Homogeneous Catalysis

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Copper-Catalyzed Site-Selective Intramolecular Amidation of Unactivated C(sp^3)–H Bonds**

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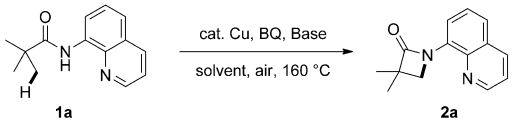
Abstract: *The intramolecular dehydrogenative amidation of aliphatic amides, directed by a bidentate ligand, was developed using a copper-catalyzed sp^3 C–H bond functionalization process. The reaction favors predominantly the C–H bonds of β-methyl groups over the unactivated methylene C–H bonds. Moreover, a preference for activating sp^3 C–H bonds of β-methyl groups, via a five-membered ring intermediate, over the aromatic sp^2 C–H bonds was also observed in the cyclometalation step. Additionally, sp^3 C–H bonds of unactivated secondary sp^3 C–H bonds could be functionalized by favoring the ring carbon atoms over the linear carbon atoms.*

Despite being a challenging process, direct C–H bond functionalization of unactivated sp^3-carbon atoms by transition-metal catalysis has received a great deal of attention in the last couple of decades.[1] Notably, this process does not require the prefunctionalization of unactivated sp^3 C–H bonds and the use of stoichiometric amounts of organometallic reagents, and thus is economically and ecologically favorable compared with the traditional approaches. Within this reaction class, the bidentate-ligand-directed process is of current research interest, and significant progress has been achieved in recent years.[2] In 2002, Sames and co-workers reported the oxidative Heck coupling of sp^3-carbon atoms by palladium catalysis.[3] Subsequently, the group of Daugulis developed a series of bidentate ligands, and a variety of coupling reactions, including acetoxylation, alkoxylation, alkylation, amination, amidation, arylation, and ethynylation, have been discovered since then.[4] Recently, ruthenium-catalyzed carbonylation of unactivated C(sp^3)–H bonds was developed in the group of Chatani.[5] Furthermore, iron-catalyzed direct arylation and alkylation reaction of sp^3-carbon atoms was also demonstrated by Nakamura and co-workers.[6] Very recently, nickel-catalyzed site-selective alkylation of unactivated sp^3 C–H bonds was established in our laboratory.[7] Inspired by recent reports on the palladium-catalyzed aminoquinoline-directed intramolecular amidation of unactivated C(sp^3)–H bonds, we report herein the copper-catalyzed bidentate-ligand-directed intramolecular amidation of sp^3-carbon atoms.[4h,i,p,8] This novel method provides a complementary approach to access mono-, spiro-, and bicyclic β-lactam derivatives, which are important structural units in biologically active natural products and medicines.[9] It should also be mentioned that although copper-catalyzed coupling reactions through an sp^2 or sp^3 C–H activation process have been extensively studied,[10] there are only few examples involving direct functionalization of unactivated sp^3-carbon atoms.[11]

Our investigation began with the oxidative cyclization of *N*-(quinolin-8-yl)pivalamide (**1a**) using catalytic Cu(OAc)$_2$ in the presence of 1.5 equivalents of $KHCO_3$ as the base and 1.2 equivalents of benzoquinone (BQ) as the oxidant at 160 °C (Table 1). After an extensive solvent screening, *o*-

Table 1: Optimization of reaction conditions.[a]



1a **2a**

Entry	Cu source	Base	Solvent	Yield [%][b]
1	$Cu(OAc)_2$	$KHCO_3$	1,2-dichlorobenzene	15
2	$Cu(OAc)_2$	$KHCO_3$	toluene	<5
3	$Cu(OAc)_2$	$KHCO_3$	mesitylene	25
4	$Cu(OAc)_2$	$KHCO_3$	*m*-xylene	24
5	$Cu(OAc)_2$	$KHCO_3$	*p*-xylene	22
6	$Cu(OAc)_2$	$KHCO_3$	*o*-xylene	29
7	$Cu(OTf)_2$	$KHCO_3$	*o*-xylene	<5
8	$CuBr_2$	$KHCO_3$	*o*-xylene	24
9	$CuCl_2$	$KHCO_3$	*o*-xylene	16
10	CuOAc	$KHCO_3$	*o*-xylene	20
11	CuI	$KHCO_3$	*o*-xylene	<5
12	CuBr	$KHCO_3$	*o*-xylene	<5
13	CuCl	$KHCO_3$	*o*-xylene	35
14	CuCl	$NaHCO_3$	*o*-xylene	33
15	CuCl	K_2CO_3	*o*-xylene	<5
16	CuCl	Na_2CO_3	*o*-xylene	22
17	CuCl	K_3PO_4	*o*-xylene	<5
18	CuCl	K_2HPO_4	*o*-xylene	32
19	CuCl	$PhCO_2K$	*o*-xylene	54
20	CuCl	$PhCO_2Na$	*o*-xylene	81
21[c]	CuCl	$PhCO_2Na$	*o*-xylene	90(87)[d]

[a] Reaction conditions: **1a** (0.3 mmol), Cu source (20 mol%), benzoquinone (1.2 equiv), base (1.5 equiv), air, 2.0 mL of solvent, 160 °C, 24 h. [b] Yields and conversions are based on **1a** and determined by ^{1}H NMR spectroscopy using dibromomethane as the internal standard. [c] Duroquinone (1.2 equiv) instead of benzoquinone. [d] Yields of isolated products. Tf = trifluoromethanesulfonyl.

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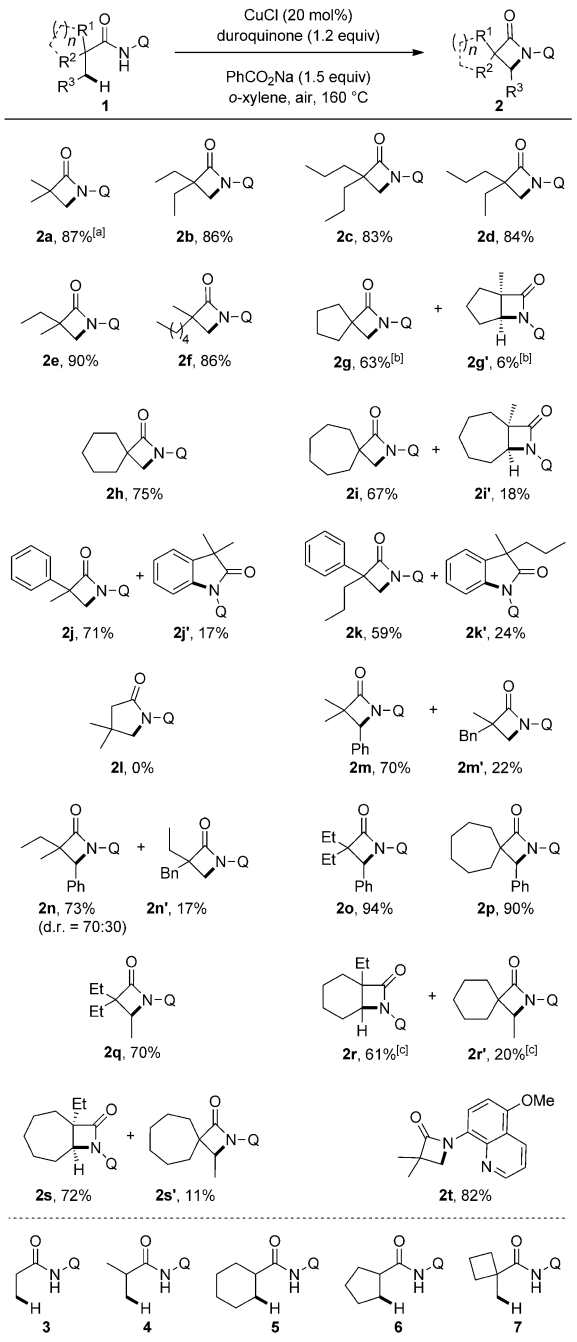
xylene proved to be optimal, albeit with a low yield (entry 6). Next, the investigation of the effect of different copper catalysts towards the reaction was carried out, and it showed that this reaction could be catalyzed by either a copper(II) or copper(I) source, and CuCl was identified as the optimal catalyst (entry 13). Following the above investigation, an extensive screening of bases was carried out, and it turned out that although low yields were typically observed with the common organic and inorganic bases, the reaction was significantly improved by the use of $PhCO_2Na$ as the base (entry 20). Additionally, the reaction yield was improved by replacing benzoquinone with duroquinone as the oxidant (entry 21).

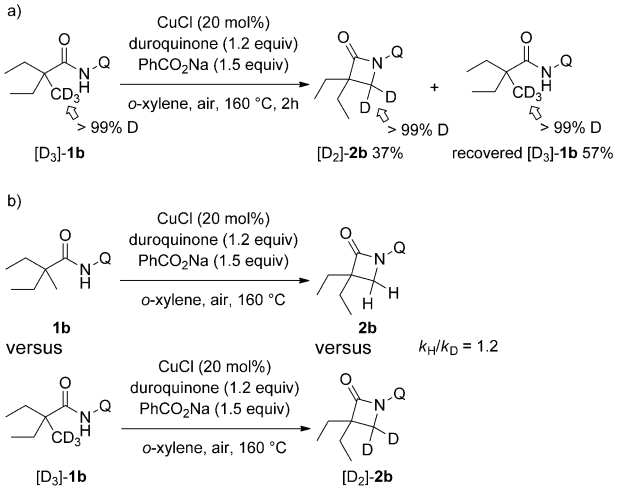
With the optimized reaction conditions in hand, we carried out the substrate scope study of this reaction (Scheme 1). As expected, all kinds of linear aliphatic amide derivatives provided the corresponding desired products in high yields (**2a–f**). It was also observed that this reaction showed excellent site selectivity of the β-methyl groups over the methylene groups. Furthermore, the amidation of the C–H bonds of the γ- or δ-methyl group on the ethyl or propyl group, respectively, was not observed, thus indicating that the formation of a five-membered ring intermediate in the cyclometalation step is predominantly favored over the six- or seven-membered ring intermediate. Interestingly, with α-cyclic substrates 1-methyl-*N*-(quinolin-8-yl)cyclopentane-1-carboxamide and 1-methyl-*N*-(quinolin-8-yl)cycloheptane-1-carboxamide, the selectivity of the β-methyl groups over the β′-methylene groups was slightly decreased, and small amounts of bicyclic compounds (**2g′** and **2i′**) were isolated along with the major spiroproducts (**2g** and **2i**). However, this phenomenon was not observed with 1-methyl-*N*-(quinolin-8-yl)cyclohexane-1-carboxamide, and the spiro-β-lactam **2h** was obtained as the predominant product. Surprisingly, with the 2-phenyl-substituted substrates, the reaction showed a preference for the sp^3 C–H bonds of the β-methyl group over the aromatic C–H bonds of the phenyl group (**2j** and **2m**), and indicates that the formation of a five-membered ring aliphatic copper intermediate should be favored over a six-membered ring aromatic copper intermediate in the metalation step. Furthermore, with 3,3-dimethyl-*N*-(quinolin-8-yl)butanamide as the substrate, the γ-lactam **2l** was not produced, thus indicating that the formation of the six-membered ring cyclometalation intermediate is not feasible in the process under the current catalytic system. It is also worthy of mention that the introduction of a methoxy group at C5 of the quinoline moiety had no apparent effect on the reaction (**2t**).



Scheme 1. Direct amidation on sp^3-carbon atoms. Reaction conditions: 1 (0.3 mmol), CuCl (20 mol%), duroquinone (1.2 equiv), $PhCO_2Na$ (1.5 equiv), 2.0 mL *o*-xylene, 160 °C, 12-24 h. [a] Yields of isolated products. [b] 170 °C. [c] Unseparable mixture. Q = quinolin-8-yl.

Next, we focused our study on the direct functionalization of secondary β-sp^3-carbon atoms. It was quickly noticed that secondary benzylic β-carbon atoms are more reactive than the β′-methyl groups and other unactivated β′-methylene carbon atoms (**2m–p**; Scheme 1. As expected, the predominant preference for C–H bonds of unactivated secondary β-carbon atoms over γ-methyl groups was observed because the formation of a six-membered ring intermediate is not feasible, as discussed above (**2q**). Furthermore, functionalization of ring β-carbon atoms was favored over acyclic β′-carbon atoms (**2r** and **2s**). Interestingly, high *syn* diastereoselectivity was also observed for the formation of the bicyclic β-lactam compound **2s**.

Furthermore, it was found that a tertiary α-carbon atom is necessary for this reaction since the amides **3–6** failed to provide the desired products. In addition, subjection of the cyclobutanecaroxamide **7** to the reaction conditions provided no desired product. As suggested by Nakamura and co-workers, the CH_3-C-C(=O) bond angle of this substrate is

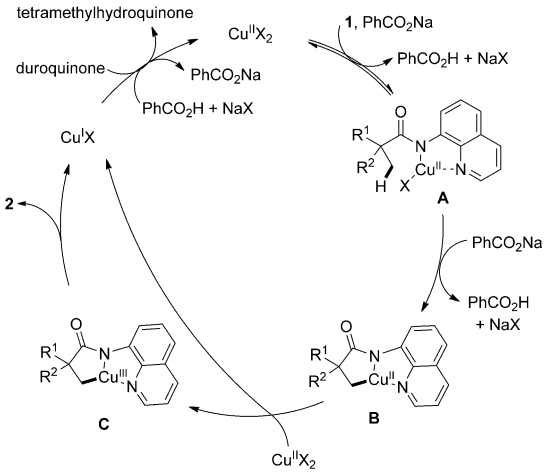


Scheme 2. Deuterium-labeling experiments.

much wider than its cyclopentyl or cyclohexyl derivative,[6] and thus the cyclometalation of **7** is less feasible.

To further explore the reaction mechanism, we carried out the deuterium-labeling experiments of 2-ethyl-2-methyl-*N*-(quinolin-8-yl)butanamide (**1b**; Scheme 2). It was noticed that there was no apparent H–D exchange in this process (Scheme 2a). Furthermore, a secondary kinetic isotope effect was observed, thus suggesting that the sp^3 C–H bond cleavage of the amide **1** should not be the rate-limiting step in this catalytic process (Scheme 2b).[12]

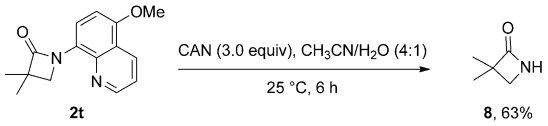
On the basis of the above observation and the previous reports,[8,13] a plausible catalytic cycle of this transformation is proposed (Scheme 3). Coordination of **1** to a copper(II)



Scheme 3. Plausible reaction mechanism.

species and subsequent ligand exchange in the presence of sodium benzoate generates the copper complex **A**, which forms the alkyl/Cu^{II} species **B** by a cyclocupration process. Oxidation of **B** with another copper(II) species gives rise to the alkyl/Cu^{III} complex **C** and a copper(I) species. Reductive elimination of **C** produces the β-lactam derivative **2** and another copper(I) species. The generated copper(I) species is then oxidized to the copper(II) species by duroquinone, and the reduced anionic species is quenched by benzoic acid through an acid/base reaction. It should be mentioned that a sequential chlorination amidation process could not be ruled out.[14]

To further broaden the synthetic application of this methodology, removal of the 5-methoxyquinolyl group of 1-(5-methoxyquinolin-8-yl)-3,3-dimethylazetidin-2-one (**2t**) was carried out based on the report from the group of Chen, and the desired β-lactam product **8** was obtained in 63% yield (Scheme 4).[4p]



Scheme 4. Oxidative cleavage of the 5-methoxyquinolyl group. CAN = ceric ammonium nitrate.

In summary, a site-selective intramolecular amidation of *N*-(quinolin-8-yl)pivalamide derivatives with an 8-aminoquinolinyl group as the bidentate ligand was developed by a copper-catalyzed sp^3 C–H bond functionalization process. This reaction proceeds with a preference for sp^3 C–H bonds of β-methyl groups over the unactivated methylene C–H bonds. Unexpectedly, this reaction favors sp^3 C–H bonds of β-methyl groups, which form a five-membered ring intermediate in the cyclometalation step; the aromatic sp^2 C–H bonds are less reactive as the reaction proceeds via a six-membered ring intermediate. Furthermore, regioselective C–H functionalization of secondary β-sp^3-carbon atoms was also observed among methylene groups with the reactivity order of benzylic > ring > linear carbon atoms. Additionally, the formation of the bicyclic β-lactam derivative **2s** by functionalization of the ring β-carbon atom was performed in a highly diastereoselective manner by favoring the *syn* products. Moreover, direct C–H functionalization of secondary benzylic β-carbon atoms is preferred over the β′-methyl groups, and gives the overall reactivity order of this process as β-benzylic > β-methyl > β-ring > β-linear carbon atoms. With this method, α,α-disubstituted mono-, spiro-, and bicyclic β-lactam derivatives could be prepared. The detailed mechanistic studies of this transformation are currently ongoing in our laboratory.

Experimental Section

A 50 mL Schlenk tube was charged with the α,α,α-trisubstituted *N*-(quinolin-8-yl)acetamides **1** (0.3 mmol), CuCl (5.9 mg, 0.06 mmol), duroquinone (59 mg, 0.36 mmol), $PhCO_2Na$ (65 mg, 0.45 mmol), and 2.0 mL of *o*-xylene. Then the vial was sealed, and stirred rigorously at 160 °C for 12–24 h. After removal of the solvent, the residue was

purified by flash chromatography on silica gel (gradient eluent of 2% EtOAc in hexanes, v/v) to give the desired product.

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[14] While 3-chloro-2,2-dimethyl-*N*-(quinolin-8-yl)propanamide (**1u**) was subjected to the standard reaction conditions, **2a** was observed as the product. This result indicates that a sequential chlorination amidation process is also possible.