.77, 119.76, 118.32, 111.19, 108.46, 24.57



2,6-di(1*H*-pyrrol-1-yl)pyridine (30): Following the general procedure B, the title compound was isolated as a white solid (Yield: 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (t, J = 8.0 Hz, 1H), 7.51 – 7.48 (m, 4H), 7.03 (d, J = 8.0 Hz, 2H), 6.31 (dd, J = 5.0, 2.8 Hz, 4H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 141.51, 131.98, 109.31, 106.15, 102.62, 97.89. HRMS (ESI-TOF) m/z: $[M+H]^+$Calcd for $C_{13}H_{11}N_3$ 210.0953; Found 210.1021.



2-(4-isopropylphenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole (31) [24]: Following the general procedure B, the title compound was isolated as a white solid (Yield: 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.08 (m, 2H), 7.06 (s, 4H), 6.88 – 6.81 (m, 3H), 6.39 (dd, J = 3.5, 1.8 Hz, 1H), 6.35 – 6.30 (m, 1H), 3.82 (s, 3H), 2.85 (hept, J = 6.9 Hz, 1H), 1.22 (d, J = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ158.21, 146.81, 134.11, 133.97, 130.55, 128.17, 127.07, 126.18, 124.29, 114.15, 109.80, 108.79, 55.53, 33.75, 23.98.



[3B.5] Spectra of selected compounds

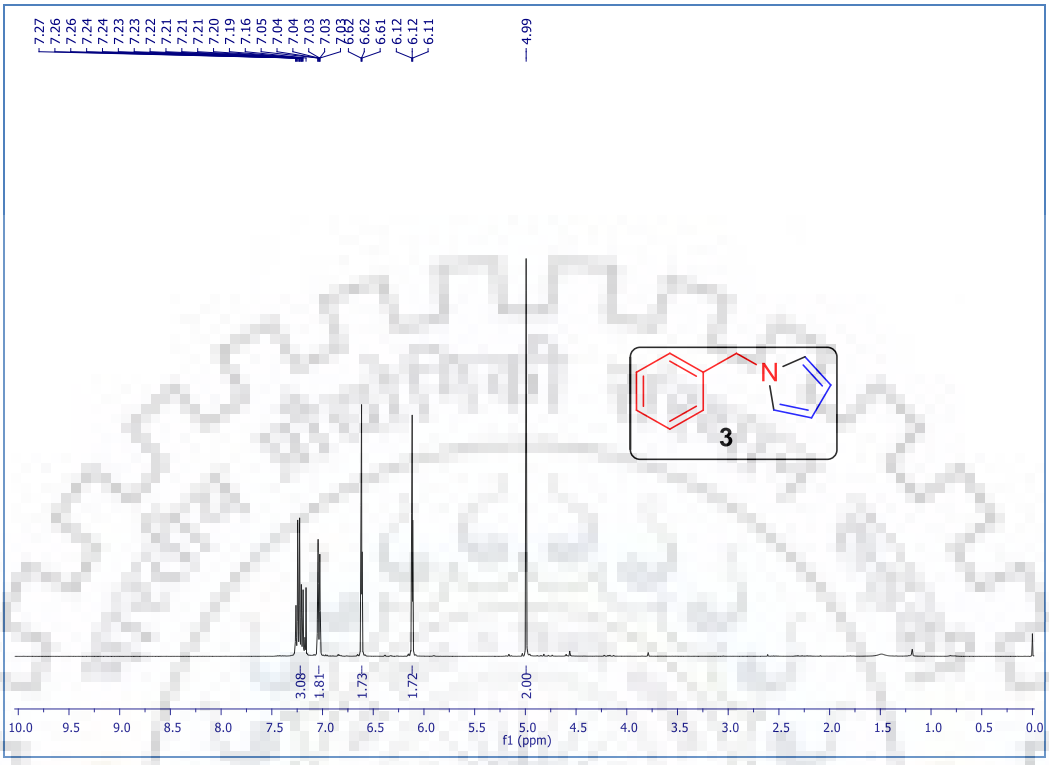


Figure 2a: ^{1}H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **3**

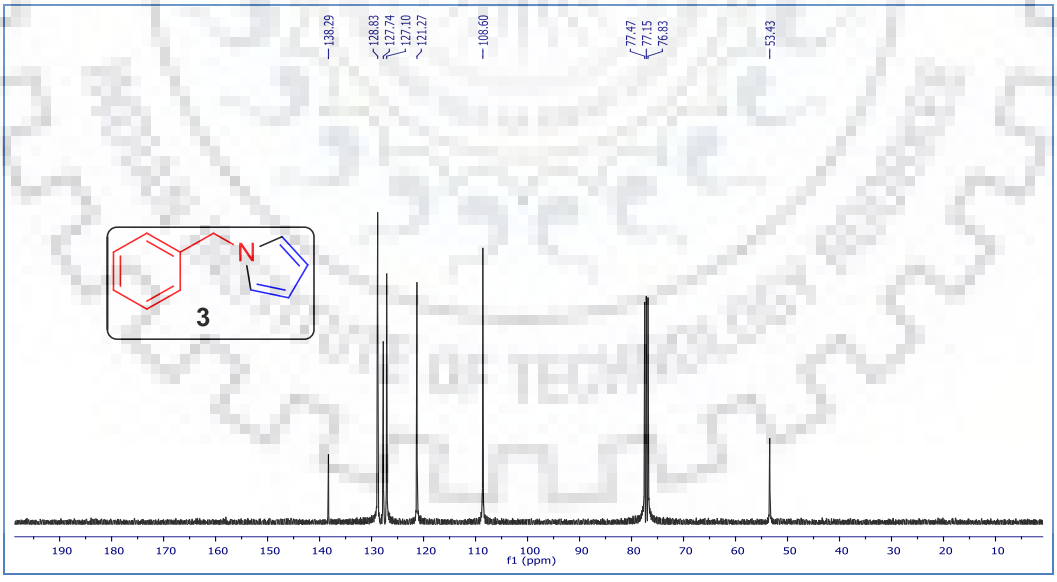


Figure 2b: ^{13}C NMR ($CDCl_3$, 125 MHz) Spectrum of Compound **3**

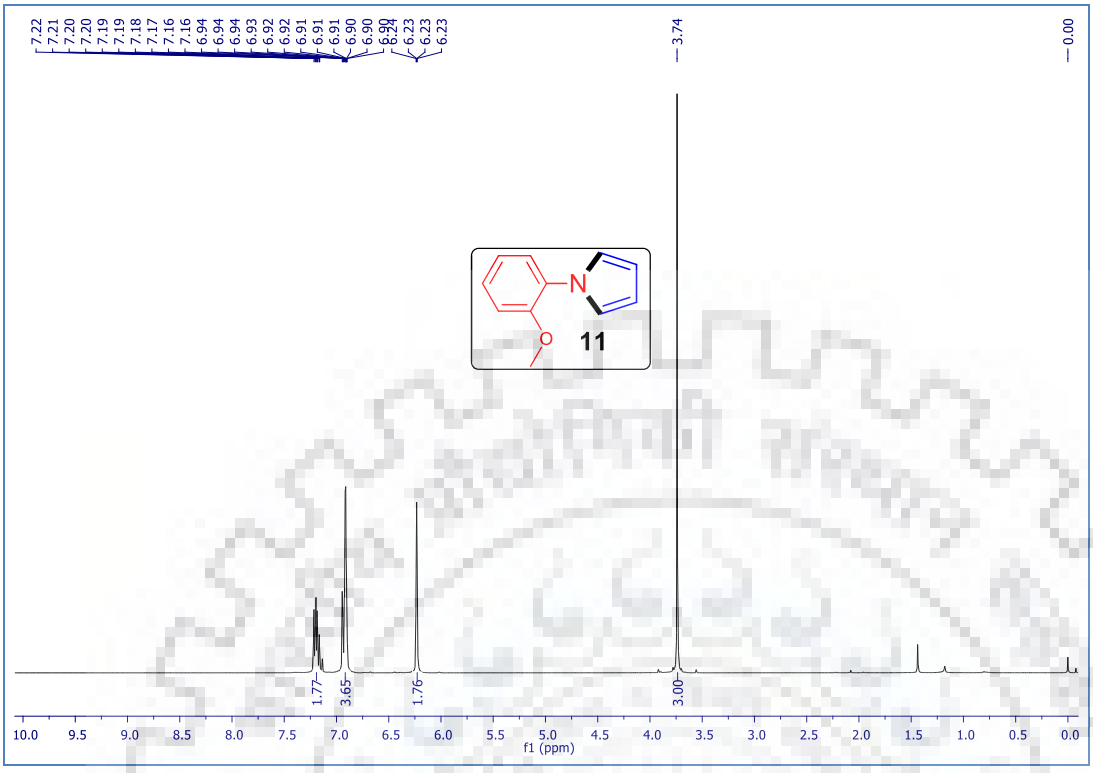


Figure 3a: ^{1}H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **11**

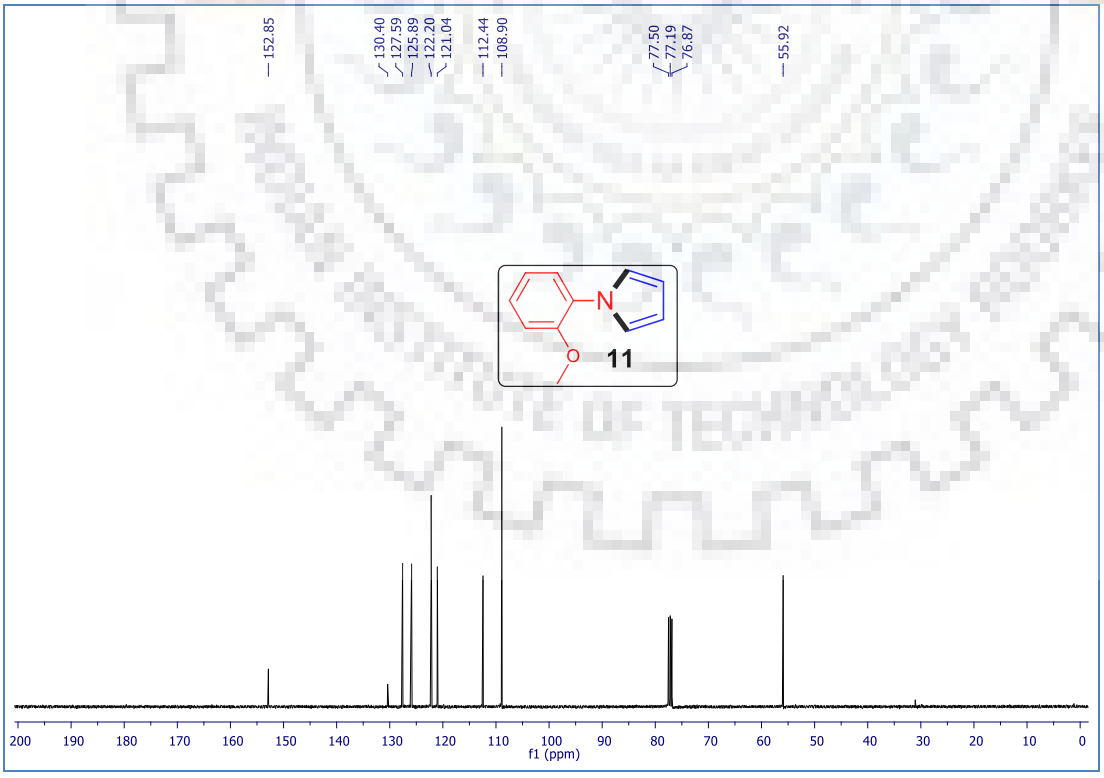


Figure 3b: ^{13}C NMR ($CDCl_3$, 125 MHz) Spectrum of Compound **11**

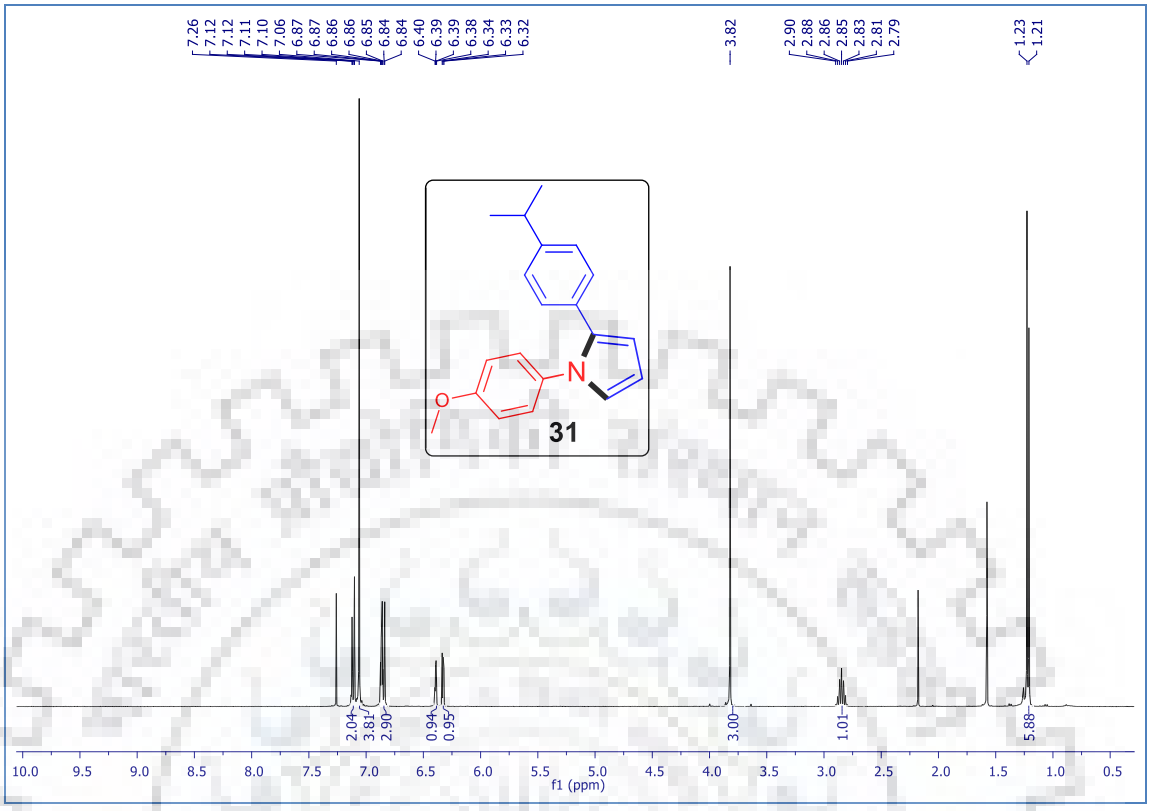


Figure 4a: ^{1}H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **31**

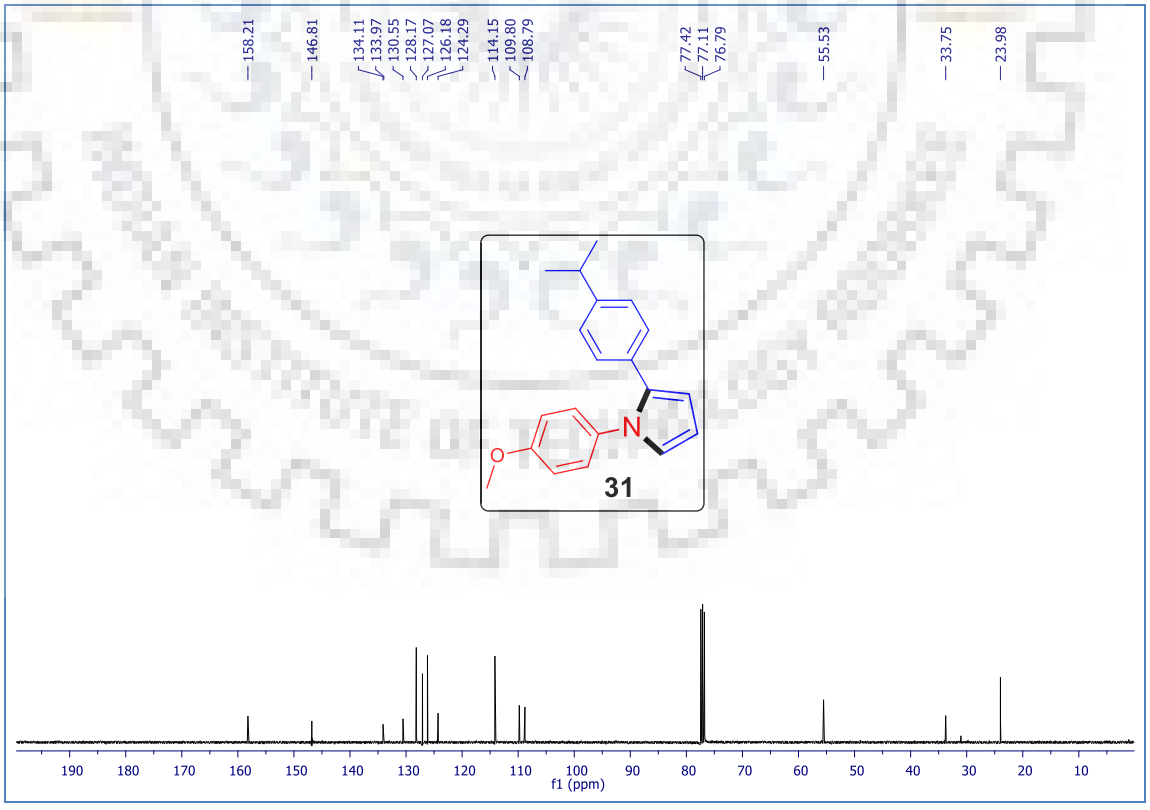


Figure 4b: ^{13}C NMR ($CDCl_3$, 100 MHz) Spectrum of Compound **31**

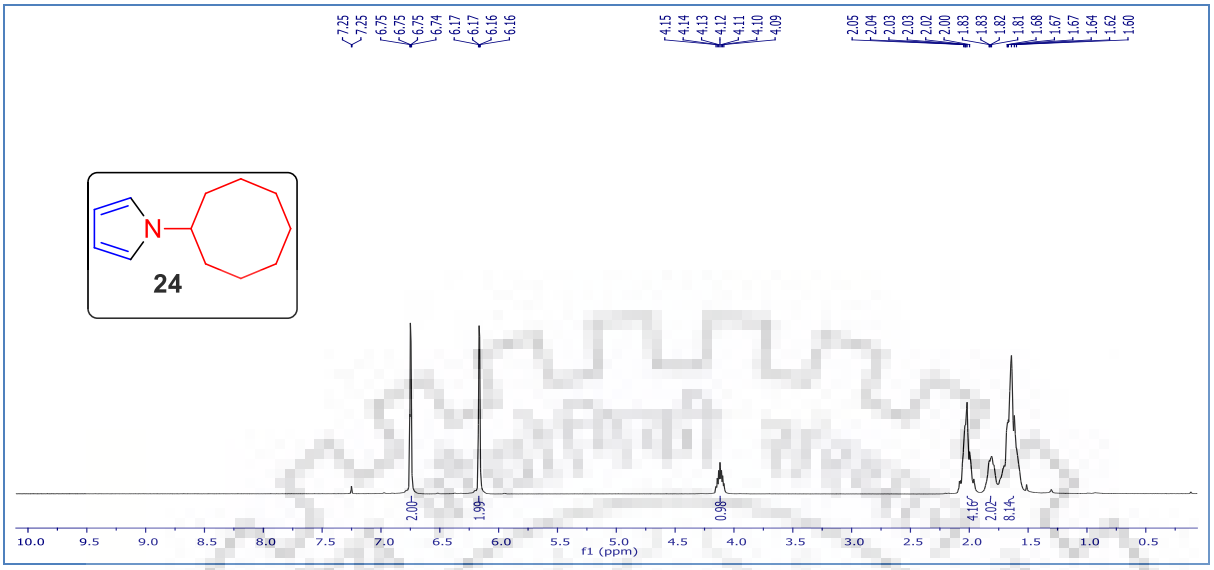


Figure 5a: ^{1}H NMR ($CDCl_3$, 400 MHz) Spectrum of Compound **24**

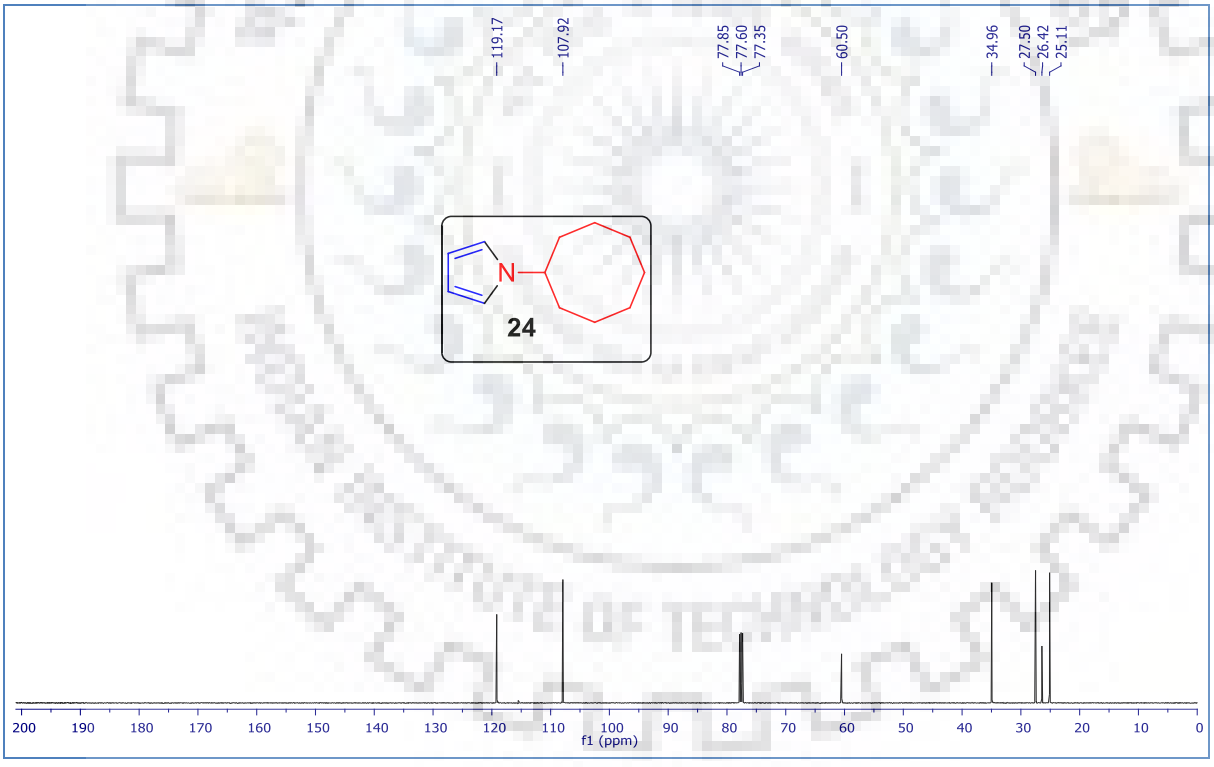


Figure 5b: ^{13}C NMR ($CDCl_3$, 125 MHz) Spectrum of Compound **24**

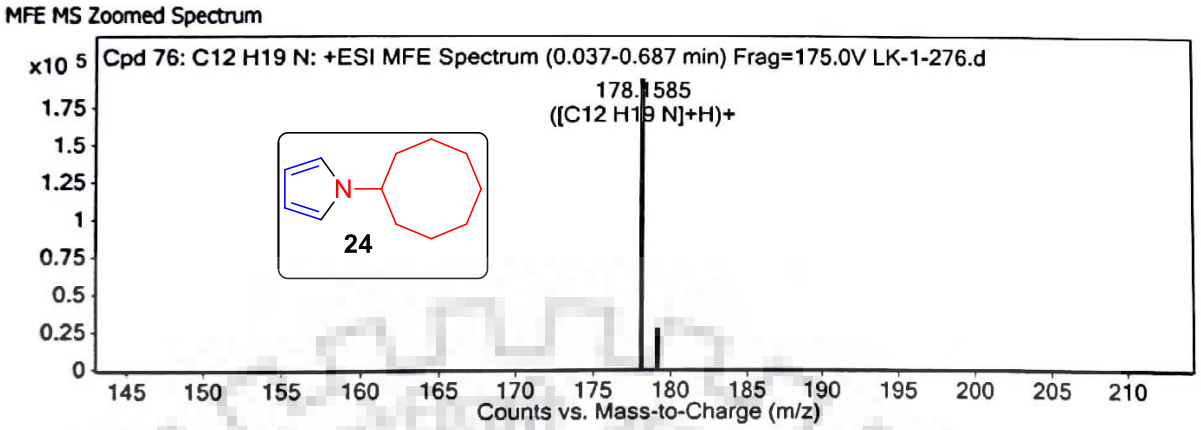
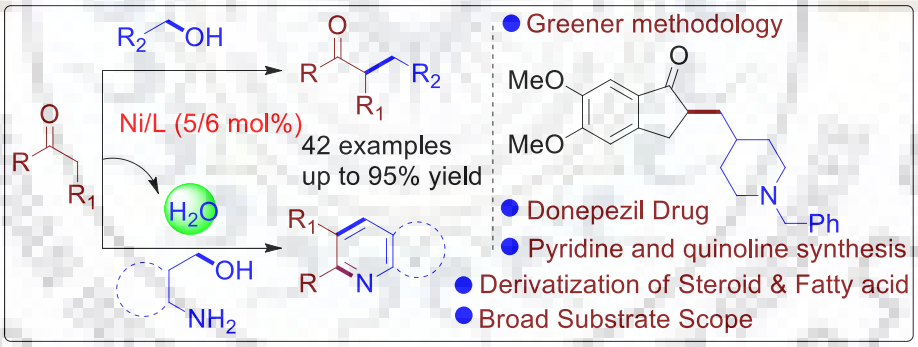


Figure 5c: HRMS (ESI) Spectrum of Compound **24**

Chapter-4: Nickel-catalyzed synthesis of gem-bis-alkylkated ketones

Herein we report the α-alkylation of methylene ketones using an earth-abundant and non-precious $NiBr_2$/**L1** system that enables the transformations to a range of branched gem-bis(alkyl) ketones using renewable primary alcohols. This nickel catalyzed system could be performed in gram scale and successfully applied in the synthesis of donepezil (Alzheimer's drug), functionalization of steroid hormone, and fatty acid derivatives. Green synthesis to N-heterocycles, α-methylation of ketones using methanol and one pot double alkylation to bis-hetero aryl ketones using two different alcohols with a single catalyst broaden the scope of the catalytic protocol. A detailed mechanistic studies involving isolation of defined Ni-intermediate species, Ni-H species, Ni-alkoxy complex, determination of rate and order of the reaction, competition reactions of electronically different alcohols and a series of deuterium labelling experiments established the participation of borrowing-hydrogen strategy for nickel-catalyzed α-alkylation of methylene ketones with alcohols.



Org. Lett. ***2018****, 20, 5587–5591*

Chapter 4: Nickel-Catalyzed Synthesis of gem-Bis alkylated Ketones

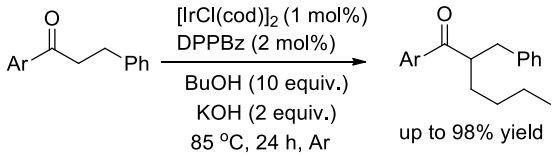
The work presented in this Chapter has recently been published in Org. Lett. **2018***, 20,* 5587-5591. *This work has been contributed equally by another author. Therefore, in this chapter we will only discuss those part of the work mainly contributed by me.*

[4.1] Introduction:

Transition-metal catalysis for α-alkylation of carbonyl compounds using renewable feedstocks is a green and sustainable strategy for construction of new C-C bonds in organic chemistry, [1] which provides valuable access to various functionalized organic compounds with applications in agrochemicals, pharmaceutical and material sciences. Advantageously, the application of readily available alcohols for α-alkylation of ketones using borrowing hydrogen strategy avoids the use of pre-synthesized alkyl halides, cryogenic temperature and toxic amide bases, relieving water as the only byproduct.[2] However, the α-alkylation of ketones is often limited with mono-alkylation of an activated methyl-ketone derivative pertain to the linear products.[3] In contrast, the use of α-substituted methylene ketones to incorporate a higher member alkyl substitution beyond methyl group for the formation of α,α-di-substituted branched products is more challenging and relatively underdeveloped due to adverse steric reason. Moreover, achieving such germinal α,α-di-substituted ketones through standard enolate chemistry in a selective and control fashion represents a significant challenge in catalysis.

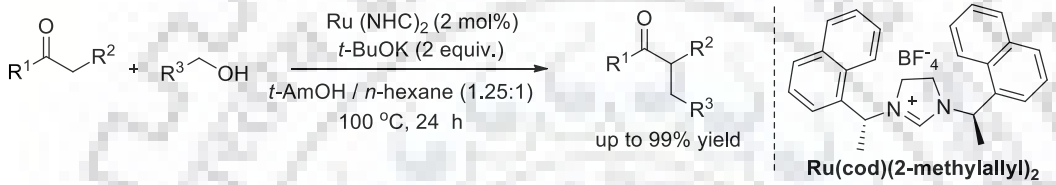
[4.2] Relevant Literature:

Branched gem-bis(alkyl) ketones are privileged structural motifs extensively used as intermediate in organic synthesis.[3a] Though, substantial progress has been made for α-alkylation of methyl ketones using Ru- and Ir-catalysts with alcohols as coupling partner, surprisingly, only handful examples are known for the synthesis of geminal di-substituted ketones. In this direction, Donohoe and co-workers established this field of chemistry by employing an Ir-catalyst for *α*-alkylation of various *o*-substituted hindered phenyl and cyclopropyl ketones. They successfully design the ketone substrates and employed ten equivalent of alcohols to achieve higher selectivity of product. Importantly, application of excess strong base is the key to control the product selectivity (Scheme 1).[4]



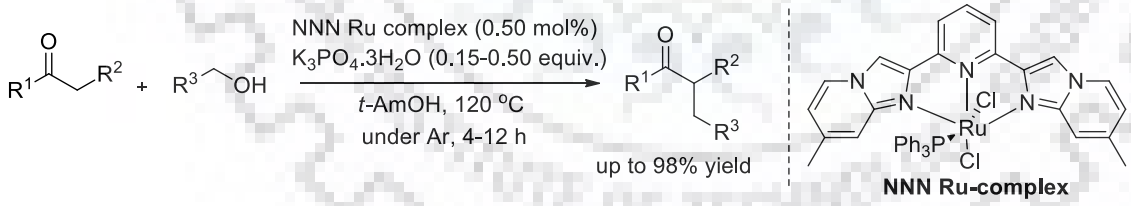
Scheme 1: Ir-catalyzed *α*-alkylation of *o*-substituted phenyl and cyclopropyl ketones

In 2016, Glorious and co-workers established the Ru-NHC-catalyzed *α*-alkylation of methylene ketones and provides a series of functionalized di-substituted branched products following borrowing hydrogen strategy with excellent yields. Notably, the catalytic protocol required 2-3 equivalents of strong base, *t*-BuOLi to achieve higher product yield (Scheme 2). [5]



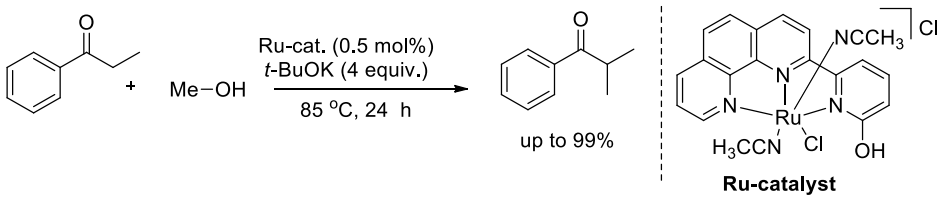
Scheme 2: *α*-alkylation of methylene ketones using Ru-NHC catalyst

Very recently, Song and co-workers, reported the synthesis of novel Ru(III)-based NNN-pincer catalyst and employed for the synthesis of various α-,α-di-substituted branched ketones. The catalyst also broadly applicable for the preparation of linear ketones as well in moderate to good yields. As an application they have demonstrated the synthesis of donepezil drug (Scheme 3). [6]



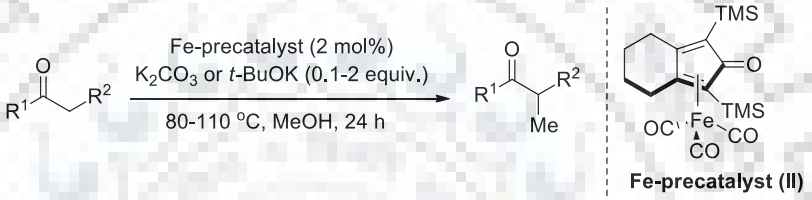
Scheme 3: *α*-alkylation of methylene ketones using NNN Ru-pincer catalyst

In a recent report, Kundu and co-workers demonstrated a three-component coupling of ketones, alcohols and methanol using Ru(II)-NNN-catalyst to access corresponding α-methylated ketones under mild conditions. The catalyst is air and moisture stable and a series of kinetic studies as well as DFT calculation were performed to understand the hydrogen borrowing process for the multi-component reactions (Scheme 4).[7]



Scheme 4: Multi-component synthesis of methylated ketones using Ru(II)-catalyst

To date, direct synthesis of α,α-di-substituted ketones are only limited with precious metal-catalysts. Applications of earth abundant and non-precious Co, Mn, Fe and Ni would be more attractive and sustainable technology in this direction. Towards this, very recently, Morril and co-workers reported an efficient defined Fe-catalyst for mono or bis-methylation of various aromatic and aliphatic ketones using methanol as a methylating agent (Scheme 5). [8]



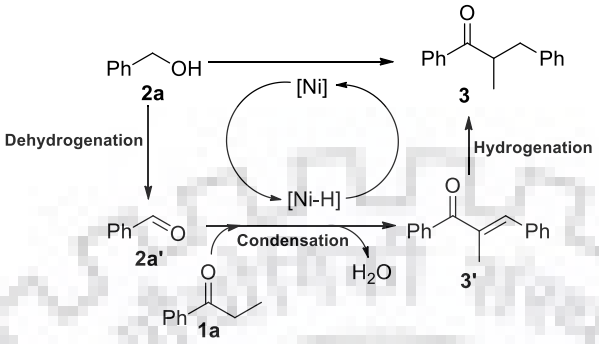
Scheme 5: Fe-catalyzed methylation of ketones.

In this direction use of earth-abundant non-precious base metals, such as, (Fe, Mn, Ni, Co) would be more sustainable and attractive alternative.[9-12] However, such processes is only known to catalyze the mono alkylation of an activated methyl-ketone derivative and has never been demonstrated for the synthesis of geminal α,α-di-substituted ketones. Till date, to the best of our knowledge, nickel-catalyzed alkylation of α-substituted methylene ketones using primary alcohols for the synthesis of α,α-disubstituted branched products has not been developed. More specifically, this represents the first example of an earth-abundant non-precious base metal-catalyzed a practical route to branched gem-bis(alkyl) ketones. Herein we demonstrated the high catalytic activity with broad substrate scope for the synthesis of α,α-dialkyl/aryl branched ketones. The key to success is the application of diversely available nitrogen ligands for nickel to forge the C-C coupling for a broad range of alcohol electrophiles. This strategy provides a new method for the facile synthesis of branched gem-bis(alkyl) ketones, substituted pyridines and quinolines.

[4.3] Results and discussion:

We have established an efficient nickel catalyzed system for amination of primary alcohols as well as intermolecular cyclization to *N*-heterocycles in chapter (2and3). Our mechanistic

studies revealed that, nickel-catalyst facilitate the dehydrogenation of alcohol to aldehyde and a Ni-H intermediate is formed. Selective hydrogenation of intermediate enone **3'** by *in situ* formed nickel hydride transformed to the product **3,** a conceptually different strategy to branched gem-bis(alkyl) ketones earlier reported by Itami and co-workers (scheme 6). [13]

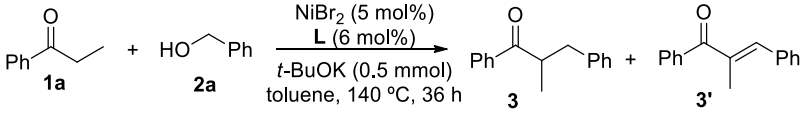


Scheme 6: Ni-catalyzed synthesis of di-substituted ketones.

Nevertheless, we realized the inevitable role for the use of nitrogen ligands for such nickel catalyzed dehydrogenative coupling of alcohols. Being anticipated the aforementioned challenge for α-substituted methylene ketones, we hypothesized few key challenges, such as, (i) selective hydrogenation of C=C bond of **3'**, (ii) control to reduce the nickel catalyzed hydrogenation of C=O bond of **3** and **3'** and (iii) minimize the self-condensation of ketones (Table 1). To this end, we envisioned that, an appropriate nickel catalyst in combination with suitable nitrogen ligand is highly desirable for this transformations.

Therefore, initially, we studied the efficacy of different nickel catalysts by the reaction of propiophenone **1a** and benzyl alcohol **2a** as model reaction of our choice for α-substituted methylene ketones to **3** (Table 1, entries 1-5). To our delight, we identified 1,10-phenanthroline **L1** as a superior ligand for the present *α*-alkylation of methylene ketone. Under identical conditions, other nitrogen and phosphine ligands, **L2**-**L8**, resulted only 44-62% of **3** along with (22-36%) of corresponding enone (Table 2, Table-1, entries 6-12). Gratifyingly, use of little excess of alcohol in the presence of 5 mol% $NiBr_2$ and 6 mol% **L1** in toluene **3** was obtained in 92% isolated yield (Table 1, entry 13).

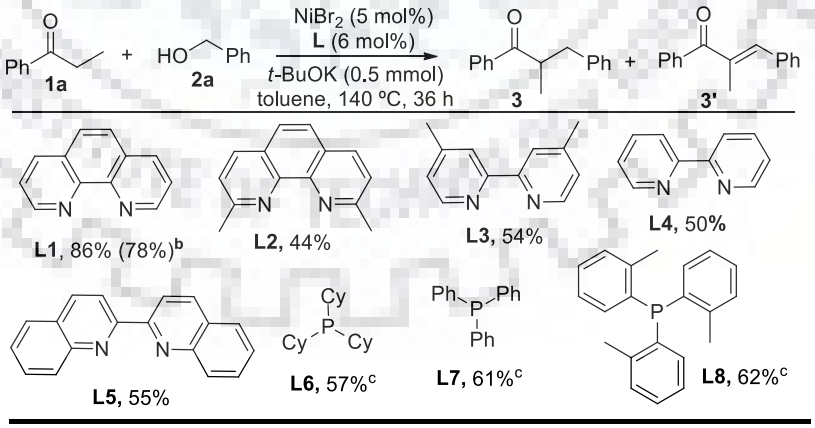
Table 1: Optimization studies for Ni-catalyzed *α*-alkylation of methylene ketones [a]



Entry	Catalyst	Ligand	Conv. (%)[b]	
			3	**3'**
1	$NiCl_2$	**L1**	50	39
2	$NiBr_2$	**L1**	86(78)	10
3	$Ni(acac)_2$	**L1**	62	15
4	$Ni(cod)_2$	**L1**	55	32
5	$NiCl_2$.DME	**L1**	37	42
6	$NiBr_2$	**L2**	44	22
7	$NiBr_2$	**L3**	54	36
8	$NiBr_2$	**L4**	55	32
9	$NiBr_2$	**L5**	50	30
10	$NiBr_2$	**L6**	57	24
11	$NiBr_2$	**L7**	61	30
12	$NiBr_2$	**L8**	62	34
13[c]	**$NiBr_2$**	**L1**	**95(92)**	**1**
14[d]	-	-	10	35

[a] Unless specified, the reaction was carried out with **1a** (0.5 mmol), **2a** (0.625 mmol), Ni cat. (0.025 mmol), **L** (0.03 mmol), and *t*-BuOK (0.5 mmol) 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] **2a** (0.75 mmol) was used. [d] *t*-BuOK (0.5 mmol) was used.

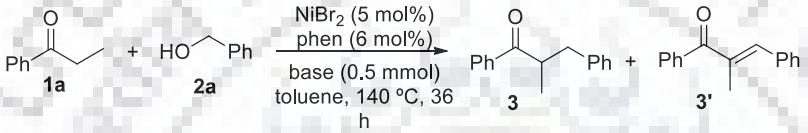
Table 2: Screening of ligands for Ni-catalyzed α-alkylation of **1a** with **2a** [a,b]



[a] Unless specified, the reaction was carried out with **1a** (0.5 mmol), **2a** (0.625 mmol), Ni-cat. (0.025 mmol), **L** (0.03 mmol), and *t*-BuOK (0.5 mmol) under an N_2 atmosphere at 140 °C (oil bath) in toluene (2.0 mL) for 36 h in Schlenk tube. [b] Conversion was determined by GC-MS (isolated yield in parentheses, average yield of two runs). [c] Ligand (0.05 mmol) was used.

Notably, under optimized conditions, influence and scope of different bases, such as, *t*-BuOK, *t*-BuONa, Na_2CO_3, K_2CO_3, Cs_2CO_3, K_3PO_4 were tested (Table 3, enteries 1-6). Control experiment revealed that no reaction occurred in absence of base (Table 3, entry 7). Further, applications of various non-polar and polar solvents, such as, xylene, 1,4-dioxane, DMA, DMF as well as pentanol did not improve the product yield further (Table 4, enteries 1-6) It is noteworthy to mention that, we also observed 2-10% reduced alcohols of **3** and **3'** using GC-MS analysis of crude reaction mixture (Table 1). Again, variation of alcohol amount also changes the product yield and we observed that, 1.5 equivalent of alcohols is required to get maximum yield (Table 5, entry 1).

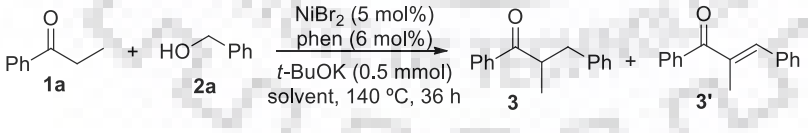
Table 3: Screening of base [a]



Entry	Base	GC-MS Conversion **3** (%)	GC-MS Conversion **3'** (%)
1	*t*-BuOK	86 (78)[b]	10
2	*t*-BuONa	70	20
3	Na_2CO_3	5	0
4	K_2CO_3	7	0
5	Cs_2CO_3	50	40
6	K_3PO_4	25	26
7	No Base	0	0

Reaction condition: [a] Propiophenone (0.5 mmol), benzyl alcohol (0.625 mmol), $NiBr_2$ (5 mol%), phen (6 mol%), base (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 140 °C oil bath, 36 h reaction time. [b] Isolated yield (average of two runs).

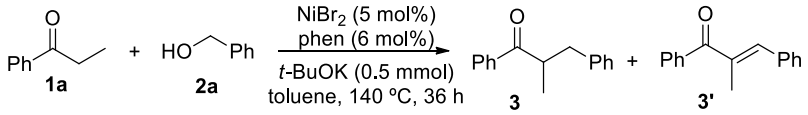
Table 4: Screening of solvents [a]



Entry	Solvent	GC-MS Conversion **3** (%)	GC-MS Conversion **3'** (%)
1	Toluene	86 (78) [b]	10
2	*p*-Xylene	62	19
3	1,4-dioxane	61	25
4	DMA	18	10
5	DMF	5	<1
6	Pentanol	5	<1

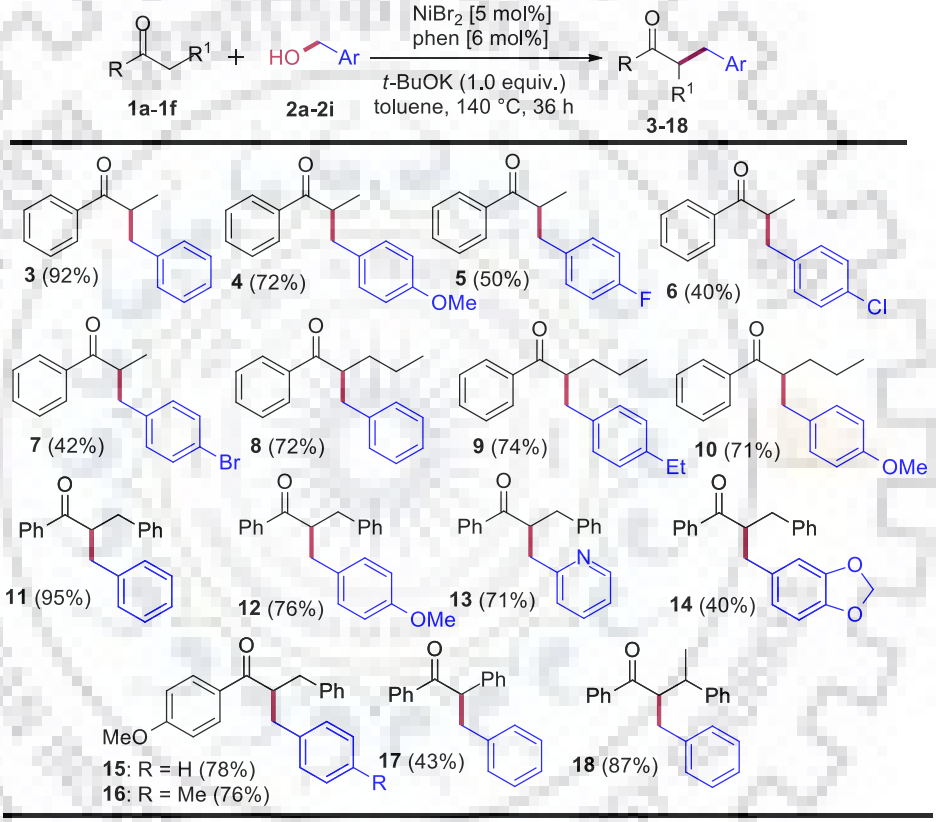
Reaction condition: [a] Propiophenone (0.5 mmol), benzyl alcohol (0.625mmol), $NiBr_2$ (5 mol%), phen (6 mol%), *t*-BuOK (0.5 mmol), solvent (2.0 mL), Schlenk tube under N_2 atmosphere, 140 °C oil bath, 36 h reaction time. [b] Isolated yield (average of two runs).

Table 5. Screening of alcohol equivalents [a]



Entry	Benzyl alcohol (X equiv.)	GC-MS Conversion **3** (%)	GC-MS Conversion **3'** (%)
1	1.5	95 (92)[b]	1
2	1.25	86 (78)[b]	10
3	1.1	79	16

Reaction condition: [a] Propiophenone (0.5 mmol), benzyl alcohol (0.75, 0.625, 0.55 mmol), $NiBr_2$ (5 mol%), phen (6 mol%), *t*-BuOK (0.5 mmol), toluene (2.0 mL), Schlenk tube under nitrogen atmosphere, 140 °C oil bath, 36 h reaction time. [b] Isolated yield (average of two runs).



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.

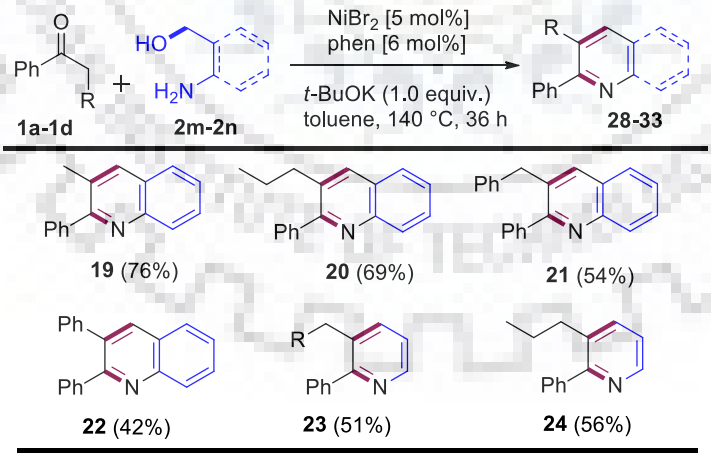
Scheme 7: Scope of methylene ketones with alcohols to branched α-alkylated ketones.

α-Alkylation of methylene ketones with alcohol: After having the optimal conditions in hand, a range of α-substituted methylene ketones and alcohols were alkylated in good to excellent yields (Scheme 7). For instance, propiophenone could be transformed to a series of branched alkylated ketones **3-7** in up to 92% yield. Gratifyingly, unsubstituted phenyl ketones bearing sterically demanding n-propyl (**1b**), benzyl (**1c**), phenyl (**1e**) or secondary alkyl

substituent (**1f**), efficiently converted to the corresponding branched products in moderate to excellent yields (Scheme 7, entries **8-10** and **11**, **17-18**).

To our delight, 2-pyridinemethanol furnished the desired product **13** in 71% yield. Advantageously, when 4-methoxy substituted phenyl ketone **1d** was employed, desired gem-bis (benzyl substituted) ketones **15-16** were obtained in 76-78% yield respectively. It is noteworthy to mention that, benzyl alcohol bearing halides (F, Cl or Br) as well as methoxy and 1,3-dioxolone groups could be tolerated under the standard catalytic conditions including pyridine moiety

Intermolecular cyclization for synthesis of quinolines and pyridines. The generality of our catalytic protocol was further explored in the green synthesis of C-2 and C-3 substituted quinolines and pyridines using 2-amino benzyl alcohol with a range of methylene substituted ketones (Scheme 8). Surprisingly, till date, mostly Ir- and Ru-based precious metal complexes are used for their synthesis. Importantly, synthesis of five and six-membered *N*-heterocycles using renewable resources under nickel catalysis would be more sustainable because of their interesting bioactivity. Gratifyingly, when 2-amino benzyl alcohol was employed with steric and electronically different methylene ketones, a range of C-2 and C-3 substituted quinolines and pyridines **19-24** were obtained in up to 76% yields (Scheme 8). Pleasingly, we established an alternative green synthesis of substituted pyridines and quinolines using an inexpensive nickel catalyst. Notably, the catalytic system is tolerant to halides, alkyl, alkoxy and dioxolone functionalities, including benzyl and pyridine moiety.

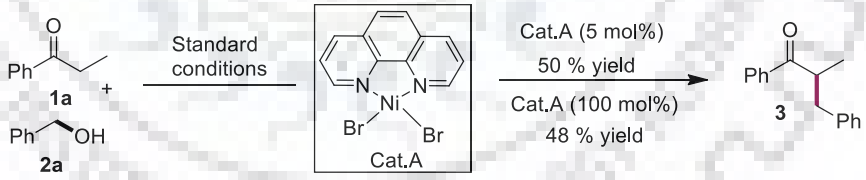


Reaction condition:[a] Unless otherwise specified, the reaction was carried out with **1** (0.25 mmol), **2** (0.3125 mmol), $NiBr_2$ (0.0125 mmol), phen (0.015 mmol), *t*-BuOK (0.25 mmol) in toluene (2.0 mL) at 140 °C for 36 h.

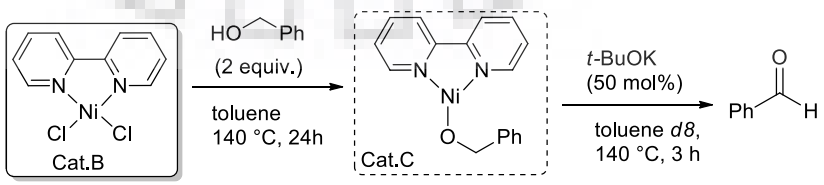
Scheme 8: Intermolecular cyclization: Green synthesis to quinoline and pyridine.

Kinetic and mechanistic studies

To the best of our knowledge, till date there is no detailed mechanistic studies reported for α-alkylation of methylene ketones. As a part of our on-going studies, we were interested to gain insight about the Ni-catalyzed α-alkylation of ketones. Therefore, to identify the key Ni-intermediate species, **Cat.A** was prepared, isolated and separately employed in stoichiometric (100 mol%) and in catalytic (10 mol%) equiv. in model reaction under standard conditions, **3** was obtained in 48% and 50% yield (Scheme 9). Mechanistically we postulated that, Ni-catalyzed α-alkylation of methylene ketones is a multi-step process: dehydrogenation of alcohol to aldehyde followed by base mediated condensation with ketone to an enone intermediate and finally *in situ* hydrogenation of enone by Ni-H species led to the desired product (Scheme 6). It is to be noted that, control experiments revealed the crucial role of base to achieve higher product yield (Table 3). We envisioned that, base enables the activation of nickel pre-catalysts *via* dehalogenation of NiX_2, followed by resulted the formation of alkoxy-nickel species with alcohol. Further, this pre-formed alkoxy-nickel species undergoes base mediated β-hydride elimination, during this process aldehyde is formed and more importantly, active nickel-hydride species is generated. Therefore to validate this hypothesis, defined Ni-alkoxy species of **Cat.B**, such as, **Cat.C** was prepared and employed under standard catalytic conditions. After three hours, GC-MS analysis of the crude reaction mixture detected benzaldehyde formation (Scheme 10). These experimental evidences are in agreement for the participation of the nickel-alkoxy intermediate during α-alkylation of methylene ketones.

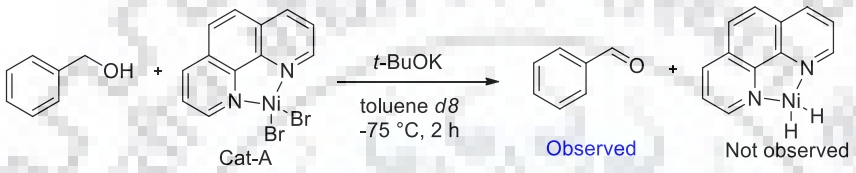


Scheme 9: Stoichiometric and catalytic studies using defined Ni-catalyst



Scheme 10: Evidence for intermediate nickel-alkoxy species

On the basis of the above findings, further we made an attempt to prepare the Ni-hydride species of **Cat. A**. Unfortunately, the experiments were not successful, after several attempt at variable temperature. These experiments revealed that, the desired Ni-H species is highly unstable to identify using an *in situ* NMR studies even at -75 °C (Scheme 11). At this point we realized that electron rich phosphine ligand might be useful to form stable Ni-H species. Therefore, tri-cyclohexyl phosphine, **L6** was used to prepare the defined complex, $(Cy_3)_2PNiBrH$, **Cat.B-H**, and subjected to employ with enone **3'** in stoichiometric equiv. using standard conditions. Gratifyingly, **3** was obtained in 21% yield (Scheme 12). The above experimental findings strongly evident for the participation of Ni-H species.

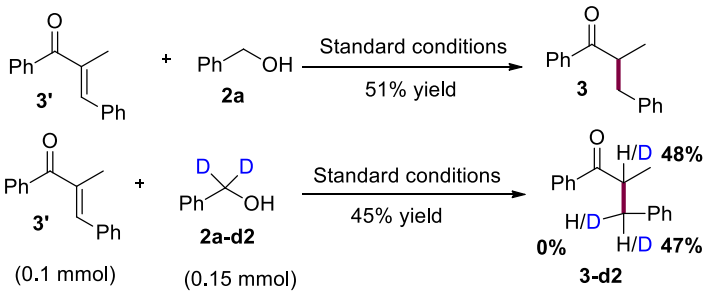


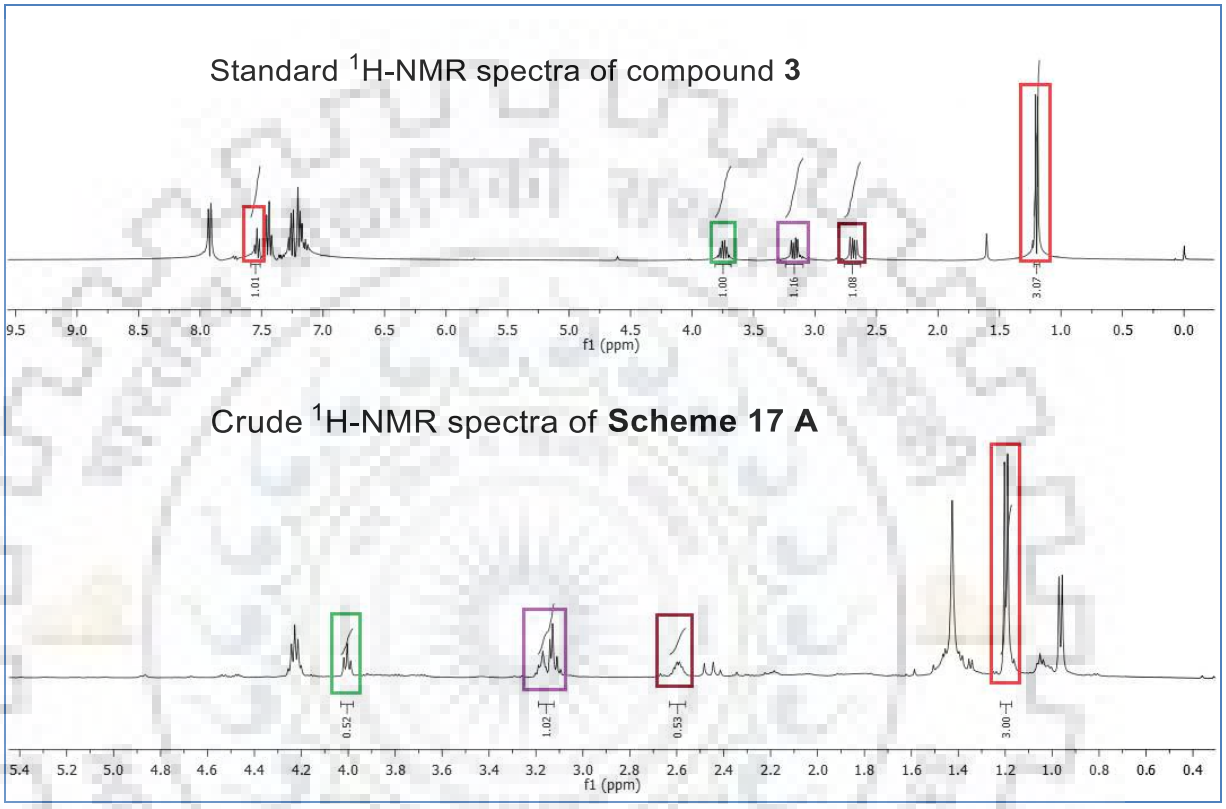
Reaction condition**:** [a] Benzyl alcohol (0.2 mmol), $NiBr_2$.phen complex (0.02 mmol), *t*-BuOK (0.2 mmol), toluene d_8 (0.4 mL), in NMR tube under N_2 atmosphere, ^1H NMR was recorded at -70 °C.

Scheme 11: Metal hydride trapping method *via* ^1H NMR

Scheme 12: Stoichiometric studies using defined Ni-H species

Again, to understand the deeper insight into the reaction mechanism, we performed a series of deuterium labelling experiments (Scheme 13-14). Enone **3'** was allowed to react with **2a** and **2a-d2** and under standard conditions afforded **3-d2** in 45-51% yield and exhibited 47-48% incorporation of deuterium. When we performed a crossover experiment using 1:1 mixture of **2a** and **2a-d2** under standard conditions, and observed the formation of H/D-scrambled product **3-d2''** in 25% yield and exhibited 20-24% incorporation of deuterium at C-2 and C-3 position of **3** (Scheme 15). Furthermore, we conducted α-alkylation of **1a** using **2a-d1** and **2a-d2,** ^1H-NMR and GC-MS analysis indicated the formation of **3-d2'** and **3-d3** having variable deuterium substitutions at C-2 and C-3 position of **3** (Scheme 16).

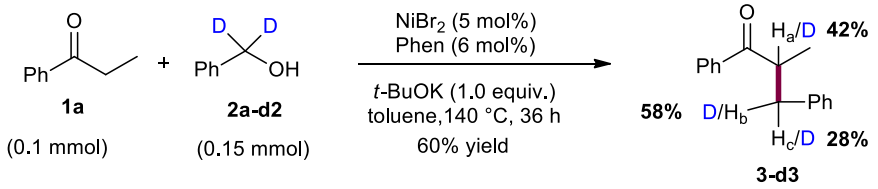


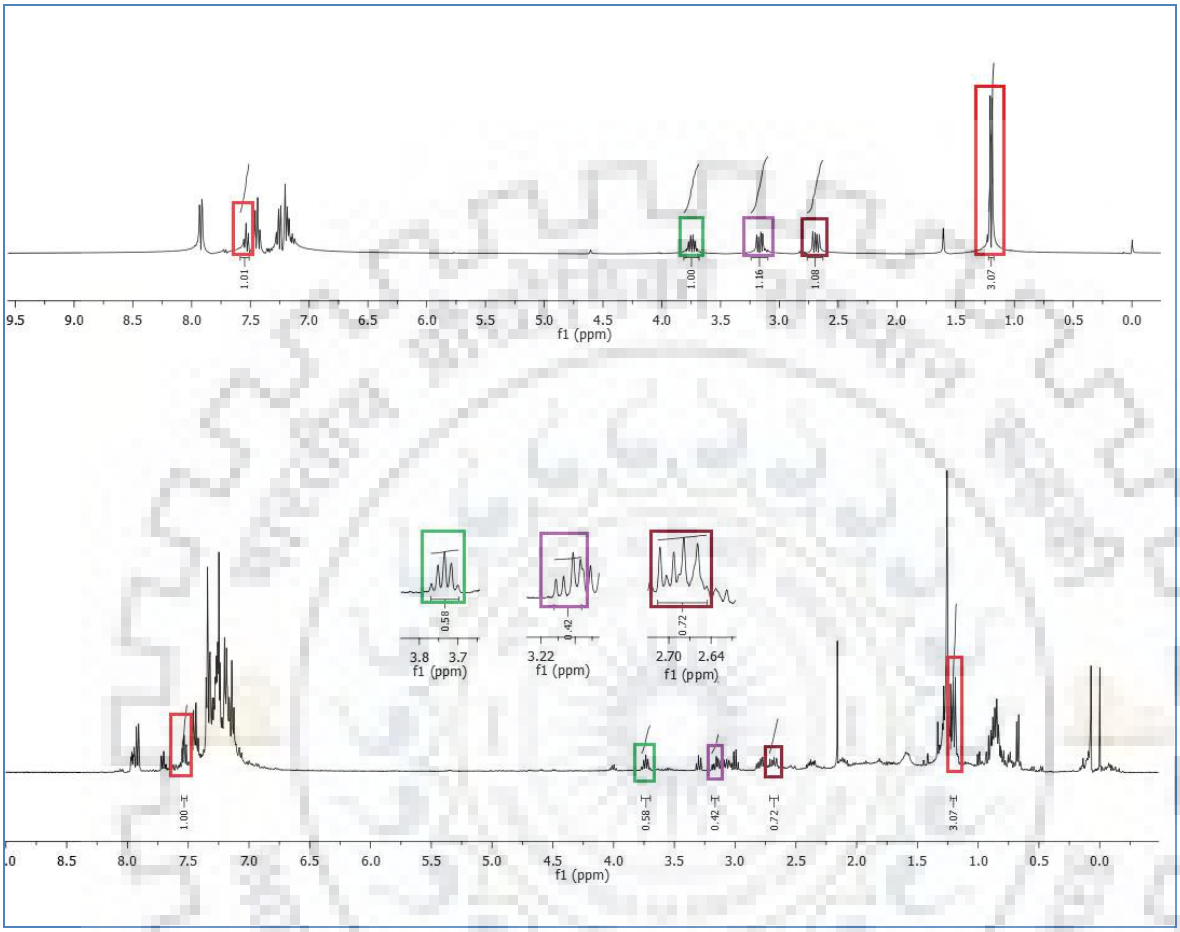


Conversion was calculated by ^{1}H-NMR integration value

		Deuterium incorporation in **H_a** Position	Deuterium incorporation in **H_b** Position	Deuterium incorporation in **H_c** Position
Signal δ ppm	1.2 [d, CH_3, (3H)]	3.75 (1H)	3.17 (1H)	2.69 (1H)
Integral Value	3.0	0.52	1.0	0.53
Calculated ratio		(1-0.52)×100 = **48%**	(1-1)×100 = **0%**	(1-0.53)×100 = **47%**

Scheme 13: Evidence for enone intermediate and catalytic deuteration studies

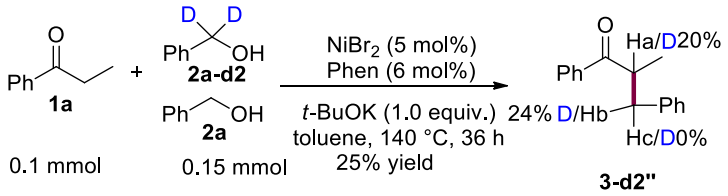


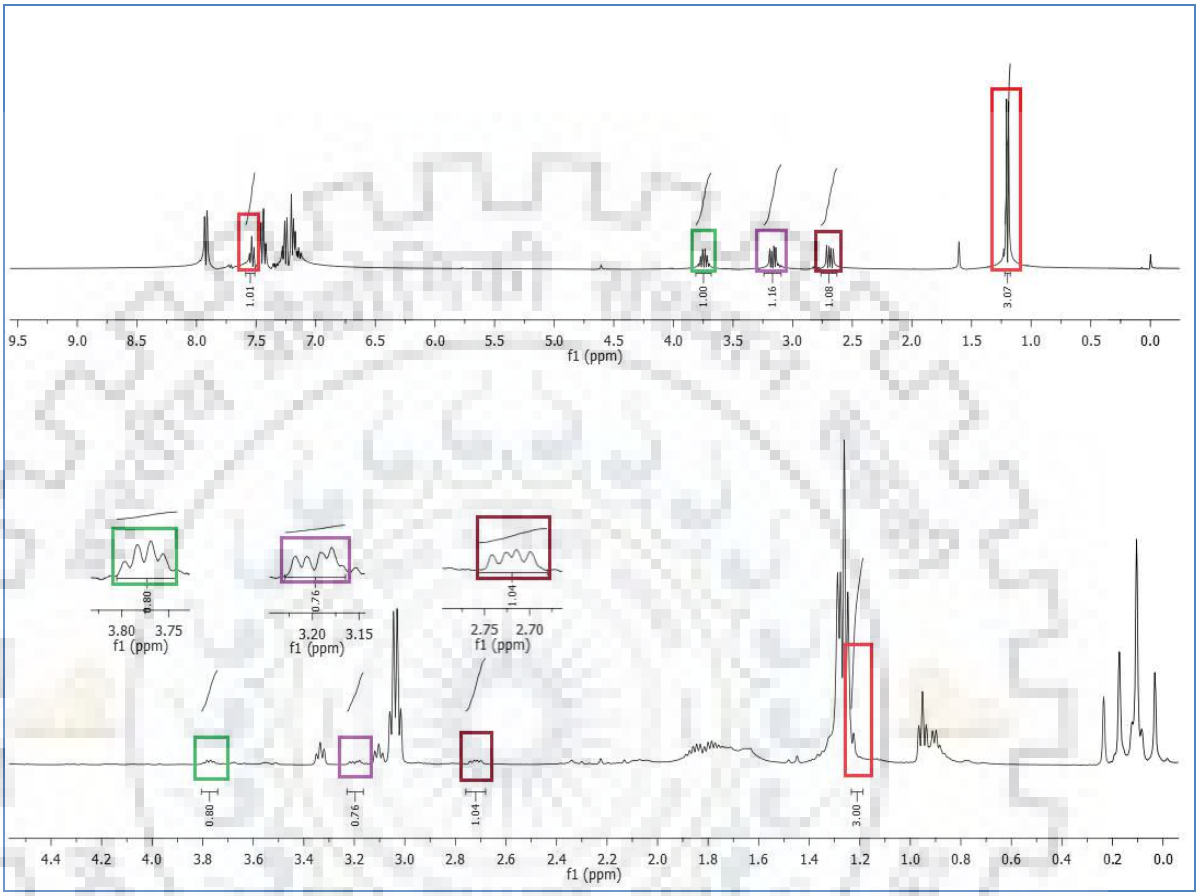


Conversion was calculated by ^{1}H-NMR integration value

		Deuterium incorporation in **H_a** Position	Deuterium incorporation in **H_b** Position	Deuterium incorporation in **H_c** Position
Signal δ ppm	1.2 [d, CH_3, (3H)]	3.75 (1H)	3.17 (1H)	2.69 (1H)
Integral Value	3.0	0.58	0.42	0.72
Calculated ratio		(1-0.58)×100=**42%**	(1-0.42)×100 = **58%**	(1-0.72)×100 = **28%**

Scheme 14: Deuterium incorporation and control experiments

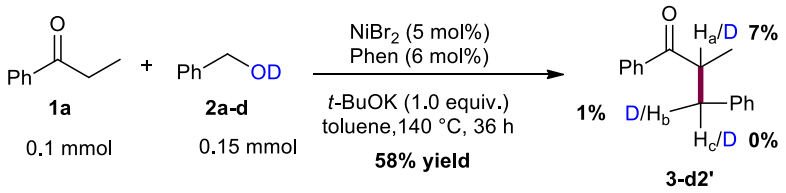


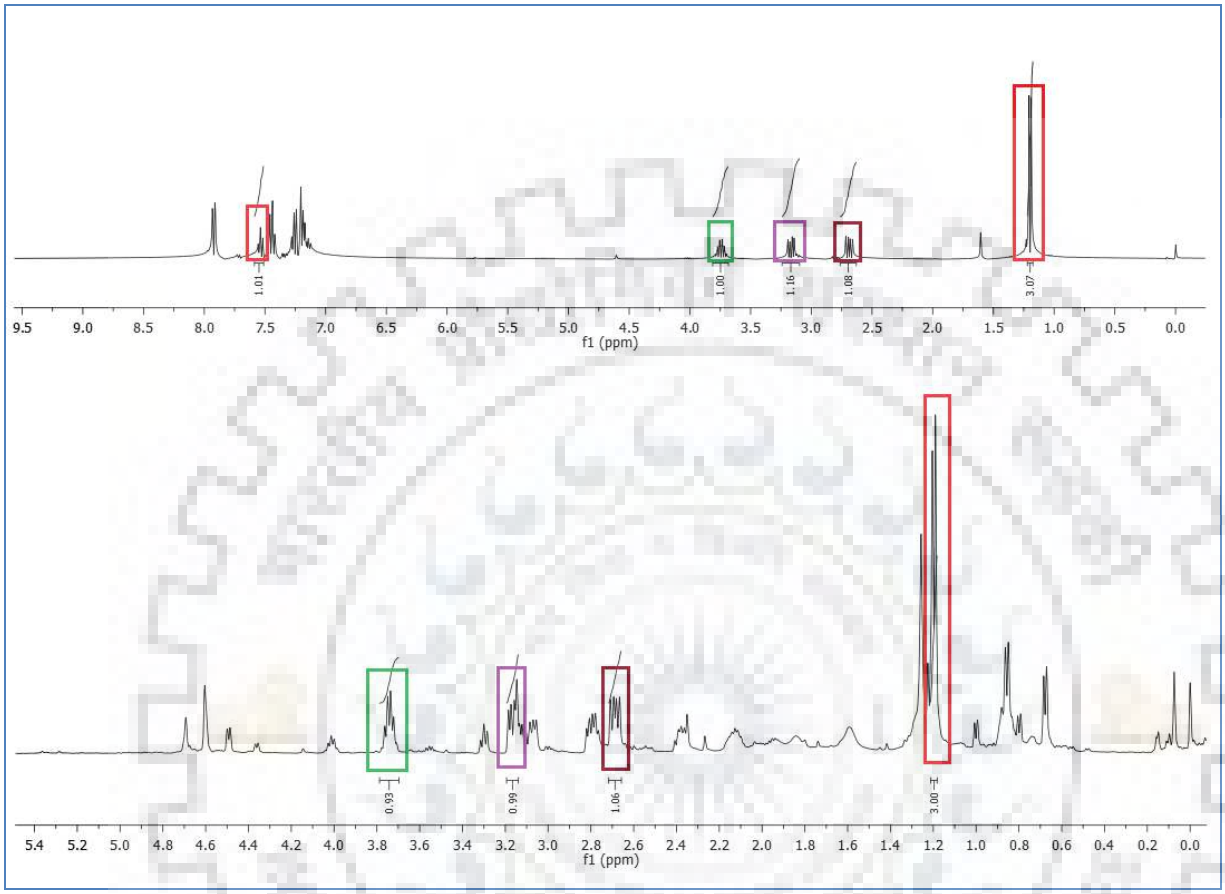


Conversion was calculated by ^{1}H-NMR integration value

		Deuterium incorporation in **H_a** Position	Deuterium incorporation in **H_b** Position	Deuterium incorporation in **H_c** Position
Signal δ	1.2 [d,CH_3, (3H)]	3.75 (1H)	3.17 (1H)	2.69 (1H)
Integral Value	3.0	0.80	0.76	1.0
Calculated ratio		(1-0.80)×100 = **20%**	(1-0.76)×100 = **24%**	(1-1)×100 = **0%**

Scheme 15: Competitive and parallel experiments

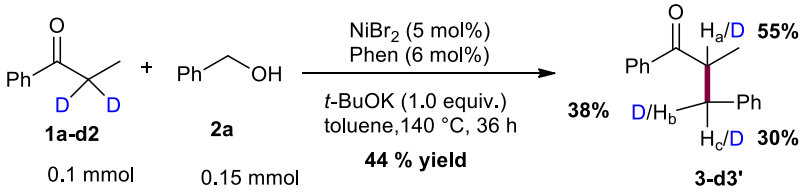


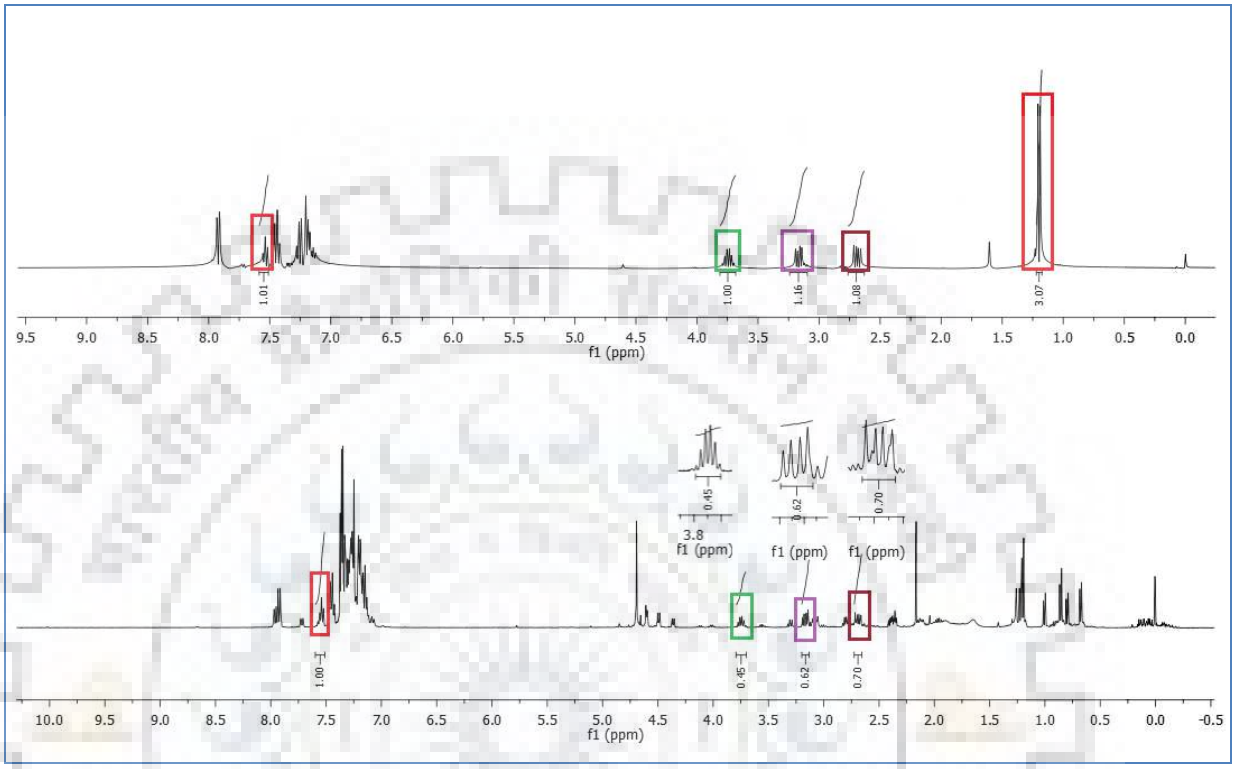


Conversion was calculated by ^{1}H-NMR integration value

		Deuterium incorporation in **H_a** Position	Deuterium incorporation in **H_b** Position	Deuterium incorporation in **H_c** Position
Signal δ ppm	1.2 [d, CH_3, (3H)]	3.75 (1H)	3.17 (1H)	2.69 (1H)
Integral Value	3.0	0.93	0.99	1.0
Calculated ratio		(1-0.93)×100 = **7%**	(1-0.99)×100 = **1%**	(1-1)×100 = **0%**

Scheme 16: Experiments with deuterated benzyl alcohol





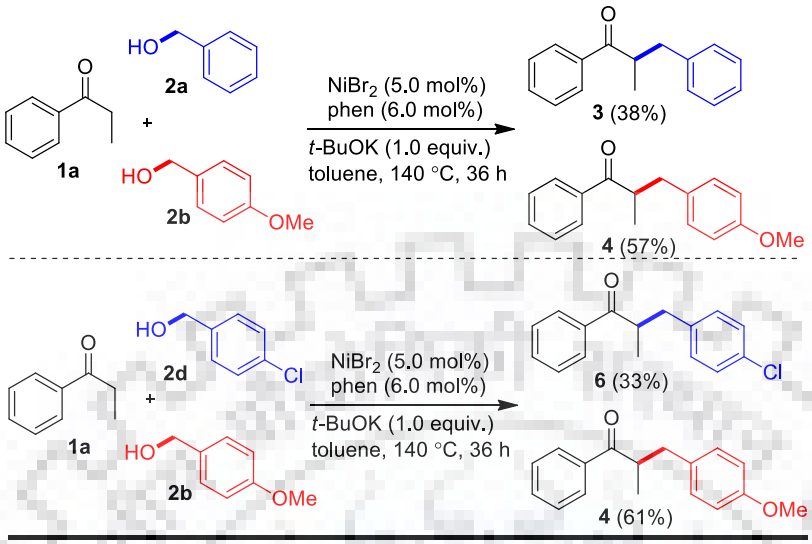
Conversion was calculated by ^{1}H-NMR integration value

		Deuterium incorporation in **H_a** Position	Deuterium incorporation in **H_b** Position	Deuterium incorporation in **H_c** Position
Signal δ ppm	7.54 [m, *p*-Ar-H, (1H)]	3.75 (1H)	3.17 (1H)	2.69 (1H)
Integral Value	1.0	0.45	0.62	0.70
Calculated ratio		(1-0.45)×100 = **55%**	(1-0.62)×100 = **38%**	(1-0.70)×100 = **30%**

Scheme 17: Experiments with deuterated acetophenone and benzyl alcohol

Reaction with **1a-d2** with benzylalcohol **2a** also resulted the formation of **3-d3'** in 44% yield with variable deuterium incorporation at C-2 and C-3 position of **3** (Scheme 17). These deuterated experimental observations strongly support our findings and are in agreement with the literature report of D/H exchange following hydrogen auto-transfer strategy. It is

noteworthy to mention that, alcohol acts as generic hydride source and nickel-hydride species is the active catalytic intermediate for α-alkylation of methylene ketones.[15]



Competitive experiments. Reaction condition: [a] Unless specified, the reaction was carried out with **1** (0.25 mmol), **2** (0.375 mmol (1:1), $NiBr_2$ (0.0125 mmol), phen (0.015 mmol), *t*-BuOK (0.25 mmol) in toluene (2.0 mL) at 140 °C for 36 h. [b] Conversion was calculated by GC-MS.

Scheme 18: Competition reactions between **1a** and benzyl alcohols of different electronics

In addition, to understand the electronic effects of different substrate motif, we performed two competition experiments. A mixture of 4-methoxy benzyl alcohol **2b** and methylene ketone **1a** were independently reacted with benzyl alcohol **2a** and 4-chlorobenzyl alcohol **2d** under standard catalytic conditions. GC-MS analysis of the crude reaction mixture revealed that, α-alkylation of methylene ketones occurred at higher rates for electron-rich substituent.

[4.4] Conclusions:

In conclusion, we have developed an operational simple and practical route for the synthesis of branched gem-bis(alkyl) ketones using earth abundant non-precious Ni-catalyst. Readily available renewable alcohols could be used for this α-alkylation of methylene ketones using borrowing hydrogen approach. A range of aryl, and alkyl derivatives including pyridine yielded the α-branched products in up to 95% yield. Green synthesis of C-2/C-3 substituted quinolines and pyridines significantly broaden the scope of this methodology. A detailed mechanistic studies involving isolation of a putative Ni-intermediate, defined Ni-H species as well as intermediate Ni-alkoxy species were performed. Additionally, studies of substrate

dependent electronic effect and a series of deuterium labelling experiments were found crucial for α-alkylation of methylene ketones.

[4.5] Experimental details

[4.5.1] General Procedure for Ni-catalyzed alkylation with Ketones:

Procedure A:

In a 15 mL oven dried schlenk tube, propiophenone (0.25 mmol), *t*-BuOK (0.25 mmol), $NiBr_2$ (0.0125 mmol), phen (0.015 mmol), and alcohols (0.375 mmol, 1.5 equiv.) were added followed by toluene (2.0 mL) under an atmosphere of N_2 and the reaction mixture was heated at 140 ^oC 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 B:

In a 15 mL oven dried schlenk tube, propiophenone (0.25 mmol), *t*-BuOK (0.5 mmol), $NiBr_2$ (0.01875 mmol), phen (0.0225 mmol), and alcohols (0.375 mmol, 1.5 equiv.) were added followed by toluene (2.0 mL) under an atmosphere of N_2 and the reaction mixture was heated at 140 ^oC 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, propiophenone (0.25 mmol), *t*-BuOK (0.625 mmol), $NiBr_2$ (0.0125 mmol), phen (0.015 mmol) were added followed by alcohols (1.0 mL) under an atmosphere of N_2 and the reaction mixture was refluxed at 140 ^oC 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 D:

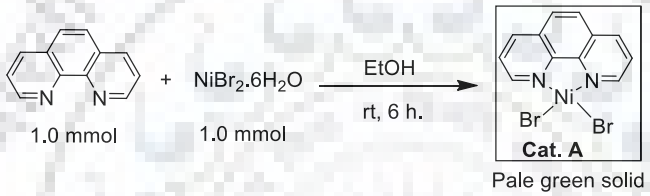
In a 15 mL oven dried schlenk tube, propiophenone (0.25 mmol), *t*-BuOK (0.0625 mmol), $NiBr_2$ (0.0125 mmol), phen (0.015 mmol), and alcohols (0.3125 mmol, 1.25 equiv.) were added followed by toluene (2.0 mL) under an atmosphere of N_2 and the reaction mixture was heated at 140 ^oC for 36 h in a closed 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 E:

In a 15 mL oven dried schlenk tube, propiophenone (0.25 mmol), *t*-BuOK (0.25 mmol), $NiBr_2$ (0.0125 mmol), phen (0.015 mmol), and alcohols (0.3125 mmol, 1.25 equiv.) were added followed by toluene (2.0 mL) under an atmosphere of N_2 and the reaction mixture was heated at 140 ^oC 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.

Synthesis of [$NiBr_2$(1,10-phen)] complex:

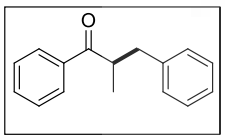


A solution of phen (124 mg, 0.69 mmol) in EtOH (2 mL) was added to a solution of $NiBr_2$•$6H_2O$ (152 mg, 0.69 mmol) in EtOH (2 mL) at rt. After stirring for 6 h, a pale green precipitate formed and was filtered off, washed with EtOH (3×3 mL), and dried *in vacuo* to afford **Cat. A** as a pale green solid.[14]

Characterization of ***Cat.A****:* Chemical Formula: $C_{12}H_8Br_2N_2Ni$; Elemental Analysis calculated (%): C, 36.15; H, 2.02; Br, 40.08; N, 7.03; Ni, 14.72; Found (%): C, 35.57; H, 2.66; N, 6.91.

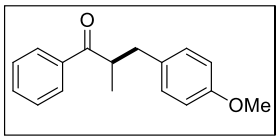
[4.5.2] Analytical Data:

2-Methyl-1,3-diphenylpropan-1-one (3) [17]:



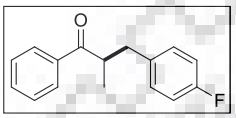
Following the general procedure A, the title product was obtained as a colourless oil (92% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, J = 8.7, 1.4 Hz, 2H), 7.56 – 7.52 (m, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.28 – 7.21 (m, 2H), 7.19 – 7.13 (m, 3H), 3.75 (dq, J = 13.9, 7.0 Hz, 1H), 3.17 (dd, J = 14.0, 6.5 Hz, 1H), 2.69 (dd, J = 14.0, 8.0 Hz, 1H), 1.20 (d, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.85, 140.04, 136.52, 133.02, 129.18, 128.73, 128.47, 128.37, 126.29, 42.84, 39.44, 17.49.

3-(4-Methoxyphenyl)-2-methyl-1-phenylpropan-1-one (4) [18]**:**



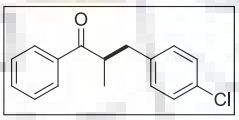
Following the general procedure A, the title product was obtained as a colourless oil (72% yield); ^{1}H NMR (400 MHz, (100 MHz, $CDCl_3$) δ 7.91 (d, J = 7.3 Hz, 2H), 7.53 (m, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 3.74 (s, 3H), 3.76-3.65 (m, 1H), 3.09 (dd, J = 13.8, 6.4 Hz, 1H), 2.62 (dd, J = 13.8, 7.7 Hz, 1H), 1.17 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.35, 154.11, 133.00, 132.06, 130.10, 128.70, 128.31, 113.86, 109.48, 55.29, 43.04, 38.58, 17.40.

3-(4-Fluorophenyl)-2-methyl-1-phenylpropan-1-one (5) [19]**:**



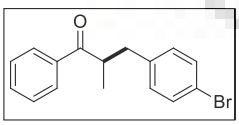
Following the general procedure A, the title product was obtained as a colourless oil (50% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.84 (m, 2H), 7.53 (dd, J = 10.8, 4.4 Hz, 1H), 7.43 (t, J = 7.9 Hz, 2H), 7.13 (dd, J = 9.0, 5.6 Hz, 2H), 6.92 (t, J = 8.9 Hz, 2H), 3.77 – 3.64 (m, 1H), 3.12 (dd, J = 14.1, 7.0 Hz, 1H), 2.67 (dd, J = 14.0, 7.5 Hz, 1H), 1.19 (d, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.31, 161.42 (d, $J_{C\text{-}F}$ = 242.7 Hz), 136.72, 136.58, 133.29, 130.19 (d, $J_{C\text{-}F}$ = 8 Hz), 128.65, 128.18, 115.36 (d, $J_{C\text{-}F}$ = 20.8 Hz), 40.14, 29.38, 17.38.

3-(4-Chlorophenyl)-2-methyl-1-phenylpropan-1-one (6):



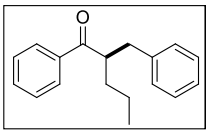
Following the general procedure A, the title product was obtained as a colourless liquid (40% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.7 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 8.3 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.9 Hz, 2H), 3.81 – 3.70 (m, 1H), 3.17 (dd, J = 14.4, 7.2 Hz, 1H), 2.71 (dd, J = 14.4, 7.6 Hz, 1H), 1.23 (d, J = 7.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.29, 138.44, 132.99, 132.02, 130.40, 128.66, 128.57, 128.47, 128.22, 42.67, 38.64, 17.57. Elemental Analysis: Calculated C, 74.27; H, 5.84; Found C, 73.48; H, 5.51.

3-(4-Bromophenyl)-2-methyl-1-phenylpropan-1-one (7) [18]**:**



Following the general procedure A, the title product was obtained as a colourless oil (42% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, J = 8.6, 1.4 Hz, 2H), 7.61 – 7.56 (m, 1H), 7.49 (t, J = 7.9 Hz, 2H), 7.38 (d, J = 5.9 Hz, 2H), 7.15 (d, J = 5.5 Hz, 2H), 3.81 – 3.70 (m, 1H), 3.16 (dd, J = 14.1, 6.7 Hz, 1H), 2.69 (dd, J = 14.0, 7.8 Hz, 1H), 1.23 (d, J = 7.1 Hz, 3H). GC-MS (EI) m/z = 302.1

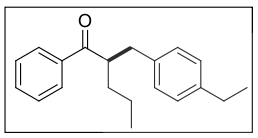
2-benzyl-1-phenylpentan-1-one (8):



Following the general procedure A, the title product was obtained as a colourless oil (72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.84 (m, 2H), 7.52 – 7.49 (m, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.24 – 7.14 (m, 5H), 3.76

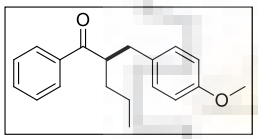
– 3.70 (m, 1H), 3.10 (dd, *J* = 13.5, 7.7 Hz, 1H), 2.77 (dd, *J* = 13.6, 6.5 Hz, 1H), 1.76 (m, 1H), 1.52 (m, 1H), 1.31 – 1.25 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.14, 140.12, 137.62, 132.90, 129.09, 128.63, 128.43, 128.21, 126.20, 48.24, 38.32, 34.68, 20.69, 14.29. Elemental Analysis: Calculated C, 85.67; H, 7.99; Found C, 84.98; H, 7.51

2-(4-Ethylbenzyl)-1-phenylpentan-1-one (9):



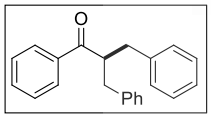
Following the general procedure A, the title product was obtained as a colourless liquid (74% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.2, 3.4 Hz, 2H), 7.52 – 7.48 (m, 1H), 7.39 (dd, *J* = 10.5, 4.7 Hz, 2H), 7.08 – 7.03 (m, 4H), 3.73 – 3.68 (m, 1H), 3.06 (dd, *J* = 13.7, 7.5 Hz, 1H), 2.72 (dd, *J* = 13.7, 6.6 Hz, 1H), 2.59 – 2.53 (m, 2H), 1.79 – 1.72 (m, 1H), 1.55 – 1.46 (m, 1H), 1.32 - 1.22 (m, 2H), 1.19 – 1.14 (m, 3H), 0.84 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.19, 142.07, 137.69, 137.24, 132.80, 129.00, 128.59, 128.31, 127.90, 48.30, 37.89, 34.57, 28.47, 20.68, 15.64, 14.27. Elemental Analysis: Calculated C, 85.67; H, 8.63; Found C, 86.08; H, 7.81.

2-(4-Methoxybenzyl)-1-phenylpentan-1-one (10):



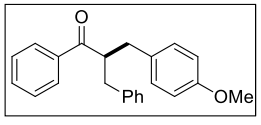
Following the general procedure A, the title product was obtained as a colourless oil (71% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.51 – 7.48 (m, 1H), 7.43 – 7.41 (m, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 3.74 (s, 3H), 3.72 – 3.66 (m, 1H), 3.04 (dd, *J* = 13.7, 7.7 Hz, 1H), 2.71 (dd, *J* = 13.7, 6.4 Hz, 1H), 1.77 – 1.75 (m, 1H), 1.56 – 1.46 (m, 1H), 1.34 – 1.22 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.31, 158.01, 137.68, 132.87, 132.15, 130.02, 128.63, 128.27, 113.84, 55.29, 48.47, 37.47, 34.63, 20.71, 14.31. Elemental Analysis: Calculated C, 80.82; H, 7.85; Found C, 79.99; H, 7.52.

2-benzyl-1,3-diphenylpropan-1-one (11) [17]**:**



Following the general procedure A, the title product was obtained as a colourless oil (95% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 203.46, 139.59, 137.45, 132.88, 129.11, 128.53, 128.50, 128.19, 126.36, 50.57, 38.30.

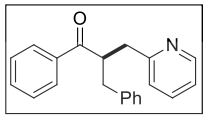
2-Benzyl-3-(4-methoxyphenyl)-1-phenylpropan-1-one (12) [17]**:**



Following the general procedure A, the title product was obtained as a colourless oil (76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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 –

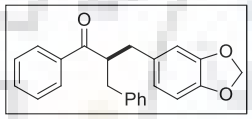
7.18 (m, 2H), 7.13 – 7.10 (m, 3H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 8.6 Hz, 2H), 4.00 – 3.93 (m, 1H), 3.73 (s, 3H), 3.12 – 3.03 (m, 2H), 2.80 – 2.71 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.60, 158.11, 139.68, 137.50, 132.82, 131.60, 130.05, 129.08, 128.51, 128.46, 128.18, 126.29, 113.89, 55.29, 50.80, 38.21, 37.45.

2-Benzyl-1-phenyl-3-(pyridin-2-yl)propan-1-one (13):



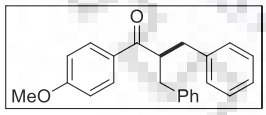
Following the general procedure A, the title product was obtained as a pale yellow oil (71% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 4.0 Hz, 1H), 7.77 (dd, *J* = 8.1, 0.9 Hz, 2H), 7.40 – 7.36 (m, 2H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.14 – 6.96 (m, 6H), 6.94 (dd, *J* = 6.9, 5.2 Hz, 1H), 4.43 – 4.36 (m, 1H), 3.23 (dd, *J* = 14.1, 8.5 Hz, 1H), 3.08 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.90 (dd, *J* = 14.1, 5.8 Hz, 1H), 2.74 (dd, *J* = 13.6, 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.58, 159.38, 149.34, 139.31, 137.36, 136.25, 136.23, 132.76, 129.18, 128.45, 128.42, 126.34, 123.99, 121.32, 47.98, 40.20, 38.53. HRMS (ESI): Calculated for $[C_{21}H_{20}NO]^+$ 302.1539; Found 302.1547.

3-(Benzo[*d*][1,3]dioxol-5-yl)-2-benzyl-1-phenylpropan-1-one (14):



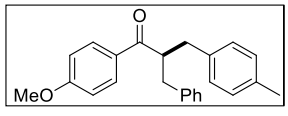
Following the general procedure A, the title product was obtained as a colourless liquid (40% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.46 (dd, *J* = 11.9, 4.4 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 2H), 7.25 – 7.18 (m, 2H), 7.14 – 7.10 (m, 3H), 6.65 – 6.57 (m, 3H), 5.86 (dd, *J* = 3.3, 1.5 Hz, 2H), 3.98 – 3.91 (m, 1H), 3.12 – 3.01 (m, 2H), 2.80 – 2.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.40, 147.61, 145.99, 139.54, 137.44, 133.34, 132.89, 129.08, 128.55, 128.50, 128.18, 126.36, 122.09, 109.46, 108.24, 100.85, 50.79, 38.27, 37.95. Elemental Analysis: Calculated C, 80.21; H, 5.85; Found C, 80.84; H, 6.50

2-Benzyl-1-(4-methoxyphenyl)-3-phenylpropan-1-one (15) [20]**:**



Following the general procedure A, the title product was obtained as a colourless oil (78% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 201.76, 163.37, 139.79, 130.53, 130.45, 129.09, 128.46, 126.29, 113.70, 55.49, 50.06, 38.43.

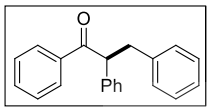
2-Benzyl-1-(4-methoxyphenyl)-3-(*p*-tolyl)propan-1-one (16) [21]**:**



Following the general procedure A, the title product was obtained as a colourless liquid (76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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),

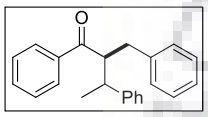
2.79 – 2.72 (m, 2H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.79, 163.33, 139.88, 136.63, 135.71, 130.53, 130.45, 129.08, 128.95, 128.41, 127.69, 126.21, 113.69, 55.50, 50.09, 38.26, 37.95, 21.13.

1,2,3-Triphenylpropan-1-one (17) [17]**:**



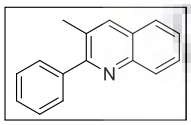
Following the general procedure A, the title product was obtained as a colourless solid (43% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, J = 8.3, 1.2 Hz, 2H), 7.44 – 7.42 (m, 1H), 7.33 (dd, J = 8.0, 7.3 Hz, 2H), 7.25 – 7.21 (m, 4H), 7.20 – 7.17 (m, 3H), 7.14 – 7.12 (m, 1H), 7.08 – 7.06 (m, 2H), 4.80 (t, J = 7.3 Hz, 1H), 3.56 (dd, J = 13.7, 7.5 Hz, 1H), 3.06 (dd, J = 13.7, 7.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.32, 139.86, 139.17, 136.84, 132.91, 129.21, 128.97, 128.81, 128.54, 128.37, 128.30, 127.22, 126.19, 55.96, 40.20.

2-Benzyl-1,3-diphenylbutan-1-one (18):



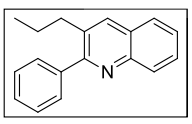
Following the general procedure A, the title product was obtained as a colourless liquid (87% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.2 Hz, 2H), 7.55 – 7.52 (m, 1H), 7.43 (t, J = 7.6 Hz, 3H), 7.31 – 7.25 (m, 6H), 7.20 – 7.12 (m, 3H), 3.54 – 3.46 (m, 1H), 3.32 – 3.11 (m, 3H), 1.33 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.16, 146.66, 137.31, 133.07, 129.09, 128.63, 128.61, 128.47, 128.23, 128.08, 128.05, 126.93, 126.35, 47.11, 35.66, 29.76, 21.93. Elemental Analysis: Calculated C, 87.86; H, 7.05; O, 5.09; Found C, 79.68; H, 7.01.

3-Methyl-2-phenylquinoline (19) [20]**:**



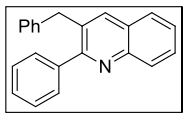
Following the general procedure E, the title product was obtained as a pale yellow oil (76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.5 Hz, 1H), 8.01 (s, 1H), 7.77 (dd, J = 8.1, 0.6 Hz, 1H), 7.65 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.60 – 7.58 (m, 2H), 7.53 – 7.41 (m, 4H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.63, 146.74, 140.99, 136.78, 129.45, 129.30, 128.94, 128.81, 128.39, 128.26, 127.69, 126.78, 126.48, 20.69.

2-Phenyl-3-propylquinoline (20) [26]**:**



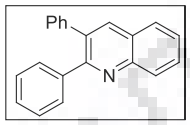
Following the general procedure E, the title product was obtained as a pale yellow oil (69% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.4 Hz, 1H), 8.02 (s, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.54 (dd, J = 8.2, 1.2 Hz, 2H), 7.51 – 7.41 (m, 4H), 2.77 – 2.73 (m, 2H), 1.57 (dd, J = 15.2, 7.6 Hz, 2H), 0.86 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.86, 146.49, 141.10, 135.84, 133.91, 129.38, 128.84, 128.36, 128.13, 127.71, 127.00, 126.45, 126.40, 35.00, 23.77, 13.98.

3-Benzyl-2-phenylquinoline (21) [27]**:**



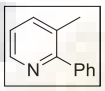
Following the general procedure E, the title product was obtained as a pale yellow oil (54% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.7 Hz, 1H), 7.91 (s, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.67 (ddd, J = 8.6, 7.0, 1.6 Hz, 1H), 7.54 – 7.38 (m, 4H), 7.31 – 7.14 (m, 5H), 7.03 – 6.92 (m, 2H), 4.12 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.96, 132.40, 129.31, 129.06, 128.90, 128.77, 128.74, 128.67, 128.39, 128.37, 128.34, 128.18, 128.07, 128.03, 126.92, 126.37, 126.15, 29.58.

2,3-Diphenylquinoline (22) [26]**:**



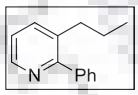
Following the general procedure E, the title product was obtained as a pale yellow oil (42% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 1H), 8.17 (s, 1H), 7.86 (dd, J = 8.0, 0.6 Hz, 1H), 7.73 (ddd, J = 8.3, 6.9, 1.4 Hz, 1H), 7.58 – 7.54 (m, 1H), 7.47 – 7.43 (m, 2H), 7.33 – 7.27 (m, 6H), 7.25 (dd, J = 4.3, 3.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.51, 147.41, 140.53, 140.09, 137.71, 137.60, 134.64, 130.12, 129.85, 129.58, 129.49, 128.32, 128.09, 128.02, 127.63, 127.26, 126.81.

3-Methyl-2-phenylpyridine (23) [28]**:**



Following the general procedure E, the title product was obtained as a pale yellow oil (51% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, J = 3.9 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 7.7 Hz, 2H), 7.21 (dd, J = 7.7, 4.8 Hz, 2H), 7.03 (d, J = 8.7 Hz, 1H), 2.38 (s, 3H). GC-MS (EI) m/z = 169.2

2-Phenyl-3-propylpyridine (24) [28]**:**



Following the general procedure E, the title product was obtained as a pale yellow oil (56% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 – 8.51 (m, 1H), 7.89 – 7.85 (m, 2H), 7.54 – 7.45 (m, 3H), 7.24 (dd, J = 7.8, 4.8 Hz, 2H), 2.70 – 2.61 (m, 2H), 1.60 – 1.54 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H). GC-MS (EI) m/z = 197.2

[4.6] Spectra of selected compounds:

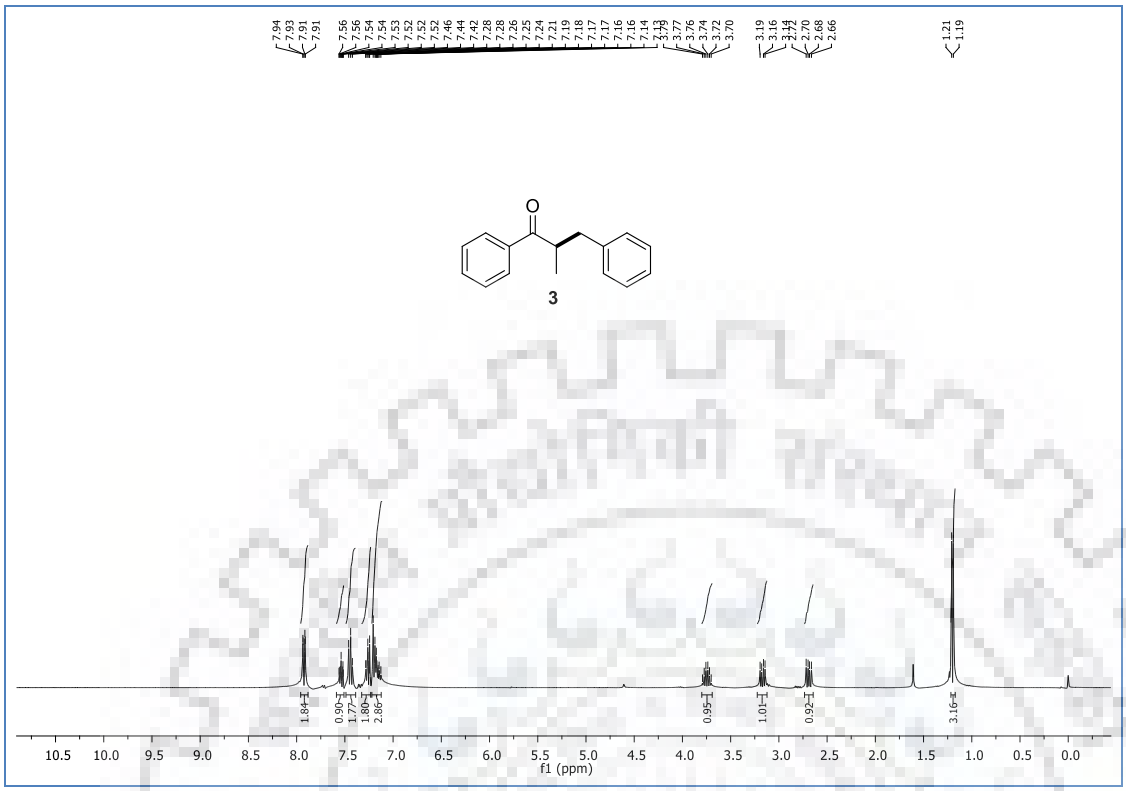


Figure 1a: ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of Compound **3**

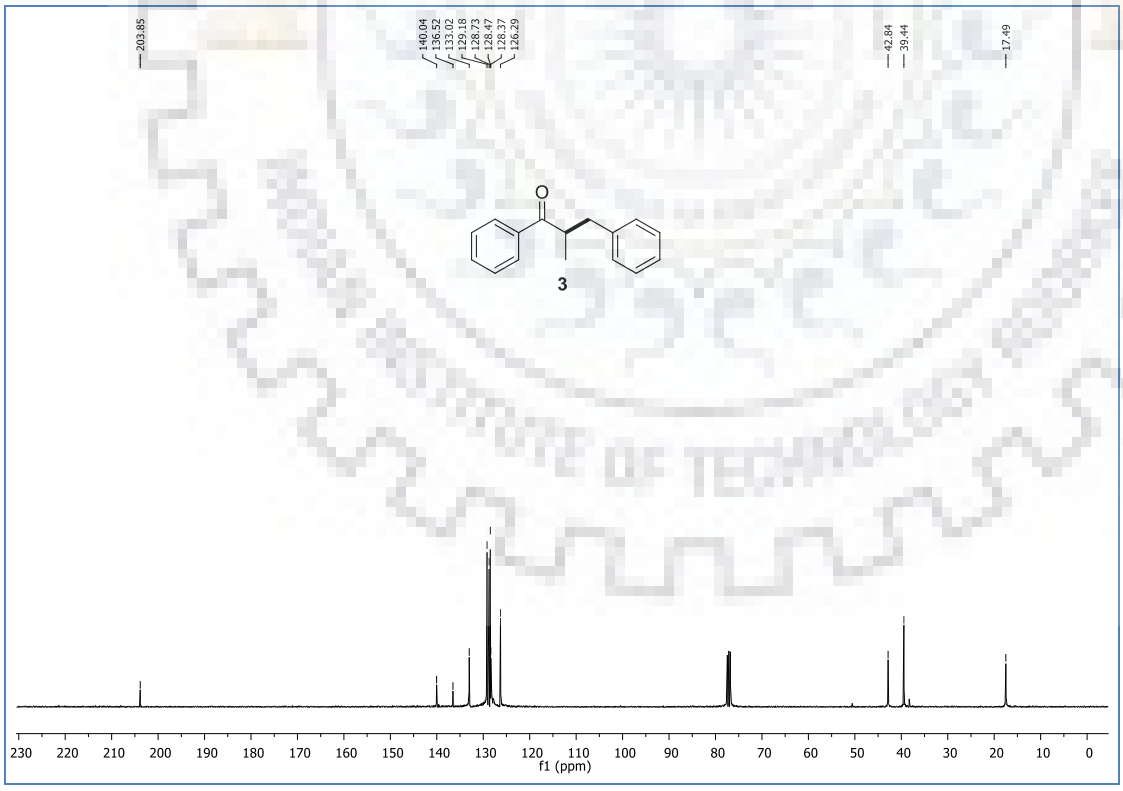


Figure 1b: ^{13}C NMR ($CDCl_3$, 400 MHz) spectrum of Compound **3**

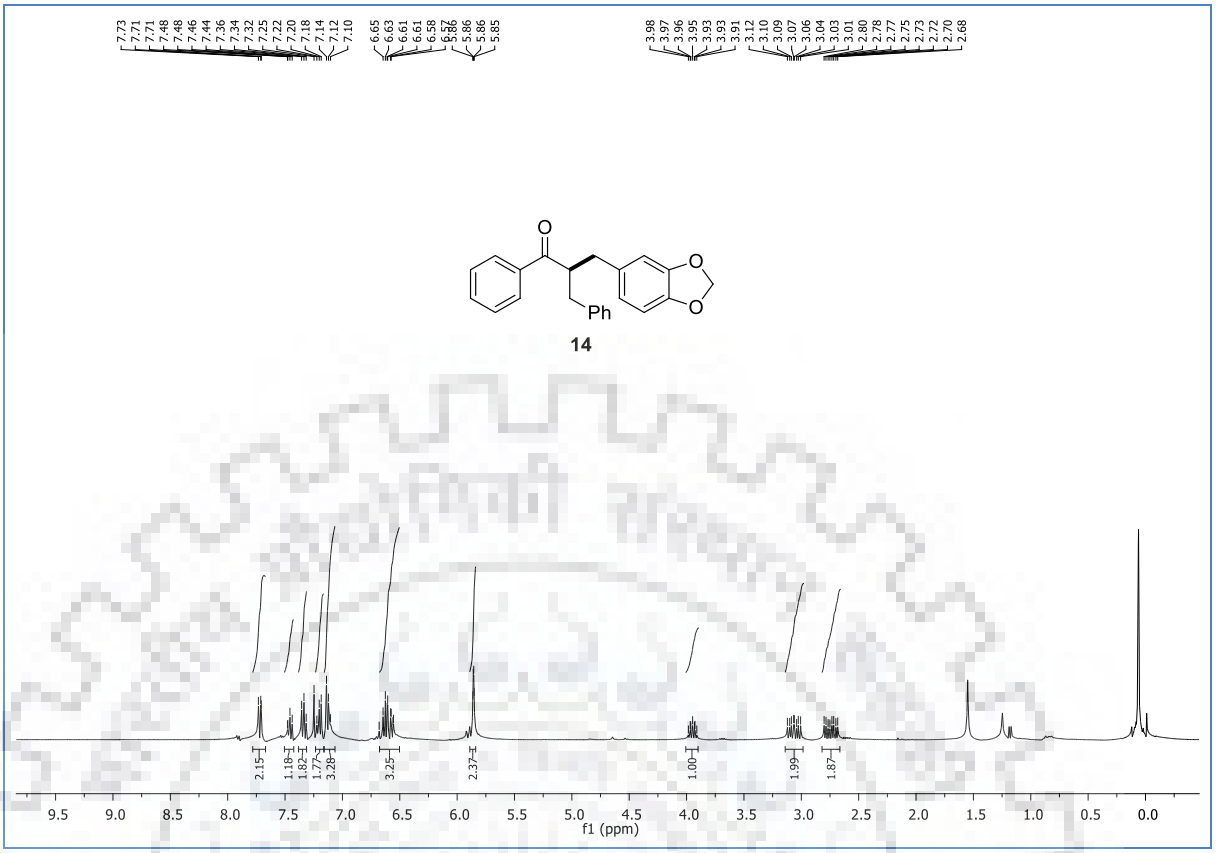


Figure 2a: ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of Compound **14**

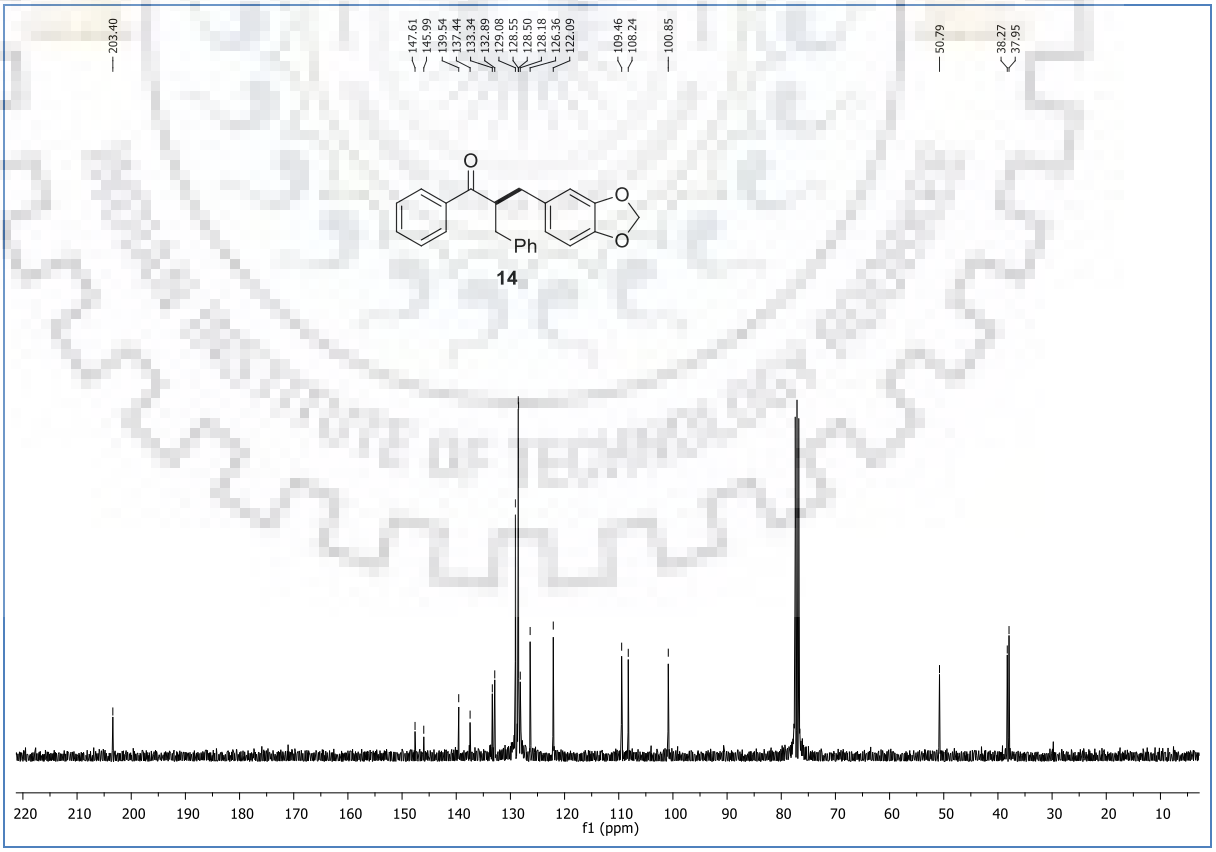


Figure 2b: ^{13}C NMR ($CDCl_3$, 400 MHz) spectrum of Compound **14**

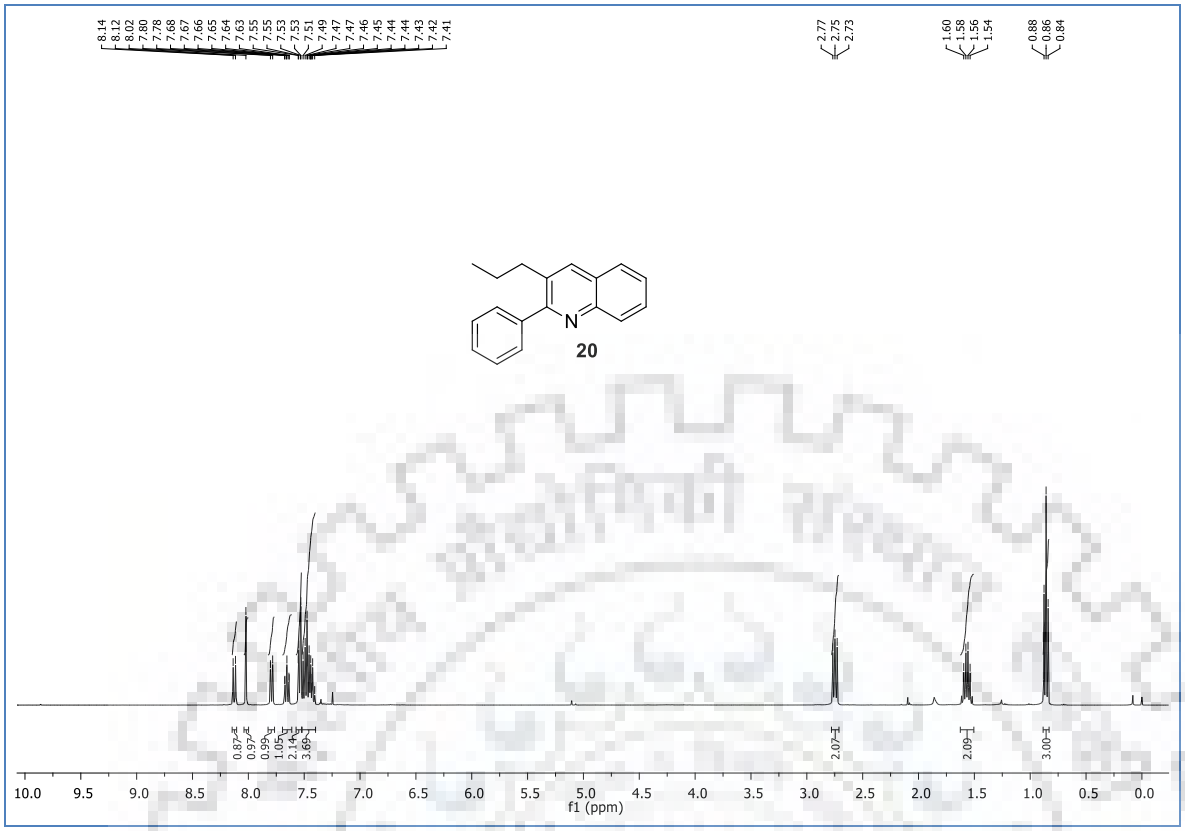


Figure 3a: ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of Compound **20**

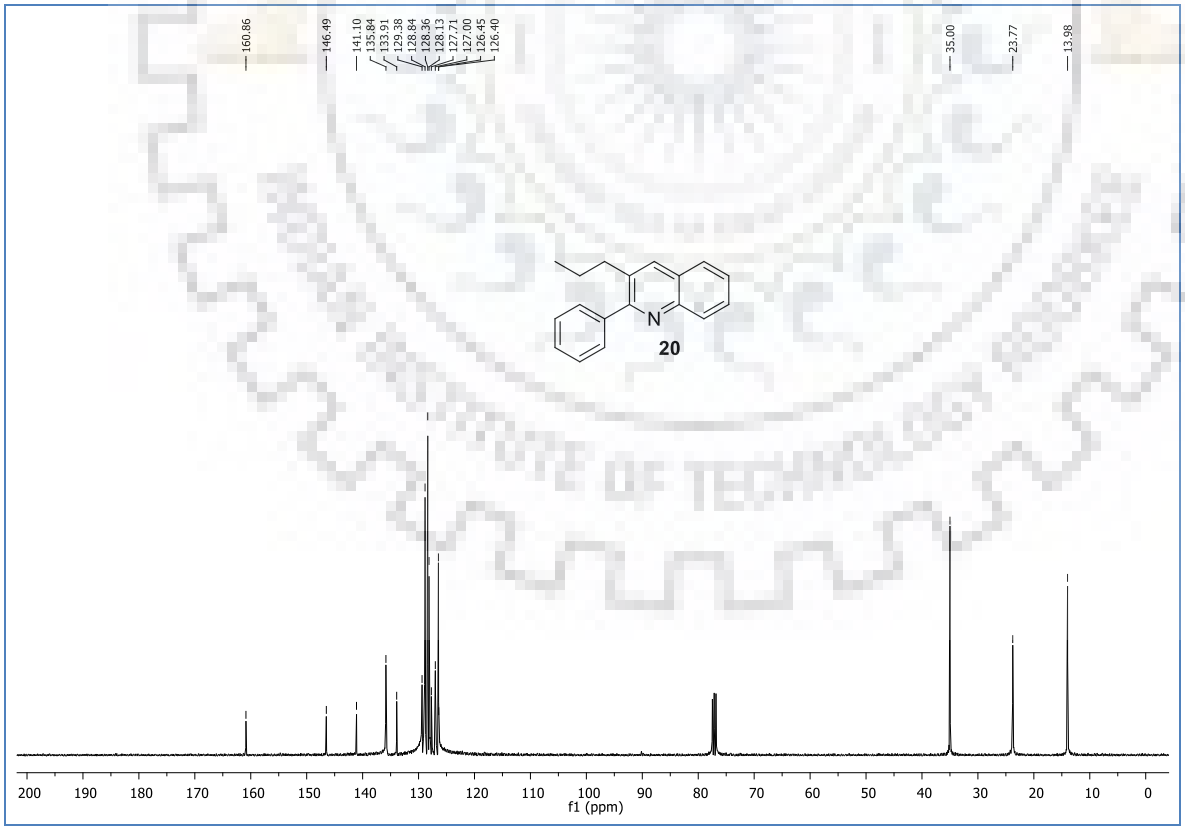


Figure 3b: ^{13}C NMR ($CDCl_3$, 400 MHz) spectrum of Compound **20**

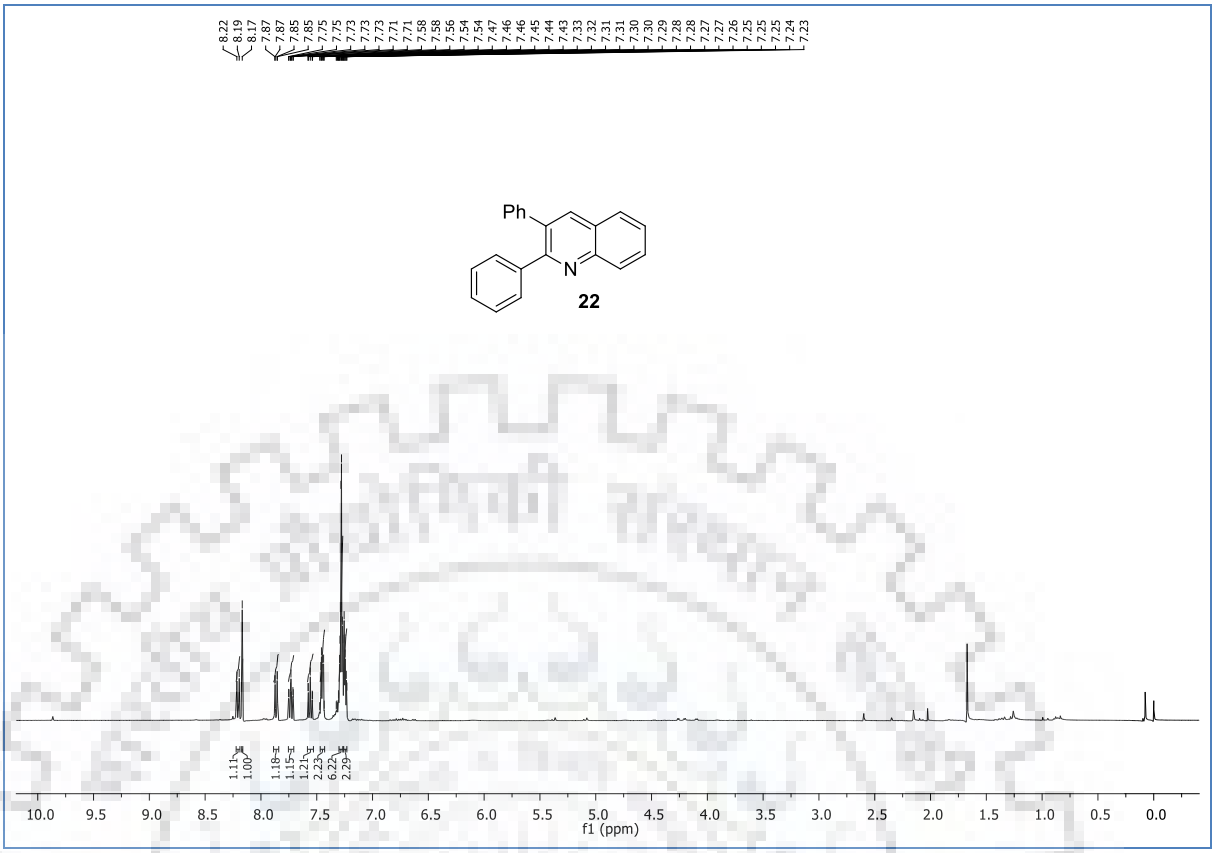


Figure 4a: ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of Compound **22**

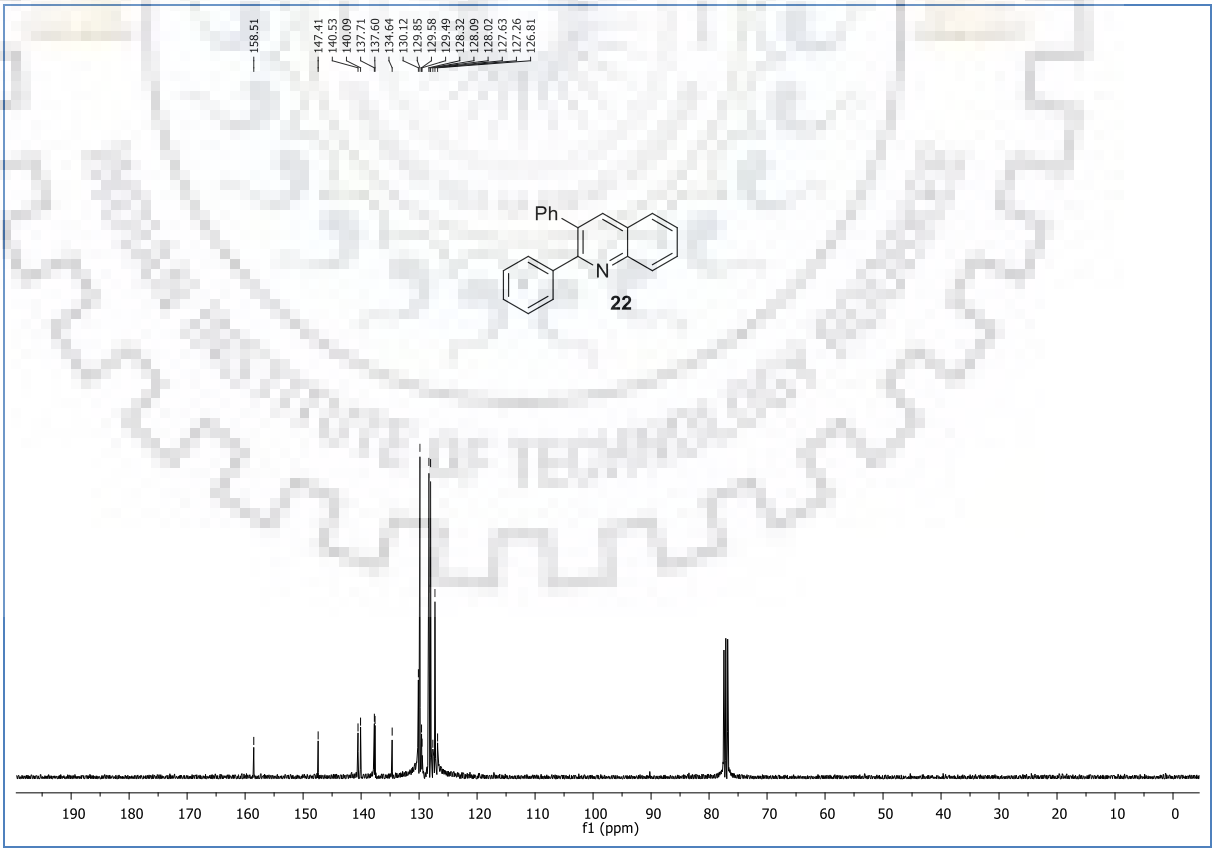


Figure 4b: ^{13}C NMR ($CDCl_3$, 400 MHz) spectrum of Compound **22**

Chapter 5: References

[5.1] Chapter 1: Metal-Catalyzed Sustainable Synthesis of C-C and C-N Bonds: A Brief Literature Summary

[1] (a) De Meijere, A., Diederich, F., Eds. Metal-Catalyzed Cross-Coupling Reactions, Wiley-VCH: Weinheim, Germany, **2004**. (b) Mueller, W. M.; Blackedge, J. P.; Libowitz, G. G. Metal Hydrides, *Academic Press Inc.* **1968**, 119.

[2] (a) Bullock, R. M. Catalysis Without Precious Metals; Wiley-VCH: Weinheim, **2010**. (b) Smithson, H.; Marianetti, C. A.; Morgan, D.; Vander Ven, A.; Predith, A.; Ceder, G. First-principles study of the stability and electronic structure of metal hydrides. *Phys. Rev*. B. **2002**, *66*, 144107.

[3] Hofmann, A. W. Contributions to the knowledge of volatile organic bases. *Justus Liebigs Ann. Chem.* **1851**, *78*, 253.

[4] (a) Magano, J.; Dunetz, J. R. Large-scale applications of transition metal-catalyzed couplings for the synthesis of pharmaceuticals. *Chem. Rev*. **2011**, *111*, 2177. (b) Aubin, Y.; Fischmeister, C.; Thomas, C. M.; Renaud, J.-L. Direct amination of aryl halides with ammonia. *Chem. Soc. Rev*. **2010**, *39*, 4130. (c) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. Industrial-Scale Palladium-Catalyzed Coupling of Aryl Halides and Amines–A Personal Account *Adv. Synth. Catal*. **2006**, *348*, 23

[5] (a) Sperotto, E.; van Klink, G. P. M.; van Koten, G.; de Vries, J. G. The mechanism of the modified Ullmann reaction. *Dalton Trans*. **2010**, *39*, 10338. (b) Monnier, F.; Taillefer, M. Catalytic C-C, C-N, and C-O Ullmann-Type Coupling Reactions. *Angew. Chem*. **2008**, *120*, 3140. *Angew. Chem. Int. Ed*. **2008**, *47*, 3096.

[6] For reviews about hydroamination: (a) Yadav, J. S.; Antony, A.; Rao, T. S.; B. V. Reddy, S. Recent progress in transition metal catalyzed hydrofunctionalisation of less activated olefins. *J. Organomet. Chem*. **2011**, *696*, 16. (b) Hesp, K. D.; Stradiotto, M. Rhodium-and Iridium-Catalyzed Hydroamination of Alkenes. *ChemCatChem* **2010**, *2*, 1192.

[7] Crozet, D.; Urrutigoity, M.; Kalck, P. Recent advances in amine synthesis by catalytic hydroaminomethylation of alkenes. *ChemCatChem* **2011**, *3*, 1102.

[8] Reguillo, R.; Grellier, M.; Vautravers, N.; Vendier, L.; Sabo-Etienne, S. Ruthenium-catalyzed hydrogenation of nitriles: insights into the mechanism. *J. Am. Chem. Soc.* **2010**, *132*, 7854.

[9] Lou, X.-B.; He, L.; Qian, Y.; Liu, Y.-M.; Cao, Y.; Fan, K.-N. Highly Chemo-and Regioselective Transfer Reduction of Aromatic Nitro Compounds using Ammonium Formate Catalyzed by Supported Gold Nanoparticles. *Adv. Synth. Catal*. **2011**, *353*, 281.

[10] Dangerfield, E. M.; Plunkett, C. H.; Win-Mason, A. L.; Stocker, B. L.; Timmer, M. S. M. Protecting-group-free synthesis of amines: synthesis of primary amines from aldehydes via reductive amination. *J. Org. Chem*. **2010**, *75*, 5470.

[11] Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. Transition metal-catalyzed N-alkylation of amines by alcohols. *J. Chem. Soc. Chem. Commun.* **1981**, 611.

[12] Watanabe, Y.; Tsuji, Y.; Ohsugi, Y. The ruthenium catalyzed N-alkylation and N-heterocyclization of aniline using alcohols and aldehydes. *Tetrahedron Lett.* **1981,** *22*, 2667.

[13] Zotto, A. D.; Baratta, W.; Sandri, M.; Verardo, G.; Rigo, P. Cyclopentadienyl RuII Complexes as Highly Efficient Catalysts for the N-Methylation of Alkylamines by Methanol. *Eur. J. Inorg. Chem.* **2004**, 524.

[14] Hamid, M. H. S. A.; Williams, J. M. J. Ruthenium catalyzed N-alkylation of amines with alcohols. *Chem. Commun*. **2007**, 725.

[15] Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. Ruthenium-Catalyzed N-Alkylation of Amines and Sulfonamides Using Borrowing Hydrogen Methodology. *J. Am. Chem. Soc*. **2009**, *131*, 1766.

[16] Bhan, S.; Imm, S.; Mevius, K.; Neubert, L.; Tillack, A.; Williams, J. M. J.; Beller, M. Selective Ruthenium-Catalyzed N-Alkylation of Indoles by Using Alcohols. *Chem. Eur. J.* **2010**, *16*, 3590.

[17] Enyong, A. B.; Moasser, B. Ruthenium-Catalyzed N-Alkylation of Amines with Alcohols under Mild Conditions Using the Borrowing Hydrogen Methodology. *J. Org. Chem.* **2014**, *79*, 7553.

[18] Fujita, K.; Li, Z.; Ozeki, N.; Yamaguchi, R. N-Alkylation of amines with alcohols catalyzed by a Cp* Ir complex. *Tetrahedron Lett.* **2003**, *44*, 2687.

[19] Kawahara, R.; Fujita, K-i.; Yamaguchi, R. N-Alkylation of Amines with Alcohols Catalyzed by a Water-Soluble Cp*Iridium Complex: An Efficient Method for the Synthesis of Amines in Aqueous Media. *Adv. Synth. Catal*. **2011**, *353*, 1161.

[20] Gnanamgari, D.; Sauer, E. L. O.; Schley, N. D.; Butler, C.; Incarvito, C. D.; Crabtree, R. H. Iridium and Ruthenium Complexes with Chelating N-Heterocyclic Carbenes: Efficient Catalysts for Transfer Hydrogenation, β-Alkylation of Alcohols, and N-Alkylation of Amines. *Organometallics* **2009**, *28*, 321.

[21] Blank, B.; Madalska, M.; Kempe, R. An Efficient Method for the Selective Iridium-Catalyzed Monoalkylation of (Hetero) aromatic Amines with Primary Alcohols. *Adv. Synth. Catal*. **2008**, *350*, 749.

[22] Blank, B.; Michlik, S.; Kempe, R. Synthesis of Selectively Mono-N-Arylated Aliphatic Diamines via Iridium-Catalyzed Amine Alkylation. *Adv. Synth. Catal*. **2009**, *351*, 2903.

[23] Blank, B.; Michlik, S.; Kempe, R. Selective Iridium-Catalyzed Alkylation of (Hetero) Aromatic Amines and Diamines with Alcohols under Mild Reaction Conditions. *Chem. Eur. J.* **2009**, *15*, 3790.

[24] Zhang, Y.; Lim, C. S.; Sim, D. S. B.; Pan, H.-J.; Zhao, Y. Catalytic enantioselective amination of alcohols by the use of borrowing hydrogen methodology: Cooperative catalysis by iridium and a chiral phosphoric acid. *Angew. Chem. Int. Ed*. **2014**, *53*, 1399.

[25] Bertoli, M.; Choualeb, A.; Lough, A. J.; Moore, B.; Spasyuk, D.; Gusev, D. G. Osmium and ruthenium catalysts for dehydrogenation of alcohols. *Organometallics* **2011**, *30*, 3479.

[26] Bala, M.; Verma, P. K.; Sharma, U.; Kumar, N.; Singh, B. Iron phthalocyanine as an efficient and versatile catalyst for N-alkylation of heterocyclic amines with alcohols: one-pot synthesis of 2-substituted benzimidazoles, benzothiazoles and benzoxazoles. *Green Chem*. **2013**, *15*, 1687.

[27] (a) Yan, T.; Feringa, B. L.; Barta, K. Iron catalyzed direct alkylation of amines with alcohols. *Nat. Commun,* **2014**, *5*, 5602. (b) Yan, T.; Feringa B. L.; Barta, K. Benzylamines via iron-catalyzed direct amination of benzyl alcohols. *ACS Catal*. **2016**, *6*, 381. (c) Yan, T.; Feringa, B. L.; Barta, K. Direct N-alkylation of unprotected amino acids with alcohols. *Sci. Adv*. **2017**, *3*, 6494.

[28] Rawlings, A. J.; Diorazio, L. J.; Wills, M. C–N bond formation between alcohols and amines using an iron cyclopentadienone catalyst. *Org. Lett.* **2015**, *17*, 1086.

[29] Pan, H.-J.; Ng, T. W.; Zhao, Y. Iron-catalyzed amination of alcohols assisted by Lewis acid. *Chem. Commun*. **2015**, *51*, 11907.

[30] Mastalir, M.; Glatz, M.; Gorgas, N.; Stöger, B.; Pittenauer, E.; Allmaier, G.; Veiros, L. F.; Kirchner, K. Divergent Coupling of Alcohols and Amines Catalyzed by Isoelectronic Hydride MnI and FeII PNP Pincer Complexes. *Chem. – Eur. J.* **2016***, 22*, 12316.

[31] Polidano, K.; Allen, B. D. W.; Williams, J. M. J.; Morrill, L. C. Iron-Catalyzed Methylation Using the Borrowing Hydrogen Approach. *ACS Catal*. **2018**, *8*, 6440.

[32] Yin, Z.; Zeng, H.; Wu, J.; Zheng, S.; Zhang, G. Cobalt-Catalyzed Synthesis of Aromatic, Aliphatic, and Cyclic Secondary Amines via a "Hydrogen-Borrowing" Strategy. *ACS Catal*. **2016**, *6*, 6546.

[33] Mastalir, M.; Tomsu, G.; Pittenauer, E.; Allmaier, G.; Kirchner, K. Co (II) PCP Pincer Complexes as Catalysts for the Alkylation of Aromatic Amines with Primary Alcohols. *Org. Lett*. **2016**, *18*, 3462.

[34] Liu, Z.; Yang, Z.; Yu, X.; Zhang, H.; Yu, B.; Zhao, Y.; Liu, Z. Efficient Cobalt-Catalyzed Methylation of Amines Using Methanol. *Adv. Synth. Catal*. **2017**, *359*, 4278.

[35] Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. Transition metal catalyzed reactions of alcohols using borrowing hydrogen methodology. *Dalton Trans*. **2009**,753.

[36] Krîger, K.; Tillack, A.; Beller, M. Recent Innovative Strategies for the Synthesis of Amines: From C-N Bond Formation to C-N Bond Activation. *ChemSusChem*. **2009**, *2*, 715.

[37] Caine, D. *in Comprehensive Organic Synthesis*, Vol. 3 (Ed.: Trost, B. M.; Fleming, I.;), Pergamon, Oxford, **1991**, pp. 1–63.

[38] Cho, C. S.; Kim, B.T.; Kim, T.-J.; Shim, S. C. An Unusual Type of Ruthenium-Catalyzed Transfer Hydrogenation of Ketones with Alcohols Accompanied by C− C Coupling. *J. Org. Chem.* **2001**, *66*,9020.

[39] Cho, C. S. Ruthenium-catalyzed one-pot β-alkylation of secondary alcohols with primary alcohols. *Organometallics* **2003**, *22*, 3608.

[40] Gnanamgari, D.; Leung, C. H.; Schley, N. D.; Hilton, S. T.; Crabtree, R. H. Alcohol cross-coupling reactions catalyzed by Ru and Ir terpyridine complexes. *Org. Biomol. Chem*. **2008**, *6*, 4442.

[41] Rueping, M.; Phapale, V. B. Effective synthesis of 2,5-disubstituted tetrahydrofurans from glycerol by catalytic alkylation of ketones. *Green Chem*. **2012**, *14*, 55.

[42] Ogawa, S.; Obora, Y. Iridium-catalyzed selective α-methylation of ketones with methanol. *Chem. Commun*. **2014**, *50*, 2491.

(43) Iuchi, Y.; Obora, Y.; Ishii, Y. Iridium-catalyzed α-alkylation of acetates with primary alcohols and diols. *J. Am. Chem. Soc.***2010**, *132*, 2536.

[44] Shen, D.; Poole, D. L.; Shotton, C. C.; Kornahrens, A. F.; Healy, M. P.; Donohoe, T. J. Hydrogen-Borrowing and Interrupted-Hydrogen-Borrowing Reactions of Ketones and Methanol Catalyzed by Iridium. *Angew. Chem. Int. Ed.* **2015**, *54*, 1642.

[45] Genç, S.; Günnaz, S.; Çetinkaya, B.; Gülcemal, S.; Gülcemal, D. Iridium (I)-Catalyzed Alkylation Reactions To Form α-Alkylated Ketones. *J. Org. Chem*. **2018**, *83*, 2875.

[46] Kuwahara, T.; Fukuyama, T.; Ryu. I. $RuHCl(CO)(PPh_3)_3$-Catalyzed α-Alkylation of Ketones with Primary Alcohols. *Org. Lett*. **2012,** *14*, 4703.

[47] Dowson, G. R. M.; Haddow, M. F.; Lee, J.; Wingad, R. L.; Wass, D. F. Catalytic Conversion of Ethanol into an Advanced Biofuel: Unprecedented Selectivity for n-Butanol. *Angew. Chem.* **2013**, *125*, 9175.

[48] Yan, F. X.; Zhang, M.; Wang, X.T.; Xie, F.; Chen, M. M.; Jiang, H. Efficient ruthenium-catalyzed α-alkylation of ketones using pyridyl methanols. *Tetrahedron* **2014**, *70*, 1193.

[49] Jumde, V. R.; Gonsalvi, L.; Guerriero, A.; Peruzzini, M.; Taddeo, M. A Ruthenium-Based Catalytic System for a Mild Borrowing-Hydrogen Process. *Eur. J. Org. Chem*. **2015**, 1829.

[50] Chan, L. K. M.; Poole, D. L.; Shen, D.; Healy, M. P.; Donohoe, T. J. Rhodium-Catalyzed Ketone Methylation Using Methanol Under Mild Conditions: Formation of α-Branched Products. *Angew. Chem. Int. Ed*. **2014**, *53*, 761.

[51] Mamidala, R.; Samser, S.; Sharma, N.; Lourderaj, U.; Venkatasubbaiah, K. Isolation and Characterization of Regioisomers of Pyrazole-Based Palladacycles and Their Use in α-Alkylation of Ketones Using Alcohols. *Organometallics* **2017**, *36*, 3343.

[52] Elangovan, S.; Sortais, J.-B.; Beller, M.; Darcel, C. Iron-Catalyzed α-Alkylation of Ketones with Alcohols. *Angew. Chem., Int. Ed*. **2015**, *54*, 14483.

[53] Seck, C.; Mbaye, M. D.; Coufourier, S.; Lator, A.; Lohier, J.-F.; Poater, A.; Ward, T. R.; Gaillard, S.; Renaud, J.-L. Alkylation of Ketones Catalyzed by Bifunctional Iron Complexes: From Mechanistic Understanding to Application. *ChemCatChem* **2017**, *9*, 4410.

[54] Zhang, G.; Wu, J.; Zeng, H.; Zhang, S.; Yin, Z.; Zheng, S. Cobalt-Catalyzed α-Alkylation of Ketones with Primary Alcohols. *Org. Lett.* **2017**, *19*, 1080.

[55] Liu, Z.; Yang, Z.; Yu, X.; Zhang, H.; Yu, B.; Zhao, Y.; Liu, Z. Methylation of C(sp3)–H/C(sp2)–H Bonds with Methanol Catalyzed by Cobalt System. *Org. Lett*. **2017**, *19*, 5228.

[56] Freitag, F.; Irrang, T.; Kempe, R. Cobalt-Catalyzed Alkylation of Secondary Alcohols with Primary Alcohols via Borrowing Hydrogen/Hydrogen Autotransfer. *Chem. – Eur. J*. **2017**, *23*, 12110.

[57] Peña-López, M.; Piehl, P.; Elangovan, S.; Neumann, H.; Beller, M. Manganese-Catalyzed Hydrogen-Autotransfer C− C Bond Formation: α-Alkylation of Ketones with Primary Alcohols. *Angew. Chem., Int. Ed.* **2016**, *55*, 14967.

[58] Fu, S.; Shao, Z.; Wang, Y.; Liu, Q. Manganese-Catalyzed Upgrading of Ethanol into 1-Butanol. *J. Am. Chem. Soc*. **2017**, *139*, 11941.

[59] (a) Guillena, G.; Ramon, D. J.; Yus, M. Hydrogen Autotransfer in the N-Alkylation of Amines and Related Compounds using Alcohols and Amines as Electrophiles. *Chem. Rev.* **2010**, *110*, 1611. (b) Gunanathan, C.; Milstein, D. Applications of acceptorless dehydrogenation and related transformations in chemical synthesis, *Science* **2013**, *341*, 249. (c) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. Catalytic Enantioselective C-H Functionalization of Alcohols by Redox-Triggered Carbonyl Addition: Borrowing Hydrogen, Returning Carbon. *Angew. Chem., Int. Ed.* **2014**, *53*, 9142.

[60] Su, T. L.; Lee, T. C.; Kakadiya, R. The development of bis (hydroxymethyl) pyrrole analogs as bifunctional DNA cross-linking agents and their chemotherapeutic potential. *Eur. J. Med. Chem*. **2013**, *69*, 609.

[61] (a) Hantzsch, A. New mode of formation of pyrrole derivatives. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474. (b) Paal, C. Synthesis of thiophene and pyrrole derivatives. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367.

[62] Zhang, M.; Neumann, H.; Beller, M. Selective ruthenium-catalyzed three-component synthesis of pyrroles. *Angew. Chem. Int. Ed.* **2013**, *52*, 597.

[63] Srimani, D.; Ben-David, Y.; Milstein, M. Direct Synthesis of Pyrroles by Dehydrogenative Coupling of β-Aminoalcohols with Secondary Alcohols Catalyzed by Ruthenium Pincer Complexes. *Angew. Chem. Int. Ed*. **2013**, *52*, 4012.

[64] Zhang, M.; Fang, H.; Neumann, H.; Beller, M. General and regioselective synthesis of pyrroles *via* ruthenium-catalyzed multicomponent reactions. *J. Am. Chem. Soc*. **2013**, *135*, 11384.

[65] Michlik, S.; Rhett Kempe, R. A sustainable catalytic pyrrole synthesis. *Nature Chemistry* **2013**, *5*, 140.

[5.2] Chapter 2: Ni-Catalyzed Direct *N*-Alkylation of Anilines with Alcohols

[1] Yan, T.; Feringa B. L.; Barta, K. Benzylamines via Iron-Catalyzed Direct Amination of Benzyl Alcohols. *ACS Catal*. **2016**, *6*, 381.

[2] Rösler, S.; Ertl, M.; Irrgand, T.; Kempe, R. Cobalt-Catalyzed Alkylation of Aromatic Amines by Alcohols. *Angew. Chem., Int. Ed.* **2015**, *54*, 15046.

[3] Elangovan, S.; Neumann, J.; Sortais, J.-B.; Junge, K.; Darcel, C.; Beller, M. Efficient and selective *N*-alkylation of amines with alcohols catalysed by manganese pincer complexes. *Nat. Commun.* 2016, *7*, 12641.

[4] Neumann, J.; Elangovan, S.; Spannenberg, A.; Junge, K.; Beller, M. Improved and General Manganese-Catalyzed N-Methylation of Aromatic Amines Using Methanol. *Chem. Eur. J.* **2017**, *23*, 5410.

[5] Shimizu, K.-I.; Imaiida, N.; Kon, K.; Siddiki, S. M. A. H.; Satsuma, A. Heterogeneous Ni Catalysts for N-Alkylation of Amines with Alcohols. *ACS Catal.* **2013**, *3*, 998.

[6] Shimizu, K.-I.; Kon, K.; Onodera, W.; Yamazaki, H.; Kondo, Junko N. Heterogeneous Ni Catalyst for Direct Synthesis of Primary Amines from Alcohols and Ammonia. *ACS Catal.* **2013**, *3*, 112.

[7] Xu, Z.; Wang, D.-S.; Yu, X.; Yang, Y.; Wang, D. Tunable Triazole-Phosphine-Copper Catalysts for the Synthesis of 2-Aryl-1*H*-benzo[*d*]imidazoles from Benzyl Alcohols and Diamines by Acceptorless Dehydrogenation and Borrowing Hydrogen Reactions. *Adv. Synth. Catal*. **2017**, *359*, 3332.

8] Khrizanforov, M.; Khrizanforova, V.; Mamedov, V.; Zhukova, N.; Strekalova, S.; Grinenko, V.; Gryaznova, T.; Sinyashin, O.; Budnikova, Y. Single-stage synthetic route to perfluoroalkylated arenes via electrocatalytic cross-coupling of organic halides using Co and Ni complexes. *J. Organomet. Chem.* **2016**, *820*, 82.

[9] (a) Green, M. L. H.; Saito, T.; Tanfield, P. J. Stable nickel hydride complexes of tricyclohexylphosphine and triisopropylphosphine. *J. Chem. Soc. A* **1971**, 152. (b) Lindner, M. M.; Beckmann, U.; Frank, W.; Kläui, W. Influence of the Steric Demand of Coligands on the Catalytic Activity of Nickel(II) Complexes in the Copolymerization of Ethene and Carbon Monoxide. *ISRN Inorg. Chem.* **2013,** 1.

[10] Zhang, G.; Yin, Z.; Zheng, S. Cobalt-Catalyzed *N*-Alkylation of Amines with Alcohols. *Org. Lett*. **2016**, *18*, 300.

[11] Kawahara, G.; Fujita, K.I.; Yamaguchi, R. *N*-Alkylation of Amines with Alcohols Catalyzed by a Water-Soluble Cp*Iridium Complex: An Efficient Method for the Synthesis of Amines in Aqueous Media. *Adv. Synth. Catal*. **2011**, *353*, 1161.

[12] Zhang, H.; Cai, Q.; Ma, D. Amino Acid Promoted CuI-Catalyzed C−N Bond Formation between Aryl Halides and Amines or N-Containing Heterocycles. *J. Org. Chem.* **2005**, *70*, 5164.

[13] Zou, Q.; Wang, C.; Smith, J.; Xue, D.; Xiao, J. Alkylation of Amines with Alcohols and Amines by a Single Catalyst under Mild Conditions. *Chem. A European J*. **2015**, *21*, 9656.

[14] Yu, J. X.; He,Y. H.; Yang, L.; Fu, Y. H.; Xue-Li, Z.; Chen, H.; Rui-Xiang, L. Hemilabile *N*-heterocyclic carbene (NHC)-nitrogen-phosphine mediated Ru (II)-catalyzed *N*-alkylation of aromatic amine with alcohol efficiently. *Catal. Commun*. **2017**, *95*, 54.

[15] Dai, X.; Cui, X.; Deng, Y.; Shi, F. A conjugated ketone as a catalyst in alcohol amination reactions under transition-metal and hetero-atom free conditions. *RSC Adv.***2015**, *5*, 43589.

[16] Xu, T.; Zhou, W.; Wang, J.; Li, X.; Jun-Wen, G.; Wan, B. A mild method for the regioselective bromination of 2-aminopyridines. *Tetrahedron* **2014**, *55*, 5058-5061

[17] Liu, C.; Liao, S.; Li, Q.; Feng, S.; Sun, Q.; Yu, X.; Xu, Q. Discovery and Mechanistic Studies of a General Air-Promoted Metal-Catalyzed Aerobic *N*-Alkylation Reaction of Amides and Amines with Alcohols. *J. Org. Chem*. **2011**, *76*, 5759.

[18] Fioravanti, R.; Biaval, M.; Porrettal, C. G.; Landolfil, C.; Simonetti, N.; Villa, A.; Conte, E.; Porta-Puglia, A. Research on antibacterial and antifungal agents. XI. Synthesis and antimicrobial activity of N-heteroaryl benzylamines and their Schiff bases. *Eur. J. Med. Chem*. **1995**, *30*, 123.

[19] Cui, X.; Zhang, Y.; Shi, F.; Deng, Y. Organic Ligand-Free Alkylation of Amines, Carboxamides, Sulfonamides, and Ketones by Using Alcohols Catalyzed by Heterogeneous Ag/Mo Oxides. *Chem A Eur. J.* **2011**, *17*, 1021.

[20] Prakash, S. K. G.; Clement, D.; Mathew, T.; Olah, A. G. Gallium(III) Triflate Catalyzed Direct Reductive Amination of Aldehydes. *Catal. Letters* **2010**, *137*, 111.

[21] (a) Lia, J.; Andersson, G. P. Room temperature and solvent-free iridium-catalyzed selective alkylation of anilines with alcohols. *Chem.Commun.***2013**, *49*, 6131. (b) Wang, C.; Chen, C.; Han, J.; Zhang, J.; Yao, Y.; Zhao, Y. Insight into O_2-Promoted Base-Catalyzed N-Alkylation of Amines with Alcohols. *Eur. J. Org. Chem*. **2015**, 2972.

[22] Zhao, Y.; Wan Foo, S.; Saito, S. Iron/Amino Acid Catalyzed Direct N-Alkylation of Amines with Alcohols. *Angew. Chem. Int. Ed*. **2011**, *50*, 3006.

[23] Ricardo, M.; Ramon, J. D.; Yus, M. Selective *N*-monoalkylation of aromatic amines with benzylic alcohols by a hydrogen autotransfer process catalyzed by unmodified magnetite. *Org. Biomol. Chem.***2009**, *7*, 2176.

[24] Kaloglu, N.; Özdemir, I.; Gürbüz, N.; Achard, M.; Bruneau, C. Benzimidazolium sulfonate ligand precursors and application in ruthenium-catalyzed aromatic amine alkylation with alcohols. *Catal. Commun.***2016**, *74*, 33.

[25] Zhang, W.; Dong, X.; Zhao, W. Microwave-Assisted Solventless Reaction of Iridium-Catalyzed Alkylation of Amines with Alcohols in the Absence of Base. *Org. Lett.***2011**, *13*, 5386.

[26] Abbenhuis, M. T. A. R.; Boersma, J.; Koten, V. G. Ruthenium-Complex-Catalyzed N-(Cyclo)alkylation of Aromatic Amines with Diols. Selective Synthesis of *N*-(ω-Hydroxyalkyl) anilines of Type $PhNH(CH_2)_nOH$ and of Some Bioactive Arylpiperazines. *J. Org. Chem*. **1998**, *63*, 4282.

[27] Gogate, N. P.; Ethirajan, M.; Kurenova, V. E.; Magis, T. A.; Pandey, K. R.; Cance, G. W. Design, synthesis, and biological evaluation of novel FAK scaffold inhibitors targeting the FAK-VEGFR3 protein-protein interaction. *Eur. J. Med. Chem.* **2014**, *80*, 154.

[28] Hsin-Ya, K.; Yi-Hong, L.; Shie-Ming, P.; Shiuh-Tzung, L. N,N′-Dialkylation Catalyzed by Bimetallic Iridium Complexes Containing a Saturated Bis-*N*-Heterocyclic Carbene (NHC) Ligand. *Organometallics* **2012**, *31*, 7248.

[29] Shu-Jie, C.; Guo-Ping, L.; Chun, C. Iridium-catalyzed methylation of indoles and pyrroles using methanol as feedstock. *RSC Adv.***2015**, *5*, 70329.

[5.3] Chapter 3 Section A: Ni-Catalyzed Intermolecular Cyclization for the Synthesis of Five and Six Membered *N*-Heterocycles

[1] (a) Hagfeldt, A.; Boschloo, G.; Sun, L.; Kloo, L.; Pettersson, H. Dye-Sensitized Solar Cells: A review. *Chem. Rev.* **2010**, *110*, 6595. (b) Nishide, H.; Oyaizu, K. Toward Flexible Batteries. Science **2008**, *319*, 737.

[2] (a) Knorr, L. "Synthese von Pyrrolderivaten," *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1635. (b) Paal, C. "Synthese von Thiophen- und Pyrrolderivaten," *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367. (c) Hantzsch, A. "Neue Bildungsweise von Pyrrolderivaten," *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474. (d) Rakshit, S.; Patureau, F. W.; Glorius, F. "Pyrrole Synthesis via Allylic sp^3 C−H Activation of Enamines Followed by Intermolecular Coupling with Unactivated Alkynes," *J. Am. Chem. Soc.* **2010**, *132*, 9585. (e) Chen, Z.; Lu, B.; Ding, Z.; Gao, K.; Yoshikai, N. "α-Palladation of Imines as Entry to Dehydrogenative Heck Reaction: Aerobic Oxidative Cyclization of *N*-Allylimines to Pyrroles," *Org. Lett.* **2013**, *15*, 1966.

[3] Chelucci, G. "Metal-catalyzed dehydrogenative synthesis of pyrroles and indoles from alcohols," *Coord. Chem. Rev*. **2017**, *331*, 37.

[4] For selected reviews: (a) Guillena, G.; Ramon, D. J.; Yus, M. "Hydrogen Autotransfer in the N-Alkylation of Amines and Related Compounds using Alcohols and Amines as Electrophiles," *Chem. Rev.* **2010**, *110*, 1611. (b) Bower, J. F.; Krische, M. J. "Formation of C–C Bonds via Iridium-Catalyzed Hydrogenation and Transfer Hydrogenation," *Top. Organomet. Chem*. **2011**, *34*, 107. (c) Watson, A. J. A.; Williams, J. M. J. "The give and take of alcohol activation," *Science* **2010**, *329*, 635. (d) Bähn, S.; Sebastian, I.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. "The Catalytic Amination of Alcohols," *ChemCatChem* **2011**, *3*, 1853. (e) Dobereiner, G. E.; Crabtree, R. H. "Dehydrogenation as a substrate-activating strategy in homogeneous transition-metal catalysis," *Chem. Rev.* **2010**, *110*, 681. (f) Gunanathan, C.; Milstein, D. "Applications of acceptorless dehydrogenation and related transformations in chemical synthesis," *Science* **2013**, *341*, 249. For selected pioneering examples: (g) Bower, J. F.; Skucas, E.; Patman, R. L.; Krische, M. J. "Catalytic C−C Coupling via Transfer Hydrogenation: Reverse Prenylation, Crotylation, and Allylation from the Alcohol or Aldehyde Oxidation Level," *J. Am. Chem. Soc.* **2007**, *129*, 15134. (h) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. "Catalytic enantioselective C-H functionalization of alcohols by redox-triggered carbonyl addition: borrowing hydrogen, returning carbon," *Angew. Chem., Int. Ed.* **2014**, *53*, 9142.

[5] Forberg, D.; Obenauf, J.; Friedrich, M.; Hghne, S. M.; Mader, W.; Motz, G.; Kempe, R. "The synthesis of pyrroles *via* acceptorless dehydrogenative condensation of secondary alcohols and 1,2-amino alcohols mediated by a robust and reusable catalyst based on nanometer-sized iridium particles," *Catal. Sci. Technol.* **2014**, *4*, 4188.

[6] Siddiki, S. M. A. H.; Touchy, A. S.; Chaudhari, C.; Kon, K.; Toyaoa, T.; Shimizu, K. "Synthesis of 2,5-disubstituted pyrroles *via* dehydrogenative condensation of secondary alcohols and 1,2-amino alcohols by supported platinum catalysts," *Org. Chem. Front.* **2016,** *3*, 846.

[7] Daw, P.; Chakraborty, S.; Garg, J. A.; Ben-David, Y.; Milstein, D. "Direct Synthesis of Pyrroles by Dehydrogenative Coupling of Diols and Amines Catalyzed by Cobalt Pincer Complexes," *Angew. Chem., Int. Ed.* **2016**, *55*, 14373. "Direct Synthesis of Pyrroles by Dehydrogenative Coupling of Diols and Amines Catalyzed by Cobalt Pincer Complexes," *Angew. Chem.* **2016**, *128*, 14585.

[8] Midya, S. P.; Landge, V. G.; Sahoo, M. K.; Rana, J.; Balaraman, E. "Cobalt-catalyzed acceptorless dehydrogenative coupling of aminoalcohols with alcohols: direct access to pyrrole, pyridine and pyrazine derivatives," *Chem. Commun.* **2018**, *54*, 90.

[9] Kallmeier, F.; Dudziec, B.; Irrgang, T.; Kempe, R. "Manganese-Catalyzed Sustainable Synthesis of Pyrroles from Alcohols and Amino Alcohols," *Angew. Chem., Int. Ed.* **2017**, *56*, 7261.

[10] Jones, G. in *Comprehensive Heterocyclic Chemistry*, ed. Katritzky, A. R.; Rees, C. W. Pergamon, New York, 5th edn, **1984**, *2*, 395.

[11] Srimani, D.; Ben-David, Y.; Milstein, D. "Direct synthesis of pyridines and quinolines by coupling of γ-amino-alcohols with secondary alcohols liberating H_2 catalyzed by ruthenium pincer complexes," *Chem. Commun*. **2013**, *49*, 6632.

[12] Ruch, S.; Irrgang, T.; Kempe, R. "New Iridium Catalysts for the Selective Alkylation of Amines by Alcohols under Mild Conditions and for the Synthesis of Quinolines by Acceptor-less Dehydrogenative Condensation," *Chem.-Eur. J.* **2014**, *20*, 13279.

[13] Michlik, S.; Kempe, R. "Regioselectively Functionalized Pyridines from Sustainable Resources," *Angew. Chem., Int. Ed.* **2013**, *52*, 6326.

[14] Hille, T.; Irrgang, T.; Kempe, R. "Synthesis of meta-Functionalized Pyridines by Selective Dehydrogenative Heterocondensation of β- and γ-Amino Alcohols," *Angew. Chem., Int. Ed.* **2017**, *56*, 371.

[15] Xiong, B.; Wang, Y.; Liu, Y.; Bao, Y.; Liu, Z.; Zhang, Y.; Ling Y. "Straight forward synthesis of quinolines from enones and 2-aminobenzyl alcohols using an iridium-catalyzed transfer hydrogenative strategy," *Org. Biomol. Chem.* **2018**, *16*, 5707.

[16] (a) Chen, F.; Shen, T.; Cui, Y.; Jiao, N. *Org. Lett.* **2012**, *14*, 4926. (b) Miura, T.; Hiraga, K.; Biyajima, T.; Nakamuro, T.; Murakami, M. *Org. Lett*. **2013**, *15*, 3298. (c) Thompson, B. B.; Montgomery, J. *Org. Lett.* **2011**, *13*, 3289.

[17] (a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. "Recent advances in homogeneous nickel catalysis," *Nature* **2014**, *509*, 299. (b) Ananikov, Valentine P. "Nickel: The "Spirited Horse" of Transition Metal Catalysis," *ACS Catal.* **2015**, *5*, 1964. (c) Jolly, P. W.; Wilke, G. *The Organic Chemistry of Nickel*, Academic Press: New York, **1974**. (d) Wilke, G. "Contributions to Organo-Nickel Chemistry," *Angew. Chem., Int. Ed.* **1988**, *27*, 185. (e) Tamaru, Y. *Modern Organonickel Chemistry*, Eds.: Wiley-VCH, Weinheim, Germany, **2005**, pp 327. (f) Dander, J. E.; Garg, N. K. "Breaking Amides using Nickel Catalysis," *ACS Catal*. **2017**, *7*, 1413. (g) Tobisu, M.; Chatani, N. "Cross-Couplings Using Aryl Ethers via C–O Bond Activation Enabled by Nickel Catalysts," *Acc. Chem. Res.* **2015**, *48*, 1717. (h) Cornella, J.; Zarate, C.; Martin, R. "Metal-catalyzed activation of ethers *via* C–O bond cleavage: a new strategy for molecular diversity," *Chem. Soc. Rev.* **2014**, *43*, 8081.

[18] Vellakkaran, M.; Singh, K.; Banerjee, D. "An Efficient and Selective Nickel-Catalyzed Direct N-Alkylation of Anilines with Alcohols," *ACS Catal.* **2017**, *7*, 8152.

[19] Yakhvarov, D. G.; Hawkins, E. H.; Kagirov, R. M.; Budnikova, Y. H.; Ganushevich, Y. S.; Sinyashin, O. G. *Russian Chemical Bulletin, Int. Ed.* **2007**, *56*, 935.

[5.4] Chapter 3 Section B: Nickel-Catalyzed Sustainable Synthesis of Pyrroles from Unsaturated Diols and Primary Amines

[1] (a) Joule, J. A.; Mills, K. Heterocyclic Chemistry 5th ed., Wiley, Chichester, **2010.** (b) Bhardwaj, V.; Gumber, D.; Abbot, V.; Dhiman, S.; Sharma, P. Pyrrole: a resourceful small molecule in key medicinal hetero-aromatics. *RSC Adv.* **2015**, *5*, 15233.

[2] (a) Hagfeldt, K. A.; Boschloo, G.; Sun, L.; Kloo, L.; Pettersson, H. Dye-Sensitized Solar Cells. *Chem. Rev.* **2010**, *110*, 6595-6663. (b) Nishide, H.; Oyaizu, K. Toward Flexible Batteries. *Science* **2008**, *319*, 737-738.

[3] (a) Knorr, L. Synthese von Pyrrolderivaten. Ber. Dtsch. Chem. Ges. **1884**, *17*, 1635-1642. (b) Paal, C. Synthese von Thiophen- und Pyrrolderivaten. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367-371. (c) Hantzsch, A. Neue Bildungsweise von Pyrrolderivaten. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474-1483. (d) Rakshit, S.; Patureau, F. W.; Glorius, F. Pyrrole Synthesis via Allylic sp^3 C−H Activation of Enamines Followed by Intermolecular Coupling with Unactivated Alkynes. *J. Am. Chem. Soc.* **2010**, *132*, 9585-9587. (e) Chen, Z.; Lu, B.; Ding, Z.; Gao, K.; Yoshikai, N. α-Palladation of Imines as Entry to Dehydrogenative Heck Reaction: Aerobic Oxidative Cy-clization of N-Allylimines to Pyrroles. *Org. Lett.* **2013**, *15*, 1966-1969.

[4] Tuck, C. O.; Pérez, E.; Horváth, I. T.; Sheldon, R. A.; Poliakoff, M. Valorization of biomass: deriving more value from waste. *Science* **2012**, *337*, 695-699.

[5] (a) Barta, K.; Ford, P. C. Catalytic Conversion of Nonfood Woody Biomass Solids to Organic Liquids. Acc. *Chem. Res.* **2014**, *47*, 1503-1512. (b) Vispute, T. P.; Zhang, H.; Sanna, A.; Xiao, R.; Huber, G. W. Renewable Chemical Commodity Feedstocks from Integrated Catalytic Processing of pyrrolysis Oils. *Science* **2010**, *330*, 1222-1227.

[6] For selected reviews: (a) Guillena, G.; Ramon, D. J.; Yus, M. Hydrogen Autotransfer in the N-Alkylation of Amines and Related Compounds using Alcohols and Amines as Electrophiles. *Chem. Rev.* **2010**, *110*, 1611-1641. (b) Bower, J. F.; Krische, M. J. For-mation of C-C Bonds via Iridium-Catalyzed Hydrogenation and Transfer Hydrogenation. *Top. Organomet. Chem.* **2011**, *34*, 107-138. (c) Watson, A. J. A.; Williams, J. M. J. The Give and Take of Alcohol Activation. *Science* **2010**, *329*, 635-636. (d) Bähn, S.; Se-bastian, I.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. The Catalytic Amination of Alcohols. *ChemCatChem* **2011**, *3*, 1853-1864. (e) Dobereiner, G. E.; Crabtree, R. H. Dehydrogenation as a Substrate-Activating Strategy in Homogeneous Transition-Metal Catalysis. *Chem. Rev.*

2010, *110*, 681-703. (f) Gunanathan, C.; Milstein, D. Applications of Acceptorless Dehydrogenation and Related Transformations in Chemical Synthesis. *Science* **2013**, *341*, 249-260. For selected pioneering examples: (a) Bower, J. F.; Skucas, E.; Patman, R. L.; Krische, M. J. Catalytic C−C Coupling via Transfer Hydrogenation: Reverse Prenylation, Crotylation, and Allylation from the Alcohol or Aldehyde Oxidation Level. *J. Am. Chem. Soc.* **2007**, *129*, 15134-15135. (b) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. Catalytic Enantioselective C-H Functionalization of Alcohols by Redox-Triggered Carbonyl Addition: Borrowing Hydrogen, Returning Carbon. *Angew. Chem., Int. Ed.* **2014**, *53*, 9142-9150.

[7] Chelucci, G. Metal-catalyzed dehydrogenative synthesis of pyrroles and indoles from alcohols. *Coord. Chem. Rev.* **2017**, *331*, 37-53.

[8] Pridmore, S. J.; Slatford, P. A.; Daniel, A.; Whittlesey, M. K.; Williams, J. M. J. Ruthenium-catalysed conversion of 1,4-alkynediols into pyrroles. *Tetrahedron Lett*. **2007**, *48*, 5115-5120.

[9] Pridmore, S. J.; Slatford, P. A.; Taylor, J. E.; Whittlesey, M. K.; Williams, J. M. J. Synthesis of furans, pyrroles and pyri-dazines by a ruthenium-catalysed isomerisation of alkynediols and in situ cyclisation. *Tetrahedron* **2009**, *65*, 8981-8986.

[10] Yan, T.; Barta, K. Sustainable Pathways to Pyrroles through Iron-Catalyzed N-Heterocyclization from Unsaturated Diols and Primary Amines. *ChemSusChem* **2016**, *9*, 2321-2325.

[11] Emayavaramban, B.; Sen, M.; Sundararaju, B. Iron-Catalyzed Sustainable Synthesis of Pyrrole. *Org. Lett*. **2017**, *19*, 6-9.

[12] Yakhvarov, D.; GHawkins, E. H.; Kagirov, R. M.; Budnikova, Y. H.; Ganushevich, Y. S.; Sinyashin, O. G. *Russian Chemical Bulletin, Int. Ed.* **2007**, *56*, 935-942.

[13] Molander, G. A.; Ryu, D.; Sarvari, M. H.; Devulapally, R.; Seapy, D. G. Suzuki–Miyaura Cross-Coupling of Potassium Trifluoro(N-methylheteroaryl)borates with Aryl and Heteroaryl Halides. *J. Org. Chem*. **2013**, *78*, 6648-6656.

[14] Taylor, J. E.; Jones, M. D.; Williams, J. M. J.; Bull, S. D. Friedel−Crafts Acylation of Pyrroles and Indoles using 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) as a Nucleophilic Catalyst. *Org. Lett*. **2010**, *12*, 5740-5743.

[15] Baig, R. B. N.; Varma, R. S. Organic synthesis via magnetic attraction: benign and sustainable protocols using magnetic nanoferrites. *Green Chem*. **2013**, *15*, 398-417.

[16] Chang, J. W. W.; Xu, X.; Chan, P. W. H. Practical copper-catalyzed N-arylation of nitrogen heterocycles with aryl halides un-der ligand and additive free conditions. *Tetrahedron Lett*. **2007**, *48*, 245-248.

[17] Sarvari, M. H.; Derikvandi, S. N.; Jarrahpour, A.; Heiran, R. Nano Sulfated Titania as a Heterogeneous Solid Acid Catalyst for the Synthesis of Pyrroles by Clauson–Kaas Condensation under Solvent-free Conditions. *Chem. Heterocycl. Compd*. **2014**, *49*, 1732-1739.

[18] Li, H.; Bai, J.; Wang, J.; Li, C. A facile method to fabricate Cu0 supported on nanofibers as efficient catalyst using N-arylation reactions. *Mol. Catal*. **2017**, *431*, 49-56.

[19] Wang, P.; Ma F. P.; Zhang, Z. H. L-(+)-Tartaric acid and choline chloride based deep eutectic solvent: An efficient and reusable medium for synthesis of N-substituted pyrroles via Clauson-Kaas reaction. *J. Mol. Liq*. **2014**, *198*, 259-262.

[20] Rivera, S.; Bandyopadhyay, D.; Banik, B. K. Facile synthesis of N-substituted pyrroles via microwave-induced bismuth nitrate-catalyzed reaction. *Tetrahedron Lett*. **2009**, *50*, 5445-5448.

[21] Satish, G.; Reddy, K. H. V.; Ramesh, K.; Kumar, B. S. P. A.; Nageswar, Y. V. D. An elegant protocol for the synthesis of N-substituted pyrroles through C–N cross coupling/aromatization process using CuFe2O4 nanoparticles as catalyst under ligand-free conditions. *Tetrahedron Lett*. **2014**, *55*, 2596-2599.

[22] Sun, J.; Chen, L.; Liu, C.; Wang, Z.; Zuo, D.; Pan, J.; Qi, H.; Bao, K.; Wu, Y.; Zhang, W. Synthesis and Biological Evaluations of 1,2-Diaryl Pyrroles as Analogues of Combretastatin A-4. *Chem. Biol. Drug Des*. **2015**, *86*, 1541-1547.

[23] Deng, H. J.; Fang, Y. J.; Chen, G. W.; Liu, M. C.; Wu, H. Y.; Chen, J. X. Copper-catalyzed Clauson–Kass pyrroles synthesis in aqueous media. *Appl. Organomet. Chem*. **2012**, *26*, 164-167.

[24] Biava, M.; Porretta, G. C.; Poce, G.; Battilocchio, C.; Alfonso, S.; DeLogu, A.; Serra, N.; Manetti, F.; Botta, M. Identification of a novel pyrrole derivative endowed with antimycobacterial activity and protection index comparable to that of the current antitubercular drugs streptomycin and rifampin. *Bioorg. Med. Chem*. **2010**, *18*, 8076-8084.

[25] Le, Z. G.; Chen, Z. C.; Hu, Y.; Zheng, Q. G. Organic Reactions in Ionic Liquids: A Simple and Highly Regioselective N-Substitution of Pyrrole. *Synthesis* **2004**, *12*, 1951-1954.

[26] Lion, C.; Baudry, R.; Hedayatullah, M.; Conceicao, L. D. Reaction of pyrroles with naphthoquinones. Synthesis of new pyrrolylnaphthoquinone dyes. *J. Heterocycl. Chem*. **2000**, *37*, 1635-1640.

[27] Daw, P.; Chakraborty, S.; Garg, J. A.; David, Y. B.; Milstein, D. Direct Synthesis of Pyrroles by Dehydrogenative Coupling of Diols and Amines Catalyzed by Cobalt Pincer Complexes. *Angew. Chem., Int. Ed*. **2016**, *55*, 14373-14377.

[28] Hamaide, T. Efficient *N*-Alkylation of Pyrrole Under Solid Triphase Transfer Catalysis Conditions. Application to *N*-Oxyalkyl Pyrroles. *Synth. Commun*. **1990**, *20*, 2913-2920.

[29] Bing, Z.; Jiuxi, C.; Miaochang, L.; Jinchang, D.; Huayue, W.; Weike, S. Scandium triflate-catalysed synthesis of *N*-substituted pyrroles from amine and 2,5-dimethoxytetrahydrofuran. *J. Chem. Res*. **2009**, *1*, 14-16.

[30] Tao, S.; Ji, E.; Shi, L.; Liu, N.; Xu, L.; Dai, B. Copper-Catalyzed C–N Bond Exchange of *N*-Heterocyclic Substituents around Pyridine and Pyrimidine Cores. *Synthesis* **2017**, *49*, 5120-5130.

[31] Patil, P. H.; Nallasivam, J. L.; Fernandes, R. A. Unimolecular 4-Hydroxypiperidines: New Ligands for Copper-Catalyzed *N*-Arylation. *Asian J. Org. Chem*. **2015**, *4*, 552-559.

[5.5] Chapter 4: Nickel-Catalyzed Synthesis of gem-Bis alkylated Ketones

[1] Barta, K.; Ford, P. C. Catalytic Conversion of Nonfood Woody Biomass Solids to Organic Liquids. *Acc. Chem. Res*. **2014**, *47*, 1503-1512.

[2] For selected reviews: (a) Guillena, G.; Ramon, D. J.; Yus, M. Hydrogen Autotransfer in the *N*-Alkylation of Amines and Related Compounds using Alcohols and Amines as Electrophiles. *Chem. Rev*. **2010**, *110*, 1611-1641. (b) Bower, J. F.; Krische, M. J. For-mation of C-C Bonds via Iridium-Catalyzed Hydrogenation and Transfer Hydrogenation. *Top. Organomet. Chem*., **2011**, *34*, 107–138. (c) Watson, A. J. A.; Williams, J. M. J. The give and take of alcohol activation. *Science* **2010**, *329*, 635-636. (d) Bähn, S.; Sebas-tian, I.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. The Catalytic Amination of Alcohols. *ChemCatChem*, **2011**, *3*, 1853-1864. (e) Dobereiner, G. E.; Crabtree, R. H. Dehydrogenation as a Substrate-Activating Strategy in Homogeneous Transition-Metal Catalysis. *Chem. Rev*. **2010**, *110*, 681-703. (f) Gunanathan, C.; Milstein, D. Applications of acceptorless dehydrogenation and related trans-formations in chemical synthesis. *Science*, **2013**, *341*, 249-260.

[3] For reviews on the α-alkylation of ketones, see: (a) Modern Carbonyl Chemistry (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**. For selective recent examples, see: (b) Alonso, F.; Riente, P.; Yus, M. The α-Alkylation of Methyl Ketones with Primary Alcohols Promoted by Nickel Nanoparticles under Mild and Ligandless Conditions. *Synlett* **2007**, 1877−1880. (c) Alonso, F.; Riente, P.; Yus, M. Alcohols for the α-Alkylation of Methyl Ketones and Indirect Aza-Wittig Reaction Promoted by Nickel Nanoparticles. *Eur. J. Org. Chem*. **2008**, 4908−4914. (d) Srimani, D.; Balaraman, E.; Gnanaprakasam, B.; Ben-David, Y.; Milstein, D. Ruthenium Pincer-Catalyzed Cross-Dehydrogenative Coupling of Primary Alcohols with Secondary Alcohols under Neutral Conditions. *Adv. Synth. Catal.* **2012**, *354*, 2403−2406. (e) Kuwahara, T.; Fukuyama, T.; Ryu, I. RuHCl(CO)(PPh3)3-Catalyzed α-Alkylation of Ketones with Primary Alcohols. *Org. Lett*. **2012**, *14*, 4703−4705. (f) Chan, L. K. M.; Poole, D. L.; Shen, D.; Healy, M. P.; Donohoe, T. J. Rhodium-Catalyzed Ketone Methylation Using Methanol Under Mild Conditions: Formation of α-Branched Products. *Angew. Chem., Int. Ed*. **2014**, *53*, 761−765. (g) Elangovan, S.; Sortais, J. -B.; Beller, M.; Darcel, C. Iron-Catalyzed α-Alkylation of Ketones with Alcohols. *Angew. Chem., Int. Ed*. **2015**, *54*, 14483−14486. (h) Peña-López, M.; Piehl, P.; Elangovan, S.; Neumann, H.; Beller, M. Manganese Catalyzed Hydrogen-Autotransfer C−C Bond Formation: α-Alkylation of

Ketones with Primary Alcohols. *Angew. Chem., Int. Ed*. **2016**, *55*, 14967−14971. (i) Zhang, G.; Wu, J.; Zeng, H.; Zhang, S.; Yin, Z.; Zheng, S. Cobalt-Catalyzed α-Alkylation of Ketones with Primary Alcohols. *Org. Lett*. **2017**, *19*, 1080−1083. (j) Genç, S.; Günnaz, S.; Çetinkaya, B.; Gülcemal, S.; Gülcemal, D. Iridium(I)-Catalyzed Alkylation Reactions To Form α-Alkylated Ke-tones. *J. Org. Chem*. **2018**, *83*, 2875−2881 and references cited therein.

[4] Frost, J. R.; Cheong, C. B.; Akhtar, W. M.; Caputo, D. F. J.; Stevenson, N. G.; Donohoe, T. J. Strategic Application and Transformation of ortho-Disubstituted Phenyl and Cyclopropyl Ketones To Expand the Scope of Hydrogen Borrowing Catalysis. *J. Am. Chem. Soc*. **2015**, *137*, 15664−15667.

[5] Schlepphorst, C.; Maji, B.; Glorius, F. Ruthenium-NHC Catalyzed α-Alkylation of Methylene Ketones Provides Branched Products through Borrowing Hydrogen Strategy. *ACS Catal*. **2016**, *6*, 4184−4188.

[6] Cao, X.-N.; Wan, X.-M.; Yang, F.-L.; Li, K.; Hao, X.-Q.; Shao, T.; Zhu, X.; Song, M.-P. NNN Pincer Ru(II)-Complex-Catalyzed α-Alkylation of Ketones with Alcohols. *J. Org. Chem.* **2018**, *83*, 3657.

[7] Chakrabarti, K.; Maji, M.; Panja, D.; Paul, B.; Shee, S.; Das, G. K.; Kundu, S. Utilization of MeOH as a C1 Building Block in Tandem Three Component Coupling Reaction. *Org. Lett.* **2017**, *19*, 4750.

[8] Polidano, K.; Allen, B. D. W.; Williams, J. M. J.; Morrill, L. C. Iron-Catalyzed Methylation Using the Borrowing Hydrogen Approach. *ACS Catal*. **2018**, *8*, 6440.

[9] Martínez, R.; Ramón, D. J.; Yus, M. $RuCl_2(dmso)_4$ Catalyzes the Solvent-Free Indirect Friedländer Synthesis of Polysubstituted Quinolines from Alcohols. *Eur. J. Org. Chem.* **2007**, 1599.

[10] Mierde, H. V.; Voort, P. V. D.; Vos, D. D.; Verpoort, F. A Ruthenium-Catalyzed Approach to the Friedländer Quinoline Synthesis. *Eur. J. Org. Chem.* **2008**, 1625.

[11] Mastalir, M.; Glatz, M.; Pittenauer, E.; Allmaier, G.; Kirchner, K. Sustainable Synthesis of Quinolines and Pyrimidines Catalyzed by Manganese PNP Pincer Complexes. *J. Am. Chem. Soc.* **2016**, *138*, 15543.

[12] Bullock, R. M. Catalysis Without Precious Metals, Eds.: Wiley-VCH, Weinheim, **2010**.

[13 Takise, R.; Muto, K.; Yamaguchi, J.; Itami, K. Nickel-Catalyzed α-Arylation of Ketones with Phenol Derivatives. *Angew. Chem. Int. Ed*. **2014**, *53*, 6791-6794.

[14] Khrizanforov, M.; Khrizanforova, V.; Mamedov, V.; Zhukova, N.; Strekalova, S.; Grinenko, V.; Gryaznova, T.; Sinyashin, O.; Budnikova, Y. Single-stage synthetic route to perfluoroalkylated arenes via electrocatalytic cross-coupling of organic halides using Co and Ni complexes. *J. Organomet. Chem.* **2016**, *820*, 82.

[15] (a) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watsom, A. J. A.; Williams, J. M. J. Ruthenium-Catalyzed N-Alkylation of Amines and Sulfonamides Using Borrowing Hydrogen Methodology. *J. Am. Chem. Soc*. **2009**, *131*, 1766-1774. (b) Samec, J. S. M.; Backvall, J. -E.; Andersson, P. G.; Brandt, P. Mechanistic aspects of transition metal-catalyzed hydrogen transfer reactions. *Chem. Soc. Rev*. **2006**, *35*, 237-248.

[16] For selected syntheses of donepezil, see: (a) Dubey, S. K.; Kharbanda, M.; Mathela, C. S. A New Commercially Viable Synthetic Route for Donepezil Hydrochloride: Anti-Alzheimer's Drug. *Chem. Pharm. Bull*. **2010**, *58*, 1157−1160. (b) Sugimoto, H.; Iimura, Y.; Yamanishi, Y.; Yamatsu, K. Synthesis and Structure-Activity Relationships of Acetylcholinesterase Inhibitors: l-Benzyl-4-[(5,6-dimethoxy-l-oxoindan-2-yl)methyl]piperidine Hydrochloride and Related Compounds. *J. Med. Chem*. **1995**, *38*, 4821−4829. (c) Lensky, S. Process for the preparation of benzyl-piperidylmethyl-indanones. U.S. Patent US5606064A, February 25, **1997**. (d) Elati, C. R.; Kolla, N.; Chalamala, S. R.; Vankawala, P. J.; Sundaram, V.; Vurimidi, H.; Mathad, V. T. New Synthesis of Donepezil Through Palladium-Catalyzed Hydrogenation Approach. *Synth*. Commun. **2006**, *36*, 169−174. (e) Reddy, K. K. V. S. R.; Babu, J. M.; Kumar, P. A.; Chandrasekhar, E. R. R.; Mathad, V. T. S.; Eswaraiah, M. S.; Reddy, K.; Vyas, K. Identification and characterization of potential impurities of donepezil. *J. Pharm. Biomed. Anal*. **2004**, *35*, 1047−1058.

[17] Schlepphorst, C.; Maji, B.; Glorius, F. Ruthenium-NHC Catalyzed α-Alkylation of Methylene Ketones Provides Branched Products through Borrowing Hydrogen Strategy. *ACS Catal.* **2016**, *6*, 4184−4188.

[18] Chakrabarti, K.; Maji, M.; Panja, D.; Paul, B.; Shee, S.; Das, G. K.; Kundu, S. Utilization of MeOH as a C1 Building Block in Tandem Three-Component Coupling Reaction. *Org. Lett.* **2017**, *19*, 4750−4753.

[19] Berthiol, F.; Doucet, H.; Santelli, M. Synthesis of β-aryl ketones by tetraphosphine/palladium catalysed Heck reactions of 2- or 3-substituted allylic alcohols with aryl bromides. *Tetrahedron* **2006**, *62*, 4372–4383.

[20] Shen, D.; Poole, D. L.; Shotton, C. C.; Kornahrens, A. F.; Healy, M. P.; Donohoe, T. J. Hydrogen-Borrowing and Interrupted-Hydrogen-Borrowing Reactions of Ketones and Methanol Catalyzed by Iridium. *Angew. Chem. Int. Ed.* **2015**, *54*, 1642 –1645.

[21] Mamidala, R.; Samser, S.; Sharma, N.; Lourderaj, U.; Venkatasubbaiah, K. Isolation and Characterization of Regioisomers of Pyrazole-Based Palladacycles and Their Use in α-Alkylation of Ketones Using Alcohols. *Organometallics* **2017**, *36*, 3343−3351.

[22] Ogawa, S.; Obora, Y. Iridium-catalyzed selective α-methylation of ketones with methanol. *Chem. Commun.* **2014**, *50*, 2491.

[23] Poisson, T.; Gembus, V.; Dalla, V.; Oudeyer, S.; Levacher, V. Organocatalyzed Enantioselective Protonation of Silyl Enol Ethers: Scope, Limitations, and Application to the Preparation of Enantioenriched Homoisoflavones. *J. Org. Chem.* **2010**, *75*, 7704–7716.

[24] Wang, R.; Huang, L.; Du, Z.; Feng, H. $RhCl(CO)(PPh_3)_2$ catalyzed α-alkylation of ketones with alcohols. *J. Organomet. Chem.* **2017**, *846*, 40-43.

[25] Ranu, B. C.; Dutta, J.; Guchhait, S. K. Indium Metal as a Reducing Agent. Selective Reduction of the Carbon−Carbon Double Bond in Highly Activated Conjugated Alkenes. *Org. Lett.* **2001**, *3*, 2603-2605.

[26] Xi, L.; Zhang, R.; Zhang, L.; Chen, S. Y.; Yu, X. An efficient synthesis of quinolines *via* copper-catalyzed C–N cleavage. *Org. Biomol. Chem.* **2015**, *13*, 3924–3930.

[27] Zhu, Y.; Cai, C. An N-heterocyclic carbene-catalyzed approach to the indirect Friedländer quinoline synthesis. *RSC Adv.***2014**, *4*, 52911–52914.

[28] Xi, L.Y.; Zhang, R. Y.; Liang, S.; Chen, S. Y.; Yu, X. Q. Copper-Catalyzed Aerobic Synthesis of 2-Arylpyridines from Acetophenones and 1,3-Diaminopropane. *Org. Lett.* **2014**, *16*, 5269−527.

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An Efficient and Selective Nickel-Catalyzed Direct N-Alkylation of Anilines with Alcohols

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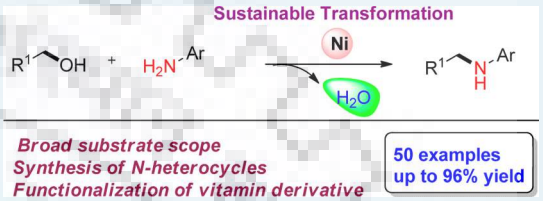
Supporting Information

ABSTRACT: Herein, we developed an efficient and selective nickel-catalyzed monoalkylation of various primary alcohols with aryl and heteroaryl amines together with diols and amino alcohol derivatives. Notably, the catalytic protocol consisting of an earth-abundant and non-precious $NiBr_2$/**L1** system enables the transformations in the presence of hydroxyl, alkene, nitrile, and nitro functionalities. As a highlight, we have demonstrated the alkylation of diamine, intramolecular cyclization to N-heterocycles, and functionalization of complex vitamin E, an (±)-α-tocopherol derivative. Preliminary mechanistic studies revealed the participation of a benzylic C−H bond in the rate-determining step.



KEYWORDS: *alcohols, nickel, borrowing-hydrogen catalysis, N-Alkylation, earth-abundant metal, amines*

INTRODUCTION

The development of new sustainable and atom-economical synthetic methodologies that utilize renewable feedstocks and convert them into key chemicals is a crucial challenge in chemical research.[1] From past decades, the borrowing-hydrogen or hydrogen-autotransfer (BH/HA) approach[2] represents a promising alternative for tandem C−C and C−N bond formations using readily available alcohols as coupling partners.[3] Notably, the direct use of an alcohol generates only water as a byproduct and avoids the use of multistep production of hazardous alkylating agents.[4]

Amines are valuable targets in chemical transformations, are ubiquitous in biologically active natural products, and are extensively used in pharmaceuticals (Figure 1), agrochemicals, ligands for catalysis, and material chemistry.[5] There are many powerful classical processes and catalytic protocols for the synthesis of amines.[6] Notably, the vibrant catalytic protocols reported in this area is evidence of the significant potential for C−N bond forming reactions.[7] The great demand for new reactions that fully or partially use renewable resources in combination with earth-abundant non-precious metals is highly desirable.[3,4,8−10]

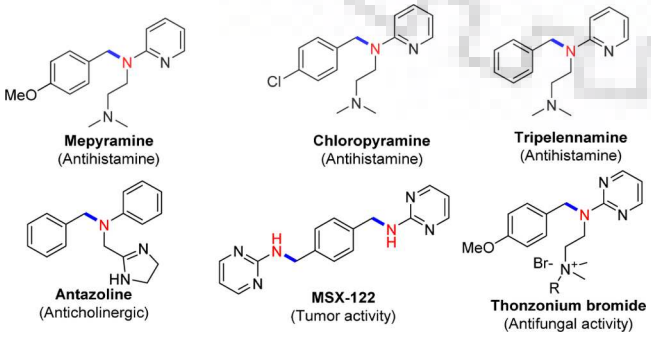


Figure 1. Selected examples of important pharmaceuticals with alkylated amine functionalities.

In this direction, pioneering studies by the groups of Watanabe and Grigg[11,12] (Ru, Rh, and Ir catalysts) followed by significant contributions by the groups of Saito,[13] Feringa and Barta (Fe catalysts),[14] Kempe[15a] (Co catalyst), Beller,[15b] and Milstein[15c] (Mn pincer complexes) are worth mentioning. More recently, Shi and co-workers reported the nickel-catalyzed synthesis of diarylmethanes using benzyl alcohols in the presence of Grignard reagents.[16a] The current surge is to develop more exciting and challenging nickel-based methodologies. Toward this goal, inexpensive, high-natural-abundance and low-toxicity nickel would serve as an ultimate sustainable alternative to palladium.[17]

To date, the applications of nickel catalysts are often limited to activated benzylic and phenolic substrates, such as carbonates, carbamates, ethers, and esters as electrophilic coupling partners (Scheme 1).[18] The substantially poor leaving ability and strong coordination properties of the hydroxyl group make it an inferior substrate class toward nickel-catalyzed transformations.[19]

However, to the best of our knowledge, the application of homogeneous nickel catalysts for amination of benzyl and alkyl alcohols has remained elusive to date.[20] Herein we disclose an efficient Ni catalyst system which enables the amination of primary alcohols with a variety of anilines and affords diversely substituted functionalized secondary amine derivatives. The key features of the optimized protocol include selective mono-

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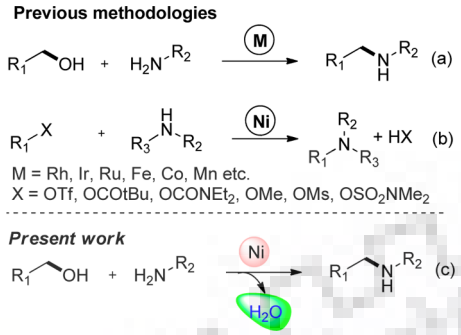
Scheme 1. Various Approaches for C−N Bond Formation: (a) Metal-Catalyzed N-Alkylation of Amines with Alcohols; (b) Nickel-Catalyzed Amination Reactions with Activated Derivatives; (c) Nickel-Catalyzed Amination of Alcohols



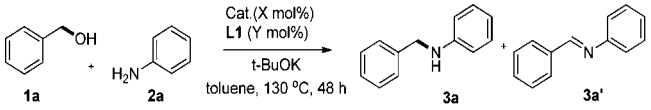
alkylation of a variety of alcohols, diols, and amino alcohols with anilines. Notably, intramolecular cyclization to N-heterocycles and functionalization of complex vitamin derivatives are of special interest.

RESULTS AND DISCUSSION

Optimization of the Catalytic Protocol. The key challenge in the direct amination of alcohols using a Ni catalyst is to attain alcohol dehydrogenation and the ability of the in situ formed Ni hydride species to carry out imine hydrogenation. A recent report by Jones and co-workers for dehydrogenation of alcohols and hydrogenation of carbonyl compounds using nickel catalysts attracted our attention, and we reasoned that it could be possible to explore the bifunctional nature of a homogeneous Ni catalyst for direct C−N bond formation.[21]

To achieve this goal, we initiated our investigations with five different nickel precatalysts having oxidation states of Ni(0) and Ni(II), aniline (**2a**), and benzyl alcohol (**1a**) as the model reaction of our choice. Notably, a combination of 10 mol % of $NiBr_2$, 20 mol % of 1,10-phenthroline (**L1**), and 0.25 mmol of *t*-BuOK at 130 °C in toluene resulted in the formation of *N*-benzyl aniline (**3a**) with 99% selectivity as determined by GC-MS analysis of the crude reaction mixture (Table 1, entries 1−5). Under identical conditions, a variety of nitrogen and phosphine ligands **L2**−**L15** with variable electronic and steric natures were tested and 15−76% of **3a** was obtained along with the corresponding imine (21−73%) (Table 2 and Table S3 in the Supporting Information). We anticipated that generation of an inadequate amount of nickel hydride species is the key issue for insufficient imine reduction. However, the use of various polar solvents, such as *i*-PrOH, *n*-BuOH, EtOH, *N*,*N*-dimethylacetamide (DMA), and *N*,*N*-dimethylformamide (DMF), as well as replacement of toluene with xylene and 1,4-dioxane did not improve the product yield and we observed fast deactivation of the catalytic system (Table S4 in the Supporting Information). In addition, different organic and inorganic bases were found to be inefficient for the alkylation of aniline (Table S2 in the Supporting Information). As usual, product conversion was suppressed significantly when a smaller amount of base was used (Table 1, entries 7 and 8). No amination was observed in the absence of catalyst, whereas a control experiment in the absence of ligand and reduced catalyst loading resulted in poor product conversion (Table 1, entries 10−13).

Table 1. Optimization Studies for Nickel-Catalyzed N-Alkylation of 1a with 2a[a,b]



		conversion (%)	
entry	catalyst	3a	3a′
1	$NiBr_2$	99 (96)	0
2	$NiCl_2$	87	13
3	$Ni(acac)_2$	81	19
4	$Ni(cod)_2$	83	17
5	$NiCl_2$·DME	35	55
6[c]	$NiBr_2$	49	40
7[d]	$NiBr_2$	65	35
8[e]	$NiBr_2$	40	60
9[f]	$NiBr_2$	0	0
10[g]	$NiBr_2$	31	51
11[h]	$NiBr_2$	79	5
12[i]	$NiBr_2$	70	26
13		0	0

[a]Unless specified otherwise, the reaction was carried out with **1a** (1.0 mmol), **2a** (0.25 mmol), Ni cat. (0.025 mmol), **L1** (0.05 mmol), and *t*-BuOK (0.25 mmol) under an N_2 atmosphere at 130 °C (oil bath) in toluene (2.0 mL) for 48 h in a Schlenk tube. [b]Conversion was determined by GC-MS (isolated yield in parentheses, average yield of two runs). [c]Reaction was performed for 36 h at 120 °C. [d]0.187 mmol of base was used. [e]0.125 mmol of base was used. [f]No base was used. [g]No ligand was used. [h]Ni cat. (0.0125 mmol) and **L1** (0.025 mmol) were used. [i]Ni cat. (0.00625 mmol) and **L1** (0.0125 mmol) were used.

It is worth mentioning that no product formation was detected when the reaction was performed in the absence of base (Table 1, entry 9).[19] We envisioned that the base plays a key role in the activation of nickel precatalysts via dehalogenation of the halide ion followed by substitution with the incoming alcohol resulting in the formation of an alkoxy nickel species.[21] Further *β*-hydride elimination of the preformed alkoxy nickel species in the presence of base leads to the formation of a carbonyl compound and generates the active nickel hydride responsible for imine reduction.[15b]

N-Alkylation of Aniline Derivatives with Benzyl Alcohol. Further, to demonstrate the general applicability of the optimized novel catalytic system, a variety of substituted aniline derivatives were tested for the selective monoalkylation using benzyl alcohol **1a** (Table 3). We observed that functionalities such as methoxy, methyl, and *n*-butyl as well as halide substituents on the aryl ring of aniline are well tolerated and furnished a 49−88% yield of selective monoalkylated anilines irrespective of their electronic properties (Table 3, **3b**−**e**,**i**). It should be noted that sterically hindered *o*-methoxy- and *o*-trifluoromethylaniline transformed efficiently into the desired secondary amines (Table 3, **3f**,**h**). Importantly, the pharmaceutically active trifluoromethyl- and 1,4-dioxalone-substituted anilines gave the corresponding products with excellent isolated yields, 77 and 86%, respectively (Table 3, **3g**,**k**). To our delight, anilines substituted with reducible functionalities are well tolerated and furnished 60 and 32% yields of **3l**,**m**, respectively (Table 3). Under identical conditions the application of aniline derivatives having ester, amide, carbonyl, epoxide, and alkyne functionalities was not successful (see Scheme S2 in the Supporting Information). The

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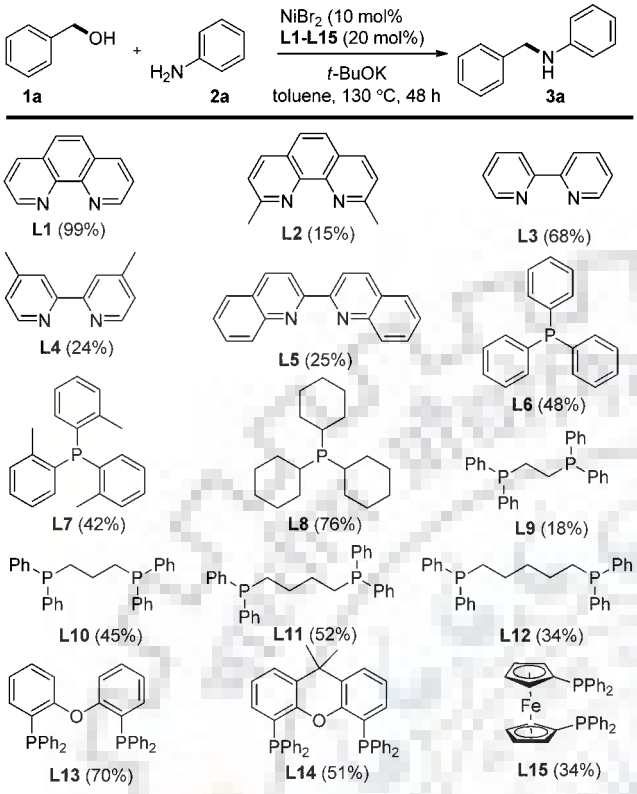
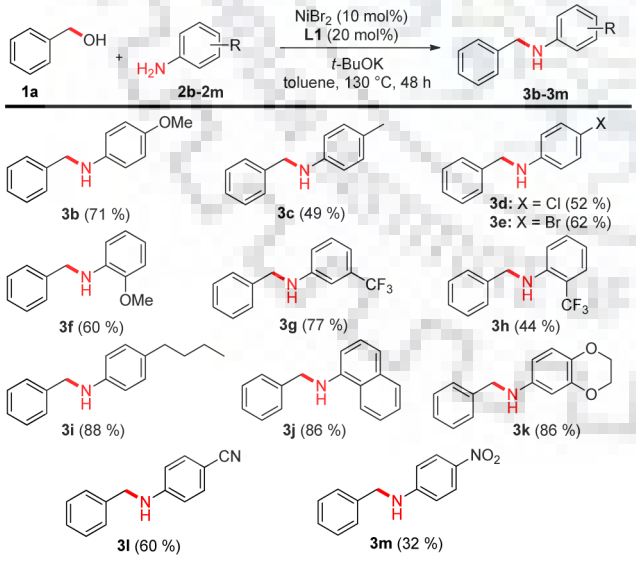
Table 2. Ligand Screening for Nickel-Catalyzed N-Alkylation of 1a with 2a[a,b]



[a]The reaction was carried out with **1a** (1.0 mmol), **2a** (0.25 mmol), Ni cat. (0.025 mmol), ligand (0.05 mmol), and base (0.25 mmol) under an N_2 atmosphere at 130 °C in toluene (2.0 mL) for 48 h. [b]Conversion was determined by GC-MS.

Table 3. Scope of Amines: Synthesis of *N*-Benzyl Aryl Amine Derivatives[a]

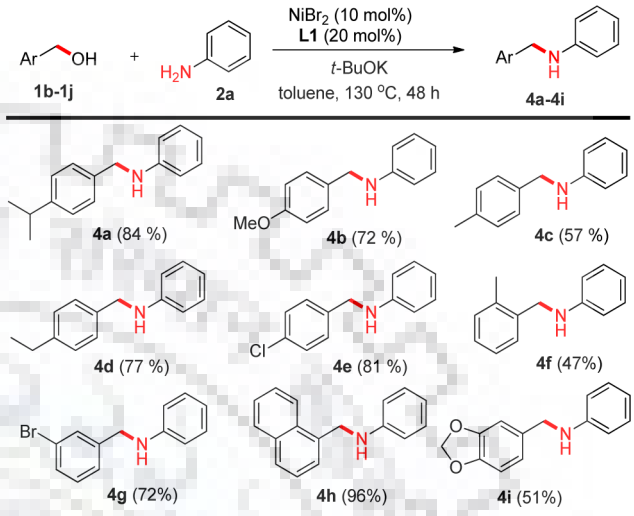


[a]The reaction was carried out with **1a** (1.0 mmol), **2** (0.25 mmol), $NiBr_2$ (0.025 mmol), **L1** (0.05 mmol), and *t*-BuOK (0.25 mmol) at 130 °C in toluene (2.0 mL) for 48 h.

catalytic protocol is highly selective for monoalkylation; however, we did not observe any desired product in the case of secondary amine derivatives (see Scheme S2).

N-Alkylation of Aniline with Various Benzyl Alcohols. Inspired by the excellent catalytic activity of anilines with benzyl alcohol, next we studied the reactivity profile and scope of various benzyl alcohols with aniline (Table 4). Benzyl

Table 4. Scope of Alcohols: Synthesis of *N*-Benzyl Aniline Derivatives[a]

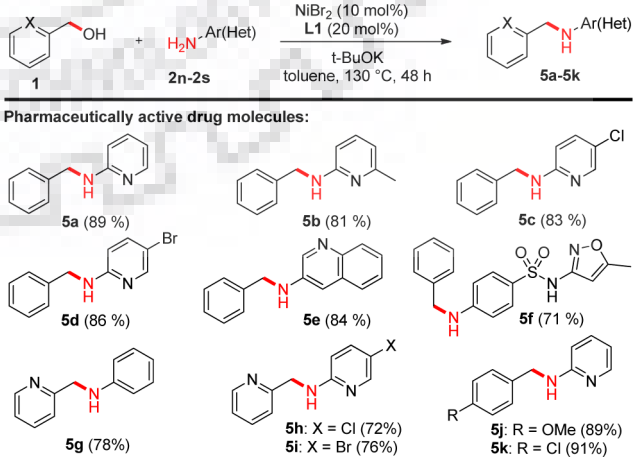


[a]The reaction was carried out with **1** (1.0 mmol), **2** (0.25 mmol), $NiBr_2$ (0.025 mmol), **L1** (0.05 mmol), and *t*-BuOK (0.25 mmol) at 130 °C in toluene (2.0 mL) for 48 h.

alcohols bearing electron-rich and electron-withdrawing functionalities as well as a fused ring system and an oxygen heterocycle at the aryl ring efficiently transformed to the corresponding monoalkylated aniline in 57−96% isolated yields (Table 4, **4a−e,g−i**). Advantageously, a sterically hindered *o*-methyl-substituted benzyl alcohol furnished the N-alkylated amine **4f** (47%).

N-Alkylation Using Heteroaromatic Amines and Alcohols. Gratifyingly, the application of substituted aminopyridine, quinoline, and sulfonamide derivatives gave efficient alkylation with excellent chemoselectivity (Table 5, **5a−f**). Notably, alkylation of 2-pyridinemethanol with aniline and

Table 5. Scope of Heteroaromatic Amines/Alcohols[a]



[a]The reaction was carried out with **1** (1.0 mmol), **2** (0.25 mmol), $NiBr_2$ (0.025 mmol), **L1** (0.05 mmol), and *t*-BuOK (0.25 mmol) at 130 °C in toluene (2.0 mL) for 48 h.

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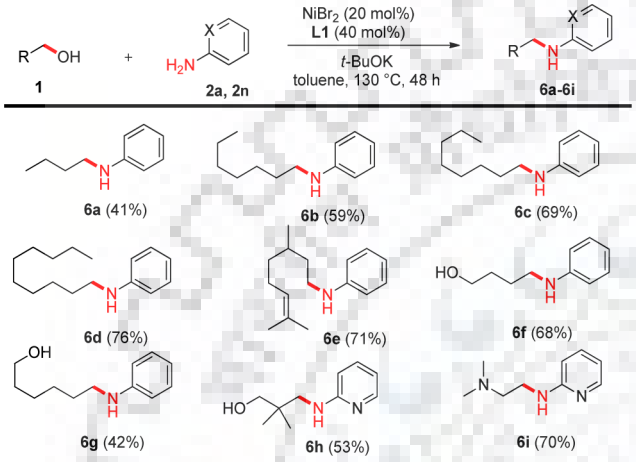
halide-substituted 2-aminopyridine delivered pharmaceutically active products **5g–i** in 72–78% yields, respectively. It is worth mentioning that the catalytic protocol is highly chemoselective and successfully transformed 2-aminopyridine into the intermediates of bioactive drugs mepyramine (**5j**) and chloropyramine (**5k**), extensively used in antihistamine activity.[22]

N-Alkylation of Alkyl Alcohols with Amines. Next we explored the reactivity of more challenging alkyl alcohols with aniline and 2-aminopyridine (Table 6). For instance, butanol,

Table 6. Scope of Aliphatic Alcohols[a]



[a]The reaction was carried out with **1** (1.25 mmol), **2** (0.25 mmol), $NiBr_2$ (0.05 mmol), **L1** (0.1 mmol), and *t*-BuOK (0.25 mmol) at 130 °C in toluene (2.0 mL) for 48 h.

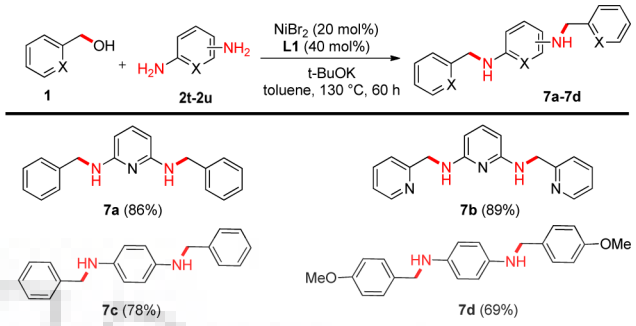
heptanol, octanol, and decanol efficiently converted to monosubstituted aniline derivatives **6a–d** in 41–76% isolated yields. It should be noted that the renewable terpenoid intermediate citronellol readily alkylated to **6e** under the optimized reaction conditions. Importantly, this is a rare example of the chemoselective transformation of an unsaturated alcohol under a Ni-catalyzed protocol, which is otherwise impossible under noble-metal catalysis.[15b] The remarkable activity of functionalized alcohols such as 2,2-dimethyl-1,3-propanediol, butane-1,4-diol, hexane-1,6-diol, and *N*,*N*-dimethyl ethanol selectively furnished valuable amino alcohols **6f–i** in 42–70% yields (Table 6). Unfortunately, under identical conditions the application of methanol did not result in any desired product.

Alkylation of Diamines. Further, we were interested in exploring the activity of pyridine-2,6-diamine and benzene-1,4-diamine with aryl as well as heteroaryl alcohols. To our delight, the resulting multifunctional amines **7a–d** are important structural motifs used as ligands in catalysis and in materials chemistry applications (Table 7 and Scheme S1 in the Supporting Information).[5,7]

Synthesis of N-Heterocycles. To establish the synthetic potential of the catalytic process, attempts at intramolecular cyclization of substituted 2-(2-aminophenyl)ethanol derivatives were carried out. We were pleased to witness an alternative synthesis of indole derivatives via a tandem borrowing-hydrogen/intramolecular cyclization (Scheme 2, **8a,b**).[23]

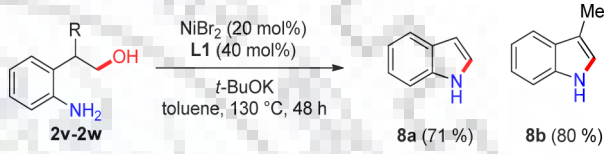
Functionalization of Vitamin Derivative. Next, the synthetic application of the catalytic protocol again was demonstrated using vitamin E, (±)-α-tocopherol, derivative of 4-bromoaniline (**2x**) with benzyl alcohols. Gratifyingly, 73

Table 7. Alkylation of Diamines[a]



[a]The reaction was carried out with **1** (2.0 mmol), **2** (0.25 mmol), $NiBr_2$ (0.05 mmol), **L1** (0.1 mmol), and *t*-BuOK (0.50 mmol) at 130 °C in toluene (2.0 mL) for 60 h.

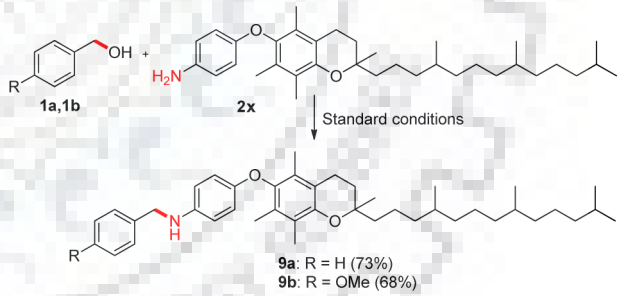
Scheme 2. Intramolecular Cyclization to Indole[a]



[a]The reaction was carried out with **2** (0.3 mmol), $NiBr_2$ (0.06 mmol), **L1** (0.12 mmol), and *t*-BuOK (0.3 mmol) at 130 °C in toluene (2.0 mL) for 48 h.

and 68% yields of secondary amines **9a,b** were respectively obtained without affecting the parent tocopherol moiety (Scheme 3).

Scheme 3. Functionalization of Complex Vitamin E Derivative[a]



[a]The reaction was carried out with **1** (1.0 mmol), **2** (0.25 mmol), $NiBr_2$ (0.025 mmol), **L1** (0.05 mmol), and *t*-BuOK (0.25 mmol) at 130 °C in toluene (2.0 mL) for 60 h.

Notably, the catalytic system is tolerant to extensive functional groups, such as halides, hydroxyl, trifluoromethyl, 1,4-dioaxlone, dimethylamino, pyridine, quinolone, and sulfonamide derivatives including the tocopherol moiety. Gratifyingly, the transformation proceeds in the presence of reducible functionalities, including alkene, nitrile, and nitro substituent, revealing the synthetic potential of the catalytic protocol.

Kinetic and Mechanistic Studies. After having established the excellent catalytic activity of the homogeneous nickel catalysts for amination of alcohols, we intended to study the preliminary mechanistic investigation of the process. To the best of our knowledge, to date no systematic mechanism is known for Ni-catalyzed C–N bond formation using an alcohol as an electrophilic coupling partner. Notably, we revealed that

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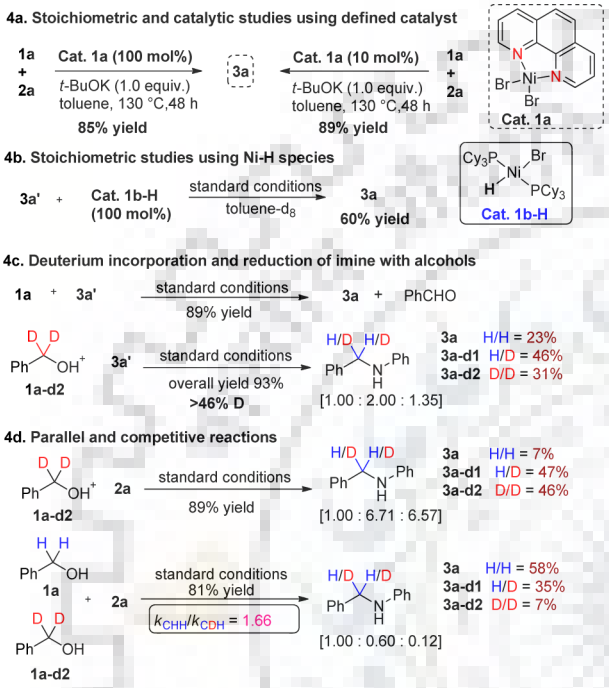
the proposed Ni-catalyzed amination of alcohol was a formal multistep process, mainly a borrowing-hydrogen methodology, as described in formal in situ NMR studies (Scheme S3 in the Supporting Information). As further confirmation of the putative Ni intermediate species, **cat.1a** was readily prepared[24] and employed in catalytic as well as in stoichiometric amounts in the reaction of **1a** with **2a** under optimized conditions and gave **3a** in good yields (Scheme 4a).

Scheme 4. Preliminary Mechanistic Studies[a]



[a]All mechanistic studies were carried out with **2** or **3a′** (0.1 mmol) and **1a** and **1a-d2** (0.4 mmol).

Additionally, the preparation of the Ni hydride species **Cat.1a** was not successful after several attempts using different hydride donors at variable temperature.[21] The experimental results suggest that the nickel hydride species is too unstable to detect even in in situ NMR studies at −75 °C (Scheme S8 in the Supporting Information). Further, in an attempt to prepare the stable Ni hydride species using an electron-rich phosphine ligand we chose tricyclohexylphosphine (**L8**) (Table 2). The defined complex $(Cy)_3PNiBr_2$ and the Ni hydride species $(Cy)_3PNiBrH$ (**Cat.1b-H**) were readily prepared according to the reported procedure,[25] and **Cat.1b-H** allowed reaction with the imine **3a′** in a stoichiometric amount under standard catalytic conditions. The desired product **3a** was obtained in 60% yield (Scheme 4b). This experimental findings are in strong agreement with the participation of Ni−H species and a Ni-catalyzed hydrogen-autotransfer strategy.

Again, in order to prove the nickel hydride species to be the active catalytic intermediate and the alcohol as a generic hydride source, the imine **3a′** was allowed to react with **1a** and **1a-d2** under the standard reaction conditions. The product distribution analysis using ^{1}H NMR as well as HRMS revealed the selective transformation of *N*-benzylaniline **3a-d1** along with **3a** and **3a-d2** and exhibited 46% incorporation of deuterium at the benzylic position of **3a-d1** (Scheme 4c and Scheme S3 in the Supporting Information).

Gratifyingly, a small amount of deuterated benzaldehyde was also detected by GC-MS analysis of the reaction mixture. All of this deuterated experimental evidence is in agreement with the literature observation of D/H exchange and the microreversible transformation of the catalytic process (Scheme 4c,d and Schemes S4−S7 in the Supporting Information).[26a] Notably, the hydride on the nickel species originated from the benzylic proton of the alcohol during dehydrogenation to benzaldehyde.[26]

Further, kinetic isotope effect (KIE) studies were performed to gain more insight into the reaction mechanism for the N-alkylation of alcohols.[27a] The intermolecular competition reactions of **1a** and **1a-d2** with **2a** were studied under the standard catalytic conditions, and the observed product ratio gave k_{CHH}/k_{CDH} = 1.66 on the basis of ^{1}H NMR as well as HRMS analysis. The experimental findings revealed the participation of benzylic C−H bond cleavage in the rate-determining step (Scheme 4d and Schemes S4−S7 in the Supporting Information).[27d]

CONCLUSIONS

In summary, we have developed the nickel-catalyzed direct application of various primary alcohols including diols and amino alcohols for selective N-alkylation of anilines. The catalytic protocol is tolerant to extensive functional groups and enables catalytic transformations in the presence of hydroxyl, alkene, nitrile, nitro, and trifluoromethyl functionalities in up to 96% yield. As a special highlight, we have demonstrated the synthetic potential of this protocol in the intramolecular cyclization to indoles, alkylation of diamine, and functionalization of a complex vitamin E derivative. Initial mechanistic studies revealed the involvement of the benzylic C−H bond in the rate-determining step. Mechanistic studies of the Ni-catalyzed amination reactions are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b02817.

Detailed experimental procedures, analytical data, and ^{1}H and ^{13}C NMR spectra for the compounds prepared (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Butters, M.; Catterick, D.; Craig, A.; Curzons, A.; Dale, D.; Gillmore, A.; Green, S. P.; Marziano, I.; Sherlock, J. P.; White, W. *Chem. Rev.* **2006**, *106*, 3002−3027.

(2) (a) Yang, Q.; Wang, Q.; Yu, Z. *Chem. Soc. Rev.* **2015**, *44*, 2305−2329. (b) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681−703. (c) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555−1575. (d) Bähn, S.; Sebastian, I.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. *ChemCatChem* **2011**, *3*, 1853−1864. (e) Guillena, G.; Ramon, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611−1641. (f) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 1229712. (g) Watson, A. J. A.; Williams, J. M. J. *Science* **2010**, *329*, 635−636.

(3) Barta, K.; Ford, P. C. *Acc. Chem. Res.* **2014**, *47*, 1503−1512.

(4) (a) Trost, B. M. *Science* **1991**, *254*, 1471−1477. (b) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, U.K., 1998. (c) Beller, M.; Centi, G. *ChemSusChem* **2009**, *2*, 459−460.

(5) (a) McGuire, J. L. *Pharmaceuticals: Classes, Therapeutic Agents, Areas of Application*; Wiley-VCH: Weinheim, Germany, 2000; Vols. *1*−*4*. (b) Hansch, C.; Sammes, P. G.; Taylor, J. B. *Comprehensive Medicinal Chemistry*; Pergamon Press: Oxford, U.K., 1990; Vol. *2*, Chapter 7.1. (c) Ricci, A. *Amino Group Chemistry: From Synthesis to the Life Sciences*; Wiley-VCH: Weinheim, Germany, 2008.

(6) (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338−6361. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860. (c) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177−2250. (d) Sperotto, E.; van Klink, G. P. M.; van Koten, G.; de Vries, J. G. *Dalton Trans.* **2010**, *39*, 10338−10351. (e) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem. Rev.* **2015**, *115*, 2596−2697.

(7) (a) Brown, D. G.; Boström, J. *J. Med. Chem.* **2016**, *59*, 4443−4458. (b) Lawrence, S. A. *Amines: Synthesis, Properties, and Applications*; Cambridge University Press: Cambridge, U.K., 2006.

(8) Bullock, R. M. *Catalysis Without Precious Metals*; Wiley-VCH: Weinheim, Germany, 2010.

(9) Selected recent examples with Ru catalysts: (a) Jumde, V. R.; Gonsalvi, L.; Guerriero, A.; Peruzzini, M.; Taddei, M. *Eur. J. Org. Chem.* **2015**, *2015*, 1829−1833. (b) Jumde, V. R.; Cini, E.; Porcheddu, A.; Taddei, M. *Eur. J. Org. Chem.* **2015**, *2015*, 1068−1074. (c) Balaraman, E.; Diskin-Posner, D. S. Y.; Milstein, D. *Catal. Lett.* **2015**, *145*, 139−144. (d) Oldenhuis, N. J.; Dong, V. M.; Guan, Z. *J. Am. Chem. Soc.* **2014**, *136*, 12548−12551. (e) Enyong, A. B.; Moasser, B. *J. Org. Chem.* **2014**, *79*, 7553−7563.

(10) Selected recent examples with Ir catalysts: (a) Wöckel, S.; Plessow, P.; Chelwies, M.; Brinks, M. K.; Rominger, F.; Hofmann, P.; Limbach, M. *ACS Catal.* **2014**, *4*, 152−161. (b) Zhang, Y.; Lim, C.-S.; Sim, D. S. B.; Pan, H.-J.; Zhao, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 1399−1403. (c) Ruch, S.; Irrgang, T.; Kempe, R. *Chem. - Eur. J.* **2014**, *20*, 13279−13285. (d) Chang, Y.-H.; Nakajima, Y.; Ozawa, F. *Organometallics* **2013**, *32*, 2210−2215.

(11) (a) Watanabe, Y.; Tsuji, Y.; Ohsugi, Y. *Tetrahedron Lett.* **1981**, *22*, 2667−2670. (b) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc., Chem. Commun.* **1981**, 611−612.

(12) For selected examples, see: (a) Fujita, K.-I.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525−3528. (b) Gnanamgari, D.; Sauer, E. L. O.; Schley, N. D.; Butler, C.; Incarvito, C. D.; Crabtree, R. H. *Organometallics* **2009**, *28*, 321−325. (c) Hamid, M. H. S. A.; Williams, J. M. J. *Chem. Commun.* **2007**, 725−727. (d) Gunanathan, C.; Milstein, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8661−8664. (e) Kawahara, R.; Fujita, K.-I.; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, *132*, 15108−15111.

(13) Zhao, Y. S.; Foo, S. W.; Saito, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3006−3009.

(14) (a) Yan, T.; Feringa, B. L.; Barta, K. *Nat. Commun.* **2014**, *5*, 5602. (b) Rawlings, A. J.; Diorazio, L. J.; Wills, M. *Org. Lett.* **2015**, *17*, 1086−1089. (c) Yan, T.; Feringa, B. L.; Barta, K. *ACS Catal.* **2016**, *6*, 381−388.

(15) (a) Rosler, S.; Ertl, M.; Irrgang, T.; Kempe, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 15046−15050. (b) Elangovan, S.; Neumann, J.; Sortais, J.-B.; Junge, K.; Darcel, C.; Beller, M. *Nat. Commun.* **2016**, *7*, 12641. (c) Mukherjee, A.; Nerush, A.; Leitus, G.; Shimon, L. J. W.; David, Y. B.; Jalapa, N. A. E.; Milstein, D. *J. Am. Chem. Soc.* **2016**, *138*, 4298−4301. (d) Zhang, G.; Yin, Z.; Zheng, S. *Org. Lett.* **2016**, *18*, 300−303. (e) Mastalir, M.; Tomsu, G.; Pittenauer, E.; Allmaier, G.; Kirchner, K. *Org. Lett.* **2016**, *18*, 3462−3465.

(16) (a) Yu, D.-G.; Wang, X.; Zhu, R.-Y.; Luo, S.; Zhang, X.-B.; Wang, B.-Q.; Wang, L.; Shi, Z.-J. *J. Am. Chem. Soc.* **2012**, *134*, 14638−14641. For selected examples of benzylic coupling, see: (b) Guan, B.-T.; Xiang, S.-K.; Wang, B.-Q.; Sun, Z.-P.; Wang, Y.; Zhao, K.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 3268−3269. (c) Harris, M. R.; Hanna, L. E.; Green, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303−3306. (d) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307−3310. (e) León, T.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 1221−1224. (f) Cao, Z.-C.; Luo, Q.-Y.; Shi, Z.-J. *Org. Lett.* **2016**, *18*, 5978−5981 and references cited therein.

(17) For selected reviews, see: (a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299−309. (b) Ananikov, V. P. *ACS Catal.* **2015**, *5*, 1964−1971. (c) Jolly, P. W.; Wilke, G. *The Organic Chemistry of Nickel*; Academic Press: New York, 1974. (d) Wilke, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 185−206. (e) Tamaru, Y. *Modern Organonickel Chemistry*; Wiley-VCH: Weinheim, Germany, 2005; p 327. (f) Dander, J. E.; Garg, N. K. *ACS Catal.* **2017**, *7*, 1413−1423.

(18) For reviews of Ni-catalyzed C−O bond activation, see: (a) Zarate, C.; Van Gemmeren, M.; Somerville, R. J.; Martin, R. *Adv. Organomet. Chem.* **2016**, *66*, 143−222. (b) Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48*, 1717−1726. (c) Tollefson, E. J.; Hanna, L. E.; Jarvo, E. R. *Acc. Chem. Res.* **2015**, *48*, 2344−2353. (d) Su, B.; Cao, Z.-C.; Shi, Z.-J. *Acc. Chem. Res.* **2015**, *48*, 886−896. (e) Cornella, J.; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081−8097. (f) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346−1416.

(19) For selected examples of Ni-catalyzed C−N bond formation reactions, see: (a) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054−6058. (b) Park, N. H.; Teverovskiy, G.; Buchwald, S. L. *Org. Lett.* **2014**, *16*, 220−223. (c) Shimasaki, T.; Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 2929−2932. (d) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598−15599. (e) Ramgren, S. D.; Silberstein, A. L.; Yang, Y.; Garg, N. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2171−2173. (f) Mesganaw, T.; Silberstein, A. L.; Ramgren, S. D.; Nathel, N. F.; Hong, X.; Liu, P.; Garg, N. K. *Chem. Sci.* **2011**, *2*, 1766−1771.

(20) (a) Shimizu, K.; Kon, K.; Onodera, W.; Yamazaki, H.; Kondo, J. N. *ACS Catal.* **2013**, *3*, 112−117. (b) Shimizu, K.; Imaiida, N.; Kon, K.; Siddiki, S. M. A. H.; Satsuma, A. *ACS Catal.* **2013**, *3*, 998−1005.

(21) Chakraborty, S.; Piszel, P. E.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2015**, *34*, 5203−5206.

(22) (a) Vaughan, J. R.; Anderson, G. W.; Clapp, R. C.; Clark, J. H.; English, J. P.; Howard, K. L.; Marson, H. W.; Sutherland, L. H.; Denton, J. J. *J. Org. Chem.* **1949**, *14*, 228−234. (b) Parsons, M. E.; Ganellin, C. R. *Br. J. Pharmacol.* **2006**, *147*, S127−S135.

(23) (a) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 1229712. (b) Fujita, K.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2002**, *4*, 2691−2694.

(24) Khrizanforov, M.; Khrizanforova, V.; Mamedov, V.; Zhukova, N.; Strekalova, S.; Grinenko, V.; Gryaznova, T.; Sinyashin, O.; Budnikova, Y. *J. Organomet. Chem.* **2016**, *820*, 82−88.

(25) (a) Green, M. L. H.; Saito, T.; Tanfield, P. J. *J. Chem. Soc. A* **1971**, 152−154. (b) Lindner, M. M.; Beckmann, U.; Frank, W.; Kläui, W. *ISRN Inorg. Chem.* **2013**, *2013*, 1−13.

(26) (a) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watsom, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766−1774. (b) Samec, J. S. M.; Backvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237−248.

DOI: 10.1021/acscatal.7b02817
ACS Catal. 2017, 7, 8152−8158

(27) (a) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066−3072. (b) Wong, C. M.; McBurney, R. T.; Binding, S. C.; Peterson, M. B.; Gonçales, V. R.; Gooding, J. J.; Messerle, B. A. *Green Chem.* **2017**, *19*, 3142−3151. (c) Bartoszewicz, A.; Miera, G. G.; Marcos, R.; Norrby, P.; Matute, B. M. *ACS Catal.* **2015**, *5*, 3704−3716. (d) Hikawa, H.; Izumi, K.; Ino, Y.; Kikkawa, S.; Yokoyama, Y.; Azumaya, I. *Adv. Synth. Catal.* **2015**, *357*, 1037−1048.

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A nitrogen-ligated nickel-catalyst enables selective intermolecular cyclisation of β- and γ-amino alcohols with ketones: access to five and six-membered N-heterocycles†

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Owing to the great demand for the synthesis of N-heterocycles, development of new reactions that utilise renewable resources and convert them into key chemicals using non-precious base metal-catalysts is highly desirable. Herein, we demonstrated a sustainable Ni-catalysed dehydrogenative approach for the synthesis of pyrroles, pyridines, and quinolines by the reaction of β- and γ-amino alcohols with ketones *via* C–N and C–C bond formations in a tandem fashion. A variety of aryl, hetero-aryl, and alkyl ketones having free amine, halide, alkyl, alkoxy, alkene, activated benzyl, and pyridine moieties were converted into synthetically interesting 2,3 and 2,3,5-substituted bicyclic as well as tricyclic N-heterocycles with up to 90% yields. As a highlight, we demonstrated the synthesis of an interesting pyrrole derivative by intermolecular cyclisation of a steroid hormone with phenylalaninol.

1. Introduction

The development of a sustainable and atom-economic technology that utilises environmentally benign and highly abundant renewable resources for the production of key chemicals represents a crucial challenge in chemical research.[1] In this regard, readily available alcohols, derived from lignocellulose biomass,[2] are an attractive and potential green feedstock for dehydrogenative coupling using transition metal complexes. Note that this dehydrogenative transformation of alcohols is often limited to the formation of C–C and C–N bonds *via* a hydrogen auto-transfer approach.[3] However, application of hydrogen transfer methodology for the construction of aromatic N-heterocycles employing N–H/C–H coupling in a tandem fashion is scarcely reported.[4]

Pyrroles and their derivatives are privileged structural motifs that are used as intermediates in the synthesis of bioactive natural products, drugs, and functional materials and as ligands in catalysis.[4] Polypyrroles have significant applications as conducting polymers in batteries, solar cell devices, and material chemistry.[5] Despite several elegant methods for pyrrole synthesis, poor substrate availability, stoichiometric waste generation, and multi-step transformations are key issues.[6] Unfortunately, synthesis of pyrroles from easily available biomass-derived sustainable feedstock is a challenging task and has rarely been explored. Notably, pyrrole derivatives due to their substantial importance and aromatic heterocycles that utilise fully or partially renewable resources are highly desirable.[1,2,7]

However, in recent years, significant progress has been made in pyrrole synthesis employing acceptorless dehydrogenation of alcohols using precious metal catalysts mainly Ru- and Ir-catalysts.[8,9] Interestingly, in a recent study, Beller and co-workers have studied Ru-catalysed multi-component synthesis of substituted pyrroles using ketones, vicinal diols, and amines (Scheme 1a and b).[8b,c] More recently, Saito *et al.* demonstrated Ru-catalysed process as an alternative synthesis of pyrroles using ketones in combination with readily available β-amino alcohols.[8e] However, apart from the conversion of renewable resources, application of inexpensive and rare noble metal catalysts is equally important for key catalytic transformations.[10,11] Processes that facilitate the synthesis of N-heterocycles using a combination of both sustainable technology and earth-abundant non-precious base metals (Fe, Mn, Ni, and Co) are highly desirable. For instance, notable contribution by the groups of Milstein,[12] Kempe,[13] Barta,[14a] and others[14] for the construction of pyrroles employing Co-, Fe-, and Mn-complexes is worth mentioning.

The recent surge is to develop a sustainable and inexpensive Ni-catalysed protocol for the construction of pyrroles from readily available β-amino alcohols to avoid the use of hazardous alkylating agents.[3] To date, nickel-catalysed pyrrole

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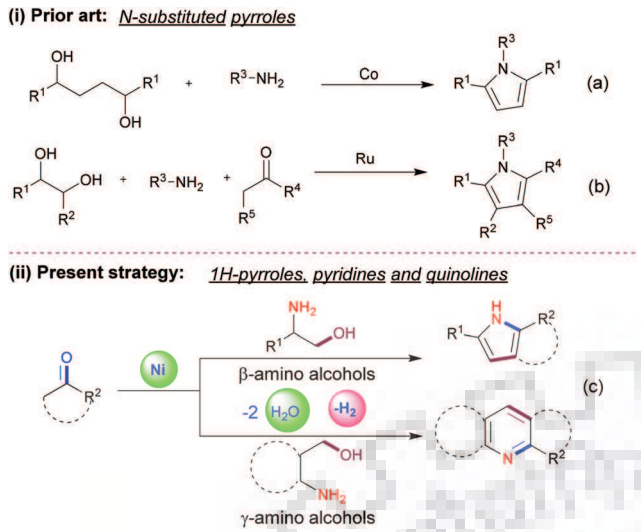
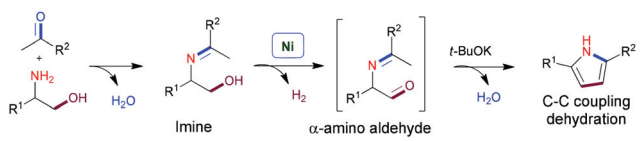


Scheme 1 (i) Metal-catalysed dehydrogenative coupling for pyrrole synthesis. (ii) Nickel-catalysed sustainable synthesis of pyrroles, pyridines, and quinolines.

synthesis is only limited to the annulation of azides with alkynes/allenes or aryl aldehydes as well as to enone alkyne reductive coupling.[15]

In general, strong binding and poor leaving ability of the hydroxyl group limit its application in nickel-catalysed transformations.[16] To overcome these limitations, recently, we have established an efficient Ni-catalysed protocol for the first time for the selective alkylation of amines and intra-molecular cyclisation to indole derivatives using 2-(2-aminophenyl)ethanol.[17] The catalytic system is tolerant to hydroxyl and amino groups. Thus, inspired by these promising results, we realised that unprotected aliphatic amino alcohols could be used to construct N-heterocycles. Therefore, we explored nickel-catalysed direct pyrrole synthesis *via* a reaction of readily abundant β-amino alcohols with ketones (Scheme 1c).

Based on our previous observations for acceptorless dehydrogenation of alcohols to aldehydes using nickel catalysts, we anticipated that α-amino aldehyde could be formed *in situ* from β-amino alcohol by a nickel catalyst, and sequential dehydration, alkylation, and base-catalysed condensation could lead to the construction of substituted pyrroles in one pot operation (Scheme 2). To our delight, herein, we established the first base metal-catalysed reaction of β-amino alcohols with ketones to substituted pyrroles in a tandem fashion *via* C–C and C–N bond formations.



Scheme 2 Proposed mechanism for Ni-catalysed tandem synthesis of pyrroles through selective C–C and C–N bond formation.

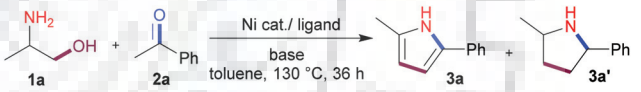
2 Results and discussion

2.1 Optimisation of the catalytic protocol

Notably, it is observed that β-amino alcohol is highly prone to undergo self-condensation to substituted pyrazine and results in lower product yield of pyrroles.[13] Hence, there is still a need for more selective and improved catalytic protocol. However, to explore the possibilities for pyrrole synthesis using nickel catalysis, initially, we envisioned the following key challenges: (i) selective control towards the reduced product **3a′**, (ii) minimization of the self-condensation of β-amino alcohol **1a** to 2,5-dimethyl-pyrazine, and (iii) catalytic selectivity to control the base-catalysed self-condensation of ketones (Table 1 and ESI, Schemes S4 and S6†).

To achieve this goal, primarily, we investigated the model reaction between 2-aminopropan-1-ol **1a** and acetophenone **2a** using five different nickel pre-catalysts having the oxidation state of Ni(0) and Ni(II) (Table 1, entries 1–5). However, a combination of $NiCl_2$/**L1** resulted in only 30% selectivity of **3a** along with the reduced product **3a′** (Table 1, entry 1). Next, influences of various phosphine and nitrogen ligands **L2–L11** were tested (Table 2 and ESI, Table S2†); however, best results were obtained with 10 mol% $NiCl_2$, 12 mol% bipyridine **L7**, 1 equiv. of *t*-BuOK, and toluene as an efficient solvent (Table 1, entry 6). Additionally, different bases, solvents, and control experiments were investigated, and no improvement in the

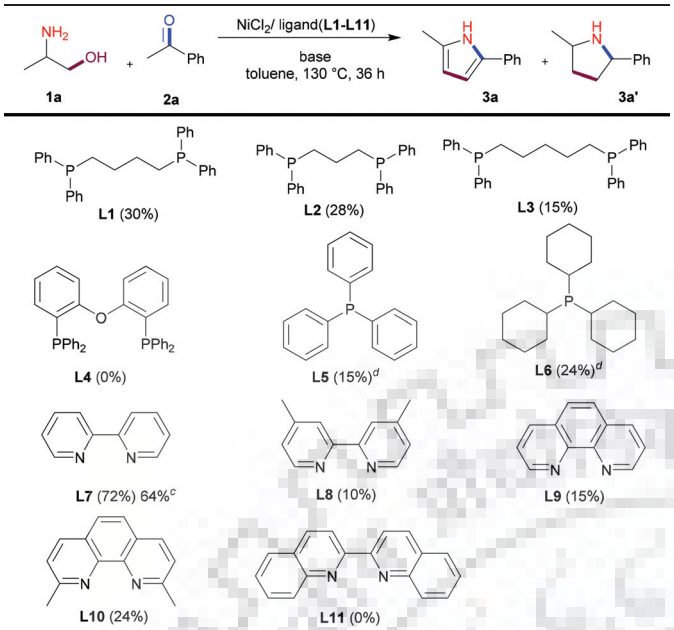
Table 1 Optimisation studies for nickel-catalysed pyrrole synthesis[a,b]



Entry	Catalyst	Ligand	Conv. (%) 3a	3a′
1	$NiCl_2$	**L1**	30	8
2	$NiBr_2$	**L1**	12	13
3	$Ni(acac)_2$	**L1**	18	9
4	$Ni(cod)_2$	**L1**	17	12
5	$NiCl_2$·DME	**L1**	25	0
6	**$NiCl_2$**	**L7**	**72(64)**	**0**
7[c]	$NiCl_2$	**L7**	50	0
8[d]	$NiCl_2$	**L7**	41	0
9[e]	$NiCl_2$	**L7**	29	0
10[f]	$NiCl_2$	**L7**	54	0
11[g]	$NiCl_2$	**L7**	42	0
12[h]	$NiCl_2$	**L7**	0	0
13[i]	—	—	5	0
14[j]	$NiCl_2$	**L7**	49	0
15[k]	$NiCl_2$	**L7**	36	0

[a] Unless specified otherwise, the reaction was carried out with **1a** (0.5 mmol), **2a** (1.0 mmol), Ni cat. (0.05 mmol), **L** (0.06 mmol), and *t*-BuOK (0.5 mmol) under a N_2 atmosphere at 130 °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] *t*-BuONa (0.5 mmol) was used. [d] 0.375 mmol of base was used. [e] 0.25 mmol of base was used. [f] $NiCl_2$ (0.0375 mmol) and **L7** (0.045 mmol) were used. [g] $NiCl_2$ (0.025 mmol) and **L7** (0.03 mmol) were used. [h] No base was used. [i] No catalyst was used. [j] Reaction was performed at 120 °C. [k] Reaction was performed at 110 °C.

Table 2 Ligand screening for nickel-catalysed pyrrole synthesis[a,b]



[a] Unless specified, the reaction was carried out with **1a** (0.5 mmol), **2a** (1.0 mmol), $NiCl_2$ (10 mol%), ligand (12 mol%), base (1.0 equiv.) under a N_2 atmosphere at 130 °C in toluene (2.0 mL) for 36 h. [b] Conversion of **3a** was determined by GC-MS. [c] Isolated yield. [d] Ligand (20 mol%) was used.

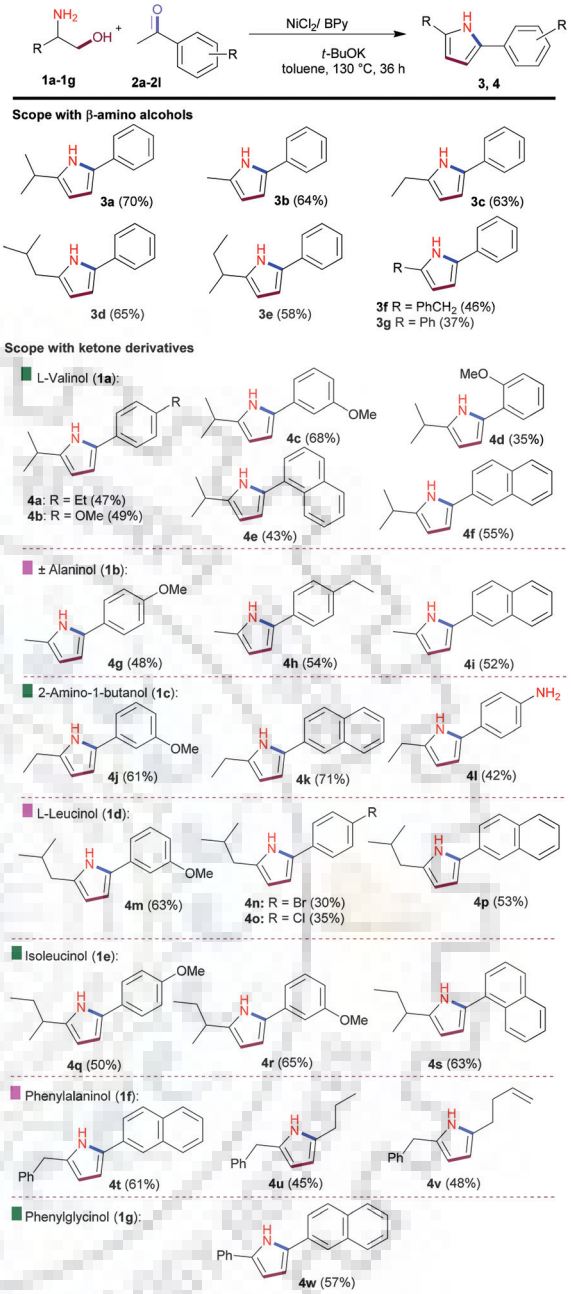
product yields was observed (Table 1, entries 6–13 and ESI Tables S1–S7†). Moreover, lowering of reaction temperature under identical conditions did not significantly improve the yield of **3a** (Table 1, entries 14, 15 and ESI Table S8†). Note that we did not observe any reduced product **3a′** when 2 equiv. of acetophenone was used with respect to β-amino alcohol. Interestingly, under optimized conditions, **3a** was obtained in 64% isolated yield, and only negligible amount of 2,5-dimethylpyrazine was observed *via* the GC-Ms analysis (Table 1, entry 6 and ESI, Schemes S4 and S6†).

2.2 Access to 2,5-disubstituted N-heterocycles

After optimising the synthetic conditions, we next studied the substrate scope and limitations of the catalytic protocol using seven different amino alcohols substituted with alkyl and aryl groups. The reaction of acetophenone with less reactive methyl, ethyl, iso-propyl, secondary-butyl as well as iso-butyl-substituted β-amino alcohols furnished the desired products in up to 70% isolated yields (Scheme 3, **3a–3e**). Interestingly, under identical conditions, phenylalaninol and phenylglycinol could be converted into 2,5-diaryl-substituted pyrroles (Scheme 3, **3f–3g**).

2.3 Pyrroles synthesis using ketone derivatives

Further, to demonstrate the general applicability of the protocol, a variety of acetophenone, including 1-acetyl and 2-acetyl naphthalene, derivatives substituted with ethyl or methoxy groups were examined with different β-amino alcohols, which



Scheme 3 Synthesis of 2,5-disubstituted pyrroles. Reaction conditions: Unless specified, the reaction was carried out with **1** (0.5 mmol), **2** (1.0 mmol), $NiCl_2$ (0.05 mmol), bpy (0.06 mmol), *t*-BuOK (0.5 mmol), 130 °C in toluene (2.0 mL) for 36 h.

resulted in a series of interesting 2,5-disubstituted pyrroles with up to 71% isolated yields (Scheme 3, **4a–4w**). It is to be noted that sterically hindered *ortho*-methoxy and halide-substituted 1-(4′-chlorophenyl) and 1-(4′-bromophenyl) acetophenone is smoothly converted into the desired pyrroles in moderate yields (Scheme 3, **4d** and **4n–4o**). Further, aliphatic ketones containing long chain as well as terminal double bond efficiently transformed into the corresponding pyrroles **4u–4v** (Scheme 3).

2.4 Synthesis of N-heterocyclic 2,5-disubstituted pyrroles

Next, more challenging 3-acetylpyridine **2m** was used as a substrate, which yielded the pharmaceutically active 3-(1*H*-pyrrol-2yl)pyridines **5a–5f** in 45–58% yields. Surprisingly, irrespective of their electronic properties, methyl, ethyl, iso-propyl, *sec*-butyl, iso-butyl, and benzyl-substituted β-amino alcohols are well tolerated (Scheme 4). Importantly, this represents a rare example of selective transformation of di-substituted N-heterocyclic pyrrole derivatives using nickel, otherwise previously not reported with other metal-catalysts.[12–14]

2.5 Synthesis of 2,3,5-trisubstituted bi-and tricyclic pyrroles

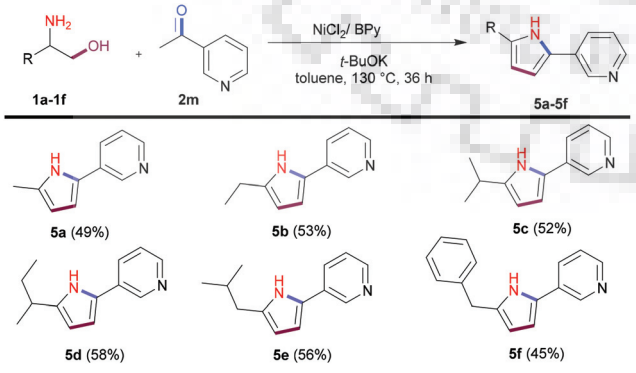
Inspired by the excellent catalytic activity, further, we explored the synthesis of 2,3,5-trisubstituted bicyclic pyrroles. Note that the application of 7-methoxy-tetralone with β-amino alcohols furnished the desired tri-substituted pyrroles in good isolated yields, 63–70% (Scheme 5, **6a–6d**). Again, we studied the reactivity of more challenging acyclic and cyclic ketones. Intermolecular cyclisation of propiophenone and valerophenone resulted in 2,3,5-trisubstituted pyrroles (Scheme 5, **6e–6f**). However, the reaction of alkyl cyclic ketones, such as cyclopentanone, cyclohexanone as well as cycloheptanone, resulted in various annulated tri-substituted bicyclic products (Scheme 5, **6g–6i**). These examples established the potential application of the present catalytic protocol.

2.6 Intermolecular cyclisation using a steroid hormone

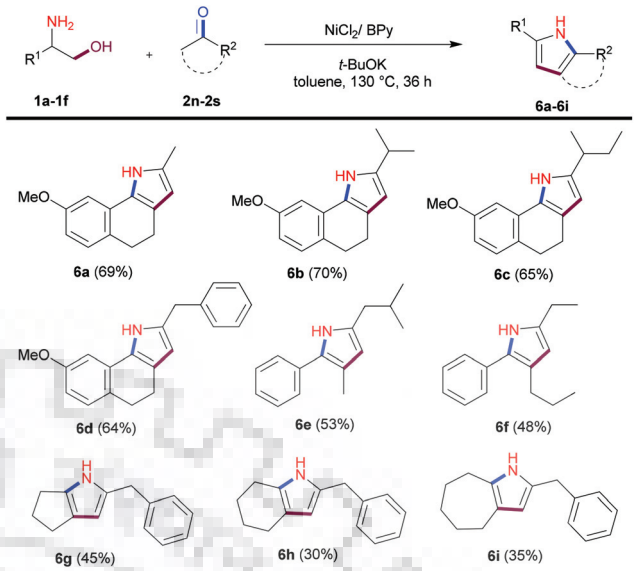
Next, to establish the versatility of the intermolecular cyclisation, we studied the catalytic pyrrole synthesis using an interesting steroid hormone. Indeed, 3-methyl ether of 5-pregnen-3-β-ol-20-one (pregnenolone) was efficiently converted into the desired 2,5-disubstituted pyrrole **7** using phenylalaninol without affecting the parent steroid framework (Scheme 6).

2.7 Intermolecular cyclization using γ-amino alcohols

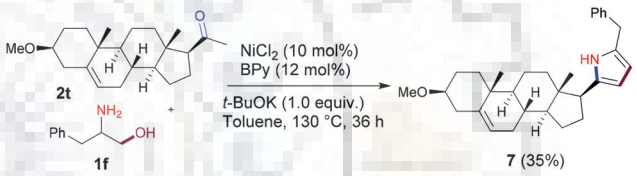
After having demonstrated the excellent catalytic activity of β-amino alcohols for pyrrole synthesis, finally, the generality of our nickel-catalysed protocol was further evaluated using



Scheme 4 Synthesis of N-heterocyclic 2,5-disubstituted pyrroles. Reaction conditions: Unless specified, the reaction was carried out with **1** (0.5 mmol), **2** (1.0 mmol), $NiCl_2$ (0.05 mmol), bpy (0.06 mmol), *t*-BuOK (0.75 mmol), 130 °C in toluene (2.0 mL) for 36 h.



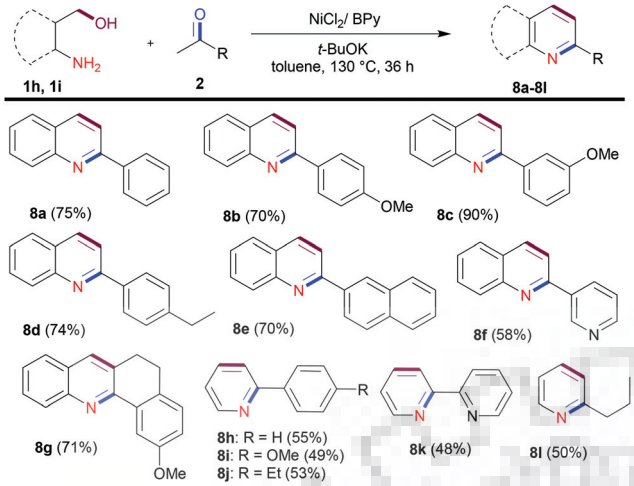
Scheme 5 Synthesis of 2,3,5-tri-substituted bi-cyclic and tri-cyclic pyrroles. Reaction conditions: Unless specified, the reaction was carried out with **1** (0.5 mmol), **2** (1.0 mmol), $NiCl_2$ (0.05 mmol), bpy (0.06 mmol), *t*-BuOK (0.5 mmol), 130 °C in toluene (2.0 mL) for 36 h.



Scheme 6 Synthetic conditions: Pyrrole synthesis using steroid hormone. Reaction conditions: Unless specified, the reaction was carried out with **1** (0.2 mmol), **2** (0.25 mmol), $NiCl_2$ (0.02 mmol), bpy (0.024 mmol), *t*-BuOK (0.2 mmol), 130 °C in toluene (2.0 mL) for 36 h.

γ-amino alcohols as a coupling partner to access six-membered N-heterocycles, pyridine and quinoline derivatives. Because of the significant importance and interesting bio-activity of pyridine and quinoline, a general and versatile method for the synthesis of pyridine and quinoline is highly desirable.[18] However, to date, their synthesis is often limited with Ir- and Ru-based precious metals complexes.[19,20] In this direction, recent advancement by Kirchner and co-workers for synthesis of quinolines is noteworthy.[21]

Surprisingly, using our optimized protocol, application of 2-amino benzyl alcohol with electronically different acetophenones furnished C-2 substituted quinolines **8a–8f** in up to 90% yields (Scheme 7). Additionally, when 3-amino-1-propanol was used as a coupling partner, the C-2-substituted pyridines **8h–8j** were obtained in 49–55% yield (Scheme 7). Notably, 2-acetylpyridine efficiently transformed into the ligand bi-pyridine **8k**. Furthermore, application of more challenging 7-methoxytetralone and 2-pentanone yielded the desired 2,3-disubstituted quinoline as well as 2-^{n}propyl pyridine **8g** and **8l** in 50–71% yield (Scheme 7). To our delight, we are pleased to



Scheme 7 Intermolecular cyclisation for C-2 substituted quinoline and pyridine derivatives. Reaction conditions: Unless specified, the reaction was carried out with **1** (0.5 mmol), **2** (1.0 mmol), $NiCl_2$ (0.05 mmol), bpy (0.06 mmol), *t*-BuOK (0.5 mmol), 130 °C in toluene (2.0 mL) for 36 h.

report an alternative synthesis of pyridine and quinoline derivatives under nickel catalysis *via* a tandem intermolecular cyclisation.

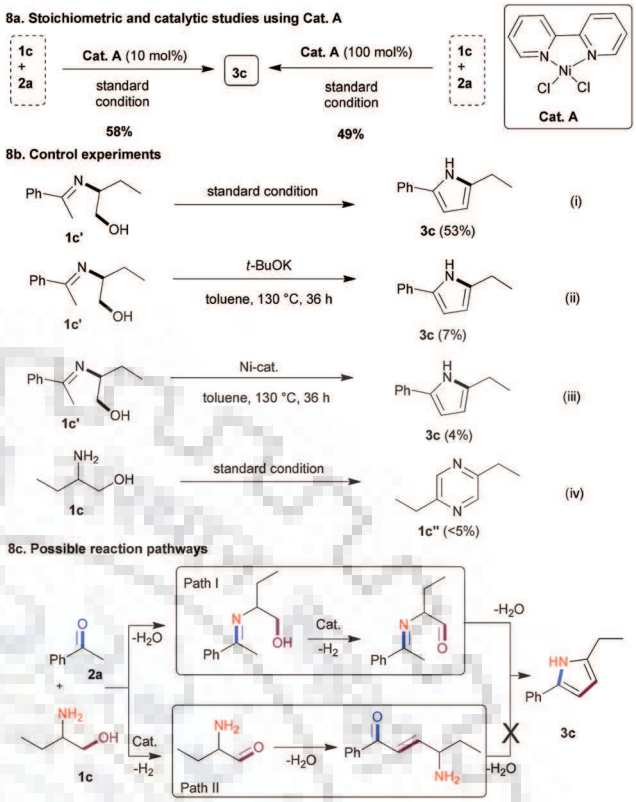
It is noteworthy to mention that the catalytic protocol is tolerant to primary amine, halides, alkyl and alkoxy groups, including benzyl and pyridine derivatives. Gratifyingly, remarkable transformations in the presence of reducible functionalities, such as terminal alkene, as well as steroid framework reveal the synthetic potential of the catalytic system. Unfortunately, application of 1-phenylbutane-1,3-dione and 4-phenylbut-3-yn-2-one under standard catalytic conditions did not result in any desired product.

2.8 Preliminary mechanistic studies

To gain insight about the reaction mechanism and the nature of the putative Ni-intermediate species, **Cat. A** was prepared,[22] isolated separately, and employed in catalytic as well as in stoichiometric equiv. for intermolecular pyrrole synthesis (ESI, Scheme S2†). Using 10 mol% and 100 mol% of **Cat. A** in the reaction of **1c** with **2a** under standard conditions, 58% and 49% yields of **3c** were obtained, respectively, comparable to the result obtained under optimized conditions (**3c**, Schemes 3 and 8a).

However, mechanistically, we anticipated that Ni-catalysed pyrrole synthesis was composed of a formal multi-step process: (i) condensation of ketone with a β-amino alcohol to an imine intermediate and (ii) Ni-catalysed *in situ* dehydrogenation to an α-amino aldehyde followed by sequential intramolecular C–C coupling and dehydration to thermodynamically favourable substituted pyrroles (Scheme 2).

Further, to elucidate the reaction pathways, imine **1c′** was independently prepared and employed under standard catalytic conditions. The desired pyrrole **3c** was obtained in a 53% yield (Scheme 8b, eqn (i) and ESI, Schemes S3–S7†). However,



Scheme 8 Control experiments to understand the reaction pathways for pyrrole formation.

intramolecular cyclisation of intermediate **1c′** in the absence of a base and catalyst revealed their potential role (Scheme 8b, eqn (ii)–(iii) and ESI, Scheme S5†). Alternatively, control experiments using *N*,*N*-dimethyl-ethanol with acetophenone did not yield any desired product (Scheme 8c and ESI, Scheme S8†). However, to identify the possible imine intermediate **1c′**, a control experiment was carried out using β-amino alcohol **1a** with acetophenone. The reaction was interrupted after 12 h, and no imine intermediate was detected by ^{1}H-NMR studies (ESI, Scheme S1†). Thus, present experimental observations suggest that the intramolecular alkylation or cyclisation is quite fast to be detected even in NMR analysis. These mechanistic findings are in agreement with the observation proposed by Kempe and co-workers.[9a] Additionally, we observed the formation of 1-phenyl ethanol as a side product derived from acetophenone (ESI, Scheme S1†); this supported the bi-functional activity of our nickel catalyst.[17,23]

3. Conclusions

In conclusion, we have demonstrated Ni-catalysed sustainable dehydrogenative coupling of β- and γ-amino alcohols with ketones to access five and six-membered N-heterocycles. This is the first example of such base metal-catalysed pyrrole synthesis using amino acid-derived alcohols. This catalytic proto-

col is highly regioselective, and a variety of aryl and alkyl ketones, including nine amino alcohols having free amine, halides, alkyl, alkoxy, alkenes, activated benzyl and pyridines, smoothly transform into 2,3 and 2,3,5-substituted bicyclic as well as tricyclic pyrroles, quinolines and pyridine derivatives in up to 90% yields. As a highlight, we demonstrated an interesting pyrrole derivative employing intermolecular cyclisation of a steroid hormone with phenylalaninol.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 C. O. Tuck, E. Pérez, I. T. Horváth, R. A. Sheldon and M. Poliakoff, *Science*, 2012, **337**, 695.
2 (*a*) K. Barta and P. C. Ford, *Acc. Chem. Res.*, 2014, **47**, 1503; (*b*) T. P. Vispute, H. Zhang, A. Sanna, R. Xiao and G. W. Huber, *Science*, 2010, **330**, 1222.
3 For selected reviews: (*a*) G. Guillena, D. J. Ramon and M. Yus, *Chem. Rev.*, 2010, **110**, 1611; (*b*) J. F. Bower and M. J. Krische, *Top. Organomet. Chem.*, 2011, **34**, 107; (*c*) A. J. A. Watson and J. M. J. Williams, *Science*, 2010, **329**, 635; (*d*) S. Bähn, I. Sebastian, L. Neubert, M. Zhang, H. Neumann and M. Beller, *ChemCatChem*, 2011, **3**, 1853; (*e*) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681; (*f*) C. Gunanathan and D. Milstein, *Science*, 2013, **341**, 249. For selected pioneering examples: (*g*) J. F. Bower, E. Skucas, R. L. Patman and M. J. Krische, *J. Am. Chem. Soc.*, 2007, **129**, 15134; (*h*) J. M. Ketcham, I. Shin, T. P. Montgomery and M. J. Krische, *Angew. Chem., Int. Ed.*, 2014, **53**, 9142.
4 J. A. Joule and K. Mills, *Heterocyclic Chemistry*, Wiley, Chichester, 5th edn, 2010.
5 (*a*) A. Hagfeldt, G. Boschloo, L. Sun, L. Kloo and H. Pettersson, *Chem. Rev.*, 2010, **110**, 6595; (*b*) H. Nishide and K. Oyaizu, *Science*, 2008, **319**, 737.
6 (*a*) L. Knorr, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 1635; (*b*) C. Paal, *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 367; (*c*) A. Hantzsch, *Ber. Dtsch. Chem. Ges.*, 1890, **23**, 1474; (*d*) S. Rakshit, F. W. Patureau and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 9585; (*e*) Z. Chen, B. Lu, Z. Ding, K. Gao and N. Yoshikai, *Org. Lett.*, 2013, **15**, 1966.
7 G. Chelucci, *Coord. Chem. Rev.*, 2017, **331**, 37.
8 Selected recent examples with Ru-catalysts: (*a*) D. Srimani, Y. Ben-David and D. Milstein, *Angew. Chem., Int. Ed.*, 2013, **52**, 4012, (*Angew. Chem.*, 2013, **125**, 4104); (*b*) M. Zhang, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2013, **52**, 597, (*Angew. Chem.*, 2013, **125**, 625); (*c*) M. Zhang, X. Fang, H. Neumann and M. Beller, *J. Am. Chem. Soc.*, 2013, **135**, 11384; (*d*) N. D. Schley, G. E. Dobereiner and R. H. Crabtree, *Organometallics*, 2011, **30**, 4174; (*e*) K. Iida, T. Miura, J. Ando and S. Saito, *Org. Lett.*, 2013, **15**, 1436.
9 Selected recent examples with Ir-catalysts: (*a*) S. Michlik and R. Kempe, *Nat. Chem.*, 2013, **5**, 140; (*b*) D. Forberg, J. Obenauf, M. Friedrich, S. M. Hghne, W. Mader, G. Motz and R. Kempe, *Catal. Sci. Technol.*, 2014, **4**, 4188. For a recent example with Pt-catalyst see: (*c*) S. M. A. H. Siddiki, A. S. Touchy, C. Chaudhari, K. Kon, T. Toyaoa and K. Shimizu, *Org. Chem. Front.*, 2016, **3**, 846.
10 (*a*) R. M. Bullock, *Catalysis Without Precious Metals*, Wiley-VCH, Weinheim, 2010; (*b*) M. Albrecht, R. Bedford and B. Plietker, *Organometallics*, 2014, **33**, 5619; (*c*) I. Bauer and H.-J. Knölker, *Chem. Rev.*, 2015, **115**, 3170; (*d*) B. Su, Z.-C. Cao and Z.-J. Shi, *Acc. Chem. Res.*, 2015, **48**, 886; (*e*) S. J. C. Robinson and D. M. Heinekey, *Chem. Commun.*, 2017, **53**, 669.
11 For selected recent examples, see: (*a*) S. Rosler, M. Ertl, T. Irrgang and R. Kempe, *Angew. Chem., Int. Ed.*, 2015, **54**, 15046; (*b*) S. Elangovan, J. Neumann, J.-B. Sortais, K. Junge, C. Darcel and M. Beller, *Nat. Commun.*, 2016, **7**, 12641; (*c*) A. Mukherjee, A. Nerush, G. Leitus, L. J. W. Shimon, Y. B. David, N. A. E. Jalapa and D. Milstein, *J. Am. Chem. Soc.*, 2016, **138**, 4298; (*d*) M. Mastalir, G. Tomsu, E. Pittenauer, G. Allmaier and K. Kirchner, *Org. Lett.*, 2016, **18**, 3462; (*e*) T. Yan, B. L. Feringa and K. Barta, *Nat. Commun.*, 2014, **5**, 5602; (*f*) T. Yan, B. L. Feringa and K. Barta, *ACS Catal.*, 2016, **6**, 381.
12 For Co-catalyzed pyrrole synthesis, see: (*a*) P. Daw, S. Chakraborty, J. A. Garg, Y. Ben-David and D. Milstein, *Angew. Chem., Int. Ed.*, 2016, **55**, 14373, (*Angew. Chem.*, 2016, **128**, 14585); (*b*) S. P. Midya, V. G. Landge, M. K. Sahoo, J. Rana and E. Balaraman, *Chem. Commun.*, 2018, **54**, 90.
13 For Mn-catalyzed reactions, see: F. Kallmeier, B. Dudziec, T. Irrgang and R. Kempe, *Angew. Chem., Int. Ed.*, 2017, **56**, 7261.
14 For Fe-catalyzed reactions, see: (*a*) T. Yan and K. Barta, *ChemSusChem*, 2016, **9**, 2321; (*b*) B. Emayavaramban, M. Sen and B. Sundararaju, *Org. Lett.*, 2017, **19**, 6.
15 (*a*) F. Chen, T. Shen, Y. Cui and N. Jiao, *Org. Lett.*, 2012, **14**, 4926; (*b*) T. Miura, K. Hiraga, T. Biyajima, T. Nakamuro and M. Murakami, *Org. Lett.*, 2013, **15**, 3298; (*c*) B. B. Thompson and J. Montgomery, *Org. Lett.*, 2011, **13**, 3289.
16 For selected Ni-catalyzed reviews, see: (*a*) S. Z. Tasker, E. A. Standley and T. F. Jamison, *Nature*, 2014, **509**, 299; (*b*) V. P. Ananikov, *ACS Catal.*, 2015, **5**, 1964; (*c*) P. W. Jolly and G. Wilke, *The Organic Chemistry of Nickel*, Academic Press, New York, 1974; (*d*) G. Wilke, *Angew. Chem., Int. Ed.*, 1988, **27**, 185; (*e*) Y. Tamaru, *Modern Organonickel Chemistry*, Wiley-VCH, Weinheim, Germany, 2005, p. 327; (*f*) J. E. Dander and N. K. Garg, *ACS Catal.*, 2017, **7**, 1413;

(*g*) M. Tobisu and N. Chatani, *Acc. Chem. Res.*, 2015, **48**, 1717; (*h*) J. Cornella, C. Zarate and R. Martin, *Chem. Soc. Rev.*, 2014, **43**, 8081.

17 (*a*) M. Vellakkaran, K. Singh and D. Banerjee, *ACS Catal.*, 2017, **7**, 8152; (*b*) J. Das and D. Banerjee, *J. Org. Chem.*, 2018, **83**, 3378.

18 J. A. Joule and K. Mills, *Heterocyclic Chemistry*, Blackwell, Oxford, 4th edn, 2000.

19 Selected recent examples for pyridine synthesis: (*a*) S. Michlik and R. Kempe, *Angew. Chem., Int. Ed.*, 2013, **52**, 6326; (*b*) N. Deibl, K. Ament and R. Kempe, *J. Am. Chem. Soc.*, 2015, **137**, 12804; (*c*) T. Hille, T. Irrgang and R. Kempe, *Angew. Chem., Int. Ed.*, 2017, **56**, 371; (*d*) D. Srimani, Y. Ben-David and D. Milstein, *Chem. Commun.*, 2013, **49**, 6632; (*e*) S. Ruch, T. Irrgang and R. Kempe, *Chem. – Eur. J.*, 2014, **20**, 13279.

20 (*a*) C. C. Cho, B. T. Kim, T.-J. Kim and S. C. Shim, *Chem. Commun.*, 2001, 2576; (*b*) H. Vander Mierde, N. Ledoux, B. Allaert, P. Vander Voort, R. Drozdzak, D. De Vos and F. Verpoort, *New J. Chem.*, 2007, **31**, 1572; (*c*) R. Martinez, D. J. Ramon and M. Yus, *Eur. J. Org. Chem.*, 2007, 1599; (*d*) H. V. V. Mierde, P. V. Voort, D. De Vos and F. Verpoort, *Eur. J. Org. Chem.*, 2008, 1625; (*e*) B. Pan, B. Liu, E. Yue, Q. Liu, X. Yang, Z. Wang and W. H. Sun, *ACS Catal.*, 2016, **6**, 1247.

21 M. Mastalir, M. Glatz, E. Pittenauer, G. Allmaier and K. Kirchner, *J. Am. Chem. Soc.*, 2016, **138**, 15543.

22 D. G. Yakhvarov, E. H. Hawkins, R. M. Kagirov, Y. H. Budnikova, Y. S. Ganushevich and O. G. Sinyashin, *Russ. Chem. Bull. Int. Ed.*, 2007, **56**, 935.

23 S. Chakraborty, P. E. Piszel, W. W. Brennessel and W. D. Jones, *Organometallics*, 2015, **34**, 5203.

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Nickel-Catalyzed Synthesis of *N*-Substituted Pyrroles Using Diols with Aryl- and Alkylamines

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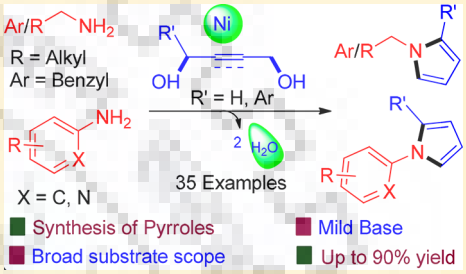
Supporting Information

ABSTRACT: Herein, nickel-catalyzed sustainable strategy for the synthesis of *N*-substituted pyrroles using butene-1,4-diols and butyne-1,4-diols with a series of aryl-, alkyl-, and heteroarylamines is reported. The catalytic protocol is tolerant of free alcohol, halide, alkyl, alkoxy, oxygen heterocycles, activated benzyl, and the pyridine moiety and resulted in up to 90% yield. Initial mechanistic studies involving defined nickel catalyst, determination of rate, and order of reaction including deuterium-labeling experiments were performed for pyrrole synthesis.

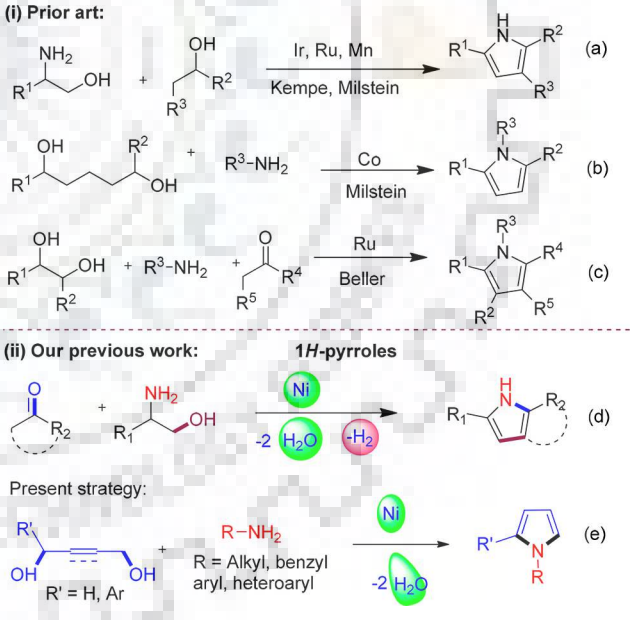


INTRODUCTION

The use of renewable resources to establish sustainable, atom-economic, and environmentally benign technology for the production of bulk and specialty chemicals is a challenging goal in chemical research.[1] In this direction, application of lignocellulose-derived inexpensive alcohols are a potential and attractive green alternative to the existing metal-catalyzed transformations.[2] Notably, such catalytic dehydrogenative transformations produced water as the sole byproduct and are in high demand in organic synthesis.[3] Therefore, such processes could be more attractive if selectively used for pyrrole synthesis in a tandem fashion in one-pot operations.[4]

Pyrroles are omnipresent in natural products, drugs, and functional materials and are used as intermediates in the synthesis of bioactive molecules and as ligands in catalysis.[4] Polypyrroles have been extensively used in material chemistry, batteries, and solar cells.[5] Classical methodologies such as Hantzsch, Knorr, and Paal−Knorr synthesis as well as other multistep transformations are known for pyrroles; unfortunately, harsh reaction conditions and special substrate designs including generation of stoichiometric waste are key limitations.[6] As a result, the recent goal has been to develop more vibrant and potential sustainable technologies that utilize abundantly available renewable resources and significantly extend the scope of existing methodologies,[1,2,7] although acceptorless dehydrogenation of alcohols has been widely used for pyrrole synthesis, often limited with noble metal catalysts, such as Ru and Ir complexes (Scheme 1, a).[8,9] For instance, Kempe and Milstein independently reported the intermolecular cyclization to pyrroles using secondary alcohol and amino alcohol with Ir and Ru catalysts. Similarly, an interesting contribution by Beller using Ru-catalyzed multicomponent transformations to substituted pyrroles involving ketones and vicinal diols in combination with amines is noteworthy (Scheme 1, c).[8b,c] Further, unsaturated diols, such as, *cis*-butene-1,4-diol or butyne-1,4-diol, were also used for construction of substituted pyrroles with suitable amines using Pd[8f] and Ru catalysts.[8g,i] However, most of these reported precious-metal-catalyzed protocols are often limited with poor selectivity of pyrroles using butyne-1,4-diols, and use of acids in the presence of phosphine ligands resulted other heterocycles.[8f,i]

Scheme 1. (i) Metal-Catalyzed Pyrrole Synthesis. (ii) Nickel-Catalyzed Sustainable Synthesis of Pyrroles



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Nevertheless, in terms of sustainability, application of renewable resources in combination with nonprecious earth-abundant and rare noble metal catalysts is equally important for such key catalytic conversions.[10,11] Therefore, development of new catalytic protocols using base metal catalysts, such as, Fe, Mn, Ni, Co, etc., is in demand. Toward this goal, several approaches were established for pyrrole synthesis using Co,[12] Mn,[13] and Fe catalysts (Scheme 1, a,b).[14,15] Notably, often these Mn- and Co-based metal complexes used diethylamine-core PNP ligands, pyridinyl-core PNP ligands, and PN^{3}P ligands as well as triazinyl-core PN^{5}P ligands for selective catalytic transformations.[12,13] The major concerns associated with these phosphine-based pincer ligands as well as Knölker-type Fe complexes are their highly expensive nature, required multistep synthesis, as well as storage and handling under standard laboratory environments.[14] Overall, in terms of cost efficiency, these ligand systems are quite expensive in comparison to the base-metal catalysts.

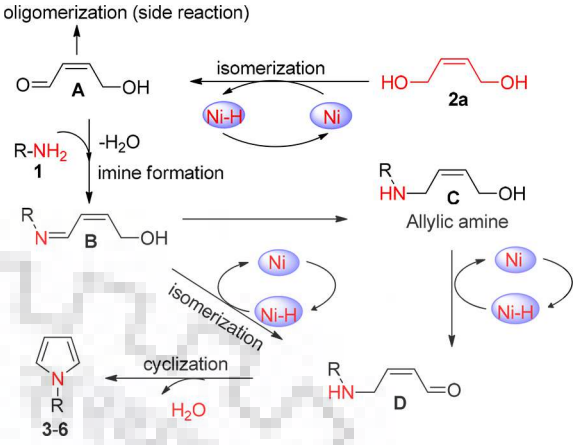
On the other hand, as part of our continuous efforts, we recently established the application of commercially available bench-stable ligands with nickel using renewable resources.[17] Overall, use of a phosphine-free catalytic system, inexpensive alcohols, and metal catalysts rendered these transformations sustainable. Herein, we demonstrated a general, operationally simple, and improved Ni-catalyzed protocol for construction of *N*-substituted pyrroles using unsaturated 1,4-diol with aryl-, alkyl-, and heteroarylamines in up to 90% yield (Scheme 1, e).[8f,i] Preliminary catalytic and mechanistic studies using deuterium-labeling experiments were performed to establish the elementary steps for pyrrole synthesis.[8f,i]

RESULTS AND DISCUSSION

In general, a free hydroxyl group in unprotected alcohol has very strong binding affinity with Ni catalyst and resists further transformations.[16] We envisioned that application of suitable Ni catalysts with specific nitrogen ligands could facilitate overcoming these long-standing problems. To our delight, we recently established an efficient and general Ni-catalyzed system for selective monoalkylation of amines and amides. Further, we realized the application of 2-(2-aminophenyl)-ethanol as well as β-amino alcohols, having free amines and hydroxyl groups, for intramolecular cyclization to indole, pyrroles, pyridine, and quinolines using Ni catalysts (Scheme 1, d).[17] Having witnessed these impressive results, we envisioned that *cis*-butene-1,4-diol could be used with primary amines for Ni-catalyzed pyrrole synthesis (Scheme 2).

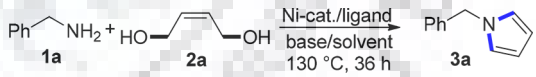
Previously, we observed that using a combination of β-amino alcohols with acetophenones resulted in base-catalyzed condensation to imine. Thereafter, in situ Ni-catalyzed dehydrogenation of alcohol followed by condensation resulted substituted pyrroles in a one-pot operation (Scheme 1d).[17c] On the other hand, based on a previous report,[14] we hypothesized that, initially, metal-catalyzed dehydrogenation or isomerization of *cis*-butene-1,4-diol **2a** followed by condensation with primary amine **1** resulted the formation of allylic amine intermediate **C** from intermediate **B**. Thereafter, nickel-catalyzed second isomerization of alcohol **C** to intermediate **D**, followed by intermolecular cyclization and dehydration, led to the construction of *N*-substituted pyrroles **3**–**6** in a one-pot operation (Scheme 2). Additionally, another possibility is that intermediate **B** could undergo metal-catalyzed isomerization to intermediate **D** followed by intermolecular cyclization to facilitate *N*-substituted pyrroles **3**–**6**. To the best of our knowledge, this represents the first report for Ni-catalyzed phosphine-free intermolecular cyclization of various *cis*-butene-1,4-diols and butyne-1,4-diols with a range of primary amines to substituted pyrroles in a tandem fashion.

Scheme 2. Postulated Ni-Catalyzed Intermolecular Cyclization to Pyrroles Based on ref 14



Optimization of the Catalytic Protocol for Ni-Catalyzed Synthesis of *N*-Substituted Pyrroles. To extend the possibilities for optimization of the efficient catalytic system, initially we investigated the efficacy of four different nickel precatalysts with bipyridine **L1** as our ligand of choice using benzylamine **1a** and *cis*-butene-1,4-diol **2a** (Table 1, entries 1–4, and Supporting Information Table S1). Using a combination $NiCl_2$/**L1** system, only 32% selectivity to pyrrole was obtained (Table 1, entry 2). Further, the use of two equivalent butene-1,4-diol **2a** significantly increased the product conversion to 75%, with 55% isolated yield of **3a** (Table 1, entry 5, and Supporting Information Table S2).

Table 1. Catalytic Screening for Ni-Catalyzed Synthesis of Pyrrole from 1a with 2a[a]



entry	catalyst	ligand	base	3a conv[b,c] (%)
1	$NiBr_2$	**L1**	*t*-BuOK	22
2	$NiCl_2$	**L1**	*t*-BuOK	32
3	$Ni(acac)_2$	**L1**	*t*-BuOK	5
4	$NiCl_2$.DME	**L1**	*t*-BuOK	18
5	$NiCl_2$	**L1**	*t*-BuOK	75 (55)
6	$NiCl_2$	**L1**	Na_2CO_3	92 (66)
7[d]	$NiCl_2$	**L1**	Na_2CO_3	62
8[e]	$NiCl_2$	**L1**	Na_2CO_3	55
9	$NiCl_2$	**L1**		9
10		**L1**	Na_2CO_3	13
11	$NiCl_2$		Na_2CO_3	35
12			Na_2CO_3	7

[a]Unless specified otherwise (entries 1–4), the reaction was carried out with benzylamine **1a** (0.5 mmol), *cis*-2-butene-1,4-diol **2a** (1.0 mmol), Ni cat. (0.05 mmol), **L1** (0.06 mmol), and *t*-BuOK (0.5 mmol) under an N_2 atmosphere at 130 °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]Entries 5–12: **2a** (2.0 mmol) was used. [d]120 °C was used. [e]110 °C was used.

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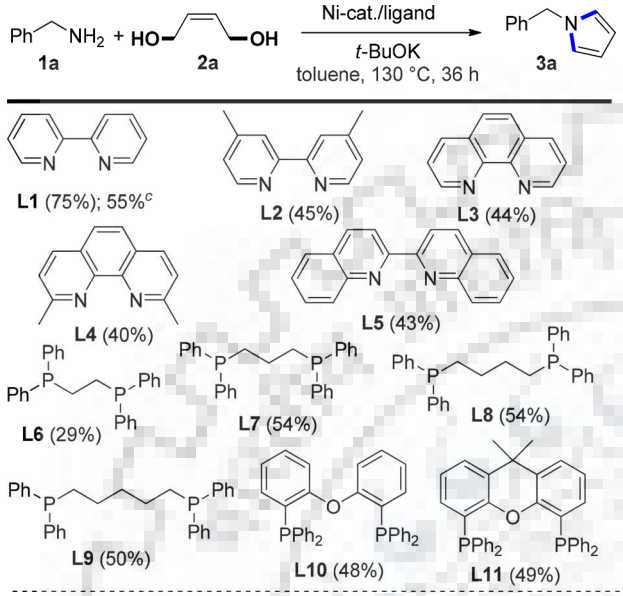
Next, application of a series of nitrogen and phosphorus ligands **L2**–**L11** with variable electronic and steric natures did not influence the product selectivity and resulted only 29–54% conversion to product (Table 2 and Supporting Information Table S3). However, when the reaction was performed using a milder base, such as Na_2CO_3, almost quantitative conversion to product **3a** was obtained (Table 1, entry 6, and Supporting Information Table S4). Thereafter, when toluene was replaced by different nonpolar and polar solvents, such as xylene, 1,4-dioxane, *N*,*N*-dimethylformamide, *N*-*N*-dimethylacetamide, and tetrahydrofuran as well as *tert*-amyl alcohol, moderate to poor product yields resulted (Supporting Information Table S5). Moreover, pyrrole synthesis could also be performed using a lower reaction temperature albeit with moderate product conversions (Table 1, entries 7 and 8, and Supporting Information Table S8).

Table 2. Ligand Screening for Ni-Catalyzed Pyrrole Synthesis[a,b]

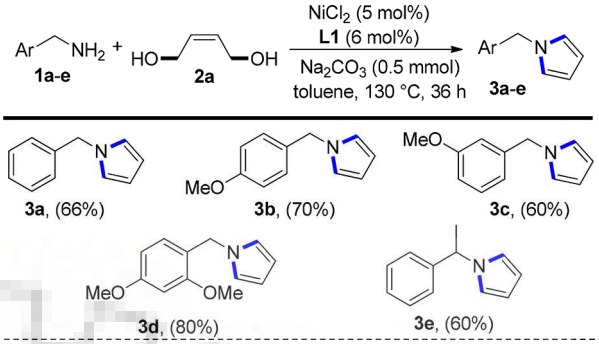


[a]Unless specified, the reaction was carried out with benzylamine **1a** (0.5 mmol), *cis*-2-butene-1,4-diol **2a** (1.0 mmol), $NiCl_2$ (5 mol %), ligand (6 mol %), and *t*-BuOK (0.5 mmol) under N_2 atmosphere at 130 °C in toluene (2.0 mL) for 36 h. [b]Conversion of **3a** was determined by GC–MS. [c]Isolated yield.

Further, control experiments revealed their potential role as individual catalytic components to achieve higher product conversions. For instance, in the absence of base, ligand, and catalyst only poor product conversions were observed (Table 1, entries 9–12, and Supporting Information Tables S1–S7). Notably, a combination of 5 mol % of $NiCl_2$, 6 mol % of bipyridine **L1**, 0.5 mmol of Na_2CO_3, and toluene, as the best solvent, led to a 66% isolated yield of **3a** (Table 1, entry 6).

With the optimized conditions in hand, we explored the scope and limitations of the catalytic protocol using electronically different benzylamines with *cis*-butene-1,4-diol (Table 3). *p*- and *m*-Methoxybenzylamines resulted in the desired pyrroles in 60–70% yields (**3b** and **3c**). However, when 2,4-dimethoxybenzylamine was used as coupling partner, an excellent yield of pyrrole was obtained (**3d**). To our delight, α-methylbenzylamine efficiently transformed into the desired pyrrole in 60% yield (Table 3, **3e**).

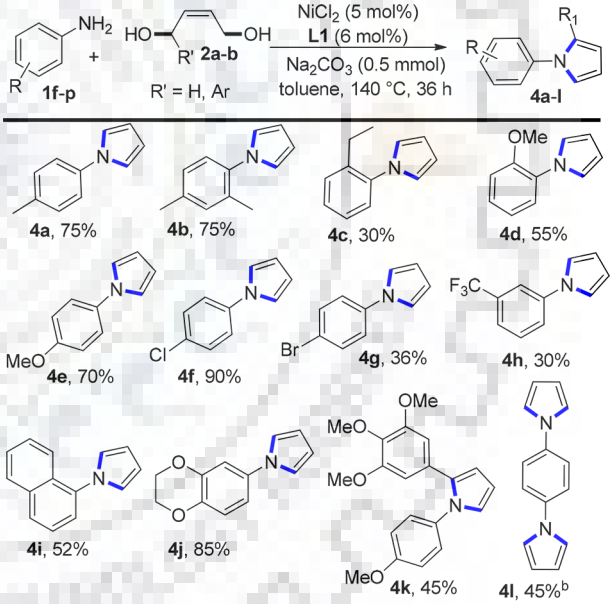
Table 3. Scope of Benzylamines[a]



[a]Reaction conditions: **1** (0.5 mmol), *cis*-2-butene-1,4-diol **2a** (2.0 mmol), $NiCl_2$ (0.025 mmol), **L1** (0.03 mmol), Na_2CO_3 (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 130 °C oil bath, 36 h reaction time. Isolated yield in parentheses.

Further, we studied the pyrrole synthesis using a series of electronically different anilines with *cis*-butene-1,4-diols. For instance, anilines substituted with methyl or methoxy groups afford a series of interesting pyrroles in up to 75% yields (Table 4, **4a**,**b**, and **4d**,**e**). Sterically hindered *o*-ethylaniline as well as *p*-bromo- and *m*-(trifluoromethyl)anilines resulted in only poor product yield (Table 4, **4c**,**g**,**h**). An excellent yield of pyrrole was obtained with *p*-chloroaniline (**4f**) and 1,4-dioxolone aniline (**4j**). Pleasingly, 1-naphthylaniline resulted in the corresponding pyrrole in moderate yield (**4i**). To our delight, C-2-substituted pyrrole was obtained when 3,4,5-trimethoxyphenyl-substituted *cis*-butene-1,4-diol was used as the coupling partner (**4k**).

Table 4. Scope of Anilines and Alcohols[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (2.0 mmol), $NiCl_2$ (0.025 mmol), **L1** (0.03 mmol), Na_2CO_3 (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 140 °C oil bath, 36 h reaction time. [b]**2a** (4.0 mmol), $NiCl_2$ (0.05 mmol), **L1** (0.06 mmol), Na_2CO_3 (1.0 mmol) was used. Isolated yield was reported.

Next, we studied the reactivity profile of more challenging acyclic and cyclic alkylamines with *cis*-butene-1,4-diol as

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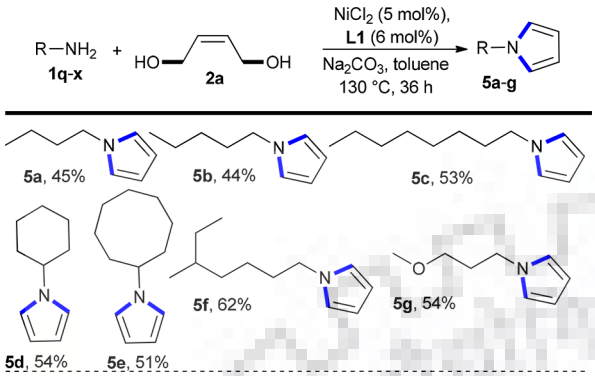
coupling partners for pyrrole synthesis (Table 5). Gratifyingly, alkylamines, such as, *n*-butyl-, *n*-pentyl-, *n*-octyl-, and 3-

Table 5. Synthesis of *N*-Alkylpyrroles[a]

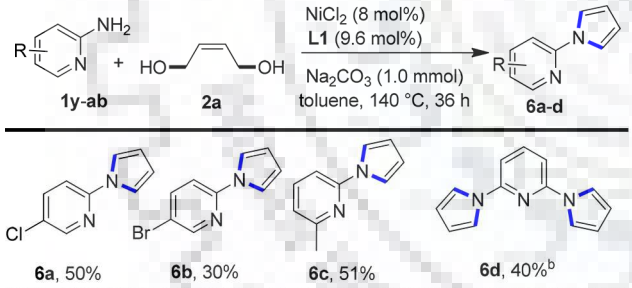


[a]Reaction conditions: **1** (0.5 mmol), *cis*-2-butene-1,4-diol **2a** (2.0 mmol), $NiCl_2$ (0.025 mmol), **L1** (0.03 mmo), Na_2CO_3 (0.5 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 130 °C oil bath, 36 h reaction time. Isolated yield was reported.

methylheptylamines as well as cyclohexyl- and cyclooctyl-amines resulted in up to 62% yield of *N*-alkylated pyrroles (**5a−f**). Additionally, methoxy-substituted γ-amino alcohol could be used efficiently for pyrrole synthesis and resulted in a 54% yield of **5g** (Table 5).

Again, more exciting 2-aminopyridines were employed for catalytic pyrrole synthesis using our optimized protocol (Table 6). In general, pyridines are often known to poison the

Table 6. Synthesis of Pyrroles from 2-Aminopyridines[a]

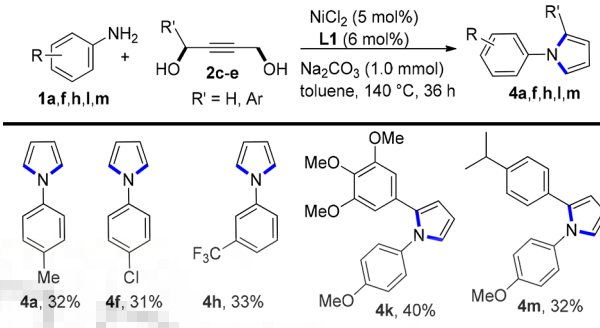


[a]Reaction conditions: **1** (0.5 mmol), *cis*-2-butene-1,4-diol **2a** (2.0 mmol), $NiCl_2$ (0.04 mmol), **L1** (0.048 mmol), Na_2CO_3 (1.0 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 140 °C oil bath, 36 h reaction time. Isolated yield was reported. [b]**2a** (4.0 mmol), $NiCl_2$ (0.05 mmol), **L1** (0.06 mmol), was used.

catalysts and, hence, diminish the reactivity.[12−14] Notably, we observed moderate to fair reactivity with chloro-, bromo-, as well as methyl-substituted 2-aminopyridines, which resulted in pharmaceutically active *N*-heterocyclic pyrrole derivatives (Table 6, **6a−c**). Additionally, we extended the catalytic protocol in the synthesis of symmetrical bis-pyrroles. Importantly, *cis*-butene-1,4-diol **2a** was utilized as a coupling partner with 1,4-diaminobenzene and 2,6-diaminopyridine. To our delight, the respective bis-pyrroles were obtained in reasonable yields (Table 4, **4l**, and Table 6, **6d**).

After having established the excellent catalytic activity with *cis*-butene-1,4-diols, the generality of our nickel-catalyzed protocol was further evaluated using butyne-1,4-diols as coupling partners for pyrrole synthesis (Table 7). For instance,

Table 7. Synthesis of Pyrroles from Butyne-1,4-diols[a]



[a]Reaction conditions: **1** (0.5 mmol), *cis*-2-butene-1,4-diol **2** (2.0 mmol), $NiCl_2$ (0.05 mmol), **L1** (0.03 mmol), Na_2CO_3 (1.0 mmol), toluene (2.0 mL), Schlenk tube under N_2 atmosphere, 140 °C oil bath, 36 h reaction time. Isolated yield was reported.

application of electronically different anilines with butyne-1,4-diols **2c−e** resulted respective pyrroles in moderate yields (Table 7). We are pleased to witness an alternative synthesis of pyrroles using nickel catalysts via intermolecular cyclization. Notably, the catalytic protocol is tolerant to primary alcohol, halides, alkylalkoxy, trifluoromethyl, and oxygen heterocycles, including benzyl and the pyridine derivatives. Gratifyingly, remarkable transformations in the presence of alkylamines and 2-aminopyridines show the synthetic potential of the catalytic system.

Further, to establish the reaction pathways for pyrrole synthesis and to understand the nature of the putative Ni intermediate species, **Cat. A** was radially prepared using the literature procedure.[18] Next, **Cat. A** was independently employed in catalytic (10 mol %) as well as in stoichiometric amounts (100 mol %) for intermolecular pyrrole synthesis in the reaction of **1a** with **2a** under standard conditions. To our delight, we observed 58% and 82% conversion of **3a** (Scheme 3a and Table 1, entry 6). Additionally, to confirm the participation of Ni-alkoxy species, we attempted the in situ preparation of Ni-alkoxy species of **Cat. A** (Supporting Information Scheme S1C). Initially, **2a** was allowed to react with **Cat. A** under reflux conditions for 24 h, and the solid residue was allowed to react with aniline **1j** under the standard conditions using toluene-d_8 at 140 °C. The reaction was interrupted after 12 h, and ^{1}H NMR analysis of the crude reaction mixture detected the formation of pyrrole **4e** (Supporting Information Scheme S1C). These experiments support for the involvement of the intermediate Ni-alkoxy species for pyrrole synthesis.

Next, to understand the involvement of the intermediate species **C** (Scheme 2), we used the model reaction of **1a** with **2a** under the standard conditions and monitored it using GC−MS analysis (Scheme 3b and Supporting Information Scheme S1A). Gratifyingly, we detected intermediate species **C** as well as pyrrole **3a** using GC−MS analysis. Further, a competitive experiment was performed using a 1:1 mixture of anilines **1j** and **1m** with alcohol **2a** under the standard catalytic conditions. We observed the formation of pyrroles **4e** and **4h** at a ratio of 3:1 (Scheme 3c). These experiments show that pyrrole formation occurred at higher rates for electron-rich aniline (Supporting Information Scheme S1B).

However, when we used **1a** with **2a-d2**(89% D) under optimized conditions, we did not observe any deuterium incorporation in pyrrole and detected **3a** in 10% yield using ^{1}H

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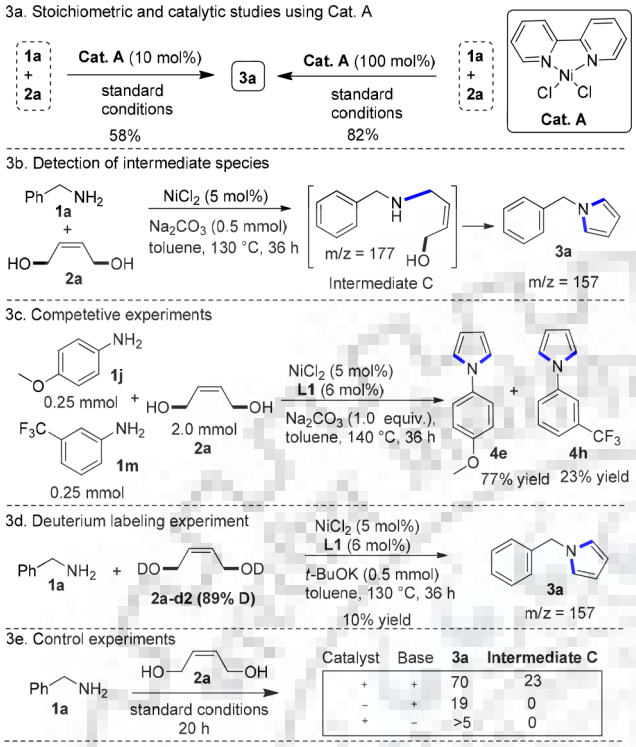
Scheme 3. Mechanistic Studies and Control Experiments for Pyrrole Synthesis



NMR and GC−MS analysis (Scheme 3d).[17,19] Additionally, control experiments in the absence of base and catalyst were performed and interrupted after 20 h. GC−MS analysis of the crude reaction mixture revealed their potential role as individual components to achieve higher catalytic selectivity of **3a** (Scheme 3e). Notably, we detected intermediate **C**, and these reactions showed the potential role of base and catalyst in the intermolecular cyclization involving C−C and C−N bond formation to pyrroles. Finally, we studied the rate and order of the pyrrole formation. To determine the rate laws, we performed kinetic studies using two sets of experiments using our model reaction of Table 1 (Supporting Information Scheme S2). Considering a steady-state approximation for *cis*-butene-1,4-diol **2a**, first-order kinetics with respect to **3a** was observed for pyrrole formation.

It is noteworthy to mention that, in general, using our standard catalytic conditions we observed good to excellent substrate conversions and selectivity using GC−MS analysis (Tables 3−7). However, in some cases, isolated yields of the desired pyrroles were quite lower. Indeed, there might be unwanted side reactions involving different active species not possible to detect using GC−MS analysis of the crude reaction mixtures. For instance, when *cis*-2-butene-1,4-diol **2a** and 2-butyne-1,4-diol **2c** were used independently under the standard conditions of Table 1, we did not detect any isomerized product using ^{1}H NMR. However, in the case of **2a**, the reaction mixture turned brown, and we observed unreacted diols, but in the case of **2c**, the entire reaction mixture turned into a black precipitate as reported in previous studies (Supporting Information Scheme S3).[14a]

CONCLUSIONS

In conclusion, for the first time, we established a straightforward and sustainable Ni-catalyzed dehydrogenative coupling for pyrrole synthesis using butene-1,4-diols and butyne-1,4-diols with a series of aryl-, alkyl-, and heteroarylamines. We demonstrated the broad substrate scopes with high selectivity to pyrroles including catalytic and mechanistic studies.[8f,i] The catalytic protocol is tolerant to amino alcohol derivatives, halides, alkyl, alkoxy, and oxygen heterocycles as well as activated benzyl and the pyridine moiety. Initial mechanistic studies using defined intermediate Ni species, competitive experiments between two electronically different anilines, deuterium-labeling experiments, as well as rate and order of reactions were crucial elementary steps for nickel-catalyzed pyrrole formations. Further studies regarding detailed mechanistic investigations will be addressed in future communications.

EXPERIMENTAL SECTION

General Experimental Details. All solvents and reagents were used as received from the suppliers. TLC was performed on Merck Kieselgel 60 F_{254} plates with a 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 500 MHz (Bruker), and ^{13}C NMR were recorded at 100 and 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 a Bruker high-resolution mass spectrometer. GC−MS were recorded using an Agilent GC mass spectrometer.

General Procedure for Ni-Catalyzed Synthesis of Pyrroles. In a 15 mL oven-dried Schlenk tube, amine (0.50 mmol), Na_2CO_3 (0.50 mmol), bipyridine **L1** (6 mol %), $NiCl_2$ (5 mol %), and diol (2.0 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 36 h in a closed system. Next, 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.

*1-Benzyl-1H-pyrrole (**3a**).*[14a] Following the general procedure, the title compound was isolated as a colorless oil using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 66%, 51 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27−7.17 (m, 3H), 7.06−7.01 (m, 2H), 6.62 (t, J = 2.1 Hz, 2H), 6.12 (t, J = 2.1 Hz, 2H), 4.99 (s, 2H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 138.1, 128.7, 127.6, 126.9, 121.1, 108.4, 53.3.

*1-(4-Methoxybenzyl)-1H-pyrrole (**3b**).*[20] Following the general procedure, the title compound was isolated as a colorless oil using silica gel column chromatography eluting with 2% ethyl acetate in hexane. Yield: 70%, 65 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.67 (t, J = 2.1 Hz, 2H), 6.19−6.14 (m, 2H), 5.00 (s, 2H), 3.79 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 159.1, 130.1, 128.5, 120.9, 114.1, 108.3, 55.3, 52.8.

*1-(3-Methoxybenzyl)-1H-pyrrole (**3c**).*[20] Following the general procedure, the title compound was isolated as a colorless oil using silica gel column chromatography eluting with 2% ethyl acetate in hexane. Yield: 60%, 56 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29−7.22 (m, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.72 (dd, J = 6.2, 4.2 Hz, 4H), 6.25−6.17 (m, 2H), 5.05 (s, 2H), 3.78 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$): δ 159.9, 139.8, 129.7, 121.1, 119.2, 112.9, 112.7, 108.5, 55.1, 53.2.

*1-(2,4-Dimethoxybenzyl)-1H-pyrrole (**3d**).*[21] Following the general procedure, the title compound was isolated as a colorless oil using silica gel column chromatography eluting with 3% ethyl acetate in hexane. Yield: 80%, 86 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (d, J = 8.3 Hz, 1H), 6.70 (t, J = 2.1 Hz, 2H), 6.44 (d, J = 2.4 Hz, 1H), 6.40 (dd, J = 8.3, 2.4 Hz, 1H), 6.14 (t, J = 2.1 Hz, 2H), 4.99 (s, 2H), 3.81

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(s, 3H), 3.77 (s, 3H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 160.6, 157.8, 129.4, 121.0, 119.2, 107.9, 104.2, 98.5, 55.4, 55.4, 47.8.

1-(1-Phenylethyl)-1H-pyrrole (**3e**).[22] Following the general procedure, the title compound was isolated as a colorless oil using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 60%, 51 mg. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.28 (m, 2H), 7.27−7.24 (m, 1H), 7.09 (dd, *J* = 7.8, 1.0 Hz, 2H), 6.76 (t, *J* = 2.1 Hz, 2H), 6.19 (t, *J* = 2.1 Hz, 2H), 5.28 (q, *J* = 7.1 Hz, 1H), 1.83 (d, *J* = 7.1 Hz, 3H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 143.6, 128.6, 127.4, 125.9, 119.5, 108.0, 58.1, 22.1.

1-(p-Tolyl)-1H-pyrrole (**4a**).[19] Following the general procedure, the title compound was isolated as a white solid using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 75%, 58 mg. ^1H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, *J* = 7.4 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.09 (s, 2H), 6.37 (s, 2H), 2.41 (s, 3H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 138.5, 135.3, 130.0, 120.5, 119.4, 110.0, 20.8.

1-(2,4-Dimethylphenyl)-1H-pyrrole (**4b**).[23] Following the general procedure, the title compound was isolated as a white solid using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 75%, 64 mg. ^1H NMR (400 MHz, $CDCl_3$): δ 7.16−7.08 (m, 2H), 7.05 (d, *J* = 7.9 Hz, 1H), 6.76 (dd, *J* = 2.5, 1.6 Hz, 2H), 6.30 (dd, *J* = 2.5, 1.6 Hz, 2H), 2.36 (s, 3H), 2.16 (s, 3H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 138.2, 137.3, 133.6, 131.6, 127.1, 126.5, 122.1, 108.5, 20.9, 17.6.

1-(2-Ethylphenyl)-1H-pyrrole (**4c**).[24] Following the general procedure, the title compound was isolated as a white solid using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 30%, 25 mg. ^1H NMR (500 MHz, $CDCl_3$): δ 7.36 (m, 2H), 7.28 (d, *J* = 5.1 Hz, 2H), 6.78 (s, 2H), 6.31 (s, 2H), 2.51 (q, *J* = 7.4 Hz, 2H), 1.10 (t, *J* = 7.3 Hz, 3H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 140.2, 140.1, 129.3, 127.9, 127.1, 126.4, 122.4, 108.6, 24.1, 15.1.

1-(2-Methoxyphenyl)-1H-pyrrole (**4d**).[25] Following the general procedure, the title compound was isolated as a white solid using silica gel column chromatography eluting with 2% ethyl acetate in hexane. Yield: 55%, 47 mg. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22−7.16 (m, 2H), 6.96−6.87 (m, 4H), 6.23 (dd, *J* = 2.5, 1.7 Hz, 2H), 3.74 (s, 3H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 152.7, 130.2, 127.4, 125.7, 122.0, 120.9, 112.3, 108.7, 55.7.

1-(4-Methoxyphenyl)-1H-pyrrole (**4e**).[19] Following the general procedure, the title compound was isolated as a white solid using silica gel column chromatography eluting with 2% ethyl acetate in hexane. Yield: 70%, 60 mg. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34−7.30 (m, 2H), 7.02 (td, *J* = 2.3, 0.7 Hz, 2H), 6.98−6.93 (m, 2H), 6.34 (td, *J* = 2.2, 0.7 Hz, 2H), 3.84 (s, 3H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 157.6, 134.5, 122.1, 119.6, 114.6, 109.8, 55.5.

1-(4-Chlorophenyl)-1H-pyrrole (**4f**).[19] Following the general procedure, the title compound was isolated as a white solid using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 90%, 79 mg. ^1H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.08−7.04 (m, 2H), 6.35 (m, 2H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 139.3, 131.1, 129.6, 121.6, 119.3, 110.8.

1-(4-Bromophenyl)-1H-pyrrole (**4g**).[19] Following the general procedure, the title compound was isolated as a white solid using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 36%, 39 mg. ^1H NMR (500 MHz, $CDCl_3$): δ 7.56−7.52 (m, 2H), 7.28 (d, *J* = 2.1 Hz, 2H), 7.07−7.04 (m, 2H), 6.37−6.35 (m, 2H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 139.8, 132.6, 121.9, 119.2, 118.7, 110.9.

1-(3-(Trifluoromethyl)phenyl)-1H-pyrrole (**4h**).[26] Following the general procedure, the title compound was isolated as a white solid using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 30%, 31 mg. ^1H NMR (500 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.53−7.38 (m, 3H), 7.11 (t, *J* = 2.1 Hz, 2H), 6.38 (t, *J* = 2.2 Hz, 2H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 141.1, 132.1 (d, J_{F-C} = 30 Hz), 130.2, 123.7 (d, J_{F-C} = 270 Hz), 123.4, 122.1 (q, J_{F-C} = 3.0 Hz), 119.2, 117.2 (q, J_{F-C} = 3.9 Hz), 111.3.

1-(Naphthalene-1-yl)-1H-pyrrole (**4i**).[27] Following the general procedure, the title compound was isolated as a white solid using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 52%, 50 mg. ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 18.2, 7.9 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.54−7.43 (m, 4H), 6.99 (t, *J* = 2.1 Hz, 2H), 6.41 (t, *J* = 2.1 Hz, 2H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 138.2, 134.2, 129.9, 128.1, 127.8, 126.9, 126.5, 125.3, 123.2, 123.2, 109.0.

1-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-1H-pyrrole (**4j**).[28] Following the general procedure, the title compound was isolated as a white solid using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 85%, 85 mg. ^1H NMR (400 MHz, $CDCl_3$): δ 6.99 (t, *J* = 2.2 Hz, 2H), 6.92 (d, *J* = 2.6 Hz, 1H), 6.89−6.85 (m, 2H), 6.31 (t, *J* = 2.2 Hz, 2H), 4.31−4.26 (m, 4H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 143.9, 141.6, 135.0, 119.6, 117.7, 113.8, 110.1, 109.9, 64.5, 64.2.

1-(4-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-1H-pyrrole (**4k**).[29] Following the general procedure, the title compound was isolated as a white solid using silica gel column chromatography eluting with 3% ethyl acetate in hexane. Yield: 45%, 76 mg. ^1H NMR (400 MHz, $CDCl_3$): δ 7.13−7.09 (m, 2H), 6.88−6.83 (m, 3H), 6.40 (dd, *J* = 3.6, 1.8 Hz, 1H), 6.33−6.31 (m, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.62 (s, 6H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 158.4, 152.8, 152.4, 136.6, 134.0, 133.8, 132.2, 128.6, 114.1, 105.6, 105.6, 103.4, 63.6, 56.0, 55.9, 55.8.

1,4-Di(1H-pyrrol-1-yl)benzene (**4l**).[30] Following the general procedure, the title compound was isolated as a white solid using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 45%, 46 mg. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37−7.18 (m, 4H), 7.02−7.01 (m, 4H), 6.38−6.35 (m, 4H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 138.4, 121.5, 119.3, 115.0, 110.6.

2-(4-Isopropylphenyl)-1-(4-methoxyphenyl)-1H-pyrrole (**4m**).[31] Following the general procedure, the title compound was isolated as a white solid using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 32%, 46 mg. ^1H NMR (400 MHz, $CDCl_3$): δ 7.14−7.08 (m, 2H), 7.06 (s, 4H), 6.88−6.81 (m, 3H), 6.39 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.35−6.30 (m, 1H), 3.82 (s, 3H), 2.85 (hept, *J* = 6.9 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 6H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.1, 146.7, 134.0, 133.9, 130.4, 128.1, 127.0, 126.1, 124.2, 114.0, 109.7, 108.7, 55.4, 33.6, 23.9.

1-Butyl-1H-pyrrole (**5a**).[32] Following the general procedure, the title compound was isolated as a colorless oil using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 45%, 27 mg. ^1H NMR (400 MHz, $CDCl_3$): δ 6.57 (t, *J* = 1.7 Hz, 2H), 6.06 (t, *J* = 1.7 Hz, 2H), 3.80 (t, *J* = 7.2 Hz, 2H), 1.67 (dt, *J* = 14.9, 7.4 Hz, 2H), 1.26−1.20 (m, 2H), 0.86 (dt, *J* = 7.4, 3.7 Hz, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$): δ 120.5, 107.7, 49.3, 33.6, 19.9, 13.6.

1-Pentyl-1H-pyrrole (**5b**).[33] Following the general procedure, the title compound was isolated as a colorless oil using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 44%, 30 mg. ^1H NMR (400 MHz, $CDCl_3$): δ 6.57 (s, 2H), 6.06 (s, 2H), 3.78 (t, *J* = 7.2 Hz, 2H), 1.69 (dt, *J* = 14.7, 7.3 Hz, 2H), 1.29−1.17 (m, 4H), 0.82 (dd, *J* = 8.2, 6.0 Hz, 3H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 120.4, 107.7, 49.6, 31.2, 28.9, 22.2, 13.9.

1-Heptyl-1H-pyrrole (**5c**).[34] Following the general procedure, the title compound was isolated as a colorless oil using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 53%, 43 mg. ^1H NMR (400 MHz, $CDCl_3$): δ 6.64 (t, *J* = 2.1 Hz, 2H), 6.12 (t, *J* = 2.1 Hz, 2H), 3.87−3.83 (m, 2H), 1.79−1.71 (m, 2H), 1.30−1.25 (m, 8H), 0.89−0.85 (m, 3H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 120.4, 107.7, 49.6, 31.7, 31.6, 28.9, 26.7, 22.6, 14.0.

1-Cyclohexyl-1H-pyrrole (**5d**).[19] Following the general procedure, the title compound was isolated as a colorless oil using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 54%, 40 mg. ^1H NMR (400 MHz, $CDCl_3$): δ 6.73 (t, *J* = 2.1 Hz, 2H), 6.13 (t, *J* = 2.1 Hz, 2H), 3.84−3.76 (m, 1H), 2.10 (dd, *J* = 13.2, 1.9 Hz, 2H), 1.92−1.83 (m, 2H), 1.76−1.68 (m, 1H), 1.62 (ddd, *J* = 24.6, 12.4, 3.2 Hz, 2H), 1.45−1.33 (m, 2H), 1.28−1.19 (m, 1H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 118.4, 107.3, 58.6, 34.7, 25.7, 25.5.

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*1-Cyclooctyl-1H-pyrrole (**5e**).* Following the general procedure, the title compound was isolated as a colorless oil using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 51%, 45 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (dd, J = 3.8, 1.9 Hz, 2H), 6.16 (dd, J = 3.9, 1.9 Hz, 2H), 4.12 (dq, J = 13.4, 4.4 Hz, 1H), 2.03 (dt, J = 12.0, 6.3 Hz, 4H), 1.82 (dd, J = 6.0, 2.1 Hz, 2H), 1.72−1.53 (m, 8H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ 118.6, 107.3, 59.9, 34.4, 26.9, 25.8, 24.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{19}N$178.1517, found 178.1585.

*1-(5-Methylheptyl)-1H-pyrrole (**5f**).* Following the general procedure, the title compound was isolated as a colorless oil using silica gel column chromatography eluting with 1% ethyl acetate in hexane. Yield: 62%, 55 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (t, J = 2.1 Hz, 2H), 6.12 (t, J = 2.0 Hz, 2H), 3.76 (dd, J = 7.0, 3.7 Hz, 2H), 1.69 (dt, J = 12.4, 6.3 Hz, 1H), 1.31−1.22 (m, 8H), 0.88 (td, J = 6.9, 3.7 Hz, 6H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ 121.0, 107.6, 53.2, 41.3, 30.6, 28.6, 23.8, 23.0, 14.0, 10.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{21}N$180.1674, found 180.1739.

*1-(3-Methoxypropyl)-1H-pyrrole (**5g**).*[35] Following the general procedure, the title compound was isolated as a colorless oil using silica gel column chromatography eluting with 2% ethyl acetate in hexane. Yield: 54%, 37 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65−6.62 (t, J = 3.1 Hz, 2H), 6.14−6.11 (t, J = 3.2 Hz,2H), 3.99 (td, J = 6.9, 1.7 Hz, 2H), 3.34−3.28 (m, 5H), 2.04−1.93 (m, 2H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ 120.7, 107.9, 69.1, 58.7, 46.2, 31.6.

*5-Chloro-2-(1H-pyrrol-1-yl)pyridine (**6a**).*[36] Following the general procedure, the title compound was isolated as a colorless oil using silica gel column chromatography eluting with 3% ethyl acetate in hexane. Yield: 50%, 44 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (dd, J = 2.7, 0.8 Hz, 1H), 7.78−7.63 (m, 1H), 7.45 (dd, J = 3.3, 1.5 Hz, 2H), 7.28−7.22 (m, 1H), 6.35 (dd, J = 3.3, 1.5 Hz, 2H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ 149.6, 147.3, 138.2, 127.6, 118.1, 112.0, 111.7.

*5-Bromo-2-(1H-pyrrol-1-yl)pyridine (**6b**).*[37] Following the general procedure, the title compound was isolated as a colorless oil using silica gel column chromatography eluting with 3% ethyl acetate in hexane. Yield: 30%, 26 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, J = 2.4 Hz, 1H), 7.82 (dd, J = 8.8, 2.4 Hz, 1H), 7.45 (t, J = 2.3 Hz, 2H), 7.20 (s, 1H), 6.37−6.34 (m, 2H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ 149.6, 140.9, 118.1, 115.6, 115.0, 112.5, 111.8.

*2-Methyl-6-(1H-pyrrol-1-yl)pyridine (**6c**).*[38] Following the general procedure, the title compound was isolated as a colorless solid using silica gel column chromatography eluting with 3% ethyl acetate in hexane. Yield: 51%, 40 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64−7.57 (m, 1H), 7.52−7.49 (m, 2H), 7.10 (d, J = 8.2 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.36−6.31 (m, 2H), 2.53 (s, 3H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ 158.0, 150.8, 138.5, 119.5, 118.1, 111.0, 108.2, 24.3.

*2,6-Di(1H-pyrrol-1-yl)pyridine (**6d**).* Following the general procedure, the title compound was isolated as a white solid using silica gel column chromatography eluting with 3% ethyl acetate in hexane. Yield: 40%, 41 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (t, J = 8.0 Hz, 1H), 7.51−7.48 (m, 4H), 7.03 (d, J = 8.0 Hz, 2H), 6.31 (dd, J = 5.0, 2.8 Hz, 4H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ 150.4, 140.8, 118.2, 115.0, 111.5, 106.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{11}N_3$210.0953, found 210.1021.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02666.

^{1}H and ^{13}C NMR and HRMS spectra, screening of the reaction conditions, and mechanistic studies (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Tuck, C. O.; Pérez, E.; Horváth, I. T.; Sheldon, R. A.; Poliakoff, M. Valorization of Biomass: Deriving More Value from Waste. *Science* **2012**, *337*, 695−699.

(2) (a) Barta, K.; Ford, P. C. Catalytic Conversion of Nonfood Woody Biomass Solids to Organic Liquids. *Acc. Chem. Res.* **2014**, *47*, 1503−1512. (b) Vispute, T. P.; Zhang, H.; Sanna, A.; Xiao, R.; Huber, G. W. Renewable Chemical Commodity Feedstocks from Integrated Catalytic Processing of pyrrolysis Oils. *Science* **2010**, *330*, 1222−1227.

(3) For selected reviews, see: (a) Guillena, G.; Ramon, D. J.; Yus, M. Hydrogen Autotransfer in the *N*-Alkylation of Amines and Related Compounds using Alcohols and Amines as Electrophiles. *Chem. Rev.* **2010**, *110*, 1611−1641. (b) Bower, J. F.; Krische, M. J. Formation of C-C Bonds via Iridium-Catalyzed Hydrogenation and Transfer Hydrogenation. *Top. Organomet. Chem.* **2011**, *34*, 107−138. (c) Watson, A. J.A.; Williams, J. M. J. The Give and Take of Alcohol Activation. *Science* **2010**, *329*, 635−636. (d) Bähn, S.; Imm, S.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. The Catalytic Amination of Alcohols. *ChemCatChem* **2011**, *3*, 1853−1864. (e) Dobereiner, G. E.; Crabtree, R. H. Dehydrogenation as a Substrate-Activating Strategy in Homogeneous Transition-Metal Catalysis. *Chem. Rev.* **2010**, *110*, 681−703. (f) Gunanathan, C.; Milstein, D. Applications of Acceptorless Dehydrogenation and Related Transformations in Chemical Synthesis. *Science* **2013**, *341*, 1229712. For selected examples, see: (g) Bower, J. F.; Skucas, E.; Patman, R. L.; Krische, M. J. Catalytic C−C Coupling via Transfer Hydrogenation: Reverse Prenylation, Crotylation, and Allylation from the Alcohol or Aldehyde Oxidation Level. *J. Am. Chem. Soc.* **2007**, *129*, 15134−15135. (h) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. Catalytic Enantioselective C-H Functionalization of Alcohols by Redox-Triggered Carbonyl Addition: Borrowing Hydrogen, Returning Carbon. *Angew. Chem., Int. Ed.* **2014**, *53*, 9142−9150.

(4) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Wiley: Chichester, 2010.

(5) (a) Hagfeldt, K. A.; Boschloo, G.; Sun, L.; Kloo, L.; Pettersson, H. Dye-Sensitized Solar Cells. *Chem. Rev.* **2010**, *110*, 6595−6663. (b) Nishide, H.; Oyaizu, K. Toward Flexible Batteries. *Science* **2008**, *319*, 737−738.

(6) (a) Knorr, L. Synthese von Pyrrolderivaten. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1635−1642. (b) Paal, C. Synthese von Thiophen-und Pyrrolderivaten. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367−371. (c) Hantzsch, A. Neue Bildungsweise von Pyrrolderivaten. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474−1483. (d) Rakshit, S.; Patureau, F. W.; Glorius, F. Pyrrole Synthesis via Allylic sp^3 C−H Activation of Enamines Followed by Intermolecular Coupling with Unactivated Alkynes. *J. Am. Chem. Soc.* **2010**, *132*, 9585−9587. (e) Chen, Z.; Lu, B.; Ding, Z.; Gao, K.; Yoshikai, N. α-Palladation of Imines as Entry to Dehydrogenative Heck Reaction: Aerobic Oxidative Cyclization of *N*-Allylimines to Pyrroles. *Org. Lett.* **2013**, *15*, 1966−1969.

(7) Chelucci, G. Metal-Catalyzed Dehydrogenative Synthesis of Pyrroles and Indoles from Alcohols. *Coord. Chem. Rev.* **2017**, *331*, 37−53.

(8) Selected recent examples with Ru and Pd catalysts: (a) Srimani, D.; Ben-David, Y.; Milstein, D. Direct Synthesis of Pyrroles by Dehydrogenative Coupling of β-Aminoalcohols with Secondary

Alcohols Catalyzed by Ruthenium Pincer Complexes. *Angew. Chem., Int. Ed.* **2013**, *52*, 4012−4015. (b) Zhang, M.; Neumann, H.; Beller, M. Selective Ruthenium-Catalyzed Three-Component Synthesis of Pyrroles. *Angew. Chem., Int. Ed.* **2013**, *52*, 597−601. (c) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. General and Regioselective Synthesis of Pyrroles via Ruthenium-Catalyzed Multicomponent Reactions. *J. Am. Chem. Soc.* **2013**, *135*, 11384−11388. (d) Schley, N. D.; Dobereiner, G. E.; Crabtree, R. H. Oxidative Synthesis of Amides and Pyrroles via Dehydrogenative Alcohol Oxidation by Ruthenium Diphosphine Diamine Complexes. *Organometallics* **2011**, *30*, 4174−4179. (e) Iida, K.; Miura, T.; Ando, J.; Saito, S. The Dual Role of Ruthenium and Alkali Base Catalysts in Enabling a Conceptually New Shortcut to *N*-Unsubstituted Pyrroles through Unmasked α-Amino Aldehydes. *Org. Lett.* **2013**, *15*, 1436−1439. (f) Murahashi, S.-I.; Shimamura, T.; Moritani, I. Conversion of Alcohols into Unsymmetrical Secondary or Tertiary Amines by a Palladium Catalyst. Synthesis of *N*-substituted Pyrroles. *J. Chem. Soc., Chem. Commun.* **1974**, 931−932. (g) Tsuji, Y.; Yokoyama, Y.; Huh, K.-T.; Watanabe, Y. Ruthenium in Organic Synthesis. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3456−3458. (h) Pridmore, S. J.; Slatford, P. A.; Daniel, A.; Whittlesey, M. K.; Williams, J. M. J. Ruthenium-Catalysed Conversion of 1,4-Alkynediols into Pyrroles. *Tetrahedron Lett.* **2007**, *48*, 5115−5120. (i) Pridmore, S. J.; Slatford, P. A.; Taylor, J. E.; Whittlesey, M. K.; Williams, J. M. J. Synthesis of Furans, Pyrroles and Pyridazines by a Ruthenium-Catalysed Isomerisation of Alkynediols and in situ Cyclisation. *Tetrahedron* **2009**, *65*, 8981−8986.

(9) Selected recent examples with Ir catalysts: (a) Michlik, S.; Kempe, R. A Sustainable Catalytic Pyrrole Synthesis. *Nat. Chem.* **2013**, *5*, 140−144. (b) Forberg, D.; Obenauf, J.; Friedrich, M.; Huhne, S. M.; Mader, W.; Motz, G.; Kempe, R. The Synthesis of Pyrroles via Acceptorless Dehydrogenative Condensation of Secondary Alcohols and 1,2-Amino Alcohols Mediated by a Robust and Reusable Catalyst Based on Nanometer-Sized Iridium Particles. *Catal. Sci. Technol.* **2014**, *4*, 4188−4192. For a recent example with Pt catalyst, see: (c) Siddiki, S. M. A. H.; Touchy, A. S.; Chaudhari, C.; Kon, K.; Toyao, T.; Shimizu, K. Synthesis of 2,5-Disubstituted Pyrroles via Dehydrogenative Condensation of Secondary Alcohols and 1,2-Amino Alcohols by Supported Platinum Catalysts. *Org. Chem. Front.* **2016**, *3*, 846−851.

(10) (a) Bullock, R. M. *Catalysis without Precious Metals*; Wiley-VCH, Weinheim, 2010. (b) Albrecht, M.; Bedford, R.; Plietker, B. Catalytic and Organometallic Chemistry of Earth-Abundant Metals. *Organometallics* **2014**, *33*, 5619−5621. (c) Bauer, I.; Knölker, H.-J. Iron Catalysis in Organic Synthesis. *Chem. Rev.* **2015**, *115*, 3170−3387. (d) Su, B.; Cao, Z.-C.; Shi, Z.-J. Exploration of Earth-Abundant Transition Metals (Fe, Co, and Ni) as Catalysts in Unreactive Chemical Bond Activations. *Acc. Chem. Res.* **2015**, *48*, 886−896. (e) Robinson, S. J.C.; Heinekey, D. M. Hydride & Dihydrogen Complexes of Earth Abundant Metals: Structure, Reactivity, and Applications to Catalysis. *Chem. Commun.* **2017**, *53*, 669−676.

(11) For selected recent examples, see: (a) Rosler, S.; Ertl, M.; Irrgang, T.; Kempe, R. Cobalt-Catalyzed Alkylation of Aromatic Amines by Alcohols. *Angew. Chem., Int. Ed.* **2015**, *54*, 15046−15050. (b) Elangovan, S.; Neumann, J.; Sortais, J.-B.; Junge, K.; Darcel, C.; Beller, M. Efficient and Selective *N*-Alkylation of Amines with Alcohols Catalysed by Manganese Pincer Complexes. *Nat. Commun.* **2016**, *7*, 12641−12648. (c) Mukherjee, A.; Nerush, A.; Leitus, G.; Shimon, L. J.W.; David, Y. B.; Jalapa, N. A.E.; Milstein, D. Manganese-Catalyzed Environmentally Benign Dehydrogenative Coupling of Alcohols and Amines to Form Aldimines and H_2A Catalytic and Mechanistic Study. *J. Am. Chem. Soc.* **2016**, *138*, 4298−4301. (d) Mastalir, M.; Tomsu, G.; Pittenauer, E.; Allmaier, G.; Kirchner, K. Co(II) PCP Pincer Complexes as Catalysts for the Alkylation of Aromatic Amines with Primary Alcohols. *Org. Lett.* **2016**, *18*, 3462−3465. (e) Yan, T.; Feringa, B. L.; Barta, K. Iron Catalysed Direct Alkylation of Amines with Alcohols. *Nat. Commun.* **2014**, *5*, 5602−5608. (f) Yan, T.; Feringa, B. L.; Barta, K. Benzylamines via Iron-Catalyzed Direct Amination of Benzyl Alcohols. *ACS Catal.* **2016**, *6*, 381−388.

(12) For Co-catalyzed pyrrole synthesis, see: (a) Daw, P.; Chakraborty, S.; Garg, J. A.; Ben-David, Y.; Milstein, D. Direct Synthesis of Pyrroles by Dehydrogenative Coupling of Diols and Amines Catalyzed by Cobalt Pincer Complexes. *Angew. Chem., Int. Ed.* **2016**, *55*, 14373−14377; Direct Synthesis of Pyrroles by Dehydrogenative Coupling of Diols and Amines Catalyzed by Cobalt Pincer Complexes. *Angew. Chem.* **2016**, *128*, 14585−14589. (b) Midya, S. P.; Landge, V. G.; Sahoo, M. K.; Rana, J.; Balaraman, E. Cobalt-Catalyzed Acceptorless Dehydrogenative Coupling of Amino Alcohols with Alcohols: direct Access to Pyrrole, Pyridine and Pyrazine Derivatives. *Chem. Commun.* **2018**, *54*, 90−93.

(13) For Mn-catalyzed reactions, see: Kallmeier, F.; Dudziec, B.; Irrgang, T.; Kempe, R. Manganese-Catalyzed Sustainable Synthesis of Pyrroles from Alcohols and Amino Alcohols. *Angew. Chem., Int. Ed.* **2017**, *56*, 7261−7265.

(14) For Fe-catalyzed reactions, see: (a) Yan, T.; Barta, K. Sustainable Pathways to Pyrroles through Iron-Catalyzed *N*-Heterocyclization from Unsaturated Diols and Primary Amines. *ChemSusChem* **2016**, *9*, 2321−2325. (b) Emayavaramban, B.; Sen, M.; Sundararaju, B. Iron-Catalyzed Sustainable Synthesis of Pyrrole. *Org. Lett.* **2017**, *19*, 6−9.

(15) (a) Chen, F.; Shen, T.; Cui, Y.; Jiao, N. 2,4- vs 3,4-Disubsituted Pyrrole Synthesis Switched by Copper and Nickel Catalysts. *Org. Lett.* **2012**, *14*, 4926−4929. (b) Miura, T.; Hiraga, K.; Biyajima, T.; Nakamuro, T.; Murakami, M. Regiocontrolled Synthesis of Polysubstituted Pyrroles Starting from Terminal Alkynes, Sulfonyl Azides, and Allenes. *Org. Lett.* **2013**, *15*, 3298−3301. (c) Thompson, B. B.; Montgomery, J. Enone−Alkyne Reductive Coupling: A Versatile Entry to Substituted Pyrroles. *Org. Lett.* **2011**, *13*, 3289−3291.

(16) For selected Ni-catalyzed reviews, see: (a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. Recent Advances in Homogeneous Nickel Catalysis. *Nature* **2014**, *509*, 299−309. (b) Ananikov, V. P. Nickel: The "Spirited Horse" of Transition Metal Catalysis. *ACS Catal.* **2015**, *5*, 1964−1971. (c) Jolly, P. W.; Wilke, G. *The Organic Chemistry of Nickel*; Academic Press: New York, 1974. (d) Wilke, G. Contributions to Organo Nickel Chemistry. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 185−206. (e) Tamaru, Y. *Modern Organonickel Chemistry*; Wiley-VCH: Weinheim, 2005; p 327. (f) Dander, J. E.; Garg, N. K. Breaking Amides using Nickel Catalysis. *ACS Catal.* **2017**, *7*, 1413−1423. (g) Tobisu, M.; Chatani, N. Cross-Couplings Using Aryl Ethers via C−O Bond Activation Enabled by Nickel Catalysts. *Acc. Chem. Res.* **2015**, *48*, 1717−1726.

(17) (a) Vellakkaran, M.; Singh, K.; Banerjee, D. An Efficient and Selective Nickel-Catalyzed Direct *N*-Alkylation of Anilines with Alcohols. *ACS Catal.* **2017**, *7*, 8152−8158. (b) Das, J.; Banerjee, D. Nickel-Catalyzed Phosphine Free Direct *N*-Alkylation of Amides with Alcohols. *J. Org. Chem.* **2018**, *83*, 3378−3384. (c) Singh, K.; Vellakkaran, M.; Banerjee, D. A Nitrogen-Ligated Nickel-Catalyst Enables Selective Intermolecular Cyclisation of β- and γ-Amino Alcohols with Ketones: Access to Five and Six-Membered *N*-Heterocycles. *Green Chem.* **2018**, *20*, 2250−2256. (d) 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.

(18) Yakhvarov, D. G.; Hey-Hawkins, E.; Kagirov, R. M.; Budnikova, Y. H.; Ganushevich, Y. S.; Sinyashin, O. G. Electrocatalytic Reduction of Aryldichlorophosphines with the (2,2'-bipyridine) Nickel Complexes. *Russ. Chem. Bull.* **2007**, *56*, 935−942.

(19) Vellakkaran, M.; Das, J.; Banerjee, D. Nickel-Catalysed Alkylation of $C(sp^3)$-H Bond with Alcohols: Direct Access to Functionalised N-Heteroaromatics. *Chem. Commun.* **2018**, *54*, 12369−12372.

(20) Molander, G. A.; Ryu, D.; Sarvari, M. H.; Devulapally, R.; Seapy, D. G. Suzuki−Miyaura Cross-Coupling of Potassium Trifluoro(*N*-methylheteroaryl)borates with Aryl and Heteroaryl Halides. *J. Org. Chem.* **2013**, *78*, 6648−6656.

DOI: 10.1021/acs.joc.8b02666
J. Org. Chem. 2018, 83, 15406−15414

(21) Taylor, J. E.; Jones, M. D.; Williams, J. M. J.; Bull, S. D. Friedel−Crafts Acylation of Pyrroles and Indoles using 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) as a Nucleophilic Catalyst. *Org. Lett.* **2010**, *12*, 5740−5743.
(22) Nasir Baig, R. B.; Varma, R. S. Organic Synthesis via Magnetic Attraction: Benign and Sustainable Protocols Using Magnetic Nanoferrites. *Green Chem.* **2013**, *15*, 398−417.
(23) Chang, J. W.W.; Xu, X.; Chan, P. W. H. Practical Copper-Catalyzed *N*-Arylation of Nitrogen Heterocycles with Aryl Halides under Ligand and Additive free Conditions. *Tetrahedron Lett.* **2007**, *48*, 245−248.
(24) Hosseini-Sarvari, M.; Najafvand-Derikvandi, S.; Jarrahpour, A.; Heiran, R. Nano Sulfated Titania as a Heterogeneous Solid Acid Catalyst for the Synthesis of Pyrroles by Clauson−Kaas Condensation under Solvent-free Conditions. *Chem. Heterocycl. Compd.* **2014**, *49*, 1732−1739.
(25) Li, H.; Bai, J.; Wang, J.; Li, C. A Facile Method to Fabricate CuO Supported on Nanofibers as Efficient Catalyst using *N*-Arylation Reactions. *Mol. Catal.* **2017**, *431*, 49−56.
(26) Wang, P.; Ma, F. P.; Zhang, Z. H. L-(+)-Tartaric Acid and Choline Chloride Based Deep Eutectic Solvent: An Efficient and Reusable Medium for Synthesis of *N*-Substituted Pyrroles via Clauson-Kaas Reaction. *J. Mol. Liq.* **2014**, *198*, 259−262.
(27) Rivera, S.; Bandyopadhyay, D.; Banik, B. K. Facile Synthesis of *N*-Substituted Prroles via Microwave-Induced Bismuth Nitrate-Catalyzed Reaction. *Tetrahedron Lett.* **2009**, *50*, 5445−5448.
(28) Satish, G.; Reddy, K. H.V.; Ramesh, K.; Kumar, B. S.P.A.; Nageswar, Y. V. D. An Elegant Protocol for the Synthesis of *N*-Substituted Pyrroles through C−N Cross Coupling/Aromatization Process using $CuFe_2O_4$ Nanoparticles as Catalyst under Ligand-free Conditions. *Tetrahedron Lett.* **2014**, *55*, 2596−2599.
(29) Sun, J.; Chen, L.; Liu, C.; Wang, Z.; Zuo, D.; Pan, J.; Qi, H.; Bao, K.; Wu, Y.; Zhang, W. Synthesis and Biological Evaluations of 1,2-Diaryl Pyrroles as Analogues of Combretastatin A-4. *Chem. Biol. Drug Des.* **2015**, *86*, 1541−1547.
(30) Deng, H. J.; Fang, Y. J.; Chen, G. W.; Liu, M. C.; Wu, H. Y.; Chen, J. X. Copper-Catalyzed Clauson−Kass Pyrroles Synthesis in Aqueous Media. *Appl. Organomet. Chem.* **2012**, *26*, 164−167.
(31) Biava, M.; Porretta, G. C.; Poce, G.; Battilocchio, C.; Alfonso, S.; De Logu, A.; Serra, N.; Manetti, F.; Botta, M. Identification of a Novel Pyrrole Derivative Endowed with Antimycobacterial Activity and Protection Index Comparable to that of the Current Antitubercular Drugs Streptomycin and Rifampin. *Bioorg. Med. Chem.* **2010**, *18*, 8076−8084.
(32) Le, Z. G.; Chen, Z. C.; Hu, Y.; Zheng, Q. G. Organic Reactions in Ionic Liquids: A Simple and Highly Regioselective N-Substitution of Pyrrole. *Synthesis* **2004**, *2004*, 1951−1954.
(33) Lion, C.; Baudry, R.; Hedayatullah, M.; Conceicao, L. D. Reaction of Pyrroles with Naphthoquinones. Synthesis of New Pyrrolylnaphthoquinone Dyes. *J. Heterocycl. Chem.* **2000**, *37*, 1635−1640.
(34) Daw, P.; Chakraborty, S.; Garg, J. A.; David, Y. B.; Milstein, D. Direct Synthesis of Pyrroles by Dehydrogenative Coupling of Diols and Amines Catalyzed by Cobalt Pincer Complexes. *Angew. Chem., Int. Ed.* **2016**, *55*, 14373−14377.
(35) Hamaide, T. Efficient N-Alkylation of Pyrrole Under Solid Triphase Transfer Catalysis Conditions. Application to *N*-Oxyalkyl Pyrroles. *Synth. Commun.* **1990**, *20*, 2913−2920.
(36) Zuo, B.; Chen, J.; Liu, M.; Ding, J.; Wu, H.; Su, W. Scandium Triflate-Catalysed Synthesis of *N*-Substituted Pyrroles from Amine and 2,5-Dimethoxytetrahydrofuran. *J. Chem. Res.* **2009**, *2009*, 14−16.
(37) Tao, S.; Ji, E.; Shi, L.; Liu, N.; Xu, L.; Dai, B. Copper-Catalyzed C−N Bond Exchange of *N*-Heterocyclic Substituents around Pyridine and Pyrimidine Cores. *Synthesis* **2017**, *49*, 5120−5130.
(38) Patil, P. H.; Nallasivam, J. L.; Fernandes, R. A. Unimolecular 4-Hydroxypiperidines: New Ligands for Copper-Catalyzed *N*-Arylation. *Asian J. Org. Chem.* **2015**, *4*, 552−559.

DOI: 10.1021/acs.joc.8b02666
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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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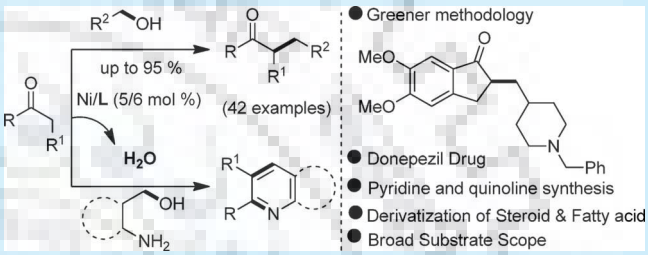
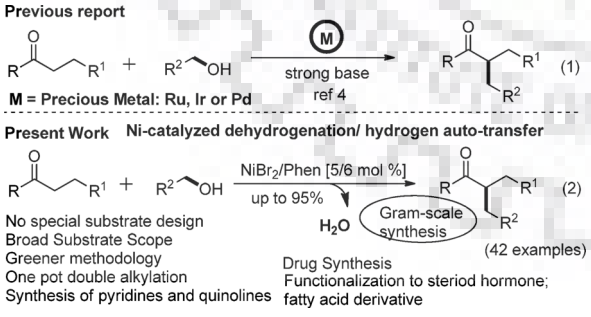
Supporting Information

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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(Figure 1). Selective hydrogenation of intermediate enone **3a′** by in situ formed nickel hydride transformed to the product **3a**,

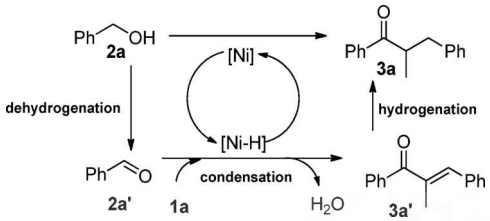
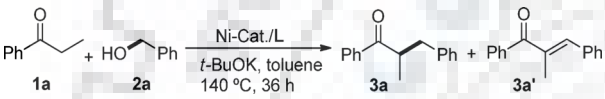


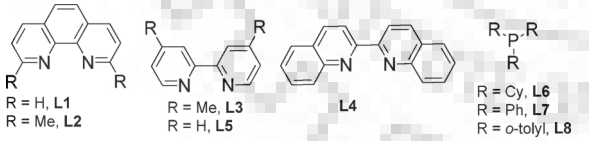
Figure 1. Proposed Ni-catalyzed α-alkylation of ketones.

a conceptually different strategy to branched *gem*-bis(alkyl) ketones previously reported by Itami and co-workers (Scheme S8).[6b] Anticipating the aforementioned issues, we hypothesized a few key challenges, such as (i) selective hydrogenation of the C═C bond of **3a′**, (ii) control to reduce the nickel-catalyzed hydrogenation of the C═O bond of **3a** and **3a′**, and (iii) how to minimize the self-condensation of ketones (Table 1 and Supporting Information (SI), Tables S1−S5).[5c] To this

Table 1. Ni-Catalyzed α-Alkylation: Optimization Studies[a]



entry	catalyst	ligand	conv[b] (%) 3a	3a′
1	$NiCl_2$	**L1**	50	39
2	$NiBr_2$	**L1**	86 (78)	10
3	$Ni(acac)_2$	**L1**	62	15
4	$Ni(cod)_2$	**L1**	55	32
5	$NiCl_2$·DME	**L1**	37	42
6	$NiBr_2$	**L2**	44	22
7	$NiBr_2$	**L3**	54	36
8	$NiBr_2$	**L4**	55	32
9	$NiBr_2$	**L5**	50	30
10	$NiBr_2$	**L6**	57	24
11	$NiBr_2$	**L7**	61	30
12	$NiBr_2$	**L8**	62	34
13[c]	$NiBr_2$	**L1**	95 (92)	1
14[d]			10	35



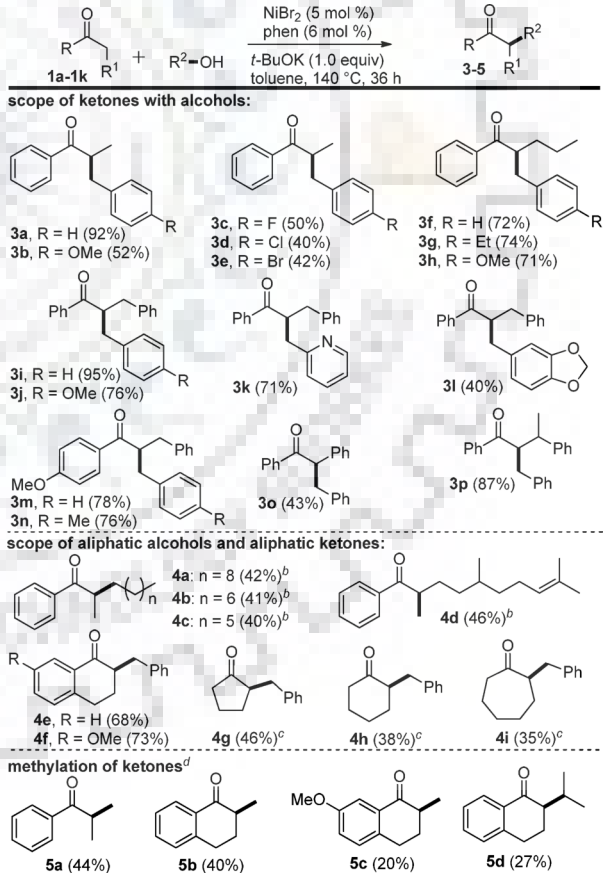
[a]Unless specified otherwise, the reaction was carried out with **1a** (0.5 mmol), **2a** (0.625 mmol), Ni cat. (0.025 mmol), **L** (0.03 mmol), and *t*-BuOK (0.5 mmol) under an N_2 atmosphere at 140 °C (oil bath) in toluene (2.0 mL) for 36 h in a Schlenk tube. [b]Conversion was determined by GC−MS (isolated yields in parentheses, average yield of two runs). [c]**2a** (0.75 mmol) was used. [d]*t*-BuOK (0.5 mmol) was used.

end, we envisioned that an appropriate nickel catalyst in combination with a suitable nitrogen ligand is highly desirable for this transformation. Primarily, we studied the efficacy of different nickel catalysts by the reaction of propiophenone **1a** with benzyl alcohol **2a** as a model reaction (Table 1, entries 1−5).

To our delight, we identified 1,10-phenanthroline **L1** as a superior ligand for the α-alkylation of ketone. Under identical conditions, other nitrogen and phosphine ligands, **L2**−**L8**, resulted in 44−62% of **3a** along with 22−36% of the corresponding enone (Table 1, entries 6−12, and SI Table S3). Gratifyingly, when a small excess of alcohol in the presence of 5 mol % $NiBr_2$ and 6 mol % **L1** in toluene was used , **3a** was obtained in 92% isolated yield (Table 1, entry 13).

Notably, under optimized conditions, influence and scope of different bases, solvents, and control experiments further did not improve product yields (Table 1, SI Tables S1−S5). It is noteworthy to mention that, in lower product yields we observed 2−10% reduced alcohols of **3a** and **3a′** by GC−MS analysis of the crude reaction mixture (Table 1). Under optimal conditions, a range of ketones and alcohols were alkylated in good to excellent yields (Scheme 2). For instance, propiophenone could be transformed to a series of branched alkylated ketones **3a**−**e** in up to 92% yield. Gratifyingly, phenyl ketones bearing sterically demanding *n*-propyl (**1b**), benzyl (**1c**), phenyl (**1e**), or secondary alkyl (**1f**) substituents efficiently converted to the corresponding branched products **3f**−**h**, **3i**,**j**,**l**, **3o**, and **3p** in moderate to excellent yields

Scheme 2. Synthesis of Disubstituted Ketones[a]



[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), and *t*-BuOK (0.5 mmol) were used. [c]*t*-BuOK (0.0625 mmol) and **2** (0.3125 mmol) were used, 24 h. [d]GC−MS and ^1H NMR yield; *t*-BuOK (0.625 mmol) and alcohol (1 mL) were used.

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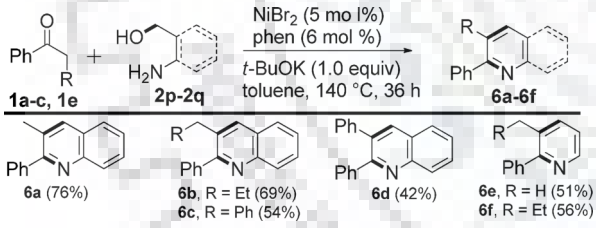
(Scheme 2). To our delight, 2-pyridinemethanol furnished the desired product **3k** in 71% yield. Advantageously, when 4-methoxy-substituted phenyl ketone **1d** was employed, the desired *gem*-bis(benzyl substituted) ketones **3m−n** were obtained in 76−78% yields, respectively. It is noteworthy to mention that benzyl alcohol bearing halides (F, Cl, or Br) as well as methoxy and 1,3-dioxolone groups could be tolerated under the standard catalytic conditions including the pyridine moiety.

Next, we explored the reactivity of more challenging primary alkyl alcohols and alkyl ketones (Scheme 2). Readily abundant C7−C10 primary alcohols as well as the renewable terpenoid intermediate citronellol efficiently converted to branched *gem*-dialkyl-substituted ketones **4a−d**. Notably, this represents a rare chemoselective transformation of unsaturated alcohol under Ni catalysis.[7] Again, the reaction of tetralone derivatives **1g,h** and cyclic alkyl ketones, such as cyclopentanone, cyclohexanone, and cycloheptanone, converted into α-benzyl cyclic ketones in up to 73% yield (Scheme 2, **4e−i**). These examples show the potential of the present catalytic protocol. Next, we utilize methanol as a C1 source for α-methylation of ketones under standard conditions. The high energy barrier for activation of smaller alcohols often limits its applications, and to date, use of Ir, Rh, and Ru catalysts are known for such processes.[9] To our delight, when using propiophenone and tetralone derivatives with methanol, α-methylated ketones **5a−c** were obtained in up to 44% yield (Scheme 2). Under identical conditions, we also observed α-isopropyl tetralone **5d** in moderate yield.

Finally, we studied the synthesis of quinolines and pyridines using γ-amino benzyl alcohols with a range of substituted ketones (Scheme 3). Surprisingly, to date, only a handful of

Scheme 3. Green Synthesis of Quinolines and Pyridines

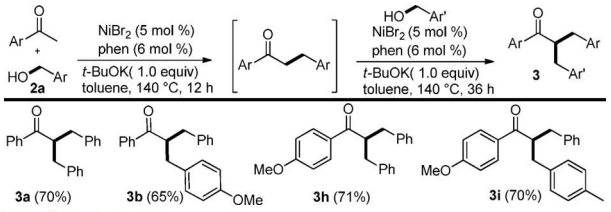


[a]Reaction was carried out with **1** (0.25 mmol), **2** (0.3125 mmol), $NiBr_2$ (0.0125 mmol), phen (0.015 mmol), and *t*-BuOK (0.25 mmol) in toluene (2.0 mL) at 140 °C for 36 h.

examples based on Ir, Ru, and Mn complexes are known for their synthesis.[8c,10−12] Gratifyingly, application of 2-amino-benzyl alcohol and 3-aminopropanol with ketones **1a−c** and **1e** resulted the formation of C-2- and C-3-substituted quinolines and pyridines **6a−f** in up to 76% yields (Scheme 3). Pleasingly, we established an alternative green synthesis of substituted pyridines and quinolines using an inexpensive nickel catalyst.

Next, we studied the one-pot sequential double alkylation of acetophenone and 4-methoxyphenyl acetophenone using primary alcohols (Scheme 4). Notably, in the first step, we observed that a selective monobenzylation followed by a second addition of similar catalyst composition and different benzyl alcohols resulted in hetero bis-alkylated ketones (Scheme 4). We also demonstrated one-step direct synthesis of donepezil **7** from commercially available starting materials

Scheme 4. Sequential One-Pot Double Alkylation of Acetophenone



(Figure 2).[13] Donepezil is a best-selling drug used for the treatment of Alzheimer's disease.[14] Interestingly, application of

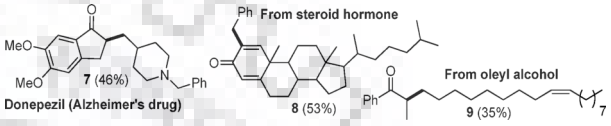


Figure 2. Application in drug synthesis and steroid hormone.

4-cholesten-3-one resulted in α-benzylated product **8** in 53% yield without affecting the parent cholesten moiety (Figure 2). Similarly, fatty acid alcohol derived from oleic acid efficiently alkylated with **1a** and resulted in a moderate yield of **9** without significantly affecting the double bond (Figure 2).

Notably, the catalytic system is tolerant to halides and alkyl, alkoxy, and dioxolone functionalities, including benzyl and the pyridine moiety. Remarkable transformations in the presence of reducible groups, such as terminal alkene and the steroid framework, provide evidence for the synthetic potential of the established protocol. To our delight, when a gram-scale reaction was performed using propiophenone **1a** with benzyl alcohol **2a**, **3a** was obtained in 71% yield (SI Scheme S7). Nevertheless, application of ketones or alcohols with electron-deficient functionalities, such as, nitro, amino, esters, and formyl as well as nitrile groups, did not result any desired products under standard catalytic conditions.

Furthermore, as part of our ongoing studies, we were interested in gaining insight about the Ni-catalyzed α-alkylation of ketones. To the best of our knowledge, to date there are no detailed mechanistic studies reported for such processes. Therefore, to identify the key Ni intermediate species, **cat. A** was prepared,[15] isolated, and separately employed in a stoichiometric (100 mol %) and catalytic (10 mol %) amount in the model reaction under standard conditions; **3a** was obtained in 48% and 50% yields (Scheme 5a). Mechanistically, we hypothesized that Ni-catalyzed α-alkylation of ketones is a multistep process: dehydrogenation of alcohol to aldehyde followed by base-mediated condensation with ketone to an enone intermediate and finally in situ hydrogenation of enone by Ni−H species led to the desired product (Figure 1 and SI Scheme S8).

On the basis of the above findings, we prepared the Ni hydride species of **cat. A**. Unfortunately, the experiments were not successful, even after several attempts at variable temperatures (SI Scheme S6).[8a,b,16] At this point, we realized that electron-rich phosphine ligand might be useful to form stable Ni−H species. Therefore, tricyclohexylphosphine **L6** was used to prepare the defined complex, $(Cy)_3PNiBrH$, **cat. B−H**.[17] Gratifyingly, **3a** was obtained in 21% yield when enone **3a′** was reacted with a stoichiometric equiv of **cat. B−H** under standard conditions (Scheme 5b and SI Scheme S6).

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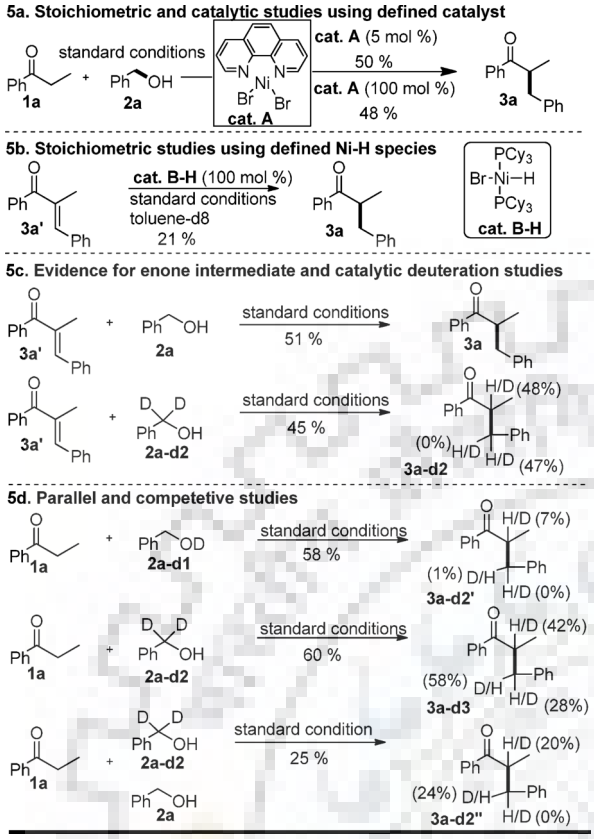
Scheme 5. Catalytic and Mechanistic Studies



The above experimental findings provide strong evidence for the participation of Ni−H species. Thereafter, we prepared the defined Ni-alkoxy species **cat. C**, employed under standard catalytic conditions. GC−MS analysis of the crude reaction mixture detected benzaldehyde formation, which is in agreement for the participation of the nickel−alkoxy intermediate (SI Scheme S6C).

Next, to gain deeper insight into the reaction mechanism, we performed a series of deuterium-labeling experiments (Scheme 5c,d). The enone **3a′** reacted with **2a** and **2a-d2** under standard conditions to afford **3a-d2** in 45−51% yield and exhibited 47−48% incorporation of deuterium (Scheme 5c and SI Scheme S3). Thereafter, we conducted α-alkylation of **1a** using benzylalcohol **2a-d1**, ^{1}H NMR, and GC−MS analysis indicating the formation of **3a-d2′** (Scheme 5d and SI Scheme S4). Additionally, we performed a crossover experiment using a 1:1 mixture of **2a** and **2a-d2** under standard conditions and observed the formation of H/D-scrambled product **3a-d2′′** (Scheme 5d and SI Schemes S1 and S2). Notably, the reaction of **1a-d2** with benzyl alcohol **2a** also resulted in the formation of **3a-d3′** in 44% yield (SI Scheme S5). These deuterated experimental observations strongly support our findings and are in agreement with the literature report of D/H exchange following hydrogen autotransfer strategy (Scheme 5 and SI Schemes S1−S5).[18]

Additionally, competition experiments using a mixture of 4-methoxybenzyl alcohol **2b** and methylene ketone **1a** were independently reacted with benzyl alcohol **2a** and 4-chlorobenzyl alcohol **2d** under standard catalytic conditions. We observed that, α-alkylation occurred at higher rates for ketones with electron-rich substituent (SI Scheme S9). Finally, we explored our interest in the determination of rate and order of the reaction. To calculate the rate laws, we performed kinetic studies using two sets of experiments (SI Scheme S10). Considering a steady-state approximation for benzyl alcohol, first-order kinetics with respect to **1a** was observed for α-alkylation of ketones.

In summary, we have developed an operationally simple and practical route for the synthesis of branched *gem*-bis(alkyl) ketones using Ni catalyst. Readily available alcohols and a series of aryl and alkyl ketones including pyridine functionality resulted in up to 95% yield. A sequential one-pot double alkylation to hetero bis-alkylated ketones is reported. Successful synthetic application to Alzheimer's drugs and functionalization of steroid hormones and fatty acid derivatives shows the potential of the present protocol. Methylation of ketones and green synthesis to N-heterocycles significantly broadens the scope of this methodology. Initial mechanistic studies using defined Ni−H species and a series of deuterium-labeling experiments established the hydrogen-borrowing strategy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02256.

Experimental procedures, screening of the reaction conditions and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Barta, K.; Ford, P. C. *Acc. Chem. Res.* **2014**, *47*, 1503−1512.

(2) For selected reviews, see: (a) Guillena, G.; Ramon, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611−1641. (b) Bower, J. F.; Krische, M. J. *Top. Organomet. Chem.* **2011**, *34*, 107−138. (c) Watson, A. J. A.; Williams, J. M. J. *Science* **2010**, *329*, 635−636. (d) Bähn, S.; Imm, S.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. *ChemCatChem* **2011**, *3*, 1853−1864. (e) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681−703. (f) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 249−260.

(3) For α-alkylation of ketones, see: (a) Alonso, F.; Riente, P.; Yus, M. *Synlett* **2007**, *2007*, 1877−1880. (b) Alonso, F.; Riente, P.; Yus, M. *Eur. J. Org. Chem.* **2008**, *2008*, 4908−4914. (c) Srimani, D.; Balaraman, E.; Gnanaprakasam, B.; Ben-David, Y.; Milstein, D. *Adv. Synth. Catal.* **2012**, *354*, 2403−2406. (d) Kuwahara, T.; Fukuyama,

DOI: 10.1021/acs.orglett.8b02256
Org. Lett. 2018, 20, 5587−5591

T.; Ryu, I. *Org. Lett.* **2012**, *14*, 4703−4705. (e) Chan, L. K. M.; Poole, D. L.; Shen, D.; Healy, M. P.; Donohoe, T. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 761−765. (f) Elangovan, S.; Sortais, J.-B.; Beller, M.; Darcel, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 14483−14486. (g) Peña-López, M.; Piehl, P.; Elangovan, S.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 14967−14971. (h) Zhang, G.; Wu, J.; Zeng, H.; Zhang, S.; Yin, Z.; Zheng, S. *Org. Lett.* **2017**, *19*, 1080−1083. (i) Genç, S.; Günnaz, S.; Çetinkaya, B.; Gülcemal, S.; Gülcemal, D. *J. Org. Chem.* **2018**, *83*, 2875−2881.

(4) (a) Shen, D.; Poole, D. L.; Shotton, C. C.; Kornahrens, A. F.; Healy, M. P.; Donohoe, T. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 1642−1645. (b) Frost, J. R.; Cheong, C. B.; Akhtar, W. M.; Caputo, D. F. J.; Stevenson, N. G.; Donohoe, T. J. *J. Am. Chem. Soc.* **2015**, *137*, 15664−15667. (c) Yan, F.-X.; Zhang, M.; Wang, X.-T.; Xie, F.; Chen, M.-M.; Jiang, H. *Tetrahedron* **2014**, *70*, 1193−1198. (d) Akhtar, W. M.; Cheong, C. B.; Frost, J. R.; Christensen, K. E.; Stevenson, N. G.; Donohoe, T. J. *J. Am. Chem. Soc.* **2017**, *139*, 2577−2580. (e) Li, F.; Ma, J.; Wang, N. *J. Org. Chem.* **2014**, *79*, 10447−10455. (f) Schlepphorst, C.; Maji, B.; Glorius, F. *ACS Catal.* **2016**, *6*, 4184−4188. (g) Cho, C. S. *J. Mol. Catal. A* **2005**, *240*, 55−60. (h) Yamada, Y. M. A.; Uozumi, Y. *Org. Lett.* **2006**, *8*, 1375−1378. (i) Kwon, M. S.; Kim, N.; Seo, S. H.; Park, I. S.; Cheedrala, R. K.; Park, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6913−6915. (j) Cui, X.; Zhang, Y.; Shi, F.; Deng, Y. *Chem. - Eur. J.* **2011**, *17*, 1021−1028.

(5) (a) Bullock, R. M. *Catalysis Without Precious Metals*; Wiley-VCH: Weinheim, 2010. (b) Su, B.; Cao, Z.-C.; Shi, Z.-J. *Acc. Chem. Res.* **2015**, *48*, 886. For recent examples of nickel-catalyzed hydrogenation of ketone, see: (c) Castellanos-Blanco, N.; Flores-Alamo, M.; García, J. J. *Inorg. Chim. Acta* **2017**, *466*, 324−332.

(6) (a) Grigalunas, M.; Ankner, T.; Norrby, P.; Wiest, O.; Helquist, P. *J. Am. Chem. Soc.* **2015**, *137*, 7019−7022. (b) Takise, R.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 6791−6794.

(7) For selected Ni-catalyzed reviews, see: (a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299−309. (b) Ananikov, V. P. *ACS Catal.* **2015**, *5*, 1964−1971. (c) Jolly, P. W.; Wilke, G. *The Organic Chemistry of Nickel*; Academic Press: New York, 1974. (d) Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48*, 1717−1726.

(8) (a) Vellakkaran, M.; Singh, K.; Banerjee, D. *ACS Catal.* **2017**, *7*, 8152−8158. (b) Das, J.; Banerjee, D. *J. Org. Chem.* **2018**, *83*, 3378−3384. (c) Singh, K.; Vellakkaran, M.; Banerjee, D. *Green Chem.* **2018**, *20*, 2250−2256.

(9) Selected recent reviews: (a) Natte, K.; Neumann, H.; Beller, M.; Jagadeesh, R. V. *Angew. Chem., Int. Ed.* **2017**, *56*, 6384−6394. (b) Shen, D.; Poole, D. L.; Shotton, C. C.; Kornahrens, A. F.; Healy, M. P.; Donohoe, T. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 1642−1645. (c) Quan, X.; Kerdphon, S.; Andersson, P. G. *Chem. - Eur. J.* **2015**, *21*, 3576−3579. (d) Ogawa, S.; Obora, Y. *Chem. Commun.* **2014**, *50*, 2491−2493.

(10) Selected recent examples for pyridine synthesis: (a) Michlik, S.; Kempe, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 6326. (b) Deibl, N.; Ament, K.; Kempe, R. *J. Am. Chem. Soc.* **2015**, *137*, 12804. (c) Hille, T.; Irrgang, T.; Kempe, R. *Angew. Chem., Int. Ed.* **2017**, *56*, 371. (d) Srimani, D.; Ben-David, Y.; Milstein, D. *Chem. Commun.* **2013**, *49*, 6632. (e) Ruch, S.; Irrgang, T.; Kempe, R. *Chem. - Eur. J.* **2014**, *20*, 13279.

(11) (a) Cho, C. C.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2001**, 2576. (b) Vander Mierde, H.; Ledoux, N.; Allaert, B.; Van Der Voort, P.; Drozdzak, R.; De Vos, D.; Verpoort, F. *New J. Chem.* **2007**, *31*, 1572. (c) Martinez, R.; Ramon, D. J.; Yus, M. *Eur. J. Org. Chem.* **2007**, *2007*, 1599. (d) Vander Mierde, H.; Van Der Voort, P.; De Vos, D.; Verpoort, F. *Eur. J. Org. Chem.* **2008**, *2008*, 1625. (e) Pan, B.; Liu, B.; Yue, E.; Liu, Q.; Yang, X.; Wang, Z.; Sun, W. H. *ACS Catal.* **2016**, *6*, 1247.

(12) Mastalir, M.; Glatz, M.; Pittenauer, E.; Allmaier, G.; Kirchner, K. *J. Am. Chem. Soc.* **2016**, *138*, 15543.

(13) Sugimoto, H.; Ogura, H.; Arai, Y.; Iimura, Y.; Yamanishi, Y. *Jpn. J. Pharmacol.* **2002**, *89*, 7−20.

(14) For selected syntheses of donepezil, see: (a) Dubey, S. K.; Kharbanda, M.; Mathela, C. S. *Chem. Pharm. Bull.* **2010**, *58*, 1157−1160. (b) Elati, C. R.; Kolla, N.; Chalamala, S. R.; Vankawala, P. J.; Sundaram, V.; Vurimidi, H.; Mathad, V. T. *Synth. Commun.* **2006**, *36*, 169−174.

(15) (a) Yakhvarov, D. G.; Hawkins, E. H.; Kagirov, R. M.; Budnikova, Y. H.; Ganushevich, Y. S.; Sinyashin, O. G. *Russ. Chem. Bull.* **2007**, *56*, 935−942. (b) Khrizanforov, M.; Khrizanforova, V.; Mamedov, V.; Zhukova, N.; Strekalova, S.; Grinenko, V.; Gryaznova, T.; Sinyashin, O.; Budnikova, Y. *J. Organomet. Chem.* **2016**, *820*, 82−88.

(16) Chakraborty, S.; Piszel, P. E.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2015**, *34*, 5203−5206.

(17) (a) Green, M. L. H.; Saito, T.; Tanfield, P. J. *J. Chem. Soc. A* **1971**, 152−154. (b) Lindner, M. M.; Beckmann, U.; Frank, W.; Kläui, W. *ISRN Inorg. Chem.* **2013**, *2013*, 1−13.

(18) (a) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766−1774. (b) Samec, J. S. M.; Backvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237−248.

DOI: 10.1021/acs.orglett.8b02256
Org. Lett. 2018, 20, 5587−5591