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Decarboxylative C(sp^3)−N Cross-Coupling of Diacyl Peroxides with Nitrogen Nucleophiles

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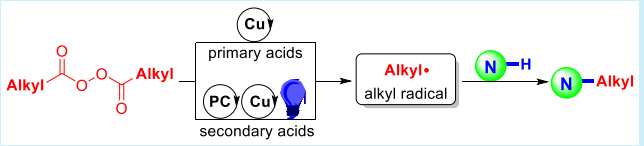
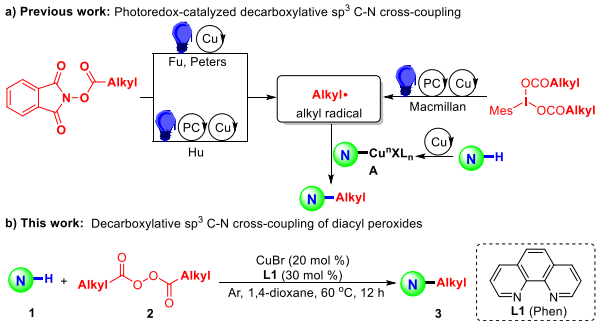
ABSTRACT: We have disclosed a new radical-mediated decarboxylative C(sp^3)−N cross-coupling of diacyl peroxides with nitrogen nucleophiles. The primary and secondary alkyl radicals derived from corresponding diacyl peroxides were generated by copper catalysis or by merging copper catalysis and photoredox catalysis, respectively. Various *N*-alkyl nitrogen nucleophiles, including indazoles, triazoles, indoles, purine, carbazole, anilines, and sulfonamide, were provided with a broad substrate scope and good functional group tolerance.



Over the past decades, the construction of the C−N bond has always been the field of focus in organic synthesis owing to its important role in pharmaceuticals, natural products, and agrochemicals.[1] The formation of the C(sp^3)−N bond has attracted much attention.[2,6−9] Thus many strategies have been proposed toward the formation of the C(sp^3)−N bond, including coupling a nitrogen nucleophile to an alkyl electrophile (e.g., aliphatic halides, alcohols),[3a,e] reductive amination,[3f,g] the hydroamination of alkene,[3h,i] and the carboamination of alkene.[3j,l] Whereas great achievements have been made, such available approaches are still limited by strong bases, a narrow scope of substrates, a great amount of waste.

Aliphatic carboxylic acids and their derivatives have low toxicity and are inexpensive, stable, and readily available in addition to being widely found in natural products and pharmaceuticals,[4] allowing the radical decarboxylative alkylation reaction to be a powerful transformation to rapidly construct C(sp^3)−X (X = C, N, O, S, etc.) bonds.[5−10] In 2017, Fu, Peters, and coworkers[6] developed a decarboxylative C(sp^3)−N coupling of alkyl *N*-hydroxyphthalimide (NHPI) ester to afford alkyl phthalimides by using photoexcitation of a copper complex to achieve the single-electron reduction (Scheme 1a). In 2018, Macmillan[7] and Hu[8] independently reported dual copper-catalyzed and photoredox-catalyzed decarboxylative C(sp^3)−N coupling by using alkyl *N*-hydroxyphthalimide (NHP) ester and iodomesitylene dicarboxylates as an alkyl radical precursor, respectively (Scheme 1a). On the basis of these results, masked alkyl carboxylic acids, such as alkyl NHPI esters[9] and iodomesitylene dicarboxylates,[7,10] undergo single-electron reduction in the presence of photoredox catalysis or transition-metal catalysis to form an alkyl radical intermediate that easily reacts with the L_nCu^nX−nitrogen nucleophile complex **A** (Scheme 1a). Despite the great achievements in decarboxylative sp^3 C−N coupling, it is still highly desired to realize the construction of

Scheme 1. Decarboxylative C(sp^3)−N Cross-Coupling of Redox-Active Esters



sp^3 C−N bonds with a new alkylating reagent. Diacyl peroxides are a class of redox-active esters that are easily prepared from aliphatic carboxylic acids and are readily decarboxylated to provide alkyl radicals under cheap transition-metal catalysis and heating.[11] Inspired by these pioneering works, we hypothesized that if the oxidizing diacyl peroxides could generate alkyl radical species in the presence of photoredox catalysis or copper catalysis, then the alkyl radical species could further react with L_nCu^nX−nitrogen nucleophile complex **A** to build C(sp^3)−N bonds (Scheme 1a). Here we have developed a new decarboxylative C(sp^3)−N cross-coupling of diacyl peroxides with nitrogen nucleophiles (Scheme 1b) to provide various alkylated nitrogen products, including indazoles,

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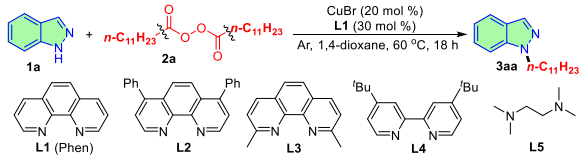
triazoles, indoles, purine, carbazole, anilines, sulfonamide, and other nitrogen nucleophiles.

We initially choose 1*H*-indazole **1a** and lauroyl peroxide (LPO) **2a** as the template reaction to investigate the decarboxylative C(sp^3)−N coupling. The desired product **3aa** was offered in 96% yield in the presence of CuBr (20 mol %) and Phen (30 mol %) in 1,4-dioxane under thermal conditions (Table 1, entry 1). Both copper catalysis and

Table 1. Screening of Optimal Reaction Conditions[a]



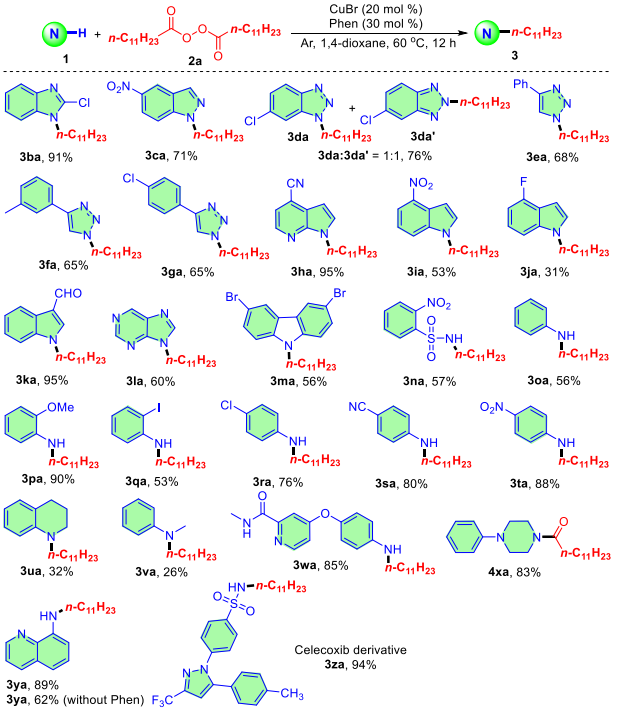
entry	variation from the standard conditions	yield (%)[b]
1	none	96
2	without CuBr	trace
3	without Phen	trace
4	$Cu(OTf)_2$ instead of CuBr	86
5	$Cu(MeCN)_4PF_6$ instead of CuBr	88
6	CuTc instead of CuBr	93
7	CuI instead of CuBr	89
8	L2 instead of L1	90
9	L3 instead of L1	50
10	L4 instead of L1	42
11	L5 instead of L1	32
12	PPh_3 instead of L1	21
13	MeOH instead of 1,4-dioxane	85
14	MeCN instead of 1,4-dioxane	79
15	PhMe instead of 1,4-dioxane	64
16	DMSO instead of 1,4-dioxane	37
17	at room temperature	75
18	at 80 °C	91
19[c]	at room temperature	95
20[d]	none	90

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv), CuBr (20 mol %), Phen (30 mol %), 1,4-dioxane (2 mL), and argon at 60 °C for 12 h. [b]Isolated yield. [c]$[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol %) 18 W blue LED for24 h [d]**1a** (1 mmol) for 24 h.

nitrogen ligands are indispensable for the decarboxylative cross-coupling reaction (entries 2 and 3). Other copper catalysts, such as $Cu(OTf)_2$, $Cu(MeCN)_4PF_6$, CuTc, and $Cu(acac)_2$, can effectively promote the decarboxylative coupling reaction to obtain the target product **3aa** in slightly lower yields (entry 1 vs entries 4−7). A series of nitrogen ligands were tested, and other ligands were not as good as 1,10-phenanthroline (**L1**) (entries 8−12). The optimization of solvents, including MeOH, MeCN, toluene, and DMSO, indicates that 1,4-dioxane is the best choice (entries 13−16). The optimization of the reaction temperature indicates that 60 °C is the best choice (entries 17 and 18). Moreover, we found that the photoredox catalysis can promote the reaction under an 18 W blue LED at room temperature, offering the product **3aa** in 95% yield (entry 19). Gratifyingly, when the reaction scale is increased to 1 mmol of 1*H*-indazole **1a**, product **3aa** can still be obtained in 90% yield (entry 20).

With the optimal reaction conditions in hand, we then investigated the scope of nitrogen nucleophiles (Scheme 2). Overall, a wide range of nitrogen nucleophiles, including nitrogen heterocycles, carbazole, anilines, and sulfonamide,

Scheme 2. Variations of the Nitrogen Nucleophiles (1)[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv), CuBr (20 mol %), Phen (30 mol %), 1,4-dioxane (2 mL), and argon at 60 °C for 12 h.

could smoothly undergo the copper-catalyzed decarboxylative coupling of lauroyl peroxide to give the alkylated products **3ba**−**wa** in moderate to good yields. Benzimidazole **1b** and indazole **1c** were all tolerated, furnishing the alkylated products in 91 and 71% yields, respectively. Benzotriazole **1d** is a suitable substrate, providing the isomer products **3da** and **3da′** in a 1:1 ratio. Heterocycles bearing three nitrogen atoms, such as triazoles **1e**−**g**, were all converted to *N*-alkyl products **3ea**−**ga** in medium yields. Indoles with electron-withdrawing group were suitable substrates, offering the corresponding products **3ha**−**ka**. Purine and carbazole were compatible with the reaction system. Benzenesulfonamide and aniline were successfully reacted with LPO to afford the products **3na** and **3oa** in 57 and 56% yields, respectively. Primary anilines bearing an OMe, an iodo, a chloro, a nitro, or a cyano on the aromatic ring were suitable nitrogen nucleophiles to deliver the *N*-alkyl anilines **3pa**−**ta** in moderate and good yields, providing the possibility of further modification. However, secondary anilines **1u,v** were coupled to obtain the tertiary amines **3ua,va** in low yields. The nitrogen nucleophile **1x** with multiple sites achieves the regioselective alkylation product **3wa**. Unfortunately, the alkyl amine **1x** tends to give the amidation product **4xa** in 83% yield. Performing quinoline-8-amine **1y** gave the corresponding target product **3ya** in 89 and 62% yields under standard conditions and without ligands, respectively. Strikingly, the decarboxylation protocol was applicable to the modification of Celecoxib **1z**, providing the alkylated product **3za** in 94% yield.

We next examined the applicability of decarboxylative C(sp^3)−N cross-coupling by assessing the scope of diacyl peroxides. As shown in Scheme 3, a variety of diacyl peroxides derived from alkyl carboxylic acids were tolerated, providing the *N*-alkyl products in moderate to good yields. Primary acids

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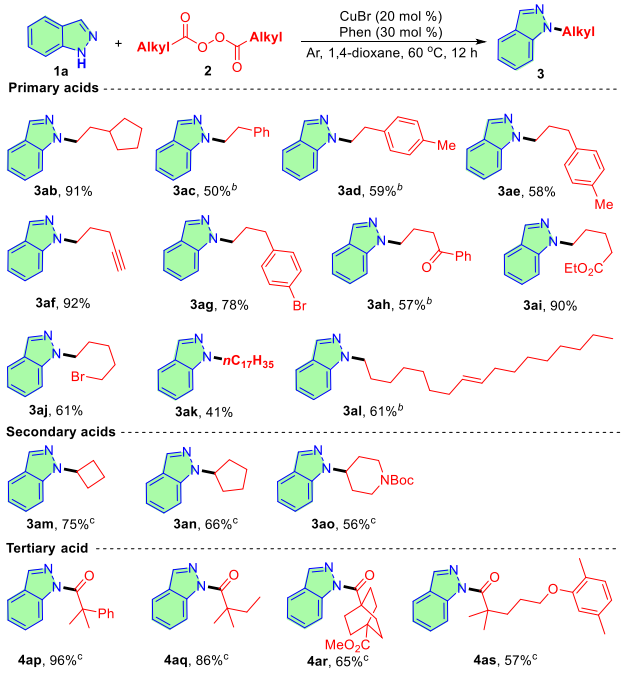
Scheme 3. Variations of Diacyl Peroxides (2)[a]



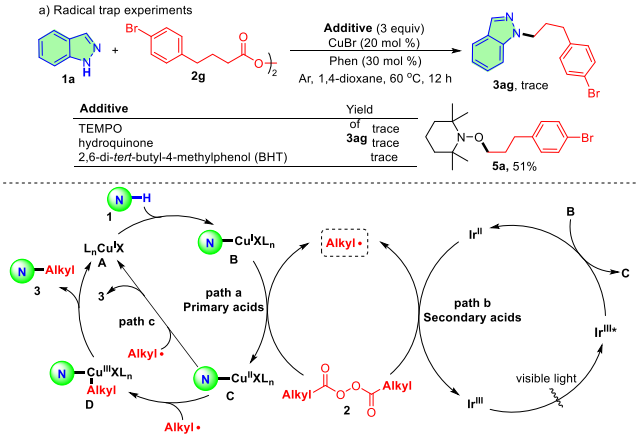
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv), CuBr (20 mol %), Phen (30 mol %), 1,4-dioxane (2 mL), and argon at 60 °C for 12 h. [b]At 100 °C. [c][Ir(dtbbpy)(ppy)$_2$]PF$_6$ (1 mol %) 18 W blue LED at 100 °C for 24 h.

with various alkyl-substituted groups could be smoothly converted to the desired products **3ab**−**ae** in 50−91% yields. Primary acids containing a series of functional groups, such as alkynyl **2f**, bromo **2g**, carbonyl **2h**, and ester **2i**, were well tolerated, offering the corresponding products **3af**−**ai** in 61−92% yields. The complex natural products, including stearic acid **2k** and oleic acid **2l**, were compatible with the reaction to supply the products **3ak**,**al** in moderate yields. The secondary alkyl groups, such as cyclobutyl, cyclopentyl, and piperidin-4-yl, were also investigated under a copper catalyst to afford the amidation products, whereas the combination of a copper and photoredox catalyst resulted in decarboxylation products **3am**−**3ao** in 56−75% yields. Unfortunately, tertiary acids **2p**−**s** failed to achieve the decarboxylative coupling of diacyl peroxides under copper catalysis or dual copper and photoredox catalysis. This may be due to the bulky sterically hindered tertiary alkyl group leading to the amidation products **4ap**−**as** in 57−96% yields.[8]

To gain mechanistic insights into the decarboxylative cross-coupling, we carried out some radical-trapping experiments that add 3 equiv of free-radical scavengers, such as TEMPO, hydroquinone, and butylated hydroxytoluene (BHT) in the presence of 1*H*-indazole **1a** and diacyl peroxide **2g** under standard conditions (Scheme 4). The decarboxylative C(sp^3)−N cross-coupling was shut down, and the TEMPO-trapping product **5a** was afforded in 51% yield, indicating that the alkyl radical was generated under the standard reaction conditions. Moreover, when quinoline-8-amine was used as the nitrogen nucleophile, the product **3ya** was supplied in the absence of 1,10-phenanthroline, showing that the copper(I)−amido species had formed.

On the basis of the experimental results and previous literature reports,[6−10,12] a plausible mechanism is proposed in

Scheme 4. Control Experiments and Possible Mechanism



Scheme 4. First, copper(I)−amido species **B** readily forms through the coordination of copper(I) catalyst **A** with nitrogen nucleophile **1**. The primary alkyl peroxides **2** easily oxidizes the intermediate **B** to produce an alkyl radical and copper(II)−amido species **C** by releasing CO_2 (path a). On the contrary, the excited photocatalyst Ir^{III}* could rapidly oxidize copper(I)−amido species **B** to copper(II)−amido species **C** and generate the Ir^{II} intermediate, which could reduce secondary alkyl peroxides by a single-electron transfer (SET), affording an alkyl radical and regenerating Ir^{III} catalysis. Then, the alkyl radical intermediate reacts with copper(II)−amido species **C** to afford the copper(III)−alkyl−amido complex **D**, which would undergo reductive elimination to provide *N*-alkyl products **3** and to regenerate **A**. In addition, copper(II)−amido species **C** may undergo a direct group transfer in the presence of the alkyl radical (path c) to afford *N*-alkyl products **3** and to regenerate **A**.[12i,j]

In summary, a new radical-mediated decarboxylative C(sp^3)−N cross-coupling of diacyl peroxides has been developed. Copper catalysis or the combination of copper catalysis and photocatalysis is the key to the generation of primary and secondary alkyl radicals, respectively. This protocol has shown mild conditions, good functional group tolerance, and a broad substrate scope, which provides a new way to approach a variety of *N*-alkyl products. The further application of this strategy is being explored in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04203.

Descriptions of experimental procedures for compounds and analytical characterization (PDF)

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Notes

The authors declare no competing financial interest.

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