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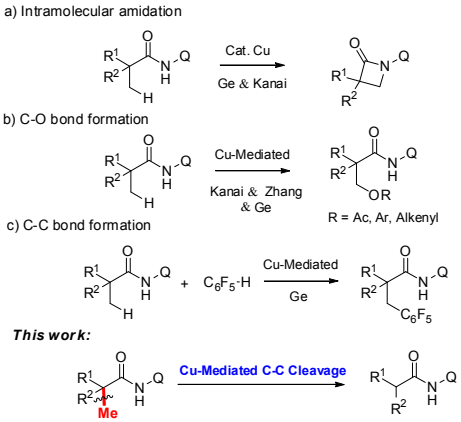
A copper-mediated directed demethylation of propionamides has been developed. This reaction proceeds predominantly at the α-methyl groups of aliphatic amides with high efficiency and provides a unique tool for the direct cleavage of unactivated C(sp^3)-C(sp^3) bonds. The directing groups can be smoothly removed to afford corresponding alkyl carboxylic acids.

In the past several decades, transition-metal-mediated C-H functionalization has emerged as one of the most powerful and versatile strategy for the modification of functionalized molecules.[1] This strategy enables the direct variation of ubiquitous C−H bonds by avoiding the inevitable prefunctionalization steps in conventional cross-coupling reactions. Among them, copper-mediated C-H functionalization has received tremendous interest in recent years due to the abundance, hypotoxicity and versatile reactivity of copper catalysts.[2] Since the Yu group's pioneering work on copper-mediated C−H functionalization of 2-arylpyridines,[3] significant progress has been made for the construction of C-C,[4] C-N,[5] C-O,[6] C-X[7] and C-S[8] bonds via copper-mediated C(sp^2)-H activation. By comparison, much less effort has been taken to the activation of C(sp^3)-H bonds. Several successful transformations are limited to the functionalization of relatively activated C(sp^3)-H bonds such as allylic and benzylic C-H bonds.[9] For unactivated C(sp^3)-H bonds, due to their inherent low reactivity and the lack of metal-coordination ability, it is even more challenging to develop reliable methods to achieve highly regioselective C-H functionalization with copper catalysts.[10] In 2014, the group of Ge and Kanai independently reported the first copper-catalyzed intramolecular C(sp^3)-H amidation reaction (Scheme 1a).[11] It was found that an external bidentate amidoquinoline directing group, which was first developed by Daugulis and co-workers in Pd-catalyzed C(sp^3)-H functionalization,[12] could facilitate the regioselective C(sp^3)-H metalation-deprotonation process with copper catalyst. Subsequently, The copper-mediated 8-amidoquinoline directed acetoxylation, aryloxylation and vinyloxylation of unactivated C(sp^3)-H bonds has also been discovered (Scheme 1b).[11d-f] Very recently, Ge and co-workers demonstrated the copper-mediated dehydrogenative coupling of polyfuoroarenes and unactivated C(sp^3)-H bonds with the 8-amidoquinoline-derivied bidentate auxiliary (Scheme 1c).[11c]



Scheme 1. Copper-mediated directed C(sp3)-H functionalization. Q = quinolin-8-yl

Inspired by recent elegant work on copper-mediated unactivated C(sp^3)-H functionalization, we report herein the first copper-mediated bidentate-ligand-directed demethylation of propionamides. This reaction provides an unprecedented C(sp^3)-C(sp^3) cleavage result with a mechanism of initial C(sp^3)-H activation followed by oxidative decarboxylation. It exhibits the unique features of copper catalysts and expands the concept and scope of both copper-mediated C(sp^3)-H bond functionalization and Cu-mediated aerobic oxidation reactions.[13] Moreover, it affords a straightforward way to the modification of α-methyl carboxylic acid derivatives, which are common structural moieties in bioactive natural products and medicines.[14]

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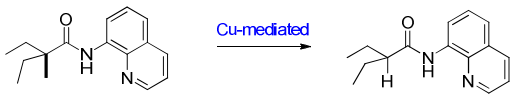
Table 1. Copper-mediated demethylation under various conditions.[a]



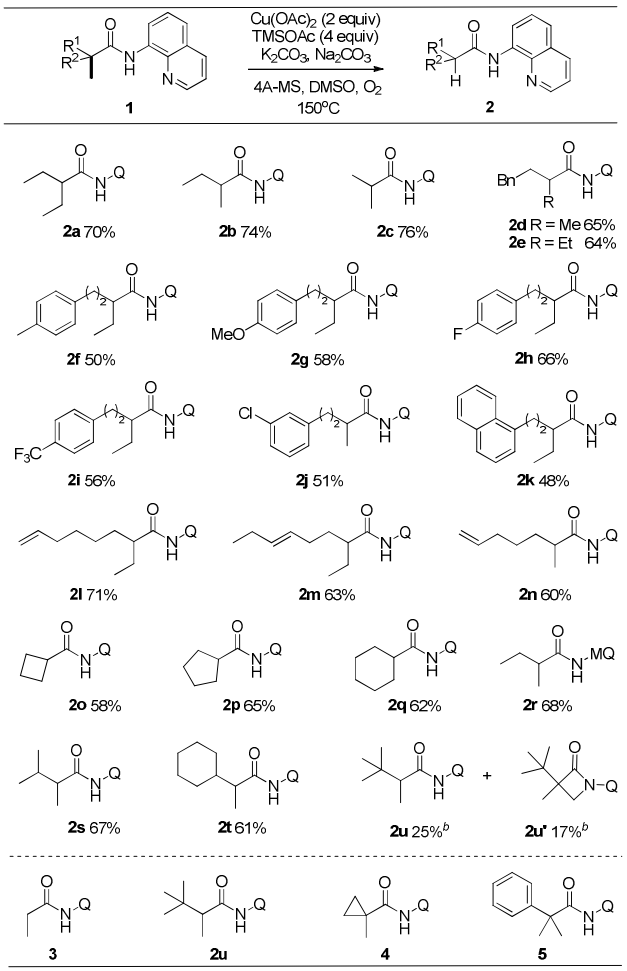
1a **2a**

Entry	Copper Salt	Base	Additive	Solvent	Yield[a] (%)
1	$Cu(OAc)_2$	Na_2CO_3	-	DMSO	21
2	$Cu(OAc)_2$	Na_2CO_3	Ag_2O	DMSO	20
3	$Cu(OAc)_2$	Na_2CO_3	Ag_2CO_3	DMSO	16
4	$Cu(OAc)_2$	Na_2CO_3	AgOAc	DMSO	41
5	$Cu(OAc)_2$	Na_2CO_3	$(BOC)_2O$	DMSO	22
6	$Cu(OAc)_2$	Na_2CO_3	TMSOAc	DMSO	38
7	$Cu(OAc)_2$	K_2CO_3	TMSOAc	DMSO	45
8	$Cu(OAc)_2$	Cs_2CO_3	TMSOAc	DMSO	40
9	$Cu(OAc)_2$	KOAc	TMSOAc	DMSO	trace
10	$Cu(OAc)_2$	K_2HPO_4	TMSOAc	DMSO	trace
11[c]	$Cu(OAc)_2$	K_2CO_3+Na_2CO_3	TMSOAc	DMSO	48
12[c, e]	$Cu(OAc)_2$	K_2CO_3+Na_2CO_3	TMSOAc	DMSO	56
13[c, e]	$Cu(OAc)_2$	K_2CO_3+Na_2CO_3	TMSOAc	DMF	32
14[c, e]	$Cu(OAc)_2$	K_2CO_3+Na_2CO_3	TMSOAc	NMP	19
15[c, d, e]	$Cu(OAc)_2$	K_2CO_3+Na_2CO_3	TMSOAc	DMSO	72(70[b])
16[c, e]	-	K_2CO_3+Na_2CO_3	TMSOAc	DMSO	trace

[a] Reaction conditions: **1a** (0.1 mmol), copper salt (0.1 mmol), base (0.3 mmol), additive (0.4 mmol) in 1 mL solvent at 150 °C for 16 h under O_2. Yields (average of two runs) were determined by GC with triphenylmethane as the internal standard. [b] Isolated yields. [c] The reaction was conducted with K_2CO_3 (0.2 mmol) and Na_2CO_3 (0.1 mmol). [d] $Cu(OAc)_2$ (0.2 mmol) was added. [e] 4A-MS (30 mg) was added. $(BOC)_2O$ = Di-tert-butyl dicarbonate, TMSOAc = trimethylsilyl acetate.

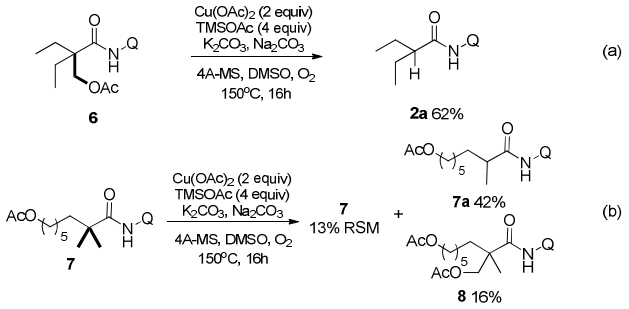
Our study began with the functionalization of **1a**, which was prepared from 2-ethyl-2-methylbutanoic acid and 8-aminoquinoline (Table 1). Treatment of **1a** with $Cu(OAc)_2$ (1 equiv) and Na_2CO_3 (3 equiv) under O_2 atmosphere in DMSO at 150 °C provided an unprecedented demethylated product **2a** in 21% yield (entry 1). In order to increase the yield, We tested several silver salts as additives and AgOAc proved to be particularly effective with yield up to 41%(entry 2-4). Encouraged by this observation, we speculated that the additional carboxylic acid ion may facilitate the demethylation. Through further evaluation of various carboxylic acid sources, it was found that a similar yield of 38% can be obtained when TMSOAc was used instead of AgOAc (entry 5-6). The choice of base also appeared to be crucial. Whereas the use of carbonate salts could smoothly promote the demethylation, acetate and phosphate salts had no effects on the reactions (entry 7-10). After a brief screen of different bases, a combination of K_2CO_3 and Na_2CO_3 gave the best result (48% GC yield, entry 11). The yield could be further improved to 56% by adding 4A molecular sieves (entry 12). Compared with other polar aprotic solvents such as DMF and NMP, DMSO provided a superior outcome (entry 13-14). It may be ascribed to the metal-coordinating properties of DMSO,[15] which can stabilize the copper catalyst and promote the aerobic oxidation. Higher the loading of $Cu(OAc)_2$ gave the optimal result (72% GC yield and 70% isolated yield, entry 15). Finally, in a control experiment without $Cu(OAc)_2$, this reaction does not occur (entry 16).

Table 2. Substrate scope of copper-mediated demethylation [a].



[a] Reaction conditions: Propionamide (0.1 mmol), $Cu(OAc)_2$ (0.2 mmol), K_2CO_3 (0.2 mmol), Na_2CO_3 (0.1 mmol), TMSOAc (0.4 mmol), 4A-MS (30 mg) in 1 mL DMSO at 150 °C for 16 h under O_2. Isolated yields. [b] Yields were determined by ^{1}HNMR analysis with a ratio of **2u** : **2u'** = 1 : 0.7. Q = quinolin-8-yl, TMSOAc = trimethylsilyl acetate. MQ = 5-methoxyquinoline-8-yl.

With the optimized conditions in hand, we investigated the scope of the copper-mediated demethylation. As depicted in Table 2, a variety of linear aliphatic amides provided the corresponding demethylated products in moderate to good yields (**2a**-**2e**). It was found that this reaction occurred preferentially at the α-methyl groups with the ethyl and methylene groups unaffected (**2a, 2e**). This reaction also showed excellent regioselectivity to give only the monodemethylated products when more than one α-methyl group exists in the starting substrates (**2b**-**2d**). A variety of functional groups, including methyl (**2f**), methoxy (**2g**), fluoro (**2h**), trifluoromethyl (**2i**), chloro (**2j**), naphthyl (**2k**), terminal (**2l**, **2n**) and internal alkenyl **(2m)** groups, could be tolerated in the present reaction. It is worth noting that no demethylated cyclization products were detected in the reaction of **2l**-**2n**, indicating that a α-carbonyl radical intermediate was not involved in the copper-mediated demethylation.[16] Cyclocarboxamides also reacted well (**2o**-**2q**). Increasing the

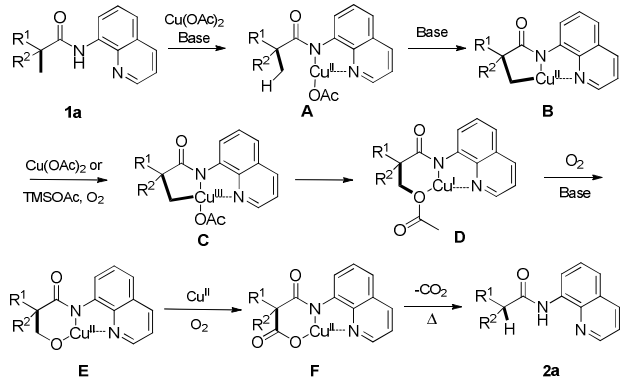


Scheme 2. Mechanistic studies for copper-mediated demethylation.

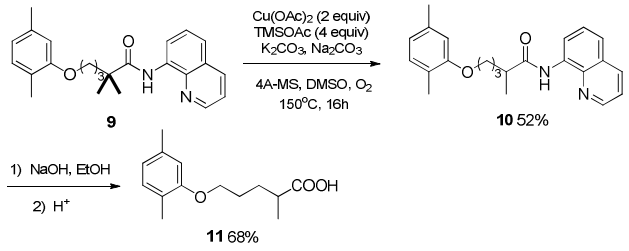
steric hindrance at α-carbonyl position led to a decreased demethylation yield (**2s-2u**). When α-tertiary butyl substituted substrate was taken into this reaction, a mixture of demethylated product **2u** and intramolecular amidation product **2u'** was obtained with a ratio of 1 : 0.7. Additionally, the methylation also proceeded well with a 5-methoxyquinolyl directing group instead of the quinolyl group (**2r**).

Furthermore, the tertiary α-carbon moiety of starting substrates plays a crucial role in this reaction. Both amides **3** and **2u** failed to give the demethylated products. The reaction of α-phenyl substituted substrate **5** was also inefficient. Moreover, subjection of the cyclopropanecaroxamide **4** to the reaction resulted in no desired product. It may attributed to the wider CH_3-C-C(=O) bond angle of **4** compared with its cyclobutyl, cyclopentyl or cyclohexyl derivatives, which made the cyclometalation process less feasible.[17]

Although the detailed reaction mechanism is still not clear, a series of preliminary studies were conducted to get some insights into this copper-mediated oxidative demethylation (scheme 2). First, an acetoxylated aliphatic amide **6** was synthesized and employed in the standard reaction conditions. The copper-mediated demethylation proceeded smoothly to afford the desired product **2a** in 62% yield, suggesting that an acetoxylated intermediate generated by C(sp^3)-H activation is possibly involved in the reaction process. Next, the reaction of substrate **7**, which has a distal substituted acetoxy group, provided a mixture of unreacted **7** (13% RSM), demethylated product **7a** (42% yield), and monoacetoxylated product **8** (16% yield).[18] It also confirmed the participation of a copper-mediated C(sp^3)-H acetoxylation process in this transformation.



Scheme 3. Plausible reaction mechanism.



Scheme 4. Modification of Gemfibrozil and removal of the directing group.

The fact that the majority of distal acetoxy groups maintained to be untouched also indicated that the 8-amidoquinoline-derivied chelation assistance was present in both courses of C(sp^3)-H acetoxylation and aerobic oxidation.[19]

Based on the above experiment results and previous reports,[11] a plausible reaction mechanism for the copper-mediated oxidative demethylation is proposed (scheme 3). First, the complexation of **1a** with $Cu(OAc)_2$ through ligand exchange yielded the Cu(II)-species **A**. A base-promoted cyclocupration then occurred to generate the Cu(II)-alkyl species **B**, which was oxidized by $Cu(OAc)_2$ or $TMSOAc/O_2$ to give the Cu(III)-alkyl intermediate **C**. The reductive elimination of **C** gave rise to the acetoxylated product and the Cu(I)-species **D**, which was oxidized to the Cu(II)-species and hydrolyzed to produce intermediate **E**. Further oxidation of **E** led to the Cu(II)-carboxyl species **F**, which underwent the thermal decarboxylation and protonation to give the demethylated product **2a**.

To further explore the usefulness of this new reaction, the Gemfibrozil derivative **9** was synthesized and subjected to the standard reaction conditions. The copper-mediated demethylation proceeded smoothly to afford the desired product **10** in 52% yield. The 8-aminoquinoline group of **10** could be removed according to the report of Daugulis and coworkers[7b] and the corresponding alkyl carboxylic acid **11** could be obtained in 68% yield (scheme 4).

In conclusion, we report the first Copper-mediated oxidative demethylation of propionamides with the assistance of a removable bidentate directing group. This novel transformation exhibits excellent regioselectivity for preferential cleavage of the C(sp^3)-C(sp^3) bonds at α-methyl positions and allows the efficient modification of substituted α-methyl amides. Preliminary mechanistic studies indicated that this reaction might proceed via a mechanism of initial C(sp^3)-H acetoxylation followed by subsequent oxidative decarboxylation. Further exploration of the detailed reaction mechanism is currently in progress.

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