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Copper-Catalyzed Intramolecular Amination of $C(sp^3)$−H Bond of Secondary Amines to Access Azacycles

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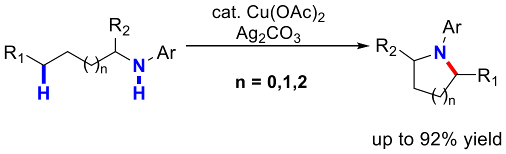
ABSTRACT: The cross-coupling of C−N bond directly from inert C−H bonds is an ideal approach to synthesize saturated azacycles due to its high efficiency and atom economy. In this article, a copper-catalyzed intramolecular amination via the cross coupling of $C(sp^3)$−H and N−H bonds of secondary amine has been reported, which exhibit excellent chemo- and regioselectivity, extensive substrate scope, and functional group tolerance in good to excellent yield, offering an efficient pathway to build nitrogen-containing heterocycle skeletons.



Nitrogen-containing heterocycles served as one of the most important core skeletons widely existing in natural products, pharmaceutics, agrochemicals, etc.[1] (Figure 1). As a result, construction of various azacycles in an efficient and facile manner is in highly demand in organic synthesis, especially for drug design and discovery. With increasing interest over the past several decades to access diverse fundamental nitrogen-containing key motifs, methods that utilized commercially available or easily prepared starting materials in an atom- and step-economic fashion are highly appreciated. Although transition-metal-catalyzed C−H activation has recently emerged as a promising approach to synthesize azacycles via C−N[2] or C−C[3] bond formation, the use of a large amount of noble metal as catalyst still limited their applications in large-scale synthesis and total synthesis of complex bioactive molecules. As an alternative path to activate the inert C−H bond, radical hydrogen-atom abstraction offered a solution for selectively cleaving the remote $C(sp^3)$−H bond via 1,*n*-hydrogen atom transfer.[4] As early as 1883 from Hofmann's pioneering work, which was next well established as the Hofmann−Löffler−Freytag (HLF) reaction, the in situ generated N-centered radical could promote the generation of remote alkyl radical for halogenation, furnishing azacycle through the following intramolecular nucleophilic attack by nitrogen atom (Scheme 1a).[5] The site-selectivity of C−H cleavage in this transformation was controlled by an entropically favorable 1,5-hydrogen atom transfer (1,5-HAT), and the nucleophilic cyclization only furnished five-membered pyrrolidines,[6] while for the construction of other membered azacycles (4- and 6-membered rings) using this tactic still remains elusive.

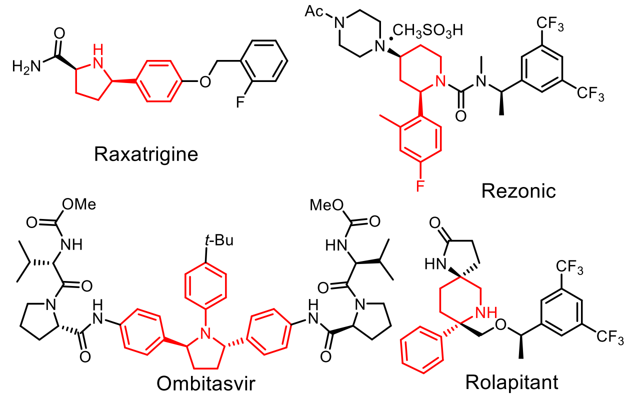


Figure 1. Selected pharmaceuticals containing 5- or 6-membered azacycles.

To expand the application of the HLF reaction, diverse functionalization of a remote C−H bond via 1,5-HAT was established to afford a variety of functionalized alkanes.[7] As part of our continuous efforts to design innovative routes for directed functionalization of remote $C(sp^3)$−H bonds, we have reported a selective C−H functionalization through intramolecular remote arylation for facile construction of a six-membered carbocyclic ring; the reactions undergo a copper-catalyzed oxidative cross-coupling of inert $C(sp^3)$−H and $C(sp^2)$−H bonds (Scheme 1b).[8] As the aryl ring could trap the alkyl radical more effectively, C−N bond formation is thus harder to realize for synthesis of pyrrolidine.

Alternatively, we envisioned with the further oxidation of in situ generated remote alkyl radical that the intramolecular amination to form the N-heterocycles would outcompete

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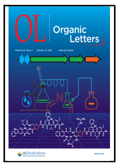


Scheme 1. Radical Cyclization via 1,*n*-Hydrogen Atom Transfer

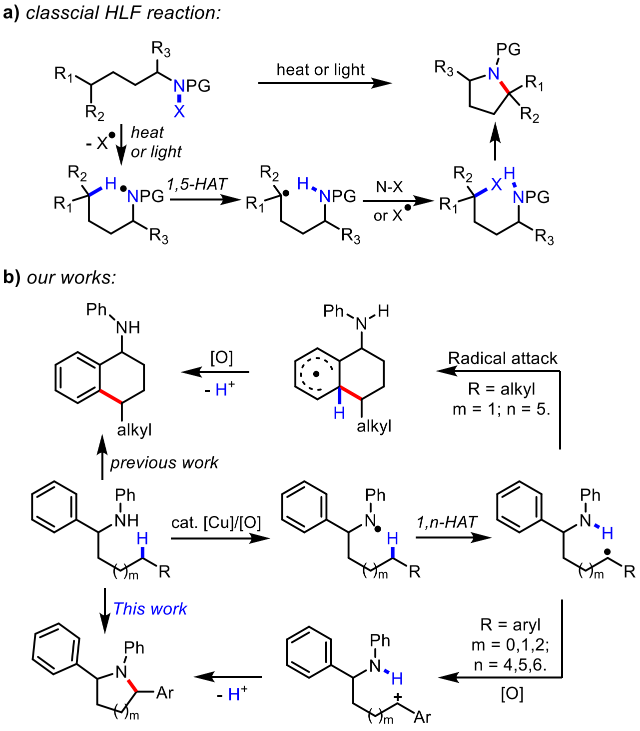
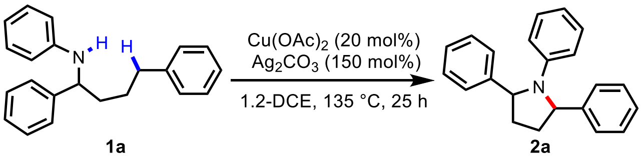


Table 1. Control Experiments and Effects Reaction Parameters[a]



entry	variation from the standard conditions	yield[b] (%)
1	none	90[c] (75[d])
2	without $Cu(OAc)_2$	nd
3	toluene instead of 1,2-DCE	nd
4	1,4-dioxane instead of 1,2-DCE	81
5	$Cu(OTFA)_2$ instead of $Cu(OAc)_2$	nd
6	CuO instead of $Cu(OAc)_2$	14
7[b]	CuCl instead of $Cu(OAc)_2$	9
8[b]	Ag_2O instead of Ag_2CO_3	61
9	$AgNO_3$ instead of Ag_2CO_3	nd
10	TEMPO instead of Ag_2CO_3	nd
11	120 °C instead of 135 °C	59
12	10 mol % $Cu(OAc)_2$ instead of 20 mol % $Cu(OAc)_2$	91
13	100 mol % Ag_2CO_3 instead of 150 mol % Ag_2CO_3	52

[a] Reaction conditions: **1** (0.1 mmol), $Cu(OAc)_2$ (20 mol %), and Ag_2CO_3 (1.5 equiv) in 1,2-DCE (2.0 mL) at 135 °C for 25 h under air. [b] GC yield; nd = not detected. [c] Isolated yield, the ratio of the diastereomer is 1.3:1. [d] 1 mmol scale, 48 h.

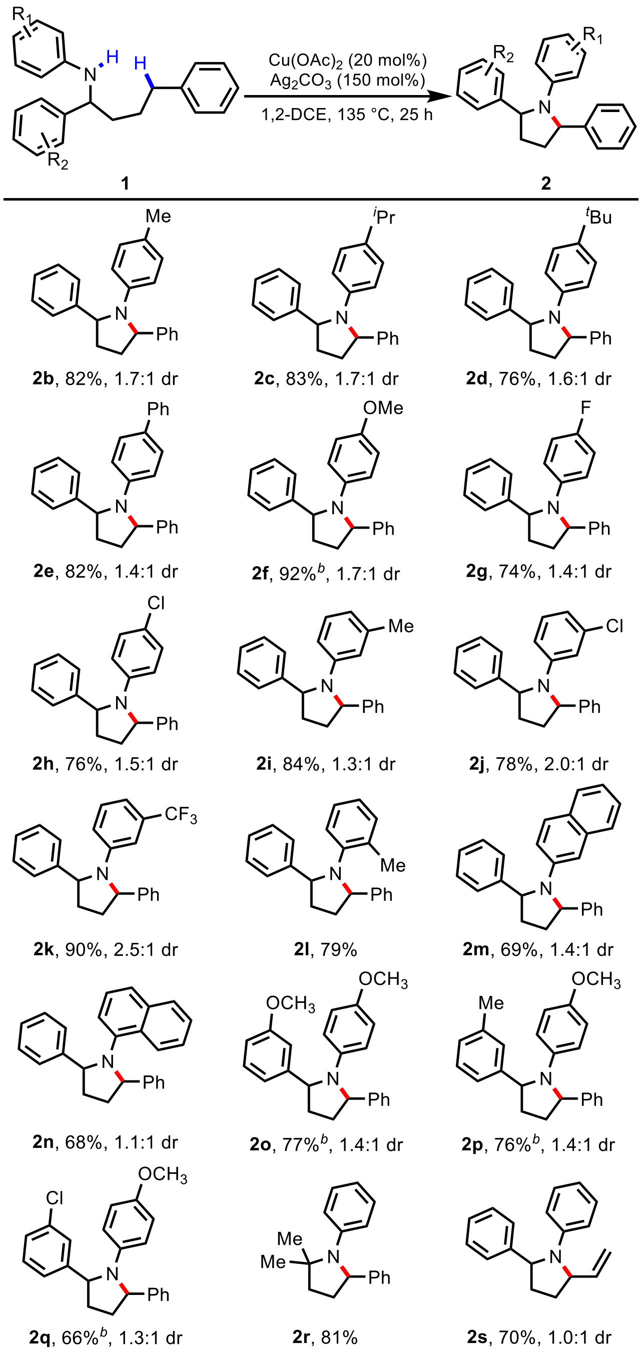
intramolecular arylation, giving the corresponding azacycle followed by a deprotonation. Accordingly, a relatively stable carbocation at the benzylic position may play a key role in realizing such cyclization for the construction of nitrogen-containing heterocycles.

Herein, we report a copper-catalyzed intramolecular amination via the cross coupling of $C(sp^3)$−H and N−H bonds of the secondary amine, which offers an efficient solution to construction of a range of nitrogen-containing heterocycles. The key to this reaction is the second oxidation of in situ generated benzylic radical to carbocation for facile intramolecular amination. Besides the well-established five-membered ring that can be synthesized via a traditional HLF-route, in our system, we can also achieve the equally important four- and six-membered azacycles via a 1,*n*-HAT process (Scheme 1b).

Initially, we commenced the intramolecular amination with secondary benzylamine **1a** as the model substrate in the presence of $Cu(OAc)_2$ (20 mol %) as the catalyst. After careful optimization (Tables S1−S4), we found that the model substrate **1a** could afford the desired product **2a** with 90% yield by using $Cu(OAc)_2$ (20 mol %) as catalyst, Ag_2CO_3 (1.5 equiv) as oxidant and 1,2-dichloroethane (1,2-DCE, 2.0 mL) as solvent at 135 °C for 25 h (entry 1, Table 1). Not surprisingly, **2a** could not be obtained in the absence of copper salt (entry 2, Table 1). We found that the investigation of copper source indicated that $Cu(OAc)_2$ played key roles as the catalyst in this radical cyclization, while almost none of the desired product was obtained using $Cu(OTFA)_2$ or CuCl as the catalyst instead of $Cu(OAc)_2$ (entries 5−7, Table 1). Moreover, the replacement of Ag_2CO_3 with other silver salts or other oxidants afforded poor results to even no reactivity, while only Ag_2O could give a moderate yield at 61% (entries 8−10, Table 1). All of these results further confirmed that $Cu(OAc)_2$ as the catalyst, Ag_2CO_3 as the oxidant were essential for the catalytic cycle. Reducing the catalyst loading of $Cu(OAc)_2$ to 10 mol % only gave a slight decrease of the yield of **2a** at 91% yield (entry 12, Table 1). However, while using 1 equiv of Ag_2CO_3 as the oxidant, the yield of this reaction diminished sharply (entry 13, Table 1). Meanwhile, lowering the reaction temperature to 120 °C decreased the yield evidently, possibly due to the high bond dissociation energy of N−H bond in secondary amine (entry 11, Table 1).

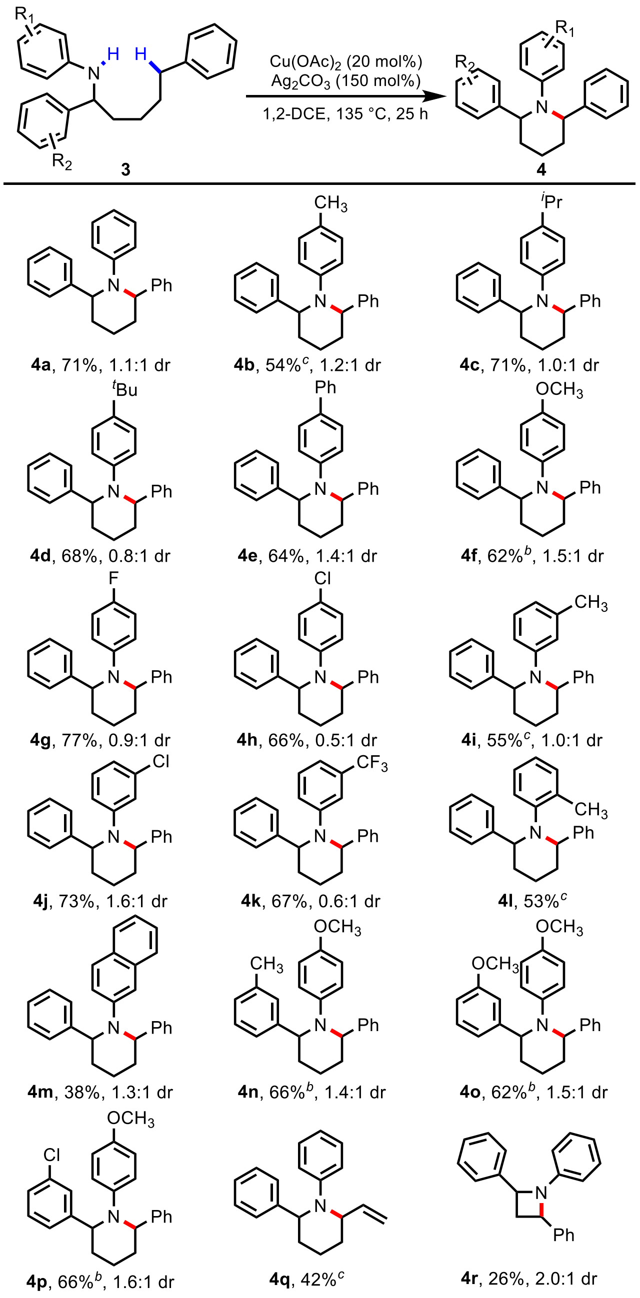
With the optimal conditions in hand, we sought to test the scope of this intramolecular amination and found a variety of nitrogen-containing heterocycles were obtainable (Scheme 2). With respect to the substituent effect on the phenyl ring of anilines (R^1), the results for pyrrolidine synthesis (m = 1) indicated that both electron-donating and -withdrawing groups were well tolerated in this catalytic reaction. As for the *para*-substituents, including alkyl (**2b−d**), phenyl (**2e**), methoxy (**2f**), and halogen (**2g−h**), the corresponding pyrrolidines could be smoothly obtained with moderate to excellent yields. Generally, *meta*-substituents, such as methyl (**2i**), chloro (**2j**), and trifluoromethyl (**2k**), on the aniline were compatible with this cyclization reaction in good yield. Notably, the *o*-methyl group on the phenyl rings was also properly tolerated in this transformation with good yield (**2l**). Furthermore, by replacing the phenyl ring on the aniline to naphthyl ring, the reaction proceeded effectively with relatively lower yield (**2m,n**). The substituent effect on the phenyl ring linked to α-position of nitrogen atom was next investigated, which also revealed that various substituted groups were well compatible for this reaction (**2o−q**). Of note is that changing the phenyl substituent to an alkyl substituent had little impact to the reactivity of this reaction, providing the cyclization product (**2r**) with good yield. To our delight, besides the benzylic $C(sp^3)$−H bond, the allylic $C(sp^3)$−H bond could be aminated successfully in good yield with pyrrolidine as the

Scheme 2. Scope of Pyrrolidine Synthesis[a]



[a]Reaction conditions: **1** (0.3 mmol), $Cu(OAc)_2$ (20 mol %) and Ag_2CO_3 (1.5 equiv) in 1,2-DCE (6.0 mL) at 135 °C for 25 h under air. Isolated yield. [b]125 °C, 25 h.

Scheme 3. Scope of Piperidine Synthesis[a]



[a]Reaction conditions: **1** (0.3 mmol), $Cu(OAc)_2$ (20 mol %) and Ag_2CO_3 (1.5 equiv) in 1,2-DCE (6.0 mL) at 135 °C for 25 h under air. Isolated yield. [b]125 °C, 15 h. [c]35 h.

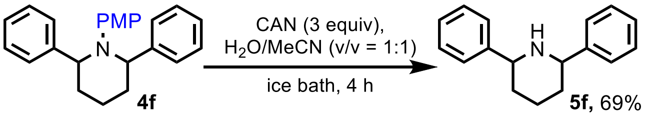
only product (**2s**), and none of the olefin-trapping product was observed.

For further elucidation of the synthetic utility of our strategy, more challenging synthesis of piperidines, which were constructed through a 1,6-HAT followed by a six-membered cyclization under the general conditions, was next probed (*m* = 2) (Scheme 3). Related iodinated precursors for classical HLF reactions only generate pyrrolidines due to the superiority of the 1,5-HAT.[6d] Compared with the 1,5-HAT, the elongation of the carbon chain in secondary benzylamines would render the 1,6-HAT more difficult. However, in our system, such six-membered cyclizations proceeded equally well, with moderate to good yield (**4a**−**q**).

Of note is that apart from recent strategy of electrochemistry,[9] cobalt-catalyzed amination,[10] and N−F bond dissociation reaction,[11] direct ε-C−H amination from bare amine has not been explored. It should be mentioned that azetidine (**4r**) was also synthesized under the standard conditions via a less common 1,4-HAT pathway. A sharp decrease of yield was due to the higher activation energy for 1,4-HAT, which can be attributed to increased C−H−C strain in the transition state.

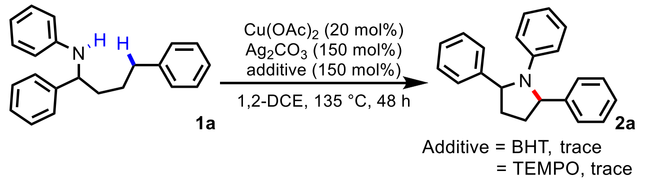
To demonstrate the synthetic utility of this strategy, a scale-up reaction and derivatization study were next carried out. A 1 mmol amount of **1a** afforded the desired product smoothly with slightly lower yield (75% yield). Moreover, since the modified amines produced via this intramolecular C−N coupling reactions are versatile synthetic precursors to various pyrrolidines and piperidines, we conducted the oxidative cleavage of the PMP group in **4f** and afforded 2,6-diphenylpiperidine (Scheme 4) with synthetically useful yield (69% yield).

Scheme 4. Further Transformation



To gain some insights into the mechanism of this intramolecular amination, free radical inhibitors such as BHT and TEMPO, were subjected to the standard conditions. Both radical inhibitors showed strong inhibiting effects for this catalytic reaction, giving only a trace amount of the desired cyclic products (Scheme 5). On the basis of all results above and the previous reports, especially our mechanistic studies on radical $C(sp^3)$−H/$C(sp^2)$−H coupling reaction under almost the same conditions,[8] a plausible mechanism for this intramolecular $C(sp^3)$−H amination is outlined.

Scheme 5. Control Experiments



The nitrogen-centered radical is generated by the initial interaction of $Cu(OAc)_2$ with amine, which selectively abstracts a remote aliphatic C−H bond via 1,*n*-hydrogen-atom transfer to afford the benzylic radical. It is noted that a direct 1,6-HAT process is more plausible compared with a 1,5-HAT followed by subsequent 1,2-HAT process according to our previous report.[12] Lastly, this carbon radical is oxidized into the carbon cation, which is attacked via the intramolecular nucleophilic amination followed by deprotonation to afford the desired cyclic product.

In conclusion, we have developed a copper-catalyzed intramolecular amination via the cross coupling of $C(sp^3)$−H and N−H bonds of secondary amine. The 1,*n*-HAT process provides a new route to synthesize pyrrolidine and piperidine products with high efficiency and broad scope. Further efforts to contruct diverse N-heterocycles with this strategy is ongoing in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03934.

Experimental procedures, spectral and analytical data, and copies of ^1H, ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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