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Direct Alkoxycarbonylation of Heteroarenes via Cu-Mediated Trichloromethylation and In Situ Alcoholysis

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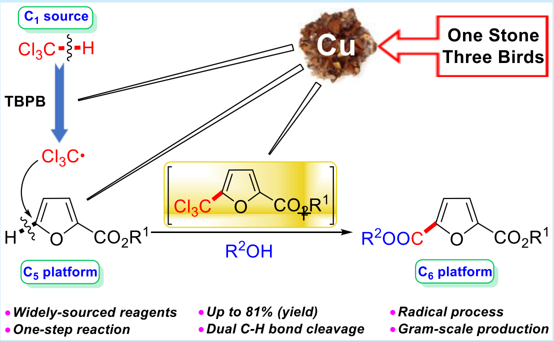
ABSTRACT: We report an efficient approach for direct alkoxycarbonylation of furans as well as other heteroarenes via a one-step copper-mediated reaction of three components (i.e., heteroarene, alcohol, and $CHCl_3$). The copper additive was confirmed to simultaneously promote the reaction in three pathways: oxidant cracking, single electron transfer, and alcoholysis. By means of this protocol, various functionalized furancarboxylates and other heteroarenecarboxylates were facilely obtained in moderate to good yields.



Heteroaromatic carboxylic esters are ubiquitous core structures in numerous functional molecules.[1] Over the last few decades, alkoxycarbonylation of heteroarenes has achieved a huge advance through the rapid development of organometallic chemistry and has become an alternative way to establish carboxylic esters compared with traditional esterification of carboxylic acid derivatives.[2] Thereinto, the cleavage of heteroaromatic C−X and C−H bonds are two main pathways before the final formation of the C−C bond.[3] However, for both of these cleavages, prefunctionalized substrates or noble metal catalysts may inevitably be involved, despite exposure of a briefer step for dual C−H bond cleavage in certain reports.[4] Meanwhile, compared with arenes[5] and N-heteroarenes,[6] furan is less explored in alkoxycarbonylation because it possesses a vulnerable structure with low aromaticity as well as an electron-rich nature and therefore is easily destroyed under oxidative and other dramatic conditions or leads to side reactions.[7] Hence, the establishment of a cost-effective method based on dual C−H bond cleavage to direct alkoxycarbonylation of heteroarenes, especially electron-rich ones (e.g., furans), is still a great challenge but with notable value.

Furan-2,5-dicarboxylic acid (FDCA), one of the most representative precursors with a furan-based scaffold, is extensively covered in production of degradable polymers and versatile applicable materials such as aromatic polyesters,[8] polyamides,[9] and plasticizers.[10] As an example of a burgeoning FDCA-derived polymer, poly(ethylene 2,5-furandicarboxylate) (PEF) is broadly acknowledged as a remarkable alternative to traditional petroleum-derived poly(ethylene terephthalate) (PET),[11] which largely contributes to the reduction of social dependence on fossil resources.[12] Currently, abundant approaches have been developed with respect to the synthesis of FDCA and its ester derivatives. Using starting materials from a C_6 platform (e.g., 5-(hydroxymethyl)furfural (HMF) in Scheme 1a, method A) is a traditional and principal pathway in the present circumstance.[13,14] However, it may compete with human foodstuffs since the C_6 platform is majorly produced by glucose and fructose. In response to this, the exploration of the renewable and nonedible C_5 platform from agricultural residues achieved a breakthrough. Among the rest, Pd-catalyzed carbonyl insertion of 5-bromofuroic acid to construct FDCA and its derivatives using CO has been reported by Yin (Scheme 1b, method B).[15] In addition to following the strategy of using CO, FDCA can be obtained via green conversion from CO_2 and furan-2-carboxylate developed by Kanan[16] and Fu[17] (Scheme 1b, method C). Although the above-reported approaches opened new avenues for employing C_5 platform, they are the only cases of the C_5 platform to date, and there is a significant vacancy in terms of other readily accessible carbonyl sources or reaction patterns. Therefore, the development of a scalable and alternative instrument for constructing difuroates (FDCA esters, as precursors that are one-step closer to PEF via interesterification) on the basis of a C_5 platform is highly desirable as an important supplement for synthetic chemistry.

With regard to oxidative radical coupling of alkenes, copper salts are frequently utilized as either catalysts or stoichiometric additives.[18] On the other hand, $CHCl_3$ as a common and

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Scheme 1. Synthesis of 2,5-Furandicarboxylates and FDCA Based on C_6 and C_5 Platforms

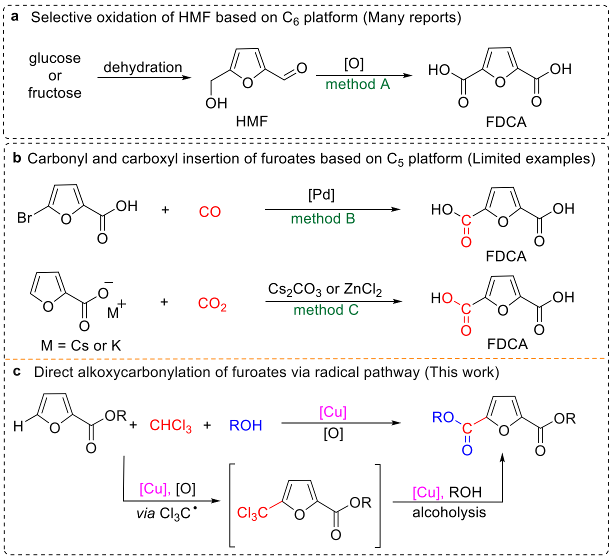
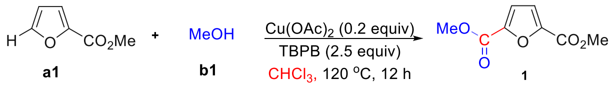


Table 1. Optimization of the Reaction Conditions



entry	variation from the initial conditions[a]	yield (%)[b]
1	none	80
2	MeOH (2.5 equiv)	74
3	MeOH (12.5 equiv)	33
4	MeOH (40 equiv)	15
5	without TBPB	0
6	without $Cu(OAc)_2$	54
7	CuOAc instead of $Cu(OAc)_2$	72
8	$Cu(acac)_2$ instead of $Cu(OAc)_2$	80
9	$Fe(acac)_2$ instead of $Cu(OAc)_2$	25
10	$Ni(acac)_2$ instead of $Cu(OAc)_2$	27
11	$Pd(OAc)_2$ instead of $Cu(OAc)_2$	0
12	$Mn(OAc)_2$ instead of $Cu(OAc)_2$	14
13	TBPB (1.5 equiv)	44
14	TBPB (3.5 equiv)	78

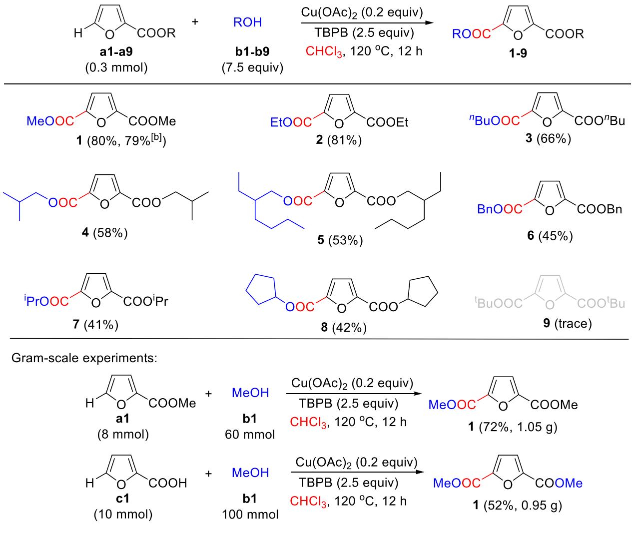
[a] Initial conditions: **a1** (0.3 mmol, 1 equiv, 0.3 M), **b1** (7.5 equiv), $Cu(OAc)_2$ (0.2 equiv), TBPB (2.5 equiv), $CHCl_3$, 120 °C, 12 h, under air. TBPB = *tert*-butyl peroxybenzoate. [b] Isolated yields.

pivotal organic solvent was explored as a trichloromethyl radical precursor for trichloromethylation of alkenes.[19] However, direct alkoxycarbonylation of C(sp^2)−H bonds of heteroarenes with $CHCl_3$ as the carbonyl source has not been reported previously, although many endeavors on radical alkylation reactions of heteroarenes (Minisci-type reactions) have been made over the past decade.[20,21] Inspired by the above facts as well as our previous research on furans serving as masked alkenes,[22] we envisaged that heteroaromatic carboxylic esters, including 2,5-furandicarboxylates, could be accessed by copper-promoted alkoxycarbonylation via trichloromethylation of the heteroaryl ring with $CHCl_3$-generated trichloromethyl radical followed by in situ alcoholysis, thereby allowing us to implement this seemingly simple but important conversion using an innovative carbonyl source and radical process on an economically viable C_5 platform (Scheme 1c).

We started the exploration of reactions with methyl 2-furoate (**a1**), which has an electron-deficient furan ring, as a model substrate (Table 1). Treatment of **a1** (0.3 mmol, 1 equiv, 0.3 M) with MeOH (**b1**, 7.5 equiv), $Cu(OAc)_2$ (0.2 equiv), and *tert*-butyl peroxybenzoate (TBPB) (2.5 equiv) in $CHCl_3$ (which serves as both reactant and solvent) under air at 120 °C afforded the desired dimethyl furan-2,5-dicarboxylate (**1**) in 80% yield (entry 1). The amount of MeOH strongly influenced the yield of **1**. Specifically, the yield decreased slightly (to 74%) when the amount of MeOH was reduced to 2.5 equiv (entry 2) and decreased markedly (to 33%) when it was increased to 12.5 equiv (entry 3). When 40 equiv of MeOH was used, the yield of **1** was only 15% (entry 4). When the reaction was carried out in the absence of TBPB, most of the **a1** was recovered, and **1** was not isolated (entry 5). The decreased yield of **1** (54%) in the absence of $Cu(OAc)_2$ suggested that the copper additive served as a promoter rather than a catalyst at this temperature (entry 6). The use of $Cu(acac)_2$ also promoted the yield more effectively than that of CuOAc (entries 7 and 8), indicating that Cu(II) is preferred over Cu(I) in this conversion. Furthermore, other metal additives such as Fe, Ni, Pd, and Mn were confirmed to have a negative effect on the yield (entries 9−12). Reducing the loading of TBPB to 1.5 equiv decreased the yield of **1** to 44% (entry 13), and **a1** was not completely consumed. A TBPB loading of 3.5 equiv gave almost the same yield as a loading of 2.5 equiv (entry 14).

With the optimal conditions in hand (Table 1, entry 1), we carried out reactions of a series of furoates and alcohols with the goal of synthesizing symmetrical difuroates (Scheme 2).

Scheme 2. Synthesis of Symmetrical Difuroates[a]

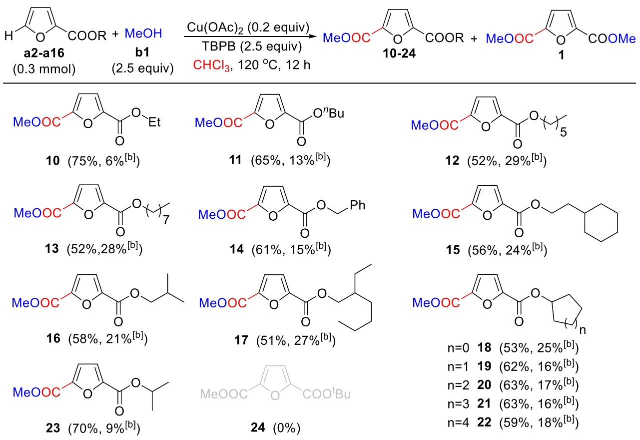


[a] Unless otherwise noted, reactions were performed on a 0.3 mmol scale in $CHCl_3$ (0.3 M) containing $Cu(OAc)_2$ (0.2 equiv), TBPB (2.5 equiv), and MeOH (7.5 equiv) at 120 °C for 12 h. [b] The reaction was performed on a 1 mmol scale in $CHCl_3$ (0.3 M).

Several primary alkyl furoates **a2−6** and alcohols **b2−6** were able to produce the corresponding difuroates **2−6** in moderate to good yields (45−81%). The particularly low yield of dibenzyl furan-2,5-dicarboxylate (**6**) (45%) may be due to oxidation of the benzyl alcohol (**b6**). The yields of the corresponding products (**7** and **8**) from secondary alkyl alcohols (**b7** and **b8**) were lower than those of products from primary alkyl alcohols, and considerable amounts of **a7** and **a8** were recovered. A reaction involving sterically bulky *tert*-butyl alcohol (**a9**) gave only a trace of product **9**. To evaluate the synthetic utility of this alkoxycarbonylation protocol, we scaled up the reaction of **a1** (8 mmol, 0.3 M) with MeOH (60 mmol), which gave **1** in 72% isolated yield. To our delight, we also found that the reaction of furoic acid (**c1**) (10 mmol, 0.3 M) in MeOH gave **1** (52%) in a single step.

Because unsymmetrical difuroates have potential applications in plastification,[23] we next turned our attention to the synthesis of these compounds by means of our alkoxycarbonylation protocol (Scheme 3). Reactions of MeOH and $CHCl_3$ with various 2-furoates (R ≠ Me, **a2**−**16**) were examined. Predictably, ester exchange was unavoidable; however, it could be partially suppressed by decreasing the amount of MeOH to 2.5 equiv, despite the formation of a small amount of **1**. When R was a linear primary alkyl group (Et, *n*-butyl, *n*-hexyl, *n*-octyl, or benzyl), the desired products **10**−**14** were obtained in moderate to good yields (52−75%), accompanied by small amounts of **1**. A set of furoates bearing a branched primary alkoxyl group (2-cyclohexylethyl, isopropyl, or 2-ethyloctyl) were also effective substrates, giving **15**−**17** in moderate yields. Furoates with secondary alkyl groups afforded the corresponding difuroates **18**−**23** in 53−70% yield. However, difuroate **24** was not detected when sterically bulky *tert*-butyl furoate was used as the substrate.

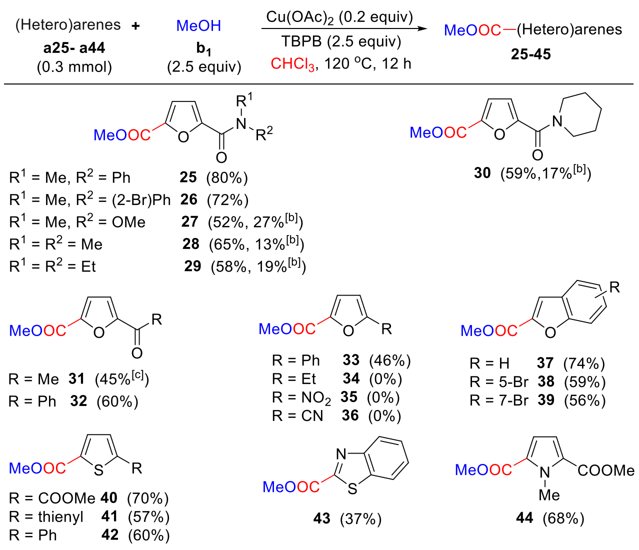
Scheme 3. Synthesis of Unsymmetrical Difuroates[a]



[a]Reactions were performed on a 0.3 mmol scale in $CHCl_3$ (0.3 M) containing $Cu(OAc)_2$ (0.2 equiv), TBPB (2.5 equiv), and MeOH (2.5 equiv) at 120 °C for 12 h. [b]Isolated yield of byproduct **1**.

We further explored the scope of this transformation by evaluating a variety of structurally diverse heteroarene substrates (Scheme 4). First, furans with *α*-substituents other than an alkoxycarbonyl group were screened, and the electronic nature of the substituent was found to strongly influence the reaction. Specifically, furans substituted with a moderately electron-withdrawing *α*-amide smoothly afforded the desired products **25**−**30**. Furthermore, furans bearing acyl groups also underwent the reaction, giving the desired products **31** and **32** in moderate yields, and an electron-neutral phenyl-substituted furan gave a 46% yield of the desired product **33**. However, the reaction of a substrate bearing an electron-donating ethyl group generated a complex mixture that contained none of the desired product **34**, possibly because of oxidative polymerization of the furan ring.

Scheme 4. Alkoxycarbonylation Reactions of Various Heteroarenes[a]

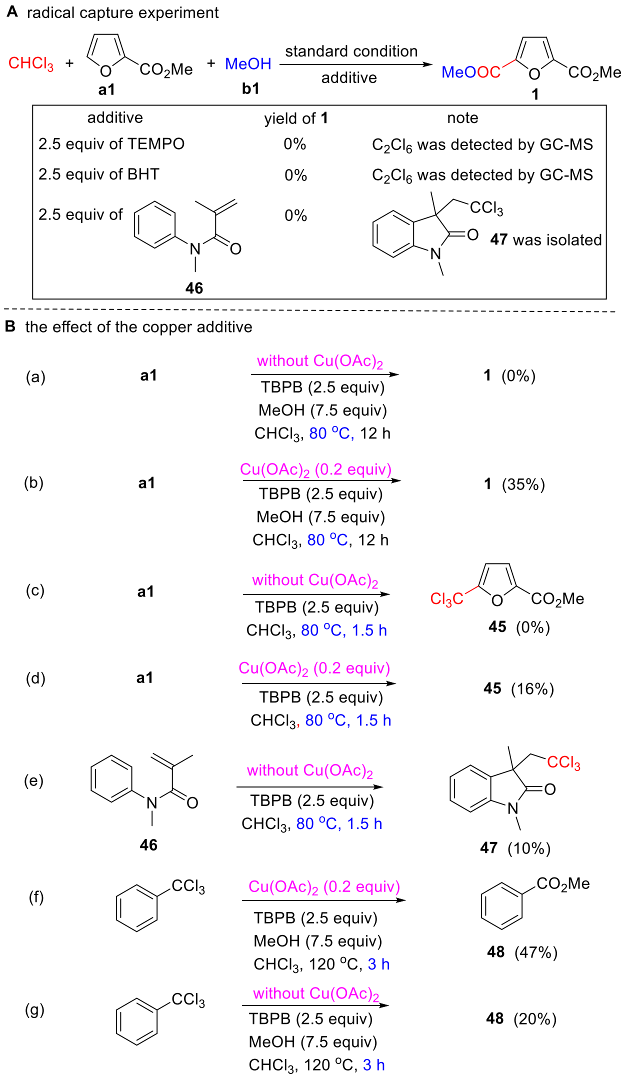


[a]Reactions were performed on a 0.3 mmol scale in $CHCl_3$ (0.3 M) containing $Cu(OAc)_2$ (0.2 equiv), TBPB (2.5 equiv), and MeOH (2.5 equiv) at 120 °C for 12 h. [b]Isolated yield of byproduct **1**. [c]The reaction was carried out at 110 °C for 9 h.

In addition, furans bearing a strongly electron-withdrawing group (nitro or cyano) also afforded complex mixtures in which the desired products (**35** and **36**) were not detected. The above-described results clearly indicate that a moderately electron-deficient furan ring is required for this transformation. It is noteworthy that further investigation revealed that benzofuran and thiophene rings, which have greater aromaticity than the furan ring, were also suitable, affording products **37**−**42**. Finally, benzothiazole and 1-methyl-1*H*-pyrrole-2-carboxylate afforded **43** and **44**, respectively.

To gain insight into the reaction mechanism, we carried out several control experiments (Scheme 5). Under the standard conditions, the reaction was completely inhibited by the radical scavengers TEMPO and BHT. In both of these experiments, C_2Cl_6 was detected by GC−MS, which indicates that $\cdot CCl_3$ radical may be generated as an intermediate. However, no direct evidence of the formation of a $\cdot CCl_3$ radical intermediate was obtained until we used highly reactive alkene **46** as a radical quencher to obtain trichloromethylated product **47** (Scheme 5A). Next, to elucidate the origin of the promotional effect of the $Cu(OAc)_2$ additive, we conducted several experiments. First, when the reaction temperature was decreased from 120 to 80 °C and $Cu(OAc)_2$ was omitted, target product **1** was not produced from methyl 2-furoate. In contrast, reaction at 80 °C in the presence of $Cu(OAc)_2$ generated **1** in 35% yield (Scheme 5B, eqs (a) and (b)). In the absence of both MeOH and $Cu(OAc)_2$ at 80 °C, intermediate **45** was not detected after reaction for 1.5 h (which is shorter than the standard duration of 12 h); however, when the copper salt was present, **45** was acquired after 1.5 h in 16% yield (Scheme 5B, eqs (c) and (d)). When amide **46** was used as the substrate instead of **a1**, trichloromethylated product **47** was formed (Scheme 5B, eq (e)), indicating that $\cdot CCl_3$ radical was not reactive enough to attack the furan ring at 80 °C. On the basis of these results, at 80 °C the copper salt acted as a catalyst rather than as a promoter, which is in sharp contrast to its role at 120 °C. Finally, the reaction of trichloromethylben-

Scheme 5. Control Experiments[a]

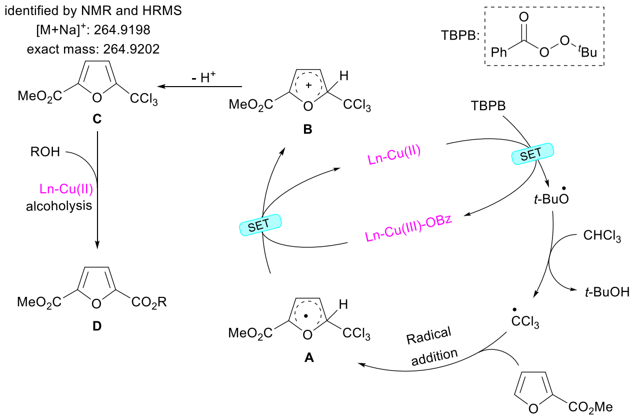


[a]Unless otherwise noted, reactions were performed on a 0.3 mmol scale in $CHCl_3$ (0.3 M) containing $Cu(OAc)_2$ (0.2 equiv), TBPB (2.5 equiv), and MeOH (7.5 equiv) at 120 °C for 12 h. TEMPO = 2,2,6,6-tetramethyl-1-piperidin-1-oxyl. BHT = butylated hydroxytoluene.

zene in the presence of $Cu(OAc)_2$ consumed most of the starting material and generated methyl benzoate (**48**) in 47% isolated yield. In contrast, in the absence of $Cu(OAc)_2$, a large amount of the trichloromethylbenzene remained unconsumed, and the yield of **48** was only 20%, indicating that $Cu(OAc)_2$ also acted as a Lewis acid, promoting esterification in the alcoholysis of the trichloromethylated aromatic rings (Scheme 5B, eqs (f) and (g)). Moreover, additional control experiments (see Schemes S1 and S2) suggested that cleavage of the $C(sp^3)$−H bond of chloroform was involved in the rate-determining step.

On the basis of the above-described control experiments, we propose the mechanism outlined in Scheme 6. In the presence of copper, initially homolytic cleavage of TBPB accelerated by Ln-Cu(II) forms an Ln-Cu(III)-OBz complex and *tert*-butoxyl radical,[24] which abstracts the hydrogen atom of $CHCl_3$ to generate $\cdot CCl_3$ radical. Addition of $\cdot CCl_3$ radical to methyl 2-furoate generates intermediate **A**, after which single electron transfer (SET) of the Ln-Cu(III)-OBz species takes place to produce the corresponding carbocation intermediate **B** and regenerate the Ln-Cu(II) species. Subsequently, intermediate **B** forms intermediate **C**, which undergoes aromatization-driven deprotonation. The results of both HRMS and NMR analyses supported the possible formation of intermediate **C**. Finally, copper-mediated alcoholysis and reaction with intermediate **C** produce target product **D**. Another possible mechanism in the absence of copper species is given in the Supporting Information (see more detail in Scheme S2).

Scheme 6. Proposed Mechanism



In conclusion, we have developed a novel approach for the direct alkoxycarbonylation of furans as well as other heteroarenes via one-step copper-mediated reaction of three components, i.e., heteroarene, alcohol, and $CHCl_3$. This method was found as the first use of a radical pathway to construct FDCA derivatives based on a C_5 platform. The copper additive used in this reaction probably engages and benefits in three significant processes: facilitating the formation of trichloromethyl radical, contributing to the single electron transfer, and devoting to in situ alcoholysis, which also has been found to be rarely reported to date. Supported by HRMS, NMR analyses and an enormous number of control assays, this Cu-promoted radical process has been fully described. More importantly, avoidance of precious or stoichiometric alkali metals, wide applicability for heteroaryl carboxylates, and success in gram-scale reaction indicate it to be a promising method for dual C−H bond cleavage and direct alkoxycarbonylation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00582.

> Experimental procedures, characterization data, optimization and additional control experiments, possible mechanism in the absence of copper, and NMR spectra of starting materials and products (PDF)

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Notes

The authors declare no competing financial interest.

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