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Directing Group in Decarboxylative Cross-Coupling: Copper-Catalyzed Site-Selective C–N Bond Formation from Nonactivated Aliphatic Carboxylic Acids

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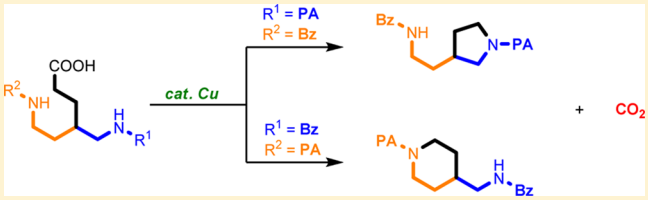
Supporting Information

ABSTRACT: Copper-catalyzed directed decarboxylative amination of nonactivated aliphatic carboxylic acids is described. This intramolecular C–N bond formation reaction provides efficient access to the synthesis of pyrrolidine and piperidine derivatives as well as the modification of complex natural products. Moreover, this reaction presents excellent site-selectivity in the C–N bond formation step through the use of directing group. Our work can be considered as a big step toward controllable radical decarboxylative carbon–heteroatom cross-coupling.

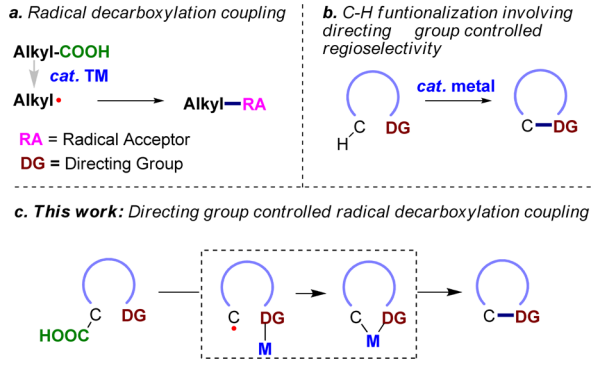


1. INTRODUCTION

The use of carboxylic acids, especially for nonactivated aliphatic carboxylic acids, as "cross-coupling" partners is gaining increasing attention recent years.[1] There are various factors that contribute to making nonactivated aliphatic carboxylic acids potentially useful for utilization in organic synthesis and industrial production: abundant resources (e.g., natural products and biomass resources) and their natural properties (e.g., air- and moisture-stable).[2−4] On the other hand, aliphatic carbon–heteroatom bonds are ubiquitous in biologically active molecules, such as natural products and drugs.[5] Therefore, an efficient approach for the construction of aliphatic carbon–heteroatom bonds via a transition-metal-catalyzed decarboxylative reaction would be useful and user-friendly.[3]

The earliest decarboxylative coupling reaction of aliphatic carboxylic acids to construct carbon–heteroatom bonds dates back to the Hunsdiecker reaction.[6] The disadvantage of this reaction, however, is the required use of stoichiometric quantities of silver salts, which then makes the reaction expensive and environmentally unfriendly. In 2012, Li and co-workers reported the silver-catalyzed decarboxylative radical chlorination reaction as the pioneer work of the catalytic Hunsdiecker reaction.[3a] Shortly thereafter, they successfully constructed aliphatic C–F[3b] and C–N_3[3f] bonds with a slightly modified catalytic system. Shen and co-workers have also reported the silver-catalyzed decarboxylative trifluoromethylthiolation reaction to construct aliphatic C–S bonds.[3c] In the above reactions, aliphatic carboxylic acids were converted to radical species, promoted by the transition metal catalysts. However, in the subsequent coupling processes, the generated alkyl radicals did not coordinate to the metal catalysts (Scheme 1a).[3] Therefore, the chemoselectivity of these reactions could not be controlled by transition metal catalysts. Specifically, when there is more than one possible coupling site, difficulties arise regarding the selectivity of the coupling reaction.

Scheme 1. Transition Metals in Decarboxylative Carbon–Heteroatom Cross-Coupling Reactions



To achieve controllable site-selectivity for decarboxylative carbon–heteroatom coupling reactions, we introduced the "directing" concept to facilitate the transition metal catalyst participating in the subsequent coupling process.[7] We expected that by using a directing group, which has strong coordinating ability for catalysts, instead of simple protecting groups, we might achieve our goal (Scheme 1c). The directing group would enhance the coupling process to take place on a certain site through the proximity of the catalyst center with the coupling site. It should be noted that directing groups have been widely used in the field of transition-metal-catalyzed C–H functionalization to control the site-selectivity (Scheme 1b).[7] A closely related example is the picolinamide (PA)-directed

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intramolecular C(sp^3)−H amination reaction, recently developed by Daugulis[8] and Chen.[9] They reported on the excellent control of site-selectivity, which now provides access to N-containing heterocyclic compounds.[10]

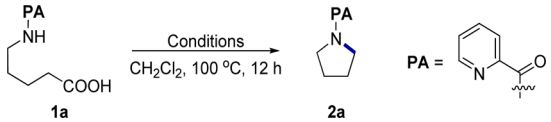
Herein, we report on the copper-catalyzed intramolecular decarboxylative amination reaction of nonactivated aliphatic carboxylic acids. This reaction presents the first example of a directed decarboxylative C−N bond formation reaction. In this study, the concept of using a directing group in C−H functionalization reaction was successfully introduced to decarboxylative carbon−heteroatom cross-coupling reaction. This new combination of two important concepts realized complete site-selectivity in the presence of more than one potential radical acceptor for the decarboxylative carbon−heteroatom cross-coupling reaction. Our work demonstrated that a copper catalyst played an important role in this decarboxylative C−N coupling reaction. This is a big step toward achieving controllable radical decarboxylative carbon−heteroatom cross-coupling with a transition metal catalyst. Furthermore, most remote amino carboxylic acids are prepared from cyclic ketones via the classic Beckmann rearrangement reaction,[11] followed by hydrolytic ring opening. Our reaction would not only be beneficial for the transformation of remote amino carboxylic acids but also extend the application of classic Beckmann rearrangement reaction.

2. RESULTS AND DISCUSSION

At the commencement of our work, 5-aminovaleric acid was selected for our model reaction. (It is commercially available and easily derived from cyclopentanone.) The PA group was used as the directing group. The desired product **2a** was obtained in 43% GC yield when using $Cu(OTf)_2$ and pyridine as the catalyst system, and PhIO as oxidant (entry 2, Table 1). This finding encouraged us to examine pyridine family additives (entries 3−5, Table 1). 4-Dimethylaminopyridine (DMAP) performed best and the yield increased significantly to 64% (entry 5, Table 1). Furthermore, we screened several oxidants (entries 6−7, Table 1) and made a critical finding that PhIO was suitable for this reaction and it was better to add it in two batches (entry 8, Table 1).[12] Under optimal conditions, the GC yield was 73%. We also noticed that the reaction was completed within 4 h (entry 9, Table 1). With control experiments, we found that the reaction did not take place when $Cu(OTf)_2$ was replaced by Pd, Ni, or Ag salts (entries 10−12, Table 1). Finally, we found that when the protecting group PA was replaced by Bz, the desired cyclization reaction was almost suppressed (entry 13, Table 1).

With the optimal reaction conditions in hand, we examined the substrate scope of this decarboxylative C−N coupling reaction (Table 2). This new catalysis strategy was efficient for construction of 5- and 6-membered heterocycles (e.g., **2a** and **2b**); however, it did not enable construction of 4- or 7-membered heterocycles. We also noted that a substrate containing aryl bromide (**2c**) was well tolerated in this reaction. This feature provided additional opportunities for further functionalization. Substrates with sterically bulky groups at the α position of the amino group converted to desired products smoothly (**2d**−**2g**). The absolute configuration at the α position of amino group in compound **2h** was retained during the transformation. Our protocol therefore provides a new method for the synthesis of chiral pyrrolidine and piperidine derivatives, which are common chemical skeletons in drugs and natural products (e.g., Relpax, an antimigraine medication). It should be noted that the preparation of six-membered ring products (**2i**−**2l**), which could be easily synthesized via this

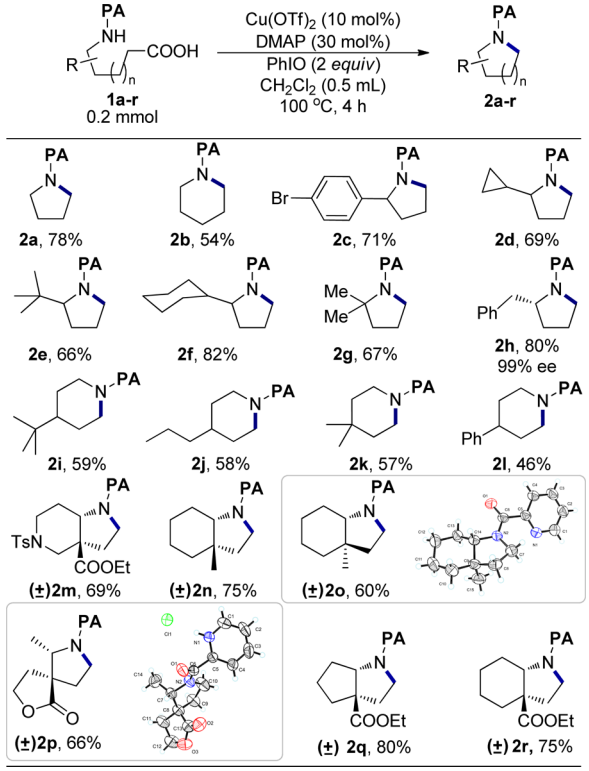
Table 1. Optimization of the Reaction Conditions for 2a



entry[a]	catalyst (10 mol %)	additive (30 mol %)	oxidant (2.0 equiv)	GC yield (%)
1	$Cu(OTf)_2$	-	PhIO	trace
2	$Cu(OTf)_2$	Pyridine	PhIO	43
3	$Cu(OTf)_2$	4-CF_3-Pyridine	PhIO	8
4	$Cu(OTf)_2$	2,4,6-Collidine	PhIO	35
5	$Cu(OTf)_2$	DMAP	PhIO	64
6	$Cu(OTf)_2$	DMAP	$K_2S_2O_8$	0
7	$Cu(OTf)_2$	DMAP	H_5IO_6	0
8[b]	$Cu(OTf)_2$	DMAP	PhIO	73
9[b,c]	$Cu(OTf)_2$	DMAP	PhIO	75
10	$Pd(OAc)_2$	DMAP	PhIO	0
11	$Ni(OTf)_2$	DMAP	PhIO	0
12	$AgNO_3$	DMAP	PhIO	0
13[d]	$Cu(OTf)_2$	DMAP	PhIO	trace

[a]Reaction conditions: **1a** (0.2 mmol), CH_2Cl_2 (0.5 mL), 100 °C, 12 h. [b]PhIO was added in two batches. [c]The reaction was carried out for 4 h. [d]The protecting group **PA** was replaced by **Bz**.

Table 2. Scope of Copper-Catalyzed Intramolecular Decarboxylative C−N Coupling of Primary Aliphatic Carboxylic Acids[a,b]



[a]Reaction conditions: **1** (0.2 mmol), $Cu(OTf)_2$ (10 mol %), DMAP (30 mol %), PhIO (0.2 mmol ×2), CH_2Cl_2 (0.5 mL), 100 °C, 4 h. [b]Isolated yield.

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newly developed reaction, was rather difficult to achieve by C−H activation reaction[8,9] or the classic Hofmann−Löffler reaction.[13] Similarly, fused-ring (**2m**−**2r**) and spiro-ring (**2p**) structures were also easily prepared in the presence of synthetically important functional groups, such as sulfonamide (**2m**) and lactone (**2p**) groups.

In addition to primary aliphatic carboxylic acids, secondary aliphatic carboxylic acids can also undergo this transformation smoothly with moderate yields (Table 3; **2s**−**2v**). However, the diastereocontrol of this reaction was not good enough when using secondary aliphatic carboxylic acid **1v**, which has a diastereoisomeric ratio of 1:1, but the product **2v** was formed in 42% yield and only with a *trans*/*cis* ratio of 2.5:1. Besides, the attempt to construct six-membered ring product **2w** by using secondary aliphatic carboxylic acid **1w** was unsuccessful, we suspect that this is probably as a result of the steric hindrance and instability of seven-membered ring intermediate. For tertiary aliphatic carboxylic acid, the attempt to get even for the five-membered ring product **2x** was failed.

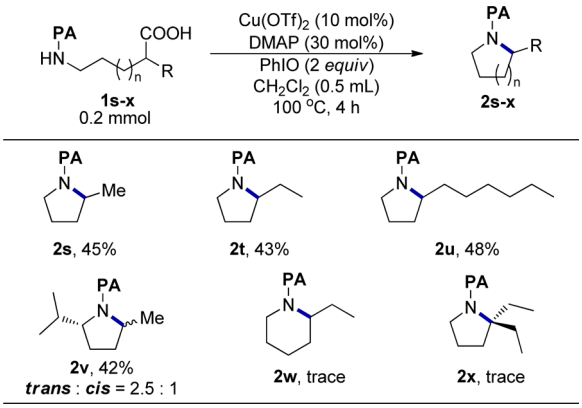
We then utilized this newly developed decarboxylative C−N coupling reaction for the modification of chemical skeletons in biologically interesting compounds[14,15] (Scheme 2). Estrone was easily transformed to the corresponding carboxylic acid **1y** through a Beckmann rearrangement reaction.[11,15a] It was then converted to the desired product **2y** with an isolated yield of 73% (Scheme 2a). Overall, we accomplished the conversion of cyclic ketones to cyclic amines, which, to date, was extremely difficult to achieve.[16]

Another interesting, and common, transformation applicable to natural products was that six-membered cyclic α,β-enones could be oxidized to δ-carbonyl carboxylic acids in the role of sodium periodate[15b] and, subsequently, the carbonyl group converted to an amino group via a reductive amination reaction. Following the above methods, the carboxylic acid **1z** was obtained from testosterone benzoate in 52% overall yield (for more details, see Supporting Information). This amino acid was converted to the desired cyclic amine **2z** in 64% yield (Scheme 2b). Furthermore, single-crystal X-ray diffraction data of **2z** confirmed that the chemical skeleton of testosterone was fully maintained during our modification process.

C-alkyl glycosides are important bioactive candidates. It would therefore be interesting to use our new reaction to modify C-alkyl glycosides to form more complex structures.[15c,d] Under our optimal reaction conditions, C-alkyl glycoside **1a′** was converted to the cyclization product **2a′** in 60% yield (Scheme 3a). Furthermore, the substrate **1b′**, which was derived from *R*-glyceraldehyde-acetonide, can be transformed into **2b′** in 52% yield with the protecting group acetonide well tolerated, which is a frequently used protecting group in carbohydrate chemistry (Scheme 3b). These transformations demonstrated the high degree of functional group compatibility of our newly developed reaction. We therefore expect that this new C−N coupling reaction will find many applications in carbohydrate chemistry.

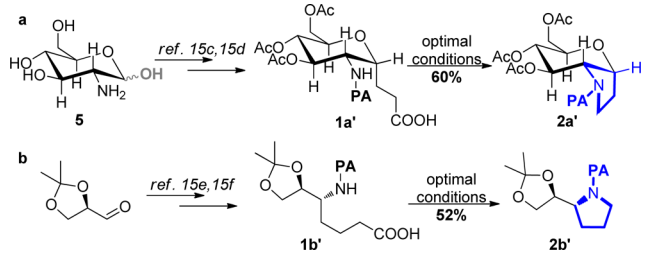
To obtain insight into the mechanism of this decarboxylative C−N coupling reaction, several control experiments were carried out. The model reaction was completely shut down when $Cu(OTf)_2$ was absent or PhIO was not added (1 equiv $Cu(OTf)_2$ was used instead of PhIO as oxidant). Meanwhile, starting materials were fully recovered (eq 1), indicating that the copper-catalyst might be necessary for the decarboxylation step, although the specific contribution was not clear.

Table 3. Scope of Copper-Catalyzed Intramolecular Decarboxylative C−N Coupling of Secondary and Tertiary Aliphatic Carboxylic Acids[a,b]

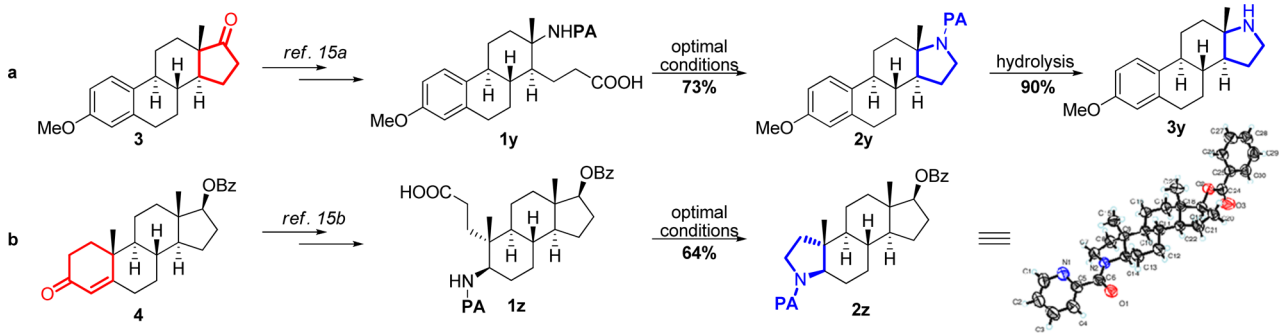


[a]Reaction conditions: **1** (0.2 mmol), $Cu(OTf)_2$ (10 mol %), DMAP (30 mol %), PhIO (0.2 mmol ×2), CH_2Cl_2 (0.5 mL), 100 °C, 4 h. [b]Isolated yield.

Scheme 3. Modification of Carbohydrate Derivatives



Scheme 2. Modification of Steroidal Compounds



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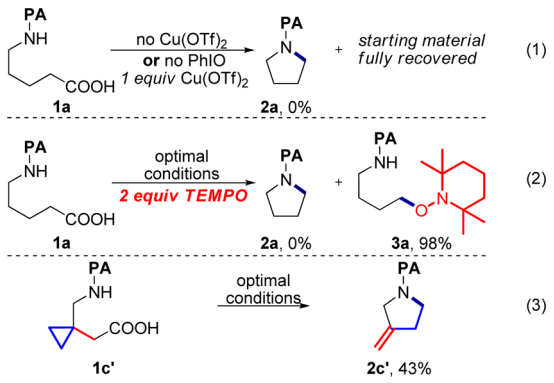


A radical trapping experiment using TEMPO (2,2,6,6-tetramethylpiperidinooxy) as radical scavenger was also carried out (eq 2). The present reaction was completely shut down, with the quantitative formation of **3a**. Finally, we examined the decarboxylative C−N coupling reaction of a cyclopropyl-derived carboxylic acid **1c′**. In this reaction, the ring-opening rearrangement product **2c′** was obtained as a single product in 43% isolated yield (eq 3).

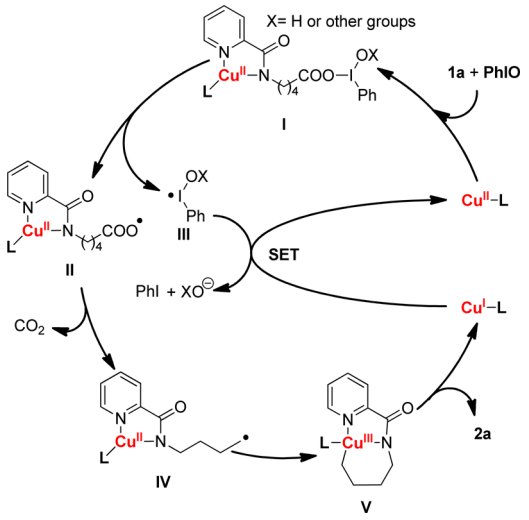
With the above mechanism experiments in hand as well as the guidance of important literature, we tried to carry out the proposed mechanism. A closely related work was reported by Minakata's group as a hypervalent iodine(III)-mediated oxidative decarboxylation of β,γ-unsaturated carboxylic acid to construct C−N bonds, which is of significantly broad substrate scopem and lack of metal catalyst made this reaction synthetically useful.[3i] The mechanistic study suggested that an ionic oxidative decarboxylation process was involved, in which the formation of allyl-λ^3-iodane intermediate was crucial. However, the formation of allyl-λ^3-iodane intermediate was not a suitable pathway for explaining our reaction which uses nonactivated alkyl carboxylic acids.

Another decarboxylation mechanism involves a SET (single electron transfer) process of an ion-pair which was produced via heterolytic cleavage of one I−O bond of (diacyloxyiodo)-benzene.[2b,c] This process must be triggered by low-valence copper species (e.g., Cu^{I}) other than $Cu^{II}(OTf)_2$ at the initial stage of the reaction.[17] Moreover, two copper species were required to work in parallel to maintain the catalysis proceeding, which could not be supported by the research data on the relationship between copper concentration and yield,[18] making this mechanism inconsequential.

According to the recent work reported by Maruoka's group,[19] a more reasonable mechanism was carried out and shown in Scheme 4. In the presence of Cu^{II}-**L**, **1a** reacts with PhIO to form hypervalent iodine(III) intermediate **I**,[20,21] which undergoes a homolytic cleavage of one I−O bond to produce two radical intermediates **II** and **III** at 100 °C.[19] The intermediate **II** goes through a decarboxylation process to generate an alkyl radical intermediate **IV** and releases CO_2. Then, by oxidative addition of the alkyl radical to the Cu^{II} which is chelated by the directing group, intermediate **V** is generated.[22] Followed by reductive elimination, the desired product **2a** is produced and the intermediate Cu^{I}-**L** is released simultaneously. Finally, the whole catalytic cycle is accomplished with the intermediate Cu^{I}-**L** oxidized to Cu^{II}-**L** by intermediate **III** or decomposition products thereof.[23]

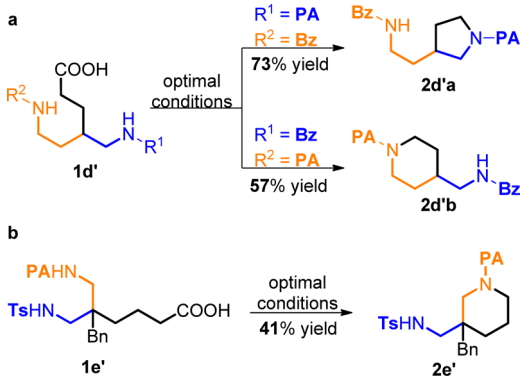
As an important component of this study, efforts were devoted to the control of selectivity in the coupling process by using a directing group. Comparative experiments were carried

Scheme 4. Proposed Mechanistic Cycle



out to verify our ideas (Scheme 5a). For each of the substrates, a single product was observed (**2d′a** and **2d′b**); hence, the

Scheme 5. Site-Selectivity Controlled by a Directing Group (PA)



coupling process took place on the PA-protected amino group selectively. The selectivity of this reaction was determined by the N-protecting groups (Bz or PA) on the substrates. The size of newly forming rings would not affect the site-selectivity. As mentioned above, the alkyl carboxylic acid was converted to an alkyl radical species and trapped by radical acceptors. In terms of the ability to capture free radicals, there is no essential difference between BzNH and PANH as they have similar arylamide structures. Furthermore, we tested the comparative experiment between TsNH and PANH (Scheme 5b). Similarly, we only got the product cyclized at the PANH side. We believe that chelation of the PA-protected amino group promotes the metal to participate further in the coupling process after the decarboxylation step. Results of these comparative experiments indicated that control of the reaction selectivity is due to the "directing" concept.

3. CONCLUSION

To summarize, we report the first Cu-catalyzed intramolecular decarboxylative C−N coupling of nonactivated aliphatic carboxylic acids. The concept of a directing group is introduced to decarboxylative carbon−heteroatom cross-coupling reaction for the control of site-selectivity. Remote amino carboxylic

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acids could be easily obtained from the transformation of natural products. Therefore, this newly developed reaction provides an efficient approach for the late-stage modification of some core structures. Of particular note is that, in the presence of a directing group, a copper catalyst plays an important role in the C−N bond formation step. It is the basis of the controllable site-selectivity of this reaction. Our work may also be considered as a big step toward controllable radical decarboxylative carbon−heteroatom cross-coupling.

4. EXPERIMENTAL SECTION

General Procedure for Copper-Catalyzed Intramolecular Decarboxylative C−N Coupling of Aliphatic Carboxylic Acids. To a 10 mL thick-walled pressure tube was sequentially added $Cu(OTf)_2$ (7.2 mg, 0.02 mmol), DMAP (7.3 mg, 0.06 mmol), **1** (0.2 mmol), PhIO (44 mg, 0.2 mmol), and 0.5 mL of CH_2Cl_2. The tube was sealed with a Teflon lined cap and the reaction mixture was stirred at 100 °C for 1 h. After cooling to room temperature, another portion of PhIO (44 mg, 0.2 mmol) was added and the reaction mixture was stirred at 100 °C for another 3 h. After complete consumption of **1** (the reaction progress was monitored by TLC; for some substrates with slower reaction rate, it is necessary to prolong the reaction time), the product **2** could be obtained by silica gel column chromatography.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05788.

Experimental details and compound characterizations (PDF)
Crystallographic data (CIF)
Crystallographic data (CIF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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