

Chapter III

Vanadium-Catalyzed Oxidative Cross Dehydrogenative-Coupling of C(sp³)-H Bond: Functionalization of Imidazo[1,2-*a*]pyridines

Transition metal-catalyzed C–C or C–X (X = F, O, N, S, P ...) bond formation reactions are very important tools in organic synthesis, allowing the construction of complex molecules from simple precursors.^[1-2] Many efficient methodologies using transition metal have been built and applied in natural products and pharmaceuticals synthesis, or in material science.^[3-4] Carbon–carbon bond formation reactions are very special among the numerous reactions described throughout the history of organic chemistry, due to formation of new framework of complex organic molecule particularly transition metal-catalyzed C–H bond activation and subsequent C–C bond formations have attracted much interest in recent years.^[5] Transition metal-catalyzed C–H bond functionalization could present green and sustainable methodology to construct diverse complex structures using simple organic molecule.^[6] The most explored reactions includes Negishi, Suzuki, Stille, Sonagashira, Heck, Hiyama coupling reaction for C–C bond construction and the most recently developed Ullmann and Buchwald–Hartwig reaction for C–N bond construction.^[7] These name reactions are useful to create new bond between sp, sp² C–H bond. However, in spite of the great success of both classical C–C bond formation methods and the modern extraordinary achievements of transition metal catalysis, C–C bond formation reactions are required to have pre-functionalized starting materials, which require extra steps (sometimes multiple steps).^[8] The necessity of these repetitive pre-functionalization and de-functionalization steps are associated with isolations and purifications, ultimately diminishes the overall material efficiency in the synthesis of complex organic molecules and increases chemical waste.^[9] To reduce the number of steps involved and increase the efficiency in synthetic chemistry, we must explore new frontiers of chemical reactions. Outstanding achievements have been made in the area of C–C bond formation and many complex compounds have been synthesized much more rapidly, although these reactions still require at least one functionalized partner in order to generate the desired C–C bond formation products.^[10] The Eglinton reaction which gives the homo-coupled product of alkynes was the first example of formation of C–C bond between two C–H bonds in presence of copper salt^[11-12] but the reaction required stoichiometric amount of copper salt. The same reaction was further improved and named as Glaser–Hay coupling reaction using catalytic amount of copper in the presence of oxidant as oxygen.^[13]

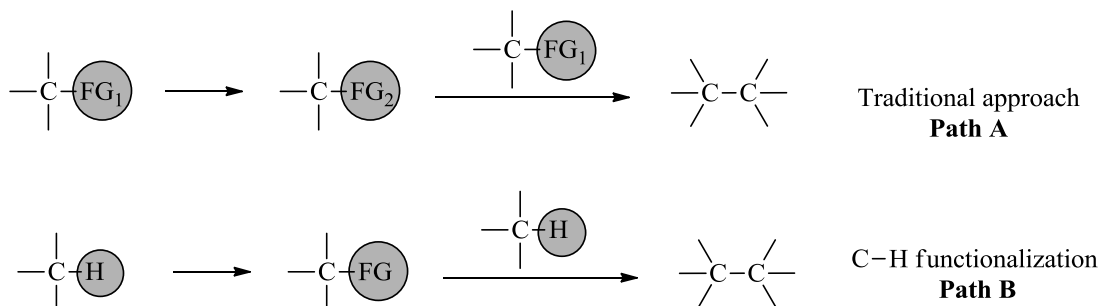
Several transition metal have been widely used for formation of C–C bond mostly, vanadium (V),^[14] molybdenum (Mo),^[15-16] iron (Fe),^[17-18] nickel (Ni),^[19] cobalt (Co)^[20-21] and copper

(Cu)^[22] are demonstrated to serve as an important catalyst in the presence of external oxidant in the field of oxidative dehydrogenation coupling reactions. Vanadium is nontoxic, readily available, cheap, and also present as natural occurring enzyme in many biological systems. Thus, its exploration *via* dehydrogenative cross-coupling, employing various oxidants under environmentally benign organic reaction conditions would be valuable.^[23]

Nitrogen-containing heterocycles are of immense importance in organic chemistry as well as in medicinal chemistry because they constitute the main structure within huge number of natural products and pharmaceutical compounds.^[24-25] Particularly, condensed heterocycles act as synthetic building blocks and pharmacophores for several potent drug molecules.^[26] Fused azaheterocycles comprise family of biological agents with interesting pharmacological properties related to planarity of the system and their DNA-chain intercalating ability, which make them suitable for anti-neoplastic and mutagenic applications.^[27] Imidazo[1,2-*a*]pyridines are the privileged structural motifs with endowed applications in multidisciplinary fields such as material science, organometallics, and medicinal chemistry.^[28] Although, imidazo[1,2-*a*]pyridines are structurally different from benzodiazepines, their pharmacological properties are quite similar to that of benzodiazepine drugs, hence they are termed as nonbenzodiazepines.^[29] These scaffolds are the key structures in many natural products and in commercially available drugs such as zolpidem, alpidem, necopidem, and saripidem. Furthermore, analogues of imidazo[1,2-*a*]pyridines were also studied against broad spectrum of biological targets. Because of their diverse applications, synthesis and functionalization of imidazo[1,2-*a*]pyridines is the subject of current interest in many laboratories.^[30]

3.1. Introduction

The aliphatic C(sp³)-H bonds, which are present in almost all organic molecules, are most challenging targets for effective and selective functionalization to construct variety of C-C and C-X bonds (X = N, O, S).^[31] In this context, construction of C-C bonds *via* oxidative cross dehydrogenative coupling (CDC) of C(sp³)-H bonds has gained intense interest resulting in the development of numerous new synthetic methods.^[32] The additional advantage of CDC reactions is that there is no necessity for pre-functionalization of precursors (**Scheme 3.1**).^[33-34]



Scheme 3.1: (A) Organic synthesis by traditional approach (B) Organic synthesis by C-H functionalization

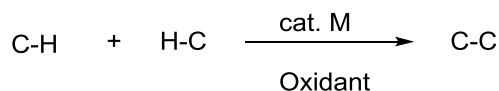
3.1.1. Cross dehydrogenative coupling

The direct functionalization of C-H bonds has two fundamental challenges to an organic chemist:

- Reactivity: Activation of single C-H bond to make it prone to chemical attack.
- Selectivity: Differences in reactivity of various C-H bonds are not much differ to each other so to target specific C-H bond is very difficult.

The challenge for selective C(sp³)-H bond activation in molecule as functional group can be prevailed by discriminating the relative strength of electronic properties of particular C-H bond. Presence of unsaturation (benzylic and allylic C-H bond) or heteroatom such as oxygen, nitrogen and sulphur adjacent to C(sp³)-H bond make them special relative to other isolated alkyl C-H bond.^[35]

Formation of carbon-carbon bonds directly from two different C-H bonds under oxidative conditions *via in situ* generation of various reactive intermediates is considered as cross-dehydrogenative coupling. The oxidative coupling of two different C-H bonds was termed cross-dehydrogenative coupling (CDC) by Chao-Jun Li and has become growing field of interest for organic chemist (**Scheme 3.2**).^[36]

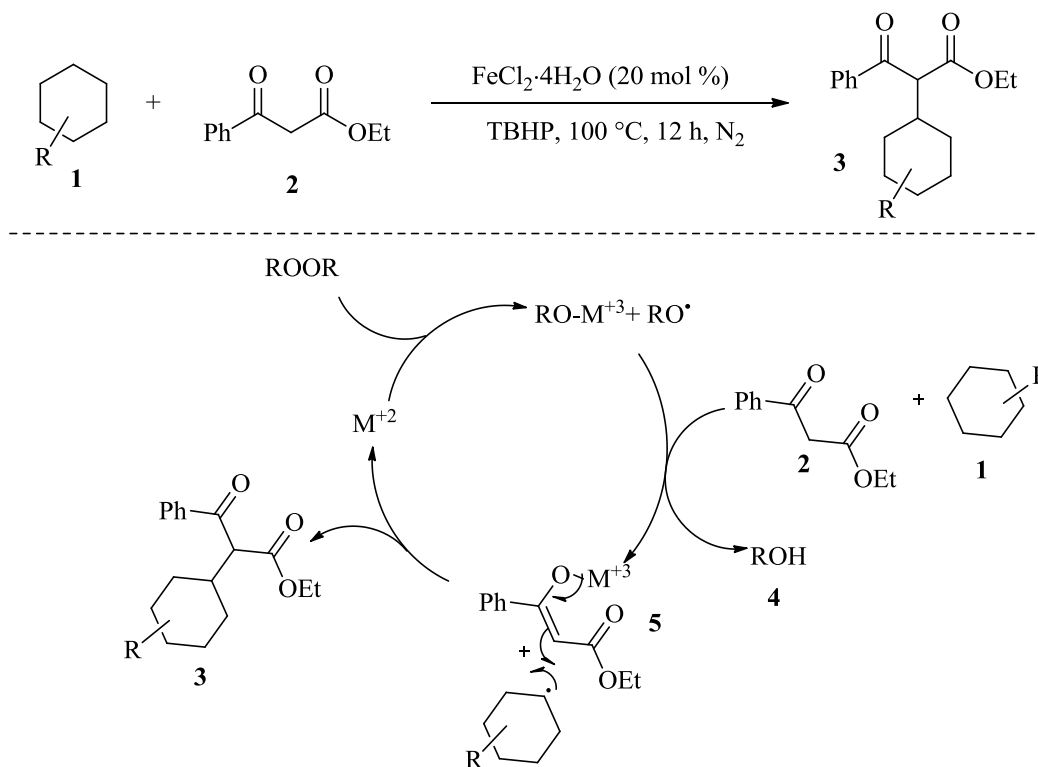


Scheme 3.2: Cross dehydrogenative coupling

Based on reactivity of different hybridized C-H bond of coupling partner cross-dehydrogenative coupling reaction can be divided into six classes.

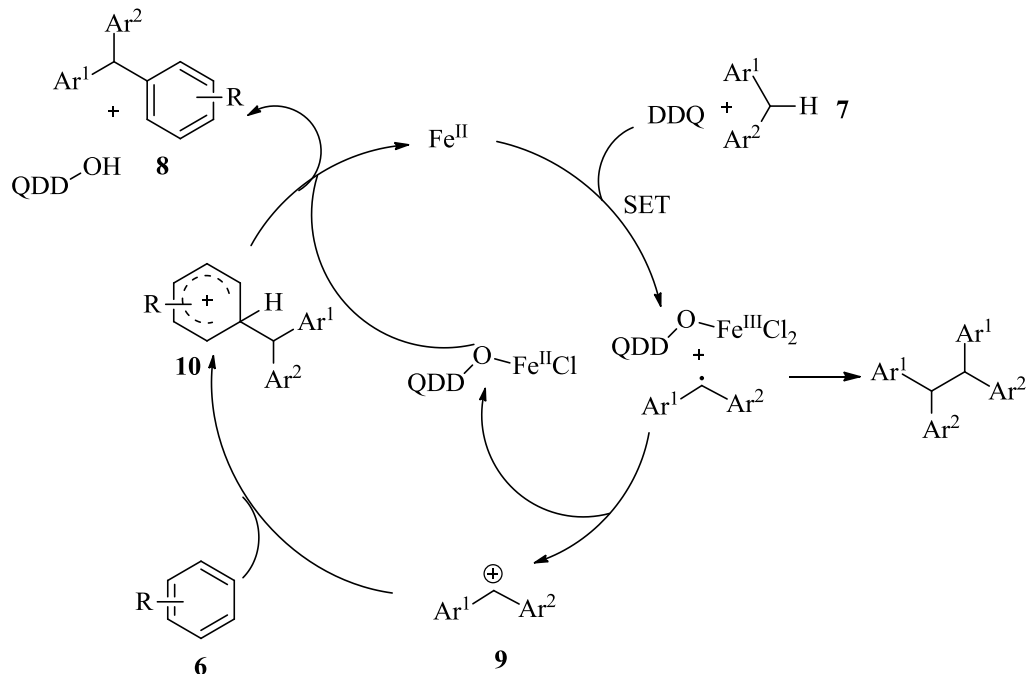
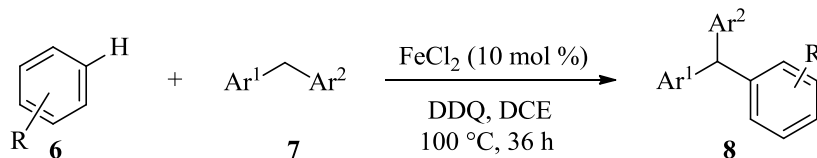
- Coupling of C(sp³)-H with C(sp³)-H:** Oxidative couplings involving C(sp³)-H bonds remain challenging task, due to their low reactivity and lack of suitable coordination site for the

catalyst. Relatively more reactive $C(sp^3)-H$ bonds such as dialkyl malonates, $\alpha-C(sp^3)-H$ bond of nitrogen in amines, $\alpha-C-H$ bond of oxygen in ethers, allylic $C(sp^3)-H$ and benzylic $C-H$ bonds^[37] could be used as substrate for $C(sp^3)-H$, $C(sp^3)-H$ cross-dehydrogenative coupling. The mechanism involves metal catalyzed decomposition of oxidant to generate radical which immediately react with $C(sp^3)-H$ bond to give alkyl radical. Further reaction of enolate (**5**) with alkyl radical give alkylated β -ketoester (**3**) and metal catalyst (**Scheme 3.3**).^[38]



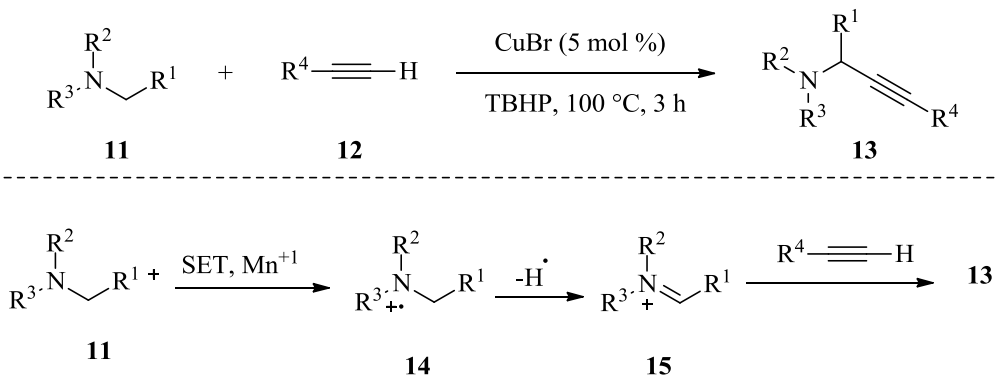
Scheme 3.3: Coupling of $C(sp^3)-H$ with $C(sp^3)-H$

b) Coupling of $C(sp^3)-H$ with $C(sp^2)-H$: Aromatic $C(sp^2)-H$ of aryl ring, indole, phenol, thiophenes and furans reacts with relatively active $C(sp^3)-H$ bond of other coupling partner in the presence of suitable oxidant and catalyst. Metal-assisted SET mechanism generates benzyl radical in the presence of oxidant which further converts to corresponding cation. Friedel–Crafts-type alkylation and abstraction of the proton by the reduced hydroquinone produce the target product and complete the catalytic cycle (**Scheme 3.4**).^[39]



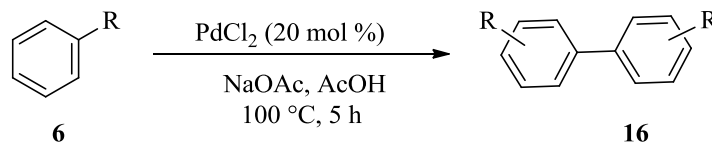
Scheme 3.4: Coupling of $\text{C}(\text{sp}^3)\text{-H}$ with $\text{C}(\text{sp}^2)\text{-H}$

c) **Coupling of $\text{C}(\text{sp}^3)\text{-H}$ with $\text{C}(\text{sp})\text{-H}$:** $\text{C}(\text{sp}^3)\text{-H}$ bond reacts with alkyne $\text{C}(\text{sp})\text{-H}$ bond in the presence of metal and oxidant and produce propargylamines (**13**) which have been considered as great synthetic intermediates in pharmaceutical interest.^[40] Reaction proceeds through SET and iminium intermediate (**5**) via metal-catalyzed oxidative cross dehydrogenative coupling (**Scheme 3.5**).^[41]



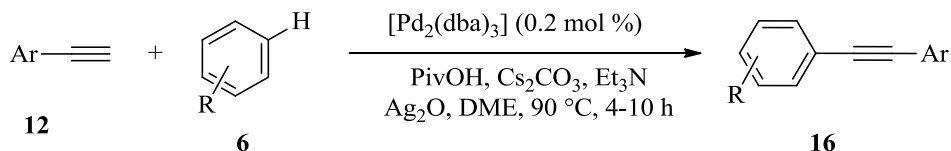
Scheme 3.5: Coupling of $\text{C}(\text{sp}^3)\text{-H}$ with $\text{C}(\text{sp})\text{-H}$

d) Coupling of C(sp²)-H with C(sp²)-H: Aromatic C-H bonds are efficiently activated for coupling with second C(sp²)-H bond in the presence of metal salts to achieve CDC reactions of C(sp²)-H with C(sp²)-H bonds. Transition metal-catalyzed direct arylation and oxidative dehydrogenation reaction occurs through Coupling of C(sp²)-H with C(sp²)-H (Scheme 3.6).^[42]



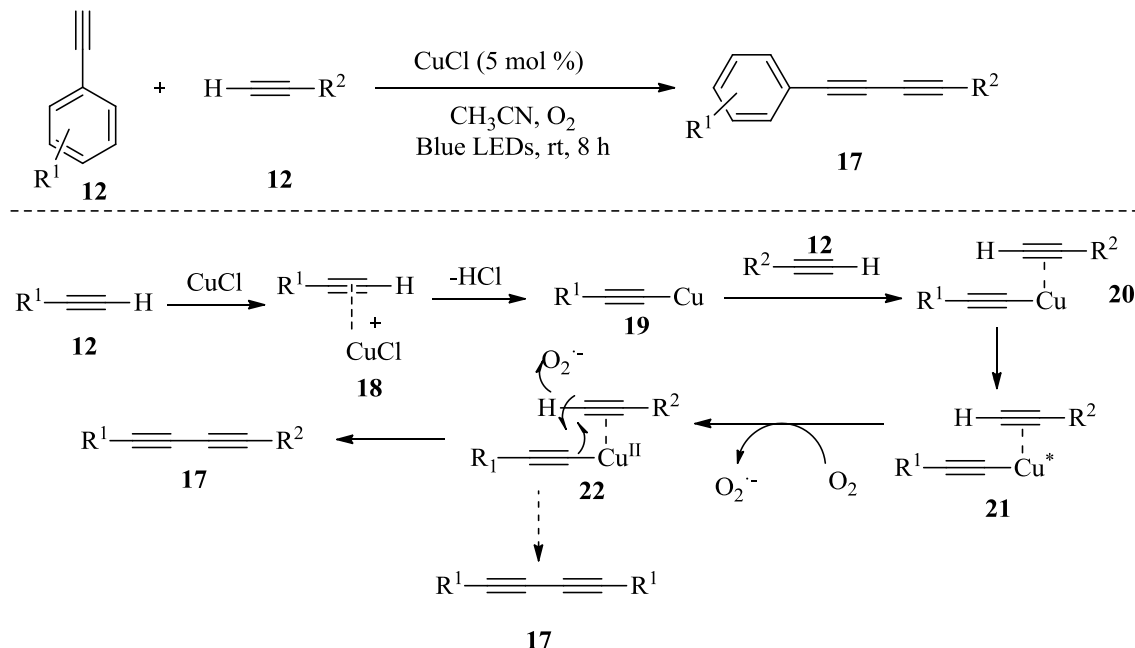
Scheme 3.6: Coupling of C(sp²)-H with C(sp²)-H

e) Coupling of C(sp²)-H with C(sp)-H: Direct alkylation of (hetero)aromatic compounds has appeared as an alternative reaction to the Sonogashira reaction by using the alkynyl reagents which can be prepared from terminal alkynes, such as alkynyl halides, benziodoxolone-based hypervalent iodine reagents, or arylsulfonylacetylenes. Although homocoupling of terminal alkyne create undesired product and can be suppressed by using excess of coupling partner or lower loading of catalyst (Scheme 3.7).^[43]



Scheme 3.7: Coupling of C(sp²)-H with C(sp)-H

f) Coupling of C(sp)-H with C(sp)-H: The methods for C(sp)-C(sp) coupling reactions are rare but useful method for synthesis of conjugated diynes. Recently palladium catalyzed C(sp)-C(sp) cross-dehydrogenative coupling reactions have been developed for homocoupling of alkynes (12). Gold, palladium and copper are effective metal catalyst for terminal alkynes to furnish conjugated diynes (17). Reaction proceeds through copper insertion to triple bond of alkyne, followed by SET mechanism by copper (Scheme 3.8).^[44]



Scheme 3.8: Coupling of C(sp)-H with C(sp)-H

The research presented in this chapter has been focused on the transition metal-catalyzed functionalization of C(sp³)-H bond *via* oxidative cross dehydrogenative coupling reactions. Direct functionalization of C(sp³)-H bond adjacent to the nitrogen atom through the oxidation of amines to iminium ions and the subsequent addition of nucleophiles are extensively studied.^[32, 45-46]

3.1.2. Vanadium-catalyzed oxidation and oxidative cross dehydrogenative coupling

Andrés Manuel del Río discovered compounds of vanadium in 1801 in Mexico by analyzing lead-containing mineral (brown lead) which he named erythronium (derived from Greek for "red") and found to be responsible for some specific properties in mineral of brown lead. In 1830 Nils Gabriel Sefström named it "vanadium" as the symbol of Scandinavian goddess of beauty and fertility, Vanadís (Freyja). Vanadium is harder than most other metals such as steel and iron and it has good resistance to corrosion and almost inactive against harsh chemicals as sulfuric and hydrochloric acids.^[47] Vanadium products are used as steel additive which make it very tough and are used for armour plate, axles, tools, piston rods and crankshafts. Vanadium pentaoxide is used as pigment for ceramics and glasses. Vanadium atom is an essential component of some enzymes; particularly nitrogen-fixing microorganisms have vanadium nitrogenase.^[48] Vanadium is the 22nd most abundant element in the earth's crust although metallic

vanadium is rare in nature but it is found in 65 different minerals in nature (**Figure 3.1**).^[49] Electronic configuration of vanadium is $[\text{Ar}] 3d^3 4s^2$ and it shows +5, +4, +3, +2, +1, -1, -3 oxidation states.

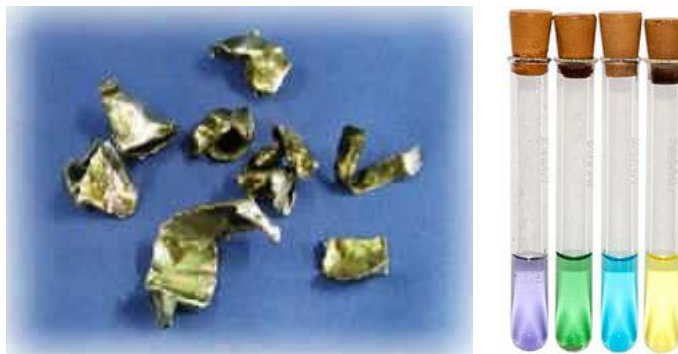


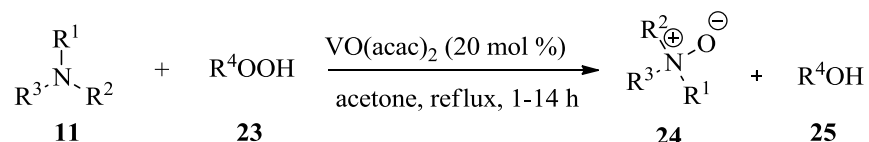
Figure 3.1: Vanadium metal, vanadium aqua complex $[\text{V}(\text{H}_2\text{O})_6]^{2+}$ (lilac), $[\text{V}(\text{H}_2\text{O})_6]^{3+}$ (green), $[\text{VO}(\text{H}_2\text{O})_5]^{2+}$ (blue) and $[\text{VO}(\text{H}_2\text{O})_5]^{3+}$ (yellow)

Having variable positive oxidation state of 2 to 5, vanadium can be used as good alternate of expensive transition metal such as palladium, ruthenium, rhodium, and gold in the field of modern growing chemical synthesis.^[50] Earth abundant vanadium catalyst is actively used for industrial purposes, which includes, metallurgy along with redox chemistry which are the main consumer of vanadium and its consumption from primary sources is actively growing for industrial purpose but in the field of catalytic properties for oxidative cross-dehydrogenative coupling reactions, vanadium is not much explored. Vanadium is nontoxic, readily available, cheap, and also present in natural occurring enzyme in many biological systems. Thus, its exploration *via* cross-dehydrogenative coupling, employing various oxidants under environmentally benign organic reaction conditions would be valuable. Vanadium exhibits remarkable diversity of reactivity due to variable oxidation state. Away from synthetic applications in industries, vanadium complexes have been used as catalysts for C–O and C–C bond cleavage reactions in lignin model compounds and vanadium is present as an active site of some metalloenzymes nitrogenase, vanadium peroxidase which reveals the significance of redox chemistry of vanadium.^[51-52] Bromoperoxidase created new attention towards the synthetic methodology which was isolated from marine algae.^[53] Vanadium has unique one-electron transfer redox property which provides variety of novel oxidation and reduction methods for organic synthesis.^[14] A variety of oxidative synthetic reactions catalyzed by vanadium oxides have been developed as oxidative coupling of phenols, oxygenation, epoxidation and activation

of molecular oxygen for oxygenation.^[14, 54] Vanadium pentoxide is used in different industrial processes as catalyst, in the contact process it serves for the oxidation of SO₂ to SO₃ with oxygen at 440 °C. Besides it is used in the oxidation of ethanol to ethanale and in the production of phthalic anhydride, polyamide, oxalic acid and various products.^[55] The compatibility of vanadium catalysts for variety of aerobic oxidations and the synergy between the reactions catalyzed by vanadium and copper has increased the interest of scientist for development of vanadium-catalyzed reaction.^[56]

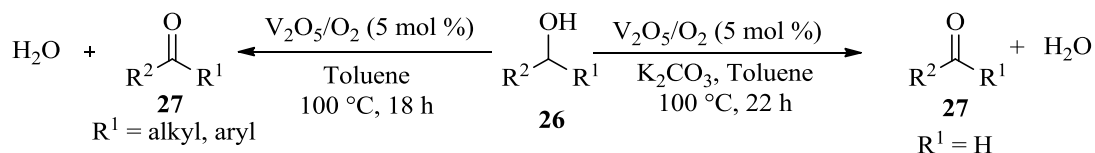
The applications of vanadium in modern organic synthesis are widely studied.^[57] The redox property of vanadium metal can be utilized for oxidation and reduction of different substrates.^[58] Also the Lewis acidity and ability to transfer oxygen are widely used application of vanadium in industrial synthesis.^[14]

Zajasek group studied series of transition metals for oxidation of tertiary amine (**11**) to amine oxide (**24**) (**Scheme 3.9**).^[59] The reaction was catalyzed by vanadium, molybdenum, and titanium compounds in less time at room temperature in the presence of hydroperoxides (**23**) but the vanadium catalyst was more effective. The reactivity of the hydroperoxides increases in the order of ^tbutyl < cumene < amylene hydroperoxide.



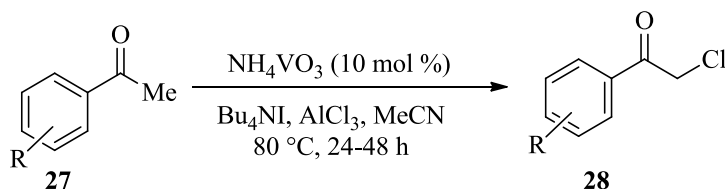
Scheme 3.9: Vanadium-catalyzed oxidation of tertiary amine to amine oxide

Punniyamurthy *et al.* oxidized aliphatic and aromatic alcohols (**26**) to corresponding aldehyde (R¹ = H, **27**) and ketone (R¹ = alkyl, aryl, **27**) using V₂O₅ catalyst in the presence of atmospheric oxygen (**Scheme 3.10**).^[60] Secondary alcohols and cyclic alcohols oxidized to the corresponding ketones in high yields and primary alcohols to aldehyde in the presence of K₂CO₃. When the reaction was carried out without base primary alcohol resulted ester of corresponding product. Reaction methodology is more selective to secondary alcohol in the presence of primary alcohol group which prove the chemoselectivity of reaction.



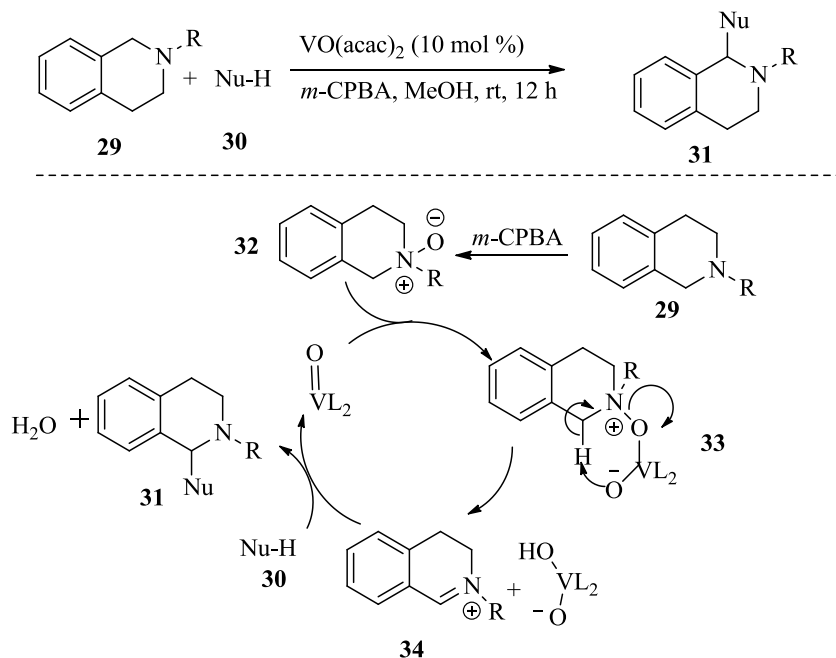
Scheme 3.10: Aerobic oxidation of alcohols with vanadium catalyst

Hirao *et al.* reported chlorination of ketones (**27**) in the presence of vanadium catalyst under molecular oxygen (**Scheme 3.11**).^[61] The combination of tetrabutylammonium iodide and aluminumtrihalide has been reported as good source of halogen in the presence of vanadium catalyst. This catalytic system was also extended to catalytic chlorination of alkenes to afford the corresponding *vic*-dichlorides.



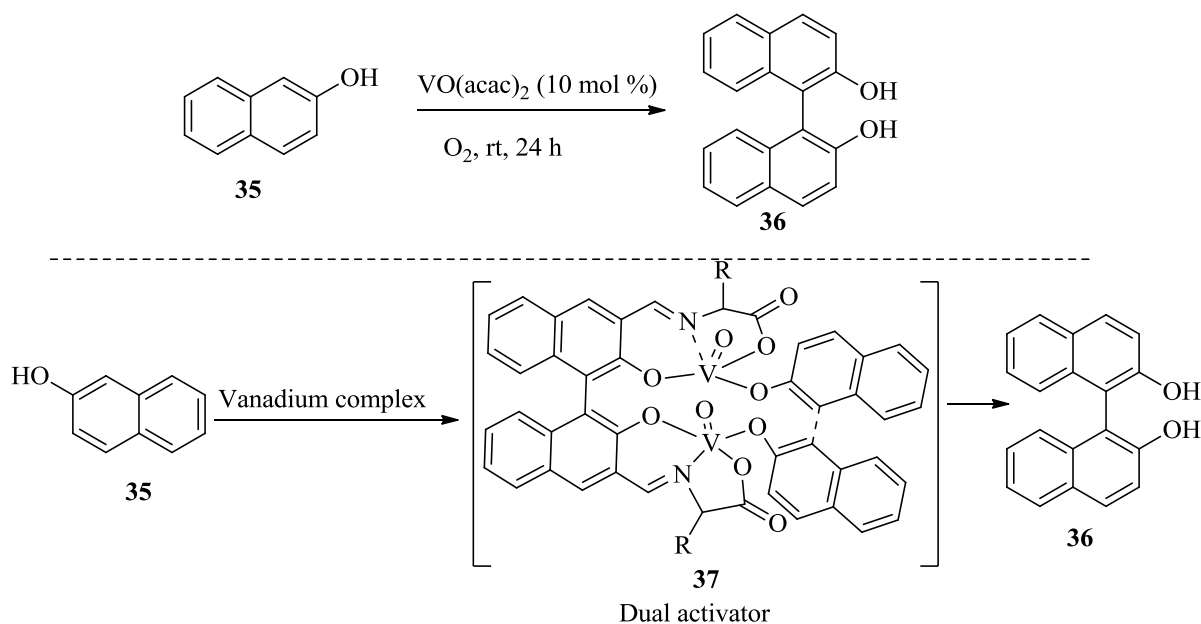
Scheme 3.11: Vanadium-catalyzed α -chlorination of ketones

Klussmann group described simple method for the oxidative coupling of *N*-alkyltetrahydroisoquinolines (**29**) with broad range of nucleophiles (**30**) such as indoles and pyrroles in the presence of *meta*-chloroperoxybenzoic acid (*m*-CPBA) and vanadyl acetylacetonate catalyst (**Scheme 3.12**).^[62] Reaction is supposed to proceed through formation of *N*-oxide (**32**) of *N*-alkyltetrahydroisoquinoline (**29**) in the presence of *m*-CPBA which reacts with vanadium catalyst to give intermediate **33** forming six member cyclic ring of vanadium and abstraction of proton produces iminium ion (**34**). Iminium ion is further attacked by suitable nucleophile to give the desired product (**31**).



Scheme 3.12: Vanadium-catalyzed C–C bond formation

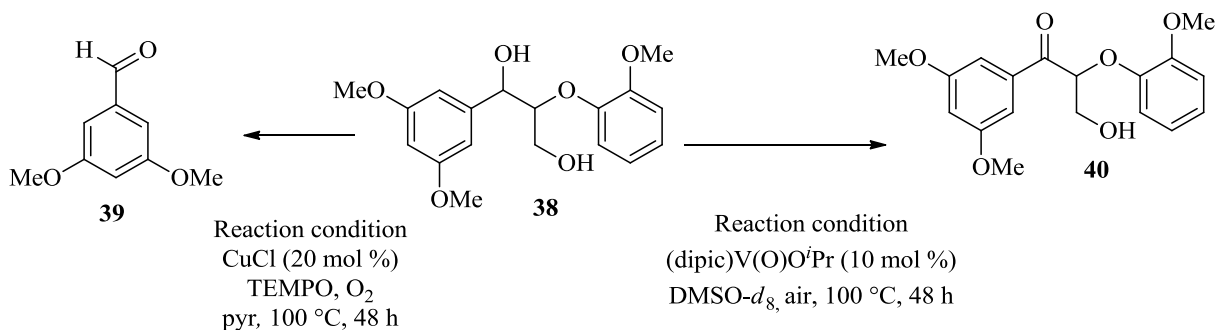
Uang *et al.* reported vanadium-catalyzed oxidative coupling of 2-naphthol (**35**) or phenol derivatives with molecular oxygen at room temperature to give the corresponding *ortho-ortho* coupled products (**36**) (**Scheme 3.13**).^[63] Molecular oxygen oxidizes V^{IV} to V^V and does not interfere with the coupling reaction and complete the catalytic cycle of catalyst. Coupling reaction with different substituent resulted in different yield of corresponding products although un-substituted phenol did not react in the standard reaction condition, but reaction of electron rich phenols such as 2,4-dimethylphenol and 2,3,5-trimethylphenol produce the corresponding product in moderate yield with standard reaction conditions. Reaction is proposed to proceed through dinuclear vanadium complex (**37**) which acts as dual activator. Kinetic study of mononuclear and dinuclear vanadium complex showed the result in favors to proposed mechanism and revealed that two vanadium metals in one chiral complex activate two molecules of 2-naphthol simultaneously in homolytic coupling reaction, achieving high reaction rate with high enantioselectivity (**Scheme 3.13**).^[64]



Scheme 3.13: Oxidative coupling of 2-naphthols in the presence of vanadium catalyst

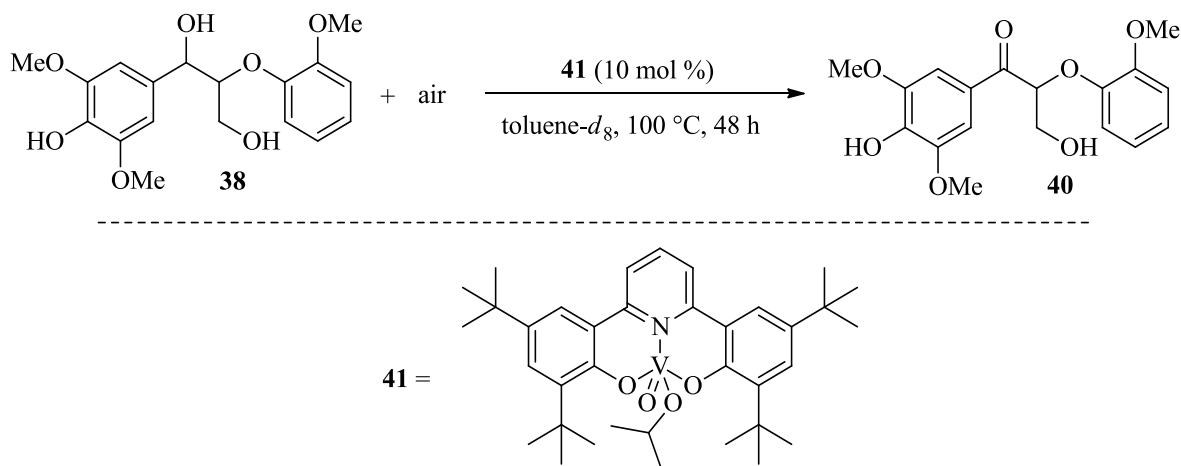
Chiral dinuclear vanadium complexes (**37**) work as dual activating catalysts for the oxidative coupling of 2-naphthols. 2-naphthols, with the C3, C4, C6 or C7 substituted, electron withdrawing as well as electron donating groups were investigated with dinuclear vanadium complexes and resulted good to excellent yield of corresponding product with high enantioselectivities.^[65]

Hanson *et al.* compared the reactivity of vanadium and copper salt for the aerobic oxidative C–C bond cleavage of bis(phenolate) ligands (**38**) (**Scheme 3.14**).^[56] Both the copper and the vanadium complexes catalyzed the aerobic oxidation of lignin model compounds under mild conditions but site of reaction for both catalysts were different and copper cleaved the C–C bond whereas vanadium preferred to cleave the C–H bond.



Scheme 3.14: Comparison of copper and vanadium catalyst for aerobic oxidative C–C bond cleavage of bis(phenolate) ligands

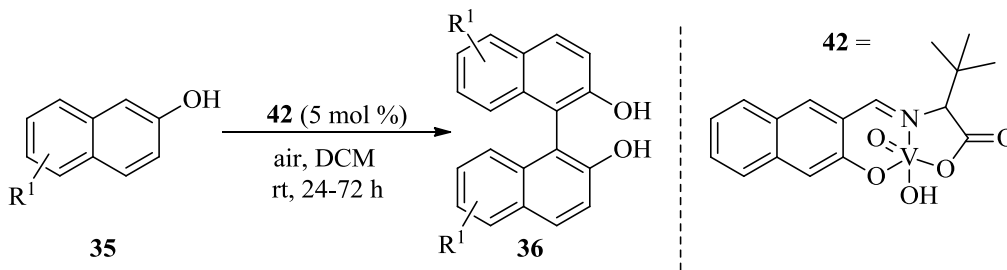
The same group reported the catalytic oxidation of alcohols as pinacol, benzyl alcohol and lignin model compounds (**38**) (**Scheme 3.15**).^[66] Homogeneous catalysts such as vanadium salts are attractive candidates for the aerobic oxidation of lignin complex molecules, by tuning the metal and ligand framework to direct the reaction toward specific bond or toward desired product.



Scheme 3.15: Vanadium-catalyzed oxidation of lignin model compound

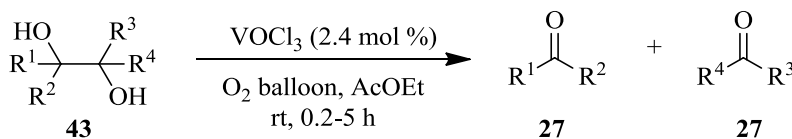
Sasai *et al.* synthesized dinuclear vanadium complex (**42**) for oxidative coupling of 2-naphthols (**35**) giving useful BINOL (**36**) which is actively used as chiral auxiliaries and ligands for asymmetric synthesis (**Scheme 3.16**).^[67] Vanadium-mediated coupling reaction occurred through one electron transfer *via* phenolic oxidation to yield BINOL. A variety of product could be

synthesized by varying different functional group on phenols using mild reaction condition and short time with water as a side product in the presence of air.^[64, 68]

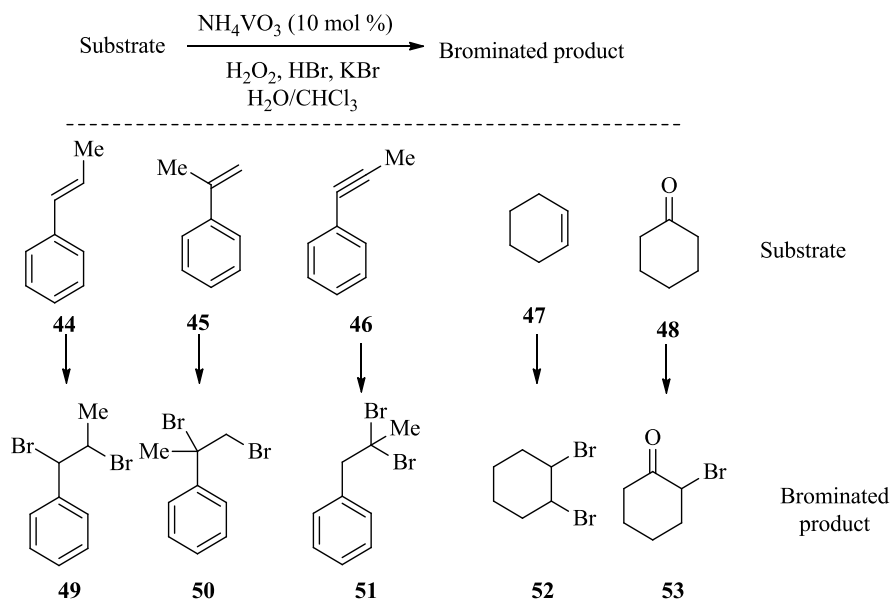


Scheme 3.16: Synthesis of BINOL in the presence of vanadium catalyst

A variety of substrates such as primary and secondary alcohols, α -hydroxy ketones, glycols, tertiary cyclopropanol (**43**) can be chemo selectively oxidized to their corresponding product using vanadium-catalyzed aerobic oxidation reaction (**Scheme 3.17**).^[69]



Scheme 3.17: Vanadium(V)-catalyzed aerobic oxidative cleavage of acyclic ditertiary glycols
Hirao group developed synthetic application of vanadium catalyst and described an efficient catalytic oxidative bromination of alkenes (**44**, **45**, **47**), alkynes (**46**) and ketone (**48**) in aqueous media using NH_4VO_3 and combination of H_2O_2 , HBr , and KBr under mild reaction conditions (**Scheme 3.18**).^[70]



Scheme 3.18: Vanadium-catalyzed oxidative bromination of different substrates

Owing to great importance of transition metal in C–H bond activation and application of vanadium catalyst for oxidative coupling reactions, encouraged us to explore the application of vanadium catalyst for aminomethylation reaction *via* Mannich base intermediate.

Chapter III

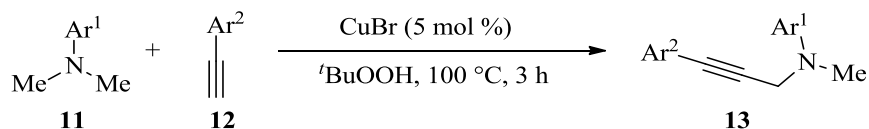
PART A

Oxidative Cross-Coupling of C(sp³)-H and C(sp²)-H Bonds: Aminomethylation of Imidazo[1,2-*a*]pyridines using NMO

3.2. Introduction

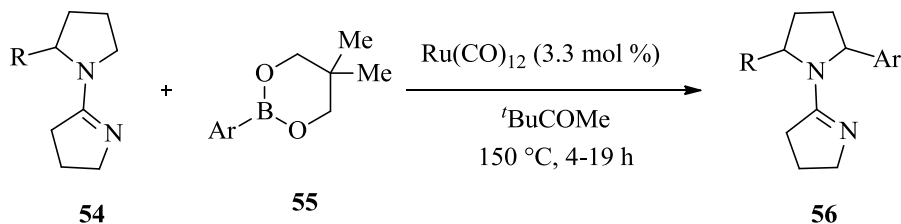
Synthetic chemists have been interested in the elaboration of the cheapest and cleanest routes for the synthesis of organic molecules. Incorporation of new carbon–carbon and carbon–nitrogen bonds into organic molecules is an apparent need in modern chemical industry. There are many recent advances in this field, mostly use of metal catalysis; however, these methods require pre-functionalization steps, thus diminishing the overall atom economy of the process. In these classic cross-couplings reactions generally an electrophile reacts with nucleophile in the presence of transition metal catalyst while oxidative cross-coupling reactions take place in between two different nucleophiles in the presence of proper oxidant with transition metal catalyst.^[71]

The development of new process for the cross-dehydrogenative coupling is challenging field for modern organic chemistry where two C–H bond are linked by new bond accompanied by the elimination of hydrogen atom from each molecule. The same is true for the synthesis of carbon–nitrogen (C–N) bonds from the coupling of C–H and nitrogen–hydrogen (N–H) bonds. Chao-Jun Li and coworkers developed CuBr-catalyzed alkylation of C(sp³)–H bonds attached to nitrogen atom. Direct construction of propargylic amines (**13**) could be achieved by the catalytic coupling of C(sp³)–H bond adjacent to nitrogen with terminal alkyne (**12**) using oxidative cross dehydrogenative coupling (**Scheme 3.19**).^[40] Aromatic terminal alkyne resulted higher yield of product as compared to aliphatic alkynes.



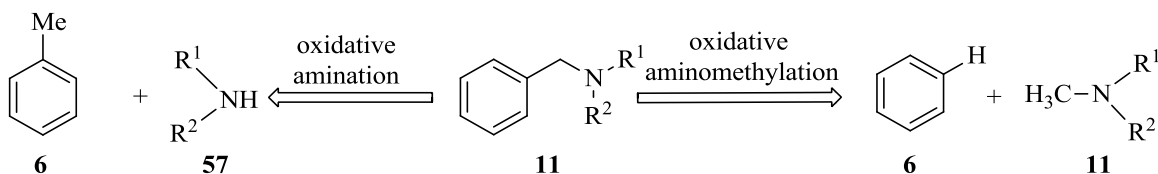
Scheme 3.19: Copper-catalyzed alkylation of amines

Sames *et al.* developed amidine directed arylation of C(sp³)–H bond of pyrrolidines (**54**) and piperidines using Ru catalyst. Synthesis of mono- and bis-arylated products (**56**) using different 2-substituted pyrrolidines with variety of arenes could be generated using easily removable directing group (**Scheme 3.20**).^[72]



Scheme 3.20: Amidine group directed arylation of C(sp³)-H bond

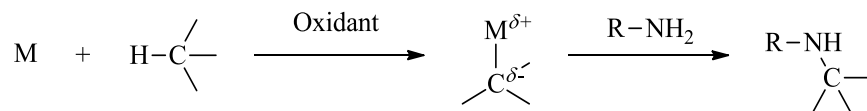
One can envision the incorporation of new C–N bonds *via* cross-dehydrogenative coupling through either oxidative amination or oxidative aminomethylation (**Scheme 3.21**).



Scheme 3.21: Oxidative amination versus oxidative aminomethylation

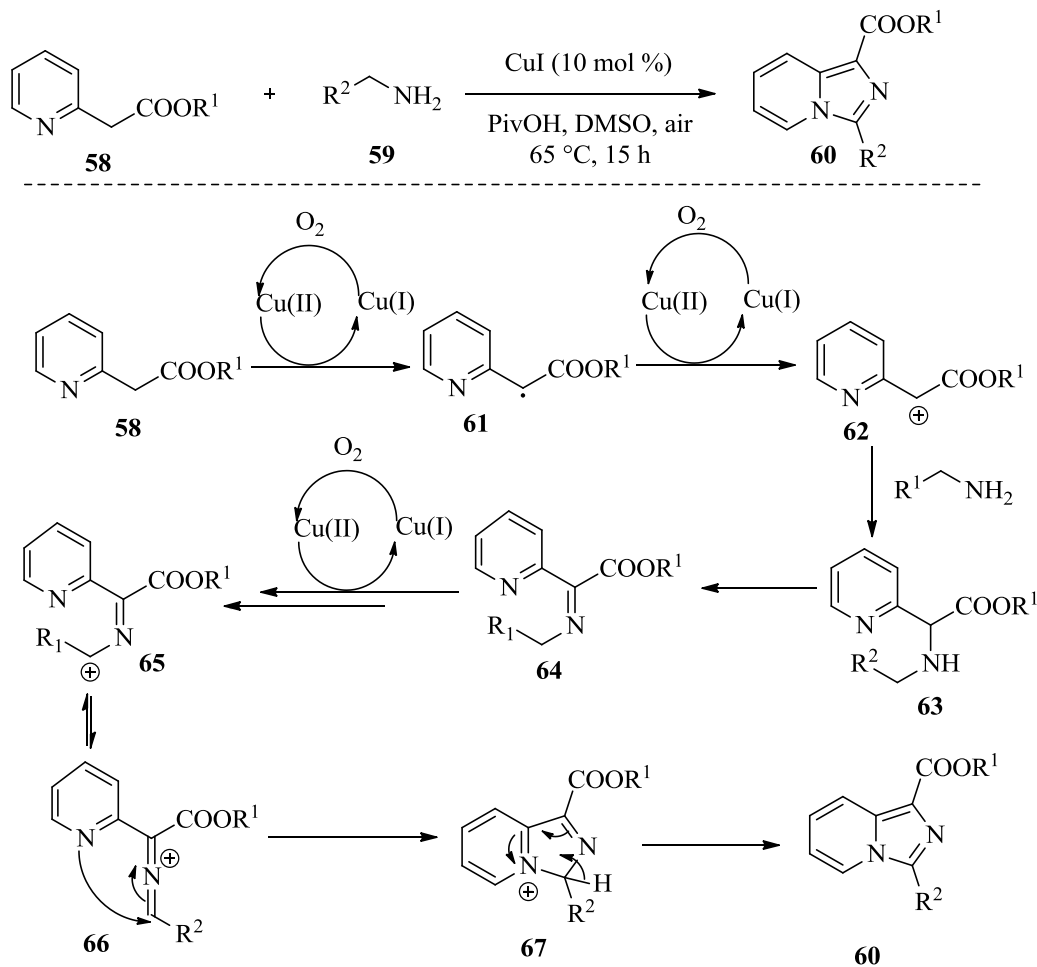
3.2.1. Oxidative amination

Direct oxidative amination, has been reported by Fritz Ullmann which suddenly opened new way for organic synthetic chemist for heterocyclic synthesis. In the field of oxidative amination further Buchwald and Hartwig independently developed modern path for the formation of C(sp²)-N bond, commonly called as Buchwald–Hartwig reaction (**Scheme 3.22**).^[73]



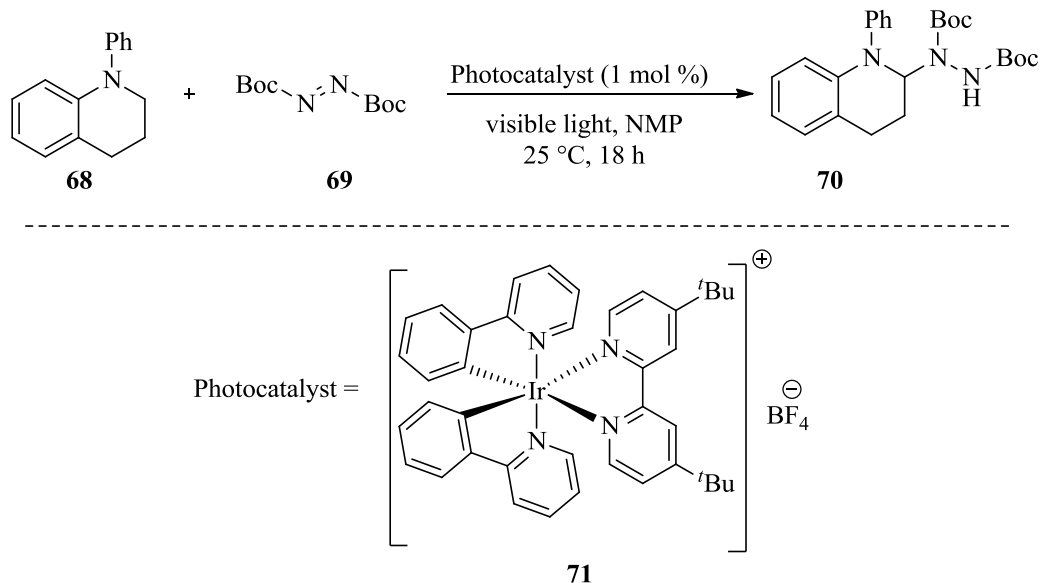
Scheme 3.22: Oxidative amination through cross-dehydrogenative couplings in the presence of metal and oxidant

Gaunt *et al.* reported Pd(II)-catalyzed oxidative C–H amination reaction for the synthesis of carbazoles.^[74] Adimurthy and his co workers recently synthesized imidazo[1,5-*a*]pyridine-1-carboxylates (**60**) *via* oxidative amination of C(sp³)-H bond. The reaction of pyridyl esters (**58**) was done with substituted benzylamines (**59**) in the presence of CuI and PivOH/air in DMSO at 65 °C (**Scheme 3.23**).^[75] The reaction believed to proceed through single electron transfer mechanism. Copper (I) oxidized to copper (II) in the presence of air and generate intermediate **56** to produce benzylic cabocation (**62**) and react with benzylamine (**59**) to form intermediate **63** and followed the SET mechanism to give intermediate **65** and **66**. Further lone pair of nitrogen assist rearrangement for cyclization process followed by aromatization to give the desired product (**60**).



Scheme 3.23: Copper-catalyzed aerobic oxidative amination of C(sp³)-H bonds

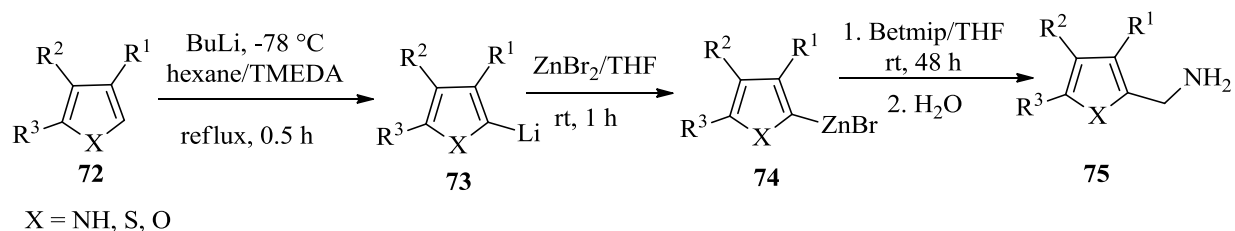
Nishibayashi and co-workers demonstrated visible light mediated photocatalyst assisted direct C(sp³)-H amination of benzocyclic amines. The author targeted to direct α -C-H amination of 1,2,3,4-tetrahydroquinolines (**68**) and indolines to give *N,N*-acetals (**70**), which were further functionalized to benzocyclic amines (**Scheme 3.24**).^[76]



Scheme 3.24: α -C–H amination of 1,2,3,4-tetrahydroquinolines

3.2.2. Oxidative aminomethylation

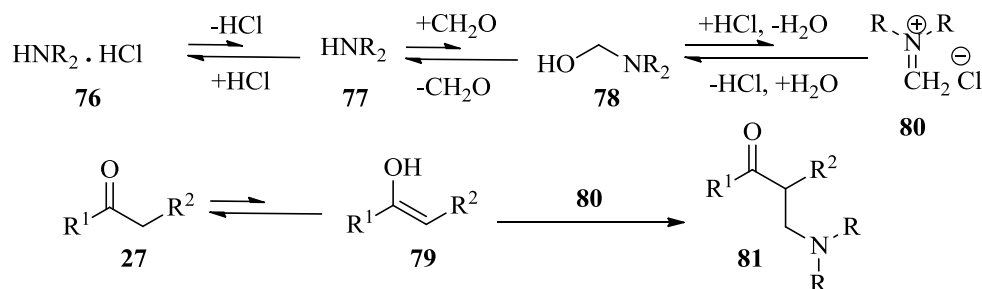
Katritzky group reported aminomethylation on 2-position of electron rich heterocycles (**72**) using sequence of reaction as lithiation, transmetalation into an organozinc reagent and treatment with 1-(triphenylphosphoroylideneaminomethyl)benzotriazole (**Scheme 3.25**).^[77]



Scheme 3.25: Aminomethylation of heterocycles *via* sequence of reactions

The aminoalkylation of compounds having acidic C–H bond was developed by several chemists in 19th century. But Carl Mannich represented and extended the significance of this type of reaction in systematic manner and since then the reaction is known as Mannich reaction. Mannich reaction is an important classical method for the synthesis of carbon-carbon bond for secondary and tertiary amine derivative (**81**) and used as key step for bioactive molecule synthesis.^[78] The aldehyde or ketone (**27**) is heated with formaldehyde and amine hydrochloride (**76**) in protic solvent to give the Mannich product (**81**) which shows significance in the synthesis of numerous pharmaceuticals and natural products. The reaction is simply believed to proceed through the iminium salt (**80**) which formed through the reaction of aldehyde and amine

(Scheme 3.26). Iminium ion attack on tautomer (79) of carbonyl compound to give the β -aminocarbonyl compounds (81) which is called as Mannich bases.^[78] These Mannich bases further can be converted to useful and valuable derivative such as Michale acceptor, 1,3-amino alcohol and functionalized carbonyl compounds.



Scheme 3.26: Mechanism of Mannich reaction

Classical Mannich reaction has several drawbacks such as harsh reaction condition, long reaction time and formation of unwanted side product such as deaminated product and methylene bisketones skeleton. Use of primary amine and ammonia may result the formation of unwanted products and also ketone with different reactive site and unsymmetrical condition can generate bis-Mannich bases and shows regioselective issues (**Figure 3.2**). The major problem with classical Mannich reaction is normally used for only carbonyl compound such as aldehyde and ketone and cannot be used for carboxylic acid and other derivatives.

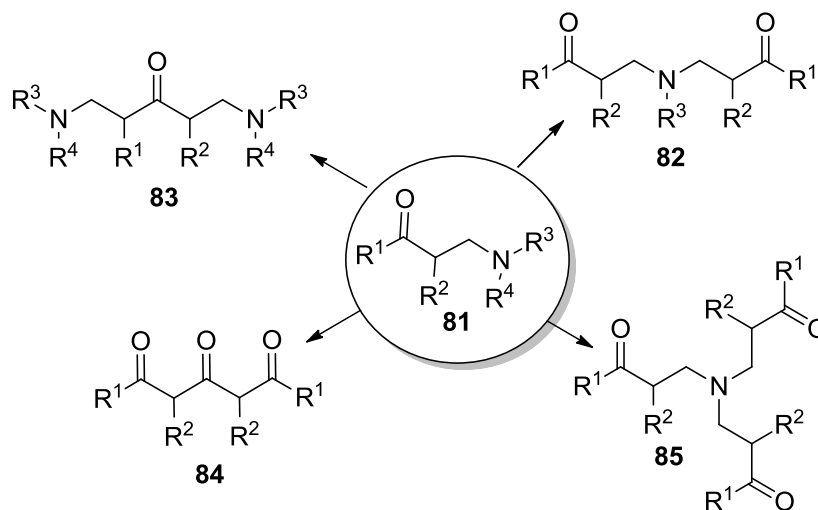


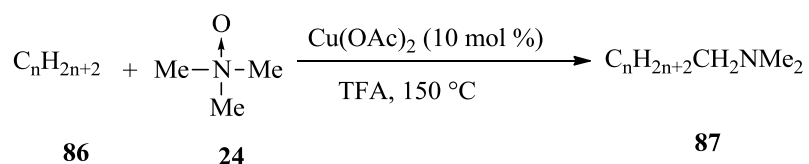
Figure 3.2: Side reaction and drawback of Mannich base

Owing to attractive application of Mannich base in pharmaceutical and bioactive compounds many synthetic modification have been attempted to overcome the drawback of classical Mannich reaction and many performed or modified Mannich reagents has been prepared.^[79-84]

Generation of iminium ion by tertiary amine oxides in the presence of promoter such as acetic anhydride, trifluoroacetic anhydride, sulfur dioxide, or ferrous salt have been well documented in literature. However these methods require harsh reaction condition like use of expensive reagents, which are difficult to handle and required in stoichiometric amount.

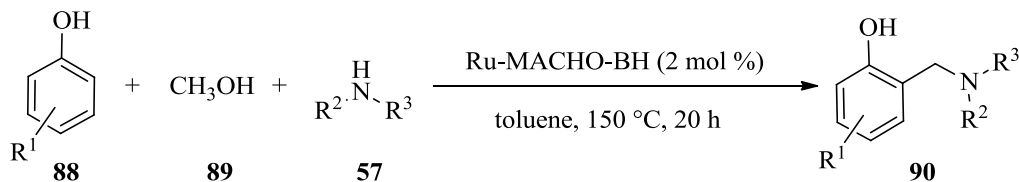
Transition metal mediated oxidative aminomethylation

In pursuit of environmentally benign synthesis without pre-activation of substrates, development of new transition metal catalyst for aminomethylation of heterocycles compounds utilizing different methylation source has been achieved great interest. Direct catalytic introduction of amino groups to organic compounds should be very important reaction for the synthesis of *N*-heterocyclic compounds. However, few reports are available on such transformation. Fujiwara *et al.* reported Cu-catalyzed C–H bond activation reaction of alkanes (**86**) with *N,N*-dialkylmethylamine *N*-oxide (**24**) in TFA to afford *N,N*-dialkylaminomethylated alkanes (**87**) (Scheme 3.27).^[85] Aminomethylation of ethane with trimethylamine *N*-oxide gave *N,N*-dimethyl-propylamine as the sole product. Possible intermediate such as the Manich iminium base, alkyl radicals, and alkyl-Cu has been suggested as reactive species in this reaction.



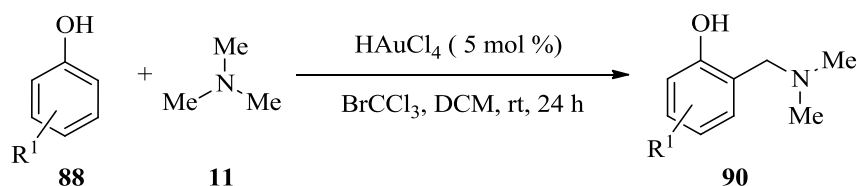
Scheme 3.27: Copper catalyzed aminomethylation of alkanes

Hong and co-workers recently reported the *ortho*-aminomethylation of phenol (**88**) via ruthenium-catalyzed dehydrogenation of methanol (**90**) which acts as one carbon source *via in situ* generated aldehyde (Scheme 3.28).^[86] A variety of functional group of phenols were well tolerated the reaction condition but in case of naphthol substrates methylation product was observed. Reaction mechanism was proposed based on control experiments and literature reports and believed to proceed through iminium cation. In the presence of ruthenium catalyst methanol dehydrogenate to formaldehyde which further react with amine (**57**) to generate iminium ion followed by attack of phenolate anion to give the product (**90**).



Scheme 3.28: *Ortho*-aminomethylation of phenol using ruthenium catalyst

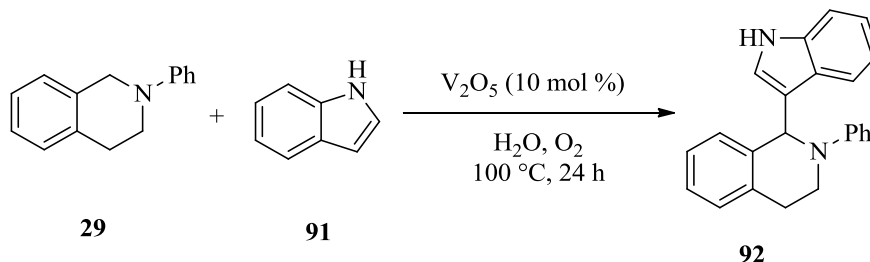
Zhou *et al.* accounted *ortho*-selective oxidative cross dehydrogenative coupling (CDC) of trimethylamine (**11**) and phenols (**88**) which is initiated by CCl_3Br *via* either C–C or C–H bond cleavage (**Scheme 3.29**).^[87] the rate of formation of radical and iminium intermediate was accelerated by gold salt in the presence of visible light.



Scheme 3.29: Gold-catalyzed aminomethylation of phenols

Tanaka *et al.* used sodium phthalimidomethyltrifluoroborate as an aminomethylated source for the one-pot, palladium-catalyzed primary aminomethylation of aryl and heteroaryl halides. Reaction occurs through Suzuki-Miyaura cross-coupling reactions with sodium phthalimidomethyltrifluoroborate followed by deamidation with ethylenediamine.^[88]

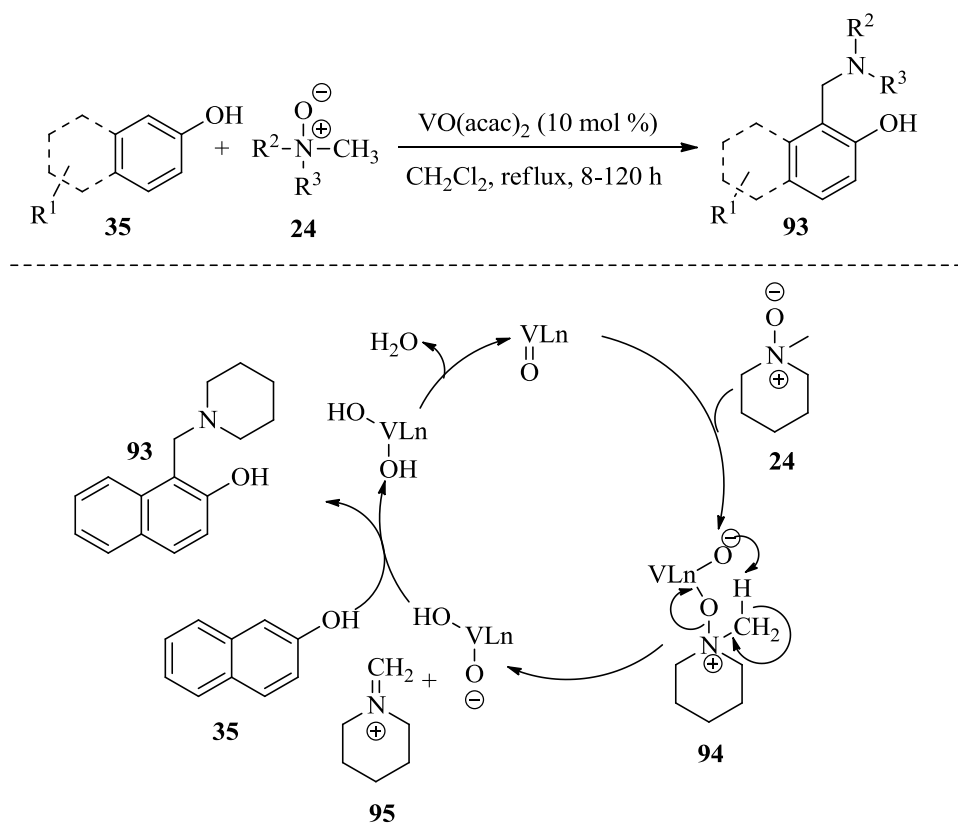
Recently, Prabhu *et al.* developed mild and efficient vanadium-catalyzed method for the synthesis of indolyl-tetrahydroisoquinoline (**92**) derivatives using aqueous media by the reaction of *N*-alkyltetrahydroisoquinoline (**29**) and indoles (**91**) (**Scheme 3.30**).^[33] Larger substrate scope, high regioselectivity, synthetic simplicity and greener reaction conditions provides an elegant method for the construction of biologically active natural products and alkaloids.



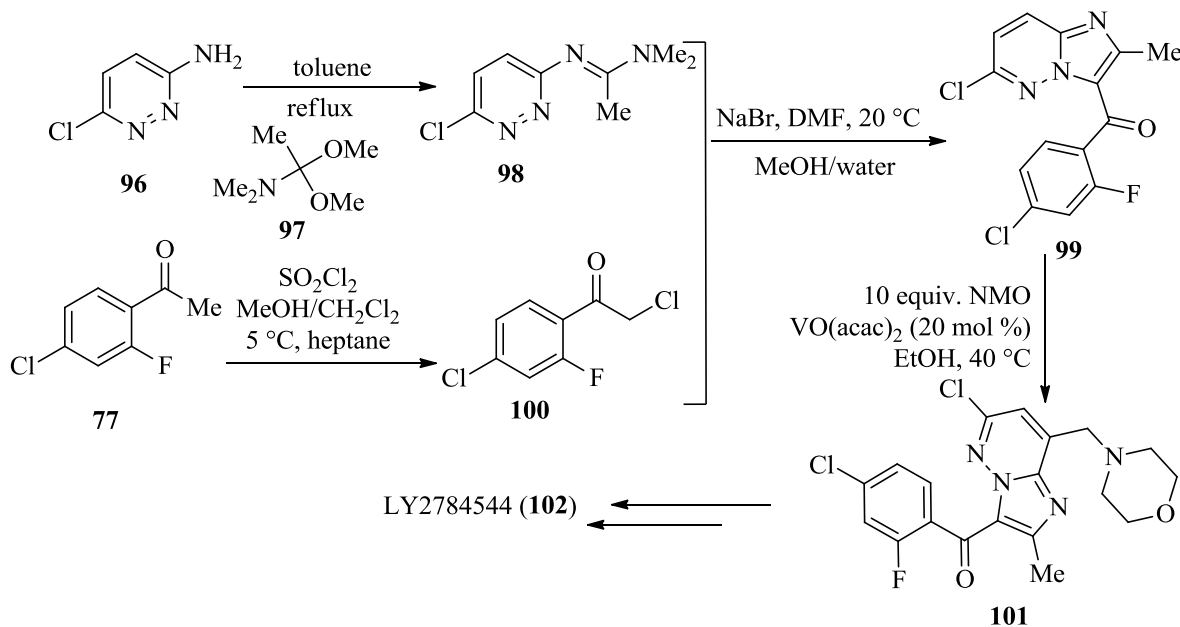
Scheme 3.30: Synthesis of indolyl-tetrahydroisoquinoline using vanadium catalyst

Hwang and Uang improved the generation of iminium ion using vanadium catalyst and achieved the regioselective aminomethylation of naphthols (**23**) to synthesize corresponding Mannich base

product (**93**). Reaction of 2-naphthol (**35**) with amine *N*-oxides (**24**) was carried out in the presence of VO(acac)₂ 10 mol % of catalyst in DCM at reflux condition for 8-120 h (**Scheme 3.31**). Generality of reaction was evaluated with different naphthol and phenol as nucleophiles with good to excellent yield but in ester substituted phenols comparatively less yield was observed. A variety of amine *N*-oxides were smoothly reacted with 1-naphthol and 2-naphthol. Reaction starts with formation of six member complex (**94**) of vanadium with amine *N*-oxide to produce iminium ion (**95**) and attack of nucleophiles followed by abstraction of proton generate the desired product and removal of water molecule complete the catalytic cycle of vanadium (**Scheme 3.31**).^[89]



Scheme 3.31: Reactions of naphthols and phenols with amine *N*-oxide catalyzed by VO(acac)₂ Mitchell *et al.* used an oxidative aminomethylation process in the large-scale synthesis of LY2784544, JAK2 inhibitor and active pharmaceutical ingredient for the treatment of myeloproliferative disorders. The molecule LY2784544 was synthesized by multistep synthesis using series of reagents. Reaction of *N*-methylmorpholine-*N*-oxide and **99** in the presence of VO(acac)₂ catalyst resulted the corresponding product (**Scheme 3.32**).^[90]



Scheme 3.32: LY2784544 synthesis *via* multi-step process

There are numerous methods to oxidatively couple two sp^2 -hybridized C–H bonds in high yields; however, the cross coupling of sp^3 - and sp^2 -hybridized C–H bonds is much less common, as sp^3 -hybridized C–H bonds are generally less reactive. In fact, in order to achieve C(sp^3)–H bond activation, directing groups are often needed. A combination of C–H activation with amination cross coupling is straightforward and simple methodology which deals as *N*-electrophile instead of *N*-nucleophile and facilitate the attack of the (nucleophilic) C–M metallated intermediate. Usual pre-functionalizations of amine partners such as *N*-carboxylates, *N*-tosylates or more often *N*-halides are common for this reactivity.^[91-93]

In the absence of directing group, and occasionally even when these groups are employed, β -hydride elimination, as opposed to cross-coupling, is often observed during the C(sp^3)–H activation step which is drawback and oppose the cross-coupling reaction. Despite these challenges, we sought to develop novel aminomethylation *via* the oxidative coupling of sp^3 - and sp^2 - hybridized C–H bonds.

Specifically, we sought to find method for the aminomethylation of imidazo[1,2-*a*]pyridine substrates. Neuroactive pharmaceuticals such as necopidem, saripidem, and zolpidem contain substituted imidazo[1,2-*a*]pyridine backbone (**Figure 3.3**). Also methylene linked morpholine heterocycles showed promising biological activity, so combining these two biologically active species will lead to some improvements in bioactivity (**Figure 3.3**). Janus kinase 2 (JAK2) is

human protein tyrosine kinase established in the cytosol which work as nucleotide binding, ATP binding, and transferase activities. Morpholine attached heterocycles CYT_{387} an orally bioavailable small-molecule inhibitor of Janus kinases 1 and 2 which is under human clinical trial as JAK2 inhibitors (**Figure 3.3**).

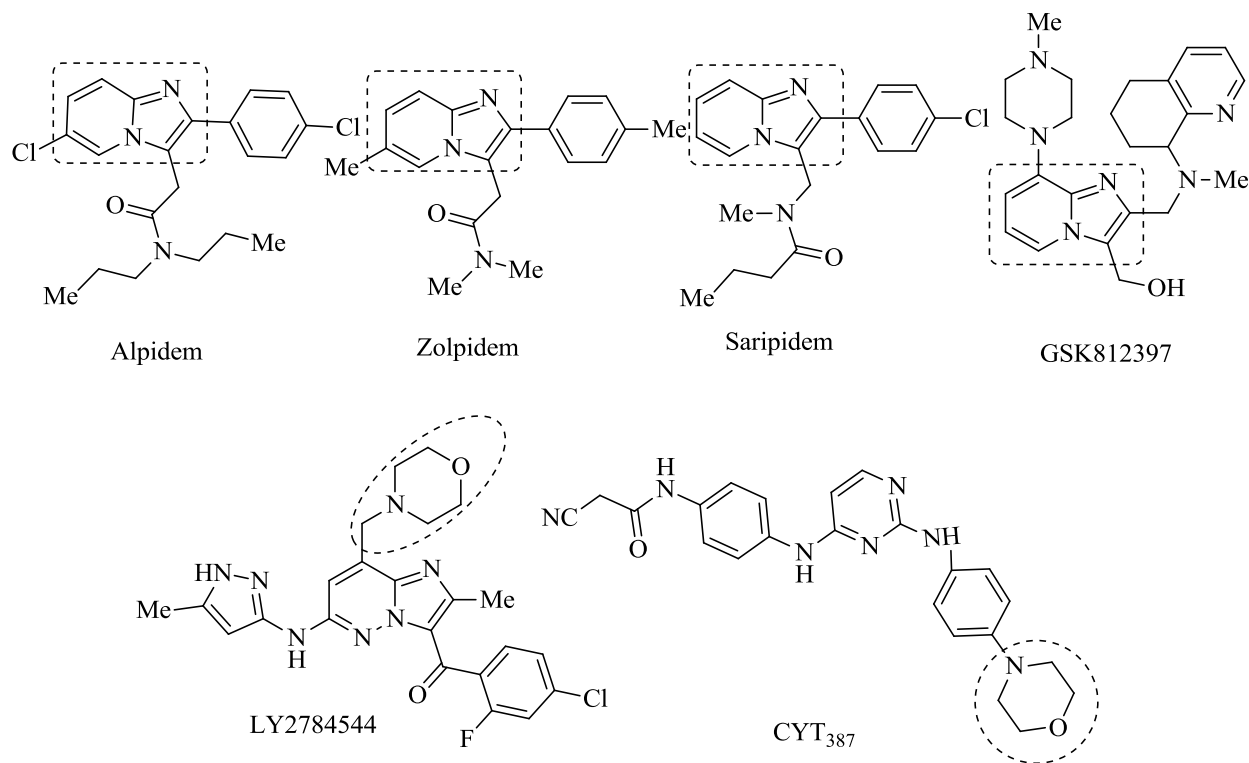


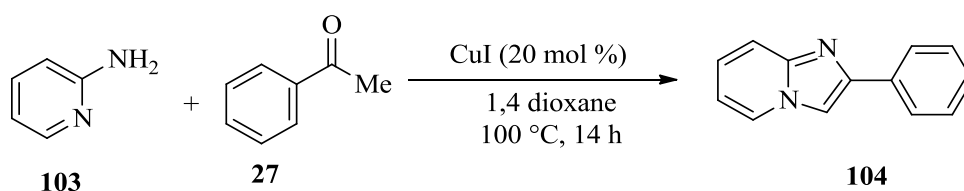
Figure 3.3: Imidazo[1,2-*a*]pyridine drug molecule and morpholine linked bioactive heterocycles

Providing a way to oxidative coupling of the 3-position of 2-arylimidazo[1,2-*a*]pyridine with alkylamines would be useful tool for the synthesis of derivatives of these nonbenzodiazepine GABA potentiators.

N-oxide amines are attractive material to generate iminium ion through the oxidation of $\text{C}(\text{sp}^3)\text{-H}$ bond α to nitrogen, catalyzed by transition-metal such as Cu, Fe, Ru, Rh, Au and V. Herein, we disclose the discovery of vanadium-catalyzed oxidative coupling of imidazo[1,2-*a*]pyridines with *N*-methylmorpholine oxide (NMO), which serves as both the sp^3 -hybridized coupling partner and the oxidant.

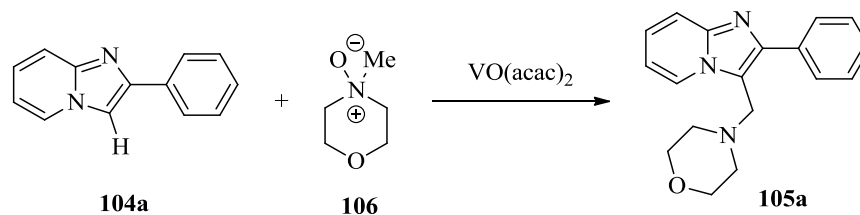
3.3. Result and discussion

The starting material 2-arylimidazo[1,2-*a*]pyridines (**104**) were synthesized using our previous reported method.^[94] Reaction of acetophenone (**27**) and 2-aminopyridine (**103**) in the presence of CuI was refluxed for 12 h to get the corresponding product (**104**) (Scheme 3.33). The synthesized **104a** was characterized by ¹H NMR and ¹³C NMR. In the ¹H NMR spectrum of **104a**, singlet appeared at δ 7.85 ppm for C₃-H along with other protons at their respective positions (Figure 3.4). The other starting materials were also characterized by matching their melting point with literature reports.^[94]

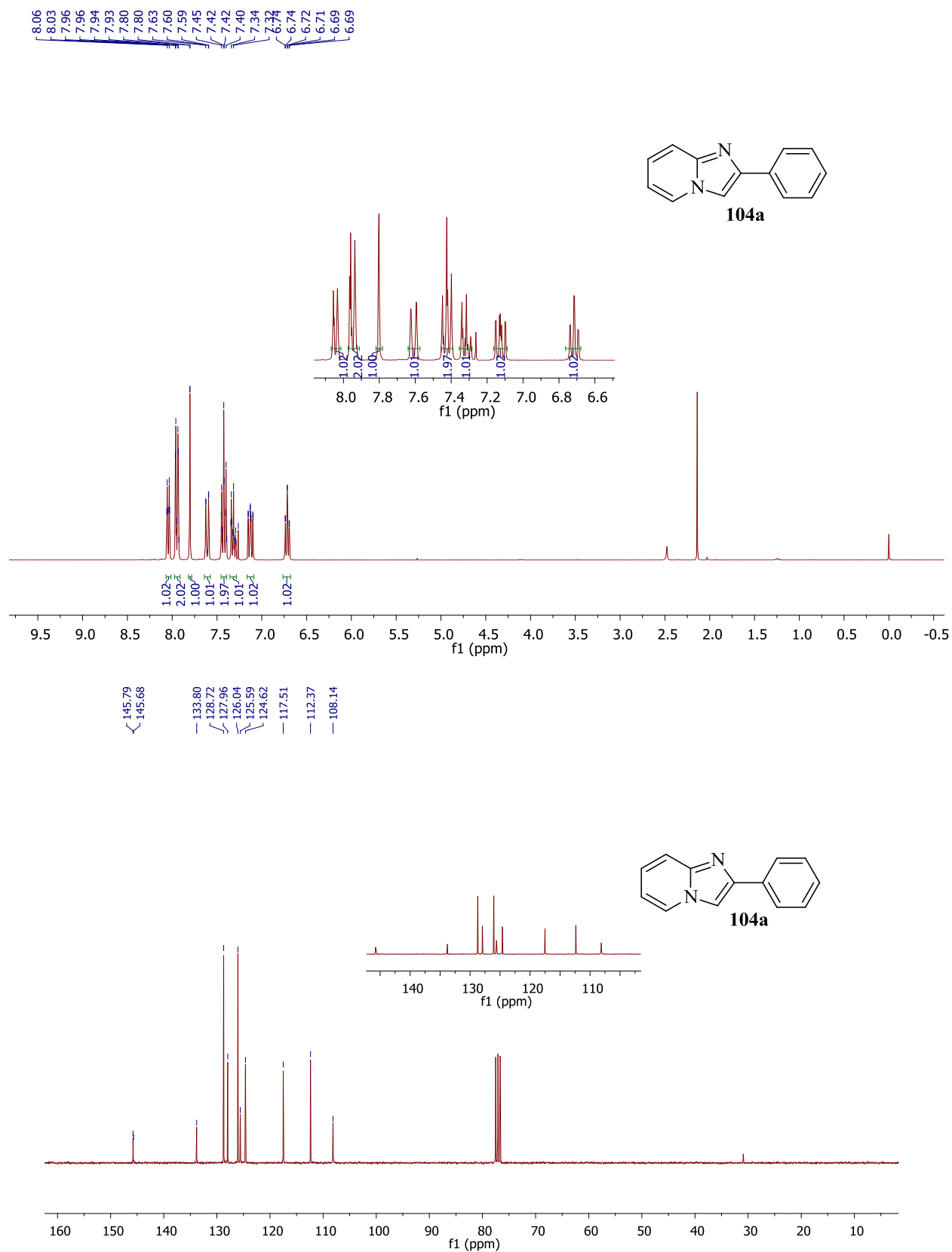


Scheme 3.33: Synthesis of 2-phenylimidazo[1,2-*a*]pyridine (**104**)

Based on the previous work of Hwang and Uang, we chose to commence our studies using vanadyl acetylacetonate, VO(acac)₂, as the catalyst for the oxidative aminomethylation of 2-arylimidazo[1,2-*a*]pyridine (Scheme 3.34). The reaction of 2-phenylimidazo[1,2-*a*]pyridine (**104a**) with NMO in the presence of VO(acac)₂ in DCM was stirred for 18 h at 120 °C to give 70% yield of 4-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (**105a**). The structure of **105a** was characterized by NMR data and characteristic peak in ¹H NMR at δ 3.98 ppm for two protons of methylene link as well as two set of triplet for four protons confirmed the link of morpholine to 2-phenylimidazo[1,2-*a*]pyridine. The product formation was also confirmed by ¹³C NMR and peak at δ 66.97 ppm corresponds to methylene carbon with well agreement of all other aromatic carbon. ¹H and ¹³C NMR spectra of 4-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (**105a**) is shown in figure 3.5



Scheme 3.34: Vanadium-catalyzed aminomethylation of 2-phenylimidazo[1,2-*a*]pyridine

Figure 3.4: ^1H and ^{13}C NMR spectra of **104a**

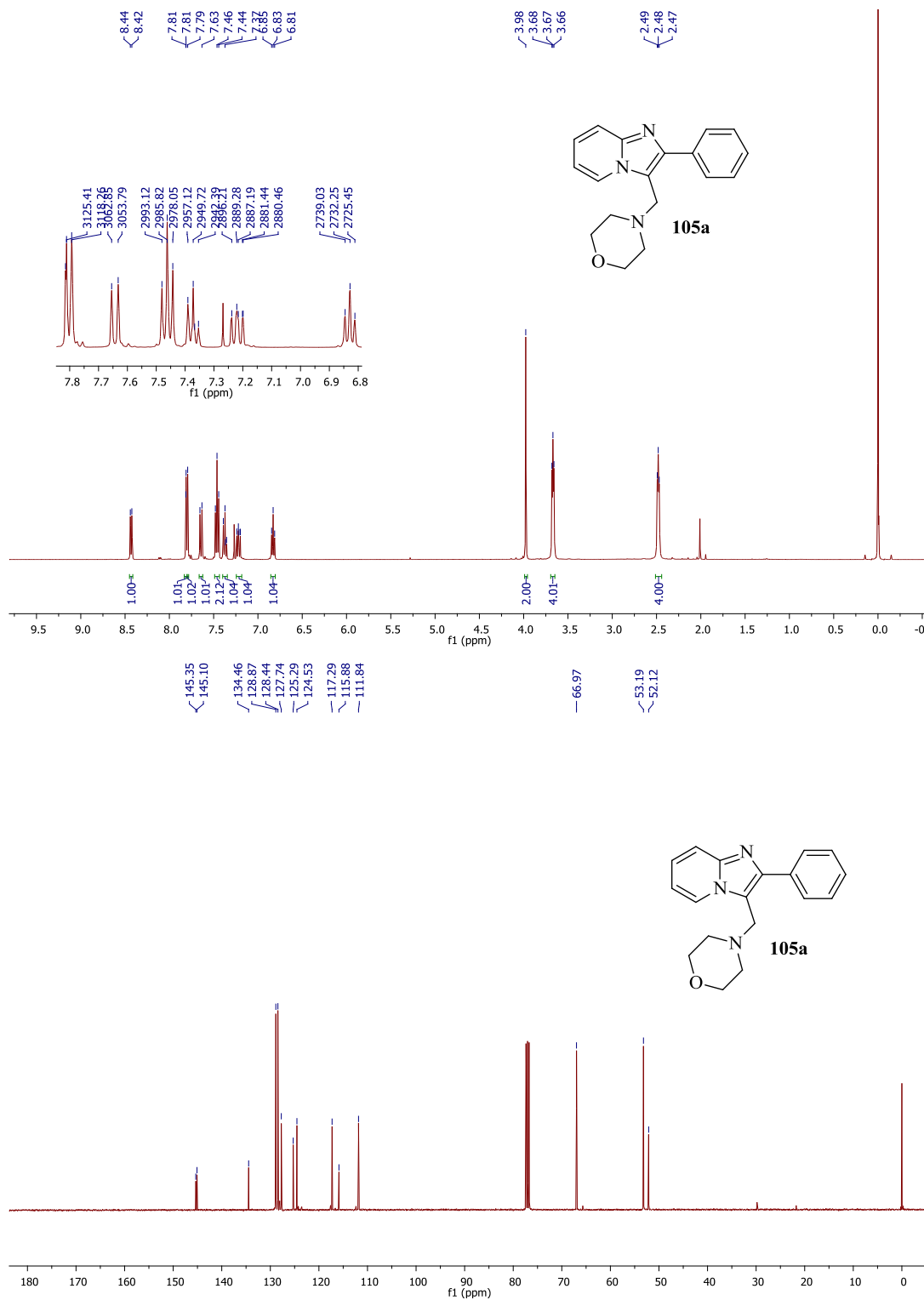
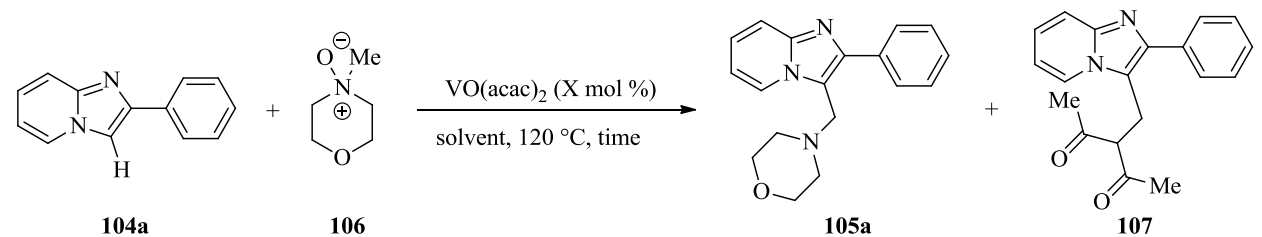


Figure 3.5: ¹H and ¹³C NMR spectra of 4-((2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)morpholine (**105a**)

We systematically studied the effect of solvent, catalyst loading, time, and NMO loading (Table 3.1). Ethanol, toluene, and tetrahydrofuran were initially tested (Table 3.1 entries 4–6), but the yields were lower compared to methylene chloride (DCM). To our surprise, the aminomethylation reactions consistently formed the acetylacetonate by-product **107**, which was very difficult to remove from the desired product **105a** by flash chromatography.

Table 3.1: Optimization of the oxidative aminomethylation conditions for the synthesis of **105a**



| Entry | Catalyst | (mol %) of catalyst | NMO (equiv) | Solvent | Time (h) | Yield (%) ^a | |
|-----------|-------------------------------|---------------------|-------------|--------------------|-----------|------------------------|----------------|
| | | | | | | 105a | 107 |
| 1 | VO(acac) ₂ | 25 | 10 | DCM | 18 | 70 | 4 |
| 2 | VO(acac) ₂ | 20 | 10 | DCM | 18 | 65 | 3 |
| 3 | VO(acac) ₂ | 25 | 10 | DCM | 18 | 59 ^c | - ^b |
| 3 | VO(acac) ₂ | 10 | 10 | DCM | 18 | 62 | - ^b |
| 4 | VO(acac) ₂ | 20 | 10 | ethanol | 18 | 33 | 2 |
| 5 | VO(acac) ₂ | 20 | 10 | toluene | 18 | 30 | 29 |
| 6 | VO(acac) ₂ | 20 | 10 | THF | 18 | 57 | 1 |
| 7 | VO(acac) ₂ | 10 | 5 | DCM | 6 | 88 | 6 |
| 8 | V ₂ O ₅ | 20 | 10 | DCM | 6 | 58 ^c | 0 |
| 9 | VO(acac) ₂ | 20 | 10 | 1,4-dioxane | 12 | 80 ^c | 0 |
| 10 | VO(acac)₂ | 20 | 5 | 1,4-dioxane | 12 | 80^c | 0 |
| 11 | VO(acac) ₂ | 20 | 3 | 1,4-dioxane | 12 | 69 ^c | 0 |
| 12 | VO(acac) ₂ | 20 | 1 | 1,4-dioxane | 12 | 36 ^c | 7 |

^aProduct yield determined by NMR.

^bTraces of **107** were observed. ^cIsolated yield.

The loading of VO(acac)₂ was varied from 25 mol % to 10 mol %, showing that lower catalyst loading provided lower yields but also lower impurities (Table 3.1, entries 1–4). This study indicated that the optimal yield of **105a** could be achieved using 10 mol % VO(acac)₂ and 5

equiv of NMO for 6 h in DCM (Table 3.1, entry 7), but as previously mentioned, the product **105a** was nearly impossible to purify from the by-product **107**. Consequently, we chose to study vanadyl catalyst V_2O_5 , that did not contain organic ligands (Table 3.1, entry 8), but the yield of **105a** was lower. Finally, we found that changing the solvent to 1,4-dioxane and increasing the catalyst loading of $VO(acac)_2$ to 20 mol % allowed for the facile synthesis of **105a** in 80% yield in high purity. Decreasing the amount of NMO below 5 equiv decreased the yield of **105a**, and when it became 1 equiv the yield of the unwanted by-product **107** increased to 7% (Table 3.1, entries 10–12).

Performing careful study of the reaction over time gave further insight into the reaction's profile. An aminomethylation reaction of **104a** was set up according to the typical procedure with solvent DCM. 0.1 mL aliquots were removed from the reaction every two hours and were analyzed by gas chromatography. *n*-Dodecane was used as an internal standard. Figure 3.6 represents the time dependent reaction progress using gas chromatography technique.

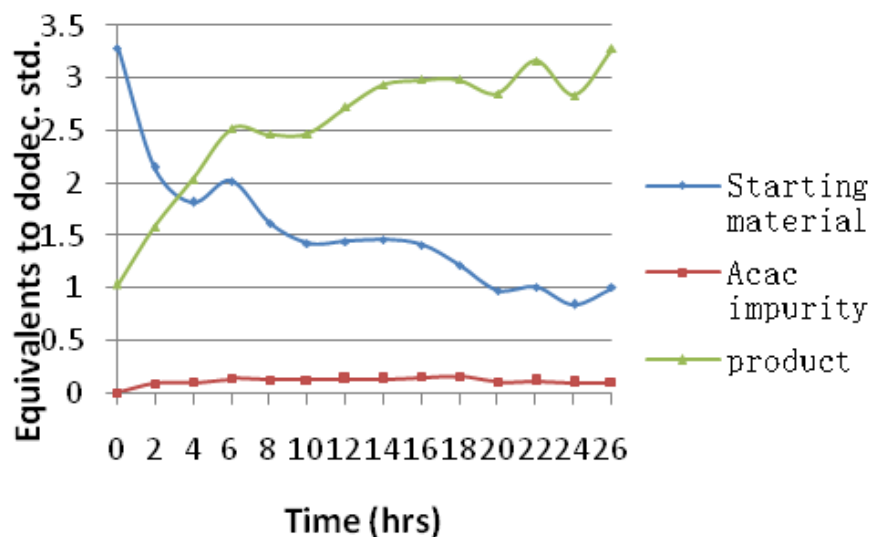


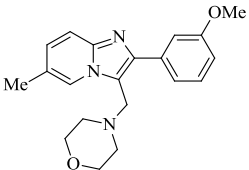
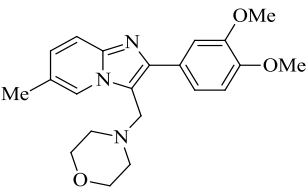
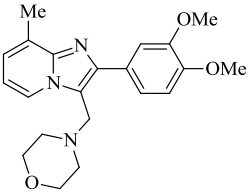
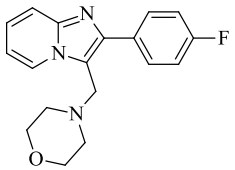
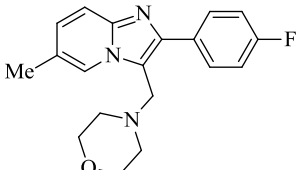
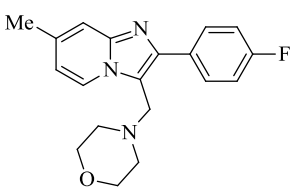
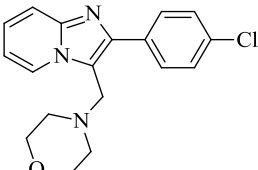
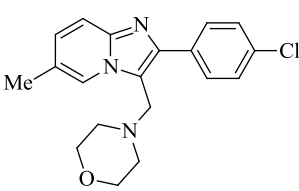
Figure 3.6: GC time study of reaction mixture

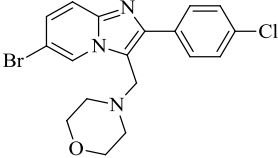
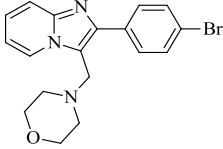
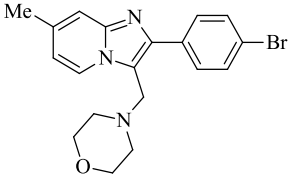
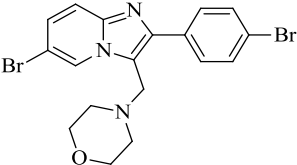
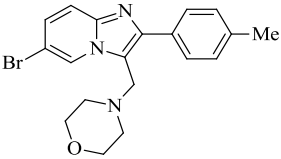
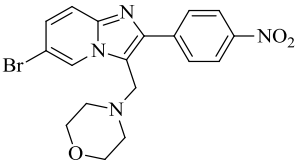
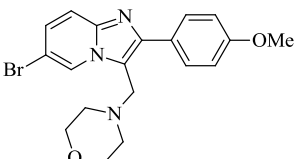
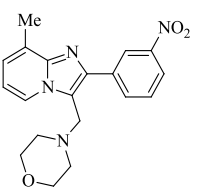
Once the optimal conditions were obtained, the oxidative aminomethylation was performed on wide variety of substrates (Table 3.2). 2-Arylimidazo[1,2-*a*]pyridines (**104**) containing electron-withdrawing groups on the *para*-position of the aryl substituent resulted in lower yields, while electron donating groups on the *para*-position generally led to higher yields. For example, **105r**, which contains nitro substituent on the *para*-position, could not be formed, while **105s**, with methyl ether substituent on the same position was easily synthesized in 84% yield. The addition

of second electron-donating substituent at the *meta*-position did not improve the yield of the reaction; rather, it produced slightly lower yield (compare **105d** and **105f**). Changing the position of an electron-donating methyl group on the imidazo[1,2-*a*]pyridine ring from the C6-position (Table 3.2, entry 6) to the C8-position (Table 3.2, entry 7) did not appear to significantly affect the reaction. Importantly, halogens as substituent in both imidazo[1,2-*a*]pyridine as well as 2-aryl ring could be tolerated by the reactions and resulted good to excellent yield of corresponding product (Table 3.2, entries 8-16), indicating that subsequent coupling reactions could be performed on the aminomethylated products.

Table 3.2: Substrate scope for oxidative aminomethylation of imidazo[1,2-*a*]pyridines^a

| Entry | R ¹ | R ² | Product | Yield (%) ^b |
|-------|----------------|----------------|---------|------------------------|
| 1 | H | H | | 80 |
| 2 | H | 4-Me | | 74 |
| 3 | 6-Me | 4-Me | | 70 |
| 4 | 6-Me | 4-OMe | | 90 |

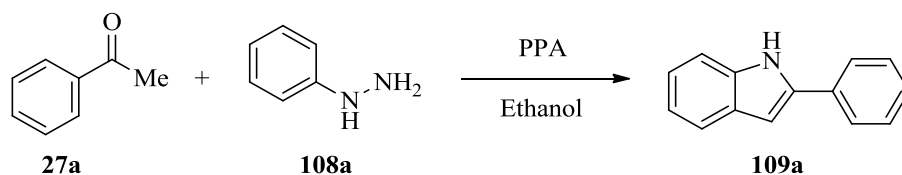
| Entry | R ¹ | R ² | Product | Yield (%) ^b |
|-------|----------------|------------------------|--------------------------------------------------------------------------------------|------------------------|
| 5 | 6-Me | 3-OMe |  | 105e 76 |
| 6 | 6-Me | 3,4-(OMe) ₂ |  | 105f 81 |
| 7 | 8-Me | 3,4-(OMe) ₂ |  | 105g 83 |
| 8 | H | 4-F |  | 105h 70 |
| 9 | 6-Me | 4-F |  | 105i 77 |
| 10 | 7-Me | 4-F |  | 105j 75 |
| 11 | H | 4-Cl |  | 105k 80 |
| 12 | 6-Me | 4-Cl |  | 105l 82 |

| Entry | R ¹ | R ² | Product | Yield (%) ^b |
|-------|----------------|-------------------|--------------------------------------------------------------------------------------|------------------------|
| 13 | 6-Br | 4-Cl |  | 105m 79 |
| 14 | H | 4-Br |  | 105n 56 |
| 15 | 7-Me | 4-Br |  | 105o 55 |
| 16 | 6-Br | 4-Br |  | 105p 58 |
| 17 | 6-Br | 4-Me |  | 105q 69 |
| 18 | 6-Br | 4-NO ₂ |  | 105r 0 |
| 19 | 6-Br | 4-OMe |  | 105s 84 |
| 20 | 8-Me | 3-NO ₂ |  | 105t 63 |

^aReaction conditions: **104** (1.0 mmol), **106** (5.0 mmol), VO(acac)₂ (20 mol %), 1,4-dioxane (3.0 mL), stirred for 12 h at 120 °C.

^bIsolated yield.

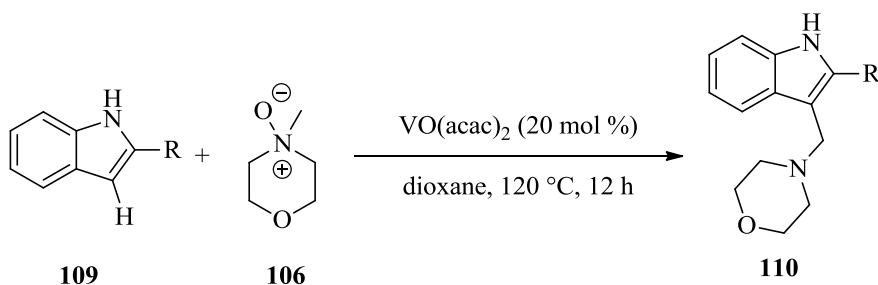
In addition to 2-arylmidazo[1,2-*a*]pyridines (**104**), 2-substituted indoles (**109**) could also be aminomethylated. 2-Arylindoles (**109**) were prepared using reported methodology *via* Fischer indole synthesis by the reaction of acetophenone (**27**) and phenylhydrazine (**108**) in the presence of polyphosphoric acid (**Scheme 3.35**).



Scheme 3.35: Synthesis of 2-arylindole *via* Fischer indole synthesis

As shown in **table 3.3**, both 2-phenyl and 2-methylindole were oxidatively aminomethylated in 60% and 73% yields respectively (**110a**, **110b**).

Table 3.3: Substrate scope for oxidative aminomethylation of 2-substituted indoles (**109**)^a



| Entry | R | Product | Yield (%) ^b |
|-------|-------------------------------|---------|------------------------|
| 1 | C ₆ H ₅ | | 60 |
| 2 | Me | | 73 |

^aReaction conditions: **109** (1.0 mmol), **106** (5 mmol), VO(acac)₂ (20 mol %), 1,4-dioxane (3.0 mL), stirred for 12 h at 120 °C.

^bIsolated yield.

Product **110a** was confirmed by ^1H and ^{13}C NMR and peak at 8.48 ppm belongs to *NH* protons and morpholine peaks appeared in aliphatic region in ^1H NMR confirming the attachment of morpholine to indole. Also methylene carbon in ^{13}C NMR appeared at 67.25 ppm which confirmed the product structure (**Figure 3.7**).

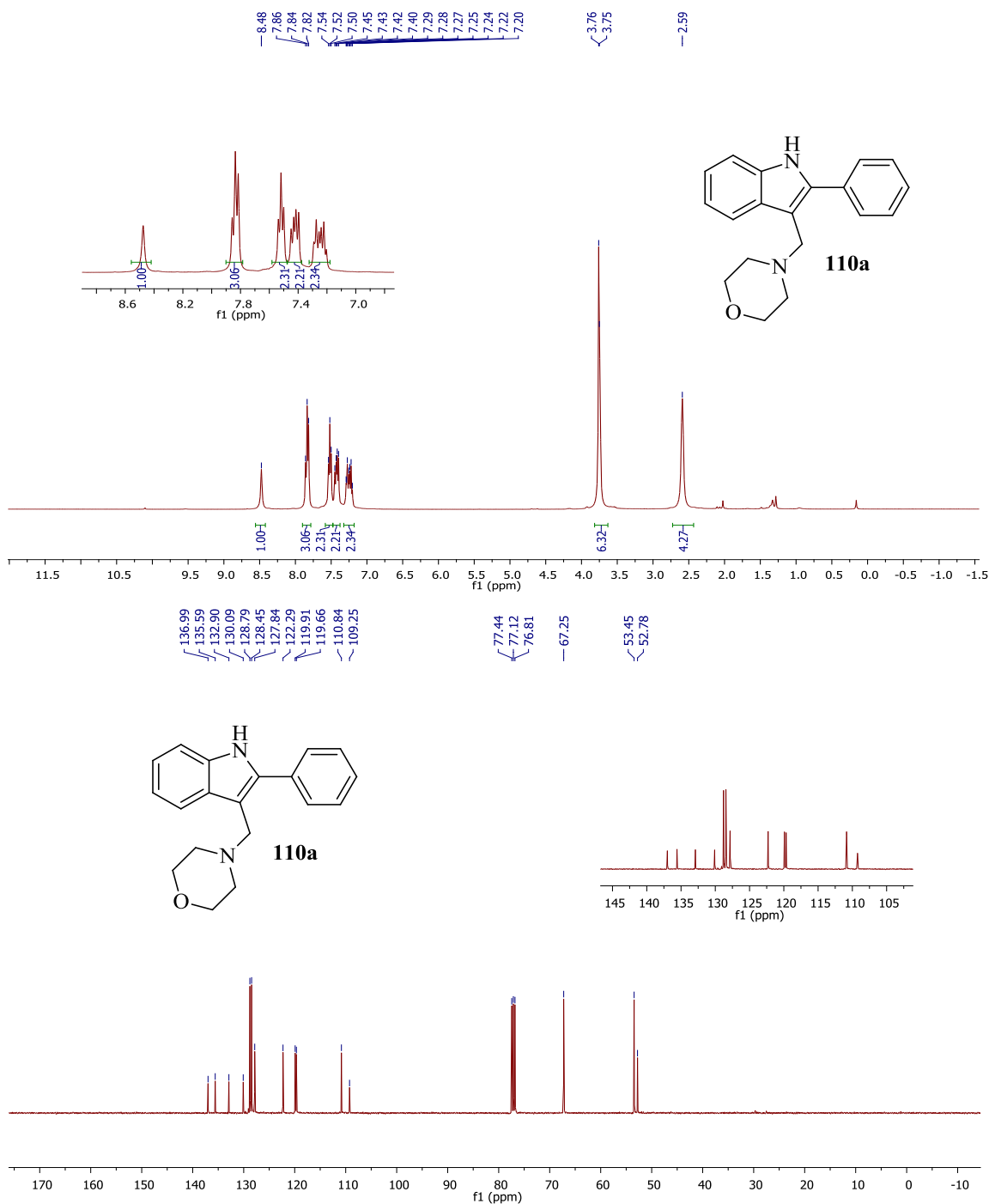
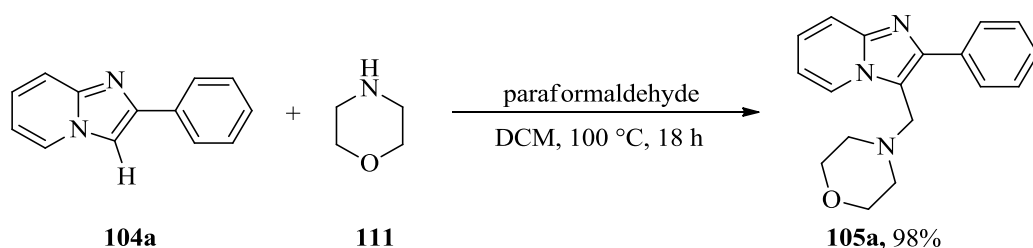


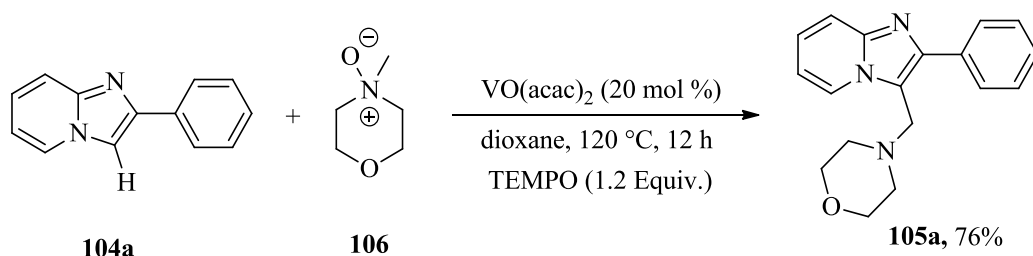
Figure 3.7: ^1H and ^{13}C NMR spectra of 4-((2-phenyl-1H-indol-3-yl)methyl)morpholine (**110a**)

Previous studies of vanadium-catalyzed oxidative coupling of structures similar to **105a** proposed radical mechanism; while others hypothesized that the product was formed by way of Mannich-type reaction. We propose that Mannich-type mechanism is responsible for the formation of both **105** and **107**. This was determined by running conventional Mannich reaction using **104a**, paraformaldehyde (**52**), and morpholine (**111**) to make the iminium ion *in situ*. The reaction of 2-phenylimidazo[1,2-*a*]pyridine (**104a**) with morpholine and paraformaldehyde in DCM was stirred for 18 h at reflux condition to give the desired product in 98% yield (**Scheme 3.36**).



Scheme 3.36: Conventional Mannich reaction for synthesis of **105a**

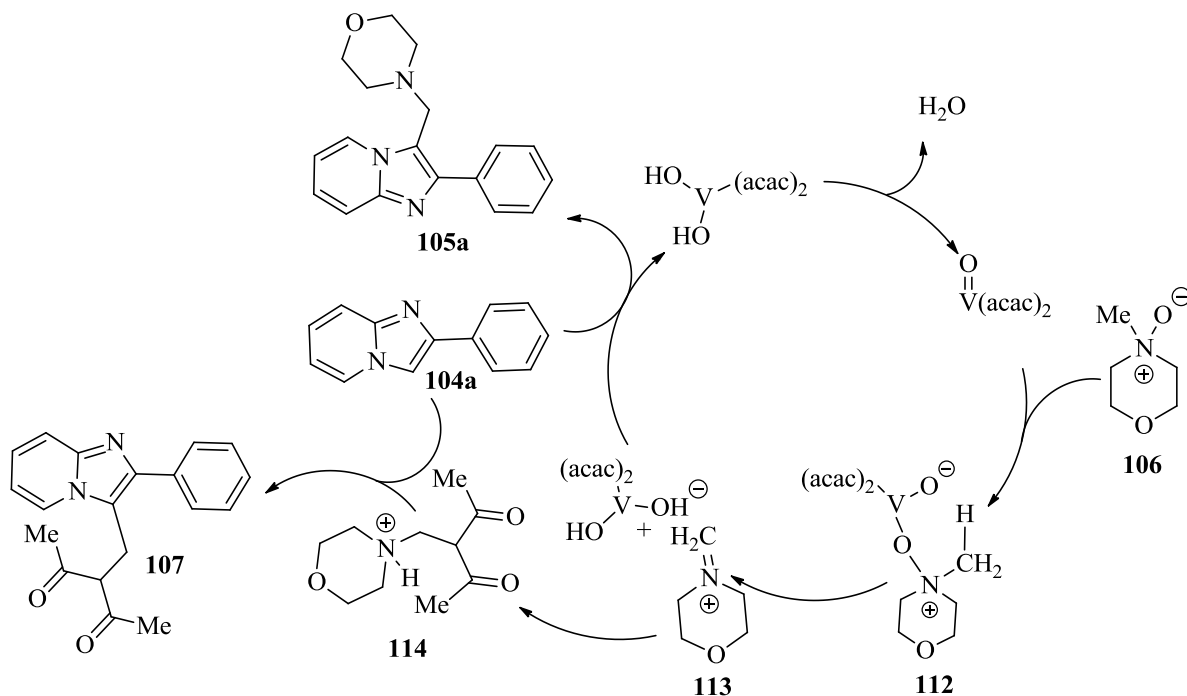
Performing the control experiment with aminomethylation for the synthesis of **105a** using our optimal reaction conditions in the presence of TEMPO, radical inhibitor, did not prevent product formation, further indicating that the reaction is likely not radical mediated (**Scheme 3.37**).



Scheme 3.37: Reaction of 2-phenylimidazo[1,2-*a*]pyridine with NMO in the presence of TEMPO

Consequently, we proposed that the product **105** and by-product **107** were formed by the mechanism shown in **scheme 3.38**. The *N*-methylmorpholine oxide reacts with VO(acac)₂ catalyst and forms complex **112** resulting in the formation of an iminium ion (**113**) and vanadium complex. Vanadium species abstract proton from 2-phenylimidazo[1,2-*a*]pyridine (**104a**) and attack on iminium ion to result desired product (**105a**). Elimination of water from vanadium complex regenerates the VO(acac)₂ to complete the catalytic cycle. We believe **107** is formed when the iminium ion reacts with one of the ligands from the vanadium catalyst producing

intermediate **114**, thus formally incorporating the acac ligand and the methyl from the NMO in the observed by-product (**107**).



Scheme 3.38: Proposed mechanism for synthesis of **105a** and **107**

3.4. Conclusions

In summary, the vanadium-catalyzed oxidative coupling of substituted imidazo[1,2-*a*]pyridines and *N*-methylmorpholine was achieved in yields up to 90%. Despite the ability to produce this product using conventional Mannich conditions, we believe this is useful, orthogonal method to synthesize tertiary amines.

3.5. Experimental section

3.5.1. General information

Melting points were determined in open capillary tubes using an EZ-Melt automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck). The chemical structures of final products were determined by nuclear magnetic resonance spectra (^1H NMR and ^{13}C NMR) using Bruker Avance 300 MHz spectrometer. ^{13}C NMR spectra are fully decoupled. Chemical shifts are reported in parts per million (ppm) using the residual protonated solvent peak or

tetramethylsilane (internal) as the standard. Gas chromatography and low resolution mass spectroscopy data were acquired using an Agilent 6870 GC, DB-1MS capillary column, and an Agilent 5973 mass selective detector (EI ionization). Compounds that were not sufficiently volatile for GCMS analysis were directly injected into an Agilent 6120 single quad mass spectrometer (ESI ionization). Both mass spectrometers were calibrated using Agilent's internal calibrant. Chemicals were obtained from commercial suppliers such as Fisher Scientific and Sigma- Aldrich and were used without further purification.

3.5.2. Experimental procedure for the synthesis of 4-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (105a): A 10 mL RB flask was charged with 2-phenylimidazo[1,2-*a*]pyridine (100 mg, 0.515 mmol), *N*-methylmorpholine-*N*-oxide (301 mg, 2.58 mmol), VO(acac)₂ (27 mg, 0.103 mmol), and dioxane (2.0 mL). The resulting solution was stirred at 120 °C in an oil bath for 12 h. On completion of the reaction, the reaction mass was filtered through celite and washed with ethyl acetate. The filtrate was washed with water, and the organic solvent was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude residue was purified by column chromatography (EtOAc: hexane, 1:4) to obtain the pure product, 4-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (**105a**).

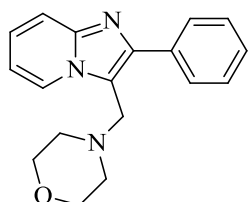
3.5.3. Experimental procedure for the synthesis of 2-phenylindole (109a): A round bottom flask was charged with acetophenone (1 gm, 0.082 mol) and phenylhydrazine (0.9 gm, 0.082 mol) in 5 mL ethanol and few drops of glacial acetic acid and heated in oil bath. The reaction was cooled and filtered and washed with spirit and dried. The crude was transferred to 50 ml beaker and added 9 gm of polyphosphoric acid. The reaction mixture was heated to 120 °C and stirred with glass rod. After 15 minutes reaction mixture was cooled and washed with excess of water and filtered. The reaction mixture was heated with rectified spirit and cooled and filtered. The product was dried over vacuum.

3.5.4. Experimental procedure for the synthesis of 4-((2-phenyl-1*H*-indol-3-yl)methyl)morpholine (110a): A 10 mL RB flask was charged with 2-phenylindole (100 mg, 0.518 mmol), *N*-methylmorpholine-*N*-oxide (303 mg, 2.59 mmol), VO(acac)₂ (27 mg, 0.103 mmol), and dioxane (2.0 mL). The resulting solution was stirred at 120 °C in an oil bath for 12 h. On completion of the reaction, the reaction mass was filtered through celite and washed with ethyl acetate. The filtrate was washed with water, and the organic solvent was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude residue was purified by

column chromatography (EtOAc: hexane, 1:6) to obtain the pure product, 4-((2-phenyl-1*H*-indol-3-yl)methyl)morpholine (**110a**).

3.5.5. Physical and spectral data of 105a-t, 110a-b

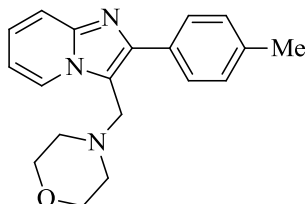
4-((2-Phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (105a): Yield 80%; Off-white



solid; mp 138-140 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.43 (d, $J = 6.9$ Hz, 1H), 7.81 (d, $J = 1.4$ Hz, 1H), 7.79 (s, 1H), 7.64 (d, $J = 9.1$ Hz, 1H), 7.46 (t, $J = 7.5$ Hz, 2H), 7.37 (dd, $J = 8.4, 6.4$ Hz, 1H), 7.26 – 7.18 (m, 1H), 6.83 (t, $J = 6.8$ Hz, 1H), 3.98 (s, 2H), 3.65 (t, $J = 4.5$ Hz, 4H), 2.46 (t, $J = 4.4$ Hz,

4H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.4, 145.1, 134.5, 128.9, 128.4, 127.7, 125.3, 124.5, 117.3, 115.9, 111.8, 67.0, 53.2, 52.1; MS (EI, m/z) calculated for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}$ 293.15, found 293.15 $[\text{M}]^+$.

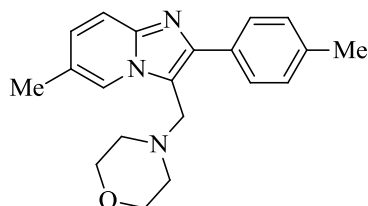
4-((2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (105b): Yield 74%; Off-white



solid; mp 119-121 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.42 (d, $J = 6.9$ Hz, 1H), 7.70 (d, $J = 8.1$ Hz, 2H), 7.63 (d, $J = 9.1$ Hz, 1H), 7.29 – 7.25 (m, 2H), 7.23 – 7.17 (m, 1H), 3.96 (s, 2H), 3.67 (t, $J = 4.5$ Hz, 4H), 2.48 (t, $J = 4.4$ Hz, 4H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.4, 145.0, 137.5, 131.6, 129.2, 128.7, 125.2, 124.4,

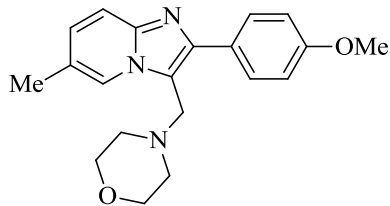
117.2, 115.6, 111.8, 67.0, 53.2, 52.2, 21.3; MS (EI, m/z) calculated for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}$ 307.17, found 307.17 $[\text{M}]^+$.

4-((6-Methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (105c): Yield 70%;



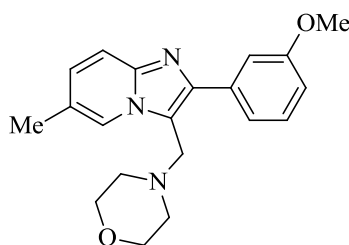
Pale yellow solid; mp 168-170 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 7.69 (d, $J = 8.1$ Hz, 2H), 7.53 (d, $J = 9.1$ Hz, 1H), 7.26 (d, $J = 7.4$ Hz, 2H), 7.06 (dd, $J = 9.2, 1.5$ Hz, 1H), 3.93 (s, 2H), 3.67 (t, $J = 4.5$ Hz, 4H), 2.48 (t, $J = 4.4$ Hz, 4H), 2.40 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.2, 144.1,

137.3, 131.7, 129.1, 128.7, 127.5, 122.7, 121.3, 116.5, 115.4, 67.0, 53.2, 52.1, 21.3, 18.5; MS (EI, m/z) calculated for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}$ 321.18, found 321.18 $[\text{M}]^+$.

4-((2-(4-Methoxyphenyl)-6-methylimidazo[1,2-a]pyridin-3-yl)methyl)morpholine (105d):

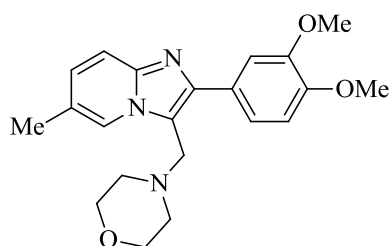
Yield 90%; Off-white solid; mp 139-141 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.15 (s, 1H), 7.75 (d, $J = 8.7$ Hz, 2H), 7.54 (d, $J = 9.2$ Hz, 1H), 7.07 (d, $J = 9.1$ Hz, 1H), 7.00 (d, $J = 8.7$ Hz, 2H), 3.92 (s, 2H), 3.87 (s, 3H), 3.68 (bs, 4H), 2.49 (bs, 4H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 149.0, 145.3, 144.8, 127.1, 123.5,

122.8, 121.4, 115.8, 112.4, 112.0, 111.0, 67.0, 55.9, 53.2, 52.2, 17.2; MS (ESI, m/z) calculated for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_2$ 337.18, found 337.18 $[\text{M}+\text{H}]^+$.

4-((2-(3-Methoxyphenyl)-6-methylimidazo[1,2-a]pyridin-3-yl)methyl)morpholine (105e):

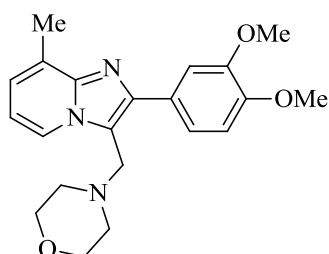
Yield 76%; Colourless solid; mp 143-145 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.15 (s, 1H), 7.55 (d, $J = 8.9$ Hz, 1H), 7.46 – 7.31 (m, 3H), 7.07 (d, $J = 8.9$ Hz, 1H), 6.92 (d, $J = 6.4$ Hz, 1H), 3.94 (s, 2H), 3.88 (s, 3H), 3.68 (bs, 4H), 2.50 (bs, 4H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.7, 145.1, 144.1, 136.0, 129.4, 127.7, 122.7,

121.5, 121.2, 116.7, 115.7, 113.9, 113.8, 67.0, 55.3, 53.2, 52.0, 18.5; MS (EI, m/z) calculated for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_2$ 337.18, found 337.19 $[\text{M}]^+$.

4-((2-(3,4-Dimethoxyphenyl)-6-methylimidazo[1,2-a]pyridin-3-yl)methyl)morpholine (105f):

Yield 81%; Off-white solid; mp 151-153 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.13 (s, 1H), 7.55 (d, $J = 9.1$ Hz, 1H), 7.49 (s, 1H), 7.37 (d, $J = 8.2$ Hz, 1H), 7.08 (d, $J = 9.4$ Hz, 1H), 6.96 (d, $J = 8.2$ Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 3.93 (s, 2H), 3.69 (t, $J = 3.9$ Hz, 4H), 2.53 (t, $J = 3.8$ Hz, 4H), 2.38 (s, 3H); ^{13}C NMR (75

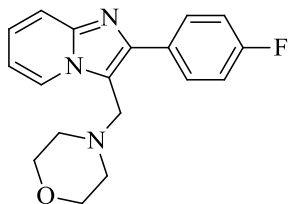
MHz, CDCl_3) δ 149.0, 148.8, 145.0, 143.9, 127.7, 127.3, 122.5, 121.6, 121.1, 116.4, 115.2, 112.0, 110.9, 67.0, 56.0, 55.9, 53.2, 52.0, 18.6; MS (ESI, m/z) calculated for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_3$ 368.20, found 368.20 $[\text{M}+\text{H}]^+$.

4-((2-(3,4-Dimethoxyphenyl)-8-methylimidazo[1,2-a]pyridin-3-yl)methyl)morpholine (105g):

Yield 83%; Viscous liquid; ^1H NMR (300 MHz, CDCl_3) δ 8.26 (d, $J = 6.8$ Hz, 1H), 7.44 (d, $J = 1.5$ Hz, 1H), 7.33 (dd, $J = 8.3$, 1.7 Hz, 1H), 7.02 (d, $J = 6.8$ Hz, 1H), 6.96 (d, $J = 8.3$ Hz, 1H), 6.76 (t, $J = 6.8$ Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 3.93 (s, 2H), 3.69 (t, $J = 4.3$ Hz, 4H), 2.67 (s, 3H), 2.50 (t, $J = 4.2$ Hz, 4H); ^{13}C NMR (75

MHz, CDCl₃) δ 149.0, 148.8, 145.3, 144.8, 127.3, 127.1, 123.5, 122.8, 121.4, 115.8, 112.4, 112.0, 111.0, 67.0, 56.0, 55.96, 55.94, 53.2, 52.2, 17.2; MS (ESI, m/z) calculated for C₂₁H₂₆N₃O₃ 368.20, found 368.20 [M+H]⁺.

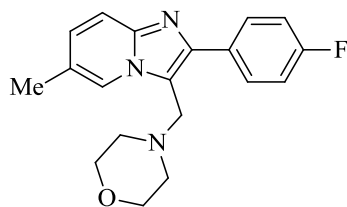
4-((2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (105h): Yield 70%;



White solid; mp 177-179 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, J = 6.9 Hz, 1H), 7.96 – 7.70 (m, 2H), 7.63 (d, J = 9.1 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.15 (t, J = 8.6 Hz, 2H), 6.84 (t, J = 6.6 Hz, 1H), 3.94 (s, 2H), 3.67 (t, J = 4.5 Hz, 4H), 2.44 (t, J = 4.5 Hz, 4H); ¹³C NMR (100

MHz, CDCl₃) δ 162.6 (d, J = 247.1 Hz), 145.1, 144.5, 130.6 (d, J = 3.3 Hz), 130.5 (d, J = 8.1 Hz), 125.2, 124.7, 117.3, 115.8, 115.4 (d, J = 21.4 Hz), 112.0, 67.0, 53.2, 52.1; MS (EI, m/z) calculated for C₁₈H₁₈FN₃O 311.14, found 311.13 [M]⁺.

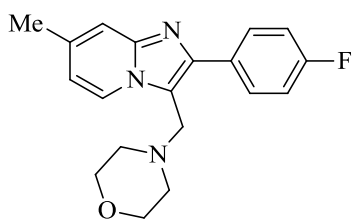
4-((2-(4-Fluorophenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (105i):



Yield 77%; Off-white solid; mp 140-142 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.14 (s, 1H), 7.79 (dd, J = 8.6, 5.5 Hz, 2H), 7.53 (d, J = 9.1 Hz, 1H), 7.14 (t, J = 8.7 Hz, 2H), 7.08 (dd, J = 9.2, 1.4 Hz, 1H), 3.90 (s, 2H), 3.68 (t, J = 4.5 Hz, 4H), 2.48 (t, J = 4.4 Hz, 4H), 2.38

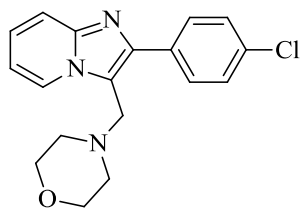
(s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 162.5 (d, J = 246.9 Hz), 144.3, 144.1, 130.8 (d, J = 3.2 Hz), 130.5 (d, J = 8.1 Hz), 127.8, 122.6, 121.6, 116.6, 115.5, 115.4 (d, J = 21.4 Hz), 67.0, 53.2, 52.0, 18.5; MS (EI, m/z) calculated for C₁₉H₂₀FN₃O 325.16, found 325.16 [M]⁺.

4-((2-(4-Fluorophenyl)-7-methylimidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (105j):

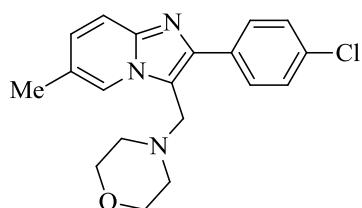


Yield 75%; Off-white solid; mp 170-172 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, J = 7.0 Hz, 1H), 7.84 – 7.71 (m, 2H), 7.38 (s, 1H), 7.14 (t, J = 8.7 Hz, 2H), 6.67 (dd, J = 7.0, 1.6 Hz, 1H), 3.90 (s, 2H), 3.67 (t, J = 4.5 Hz, 4H), 2.47 (t, J = 4.4 Hz, 4H), 2.42 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 162.5 (d, J = 246.9 Hz),

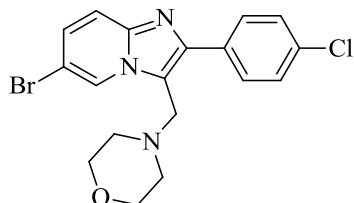
145.5, 144.1, 135.6, 130.8 (d, J = 3.2 Hz), 130.4 (d, J = 8.1 Hz), 124.4, 115.6, 115.4 (d, J = 21.4 Hz), 115.2, 114.6, 67.0, 53.2, 52.0, 21.3; MS (EI, m/z) calculated for C₁₉H₂₀FN₃O 325.16, found 325.16 [M]⁺.

4-((2-(4-Chlorophenyl)imidazo[1,2-a]pyridin-3-yl)methyl)morpholine (105k): Yield 80%;

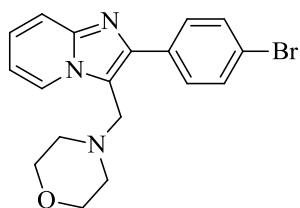
Off-white solid; mp 164-166 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.41 (d, $J = 6.9$ Hz, 1H), 7.81 – 7.72 (m, 2H), 7.63 (d, $J = 9.1$ Hz, 1H), 7.43 (d, $J = 8.5$ Hz, 2H), 7.26 – 7.20 (m, 1H), 6.84 (t, $J = 6.8$ Hz, 1H), 3.94 (s, 2H), 3.67 (t, $J = 4.5$ Hz, 4H), 2.48 (t, $J = 4.4$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.1, 144.2, 133.7, 133.0, 130.1, 128.7, 125.2, 124.8, 117.3, 116.1, 112.1, 67.0, 53.2, 52.0; MS (EI, m/z) calculated for $\text{C}_{18}\text{H}_{18}\text{ClN}_3\text{O}$ 327.11, found 327.11 $[\text{M}]^+$.

4-((2-(4-Chlorophenyl)-6-methylimidazo[1,2-a]pyridin-3-yl)methyl)morpholine (105l):

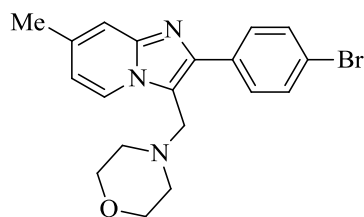
Yield 82%; White solid; mp 151-154 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.14 (s, 1H), 7.77 (d, $J = 8.5$ Hz, 2H), 7.53 (d, $J = 9.2$ Hz, 1H), 7.42 (d, $J = 8.5$ Hz, 2H), 7.08 (dd, $J = 9.2, 1.5$ Hz, 1H), 3.90 (s, 2H), 3.68 (t, $J = 4.5$ Hz, 4H), 2.49 (t, $J = 4.4$ Hz, 4H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.2, 144.0, 133.6, 133.2, 130.0, 128.6, 127.9, 122.6, 121.7, 116.7, 115.8, 67.0, 53.2, 52.0, 18.5; MS (EI, m/z) calculated for $\text{C}_{19}\text{H}_{20}\text{ClN}_3\text{O}$ 341.13, found 341.13 $[\text{M}]^+$.

4-((6-Bromo-2-(4-chlorophenyl)imidazo[1,2-a]pyridin-3-yl)methyl)morpholine (105m):

Yield 79%; White solid; mp 158-160 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.59 (d, $J = 1.2$ Hz, 1H), 7.76 – 7.69 (m, 2H), 7.52 (d, $J = 9.5$ Hz, 1H), 7.45 – 7.40 (m, 2H), 7.32 – 7.26 (m, 1H), 3.93 (s, 2H), 3.71 (t, $J = 4.5$ Hz, 4H), 2.46 (t, $J = 4.5$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.9, 143.6, 134.1, 132.5, 130.0, 128.8, 128.2, 125.4, 118.0, 116.5, 106.7, 66.9, 53.2, 52.0; MS (ESI, m/z) calculated for $\text{C}_{18}\text{H}_{18}\text{BrClN}_3\text{O}$ 406.03, found 406.02 $[\text{M}+\text{H}]^+$.

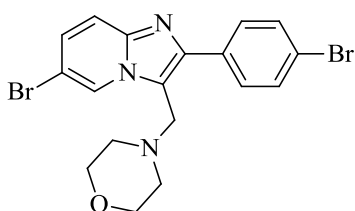
4-((2-(4-Bromophenyl)imidazo[1,2-a]pyridin-3-yl)methyl)morpholine (105n): Yield 56%;

Off-white solid; mp 167-169 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.41 (d, $J = 6.9$ Hz, 1H), 7.71 (d, $J = 8.5$ Hz, 2H), 7.63 (d, $J = 9.1$ Hz, 1H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.31 – 7.18 (m, 1H), 6.85 (td, $J = 6.8, 1.0$ Hz, 1H), 3.94 (s, 2H), 3.68 (t, $J = 4.4$ Hz, 4H), 2.46 (t, $J = 4.4$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.2, 144.2, 133.5, 131.6, 130.4, 125.2, 124.8, 122.0, 117.4, 116.1, 112.1, 66.9, 53.2, 52.0; MS (ESI, m/z) calculated for $\text{C}_{18}\text{H}_{19}\text{BrN}_3\text{O}$ 372.07, found 372.07 $[\text{M}+\text{H}]^+$.

4-((2-(4-Bromophenyl)-7-methylimidazo[1,2-a]pyridin-3-yl)methyl)morpholine (105o):

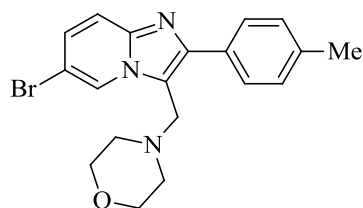
Yield 55%; Off-white solid; mp 181-183 °C; ^1H NMR (300 MHz, CDCl_3) δ 8.29 (d, $J = 7.0$ Hz, 1H), 7.70 (d, $J = 8.5$ Hz, 2H), 7.58 (d, $J = 8.4$ Hz, 2H), 7.38 (s, 1H), 6.68 (d, $J = 7.0$ Hz, 1H), 3.92 (s, 2H), 3.68 (t, $J = 4.4$ Hz, 4H), 2.47 (t, $J = 4.3$ Hz, 4H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.6, 143.8, 135.9, 133.5,

131.6, 130.3, 124.4, 121.9, 115.7, 115.5, 114.8, 67.0, 53.2, 52.0, 21.4; MS (ESI, m/z) calculated for $\text{C}_{19}\text{H}_{21}\text{BrN}_3\text{O}$ 386.09, found 386.11 $[\text{M}+\text{H}]^+$.

4-((6-Bromo-2-(4-bromophenyl)imidazo[1,2-a]pyridin-3-yl)methyl)morpholine (105p):

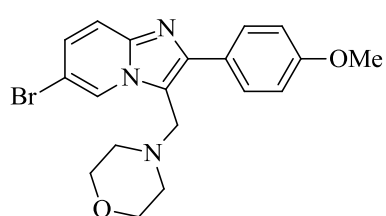
Yield 58%; White solid; mp 154-156 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.59 (d, $J = 1.1$ Hz, 1H), 7.66 (d, $J = 8.5$ Hz, 2H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.53 (d, $J = 9.5$ Hz, 1H), 7.29 (dd, $J = 9.5$, 1.9 Hz, 1H), 3.93 (s, 2H), 3.66 (t, $J = 4.3$ Hz, 4H), 2.42 (t, $J = 4.3$

Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.9, 143.6, 132.9, 131.7, 130.3, 128.2, 125.4, 122.4, 118.0, 116.5, 106.8, 66.9, 53.2, 52.0; MS (ESI, m/z) calculated for $\text{C}_{18}\text{H}_{18}\text{Br}_2\text{N}_3\text{O}$ 449.98, found 449.99 $[\text{M}+\text{H}]^+$.

4-((6-Bromo-2-(*p*-tolyl)imidazo[1,2-a]pyridin-3-yl)methyl)morpholine (105q):

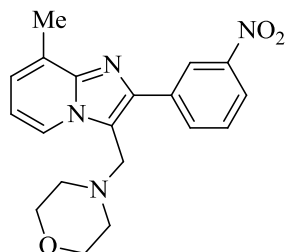
Yield 69%; White solid; mp 141-143 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.59 (d, $J = 1.2$ Hz, 1H), 7.65 (d, $J = 8.1$ Hz, 2H), 7.52 (d, $J = 9.5$ Hz, 1H), 7.29 – 7.24 (m, 3H), 3.95 (s, 2H), 3.68 (t, $J = 4.4$ Hz, 4H), 2.48 (t, $J = 4.4$ Hz, 4H), 2.41 (s, 3H); ^{13}C NMR (100 MHz,

CDCl_3) δ 146.2, 143.5, 137.9, 131.0, 129.3, 128.7, 127.8, 125.4, 117.8, 116.1, 106.4, 66.9, 53.2, 52.1, 21.3; MS (ESI, m/z) calculated for $\text{C}_{19}\text{H}_{21}\text{BrN}_3\text{O}$ 386.09, found 386.09 $[\text{M}+\text{H}]^+$.

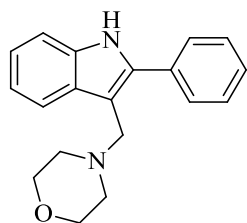
4-((6-Bromo-2-(4-methoxyphenyl)imidazo[1,2-a]pyridin-3-yl)methyl)morpholine (105s):

Yield 84%; Off-white solid; mp 145-147 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.57 (d, $J = 1.2$ Hz, 1H), 7.74 – 7.67 (m, 2H), 7.51 (d, $J = 9.5$ Hz, 1H), 7.30 – 7.22 (m, 1H), 7.04 – 6.90 (m, 2H), 3.94 (s, 2H), 3.86 (s, 3H), 3.68 (t, $J = 4.4$ Hz, 4H), 2.46 (t, $J = 4.4$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.5, 146.0,

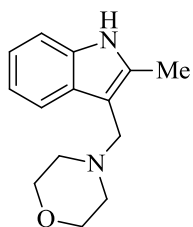
143.4, 130.0, 127.7, 126.5, 125.3, 117.7, 115.7, 114.0, 106.3, 66.9, 55.3, 53.2, 52.2; MS (ESI, m/z) calculated for $\text{C}_{19}\text{H}_{21}\text{BrN}_3\text{O}_2$ 402.08, found 402.09 $[\text{M}+\text{H}]^+$.

4-((8-Methyl-2-(3-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)methyl)morpholine (105t):

Yield 63%; Pale yellow solid; mp 162-164 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.97 – 8.88 (m, 1H), 8.29 (d, $J = 7.8$ Hz, 1H), 8.24 (d, $J = 6.9$ Hz, 1H), 8.20 (dd, $J = 8.2, 1.1$ Hz, 1H), 7.63 (t, $J = 8.0$ Hz, 1H), 7.06 (d, $J = 6.8$ Hz, 1H), 6.81 (t, $J = 6.9$ Hz, 1H), 3.92 (s, 2H), 3.70 (t, $J = 4.4$ Hz, 4H), 2.66 (s, 3H), 2.53 (t, $J = 4.2$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.4, 145.7, 142.4, 136.6, 134.7, 129.4, 127.6, 123.9, 123.8, 122.4, 122.2, 117.5, 112.6, 66.9, 53.1, 51.8, 17.0; MS (ESI, m/z) calculated for $\text{C}_{19}\text{H}_{21}\text{N}_4\text{O}_3$ 353.16, found 353.14 $[\text{M}+\text{H}]^+$.

4-((2-Phenyl-1*H*-indol-3-yl)methyl)morpholine (110a):

Yield 60%; White solid; mp 148-150 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.48 (s, 1H), 7.83 (d, $J = 7.2$ Hz, 3H), 7.51 (t, $J = 7.6$ Hz, 2H), 7.42 (dd, $J = 7.4, 6.0$ Hz, 2H), 7.28 – 7.16 (m, 2H), 3.74 (t, $J = 4.4$ Hz, 6H), 2.58 (s, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.9, 135.5, 132.9, 130.1, 128.8, 128.4, 127.8, 122.3, 119.9, 119.7, 110.8, 109.4, 67.3, 53.5, 52.8.

4-((2-Methyl-1*H*-indol-3-yl)methyl)morpholine (110b):

Yield 73%; White solid; mp 165-167 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.97 (s, 1H), 7.73 – 7.60 (m, 1H), 7.31 – 7.26 (m, 1H), 7.19 – 7.08 (m, 2H), 3.74 – 3.69 (m, 4H), 3.66 (s, 2H), 2.51 (bs, 4H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 135.1, 133.4, 129.31, 121.1, 119.4, 118.8, 110.1, 107.78, 67.2, 53.6, 52.9, 11.9.

Chapter III

PART B

**Methylenation of Imidazo[1,2-*a*]pyridines by
Using DMA as One Carbon Source: Direct Access
to Bis(imidazo[1,2-*a*]pyridin-3-yl)methanes**

3.6. Introduction

Bis(heteroaryl)methanes have attracted the attention of chemists in recent years owing to their wide spectrum of biological activities. Several reports are available on the synthesis of bis(indolyl)methanes (BIM) using different methylene source. Many of the most important BIMs are found in various terrestrial and marine natural sources. These natural products have BIM core structure and exhibit range of important biological activities. Mostly BIM has been studied for inhibition of cancer cell growth in different part of body.^[95-97] Due to versatile biological application there is continuous hunt to develop new environment benign synthetic method for bis(heteroaryl)methanes (**Figure 3.8**).

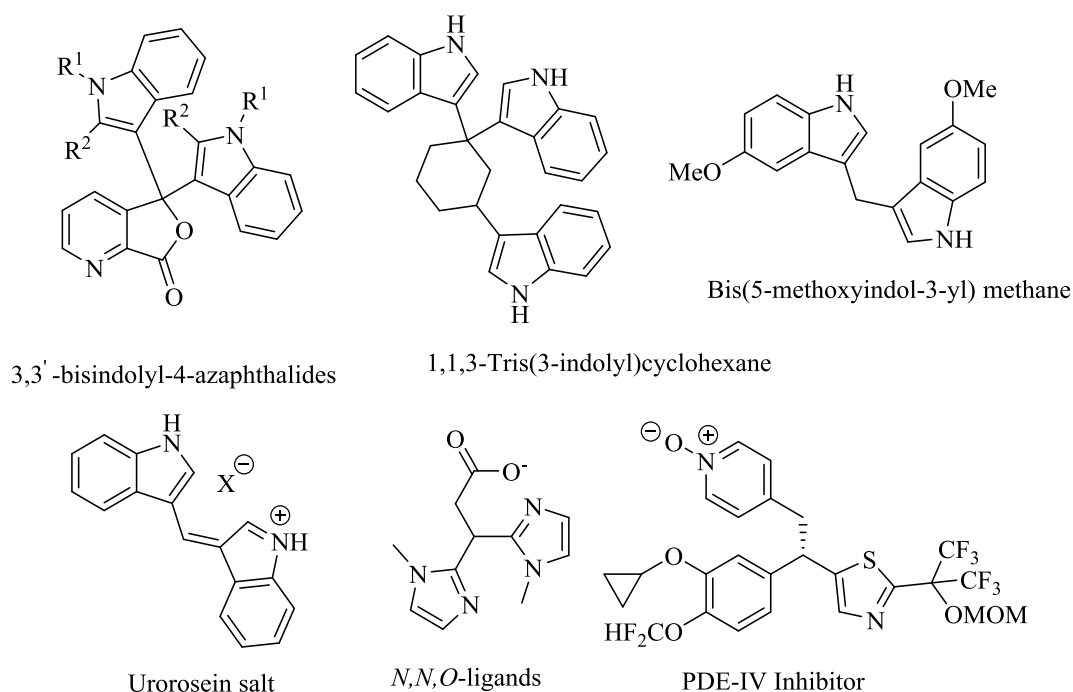
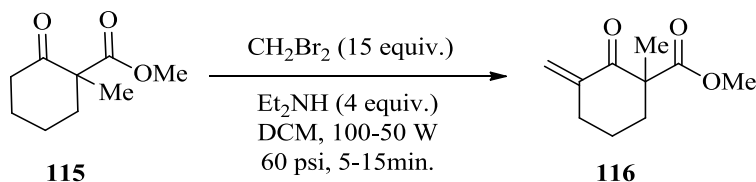


Figure 3.8: BIMS and other bis(heteroaryl)methanes having various applications

An important aspect of methylation with transition metal-catalyzed reaction is generation of methylenating reagent which avoids the use of harsh reaction condition and extends the range of substrates scope. The interest in the methylation of carbonyl compounds, which developed strongly after the discovery of the Wittig reagents, continues to generate many exciting diverse methylenation reagents.

Hon and co-workers used dibromomethane synthon as one-carbon source for α -methylenation of ketones (**115**) (**Scheme 3.39**).^[98] Reactive species was generated from Et_2NH and CH_2Br_2 by 100% irradiation in first 5 minutes and then 50% radiation was given to complete the reaction.

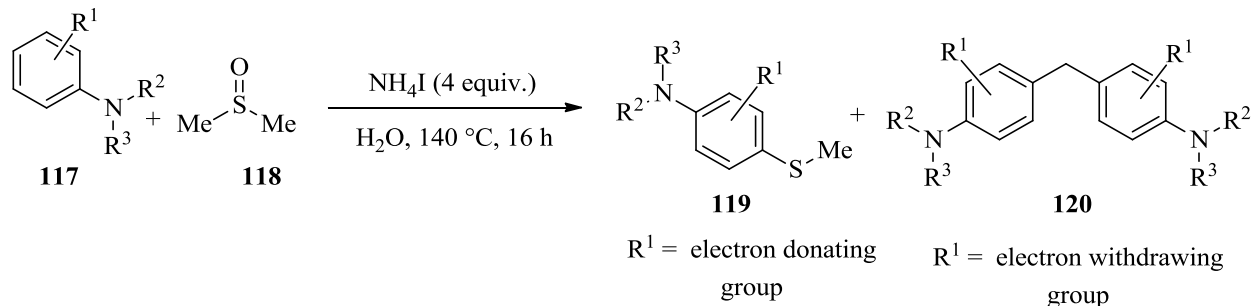
The reactive intermediate may decompose before reacting with acetophenone under conditions of long irradiation. The scope of α -methylenation of ketones was investigated by various aryl alkyl ketones, 1-naphthyl ethyl ketone, α -tetralone, heteroaryl alkyl ketones and cyclic ketones to give moderate to good yield of α -methylated ketones (**116**) although 2-norbornanone could result only corresponding Mannich base.



Scheme 3.39: α -Methylenation of ketones with dibromomethane

This procedure can be used industrially for the production of α -methylation of simple aldehydes and ketones, although their applications in the synthesis of more complex molecules with methylene linkage are very less.^[99-100] With more complex aldehydes, stoichiometric amounts of the amine salt and dibromomethane are typically required. As a result of the slow reaction rates and relatively drastic conditions (typically reflux overnight), yields tend to be lower and the reactions are often discarded due to formation of polymeric side products.^[101-102] From an atom economic and process chemistry points of view, the use of stoichiometric amount of the amine salt and the long reaction time are major disadvantages of reported methodology.

Sun *et al.* used DMSO as one carbon source for methylenation of arylamines (**117**) in the presence of NH_4I under metal-free conditions along with *para*-methylthiolation (**119**) product of arylamines. *Para*-methylthiolation (**119**) product and methylene-bridged product (**120**) formation were achieved depending on the electronic nature of arylamines (**Scheme 3.40**).^[103] Anilines with electron-donating groups resulted *para*-methylthiolation while electron withdrawing groups gave methylene-bridged products although in case of disubstituted or phenyl substituted anilines both product was obtained in moderate yield. The author revealed the mechanism through free radical for methylthiolation and through iminium ion and Mannich type reaction for methylene bridge product.



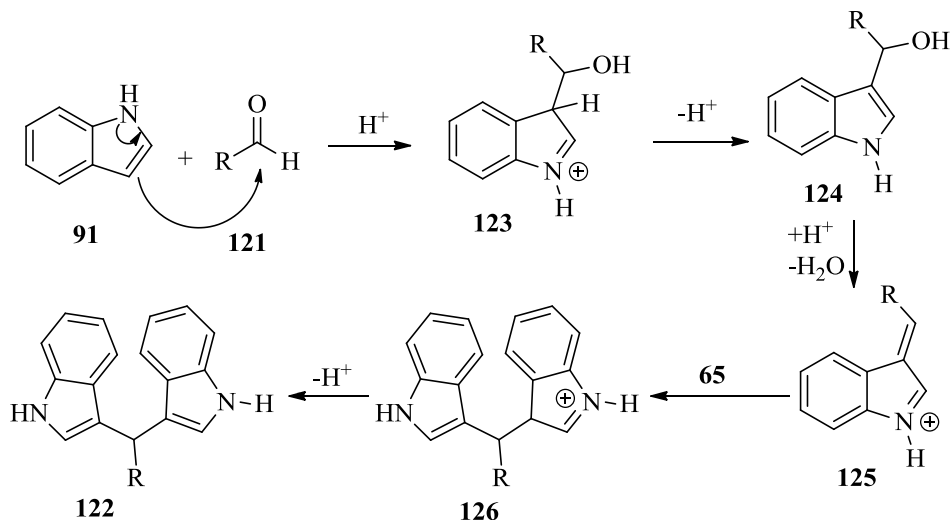
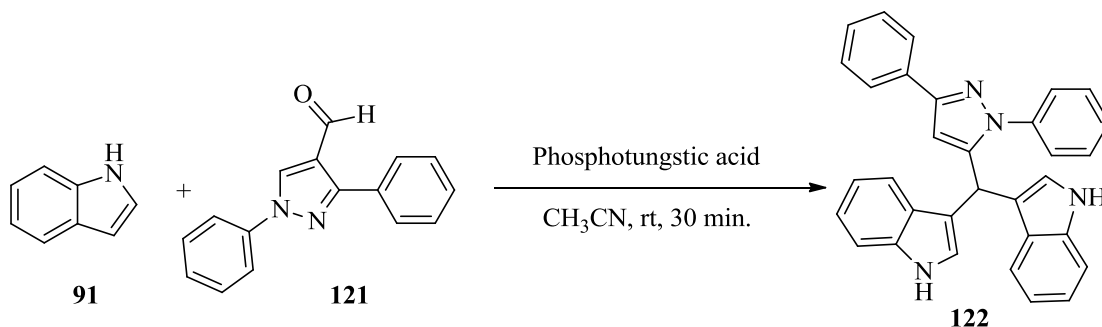
Scheme 3.40: NH_4I -mediated substrate dependent *para*-methylthiolation and synthesis of methylene bridge product

Two common approach for methylenation have been described here,

3.6.1. Acid catalyzed addition to aldehyde for methylenation

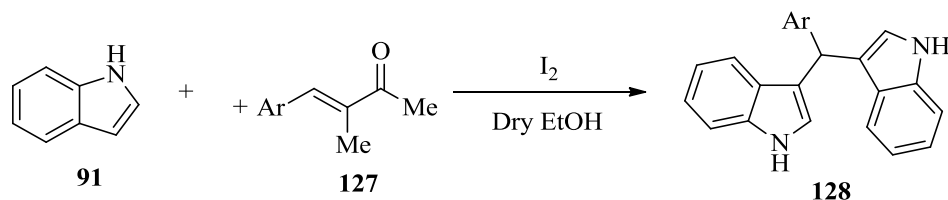
The acid catalyzed reaction of electron-rich heterocyclic compounds such as indoles and pyrroles with *p*-dimethylaminobenzaldehyde is known as the Ehrlich test. Typical protic acids are used to catalyze this type of reaction, include silica sulfuric acid (SSA), oxalic acid, HCOOH ,^[104] CH_3COOH ,^[105-107] *p*-TsOH, PEG-supported sulfonic acid^[108]. Further improvements in terms of green chemistry were added using Lewis acids, such as lanthanide resins,^[109] zeolite (ZnY),^[110] montmorillonite clay K-10,^[111] cerium ammonium nitrate (CAN), InCl_3 , $\text{In}(\text{OTf})_3$.^[110] These methods have been widely studied and well documented in literature. Green and eco-friendly conditions as the main drive have also lead to reasonable development in this field of chemistry. Ionic liquids,^[112-114] as green solvents have been largely used in the synthesis of bis(heteroaryl)methanes^[115-116].

Perumal *et al.* synthesized pyrazolylbisindoles (**122**) by the reaction of substituted pyrazole aldehydes (**121**) with substituted indoles (**91**) using phosphotungstic acid at room temperature (**Scheme 3.41**).^[117] The scope and generality of reported procedure has been illustrated with respect to various substituted pyrazole aldehydes and indoles with good to excellent yield. The synthesized compounds were studied for anti-microbial activity and showed promising anti-fungal property.



Scheme 3.41: Synthesis of pyrazolylbisindoles

The general mechanism is depicted in **scheme 3.41** which starts with nucleophilic attack on aldehyde and generates azafulven enamine (**125**). The enamine undergoes further addition of indole molecule to produce BIM. Further Mallik *et al.* reported the reaction of indoles with α,β -unsaturated ketones (**127**) to give BIMS (**128**) in good to excellent yield and reaction is supposed to proceed through azafulven (**125**) (**Scheme 3.42**).^[118]



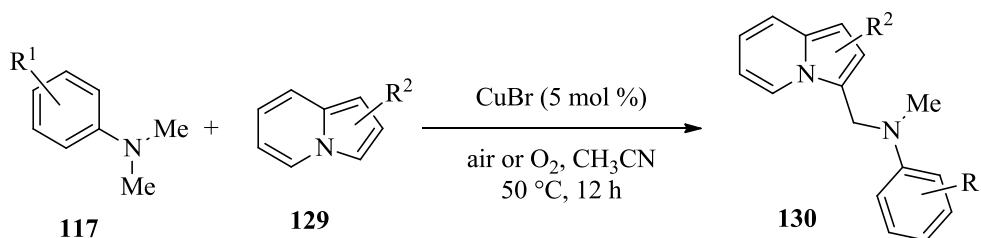
Scheme 3.42: Synthesis of BIM in the presence of I_2

Also there is range of substrates for methylene source for the synthesis of bis(heteroaryl)methanes, which includes aldehyde, alcohol, imines, iminium salts, nitrons and *N,N*-dimethylacetamide dimethylacetal.^[115-116]

3.6.2. Transition metal catalyzed methylenation

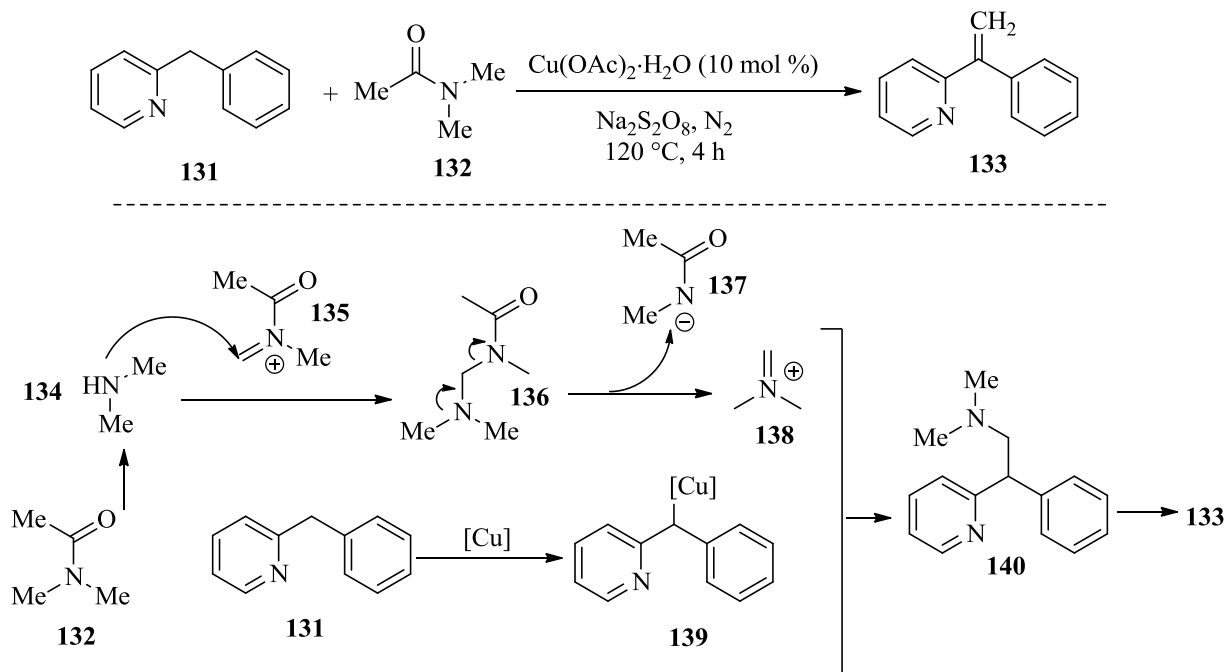
However, many new catalytic and greener alternatives have been developed for stabilizing methylenating reagent; there have been very few reports in terms of transition metal catalyzed methylenation using easily available methylenating reagents.

Zhang group reported oxidative cross-coupling of C(sp²)-H bonds with C(sp³)-H bonds using *N,N*-dimethylanilines and heteroarenes under molecular oxygen in the presence of copper catalyst. The author imagined that the electron-rich *N* fused heteroarenes work as nucleophile to access nucleophilic reaction with the iminium ion intermediate, which is generated by *N,N*-dimethylanilines (**117**) with the help of molecular oxygen and copper catalyst. Substituted indolizines (**129**), 2-phenylimidazole and *N,N*-dimethylbenzenamine with range of *N,N*-dimethylanilines could result the corresponding product in good to excellent yield (**Scheme 3.43**).^[119]

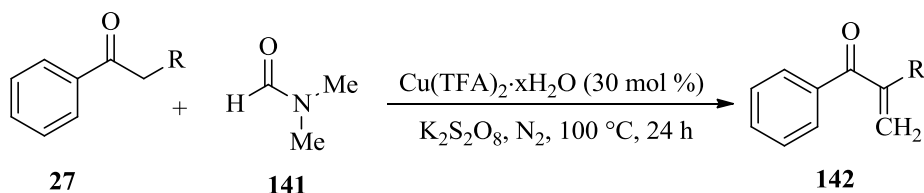


Scheme 3.43: Copper-catalyzed oxidative cross-coupling of sp² C-H bond with sp³ C-H

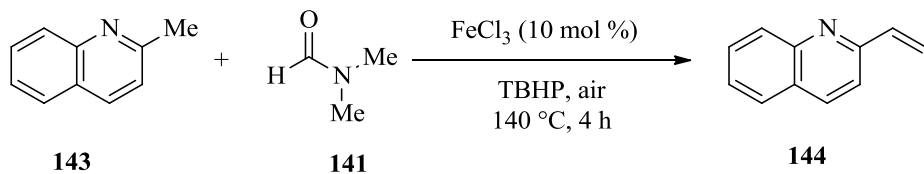
Miura group recently achieved direct α -methylenation of benzylpyridines (**131**) under copper catalysis with DMA as one carbon source. Various substituted 2-benzylpyridines, 4-benzylpyridines and 2-benzylpyrimidine could be used for the α -methylenation reaction. Reaction mechanism was proposed based on isolated intermediate and control experiments as shown in **scheme 3.44**.^[120] In the presence of oxidant DMA generate iminium ion (**137**) and benzylpyridines (**131**) produce intermediate **139** in the presence of copper catalyst. Reaction of intermediate **139** and **137** lead to the formation of intermediate **140** which convert to product (**Scheme 3.44**).



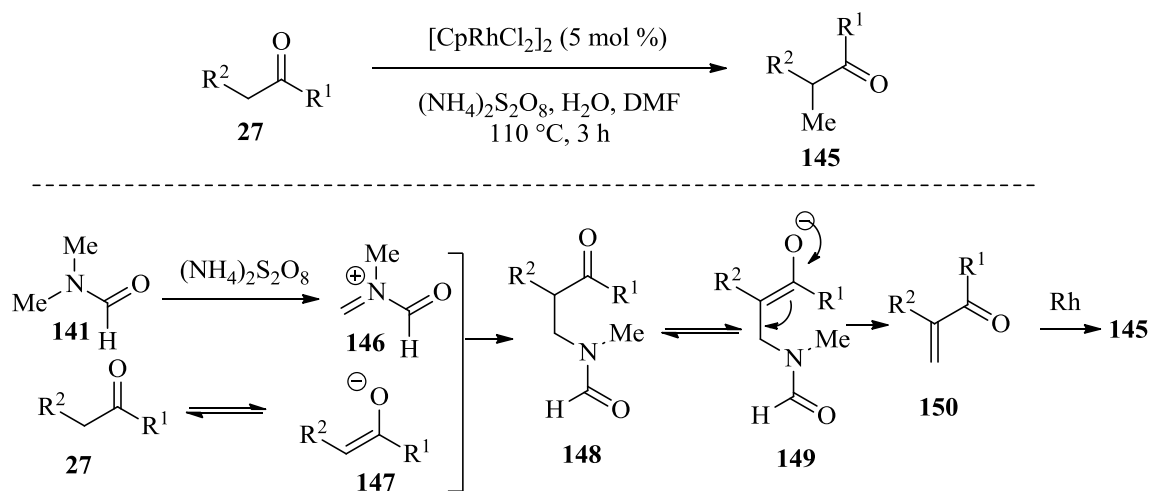
Lei and co-workers also reported the C(sp³)-H methylation of ketone (**27**) using DMF (**141**) as one carbon source in the presence of copper catalyst to construct arylvinylketones derivatives (**142**) with various functional groups (**Scheme 3.45**).^[121]



Xu and Wang group independently synthesized 2-vinylquinolines (**144**) in good to excellent yield using DMF, DMA and *N,N*-dimethylbenzamide as one carbon source under iron-catalysis (**Scheme 3.46**).^{98,99} Reaction proceeds through iminium intermediate and FeCl₃ assisted C-N bond cleavage.

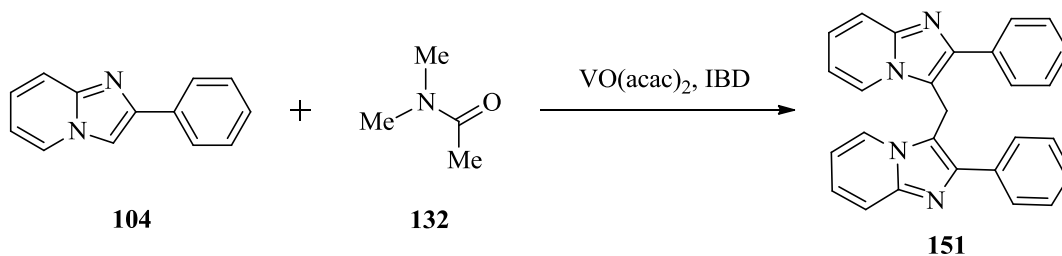


Xiao and co-workers used DMF as carbon source for the α -methylenation of ketone (**27**) using Rh-catalyst and $(\text{NH}_4)_2\text{S}_2\text{O}_8$ oxidant (**Scheme 3.47**).^[122] Broad substrate scope, including both aryl and alkyl ketones with various substituents were well tolerated to result good to excellent yield of α -methyl ketone (**145**). The reaction mechanism was proposed based on control experiments and DMF oxidized to iminium intermediate (**146**) in the presence of $(\text{NH}_4)_2\text{S}_2\text{O}_8$ and enol form of ketone (**147**) attack on iminium ion followed by C–N bond cleavage to generate unsaturated ketone (**150**) and further get reduced in the presence of Rh-catalyst.



3.7. Results and Discussion

Recently, our group and others have been involved in developing new methods of the functionalization of imidazo[1,2-*a*]pyridines.^[123-127] In this part of chapter III, we report our initial results for the vanadium-catalyzed methylenation of imidazo[1,2-*a*]pyridines using DMA as methylene source in the presence of iodobenzene diacetate (IBD) as the oxidant (**Scheme 3.48**). To the best of our knowledge, there was no report available for the synthesis of bis(imidazo[1,2-*a*]pyridin-3-yl)methanes using DMA as methylene source mediated by vanadium catalyst.



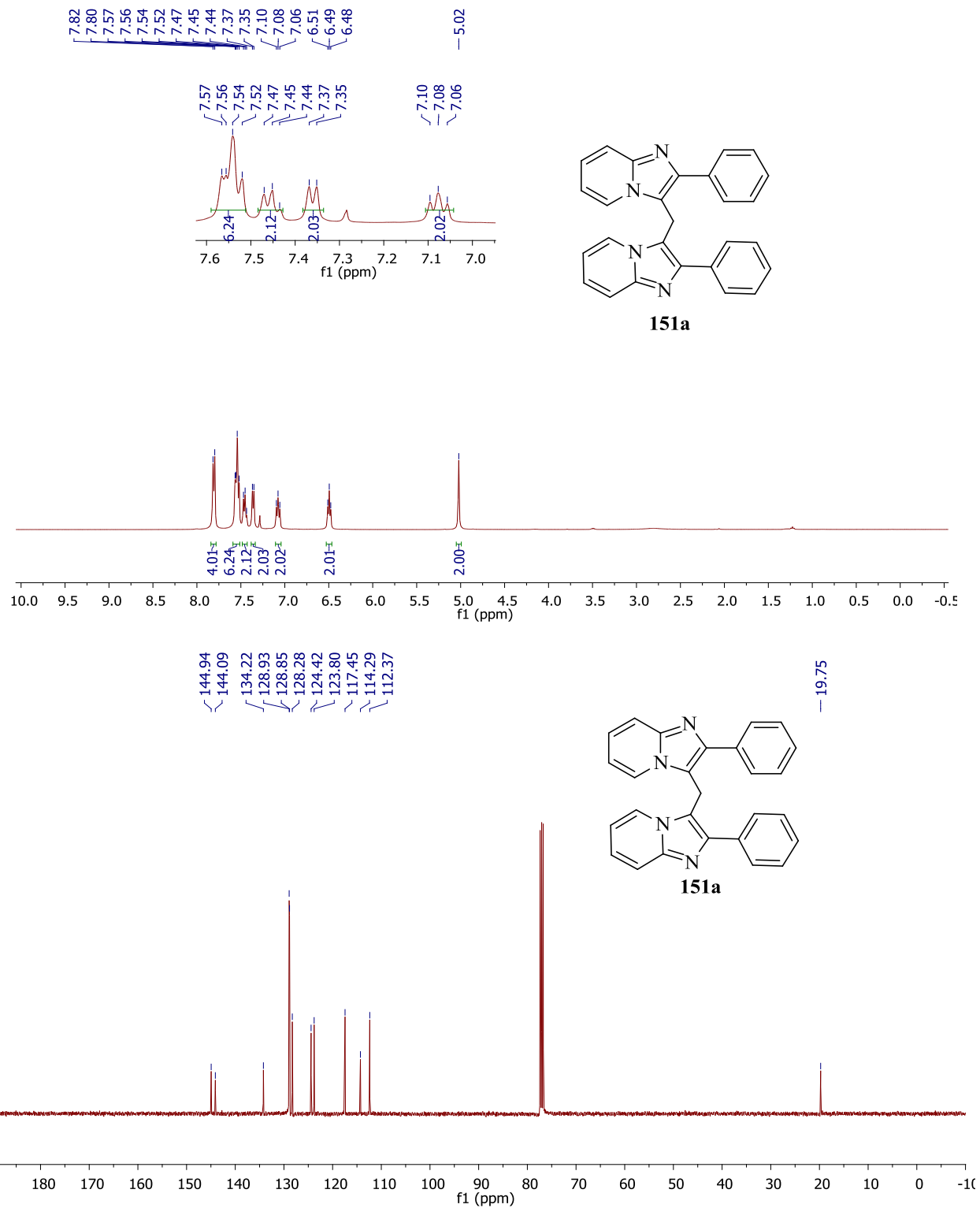
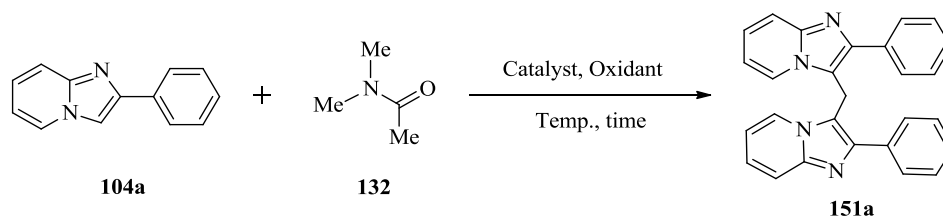


Figure 3.9: ^1H NMR and ^{13}C NMR of bis(2-phenylimidazo[1,2-a]pyridin-3-yl)methane (**151a**)

The structure of **151a** was ascertained by NMR spectroscopy and HRMS spectrometry data. A characteristic singlet peak for the methylene protons was observed at δ 5.02 in the ^1H NMR spectrum of **151a**, and the methylene carbon appeared at δ 19.75 in the ^{13}C NMR spectrum (Figure 3.9). The presence of the methylene carbon in **151a** was further confirmed by DEPT 135 experiment. The presence of peak at m/z 401.1757 for $[\text{M} + \text{H}]^+$ ion in the HRMS spectrum finally confirmed the structure of **151a**.

Our initial investigation commenced with the reaction of 2-phenylimidazo[1,2-*a*]pyridine (**104a**) with DMA in the presence of V_2O_5 (10 mol %) and *meta*-chloroperbenzoic acid (*m*-CPBA). A low yield (12%) of bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (**151a**) was obtained after heating the reaction mixture at 100 °C for 12 h (Table 3.4, entry 1). Increasing the reaction temperature to 150 °C increased the yield of **151a** to 31% after 12 h (Table 3.4, entry 3). To our delight replacing V_2O_5 with $\text{VO}(\text{acac})_2$ in the model reaction increased the yield of bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (**151a**) to 64% at 150 °C after 6 h (Table 3.4, entry 5). Subsequent screening of oxidants such as tert-butyl hydroperoxide (TBHP), $\text{K}_2\text{S}_2\text{O}_8$, ZnI_2 , $\text{Cu}(\text{OAc})_2$ and IBD revealed that IBD was the most suitable oxidant for this reaction (Table 3.4, entries 5–10). Use of IBD (2 equiv.) with $\text{VO}(\text{acac})_2$ (10 mol %) produced an 85% yield of **151a** for the model reaction at 150 °C after 6 h. On the other hand, use of ZnI_2 and $\text{Cu}(\text{OAc})_2$ failed to give the desired product. Increasing the loading of IBD did not result in an increased yield of **151a**; however, decreasing the amount of IBD resulted in lower yield of **151a** (Table 3.4, entries 10–13). Increasing the $\text{VO}(\text{acac})_2$ loading from 20 mol % to 30 mol % led to slightly improved yield of **151a** (Table 3.4, entries 15–16) and varying the amount of the methylene source revealed that 1 mL of DMA per mmol of substrate **104a** was required for good yield of **151a** (Table 3.4, entries 18–20). The yield of **151a** decreased drastically when the reaction temperature was lowered (120 °C) (Table 3.4, entry 21), and at 80 °C temperature only 29% conversion of **151a** was observed (Table 3.4, entry 2), while no product was formed at room temperature, even after 24 h (Table 3.4, entry 23).

Based on different screening conditions finally we got the best reaction conditions for the reaction using 10 mol % of $\text{VO}(\text{acac})_2$ catalyst, 2.0 equivalent of IBD in DMA solvent for 6 h at 150 °C to result 85% yield of bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (**151a**) (Table 3.4, entry 10).

Table 3.4: Optimization of the reaction condition for **151a**^a

| Entry | Catalyst | Oxidant (equiv.) | Temp. (°C) | Time (h) | % Yield ^b |
|-----------|-------------------------------|----------------------------------------------------|------------|----------|----------------------|
| 1 | V ₂ O ₅ | <i>m</i> -CPBA (2.0) | 100 | 12 | 12 |
| 2 | V ₂ O ₅ | <i>m</i> -CPBA (2.0) | 100 | 16 | 19 |
| 3 | V ₂ O ₅ | <i>m</i> -CPBA (2.0) | 150 | 12 | 31 |
| 4 | V ₂ O ₅ | <i>m</i> -CPBA (2.0) | 150 | 6 | 30 |
| 5 | VO(acac) ₂ | <i>m</i> -CPBA (2.0) | 150 | 6 | 64 |
| 6 | VO(acac) ₂ | TBHP (2.0) | 150 | 6 | 49 |
| 7 | VO(acac) ₂ | ZnI ₂ (2.0) | 150 | 6 | traces |
| 8 | VO(acac) ₂ | Cu(OAc) ₂ (2.0) | 150 | 6 | ND ^c |
| 9 | VO(acac) ₂ | K ₂ S ₂ O ₈ (2.0) | 150 | 6 | 20 |
| 10 | VO(acac)₂ | IBD (2.0) | 150 | 6 | 85 |
| 11 | VO(acac) ₂ | IBD (3.0) | 150 | 6 | 86 |
| 12 | VO(acac) ₂ | IBD (1.0) | 150 | 6 | 50 |
| 13 | VO(acac) ₂ | IBD (0.2) | 150 | 6 | 9 |
| 14 | VO(acac) ₂ | - | 150 | 6 | Traces |
| 15 | VO(acac) ₂ | IBD (2.0) | 150 | 6 | 87 ^d |
| 16 | VO(acac) ₂ | IBD (2.0) | 150 | 6 | 90 ^e |
| 17 | - | IBD (2.0) | 150 | 6 | 40 |
| 18 | VO(acac) ₂ | IBD (2.0) | 150 | 6 | 37 ^{f, i} |
| 19 | VO(acac) ₂ | IBD (2.0) | 150 | 6 | 55 ^{g, i} |
| 20 | VO(acac) ₂ | IBD (2.0) | 150 | 6 | 57 ^{h, i} |
| 21 | VO(acac) ₂ | IBD (2.0) | 120 | 24 | 63 |
| 22 | VO(acac) ₂ | IBD (2.0) | 80 | 24 | 29 |
| 23 | VO(acac) ₂ | IBD (2.0) | 25 | 24 | ND ^c |

^aReactions conditions: DMA (1.0 mL), catalyst (10 mol%), oxidant (2.0 mmol), stirred at 100 °C for 1 h followed by addition of **104a** (1.0 mmol) under air,

^bIsolated yield of pure product based on **104a**,

^cNR = No reaction,

^dCatalyst (20 mol %),

^eCatalyst (30 mol %),

^fDMA (2 equiv.),

^gDMA (5 equiv.),

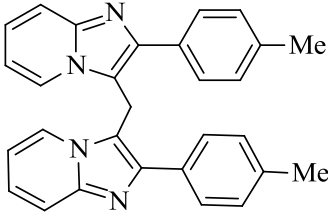
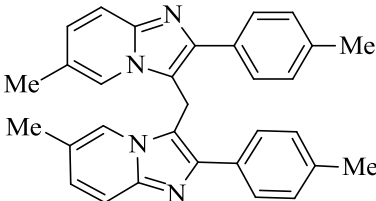
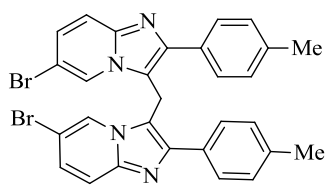
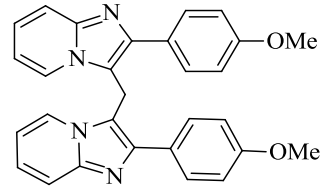
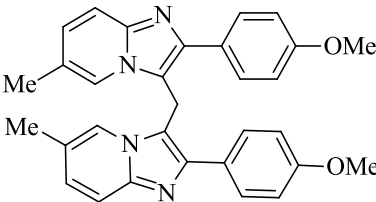
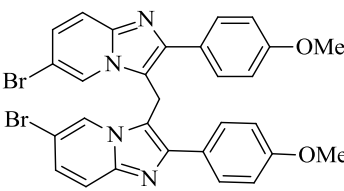
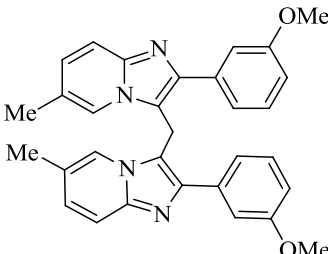
^hDMA (10 equiv.),

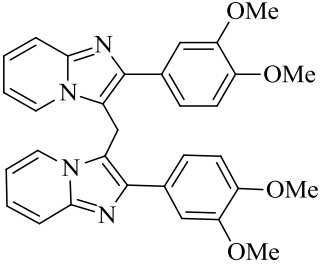
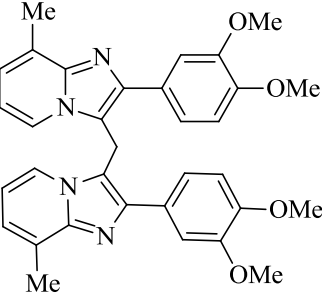
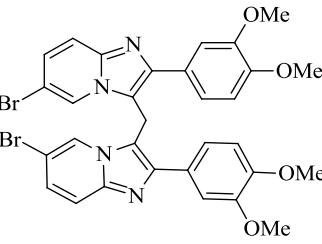
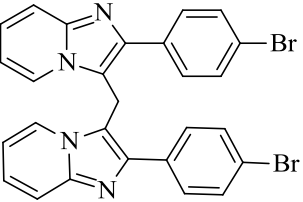
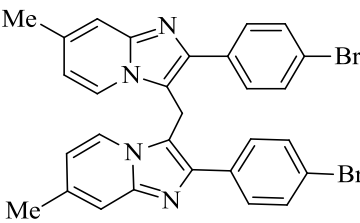
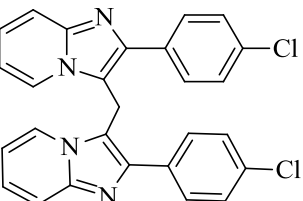
ⁱThe reaction was performed neat.

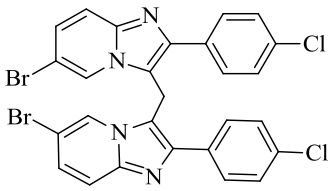
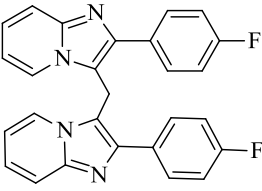
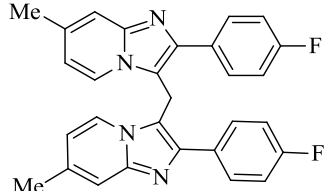
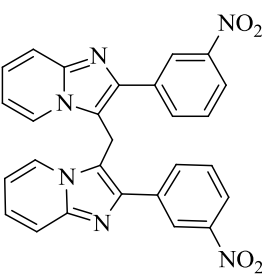
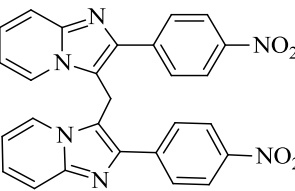
The optimized reaction conditions were then used to evaluate the scope and generality of the novel methylenation reaction. Diversely substituted 2-arylimidazo[1,2-*a*]pyridines (**104a–s**) reacted efficiently with DMA to give the corresponding bis(2-arylimidazo[1,2-*a*]pyridin-3-yl)methanes (**151a–s**) in moderate to excellent yields (29–90%; **Table 3.5**). Substrates with C-2 aryl rings containing electron-donating groups gave higher yields than substrates containing electron-withdrawing groups. For example, **104f**, with 4-methoxyphenyl substituent, gave 90% yield of **151f**, whereas **104s**, having 3-nitrophenyl group gave only 29% yield of **151s**, and **104t**, having 4-nitrophenyl group did not react under these conditions (**Table 3.5**, entries 6, 19, 20). Similarly, substrates with different substituent on the pyridine ring of the imidazo[1,2-*a*]pyridine also reacted smoothly to give good to excellent yields of the corresponding bis(imidazo[1,2-*a*]pyridin-3-yl)methanes. The presence of functional groups, such as fluorine, chlorine and bromine, were well tolerated under these conditions. The presence of these groups in the products further provides opportunities for subsequent synthetic manipulation of these compounds.

Table 3.5: Substrate scope for synthesis of bis(imidazo[1,2-*a*]pyridin-3-yl)methanes^a

| Entry | R ¹ | R ² | Product | Yield (%) ^b |
|-------|----------------|----------------|---------|------------------------|
| 1 | H | H | | 85 |
| 2 | 6-Br | H | | 29 |

| Entry | R ¹ | R ² | Product | Yield (%) ^b |
|-------|----------------|----------------|--------------------------------------------------------------------------------------|------------------------|
| 3 | H | 4-Me |  | 76 |
| 4 | 6-Me | 4-Me |  | 75 |
| 5 | 6-Br | 4-Me |  | 59 |
| 6 | H | 4-OMe |  | 90 |
| 7 | 6-Me | 4-Me |  | 86 |
| 8 | 6-Br | 4-OMe |  | 60 |
| 9 | 6-Me | 3-OMe |  | 78 |

| Entry | R ¹ | R ² | Product | Yield (%) ^b |
|-------|----------------|----------------|--------------------------------------------------------------------------------------|------------------------|
| 10 | H | 3,4-diOMe |  | 88 |
| 11 | 8-Me | 3,4-diOMe |  | 70 |
| 12 | 6-Br | 3,4-diOMe |  | 67 |
| 13 | H | 4-Br |  | 41 |
| 14 | 7-Me | 4-Br |  | 70 |
| 15 | H | 4-Cl |  | 72 |

| Entry | R ¹ | R ² | Product | Yield (%) ^b |
|-------|----------------|-------------------|--------------------------------------------------------------------------------------|------------------------|
| 16 | 6-Br | 4-Cl |  | 48 |
| 17 | H | 4-F |  | 41 |
| 18 | 7-Me | 4-F |  | 29 |
| 19 | H | 3-NO ₂ |  | 30 |
| 20 | H | 4-NO ₂ |  | 0 |

^aReaction conditions: DMA (1.0 mL), VO(acac)₂ (10 mol %), IBD (2.0 mmol) stirred at 100 °C for 1 h, after 1 h **104** (1.0 mmol) was added, stirred at 150 °C for 5 h under air.

^bIsolated yield of pure product based on **104**.

After establishing the substrate scope, we turned our attention towards synthesis of an unsymmetrical bis(imidazo[1,2-*a*]pyridin-3-yl)methane. The reaction of **104d** and **104i** (1:1 molar ratio) with DMA under the optimized reaction conditions gave **151di** in 56% yield (**Scheme 3.49**). The structure of the cross-coupled product **151di** was ascertained by NMR and mass spectrometry data (**Figure 3.10**). Homo-coupled products were not observed in this reaction.

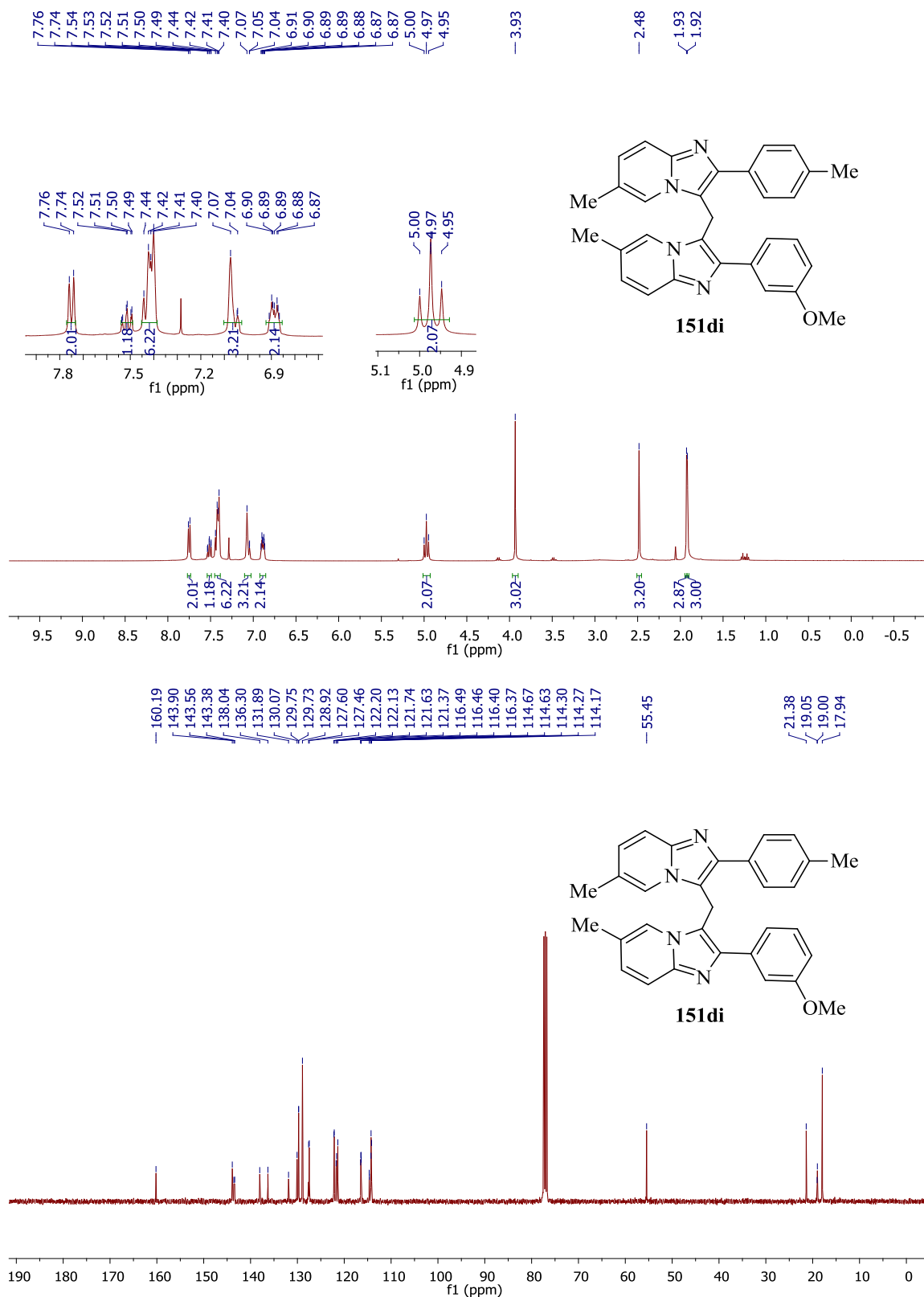
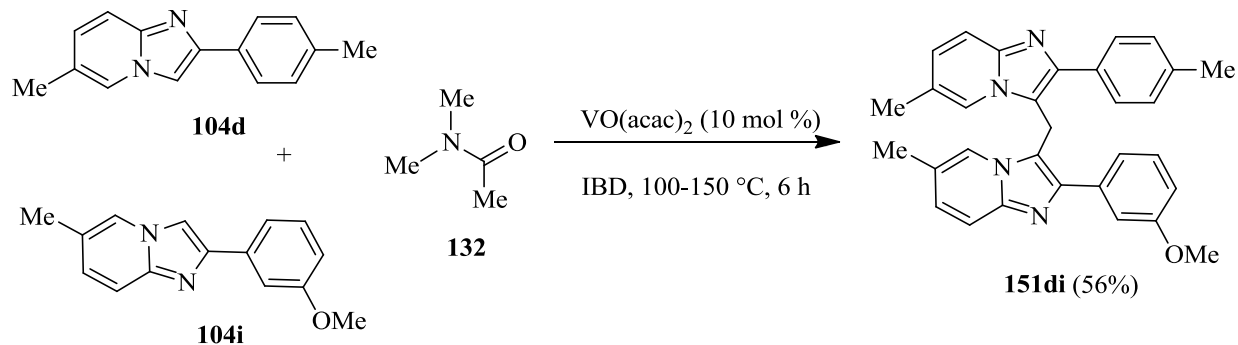
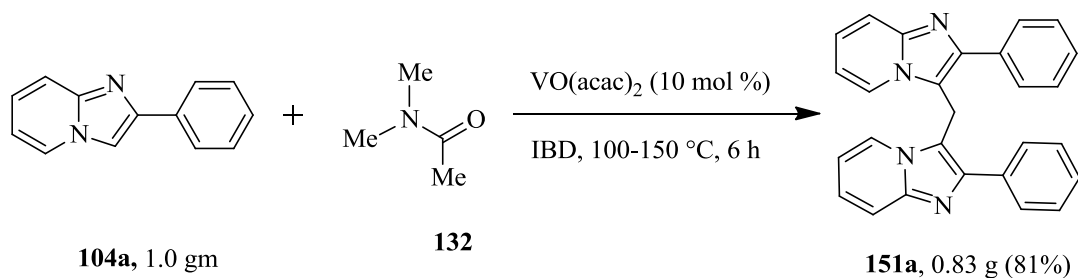


Figure 3.10: ^1H NMR and ^{13}C NMR of 2-(3-methoxyphenyl)-6-methyl-3-((6-methyl-2-(*p*-tolyl)-imidazo[1,2-*a*]pyridin-3-yl)methyl)imidazo[1,2-*a*]pyridine (**151di**)



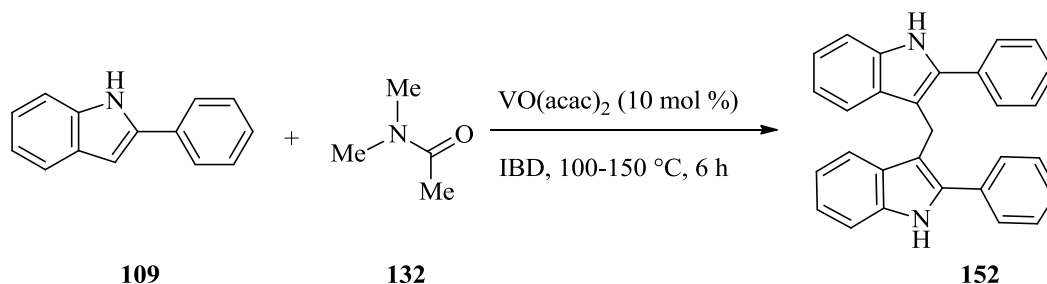
Scheme 3.49: Synthesis of unsymmetrical bis(imidazo[1,2-*a*]pyridin-3-yl)methanes (**151di**).

To further demonstrate the practicality and efficiency of the developed methodology, gram scale reaction was performed. As shown in **scheme 3.50**, **151a** (81%, 0.83 g) could be readily synthesized from 1.0 g of **104a**.



Scheme 3.50: Gram scale synthesis of **151a**

Additionally, the methylenation of 2-arylindoles (**109**) was explored. To our delight, bis(2-aryl-1*H*-indol-3-yl)methanes (**152**) were obtained in 50–71% yield after 6 h (**Scheme 3.51**). The structure of all the products was ascertained by NMR and mass spectrometry data. A characteristic singlet for methylene protons was observed around δ 4.2 ppm in the ¹H NMR of bis(2-phenyl-1*H*-indol-3-yl)methane (**152a**) and at 21.31 ppm in ¹³C NMR (**Figure 3.11**).



Scheme 3.51: Synthesis of bis(2-aryl-1*H*-indol-3-yl)methanes (**152**)

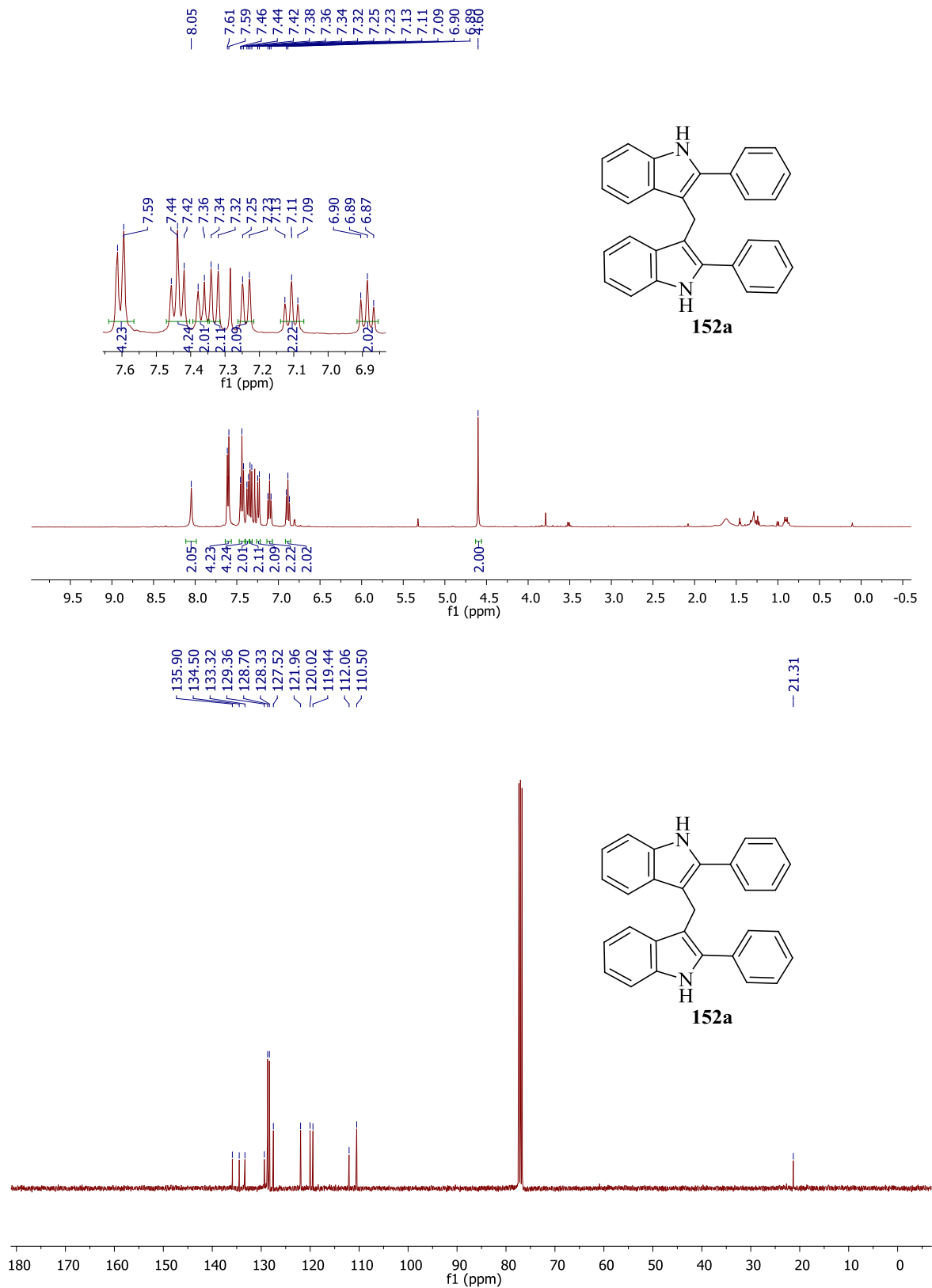
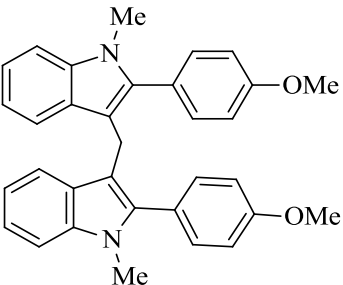
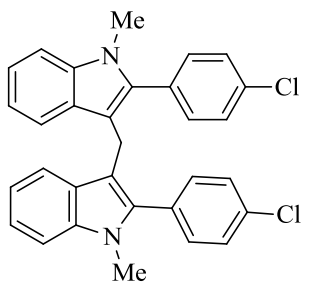


Figure 3.11: ^1H NMR and ^{13}C NMR of bis(2-phenyl-1H-indol-3-yl)methane (**152a**)

Table 3.6: Substrate scope for synthesis of bis(2-aryl-1*H*-indol-3-yl)methanes^a

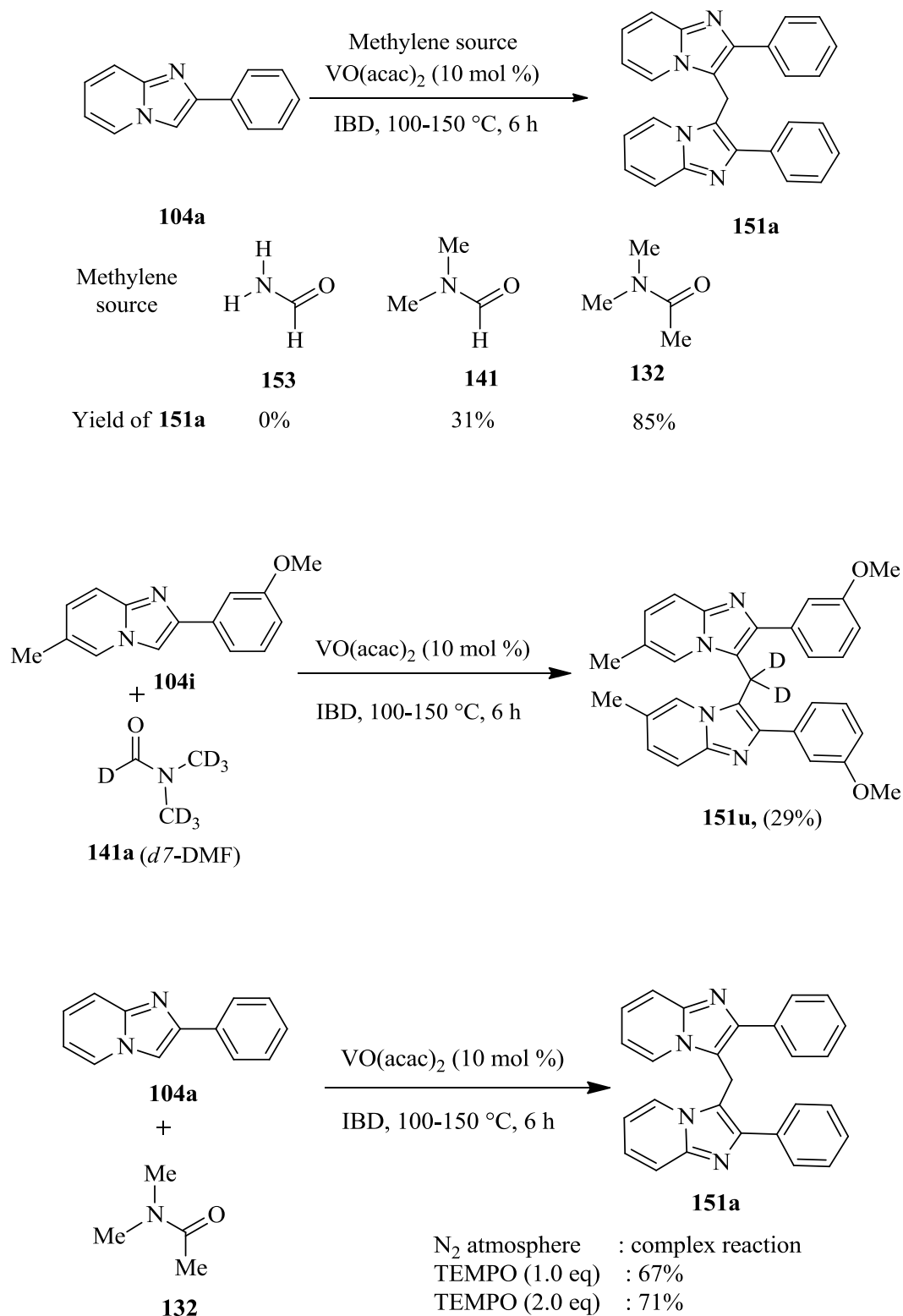
| Entry | R ¹ | R ² | Product | Yield (%) ^b |
|-------|----------------|----------------|---------|------------------------|
| 1 | H | H | | 64 |
| 2 | H | Me | | 50 |
| 3 | H | OMe | | 51 |
| 4 | H | Cl | | 69 |

| Entry | R ¹ | R ² | Product | Yield (%) | |
|-------|----------------|----------------|------------------------------------------------------------------------------------|-------------|----|
| 5 | Me | OMe |  | 152e | 66 |
| 6 | Me | Cl |  | 152f | 71 |

^aReaction conditions: DMA (1.0 mL), VO(acac)₂ (10 mol %), IBD (2.0 mmol) stirred at 100 °C for 1 h, after 1 h **109** (1.0 mmol) was added, stirred at 150 °C for 5 h under air.

^bIsolated yield of pure product based on **109**.

To understand the synthetic pathway and mechanism of the developed methylenation reaction, several control and deuterium tracking experiments were performed. First, different substrates were evaluated to find the source of methylene in the methylenation. As shown in **scheme 3.52**, formamide (**153**) could not generate the desired product under the optimized reaction conditions, whereas the use of DMF gave 31% yield of **151a**. The reaction of **104i** with deuterium labeled DMF ([*d*₇]DMF) (**141a**) under the optimized conditions produced the deuterated bis(imidazo[1,2-*a*]pyridin-3-yl)methane (**151u**) in 29% yield. The structure of **151u** was confirmed by NMR, the peak at δ 5.02 ppm was missing, when compared to the non-deuterated product (**151i**), while all other protons were present in the respective positions (**Figure 3.12**). The presence of peak at m/z 491.2500 in the mass spectrum corresponding to the molecular formula C₃₁H₂₇D₂N₄O₂ further confirmed the structure of **151u** (**Figure 3.13**). The yield of **151a** was minimally perturbed by the presence of the radical scavenger, TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxy), indicating that the reaction does not follow radical pathway. Also complex mixture was obtained when the model reaction was performed under nitrogen, and we could not isolate **151a**, indicating the involvement of air in the oxidation (**Scheme 3.52**).



Scheme 3.52: Control experiments

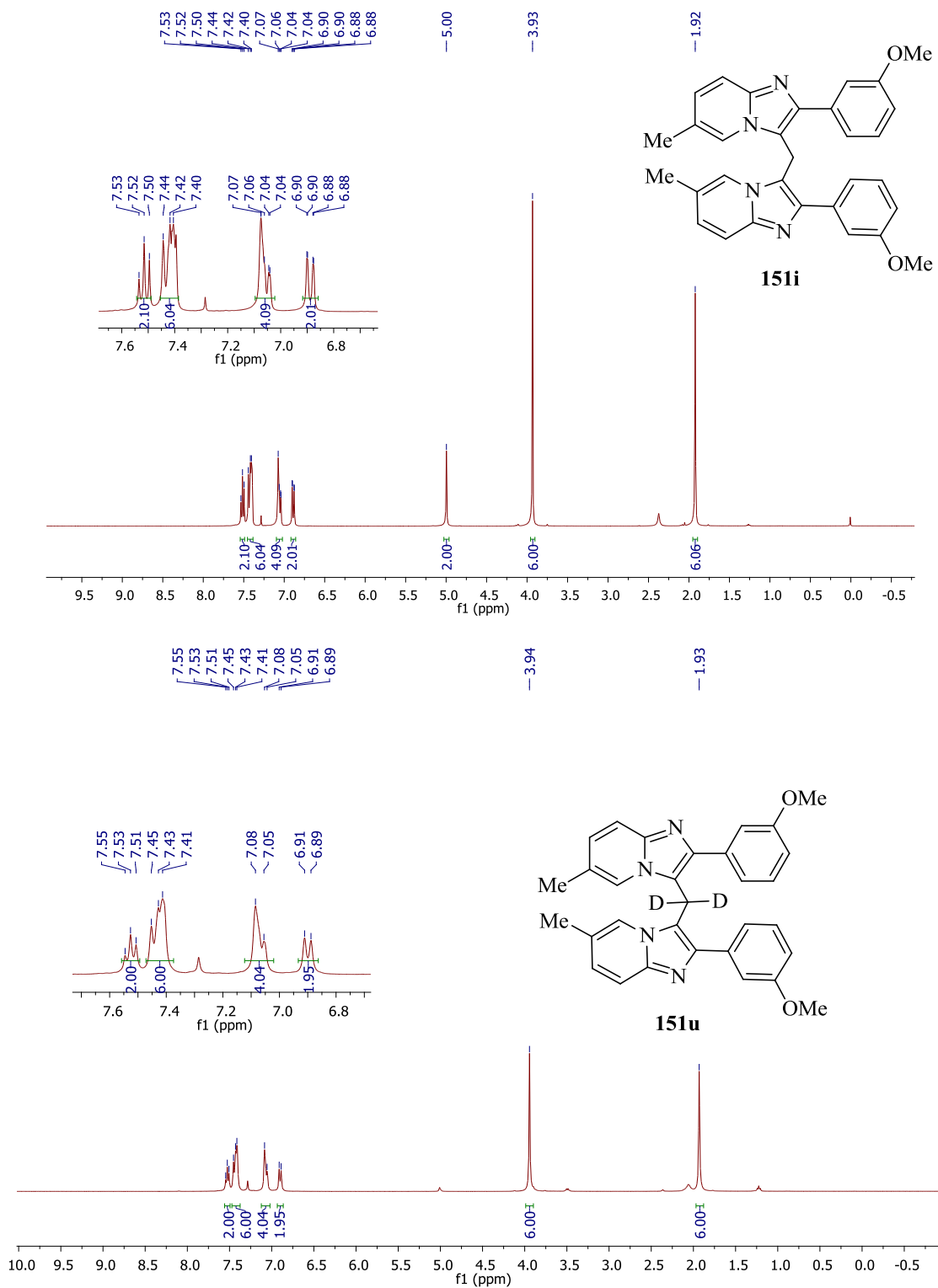


Figure 3.12: ^1H NMR of **151i** and deuterated bis(imidazo[1,2-*a*]pyridin-3-yl)methane (**151u**)

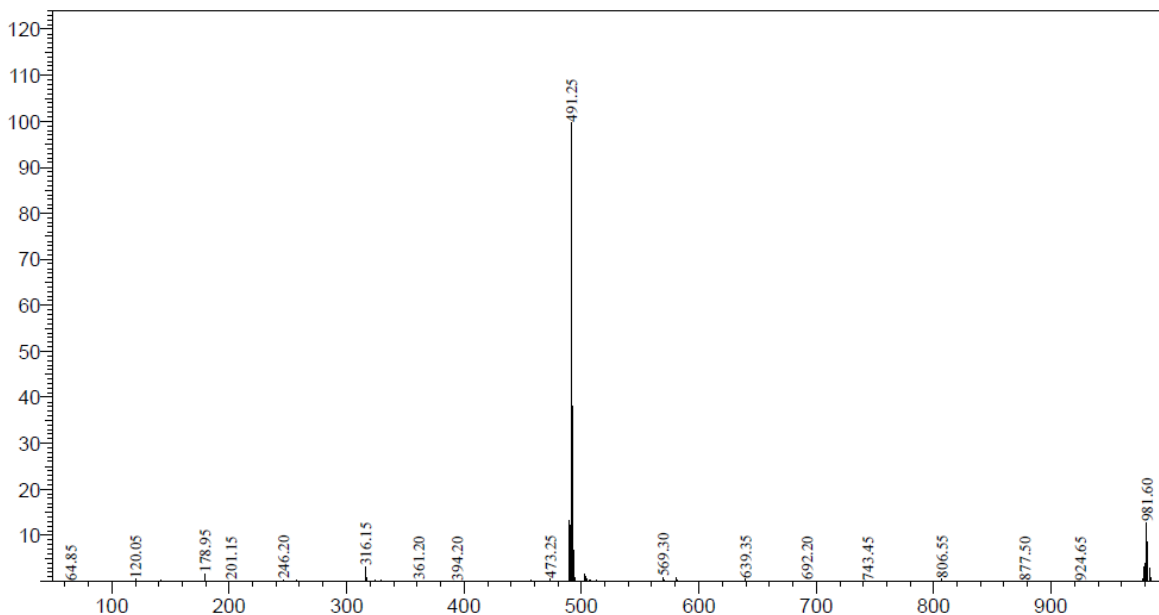
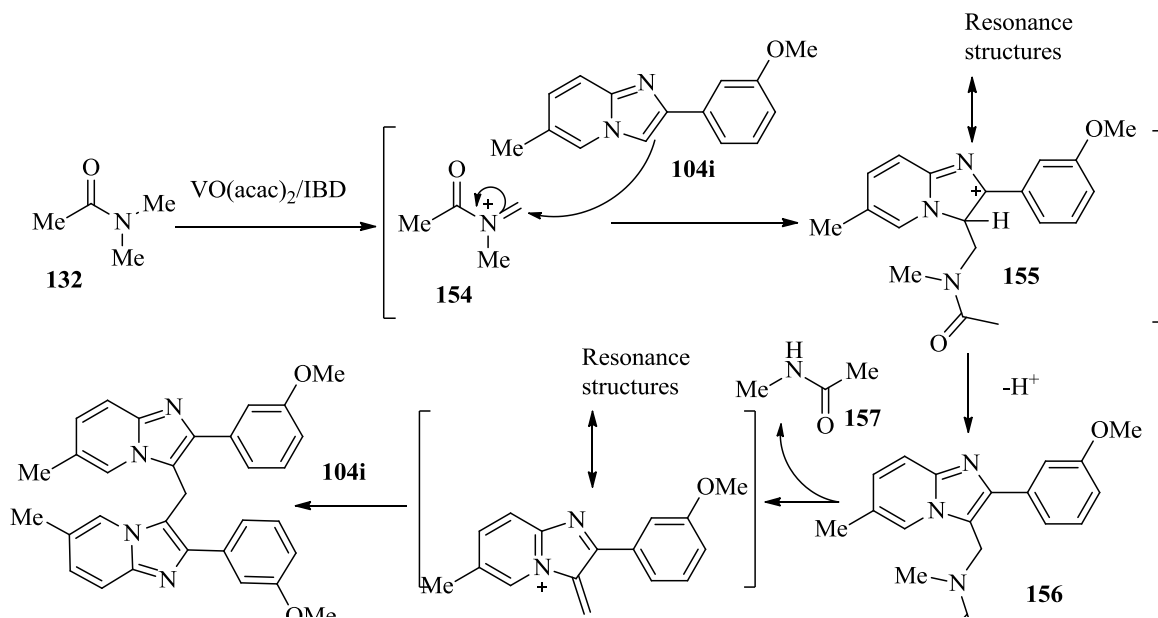


Figure 3.13: Mass of bis(2-(3-methoxyphenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl)methane-*d*₂ (**151u**)

Based on the results obtained from the control and deuterium tracking experiments, and recent literature reports^[68, 89, 121, 128] plausible mechanism has been proposed (**Scheme 3.53**). Initially the iminium intermediate **154** is generated by oxidation of DMA in the presence of VO(acac)₂, air and IBD. V^{IV} and V^V complexes are known to be efficient catalysts for oxidizing alcohols to ketones and amines to imines in the presence of air,^[14, 60, 129-131] though these reaction are thought to be mediated by V^V species; consequently we propose that the VO(acac)₂ is oxidized to an active V^V species, which then oxidizes the DMA to an iminium ion (**154**). Imidazo[1,2-*a*]pyridine (**104i**) then undergoes an electrophilic substitution with **154** followed by deprotonation to give *N*-methyl-*N*-((2-phenylimidazo[1,2-*a*]pyridin-3-yl)methyl)-acetamide (**156**). The formation of intermediate **156** was confirmed by the presence of peak at *m/z* 324.1709 in the mass spectrum of the reaction mixture after 2 h (**Figure 3.14**). Further, *in situ* elimination of *N*-methylacetamide (**157**) from **156** produces reactive intermediate **158**, which then again undergoes electrophilic substitution at the C-3 position of the imidazo[1,2-*a*]pyridine (**104i**) to produce the bis(imidazo[1,2-*a*]pyridin-3-yl)methanes (**151i**). This mechanism is supported by the observations that poor yields result from imidazo[1,2-*a*]pyridines having electron-withdrawing groups at C-2 aryl ring, and that formamide fails to produce product, while deuterated product is produced from [*d*₇]DMF. On the other hand, good yields of product in the presence of TEMPO,

radical scavenger, indicate that the reaction is not proceeding through radical-mediated mechanism.



Scheme 3.53: Plausible mechanism for dimerization of imidazo[1,2-*a*]pyridine

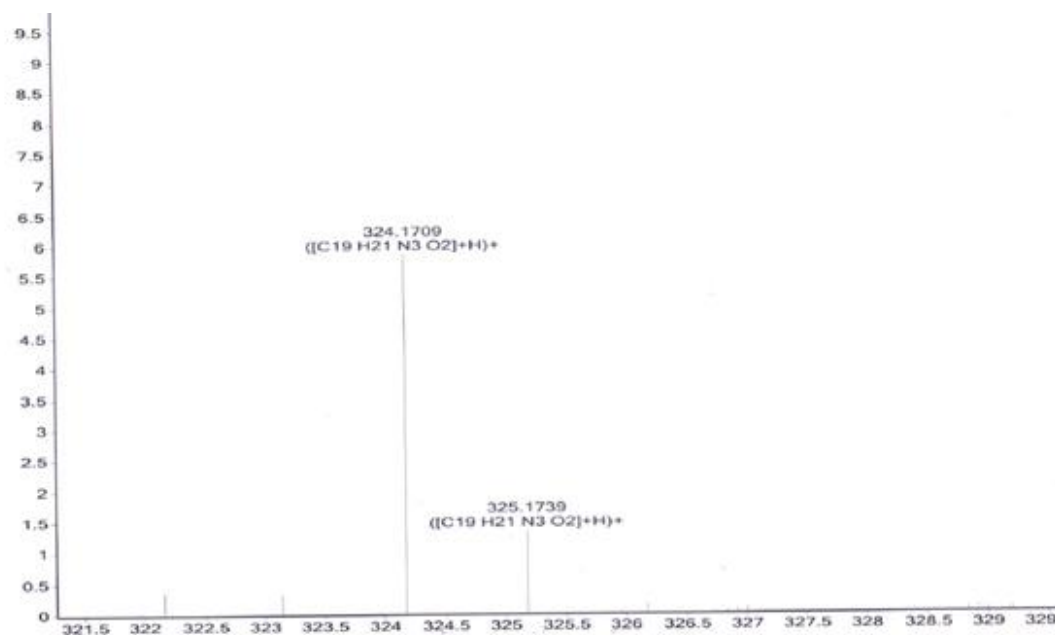


Figure 3.14: Mass spectrum of intermediate 156

3.8. Conclusion

In summary, novel and efficient vanadium-catalyzed method has been demonstrated for the synthesis of bis(2-arylimidazo[1,2-*a*]pyridin-3-yl)methane in good to excellent yields using DMA as methylene source. A catalytic amount of an earth-abundant and inexpensive vanadium catalyst, broad substrate scope, good to excellent yields, and simple isolation procedure are the salient features of the method. The reaction mechanism involves the vanadium-mediated formation of an iminium intermediate and electrophilic substitution.

3.9. Experimental section

3.9.1. General information

Melting points were determined in open capillary tubes on EZ-Melt Automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck). The chemical structures of final products were determined by their NMR spectra (^1H and ^{13}C NMR). Chemical shifts are reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane as an internal standard. The HRMS data were recorded on mass spectrometer with electrospray ionization and TOF mass analyzer. All chemicals were obtained from the commercial suppliers and used without further purification.

3.9.2. Procedure for synthesis of 151a: An oven-dried 5 mL RB flask was charged with $\text{VO}(\text{acac})_2$ (26.5 mg, 10 mol %), IBD (644 mg, 2 mmol), in 1 mL DMA and stirred at 100 °C for 1 h. After 1 h, **104a** (194 mg, 1 mmol) was added to the resulting solution and the reaction was again stirred at 150 °C for 5 h. Reaction progress was monitored by TLC, and after 5 h the reaction mass was allowed to cool to ambient temperature and filtered through cellite pad. The reaction mixture was diluted with water 30 mL and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue so obtained was purified by column chromatography (EtOAc: Hexanes, 3:1) to afford **151a**.

3.9.3. Reaction of 104i and d_7 -DMF: An oven-dried 5 mL RB flask was charged with $\text{VO}(\text{acac})_2$ (11 mg, 10 mol %), IBD (270 mg, 0.84 mmol), in 0.4 mL d_7 -DMF and stirred at 100 °C for 1 h. After 1 h, **104i** (100 mg, 0.42 mmol) was added to the resulting solution and the reaction was again stirred at 150 °C for 5 h. The reaction mass was allowed to cool to ambient

temperature and filtered through cellite pad. Then diluted with water 30 mL and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and evaporated to dryness. The crude residue so obtained was purified by column chromatography (EtOAc: Hexanes, 3:2) to afford desired product (**151u**).

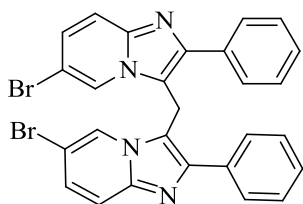
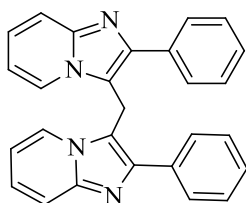
3.9.4. Characterization of intermediate 156 by HRMS: An oven-dried 5 mL RB flask was charged with VO(acac)₂ (11 mg, 10 mol %), IBD (270 mg, 2.0 equiv.), in 0.4 mL DMA and stirred at 100 °C for 1 h. After 1 h, **104i** (100 mg, 1.0 equiv.) was added to the resulting solution and the reaction was again stirred at 150 °C for 30 minutes. LC HRMS of the crude reaction mixture was recorded.

3.9.5. Procedure for synthesis of 152a: An oven-dried 5 mL RB flask was charged with VO(acac)₂ (26.5 mg, 10 mol %), IBD (644 mg, 2 mmol), in 1 mL DMA and stirred at 100 °C for 1 h. After 1 h, **109a** (193 mg, 1 mmol) was added to the resulting solution and the reaction was again stirred at 150 °C for 5 h. Reaction progress was monitored by TLC and after 5 h the reaction mass was allowed to cool to ambient temperature and filtered through cellite pad. Then diluted with water 30 mL and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and evaporated to dryness. The crude residue so obtained was purified by column chromatography (EtOAc: Hexanes, 3:2) to afford **152a**.

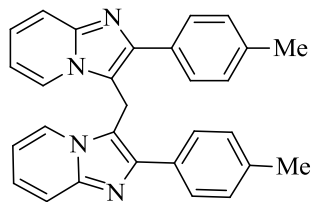
3.9.6. Physical and spectral data of 151a-u, 151di, and 152a-f

Bis(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (151a): Yield 85%; Dark brown solid; mp 211–212 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.81 (d, *J* = 7.9 Hz, 4 H), 7.58–7.51 (m, 6H), 7.49–7.42 (m, 2H), 7.36 (d, *J* = 6.8 Hz, 2 H), 7.10–7.05 (m, 2H), 6.49 (t, *J* = 6.7 Hz, 2H), 5.02 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 144.9, 144.1, 134.2, 128.9, 128.9, 128.3, 124.4, 123.8, 117.5, 114.3, 112.4, 19.8; HRMS (ESI, *m/z*) calcd for C₂₇H₂₁N₄ 401.1761, found 401.1757 [M+H]⁺.

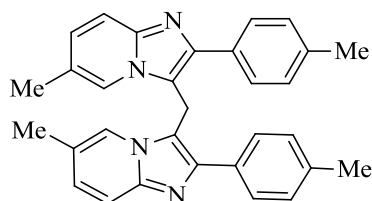
Bis(6-bromo-2-phenylimidazo[1,2-*a*]pyridin-3-yl)methane (151b): Yield 29%; Dark brown solid; mp 285–287 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, *J* = 7.4 Hz, 4H), 7.60 (t, *J* = 7.5 Hz, 4H), 7.55–7.49 (m, 2H), 7.46–7.41 (m, 4H), 7.18–7.10 (m, 2H), 4.96 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 145.2, 143.5, 133.6, 129.3, 129.1, 128.8, 128.0, 124.2, 118.1, 114.6, 107.1, 19.1; HRMS (ESI, *m/z*) calcd for C₂₇H₁₉Br₂N₄ 556.9971, found 556.9976 [M+H]⁺.



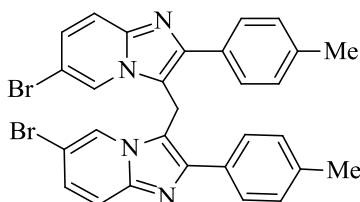
Bis(2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (151c): Yield 76%; Off-white solid; mp 260–262 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.72 (d, $J = 8.0$ Hz, 4H), 7.54 (d, $J = 9.0$ Hz, 2H), 7.39 – 7.32 (m, 6H), 7.09 – 7.01 (m, 2H), 6.48 (td, $J = 6.8, 1.1$ Hz, 2H), 5.01 (s, 2H), 2.47 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.0, 144.3, 138.1, 131.40, 129.6, 128.8, 124.2, 123.9, 117.4, 114.2, 112.2, 21.4, 19.8; HRMS (ESI, m/z) calcd for $\text{C}_{29}\text{H}_{25}\text{N}_4$ 429.2074, found 429.2077 $[\text{M}+\text{H}]^+$.



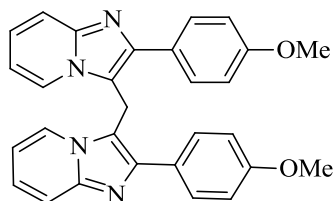
Bis(6-methyl-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (151d): Yield 75%; Off-white solid; mp 288–290 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, $J = 7.8$ Hz, 4H), 7.43 – 7.37 (m, 6H), 7.07 (s, 2H), 6.86 (d, $J = 9.1$ Hz, 2H), 4.94 (s, 2H), 2.48 (s, 6H), 1.91 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.9, 143.7, 138.0, 132.0, 129.7, 128.9, 127.3, 122.1, 121.5, 116.4, 114.3, 21.4, 19.1, 18.0; HRMS (ESI, m/z) calcd for $\text{C}_{31}\text{H}_{29}\text{N}_4$ 457.2387, found 457.2383 $[\text{M}+\text{H}]^+$.



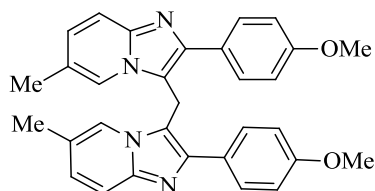
Bis(6-bromo-2-(*p*-tolyl)imidazo[1,2-*a*]pyridin-3-yl)methane (151e): Yield 59%; Off-white solid; mp 182–184 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.68 (d, $J = 8.0$ Hz, 4H), 7.44 – 7.37 (m, 8H), 7.12 (dd, $J = 9.6, 1.6$ Hz, 2H), 4.91 (s, 2H), 2.48 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.2, 143.4, 138.6, 130.7, 130.0, 128.9, 127.8, 124.2, 117.9, 114.5, 106.9, 21.5, 19.1; HRMS (ESI, m/z) calcd for $\text{C}_{29}\text{H}_{23}\text{Br}_2\text{N}_4$ 585.0284, found 585.0279 $[\text{M}+\text{H}]^+$.



Bis(2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (151f): Yield 90%; Brown solid; mp 209–211 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, $J = 8.7$ Hz, 4H), 7.53 (d, $J = 9.0$ Hz, 2H), 7.37 (d, $J = 6.9$ Hz, 2H), 7.10 – 7.04 (m, 6H), 6.49 (t, $J = 6.5$ Hz, 2H), 4.97 (s, 2H), 3.91 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.6, 144.9, 143.9, 130.1, 126.7, 124.2, 123.8, 117.2, 114.3, 113.8, 112.2, 55.4, 19.8; HRMS (ESI, m/z) calcd for $\text{C}_{29}\text{H}_{25}\text{N}_4\text{O}_2$ 461.1972, found 461.1965 $[\text{M}+\text{H}]^+$.

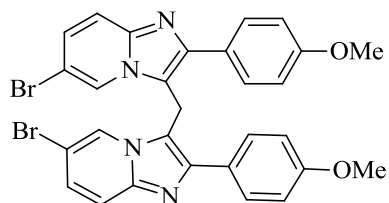


Bis(2-(4-methoxyphenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl)methane (151g): Yield 86%; Yellow solid; mp 159–161 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, $J = 8.7$ Hz, 4H), 7.39 (d, $J = 9.1$ Hz, 2H), 7.15 – 7.08 (m, 6H), 6.87 (dd, $J = 9.2, 1.5$ Hz, 2H), 4.91 (s, 2H), 3.91 (s, 6H),



1.95 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.7, 143.9, 143.5, 130.3, 127.4, 127.3, 122.1, 121.5, 116.4, 114.5, 114.0, 55.5, 19.2, 18.1; HRMS (ESI, m/z) calcd for $\text{C}_{31}\text{H}_{29}\text{N}_4\text{O}_2$ 489.2285, found 489.2289 $[\text{M}+\text{H}]^+$.

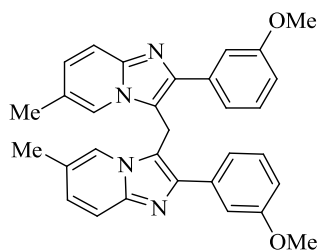
Bis(6-bromo-2-(4-methoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (151h): Yield 60%;



Dark brown solid; mp 273–275 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, $J = 8.6$ Hz, 4H), 7.49 – 7.38 (m, 4H), 7.16 – 7.08 (m, 6H), 4.89 (s, 2H), 3.92 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.1, 145.0, 143.4, 130.3, 127.8, 126.0, 124.2, 117.9, 114.7, 114.3, 106.9, 55.5, 19.1; HRMS (ESI, m/z) calcd for

$\text{C}_{29}\text{H}_{23}\text{Br}_2\text{N}_4\text{O}_2$ 617.0182, found 617.0191 $[\text{M}+\text{H}]^+$.

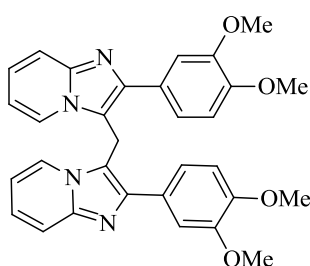
Bis(2-(3-methoxyphenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl)methane (151i): Yield 78%;



White solid; mp 223–225 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.52 (t, $J = 7.8$ Hz, 2H), 7.46 – 7.38 (m, 6H), 7.09 – 7.02 (m, 4H), 6.89 (dd, $J = 9.1, 1.0$ Hz, 2H), 5.00 (s, 2H), 3.93 (s, 6H), 1.92 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.2, 144.0, 143.5, 136.4, 130.1, 127.5, 122.2, 121.7, 121.37, 116.5, 114.6, 114.3, 114.2, 55.5, 19.0, 17.9; HRMS

(ESI, m/z) calcd for $\text{C}_{31}\text{H}_{29}\text{N}_4\text{O}_2$ 489.2285, found 489.2281 $[\text{M}+\text{H}]^+$.

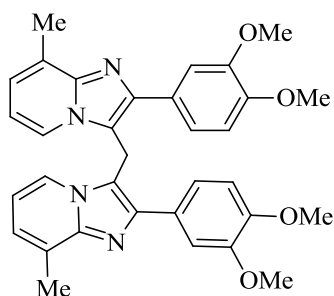
Bis(2-(3,4-dimethoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)-methane (151j): Yield 88%; Off-



white solid; mp 191–193 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.54 (d, $J = 9.0$ Hz, 2H), 7.39 (d, $J = 7.0$ Hz, 4H), 7.30 (dd, $J = 8.4, 1.6$ Hz, 2H), 7.09 – 7.04 (m, 2H), 7.00 (d, $J = 8.2$ Hz, 2H), 6.49 (t, $J = 6.6$ Hz, 2H), 5.00 (s, 2H), 4.00 (s, 6H), 3.97 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.4, 149.1, 144.9, 144.0, 127.2, 124.3, 123.9, 121.3, 117.3, 114.1, 112.2, 112.0, 111.1, 56.1, 56.0, 19.8; HRMS

(ESI, m/z) calcd for $\text{C}_{31}\text{H}_{29}\text{N}_4\text{O}_4$ 521.2183, found 521.2176 $[\text{M}+\text{H}]^+$.

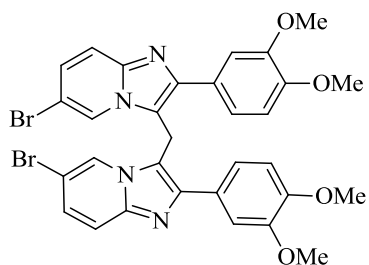
Bis(2-(3,4-dimethoxyphenyl)-8-methylimidazo[1,2-*a*]pyridin-3-yl)methane (151k): Yield



70%; Off-white solid; mp 191–193 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.37 (s, 2H), 7.33 – 7.22 (m, 4H), 6.98 (d, $J = 8.2$ Hz, 2H), 6.86 (d, $J = 6.6$ Hz, 2H), 6.41 (t, $J = 6.8$ Hz, 2H), 4.91 (s, 2H), 3.99 (s, 6H), 3.96 (s, 6H), 2.58 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 149.3, 149.0, 145.2, 143.5, 127.5, 127.1, 123.0, 121.7, 121.5, 114.7, 112.3,

112.1, 111.1, 56.1, 56.0, 19.9, 17.0; HRMS (ESI, m/z) calcd for $C_{33}H_{33}N_4O_4$ 549.2496, found 549.2489 $[M+H]^+$.

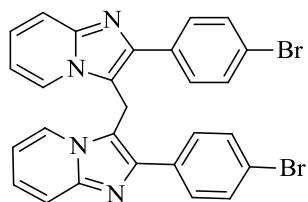
Bis(6-bromo-2-(3,4-dimethoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (151l): Yield



67%; Off-white solid; mp 229–231 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 6H), 7.30 (dd, $J = 8.3, 1.8$ Hz, 2H), 7.12 (dd, $J = 9.4, 1.7$ Hz, 2H), 7.07 (d, $J = 8.2$ Hz, 2H), 4.95 (s, 2H), 4.03 (s, 6H), 4.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 149.6, 144.8, 143.3, 127.9, 126.5, 124.4, 121.0, 117.8, 114.7, 112.1, 111.3, 107.0, 56.1, 56.0, 18.8; HRMS (ESI, m/z)

calcd for $C_{31}H_{27}Br_2N_4O_4$ 677.0394, found 677.0397 $[M+H]^+$.

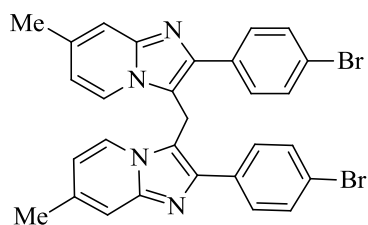
Bis(2-(4-bromophenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (151m): Yield 41%; Dark brown



solid; mp 271–274 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.59 (bs, 8H), 7.55 (d, $J = 9.1$ Hz, 2H), 7.38 (d, $J = 6.9$ Hz, 2H), 7.14 – 7.09 (m, 2H), 6.57 (t, $J = 6.5$ Hz, 2H), 4.89 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 143.1, 133.1, 131.8, 130.2, 124.7, 123.4, 122.5, 117.6, 114.0, 112.7, 20.1; HRMS (ESI, m/z) calcd for $C_{27}H_{19}Br_2N_4$ 556.9971, found

556.9979 $[M+H]^+$.

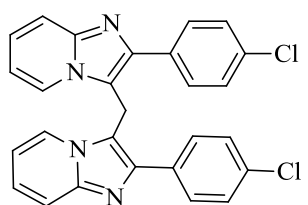
Bis(2-(4-bromophenyl)-7-methylimidazo[1,2-*a*]pyridin-3-yl)methane (151n): Yield 70%;



Dark brown solid; mp 295–297 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.60 (bs, 8H), 7.28 (s, 2H), 7.22 (d, $J = 7.0$ Hz, 2H), 6.37 (dd, $J = 7.1, 1.5$ Hz, 2H), 4.84 (s, 2H), 2.31 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 142.7, 135.7, 133.31, 131.9, 130.2, 122.7, 122.3, 115.9, 115.3, 113.7, 21.2, 20.0; HRMS (ESI, m/z) calcd for

$C_{29}H_{23}Br_2N_4$ 585.0284, found 585.0273 $[M+H]^+$.

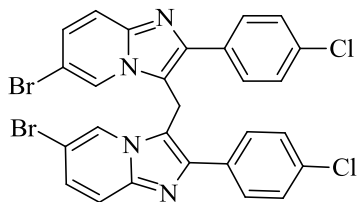
Bis(2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (151o): Yield 72%; White solid;



mp 274–276 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, $J = 8.5$ Hz, 4H), 7.55 (d, $J = 9.1$ Hz, 2H), 7.44 (d, $J = 8.5$ Hz, 4H), 7.38 (d, $J = 6.9$ Hz, 2H), 7.16 – 7.06 (m, 2H), 6.57 (td, $J = 6.8, 0.9$ Hz, 2H), 4.90 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 143.1, 134.2, 132.6, 129.9,

128.9, 124.6, 123.4, 117.6, 114.0, 112.7, 20.0; HRMS (ESI, m/z) calcd for $C_{27}H_{19}Cl_2N_4$ 469.0981, found 469.0974 $[M+H]^+$.

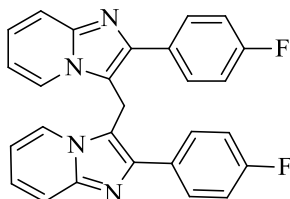
Bis(6-bromo-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (151p): Yield 48%; Off-



white solid; mp 269–273 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.69 (d, $J = 8.4$ Hz, 4H), 7.54 (d, $J = 8.4$ Hz, 4H), 7.48 – 7.41 (m, 4H), 7.18 (dd, $J = 9.6, 1.3$ Hz, 2H), 4.86 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.0, 143.5, 134.9, 132.1, 130.1, 129.4, 128.3, 123.9, 118.2, 114.4, 107.4, 19.3; HRMS (ESI, m/z) calcd for

$\text{C}_{27}\text{H}_{17}\text{Br}_2\text{Cl}_2\text{N}_4$ 624.9192, found 624.9197 $[\text{M}+\text{H}]^+$.

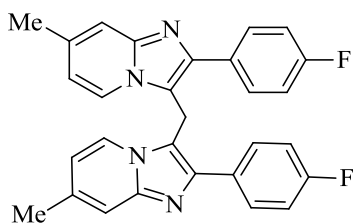
Bis(2-(4-fluorophenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (151q): Yield 41%; Dark brown



solid; mp 200–204 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.76 – 7.68 (m, 4H), 7.56 (d, $J = 9.1$ Hz, 2H), 7.40 (d, $J = 6.9$ Hz, 1H), 7.23 – 7.17 (m, 2H), 7.15 – 7.10 (m, 4H), 6.58 (td, $J = 6.8, 0.9$ Hz, 2H), 4.93 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.7 (d, $J = 248.2$ Hz), 145.0, 143.4,

130.5 (d, $J = 8.2$ Hz), 130.3 (d, $J = 3.3$ Hz), 124.5, 123.5, 117.6, 115.8 (d, $J = 21.5$ Hz), 113.9, 112.5, 19.9; HRMS (ESI, m/z) calcd for $\text{C}_{27}\text{H}_{19}\text{F}_2\text{N}_4$ 437.1572, found 437.1565 $[\text{M}+\text{H}]^+$.

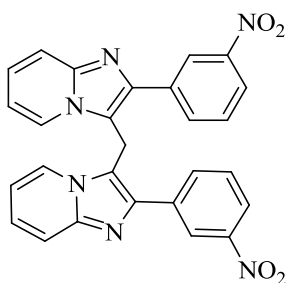
Bis(2-(4-fluorophenyl)-7-methylimidazo[1,2-*a*]pyridin-3-yl)methane (151r): Yield 29%; Off-



white solid; mp 256–258 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.76 – 7.69 (m, 4H), 7.28 (s, 2H), 7.25 – 7.16 (m, 6H), 6.37 (dd, $J = 7.0, 1.4$ Hz, 2H), 4.87 (s, 2H), 2.31 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.6 (d, $J = 247.8$ Hz), 145.4, 142.9, 135.5, 130.6 (d, $J = 3.2$ Hz), 130.5 (d, $J = 8.1$ Hz), 122.8, 115.8, 115.8 (d, $J = 21.5$

Hz), 115.1, 113.5, 21.2, 19.8; HRMS (ESI, m/z) calcd for $\text{C}_{29}\text{H}_{23}\text{F}_2\text{N}_4$ 465.1885, found 465.1892 $[\text{M}+\text{H}]^+$.

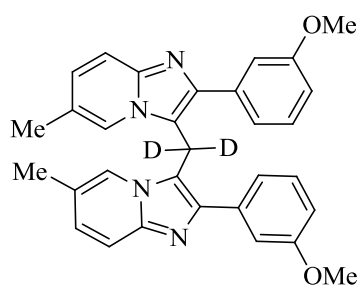
Bis(2-(3-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)methane (151s): Yield 30%; Dark brown



solid; mp 89–94 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.37 (t, $J = 1.9$ Hz, 2H), 8.19 – 8.14 (m, 2H), 7.84 – 7.81 (m, 2H), 7.64 (d, $J = 6.9$ Hz, 2H), 7.57 (d, $J = 9.1$ Hz, 2H), 7.51 (t, $J = 8.0$ Hz, 2H), 7.25 – 7.20 (m, 2H), 6.80 (td, $J = 6.8, 1.0$ Hz, 2H), 4.94 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.9, 145.0, 142.1, 135.5, 134.2, 129.3, 125.2, 123.0, 123.0, 122.8, 118.0, 114.1, 113.4, 20.4; HRMS (ESI, m/z) calcd for $\text{C}_{27}\text{H}_{19}\text{N}_6\text{O}_4$

491.1462, found 491.1458 $[\text{M}+\text{H}]^+$.

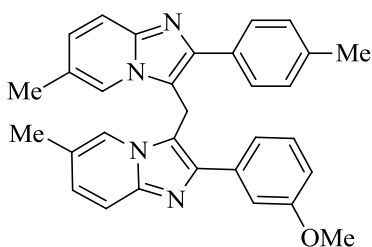
Bis(2-(3-methoxyphenyl)-6-methylimidazo[1,2-*a*]pyridin-3-yl)methane-*d*₂ (151u): Yield



29%; Dark brown solid; mp 197–199 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.53 (t, *J* = 7.7 Hz, 2H), 7.47 – 7.37 (m, 6H), 7.09 – 7.02 (m, 4H), 6.90 (d, *J* = 9.0 Hz, 2H), 3.94 (s, 6H), 1.93 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 160.2, 144.0, 143.5, 136.4, 130.1, 127.6, 122.2, 121.7, 121.4, 116.5, 114.6, 114.3, 114.2, 55.5, 19.0, 17.9; HRMS (ESI, *m/z*) calcd for C₃₁H₂₇D₂N₄O₂ 491.2411, found

491.2500 [M+H]⁺.

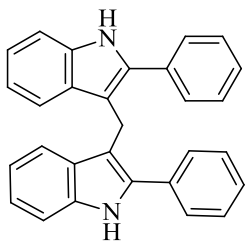
2-(3-Methoxyphenyl)-6-methyl-3-((6-methyl-2-(*p*-tolyl)-imidazo[1,2-*a*]pyridin-3-



yl)methyl)imidazo[1,2-*a*]pyridine (151di): Yield 56%; Dark brown solid; mp 222–224 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, *J* = 7.3 Hz, 2H), 7.54 – 7.49 (m, 1H), 7.45 – 7.38 (m, 6H), 7.10 – 7.02 (m, 3H), 6.92 – 6.85 (m, 2H), 4.97 (t, *J* = 10.5 Hz, 2H), 3.93 (s, 3H), 2.48 (s, 3H), 1.93 (s, 3H), 1.92 (s, 3H); ¹³C

NMR (100 MHz, CDCl₃) δ 160.2, 143.9, 143.6, 143.3, 138.0, 136.3, 131.9, 130.1, 129.8, 129.7, 128.9, 127.6, 127.5, 122.2, 122.1, 121.7, 121.6, 121.4, 116.5, 116.5, 116.4, 116.4, 114.7, 114.6, 114.3, 114.3, 114.2, 55.5, 21.4, 19.1, 19.0, 17.9; HRMS (ESI, *m/z*) calcd for C₃₁H₂₉N₄O 473.2336, found 473.2326 [M+H]⁺.

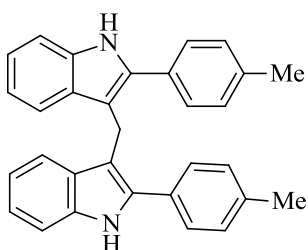
Bis(2-phenyl-1*H*-indol-3-yl)methane (152a): Yield 64%; Red solid; mp 168–170 °C; ¹H NMR



(400 MHz, CDCl₃) δ 8.05 (s, 2H), 7.60 (d, *J* = 7.2 Hz, 4H), 7.44 (t, *J* = 7.5 Hz, 4H), 7.37 (d, *J* = 7.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 2H), 6.89 (t, *J* = 7.5 Hz, 2H), 4.60 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 135.9, 134.5, 133.3, 129.4, 128.7, 128.3, 127.5, 122.0, 120.0, 119.4, 112.1, 110.5, 21.3; HRMS (ESI, *m/z*) calcd for

C₂₉H₂₃N₂ 399.1856, found 399.1861 [M+H]⁺.

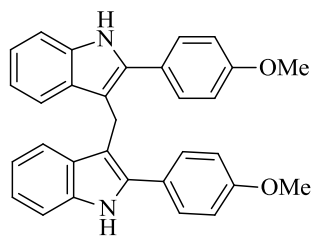
Bis(2-(*p*-tolyl)-1*H*-indol-3-yl)methane (152b): Yield 50%; Green solid; mp 206–208 °C; ¹H



NMR (400 MHz, CDCl₃) δ 8.02 (s, 2H), 7.53 (d, *J* = 7.9 Hz, 4H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 4H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 2H), 6.86 (t, *J* = 7.4 Hz, 2H), 4.57 (s, 2H), 2.43 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 137.4, 135.8, 134.5, 130.5, 129.45, 128.2, 121.8, 120.0, 119.4, 111.8, 110.4, 21.4, 21.3; HRMS

(ESI, m/z) calcd for $C_{31}H_{27}N_2$ 427.2169, found 427.2164 $[M+H]^+$.

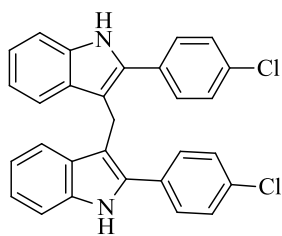
Bis(2-(4-methoxyphenyl)-1H-indol-3-yl)methane (152c): Yield 51%; Red solid; mp 196–199



°C; 1H NMR (400 MHz, DMSO) δ 11.10 (s, 2H), 7.62 (d, $J = 8.4$ Hz, 4H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.03 (t, $J = 8.0$ Hz, 6H), 6.95 (t, $J = 7.4$ Hz, 2H), 6.70 (t, $J = 7.4$ Hz, 2H), 4.44 (s, 2H), 3.81 (s, 6H); ^{13}C NMR (100 MHz, DMSO) δ 159.0, 136.3, 134.8, 129.9, 129.3, 126.0, 121.2, 119.41, 118.7, 114.5, 111.3, 110.4, 55.6, 21.7; HRMS (ESI,

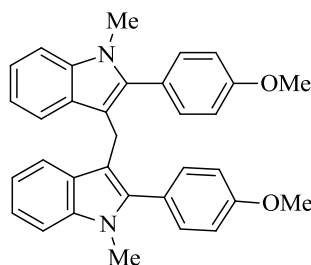
m/z) calcd for $C_{31}H_{27}N_2O_2$ 459.2067, found 459.2071 $[M+H]^+$.

Bis(2-(4-chlorophenyl)-1H-indol-3-yl)methane (152d): Yield 69%; Green solid; mp 201–203



°C; 1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 2H), 7.43 – 7.31 (m, 9H), 7.31 – 7.26 (m, 3H), 7.14 (t, $J = 7.4$ Hz, 2H), 6.94 (t, $J = 7.4$ Hz, 2H), 4.52 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 133.5, 133.4, 131.6, 129.4, 129.2, 128.8, 122.4, 119.8, 119.7, 112.3, 110.7, 21.1; HRMS (ESI, m/z) calcd for $C_{29}H_{21}Cl_2N_2$ 467.1076, found 467.1078 $[M+H]^+$.

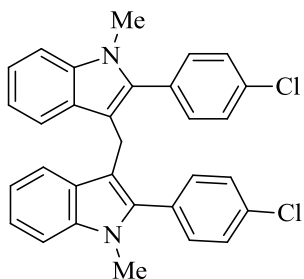
Bis(2-(4-methoxyphenyl)-1-methyl-1H-indol-3-yl)methane (152e): Yield 66%; Off-white



solid; mp 183–185 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 8H), 7.18 (t, $J = 7.5$ Hz, 2H), 6.99 (d, $J = 8.6$ Hz, 4H), 6.94 (d, $J = 7.4$ Hz, 2H), 4.24 (s, 2H), 3.91 (s, 6H), 3.58 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 137.5, 137.1, 132.0, 128.1, 124.6, 121.1, 119.7, 118.8, 113.7, 112.1, 108.9, 55.4, 30.7, 21.1; HRMS (ESI, m/z)

calcd for $C_{33}H_{31}N_2O_2$ 487.2380, found 487.2383 $[M+H]^+$.

Bis(2-(4-chlorophenyl)-1-methyl-1H-indol-3-yl)methane (152f): Yield 71%; Off-white solid;



mp 202–204 °C; 1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, $J = 8.3$ Hz, 4H), 7.32 – 7.27 (m, 4H), 7.21 (t, $J = 7.5$ Hz, 2H), 7.12 (d, $J = 8.3$ Hz, 4H), 6.99 (t, $J = 7.4$ Hz, 2H), 4.21 (s, 2H), 3.52 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.3, 133.8, 131.9, 130.5, 128.3, 127.9, 121.7, 119.6, 119.2, 112.5, 109.1, 30.8, 20.7; HRMS (ESI, m/z) calcd for $C_{31}H_{25}Cl_2N_2$ 495.1382, found 495.1382 $[M+H]^+$.

3.10. References:

- [1] Luh, T. Y.; Huang, L.-F., In *Book Wiley-VCH Verlag GmbH*: **2008**; pp 397-449.
- [2] Cahiez, G.; Duplais, C.; Buendia, J., *Chemical Reviews* **2009**, *109*, 1434-1476.
- [3] Orsini, F.; Sello, G., *Current Organic Synthesis* **2004**, *1*, 111-135.
- [4] Alan, C. S.; Christopher, J. G. G.; Joseph, P. H., *Current Organic Synthesis* **2004**, *1*, 211-226.
- [5] Shi, W.; Liu, C.; Lei, A., *Chemical Society Reviews* **2011**, *40*, 2761-2776.
- [6] Zheng, Q. Z.; Jiao, N., *Chemical Society Reviews* **2016**, *45*, 4590-4627.
- [7] Leenders, S. H. A. M.; Gramage-Doria, R.; de Bruin, B.; Reek, J. N. H., *Chemical Society Reviews* **2015**, *44*, 433-448.
- [8] Ouyang, K.; Hao, W.; Zhang, W. X.; Xi, Z., *Chemical Reviews* **2015**, *115*, 12045-12090.
- [9] Bagal, D. B.; Bhanage, B. M., *Advanced Synthesis & Catalysis* **2015**, *357*, 883-900.
- [10] Nakamura, I.; Yamamoto, Y., *Chemical Reviews* **2004**, *104*, 2127-2198.
- [11] Eglinton, G.; Galbraith, A., Soc Chemical Industry 14 Belgrave Square, London, England: **1956**; pp 737-738.
- [12] Eglinton, G.; Galbraith, A. R., *Journal of the Chemical Society* **1959**, 889-896.
- [13] Hay, A. S., *The Journal of Organic Chemistry* **1962**, *27*, 3320-3321.
- [14] Hirao, T., *Chemical Reviews* **1997**, *97*, 2707-2724.
- [15] Trost, B. M.; Hung, M. H., *Journal of the American Chemical Society* **1983**, *105*, 7757-7759.
- [16] Trost, B. M.; Zhang, Y., *Journal of the American Chemical Society* **2007**, *129*, 14548-14549.
- [17] Plietker, B., *Angewandte Chemie International Edition* **2006**, *45*, 1469-1473.
- [18] Holzwarth, M.; Dieskau, A.; Tabassam, M.; Plietker, B., *Angewandte Chemie International Edition* **2009**, *48*, 7251-7255.
- [19] Nomura, N.; RajanBabu, T. V., *Tetrahedron Letters* **1997**, *38*, 1713-1716.
- [20] Reddy, C. K.; Knochel, P., *Angewandte Chemie International Edition* **1996**, *35*, 1700-1701.
- [21] Tsuji, T.; Yorimitsu, H.; Oshima, K., *Angewandte Chemie International Edition* **2002**, *41*, 4137-4139.

- [22] Lauer, A. M.; Mahmud, F.; Wu, J., *Journal of the American Chemical Society* **2011**, *133*, 9119-9123.
- [23] Shul'pin, G. B., *Dalton Transactions* **2013**, *42*, 12794-12818.
- [24] Sandulenko, Y.; Krasavin, M., *Chemistry of Heterocyclic Compounds* **2012**, *48*, 606-612.
- [25] Chaoui B., A.; Galtier, C.; Allouchi, H.; Kherbeche, A.; Debouzy, J. C.; Teulade, J. C.; Chavignon, O.; Witvrouw, M.; Pannecouque, C.; Balzarini, J.; de, C. E.; Enguehard, C.; Gueiffier, A., *Archiv der Pharmazie* **2001**, *334*, 224-228.
- [26] Wen, L.-R.; Jiang, C.-Y.; Li, M.; Wang, L.-J., *Tetrahedron* **2011**, *67*, 293-302.
- [27] Fisher, M. H.; Lusi, A., *Journal of Medicinal Chemistry* **1972**, *15*, 982-5.
- [28] Kaminski, J. J.; Bristol, J. A.; Puchalski, C.; Lovey, R. G.; Elliott, A. J.; Guzik, H.; Solomon, D. M.; Conn, D. J.; Domalski, M. S.; et, a., *Journal of Medicinal Chemistry* **1985**, *28*, 876-892.
- [29] Hieke, M.; Roedl, C. B.; Wisniewska, J. M.; Buscato, E.; Stark, H.; Schubert, Z. M.; Steinhilber, D.; Hofmann, B.; Proschak, E., *Bioorganic & Medicinal Chemistry Letters* **2012**, *22*, 1969-1975.
- [30] Pericherla, K.; Kaswan, P.; Pandey, K.; Kumar, A., *Synthesis* **2015**, *47*, 887-912.
- [31] Gao, P.; Guo, W.; Xue, J.; Zhao, Y.; Yuan, Y.; Xia, Y.; Shi, Z., *Journal of the American Chemical Society* **2015**, *137*, 12231-12240.
- [32] Scheuermann, C. J., *Chemistry – An Asian Journal* **2010**, *5*, 436-451.
- [33] Alagiri, K.; Kumara, G. S. R.; Prabhu, K. R., *Chemical Communications* **2011**, *47*, 11787-11789.
- [34] Godula, K.; Sames, D., *Science* **2006**, *312*, 67-72.
- [35] Pandey, G.; Jadhav, D.; Tiwari, S. K.; Singh, B., *Advanced Synthesis & Catalysis* **2014**, *356*, 2813-2818.
- [36] Li, C. J., *Accounts of Chemical Research* **2009**, *42*, 335-344.
- [37] Li, Z.; Cao, L.; Li, C. J., *Angewandte Chemie* **2007**, *119*, 6625-6627.
- [38] Zhang, Y.; Li, C. J., *European Journal of Organic Chemistry* **2007**, 4654-4657.
- [39] Li, Y.-Z.; Li, B.-J.; Lu, X.-Y.; Lin, S.; Shi, Z.-J., *Angewandte Chemie International Edition* **2009**, *48*, 3817-3820.
- [40] Li, Z.; Li, C. J., *Journal of the American Chemical Society* **2004**, *126*, 11810-11811.

- [41] Beak, P.; Zajdel, W. J.; Reitz, D. B., *Chemical Reviews* **1984**, *84*, 471-523.
- [42] Van H., R.; Verberg, G., *Recueil des Travaux Chimiques des Pays-Bas* **1965**, *84*, 1263-1273.
- [43] Jie, X.; Shang, Y.; Hu, P.; Su, W., *Angewandte Chemie International Edition* **2013**, *52*, 3630-3633.
- [44] Sagadevan, A.; Lyu, P.-C.; Hwang, K. C., *Green Chemistry* **2016**, *18*, 4526-4530.
- [45] Murahashi, S.-I.; Zhang, D., *Chemical Society Reviews* **2008**, *37*, 1490-1501.
- [46] Jones, K. M.; Klusmann, M., *Synlett* **2012**, 159-162.
- [47] Murugesan, S.; Kirchner, K., *Dalton Transactions* **2016**, *45*, 416-439.
- [48] Scior, T.; Guevara, G. A.; Bernard, P.; Do, Q.-T.; Domeyer, D.; Laufer, S., *Mini-Reviews in Medicinal Chemistry* **2005**, *5*, 995-1008.
- [49] Haber, J., *Catalysis Today* **2009**, *142*, 100-113.
- [50] Santoro, S.; Kalek, M.; Huang, G.; Himo, F., *Accounts of Chemical Research* **2016**, *49*, 1006-1018.
- [51] Pessoa, J. C.; Etcheverry, S.; Gambino, D., *Coordination Chemistry Reviews* **2015**, *301-302*, 24-48.
- [52] Butler, A.; Tschirret, G. R. A.; Simpson, M. T., *ACS Symposium Series* **1998**, *711*, 202-215.
- [53] Kioseoglou, E.; Petanidis, S.; Gabriel, C.; Salifoglou, A., *Coordination Chemistry Reviews* **2015**, 87-105.
- [54] Dummer, N. F.; Bartley, J. K.; Hutchings, G. J., *Advances in Catalysis* **2011**, *54*, 189-247.
- [55] Gopinath, R.; Patel, B. K., *Organic Letters* **2000**, *2*, 577-579.
- [56] Sedai, B.; Díaz, U. C.; Baker, R. T.; Wu, R.; Silks, L. A. P.; Hanson, S. K., *ACS Catalysis* **2011**, *1*, 794-804.
- [57] Pellissier, H., *Coordination Chemistry Reviews* **2015**, *284*, 93-110.
- [58] Doan, T. N. L.; Hoang, T. K. A.; Chen, P., *RSC Advances* **2015**, *5*, 72805-72815.
- [59] Sheng, M. N.; Zajacek, J. G., *The Journal of Organic Chemistry* **1968**, *33*, 588-590.
- [60] Velusamy, S.; Punniyamurthy, T., *Organic Letters* **2004**, *6*, 217-219.
- [61] Moriuchi, T.; Fukui, Y.; Kato, S.; Kajikawa, T.; Hirao, T., *Journal of Inorganic Biochemistry* **2015**, *147*, 177-180.

- [62] Jones, K. M.; Karier, P.; Klussmann, M., *ChemCatChem* **2012**, *4*, 51-54.
- [63] Hwang, D.-R.; Chen, C.-P.; Uang, B.-J., *Chemical Communications* **1999**, 1207-1208.
- [64] Takizawa, S., *Chemical and Pharmaceutical Bulletin* **2009**, *57*, 1179-1188.
- [65] Takizawa, S.; Katayama, T.; Sasai, H., *Chemical Communications* **2008**, 4113-4122.
- [66] Zhang, G.; Scott, B. L.; Wu, R.; Silks, L. A. P.; Hanson, S. K., *Inorganic Chemistry* **2012**, *51*, 7354-7361.
- [67] Brunel, J. M., *Chemical Reviews* **2005**, *105*, 857-898.
- [68] Takizawa, S.; Katayama, T.; Kameyama, C.; Onitsuka, K.; Suzuki, T.; Yanagida, T.; Kawai, T.; Sasai, H., *Chemical Communications* **2008**, 1810-1812.
- [69] Kirihara, M., *Coordination Chemistry Reviews* **2011**, *255*, 2281-2302.
- [70] Moriuchi, T.; Yamaguchi, M.; Kikushima, K.; Hirao, T., *Tetrahedron Letters* **2007**, *48*, 2667-2670.
- [71] Liu, C.; Zhang, H.; Shi, W.; Lei, A., *Chemical Reviews* **2011**, *111*, 1780-1824.
- [72] Pastine, S. J.; Gribkov, D. V.; Sames, D., *Journal of the American Chemical Society* **2006**, *128*, 14220-14221.
- [73] Louillat, M.-L.; Patureau, F. W., *Chemical Society Reviews* **2014**, *43*, 901-910.
- [74] Jordan, H. J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J., *Journal of the American Chemical Society* **2008**, *130*, 16184-16186.
- [75] Chandra, M. D.; Nageswara, R. S.; Ravi, C.; Adimurthy, S., *Organic & Biomolecular Chemistry* **2015**, *13*, 5602-5607.
- [76] Miyake, Y.; Nakajima, K.; Nishibayashi, Y., *Chemistry – A European Journal* **2012**, *18*, 16473-16477.
- [77] Katritzky, A. R.; Wang, J.; Yang, B., *Synthetic Communications* **1995**, *25*, 2631-2637.
- [78] Arend, M.; Westermann, B.; Risch, N., *Angewandte Chemie International Edition* **1998**, *37*, 1044-1070.
- [79] Cole C., D., *Tetrahedron* **1994**, *50*, 9517-9582.
- [80] Hart, D. J.; Ha, D. C., *Chemical Reviews* **1989**, *89*, 1447-1465.
- [81] Heaney, H.; Papageorgiou, G.; Wilkins, R. F., *Tetrahedron* **1997**, *53*, 2941-2958.
- [82] Petasis, N. A.; Akritopoulou, I., *Tetrahedron Letters* **1993**, *34*, 583-586.
- [83] Polniaszek, R. P.; Bell, S. J., *Tetrahedron Letters* **1996**, *37*, 575-578.
- [84] Tidwell, T. T., In *Book* John Wiley & Sons, Inc.: **2004**.

- [85] Fujiwara, Y.; Tabaki, K.; Taniguchi, Y., *Synlett* **1996**, 591-599.
- [86] Kim, S.; Hong, S. H., *Advanced Synthesis & Catalysis* **2017**, 359, 798-810.
- [87] Sun, W.; Lin, H.; Zhou, W.; Li, Z., *RSC Advances* **2014**, 4, 7491-7494.
- [88] Murai, N.; Miyano, M.; Yonaga, M.; Tanaka, K., *Organic Letters* **2012**, 14, 2818-2821.
- [89] Hwang, D.-R.; Uang, B.-J., *Organic Letters* **2002**, 4, 463-466.
- [90] Mitchell, D.; Cole, K. P.; Pollock, P. M.; Coppert, D. M.; Burkholder, T. P.; Clayton, J. R., *Organic Process Research & Development* **2012**, 16, 70-81.
- [91] Kawano, T.; Hirano, K.; Satoh, T.; Miura, M., *Journal of the American Chemical Society* **2010**, 132, 6900-6901.
- [92] Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M., *Organic Letters* **2011**, 13, 2860-2863.
- [93] Tran, L. D.; Roane, J.; Daugulis, O., *Angewandte Chemie International Edition* **2013**, 52, 6043-6046.
- [94] Pericherla, K.; Kaswan, P.; Khedar, P.; Khungar, B.; Parang, K.; Kumar, A., *RSC Advances* **2013**, 3, 18923-18930.
- [95] Fahy, E.; Potts, B. C. M.; Faulkner, D. J.; Smith, K., *Journal of Natural Products* **1991**, 54, 564-569.
- [96] Safe, S.; Papineni, S.; Chintharlapalli, S., *Cancer Letters* 269, 326-338.
- [97] Kuethe, J. T., *CHIMIA International Journal for Chemistry* **2006**, 60, 543-553.
- [98] Hon, Y.-S.; Hsu, T.-R.; Chen, C.-Y.; Lin, Y.-H.; Chang, F.-J.; Hsieh, C.-H.; Szu, P.-H., *Tetrahedron* **2003**, 59, 1509-1520.
- [99] Snider, B. B.; Lobera, M.; Marien, T. P., *The Journal of Organic Chemistry* **2003**, 68, 6451-6454.
- [100] Marvel, C. S.; Myers, R. L.; Saunders, J. H., *Journal of the American Chemical Society* **1948**, 70, 1694-1699.
- [101] Basu, K.; Richards, J.; Paquette, L. A., *Synthesis* **2004**, 2841-2844.
- [102] Yoshida, K.; Grieco, P. A., *The Journal of Organic Chemistry* **1984**, 49, 5257-5260.
- [103] Xu, Y.; Cong, T.; Liu, P.; Sun, P., *Organic & Biomolecular Chemistry* **2015**, 13, 9742-9745.
- [104] Chakrabarty, M.; Khasnobis, S.; Harigaya, Y.; Konda, Y., *Synthetic Communications* **2000**, 30, 187-200.
- [105] Uhle, F. C.; Harris, L. S., *Journal of the American Chemical Society* **1957**, 79, 102-109.

- [106] Noland, W. E.; Venkiteswaran, M. R.; Richards, C. G., *The Journal of Organic Chemistry* **1961**, 26, 4241-4248.
- [107] Freter, K., *The Journal of Organic Chemistry* **1972**, 37, 2010-2015.
- [108] Sheng, S.-R.; Wang, Q.-Y.; Ding, Y.; Liu, X.-L.; Cai, M.-Z., *Catalysis Letters* **2008**, 128, 418-421.
- [109] Yu, L.; Chen, D.; Li, J.; Wang, P. G., *The Journal of Organic Chemistry* **1997**, 62, 3575-3581.
- [110] Karthik, M.; Tripathi, A. K.; Gupta, N. M.; Palanichamy, M.; Murugesan, V., *Catalysis Communications* **2004**, 5, 371-375.
- [111] Banerji, J.; Dutta, U.; Basak, B.; Saha, M.; Budzikiewicz, H.; Chatterjee, A., *Indian Journal of Chemistry, (Section B)* **2001**, 40B, 981-984.
- [112] Pal, C.; Dey, S.; Mahato, S. K.; Vinayagam, J.; Pradhan, P. K.; Giri, V. S.; Jaisankar, P.; Hossain, T.; Baruri, S.; Ray, D.; Biswas, S. M., *Bioorganic & Medicinal Chemistry Letters* **2007**, 17, 4924-4928.
- [113] Gu, D.-G.; Ji, S.-J.; Jiang, Z.-Q.; Zhou, M.-F.; Loh, T.-P., *Synlett* **2005**, 0959-0962.
- [114] Rad, M. K.; Sharifi, K. M., *Tetrahedron* **2009**, 65, 8816-8820.
- [115] Shiri, M., *Chemical Reviews* **2012**, 112, 3508-3549.
- [116] Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z., *Chemical Reviews* **2010**, 110, 2250-2293.
- [117] Sivaprasad, G.; Perumal, P. T.; Prabavathy, V. R.; Mathivanan, N., *Bioorganic & Medicinal Chemistry Letters* **2006**, 16, 6302-6305.
- [118] Mallik, A. K.; Pal, R.; Mandal, T. K., *Indian Journal of Chemistry* **2007**, 46B, 2056-2059.
- [119] Huang, L.; Niu, T.; Wu, J.; Zhang, Y., *The Journal of Organic Chemistry* **2011**, 76, 1759-1766.
- [120] Itoh, M.; Hirano, K.; Satoh, T.; Miura, M., *Organic Letters* **2014**, 16, 2050-2053.
- [121] Liu, J.; Yi, H.; Zhang, X.; Liu, C.; Liu, R.; Zhang, G.; Lei, A., *Chemical Communications* **2014**, 50, 7636-7638.
- [122] Li, Y.; Xue, D.; Lu, W.; Wang, C.; Liu, Z.-T.; Xiao, J., *Organic Letters* **2014**, 16, 66-69.

- [123] Saini, H. K.; Kaswan, P.; Pericherla, K.; Kumar, A., *Asian Journal of Organic Chemistry* **2015**, *4*, 1380-1385.
- [124] Bagdi, A. K.; Santra, S.; Monir, K.; Hajra, A., *Chemical Communications* **2015**, *51*, 1555-1575.
- [125] Mohan, D. C.; Rao, S. N.; Ravi, C.; Adimurthy, S., *Asian Journal of Organic Chemistry* **2014**, *3*, 609-613.
- [126] Cao, H.; Lei, S.; Li, N.; Chen, L.; Liu, J.; Cai, H.; Qiu, S.; Tan, J., *Chemical Communications* **2015**, *51*, 1823-1825.
- [127] Pericherla, K.; Khedar, P.; Khungar, B.; Kumar, A., *Chemical Communications* **2013**, *49*, 2924-2926.
- [128] Kaswan, P.; Porter, A.; Pericherla, K.; Simone, M.; Peters, S.; Kumar, A.; DeBoef, B., *Organic Letters* **2015**, *17*, 5208-5211.
- [129] Jiang, N.; Ragauskas, A. J., *Tetrahedron Letters* **2007**, *48*, 273-276.
- [130] Wang, L.; Chen, B.; Ren, L.; Zhang, H.; Lü, Y.; Gao, S., *Chinese Journal of Catalysis* **2015**, *36*, 19-23.
- [131] Amadio, E.; Di Lorenzo, R.; Zonta, C.; Licini, G., *Coordination Chemistry Reviews* **2015**, *301-302*, 147-162.