PART III

Section A

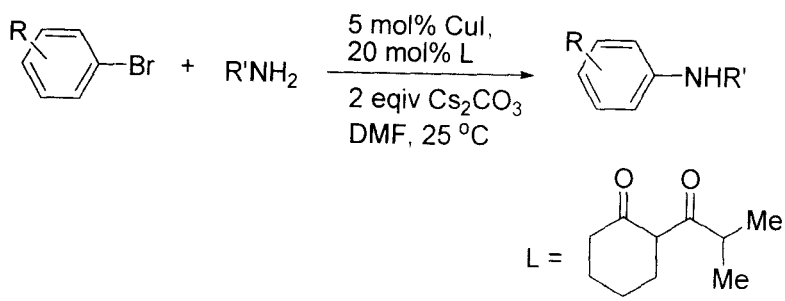
"Role of copper in catalyzing aryl and heteroaryl -Nitrogen (or -Oxygen) bond formation under ligand-free and solvent-free conditions"

III.A.1. Introduction

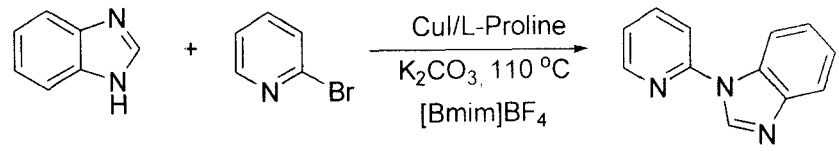
The formation of carbon-heteroatom bonds using metal catalysis is emerging as one of the most significant classes of cross-coupling reactions. In recognition of their widespread importance, over the years, transition-metal-catalyzed cross-coupling reactions of aryl halides with N– and O– containing nucleophilic compounds have emerged as the most prominent synthetic methods for the formation of these bonds.[1] The copper-catalyzed Ullmann-Goldberg coupling, a well known reaction for the introduction of amine functionality using aromatic halides, proceeds under severe reaction conditions such as heating at high temperatures without a solvent.[2] While milder reactions using transmetallating agents such as triarylbismuth,[3] aryllead triacetates,[4] arylboronic acids,[5] and hypervalent aryl siloxanes[6] have been developed, the utility of these variants is limited since the preparation of highly functionalized substrates usually requires multistep sequences. Other noteworthy reactions include the aryl coupling reactions based on Pd(0) catalysts such as the Buchwald-Hartwig coupling to form aryl-nitrogen and aryl-oxygen bonds.[7] Pd(0)-catalyzed Buchwald-Hartwig hetero cross coupling reactions have been successful by using suitable ligand based palladium complexes, preferably with bis-phosphine ligands. Although these reactions have largely supplanted the copper-mediated reactions like the Ullmann coupling and the Stephens-Castro coupling,[8] yet copper-mediated couplings are still the reactions of choice for the large scale industrial preparation of these bonds.

A growing number of papers have therefore focused on the deliberate use of ligands to facilitate copper-catalyzed aryl-nitrogen and aryl-oxygen bond forming reactions.[9] Among a variety of bidentet chelating ligands used, the N,N-, O,O-, and N,O-chelators appear to be in the majority of the copper-catalyzed coupling reaction protocols (Scheme 1-3).

Scheme 1

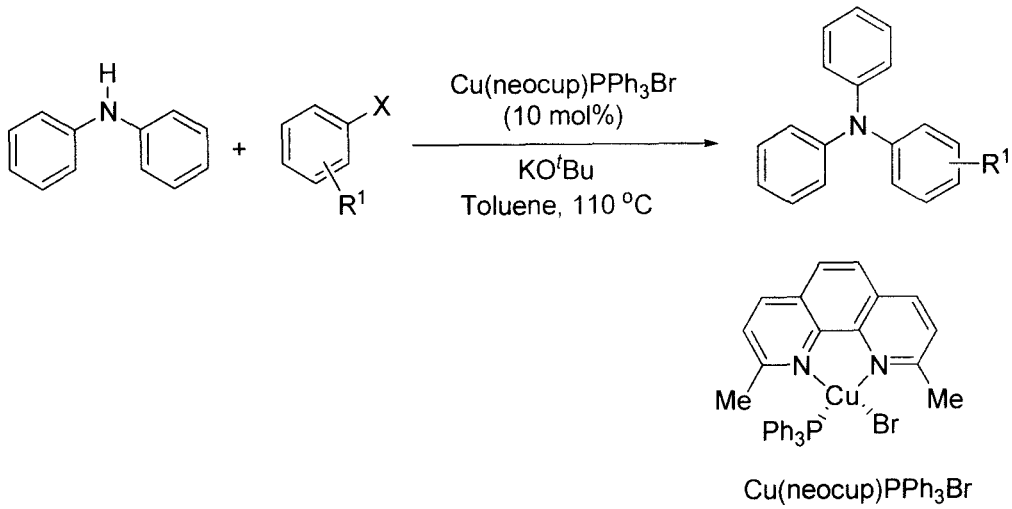


Scheme 2



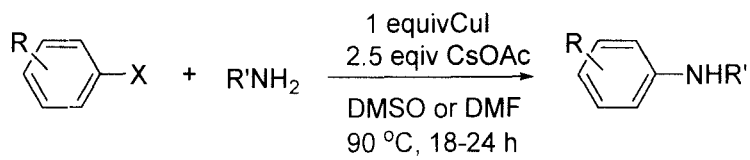
Reaction conditions: CuI (0.3-1.2 mmol), base (5.4 mmol), Proline (0.6-2.4 mmol), benzimidazole (3 mmol), 2-bromopyridine (5.4 mmol), [Bmim]BF_4 (3 ml)

Scheme 3



Cu(neocup)PPh_3Br

Scheme 4

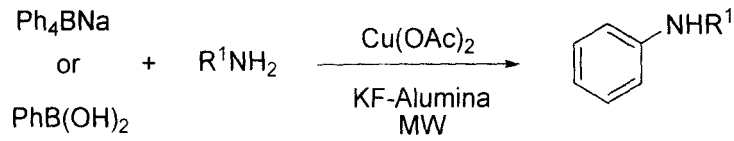


Buchwald reported a highly selective Cu-catalyzed C-N coupling reaction of aryl and heteroaryl halides (Scheme 4) in presence of CuI (5 mol%) and 1,3-diketone as the ligand (20 mol%), Venkataraman reported the use of neocuproin-based copper catalyst, (Scheme 3)[10] Fukuyama developed a ligand-free intermolecular amination of aryl iodides (Scheme 4) using stoichiometric amounts of CuI.[11] Thus, either catalytic copper salts in presence of suitable ligands or stoichiometric use of CuI at higher temperature remain the major choice for C-N coupling reaction of aryl and heteroaryl halides. Besides, such protocols were not examined for C-O coupling reactions. The development of a method with very specific ligand/metal combinations is therefore currently needed.

III.A.2. Present work: Results and Discussions

An experimentally simple microwave-assisted solvent-free *N*-arylation of primary amines with sodium tetraphenylborate or arylboronic acid has been reported previously from our laboratory (Scheme 5).[12b] The reaction promoted by cupric acetate is selective for mono-*N*-alkylation and tolerant of a variety of functional groups.

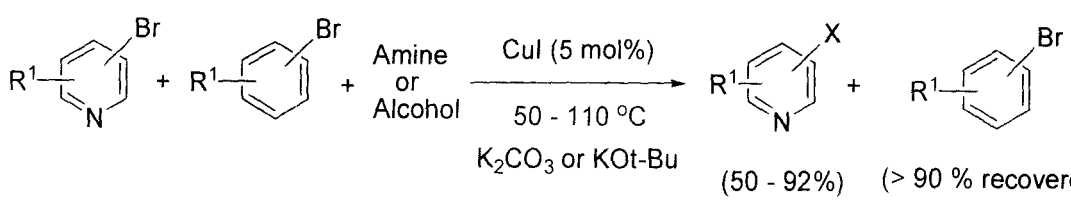
Scheme 5



R^1 = Alkyl or Aryl

In conjunction with our interest in Pd- and Cu- catalyzed cross coupling reactions coupled with the development of environmentally benign methodology,[12] Cu(I)-catalyzed ligand-free C-N (and C-O) coupling reactions under heterogeneous basic conditions were investigated. Our observations showed that the heteroaryl bromides (such as, pyridine, quinoline, pyrimidine and thiophene) can be coupled with amines selectively under Cu(I)-catalyzed ligand-free conditions, while bromoarenes remained entirely unproductive (Scheme 6). Moreover, 2-bromopyridines can be aminated with secondary amines even in the absence of any copper catalyst. To the best of our knowledge, such observations and selectivity, are not known in the literature and might be useful for selective amination in complex molecules with both types of aromatic halides. Indeed, a mixture of 4-bromoanisole and 2-bromopyridine when subjected to amination using pyrrolidine, only the corresponding aminopyridine was isolated along with the unreacted 4-bromoanisole (>90% recovered from the product mixture). We studied several other reactions where clear selectivity between aryl bromide and heteroaryl bromide has been observed. Besides, the reaction was further extended to C-O bond-forming reactions under similar conditions.

Scheme 6



(50 - 92%) (> 90 % recovered)

X = NHR, NR_2, OR

Initial experiments were carried out with the amination of 2-bromopyridine. When a mixture of 2-bromopyridine and an amine in the ratio of 1:3 was heated in the presence

of CuI (5 mol%) and base (1 equiv.) at 80-90 °C for 2-7 hr, the corresponding 2-aminopyridine was obtained in 65-92% yield. Such amination process was then extended successfully to 2,6- and 2,5-dibromopyridines affording the corresponding 2-amino-bromopyridines in good to excellent yields. Aminations of 3-bromo-heteroarenes with both primary and secondary amines using 5 mol% CuI were found to be less productive furnishing the desired product in 55-60% yield. It is interesting to observe that while 2-bromopyridines can also afford the corresponding aminated product in the absence of Cu-catalyst in almost comparable yields, 3-bromopyridines require presence of Cu-catalyst for amination. Furthermore, facile amination was observed with secondary amines as compared to its primary counterpart. Diazoles as the source of amine afforded the desired products in the range of 50-66% yields. Since the diazoles are solid compounds, a small amount of DMF was used in these cases. The results are summarized in Table 1.

Table 1

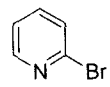
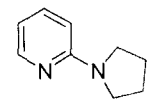
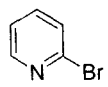
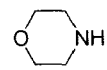
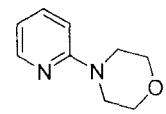
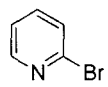
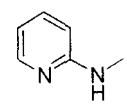
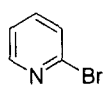
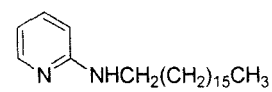
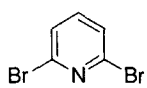
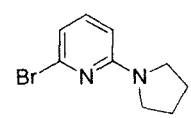
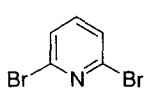
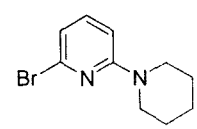
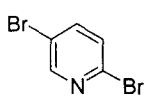
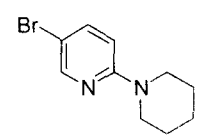
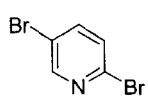
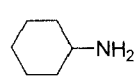
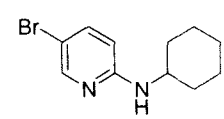
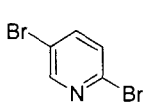
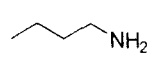
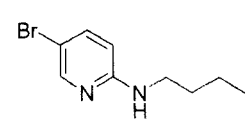
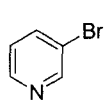
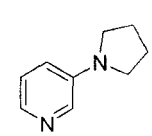
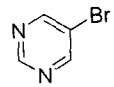
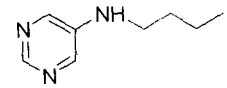
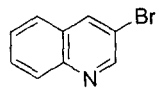
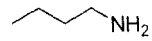
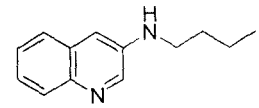
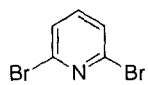
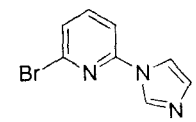
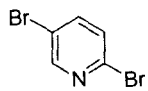
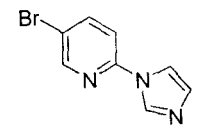
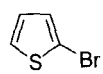
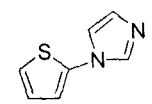
Entry No.	Bromopyridine	Amine	Condition[a] Temp./ Time	Product	% of Yield[b]
1			90 °C / 2 h		92 (85)
2			80 °C / 7 h		83 (80)
3		CH_3NH_2. HCl	80 °C / 5 h		65
4		$NH_2CH_2(CH_2)_{15}CH_3$	80 °C / 6 h		74
5			50 °C / 0.5 h		90 (82)
6			50 °C / 1 h		88 (81)
7			80 °C / 2 h		92 (83)
8			90 °C / 4 h		85 (< 5)
9			80 °C / 5 h		91 (10)
10			90 °C / 4 h		60 (< 5)

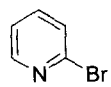
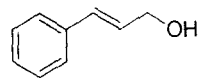
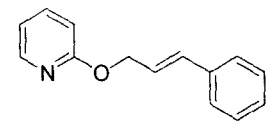
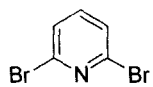
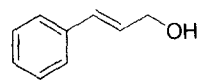
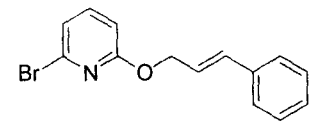
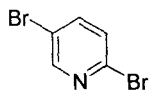
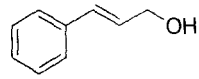
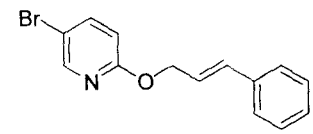
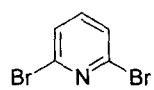
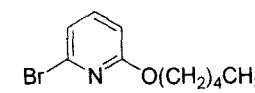
Table 1Continued .....

Entry No.	Bromopyridine	Amine	Condition[a] Temp./ Time	Product	% of Yield[b]
11			90 °C/ 6h		58 (< 5)
12			80 °C/ 8h		55
13			110 °C / 11 h		66
14			110 °C / 11 h		50
15			110 °C / 11 h		61

[a] Halopyridine: Amine is 1: 3, CuI (5 mol%) and 1 equivalent of base (K_2CO_3) are used for these reactions.
[b] Yields in the parenthesis correspond to conditions without CuI.

There has been a resurgence of interest in Cu mediated C-O ether bond forming reactions beyond that of the classical Ullmann ether synthesis. The hetero cross-coupling has been extensively studied with several organometalloids such as organo-Bi,[13] –Sn[14] and –B[12b,15] compounds. An obvious limitation of these methods is that stoichiometric amount of Cu salts is required. Extending our protocols to C-O bond-forming reactions was resulted with varied success. While phenols were not reactive due to poor nucleophilicity of the phenoxide,[16] cinnamyl alcohol and amyl alcohol could react efficiently with bromopyridines producing direct heteroaryl-O compounds. The results are presented in Table 2.

Table 2

Entry No.	Bromopyridine	Alcohol or Thiophenol	Condition[a] Temp./ Time	Product	% of Yield
1			90 °C / 1 h		85
2			90 °C / 1 h		80
3			90 °C / 1 h		80
4		$CH_3(CH_2)_3CH_2OH$	90 °C / 5h		62

[a] Halopyridine: Alcohol (1: 3), CuI (5 mol%) and 1 equivalent of base (KO^tBu) are used for these reactions.

The relation of specific requisite of ligand/metal combination with reference to substrates might be interpreted on the basis of present studies. In Ullmann type of coupling, there is compelling evidence for the involvement of arylcopper species as an intermediate, which may be stabilized in the form of a complex in presence of suitable ligands (also solvent molecules).[17] Aryl iodides can be aminated under ligand-free conditions in presence of stoichiometric Cu(I) salts.[11] Such process might involve formation of arylcopper intermediate followed by amination. On the other hand, heteroaryl bromides, in particular N-containing aryl bromides, can be aminated either in presence or in absence of Cu(I) catalyst. Amination of 2-bromopyridine with pyrrolidine at different temperature/time (rt/24 hr, 50 °C/4 hr and 90 °C/2 hr) in absence or in presence of catalytic CuI (5 mol%) has not resulted in appreciable change in the yields of the aminated product. The present studies thus led to suggest that 2-bromopyridines can be aminated possibly as a result of simple nucleophilic addition reaction (i.e. two-step addition/elimination) without involvement of the copper salts, while amination of 3-bromopyridines occurs in presence of catalytic Cu(I) salts indicating that the metal is perhaps acting as a Lewis acid and not activating the aryl-bromide bond directly.[18] On the other hand, aryl bromides (iodide) undergo amination in presence of stoichiometric amount of CuI.[11]

III.A.3. Conclusion

The present studies have clearly demonstrated the role of copper in catalyzing or mediating the formation of C-N (or C-O) bonds in amination (or etherification) of heteroaryl or aryl halides. Deliberate use of suitable ligand and copper salts could be avoided depending on the nature of the substrate. Moreover, the amination and etherification procedures are performed in air with no adverse effects on the yields of the reactions. The selectivity, mild, operationally simple protocols are attractive and might be useful in complex molecules containing both types of aromatic halides. Besides, ligand and solvent-free conditions satisfy the viewpoint of ecology and economy.

III.A.4. Experimental Procedure

III.A.4.1. Representative Procedure for Cu(I)-Catalyzed Amination

To a mixture of 2–bromopyridine (158 mg, 1mmol), CuI (9.5 mg, 5 mol%) and K_2CO_3 (138 mg, 1 mmol), pyrrolidine (213 mg, 3 mmol) was added and the final mixture was placed on a pre-heated oil- bath at 90 °C for 2 hr. After cooling to RT the reaction-mixture was extracted with dichloromethane (3 x 20 mL), dry packed with silica gel and then transferred on a column of silica gel. Elution with ethyl acetate/light petroleum (1:19) afforded the 2–(pyrrolidin–1–yl)pyridine as colourless oil (138 mg, 92%). IR (Film)-1597, 1555, 1501, 1485, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.06 (dd, 1H, J = 5.1 & 1.2 Hz), 7.33 (ddd, 1H, J = 8.7, 7.2 & 1.8 Hz), 6.41 (ddd, 1H, J = 6.3, 5.4 & 1 Hz), 6.25 (d, 1H, J = 8.7 Hz), 3.36 (t, 4H, J = 6.6 Hz), 1.91 (t, 4H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.1, 148.0, 136.8, 110.9, 106.4, 46.5, 25.4.

Reaction of 2–bromopyridine with pyrrolidine under similar conditions without using CuI afforded the desired 2–(pyrrolidin–1–yl)pyridine in 85% yield.

III.A.4.2. Representative procedure for Cu(I)-Catalyzed Etherification

To a mixture of 2–bromopyridine (158 mg, 1mmol), CuI (9.5 mg, 5 mol%) and $KOBu^t$ (112 mg, 1 mmol), cinnamyl alcohol (360 mg, 3 mmol) was added and the final mixture was placed on a pre-heated oil- bath at 90 °C for 1 hr. After cooling to RT the reaction-mixture was extracted with dichloromethane (3 x 20 mL), dry packed with silica gel and then transferred on a column of silica gel.

III.A.5. Spectral Data

Table 1: Entry 1: 2-(Pyrrolidin-1-yl)pyridine

Reaction Temp: 90 °C, Time: 2 h, Yield: 92% (obtained as liquid).

IR (neat): ν_{max} 1597, 1555, 1501, 1485, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.06 (dd, 1H, *J* = 5.1 & 1.2 Hz), 7.33 (ddd, 1H, *J* = 8.7, 7.2 & 1.8 Hz), 6.41 (ddd, 1H, *J* = 6.3, 5.4 & 1 Hz), 6.25 (d, 1H, *J* = 8.7 Hz), 3.36 (t, 4H, J = 6.6 Hz), 1.91 (t, 4H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 157.2, 148.1, 136.9, 111.0, 106.5, 46.6, 25.5.

Entry 2: 4-(Pyridin-2-yl)morpholine[12d]

Reaction Temp: 80 °C, Time: 7 h, Yield: 83% (obtained as liquid)

IR (neat): ν_{max} 2916, 2858, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.12 (dd, 1H, *J* = 4.8 & 1.2 Hz), 7.41 (ddd, 1H, *J* = 8.7, 5.1 & 1.8 Hz), 6.56 (m, 2H), 3.73 (t, 4H, *J* = 5.1 Hz), 3.41 (t, 4H, *J* = 5.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 159.5, 147.8, 137.4, 113.7, 106.8, 66.6, 45.5.

Entry 3: *N*-Methylpyridin-2-amine

Reaction Temp: 80 °C, Time: 5 h, Yield: 65% (obtained as liquid)

IR (neat): ν_{max} 2920, 2846, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.1 (s, 1H), 7.43 (dd, 1H, *J* = 8.4 & 1.2 Hz), 6.59-6.39 (m, 2H), 4.80 (br s, 1H), 2.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 159.5, 148.0, 137.4, 112.7, 106.1, 28.9.

Entry 4: *N*-Heptadecylpyridin-2-amine

Reaction Temp: 80 °C, Time: 6 h, Yield: 74%; mp. 61-63 °C (recrystallised from ether)

IR (neat): ν_{max} 2920, 2846, 2360, 1484 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.05 (br s, 1H), 7.44-7.38 (m, 1H), 6.56-6.52(m, 1H), 6.37 (d, 1H, *J* = 8.4 Hz), 3.62 (t, 1H, *J* = 6.6 Hz), 3.22 (t, 2H, *J* = 6.9 Hz), 1.64-1.56 (m, 3H), 1.38-1.19 (m, 24H), 0.879 (t, 6H, *J* = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 158.9, 148.0, 137.3, 113.1, 109.9, 62.9, 42.3, 32.9, 31.9, 29.7, 29.68, 29.62, 29.6, 29.5, 29.4, 29.3, 27.1, 25.8, 22.7, 14.15.

Entry 5: 2-Bromo-6-(pyrrolidin-1-yl)pyridine[12d]

Reaction Temp: 50 °C, Time: 0.5 h, Yield: 90%; mp. 88 °C (recrystallised from ether).

IR (Nujol): ν_{max} 2976, 1589, 1535, 1493, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.13 (dd, 1H, *J* = 8.4 & 7.5 Hz), 6.55 (d, 1H, *J* = 7.5 Hz), 6.14 (d, 1H, *J* = 8.4 Hz), 3.33 (t, 4H, *J* = 6.6 Hz), 1.90 (t, 4H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 157.2, 140.4, 138.7, 113.7, 104.5, 46.7, 25.5.

Entry 6: 2-Bromo-6-(piperidin-1-yl)pyridine[12a]

Reaction Temp: 50 °C, Time: 1 h, Yield: 88% (obtained as liquid)

IR (neat): ν_{max} 2931, 2854, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ =7.22 (d, 1H, *J* = 8.4 & 7.5 Hz), 7.65 (d, 1H, *J* = 7.5 Hz), 7.48 (d, 1H, *J* = 8.4 Hz), 3.50 (t, 4H, *J* = 6Hz), 1.62-1.57 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 159.3, 140.1, 139.3, 114.9, 104.7, 45.9, 25.4, 24.6.

Entry 7: 5-Bromo-2-(piperidin-1-yl)pyridine

Reaction Temp: 80 °C, Time: 2 h, Yield: 92% (obtained as liquid)

IR (neat): ν_{max} 2931, 2851, 1582, 1411 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.07 (d, 1H, *J* = 2.4 Hz), 7.38 (dd, 1H, *J* = 9.0 & 2.7 Hz), 6.43 (d, 1H, *J* = 9.3 Hz), 3.41-3.39 (m, 4H), 1.54-1.51 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 157.9, 148.3, 139.3, 108.6, 106.4, 46.2, 25.2, 24.5.

Entry 8: 5-Bromo-N-cyclohexylpyridin-2-amine

Reaction Temp: 90 °C, Time: 4 h, Yield: 85%; mp. 64-65 °C (recrystallised from ether).

IR (nujol): ν_{max} 2931, 2854, 1539 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.89 (d, 1H, *J* = 2.4 Hz), 7.25 (dd, 1H, *J* = 9.0 & 2.4 Hz), 6.08 (d, 1H, *J* = 9.0 Hz), 4.42 (br s, 1H), 3.36-3.24 (m, 1H), 1.85-1.80 (m, 2H), 1.57-1.38 (m, 8H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 146.6, 132.4, 115.7, 115.5, 51.0, 33.4, 23.0, 27.9.

Entry 9: 5-Bromo-N-butylpyridin-2-amine

Reaction Temp: 80 °C, Time: 5 h, Yield: 91% (obtained as liquid).

IR (neat): ν_{max} 2920, 2850, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.08 (d, 1H, *J* = 2.4 Hz), 7.46 (dd, 1H, *J* = 9.0 & 2.4 Hz), 7.28 (d, 1H, *J* = 9.0 Hz), 4.60 (br s, 1H), 3.25-3.18 (m, 2H), 1.61-1.54 (m, 2H), 1.45-1.37 (m, 2H), 0.95 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 157.4, 148.5, 139.7, 107.8, 106.5, 42.0, 31.4, 20.1, 13.8.

Entry 10: 3-(Pyrrolidin-1-yl)pyridine

Reaction Temp: 90 °C, Time: 4 h, Yield: 60% (obtained as liquid).

IR (neat): ν_{max} 2920, 2850, 2360, 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.86 (br s, 2H), 7.03 (br s, 1H), 6.71 (d, 1H, *J* = 8.4 Hz), 3.20 (t, 4H, *J* = 6.6 Hz), 1.93 (t, 4H, *J* = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 143.8, 136.7, 134.2, 123.4, 117.5, 47.1, 25.2.

Entry 11: *N*-Butylpyrimidin-5-amine

Reaction Temp: 90 °C, Time: 6 h, Yield: 58% (obtained as liquid)

IR (neat): ν_{max} 2924, 2875, 2360, 1550 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.57 (s, 1H), 8.11 (s, 2H), 3.15 (t, 2H, J = 7.2 Hz), 1.69-1.59 (m, 2H), 1.50-1.39 (m, 2H), 0.97 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 147.9, 142.0, 140.5, 42.7, 31.1, 20.0, 13.7.

Entry 12: *N*-Butylquinolin-3-amine

Reaction Temp: 80 °C, Time: 8 h, Yield: 55% (obtained as liquid)

IR (neat): ν_{max} 2924, 2850, 2360, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.43 (s, 1H), 7.95-7.92 (m, 1H), 7.63-7.58 (m, 1H), 7.42-7.35 (m, 2H), 6.98 (d, 1H, J = 2.7 Hz), 4.01 (br s, 1H), 3.18 (t, 2H, J = 6.9 Hz), 1.72-1.61 (m, 2H), 1.57-1.48 (m, 2H), 0.98 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 143.3, 141.8, 129.6, 128.8, 126.8, 125.8, 124.6, 109.7, 43.3, 31.1, 20.3, 13.8.

Entry 13: 2-Bromo-6-(1H-imidazol-1-yl)pyridine

Reaction Temp: 110 °C, Time: 11 h, Yield: 66%, mp. 92-94 °C (recrystallized from ether).

IR (nujol): ν_{max} 2924, 2875, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.12 (s, 1H), 7.47 (dd, 1H, J = 8.1 & 7.8 Hz), 7.41 (s, 1H), 7.21 (dd, 1H, J = 7.8 & 0.6 Hz), 7.11 (dd, 1H, J = 8.1 & 0.6 Hz), 6.98 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 148.7, 140.9, 140.8, 134.9, 132.9, 125.9, 116.0, 110.5.

Entry 14: 5-Bromo-2-(1H-imidazol-1-yl)pyridine

Reaction Temp: 110 °C, Time: 11 h, Yield: 50%, mp. 138-139 °C (recrystallized from ether).

IR (nujol): ν_{max} 2924, 2875, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.41 (dd, 1H, J = 2.4 & 0.6 Hz), 8.23 (s, 1H), 7.83 (dd, 1H, J = 8.4 & 2.1 Hz), 7.52 (s, 1H), 7.19 (dd, 1H, J = 8.4 & 0.6 Hz), 7.11 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 149.9, 147.5, 141.3, 134.7, 130.8, 117.5, 115.9, 113.2.

Entry 15: 1-(Thiophen-2-yl)-1H-imidazole

Reaction Temp: 110 °C, Time: 11 h, Yield: 61% (obtained as liquid)

IR (neat): ν_{max} 2924, 2875, 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.62 (s, 1H), 7.07 (s, 1H), 7.03-7.00 (m, 2H), 6.88-6.84 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 139.3, 137.0, 130.2, 126.3, 121.8, 120.2, 119.0.

Table 2: Entry 1: 2-(Cinnamyloxy)pyridine

Reaction Temp: 90 °C, Time: 1 h, Yield: 85% (obtained as liquid)

IR (neat): ν_{max} 2924, 2875, 1500, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.75-7.60 (m, 2H), 7.32-7.13 (m, 5H), 6.69-6.60 (m, 2H), 6.39-6.24 (m, 2H), 4.95 (d, 2H, J = 5.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 164.6, 147.1, 138.6, 135.4, 129.9, 128.7, 128.3, 126.2, 123.7, 110.9, 110.5, 71.8.

Entry2: 2-Bromo-6-(cinnamyloxy)pyridine

Reaction Temp: 90 °C, Time: 1 h, Yield: 80% (obtained as liquid)

IR (neat): ν_{max} 2924, 2875, 1495, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.41-7.21 (m, 6H), 7.04 (dd, 1H, J = 7.5 & 0.6 Hz), 6.79-6.68 (m, 2H), 6.45-6.36 (m, 1H), 4.96 (dd, 2H, J = 6.3 & 1.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 162.9, 140.5, 138.4, 136.4, 133.8, 128.5, 127.9, 126.5, 123.8, 120.3, 109.6, 67.1.

Entry 3: 5-Bromo-2-(cinnamyloxy)pyridine

Reaction Temp: 90 °C, Time: 1 h, Yield: 80%; mp. 100 °C (recrystallised from ether).

IR (nujol): ν_{max} 2924, 2875, 1495, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 8.21 (d, 1H, J = 2.4 Hz), 7.67 (d, 1H, J = 9 Hz), 7.42-7.29 (m, 5H), 6.73-6.70 (m, 2H), 6.50-6.41 (m, 1H), 4.96 (d, 2H, J = 5.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 162.2, 147.4, 141.2, 136.4, 133.5, 128.6, 127.9, 126.6, 124.1, 112.9, 111.8, 66.8.

Entry 4: 2-Bromo-6-(pentyloxy)pyridine

Reaction Temp: 90 °C, Time: 5 h, Yield: 62% (obtained as liquid)

IR (neat): ν_{max} 2924, 2875, 1495, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.92-7.86 (m, 1H), 7.38-7.30 (m, 1H), 7.15-7.04 (m, 1H), 3.97-3.90 (m, 2H), 1.75-1.68 (m, 2H), 1.41-1.30 (m, 4H), 0.96-1.0 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 164.9, 141.4, 140.7, 114.9, 110.1, 68.8, 29.4, 28.1, 22.6, 14.1.

NMR Spectra of Some Selected Compounds

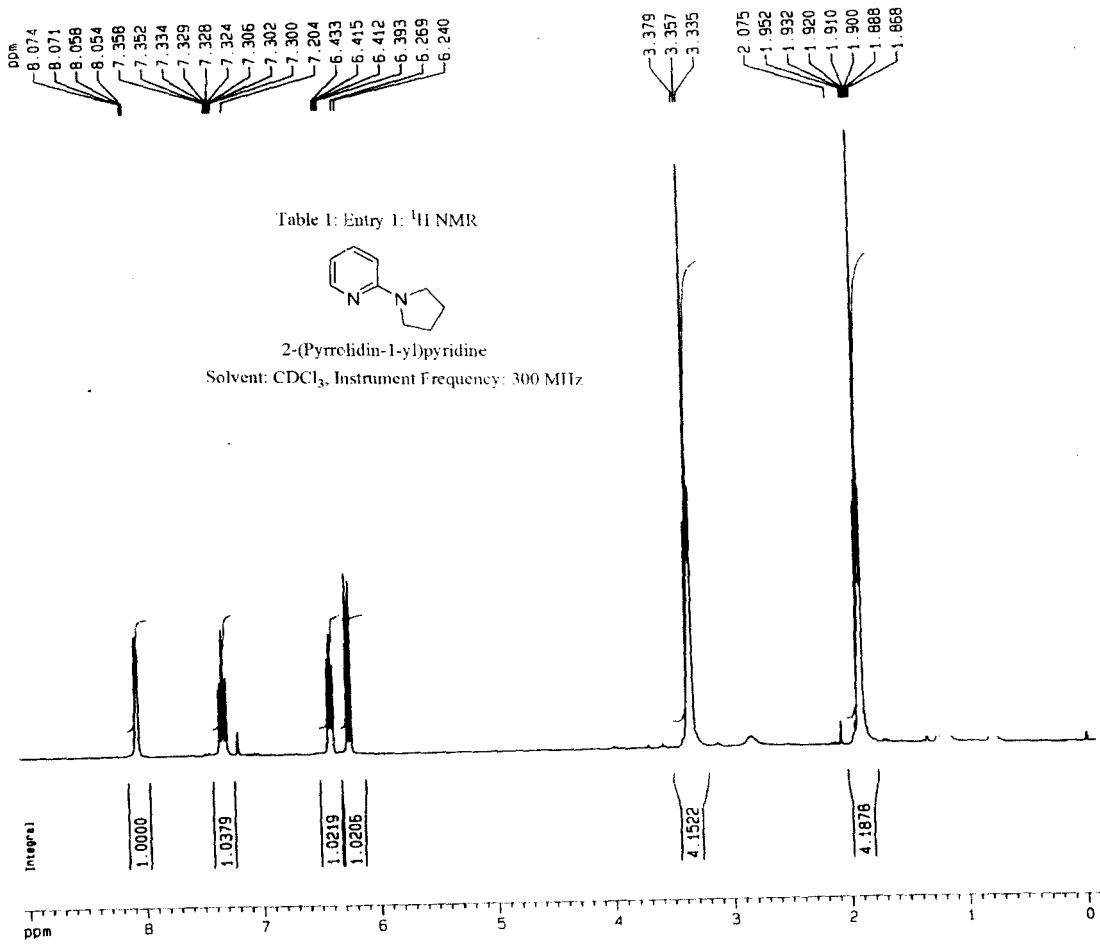


Table 1: Entry 1: ^{1}H NMR

2-(Pyrrolidin-1-yl)pyridine

Solvent: $CDCl_3$, Instrument Frequency: 300 MHz

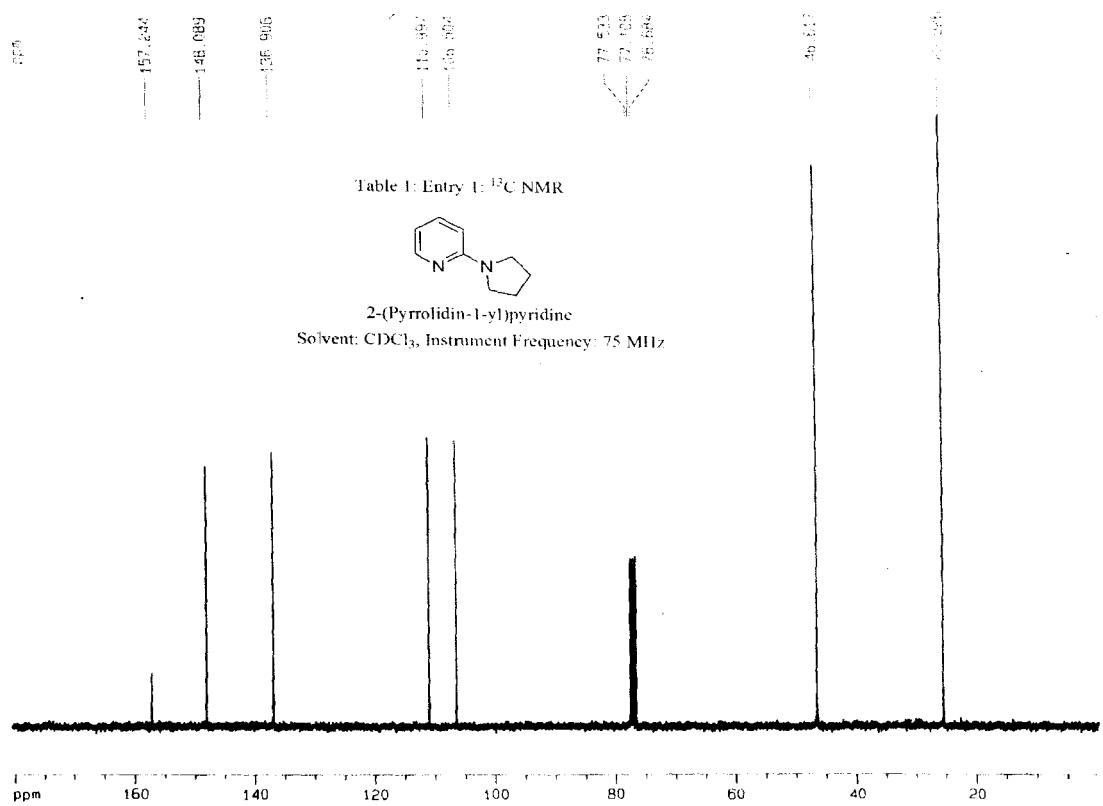


Table 1: Entry 1: ^{13}C NMR

2-(Pyrrolidin-1-yl)pyridine

Solvent: $CDCl_3$, Instrument Frequency: 75 MHz

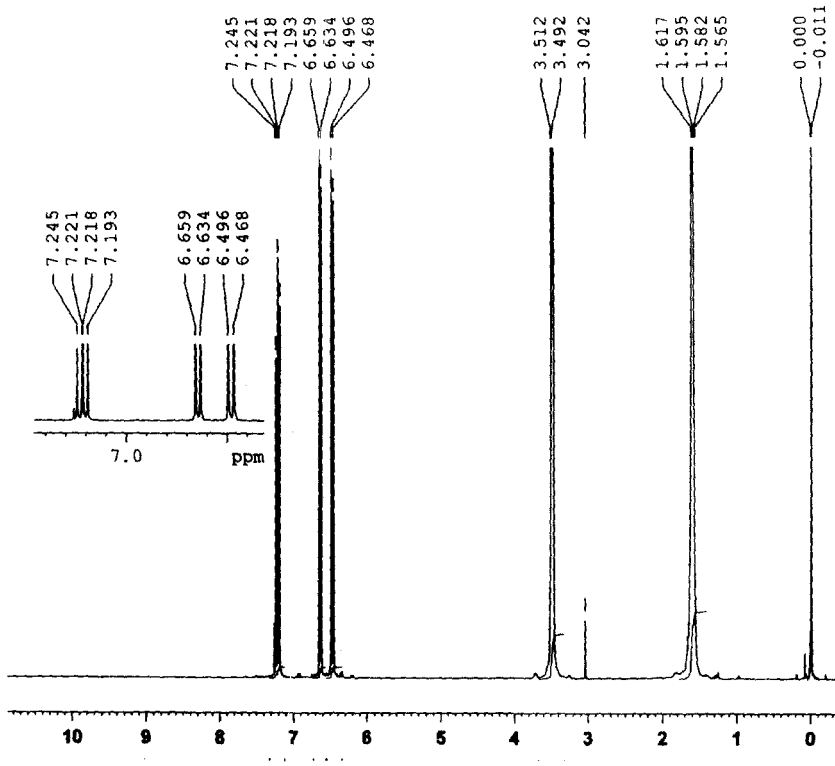
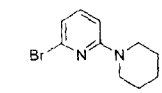


Table 1: Entry 6: ^{1}H NMR



2-Bromo-6-(piperidin-1-yl)pyridine
Solvent: $CDCl_3$, Instrument Frequency: 300 MHz

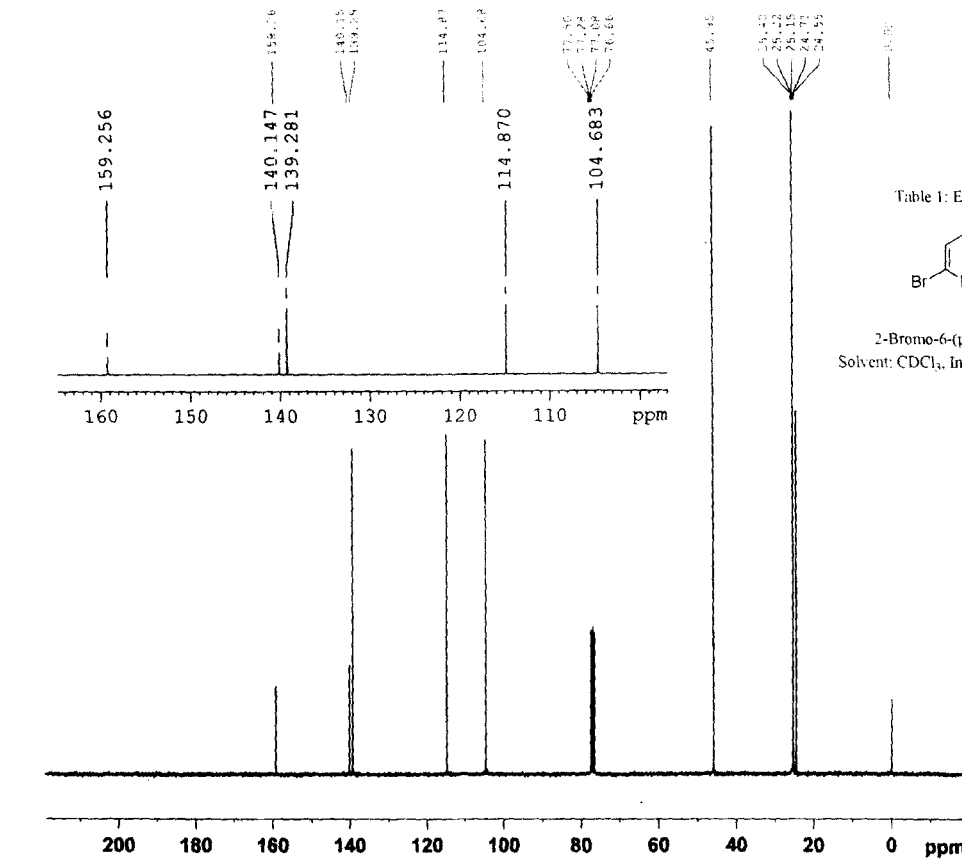
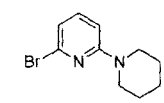


Table 1: Entry 6: ^{13}C NMR



2-Bromo-6-(piperidin-1-yl)pyridine
Solvent: $CDCl_3$, Instrument Frequency: 75 MHz

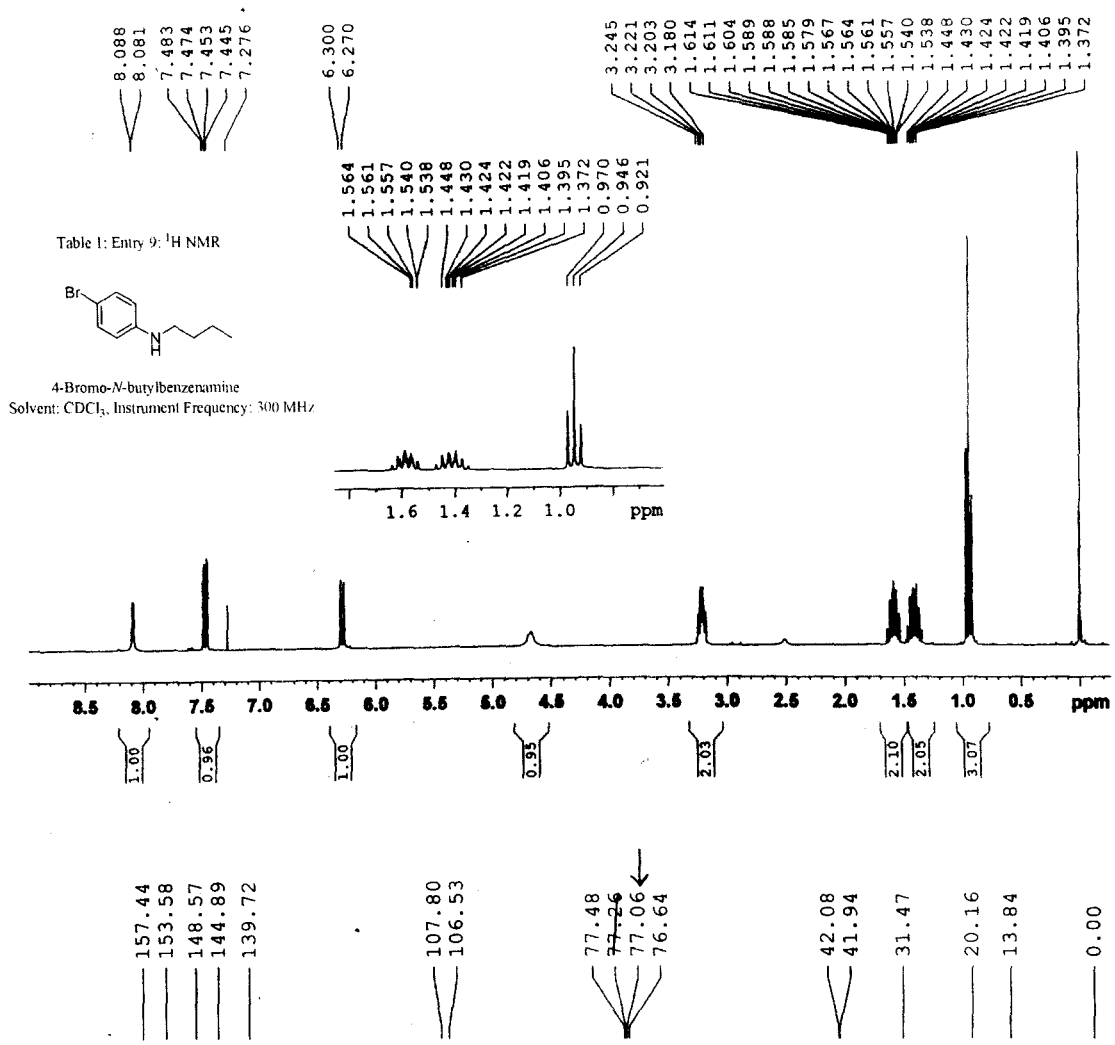
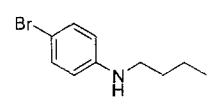


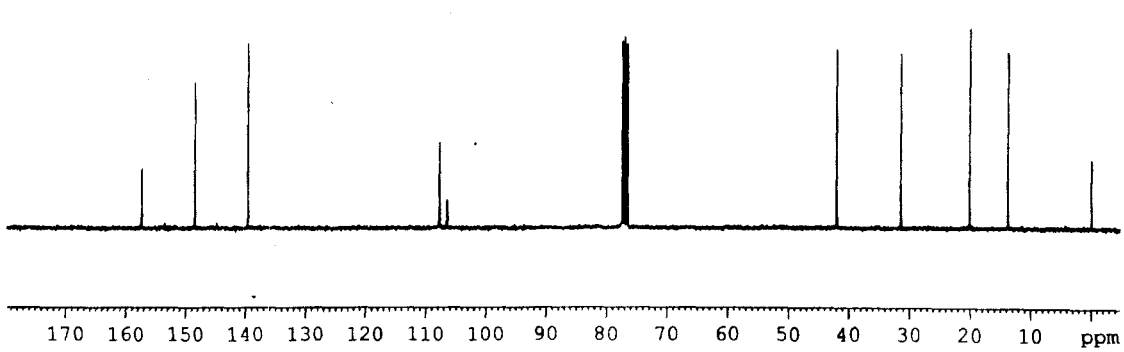
Table 1: Entry 9: ^{1}H NMR

4-Bromo-*N*-butylbenzenamine
Solvent: $CDCl_3$, Instrument Frequency: 300 MHz

Table 1: Entry 9: ^{13}C NMR



4-Bromo-*N*-butylbenzenamine
Solvent: $CDCl_3$, Instrument Frequency: 75 MHz



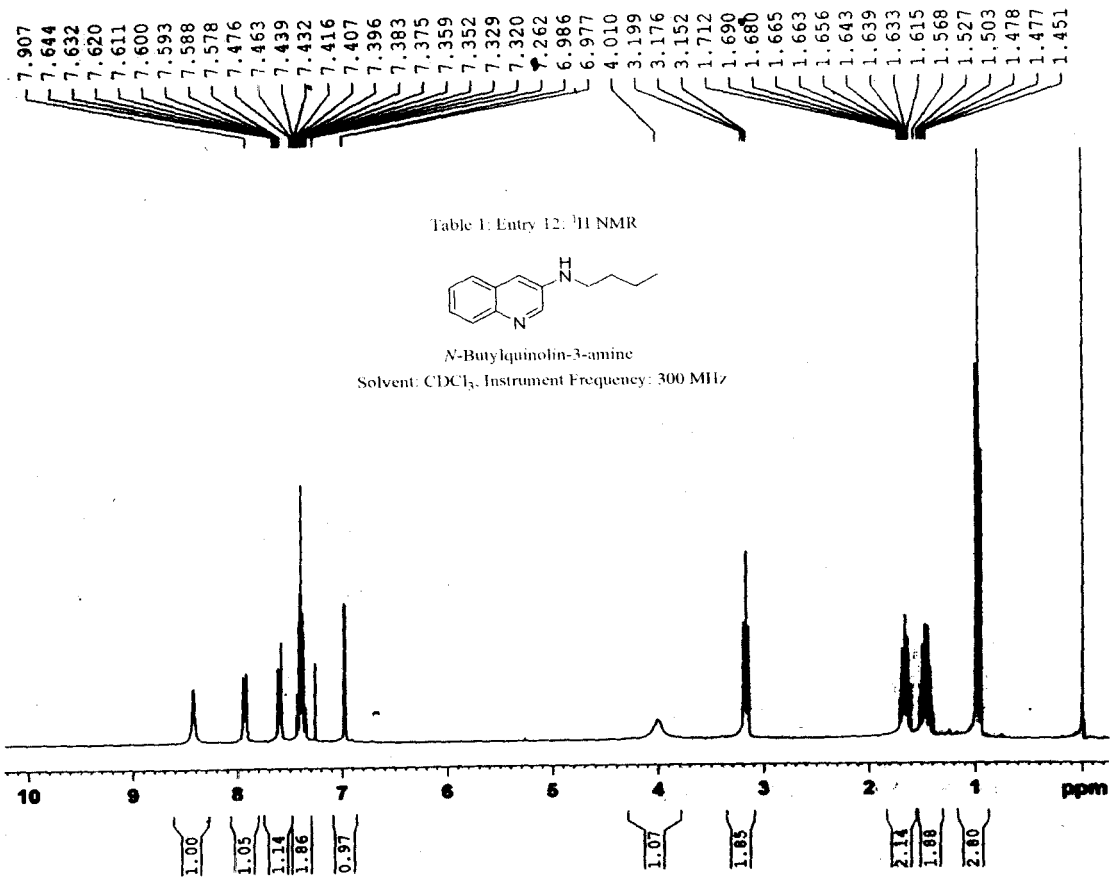


Table 1: Entry 12: ^{1}H NMR

N-Butylquinolin-3-amine

Solvent: $CDCl_3$, Instrument Frequency: 300 MHz

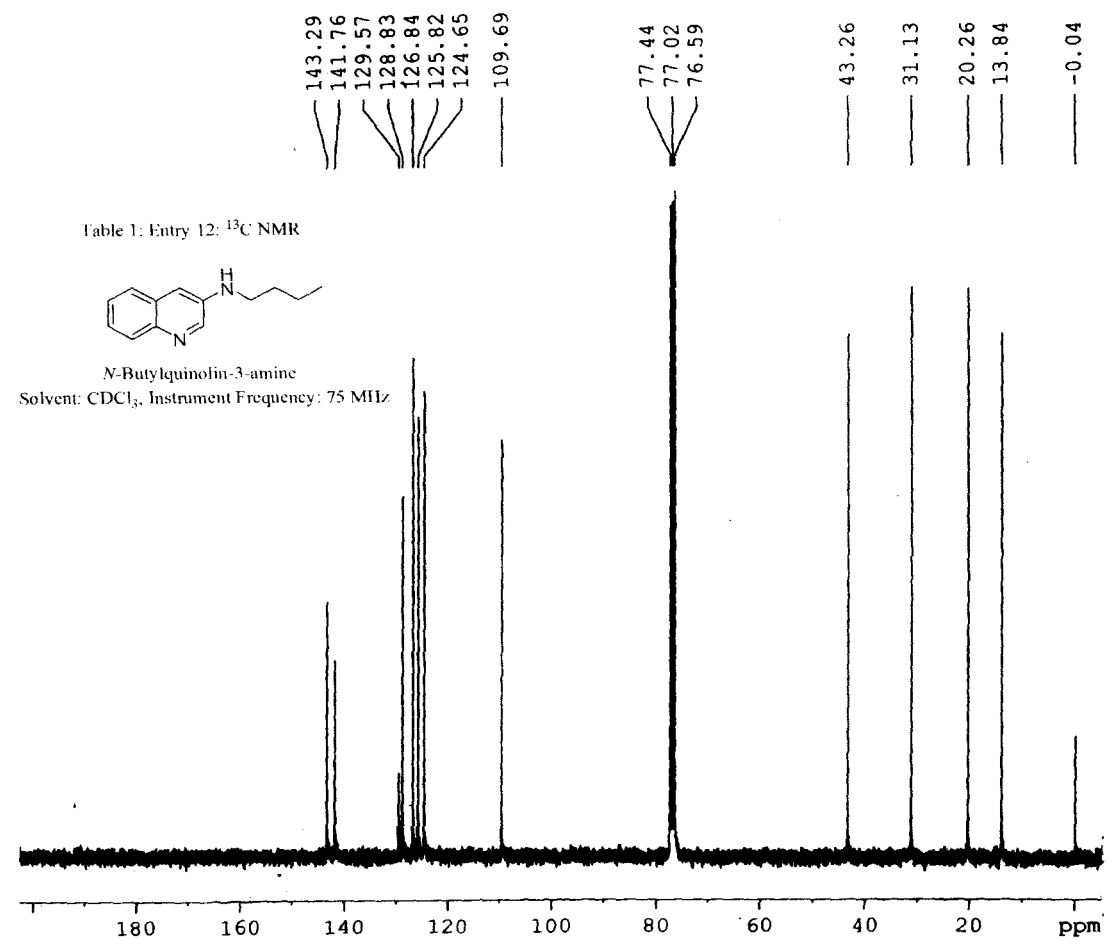
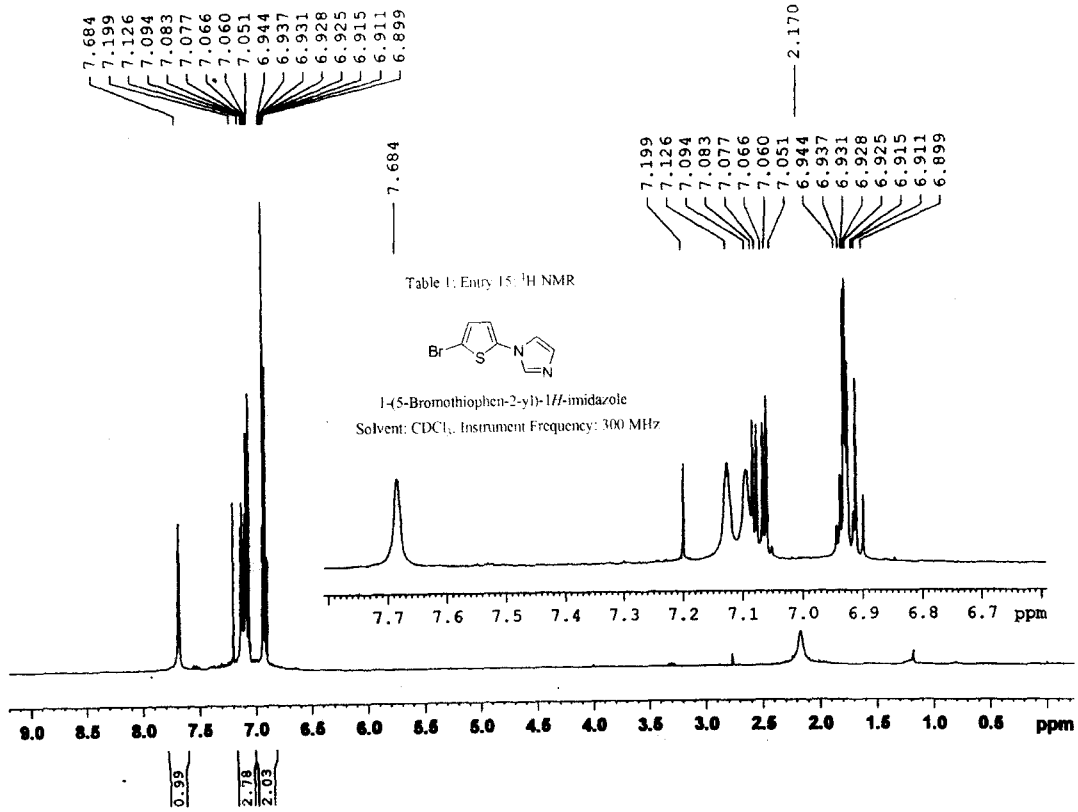
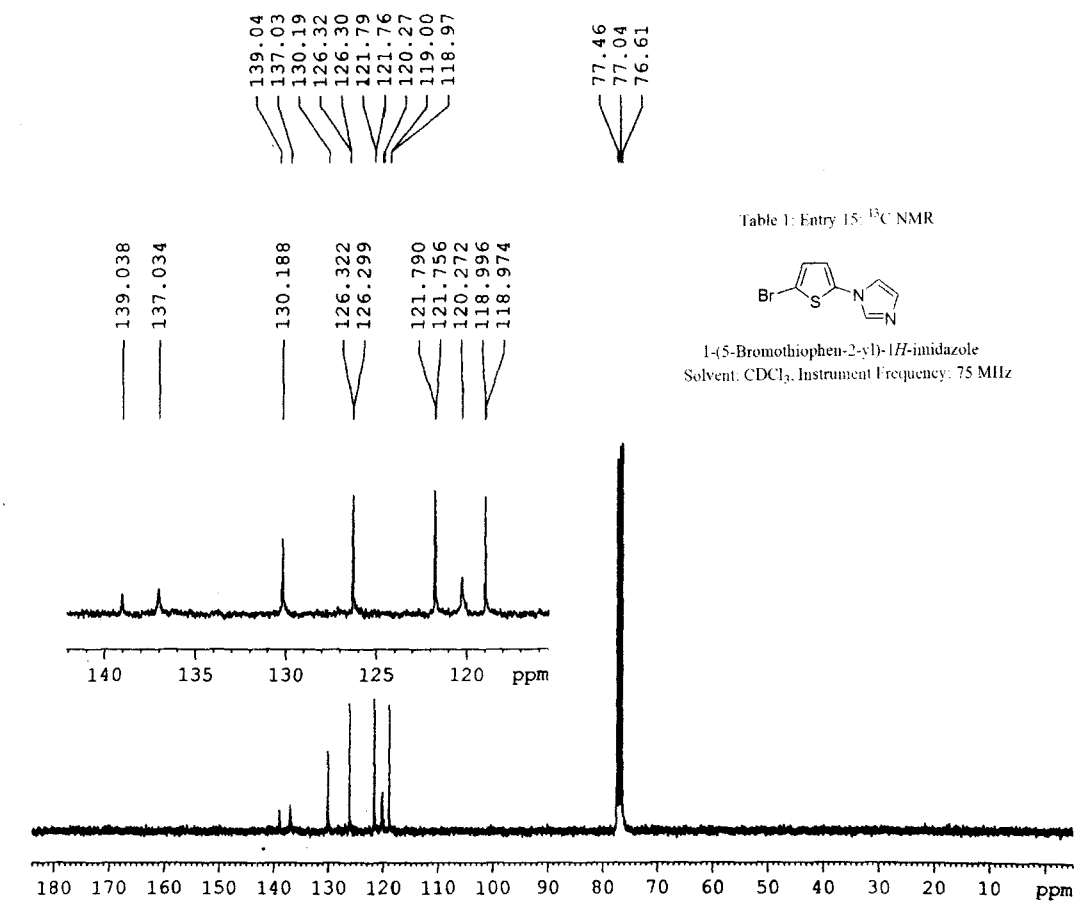


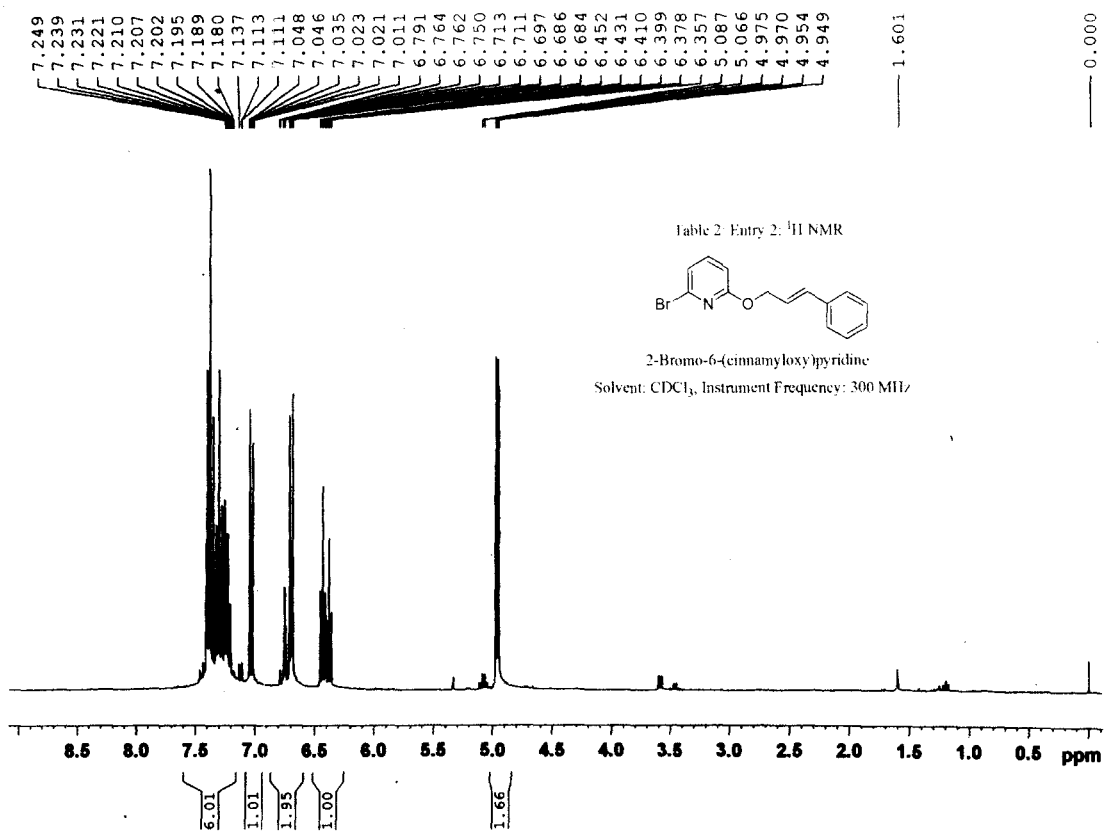
Table 1: Entry 12: ^{13}C NMR

N-Butylquinolin-3-amine

Solvent: $CDCl_3$, Instrument Frequency: 75 MHz


7.684
7.199
7.126
7.094
7.083
7.077
7.066
7.060
7.051
6.944
6.937
6.931
6.928
6.925
6.915
6.911
6.899
2.170
Table 1: Entry 15: ^{1}H NMR
Br
S
N
1-(5-Bromothiophen-2-yl)-1*H*-imidazole
Solvent: $CDCl_3$, Instrument Frequency: 300 MHz
7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 ppm
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.99
2.78
2.03


139.04
137.03
130.19
126.32
126.30
121.79
121.76
120.27
119.00
118.97
77.46
77.04
76.61
Table 1: Entry 15: ^{13}C NMR
Br
S
N
1-(5-Bromothiophen-2-yl)-1*H*-imidazole
Solvent: $CDCl_3$, Instrument Frequency: 75 MHz
139.038
137.034
130.188
126.322
126.299
121.790
121.756
120.272
118.996
118.974
140 135 130 125 120 ppm
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.249
7.239
7.231
7.221
7.210
7.207
7.202
7.195
7.189
7.180
7.137
7.113
7.111
7.048
7.046
7.035
7.023
7.021
7.011
6.791
6.764
6.762
6.750
6.713
6.711
6.697
6.686
6.684
6.452
6.431
6.410
6.399
6.378
6.357
5.087
5.066
4.975
4.970
4.954
4.949
1.601
0.000
Table 2 Entry 2: ^{1}H NMR
Br
N
O
2-Bromo-6-(cinnamyloxy)pyridine
Solvent: $CDCl_3$, Instrument Frequency: 300 MHz
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
6.01
1.01
1.95
1.00
1.66

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Role of copper in catalyzing aryl and heteroaryl-nitrogen (or -oxygen) bond formation under ligand-free and solvent-free conditions

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Formation of aryl- or heteroaryl-nitrogen (or -oxygen) bonds under ligand and solvent-free conditions are highly selective to the presence of copper. While bromoarenes undergo C-N (or -O) coupling in stoichiometric presence of copper, heteroaryl bromides require only catalytic amounts of copper(I) salts depending on the position of bromo substituents. Such selectivity coupled with ligand and solvent-free protocols appear promising from the viewpoint of ecology and economy and are more attractive as compared to the existing protocols.

Keywords: Cu catalyst, bromopyridines, C-N coupling, C-O coupling, ligand-free conditions

Heteroaryl-nitrogen and -oxygen bonds are prevalent in many compounds that are of biological, pharmaceutical, and materials interest[1]. In recognition of their widespread importance, over the years, transition-metal-catalyzed cross-coupling reactions of aryl halides with N- and O-containing nucleophilic compounds have emerged as the most prominent synthetic methods for the formation of these bonds[2]. Most noteworthy among them are the aryl coupling reactions based on Pd(0) catalysts such as the Buchwald-Hartwig coupling to form aryl-nitrogen and aryl-oxygen bonds[3]. Traditional copper-mediated Ullmann couplings generally require harsh reaction conditions besides most Cu(I) salts are insoluble in organic solvents[4]. In order to circumvent such problems, suitable ligands-based copper complexes have been used both in stoichiometric and catalytic amounts in Ullmann type coupling reactions. In recent years significant advances have been made in the development of copper-catalyzed cross-coupling methodology[5]. On the other hand, Pd(0)-catalyzed Buchwald-Hartwig hetero cross couplings reactions have been successful by using suitable ligand-based palladium complexes, preferably with bis-phosphine ligands[3].

Considering the complexity of using suitable ligand-based palladium complexes and economic aspects, yet, copper-mediated cross couplings have remained reactions of choice for large- and industrial-scale formation of these aryl-heteroatom bonds. A growing number of papers have therefore focused on the deliberate use of ligands to facilitate copper-catalyzed aryl-nitrogen and aryl-oxygen bond forming reactions[6]. Among a variety of bidentate chelating ligands used, the N,N-, O,O-, and N,O-chelators appear to be in the majority of the copper-catalyzed coupling reaction protocols. While Buchwald reported a highly selective Cu-catalyzed C-N coupling reaction of aryl and heteroaryl halides in presence of CuI (5 mol%) and 1,3-diketone as the ligand (20 mol%)[7], Fukuyama developed a ligand-free intermolecular amination of aryl iodides using stoichiometric amounts of CuI[8]. Thus, either catalytic copper salts in presence of suitable ligands or stoichiometric use of CuI at higher temperature remain the major choice for C-N coupling reaction of aryl and heteroaryl halides. Besides, such protocols were not examined for C-O coupling reactions. The development of a method with very specific ligand/metal combinations is therefore currently needed.

In conjunction with our interest in Pd- and Cu-catalyzed cross coupling reactions coupled with the development of environmentally benign methodology[9], we investigated Cu(I)-catalyzed ligand-free C-N (and C-O) coupling reactions under heterogeneous basic conditions. We observed that the heteroaryl bromides (such as, pyridine, quinoline, pyrimidine and thiophene) can be coupled with amines selectively under Cu(I)-catalyzed ligand-free conditions, while bromoarenes remained entirely

unproductive (**Scheme I**). Moreover, 2-bromopyridines can be aminated with secondary amines even in the absence of any copper catalyst. To the best of our knowledge, such observations and selectivity, are not known in the literature and might be useful for selective amination in complex molecules with both types of aromatic halides. Indeed, a mixture of 4-bromoanisole and 2-bromopyridine when subjected to amination using pyrrolidine, only the corresponding aminopyridine was isolated along with the unreacted 4-bromoanisole (>90% recovered from the product mixture). We studied several other reactions where clear selectivity between aryl bromide and heteroaryl bromide has been observed. Besides, the reaction was further extended to C-O bond-forming reactions under similar conditions.

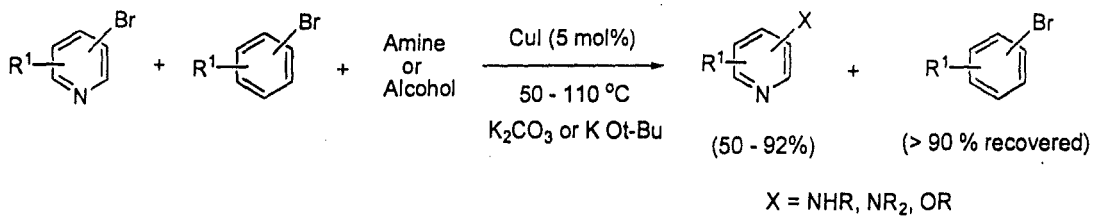
Results and Discussion

Initial experiments were carried out with the amination of 2-bromopyridine. When a mixture of 2-bromopyridine and an amine in the ratio of 1:3 was heated in the presence of CuI (5 mol%) and base (1 equiv.) at 80-90°C for 2-7 hr, the corresponding 2-aminopyridine was obtained in 65-92% yield. Such amination process was then extended successfully to 2,6- and 2,5-dibromopyridines affording the corresponding 2-amino-bromopyridines in good to excellent yields. Aminations of 3-bromo-heteroarenes with both primary and secondary amines using 5 mol% CuI were found to be less productive furnishing the desired product in 55-60% yield. It is interesting to observe that while 2-bromopyridines can also afford the corresponding aminated product in the absence of Cu-catalyst in almost comparable yields, 3-bromopyridines require presence of Cu-catalyst for amination. Furthermore, facile amination was observed with secondary amines as compared to its primary counterpart. Diazoles as the source of amine afforded the desired products in the range of 50-66% yields. Since the diazoles are solid compounds, a small amount of DMF was used in these cases. The results are summarized in **Table I**. There has been a resurgence of interest in Cu mediated C-O ether bond forming reactions beyond that of the classical Ullmann ether synthesis. The hetero cross-coupling has been extensively studied with several organometalloids such as organo-Bi (Ref. 10), -Sn (Ref. 11) and –B (Ref. 12, 9b) compounds. An obvious limitation of these methods is that stoichiometric amount of Cu salts is required. Extending our protocols to C-O bond-forming reactions met with varied success. While phenols were not reactive due to poor nucleophilicity of the phenoxide[13], cinnamyl alcohol and amyl alcohol could react efficiently with bromopyridines producing direct heteroaryl-O compounds. The results are presented in **Table II**. The relation of specific requisite of ligand/metal combination with reference to substrates might be interpreted on the basis of present studies. In Ullmann type of coupling, there is compelling evidence for the involvement of arylcopper species as an intermediate, which may be stabilized in the form of a complex in presence of suitable ligands (also solvent molecules)[14]. Aryl iodides can be aminated under ligand-free conditions in presence of stoichiometric Cu(I) salts[8]. Such process might involve formation of arylcopper intermediate followed by amination. On the other hand, heteroaryl bromides, in particular N-containing aryl bromides, can be aminated either in presence or in absence of Cu(I) catalyst. Amination of 2-bromopyridine with pyrrolidine at different temperature/time (rt/24 hr, 50°C/4 hr and 90°C/2 hr) in absence or in presence of catalytic CuI (5 mol%) has not resulted in appreciable change in the yields of the aminated product. The present studies thus led to suggest that 2-bromopyridines can be aminated possibly as a result of simple nucleophilic addition reaction (i.e. two-step addition/elimination) without involvement of the copper salts, while amination of 3-bromopyridines°Ccurs in presence of catalytic Cu(I) salts indicating that the metal is perhaps acting as a Lewis acid and not activating the aryl-bromide bond directly[15]. On the other hand, aryl bromides (iodide) undergo amination in presence of stoichiometric amount of CuI[8].

In summary, the present studies have clearly demonstrated the role of copper in catalyzing or mediating the formation of C-N (or C-O) bonds in amination (or etherification) of heteroaryl or aryl halides. Deliberate use of suitable ligand and copper salts could be avoided depending on the nature of the substrate. The selectivity, mild, operationally simple protocols are attractive and might be useful in complex molecules containing both types of aromatic halides. Besides, ligand and solvent-free conditions satisfy the viewpoint of ecology and economy.

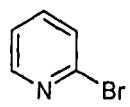
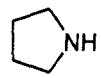
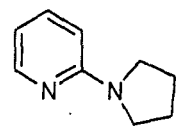
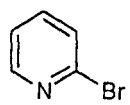
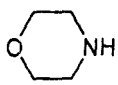
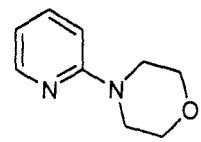
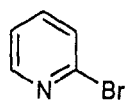
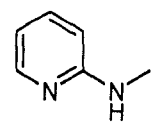
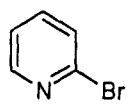
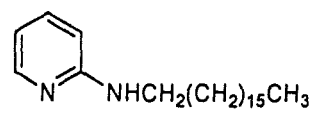
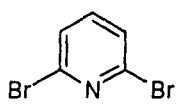
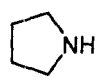
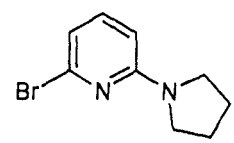
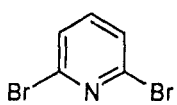
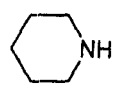
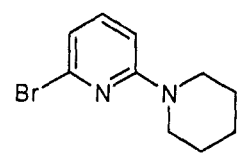
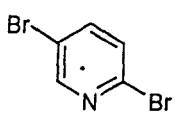
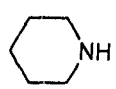
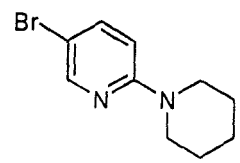
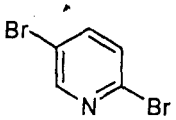
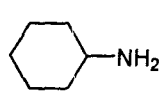
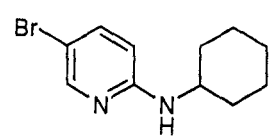
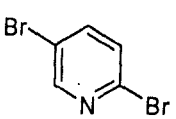
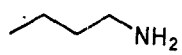
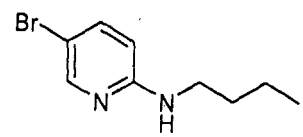
Experimental Section

All the bromopyridines, except 2-bromopyridine, were purchased from Sigma Aldrich Chemical Pvt. Ltd, India. 2-bromopyridine and *n*-heptadecylamine



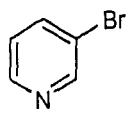
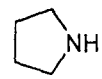
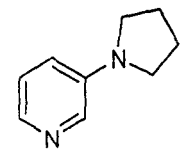
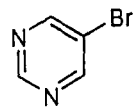
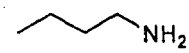
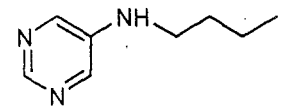
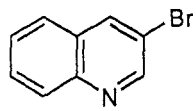
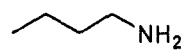
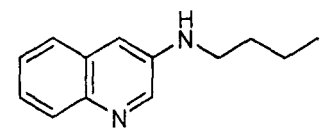
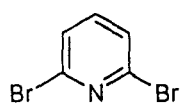
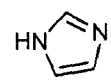
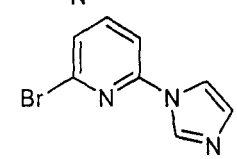
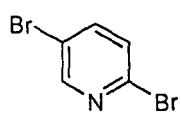
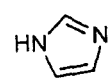
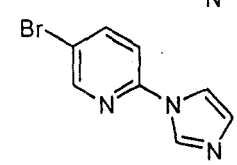
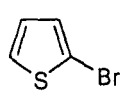
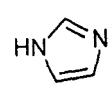
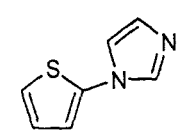
Scheme I

Table I—CuI-catalyzed ligand-free amination of bromopyridines and other heteroarenes.

Entry No.	Bromopyridine	Amine	Condition[a] Temp./ Time	Product	% of Yield[b]
1			90°C/ 2h		92 (85)
2			80°C/ 7h		83 (80)
3		CH_3NH_2. HCl	80°C/ 5h		65
4		$NH_2CH_2(CH_2)_{15}CH_3$	80°C/ 6h		74
5			50°C/ 0.5h		90 (82)
6			50°C/ 1h		88 (81)
7			80°C/ 2h		92 (83)
8			90°C/ 4h		85 (< 5)
9			80°C/ 5h		91 (10)

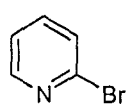
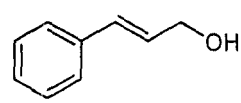
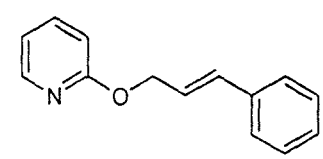
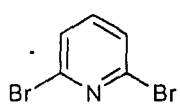
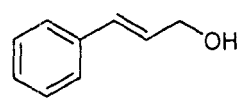
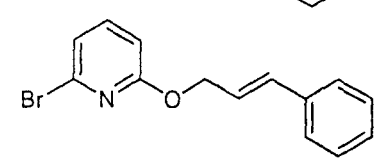
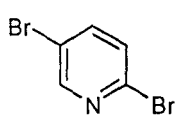
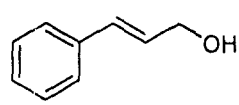
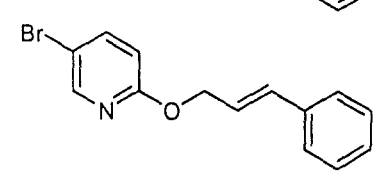
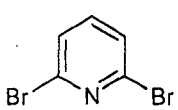
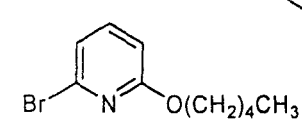
—Contd

Table I — CuI-catalyzed ligand-free amination of bromopyridines and other heteroarenes.--*Contd*

Entry No.	Bromopyridine	Amine	Condition[a] Temp./ Time	Product	% of Yield[b]
10			90°C/ 4h		60 (< 5)
11			90°C/ 6h		58 (< 5)
12			80°C/ 8h		55
13			110°C/ 11h		66
14			110°C/ 11h		50
15			110°C/ 11h		61

[a] Halopyridine:Amine is 1: 3, CuI (5 mol%) and 1equivalent of base (K_2CO_3) are used for these reactions.
[b] Yields in parenthesis correspond to conditions without CuI.

Table II — CuI-catalyzed C-O couplings of heteroaryl bromides.

Entry No.	Bromopyridine	Alcohol	Condition[a] Temp./ Time	Product	% of Yield
1			90°C/ 1h		85
2			90°C/ 1h		80
3			90°C/ 1h		80
4		$CH_3(CH_2)_3CH_2OH$	90°C/ 5h		62

[a] Halopyridine:Alcohol (1:3), CuI (5 mol%) and 1 equivalent of base (KO^tBu) are used for these reactions.

ere purchased from Fluka. Diazole was purchased om Loba Chemie Pvt. Ltd., India, pyrrolidine from ancaster, England and CuI was prepared according literature method[16]. The rest of the amines were urchased from The British Drug House Pvt. Ltd., ngland. Liquid amines were distilled prior to use and ie rest of the chemicals were used as received. The roducts were isolated by column chromatography sing silica (60-200 μm), SRL, India. TLC was done n Merck plates coated with silica gel 60, F254. FT-R spectra were recorded on a Shimadzu-8300 pectrophotometer in Nujol. NMR spectra of the ompounds were recorded with a Bruker AV 300 pectrometer using TMS as the internal standard.

A representative procedure for Cu(I)–catalyzed mination:

To a mixture of 2–bromopyridine (158 mg, mmol), CuI (9.5 mg, 5 mol%) and K_2CO_3 (138 mg, 1 mmol), pyrrolidine (213 mg, 3 mmol) was added and ie final mixture was placed on a pre-heated oil-bath t 90°C for 2 hr. After cooling to RT the reaction-ixture was extracted with dichloromethane (3×20 L), dry packed with silica gel and then transferred n a column of silica gel. Elution with ethyl cetate/light petroleum (1:19) afforded the -(pyrrolidin–1–yl)pyridine as colourless oil (138 mg, 2%). IR (Film) ν_{max} 1597, 1555, 1501, 1485, 1443 m^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.06 (dd, 1H, = 5.1 & 1.2 Hz), 7.33 (ddd, 1H, J = 8.7, 7.2 & 1.8 lz), 6.41 (ddd, 1H, J = 6.3, 5.4 & 1 Hz), 6.25 (d, 1H, = 8.7 Hz), 3.36 (t, 4H, J = 6.6 Hz), 1.91 (t, 4H, J = .6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.1, 148.0, 36.8, 110.9, 106.4, 46.5, 25.4.

Reaction of 2–bromopyridine with pyrrolidine ıder similar conditions without using CuI afforded e desired 2–(pyrrolidin–1–yl)pyridine in 85% yield.

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