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Copper-Catalyzed Remote (δ) C(sp^3)–H Bond Amination: A Practical Strategy to Construct Pyrrolidine Derivatives

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We report a copper-catalyzed remote C(sp^3) –H bond amination reaction that convert acyclic amines to pyrrolidines. This reaction occurs selectively at the carbon δ to the amine functionality. Primary, secondary and tertiary C–H bonds are all suitable for the amination reactions in the presence of an inexpensive and commercially available copper catalyst.

Nitrogen-containing heterocycles are common in natural products, pharmaceuticals and optical materials,[1] which often exhibit high levels of biological and optical activities. In particular, the pyrrolidine derivatives are privileged structural units as exemplified by the structure of nicotine, geissoschizoline, dehydrotubifoline, aspidophytine, as well as mesembrane (Figure 1).[1a,2] Therefore, the development of efficient methods to construct this ubiquitous structure unit is highly desirable.

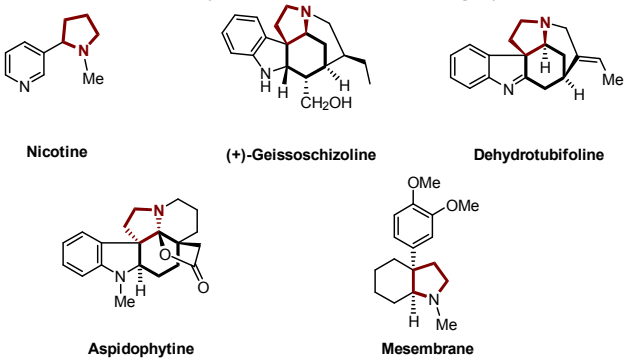

Figure 1 Natural bioactive products containing pyrroline structurals.

Transition-metal catalyzed direct functionalization of inert C–H bond is of great importance as it improves the atom- and step-economy of organic synthesis.[3] This chemistry can directly convert simple and easily available raw materials to valuable products. A notable challenge in this field is to achieve C(sp^3)–H functionalization with chemo- and regioselectivity. In particular, the selective amination reaction of inert C(sp^3)–H bond to construct nitrogen-containing heterocycles has received much attention in the synthetic community. Among them, great progress has been made in directing group assisted selective C–H bond amination reactions.[4] Nevertheless, these methods require pre-installation and removal of a directing group in a synthetic sequence. The practical remote C(sp^3)–H amination is still challenging. To solve the problem, the metalated amides and nitrene were successfully employed to confront this key synthetic challenge.[4,5,6]

Complementary to these reactions are the radical-mediated strategies that enable C–H amination with different selectivities, especially for the synthesis of pyrrolidine derivatives.[7] For example, Hofmann–Löffler–Freytag (HLF) reaction are efficient δ C–H amination reactions that occur with an N-halogen precursor.[8] Although high selectivity were obtained for the synthesis of five-membered heterocycles, the typically harsh reaction conditions for the generation of radicals greatly limited the synthetic utility. Many chemists devoted themselves to searching for more mild and practical strategies for generating and harnessing the reactivity of nitrogen-centered radicals.

Suárez modification is a major milestone in the development of HLF reaction, because the reaction conditions are milder than those of typical HLF reactions, and amine substrate can be used directely.[9] Based on Suárez modification, many modified methods have been successfully applied to achieve direct amination reactions. Fan[10] has demonstrated that δ-phenyl substituted sulfonamides can be converted to α-phenyl substituted pyrrolidines in the presence of a hypervalent iodine reagent and molecular iodine.

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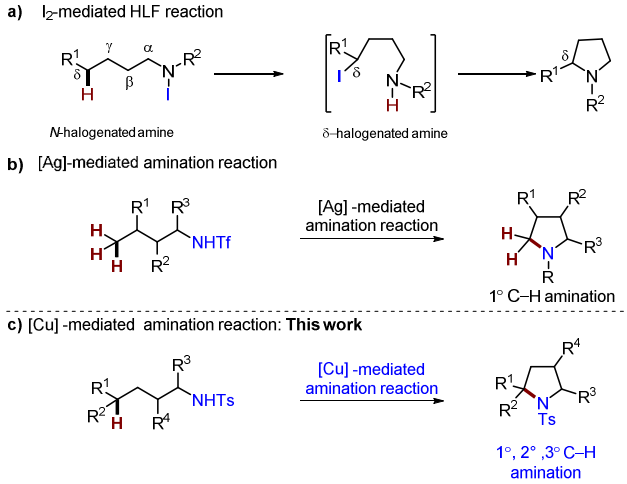
Subsequently, Yu[11] developed a visible-light-promoted amination of C(sp^3)–H bond; however, pre-functionalized sulfonamides are necessary to accomplish this transformation. Alternatively, Martínez and Muñiz developed the first example



Scheme 1. Halogen and transition-metal mediated direct C–H amination.

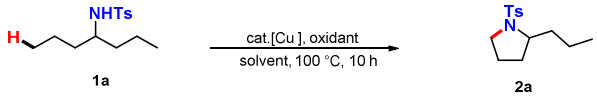
of iodine-catalyzed visible-light induced C–H amination reaction.[12] Sensitive functional groups, such as alkenes and anisoles can be well tolerated in this novel catalytic system. Nonetheless, in most cases this reaction occurred at weak C–H bonds, such as tertiary, benzylic C–H bonds and the ones α to heteroatoms. Non-constrained amines are challenging substrates for these reactions. Very recently, Nagib reported a very nice protocol of δ amination of secondary C–H bonds from simple tosylamines mediated by triiodite (I_3^-) generated in situ.[13] However, large amount of hypervalent iodide reagent and inorganic salt are necessary to generate active I_3^- species. All of these protocols relied on the halogen transfer process (Scheme 1, a).[14] As a result, the selectivity and the reactivity highly depend on the structures of the substrates and the reaction conditions.

Compared with the halogen mediated C–N bond formation, carbon-carbon and carbon-heteroatom bonds formation through the interception of remote carbon radical center by transition-metal catalysts has proved challenging. Previously, Shi has demonstrated the potential of transiton-metal silver catalyzed site-selective amination of primary C–H bonds without directing groups.[15] However, the silver catalyst is only active for amination of primary C–H bonds (Scheme 1, b).

As a first row transition metal, copper often exhibits unique and versatile reactivity. For example, copper-catalyzed C–H amination reaction is an important method to construct C–N bond.[16] A single-electron or a two-electron-transfer fashion is generally involved in copper-catalyzed redox reactions. As on our research interest in the C–N bond formation, we proposed that Cu^{II} species with d^9 configuration at the metal center could be employed as catalysts in single electron reaction events to form C–N bond. Here we report a general amination method of remote C–H bond at primary, secondary and tertiary positions catalyzed by a simple non-precious copper complex.

We began our study with sulphonamide **1a** as the model substrate because they are readily accessible and synthetically useful (Table 1). In the presence of CuI, $PhI(OTFA)_2$ and DCE at 100 ℃ for 10 hours, 79% of desired product was obtained. Encouraged by this result, we screened various oxidants, such as $PhI(OCOPh)_2$, $PhI(OAc)_2$, $K_2S_2O_8$, NFSI. However, these oxidants were not efficient to improve the product yield (entries 1-5). Further solvents screening (entries 6-11) revealed that 1,2-dichloroethane in this reaction was more efficient than others. The reactions conducted with other copper catalysts didn't improve the product yield (entries 12-15).

Table 1 Optimization of Reaction Conditions[a]



entry	catalyst	oxidant	solvent	yield[b](%)
1	CuI	$PhI(OTFA)_2$	DCE	82(79)
2	CuI	$PhI(OCOPh)_2$	DCE	18
3	CuI	$PhI(OAc)_2$	DCE	7
4	CuI	$K_2S_2O_8$	DCE	N.R.[c]
5	CuI	NFSI	DCE	N.R.[c]
6	CuI	$PhI(OTFA)_2$	THF	9
7	CuI	$PhI(OTFA)_2$	CH_3CN	7
8	CuI	$PhI(OTFA)_2$	toluene	N.R.[c]
9	CuI	$PhI(OTFA)_2$	DCM	61
10	CuI	$PhI(OTFA)_2$	PhCl	16
11	CuI	$PhI(OTFA)_2$	$PhCF_3$	69
12	CuBr	$PhI(OTFA)_2$	DCE	23
13	$CuBr_2$	$PhI(OTFA)_2$	DCE	33
14	CuCl	$PhI(OTFA)_2$	DCE	18
15	$Cu(OAc)_2$	$PhI(OTFA)_2$	DCE	41
16	[Cu][d]	$PhI(OTFA)_2$	DCE	61
17	$Cu(OTf)_2$	$PhI(OTFA)_2$	DCE	88(80)
18	$Cu(OTf)_2$	$PhI(OTFA)_2$[e]	DCE	32
19[f]	-	$PhI(OTFA)_2$	DCE	6
20[f,g]	-	$PhI(OTFA)_2$	DCE	30
21	CuI	-	DCE	N.R.[c]

[a] Reaction condition: **1a** (0.1mmol), catalyst (10 mol%), oxidant (2.0 equiv), solvent (1.0 mL), 100 ℃,10 h. [b] The yield was determined based on ^{1}H NMR with 1,1,2,2-Tetrachloroethaneas internal standard. Isolated yield in parentheses. [c] N.R. means no reaction (detected by crude ^{1}H NMR). [d] [Cu]=$Cu(CH_3CN)_4PF_6$. [e] $PhI(OTFA)_2$ (3.0 equiv). [f] Without catalyst. [g] Additive: NaI (1.0 equiv).

Notably, $Cu(OTf)_2$ showed a great advantage in promoting this amination reaction; as product **2a** was obtained cleanly with 80% yield (entry 17, see SI). In the absence of any copper catalyst, the reaction gave **2a** in very low yield (6%, entry 19). When the sodium iodide was used instead of copper iodide, the formation of the product was significantly inhibited, indicating that the copper catalyst is necessary for the reaction to occur efficiently (entry 20). No product was formed in the absence of oxidant (entry 21).

With the optimized reaction condition in hand, we studied the substrate scope with various heteroatom functionalities. To demonstrate the synthetic utility of this method, we first studied reactions with amino acid ester L-isoleu-**2a** and protected amino alcohol **3a**. To our satisfaction, the desired products 3-methylproline **2b** and 3-methylprolinol **3b** were obtained in high yields with retention of the stereogenic

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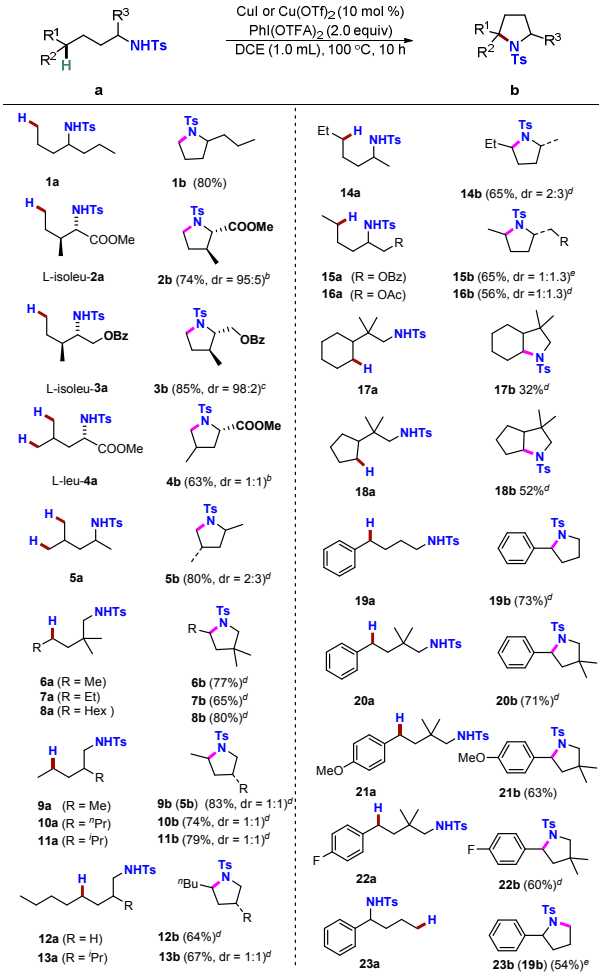
centers. Thus, our method can potentially serve as an efficient strategy to generate unnatural proline derivatives. The desymmetrization cyclization of amino acid ester L-leu-**4a** process with low diastereoselectivity. Remarkably, this method was also found to be effective in the activation of methylene C–H bond in linear sulfonamides (**5a**, **6a**, **7a**, **8a**, **9a**, **10a**, **11a**, **12a**, **13a** and **14a**). The most interesting thing is the pyrrolidine product **5b** can be obtained from different substrates **5a** and **9a** to show the synthetic varieties of this method. For substrates **6a**, **7a** and **8a**, including an alkyl group at δ position, cyclization reaction also took place to afford amination product in good yields. Non constrained substrates **9a**, **10a**,

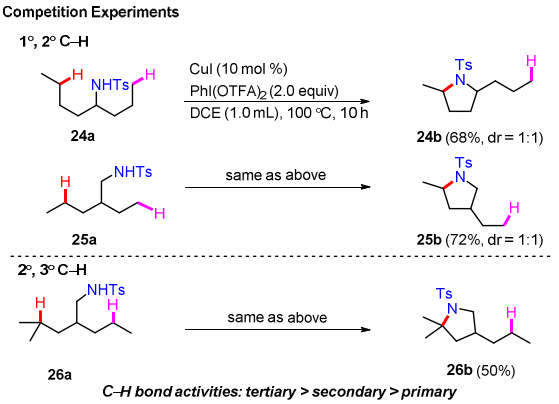
Table 2 Direct amination of sp^3 C–H bonds[a]



[a] Reaction conditions: **a** (0.1 mmol), $Cu(OTf)_2$ (0.01 mmol), $PhI(OTFA)_2$ (0.4 mmol), DCE (1.0 mL), 100 °C, 10 h. [b] Changes: $PhI(OTFA)_2$ (3.0 equiv). [c] Changes: $PhI(OTFA)_2$ (2.5 equiv). [d] Changes: CuI (0.01 mmol). [e] Changes: $PhI(OTFA)_2$ (4.0 equiv).

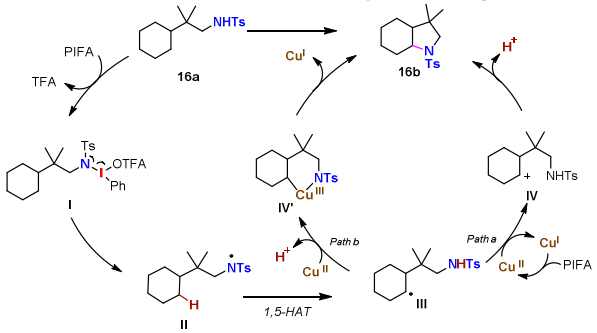
11a, **12a**, **13a** and **14a**, regarded as the challenge ones in HLF reactions, worked very well. Furthermore, the amination of protected amino alcohol derivatives **15a** and **16a** resulting in 5-methylprolino **15b** and **16b** in good yields. The amination reaction also occurred on cycloalkane (**17a**, **18a**), giving polycyclic products, albeit in moderate yields (**17b**, **18b**). In addition, the more reactive secondary benzylic C–H bonds in **19a**, **20a**, **21a** and **22a** could expand the scope of pyrolidine structures for the further application. The sulphonamide **23a** with a phenyl substitutent at α position, the amination reaction was occurred with primary C–H bond to give the same product as the sulphonamide **19a**.

To gain insight into the reaction mechanism, competition experiment between 1°/2°C–H bonds and 2°/3° C–H bonds were carried out independently (Scheme 2). In 1°/2°C–H bonds competition experiment, secondary C–H bond is more reactive than the primary one (**24a** and **25a**). And then, in 2°/3° C–H bonds competition experiment, amination selectively occurred at tertiary C–H bond than secondary (**26a**). The totally reactivity of hydrogen atoms decreases in the order tertiary> secondary > primary. Furthermore, radical captured experiments were conducted to uncover evidence for the presence of radical intermediate. Initially, 2.0 equiv of TEMPO was added, the reaction was completely inhibited. Meanwhile, in presence of 1.0 equiv 2,6-*di*-*tert*-butylphenol, the product yield was decreased significiantly, only 34% of amination product was obtained (see SI).



Scheme 2 Intromolecular competition experiment.

Based on these results, we proposed a possible pathway described as below (Scheme 3). Direct oxidation of sulphonamides (**16a**) with PIFA generating the amido-λ^3-iodane **I**,[17] which underwent the homolysis of nitrogen-iodine



Scheme 3 Proposed Mechanisms

bond forming the *N*–centered radical **II**. A subsequent 1,5–HAT of C–H bond by a polarized aminyl radical formed a carbon radical (**III**). For the next step, two possible pathways could be followed. One is the single-electron oxidation of carbon radical to give carbon cation (**IV**), which was captured

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by sulphonamide group to afford the cyclization product (**16b**) (Path a). Another is the oxidation addition of carbon radical by Cu(II) catalyst to generate Cu(III) –sulphonamide intermediate **IV'**, after reductive elimination to give the cyclization product (**16b**) (Path b).[18] The mechanistic studies are consistent with our proposed mechanism, more detailed mechanism study is on the way.

In conclusion, we developed a copper catalyzed remote (δ) selective amination of C(sp^3) –H bonds that does not require pre-installation of directing groups. The reaction proceeds in high yield, with primary, secondary, and tertiary C–H bonds, under mild reaction conditions. Notably, the methodology enables direct amination of unbiased tosylamine to access a range of pyrrolidines. Importantly, this method has achieved the potential of the interception of the remote carbon radical in the presence of a copper complex to form C–N bonds.

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18 The more details of mechanism please see **SI**.