Organic & Biomolecular Chemistry

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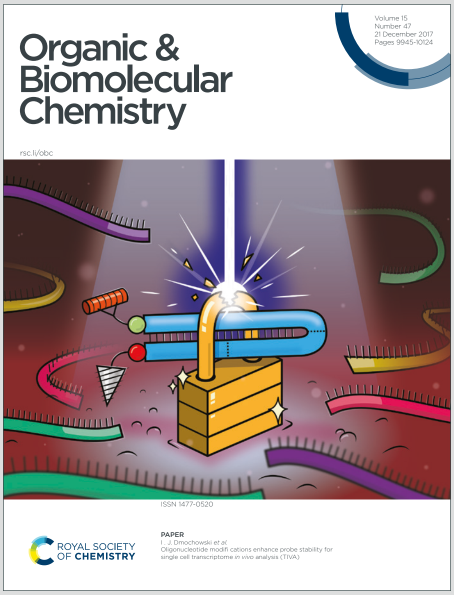

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PAPER
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Copper-catalyzed direct amination of benzylic hydrocarbons and inactive aliphatic alkanes with arylamines

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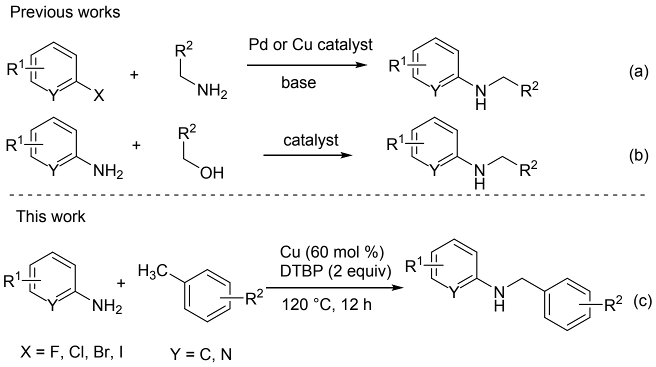
Hua Yao, Bo Xie, Xiaoyang Zhong, Shengzhou Jin, Sen Lin*, and Zhaohua Yan*

Abstract： A new synthetic method toward direct C–N bond formation through saturated C–H amination of benzylic hydrocarbons and inactive aliphatic alkanes with primary aromatic amines under an inexpensive catalyst/oxidant (Cu/DTBP) system has been developed. Both aminopyridines and anilines could react smoothly with primary and secondary benzylic C–H substrates or cyclohexane to form the corresponding aromatic secondary amines in moderate to good yield. This protocol has the advantages of wide functional group tolerance and using of readily available raw materials.

Amines are a class of important compounds that find wide application in indispensable areas of life such as pharmaceuticals, agrochemicals, dyes， and functional materials[1]. Due to their interesting physiological activities, especially their extremely important pharmacophore in many bioactive compounds, secondary amines have received extensive attention in the field of drug discovery[2]. Traditional methods of preparation of secondary amines involve treating primary amines with halogenated hydrocarbons[3] or using various reductants to completely reduce the imines[4], but these transformations are often problematic due to the harsh reaction conditions, generally low yields and poor chemical selectivity. To overcome these deficiencies, metal-catalyzed coupling reactions have been developed for the construction of aromatic amines[5]. Such as Ullman cross-coupling[6], Buchwald–Hartwig amination[7] [Scheme 1, (a)], hydroamination[8], hydroaminomethylation[9] and hydrogen borrowing methodology[10] [Scheme 1, (b)]. However, all these transformations have in common the need for a reactive functional group may leading to potential environmental problems. It would be highly attractive to direct amination of the unfunctionalized starting materials such as aromatic hydrocarbon, aliphatic hydrocarbon , or other C (sp^3)−H bond containing compounds， since formally only H_2O will be formed as a byproduct of this transformation. Within this contribution, we herein report a general method of copper-catalyzed direct amination of C (sp^3)–H with aromatic amines to afford the corresponding aromatic secondary amines [Scheme 1, (c)]. Both anilines and aminopyridines can react

Scheme 1. Synthesis of aromatic secondary amines



Department of Chemistry, Nanchang University, No. 999, Xuefu Rd. Nanchang, 330031, P. R. China. E-mail: senlin@ncu.edu.cn, yanzh@ncu.edu.cn

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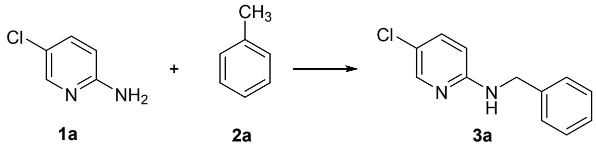
smoothly with primary and secondary benzylic C–H substrates in moderate to good yields.

Table 1. Optimization of the reaction conditions [a]

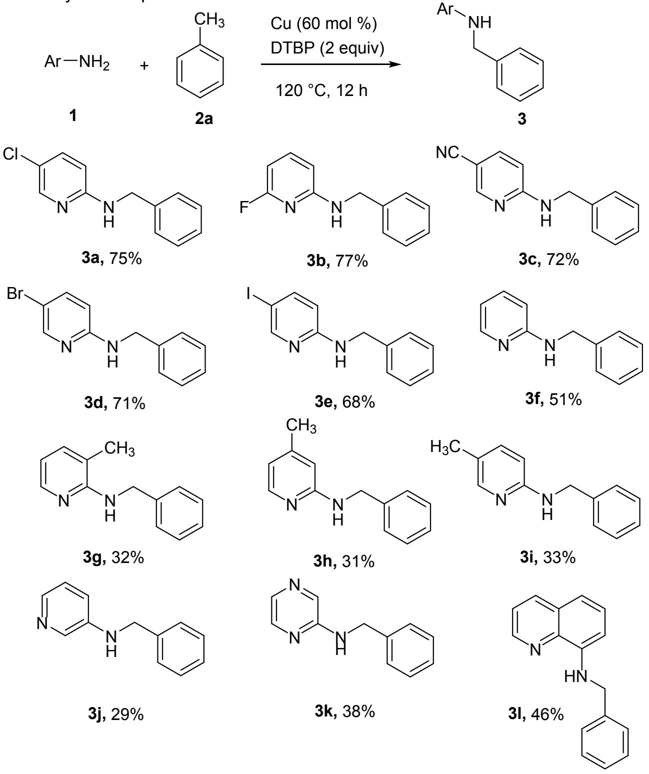


Entry	Catalyst (mol%)	Oxidant (eq.)	Solvent	Yield[b]
1	CuI (20)	DTBP (2.0)	neat	31
2	CuBr (20)	DTBP (2.0)	neat	29
3	$CuCl_2$ (20)	DTBP (2.0)	neat	38
4	$Cu(OAc)_2$ (20)	DTBP (2.0)	neat	35
5	Cu (20)	DTBP (2.0)	neat	51
6	CuSCN (20)	DTBP (2.0)	neat	34
7	$FeCl_2$ (20)	DTBP (2.0)	neat	19
8	$FeCl_3$ (20)	DTBP (2.0)	neat	trace
9	$NiCl_2$ (20)	DTBP (2.0)	neat	trace
10	$AgNO_3$ (20)	DTBP (2.0)	neat	trace
11	Cu (20)	TBHP (2.0)	neat	n.d.
12	Cu (20)	BPO (2.0)	neat	n.d.
13	Cu (20)	TBPB (2.0)	neat	n.d.
14	Cu (20)	$K_2S_2O_8$ (2.0)	neat	n.d.
15	Cu (20)	DDQ (2.0)	neat	trace
16	Cu (20)	DTBP (2.0)	DMSO	trace
17	Cu (20)	DTBP (2.0)	DMF	trace
18	Cu (20)	DTBP (2.0)	DME	28
19	Cu (20)	DTBP (2.0)	H_2O	18
20	—	DTBP (2.0)	neat	trace
21	Cu (40)	DTBP (2.0)	neat	63
22	Cu (60)	DTBP (2.0)	neat	72
23	Cu (80)	DTBP (2.0)	neat	71
24	Cu (60)	—	neat	n.d.
25	Cu (60)	DTBP (1.0)	neat	46
26	Cu (60)	DTBP (3.0)	neat	69
27[c]	**Cu (60)**	**DTBP (2.0)**	**neat**	**75**
28[d]	Cu (60)	DTBP (2.0)	neat	73

[a]Conditions: 1a (0.50 mmol), 2a (1.0 mmol), solvent (2 mL), 10 h, 120 °C, under N_2. [b] Isolated yield. [c] 12 h. [d] 14 h.

The initial explorations were completed by the inter-molecular coupling of 5-amino-2-chloropyridine (**1a**) with methyl-benzene (**2a**) as a model reaction under different reaction conditions, including optimization of catalysts, oxidants, reaction time, and solvents to yield desired compound. The results are summarized in Table 1. The reaction was initially carried out by using CuI and DTBP (Di-tert-butyl peroxide) as a catalyst and an oxidant, respectively (Table 1, entry 1). A small amount of the corresponding product was obtained after heating at 120 °C for 10 h under nitrogen atmosphere in the sealed tube. Encouraged by this result, different kinds of Cu catalysts such as CuBr, $CuCl_2$, $Cu(OAc)_2$, Cu powder and CuSCN were employed in the reaction (Table 1, entries 2-6). The results showed that Cu powder showed the best results for this reaction. Other metal catalysts (such as Fe salts, Ni salts and Ag salts) exhibited less efficient or no catalytic activity under the same conditions (Table 1, entries 7-10). Meanwhile, several oxidants (such as TBHP, BPO, TBPB, etc.) were filtrated for this transformation. It turned out that only DTBP exhibited reaction activity to the transformation, and TBHP (tert-butyl hydroperoxide) (70% in water), TBPB (tert-butyl perbenzoate), BPO (benzoyl peroxide), DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquin-one) and $K_2S_2O_8$ did not trigger the reaction (Table 1, entries 11-15). The reaction was carried out in other solvents, whereas no reaction was observed in DMSO and DMF, and reaction of DME and H_2O afforded **3a** in lower yields (Table 1, entries 16-19). Increasing the amount of Cu powder to 60% led to a higher yield of 72% (Table 1, entry 20-22); further increasing it to 80% did not improve the yield (Table 1, entries 23). The amount of the oxidant was screened, results showed that 2.0 equiv of DTBP provided **3a** in better yield (Table 1, entry 22, 24, 25,26).

Scheme 2. Substrate scope of aminopyridines and other nitrogen-containing heterocyclic compounds [a,b]



[a] Conditions: **1** (0.50 mmol), **2a** (2.0 mL), Cu powder (0.3 mmol) and DTBP (1.0 mmol) 120 °C, 12 h, under N_2. [b] Isolated yield.

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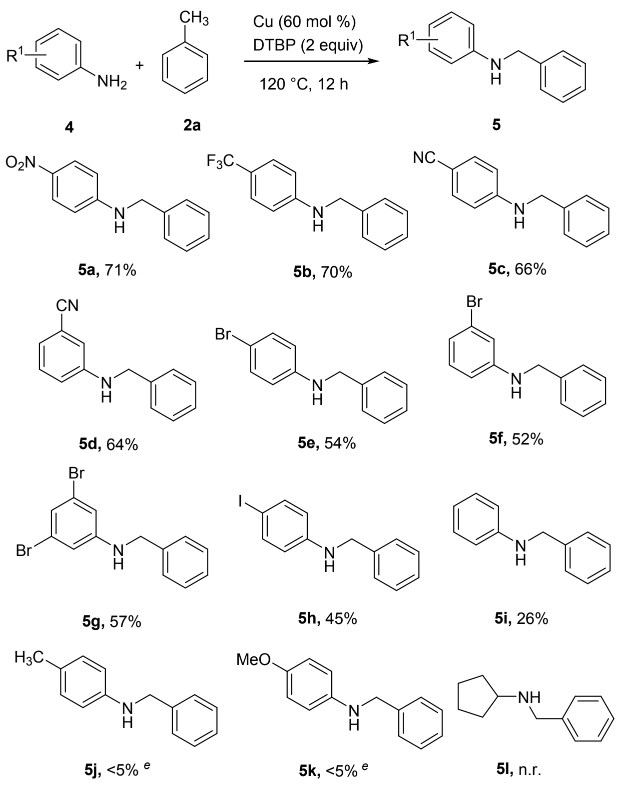
When the reaction time was extended to 12 h, the yield of **3a** increased to 75% (Table 1, entry 27), further increasing the reaction time to 14 h, there was a slight decrease in the yield of **3a** (Table 1, entry 28). On the basis of the results showed in Table 1, the reaction was carried out with 0.5 mmol of aromatic amines, 2.0 mL of toluene substrates, 0.30 mmol of Cu powder, and 1.0 mmol of DTBP at 120 °C for 12 h.

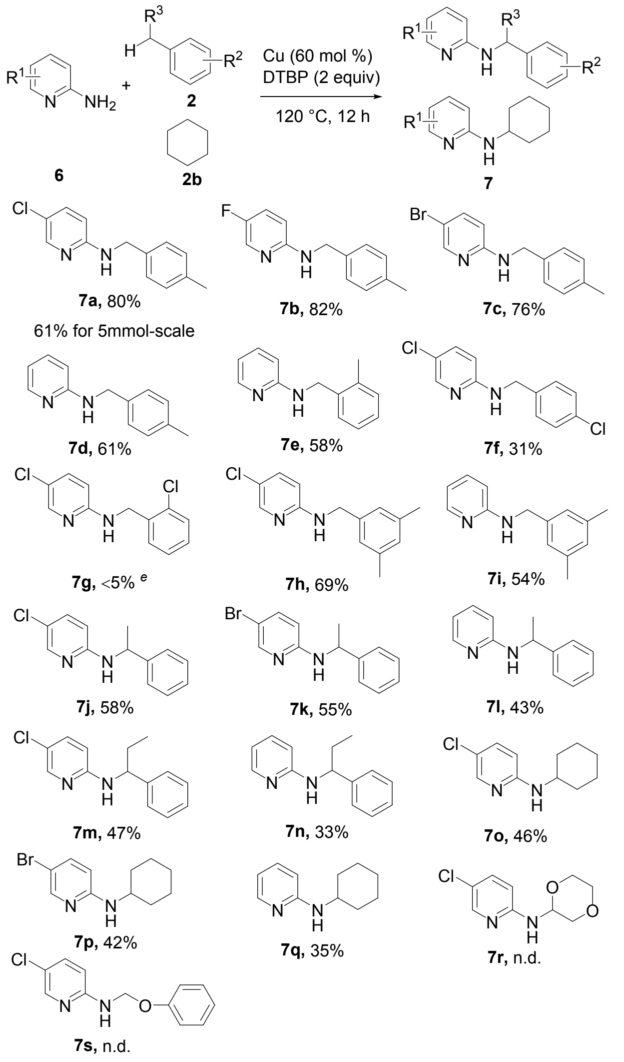
Scheme 3. Substrate scope of anilines [a,b]



[a] Conditions: **4** (0.50 mmol), **2a** (2.0 mL), Cu powder (0.3 mmol) and DTBP (1.0 mmol), 120 °C, 12 h, under N_2. [b] Isolated yield. [e] Detected by GC-MS.

With optimized conditions obtained, the scope of the process was studied for the reaction of a series of substituted aminopyridines with toluene as a representative example (Scheme 2). The electronic effect of the substituent groups on the pyridine rings had an obviously influence on the reactions. Aminopyridines containing electron-withdrawing groups such as halogen and -CN reacted with toluene affording the corresponding aromatic secondary amines with yields ranging from 68% to 77% (**3a-3e**). The reaction of aminopyridines containing the electron-donating group methyl was significantly reduced in the yield of the ammoniation products (**3g-3i**). Additionally, different positions of Methyl substituents in the pyridine ring did not appear to have a significant effect on the reaction yields. 2-aminopyridine (**3f**) and 3-aminopyridine (**3j**) which without other substituents on the pyridine rings were used to participate in the reaction, and the results showed that 2-aminopyridine was more suitable for our optimization conditions. Interestingly, other nitrogen-containing heterocyclic compounds such as aminopyrazine and 8-aminoquinoline were adopted, the results showed that they could react with methylbenzene smoothly and gave the desired product in 38-46% yields **(3k, 3l)**.

Scheme 4. Substrate Scope of benzylic hydrocarbons, aliphatic alkanes and ethers [a,b,e]



[a] Conditions: **6** (0.50 mmol), **2** (2.0 mL), Cu powder (0.3 mmol) and DTBP (1.0 mmol), 120 °C, 12 h, under N_2. [b] Isolated yield. [e] Detected by GC-MS.

Encouraged by the above research, we decided to study the amination of toluene with anilines and aliphatic amines. As showed in Scheme 3, anilines bearing strong electron-withdrawing groups, such as -NO_2, -CF_3, and -CN reacted with toluene to offer the corresponding products in good yields **(5a-5d)**. The reaction of anilines with bromo and iodo functional groups afforded the corresponding aromatic

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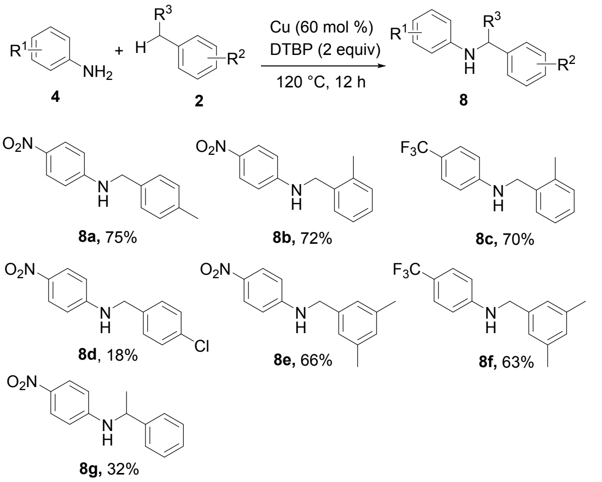
secondary amines in 45%-57% yields **(5e-5h)**. Aniline reacted with toluene giving **5i** in a low yield of 26%. 4-methylaniline and 4-methoxyaniline were unsuccessful substrates (**5j, 5k**), which may be due to the electron donor nature of the -Me and -OMe. Additionally, our optimized reaction conditions may not be suitable for aliphatic amines, and cyclopentylamine failed to react with toluene to produce corresponding secondary amine compound **(5l)**.

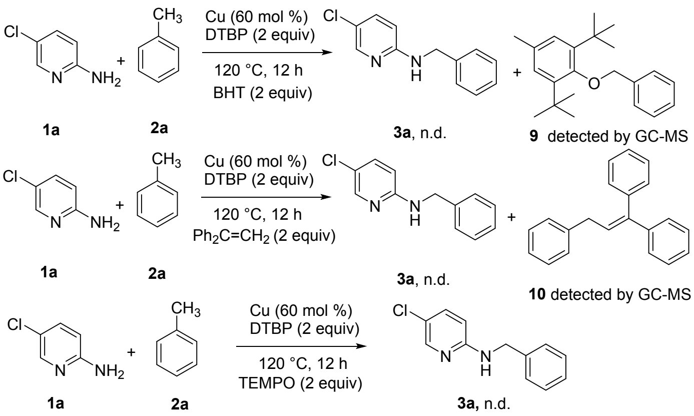
Scheme 5. Substrate scope of benzylic hydrocarbons ^{a,b}



^{a} Conditions: **4** (0.50 mmol), **2** (2.0 mL), Cu powder (0.3 mmol) and DTBP (1.0 mmol), 120 °C, 12 h, under N_2. ^{b} Isolated yield.

Substrate scope studies were also carried out on other benzylic hydrocarbons, inactive aliphatic alkanes and ethers with aromatic amines. Results were disclosed in Scheme 4 and Scheme 5. The presence of electron-donating group -Me at the para or ortho positions of toluenes could make them react smoothly with aminopyridine derivatives and aniline derivatives afforded the amination products in good yields **(7a-7e, 8a, 8b, 8c**). A significant negative effect occurred by -Cl substituents in the toluenes, providing only low conversions under standard conditions **(7f, 7g, 8d)**. Mesitylene can react with aromatic primary amines to obtain corresponding aromatic secondary amines in moderate yields **(7h, 7i, 8e, 8f)**. It is noteworthy that ethylbenzene and propylbenzene were well-tolerated in this protocol, ethylbenzene could couple with aminopyridines to give yield of 43-58% **(7j-7l)**, however, the yield of this reaction decreased significantly in the case of p-nitroaniline, 4-nitro-N-(1-phenylethyl)aniline **(8g)** was obtained with a yield of 32%, propylbenzene coupled with 5-amino-2-chloropyridine and 2-aminopyridine afforded the corresponding ammoniation products in 47% and 33% **(7m, 7n)**. Cyclohexane could react with aminopyridines smoothly, and it worked with 5-amino-2-chloropyridine, 5-amine-2-bromopyridine, and 2-aminopyridine to give the corresponding products in yields of 35%-46% **(7o-7q)**, thus providing a great opportunity for further synthetic manipulations. Unlike primary benzylic hydrocarbons or inactive aliphatic alkanes, the amination of sp^{3}C−H bonds in ethers such as 1,4-dioxane **(7r)** and anisole **(7s)** were failed under the optimized reaction conditions.

Scheme 6. Control experiments for investigation of the mechanism



Finally, a gram-scale reaction was explored, 5mmol of **1a** reacted with 10.0 mL of p-xylene, 3.0 mmol of Cu powder, and 10.0 mmol of DTBP at 120 °C for 12 h, and the product was produced in 61%.

In order to gain further insight into the plausible reaction pathway, control experiments were conducted (Scheme 6). The reactions were suppressed in the presence of butylated hydroxytoluene (BHT), ethene-1,1-diyldibenzene and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) under the standard conditions. As expected, the formation of **3a** was inhibited in the reactions, and the benzyl radical was captured by BHT and ethene-1,1-diyldibenzene offered products **9** and **10** (detected by GC−MS). These results illustrated that the reaction possibly proceeds through a radical pathway.

On the basis of these preliminary results above, together with previous studies[11], a plausible mechanism is depicted in Scheme 7 . Initially, homolysis of DTBP can produce ^{t}BuO radical **A**, benzyl radical **B** would be generated by abstracting hydrogen from toluene by **A**. Reaction of arylamines with copper produce intermediate **C** in the presence of DTBP.

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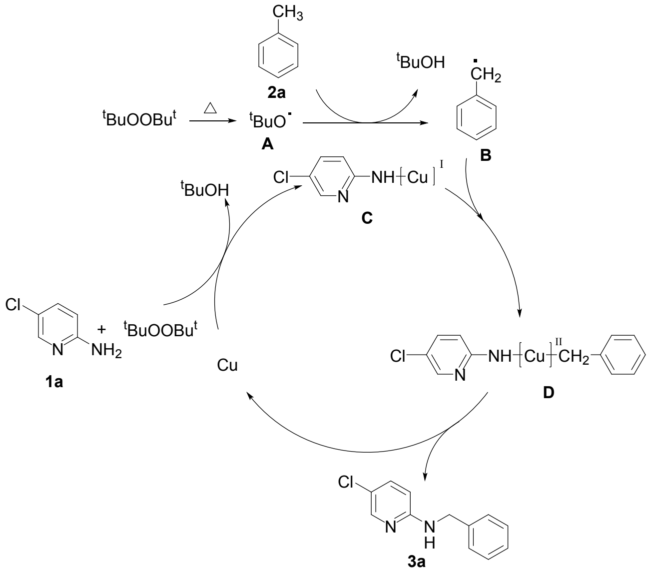
Intermediate **C** combined with the benzyl radical **B** to generate the intermediate **D**. **D** releases of the copper and form the desired product **3a** to complete the catalytic cycle.

Scheme 7. Possible mechanism.



Conclusions

In general, we have developed an effective method of copper-catalyzed direct amination of benzylic hydrocarbons and inactive aliphatic alkanes with aromatic amines. Copper powder was used as an effective promoter in this kind of transformation. A range of anilines, aminopyridines and other nitrogen-containing heterocyclic compounds are suitable substrates for this transformation to product target coupling products in moderate to good yields. This reaction provides a potential route for the selective coupling C−N functionalization from the simple substrates to functionalized aromatic secondary.

AUTHOR INFORMATION
Corresponding Authors
*Email: senlin@ncu.edu.cn
*Email: yanzh@ncu.edu.cn
Author Contribution
Hua Yao and Bo Xie contributed equally to this work.

NOTES
The authors declare no competing financial interest.

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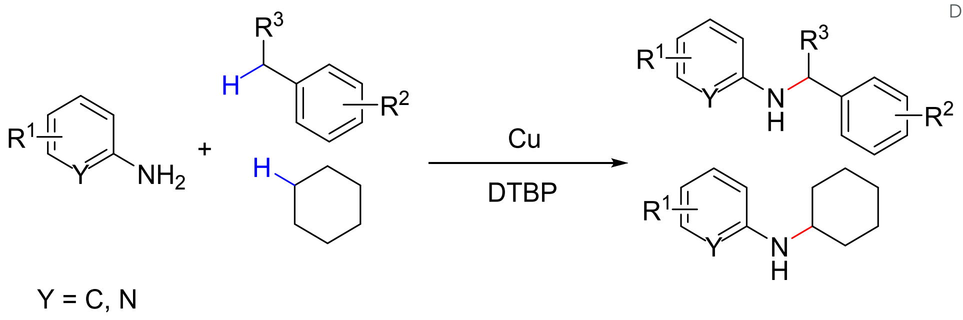

- direct amination of C (sp^3)-H
- low-cost catalyst
- wide functional group tolerance
- 48 examples up to 82%