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Nickel-Catalyzed Aminoxylation of Inert Aliphatic C(sp^3)−H Bonds with Stable Nitroxyl Radicals under Air: One-Pot Route to α-Formyl Acid Derivatives

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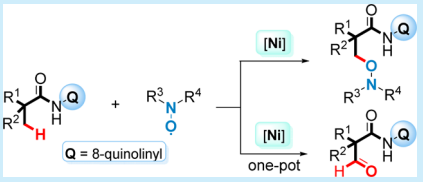
Supporting Information

ABSTRACT: Nickel-catalyzed aminoxylation of an unactivated C(sp^3)−H bond with a stable nitroxyl radical has been accomplished for the first time to offer various *N*-alkoxyamine derivatives, which further enables a one-pot approach to α-formyl acid derivatives. The aminoxylation process reported also provides direct evidence for the oxidative addition of a cyclometallic intermediate with a free radical, which is helpful for the reaction-mechanism study in transition-metal-catalyzed functionalization of inert C(sp^3)−H bonds.

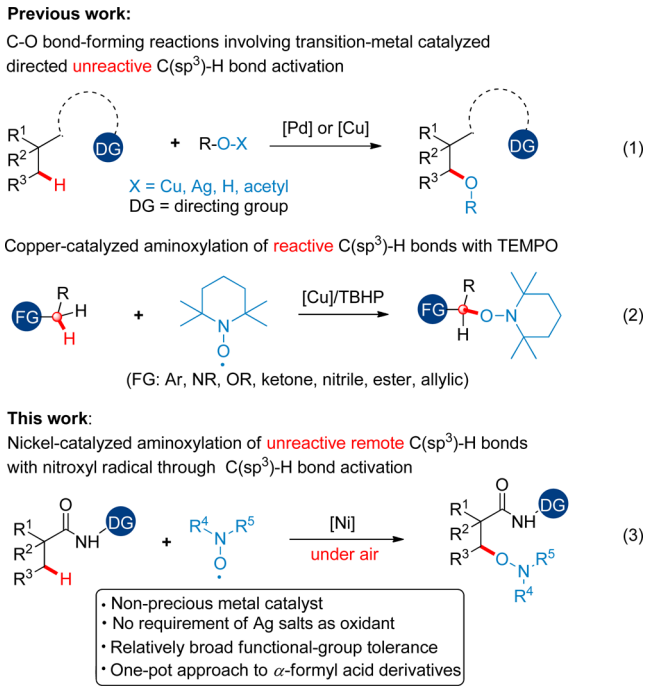


In recent years, tremendous efforts have been devoted to the formation of alkyloxy compounds.[1−3] As an effective strategy for the construction of these compounds, carbon−oxygen bond-forming reactions involving transition-metal-catalyzed unactivated C(sp^3)−H activation have emerged and attracted much attention in the organic chemistry community (Scheme 1, eq 1).[3] *N*-Alkoxyamines, as effective fireproofing agents, rheology modifiers, chiral building blocks and other polyfunctional precursors, have been widely applied in research and development of materials and drugs.[4,5] Although the past decades have witnessed substantial progress in the development of approaches for preparing *N*-alkoxyamines,[6] the aminoxylation of inert aliphatic C(sp^3)−H bond has not yet been implemented.

In the past few decades, significant progress has been made in free-radical reactions. 2,2,6,6-Tetramethylpiperidin-1-oxyl (TEMPO), a stable nitroxyl radical, has been used as radical scavenger, nonmetallic catalyst, organic single electron oxidant, and coupling partner.[7] TEMPO displays various roles in these reactions due to its unique physicochemical property. Recently, the copper-catalyzed aminoxylation of reactive C(sp^3)−H bonds, such as those which are adjacent to N, O, ketone, nitrile, ester, allylic, and aryl with TEMPO, was reported (Scheme 1, eq 2).[6f] In this work, we demonstrate that unactivated C(sp^3)−H bonds enable the aminoxylation with a stable nitroxyl radical to construct *N*-alkoxyamines by nickel-catalyzed C(sp^3)−H bond activation (Scheme 1, eq 3).

Despite significant progress in transition-metal-catalyzed carbon−oxygen bond-forming reactions of C(sp^3)−H bonds, transition-metal-catalyzed directed functionalization of inert C(sp^3)−H bonds involving free radicals has been rarely reported until now.[8] In previous reports, carbon−oxygen bond-forming reactions in the field of unactivated C(sp^3)−H activation have been developed mainly with palladium as the catalyst.[3] Considering that inexpensive and earth-abundant first-row transition metals such as iron, copper, and nickel salts have been widely used as the catalyst in the free-radical reactions,[9] these metals were thus employed to investigate this type of aminoxylation of unreactive C(sp^3)−H bonds. Choosing the 8-aminoquinoline unit as a readily removable bidentate directing group, we initiated our study with the

Scheme 1. Transition-Metal-Catalyzed C−O Bond-Forming Reactions of C(sp^3)−H Bonds



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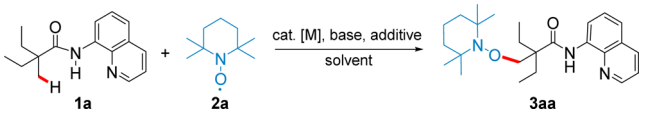
reaction of 2-ethyl-2-methyl-*N*-(quinolin-8-yl)butanamide **1a** with TEMPO (Scheme 2). Luckily, the desired cross-coupled

Scheme 2. Optimization of Reaction Conditions

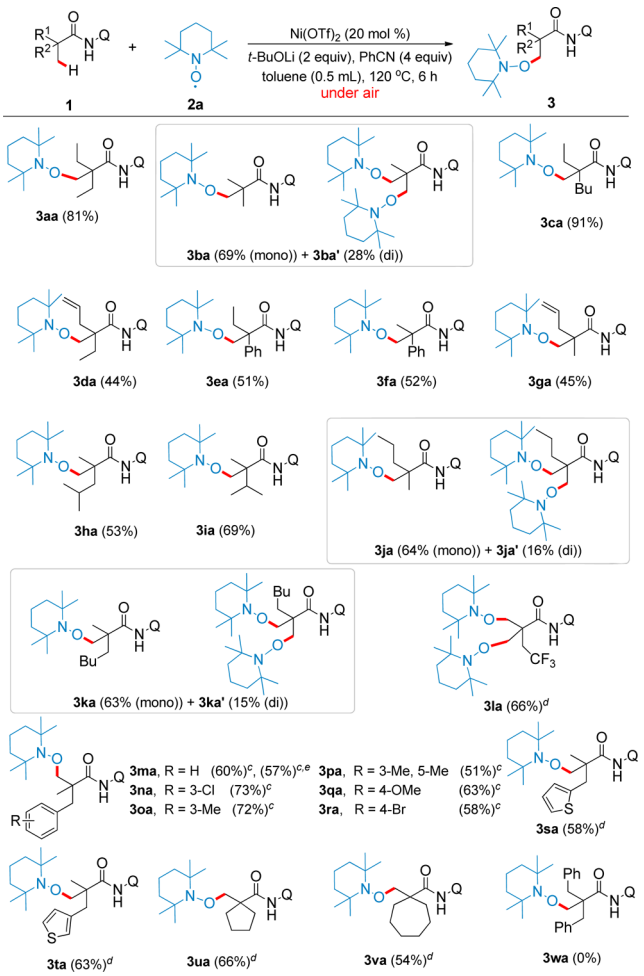


product **3aa** was obtained in toluene in 7% yield by using $NiCl_2$ as the catalyst in the presence of 2.0 equiv of *t*-BuOLi as the base (Table S1, entry 1). Other commercially available simple metal salts, such as $CoCl_2$, $CuCl_2$, and CuCl, did not give any desired product. Other bases such as *t*-BuONa, *t*-BuOK, K_3PO_4, Li_2CO_3, Na_2CO_3, NaOAc, PhCOONa, CsF, DIPEA, and DBU were screened, and no product was detected (Table S2). Next, the effect of solvents was investigated (Table S3). DCE, DMF, DMSO, and acetonitrile were incompatible in this reaction. Benzonitrile could improve the yield to 21% (Table S3, entry 9). However, some undefined side reaction was observed when PhCN was used as the solvent. Then a mixture of benzonitrile and toluene (ca. 1:5 v/v) was used as the solvent, giving the desired product in a similar yield (Table S3, entry 10). Subsequently, various Ni(II) and Ni(0) species were examined (Table S4), and $Ni(OTf)_2$ was found to afford **3aa** in 81% yield at 120 °C for 6 h under air (Table S5, entry 8). Notably, the aminoxylation occurred in 69% yield under an atmosphere of nitrogen, indicating that, besides oxygen, TEMPO could also serve as the oxidant (Table S5, entries 8, 12, and 13).

With the optimized conditions in hand, the substrate scope of aliphatic amides using TEMPO as the aminoxyl source was investigated. As summarized in Scheme 3, a series of 2,2-disubstituted propanamides bearing linear or cyclic chains could be transformed into the desired *N*-alkoxyamine products in moderate to high yields. Substrates with functional groups such as bromine, alkoxy, heteroaryl, trifluoromethyl, and alkenyl on the alkane skeletons were compatible with this reaction. However, no reactions were detected when the substrates contained functional groups such as esters, benzyl ethers, and ketones (for details, see the SI). Moreover, the disubstituted products could be obtained under the standard conditions when aliphatic amides with small steric hindrance were employed (**3ba′**, **3ja′**, and **3ka′**). Furthermore, site selectivity for the *β*-methyl group over the methylene group or *γ*- and *δ*-methyl group was revealed even though the *β*-benzylic site exists (**3aa**–**ra**). Notably, the trisubstituted product could not be detected in this catalytic system probably due to steric hindrance. 2-Benzyl-2-methyl-3-phenyl-*N*-(quinolin-8-yl)-propanamide (**1w**) did not undergo the aminoxylation.

Next, substrate scope with respect to nitroxyl radicals was explored (Scheme 4). The nitroxyl radicals with a reactive functional group such as hydroxyl (**2-a**), keto carbonyl (**2-b**), and amino (**2-c**) did not provide the desired cross-coupled products. However, this catalytic system was tolerant of the protected hydroxyl, keto carbonyl, and amino groups, delivering the desired *N*-alkoxyamines. 2,2,6,6-Tetramethyl-4-(phenylmethoxy)piperidinoxy compounds with an electron-donating or electron-drawing group on the phenyl ring could also be transformed into the desired products (**3bh**–**bk**). The presence of a diethylphosphate group did not lead to the *N*-alkoxyamine product (**2-d**).

Scheme 3. Scope of Aliphatic Acid Derivatives[a,b]



[a]Reaction conditions: **1** (0.25 mmol), **2a** (2.0 equiv), $Ni(OTf)_2$ (20 mol %), PhCN (4.0 equiv), and *t*-BuOLi (2.0 equiv) were stirred in toluene (0.5 mL) at 120 °C for 6 h under an atmosphere of air. [b]Isolated yields. [c]12 h. [d]12 h, 140 °C. [e]1.5 mmol scale. Q = 8-quinolinyl.

To gain insight into the reaction mechanism, deuterium-labeling experiments were conducted (Scheme 5). When the reaction was performed with D_2O or CD_3OD instead of nitroxyl radicals, no methyl hydrogen in [d_n]-**1a** was deuterated, indicating that the primary C(sp^3)–H bond activation was an irreversible process. We then measured both the parallel and intermolecular kinetic isotope effects (KIEs). The observed KIE values indicated that C–H bond cleavage might be related to the rate-determining step.[10]

Based on the above results and previous reports,[11] a tentative mechanism of aminoxylation is proposed in Scheme 6. Initially, a bidentate chelation process of the amide **A** with the Ni(II) species gives the Ni(II) complex **B** with the generation of HX, which is trapped by *t*-BuOLi. Then the C–H bond in complex **B** undergoes an irreversible cleavage to give the cyclometallic intermediate **C**. The Ni(III) species **D** is generated via the oxidative addition of the nickelacycle **C** with the nitroxyl radical. The reductive elimination and protonation next occur to deliver the desired product with generation of the Ni(I) species (Scheme 6, path a). Finally, the Ni(I) species is oxidized to the Ni(II) species by either the stable nitroxyl radical or oxygen in air, fulfilling the catalytic cycle. It is noted that no

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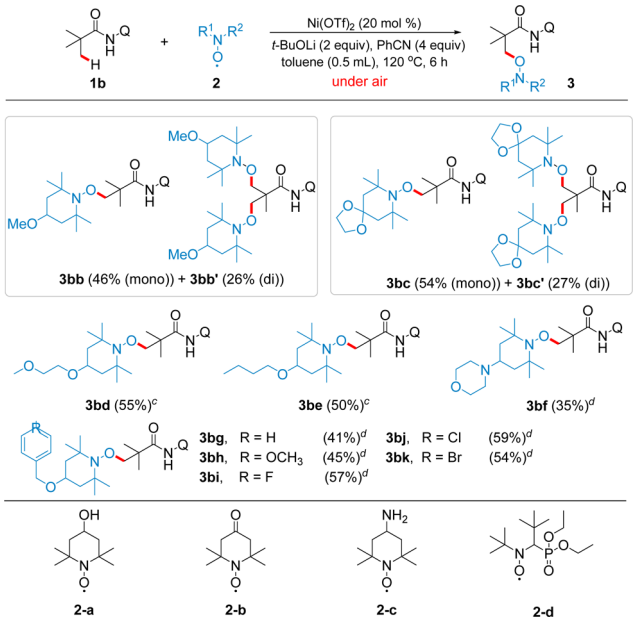
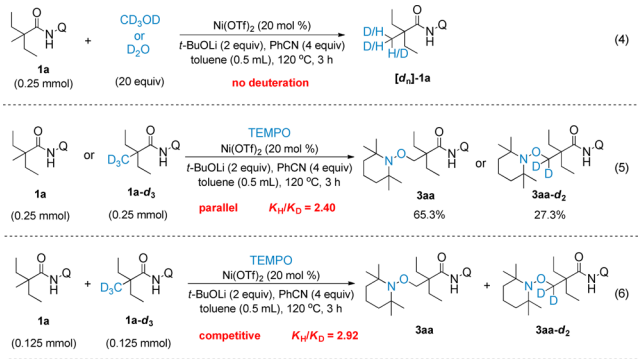
Scheme 4. Scope of Stable Nitroxyl Radicals[a,b]

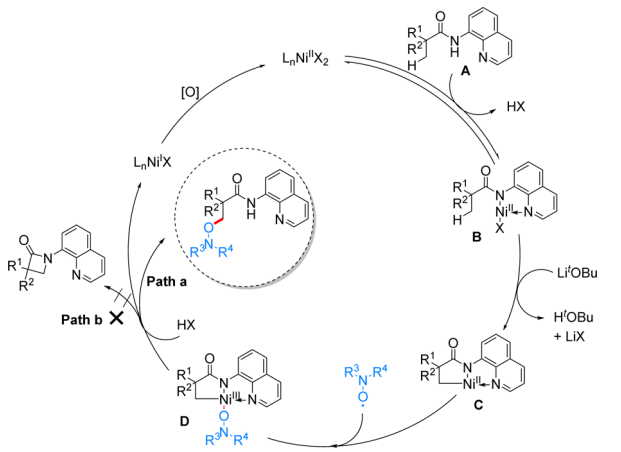


[a]Reaction conditions: **1a** (0.25 mmol), **2** (2.0 equiv), $Ni(OTf)_2$ (20 mol %), PhCN (4.0 equiv), and *t*-BuOLi (2.0 equiv) were stirred in toluene (0.5 mL) at 120 °C for 6 h under an atmosphere of air. [b]Isolated yields. [c]24 h. [d]24 h, 140 °C. Q = 8-quinolinyl.

Scheme 5. Deuterium-Labeling Experiments



Scheme 6. Plausible Mechanistic Pathway



lactam product was detected in this catalytic system (Scheme 6, path b).[7e]

As important structural motifs, α-formyl acid derivatives are widely found in pharmaceutical and natural product molecules (Figure 1).[12] To further extend the utility of this protocol, a

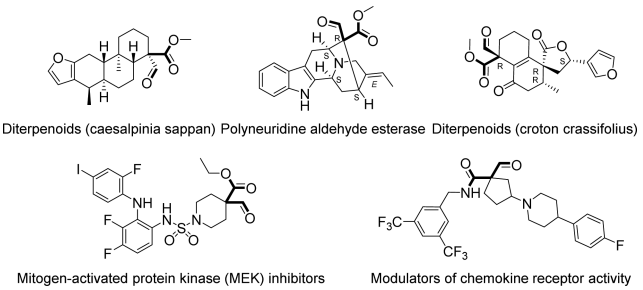
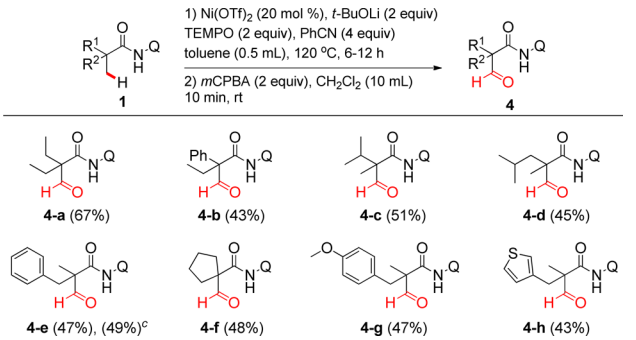


Figure 1. Selected pharmaceutical and natural product molecules containing α-formyl acid derivatives.

one-pot route to α-formyl acid derivatives was put forward. After the aminoxylation of the C(sp^3)−H bond of aliphatic amides, 2 equiv of *m*-CPBA was directly added in the same tube to yield α-formyl acid derivatives.[13] As shown in Scheme 7, a range of α-formyl acid derivatives bearing alkoxy, phenyl, and heteroaryl groups were obtained in acceptable yields.

Scheme 7. Synthesis of α-Formyl Acid Derivatives[a,b]



[a]Reaction conditions: (1) **1** (0.25 mmol), **2a** (2.0 equiv), $Ni(OTf)_2$ (20 mol %), PhCN (4.0 equiv), and *t*-BuOLi (2.0 equiv) were stirred in toluene (0.5 mL) at 120 °C for 6−12 h under an atmosphere of air; (2) 0.5 mmol of *m*-CPBA and 10 mL of dichloromethane were added in the same tube. The system was stirred for 10 min at room temperature. [b]Isolated yields. [c]1.5 mmol scale. Q = 8-quinolinyl.

The *N*-alkoxyamine product **3ma** could be converted into the corresponding carboxylic esters in the presence of $BF_3{\cdot}Et_2O$ (Scheme S1). In addition, a β-hydroxyl amide **6-e** could be easily obtained by reduction of the α-formyl acid derivative **4-e** by use of $NaBH_4$ (Scheme S2).

In summary, we have developed the nickel-catalyzed aminoxylation of an unactivated C(sp^3)−H bond with a stable nitroxyl radical, affording various *N*-alkoxyamine derivatives. This protocol can further provide a feasible synthetic approach to α-formyl acid derivatives in one pot. This protocol also offers direct evidence for an oxidative addition of a cyclometallic intermediate with a free radical, which is helpful to the study of the reaction mechanism in transition-metal-catalyzed functionalization of inert C(sp^3)−H bonds.[8] Further studies related to a radical-involved process are ongoing in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00479.

Detailed experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of final products (PDF)

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Notes

The authors declare no competing financial interest.

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