ChemPubSoc Europe

DOI: 10.1002/chem.201603370

CHEMISTRY
A European Journal
Communication

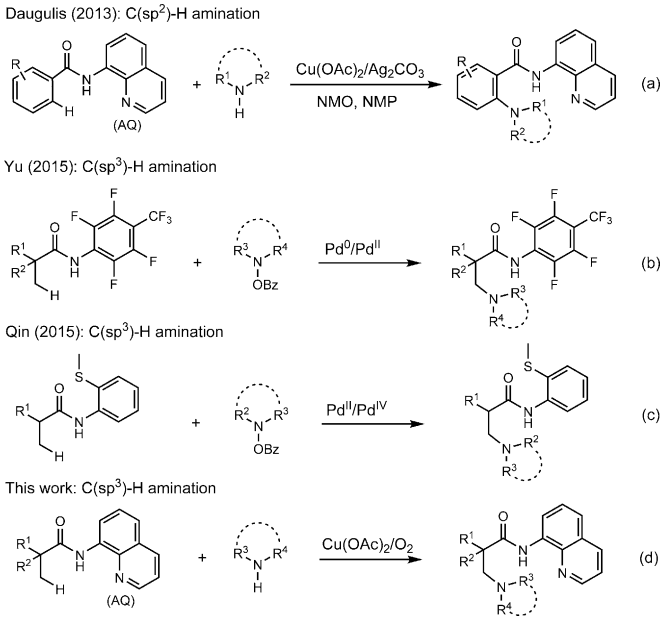
C–H Activation

Intermolecular Amination of Unactivated C(sp^3)–H Bonds with Cyclic Alkylamines: Formation of C(sp^3)–N Bonds through Copper/Oxygen-Mediated C(sp^3)–H/N–H Activation

Quan Gou, Yu-Wen Yang, Zi-Ning Liu, and Jun Qin*[a]

Abstract: The first example of intermolecular amination of unactivated C(sp^3)–H bonds by cyclic alkylamines mediated by $Cu(OAc)_2/O_2$ is reported. This method avoids the use of benzoyloxyamines as the aminating reagent, which are normally prepared from alkylamines in extra steps. A variety of unnatural $\beta^{2,2}$-amino acid analogues are synthesized by this simple and efficient procedure. This approach offers a solution to the previous unmet challenge of C(sp^3)–H/N–H activation for the formation of C(sp^3)–N bonds.

C–N bonds are important structural units that are widely present in natural products, pharmaceuticals, and agrochemicals.[1] Recent years have witnessed a rapid development of C–H activation/C–N bond-forming reactions. Nevertheless, those reactions are mainly focusing on C(sp^2)–H amination/amidation by using various preactivated aminating reagents such as benzoyloxyamines, *N*-chloroamines, *N*-nosyloxycarbamate, or sulfonyl/acyl azides catalyzed by different metals.[2–10] Amination of C(sp^2)–H bonds by alkylamines was recently reported by Daugulis (Scheme 1 a).[7d] Due to lack of π-bond coordinating character, C(sp^3)–H activation for C(sp^3)–N bond formation is challenging, and limited examples have been developed until now,[11–12] exemplified by C(sp^3)–H amidation by Che[11a] and C(sp^3)–H aminations by Yu[12b] and Qin[12c] by using benzoyloxyamines as aminating reagents (Scheme 1 b,c). Direct amination of unactivated C(sp^3)–H bonds by alkylamines to construct C(sp^3)–N bonds represents an unmet challenge and has never been reported, but offers a great advantage in that it saves extra steps for the preparation of benzoyloxyamines and simplifies the overall synthetic procedure. To achieve such challenging transformations, proper oxidative conditions are to be identified. Herein, we report the first example of intermolecular amination of unactivated C(sp^3)–H bonds with cyclic alkylamines mediated by Cu^{II}/O_2 (Scheme 1 d). This protocol directly couples β-C(sp^3)–H bonds of α,α-disubstituted propionic amides with cyclic alkylamines, producing diverse unnatural $\beta^{2,2}$-amino acid derivatives, a set of important compounds with wide biological and medicinal properties.[13] It is worth noting that this method is mediated by Cu^{II}/oxygen. Copper is an abundant and cheap metal, and oxygen is environmentally friendly and rich terminal oxidant on the earth.



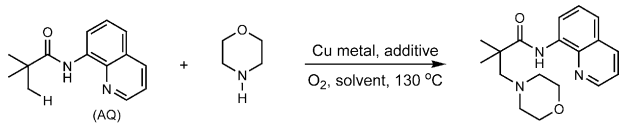
Scheme 1. Intermolecular amination of C(sp^3)–H bonds by alkylamines. NMO = *N*-methylmorpholine-*N*-oxide; NMP = *N*-methyl-2-pyrrolidone.

In our continuing efforts to develop new C(sp^3)–N bond-formation reactions,[12c] we became interested in 8-aminoquinoline (AQ)-directed[14] amination of β-C(sp^3)–H bonds of α,α-disubstituted propionic amides by alkylamines as aminating agents. This transformation could produce a variety of unnatural $\beta^{2,2}$-amino acid analogues in a straightforward fashion if it was successful. Amination of **1a** by **2a** was chosen as the model reaction for optimization (Table 1). Screening of various copper metals in DMSO revealed that 20 mol% $Cu(OAc)_2$ afforded the amination product **3aa** in 18% yield (Table 1, entry 5). Investigation of solvent showed that DMSO remained optimal (entries 6–9). Additives such as Ag_2CO_3/NMO[7d] or IBD did not improve the yield (entries 10–11). Gratifyingly, when the quantity of $Cu(OAc)_2$ used was one equivalent, the yield of **3aa** was improved to 47% (entry 12). Base Na_2CO_3 was detrimental to the reaction[7f] (entry 13). The yield was increased to

[a] Q. Gou, Y.-W. Yang, Z.-N. Liu, Prof. J. Qin
Key Laboratory of Medicinal Chemistry for Natural Resource
Ministry of Education, School of Chemical Science and Technology
Yunnan University, Kunming, Yunnan 650091 (P.R. China)
E-mail: qinjun@ynu.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201603370.

Table 1. Optimization of the reaction conditions.[a]



1a 2a 3aa

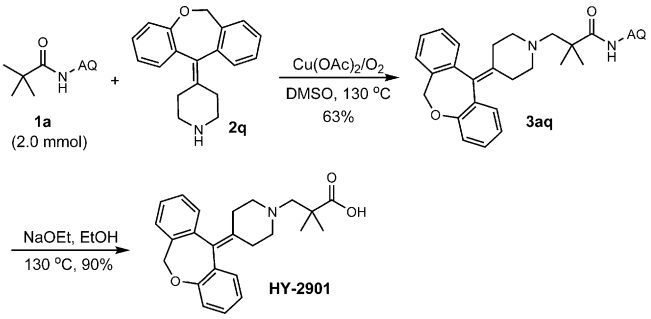
Entry	Cu metal (equiv)	Additive	Solvent	Yield [%][b]
1	CuI (0.2)		DMSO	trace
2	$CuBr_2$ (0.2)		DMSO	0
3	CuF_2 (0.2)		DMSO	5
4	$Cu(TFA)_2$ (0.2)		DMSO	0
5	$Cu(OAc)_2$ (0.2)		DMSO	18
6	$Cu(OAc)_2$ (0.2)		DMF	11
7	$Cu(OAc)_2$ (0.2)		toluene	0
8	$Cu(OAc)_2$ (0.2)		DCE	0
9	$Cu(OAc)_2$ (0.2)		CH_3CN	trace
10[c]	$Cu(OAc)_2$ (0.2)	Ag_2CO_3, NMO	DMSO	9
11[d]	$Cu(OAc)_2$ (0.2)	IBD	DMSO	trace
12	$Cu(OAc)_2$ (1.0)		DMSO	47
13[e]	$Cu(OAc)_2$ (1.0)	Na_2CO_3	DMSO	15
14[f]	$Cu(OAc)_2$ (2.0)		DMSO	72
15	$Cu(OAc)_2$ (3.0)		DMSO	71
16[g]	$Cu(OAc)_2$ (2.0)		DMSO	trace
17[h]	$Cu(OAc)_2$ (2.0)		DMSO	trace

[a] General procedure: **1a** (0.20 mmol), **2a** (0.60 mmol), Cu metal (*x* equiv), and additive (*x* equiv) in solvent (2.0 mL) under O_2 at 130 °C for 2 h. [b] Determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [c] Ag_2CO_3 (0.2 equiv), NMO (2 equiv). **1a** recovered in 90%. [d] IBD ($PhI(OAc)_2$) (2 equiv). [e] Na_2CO_3 (2 equiv). **1a** recovered in 60%. [f] **1a** recovered in 13%. [g] Reaction under Ar. [h] Reaction at 110 °C.

72% when two equivalents of $Cu(OAc)_2$ were used (entry 14). A further increase in the amount of $Cu(OAc)_2$ to three equivalents had no positive effect on the yield (entry 15). Dioxygen was essential to the reaction (entry 16). Lowering the reaction temperature to 110 °C led to no reaction (entry 17). Overall, the optimal reaction conditions were using two equivalents $Cu(OAc)_2$ in DMSO under O_2 at 130 °C.

Next, we evaluated the potential of other known directing groups in assisting this transformation, including the perfluoroaniline,[15a] 2-(pyridine-2-yl)-isopropylamine,[15b] 2-methylthioaniline,[15c] picolinamide,[15d] 2-aminopyridine *N*-oxide,[15e] and 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)aniline.[15f] We found that none of those groups were effective in directing the amination under the reaction conditions (see the Supporting Information).

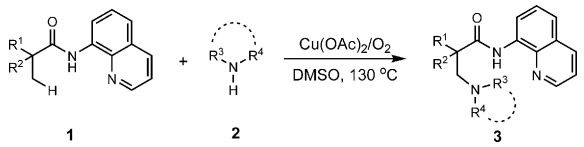
With the optimal conditions in hand, we explored the reaction scope (Table 2). Substrates with simple aliphatic chains were well tolerated to deliver the products in good yields (**3ba**–**3fa**). Sterically hindered aryl analogues afforded the product in moderate yield (**3ga**). Benzyl analogues regardless of their electronic properties were well tolerated to give the products (**3ha**–**3ma**). The aryl substitution of the substrate can be further extended to the δ-position to proceed the amination (**3na**). An olefinic substrate was also tolerated (**3oa**). Late-stage functionalization of pharmaceutical agents could diversify the chemical structure with the potential to modify the PK/PD profiles of the agent. An analogue of gemfibrozil, a lipid-lowering drug,[16] was successfully aminated in 68% yield (**3pa**). Further exploration revealed that a bulkier substrate was also tolerated (**3qa**). Finally, cyclic substrates also delivered the products, though in lower yields (**3ra**–**3sa**). Intriguingly, we found that substrates containing α-hydrogen or amination of the secondary C(sp^3)–H bond were not working. Afterwards, we explored the scope of amine partners. Diverse alkyl- or aryl-substituted piperidines proceeded the aminations in good yield (**3ab**–**3ag**). Moreover, various functional piperidines with ester, ketal, or ether groups (**3ah**–**3aj**) were also well tolerated. In addition, thiomorpholine and piperazine were successful as amine partners (**3ak**, **3al**). The scope of amine can be further expanded to azepane, pyrrolidine, and azetidine (**3am**, **3an**, **3ao**). It is worth noting that diallylamine also proceeded the amination though in low yield (**3ap**). The allyl protection of the product could be removed to release the amine group, which is a useful handle for further derivatization. However, in general, acyclic dialkylamines or primary alkylamines (e.g. Bu_2NH, $BuNH_2$) did not currently work as amine partners. It should be noted that the major mass balance of those reactions with low yields was the unreacted **1**. Overall, the reaction showed useful substrate scope of quaternary carboxylic amides and cyclic alkylamines. The resulting products are important structural motifs that widely exist in medicinally and biologically active compounds. The utility of this method was further highlighted in a synthesis of CNS disorder modulator HY-2901 (Scheme 2).[17] Under the reaction conditions, amination of 1.0 mmol **1a** by **2q** successfully afforded **3aq** in 62% yield. Removal of the AQ was achieved by NaOEt to afford HY-2901 in 90% yield.



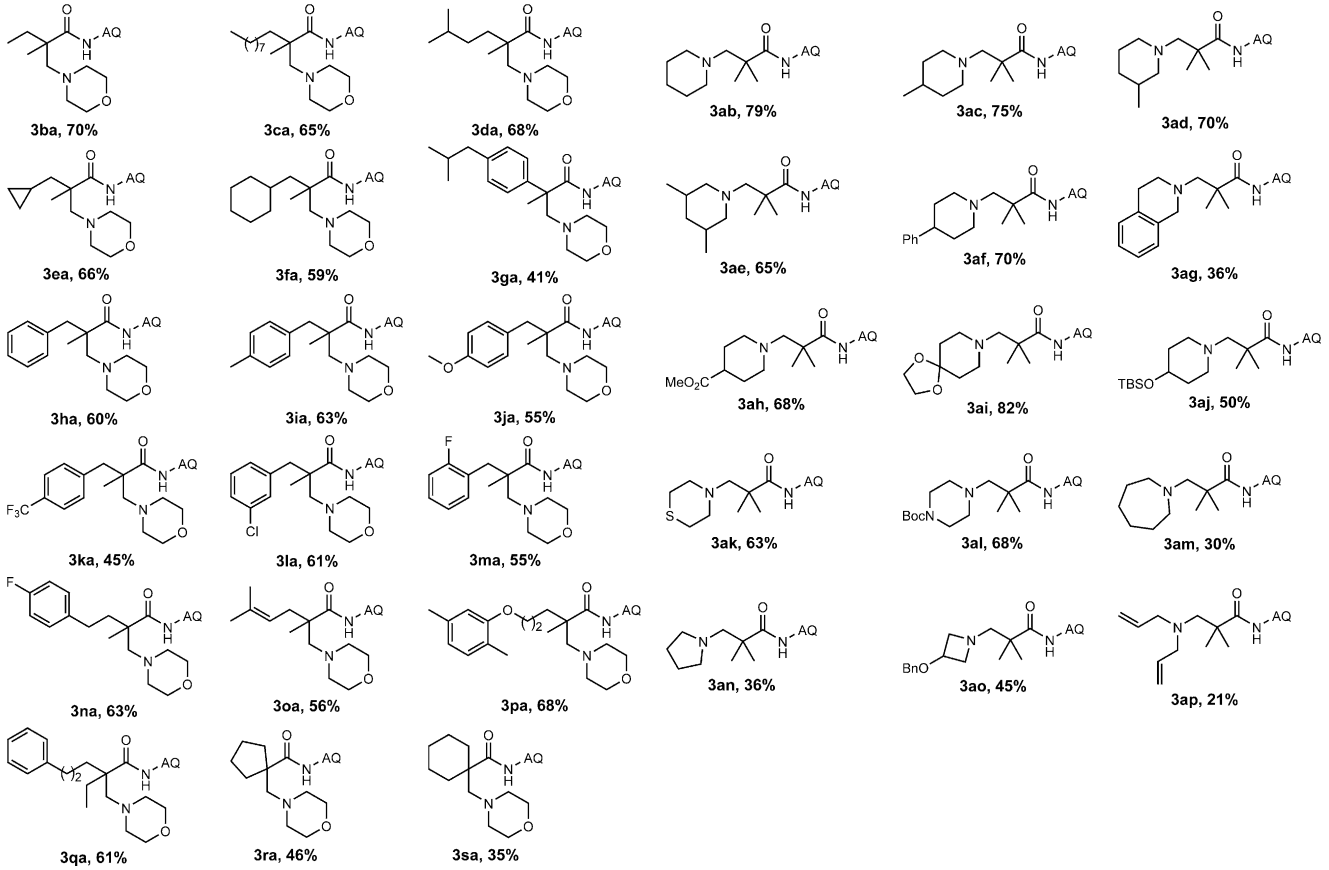
Scheme 2. Synthesis of CNS disorder modulator HY-2901.

The preliminary data of kinetic isotope experiments (parallel intermolecular KIE = 2.7, see the Supporting Information) implied that the cleavage of the β-C(sp^3)–H bond occurred as the rate-limiting step. It was found that radical quencher 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) inhibited the reaction between **1a** and **2a** completely, suggesting a radical pathway was involved. Additionally, we found that in the absence of **2a**, **1a** produced acetoxylation and hydroxylation product **5** and **6** in 8 and 21% yield, respectively, under the conditions. Based on these observations, we putatively proposed a reaction pathway (Scheme 3). First, complexation of **1a** with $Cu(OAc)_2$ generated intermediate **I**. Then a base-assisted C(sp^3)–H activa-

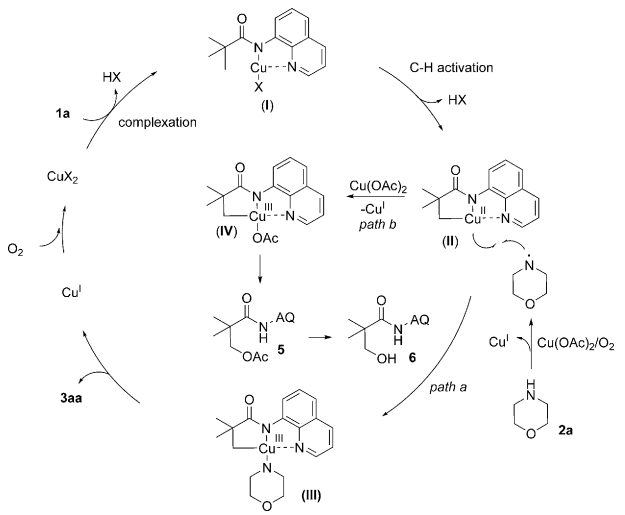
Table 2. Substrate scope of the reaction.[a]



1 2 3



[a] Reaction conditions: **1** (0.20 mmol), **2** (0.60 mmol), and $Cu(OAc)_2$ (2.0 equiv) in DMSO (2.0 mL) under O_2 at 130 °C for 2 h. Yield is the isolated yield.



Scheme 3. Proposed reaction mechanism.

tion took place to produce Cu^{II} intermediate **II**. Meanwhile, **2a** was oxidized by another equivalent $Cu(OAc)_2$ together with O_2 to afford a nitrogen radical species,[19] which then underwent an oxidative radical coupling with **II** to afford a Cu^{III} intermediate **III**. Subsequent reductive elimination led to **3aa** together with the formation of Cu^{I}, which was oxidized by O_2 to regenerate Cu^{II} (path a). In the absence of **2a**, path b was dominant. In this case, Cu^{II} intermediate **II** was further oxidized by $Cu(OAc)_2$ to form Cu^{III} intermediate **IV**, which underwent a reductive acetoxylation to give **5**, followed by hydrolysis affording **6**.[7a,20] Nevertheless, additional solid evidence is needed to fully elaborate the reaction pathway.

In summary, the first example of intermolecular amination of unactivated $C(sp^3)$–H bonds with cyclic alkylamines has been successfully developed. This protocol is mediated by $Cu(OAc)_2/O_2$. The method demonstrates useful substrate scope of quaternary carboxylic amides and cyclic alkylamines. Various unnatural $\beta^{2,2}$-amino acid analogues are prepared by the method. The utility of the method is further illustrated in a synthesis of

CNS disorder modulator HY-2901. This method offers a solution to the previous unmet challenge and simplifies the procedure for C(sp^3)–N bond formation. Future works will be directed to investigate the reaction mechanism and expand the reaction scope.

Experimental Section

General method

A 10 mL Schlenk tube was charged with **1** (0.20 mmol), **2** (0.60 mmol), $Cu(OAc)_2$ (0.40 mmol), and DMSO (2.0 mL). Then the mixture was purged with high-purity oxygen and tightly capped. It was stirred at rt for 1 min for proper mixing of the reactants, and then heated at 130 °C with vigorous stirring for 2 h. Afterwards, the tube was cooled to rt, diluted with ethyl acetate, and washed with 30% ammonium hydroxide and brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo to give the residue. The crude residue was purified by flash chromatography on silica gel to afford the title product **3**.

Acknowledgements

We gratefully acknowledge financial support from National Natural Science Foundation of China (No. 21272201), Program for Changjiang Scholars and Innovation Research Team in University (IRT13095), Program of High-End Science and Technology Talents of Yunnan Province (2012A003), Program of Hundred Oversea High-Level Talents of Yunnan Province (W8110305), and Yunnan University (XT412003).

Keywords: amination · C–H activation · C–N bonds · copper · cyclic alkylamine

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Received: August 5, 2016
Published online on ■■ ■■, 0000

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C–H Activation

*Q. Gou, Y.-W. Yang, Z.-N. Liu, J. Qin**

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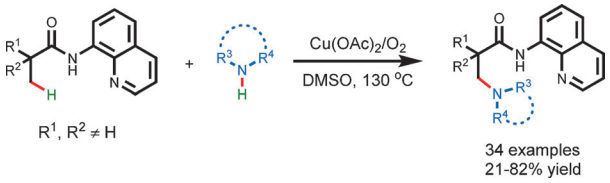
Intermolecular Amination of Unactivated C(sp^3)–H Bonds with Cyclic Alkylamines: Formation of C(sp^3)–N Bonds through Copper/Oxygen-Mediated C(sp^3)–H/N–H Activation



Intermolecular amination of unactivated C(sp^3)–H bonds by cyclic alkylamines mediated by $Cu(OAc)_2/O_2$ has been reported. This method avoids the use of benzoyloxyamines as the aminating reagent. A variety of unnatural $\beta^{2,2}$-amino acid analogues are synthesized by this simple and efficient procedure (see scheme).