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Cu(II)-Catalyzed Ortho C(sp^2)−H Diarylamination of Arylamines To Synthesize Triarylamines

Mohit Kumar, Rishabh Sharma, Raziullah, Afsar Ali Khan, Ashfaq Ahmad, Himangsu Sekhar Dutta, and Dipankar Koley*

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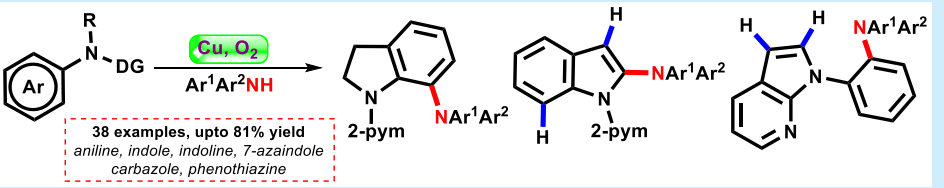

ABSTRACT: A copper-catalyzed, directed *ortho* C−H diarylamination of indoles, indolines, anilines, and *N*-aryl-7-azaindoles has been established. Only copper salt as the catalyst and oxygen as the terminal oxidant are used to synthesize triarylamines using various diarylamines including carbazole and phenothiazine. Mechanistic interrogation reveals that copper plays a dual role.

There has been a longstanding interest in the construction of C(sp^2)−N bonds owing to the ubiquity of C(sp^2)−N bonds in natural products, pharmaceuticals, agrochemicals, and multifunctional materials.[1−3]The most accomplished method to construct C−N bonds is the Pd-catalyzed Buchwald and Hartwig amination to aryl halides/boronic acids.[4,5] However, in the past decade, considerable achievements have been made in the direct C−H amination via oxidative coupling,[6] metal-catalyzed directing group assisted cross-coupling,[7] and radical induced coupling.[8] In this regard, since the independent seminal reports[7f,g] of Yu and Chatani, use of earth abundant, inexpensive copper catalysts showed great progress, especially on the directing group assisted C−H amination. Consequently, several other groups have expanded the overall scope of this strategy including the use of removable directing groups, diverse aminating sources.[3c9] For examples, Daugulis et al. used bidentate directing groups that could be removed easily.[9c] Yu et al. reported direct amination using carboxamides, sulfonamides, and anilines.[9d,g] Recently, Chang et al. showed that aqueous ammonia could directly be used as a C−H aminating reagent.[9f]

Triarylamines, with its unique structural and electronic properties, are considered to be a promising building block for novel optoelectronic devices.[10] Derivatives of triarylamine have shown enormous potential as photocatalysts[11] and redox-mediators.[12] Especially, incorporation of carbazole and phenothiazine moieties would be of immense importance owing to their proven character in organic materials.[13] In addition, triarylamine scaffolds are found to display anticancer activity.[14] However, the only available strategy for their syntheses is the conventional cross-coupling method using aryl halides and diarylamines.[15] While a number of examples are reported for the aryl C−H amination largely using dialkyl amines,[16] only a few reports have demonstrated C−H diarylamination to synthesize triarylamine derivatives (Scheme 1).[17] In 2014, Patureau et al. reported ruthenium-catalyzed diarylamination to afford anilines.[17g] However, only carbazole was effective as a diarylamine coupling partner. The same group has also been able to devise a strategy to synthesize phenothiazine- and carbazole-based triarylamines via oxidative coupling of diarylarylamines with arenes.[17a−f,h] However, the scope of the substrates was limited mostly to the phenol based arenes. The Zhang group recently reported copper catalyzed tandem reactions to synthesize indole and benzimidazole derivatives using diarylamines.[18] Very recently, in 2019, Lei's group developed aryl C−H diarylamination to produce anilines by utilizing electrochemical oxidation, albeit, furnishing the products exclusively in the *para*-selective manner.[17j] We considered whether directing group assisted C−H amination using diarylamine could be an alternative strategy to synthesize triarylamine. To the best of our knowledge, copper-catalyzed ortho C(sp^2)−H diarylamination to arylamines has not been reported. We have very recently demonstrated the use of highly abundant, less toxic, and inexpensive copper salts to functionalize the C(sp^2)−H of diverse arenes.[19] The study revealed that the reaction proceeds via disproportionation reaction. Recently, Stahl et al. demonstrated that copper catalyst can oxidatively dimerize diphenylamine to tetraarylhy-

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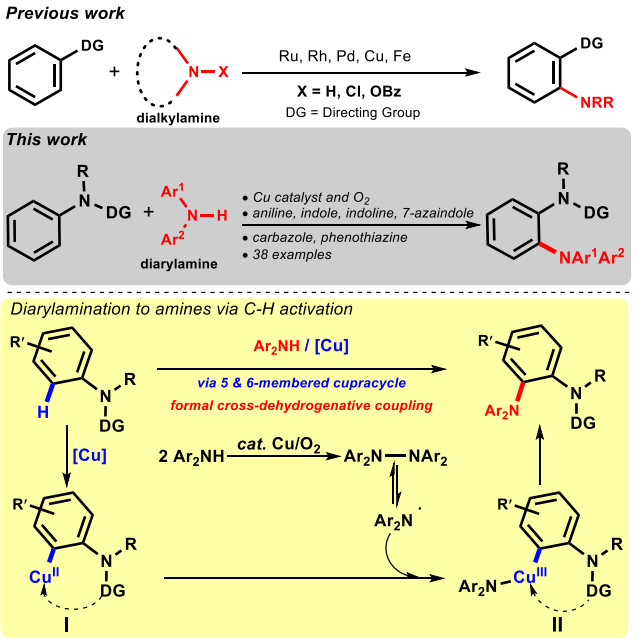
Scheme 1. Amination to Anilines via C−H Functionalization



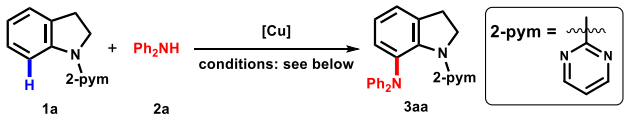
drazine under aerobic conditions via the generation of an aminyl radical.[20]

We argued that the in situ generated aminyl radical could oxidize the cyclometalated Cu(II) intermediate **I** to **II**, which should undergo reductive elimination to furnish the desired product (Scheme 1). Herein, we disclose diarylamination to synthesize indole, indoline, and aniline derivatives under aerobic conditions using a copper catalyst via direct C−H functionalization.[21] Notably, this method showed very good reactivity with not only various diarylamines including carbazoles and phenothiazine but also various *N*-aryl-7-azaindoles which were successfully aminated by diarylamines. In addition, this simple and atom-economical protocol needs only a copper catalyst and oxygen. While our work was in progress, a similar strategy was reported by Miura et al. for the diarylamination to phenols using a bidentate chelating ligand as a directing group.[17k] However, one of the major limitations of this protocol was the formation of bis-aminated products.

In a pilot reaction, we used *N*-pyrimidyl indoline (**1a**) and diphenylamine (**2a**) as the model substrates (Table 1). Delightfully, when heated in toluene at 120 °C, 30 mol % of $Cu(OAc)_2$ furnished the desired product **3aa** in 65% yield (entry 1). The same was isolated in 69% yield when the temperature was further increased up to 140 °C (entries 2,3). Next, various copper salts were tested (entries 4−7). However, none of them provided a better yield. A solvent screening study (entries 8−11) revealed that polar solvents were not suitable for this transformation, and dichloroethane (DCE) provided 71% of the desired product. 1.2 equiv of **2a** furnished the highest yield (entries 9, 12−14). Gratifyingly, no C5−H aminated product was obtained under the optimized conditions. No desired product was obtained in the absence of a copper catalyst.

Next, the reaction scope was examined by treating a variety of indoline derivatives (Scheme 2). The benzenoid moiety of indoline bearing methyl (**3ba**), methoxy (**3ca**), fluoro (**3da**), chloro (**3ea**), and iodo (**3fa**) functionality at the C5 position

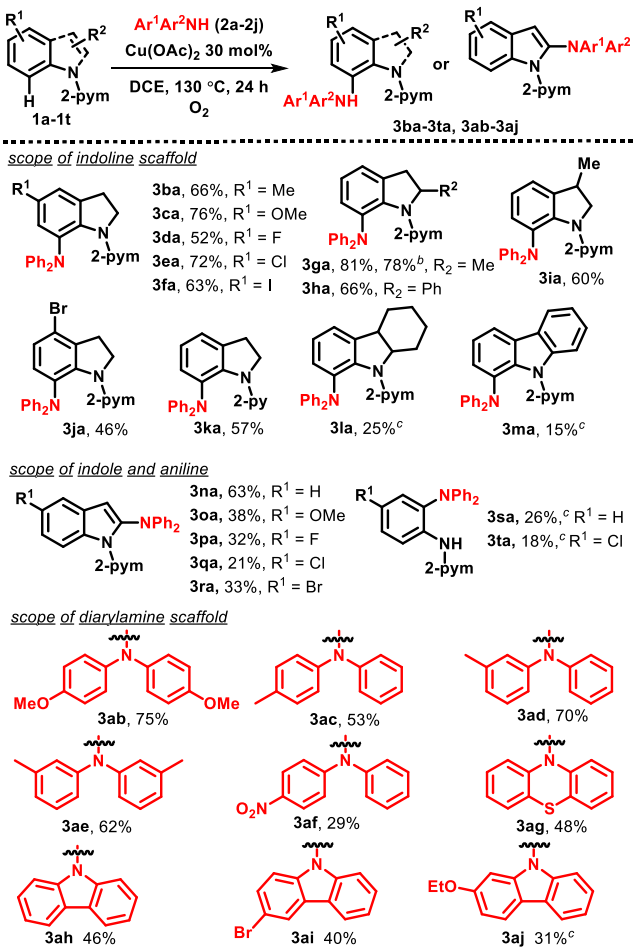
Table 1. Reaction Optimization[a]



entry	Cu-salt(mol %)	solvent	2a (equiv)	Temp (°C)	Yield[b] (%)
1	$Cu(OAc)_2$ (30)	Toluene	1.2	120	65%
2	$Cu(OAc)_2$ (30)	Toluene	1.2	130	69%
3	$Cu(OAc)_2$ (30)	Toluene	1.2	140	69%
4	CuTc (30)	Toluene	1.2	130	66%
5	$Cu(OBz)_2$ (30)	Toluene	1.2	130	63%
6	$Cu(OTf)_2$ (30)	Toluene	1.2	130	nd
7[c]	Cu_2O (30)	Toluene	1.2	130	52%
8	$Cu(OAc)_2$ (30)	DCB	1.2	130	54%
9	**$Cu(OAc)_2$ (30)**	**DCE**	**1.2**	**130**	**71%**
10	$Cu(OAc)_2$ (30)	DMF	1.2	130	traces
11	$Cu(OAc)_2$ (30)	DMSO	1.2	130	traces
12	$Cu(OAc)_2$ (30)	DCE	1.0	130	65%
13	$Cu(OAc)_2$ (30)	DCE	1.5	130	52%
14	$Cu(OAc)_2$ (30)	DCE	2.0	130	46%

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.3 mmol), solvent (2.5 mL), O_2 flush, 24 h. [b]Isolated yield. [c]With 60 mol % of BzOH

Scheme 2. Scope of Indolines and Diphenylamines[a]



[a]Reaction conditions: **1a−1t** (0.25 mmol), **2a−2j** (1.2 equiv), $Cu(OAc)_2$ (30 mol %), DCE (2.5 mL), 130 °C, 24 h; isolated yields. [b]1.0 mmol of **1g**, [c]140 °C.

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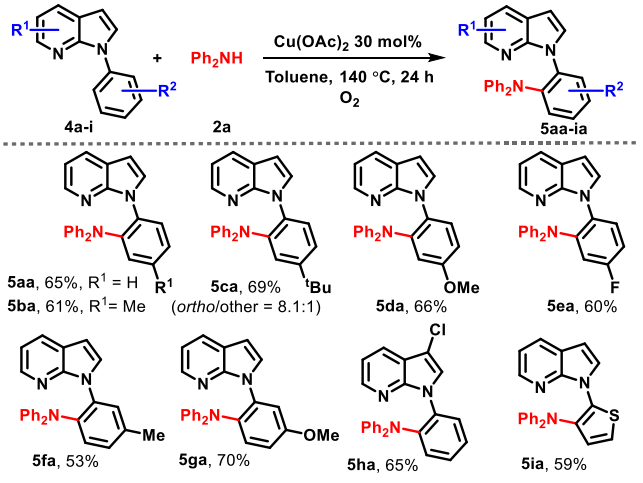
Org. Lett. XXXX, XXX, XXX−XXX

proved to be compatible with the process. Furthermore, indolines bearing substituents at the C2, C3, and C4 positions also afforded the desired products (**3ga**−**3ja**) in good yields (up to 81%). Notably, iodo- (**3fa**) and bromo- (**3ja**) substituted derivatives preferentially underwent desired C−H diarylamination over the Ullmann-type coupling. Indoline bearing pyridine as a directing group also furnished the desired product (**3ka**, 57%). Despite heating at elevated temperature (140 °C), hexahydrocarbazole (**1l**) and carbazole (**1m**) furnished the products (**3la**, **3ma**) in low yields. Our next objective was to check the possibility of amination at the C2 position of indole. Delightfully, various indoles were aminated to furnish the products (**3na**−**3ra**) in moderate yields. Aniline derivatives were also aminated by diphenylamine to yield products (**3sa**, **3ta**) in low yields (up to 26% yield). We next examined the scope of diarylamine substrates. Diarylamines bearing methyl (**3ac**−**3ae**), methoxy (**3ab**), and nitro (**3af**) efficiently furnished the products with yields up to 75%. Notably, phenothiazine, a privileged heterocycle[22] not only in medicinal chemistry but also in photoredox catalysis, has been coupled with **1a** to synthesize *N*-arylphenothiazine **3ag** in 48% yield. Gratifyingly, carbazoles, another important class of medicinally relevant scaffold,[23] were successful coupling partner as diarylamine to furnish **3ah**−**3aj**. Gratifyingly, the reaction was also tolerated on a larger scale setup as 1.0 mmol of **1g** yielded 78% of **3ga**.

We next argued whether 7-azaindole,[24] a promising privileged scaffold in medicinal chemistry, could be used as a directing group for the diarylamination to produce arene substrates (Scheme 3). Thus, various *N*-aryl-7-azaindoles were

Scheme 3. Scope of Azaindoles[a]

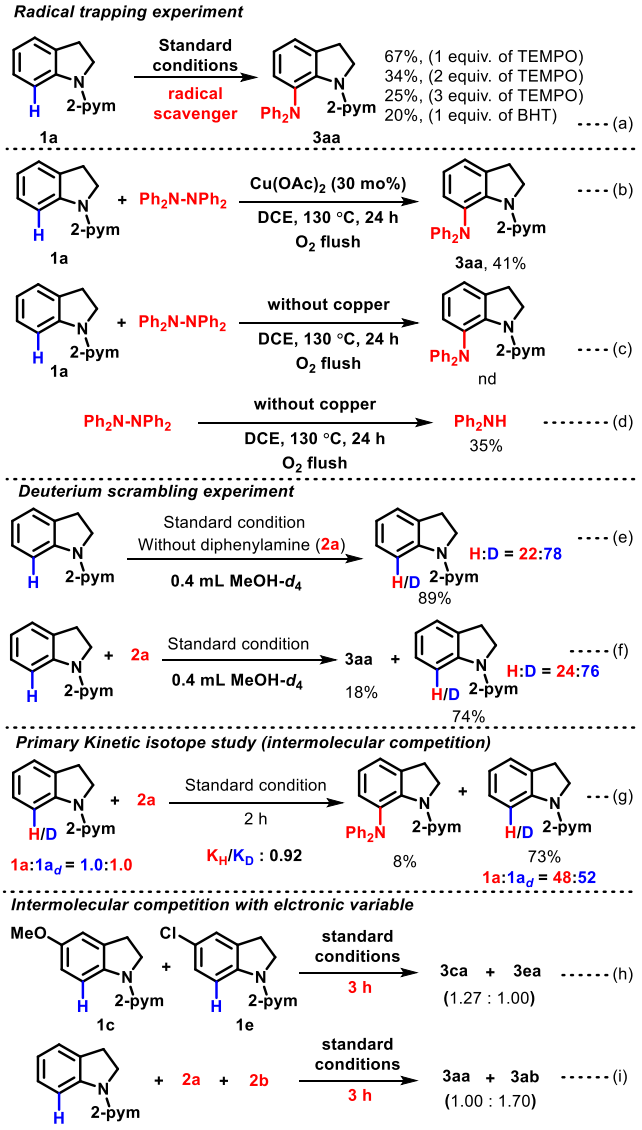


[a]Reaction conditions: **4a**−**4i** (0.25 mmol), **2a** (0.3 mmol), $Cu(OAc)_2$ (30 mol %), Toluene (2.5 mL), 140 °C, 24 h; isolated yields.

subjected to the optimized reaction conditions. To our delight, various *N*-aryl-7-azaindoles were tolerated by the method and the aminated products (**5aa**−**5ia**) were obtained in good to very good yields (53−70%). Arenes bearing an alkyl (**5ba**, **5ca**, **5fa**), alkoxyl (**5da**, **5ga**), and halogen (**5ea**, **5ha**) were well tolerated. Hetereoarene (**5ia**, 59%) also participated in the reaction. Interestingly, unlike the Miura report, in most of the cases only trace amount of bisaminated product was identified via mass spectroscopic analysis of the crude reaction mixture.

We next focused our attention toward understanding the mechanism of this reaction (Scheme 4). Our hypothesis of a

Scheme 4. Control Experiments on Mechanistic Aspect



radical mechanism was supported by the radical trap experiment (Scheme 4a), as the formation of **3aa** was suppressed by both 2,2,6,6-tetra-methylpiperidine-1-oxyl (TEMPO) and butylated hydroxytoluene (BHT). As described by Stahl et al., in the presence of a copper salt under O_2, the diarylamine exists in equilibrium with its tetraarylhydrazine derivative; thus, we wondered whether tetraarylhydrazine might serve as the source of the diarylaminyl radical. To our delight, under the optimized conditions, tetraphenylhydrazine provided 41% of **3aa** (Scheme 4b). As expected, no product was obtained when the same reaction was performed in the absence of a copper catalyst (Scheme 4c). On the contrary, upon heating, tetraphenylhydrazine undergoes smooth decomposition to diphenylamine without any copper catalyst (Scheme 4d). These results together suggest that the aminyl radical is the key intermediate in this reaction and copper is necessary to generate this radical. As observed previously by us,[19c−e] the results of deuterium scrambling experiments (Scheme 4e, 4f) suggest that the C−H metalation step is reversible. However, the primary kinetic isotope study revealed (k_H/k_d = 0.92) that the rate of the reaction does not depend on the C−H metalation step (Scheme 4g). We have also observed

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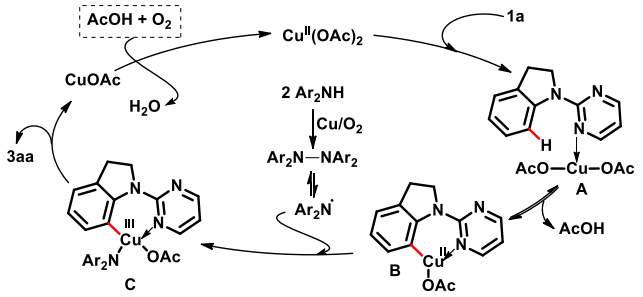
Org. Lett. XXXX, XXX, XXX−XXX

(Scheme 4h, 4i) that electronically rich indolines as well as electronically rich diarylamines react preferentially over the electronically neutral or electronically deficient substrates.

On the basis of the preliminary experimental results and previous reports,[17k,19c,d,20,25] a plausible mechanism for this reaction is outlined in Scheme 5. First, **1a** chelates with Cu(II)

Scheme 5. Plausible Reaction Mechanism



to form intermediate **A** which is then converted to the intermediate **B** via chelation assisted reversible C−H bond cleavage. Subsequently, tetraarylhydrazine formed in situ from diarylamine oxidizes the Cu(II) metallacycle to the Cu(III) intermediate **C**, which upon reductive elimination furnishes product **3aa** and Cu(I)OAc. The active catalyst is then regenerated by molecular oxygen.

In summary, we have developed a copper-catalyzed C−H amination by diarylamine derivatives to indolines and aniline under an oxygen atmosphere. Privileged scaffolds like phenothiazine and carbazole have been efficiently coupled as diarylamine precursors. Medicinally relevant *N*-aryl-7-azaindoles underwent diarylamination in good to very good yields. Overall, this method provides a simple way to synthesize triarylamine derivatives via C−H activation. Control experiments on mechanistic interrogation suggest that the reaction follows a radical pathway and copper plays a dual role in this reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00196.

Full experimental details, characterization data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Dipankar Koley − *Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, Lucknow 226031, India; Academy of Scientific and Innovative Research, New Delhi 110001, India;* orcid.org/0000-0002-4861-7232; Email: dkoley@cdri.res.in

Authors

Mohit Kumar − *Academy of Scientific and Innovative Research, New Delhi 110001, India*

Rishabh Sharma − *National Institute of Pharmaceutical Education and Research, Kolkata 700054, India*

Raziullah − *Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, Lucknow 226031, India*

Afsar Ali Khan − *Academy of Scientific and Innovative Research, New Delhi 110001, India*

Ashfaq Ahmad − *Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, Lucknow 226031, India*

Himangsu Sekhar Dutta − *Academy of Scientific and Innovative Research, New Delhi 110001, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00196

Notes

The authors declare no competing financial interest.

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