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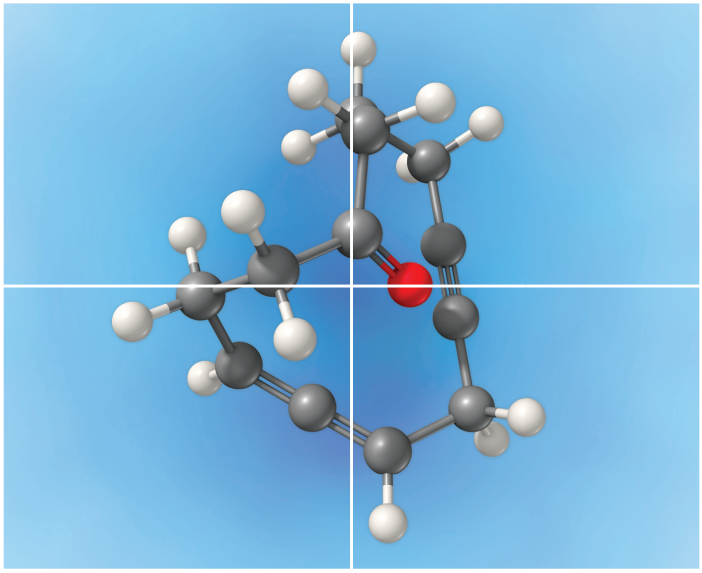

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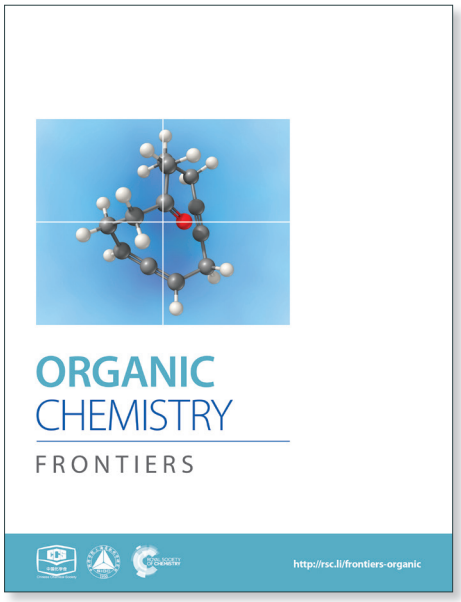

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Copper-Mediated C(sp^2)−H Amination Using $TMSN_3$ as a Nitrogen Source: Redox-neutral Access to Primary Anilines

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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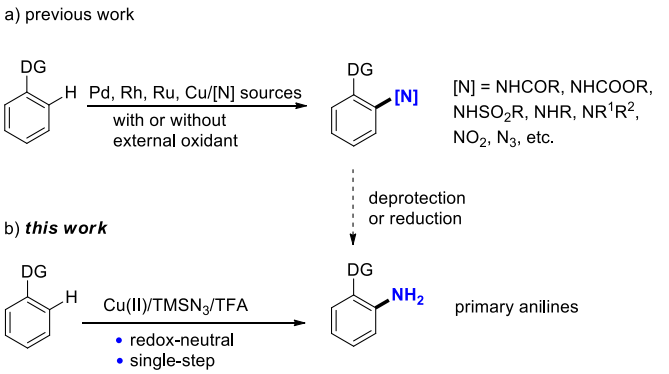
A Cu-mediated direct conversion of aromatic C−H to C−NH_2 assisted by a chelation group was developed. The reaction employed $TMSN_3$ as a nitrogen source under redox-neutral conditions to provide a variety of N-heterocycle-substituted primary anilines. Neither external oxidant nor additional deprotection or reduction step was required in this process.

Aromatic amines (anilines) are essential intermediates in the manufacture of agrochemicals, pharmaceuticals, dyes, pigment, and polymers.[1] Primary anilines are particularly useful, because they can be served as starting materials of various aniline derivatives, such as secondary or tertiary anilines, amides, imines, amidines, and carbomates. In addition, they are precursors of many other functional groups, including halides, CN, OH, SH, CF_3, etc. via diazonium salts as intermediates.[2] Common accesses to primary anilines are reduction of aromatic nitro compounds[3] and transition-metal-catalyzed amination of aryl halides with ammonia or its surrogates.[4] Recent efforts have identified that aryl boronic acids,[5] substituted cyclohexenone oximes[6] could also be transformed to primary anilines under metal-free or transition-metal-catalyzed conditions. In recent years, substantial achievements have been made in transition-metal-catalyzed C−H functionalization reactions due to their advantages over traditional transformations based on pre-functionalized substrates in atom-economy and step-efficiency.[7] Direct conversion of aromatic C−H to C−N bonds is one of the major topics in C−H functionalization due to the great importance of anilines in organic synthesis.[8] Therefore, a range of Pd-, Rh-, Ru-, or Cu-catalyzed systems employing either non-activated amino sources under oxidative conditions, such as amines, amides,[9] sodium azide/nitrite[10] or pre-activated amino sources under redox-neutral conditions, such as *N*-chloroamines,[11] *N*-hydroxycarbamates,[12] *O*-acylhydroxylamines,[13] nitrosobenzenes,[14] NFSI,[15] sulfonyl/acyl azides,[16] and aryl/alkyl azides[17] have been developed (a, Scheme 1). Corresponding secondary/tertiary aniline derivatives, azides, etc. were produced. To access to primary anilines via aforementioned C−H amination methods, an extra deprotection or reduction step is unavoidable. Therefore, direct conversion of aromatic C−H bond to C−NH_2 is highly valuable and similar reports are scarce in literature.[18]

Trimethylsilyl azide has been widely used in the synthesis of nitrogen-containing molecules,[19] such as triazoles, tetrazoles, nitriles, azirines, and so on.[20] Recently, the group of Jiao reported a copper-catalyzed C−H azidation of primary anilines with $TMSN_3$ as an azide source directed by the free amino group.[21] Monguchi and Sajiki developed a general route to primary anilines through $Cu^{(0)}$-mediated reductive amination of aryl halides with $TMSN_3$.[22] Herein, we report an unprecedented copper(II)-mediated access to primary anilines using $TMSN_3$ as an amino source in the presence of TFA via a chelation group assisted C−H activation in one pot. Neither external oxidant nor additional deprotection or reduction step is required in this process (b, Scheme 1).

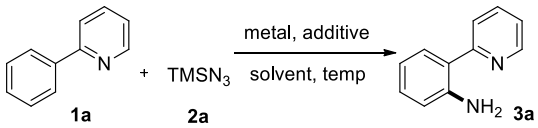


Scheme 1. Chelation Assisted C(sp^2)-H Amination

We initially studied the reaction between 2-phenylpyridine **1a** and $TMSN_3$ **2a** in the presence of CuTc (30 mol %) and TfOH (1.0 equiv) in 1,2-dichlorobenzene at 120 °C for 24 h (entry 1, Table 1). To our delight, the desired primary aniline **3a** was obtained in 24% yield together with 64% of **1a** recovered. Extended reaction times resulted in partial decomposition of the aminated product. TFA was superior to other acidic additives, improving the yield of **3a** to 32%. $Cu(TFA)_2$ can promote the reaction more efficiently than CuTc (36%). Only trace amount of **3a** was detected in the absence of acid, suggesting the essential role of acid in this amination process (entries 2-5). In all of the cases, the starting material **1a** cannot be fully consumed, presumably as a result of strong coordination of copper

with the two nitrogen atoms in **3a**. As expected, the yield of **3a** was improved to 88% when the loading of $Cu(TFA)_2$ was increased to 1.0 equivalent (entry 6). Other copper salts, including $Cu(OAc)_2$, $CuCl_2$, $Cu(OTf)_2$, $Cu(hfacac)_2$, CuI, and CuBr were also screened (see Electronic Supplementary Information). It was intriguing that when $Cu(TFA)_2$ was replaced by $Cu(OAc)_2$, no **3a** was detectable. When $CuCl_2$ was applied, only mono- and dichlorinated products were formed. It is obvious that the counter anion of copper is vital for the product formation. Screening of solvents resulted in lower yields or no product formation (entries 9-10, and ESI). It should be noted that NaN_3 can also be used as an amino source instead of $TMSN_3$, furnishing **1a** in 38% yield (entry 11). A control reaction using $Pd(TFA)_2$ (20 mol %) as catalyst didn't give any of the desired product. When the reaction temperature was lowered to 90 °C, this C−H amination reaction was shut down completely.

Table 1. Optimization of the Reaction Conditions[a]

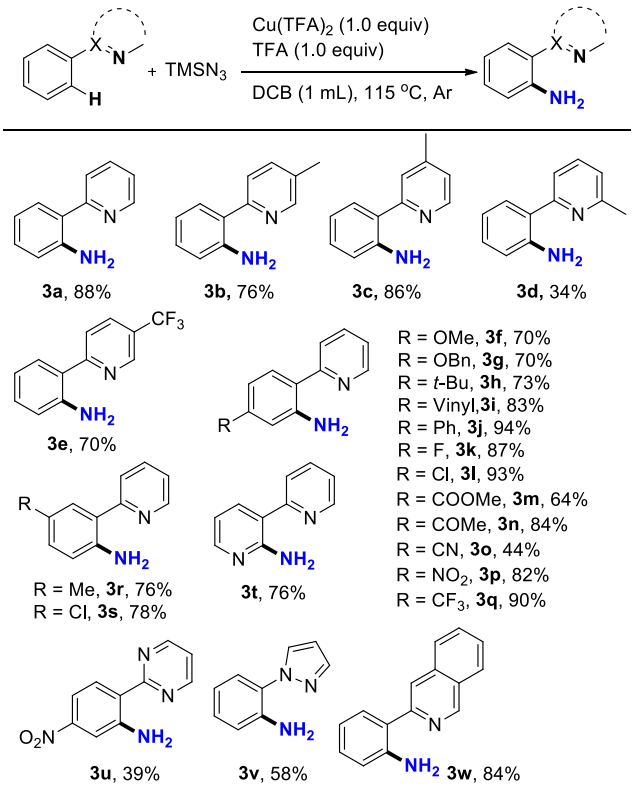


Entry	Metal (equiv)	Additive (1.0 equiv)	Solvent	Time (h)	Yield (%)[b]
1	CuTc (0.3)	TfOH	DCB	24	24
2	CuTc (0.3)	TFA	DCB	24	32
3	CuTc (0.3)	--	DCB	24	trace
4	CuTc (0.3)	*p*-TsOH	DCB	24	18
5	$Cu(TFA)_2$ (0.3)	TFA	DCB	24	36
6	**$Cu(TFA)_2$ (1.0)**	**TFA**	**DCB**	**12**	**88**
7	$Cu(OAc)_2$ (1.0)	TFA	DCB	24	N.R.
8	$CuCl_2$ (1.0)	TFA	DCB	24	N.D.[c]
9	$Cu(TFA)_2$ (1.0)	TFA	Toluene	12	47%.
10	$Cu(TFA)_2$ (1.0)	TFA	DMSO	12	N.R
11	$Cu(TFA)_2$ (1.0)	TFA	DCB	24	38%[d]
12	$Pd(TFA)_2$ (0.2)	TFA	DCB	12	N.R

[a] Conditions: **1a** (0.20 mmol), **2a** (0.4 mmol), metal salt, additive (1.0 equiv), solvent (1.0 mL), Ar, sealed tube, 115 ℃. [b] Yield of isolated **3a**, DCB = 1, 2-dichlorobenzene. [c] Mono- and dichlorinated products were formed. [d] NaN_3 (0.4 mmol) was used, 41% of **1a** was recovered.

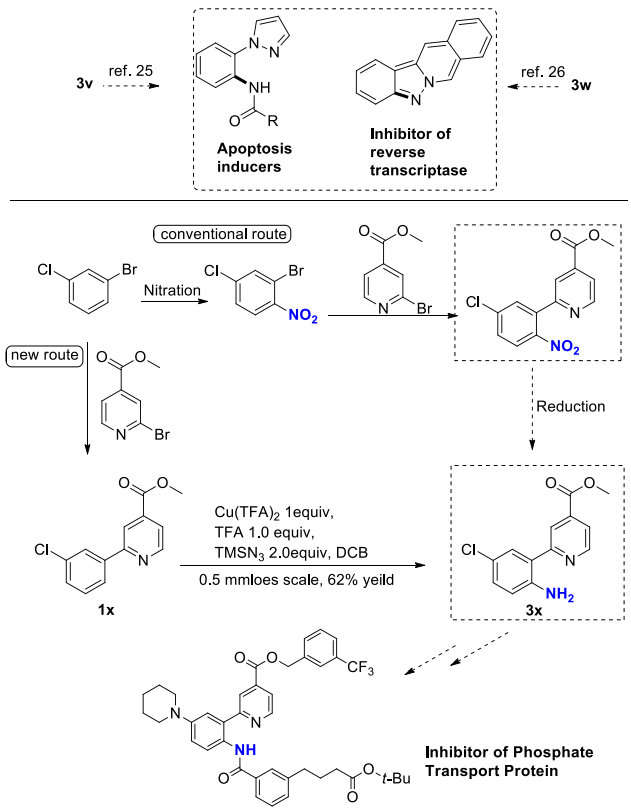
Next, the scope of this C−H amination reaction was investigated under the optimal reaction conditions. 2-Phenylpyridines bearing an electron-donating Me (**3b** and **3c**) or electron-withdrawing CF_3 (**3e**) group in the pyridine moiety aminated smoothly. However, a methyl group substituted at C6 of pyridine deteriorated the reaction dramatically (34%, **3d**) probably due to the steric hindrance around the pyridine nitrogen, proving its great importance in chelation with Cu. C−H amination also occurred efficiently on substrates with various substituents on different positions of the phenyl ring. Electron-donating OMe, OBn, and *t*-Bu (**3f-h**) as well as electron-withdrawing halogens (**3k-l**), ester (**3m**), ketone (**3n**), NO_2 (**3p**), and CF_3 (**3q**) groups on the *para* position were well tolerated, providing corresponding primary anilines in good to excellent yields. The group of nitrile was less compatible with the acidic conditions, furnishing **3o** in a lower yield of 44%. It is noteworthy that an alkene group in **3i** also survived the reaction. These functional groups provided handles for further transformations on the scaffold. For *meta*-substituted substrates, amination took place at the less steric hindered C−H bond exclusively (**3r** and **3s**). Notably, a bipyridine substrate, 2-(pyridin-3-yl)pyridine, produced only one aminated product, 3-(pyridin-2-yl)pyridin-2-amine **3t,** regioselectively in 76% yield. Besides pyridine, other heterocycles, such as pyrimidine, pyrazole, and isoquinoline, can also act as viable chelating groups in this amination reaction, providing corresponding products **3u-w** in moderate to good yields. Unlike other chelation assisted $C(sp^2)$−H functionalization reactions where difunctionalization is generally an inevitable side-reaction, no diamination products were observed in all of the cases. Recently, Jiao reported a Pd-catalyzed tandem C−H azidation and N−N bond formation by reacting 2-arylpyridines with sodium azide in the presence of oxidants.[23] However, neither 2-(2-azidophenyl)pyridines as reaction intermediates nor pyrido[1,2-*b*]indazoles was detected in the current Cu-mediated primary aniline synthesis.

Table 2. Scope of C-H Amination[a, b]



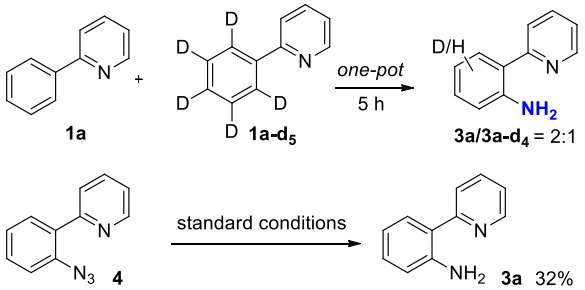
[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Cu(TFA)_2$ (1.0 equiv), TFA (1.0 equiv), 1, 2-dichlorobenzene (1.0 mL), Ar, sealed tube, 115 ℃. [b]Yield of isolated **3**.

These primary aniline products containing an *ortho*-*N*-heterocycle are useful precursors in the synthesis bidental nitrogen ligands[24] as well as bioactive agents. For example, *N*-Ts protected derivative of **3a** was an effective bidental ligand in fluorination chemistry.[25] The binding affinity of this class of ligands is tunable, since analogues of **3a** can be accessed feasibly by applying this amination method. Pyrazole and isoquinoline substituted primary anilines **3v** and **3w** are intermediates in the synthesis of apoptosis inducers[26] and inhibitors of reverse transcriptase, [27] respectively (Scheme 3). Primary aniline **3x**, a key intermediate for the synthesis of inhibitors of phosphate transport protein,[28] was prepared from **1x** under the standard reaction conditions in 62% isolated yield. The previous method to introduce the free NH_2 in **3x** involves nitration and reduction steps, which is less atom-economic and step-efficient.



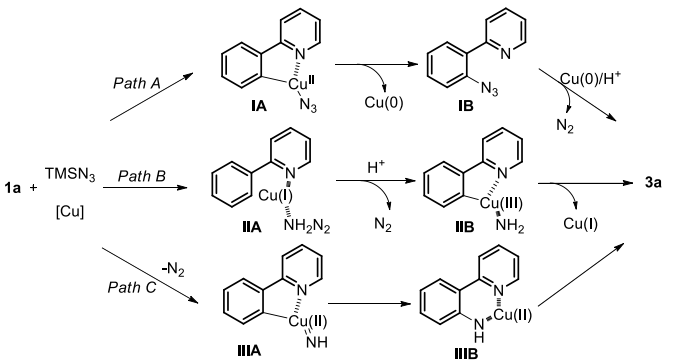
Scheme 3. Application of the Primary Aniline Products

To gain insights into this C−H amination process, a competition reaction between equal amount of **1a** and deuterated **1a-d$_5$** in one pot was carried out. The reaction was quenched in the middle and the product ratio between **3a** and **3a-d$_4$** was determined to be 2 : 1 by ^{1}HNMR, suggesting that C−H bond cleavage was likely a rate-limiting step[29] (Scheme 4). A possible intermediate, 2-(2-azidophenyl)pyridine **4**, was synthesized and subjected to the reaction. Although the yield for the transformation of azide **4** to **3a** was low under the standard conditions (32%), a reaction pathway involving azide **4** as an intermediate cannot be fully ruled out.



Scheme 4. Mechanistic Studies

Although the exact mechanism of this free aniline-forming process is not clear at current stage, possible pathways are proposed in Scheme 5.[30] In path A, the azido group may be transferred into the aryl ring first via reductive elimination of a cyclometalated intermediate **IA** after C−H bond activation. Reduction of **IB** by Cu$^{(0)}$ in the presence of acid provides **3a**. In path B, the coordinated Cu$^{(I)}$, generated by disproportionation of Cu$^{(II)}$, is oxidized to a high valent Cu$^{(III)}$ species[31] with concurrent release of N_2. After C−H bond activation and C−Cu bond formation, the cyclometalated Cu$^{(III)}$ intermediate **IIB** was formed, followed by reductive elimination. Alternatively, pathway C involving copper nitrenoid insertion to C−Cu bond is also possible.[32]



Scheme 5. Plausible reaction pathways

Conclusions

In summary, we have developed a copper-mediated process for the direct conversion of aromatic C−H to C−NH$_2$ bonds. Several N-heterocycles can act as chelation groups to assist the key C−H activation step. Corresponding primary anilines containing an *ortho* N-heterocycle are obtained under redox neutral conditions without an extra deprotection or reduction step. A range of functional groups are tolerated. The versatility of primary anilines in chemical transformations makes this method particularly useful in diversifying *N*-heterocycle substituted arenes. The exploration of related transformation and further mechanistic studies are currently under way in our laboratories.

Acknowledgements

We are grateful for financial support of this work by National Science Foundation of China (21202167).

Notes and references

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