Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Reductive Cleavage of Aromatic and Heteroaromatic Ester Functions via Copper-Catalyzed Proto-Decarbomethoxylation

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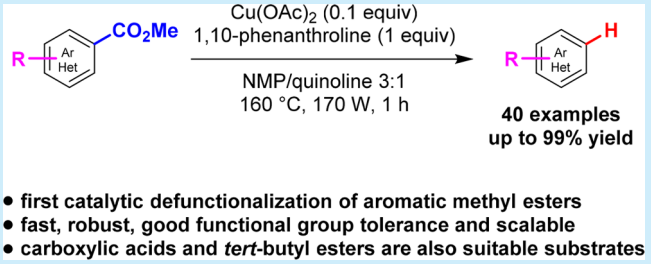
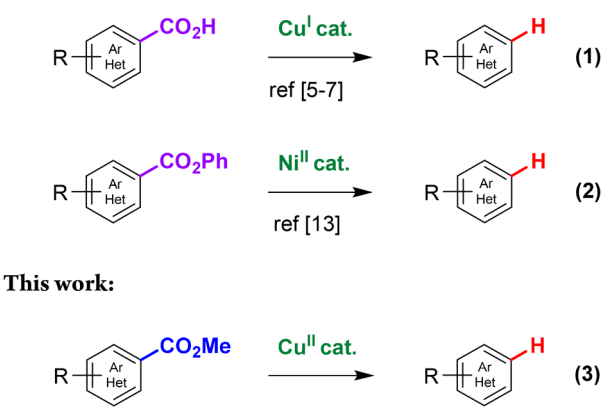
Supporting Information

ABSTRACT: An unprecedented catalytic reductive cleavage of aromatic and heteroaromatic methyl ester functions was successfully achieved with a cheap, nontoxic, and air-stable $Cu(OAc)_2$ catalyst. This reaction is fast, features good functional group tolerance, does not require inert atmosphere or anhydrous solvent, and can be scaled up to 1 g. Moreover, carboxylic acids and *t*-butyl esters also reacted smoothly under these conditions.



Esters are widely recognized as ubiquitous organic functions that can be found in synthetic building blocks as well as in natural products. Consequently, reductive removal of esters represents an important class of transformations in synthetic organic chemistry. In recent years, metal-catalyzed defunctionalization, in general, and decarboxylation, in particular, have attracted great interest.[1] Discovered in 1930, the stoichiometric decarboxylation of benzoic acids using Cu_2O has been extensively studied during the mid-20th century by Shepard,[2] Nilsonn,[3] and Cohen.[4] The potential of this reaction remained underexploited until major breakthroughs were achieved over the past decade with the development of catalytic versions using various ligands: 1,10-phenanthroline for Gooßen,[5] TMEDA for Cahiez,[6] or TEA for Cai (Scheme 1, eq 1).[7] Microwave heating was also reported to significantly reduce reaction times.[8] Currently, two main applications emerging from copper-catalyzed decarboxylation are of major importance: (i) decarboxylative cross-coupling reactions for C−C bond formation, especially as a Suzuki alternative for biaryl synthesis,[9,10] and (ii) the use of carboxylic acid as traceless directing groups for C−H activation.[11,12]

Scheme 1. Metal-Catalyzed Proto-decarbo(metho)xylation of (Hetero)aryls



More recently, nickel-catalyzed reductive defunctionalization of phenyl esters was reported for the first time by the group of Rueping (Scheme 1, eq 2).[13] Whereas phenyl esters can be advantageously used in cross-coupling reactions, mainly limited to nickel catalysis,[14,15] methyl esters are more attractive from an atom-economic point of view. Surprisingly, and to the best of our knowledge, there was no report dealing with catalytic reductive removal of methyl esters when we started our investigation. The very first example was actually disclosed by Rueping, while we were preparing this paper, who described the nickel-catalyzed conversion of methyl esters into stannane derivatives.[16]

Given the fundamental synthetic interest in the reduction of aryl esters and the green advantage of methyl versus phenyl esters, it would be highly desirable to develop a method to remove methyl esters via a catalytic process using a cheap, nontoxic, and air-stable catalyst such as copper. We report herein the first example of copper-catalyzed reductive cleavage of aryl and heteroaryl methyl esters (Scheme 1, eq 3). This reaction represents an attractive pathway for the late-stage defunctionalization of high-value polyfunctionalized natural or synthetic aromatic esters.

For our initial investigation of methyl ester defunctionalization, inspired from previous studies on protodecarboxylation,[2−8] we chose methyl 2-nitrobenzoate (***o*-1a**) and methyl 2-methoxybenzoate (***o*-1b**) as models of activated and deactivated substrates, respectively. After examination of various copper

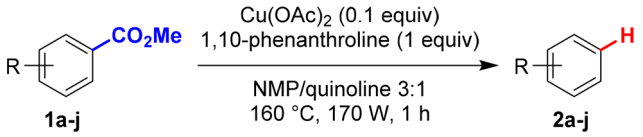
Received: March 21, 2018

DOI: 10.1021/acs.orglett.8b00930
Org. Lett. XXXX, XXX, XXX−XXX

sources and amounts, ligands, solvents, and heating conditions, we were pleased to find that 0.1 equiv of $Cu(OAc)_2$ and 1 equiv of 1,10-phenanthroline as a ligand in a mixture of 3:1 NMP/quinoline at 160 °C and 170 W for 1 h were the optimal reaction conditions (for details, see Tables S1 and S2 in the Supporting Information (SI)). Before proceeding further, control experiments were performed and demonstrated (i) that the desired product is not formed in the absence of copper and (ii) that the yield is significantly lowered when the ligand or the microwave activation is missing (for details, see Table S3 in the SI).

With these fully optimized conditions in hand, we then examined the scope and limitations of the reaction (Table 1).

Table 1. Scope of Substituted Methyl Benzoates[a]



entry	substrate	R	product	yield (%)[b]
1	***o*-1a**	*o*-NO_2	**2a**	80 [**84**] (**A**)
2	***m*-1a**	*m*-NO_2	**2a**	44 (**A**), 32 (**B**)
3	***p*-1a**	*p*-NO_2	**2a**	39 (**A**), 34[c] (**B**)
4	***o*-1b**	*o*-OMe	**2b**	26[d] (**A**), 50 (**B**)
5	***m*-1b**	*m*-OMe	**2b**	29 (**A**), 65 [**61**] (**B**)
6	***p*-1b**	*p*-OMe	**2b**	50 (**B**)
7	***o*-1c**	*o*-Me	**2c**	26 (**A**), 60 [**72**] (**B**)
8	***m*-1c**	*m*-Me	**2c**	24 (**A**), 39 (**B**)
9	***p*-1c**	*p*-Me	**2c**	15 (**A**), 53 (**B**)
10	***o*-1d**	*o*-OH	**2d**	99 [**95**] (**A**)
11	***m*-1d**	*m*-OH	**2d**	51 (**A**), 96 [**99**] (**B**)
12	***p*-1d**	*p*-OH	**2d**	53 (**A**), 83 (**B**)
13	***o*-1e**	*o*-NH_2	**2e**	0 (**A**), 72 [**70**] (**B**)
14	***m*-1e**	*m*-NH_2	**2e**	0 (**A**), 55 (**B**)
15	***p*-1e**	*p*-NH_2	**2e**	0 (**A**), 36 (**B**)
16	***o*-1f**	*o*-NMe_2	**2f**	21 (**A**), 59 [**64**] (**B**)
17	***m*-1f**	*m*-NMe_2	**2f**	15 (**A**), 55 (**B**)
18	***p*-1f**	*p*-NMe_2	**2f**	0 (**A**), 38 (**B**)
19	***o*-1g**	*o*-CN	**2g**	87 (**A**)
20	***m*-1g**	*m*-CN	**2g**	75 (**A**)
21	***p*-1g**	*p*-CN	**2g**	95 [**87**] (**A**)
22	***o*-1h**	*o*-CHO	**2h**	49 (**A**), 53 (**B**)
23	***m*-1h**	*m*-CHO	**2h**	45 (**A**), 58 (**B**)
24	***p*-1h**	*p*-CHO	**2h**	88 [**91**] (**A**)
25	***o*-1i**	*o*-Cl	**2i**	54 (**A**)
26	***m*-1i**	*m*-Cl	**2i**	65 (**A**), 85 [**76**] (**B**)
27	***p*-1i**	*p*-Cl	**2i**	73 (**A**)
28	***o*-1j**	*o*-F	**2j**	46 (**A**), 63 (**B**)
29	***m*-1j**	*m*-F	**2j**	37 (**A**), 79 (**B**)
30	***p*-1j**	*p*-F	**2j**	27 (**A**), 73 [**75**] (**B**)
31	***o*-1i**	*o*-Cl	**2i**	50[e] (**A**)
32	***o*-1i**	*o*-Cl	**2i**	63[f] (**A**)

[a]Method A: methyl benzoate **1a–i** (1 mmol), $Cu(OAc)_2$ (0.1 mmol), 1,10-phenanthroline (1 mmol), NMP (2.5 mL), quinoline (0.8 mL), μW (160 °C/170 W), 1 h. Method B: method A with 0.4 mmol of $Cu(OAc)_2$ instead of 0.1 mmol. [b]Isolated yields indicated in brackets [] are consistent with those determined by GC or NMR using tetradecane (0.1 mmol) as the internal standard. [c]Aniline was identified in 66% yield. [d]Phenol was identified in 72% yield. [e]Performed under anhydrous conditions. [f]Performed on a 1 g (150 mmol) scale.

In the first set of experiments, the reactions were carried out with our optimized conditions (method A), and when the yields were less than 50%, a second set of experiments was performed using 0.4 equiv of $Cu(OAc)_2$ (method B). In order to properly benchmark our protocol against previous reports on decarboxylation of benzoic acids,[5−8] we have chosen a wide panel of substituted methyl benzoates that systematically include *ortho*, *meta*, and *para* derivatives.

To our delight, the reaction proceeded smoothly in reasonable to quantitative yields for all of the substrates, regardless of the substituents' electronic nature on the aromatic ring. In that respect, aromatic methyl esters proved to be indeed prone to undergo proto-decarbomethoxylation under our conditions, whereas these functional groups remained stable under Gooßen[6] or Rueping[9] reductive conditions. Furthermore, a large variety of functional groups, including nitro **1a**, methoxy **1b**, methyl **1c**, hydroxy **1d**, amino **1e**, dimethylamino **1f**, cyano **1g**, formyl **1h**, chloro **1i**, and fluoro **1j** were well tolerated under these conditions, which demonstrates the generality of our method. Very few exceptions were the *p*-nitro (***p*-1a**) and *o*-methoxy (***o*-1b**) derivatives, which underwent over-reactions that, despite a full conversion of the substrates, lowered the yield of the desired product (Table 1, entries 3 and 4, respectively). Although disappointing, the 26% yield obtained for the ester ***o*-1b** is consistent with the optimized 24% yield obtained by Gooßen for the corresponding decarboxylation of 2-methoxybenzoic acid.[5]

For all the other substrates, as described in previous studies for related decarboxylation of benzoic acids,[5−8] a marked steric and electronic *ortho* effect can be observed for substrates bearing neutral or electron-donating groups in the *ortho* position, which afford better yields than their *meta* and *para* analogues (Table 1, entries 7−18). This effect seems to be offset by the presence of electron-withdrawing groups that are, on the contrary, preferred in the *para* position (Table 1, entries 19−27). These observations support the hypothesis of a negative charge on the carbon *ipso* to the carboxylate in the transition state,[13] except for fluorine-containing compounds that led to mixed results (Table 1, entries 28−30). In a few cases, methyl esters led to yields better than those reported for their carboxylic acid counterparts: 87% vs 81% for the *para*-cyano (***p*-1g**) and 91% vs 64% for the *para*-formyl (***p*-1h**) derivatives (Table 1, entries 21 and 24).[8]

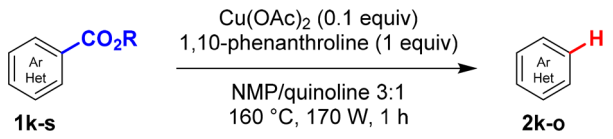
To further assess the practicality of our protocol, we performed control experiments with the substrate ***o*-1i**. Anhydrous conditions are not essential, as they do not lead to any increase of the yield (Table 1, entry 31 vs 25), and the reaction can be successfully scaled up to 1 g (150 mmol) with an even better yield of 63% (Table 1, entry 32 vs 25), which strengthens the advantages of this new reduction method.

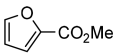
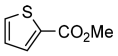
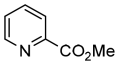
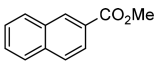
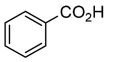
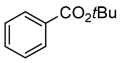
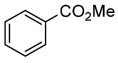
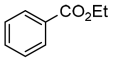
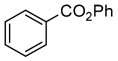
We finally explored the applicability of our conditions to pharmaceutically relevant heteroaromatic methyl esters and other types of simple aromatic esters (Table 2).

Satisfyingly, all of the desired products were obtained in moderate to quantitative yields. Furyl **1k** and thienyl **1l** derivatives reacted smoothly in good yields with 0.1 equiv of $Cu(OAc)_2$, leading to 61 and 72% of desired products **2k** and **2l**, respectively (Table 2, entries 1 and 2). Although pyridyl **1m** and naphthyl **1n** substrates failed to react nicely with 0.1 equiv of catalyst, and they both furnished 99% of the corresponding products when 0.4 equiv was used (Table 2, entries 3 and 4). Benzoic acid **1o** and the *tert*-butylbenzoate **1p** were the most reactive substrates, affording benzene **2o** in 87 and 99% yields,

DOI: 10.1021/acs.orglett.8b00930
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Scope of Other (Hetero)aromatics[a]



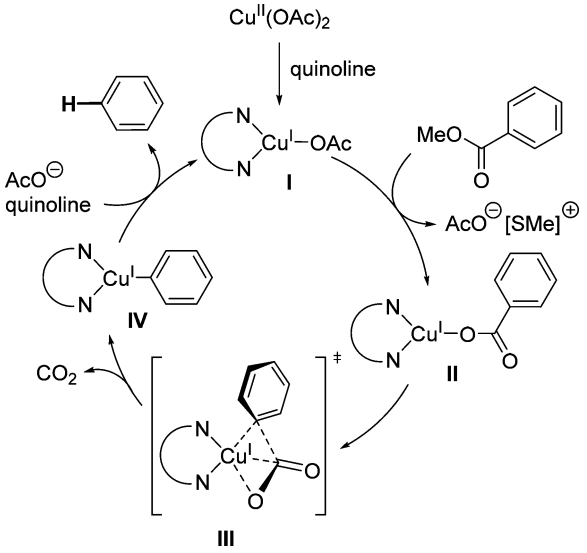
entry	substrate		product	yield (%)[b]
1	**1k**		**2k**	61 (**A**)
2	**1l**		**2l**	72 (**A**)
3	**1m**		**2m**	41 (**A**), 99 [**90**] (**B**)
4	**1n**		**2n**	41 (**A**), 99 [**85**] (**B**)
5	**1o**		**2o**	87 (**A**)
6	**1p**		**2o**	99 [**95**] (**A**)
7	**1q**		**2o**	29 (**A**), 96 (**B**)
8	**1r**		**2o**	14 (**A**), 45 (**B**)
9	**1s**		**2o**	42 (**A**), 53 (**B**)

[a]Method A: substrates **1k–s** (1 mmol), $Cu(OAc)_2$ (0.1 mmol), 1,10-phenanthroline (1 mmol), NMP (2.5 mL), quinoline (0.8 mL), μW (160 °C/170 W), 1 h. Method B: method A with 0.4 mmol of $Cu(OAc)_2$ instead of 0.1 mmol. [b]Isolated yields indicated in brackets [] are consistent with those determined by GC using tetradecane (0.1 mmol) as the internal standard.

respectively (Table 2, entries 5 and 6). On the contrary, methyl, ethyl, and phenyl benzoates that were less reactive required 0.4 equiv of $Cu(OAc)_2$ to react properly (Table 2, entries 7–9). These differences observed in reactivity highlight that chemoselective reduction could be achieved by this method. On the basis of our observations, and the conclusions of previous studies,[17,18] the mechanism could be described as follows (Scheme 2): reduction of the copper acetate by quinoline[4a] gives the catalytically active complex **I**, demethylation of the ester by the nucleophilic solvent (S) or an acetate anion (methyl acetate was isolated through distillation) affords the copper-benzoate **II**, decarboxylation occurs through the transition state **III**[17] which leads to the insertion of the metal into the aryl–carboxyl bond and provides the aryl–copper species **IV**. The last step was extensively studied by Cohen, who demonstrated that quinoline acts as a major source of hydrogen by being involved in copper-catalyzed C-H activation.[4b]

In summary, we have developed the first catalytic reductive cleavage of aromatic and heteroaromatic methyl esters. This new reaction involves a cheap, nontoxic, air- and moisture-stable $Cu(OAc)_2$ catalyst in combination with an inexpensive phenanthroline ligand. The practicality of this protocol that does not require anhydrous conditions was demonstrated from small (1 mmol) to larger (150 mmol) scale. This versatile method proved to be compatible with a large variety of functional groups and is not hampered by heteroaromatic scaffolds. This copper-catalyzed reduction can also be applied to aromatic carboxylic acid or the parent *tert*-butyl, ethyl, or

Scheme 2. Proposed Mechanism for the Copper-Catalyzed Proto-decarbomethoxylation



phenyl esters with a chemoselectivity that depends on the amount of catalyst. This new transformation represents an attractive strategy for the late-stage defunctionalization of high-value natural or synthetic aromatic esters. It also paves the way for the use of methyl esters as relevant substrates for cross-coupling reactions. Further studies in this direction are currently ongoing in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00930.

Full optimization tables and detailed experimental data, including general methods, synthetic procedures, purification methods, characterization data, and ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the Centre National de la Recherche Scientifique, the Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation, and the Agence Nationale de Recherches sur le Sida et les Hépatites Virales (Grant No. ANRS ECTZ204422) for financial support of this work. We also thank the Ecole Doctorale Médicament, Toxicologie, Chimie, Imageries for the Ph.D. grant to J.F.

DOI: 10.1021/acs.orglett.8b00930
Org. Lett. XXXX, XXX, XXX–XXX

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DOI: 10.1021/acs.orglett.8b00930
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