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Direct Aerobic Carbonylation of C(sp^2)−H and C(sp^3)−H Bonds through Ni/Cu Synergistic Catalysis with DMF as the Carbonyl Source

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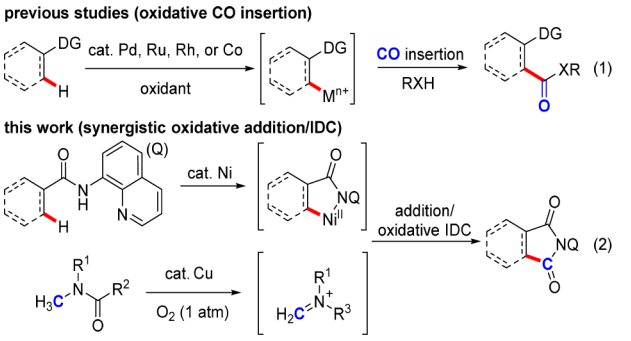
Supporting Information

ABSTRACT: The direct carbonylation of aromatic sp^2 and unactivated sp^3 C−H bonds of amides was achieved via nickel/copper catalysis under atmospheric O_2 with the assistance of a bidentate directing group. The sp^2 C−H functionalization showed high regioselectivity and good functional group compatibility. The sp^3 C−H functionalization showed high site-selectivity by favoring the C−H bonds of α-methyl groups over those of the α-methylene, β- or γ-methyl groups. Moreover, this reaction showed a predominant preference for functionalizing the α-methyl over α-phenyl group. Mechanistic studies revealed that nickel/copper synergistic catalysis is involved in this process.

Transition-metal-catalyzed C−H functionalization has experienced a tremendous development over the past decade.[1] This method allows for the direct derivatization of (hetero)-arenes and alkanes in a highly site-selective manner by avoiding the prefunctionalization in the classic coupling reactions. Within this reaction class, direct carbonylation has attracted considerable attention in recent years due to the prevalent presence of the carbonyl group in organic molecules [Scheme 1 (1)].[2] For example, Pd, Co, Rh, or Ru-catalyzed processes have been well established on sp^2 carbons.[3] Additionally, direct carbonylation of C(sp^3)−H bonds has been demonstrated with Pd, Rh, or Ru catalysis.[4] Despite a powerful strategy, the use of toxic CO (mainly at high pressure) associated with somewhat troublesome gas handling procedure limits the application of this method. Therefore, it would be highly desirable if nontoxic and inexpensive reagents, preferably the organic solvents, could serve as the carbonyl source.

Cooper-catalyzed aerobic cross dehydrogenative coupling reactions of amines have been well studied.[5] Very recently, intramolecular dehydrogenative cyclization (IDC) reactions of hydrazones have also been demonstrated in our group with copper catalysis under atmospheric O_2.[6] On the basis of these studies, it is believed that selective oxidation of *N*-methyl-*N*-alkyl substituted amides could be reached, and the *in situ* generated iminium ion intermediates could then act as highly reactive electrophiles for the nucleophilic addition of an organometallic species. Following this process, aerobic oxidative IDC could occur to provide succinimides as the products [Scheme 1 (2)]. On the basis of recent reports of nickel-catalyzed bidentate ligand-directed C−H functionalization of arenes and alkanes,[7] herein, we report the chelation-assisted site-selective carbonylation of C(sp^2)−H and C(sp^3)−H bonds via nickel/copper synergistic catalysis with *N*,*N*-dimethylforamide (DMF) as the carbonyl source under atmospheric O_2.[8] It is noteworthy that this reaction represents the first example of nucleophilic addition to a carbon-heteroatom double bond via nickel-catalyzed C−H functionalization on sp^2 carbons. Additionally, it is the first example of transition-metal-catalyzed site-selective nucleophilic addition reactions of unactivated C(sp^3)−H bonds. Moreover, the use of two distinct metals as the synergistic catalysts in an sp^3 C−H functionalization process is rare.

Scheme 1. Transition-Metal-Catalyzed Direct Carbonylation of sp^2 and sp^3 Carbons



Our investigation began with direct carbonylation of *N*-(quinolin-8-yl)benzamide (**1a**) in DMF via nickel/copper bimetallic catalysis under atmospheric oxygen (see Table S1 in Supporting Information). After an extensive screening of the catalysts, the desired product, 2-(quinolin-8-yl)isoindoline-1,3-dione (**2a**) was obtained in 23% yield by the combination of catalytic amounts of NiI_2 and $Cu(acac)_2$ with 1 equiv of Na_2CO_3 as the base (entry 8). Next, the screening of the base was carried out, and it turned out that Li_2CO_3 is optimal, providing **2a** in 37% yield (entry 11). Interestingly, a higher yield was then observed with reduced amounts of Li_2CO_3, indicating that the base might compete with the substrate for the metal coordination (entry 12). Further optimization showed that this reaction could be significantly improved by the addition of a quaternary ammonium salt, presumably due to the increased solubility of the reagents and intermediates by this ammonium salt (entries 13−16). It was also noticed that both a nickel and copper catalyst are required for this process, suggesting that this reaction is performed via a synergistic catalysis (entries 17 and 18).

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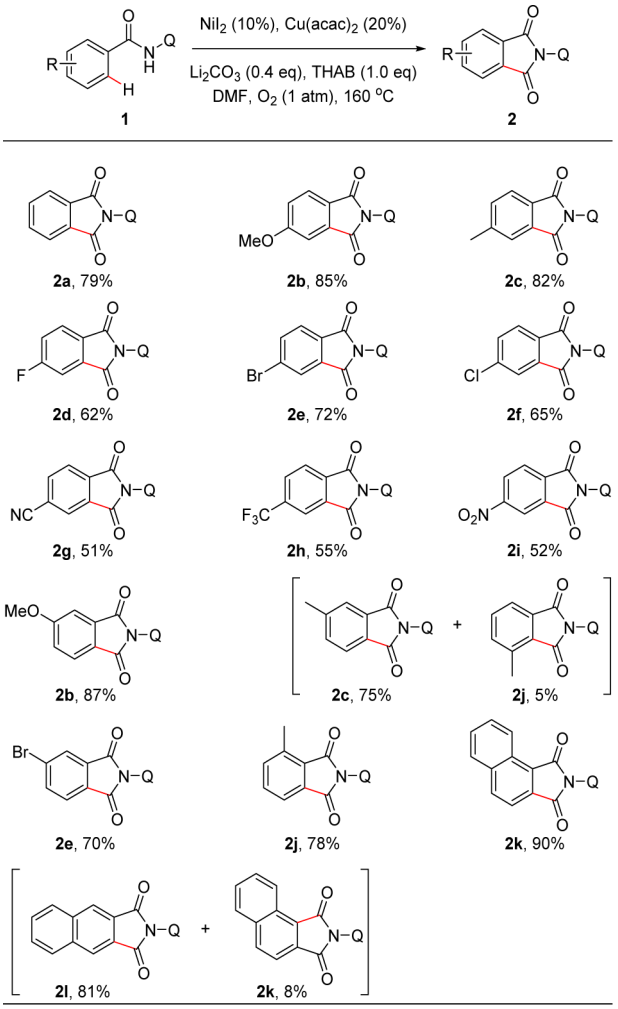
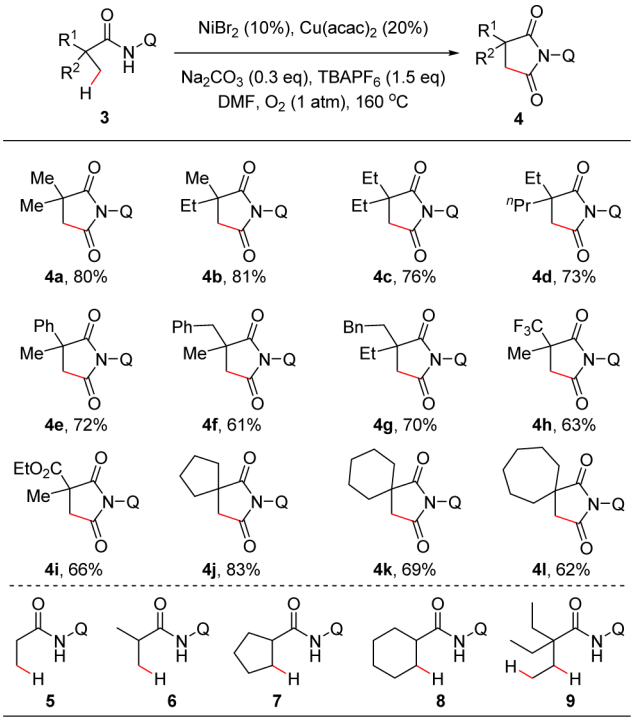
Table 1. Scope of Aromatic Amides[a,b]



[a]Reaction conditions: **1** (0.2 mmol), NiI_2 (10 mol %), $Cu(acac)_2$ (20 mol %), Li_2CO_3 (0.4 equiv), THAB (1.0 equiv), O_2 (1 atm), 3.0 mL of DMF, 160 °C, 24 h. [b]Isolated yield. THAB = tetraheptylammonium bromide. Q = 8-quinolinyl.

Table 2. Scope of Aliphatic Amides[a,b]



[a]Reaction conditions: **3** (0.2 mmol), $NiBr_2$ (10 mol %), $Cu(acac)_2$ (20 mol %), Na_2CO_3 (0.3 equiv), $TBAPF_6$ (1.5 equiv), O_2 (1 atm), 5.0 mL of DMF, 160 °C, 24 h. [b]Isolated yield. $TBAPF_6$ = tetrabutylammonium hexafluorophosphate.

With the optimized conditions in hand, the scope study of aromatic amides was carried out. As shown in Table 1, a variety of functional groups including methoxyl, methyl, halogen (F, Cl, and Br), cyano, trifluoromethyl, and nitro groups are compatible with the catalytic conditions (**2a**–**j**). In addition, substrates with an electron-withdrawing group on the benzene ring gave lower yields compared with those with an electron-donating group. Considering that a nucleophilic addition step might be involved in the process, the above observed results are not surprising since an electron-withdrawing group decreases the nucleophilicity of the *in situ* generated nucleophile. Furthermore, it was found that the benzene ring could also be effectively replaced by naphthalene moiety (**2k** and **2l**). Unfortunately, heteroaromatic substrates failed to provide any desired products.[9]

Next, we carried out the substrate scope study on aliphatic amides (Table 2). As expected, good yields were obtained with 2,2-disubstituted propanamides bearing either the linear or cyclic chains under modified reaction conditions (**4a**–**l**). As shown in the previous studies,[4,7] this reaction showed a high site-selectivity by preferring the methyl group over the methylene groups including the relatively reactive benzyl group (**4f**). Furthermore, a predominant preference of functionalizing the β-C–H over γ- or δ-C–H bonds of methyl groups was also observed, indicating that the formation of a five-membered ring intermediate in the cyclometalation step is favored over the six- or seven-membered ring intermediates. Moreover, with the 2-phenyl-substituted substrate, sp^3 C–H functionalization of the methyl group is preferred over the sp^2 C–H functionalization (**4e**). It should be mentioned that a quaternary α-carbon is required for this reaction because subjection of amides **5**–**8** to the reaction conditions did not afford any desired products. Additionally, 2,2-diethyl-*N*-(quinolin-8-yl)butanamide (**9**) failed this reaction, suggesting that the formation of a six-membered cyclometalated intermediate is not feasible under the current reaction conditions.

Following the above studies, we then carried out the investigation on the reaction mechanism. It has been reported that DMF could release carbon monoxide at high temperature, and thus the released CO could potentially participate in this process as the carbonyl source.[10] To clarify this, DMF($^{13}C{=}O$) was used as the solvent to replace regular DMF (Scheme 2). It was found that only trace amount of [^{13}C]-**2a** was obtained from the reaction, indicating that the incorporated carbonyl group mainly comes from the methyl group. On the basis of these results, we then carried out some control experiments with a series of N-containing solvents. Not surprisingly, the reaction could be performed with an *N*-methyl solvent such as *N*,*N*-dimethylacetamide or *N*-methylpyrrolidone. In an *N*-ethyl solvent (diethylformaide), only a small amount of **2a** was obtained, presumably arisen from the insertion of CO generated from the solvent upon heating.

To gain more insights on the reaction mechanism, several potential intermediates (**10**–**13**) were then synthesized and subjected to the reaction conditions (Scheme 3). Among these

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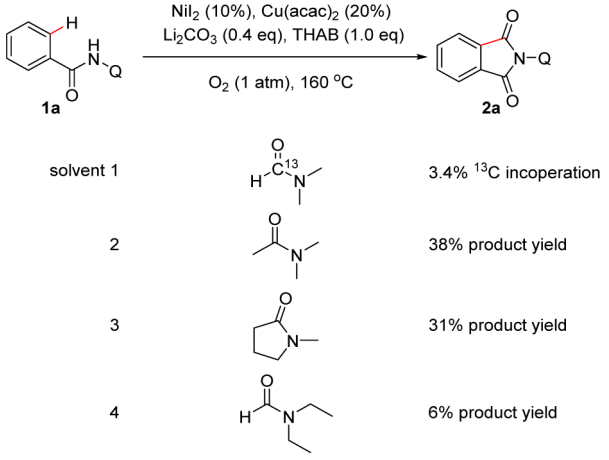
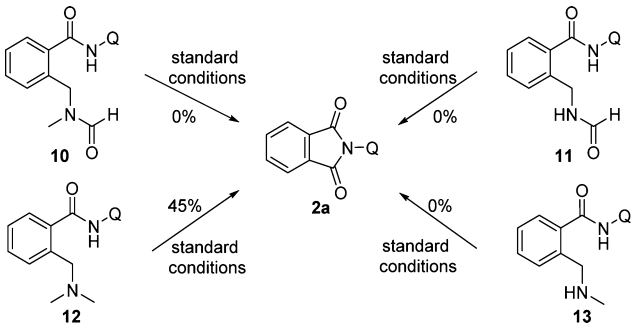
Scheme 2. Control Experiments and Isotope Studies of Aromatic Substrates



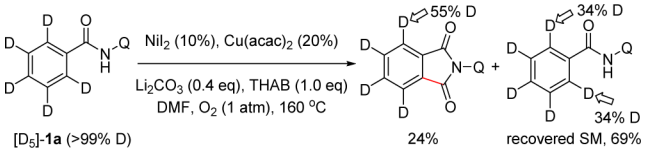
Scheme 3. Control Experiments of Aromatic Substrates



substrates, only 2-((dimethylamino)methyl)-*N*-(quinolin-8-yl)-benzamide (**12**) afforded the desired product, suggesting that an *N*-methyl-*N*-methylenemethanaminium species is involved in this process as a reactive nucleophile.

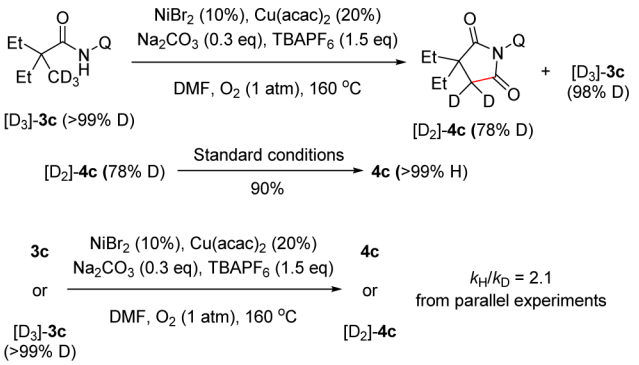
A deuterium-labeling experiment was then carried out to further probe the reaction mechanism of aromatic amides (kinetic isotope effect), and an apparent H/D exchange was observed for [D_5]-**1a** (Scheme 4). This suggests that C−H bond cleavage should be a reversible step in the sp^2 C−H functionalization process.

Scheme 4. Deuterium-Labeling Experiments of C(sp^2)−H Activation

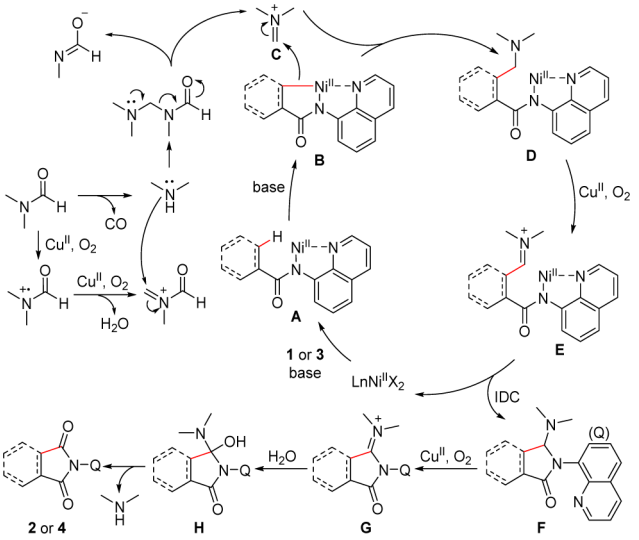


In contrast, a first-order kinetic isotope effect was observed with **3c** in the sp^3 C−H functionalization process, indicating that the cyclometalation step of an aliphatic amide is the rate-determining step (Scheme 5). Interestingly, an apparent H/D exchange also occurred with the product. Furthermore, subjection of [D_2]-**4c** into the standard reaction conditions provided **4c** in 90% yield. These results suggested that the observed H/D exchange of the product [D_2]-**4c** has arisen from the formation of an enolate ion followed by protonation.

Scheme 5. Deuterium-Labeling Experiments of C(sp^3)−H Activation



Scheme 6. Plausible Reaction Mechanism



On the basis of the above observations and the previous reports,[7] a plausible catalytic cycle is proposed (Scheme 6). It is believed that this process is initiated from coordination of amide **1** to a Ni^{II} species followed by a ligand exchange step under basic conditions to give the nickel complex **A**. Then, cyclometalation of **A** occurs via either sp^2 or sp^3 C−H bond activation to generate the intermediate **B**. It is noteworthy that sp^2 C−H bond cleavage is a reversible step, while sp^3 C−H bond cleavage is presumably an irreversible step as discussed in Schemes 4 and 5. Concurrently, an *N*-methyl-*N*-methylenemethanaminium species **C** is generated *in situ* from DMF via a sequential decarbonylation, nucleophilic addition, and elimination process under copper catalysis with oxygen as the external oxidant.[11] Nucleophilic addition of the intermediate **B** to the iminium ion intermediate **C** provides the intermediate **D**. Oxidation of intermediate **D** followed by intramolecular nucleophilic addition gives rise to the intermediate **F** which then produces the product **2** or **4** via oxidation and hydrolysis.

To further broaden the synthetic utility of this process, ring-opening reactions of succinimide **4j** were carried out (Scheme 7).[4d] Treatment of **4j** under acidic conditions provided the hydrolyzed product 1-(carboxymethyl)cyclopentane-1-carboxylic acid (**14**) in 85% isolated yield. On the other hand, selective alcoholysis of **4j** occurred with NaOMe in MeOH at room temperature, affording methyl 2-(1-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)cyclopentyl)acetate (**15**) in 74% yield. Further-

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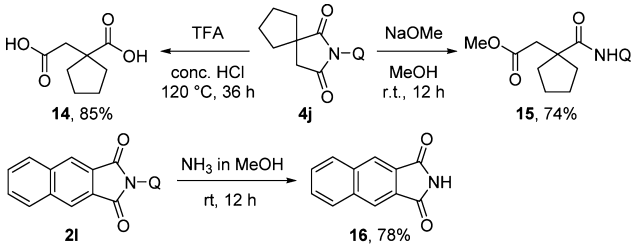
Scheme 7. Derivatization of Succinimides



more, the quinolin-8-yl moiety of **2l** could also be readily removed by treatment with ammonia, affording the corresponding naphthalimide derivative **16**.[12]

In summary, a direct carbonylation of C−H bonds of aromatic or aliphatic amides was developed through nickel/copper synergistic catalysis under atmospheric oxygen with DMF as the carbon source of carbonyl group. The sp^2 C−H bond functionalization process was featured with high regioselectivity and a good compatibility with a broad range of functional groups. The sp^3 C−H bond functionalization process showed a predominant preference for the α-methyl groups over the α-methylene and β- or γ-methyl groups. Furthermore, the preference of functionalizing the sp^3 C−H bond of the α-methyl group over the sp^2 C−H bond of the α-phenyl group was also observed. Mechanistic studies suggested that this reaction is performed via nickel/copper synergistic catalysis with the nickel species initiating the C−H activation of an amide to generate a nucleophile and DMF providing an electrophile by the copper species. Interestingly, it was found that C−H bond cleavage of aromatic amides is a reversible step, while C−H bond cleavage of aliphatic amides is the rate-limiting step, indicating that C−H activation on sp^3 carbons is a more challenging process compared with sp^2 carbons. The detailed mechanistic study and potential application of this transformation is currently undergoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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