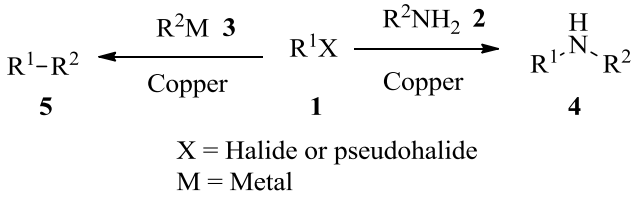
Chapter II

Copper-Catalyzed Ullmann-Type C–N Coupling: Regioselective Synthesis of Azole and Triazole-substituted Imidazo[1,2-*a*]pyridines

2.1. Introduction

The use of metal as catalyst for organic conversion has received much attention over the past half-century.[1-2] Transition metals were initially used for simple reaction and for various purpose by chemists during the mid-18th century, but the explored journey of limits and capabilities of metallic chemistry such as palladium, gold, silver, rhodium, nickel, copper and iron escalated during the last half of the 20th century.[3-5] Among them chemistry of copper is exceptionally well heeled due to availability of different oxidation state as Cu(0), Cu(I), Cu(II), Cu(III) complexes which react *via* single electron transfer or two electron transfer mechanism.[6-9]

Copper-catalyzed C−C and C−heteroatom (Heteroatom = F, N, S, P, O…) bond forming reactions have been considered as important tools in organic synthesis for allowing the construction of complex and bioactive molecules from simple precursors.[10] Copper mediated C−N bond formation is standard procedure for insertion of nitrogen heteroatom to organic molecule to make biological active heterocyclic compounds through cross-coupling reactions.[11] Many efficient methodologies have been developed and applied in the synthesis of natural products and pharmaceuticals (**Scheme 2.1**).[12]

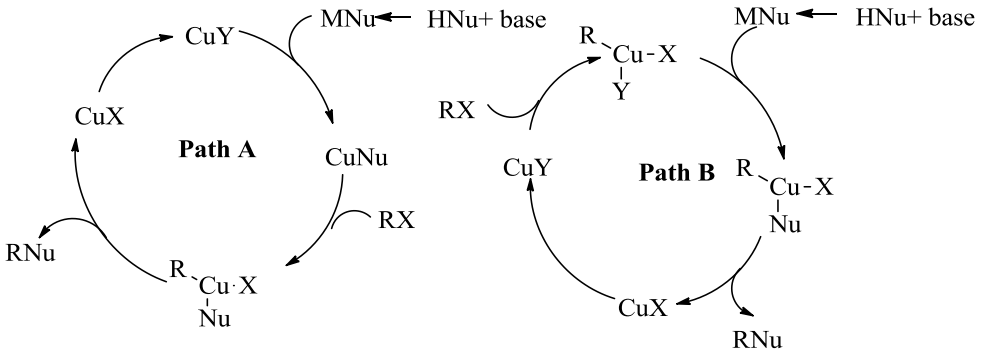


Scheme 2.1: Copper-catalyzed C−C and C−N coupling reaction

2.1.1. Ullmann C−N coupling

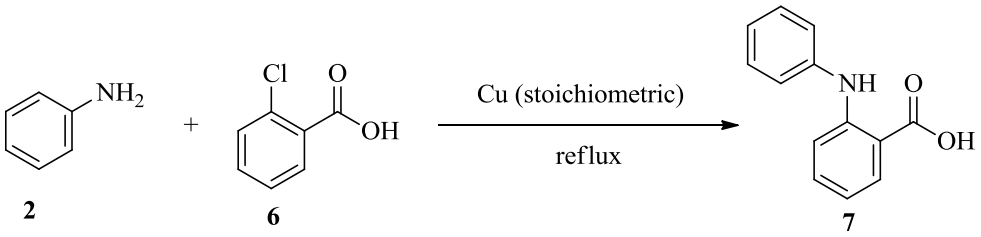
Palladium catalyst is widely used for cross-coupling reaction but recent evidence has revealed the use of copper similar to palladium in cross-coupling reaction.[11, 13] Classical Ullmann chemistry along with closely related methods have been known for a century and served well for C−N, C−S, C−O and some other bond formation reactions.[14] The Ullmann reaction or Ullmann coupling is coupling reaction between aryl halides and nucleophiles in the presence of copper. The Ullmann reaction is believed to follow two possible pathways (**Scheme 2.2**).[15] In path **A**, copper catalyst first reacts with nucleophile to generate more reactive complex which then reacts

with aryl halide to produce the coupled product. In path **B**, copper first reacts with aryl halide and creates more electrophilic intermediate which then reacts with nucleophile and results in the formation of coupled product. Unlike, Pd-catalyzed cross-coupling reaction in which firstly an oxidative addition step is believed to proceed followed by the transmetallation, the order of oxidative addition and transmetallation steps in the copper cycle is still not much known, so either of two possibilities can take place (**Scheme 2.2,** Path **A** or **B**).[7]



Scheme 2.2: Possible catalytic paths for Ullmann C−N coupling

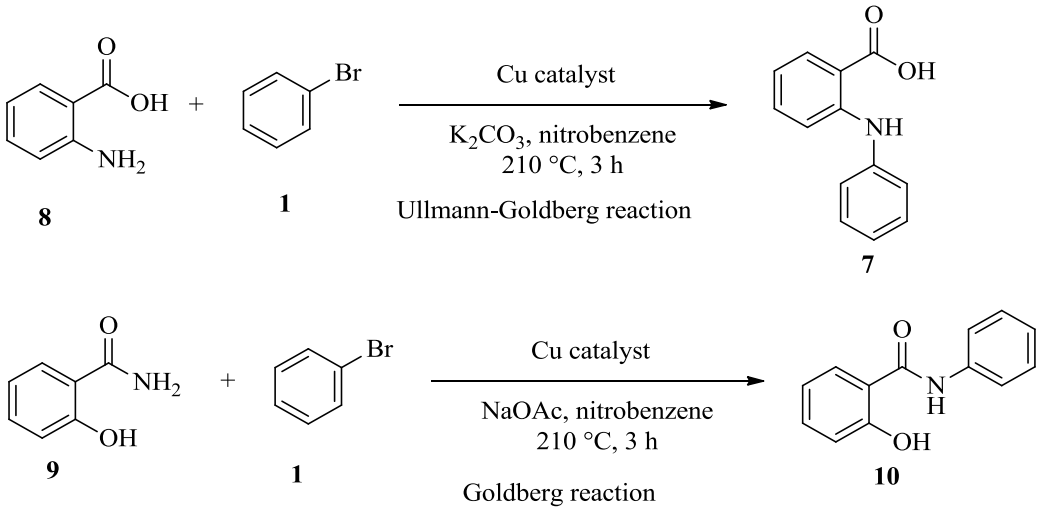
In 1903, Ullmann reported reaction of aniline (**2**) with 2-chlorobenzoic acid (**6**) in the presence of stoichiometric amount of copper to give 2-phenylaminobenzoic acid (**7**). The reaction was further improved by Goldberg in 1906 who used potassium salt of 2-aminobenzoic acid to react with phenyl bromide in the presence of catalytic amount of copper (**Scheme 2.3**).[16-19]



Scheme 2.3: Ullmann C-N coupling reaction

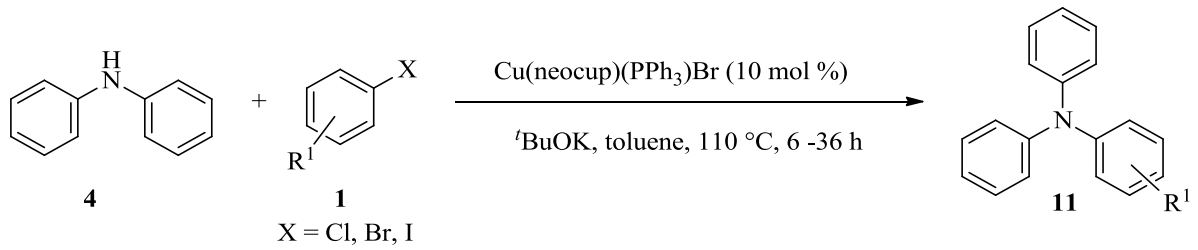
Copper-catalyzed amination as well as amidation of aryl halide (**1**) with 2-aminobenzoic acid (**8**) and 2-hydroxybenzamide (**9**) were carried out in the laboratory of Goldberg using copper catalyst which respectively known as Ullmann–Goldberg amination and Goldberg amidation (**Scheme 2.4**).[19-20] These conceptual two papers have to be considered as the starter for the basis

of the current work on the copper-catalyzed arylation reactions.



Scheme 2.4: Copper-catalyzed amination and amidation of arylhalide

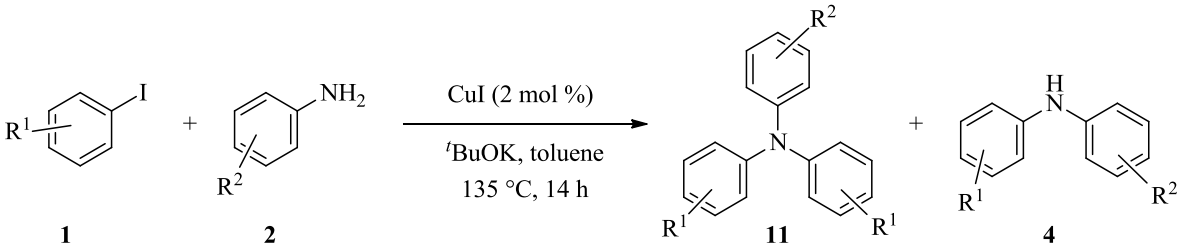
Venkataraman group reported typical example of Ullmann-type reaction using copper-phenanthroline complexes as catalyst with base. The reaction of diphenylamine (**4**) with haloarenes (**1**) in the presence of copper complex was carried out for longer reaction time to give triphenylamine (**11**) (**Scheme 2.5**).[21] The author also extended the methodology for formation of aryl-carbon and aryl-oxygen bond by slightly changing the reaction conditions. Use of copper over noble metals and use of cheaper ligand made the method more useful and economic for C−N coupling reactions.[22]



Scheme 2.5: Reactions of aryl halides with diphenylamine

Chaudhari *et al.* reported the representative ligand-free copper-catalyzed Ullmann coupling reaction for the synthesis of triarylamines (**11**) in one-step. Reaction of aryl iodide (**1**) with arylamine (**2**) in the presence of copper and ^{t}BuOK resulted diarylamine (**4**) and triarylamine (**11**) in good yield. Yield of product was further improved using ligand such as 1,10-

phenanthroline, PPh_3, DPPT and DPPH (**Scheme 2.6**).[23] The role of base was important in the development of ligand-free Cu-catalyst system and use of chelating ligands in stoichiometric amount gave triarylamines with high activity and selectivity.



Scheme 2.6: Ligand-free copper-catalyzed reaction of aryl iodide with arylamine

2.1.2. Limitation of Ullmann C−N coupling

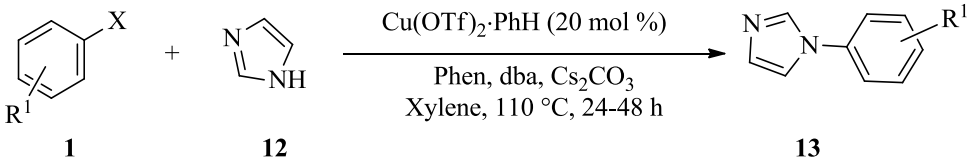
Ullmann condensations have not been fully explored until 2000 for synthetic scope due to harsh reaction conditions, limited substrate scope and moderate yields.[15] Condensations were traditionally carried out in the presence of stoichiometric amounts of copper reagents at high temperatures, preferentially with activated aryl halides for long reaction time.[24] These reactions required strong bases such as ^{t}BuONa, ^{t}BuOK making it incompatible with the broader range of functionality. Application of this methodology to various heteroaromatic compounds is still relatively unexplored process.[25] Copper-catalyzed cross-coupling chemistry was limited to iodo and bromo derivatives of arenes, while chloro derivatives have not been much considered for this chemistry with only few examples.[20]

In recent years, special attention has been given to overcome the deficiencies of conventional copper-assisted substitution methods (Ullmann chemistry) by making reaction conditions milder, extending scope towards unactivated substrates and new types of nucleophiles, and increasing tolerance to sensitive functionality.[7] This has become possible by using special ligands to promote these coupling reactions. α-Amino acids (more specifically L-proline) and *N*,*N*-dimethylglycine ligand can accelerate Cu-assisted Ullmann reactions, leading to the coupling reactions of aryl halides and ligand at lower temperature.[26] However the ligands often become inactivated during the repetitive use of these catalyst systems as well as these are expensive and not environment benign procedure in economic point of view, so new interest in development of much cheaper and more practical ligand for copper-catalyzed chemistry has been brought which can modulate the reactivity of catalyst, and generate more effective and more versatile catalytic systems.

2.2. Developments in C−N bond formation reaction

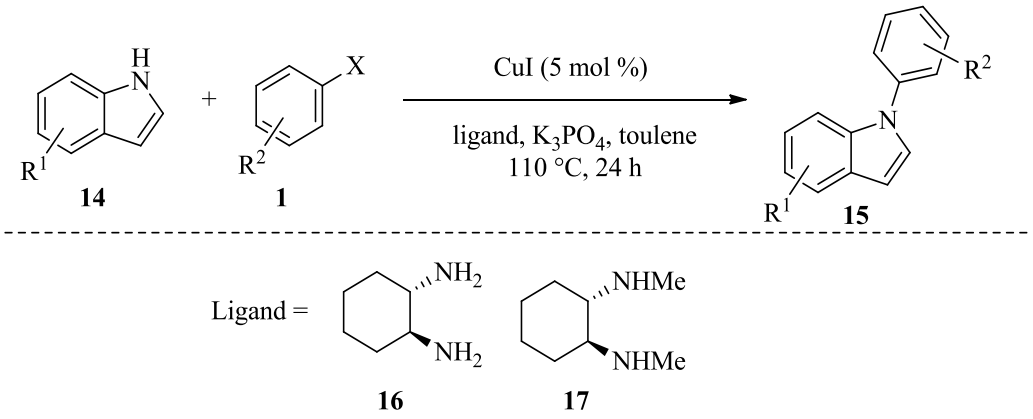
Copper catalyst has proved to be cheaper and more environment friendly catalyst than palladium for various organic transformations.[27] With the use of new ligands having lone pair of binding electrons and chelating site it has become possible to perform C−N coupling reactions under moderate conditions using copper based catalytic system.

Buchwald with his co-workers described *N*-arylation of imidazoles (**12**) using $(CuOTf)_2$.benzene as copper source and Cs_2CO_3 as base in xylene at 110-125 °C (**Scheme 2.7**).[28] The addition of 1,10-phenanthroline (phen) as ligand and *trans,trans*-dibenzylideneacetone (dba) as additives played crucial role for higher yield of corresponding product (**13**). Electron-rich and electron-poor aryl halides and imidazole resulted excellent yield of product, although substitution on either the imidazole or at the *ortho* position of the aryl halide decreased the yield and took longer time for completion of the reaction.



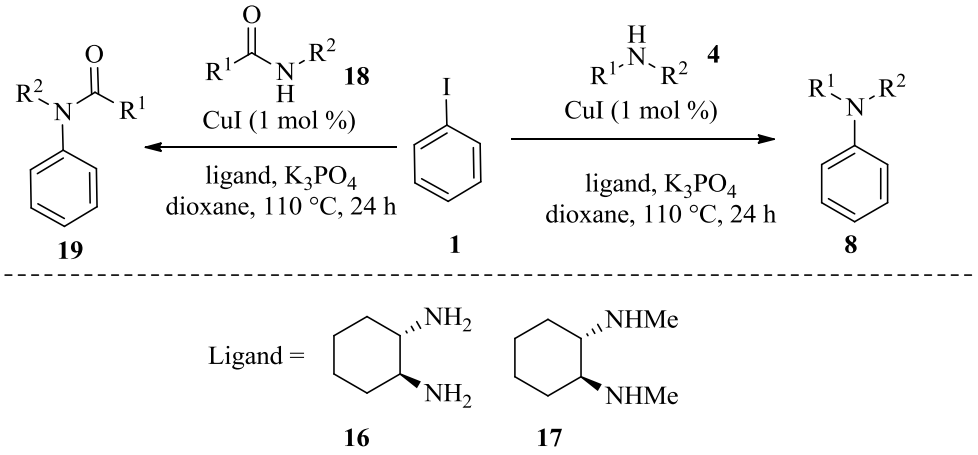
Scheme 2.7: Copper-catalyzed *N*-arylation of imidazole

Buchwald group reported an efficient method for the coupling of substituted aryl bromides and iodides (**1**) with indoles (**14**) in the presence of catalyst derived from CuI and ligand such as *N*,*N*-dimethyl-1,2-diamine (**16, 17**) (**Scheme 2.8**).[29] A variety of aryl bromides and functional groups on the aryl halide and indole such as amine (alkyl or aryl), amide, cyano, nitro, ester, allyl, and hydroxyl groups were found to be suitable for the given C−N coupling reaction.



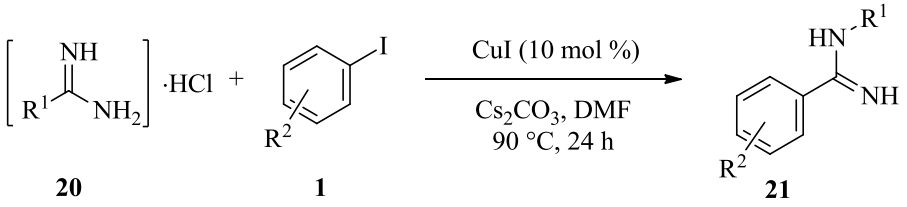
Scheme 2.8: *N*-arylation of indoles using copper catalyst

Further Buchwald *et al.* also developed general, simple, and inexpensive catalyst system for the amidation and amination of aryl halides (**1**) (**Scheme 2.9**).[30] A wide range of amide (**18**) and different *NH*-heterocycles (**4**) such as pyrazoles, indazole, 7-azaindole, phthalazinonepyrrole, and carbazole can by arylated using only 1 mol % of CuI catalyst.



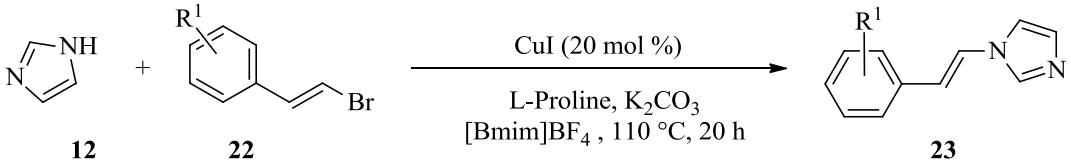
Scheme 2.9: Amidation of aryl halides and the *N*-arylation of *NH*-heterocycles

Antilla group reported copper-catalyzed arylation of amidine (**20**) using Ullmann-type reaction (**Scheme 2.10**).[31] Reaction of various steric hindered and electron rich and electron deficient aryl iodide (**1**) were reacted with aliphatic, aromatic and hetero amidine in the presence of CuI and Cs_2CO_3 without any external ligand to give the corresponding product (**21**) in moderate to good yield.



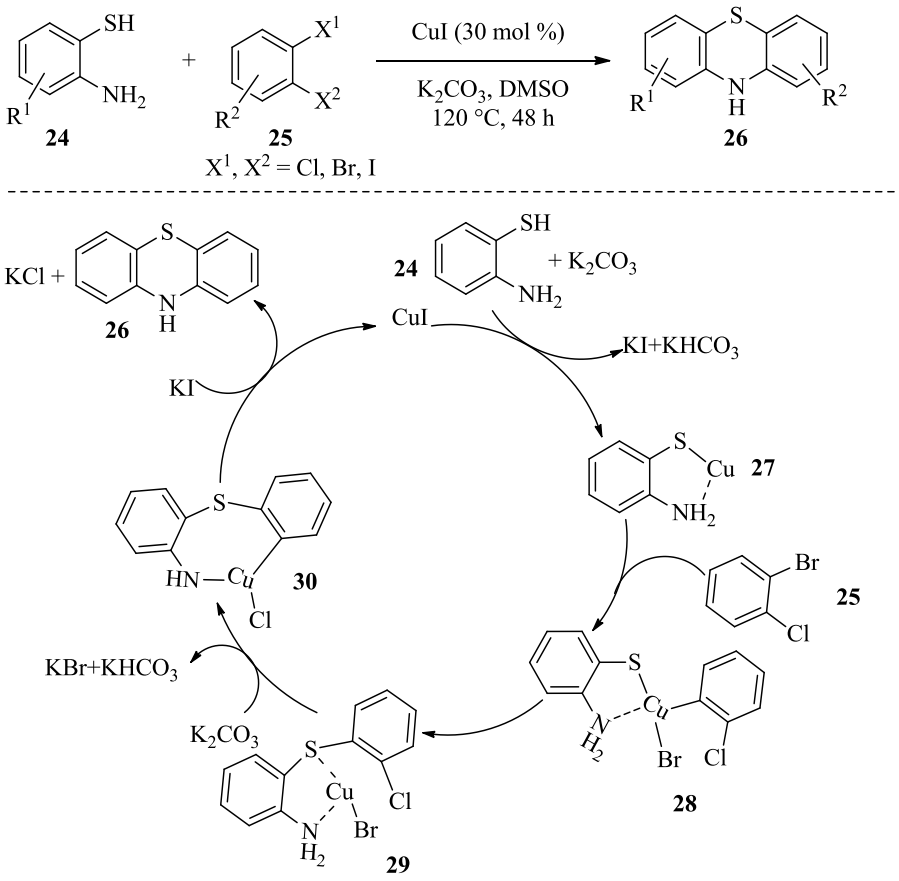
Scheme 2.10: Copper-catalyzed arylation of amidines

Bao *et al.* developed mild and efficient greener approach for the copper-catalyzed coupling of imidazoles (**12**) with vinyl bromides (**22**) by using ionic liquids as reaction media with recycling of catalyst. The reaction of imidazoles (**12**) with vinyl bromides (**22**) was carried out in the presence of CuI and K_2CO_3 in [Bmim]BF_4 ionic liquid solvent (**Scheme 2.11**).[32] Various vinyl bromides and other imidazoles as well as sterically hindered substrate were well tolerated under the reaction condition to afford good to excellent yield of stereoselective product (**23**).



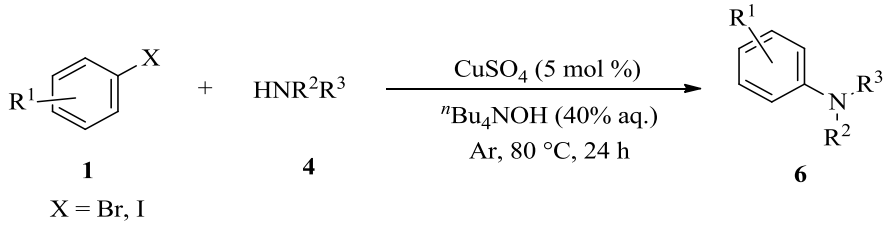
Scheme 2.11: Ullmann-type reaction of vinyl bromides with imidazoles in ionic liquid

Recently, Zeng *et al.* developed lignad-free copper-catalyzed synthesis of phenothiazine (**26**) *via* C−S and C−N bond formation in good to excellent yield. Reaction of (hetero)aryl *ortho*-dihalides (**25**) and *ortho*-aminobenzenethiols (**24**) were kept in the presence of CuI and K_2CO_3 in DMSO at 120 °C for 48 h to give the desired product in good yield without any ligand (**Scheme 2.12**).[33] Various *ortho*-aminobenzenethiols and *ortho*-bromochlorobenzenes were evaluated at standard optimized conditions to afford the corresponding product. *Ortho*-aminobenzenethiol coordinates with copper and further takes part in the formation of phenothiazine. The proposed mechanism is depicted in **scheme 2.12** and starts with abstraction of proton of thiol group by base followed by coordination of copper to generate copper complex **23**. Oxidative addition of 2-bromoiodobenezene and reductive elimination gives complex **29** by forming of C−S bond. Further K_2CO_3 abstracts proton from amino group and repetition of oxidative addition and reductive elimination produces the target product (**26**) completing the catalytic cycle (**Scheme 2.12**).



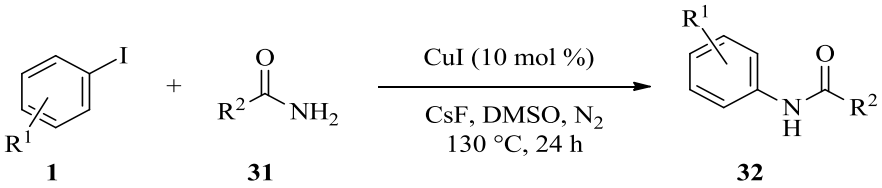
Scheme 2.12: CuI-catalyzed cascade C–S and C–N cross coupling of *ortho*-aminobenzenethiols and *ortho*-bromochlorobenzenes

Jingyu and co-workers reported Cu(I)-catalyzed C−N cross-coupling reaction of aryl halides (**1**) with alkylamines or *N*-heterocycles (**4**) without any external ligand in aqueous medium using argon inert atmosphere (**Scheme 2.13**).[34] Reaction methodology was well tolerated with different functional group to give desired product (**6**) with excellent yield, although reaction of aryliodide with pyrazol, imidazole or triazole gave lower yield of product. Moderate reaction condition, simple experimental operation and relative low amount of $CuSO_4$ catalyst and ligand-free condition make the methodology useful for industrial use.



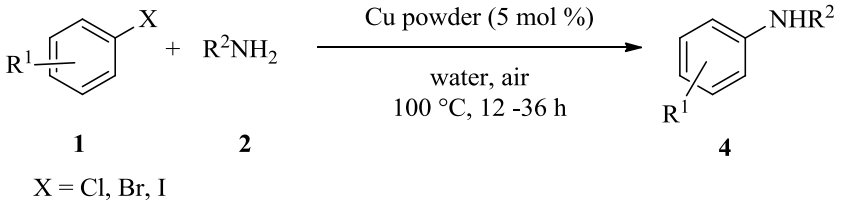
Scheme 2.13: C−N cross-coupling reaction of aryl halide and alkylamine

Recently, Wang *et al.* reported ligand-free C−N coupling of heteroarylamine and aryl halide in the presence of 10 mol % of copper catalyst.[35] In same time Ribas group also did the coupling of amide (**31**) with aryl halide (**1**) in the presence of copper catalyst without any external ligand (**Scheme 2.14**).[36] Reaction of different aryl iodides was carried out with amide family of *N*-nucleophiles in DMSO for 24 h in nitrogen atmosphere. Due to the coordinating ability of dimethyl sulfoxide and other solvents such as DMF and DMA worked as chelation as well as solvent for Ullmann-type C−N coupling reaction.



Scheme 2.14: Ligand-free *N*-arylation of amides with iodobenzene

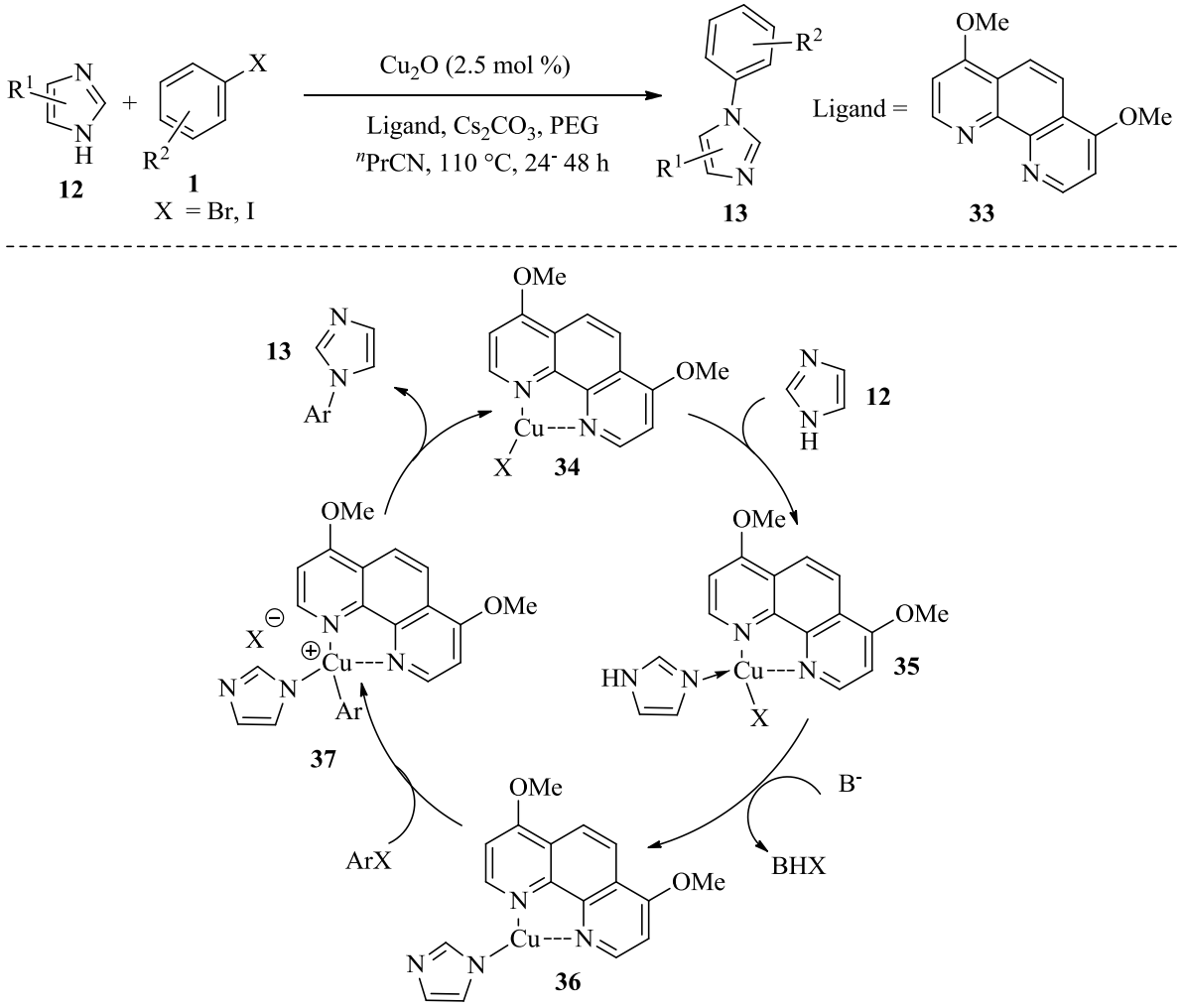
Wei *et al.* further improved the Ullmann-type reaction using aqueous media without any base and ligand. The reaction was supposed to proceed smoothly in the presence of air as oxidant. Aliphatic primary amines (**2**) showed good to very high reactivity but secondary amines and aniline resulted traces of desired product showing less reactivity. Reaction of aryl halides (**1**) and commercially available aqueous solution of amines (**2**) was treated with Cu powder at 100 ˚C for 12-36 h to give the *N*-arylamines (**4**) in good to excellent yield (**Scheme 2.15**).[37]



Scheme 2.15: Ligand and base-free Ullmann reaction of halobenzene with amines

Buchwald group extended his work methodology for *N*-arylation of imidazole (**12**) and benzimidazole using copper catalyst and 4,7-dimethoxy-1,10-phenanthroline (**33**) ligand (**Scheme 2.16**).[38] A variety of hindered and functionalized imidazoles, benzimidazoles were treated with aryl halides (**1**) and heteroaryl halides to give the corresponding product (**13**) in good to excellent yields. Study of reactivity of different ligand and steric effect of substrate as

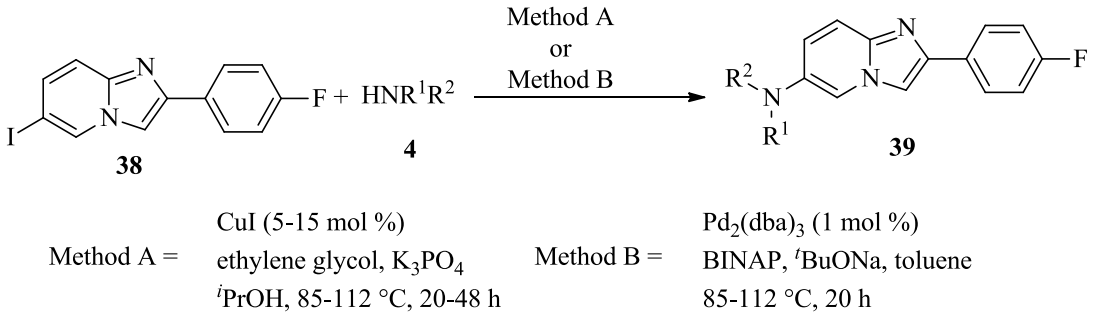
well as explanation of mechanistic study has proved the importance of the developed methodology. Reaction mechanism was proposed to proceed through interaction of lignad with copper followed by chelation with imidazole and proton abstraction by base to give the copper complex **36**. Intermediate **36** react with aryl halide (**1**) *via* oxidative insertion step to produce intermediate **37** which undergo reductive elimination to yield the corresponding product (**13**) and complete the catalytic cycle of copper.



Scheme 2.16: Coupling of imidazoles with aryl iodides using copper catalyst

Gueiffier and Buchwald together compared the reactive efficiency of copper and palladium catalyst for amination of 6-halogenoimidazo[1,2-*a*]pyridines (**38**). Reaction of 6-iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine (**38**) with variety of *NH*-heterocycles (**4**) was carried out in the presence of copper catalyst with ethylene glycol ligand and K_3PO_4 base at higher temperature

to give corresponding product (**39**) in good yield (**Scheme 2.17**).[39] Although in case of aliphatic and secondary cyclic amine lower yield of product obtained and it was improved by the addition of palladium catalyst in short reaction time. Catalyst loading was decreased to 1 mol % in case of palladium catalyst whereas 5-15 mol % of catalyst was used for copper (**Scheme 2.17**).



Scheme 2.17: Synthesis of 6-aminoimidazo[1,2-*a*]pyridines using palladium or copper catalyst

Adding to our continuous interest in the area of transition metal-catalyzed synthesis and functionalization of imidazo[1,2-*a*]pyridines,[40-43] in this chapter we focused our attention for an efficient and ligand-free copper catalyzed Ullmann-type C–N coupling reaction to give azole and triazole substituted imidazo[1,2-*a*]pyridines.

Chapter II

PART A

Copper-Catalyzed Synthesis of Azole-substituted Imidazo[1,2-*a*]pyridines

2.3. Introduction

C−N coupling reaction for the synthesis of azole substituted heterocyclic compounds has been considered as an efficient and straightforward method from the view point of synthetic simplicity and atom economy as well as environmental benefits. Owing to their broad range of biological importance of heterocyclic compounds, considerable efforts have been directed towards the copper-catalyzed reactions and Ullmann couplings over traditional methods for formation of carbon–heteroatom bonds.[17-18] However, these protocols are less favored as they require the use of stoichiometric amounts of copper reagents, harsh reaction conditions, strong bases, and extended reaction times. In last decade, great efforts have been made to overcome these shortcomings. Although the palladium catalyzed Buchwald–Hartwig reaction is an effective alternative for the C–N coupling, copper-catalyzed protocols of still have advantages such as low cost, less toxicity of the reagents and high functional-group tolerance.[44-46] Improvements include the use of organic ligands such as diamines,[29, 47] amino acids,[26, 48] diols,[39] 1,10-phenanthrolines,[49] and other heteroatom containing compounds[50-51] for Ullmann-type aminations reaction.

Azoles substituted heterocyclic molecular frameworks are found in large number of biologically active natural and synthetic compounds.[52] To a medicinal chemist, the ideal use of heterocyclic structures is the ability to synthesize library of compounds having one core scaffold and screen it against variety of different receptors, to get several biologically active compounds.[53] Almost unlimited combinations of different heterocyclic structures can be designed, resulting in novel polycyclic frameworks with the most diverse physical, chemical, and biological properties.[54-55] The combination of several heterocylic rings leads to polycyclic structures holding the promise of high functional specialization. Imidazole nucleus is biologically accepted pharmacophore in medicinal compounds and compounds with this nucleus possess wide spectrum of biological activities.[53] Miconazole, econazole, voriconazole, posaconazole and clotrimazole (**Figure 2.1**) are potent imidazole and azole skelton containing broad-spectrum antimycotics which show high *in vitro* activity against almost all fungi of clinical interest.[56-59]

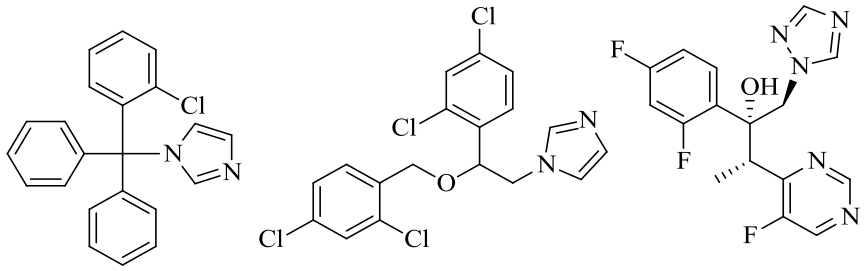


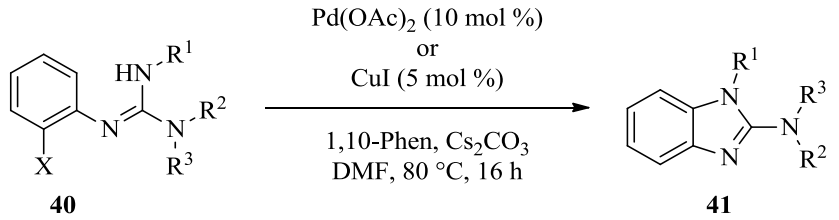
Figure 2.1: Marketed drug with azole skeleton

Imidazo[1,2-*a*]pyridine, a bicyclic *N*-fused imidazole is privileged structural motif present in several natural products and pharmacologically relevant structures with wide range of activities. Imidazo[1,2-*a*]pyridines possess biological properties such as antifungal,[60] antiviral,[61] anticonvulsant,[62] anti-ulcer,[63] anti-inflammatory,[64] antiprotozoal,[65] and antiretroviral.[66] This motif is found in commercially available drugs such as Zolpidem (treatment of insomnia and certain brain disorders), Alpidem, Necopidem and Saripidem (anxiolytics), Zolimidine (treatment of peptic ulcers), Olprinone (cardiotonic agent), and Miroprofen (analgesic).

2.4. Application of copper-catalyzed C–N coupling for synthesis of heterocycles

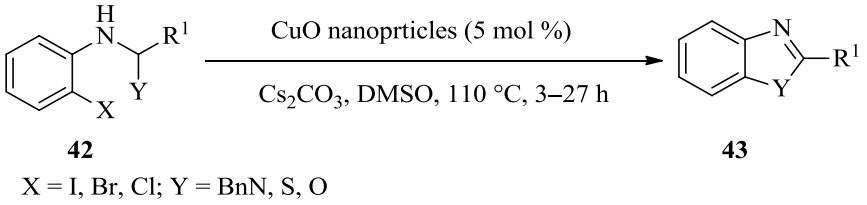
Copper catalytic system for the synthesis or the functionalization of *N*-containing heterocycles like indoles, quinolones, indoxyls or 1,2-dihydroisoquinolin-3-ones have been developed by various research group and efforts have been made to improve the methodology for synthesis of some medicinal important heterocycles.[44, 67]

Batey *et al.* described the synthesis of 2-aminobenzimidazoles (**41**) *via* intramolecular C–N bond formation reaction using copper as catalyst. The reaction of aryl halide and guanidine moiety to produce starting material (**40**) followed by Buchwald and Hartwig aryl amination reaction or CuI catalysis with 1, 10-phenanthroline ligand resulted the 2-aminobenzimidazoles (**41**) in good to excellent yield (**Scheme 2.18**).[22] The intramolecular aryl guanidinylation was applied to various aryl bromide substrates using two sets of optimized conditions which are palladium catalysis and copper catalysis. The comparison between copper and palladium catalyst was studied and the use of inexpensive copper salts such as CuI is shown to be superior to their palladium counterparts both in terms of yields and selectivity.



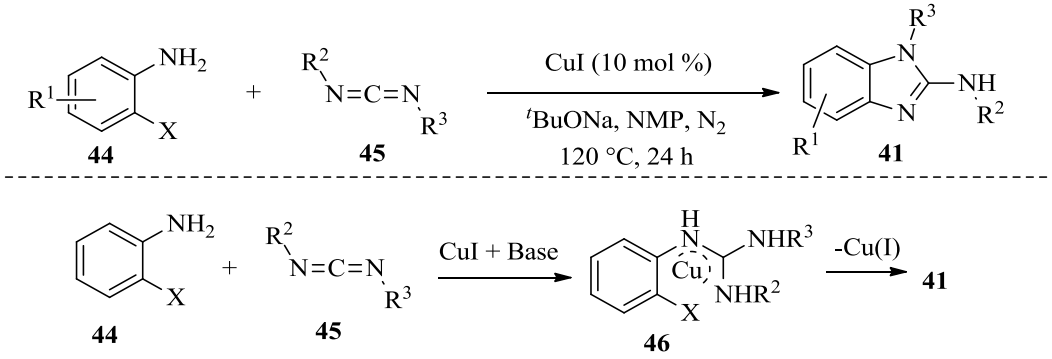
Scheme 2.18: Synthesis of 2-aminobenzimidazoles *via* C–N bond formation

Punniyamurthy group also synthesized series of heterocycles (**43**) such as substituted benzimidazoles, 2-aminobenzimidazoles, 2-aminobenzothiazoles, and benzoxazoles *via* intramolecular cyclization of *ortho*-haloaryl derivatives (**42**) using copper(II) oxide nanoparticles in DMSO under atmospheric oxygen (**Scheme 2.19**).[68] *Ortho*-iodoaryl and *ortho*-bromoaryl derivatives resulted good to excellent yield of corresponding product but *ortho*-chloroaryl derivatives gave lower yield of the product.



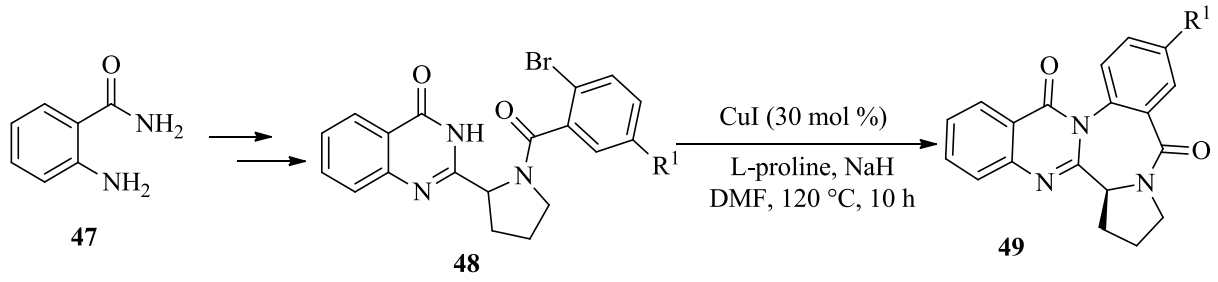
Scheme 2.19: Use of copper(II) oxide nanoparticles for C–X coupling reaction

Chanjuan and co-workers used copper(I)-catalyzed domino reaction of *ortho*-haloanilines (**44**) and carbodiimides (**45**) in the presence of *tert*-butoxide and NMP ligand to give product (**41**) in moderate to excellent yield (**Scheme 2.20**).[69] *Ortho*-iodoaniline, *ortho*-bromoaniline, and *ortho*-chloroaniline derivatives with series of carbodiimides (**45**) having symmetrical and unsymmetrical substrates with aryl or alkyl substituents can be easily used for the synthesis of 2-aminobenzimidazoles (**41**). Reaction mechanism is depicted in **scheme 2.20**. In the presence of *tert*-butoxide and copper(I), *ortho*-haloanilines attacks at the carbon atom of N=C=N of carbodiimide to give intermediate **46** which undergoes ring closure to yield product with elimination of copper halide. Peng *et al.* also synthesized benzimidazole derivative using water as reaction media in the presence of Cu_2O catalyst by intramolecular *N*-arylation of (*ortho*-haloaryl)amidines.[70]



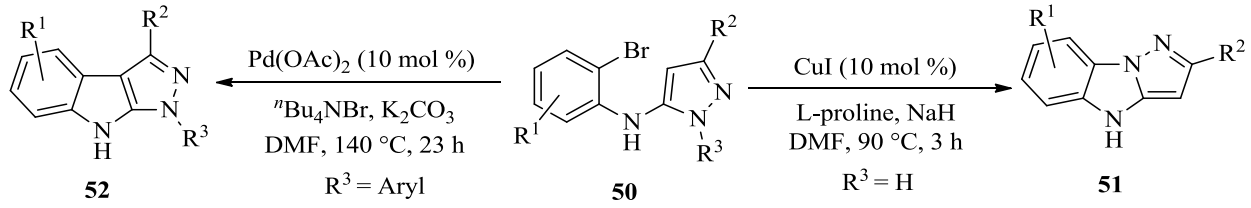
Scheme 2.20: Synthesis of 2-aminobenzimidazoles using copper catalyst

Argade *et al.* reported an efficient method for total synthesis of (-)-circumdatins H and J involving copper-catalyzed C–N coupling for its benzodiazepine core structure. Copper-catalyzed intramolecular C–N coupling reaction of quinazolinone (**48**) nucleus was carried out in the presence of L-proline and sodium hydride in DMF for 10 h at 120 °C (**Scheme 2.21**).[71]



Scheme 2.21: Total synthesis of (-)-circumdatins H and J using copper-catalyzed C–N coupling

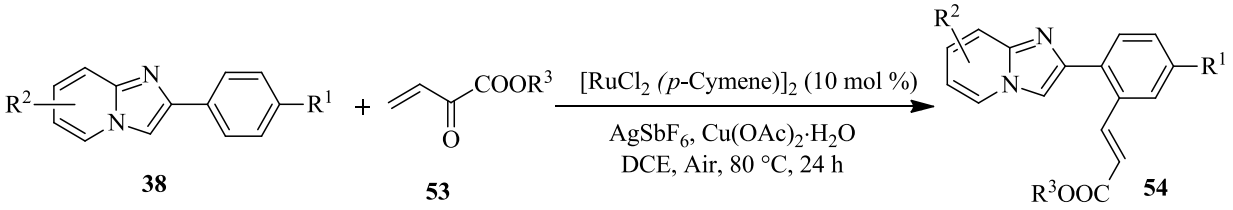
Ila group developed an intramolecular C–C and C–N coupling reaction for the synthesis of pyrazolo[3,4-*b*]indoles (**52**) and pyrazolo[1,5-*a*]benzimidazoles (**51**) *via* palladium and copper-catalyzed reactions, respectively.[72] 3(5)-(*ortho*-Bromoanilino)pyrazoles (**50**) underwent intramolecular palladium-catalyzed Heck-type heteroarylation *via* C–C coupling reaction to give pyrazolo[3,4-*b*]indoles (**52**) or copper-catalyzed *N*-arylation *via* C–N coupling reaction to give pyrazolo[1,5-*a*]benzimidazoles (**51**) (**Scheme 2.22**). Liubchak *et al.* also applied same type of methodology for the synthesis of imidazo[4,5-c]pyrazoles.[73] *N*′-(4-halopyrazol-5-yl)amidine underwent intramolecular cyclization in the presence of copper catalyst *via* Ullmann-type cross-coupling reactions.



Scheme 2.22: Synthesis of pyrazolo[3,4-*b*]indoles and pyrazolo[1,5-*a*]benzimidazoles

Ortho-directed activation of C_2-H bond of 2-phenylimidazo[1,2-*a*]pyridines *via* interaction of nitrogen with metal

Transition metal coordinates to *N*-1 of imidazo[1,2-*a*]pyridine and activates the *ortho*-position of phenyl ring by *ortho*-metalation to generate five member metallo cycle which can be used for *ortho*-directed coupling reactions. Some ligand-promoted *ortho*-directed C–C couplings on C_2–H bond of 2-phenyl ring have been reported on imidazo[1,2-*a*]pyridines, but *ortho*-directed aminations of these privileged motifs are poorly studied. Pardasani *et al.* disclosed an straightforward ruthenium catalyzed oxidative C–H bond alkenylation of 2-phenylimidazo[1,2-*a*]pyridine (**38**) with acrylates (**53**) offering monoalkenylated 2-(2′-alkenylphenyl)imidazo[1,2-*a*]pyridines (**54**) with high levels of diastereoselectivity resulting single *E*-isomer of the alkenes (**Scheme 2.23**).[74] The method was compatible with various electron rich and electron deficient substituents including 2-phenylimidazo[1,2-*a*]pyridine, irrespective of substituent either at phenyl ring or pyridyl ring. Reaction starts with coordination of Ru with N_1 of imidazo[1,2-*a*]pyridine and activating *ortho* C–H bond by *ortho*-metalation to generate the five member metal complex.

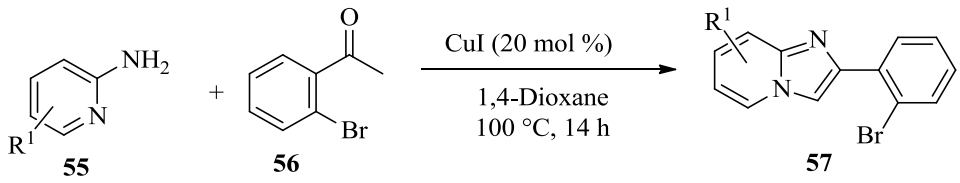


Scheme 2.23: Alkenylation of imidazo[1,2-*a*]pyridines through *ortho*-metalation

In continuation of our efforts towards designing novel heterocycles containing imidazo[1,2-*a*]pyridines, we developed regioselective, ligand-free, copper-catalyzed C–N coupling reaction for the synthesis of azole-substituted imidazo[1,2-*a*]pyridines by the reaction of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridines (**46**) with different azoles (*NH* azoles) (**47**).[75-77]

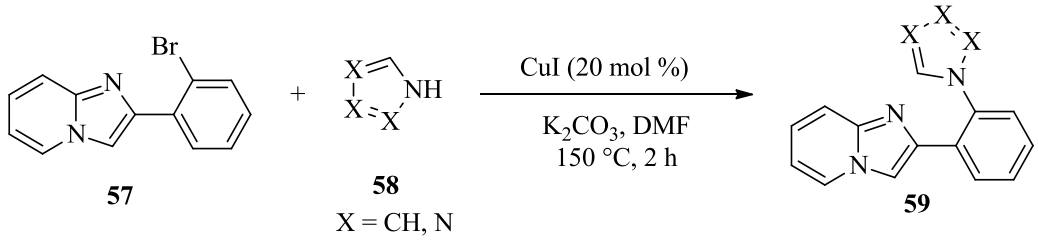
2.5. Results and discussion

The starting material 2-(2-bromophenyl)imidazo[1,2-*a*]pyridines (**57**) were synthesized using our previous reported method (**Scheme 2.24**).[8] 2-Aminopyridine (**55**) and 2-bromoacetophenone (**56**) were refluxed in the presence of CuI in 1,4-dioxane to give corresponding imidazo[1,2-*a*]pyridines (**57**).



Scheme 2.24: Synthesis of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**57**)

2-(2-Bromophenyl)imidazo[1,2-*a*]pyridine (**57a**) and 1*H*-imidazole (**58a**) were chosen as model substrates for the initial studies. After extensive examinations, we were gratified to find that 20 mol % of CuI and K_2CO_3 (2.0 equiv.) gave clean reaction in *N*,*N*-dimethylformamide (DMF) at 150 °C without any external ligand to afford the coupled product, 2-[2-(1*H*-imidazol-1-yl)phenyl]imidazo[1,2-*a*]pyridine (**59a**) in excellent (92%) yield (**Scheme 2.25**).



Scheme 2.25: Synthesis of azole-substituted imidazo[1,2-*a*]pyridines

The structure of **59a** was confirmed by the ^{1}H NMR and ^{13}C NMR (**Figure 2.2**) and HRMS data In the ^{1}H NMR spectrum of 2-(2-(1*H*-imidazol-1-yl)phenyl)imidazo[1,2-*a*]pyridine (**59a**) characteristic singlets appeared at δ 6.29 ppm and δ 7.06 ppm for the C−2 proton of imidazole ring and for C−3 proton of 2-phenylimadzo[1,2-*a*]pyridine. In the ^{13}C NMR a total number of 16 carbons peaks appeared as expected from the structure of **59a**. The HRMS of **59a** displayed peak at *m/z* 261.1119 for $[M+H]^+$, further confirming the structure of the product.

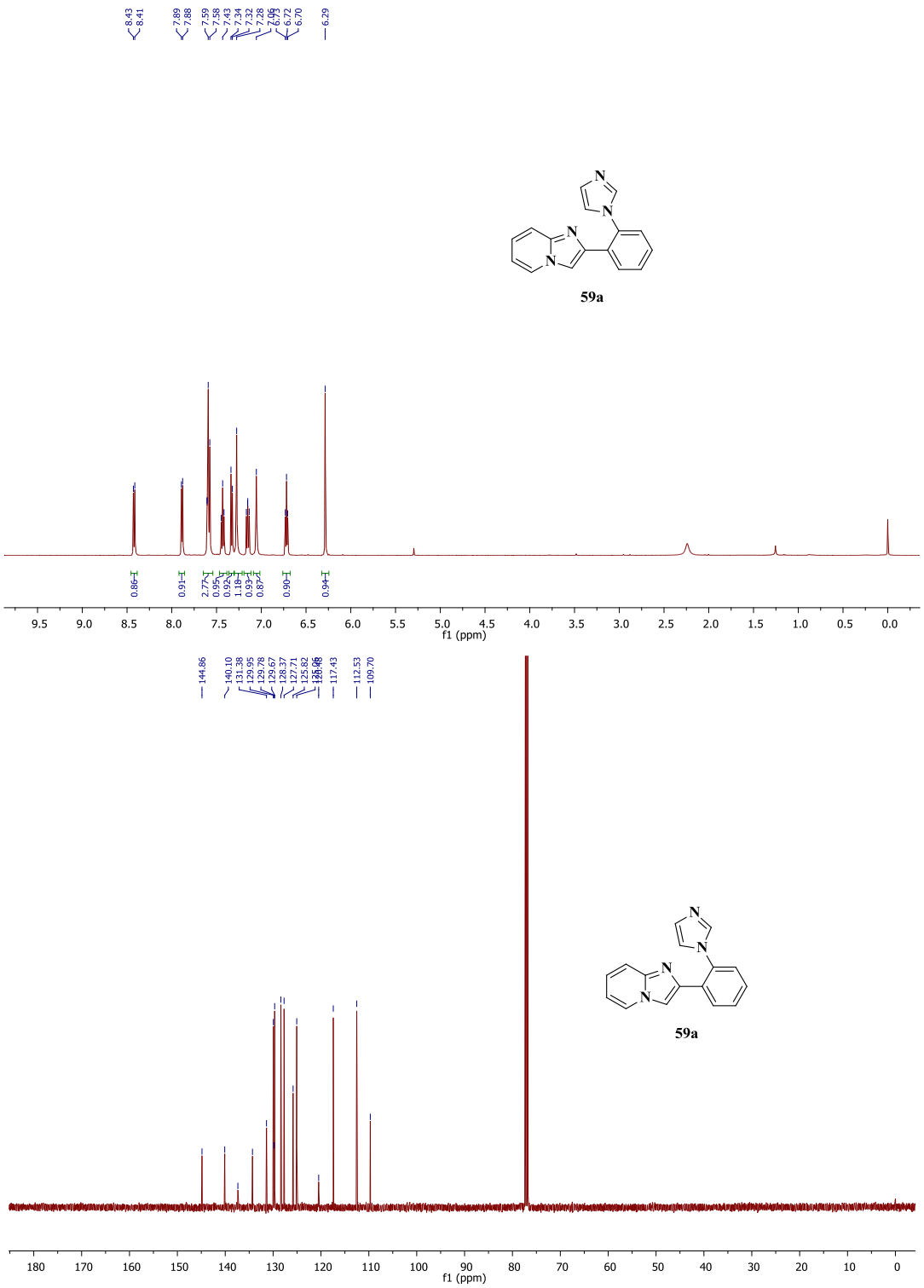
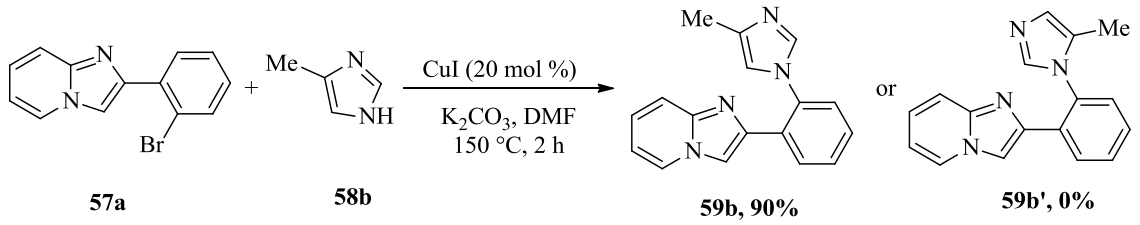


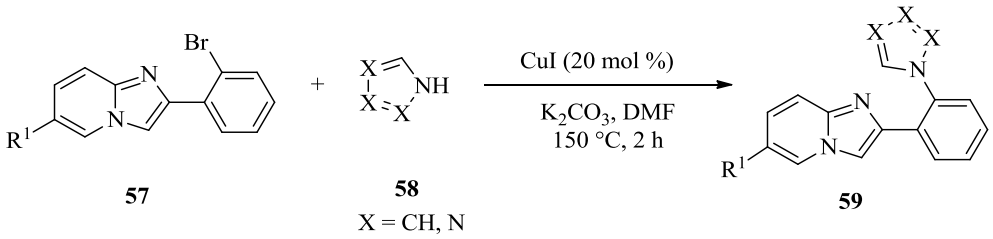
Figure 2.2: ^{1}H NMR, ^{13}C NMR spectra of 2-(2-(1*H*-imidazol-1-yl)phenyl)imidazo[1,2-*a*]pyridine (**59a**)

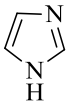
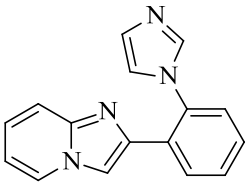
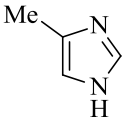
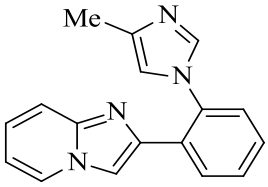
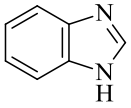
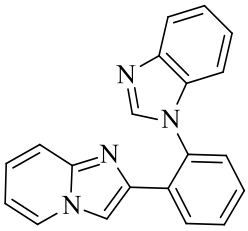
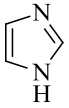
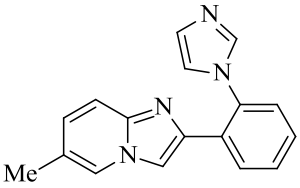
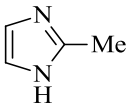
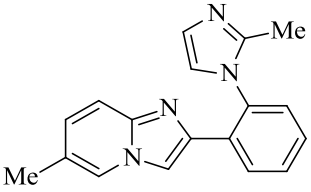
After optimization of the reaction conditions and characterisation of product, the scope and generality of this copper-catalyzed Ullmann-type C–N coupling reaction was explored using series of azoles (**58**) such as 2-methyl-1*H*-imidazole, 4-methyl-1*H*-imidazole, and 1*H*-benzimidazole. The results are summarized in **table 2.1**. The reactions were carried out under the optimized conditions without any special precautions. As can be seen from **table 2.1**, the coupling proceeded smoothly with azoles **58a–g** yielding the corresponding products in good yields (**Table 2.1**, entries 2–6). 1*H*-1,2,4-Triazole and 1*H*-tetrazole also reacted well under the optimized reaction conditions to give the corresponding coupled products in good yields (**Table 2.1**, entries 7–9). Similarly, good yield of 2-[2-(1*H*-indol-1-yl)phenyl]-6-methylimidazo[1,2-*a*]pyridine (**59j**) was obtained when indole was used under standared conditions, however the reaction required six hours for completion (**Table 2.1**, entry 10). Under the standared reaction conditions single isomer was observed in the case of 4-methyl-1*H*-imidazole instead of possible mixture of isomers (**59b**) as shown in **scheme 2.26**. (**Table 2.1**, entry 2).[78] The use of an inexpensive catalytic system, high efficiency, and simple methodology make this protocol of considerable practical utility. All the synthesized compounds were well characterized by ^{1}H NMR, ^{13}C NMR, and mass spectral data.

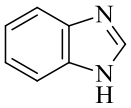
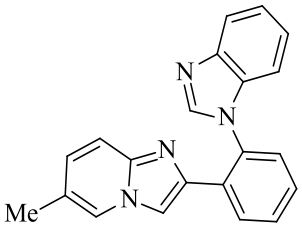
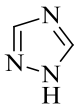
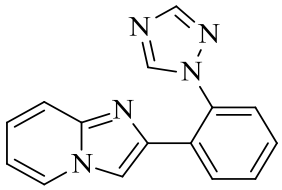
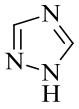
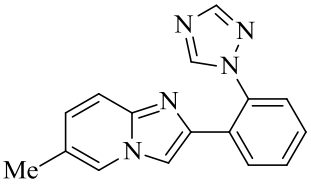
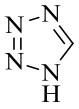
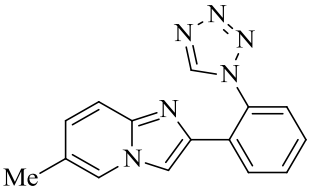
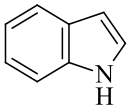
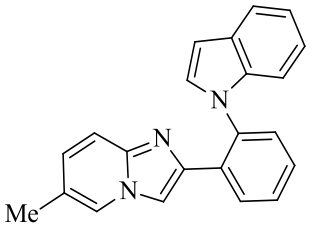
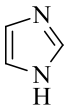
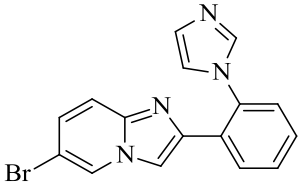


Scheme 2.26: Reaction of **57a** with 4-methyl-1*H*-imidazole

Table 2.1: Synthesis of azole-substituted imidazo[1,2-*a*]pyridines through Ullmann-type C–N coupling.[a]



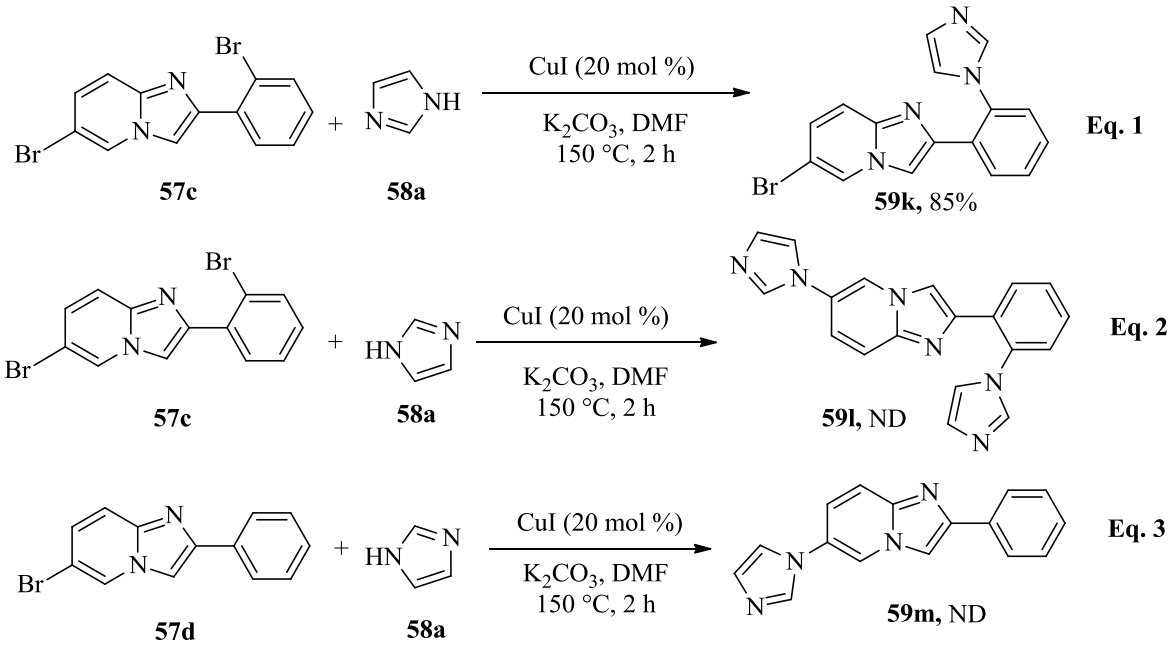
Entry	**57** (R^1)	**58**	Product		Yield (%)[b]
1	H			**59a**	92[c]
2	H			**59b**	90
3	H			**59c**	85
4	Me			**59d**	87
5	Me			**59e**	65

Entry	**57** (R^1)	**58**	Product		Yield (%)[b]
6	Me			**59f**	92
7	H			**59g**	85
8	Me			**59h**	87
9	Me			**59i**	88
10	Me			**59j**	74[c]
11	Br			**59k**	85

[a]Reaction conditions: **57** (1.0 mmol), **58** (1.2 mmol), CuI (0.2 mmol), K_2CO_3 (2.0 mmol), DMF, 150 °C, 2 h,
[b]Isolated yield
[c]Reaction time was 6 h.

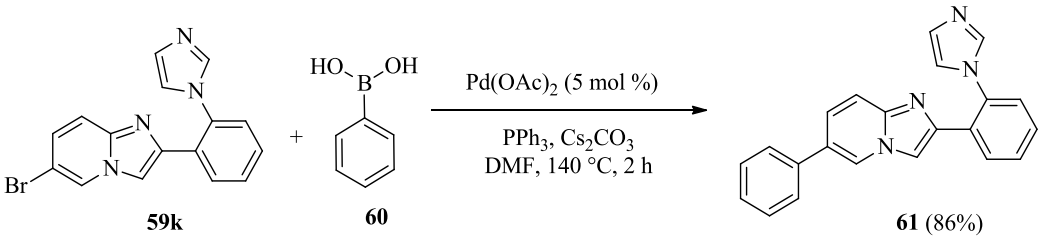
The regioselectivity of the coupling reaction was established by performing control experiments on 6-bromo-2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**57c**) and 6-bromo-2-phenylimidazo[1,2-*a*]pyridine (**57d**) (**Scheme 2.27**). When **57c** was treated with 1*H*-imidazole (**58a**) under the

optimized conditions, mono-coupled product 2-[2-(1*H*-imidazol-1-yl)phenyl]-6-bromoimidazo[1,2-*a*]pyridine (**59k**) was obtained in 85% yield (**Scheme 2.27, eq. 1**) and formation of 2-(2-(*1H*-imidazol-1-yl)phenyl)-6-(*1H*-imidazol-1-yl)imidazo[1,2-*a*]pyridine (**59l)** was not observed with **57c** even after increasing the amount of imidazole to 2 equivalent (**Scheme 2.27, eq. 2**). Regioselectively formation of **59k** product confirmed the regioselectivity of developed methodology. Further **57d** did not react under these conditions to give the desired product **59m** (**Scheme 2.27, eq. 3**). It is worth mentioning that no double C–N coupled product was detected from **57c** in this reaction (**Scheme 2.27, eq. 2**). Addition of external ligand to the **57d** in the presence of copper or palladium catalyst produce the **59m** product and it is well studied by Buchwald group.[79]



Scheme 2.27: Control experiments for regioselectivity of Ullmann-type C−N coupling reaction

These results are particularly interesting as the products can be further functionalized by transition-metal-catalyzed C–C or C–heteroatom cross-coupling reactions. To illustrate this we performed Suzuki reaction with **59k**. When **59k** (1 mmol) was separately treated with phenylboronic acid (**60**) (1.1 mmol), $Pd(OAc)_2$ (5 mol %), Ph_3P (10 mol %), Cs_2CO_3 (1.5 mmol) in DMF at 140 °C for 2 hours, the corresponding cross-coupled product 2-[2-(1*H*-imidazol-1-yl)phenyl]-6-phenylimidazo[1,2-*a*]pyridine (**61**) was obtained in 86% yield (**Scheme 2.28**). The synthesized compound (**61**) was further confirmed by spectral data (**Figure 2.3**).



Scheme 2.28: Functionalization of azole-substituted imidazo[1,2-*a*]pyridines

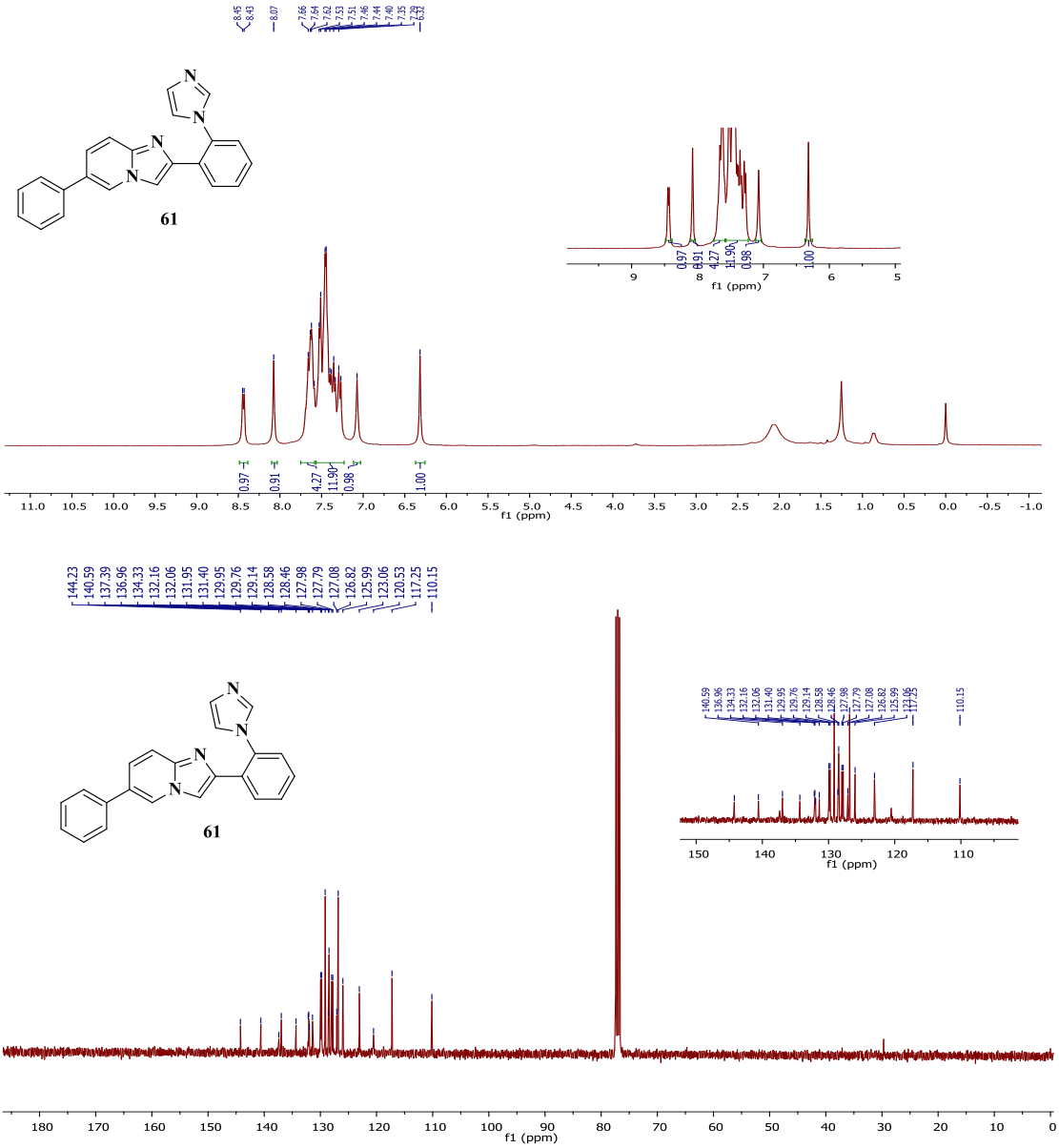
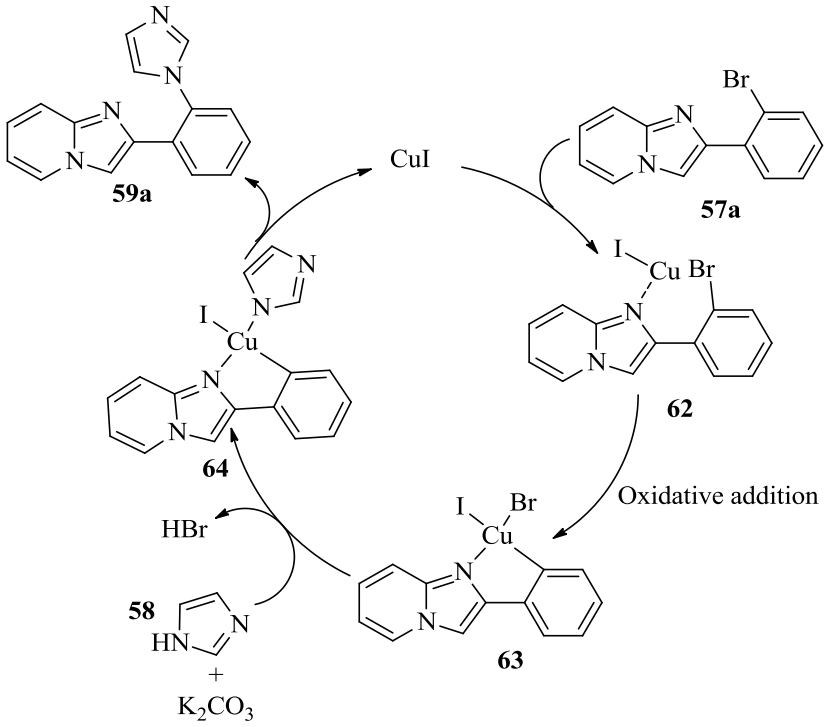


Figure 2.3: ^{1}H NMR and ^{13}C NMR spectra of **61**

Based on literature precedent[7, 45-46] the proposed mechanism of the coupling reaction is shown in **scheme 2.29**. It is proposed that the imidazo[1,2-*a*]pyridine–copper complex **62** (through *N1*-

nitrogen atom of imidazo[1,2-*a*]pyridine) on oxidative addition with C–Br bond leads to intermediate **63**. Subsequently, the halide group on the copper can be exchanged with 1*H*-imidazole in the presence of base to give intermediate **64,** which on reductive elimination, leads to the target molecule (**59a**) with the regeneration of copper catalyst.



Scheme 2.29: Plausible mechanism for copper-catalyzed Ullmann-type C–N coupling

2.6. Conclusion

A simple and highly efficient protocol for the regioselective synthesis of azole-substituted imidazo[1,2-*a*]pyridines has been developed using ligand-free, copper-catalyzed Ullmann-type C–N coupling of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridines with different azoles. The reactions proceeded smoothly to furnish azole-imidazo[1,2-*a*]pyridines in good to excellent yields (74–92%). Further functionalization of halosubstituted, azole-imidazo[1,2-*a*]pyridines was achieved *via* Suzuki–Miyaura cross-coupling.

2.7. Experimental section

2.7.1. General information

Melting points were determined in open capillary tubes on 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 (^{1}H NMR, ^{13}C NMR) determined on Bruker AV NMR 300 MHz, Bruker AV 400 MHz and Varian 500 MHz spectrometer. ^{13}C NMR spectra are fully decoupled. Chemical shifts were reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane (internal) as the standard. High resolution mass spectra (HRMS-ESI) were carried out using quadrupole time of-flight (Q-TOF) mass spectrometer (Applied Biosystem). The key starting materials (**57a-d**) was synthesized using our reported procedures.[8] All other chemicals were obtained from the commercial suppliers and used without further purification.

2.7.2. Experimental procedure for the synthesis of 2-(2-(1*H*-imidazol-1-yl)phenyl) imidazo[1,2-*a*]pyridine (59a):

A 10 mL RB flask was charged with 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**57a)** (100 mg, 0.36 mmol), 1*H*-imidazole (**58a)** (29 mg, 0.439 mmol), CuI (13.9 mg, 0.07 mmol), K_2CO_3 (101 mg, 0.732 mmol) and *N*,*N*-dimethylformamide (DMF) (2.0 mL). The resulting solution was stirred at 150 °C in an oil bath for 2 h under nitrogen atmosphere. On completion, the reaction mass was filtered through celite pad and washed with ethyl acetate (2×10 mL). The filtrate was washed with water, dried over anhydrous sodium sulfate and concentrated under vacuum. The crude residue was purified by column chromatography (EtOAc: hexane, 2: 3) to obtain the product, 2-(2-(1*H*-imidazol-1-yl)phenyl)imidazo[1,2-*a*]pyridine (**59a**).

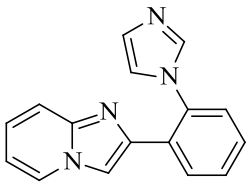
2.7.3. Experimental procedure for the synthesis of 61

A 10 mL RB flask was charged with **59k** (1.0 mmol), phenylboronic acid (**60**) (1.2 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.1 mmol), Cs_2CO_3 (1.5 mmol) and DMF (2.0 mL). The resulting solution was stirred at 140 °C in an oil bath for 2 h under nitrogen atmosphere. On completion, the reaction mass was filtered through celite pad and washed with ethyl acetate. The filtrate was

washed with water, dried over anhydrous sodium sulfate and concentrated under vacuum. The crude residue was purified by column chromatography to give **61**.

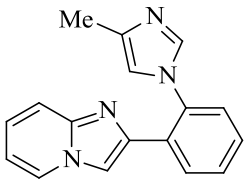
2.7.4. Physical and spectral data of 59a-j and 61

2-(2-(*1H*-Imidazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (**59a**): Yield 92%; Colourless solid;



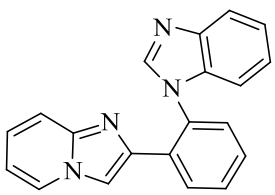
mp 149-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.89 (dt, *J* = 6.8, 1.1 Hz, 1H), 7.65 – 7.55 (m, 3H), 7.44 (td, *J* = 7.6, 1.5 Hz, 1H), 7.34 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.29 (s, 1H), 7.18 – 7.14 (m, 1H), 7.06 (s, 1H), 6.73 (td, *J* = 6.8, 1.1 Hz, 1H), 6.29 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 140.1, 137.4, 134.3, 131.4, 130.0, 129.8, 129.7, 128.4, 127.7, 125.8, 125.1, 120.5, 117.4, 112.5, 109.7; HRMS (*m/z*) calcd for $C_{16}H_{13}N_4$ 261.1135, found 261.1119 $[M+H]^+$.

2-(2-(4-Methyl-1*H*-imidazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (**59b**): Yield 90%;



Colourless solid; mp 174-177 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.90 (dt, *J* = 6.8, 1.0 Hz, 1H), 7.62 – 7.52 (m, 2H), 7.47 (s, 1H), 7.40 (td, *J* = 7.6, 1.5 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.18 – 7.11 (m, 1H), 6.76 (s, 1H), 6.72 (td, *J* = 6.8, 1.1 Hz, 1H), 6.40 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 140.3, 138.8, 136.5, 134.6, 131.3, 129.9, 129.439, 128.309, 127.8, 125.8, 125.0, 117.4, 116.8, 112.5, 109.9, 13.8; HRMS (*m/z*) calcd for $C_{17}H_{15}N_4$ 275.1291, found 275.1278 $[M+H]^+$.

1-(2-(*H*-Imidazo[1,2-*a*]pyridin-2-yl)phenyl)-1*H*-benzo[*d*]imidazole (59c): Yield 85%;



Colourless solid; mp 129-132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.97 – 7.88 (m, 2H), 7.72 – 7.62 (m, 2H), 7.59 – 7.46 (m, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.37 – 7.30 (m, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.14 – 7.05 (m, 1H), 6.61 (t, *J* = 6.7 Hz, 1H), 6.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 143.4, 143.1, 140.22, 134.5, 132.5, 132.2, 130.6, 129.9, 128.8, 128.5, 125.8, 125.1, 123.9, 122.8, 120.4, 117.4, 112.4, 110.6, 109.83; HRMS (*m/z*) calcd for $C_{20}H_{15}N_4$ 311.1291, found 311.1281 $[M+H]^+$.

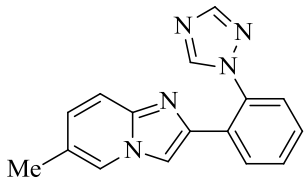
2-(2-(1*H*-Imidazol-1-yl)phenyl)-6-methyl*H*-imidazo[1,2-*a*]pyridine (59d): Yield 87%; Off-white solid; mp 167-169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.67 (s, 1H), 7.58 (td, *J* = 7.8, 1.3 Hz, 2H), 7.48 (d, *J* = 9.2 Hz, 1H), 7.41 (td, *J* = 7.6, 1.5 Hz, 1H), 7.31 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.27 (d, *J* = 3.2 Hz, 1H), 7.04 (s, 1H), 6.99 (dd, *J* = 9.2, 1.5 Hz, 1H), 6.19 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 139.8, 137.3, 134.2, 131.6, 129.8, 129.6, 128.3, 128.2, 127.7, 123.5, 122.1, 120.6, 120.5, 116.7, 109.4, 18.0; HRMS (*m/z*) calcd for $C_{17}H_{15}N_4$ 275.1291, found 275.1278 $[M + H]^+$.

6-Methyl-2-(2-(2-methyl-1*H*-imidazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (**59e**)*:* Yield 65%; Viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.79 – 7.35 (m, 4H), 7.33 – 6.88 (m, 4H), 6.06 (s, 1H), 2.26 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 144.0, 139.8, 134.1, 132.0, 129.9, 129.5, 128.5, 128.4, 128.1, 127.8, 123.7, 122.2, 120.17, 116.6, 109.6, 18.0, 12.8; HRMS (*m/z*) calcd for $C_{18}H_{17}N_4$ 289.1448, found 289.1462 $[M + H]^+$.

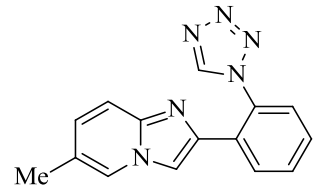
1-(2-(6-Methyl*H*-imidazo[1,2-*a*]pyridin-2-yl)phenyl)-1*H*-benzo[*d*]imidazole (**59f**): Yield 92%; Colourless solid; mp 161-164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, *J* = 7.5 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.65 (t, *J* = 7.1 Hz, 1H), 7.55 – 7.30 (m, 5H), 7.29 – 7.13 (m, 2H), 6.95 (d, *J* = 9.0 Hz, 1H), 6.03 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 143.3, 143.1, 139.9, 134.5, 132.3, 132.3, 130.4, 129.9, 128.6, 128.4, 128.4, 123.9, 123.4, 122.7, 122.1, 120.4, 116.6, 110.6, 109.6, 17.9; HRMS (*m/z*) calcd for $C_{21}H_{17}N_4$ 325.1448, found 325.1428 $[M + H]^+$.

2-(2-(1*H*-1,2,4-Triazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (**59g**): Yield 85%; Colourless solid; mp 167-169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.8 Hz, 1H), 8.21 (s, 1H), 8.16 (s, 1H), 7.91 (d, *J* = 6.7 Hz, 1H), 7.68 – 7.54 (m, 2H), 7.53 – 7.38 (m, 2H), 7.20 – 7.11 (m, 1H), 6.73 (t, *J* = 6.7 Hz, 1H), 6.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 145.1, 144.64, 140.6, 134.3, 131.3, 130.5, 130.4, 128.6, 127.6, 125.8, 125.1, 117.6, 112.7, 109.8; HRMS (*m/z*) calcd for $C_{15}H_{12}N_5$ 262.1087, found 262.1067 $[M + H]^+$.

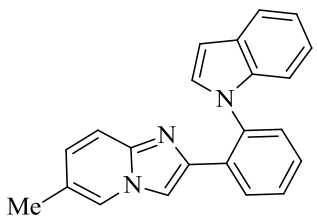
2-(2-(1*H*-1,2,4-Triazol-1-yl)phenyl)-6-methyl*H*-imidazo[1,2-*a*]pyridine (**59h**): Yield 87%; Viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 7.6 Hz, 1H), 8.20 (s, 1H), 8.14 (s, 1H), 7.70 (s, 1H), 7.64 – 7.57 (m, 1H), 7.51 – 7.39 (m, 3H), 7.01 (dd, J = 9.2, 1.3 Hz, 1H), 6.51 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 144.6, 144.2, 140.2, 134.2, 131.4, 130.4, 130.4, 128.5, 128.4, 127.5, 123.4, 122.4, 116.8, 109.5, 18.0; HRMS (*m/z*) calcd for $C_{16}H_{14}N_5$ 276.1244, found 276.1269 $[M + H]^+$.



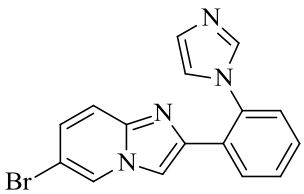
2-(2-(1*H*-Tetrazol-1-yl)phenyl)-6-methyl*H*-imidazo[1,2-*a*]pyridine (**59i**): Yield 88%; Viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 5.5 Hz, 1H), 8.07 (s, 1H), 7.74 (s, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.26 (d, J = 5.0 Hz, 3H), 6.99 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 6.7 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 143.8, 143.8, 140.2, 129.1, 128.8, 128.1, 125.4, 124.1, 123.6, 121.7, 118.8, 116.5, 112.1, 18.0; HRMS (*m/z*) calcd for $C_{15}H_{13}N_6$ 277.1196, found 277.1168 $[M +H]^+$.



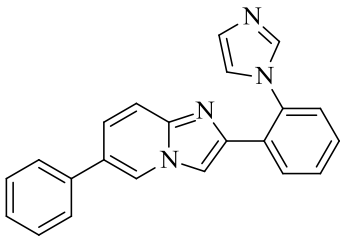
2-(2-(1*H*-Indol-1-yl)phenyl)-6-methyl*H*-imidazo[1,2-*a*]pyridine (**59j**): Yield 74%; Off-white solid; mp 134-136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 – 8.42 (m, 1H), 7.64 – 7.57z (m, 1H), 7.49 (td, J = 7.6, 1.5 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.28 – 7.23 (m, 2H), 7.08 – 6.94 (m, 4H), 6.79 (dd, J = 9.2, 1.6 Hz, 1H), 6.61 (d, J = 3.1 Hz, 1H), 5.78 (s, 1H), 2.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 140.2, 136.6, 135.8, 135.72, 132.6, 129.8, 129.2, 129.0, 128.5, 128.3, 127.9, 123.4, 122.4, 121.74, 120.8, 120.2, 116.5, 110.7, 110.4, 103.1, 17.9; HRMS (*m/z*) calcd for $C_{22}H_{18}N_3$ 324.1495, found 324.1435 $[M + H]^+$.



2-(2-(1*H*-Imidazol-1-yl)phenyl)-6-bromoimidazo[1,2-*a*]pyridine (59k): Yield 85%; Colourless solid; mp 201-203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, J = 7.9, 1.2 Hz, 1H), 8.07 (s, 1H), 7.62 (dd, J = 10.9, 4.3 Hz, 2H), 7.52 – 7.44 (m, 2H), 7.36 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 4.5 Hz, 1H), 7.23 (dd, J = 9.5, 1.7 Hz, 1H), 7.06 (s, 1H), 6.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 141.0, 137.4, 134.4, 131.0, 130.0, 129.8, 128.7, 128.6, 127.8, 125.8, 120.43, 118.0, 109.8, 107.2; HRMS (*m/z*) calcd for $C_{16}H_{12}BrN_4$ 339.0247, found 339.0240 $[M + H]^+$ and 341.0232 $[M + H +2]^+$.



2-(2-(1*H*-Imidazol-1-yl)phenyl)-6-phenyl*H*-imidazo[1,2-*a*]pyridine (**61**): Yield 86%;



Colourless solid; mp 96-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 7.5 Hz, 1H), 8.07 (s, 1H), 7.71 – 7.58 (m, 3H), 7.56 – 7.24 (m, 9H), 7.07 (s, 1H), 6.32 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 140.6, 137.0, 134.3, 132.2, 132.1, 131.4, 130.0, 129.8, 129.1, 128.6, 128.5, 128.0, 127.8, 127.1, 126.8, 126.0, 123.1, 117.3, 110.2; HRMS (*m/z*) calcd for $C_{22}H_{17}N_4$ 337.1448, found 337.1473 $[M + H]^+$.

Chapter II

Part B

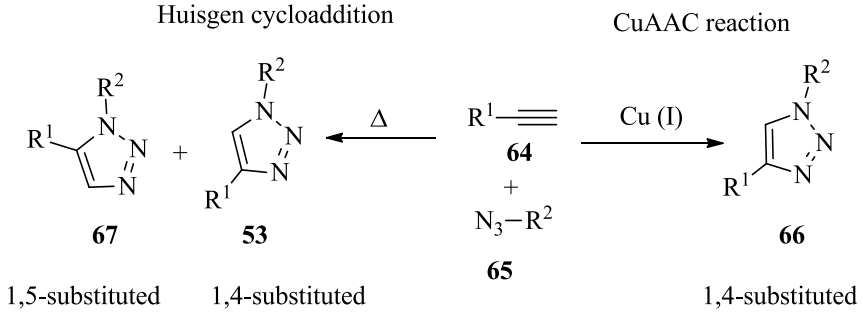
Synthesis of 1,2,3-Triazole-substituted Imidazo[1,2-*a*]pyridines

2.8. Introduction

The traditional process for synthesis of medicinally based compounds or natural secondary metabolites has often been slow, very expensive, and labor-intensive. Even after the initiation of combinatorial chemistry in the past two decades, the generation of new complex molecules is dependent on the consistency of the reactions.[80-81] The discovery of new molecular diversity inspired from nature and the continuous demand for more efficient and environmentally benign chemical methodology invites the further development of such synthetic strategies and plans as we move into new age of chemical synthesis.[82-83]

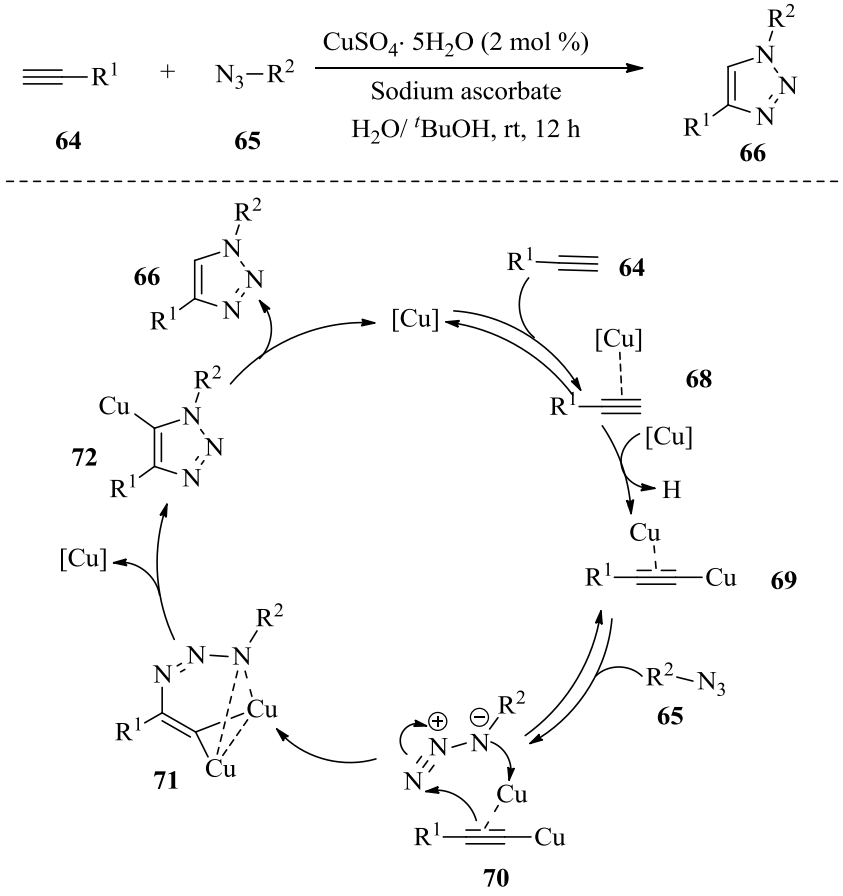
2.8.1. Click chemistry

Reaction of azides to alkynes known as Huisgen cycloaddition has gained much attention due to its potential to yield wide variety of triazoles derivatives.[84] The reaction requires high temperature and mixture of 1,4- and 1,5-regioisomeric triazoles is obtained (**Scheme 2.30**).[85] In 2002, Sharpless and Meldal presented milestone in this field and used copper catalyst to give regioselective 1,4-disubstituted triazole by the reaction of azides with alkynes and this reaction has been commonly known as copper catalyzed azide-alkyne cycloaddition (CuAAC) or click reaction.[86-87]



Scheme 2.30: Synthesis of triazoles through Huisgen cycloaddition and CuAAC

Fokin *et al.* predicted the mechanistic part by DFT study and proposed mechanism for the copper-catalyzed 1,3-dipolar cycloaddition reaction of alkyne with azide to give the triazole (**Scheme 2.31**)**.** The reaction starts with interaction of alkyne and copper to form π-complex **68** with triple bond and base abstracts proton to form Cu-acetylide intermediate (**69**) which reacts with azide *via* 1,3-dipolar cycloaddition to give copper-azide-acetylide complex (**70**) and finally it dissociates to give 1,2,3-triazole and copper catalyst.[88]

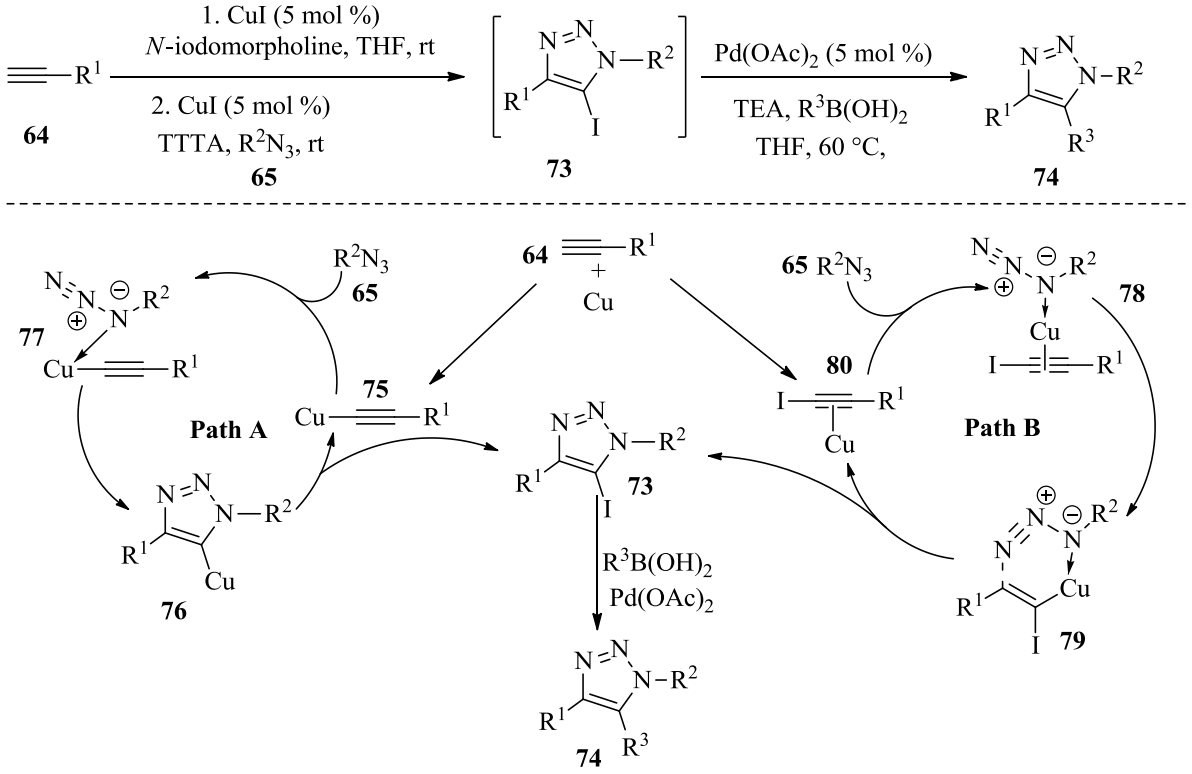


Scheme 2.31: Proposed reaction mechanism for CuAAC reaction based on DFT study

2.8.2. Post C–C coupling in click reaction *via* tandem approach

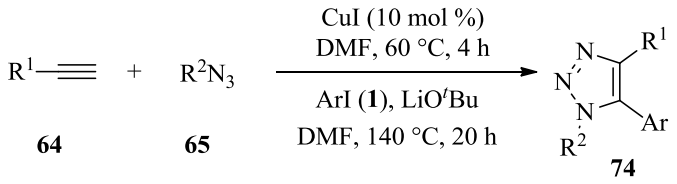
Tandem or cascade reactions catalyzed by metal salts serve as an efficient tool for the synthesis of assembly of complex biologically active heterocyclic molecules.[45] In general, Pd, Au, Ag, Rh, Ni, Cu and Fe are the most investigated and engaged metal species for coupling reactions. [15,76] The classical CuAAC reaction produce only 1,4-disubstituted 1,2,3-triazoles using terminal alkyne as an essential substrates.[89] Thus, the development of an efficient strategy to access fully substituted triazoles by tandem reaction with click chemistry is highly desirable. The combination of click chemistry and C–C coupling reaction can be utilized for the synthesis of fully substituted 1,2,3-triazoles. Two reactive intermediate (C–Cu intermediate and iodo-CuAAC intermediate) has been isolated for mechanistic study of CuAAC reaction and has been well documented in literature. These intermediates undergo rapid protonation to form the stable 1,4-disubstituted 1,2,3-triazoles but these versatile synthetic intermediates can be *in situ*

functionalized by using C–C coupling reactions. One of interesting synthetic utility of the iodo-CuAAC (**73**) intermediate was described by Hein's group. Using combination of palladium-catalyzed Suzuki–Miyaura cross-coupling reactions or direct arylation reactions with CuAAC reaction in one-pot procedure, multi-substituted 1,4,5-triaryl-1,2,3-triazoles (**74**) were prepared with regio-control (**Scheme 2.32**). The developed reaction can follow two pathways as shown in **scheme 2.32**. Path A involves formation of σ-acetylide (**75**) complex which then coordinates with azide (**77**) through the proximal nitrogen (**Path A, Scheme 2.32**) whereas path B involves copper activated iodoalkyne to form π-complex intermediate (**80**) which then interacts with azide (**79**) **(Path B, Scheme 2.32**).[90]



Scheme 2.32: Sequential synthesis of 1,4,5-triaryl-1,2,3-triazoles through iodo-CuAAC reaction

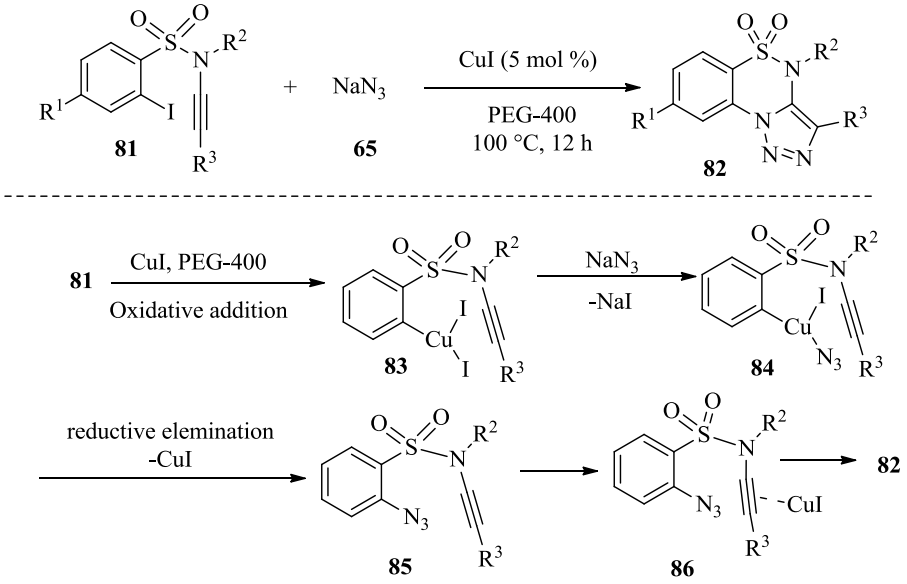
Ackermann *et al.* reported synthetic utility of cuprate−triazole intermediate *via* one-pot multi-component reaction for the synthesis of fully decorated triazoles *via* sequential click reaction and direct arylation reaction. The reaction of alkyne (**64**), alkyl halide (**1**) and alkyl azide (**65**) was carried out in the presence of CuI and base in DMF for 20 hours at 140 °C to get fully or tri-substituted triazoles (**74**) (**Scheme 2.33**).[91]



Scheme 2.33: Sequential copper-catalyzed synthesis of multi-substituted triazoles

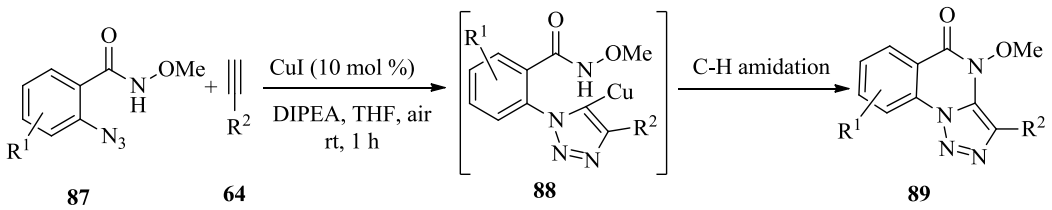
2.8.3. Post C–N coupling in CuAAC reaction *via* tandem approach

1,2,3-Triazoles fused heterocycles are core structure of many biologically active organic compounds in pesticides, medicines, and functional materials. For synthesis of these fused triazoles core structure amalgamation of click chemistry and C–N coupling reaction through one-pot tandem approach can formulate the future of synthetic medicinal chemistry. Swamy and co-workers synthesized triazolo-1,2,4-benzothiadiazine-1,1-dioxides (**82**) using one-pot tandem process with copper catalyst by the reaction of functionalized ynamides (**81**) and sodium azide (**65**) (**Scheme 2.34**).[92] The reaction proceeds through intermolecular C–N bond formation to give intermediate (**85**) and subsequent cycloaddition reaction between ynamide and azide resulted product (**82**). Three new C–N bonds are formed in single step. A range of *N*-alkynyl-2-iodo-benzenesulfonamides with electron donating group and electron withdrawing group were well tolerated to furnish the desired product in good to excellent yield.



Scheme 2.34: Synthesis of triazolo 1,2,4-benzothiadiazine 1,1-dioxides from *N*-alkynyl-2-iodo-benzene sulfonamides

Sun *et al.* synthesized triazoloquinazolinones (**89**) *via* copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction (**Scheme 2.35**).[93] The synthetic methodology involves sequential one-pot click reaction and aerobic intramolecular C–H amidation in the presence of copper catalyst without any external ligand. Control experiments proved the formation of intermediate **88** with copper catalyst.



Scheme 2.35: Synthesis of triazoloquinazolinones *via* one-pot CuAAC and C–H amidation

2.8.4. Synthesis of heterocycles with triazole *via* click reaction

Heterocyclic systems have been accounted as one of the most representative chemical building structure found in several natural and synthetic bioactive compounds, including variety of marketed drugs. Nitrogen containing heterocyclic compounds are important building-blocks for new materials with interesting electronic, mechanical, or biological properties.[94-95] In this context 1,2,3-triazole scaffold plays vital role in the medicinal area and numerous molecules having core structure of this framework are showing HIV protease inhibiting, anticancer, antituberculosis, antifungal, or antibacterial activities.[55, 96-97] 1,2,3-Triazole tethered heterocycles moieties are widely applicable in biological systems, material chemistry, and especially in the area of fluorescent sensors, dye-sensitized solar cell etc.[98-103] In recent years it has been observed that fusion of two biological prominent skeletons can lead to molecules with improved biological properties. 1,2,3-Triazoles linked organic compounds have been developed with variety of biological activities and material application (**Figure 2.4**).[104-106]

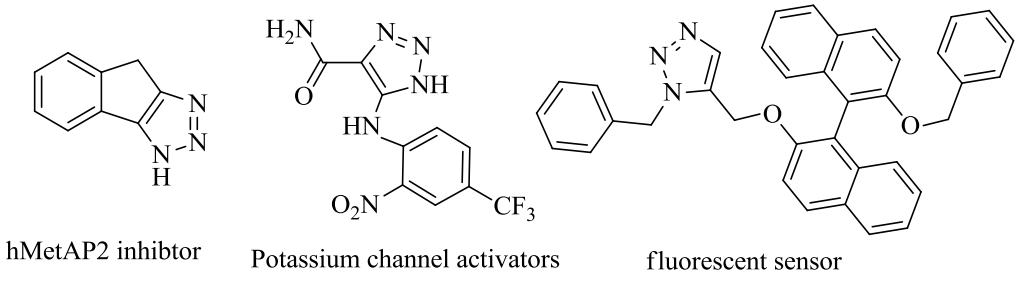
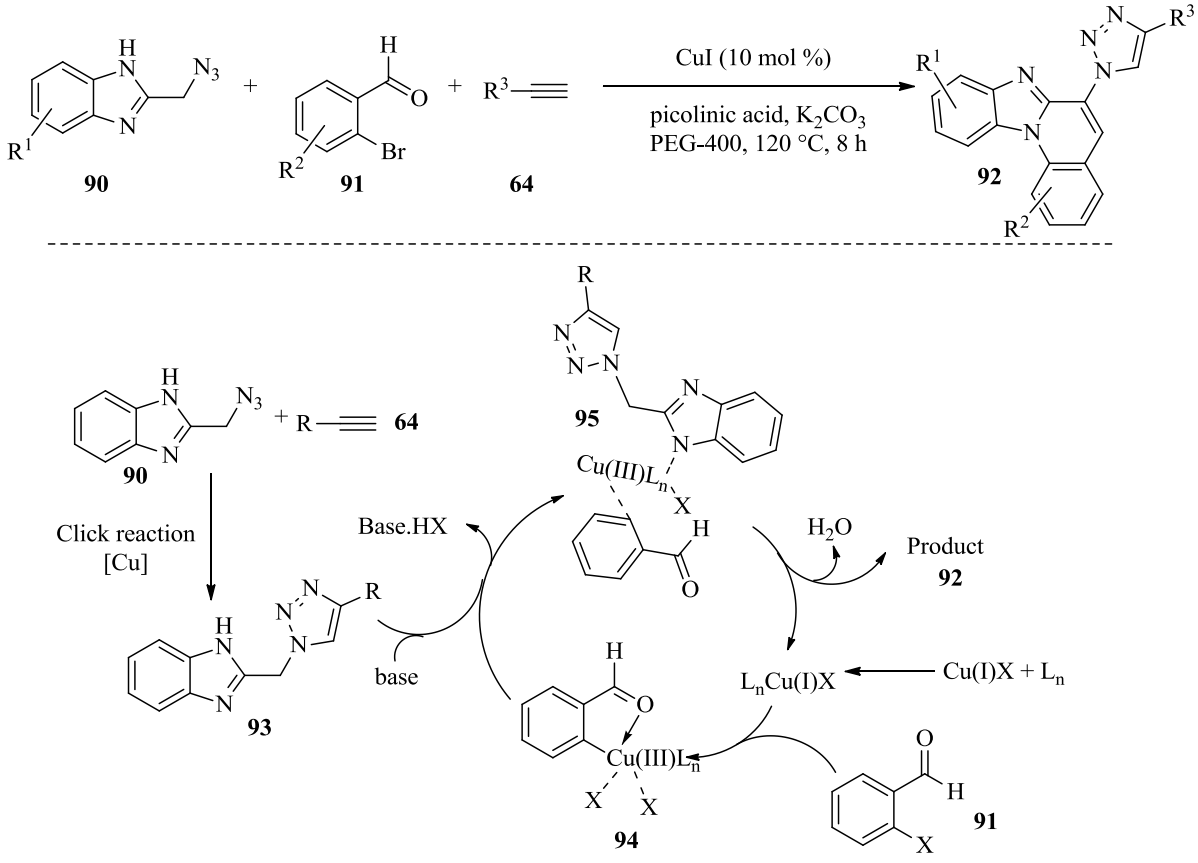


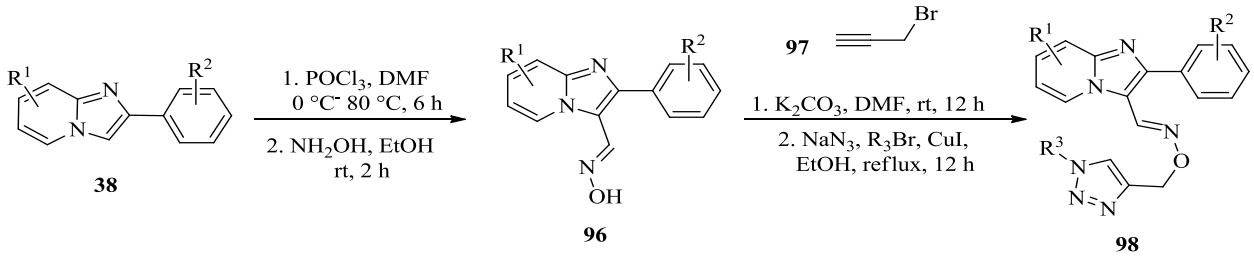
Figure 2.4: Some important 1,2,3-triazoles linked organic compounds

Recently, Sekhar *et al.* synthesized 1,2,3-triazole appended benzimidazo[1,2-*a*]quinoline (**92**) using copper catalyst (**Scheme 2.36**).[106] Reaction occurred through series of reaction as click reaction/ C–N bond formation/Knoevenagel condensation having dual role of copper in click reaction and C–N coupling reaction. The reaction of 2-(azidomethyl)-1*H*-benzo[*d*]imidazole (**90**), 2-bromobenzaldehyde (**91**) and phenylacetylene (**64**) was carried out in the presence of CuI, to form four new bonds (1C–C and 3C–N) in the desired product (**Scheme 2.36**). The reaction was also investigated under ligand-free condition but yield was less compared to that in the presence of picolinic acid as ligand. Reaction mechanism starts with click reaction between **90** and **64** to form compound **93** with active methylene group which then reacts with the intermediate **94** which is generated by the reaction of *ortho*-halo (hetero)aryl aldehyde (**91**) with copper catalyst through oxidative addition to give intermediate **95**. Intermediate **95** undergoes reductive elimination to furnish the desired product (**92**) and complete the catalytic cycle.



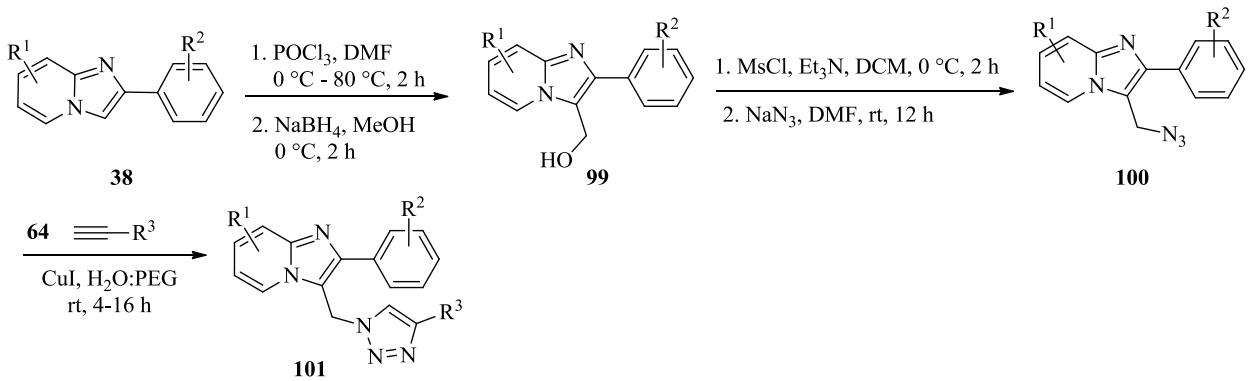
Scheme 2.36: One-pot synthesis of 1,2,3-triazole tethered benzimidazo[1,2-*a*]quinoline

Adhikari group synthesized 1,2,3-triazole substituted imidazo[1,2-*a*]pyridines (**98**) through multistep protocol.[62] Formylation of imidazo[1,2-*a*]pyridines (**38**) followed by oxime synthesis resulted intermediate **96**. Propargyl functionality was attached to the intermediate **96** by the reaction of propargyl bromide (**97**) in the presence of K_2CO_3 which reacted with alkyl azides (*in situ* generated by the reaction of sodium azide (**65**) and alkyl halide (**1**)) *via* [3+2] cycloaddition reaction to afford the targeted molecule (**98**) (**Scheme 2.37**).



Scheme 2.37: Synthesis of 1,2,3-triazole substituted imidazo[1,2-*a*]pyridines

Recently, our group reported synthesis of 1,2,3-triazole substituted imidazo[1,2-*a*]pyridines (**101**) using sequence of reactions, where azide (**65**) group reacted with imidazo[1,2-*a*]pyridine skeleton at C-3 position followed by click chemistry.[76] The developed procedure was simple and offered good yields of triazolyl imidazo[1,2-*a*]pyridines (**110**). Reaction of imidazo[1,2-*a*]pyridines with $POCl_3$ followed by reduction with $NaBH_4$ resulted alcohol of imidazo[1,2-*a*]pyridines (**99**) which was further treated with MsCl and NaN_3 to furnish azido linked imidazo[1,2-*a*]pyridines (**100**) and finally it was treated with alkyne (**64**) in the presence of copper catalyst to give the targeted product (**101**) in good to excellent yield *via* CuAAC reaction (**Scheme 2.38**).

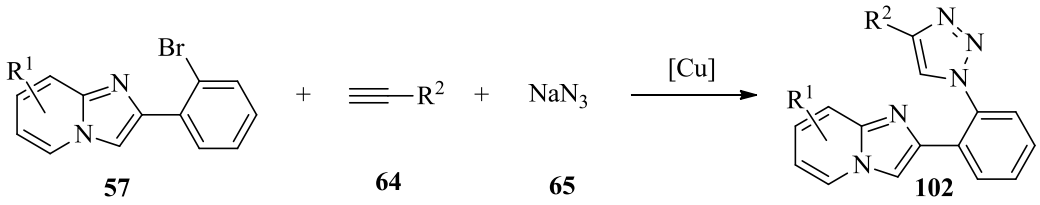


Scheme 2.38: Synthesis of 1,2,3-triazole substituted imidazo[1,2-*a*]pyridines

In the continuation of our efforts towards functionalization of heterocycles containing imidazo[1,2-*a*]pyridines using copper-catalyzed multi-component and click chemistry in this B part of this chapter we have discussed our new findings on ligand-free copper-catalyzed synthesis of *in situ* generated 1,2,3-triazoles substituted imidazo[1,2-*a*]pyridine.[76-77, 107-108]

2.9. Results and discussion

Encouraged by the success of ligand-free Ullmann coupling of azoles with imidazo[1,2-*a*]pyridines, in **part A** of this chapter, we focused our attention to develop regioselective, ligand-free, copper-catalyzed C–N coupling reaction for the synthesis of triazole-substituted imidazo[1,2-*a*]pyridines (**69**) by the reaction of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridines (**57**) with *in situ* generated 1,2,3-triazoles (**105**) (**Scheme 2.39**).

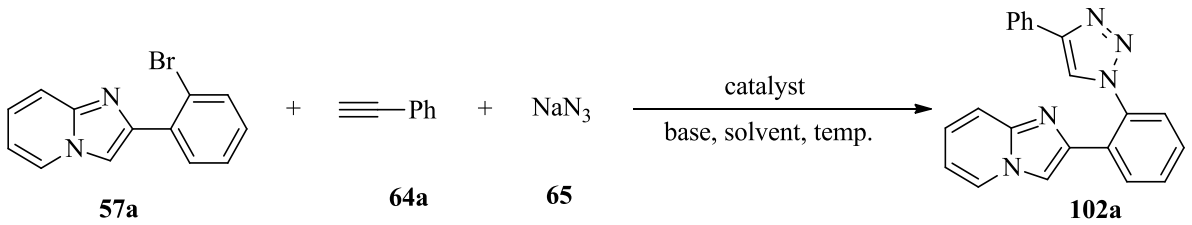


Scheme 2.39: Synthesis of triazole-substituted imidazo[1,2-*a*]pyridines

In typical experiment 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**57a**), sodium azide (**65**), and phenylacetylene (**64a**) were reacted in the presence of CuI and K_2CO_3 in DMF for 6 hours at 150 ˚C which is the optimized conditions for ligand-free Ullmann coupling of azole with 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine. Again, we were gratified to observe that 2-[2-(4-phenyl-*1H*-1,2,3-triazol-1-yl)phenyl]imidazo[1,2-*a*]pyridine (**102a**) was isolated in 55% yield (**Table 2.2**, entry 1). To improve the yield of **102a**, the reaction conditions were varied by examining catalysts such as CuBr, $CuCl_2{\cdot}2H_2O$, and $CuSO_4$ while keeping other parameters unchanged (**Table 2.2**, entry 1-3). Among the copper salts screened, $CuCl_2{\cdot}2H_2O$ provided best yields at 100 °C within three hours (**Table 2.2**, entry 5). Other parameter such as solvent and base were also varied to further improve the yield of **102a** and use of K_2CO_3 as base and DMF as solvents were found superior to other bases and solvent (**Table 2.2**, entry 6-8). Reaction was also tried at lower temperature (80 ˚C) but yield of **102a** was decreased (**Table 2.2**, entry 4). After extensive examinations of reaction conditions, we were gratified to find that 20 mol % of $CuCl_2.2H_2O$ and

K_2CO_3 (2.0 equiv.) gave clean reaction in *N*,*N*-dimethylformamide (DMF) at 100 °C without any external ligand to afford the tandem coupled product, 2-(2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (**102a**) in good yield (76%, **Table 2.2**, entry 5).

Table 2.2: Optimization of reaction conditions for the one-pot synthesis of **102a**[a]



57a **64a** **65** **102a**

Entry	Catalyst	Base	Solvent	Temperature	Yield (%)[b]
1	CuI	K_2CO_3	DMF	150	55
2	CuBr	K_2CO_3	DMF	150	49
3	$CuSO_4$	K_2CO_3	DMF	150	57
4	$CuCl_2.2H_2O$	K_2CO_3	DMF	80	66
5	**$CuCl_2.2H_2O$**	**K_2CO_3**	**DMF**	**100**	**76**
6	$CuCl_2.2H_2O$	NaOAc	DMF	150	69
7	$CuCl_2.2H_2O$	K_2CO_3	1,4-Dioxane	100	NR
8	$CuCl_2.2H_2O$	K_2CO_3	MeCN	150	37

[a]Reaction condition: **57a** (1.00 mmol), **64a** (1.20 mmol), **65** (1.20 mmol), catalyst (20 mol %), base (2.0 mmol), solvent (3.0 mL), for 3 h.
[b]Isolated yields.

The structure of **102a** was elucidated by analysis of ^{1}H NMR, ^{13}C NMR, and mass spectra. The characteristic singlets of C-3 position of imidazo[1,2-*a*]pyridine and C-5 position of triazole appeared at δ 6.93 ppm and δ 8.89 ppm respectively in ^{1}H NMR of **102a**. All protons and carbons were observed at their respective positions in ^{1}H and ^{13}C NMR of **102a**. Additionally,

HRMS (*m/z*) peak at 338.1405 for $[M+H]^+$ confirmed the structure of **102a**. The ^{1}H and ^{13}C NMR spectra of **102a** are shown in **figure 2.5**.

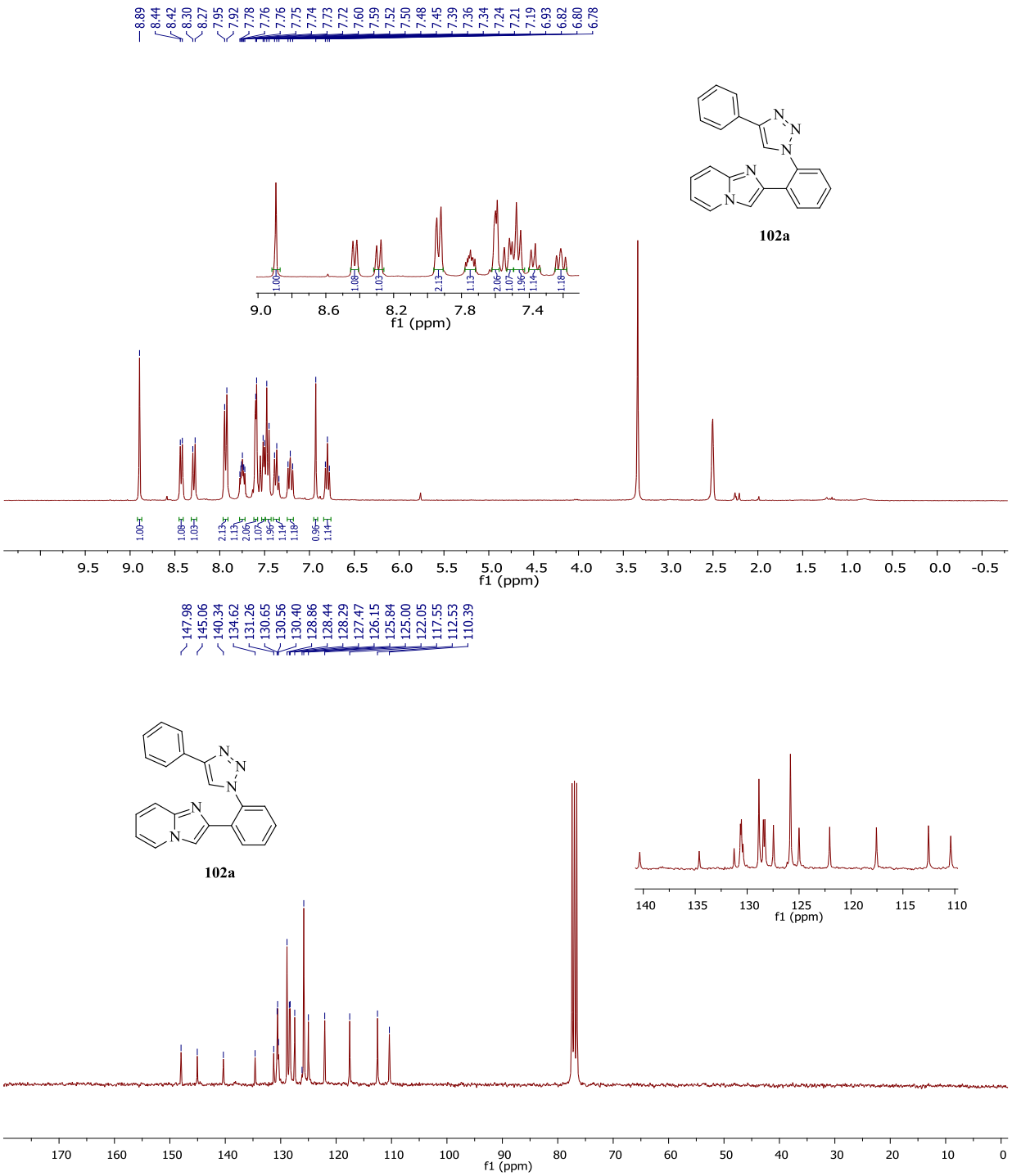
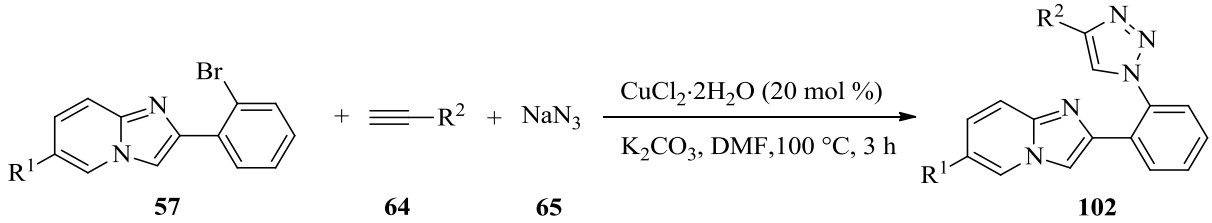


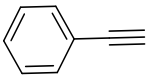
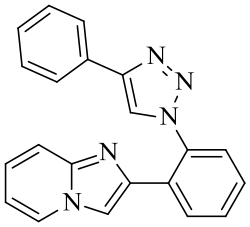
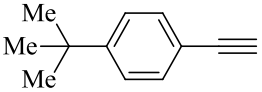
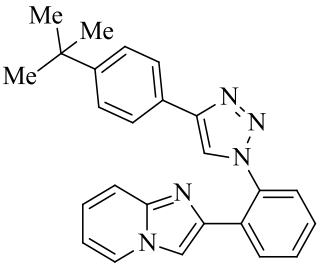
Figure 2.5 ^{1}H and ^{13}C NMR of 2-(2-(4-phenyl-*1H*-1,2,3-triazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (**102a**)

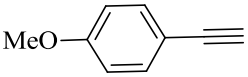
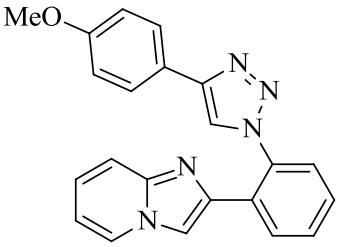
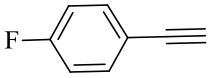
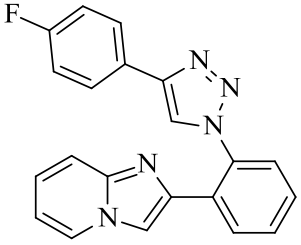
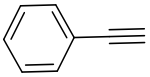
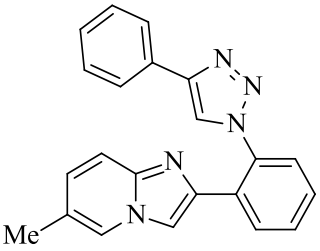
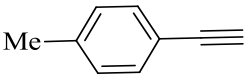
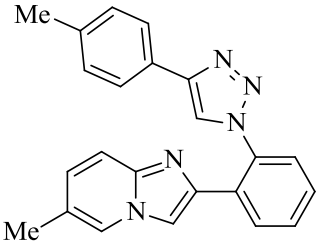
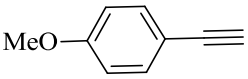
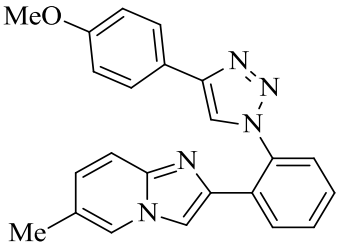
Next, we investigated substrate scope for the tandem synthesis of 1,2,3-triazole-substituted imidazo[1,2-*a*]pyridines (**Table 2.3**). In general, the scope of this reaction was found to be wide as phenylacetylenes with substitutions such as 4-^{t}Bu, 4-Me, 4-OMe, and 4-F gave the coupled products in good yields (**Table 2.3**, entries 2–7). With strong electron donating group on phenyl acetylene such as OMe, excellent yield was obtained (**Table 2.3**, entry 7). Aliphatic terminal alkynes such as pent-1-yne, hex-1-yne and hept-1-yne also efficiently participated in the reaction to form novel 1,2,3-triazolo-imidazo[1,2-*a*]pyridines in good yields (**Table 2.3**, entries 8–10). Bulkier group such as ^{t}Bu on phenylacetylene were also well tolerated the optimized reaction conditions to give the corresponding tandem product in good yield (**Table 2.3**, entry 2). Bromo substitution on the pyridine ring of imidazo[1,2-*a*]pyridines resulted the desired product in 82% yield which can be further used for several coupling reaction (**Table 2.3**, entry 11) .

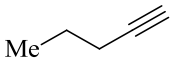
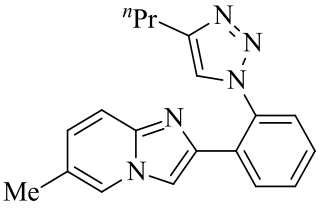
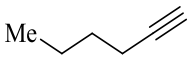
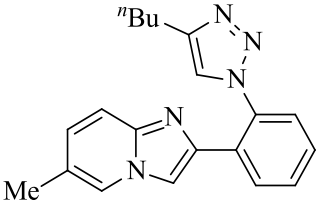
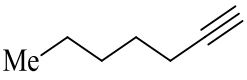
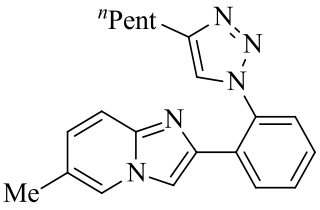
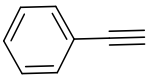
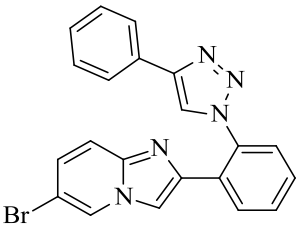
Table 2.3: Synthesis of 1,2,3-triazolo-imidazo[1,2-*a*]pyridines through tandem click–Ullmann C–N coupling reaction[a]



57 **64** **65** **102**

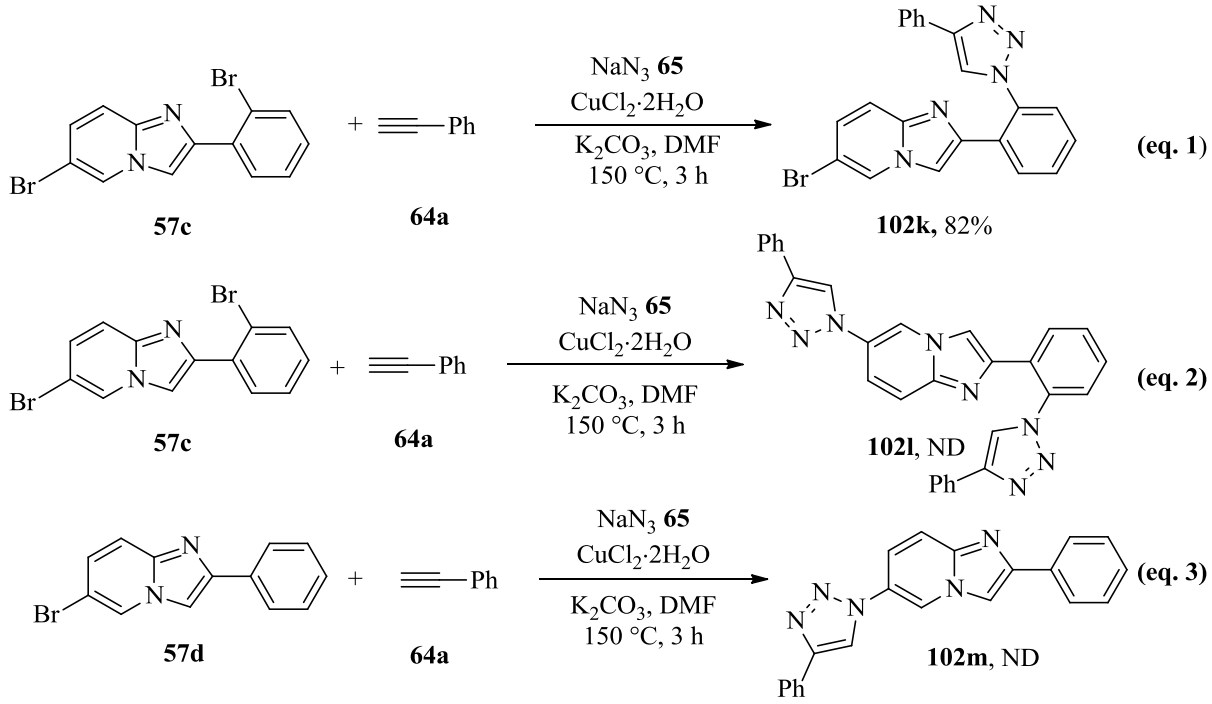
Entry	**57** (R^1)	**64**	Product	Yield (%)[b]
1	H		 **102a**	76
2	H		 **102b**	84

Entry	**57** (R^1)	**64**	Product		Yield (%)[b]
3	H			**102c**	75
4	H			**102d**	84
5	Me			**102e**	80
6	Me			**102f**	87
7	Me			**102g**	96

Entry	**57** (R^1)	**64**	Product		Yield (%)[b]
8	Me			**102h**	78
9	Me			**102i**	80
10	Me			**102j**	84
11	Br			**102k**	82

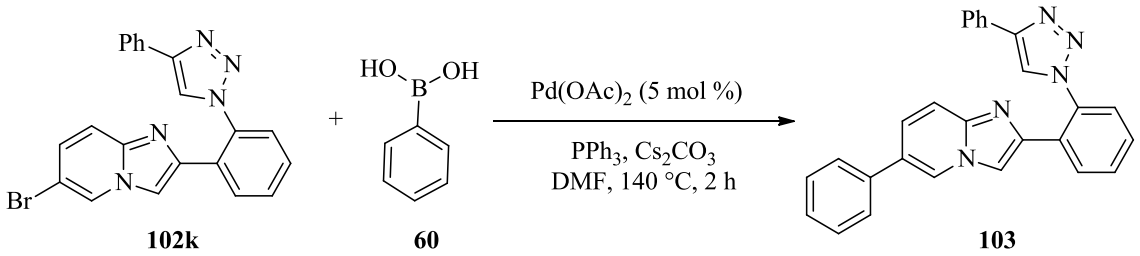
[a]Reaction conditions: **57** (1.0 mmol), **64** (1.2 mmol), **65** (1.2 mmol), $CuCl_2 \cdot 2H_2O$ (0.2 mmol), K_2CO_3 (2.0 mmol), DMF, 100 °C, 3 h,
[b]Isolated yield.

The regioselectivity of the coupling reaction was established by performing control experiments on 6-bromo-2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**57c**) and 6-bromo-2-phenylimidazo[1,2-*a*]pyridine (**57d**) (**Scheme 2.40**). When **57c** and **57d** were treated with phenylacetylene (**64a**) and sodium azide (**65**) under the optimized conditions, mono-coupled product 6-bromo-2-(2-(4-phenyl-*1H*-1,2,3-triazol-1-yl)phenyl)imidazo[1,2-*a*]pyridine (**102k**) was obtained in 82% yield from **57c** (**Scheme 2.40, eq. 1**) while **57d** did not react under these conditions (**Scheme 2.40, eq. 3**). It is worth mentioning that no double C–N coupled product (**102l**) was detected from **57c** in this reaction (**Scheme 2.40, eq. 2**).



Scheme 2.40: Control experiments for regioselective study

The synthesized product **102k** can be further functionalized by transition metal-catalyzed C–C or C–heteroatom cross-coupling reactions. To illustrate this application, we performed Suzuki reaction with **102k** (**Scheme 2.41**). When **102k** (1 mmol) was treated with phenylboronic acid (**60**) (1.1 mmol), $Pd(OAc)_2$ (5 mol %), Ph_3P (10 mol %), Cs_2CO_3 (1.5 mmol) in DMF at 140 °C for 2 hours, the corresponding cross-coupled products 6-phenyl-2-[2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl]imidazo[1,2-*a*]pyridine (**103**) was obtained in 77% yield (**Scheme 2.41**). The synthesized compound **103** was further confirmed by ^{1}H NMR, and ^{13}C NMR (**Figure 2.6**).



Scheme 2.41: Functionalization of triazole-substituted imidazo[1,2-*a*]pyridines *via* Suzuki reaction

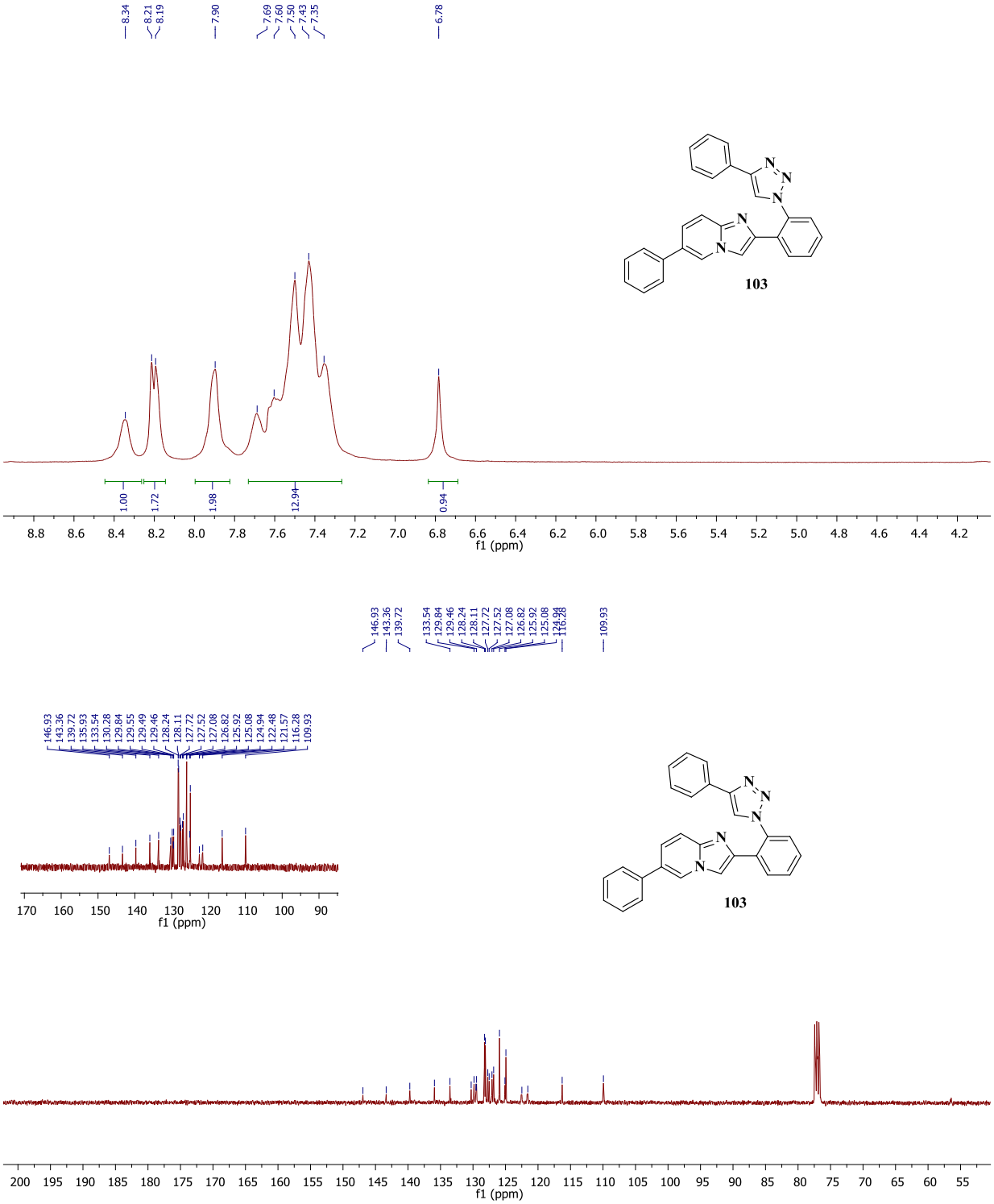
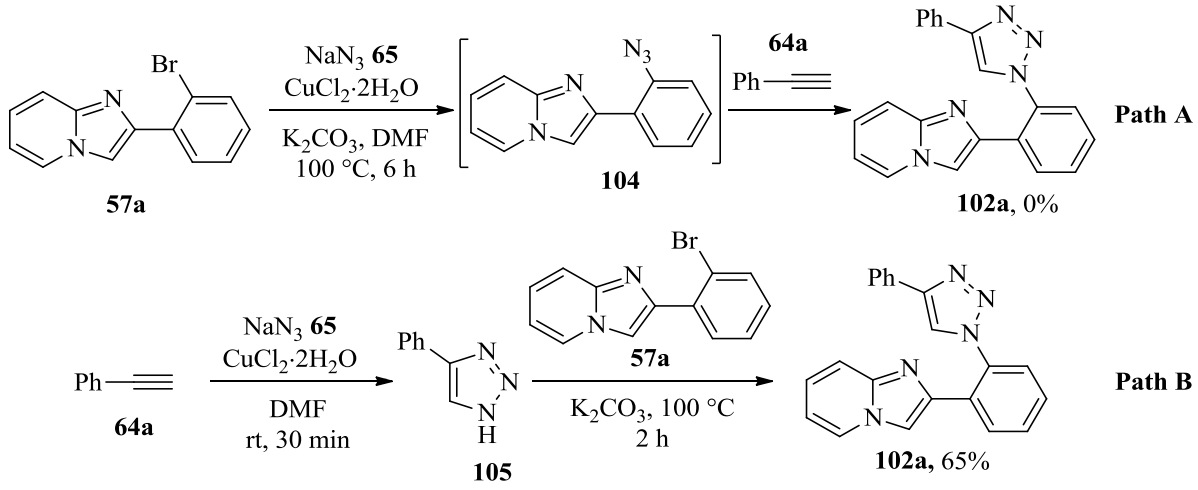


Figure 2.6: Representative ^{1}H NMR, ^{13}C NMR spectra of **103**

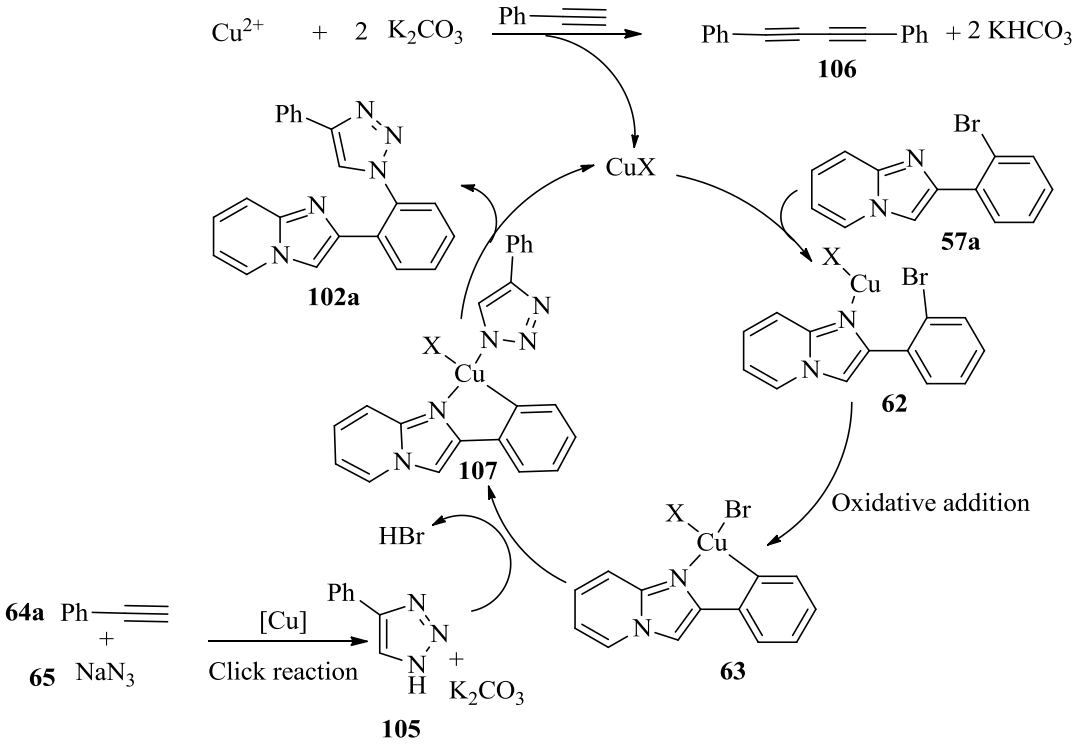
We further investigated the sequence of the tandem 1,2,3-triazole coupling as there are two possible pathways for this reaction (**path A and path B; Scheme 2.42**). To understand the sequence of reactions, **57a** was treated with sodium azide (**65**) in the absence of **64a** under the optimized reaction conditions with the expectation that azide would undergo substitution in the presence of copper to give 2-(2-azidophenyl)imidazo[1,2-*a*]pyridine (**104**) (**path A, Scheme 2.42**). However, no conversion was observed in the absence of **64a**, and **57a** was recovered quantitatively. In another experiment **64a** was treated with sodium azide (**65**) and Cu(II) in DMF to give 4-phenyl-1*H*-1,2,3-triazole (**105**) (**path B, Scheme 2.42**). After complete conversion as indicated by TLC, **57a** and K_2CO_3 were added and stirred at 100 °C for additional two hours. From this reaction **102a** was isolated in 65% yield, confirming that the sequence of reactions in this tandem protocol is as shown in **path B** (**Scheme 2.42**).



Scheme 2.42: Possible sequence of the reaction for synthesis of tandem 1,2,3-triazolo-imidazo[1,2-*a*]pyridine

Based on literature[62, 91, 102] precedent and control experiments, the proposed mechanism of the coupling reaction is shown in **scheme 2.43**. Reaction of phenylacetylene (**64a**) with sodium azide (**65**) in the presence of copper catalyst proceeds through CuACC (Click chemistry) and for further catalysis Cu(I) can be generated *in situ* from its precursor Cu(II) by reacting with phenylacetylene (**64a**) in homocoupling reaction (**Scheme 2.43**).[89, 109] It is proposed that the imidazo[1,2-*a*]pyridine–copper complex **62 (**through *N1*-nitrogen atom of imidazo[1,2-*a*]pyridine) on oxidative addition with C–Br bond leads to intermediate **63**. Subsequently, the

halide group on the copper can be exchanged with 4-phenyl-*1H*-1,2,3-triazole (**105**) in the presence of base to give intermediate **107** which, on reductive elimination, leads to the target molecule (**102a**) with the regeneration of copper catalyst (**Scheme 2.43**).



Scheme 2.43: Plausible mechanism for ligand-free, copper-catalyzed Ullmann-type C–N coupling

2.10. Conclusion

In summary, we have developed simple and practical protocol for regioselective synthesis of triazole-substituted imidazo[1,2-*a*]pyridines by ligand-free, copper-catalyzed Ullmann-type C–N coupling. The strategy has been used towards the tandem synthesis of 1,2,3-triazole-substituted imidazo[1,2-*a*]pyridines through *in situ* formation of 1,2,3-triazoles by the reaction between terminal alkynes and sodium azide followed by C–N bonding. Further functionalization of halosubstituted triazole-substituted imidazo[1,2-*a*]pyridines was achieved *via* Suzuki–Miyaura cross-coupling.

2.11. Experimental section

2.11.1. General

Melting points were determined in open capillary tubes on 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 (^{1}H NMR, ^{13}C NMR) determined on Bruker AV NMR 300 MHz, Bruker AV 400 MHz and Varian 500 MHz spectrometer. ^{13}C NMR spectra are fully decoupled. Chemical shifts were reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane (internal) as the standard. High resolution mass spectra (HRMS-ESI) were carried out using quadrupole time of-flight (Q-TOF) mass spectrometer (Applied Biosystem). The key starting materials (**57a-d**) was synthesized using our reported procedures.[8] All other chemicals were obtained from the commercial suppliers and used without further purification.

2.11.2. Experimental procedure for the synthesis of 2-(2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (102a):

A 10 mL RB flask was charged with 2-(2-bromophenyl)imidazo[1,2-*a*] pyridine (**57a)** (100 mg, 0.36 mmol), sodium azide (**65**) (28.5 mg, 0.439 mmol), phenylacetylene (**64a**) (44.8 mg, 0.439 mmol), $CuCl_2{\cdot}2H_2O$ (12.4 mg, 0.073 mmol), K_2CO_3 (101 mg, 0.732 mmol) and DMF (2.0 mL). The resulting solution was stirred at 100 °C in an oil bath for 3 h. On completion, the reaction mass was filtered through celite pad and washed with ethyl acetate. The filtrate was washed with water, dried over anhydrous sodium sulfate and concentrated under vacuum. The crude residue was purified by column chromatography (EtOAc: hexane, 3:2) to obtain product, 2-(2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)imidazo[1,2-*a*]pyridine (**102a**).

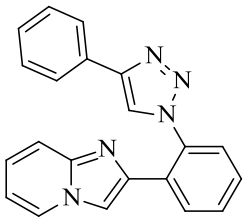
2.11.3. Procedure for the synthesis of compound 103

A 10 mL RB flask was charged with **102k** (1.0 mmol), phenylboronic acid (**60**) (1.2 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.1 mmol), Cs_2CO_3 (1.5 mmol) and DMF (2.0 mL). The resulting solution was stirred at 140 °C in an oil bath for 2 h under nitrogen atmosphere. On completion, the reaction mass was filtered through celite pad and washed with ethyl acetate. The filtrate was

washed with water, dried over anhydrous sodium sulfate and concentrated under vacuum. The crude residue was purified by column chromatography.

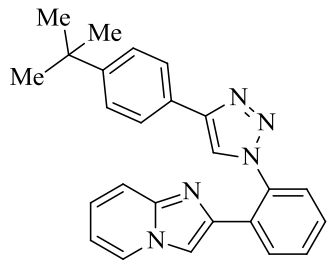
2.11.4. Physical and spectroscopic data of compound 102a-k and 103:

2-(2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (102a): Yield 76%;



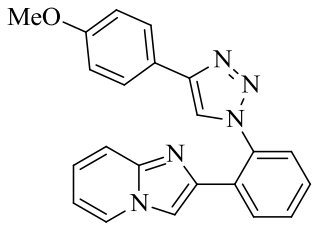
Off-white solid; mp 189-192 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.89 (s, ^{1}H), 8.43 (d, J = 6.8 Hz, 1H), 8.29 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 7.3 Hz, 2H), 7.79 – 7.69 (m, 1H), 7.59 (d, J = 3.1 Hz, 2H), 7.51 (d, J = 4.8 Hz, 1H), 7.46 (d, J = 7.7 Hz, 2H), 7.36 (t, J = 7.3 Hz, 1H), 7.27 – 7.15 (m, 1H), 6.93 (s, 1H), 6.80 (t, J = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 148.0, 145.1, 140.3, 134.6, 131.3, 130.7, 130.6, 130.4, 128.9, 128.4, 128.3, 127.5, 126.2, 125.8, 125.0, 122.1, 117.6, 112.5, 110.4; HRMS (*m/z*) calcd for $C_{21}H_{16}N_5$ 338.1400, found 338.1405 $[M + H]^+$.

2-(2-(4-(4-*tert*-Butylphenyl)-1*H*-1,2,3-triazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (102b):



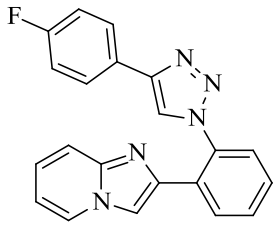
Yield 84%; Colourless solid; mp 168-171 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J = 6.3 Hz, 1H), 7.92 – 7.74 (m, 4H), 7.67 (s, 1H), 7.61 – 7.39 (m, 5H), 7.20 – 7.07 (m, 1H), 6.66 (d, J = 8.9 Hz, 2H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 148.0, 145.0, 140.1, 134.4, 131.3, 130.7, 130.4, 128.5, 127.6, 127.4, 125.9, 125.5, 125.1, 124.0, 121.8, 117.5, 112.6, 110.3, 34.1, 31.3; HRMS (*m/z*) calcd for $C_{25}H_{24}N_5$ 394.2026, found 394.1998 $[M + H]^+$.

2-(2-(4-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (102c):



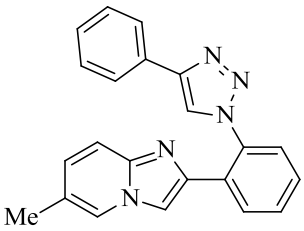
Yield 75%; Colourless solid; mp 185-186 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 8.34 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 6.8 Hz, 1H), 7.82 – 7.75 (m, 3H), 7.70 – 7.62 (m, 1H), 7.57 (d, J = 9.1 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.19 – 7.08 (m, 1H), 6.96 (d, J = 8.7 Hz, 2H), 6.72 – 6.60 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 159.7, 147.8, 144.9, 140.1, 134.4, 131.2, 130.6, 130.4, 128.4, 127.5, 127.0, 125.81 125.03 122.7, 121.14 117.41 114.3, 112.5, 110.2, 55.3; HRMS (*m/z*) calcd for $C_{22}H_{18}N_5O$ 368.1508, found 368.1496 $[M + H]^+$.

2-(2-(4-(4-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (102d):



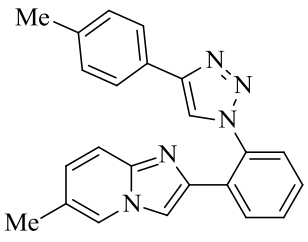
Yield 84%; Colourless solid; mp 175-177 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 8.0 Hz, 1H), 7.93 – 7.76 (m, 4H), 7.72 – 7.63 (m, 1H), 7.57 (d, J = 9.1 Hz, 1H), 7.50 (dt, J = 14.7, 4.4 Hz, 2H), 7.17 – 7.06 (m, 3H), 6.76 – 6.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8 (d, J_{C-F} = 247.8 Hz), 147.1, 145.1, 140.2, 134.3, 131.2, 130.8, 130.6, 128.5, 127.6 (d, J_{C-F} = 2.9 Hz), 127.5, 126.4(d, J_{C-F} = 3.2 Hz), 125.9, 125.2, 121.9, 117.5, 115.9 (d, J_{C-F} = 21.8 Hz), 112.6, 110.3; HRMS (*m/z*) calcd for $C_{21}H_{15}FN_5$ 356.1306, found 356.1329 $[M + H]^+$.

6-Methyl-2-(2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (102e):



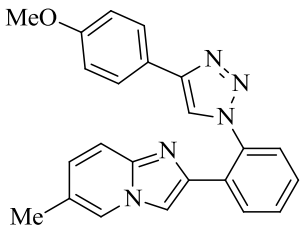
Yield 80%; Colourless solid; mp 230-234 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 7.9 Hz, 1H), 7.87 (t, J = 3.5 Hz, 3H), 7.69 – 7.60 (m, 2H), 7.50 – 7.40 (m, 5H), 7.34 (t, J = 7.2 Hz, 1H), 6.98 (d, J = 9.2 Hz, 1H), 6.56 (s, 1H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 144.1, 139.8, 134.3, 131.4, 130.7, 130.4, 130.2, 128.9, 128.4, 128.4, 128.3, 127.6, 125.8, 123.5, 122.3, 122.1, 116.7, 110.0, 18.0; HRMS (*m/z*) calcd for $C_{22}H_{18}N_5$ 352.1557, found 352.1570 $[M + H]^+$.

6-Methyl-2-(2-(4-*p*-tolyl-1*H*-1,2,3-triazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (102f):



Yield 87%; Colourless solid; mp 176-179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 – 8.26 (m, 1H), 7.83 (s, J = 11.2 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.69 – 7.58 (m, 1H), 7.48 (s, 1H), 7.45 (dd, J = 4.8, 2.6 Hz, 1H), 7.28 – 7.20 (m, 2H), 6.97 (dd, J = 9.2, 1.5 Hz, 1H), 6.54 (s, 1H), 2.38 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 144.1, 139.8, 138.3, 134.3, 131.4, 130.7, 130.3, 129.6, 128.4, 128.3, 127.6, 127.4, 125.7, 123.5, 122.2, 121.7, 116.7, 110.0, 21.3, 17.9; HRMS (*m/z*) calcd for $C_{23}H_{20}N_5$ 366.1713, found 366.1701 $[M + H]^+$.

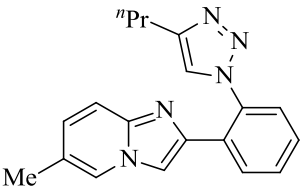
2-(2-(4-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)phenyl)-6-methyl*H*-imidazo[1,2-*a*]pyridine



(**102g**): Yield 96%; Colourless solid; 151-155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 8.4 Hz, 1H), 7.81 (s, J = 2.0 Hz, 1H), 7.78 (d, J = 1.1 Hz, 2H), 7.68 – 7.62 (m, 2H), 7.51 – 7.44 (m, 3H), 7.00 – 6.94 (m, 3H), 6.56 (s, J = 4.6 Hz, 1H), 3.84 (s, J = 5.9 Hz, 3H), 2.21 (s, J = 0.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 147.8, 144.1,

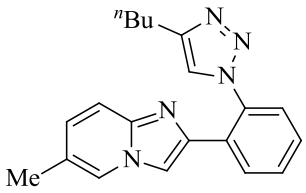
139.8, 134.3, 131.4, 130.7, 130.3, 128.4, 128.3, 127.6, 127.1, 123.5, 122.9, 122.2, 121.2, 116.7, 114.3, 110.0, 55.4, 18.0; HRMS (*m/z*) calcd for $C_{23}H_{20}N_5O$ 382.1662, found 382.1642 $[M + H]^+$.

6-Methyl-2-(2-(4-propyl-1*H*-1,2,3-triazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (102h):



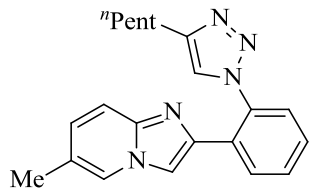
Yield 78%; Off-white solid; mp 115-119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 11.0, 3.2 Hz, 2H), 7.53 – 7.39 (m, 3H), 7.35 (s, 1H), 7.00 (dd, J = 9.2, 1.3 Hz, 1H), 6.40 (s, 1H), 2.76 (t, J = 7.5 Hz, 2H), 2.26 (s, 3H), 1.79 – 1.63 (m, 2H), 0.93 (q, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 144.1, 139.9, 134.6, 131.3, 130.5, 130.1, 128.3, 128.2, 127.5, 123.3, 123.3, 122.3, 116.8, 110.0, 27.5, 22.7, 18.0, 13.6; HRMS (*m/z*) calcd for $C_{19}H_{20}N_5$ 318.1713, found 318.1702 $[M + H]^+$.

2-(2-(4-Butyl-1*H*-1,2,3-triazol-1-yl)phenyl)-6-methyl*H*-imidazo[1,2-*a*]pyridine (102i): Yield



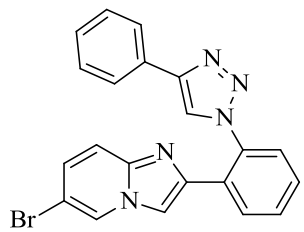
80%; Off-white solid; mp 121-123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 8.0 Hz, 1H), 7.68 – 7.54 (m, 2H), 7.53 – 7.39 (m, 3H), 7.33 (s, 1H), 7.00 (d, J = 9.2 Hz, 1H), 6.39 (s, 1H), 2.79 (t, J = 7.5 Hz, 2H), 2.26 (s, 3H), 1.73 – 1.61 (m, 2H), 1.42 – 1.27 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 144.0, 139.9, 138.8, 134.6, 131.4, 130.5, 130.1, 128.2, 127.5, 123.3, 123.2, 122.3, 116.8, 109.9, 31.6, 25.2, 22.1, 18.0, 13.8; HRMS (*m/z*) calcd for $C_{20}H_{22}N_5$ 332.1870, found 332.1840 $[M + H]^+$.

6-Methyl-2-(2-(4-pentyl-1*H*-1,2,3-triazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (102j):



Yield 84%; Colourless solid; mp 119-121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 8.1 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.50 – 7.38 (m, 3H), 7.33 (s, 1H), 7.00 (dd, J = 9.2, 1.4 Hz, 1H), 6.39 (s, 1H), 2.78 (t, J = 7.5 Hz, 2H), 2.26 (s, 3H), 1.78 – 1.62 (m, 2H), 1.38 – 1.26 (m, 4H), 0.85 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 144.0, 139.9, 134.6, 131.5, 130.5, 130.1, 128.2, 128.2, 127.5, 123.3, 123.2, 122.3, 116.8, 109.9, 31.2, 29.2, 25.5, 22.4, 18.0, 13.9; HRMS (*m/z*) calcd for $C_{21}H_{24}N_5$ 346.2026, found 346.2015 $[M + H]^+$.

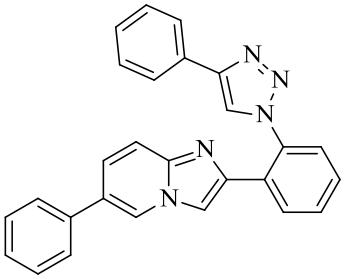
6-Bromo-2-(2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (102k):



Yield 82%; Colourless solid; mp 228-230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 7.8 Hz, 1H), 8.01 (s, 1H), 7.93 – 7.83 (m, 3H), 7.67 (t, J = 7.3 Hz, 1H), 7.56 – 7.41 (m, 5H), 7.40 – 7.32 (m, 1H), 7.19 (d, J = 9.5 Hz, 1H), 6.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1,

143.5, 141.0, 134.4, 130.8, 130.5, 130.1, 129.0, 128.8, 128.7, 128.5, 127.7, 125.8, 125.8, 122.0, 118.1, 110.4, 107.3; HRMS (*m/z*) calcd for $C_{21}H_{15}BrN_5$ 416.0505, found 416.0527 $[M + H]^+$ and 418.0513 $[M + H + 2]^+$.

6-Phenyl-2-(2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)phenyl)*H*-imidazo[1,2-*a*]pyridine (103): Yield



77%; Colourless solid; mp 90-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.20 (d, J = 7.9 Hz, 2H), 7.94 – 7.88 (m, 2H), 7.74 – 7.29 (m, 13H), 6.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 143.4, 139.7, 135.9, 133.5, 130.3, 129.8, 129.6, 129.5, 128.2, 128.1, 127.7, 127.5, 127.1, 126.8, 125.9, 125.1, 124.9, 122.5, 121.7, 121.6, 116.3, 109.9. HRMS (*m/z*) calcd for $C_{27}H_{20}N_5$ 414.1713, found 414.1731 $[M + H]^+$.

2.12. References

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