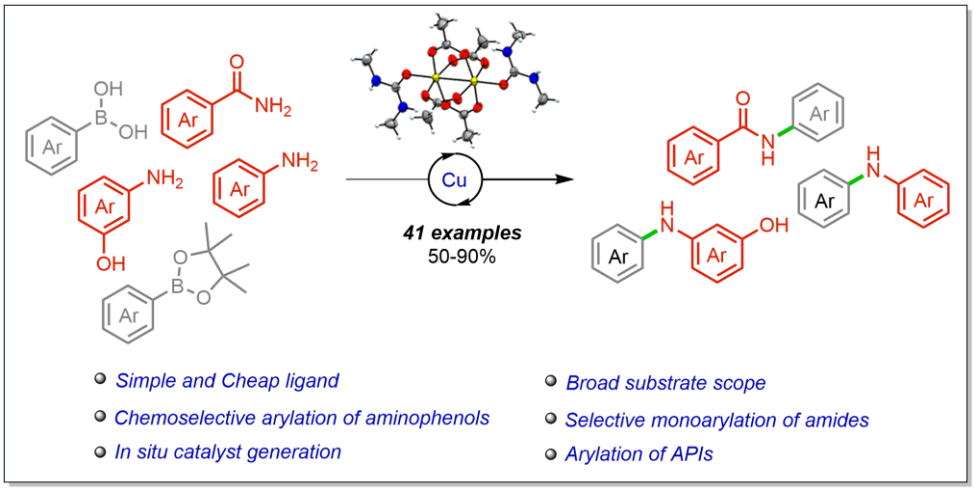
Chapter 4

N,N'-dimethylurea as an efficient ligand for Chan-Lam N-arylated pharma-relevant motifs[a]



ABSTRACT: This chapter introduces *N,N'*−dimethylurea (DMU) as a ligand to aid Chan−Lam *N*−arylation of primary amides, anilines and 3−aminophenols with arylboronic acids and its ester derivative as the arylating agents. The developed methodology is catalyzed by Cu and its *in-situ* complexation with DMU brings about efficient synthesis of *N*−arylated anilines, 3−aminophenols and primary amides in moderate to good yields (50-90%). The $[Cu_2(OAc)_4(DMU)_2]$ complex is synthesized and characterized through single crystal X-ray structure elucidation. The catalyst is cheap, free from prior synthesis of the metal-complex, provides chemoselectivity towards *N*−arylation of 3-aminophenols and suitable for mono-arylation of primary amides. The methodology is applied in a selective post-modification of two active pharmaceutical ingredients (APIs). The developed catalytic system extends the scope of *N,N'*−dimethylurea as an auxiliary in inexpensive and versatile Cu−catalysis.

[a]Saikia, R., Das, S., Almin, A., Mahanta, A., Sarma, B., Thakur, A. J., and Bora, U. *N,N'*−dimethylurea as an efficient ligand for Chan-Lam *N*-arylated pharma-relevant motifs; *Manuscript under communication*

Chapter 4

4. *N,N'*–dimethylurea as an auxiliary in Chan–Lam cross–coupling!

4.1 *Introduction*

The domain of carbon–nitrogen bond formation is predominantly occupied by three strategies: Ullmann-Goldberg reaction, Buchwald-Hartwig reaction and the Chan–Lam cross-coupling reaction [1-6]. Of these, the adopted approach depends on the starting materials, the choice of metal and the type of C–N transformation desired. Credited for a universal demand for more than 100 years, C–N bond formations remain to enthrall synthetic chemists for the notable biological activities of the products [7-10]. In this regard, it is noteworthy to mention that C–N bond containing *N*–arylamides, *N*–arylamines and 3–arylaminophenols are significant pharma–relevant scaffolds (Figure **4.1**).

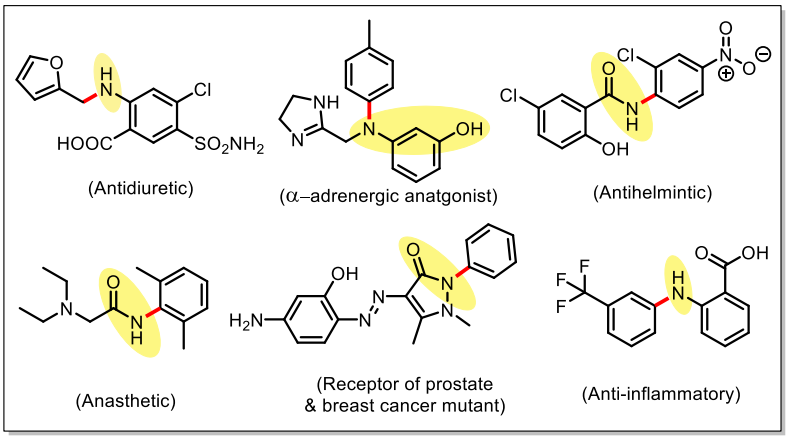


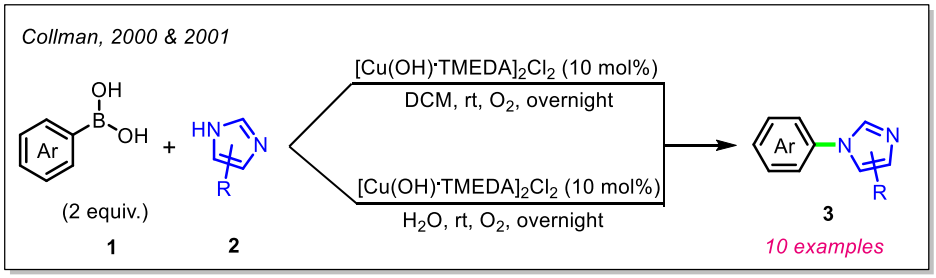
Figure **4.1** Some bioactive molecules with C–N bonds.

From high-temperature–Pd catalysis and highly complicated phosphine ligands, passing the baton on to milder Cu–catalysis, the pioneering fathers Chan, Evans and Lam, independently designed an "open flask chemistry" (Cu^{II}, mild base, ambient temperature and run in air) introducing arylboronic acids as efficient arylating agents. Arylboronic acids and their derivatives are insensitive to air, stable, permit reactions in an aqueous medium and are compatible with a wide range of substrates [11-13]. This oxidative cross–coupling can allow the formation of twelve different types of

C−heteroatom bonds and has extended its scope over the years to include a variety of *N*−nucleophiles under its ambit [14-20]. Although, the utilization of arylboronic acids may be a concern (as they are primarily synthesized from aryl halides), recent reports have suggested that arylboronic acids and their derivatives can be directly prepared from C−H borylations of arenes and indoles [21]. Traditional Chan−Lam cross-couplings were however, criticized for their long reaction duration, high catalyst loadings and need of excess amounts of arylboronic acids. Later developments have significantly contributed to overcoming these drawbacks making Chan-Lam cross-coupling a preferred C−N bond forming approach over existing protocols.

4.2 *Homogeneous catalysis in Chan-Lam cross-couplings*

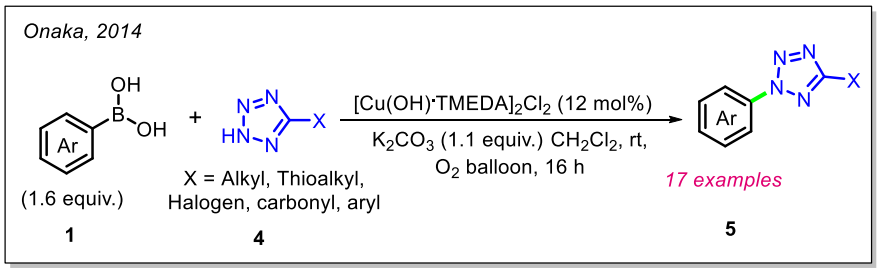
The design of a suitable ligand with Cu is the perfect answer to efficient homogeneous catalysis in Chan−Lam cross−coupling reaction. Collman [22] reported the first catalytic version of Chan-Lam cross-coupling utilizing commercially available $[Cu(OH)\cdot TMEDA]_2Cl_2$ to obtain *N*-arylimidazoles in DCM without the requirement of a base. In a consecutive report, they adopted the same methodology and documented the *N*-arylation in "water" (Scheme **4.1**) [23]. However, both the reactions employed about 2 equivalents of phenylboronic acid (**1**). The possible decomposition of phenylboronic acid by H_2O_2 formed in the disproportionation step prompted them to use large excess of phenylboronic acids.



Scheme **4.1** *N*-arylation of imidazoles in water

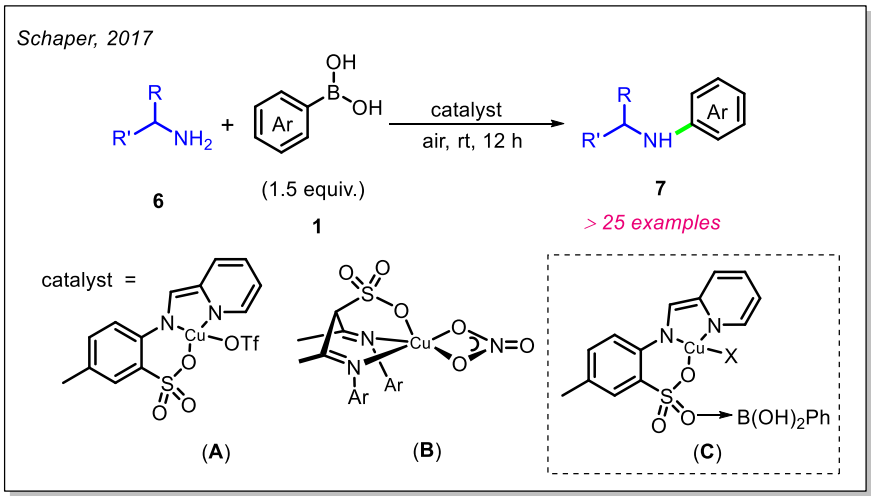
Later in 2014, Onaka et al. [24] utilized the same $[Cu(OH)\cdot TMEDA]_2Cl_2$ catalyst and found TMEDA as an effective ligand to obtain highly regioselective *N*-arylation of 5-alkyl and aryl-substituted tetrazoles at room temperature (Scheme **4.2**). Other similar ligands like DMEDA and TMPDA were found to be less effective than TMEDA. The "suitable steric environment" of TMEDA was thought to be necessary for the selectivity. The

mechanism was found similar to that proposed by Collman's group [22]. Unlike the previous protocol, a base was necessary to activate the tetrazoles because of the difference in nucleophilicities between imidazole and tetrazole.



Scheme **4.2** *N*-arylation of 5-substituted tetrazoles

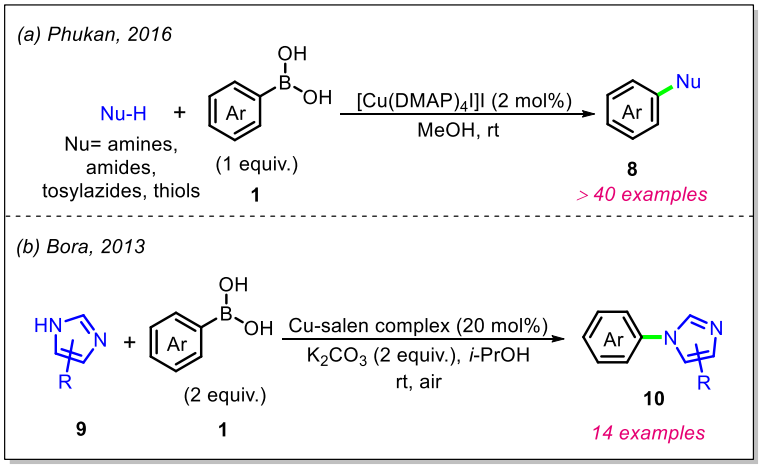
In another series of reports, Duparc et al. synthesized Cu complexes with sulfanoto-imine ligands (Scheme **4.3**, **A**) [25] and diketimino-sulfonate ligands (Scheme **4.3**, **B**) [26], and utilized the chelating nature of these ligands to achieve efficient base-free Chan-Lam cross-couplings. These chelating ligands having a sulfonate group fulfilled the role of bases/ligands as it helped the boronic acid group to coordinate to the oxygen atom and facilitated the transmetallation step (Scheme **4.3**, **C**). The coordination complexes also decreased the sensitivity of these reactions in water. The catalysts were however, sluggish towards sterically hindered substrates.



Scheme **4.3** Chan-Lam cross-coupling with chelating ligands

Likewise, the research groups of Phukan and Bora designed unique water-soluble Cu-salen type complex and a square pyramidal complex $[Cu(DMAP)_4I]I$ respectively, to facilitate Chan-Lam arylations. Phukan's group [27] designed an impressive

homogeneous Cu-complex, $[Cu(DMAP)_4I]I$ through the disproportionation of CuI in the presence of DMAP. The complex gave excellent yields of the *N*-arylated nucleophiles (amines, amides, azides and thiols) under base-free conditions (Scheme **4.4a**). Similarly, Bora's group [28] designed a unique Cu-salen complex to facilitate arylation of anilines and imidazoles in mild aqueous conditions (Scheme **4.4b**).



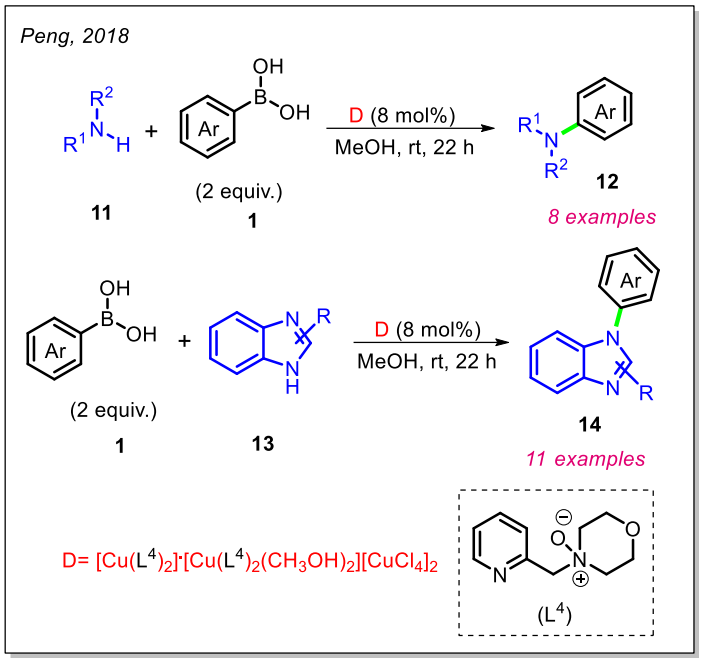
Scheme **4.4** Chan-Lam cross-coupling reaction through homogeneous catalysis

Peng's group also synthesized Cu^{II}–complexes with "tunable" *N*,*O*–bidentate ligands to obtain *N*-arylimidazoles at room temperature [29]. They designed four *N*,*O*–bidentate ligands and the activity of their corresponding Cu-complexes were tested in Chan-Lam cross-coupling reaction of 1*H*-imidazoles and 1*H*-benzimidazoles. Out of them, L^4 (as shown in Scheme **4.5**) exhibited the best activity. In the methodology, the *N*,*O*-bidentate chelating Cu–complex supposedly interacted with the boronic acid group and brought about faster transmetallation process under base-free conditions.

Thus, it is evident that Cu-coordination complexes have exhibited superior catalytic activity in comparison to their parent Cu-salts.

4.3 *Urea as auxiliaries in homogeneous catalysis*

Urea and its derivatives are small inexpensive ligands that serve as important raw materials in organic synthesis. They are excellent hydrogen bonding molecules [30], possess long shelf-life and are credited for their ability to coordinate to the metal centre in both neutral and ionic states [31]. Urea-based ligands are particularly useful in anion recognition by hydrogen bonding [32] and in asymmetric catalysis [33].



Scheme **4.5** Tunable *N*,*O*−bidentate ligands in Chan−Lam cross−coupling

With respect to organic synthesis, Bao et al. synthesized a urea-Pd/PAN composite *via* electro-spinning technique and achieved more efficient Suzuki-Miyaura cross-couplings under green catalysis [34]. Ureas are also useful as ligands to Pd for achieving phosphine ligand-free Heck couplings [35]. In addition to that, ureas and thioureas were also utilized to achieve hydrogenation of ketones and epoxides [36], enantio-selective reduction of acetophenone [37] and as alternative green ligands to reprotoxic NMP for alkylations of aryl chlorides and tosylates with Grignard reagents [38]. *N*-arylureas behaved as pro-ligands for ureates, which were used for a Pd−catalyzed heteroannulation of 1,3-dienes and haloanilines in another interesting approach [39]. Despite their tested robustness with Pd-catalysis, ureas and their derivatives are practically unexplored as auxiliaries in cheaper and more-sustainable Cu−catalysis. Figure **4.2** shows some common urea ligands that are employed in organic synthesis.

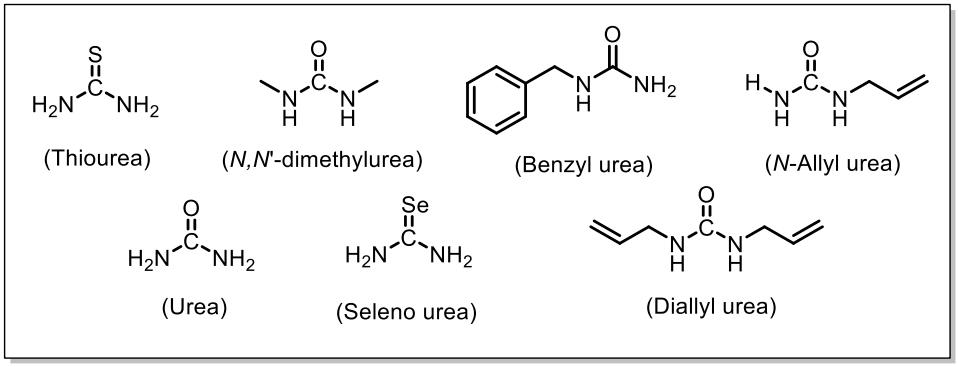
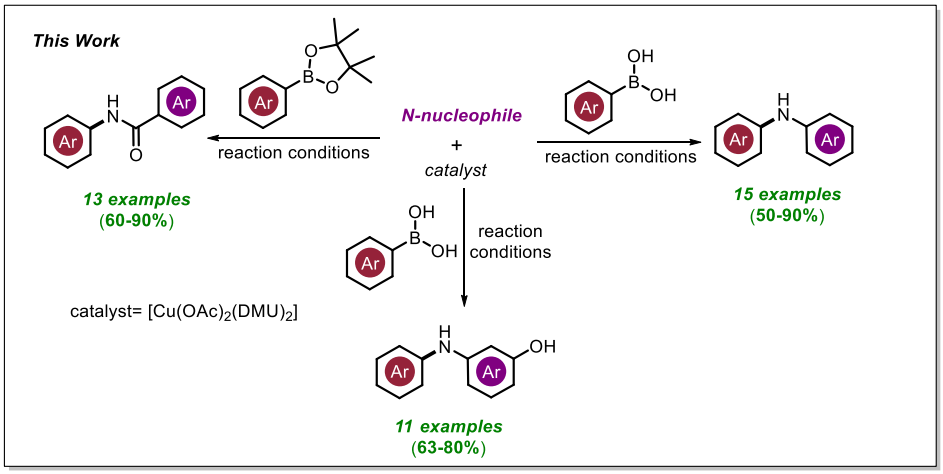


Figure **4.2** Commonly employed urea ligands

4.4 *Results and Discussion*

In this chapter, *N*,*N'*–dimethylurea (DMU) is discussed as a ligand for *N*–arylation of anilines, 3-aminophenols and mono-arylated primary amides through Chan-Lam cross-coupling strategy (Scheme **4.6**). The homogeneous catalytic system is free from prior synthesis of the Cu-complex and is generated *in situ*. It efficiently helps to establish a broad substrate scope (*up to 41 examples*) under mild reaction conditions. The methodology was successfully applied in the *N*–arylation of two active pharmaceutical ingredients (APIs). The currently developed Cu^{II}–DMU catalyst and the associated methodology mark the use of a cheap, easily available and lesser explored ligand for Cu in achieving sustainable Chan-Lam cross-couplings.



Scheme **4.6** Chan–Lam *N*–arylation with Cu^{II}–DMU catalyst

4.4.1 *Optimization of reaction conditions*

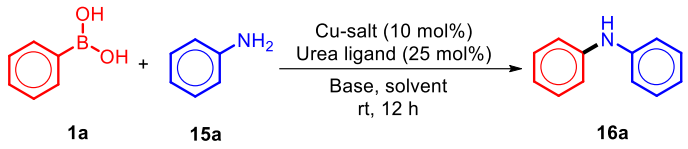
Initially, Chan−Lam amination was tested for phenylboronic acid (**1a**) and aniline (**15a**). 10 mol% of $Cu(OAc)_2 \cdot H_2O$ and 25 mol% of urea were employed at room temperature and open-air condition (open-flask chemistry) in CH_3CN:H_2O mixture as solvent and K_2CO_3 as the base (Table **4.1**, entry **1**). Water was reported to be beneficial for Cu-coordination complexes and enhanced the solubility of $Cu(OAc)_2 \cdot H_2O$, urea and base. The progress of the reaction was monitored through TLC and the reaction was allowed to stir until one of the reactants was completely consumed. After 12 hours, the reaction afforded 53% of the desired *N*-arylated product (**16a**).

Subsequently, “seven” urea derivatives were screened for their efficiency in Chan-Lam cross-coupling reaction (Table **4.1**, entries **1**-**7**). The mode of coordination of urea with the metal ions seemed to be dependent upon the type and nature of the metal. Generally, ureas are monodentate ligands and they coordinate through the nitrogen atom to a “soft” metal centre and through the oxygen atom to a “hard” metal centre. Cu^{II} ions have been reported to coordinate to the oxygen atom of urea ligands [40], where one pair of the carbonyl oxygen acts as a hydrogen-bond acceptor and the other participates in the formation of the Cu–oxygen coordination bond. Of the seven screened urea ligands, the highest yield was obtained with DMU (Table **4.1**, entry **6**). Upon coordination of DMU with Cu^{II}, the negative charge acquired by the oxygen atom of DMU (*via* resonance) is stabilized by the positively charged Cu^{II} ion enhancing the overall stability of the Cu^{II}–DMU system in the reaction medium. The reaction was thereafter carried out with DMU. Varying the ratio of CH_3CN:H_2O (Table **4.1**, entry **8**), a decent yield of the desired product was not observed. The reaction conditions in entry **6** were tested again with an oxygen balloon and a very good transformation of 80% was obtained.

To further optimize the reaction conditions, phenylboronic acid (**1a**) and aniline (**15a**) were chosen as model substrates. Results were also tested in CH_3CN or H_2O alone to eliminate the co-solvent and also at an increased temperature of 60 °C, all with unsatisfactory results (Table **4.1**, entries **10**-**12**). The reaction was screened with different polar solvents like methanol (MeOH), isopropanol (IP), ethanol (EtOH) and also without adding DMU. But, better results were not obtained (Table **4.1**, entries **13**-**16**).

Increasing the amount of phenylboronic acid increased the amount of homocoupling product, which was undesirable (Table **4.1**, entries **17** and **18**).

Table **4.1** Investigation of reaction conditions for the Chan-Lam cross-coupling reaction between aniline (**15a**) and phenylboronic acid (**1a**).[a]



1a **15a** **16a**

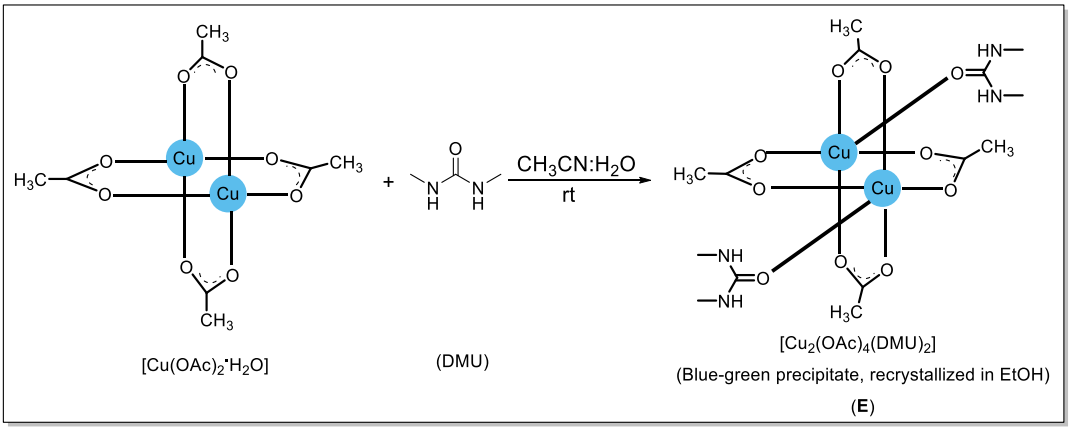
Entry	1a (mmol)	Cu salt	Ligand	Solvent (mL)	Time (h)	Yield[b](%)
1	1.2	$Cu(OAc)_2·H_2O$	Urea	$CH_3CN:H_2O$ (2:3)	12	53
2	1.2	$Cu(OAc)_2·H_2O$	Thiourea	$CH_3CN:H_2O$ (2:3)	12	NR
3	1.2	$Cu(OAc)_2·H_2O$	Benzyl urea	$CH_3CN:H_2O$ (2:3)	12	60
4	1.2	$Cu(OAc)_2·H_2O$	*N*-Allyl urea	$CH_3CN:H_2O$ (2:3)	12	68
5	1.2	$Cu(OAc)_2·H_2O$	Diallyl urea	$CH_3CN:H_2O$ (2:3)	12	65
6	1.2	$Cu(OAc)_2·H_2O$	DMU	$CH_3CN:H_2O$ (2:3)	12	70
7	1.2	$Cu(OAc)_2·H_2O$	Seleno urea	$CH_3CN:H_2O$ (2:3)	12	NR
8	1.2	$Cu(OAc)_2·H_2O$	DMU	$CH_3CN:H_2O$ (1:4)	12	60
9[c]	**1.2**	**$Cu(OAc)_2·H_2O$**	**DMU**	**$CH_3CN:H_2O$ (2:3)**	**12**	**80**
10	1.2	$Cu(OAc)_2·H_2O$	DMU	CH_3CN	12	NR
11[d]	1.2	$Cu(OAc)_2·H_2O$	DMU	CH_3CN	12	NR
12	1.2	$Cu(OAc)_2·H_2O$	DMU	H_2O	12	NR
13	1.2	$Cu(OAc)_2·H_2O$	DMU	$EtOH:H_2O$ (2:3)	12	23
14	1.2	$Cu(OAc)_2·H_2O$	DMU	$IP:H_2O$ (2:3)	12	30
15	1.2	$Cu(OAc)_2·H_2O$	DMU	$MeOH:H_2O$ (2:3)	12	25
16	1.2	$Cu(OAc)_2·H_2O$	-	$CH_3CN:H_2O$ (2:3)	12	20
17[e]	1.4	$Cu(OAc)_2·H_2O$	DMU	$CH_3CN:H_2O$ (2:3)	12	63
18[e]	2.0	$Cu(OAc)_2·H_2O$	DMU	$CH_3CN:H_2O$ (2:3)	12	53
19	1.2	$Cu(OAc)_2·H_2O$	DMU	CH_3CN: WEBPA(2:3)	12	NR
20	1.2	$Cu(OTf)_2$	-	$CH_3CN:H_2O$ (2:3)	12	55

[a]Reaction conditions: Aniline (**15a**, 0.75 mmol), Phenylboronic acid (**1a**, 1.2 mmol, 1.6 equiv.), Cu-salt (10 mol%, 0.1 mmol, 0.0135 g), ligand (25 mol%, 0.25 mmol, 0.022 g), K_2CO_3 (1 equiv.), solvent (5 mL), rt-room temperature, 12 h; [b]Isolated yield based on aniline; [c]reaction carried under O_2 balloon; [d]reaction temperature was maintained at 60 °C; [e]Homocoupling product was obtained; NR-no reaction.

The homocoupling of boronic acids has been exclusively reported with or without base by various research groups [41]. The basic properties of WEBPA were also tested by employing it as a solvent along with acetonitrile in the ratio 3:2 (Table **4.1**, entry **19**) [42]. Owing to triflate (−OTf) being a better leaving group, the reaction was screened with $Cu(OTf)_2$ too (Table **4.1**, entry **20**). However, better results were not obtained further. Acetate ion (−OAc) has proved to be the most effective counter-ion in Chan-Lam cross-coupling reactions. Therefore, at room temperature with an oxygen balloon, 10 mol% of $Cu(OAc)_2{\cdot}H_2O$, 25 mol% of DMU and 1 equiv. of K_2CO_3 in $CH_3CN{:}H_2O$ were fixed as the optimized reaction condition (Table **4.1**, entry **9**).

4.4.2 *Catalyst study*

The Cu^{II}–DMU catalyst was prepared by stirring $Cu(OAc)_2{\cdot}H_2O$ (10 mol%) and DMU (25 mol%) in $CH_3CN{:}H_2O$ solvent mixture (Scheme **4.7**). The resultant blue-green solid was filtered and re-crystallized from EtOH to obtain complex (**E**). The model reaction (Table **4.1**, entry **9**) was then tested with the synthesized $[Cu_2(OAc)_4(DMU)_2]$ complex. With similar results in hand, we decided to continue our studies with the *in-situ* generated catalyst.



Scheme **4.7** Synthesis of $[Cu_2(OAc)_4(DMU)_2]$ (**E**)

The crystal structure of **E** is solved and refined in monoclinic space group $P2_1/n$, with a half symmetry-independent molecule in the lattice. The crystal data parameter is available in Table **4.7**. ORTEP with a 50% probability ellipsoid is displayed in Figure **4.3**. The experimental section is referred to the details of the Single crystal X-ray data collection methods; CheckCIF report is available in Annexure A.

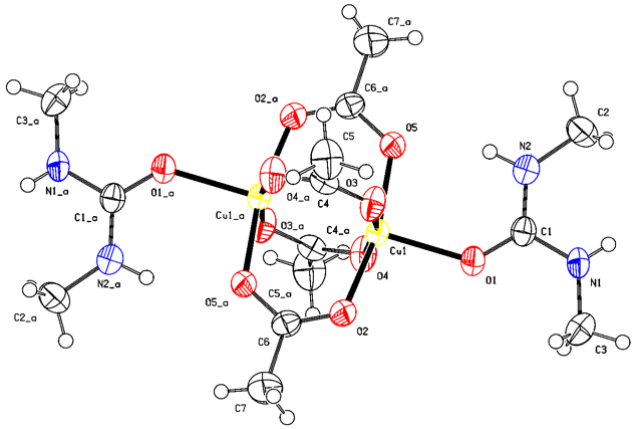


Figure **4.3** ORTEP diagram of compound **E** with 50% probability ellipsoid.

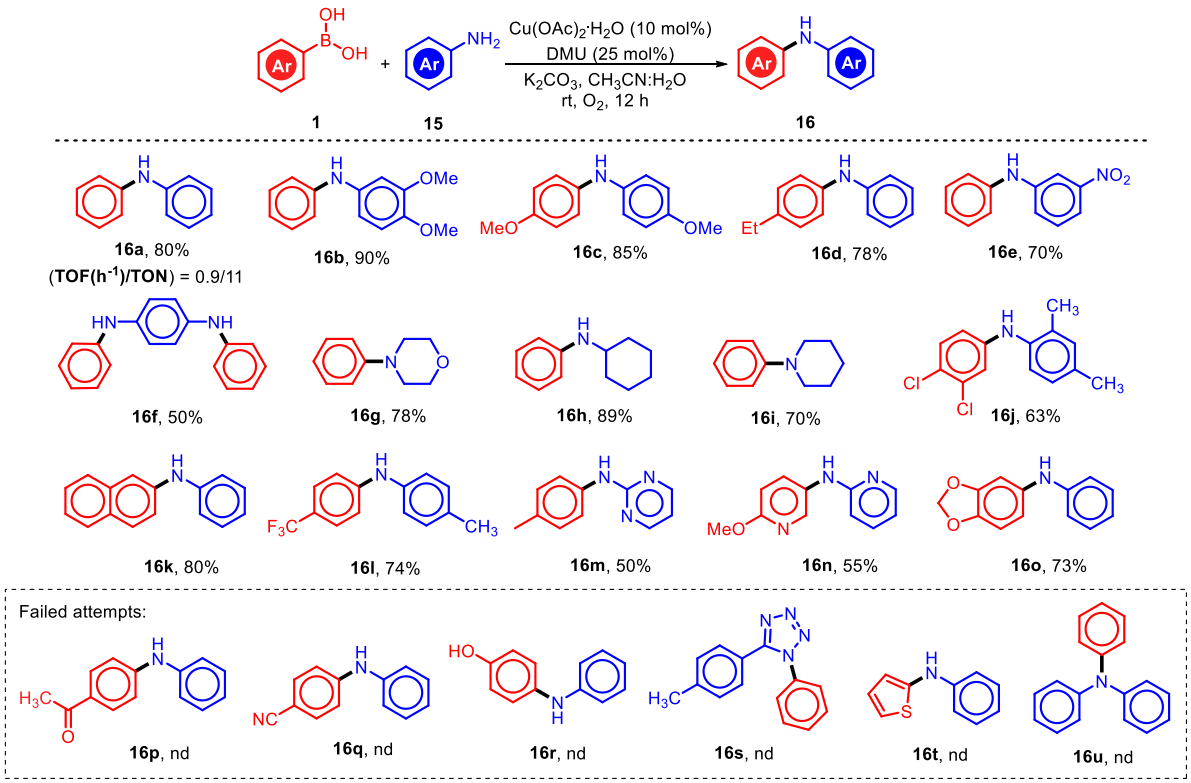
4.4.3 *Substrate scope study*

An overall picture of substrate scope of Chan-Lam cross-coupling of arylboronic acids (**1**) with anilines (**15**) using the optimized reaction condition (Table **4.1**, entry **9**) is shown in Table **4.2**.

The developed reaction condition was applied to a variety of arylboronic acids and anilines. The unsubstituted diphenylamine (**16a**) was obtained in a decent yield of 77%. Common to Chan-Lam arylation reactions, electronic factors played an interesting role in increasing or decreasing the yields of the desired products. The developed protocol was useful for boronic acids with EDGs (**16c**, **16d**) and EWGs (**16l**), along with naphthylboronic acid (**16k**). Similarly, anilines with EDGs (**16b**, **16c**) and EWGs (**16e**) were also tolerated with the methodology. Cyclic primary alkyl amines like cyclohexylamine (**16h**) and cyclic secondary amines like morpholine (**16g**) and piperidine (**16i**) exhibited decent reactivity. Interesting substrates like double *N*-arylation of *p*-phenylenediamine (**16f**) and multi-substituted diphenylamine (**16j**) could be synthesized in decent yields as well. Chan-Lam arylation products bearing a heterocyclic boronic acid (**16o**), a heteroarylamine (**16m**) and that bearing both heteroaromatic fragments (**16n**) were also produced in moderate yields.

In practice, a conventional Chan-Lam cross-coupling reaction is hindered by three side reactions: protodeboronation, oxidation and oxidative homocoupling of arylboronic acids [43]. However, meticulous screening of reaction conditions can easily help to overcome unwanted side products and maximize the formation of desired products.

Table 4.2 Scope exploration for the Chan–Lam cross–coupling of arylboronic acids (**1**) with anilines (**15**).[a]



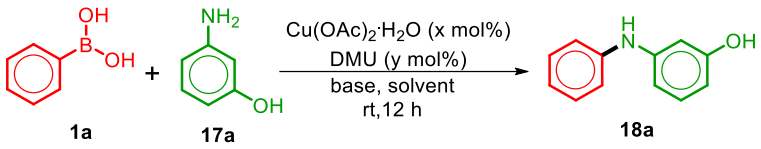
[a]*Reaction conditions*: Aniline (**15**, 0.75 mmol), Arylboronic acid (**1**, 1.2 mmol), $Cu(OAc)_2{\cdot}H_2O$ (10 mol%), DMU (25 mol%), K_2CO_3 (1 equiv.), $CH_3CN{:}H_2O$ (2:3), r.t.= room temperature (27 °C), 12 h; nd-not detected

In addition to all the above synthesized diphenylamine derivatives, some substrates did not pertain to our protocol and underwent unwanted side reactions. The boronic acid counterpart of products (**16p**) and (**16r**) i.e. 4-acetylphenylboronic acid and 4-hydroxyphenylboronic acid underwent protodeboronation predominantly to produce phenol and acetophenone respectively under the given reaction conditions. On the other hand, 4-cyanophenylboronic acid (precursor of **16q**) suffered exclusive homocoupling and did not give the desired product (**16q**). Along similar lines, attempts with **16s**, **16t** and **16u** were not obtained at all with this methodology.

4.4.4 *Chemoselectivity of the catalyst*

Next, the chemoselectivity of Cu^{II}–DMU complex was screened. 3-aminophenol (**17a**) was chosen as the model substrate for this purpose. The reaction conditions were investigated for chemoselective Chan-Lam cross-coupling of phenylboronic acid (**1a**) with 3-aminophenol (**17a**) and the results are presented in Table **4.3**.

Table 4.3 Investigation of reaction conditions for the Chemoselective Chan-Lam cross-coupling of phenylboronic acid (**1a**) with 3-aminophenol (**17a**).[a]



Entry	x (mol%)	y (mol%)	Base	Solvent	Yield[b](%)
1	10	25	K_2CO_3	CH_3CN:H_2O (2:3)	50
2	10	25	K_2CO_3	CH_3CN	45
3	10	25	K_2CO_3	1,2-DCE	60
4[c]	10	25	K_2CO_3	1,2-DCE	64
5[c],[d]	10	25	K_2CO_3	1,2-DCE	70
6[c],[d]	10	25	Et_3N	1,2-DCE	72
7[c],[d]	20	50	Et_3N	1,2-DCE	75
8[c],[d],[e]	**20**	**50**	**Et_3N**	**1,2-DCE**	**78**
9[c],[d]	20	50	Et_3N	Toluene	NR
10[c],[d]	20	50	Et_3N	^{t}BuOH	20
11[c],[d]	20	50	Et_3N	MeOH	43
12[c],[d]	20	50	Na^{t}OBu	1,2-DCE	65

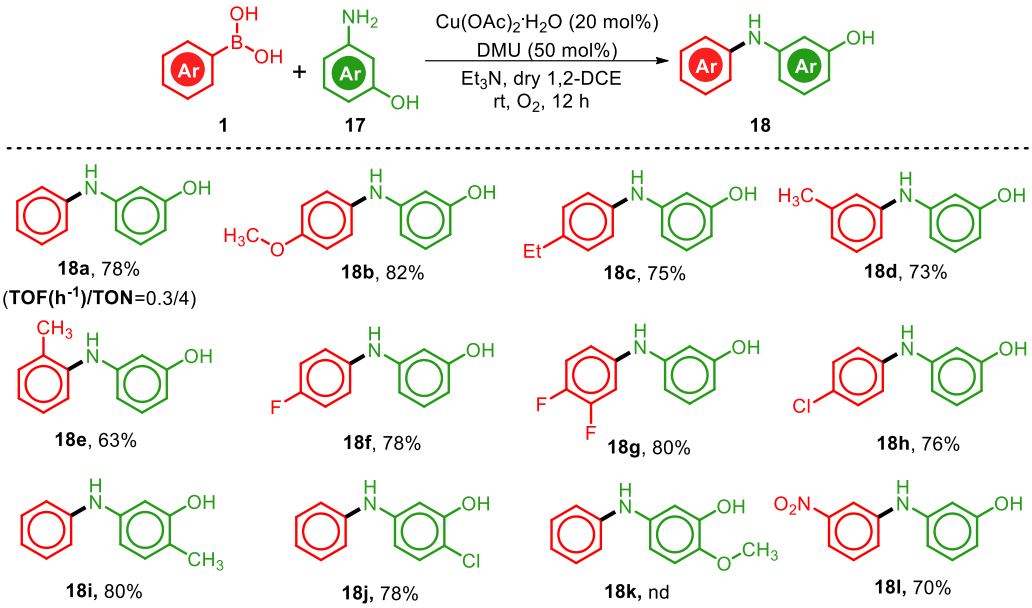
[a]*Reaction conditions*: 3-Aminophenol (**17a**, 0.75 mmol), Phenylboronic acid (**1a**, 1.3 mmol, 1.7 equiv.), $Cu(OAc)_2·H_2O$ (20 mol%), DMU (50 mol%), Et_3N (2 equiv.), dry 1,2-DCE (4 mL), r.t. = room temperature , 12 h; [b]Isolated yield with respect to 3-Aminophenol; [c]Dry solvents were used; [d]reaction carried under oxygen atmosphere; [e]1.3 mmol of Phenylboronic acid was used.

Careful optimization of the amount of Cu^{II} and DMU shows that 20 mol% of $Cu(OAc)_2·H_2O$ was necessary for the chemoselective arylation. Accordingly, the amount of DMU was fixed at 50 mol% to maintain the desired ratio in the *in-situ* generated Cu^{II}–DMU complex. Among the bases, K_2CO_3 and NaO^{t}Bu could not serve the purpose (45-70%, Table **4.3**, entries **1**-**5** and **12**) and Et_3N was screened, owing to its relevance in Chan-Lam cross-coupling. As seen, Et_3N gave the highest conversion of 78% (Table **4.3**, entries **6**-**11**). It is supposed to enhance the re-oxidation of Cu^{I} to Cu^{II}, help in better generation of the active Cu^{II}–complex and prevent its reversion to the inactive paddlewheel species [44]. Among solvents, it was observed that dry solvents were necessary to completely suppress the oxidation of phenylboronic acids. After a careful

investigation of some dry solvents, 1,2−DCE was chosen for better yield (78%, Table **4.3**, entries **3**-**8**). Subsequently, the final optimized reaction condition was fixed as 20 mol% of $Cu(OAc)_2 \cdot H_2O$, 50 mol% of DMU with 2 equiv. of Et_3N in dry 1,2-DCE (78%, Table **4.3**, entry **8**).

Table **4.4** summarises the various Chan-Lam arylated products obtained by the chemoselective *N*-arylation of 3-aminophenols under the developed reaction condition with Cu^{II}–DMU complex. The absence of electronic effects gave the unsubstituted arylated 3-aminophenol in good yield (78%, **18a**). Phenylboronic acids with EDGs like 4−OMe (**18b**), 4−Et (**18c**) and 3−Me (**18d**) have given good yields (82%, 75% and 73% respectively) of the desired Chan-Lam product. However, the conversion decreased to 63% for arylation with 2−Me phenylboronic acid, which may be due to the steric effect and competing secondary reactions (**18e**). The developed protocol also favoured arylation with phenylboronic acids having EWGs like $3-NO_2$ (**18l**) and weakly deactivating halogens (**18f**, **18g**, **18h**) in decent yields. With respect to aminophenols, EDGs provided very good yields of the corresponding *N*-arylated product (**18i** and **18j**). Initially, this reaction was very susceptible to the formation of phenol as a by-product, however, “dry” solvents and their careful optimization helped to suppress the oxidation product to a large extent. Although 3-Nitrophenylboronic acid underwent protodeboronation to nitrobenzene under the given reaction conditions, it gave the desired product (**18l**) in 70% yield. Interestingly, aminophenol with –OMe did not react at all under the developed protocol (**18k**). It probably deactivates the catalyst by the formation of an inactive Cu^{II}–amine complex [45].

Table 4.4 Scope exploration for the Chemoselective Chan-Lam cross-coupling of arylboronic acids (**1**) with 3-aminophenols (**17**).[a]

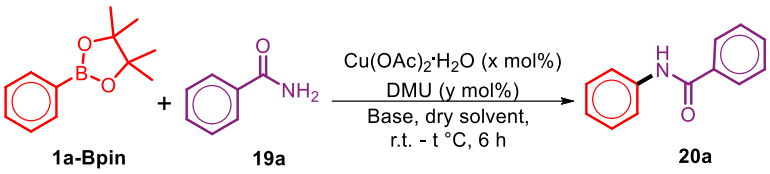


[a]*Reaction conditions*: 3-Aminophenols (**17**, 0.75 mmol), Arylboronic acid (**1**, 1.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (20 mol%), DMU (50 mol%), Et_3N (2 equiv.), dry 1,2-DCE (4 mL), rt = room temperature, 12 h; nd-not detected.

4.4.5 *Extension of scope of reaction*

The activity of the Cu^{II}–DMU complex was then targeted at the selective "monoarylation" of primary amides, owing to the dominance of the *N*-arylamide scaffold in pharmaceuticals [46]. Primary amides do not undergo *N*-arylation readily and easily adoptable methods of arylation are few. They have been previously reported to be *N*-arylated with diazonium salts [47], Goldberg arylating agent-aryl halides [48], aryltrimethoxysilane [49], Iodoferrocene [50], and hetero(aryl) electrophiles [51]. However, very few studies have been executed with boronic acid and its derivatives [52]. Hence, we attempted to study the Chan–Lam *N*–arylation of primary amides with arylboronic acid pinacol esters (BPin) as the arylating source [53]. BPin are more stable and more accessible arylating agents in comparison to phenylboronic acids and their conversion to the corresponding acid is simple [54]. The optimization of reaction conditions of Chan-Lam cross-coupling of Phenylboronic acid pinacol ester (**1a-BPin**) with benzamide (**19a**) is presented in Table **4.5**.

Table 4.5 Investigation of reaction conditions for the Chan-Lam cross-coupling of Phenylboronic acid pinacol ester (**1a-BPin**) with Benzamide (**19a**).[a]



Entry	$Cu(OAc)_2 \cdot H_2O$	DMU	Base (equiv.)	Solvent	Yield[b](%)
1	10	25	K_3PO_4 (1)	$CH_3CN:H_2O$	NR
2	10	25	K_3PO_4 (1)	1,2-DCE	NR
3	10	25	K_3PO_4 (1)	1,2-DCE:H_2O (3:2)	NR
4	10	25	K_3PO_4 (1)	^{t}BuOH	Trace
5	10	25	K_3PO_4 (1)	^{t}BuOH:DCE (3:2)	Trace
6	10	25	K_3PO_4 (2)	^{t}BuOH	Trace
7	10	25	K_3PO_4 (2)	^{t}BuOH:CH_3CN	Trace
8	10	25	K_3PO_4 (2)	^{t}BuOH:MeOH	20
9	10	25	K_3PO_4 (2)	^{t}BuOH:IP	Trace
10	10	25	K_3PO_4 (2)	^{t}BuOH:Dioxane	Trace
11	10	25	K_3PO_4 (2)	^{t}BuOH:DMF	Trace
12	10	25	K_3PO_4 (2)	^{t}BuOH:DMSO	Trace
13	10	25	K_3PO_4 (2)	Dry MeOH	30
14	10	25	K_2CO_3 (2)	Dry MeOH	NR
15	10	25	Na^{t}OBu (2)	Dry MeOH	30
16	10	25	DBU (2)	Dry MeOH	40
17	10	25	DIPEA (2)	Dry MeOH	35
18	10	25	Et_3N (2)	Dry MeOH	46
19	10	25	DABCO (2)	Dry MeOH	Trace
20	10	25	DMAP (2)	Dry MeOH	Trace
21	20	50	Et_3N (2)	Dry MeOH	45
22[c]	10	25	Et_3N (2)	Dry MeOH	48
23[d]	10	25	Et_3N (2)	Dry MeOH	55
24[e]	10	25	Et_3N (2)	Dry MeOH	54
25[d],[f]	10	25	Et_3N (2)	Dry MeOH	70
26 [d],[f],[g]	**10**	**25**	**Et_3N (2)**	**Dry MeOH**	**80**
27 [d],[f],[h]	10	25	Et_3N (2)	Dry MeOH	82

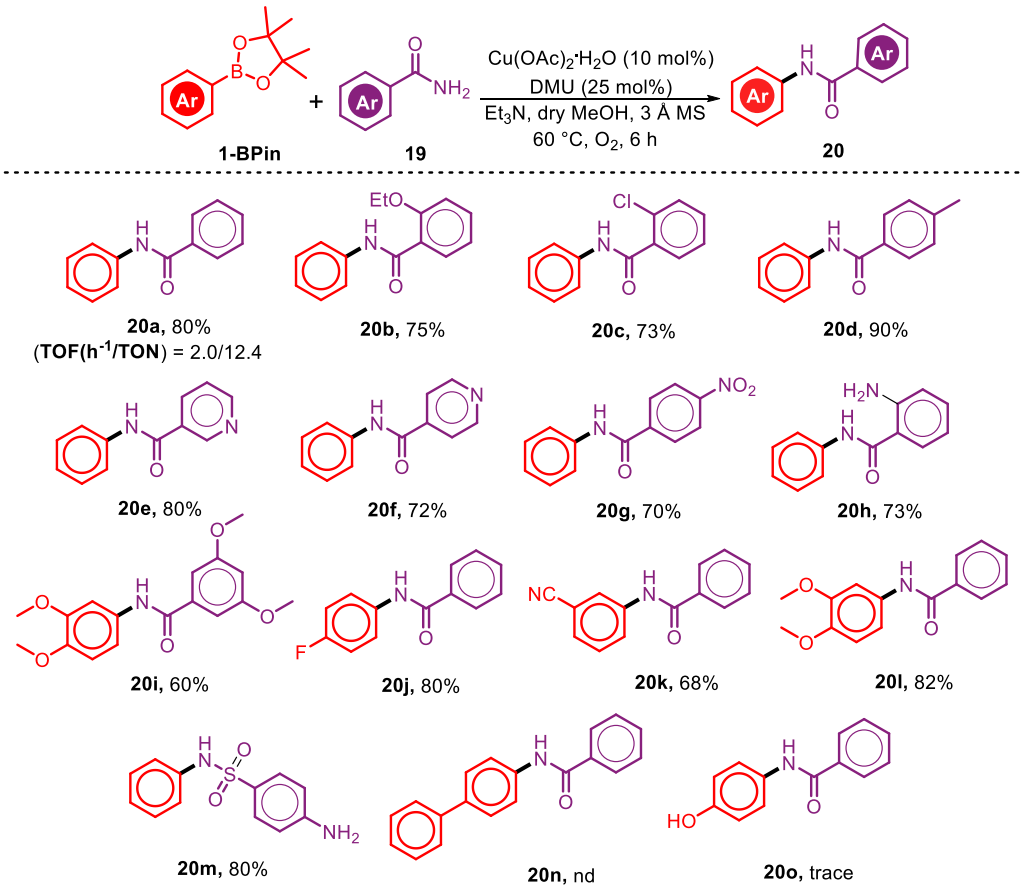
[a]*Reaction conditions:* Benzamide (**19a**, 0.75 mmol), Phenylboronic acid pinacol ester (**1a-BPin**, 1.3 mmol, 1.7 equiv.), $Cu(OAc)_2 \cdot H_2O$ (10 mol%), DMU (25 mol%), Et_3N (2 equiv.), dry MeOH (4 mL), 6 h; [b] Isolated yield based on benzamide, **19**; [c],[d],[e] Reaction was carried out with 1.25, 1.3 and 1.4 mmol of BPin respectively, [f] reaction was carried under oxygen atmosphere; [g],[h] Reaction temperature was maintained at 60 °C and 80 °C respectively; NR- no reaction.

It was observed that even after a meticulous study of polar solvents, non-polar solvents and their combination, the desired *N*-arylated product was not obtained except for an unsatisfactory 20% yield with ^{t}BuOH:MeOH solvent combination (Table **4.5**, entries **1**-**12**). Inspired by the effect of dry solvents and molecular sieves (MS) in suppressing oxidation by-products, further optimization studies were carried out with dry methanol and with 3 Å MS. Use of MS was not detrimental in the previous methodologies; however, it played an important role in case of primary amides. The effect of bases (both organic and inorganic) was then screened. The amount of base was fixed at 2 equivalents for all the optimization studies as no conversion was obtained with 1 equivalent of the base. It was seen that except for K_2CO_3, inorganic bases like K_3PO_4 and Na^{t}OBu gave slightly higher but similar yields of the corresponding secondary amides (Table **4.5**, entries **13**-**15**). On the other hand, organic bases like DBU, DIPEA, Et_3N, DABCO and DMAP provided improved yields of the product and the highest yield was obtained with Et_3N (Table **4.5**, entries **16**-**20**). An increase in the amount of Cu(II) and DMU to 20% and 50% respectively, did not provide significant conversion (Table **4.5**, entry **21**).

Subsequently, the amount of aryl BPin was also altered to check the dependence of the yield of *N*-arylated product on the equivalence of the arylating agent (Table **4.5**, entries **22**-**24**). The best yield of 55% was obtained with 1.3 mmol of aryl BPin. When the reaction was conducted in the presence of an oxygen balloon, the reaction yield rocketed as anticipated, to 70% (Table **4.5**, entry **25**). On checking the dependence of reaction yield on temperature, the *N*-arylated amide was obtained in 80% yield at 60 °C (Table **4.5**, entry **26**). Although the obtained yield slightly increased to 82% on further increasing the reaction temperature to 80 °C (Table **4.5**, entry **27**), the final optimized condition was fixed at 60 °C on energy sustainable grounds.

The optimized reaction condition (Table **4.5**, entry **26**) endured a variety of primary amides with EDGs and EWGs and transformed to the desired secondary amides (Table **4.6**).

Table 4.6 Scope exploration for the Chan–Lam cross-coupling of arylboronic acid pinacol esters (**1-BPin**) with primary amides (**19**).[a]



[a]*Reaction conditions*: benzamides (**19**, 0.75 mmol), Phenylboronic acid pinacol ester (**1-BPin**, 1.3 mmol), $Cu(OAc)_2 \cdot H_2O$ (10 mol%), DMU (25 mol%), Et_3N (2 equiv.), dry MeOH (4 mL), 6 h; nd-not detected.

Benzamides with EDGs like 2–OEt (**20b**) and 4–Me (**20d**), along with weakly deactivating 2–Cl (**20c**) gave very good yields of the corresponding secondary amide. A strongly withdrawing group 4–NO_2 on the primary amide slightly decreased the conversion to 70% (**20g**). The developed methodology was also successful in selective *N*-arylation of the primary amide group in the presence of an amine group (**20h**) and also in the synthesis of a highly crowded secondary amide in satisfactory yields of 73% and 60% respectively. APIs like nicotinamide (**20e**), isonicotinamide (**20f**) and sulfonamide (**20m**) bearing a single amide group could also be successfully arylated without significant difference in their respective yields. In the case of aryl BPin, the presence of EDG like 3,4–OMe (**20l**) and halogen 4–F (**20j**) on the boronate ester provided increased yields of the *N*-arylated secondary amine in comparison to the presence of a strong withdrawing

group like 3−CN (**20k**). For initial studies, the developed catalyst was screened with phenylboronic acids as the arylating source. However, after a series of investigations and tuning of reaction conditions, we could not suppress the homocoupling of phenylboronic acids completely. This may be because primary amides are chemically difficult substrates and competing reactions can easily take place. Further, it was observed that portion addition of boronic acids to the reaction mixture resulted in greater homocoupling products. The use of less polar solvents also resulted in greater homocoupling of boronic acids. Hence, we switched our studies to a more stable form of boronic acid, i.e. phenylboronic acid pinacol ester (**1a-BPin**). Aryl B-pin could successfully diminish the formation of coupling products. With regard to some specific substrates, it was observed that biphenylboronic pinacol ester and 4-Hydroxyphenylboronic pinacol ester underwent oxidation and protodeboronation respectively under the given reaction conditions. While the corresponding 4−Hydroxyphenylbenzamide (**20o**) was obtained in trace amount, the biphenylbenzamide (**20n**) was not obtained at all.

4.4.6 *Applications*

The prowess of the developed homogeneous catalyst Cu^{II}−DMU and the optimized protocol (Table **4.5**, entry **26**) was applied for site-selective post modification of two APIs; Acetazolamide, a diuretic (Figure **4.4**, **21a**) and Glibenclamide, a hypoglycemic (Figure **4.4**, **21b**). Each of these molecules possesses two different amide sites. It was seen that the developed protocol with Cu^{II}−DMU could selectively arylate the sulfonamide group with aryl BPin in satisfactory yields (Figure **4.4**, **22a** and **22b**). In the case of Glibenclamide, loss of an isocyanate molecule takes place which is a common metabolite of glibenclamide [55]. The remaining bioactive sulfonylurea moiety was *N*-arylated at the sulfonamide group (**22b**). The introduction of the aryl group enhances the lipophilicity of the molecule.

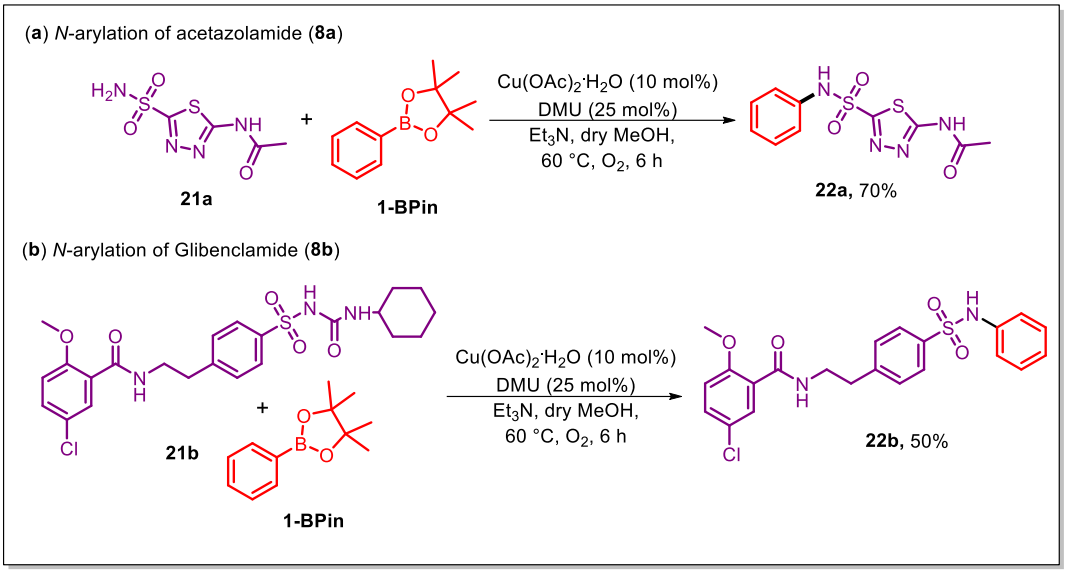


Figure **4.4** Site-selective post modifications of APIs

4.4.7 *Plausible Mechanism*

As already discussed in Chapter 1, the Chan–Lam reaction is largely dependent on the reaction conditions and the substrates, unlike other Pd-catalyzed C–N bond formation reactions. To simply put, the coordination of *N*-nucleophile promotes the denucleation of the paddlewheel complex into monomer species in solution. Subsequently abstraction of a proton from the amine takes place in the disproportionation step and the resultant Cu^{II}–aryl species is oxidized by another Cu^{II} complex to form the Cu^{III}–aryl species after transmetallation. The *O*–donor ligand *N,N'*–dimethylurea (DMU) employed in this work is expected to increase the electron density on the Cu^{II}–aryl species after transmetallation and promote faster oxidation to form the Cu^{III}–aryl species. A slower disproportionation step would lead to the accumulation of the Cu(II)-aryl species and result in the formation of unwanted side-products. The difference in the electronic environment also facilitates the rate-determining disproportionation step. The Cu^{III}–aryl species undergoes facile reductive elimination to release the *N*–arylated product. The catalyst is regenerated through re-oxidation by O_2. In the same context, although pinacol esters (BPin) are accused of inhibiting the transmetallation process through the formation of a substantially stable Cu^{II}–pinacol complex [56], such hindrances did not suppress reactivity in this methodology.

4.4.8 *Conclusion*

The current work explores *N*,*N'*−dimethylurea as an auxiliary in inexpensive and versatile Cu-catalysis. The developed Cu^{II}–DMU catalyst is cheap, free from the prior synthesis of the metal-complex, chemoselective and suitable for mono-arylation of primary amides. Unlike most homogeneous catalysts, it exhibits a general reactivity to anilines, 3-aminophenols and primary amides, and provides good to very good yields. The synthetic utility of the catalyst is demonstrated through a site-selective post-modification of two active pharmaceutical ingredients (APIs). Substrate-dependent limitations of the developed protocol are few and all of them are characteristic of Chan-Lam cross-coupling reactions. Although detailed mechanistic studies are not included in the current context, it is certainly under the scope of ongoing studies. We believe that the developed catalyst extends the scope of Chan-Lam cross-couplings through the exploration of a simple and stable Cu-catalytic system in achieving a broad functional group tolerance and can be considered as an industrially viable methodology. The homogeneous catalytic system can also be explored for achieving greater efficiency in other C−N cross−coupling reactions.

4.4.9 *Experimental Section*

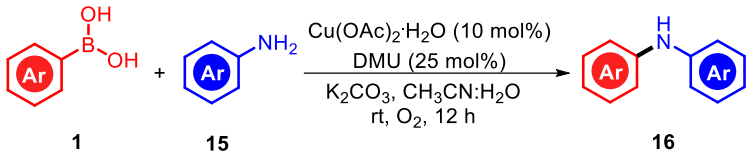
4.4.9.1 *General Information*

All the chemicals used for the reactions were procured commercially and used without further purification. The progress of the reaction was monitored through thin layer chromatography on Merck Kieselgel Silica gel $60F_{254}$ plates using short wave UV light (λ=254 nm). The products were purified by column chromatography using Silica gel (60-120 mesh). The identification of the purified products was carried out by NMR spectroscopy. The ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz JEOL NMR spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Chemical shifts for both ^{1}H (δ_H) and ^{13}C (δ_C) NMR are assigned in parts per million (ppm) using TMS (0 ppm) as the internal reference and $CDCl_3$ and DMSO-d_6 as solvent ($CDCl_3$: δ_H = 7.25 ppm and δ_C = 77.1 ppm; DMSO-d_6: δ_H = 2.5 ppm, DMSO-d_6 absorbed water = 3.3 ppm and δ_C = 40.0 ppm). The multiplicities of the signals are assigned as: s= singlet, d= doublet, t= triplet, q= quartet and m= multiplet. Raw NMR data was processed using MestReNova

software. Single crystal X-ray diffractions were collected on a Bruker SMART APEX-II CCD.

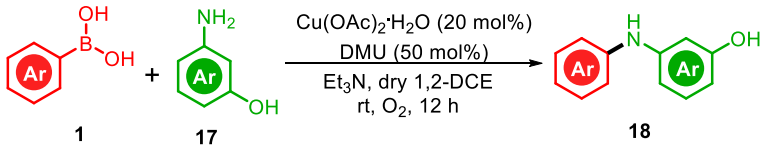
4.4.9.2 *General Experimental Procedure*

A. *General experimental procedure for N-arylation of Anilines (**16**)*



In a 50 mL round-bottomed flask with a magnetic stirring bead, 10 mol% of $Cu(OAc)_2 \cdot H_2O$ (0.0182 g) and 25 mol% of DMU (0.022 g) were taken in (2+3)= 5 mL of $CH_3CN:H_2O$. To it, arylboronic acid, **1** (1.2 mmol, 1.6 equiv.), aniline derivative, **15** (0.75 mmol) and K_2CO_3 (1 equiv.) were added. The reaction vessel was then sealed, fitted with an oxygen balloon *via* a needle and stirred at room temperature for 12 h. The progress of the reaction was monitored using TLC. After 12 h, the resulting reaction mixture was extracted in ethyl acetate, washed with brine and concentrated on a rotary evaporator under reduced pressure. The reaction mixture was purified by column chromatography using ethyl acetate-hexane as an eluent to obtain the pure product (**16**). Further, the products were checked for the presence of Cu, if any, by ICP-AES.

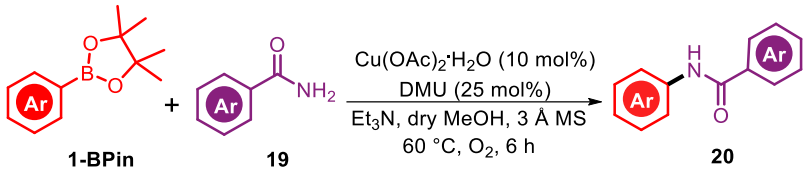
B. *General experimental procedure for N-arylation of 3-Aminophenols (**18**)*



In a 50 mL round-bottomed flask with a magnetic stirring bead, 20 mol% of $Cu(OAc)_2 \cdot H_2O$ (0.0372 g) and 50 mol% of DMU (0.044 g) were taken in 4 mL of dry 1,2-DCE. To it, arylboronic acid, **1** (1.3 mmol, 1.7 equiv.), 3-aminophenol derivative, **17** (0.75 mmol) and freshly distilled Et_3N (2 equiv.) were added. The reaction vessel was then sealed, fitted with an oxygen balloon *via* a needle and stirred at room temperature for 12 h. The progress of the reaction was monitored using TLC. After 12 h, the resulting reaction mixture was extracted in ethyl acetate, washed with brine and concentrated on a rotary evaporator under reduced pressure. The reaction mixture was purified by column chromatography using ethyl acetate-hexane as an eluent to obtain the pure

product (**18**). Further, the products were checked for the presence of Cu, if any, by ICP-AES.

C. *General experimental procedure for N-arylation of Amides (**20**)*



In a 100 mL two-neck round-bottomed flask with a magnetic stirring bead and few molecular sieves (3 Å), 10 mol% of $Cu(OAc)_2 \cdot H_2O$ (0.0182 g) and 25 mol% of DMU (0.022 g) was taken in 4 mL of dry MeOH. To it, arylboronic acid pinacol ester, **1-BPin** (1.3 mmol, 1.7 equiv.), benzamide derivative, **19** (0.75 mmol) and freshly distilled Et_3N (2 equiv.) were added. The reaction vessel was then sealed, fitted with an oxygen balloon *via* a needle and stirred at 60 °C for 6 h. The progress of the reaction was monitored using TLC. After 6 h, the resulting reaction mixture was extracted in ethyl acetate, washed with brine and concentrated on a rotary evaporator under reduced pressure. The reaction mixture was purified by column chromatography using ethyl acetate-hexane as an eluent to obtain the pure product (**20**). Further, the products were checked for the presence of Cu, if any, by ICP-AES.

4.4.9.3 *Single crystal X-ray diffraction*

Single crystal X-ray diffractions were collected on a Bruker SMART APEX-II CCD diffractometer using Mo Kα (λ =0.71073 Å) radiation. Bruker SAINT software has been employed for reducing the data and SADABS for correcting the intensities of absorption [57]. The structure was solved and refined using SHELXL with anisotropic displacement parameters for non-H atoms. In the crystal structure, H-atoms are located experimentally, whereas C–H atoms were fixed geometrically using the HFIX command in SHELX-TL [58]. No missed symmetry was observed in the final check of the CIF file using PLATON [59,60]. Information on crystallographic parameters for all structures is furnished in Table **4.7**.

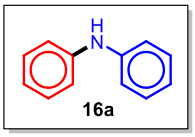
Table **4.7** Crystallographic parameters of **E**

Crystal data	**$[Cu_2(OAc)_4(DMU)_2]$ (E)**
Formula unit	$C_{14}H_{28}O_{10}Cu_2N_4$
Formula weight ($gmol^{-1}$)	539.48
Crystal system	Monoclinic
T [K]	100
a [Å]	10.240(7)
b [Å]	8.487(5)
c [Å]	13.274(9)
α [°]	90
β [°]	107.29(4)
γ [°]	90
Volume [$Å^3$]	1101.5(12)
Space group	$P2_1/n$
Z	2
D_{cal} [g/cm^3]	1.627
R_1, *w*R2	0.453, 0.0878
Instrument	Bruker CCD Apex II
CCDC No	2183901

4.4.10 *Characterization data of the N–aryl derivatives:*

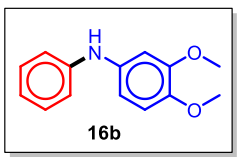
4.4.10.1 *^1H and ^{13}C NMR spectral analysis of N–arylanilines (**16**)*

Diphenylamine (**16a**)



Synthesized as per the general experimental procedure A; obtained as a colourless solid, Yield: 80% (101 mg); ^1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 6.78 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 4H), 7.19 (t, *J* = 8.0 Hz, 4H), 8.12 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 117.3, 120.1, 129.7, 143.9. Spectroscopic data was consistent with literature [27].

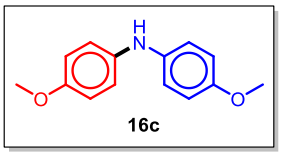
3,4–Dimethoxy-*N*-phenylamine (**16b**)



Synthesized as per the general experimental procedure A; obtained as a colourless solid, Yield: 90% (154 mg); ^1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 3.67 (s, 6H), 6.59 (d, *J* = 8 Hz, 1H), 6.66-

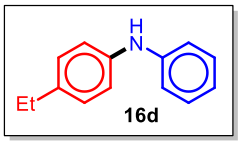
6.69 (m, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 2H), 7.12 (t, J = 8.0 Hz, 2H), 7.81 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 55.8, 56.5, 104.7, 110.4, 113.6, 115.7, 118.9, 129.6, 137.3, 143.7, 145.3, 149.9. Spectroscopic data was consistent with literature [61].

Bis−(4−methoxyphenyl)amine (**16c**)



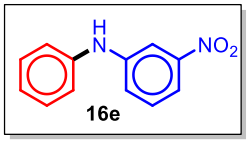
Synthesized as per the general experimental procedure A; obtained as a colourless solid, Yield: 85% (146 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 3.64 (s, 6H), 6.76 (d, J = 8.0 Hz, 4H), 6.87 (d, J = 8.0 Hz, 4H), 7.46 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 55.7, 115.0, 118.5, 138.5, 153.3. Spectroscopic data was consistent with literature [62].

4−Ethyl−*N*−phenylamine (**16d**)



Synthesized as per the general experimental procedure A; obtained as a light yellow oil, Yield: 75% (110 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.11 (t, J = 8.0 Hz, 3H), 2.48 (q, J = 8.0 Hz, 2H), 6.70-6.73 (m, 1H), 6.96-6.98 (m, 4H), 7.03 (d, J = 8.0 Hz, 2H), 7.14 (t, J = 8.0 Hz, 2H), 7.96 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 16.4, 28.0, 116.4, 118.0, 119.5, 128.8, 129.5, 135.8, 141.4, 144.5. Spectroscopic data was consistent with literature [63].

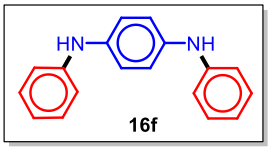
3−Nitro−*N*−phenylamine (**16e**)



Synthesized as per the general experimental procedure A; obtained as a orange solid, Yield: 70% (112 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 6.93 (t, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 8.0 Hz, 2H), 7.36-7.43 (m, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.75 (s, 1H), 8.69 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 109.2, 113.6, 119.2, 121.9, 122.2, 130.0, 130.9,

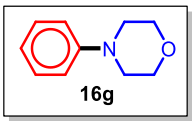
142.0, 145.8, 149.2. Spectroscopic data was consistent with literature [27].

N^1,N^4–diphenylbenzene–1,4-diamine (**16f**)



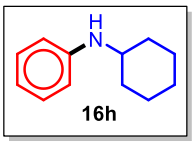
Synthesized as per the general experimental procedure A; obtained as a off-white solid, Yield: 50% (98 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 6.67 (t, J = 8 Hz, 2H), 6.91 (d, J = 8 Hz, 4H), 6.99 (s, 4H), 7.12 (t, J = 8 Hz, 4H), 7.84 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 115.5 , 118.8, 120.2, 129.5, 136.9, 145.4. Spectroscopic data was consistent with literature [64].

4–Phenylmorpholine (**16g**)



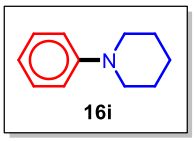
Synthesized as per the general experimental procedure A; obtained as a light yellow solid, Yield: 78% (95 mg) ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 3.03-3.05 (m, 4H), 3.68-3.70 (m, 4H), 6.76 (t, J = 8 Hz, 1H), 6.89 (d, J = 8 Hz, 2H), 7.18 (t, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 48.9, 66.6, 115.6, 119.6, 129.5, 151.6. Spectroscopic data was consistent with literature [27].

N–Cyclohexylamine (**16h**)



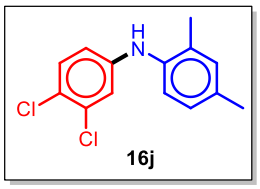
Synthesized as per the general experimental procedure A; obtained as a colourless oil, Yield: 89% (117 mg), ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.07-1.19 (m, 3H), 1.25-1.34 (m, 2H), 1.54-1.58 (m, 1H), 1.66-1.71 (m, 2H), 1.88-1.91 (m, 2H), 3.11-3.16 (m, 1H), 5.22 (s, 1H), 6.44 (t, J = 8 Hz, 1H), 6.52 (d, J = 8 Hz, 2H), 7.00 (t, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 25.1, 26.2, 33.1, 51.1, 112.8, 115.6, 129.3, 148.5. Spectroscopic data was consistent with literature [27].

1−Phenylpiperidine (**16i**)



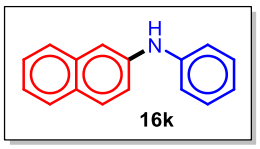
Synthesized as per the general experimental procedure A; obtained as a light yellow oil, Yield: 65% (78 mg), ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.46-1.49 (m, 2H), 1.53-1.59 (m, 4H), 3.05-3.07 (m, 4H), 6.69 (t, J = 8 Hz, 1H), 6.86 (d, J = 8 Hz, 2H), 7.14 (t, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 24.4, 25.7, 50.1, 116.3, 118.8, 129.4, 152.2. Spectroscopic data was consistent with literature [65].

N−(3,4−dichlorophenyl)−2,4−dimethylaniline (**16j**)



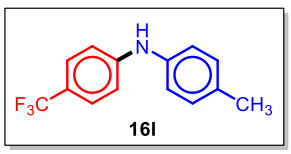
Synthesized as per the general experimental procedure A; obtained as a colourless solid, Yield: 63% (126 mg), ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.07 (s, 3H), 2.19 (s, 3H), 6.61 (d, J = 8 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 8 Hz, 2H), 7.24 (d, J = 8.0 Hz, 1H), 7.76 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 18.1, 20.9, 114.6, 115.2, 123.9, 127.8, 131.2, 131.8, 132.2, 132.50, 133.8, 137.2, 147.2.

N−phenylnapthalen−2−amine (**16k**)



Synthesized as per the general experimental procedure A; obtained as a colourless solid, Yield: 80% (131 mg), ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.18 (d, J = 8 Hz, 2H), 7.20-7.27 (m, 4H), 7.31-7.34 (m, 1H), 7.44 (s, 1H), 7.63 (d, J = 8 Hz, 1H), 7.70 (d, J = 8 Hz, 1H), 7.73 (d, J = 8 Hz, 1H), 8.40 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 109.5, 117.8, 120.4, 120.7, 123.2, 126.7, 127.9, 128.2, 128.6, 129.3, 129.7, 134.9, 141.9, 143.6. Spectroscopic data was consistent with literature [27].

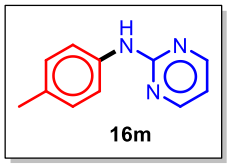
N−methyl−*N*−(4−trifluoromethyl)phenyl)aniline (**16l**)



Synthesized as per the general experimental procedure A; obtained as a yellow solid, Yield: 74% (139 mg), ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.26 (s, 3H), 7.08 (d, J = 8 Hz, 4H),

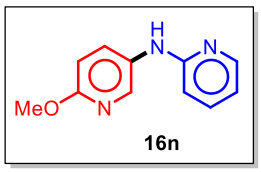
7.13 (d, *J* = 8 Hz, 2H), 7.48 (d, *J* = 8 Hz, 2H), 8.56 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 20.8, 114.5, 120.3, 124.1, 127.0, 130.2, 131.5, 139.2, 148.6. Spectroscopic data was consistent with literature [66].

N−(*p*−tolyl)pyrimidin−2−amine (**16m**)



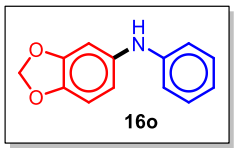
Synthesized as per the general experimental procedure A; obtained as a colourless solid, Yield: 50% (70 mg), ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.25 (s, 3H), 6.78-6.81 (m, 1H), 7.08 (d, *J* = 8 Hz, 2H), 7.63 (d, *J* = 8 Hz, 2H), 8.45 (d, *J* = 8 Hz, 2H), 9.47 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 20.8, 112.5, 119.4, 129.3, 130.6, 138.3, 158.4, 160.5. Spectroscopic data was consistent with literature [67].

N−(6−methoxypyridin−3−yl)pyridine−2−amine (**16n**)



Synthesized as per the general experimental procedure A; obtained as a yellow oil, Yield: 55% (82 mg), ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 3.76 (s, 3H), 6.64-6.67 (m, 1H), 6.71 (t, *J* = 8 Hz, 2H), 7.49 (t, *J* = 8 Hz, 1H), 7.97 (d, *J* = 8 Hz, 1H), 8.04 (d, *J* = 8 Hz, 1H), 8.35 (s, 1H), 8.87 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 53.4, 110.1, 110.5, 110.9, 114.4, 127.7, 131.4, 132.8, 133.0, 137.1, 137.7, 147.6, 149.0, 156.4, 157.3, 158.6.

N−phenylbenzo[*d*][1,3]dioxol−5−amine (**16o**)

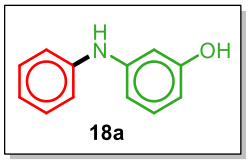


Synthesized as per the general experimental procedure A; obtained as a colourless solid, Yield: 73% (117 mg), ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 5.90 (s, 2H), 6.51 (dd, *J* = 8 Hz, 2 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.68-6.71 (m, 1H), 6.76 (d, *J* = 8 Hz, 1H), 6.90 (d, *J* = 8 Hz, 2H), 7.13 (t, *J* = 8 Hz, 2H), 7.85 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 101.3, 109.0, 111.3, 116.0, 119.3, 129.7, 138.3, 141.8, 145.2, 148.2. Spectroscopic data was

consistent with literature [61].

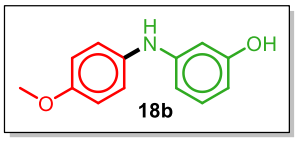
4.4.10.2 *^{1}H and ^{13}C NMR spectral analysis of 3−arylaminophenols (**18**)*

3−(Phenylamino)phenol (**18a**)



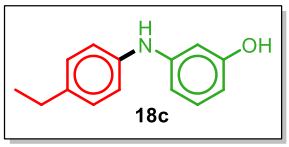
Synthesized as per the general experimental procedure B; obtained as a brown solid, Yield: 78% (108 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 6.21 (d, J = 8 Hz, 1H), 6.47 (t, J = 8 Hz, 2H), 6.76 (t, J = 8 Hz, 1H), 6.96 (t, J = 8 Hz, 1H), 7.02 (d, J = 8 Hz, 2H), 7.17 (t, J = 8 Hz, 2H), 7.98 (br s, 1H), 9.14 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 104.0, 107.4, 108.2, 117.5, 120.0, 129.6, 130.3, 143.9, 145.1, 158.7. Spectroscopic data was consistent with literature [68].

3−((4−Methoxyphenyl)amino)phenol (**18b**)



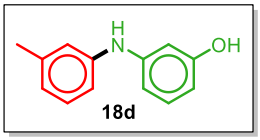
Synthesized as per the general experimental procedure B; obtained as a brown solid, Yield: 82% (132 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 3.66 (s, 3H), 6.08 (d, J = 8 Hz, 1H), 6.30 (d, J = 8 Hz, 2H), 6.81 (d, J = 8 Hz, 2H), 6.88 (t, J = 8 Hz, 1H), 6.97 (d, J = 8 Hz, 2H), 7.68 (br s, 1H), 9.04 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 55.6, 102.0, 106.2, 114.9, 121.2, 130.2, 136.6, 146.9, 154.2, 158.7. Spectroscopic data was consistent with literature [68].

3−((4−Ethylphenyl)amino)phenol (**18c**)



Synthesized as per the general experimental procedure B; obtained as a brown solid, Yield: 75% (120 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.10 (t, J = 8 Hz, 3H), 2.47 (q, J = 8 Hz, 2H), 6.15 (dd, J = 8 Hz, 1.2 Hz, 1H), 6.41 (t, J = 8 Hz, 2H), 6.90-6.95 (m, 3H), 7.02 (d, J = 8 Hz, 2H), 7.86 (br s, 1H), 9.10 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 16.4, 19.4, 103.0, 106.8, 107.5, 118.3, 128.8, 130.2, 135.7, 141.4, 145.7, 158.6.

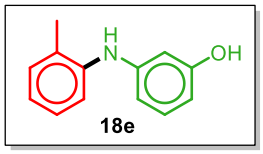
3−(*m*−tolylamino)phenol (**18d**)



18d

Synthesized as per the general experimental procedure B; obtained as a yellow solid, Yield: 73% (108 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.20 (s, 3H), 6.22 (d, J = 8 Hz, 1H), 6.48 (t, J = 8 Hz, 2H), 6.59 (d, J = 8 Hz, 1H), 6.84 (d, J = 8 Hz, 2H), 6.96 (t, J = 8 Hz, 1H), 7.06 (t, J = 8 Hz, 1H), 7.92 (br s, 1H), 9.16 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 21.7, 103.9, 107.4, 108.3, 114.7, 118.2, 120.9, 129.4, 130.3, 138.7, 143.9, 145.2, 158.7.

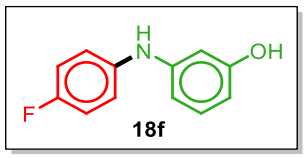
3−(*o*−tolylamino)phenol (**18e**)



18e

Synthesized as per the general experimental procedure **B**; obtained as a yellow oil, Yield: 63% (94 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.13 (s, 3H), 6.12 (dd, J = 8 Hz, 2 Hz, 1H), 6.24-6.28 (m, 2H), 6.84 (d, J = 8 Hz, 1H), 6.89 (t, J = 8 Hz, 1H), 7.05 (t, J = 8 Hz, 1H), 7.12 (t, J = 8 Hz, 2H), 7.21 (br s, 1H), 9.03 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 18.5, 103.1, 106.5, 107.6, 120.8, 122.4, 126.9, 130.2, 131.31, 141.8, 146.8, 158.6. Spectroscopic data was consistent with literature [68].

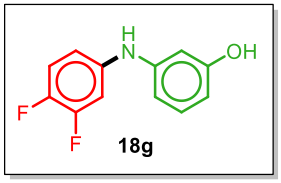
3−((4−Fluorophenyl)amino)phenol (**18f**)



18f

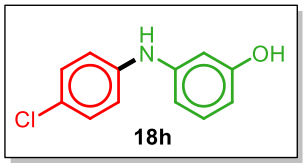
Synthesized as per the general experimental procedure B; obtained as a yellow oil, Yield: 78% (119 mg), ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 6.17 (d, J = 8 Hz, 1H), 6.37-6.41 (m, 2H), 6.92 (t, J = 8 Hz, 1H), 7.02 (d, J = 8 Hz, 4H), 7.93 (br s, 1H), 9.13 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 103.3, 107.2, 107.6, 116.1, 119.6, 130.3, 140.3, 145.7, 156.8 (d, $J_{C\text{-}F}$ = 240 Hz), 158.7. Spectroscopic data was consistent with literature [69].

3−((3,4−Difluorophenyl)amino)phenol (**18g**)



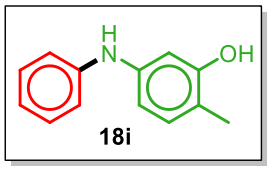
Synthesized as per the general experimental procedure B; obtained as a orange solid, Yield: 80% (132 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 6.31 (d, J = 8 Hz, 1H), 6.50 (d, J = 8 Hz, 2H), 6.83 (d, J = 8 Hz, 1H), 6.96-6.99 (m, 1H), 7.04 (m, 1H), 7.22-7.29 (m, 1H), 8.20 (br s, 1H), 9.27 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 104.4, 105.3, 105.5, 108.3, 108.6, 113.1, 118.0, 118.2, 130.4, 141.5, 143.5 (d, $J_{C\text{-}F}$ = 240 Hz), 144.3, 150.1 (d, J_{C-F} = 250 Hz), 158.7

3−((4−Chlorophenyl)amino)phenol (**18h**)



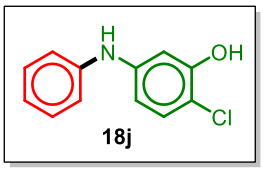
Synthesized as per the general experimental procedure B; obtained as a brown solid, Yield: 76% (125 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 6.23 (d, J = 8 Hz, 1H), 6.45 (d, J = 8 Hz, 2H), 6.95-7.01 (m, 3H), 7.19 (d, J = 8 Hz, 2H), 8.15 (br s, 1H), 9.23 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 104.4, 108.1, 108.7, 117.4, 118.5, 123.0, 129.3, 130.5, 143.1, 144.4, 158.7. Spectroscopic data was consistent with literature [69].

2−Methyl−5-(phenylamino)phenol (**18i**)



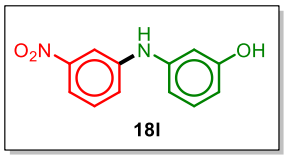
Synthesized as per the general experimental procedure B; obtained as a brown solid, Yield: 80% (119 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.98 (s, 3H), 6.38 (d, J = 8 Hz, 1H), 6.55 (s, 1H), 6.70 (t, J = 8 Hz, 1H), 6.84 (d, J = 8 Hz, 1H), 6.95 (d, J = 8 Hz, 2H), 7.13 (t, J = 8 Hz, 2H), 7.84 (br s, 1H), 9.05 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 15.9, 104.6, 108.8, 115.9, 116.6, 119.3, 129.5, 131.3, 142.4, 144.6, 156.3. Spectroscopic data was consistent with literature [70].

2−Chloro−5−(phenylamino)phenol (**18j**)



Synthesized as per the general experimental procedure B; obtained as a brown solid, Yield: 80% (132 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 6.50 (d, J = 8 Hz, 1H), 6.75 (s, 1H), 6.85 (t, J = 8 Hz, 1H), 7.06 (d, J = 8 Hz, 2H), 7.12 (d, J = 8 Hz, 1H), 7.23-7.26 (m, 2H), 8.17 (br s, 1H), 9.92 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 104.5, 109.0, 110.1, 117.9, 120.5, 129.6, 130.4, 143.4, 143.9, 153.9

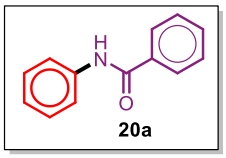
3−((3−Nitrophenyl)amino)phenol (**18l**)



Synthesized as per the general experimental procedure **B**; obtained as a yellow solid, Yield: 70% (120 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 6.41 (d, J = 8 Hz, 1H), 6.59-6.61 (m, 2H), 7.11 (t, J = 8 Hz, 1H), 7.42 (d, J = 8 Hz, 1H), 7.46 (t, J = 8 Hz, 1H), 7.58 (d, J = 8 Hz, 1H), 7.81 (s, 1H), 8.62 (br s, 1H), 9.40 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 105.9, 109.4, 109.5, 109.8, 113.5, 122.1, 130.5, 130.8, 143.2, 145.8, 149.1, 158.8. Spectroscopic data was consistent with literature [68].

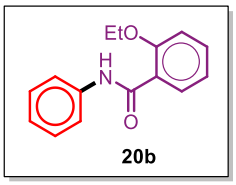
4.4.10.3 *^{1}H and ^{13}C NMR spectral analysis of N−arylamides (**20**)*

N−phenylbenzamide (**20a**)



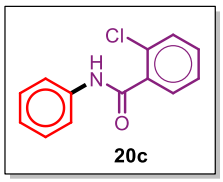
Synthesized as per the general experimental procedure C; obtained as a colourless solid, Yield: 64% (94 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.06 (t, J = 8 Hz, 1H), 7.31 (t, J = 8 Hz, 2H), 7.49 (t, J = 8 Hz, 2H), 7.55 (t, J = 8 Hz, 1H), 7.74 (d, J = 8 Hz, 2H), 7.92 (t, J = 8 Hz, 2H), 10.20 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 120.9, 124.2, 128.1, 128.8, 129.1, 132.0, 135.5, 139.7, 166.1. Spectroscopic data was consistent with literature [27].

2−Ethoxy−*N*−phenylbenzamide (**20b**)



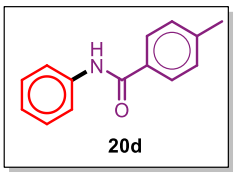
Synthesized as per the general experimental procedure C; obtained as a colourless solid, Yield: 64% (115 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.36 (t, J = 8 Hz, 3H), 4.13 (q, J = 8 Hz, 2H), 7.03 (q, J = 8 Hz, 2H), 7.12 (d, J = 8 Hz, 1H), 7.30 (t, J = 8 Hz, 2H), 7.45 (t, J = 8 Hz, 1H), 7.66-7.70 (m, 3H), 10.10 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 15.0, 64.8, 113.4, 119.9, 121.0, 123.9, 124.8, 129.3, 130.5, 132.8, 139.5, 156.4, 164.6. Spectroscopic data was consistent with literature [71].

2−Chloro−*N*−phenylbenzamide (**20c**)



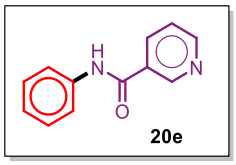
Synthesized as per the general experimental procedure C; obtained as a white solid, Yield: 64% (111 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.06 (t, J = 8 Hz, 1H), 7.31 (t, J = 8 Hz, 2H), 7.41 (t, J = 8 Hz, 1H), 7.47 (t, J = 8 Hz, 1H), 7.53 (t, J = 8 Hz, 2H), 7.68 (d, J = 8 Hz, 2H), 10.47 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 120.0, 124.3, 127.8, 129.3, 130.2, 130.4, 131.5, 137.5, 139.4, 165.4. Spectroscopic data was consistent with literature [72].

4−Methyl−*N*−phenylbenzamide (**20d**)



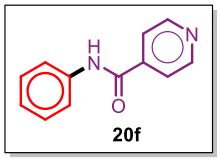
Synthesized as per the general experimental procedure C; obtained as a white solid, Yield: 64% (101 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.42 (s, 3H), 7.13 (t, J = 8 Hz, 1H), 7.36-7.40 (m, 4H), 7.82 (d, J = 8 Hz, 2H), 7.92 (d, J = 8 Hz, 2H), 10.20 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 21.4, 120.8, 124.0, 128.1, 129.0, 129.37, 132.5, 139.7, 142.0, 165.8. Spectroscopic data was consistent with literature [27].

N−Phenylnicotinamide (**20e**)



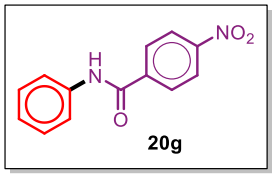
Synthesized as per the general experimental procedure C; obtained as a brown solid, Yield: 80% (119 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.16 (t, J = 8 Hz, 1H), 7.40 (t, J = 8 Hz, 2H), 7.60 (t, J = 8 Hz, 1H), 7.82 (d, J = 8 Hz, 2H), 8.33 (d, J = 8 Hz, 1H), 8.80 (s, 1H), 9.15 (s, 1H), 10.48 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 120.8, 123.9, 124.4, 129.1, 131.1, 135.9, 139.3, 149.1, 152.5, 164.5. Spectroscopic data was consistent with literature [74].

N−Phenylisonicotinamide (**20f**)



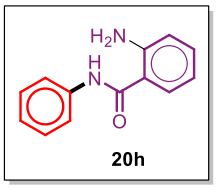
Synthesized as per the general experimental procedure C; obtained as a light brown solid, Yield: 74% (110 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.15 (t, J = 8 Hz, 1H), 7.39 (t, J = 8 Hz, 2H), 7.79 (d, J = 8 Hz, 2H), 7.88 (d, J = 8 Hz, 2H), 8.80 (d, J = 8 Hz, 2H), 10.51 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 120.9, 122.0, 124.6, 129.1, 139.0, 142.4, 150.7, 164.4. Spectroscopic data was consistent with literature [75].

4−Nitro−*N*−phenylbenzamide (**20g**)



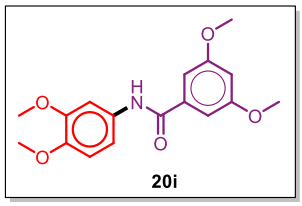
Synthesized as per the general experimental procedure C; obtained as a Off-white solid, Yield: 64% (116 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.15 (t, J = 8 Hz, 1H), 7.39 (t, J = 8 Hz, 2H), 7.79 (d, J = 8 Hz, 2H), 8.19 (d, J = 8 Hz, 2H), 8.38 (d, J = 8 Hz, 2H), 10.57 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 120.9, 124.0, 124.6, 129.1, 129.6, 139.1, 141.1, 149.6, 164.3. Spectroscopic data was consistent with literature [27].

2−Amino−*N*−phenylbenzamide (**20h**)



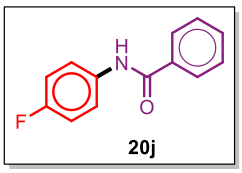
Synthesized as per the general experimental procedure C; obtained as a colourless solid, Yield: 73% (116 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 6.31 (s, 2H), 6.60 (t, J = 8 Hz, 1H), 6.76 (d, J = 8 Hz, 1H), 7.08 (t, J = 8 Hz, 1H), 7.19-7.22 (m, 1H), 7.33 (t, J = 8 Hz, 2H), 7.63 (d, J = 8 Hz, 1H), 7.72 (d, J = 8 Hz, 2H), 9.98 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 115.1, 115.7, 116.8, 121.0, 123.8, 128.9, 129.1, 132.5, 139.7, 150.1, 168.3. Spectroscopic data was consistent with literature [76].

N−(3,4−dimethoxyphenyl)−3,5−dimethoxybenzamide (**20i**)



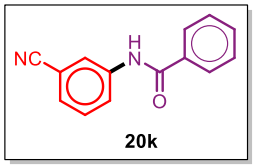
Synthesized as per the general experimental procedure C; obtained as a light purple solid, Yield: 60% (142 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 3.75 (s, 3H), 3.76 (s, 3H), 3.83 (s, 6H), 6.71 (s, 1H), 6.94 (d, J = 8 Hz, 1H), 7.11 (s, 2H), 7.32 (dd, J = 8 Hz, 2.4 Hz, 1H), 7.47 (s, 1H), 10.02 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 55.8, 55.9, 56.2, 103.6, 106.0, 106.1, 112.3, 112.9, 133.0, 137.5, 145.7, 148.9, 160.8, 165.0. Spectroscopic data was consistent with literature [77].

N−(4−fluorophenyl)benzamide (**20j**)



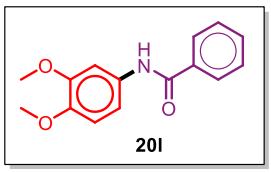
Synthesized as per the general experimental procedure C; obtained as a colourless solid, Yield: 80% (129 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.20 (d, J = 8 Hz, 2H), 7.54 (t, J = 8 Hz, 2H), 7.60 (t, J = 8 Hz, 1H), 7.80-7.83 (m, 2H), 7.97 (d, J = 8 Hz, 2H), 10.31 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 115.5, 115.7, 122.6, 122.7, 128.0, 128.8, 132.0, 135.3, 136.0, 158.7 (d, $J_{C\text{-}F}$ = 240 Hz), 165.9. Spectroscopic data was consistent with literature [48c].

N−(3−cyanophenyl)benzamide (**20k**)



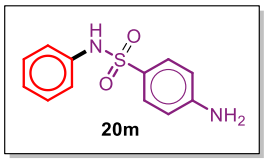
Synthesized as per the general experimental procedure C; obtained as a colourless solid, Yield: 68% (113 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 7.55 (d, J = 8 Hz, 2H), 7.59 (d, J = 8 Hz, 2H), 7.63 (t, J = 8 Hz, 1H), 7.98 (d, J = 4 Hz, 2H), 8.06 (d, J = 8 Hz, 1H), 8.27 (s, 1H), 10.56 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 111.9, 119.2, 123.4, 125.3, 127.6, 128.2, 128.9, 129.3, 130.6, 132.4, 134.8, 140.4, 166.4. Spectroscopic data was consistent with literature [78].

N−(3,4−dimethoxyphenyl)benzamide (**20l**)



Synthesized as per the general experimental procedure C; obtained as a colourless liquid, Yield: 82% (158 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 3.75 (s, 3H), 3.77 (s, 3H), 6.94 (d, J = 8 Hz, 1H), 7.36 (d, J = 8 Hz, 1H), 7.53 (t, J = 8 Hz, 3H), 7.58 (d, J = 8 Hz, 1H), 7.97 (d, J = 8 Hz, 2H), 10.11 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 55.8, 56.2, 106.0, 112.4, 112.8, 127.9, 128.8, 131.8, 133.2, 135.5, 145.6, 148.9, 165.5. Spectroscopic data was consistent with literature [79].

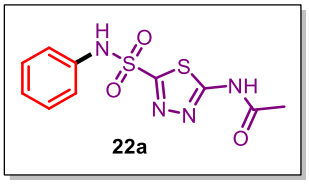
4−Amino−*N*−phenylbenzenesulfonamide (**20m**)



Synthesized as per the general experimental procedure **C**; obtained as a dark-red solid, Yield: 80% (149 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 5.94 (s, 2H), 6.54 (d, J = 8 Hz, 2H), 6.97 (t, J = 8 Hz, 1H), 7.07 (d, J = 8 Hz, 2H), 7.20 (t, J = 8 Hz, 2H), 7.40 (d, J = 8 Hz, 2H), 9.83 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 113.0, 119.9, 123.7, 124.9, 129.1, 129.4, 129.8, 138.9, 153.2. Spectroscopic data was consistent with literature [80].

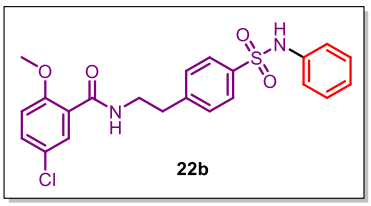
4.4.10.4 *Characterization data of **22a** and **22b***

N−(5−(*N*−phenylsulfamoyl)−1,3,4−thiadiazol-2-yl)acetamide (**22a**)



Synthesized as per the general experimental procedure C; obtained as a colourless solid, Yield: 70% (157 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.21 (s, 3H), 7.15 (d, *J* = 8 Hz, 1H), 7.20 (d, *J* = 8 Hz, 2H), 7.31 (d, *J* = 8 Hz, 2H), 11.17 (s, 1H), 13.07 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 22.7, 121.5, 125.6, 129.8, 136.7, 161.0, 162.1, 170.0; HRMS-ESI *m/z*: $[M+H]^+$ calcd for $C_{10}H_{10}N_4O_3S_2$, 298.0194; found, 299.0275

5−Chloro−2-methoxy−*N*−(4−(*N*−phenylsulfamoyl)phenethyl)benzamide (**22b**)



Synthesized as per the general experimental procedure C; obtained as a light orange oil, Yield: 50% (166 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm); 2.93-2.96 (m, 2H), 3.66 (s, 3H), 3.69-3.74 (m, 2H), 6.83 (t, *J* = 8 Hz, 1H), 7.09 (t, *J* = 8 Hz, 3H), 7.20-7.24 (m, 3H), 7.30 (d, *J* = 8 Hz, 2H), 7.36 (dd, *J* = 8 Hz , 2.8 Hz, 1H), 7.73 (d, *J* = 8 Hz, 2H), 7.78 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 35.4, 40.5, 56.1, 112.9, 121.5, 122.6, 125.3, 126.7, 127.5, 129.3, 129.5, 131.9, 132.4, 136.5, 137.5, 144.9, 155.9, 164.1; HRMS-ESI *m/z*: $[M+H]^+$ calcd for $C_{22}H_{21}ClN_2O_4S$, 444.0911; found, 445.1014

4.4.11 *Representative ^{1}H and ^{13}C NMR spectra of N-aryl derivatives*

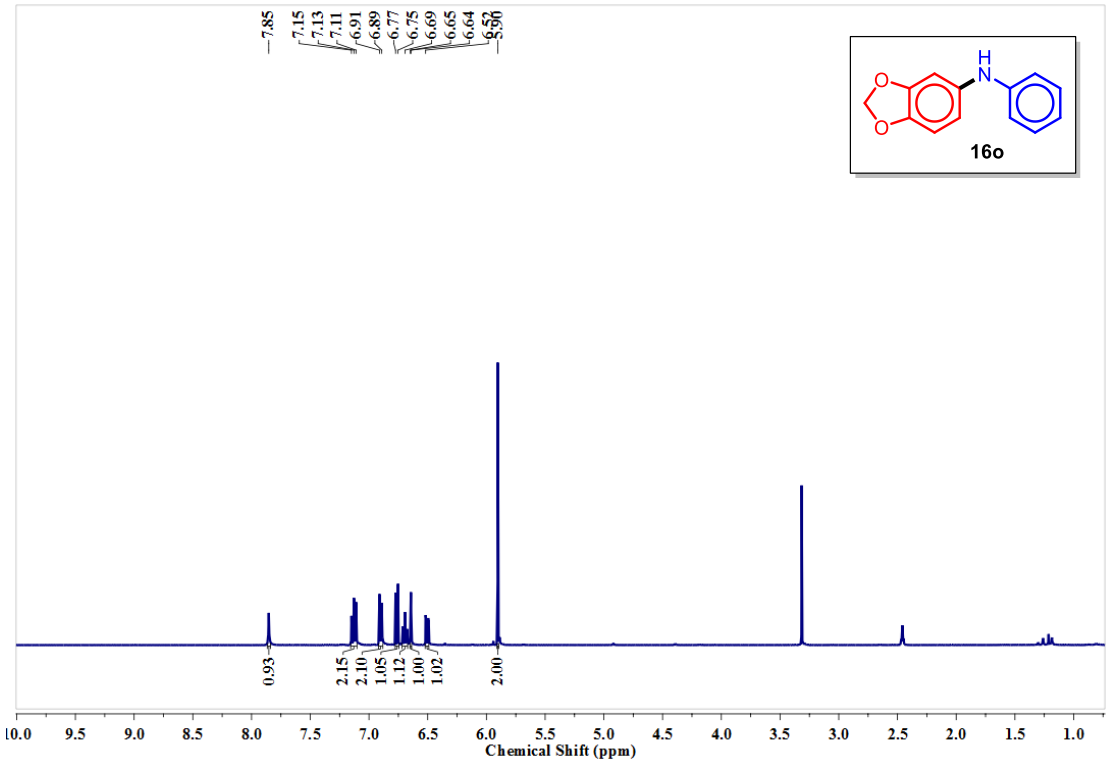


Figure **4.5** ^{1}H NMR spectrum of **16o** in DMSO-d_6 (400 MHz, 298 K)

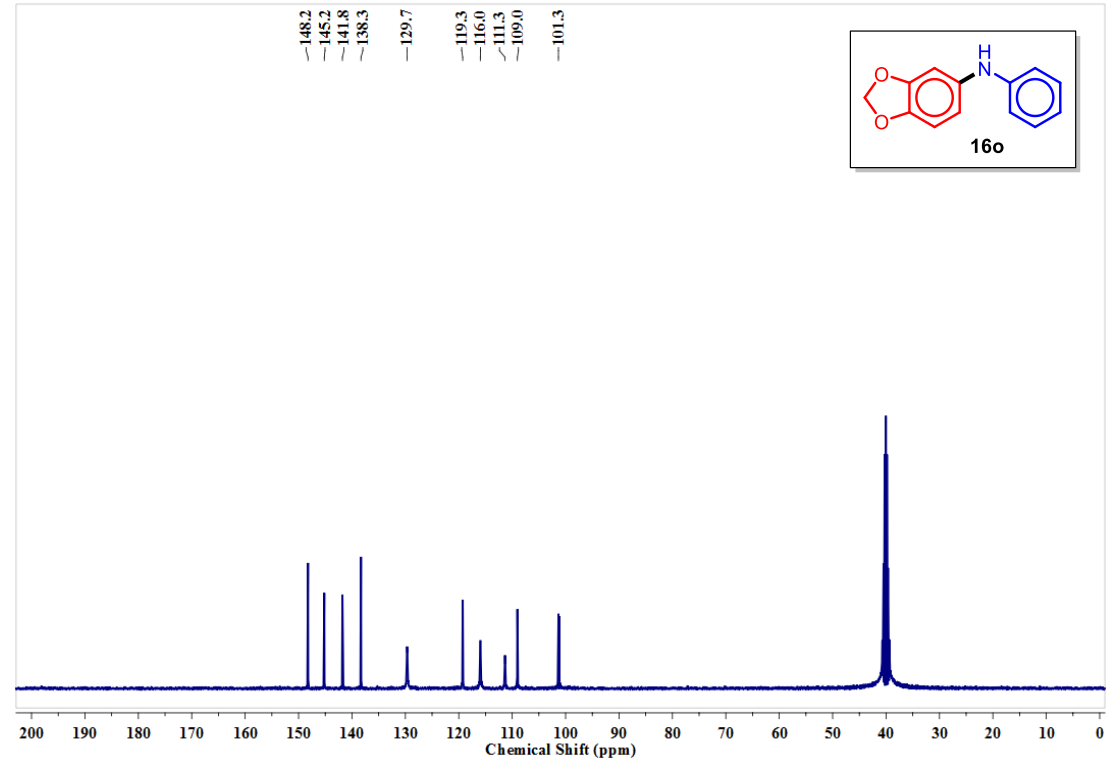


Figure **4.6** ^{13}C NMR spectrum of **16o** in DMSO-d_6 (100 MHz, 298 K)

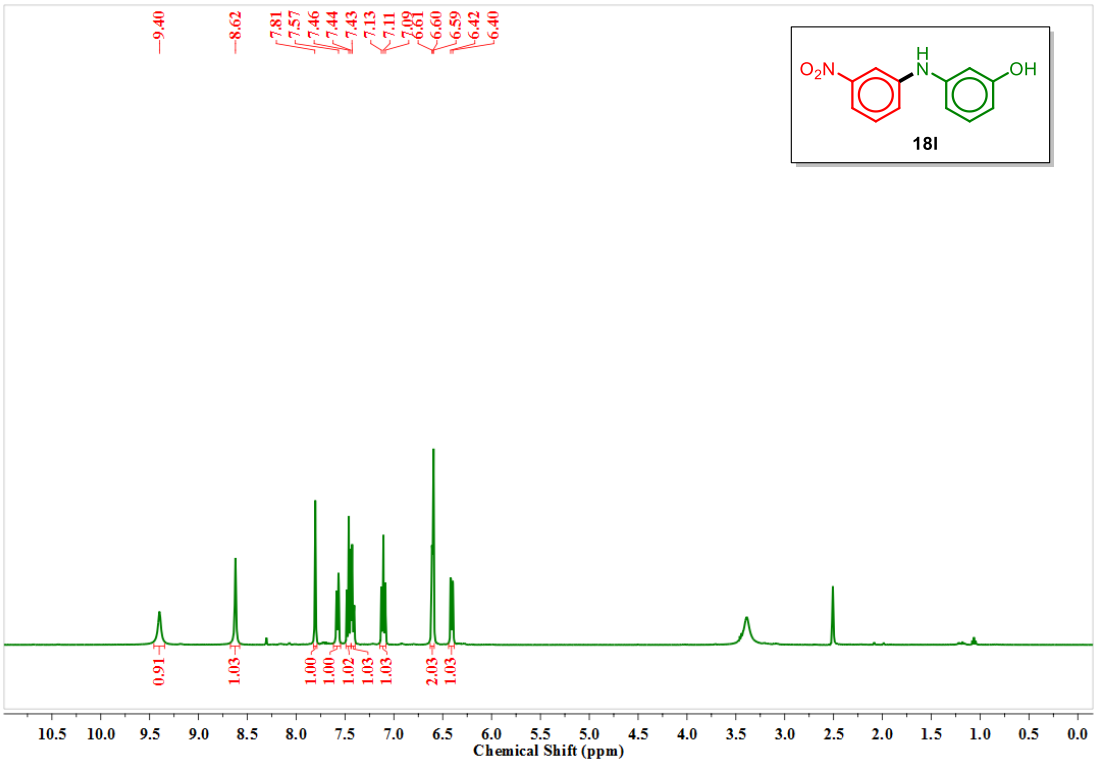


Figure **4.7** ^{1}H NMR spectrum of **18l** in DMSO-d_6 (400 MHz, 298 K)

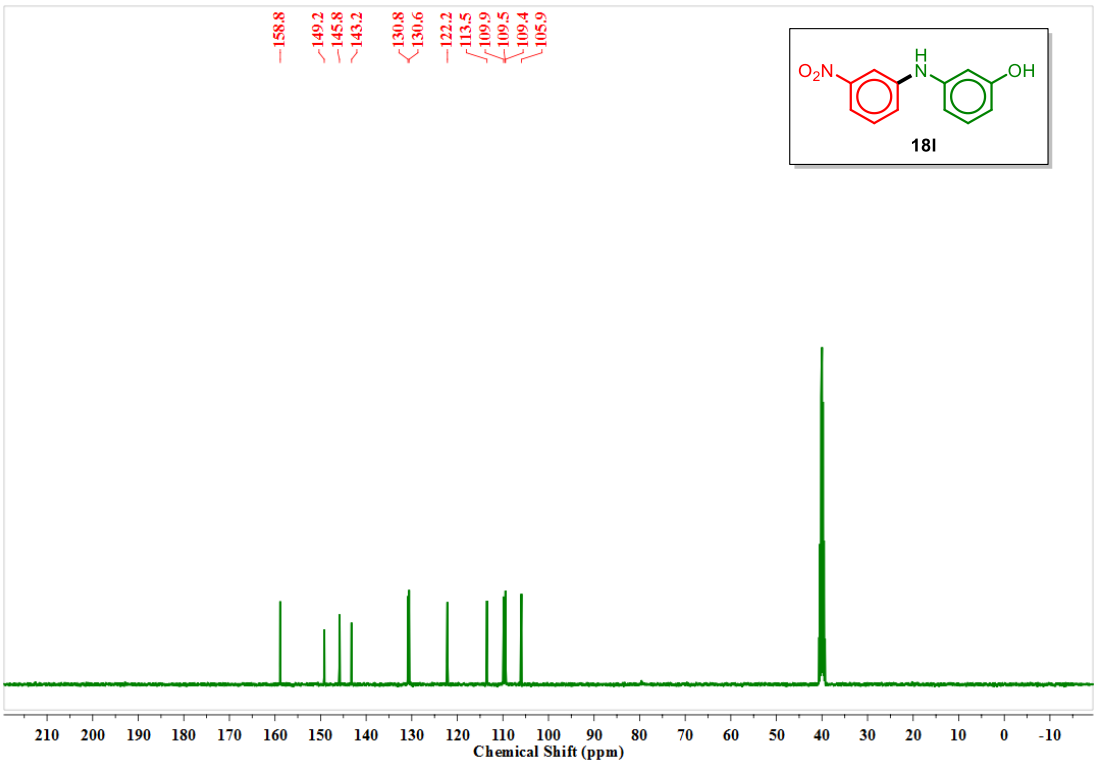


Figure **4.8** ^{13}C NMR spectrum of **18l** in DMSO-d_6 (100 MHz, 298 K)

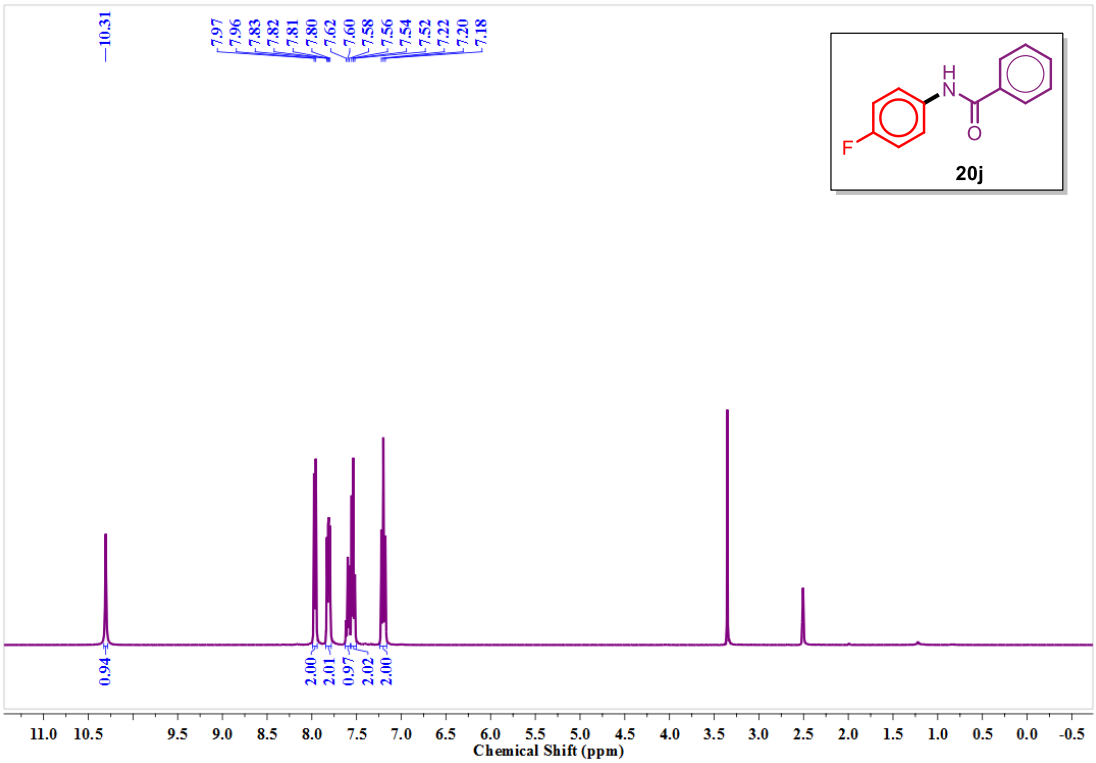


Figure **4.9** ^{1}H NMR spectrum of **20j** in DMSO-d_6 (400 MHz, 298 K)

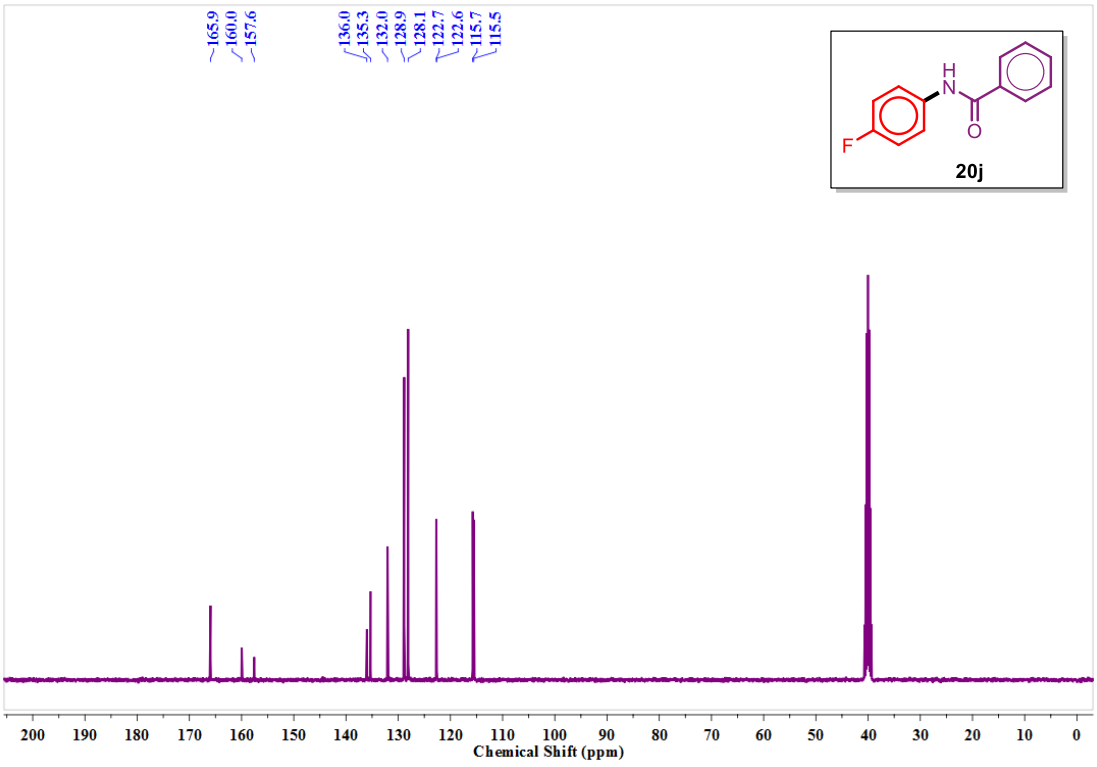


Figure **4.10** ^{13}C NMR spectrum of **20j** in DMSO-d_6 (100 MHz, 298 K)

4.5 *Bibliography*

[1] Fernandes, R. A., Bhowmik, A., and Yadav, S. S. Advances in Cu and Ni-Catalyzed Chan-Lam-Type Coupling: Synthesis of Diarylchalcogenides, Ar_2–X (X= S, Se, Te). *Organic & Biomolecular Chemistry*, 18(47):9583-9600, 2020.

[2] Chen, J. Q., Li, J. H., and Dong, Z. B. A Review on the Latest Progress of Chan-Lam Coupling Reaction. *Advanced Synthesis & Catalysis*, 362(16):3311-3331, 2020.

[3] Vijayan, A., Rao, D. N., Radhakrishnan, K. V., Lam, P. Y., and Das, P. Advances in Carbon-Element Bond Construction under Chan−Lam Cross−Coupling Conditions: A Second Decade. *Synthesis*, 53(05):805-847, 2021.

[4] West, M. J., Fyfe, J. W., Vantourout, J. C., and Watson, A. J. Mechanistic Development and Recent Applications of the Chan-Lam Amination. *Chemical Reviews*, 119(24):12491-12523, 2019.

[5] Qiao, J. X., and Lam, P. Y. Copper-Promoted Carbon-Heteroatom Bond Cross-Coupling with Boronic Acids and Derivatives. *Synthesis*, 2011(06):829-856, 2011.

[6] Abedinifar, F., Mahdavi, M., Asadi, M., and Larijani, B. Recent Developments in Arylation of *N*-Nucleophiles *via* Chan-Lam Reaction: Updates from 2012 Onwards. *Current Organic Synthesis*, 19(1):16-30, 2022.

[7] Ritleng, V., Sirlin, C., and Pfeffer, M. Ru-, Rh-, and Pd-catalyzed C-C Bond Formation Involving C-H Activation and Addition on Unsaturated Substrates: Reactions and Mechanistic Aspects. *Chemical Reviews*, 102(5):1731-1770, 2002.

[8] Hili, R., and Yudin, A. K. Making Carbon-Nitrogen Bonds in Biological and Chemical Synthesis. *Nature Chemical Biology*, 2(6):284-287, 2006.

[9] Bariwal, J., and Van der Eycken, E. C–N Bond Forming Cross-Coupling Reactions: An Overview. *Chemical Society Reviews*, 42(24):9283-9303, 2013.

[10] Ruiz-Castillo, P., and Buchwald, S. L. Applications of Palladium-Catalyzed C-N Cross-Coupling Reactions. *Chemical Reviews*, 116(19):12564-12649, 2016.

[11] António, J. P., Russo, R., Carvalho, C. P., Cal, P. M., and Gois, P. M. Boronic Acids as Building Blocks for the Construction of Therapeutically Useful Bioconjugates. *Chemical Society Reviews*, 48(13):3513-3536, 2019.

[12] Muñoz, A., Leo, P., Orcajo, G., Martínez, F., and Calleja, G. URJC−1−MOF as New Heterogeneous Recyclable Catalyst for C-Heteroatom Coupling Reactions. *ChemCatChem*, 11(15):3376-3380, 2019.

[13] Hall, D. G. Boronic Acid Catalysis. *Chemical Society Reviews*, 48(13):3475-3496, 2019.

[14] West, M. J., Thomson, B., Vantourout, J. C., and Watson, A. J. Discovery, Scope, and Limitations of an *N*−dealkylation/*N*-arylation of Secondary Sulfonamides Under Chan-Lam Conditions. *Asian Journal of Organic Chemistry*, 9(3):364-367, 2020.

[15] Györke, G., Dancsó, A., Volk, B., and Milen, M. Chan−Lam Arylation of Benzimidazole and its Derivatives in the Presence of Copper-Containing Minerals. *ChemistrySelect*, 6(4):802-807, 2021.

[16] Wang, C., Zhang, H., Wells, L. A., Liu, T., Meng, T., Liu, Q., Walsh, P. J., Koz lowski, M. C., and Jia, T. Autocatalytic Photoredox Chan-Lam Coupling of Free Diaryl Sulfoximines with Arylboronic Acids. *Nature Communications*, 12(1):1-11, 2021.

[17] Clerc, A., Bénéteau, V., Pale, P., and Chassaing, S. Chan-Lam-Type Azidation and One-Pot CuAAC Under CuI-Zeolite Catalysis. *ChemCatChem*, 12(7):2060-2065, 2020.

[18] Chen, J. Q., Liu, X., Guo, J., and Dong, Z. B. A Chemoselective and Desulfurative Chan-Lam Coupling: C-N Bond Formation between Benzimidazoline-2-Thiones and Arylboronic Acids. *European Journal of Organic Chemistry*, 2020(16):2414-2424, 2020.

[19] Jones, K. L., Porzelle, A., Hall, A., Woodrow, M. D., and Tomkinson, N. C. Copper-Catalyzed Coupling of Hydroxylamines with Aryl Iodides. *Organic Letters*, 10(5):797-800, 2008.

[20] Sahoo, H., Mukherjee, S., Grandhi, G. S., Selvakumar, J., and Baidya, M. Copper Catalyzed C-N Cross-Coupling Reaction of Aryl Boronic Acids at Room Temperature through Chelation Assistance. *The Journal of Organic Chemistry*, 82(5):2764-2771, 2017.

[21] Gupta, S., Chaudhary, P., Muniyappan, N., Sabiah, S., and Kandasamy, J. Copper Promoted *N*-alkylation of Sulfoximines with Alkylboronic Acid under Mild Conditions. *Organic & Biomolecular Chemistry*, 15(40):8493-8498, 2017.

[22] Collman, J. P., and Zhong, M. An Efficient Diamine-Copper Complex-Catalyzed Coupling of Arylboronic Acids with Imidazoles. *Organic Letters*, 2(9):1233-1236, 2000.

[23] Collman, J. P., Zhong, M., Zeng, L., and Costanzo, S. The $[Cu(OH)\cdot TMEDA]_2Cl_2$-Catalyzed Coupling of Arylboronic Acids with Imidazoles in Water. *The Journal of Organic Chemistry*, 66(4):1528-1531, 2001.

[24] Onaka, T., Umemoto, H., Miki, Y., Nakamura, A., and Maegawa, T. $[Cu(OH)\cdot TMEDA]_2Cl_2$-Catalyzed Regioselective 2-Arylation of 5-Substituted Tetrazoles with Boronic Acids Under Mild Conditions. *The Journal of Organic Chemistry*, 79(14):6703-6707, 2014.

[25] Duparc, V. H., and Schaper, F. Sulfonato-Imino Copper(II) Complexes: Fast and General Chan-Evans-Lam Coupling of Amines and Anilines. *Dalton Transactions*, 46(38):12766-12770, 2017.

[26] Hardouin Duparc, V., and Schaper, F. Sulfonato-Diketimine Copper(II) Complexes: Synthesis and Application as Catalysts in Chan-Evans-Lam Couplings. *Organometallics*, 36(16):3053-3060, 2017.

[27] Roy, S., Sarma, M. J., Kashyap, B., and Phukan, P. A quick Chan-Lam C−N and C−S Cross−Coupling at Room Temperature in the Presence of Square Pyramidal $[Cu(DMAP)_4I]I$ as a Catalyst. *Chemical Communications*, 52(6):1170-1173, 2016.

[28] Gogoi, A., Sarmah, G., Dewan, A., and Bora, U. Unique Copper−Salen Complex: An Efficient Catalyst for *N*-arylations of Anilines and Imidazoles at Room Temperature. *Tetrahedron Letters*, 55(1):31-35, 2014.

[29] Jia, X., and Peng, P. *N*,*O*−Bidentate Ligand-Tunable Copper(II) Complexes as a Catalyst for Chan-Lam Coupling Reactions of Arylboronic Acids with 1*H*-imidazole Derivatives. *Organic & Biomolecular Chemistry*, 16(46):8984-8988, 2018.

[30] Keuleers, R., Desseyn, H. O., Papaefstathiou, G. S., Drakopoulou, L., Perlepes, S. P., Raptopoulou, C. P., and Terzis, A. Hydrogen-Bonded Networks Based on Manganese(II), Nickel(II), Copper(II) and Zinc(II) Complexes of *N*,*N'*−dimethylurea. *Transition Metal Chemistry*, 28(5):548-557, 2003.

[31] Mannepalli, L. K., Gadipelly, C., Deshmukh, G., Likhar, P., and Pottabathula, S. Advances in C−C Coupling Reactions Catalyzed by Homogeneous Phosphine−Free Palladium Catalysts. *Bulletin of the Chemical Society of Japan*, 93(3):355-372, 2020.

[32] [a] Custelcean, R. Urea-Functionalized Crystalline Capsules for Recognition And Separation of Tetrahedral Oxoanions. *Chemical Communications*, 49(22):2173-2182, 2013; [b] Tovilla, J. A., Carlqvist, P., Benet-Buchholz, J., Maseras, F., and Vilar, R. Di-Palladium Complexes with Urea-Containing Ligands as Anion Receptors. *Supramolecular Chemistry*, 19(8):599-611, 2007; [c] Tovilla, J. A., Vilar, R., and White, A. J. A Di-Palladium Urea Complex as a Molecular Receptor for Anions. *Chemical Communications*, (38):4839-4841, 2005; [d] Amendola, V., Fabbrizzi, L., and Mosca, L. Anion Recognition by Hydrogen Bonding: Urea-Based Receptors. *Chemical Society Reviews*, 39(10):3889-3915, 2010; [e] Zhao, J., Yang, D., Yang, X. J., & Wu, B. Anion Coordination Chemistry: From Recognition to Supramolecular Assembly. *Coordination Chemistry Reviews*, 378:415-444, 2019; [f] Qureshi, N., Yufit, D. S., Steed, K. M., Howard, J. A., and Steed, J. W. Anion Hydrogen Bonding from a 'Revealed' Urea Ligand. *CrystEngComm*, 18(28):5333-5337, 2016.

[33] Breuzard, J. A., Christ-Tommasino, M. L., and Lemaire, M. Chiral Ureas and Thioureas in Asymmetric Catalysis. In Lemaire M., and Mangeney, P., editors, *Chiral Diazaligands for Asymmetric Synthesis*, pages 231-270, Springer, 2005.

[34] Bao, G., Fan, X., Xu, T., Li, C., and Bai, J. Preparing Pd Catalysts Based on Urea Ligand *via* Electrospinning for Suzuki–Miyaura Cross-Coupling Reactions. *Applied Organometallic Chemistry*, 34(10):e5877, 2020.

[35] [a] Cui, X., Zhou, Y., Wang, N., Liu, L., and Guo, Q. X. *N*−phenylurea as an Inexpensive and Efficient Ligand for Pd-Catalyzed Heck and Room-Temperature Suzuki Reactions. *Tetrahedron Letters*, 48(1):163-167, 2007; [b] Smith, M. R., Kim, J. Y., and Ciufolini, M. A. Pd−arylurea Complexes for the Heck Arylation of Crotonic and Cinnamic Substrates. *Tetrahedron Letters*, 54(16):2042-2045, 2013.

[36] Erathodiyil, N., Ooi, S., Seayad, A. M., Han, Y., Lee, S. S., and Ying, J. Y. Palladium Nanoclusters Supported on Propylurea-Modified Siliceous Mesocellular Foam for Coupling and Hydrogenation Reactions. *Chemistry–A European Journal*, 14(10):3118-3125, 2008.

[37] Touchard, F., Bernard, M., Fache, F., and Lemaire, M. Ureas and Thioureas as Rh-Ligands for the Enantioselective Hydride Transfer Reduction of Acetophenone. *Journal of Molecular Catalysis A*: *Chemical*, 140(1):1-11, 1999.

[38] [a] Bisz, E., and Szostak, M. Cyclic Ureas (DMI, DMPU) as Efficient, Sustainable Ligands in Iron-Catalyzed $C(sp^2)–C(sp^3)$ Coupling of Aryl Chlorides and Tosylates. *Green Chemistry*, 19(22):5361-5366, 2017; [b] Bisz, E. Iron-Catalyzed Cross-Coupling Reactions of Alkyl Grignards with Aryl Chlorobenzenesulfonates. *Molecules*, 26(19):5895, 2021.

[39] Vaith, J., Rodina, D., Spaulding, G. C., and Paradine, S. M. Pd-Catalyzed Heteroannulation Using *N*-arylureas as a Sterically Undemanding Ligand Platform. *Journal of the American Chemical Society*, 144(15):6667-6673, 2022.

[40] [a] Megahed, A. S., Ibrahim, O. B., and Adam, A. M. A. Synthesis and Structural Characterization of Urea Metal Complexes with Cu(II), Zn(II), Ag(I), Cd(II), Zn(II), Ag(I), Cd(II), and Hg(II) ions at High Temperature. *International Journal of Chemical Science*, 12:335-343, 2014; [b] Stonestreet, B. C., Bull, W. E., and Williams, R. J. Co-ordination Compounds of 1,3-Dimethylurea. *Journal of Inorganic and Nuclear Chemistry*, 28(9):1895-1900, 1966.

[41] [a] Kirai, N., and Yamamoto, Y. Homocoupling of Arylboronic Acids Catalyzed by 1,10-Phenanthroline-Ligated Copper Complexes in Air. *European Journal of Organic Chemistry*, 2009(12):1864-1867, 2009; [b] Cao, Y. N., Tian, X. C., Chen, X. X., Yao, Y. X., Gao, F., and Zhou, X. L. Rapid Ligand-Free Base-Accelerated Copper-Catalyzed Homocoupling Reaction of Arylboronic Acids. *Synlett*, 28(05):601-606, 2017.

[42] Mahanta, A., Thakur, A. J., and Bora, U. Effective Utilization of Basic Nature of WEB in Copper Catalyzed Chan-Lam *N*-arylation Reaction Under Ligand Free Conditions. *Current Research in Green and Sustainable Chemistry*, 4:100093, 2021.

[43] Vantourout, J. C., Miras, H. N., Isidro-Llobet, A., Sproules, S., and Watson, A. J. Spectroscopic Studies of the Chan-Lam Amination: A Mechanism-Inspired Solution to Boronic Ester Reactivity. *Journal of the American Chemical Society*, 139(13):4769-4779, 2017.

[44] Wexler, R. P., Nuhant, P., Senter, T. J., and Gale-Day, Z. J. Electrochemically Enabled Chan-Lam Couplings of Aryl Boronic Acids and Anilines. *Organic Letters*, 21(12):4540-4543, 2019.

[45] Hardouin Duparc, V., Bano, G. L., and Schaper, F. Chan–Evans–Lam Couplings with Copper Iminoarylsulfonate Complexes: Scope and Mechanism. *ACS Catalysis*, 8(8):7308-7325, 2018.

[46] [a] Greenberg, A., Breneman, C. M., Liebman, J. F. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*. John Wiley & Sons, 2000; [b] Stanley, M., Rotrosen, J., Press, R. *The Benzamides: Pharmacology, Neurobiology and Clinical Aspects*. Raven Press, 1982.

[47] Bhojane, J. M., Jadhav, V. G., and Nagarkar, J. M. A Novel Approach for the Synthesis of Biologically Important *N*-Aryl Amides with Arenediazonium Salts. *Synthesis*, 46(21):2951-2956, 2014.

[48] [a] Zhao, R., Dong, W., Teng, J., Wang, Z., Wang, Y., Yang, J., Jia, Q., and Chu, C. Activated Charcoal Supported Copper Nanoparticles: A Readily Available and Inexpensive Heterogeneous Catalyst for the *N*-arylation of Primary Amides and Lactams with Aryl Iodides. *Tetrahedron*, 79:131858, 2021; [b] Bhunia, S., De, S., and Ma, D. Room Temperature Cu-Catalyzed *N*-Arylation of Oxazolidinones and Amides with (Hetero) Aryl Iodides. *Organic Letters*, 24(5):1253-1257, 2022; [c] Quan, Z. J., Xia, H. D., Zhang, Z., Da, Y. X., and Wang, X. C. An Efficient Copper-Catalyzed *N*-arylation of Amides: Synthesis of *N*−arylacrylamides and 4−Amido-*N*-phenylbenzamides. *Tetrahedron*, 69(39):8368-8374, 2013; [d] Moglie, Y., Mascaró, E., Zacconi, F., and Radivoy, G. Copper Nanoparticles Supported on Zinc Oxide as Efficient Catalyst for the *N*-arylation of (Hetero)cyclic and Acyclic Amides. *ChemistrySelect*, 6(18):4412-4417, 2021.

[49] Lin, B., Liu, M., Ye, Z., Ding, J., Wu, H., and Cheng, J. Copper-TBAF Catalyzed Arylation of Amines and Amides with Aryl Trimethoxysilane. *Organic & Biomolecular Chemistry*, 7(5):869-873, 2009.

[50] Kadari, L., Erb, W., Roisnel, T., Krishna, P. R., and Mongin, F. Iodoferrocene as a Partner in *N*-arylation of Amides. *New Journal of Chemistry*, 44(37):15928-15941, 2020.

[51] [a] MacMillan, J. W., McGuire, R. T., and Stradiotto, M. Organic Base Enabled Nickel-Catalyzed Mono-α-Arylation of Feedstock Solvents. *Chemistry–A European Journal*, 28(28):e202200764, 2022; [b] Lavoie, C. M., MacQueen, P. M., and Stradiotto, M. Nickel-Catalyzed *N*-arylation of Primary Amides and Lactams with Activated (Hetero)aryl Electrophiles. *Chemistry–A European Journal*, 22(52):18752-18755, 2016.

[52] [a] Rossi, S. A., Shimkin, K. W., Xu, Q., Mori-Quiroz, L. M., and Watson, D. A. Selective Formation of Secondary Amides *via* The Copper-Catalyzed Cross-Coupling of Alkylboronic Acids with Primary Amides. *Organic Letters*, 15(9):2314-2317, 2013; [b] Hanaya, K., Miller, M., and Ball, Z. Amide N-H Arylation of Pyroglutamate-Histidine Promoted by Nickel(II) Acetate. *Organic Letters*, 21:2445-2448, 2019.

[53] [a] Matsuda, N., Hirano, K., Satoh, T., and Miura, M. Copper-Catalyzed Amination of Arylboronates with *N*,*N*-dialkylhydroxylamines. *Angewandte Chemie International Edition*, 51(15):3642-3645, 2012; [b] Rucker, R. P., Whittaker, A. M., Dang, H., and Lalic, G. Synthesis of Hindered Anilines: Copper-Catalyzed Electrophilic Amination of Aryl Boronic Esters. *Angewandte Chemie International Edition*, 51(16):3953-3956, 2012.

[54] Chan, D. M., Monaco, K. L., Li, R., Bonne, D., Clark, C. G., and Lam, P. Y. Copper Promoted C−N and C−O Bond Cross-Coupling with Phenyl and Pyridylboronates. *Tetrahedron Letters*, 44(19):3863-3865, 2003.

[55] Tiller, P. R., Land, A. P., Jardine, I., Murphy, D. M., Sozio, R., Ayrton, A., and Schaefer, W. H. Application of Liquid Chromatography−Mass Spectrometryn Analyses to the Characterization of Novel Glyburide Metabolites Formed in Vitro. *Journal of Chromatography A*, 794(1-2):15-25, 1998.

[56] Bose, S., Dutta, S., and Koley, D. Entering Chemical Space with Theoretical Underpinning of the Mechanistic Pathways in the Chan-Lam Amination. *ACS Catalysis*, 12(2):1461-1474, 2022.

[57] Bruker AXS Inc., Madison, WI, 2008.

[58] Sheldrick, G. M. SHELXS and SHELXL97 Programs for structure refinement and solution. Göttingen, Germany, 1997.

[59] Spek, A. L. PLATON. Program for the Automated Analysis of Molecular Geometry (A Multipurpose Crystallographic Tool). University of Utrecht, Utrecht, The Netherlands, 2002.

[60] Spek, A. L. J. Single-crystal structure validation with the program PLATON. *Journal of Applied Crystallography*, 36(1):7-13, 2003.

[61] Jati, A., Dey, K., Nurhuda, M., Addicoat, M. A., Banerjee, R., and Maji, B. Dual Metalation in a Two-Dimensional Covalent Organic Framework for Photo-catalytic

C−N Cross-Coupling Reactions. *Journal of the American Chemical Society*, 144(17):7822-7833, 2022.

[62] Key, R. J., and Vannucci, A. K. Nickel Dual Photo-redox Catalysis for the Synthesis of Aryl Amines. *Organometallics*, 37(9):1468-1472, 2018.

[63] Nadri, S., Rafiee, E., Jamali, S., and Joshaghani, M. 2,6-*Bis*(diphenylphosphino) pyridine: A Simple Ligand Showing High Performance in Palladium-Catalyzed C-N Coupling Reactions. *Tetrahedron Letters*, 55(30):4098-4101, 2014.

[64] Alsabeh, P. G., and Stradiotto, M. Addressing Challenges in Palladium-Catalyzed Cross-Couplings of Aryl Mesylates: Monoarylation of Ketones and Primary Alkyl Amines. *Angewandte Chemie International Edition*, 52(28):7242-7246, 2013.

[65] Kwong, F. Y., Klapars, A., and Buchwald, S. L. Copper-Catalyzed Coupling of Alkylamines and Aryl Iodides: An Efficient System Even in an Air Atmosphere. *Organic Letters*, 4(4):581-584, 2002.

[66] Semeniuchenko, V., Ovens, J. S., Braje, W. M., and Organ, M. G. NaBHT Generated *In Situ* from BHT and NaO^{t}Bu: Crystallographic Characterization and Applications in Buchwald-Hartwig Amination. *Organometallics*, 40(19):3276-3290, 2021.

[67] Ansari, T. N., Taussat, A., Clark, A. H., Nachtegaal, M., Plummer, S., Gallou, F., and Handa, S. Insights on Bimetallic Micellar Nanocatalysis for Buchwald-Hartwig Aminations. *ACS Catalysis*, 9(11):10389-10397, 2019.

[68] Reddy, A. S., Reddy, K. R., Rao, D. N., Jaladanki, C. K., Bharatam, P. V., Lam, P. Y., and Das, P. Copper(II)-Catalyzed Chan-Lam Cross-Coupling: Chemoselective *N*-arylation of Aminophenols. *Organic & Biomolecular Chemistry*, 15(4):801-806, 2017.

[69] Maiti, D., and Buchwald, S. L. Orthogonal Cu-and Pd-Based Catalyst Systems for the *O*- and *N*-arylation of Aminophenols. *Journal of the American Chemical Society*, 131(47):17423-17429, 2009.

[70] Paul, S., Joy, B. P., Sasikala, G., Raghuthaman, A. G., and Gudimetla, V. B. Copper-NHC Based Ullmann Catalysis in Water for Selective *N*-Arylation of 3-Aminophenols. *ChemistrySelect*, 5(47):15004-15009, 2020.

[71] Werbel, L. M., Hess, C. A., and Elslager, E. F. Potential Antimalarial Substances. Amides of *o*-Ethoxy-and *p*-Isopropylbenzoic Acids. *Journal of Medicinal Chemistry*, 10(3):508-509, 1967.

[72] Tang, X., Chen, S., and Wang, L. Synthesis and Antifungal Activity of 2-Chloro-*N*-phenylbenzamide. *Asian Journal of Chemistry*, 24(7):2860-2862, 2012.

[73] Wan, Y., Alterman, M., Larhed, M., and Hallberg, A. Dimethylformamide as a Carbon Monoxide Source in Fast Palladium-Catalyzed Aminocarbonylations of Aryl Bromides. *The Journal of Organic Chemistry*, 67(17):6232-6235, 2002.

[74] Schoenberg, A., and Heck, R. F. Palladium-Catalyzed Amidation of Aryl, Heterocyclic and Vinylic Halides. *The Journal of Organic Chemistry*, 39(23):3327-3331, 1974.

[75] Stanovnik, B., Tišler, M., Golob, V., Hvala, I., and Nikolić, O. Heteroacyl Azides as Acylating agents for Aromatic or Heteroaromatic Amines. *Journal of Heterocyclic Chemistry*, 17(4):733-736, 1980.

[76] ChandruáSenadi, G., and SuresháKudale, V. Sustainable Methine Sources for the Synthesis of Heterocycles Under Metal and Peroxide-Free Conditions. *Green Chemistry*, 21(5):979-985, 2019.

[77] Fujimoto, S., Matsumoto, K., Iwata, T., and Shindo, M. Aerobic Oxidative Homocoupling Reaction of Anilides Using Heterogeneous Metal Catalysts. *Tetrahedron Letters*, 58(10):973-976, 2017.

[78] Chen, Z., Liang, P., Liu, B., Luo, H., Zheng, J., Wen, X., Liu, T., and Ye, M. A Facile Tandem Decyanation/Cyanation Reaction of α−iminonitriles Toward Cyano-Substituted Amides. *Organic & Biomolecular Chemistry*, 16(44):8481-8485, 2018.

[79] Fang, W. Y., Huang, Y. M., Leng, J., and Qin, H. L. Pd-Catalyzed One-Pot Dehydroxylative Coupling of Phenols and Amines under a Carbon Monoxide Atmosphere: A Chemical-Specific Discrimination for Arylcarboxylic Amide Synthesis. *Asian Journal of Organic Chemistry*, 7(4):751-756, 2018.

[80] Nasrollahzadeh, M., Ehsani, A., and Maham, M. Copper-Catalyzed *N*-arylation of Sulfonamides with Boronic Acids in Water Under Ligand−Free and Aerobic Conditions. *Synlett*, 25(04):505-508, 2014.