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Cu-Catalyzed Mild C(sp^2)−H Functionalization Assisted by Carboxylic Acids en Route to Hydroxylated Arenes

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Supporting Information

ABSTRACT: A formal Cu-catalyzed C(sp^2)−H hydroxylation assisted by benzoic acids is described. The procedure is characterized by its mild reaction conditions and wide substrate scope utilizing simple and cheap Cu catalysts, thus becoming a user-friendly and operationally simple protocol for C(sp^2)−H hydroxylation.

The field of C−H functionalization has gained considerable momentum over recent years,[1] holding great promise for preparing highly complex molecules from simple precursors.[2] While synthetically very attractive, most of these protocols still suffer from relatively high catalyst loadings, harsh conditions, and site selectivity.[3] Despite formidable advances, the majority of C−H functionalization processes are still limited to the use of nonweakly coordinating groups that are difficult to functionalize;[1−3] additionally, the C−H functionalization arena is mainly limited to the use of expensive noble metals as catalysts such as Pd, Rh, or Ir.[4] From a synthetic perspective, the ability to prepare synthetically relevant scaffolds via C−H functionalization using weakly coordinating directing groups with cheaper catalysts and under mild conditions would be of significant importance.

Hydroxylated arenes rank among the most ubiquitous motifs in pharmaceuticals, agrochemicals, and polymers, among others.[5] Indeed, the preparation of hydroxylated arenes has become an important goal at the community level.[6] Initial studies by Rybak-Akimova and Que[7a] using stoichiometric Fe(II) complexes followed by the pioneering Pd-catalyzed protocol developed by Yu[7b] using O_2 set up the stage for promoting *ortho* C−H hydroxylation of benzoic acids. To the best of our knowledge, the development of a catalytic C(sp^2)−H functionalization with benzoic acids using cheap Cu salts remains unexplored. We hypothesized that the use of Cu catalysts might lead to pharmaceutically relevant benzolactones **2**[8] via C(sp^2)−H functionalization and subsequent hydrolysis en route to **3** (Scheme 1). While benzolactones **2** are typically prepared from the cyclization of hydroxyacids or via metal-mediated lactonization of aryl halides under harsh conditions,[9] our approach offers the alternative of using nonprefunctionalized and much simpler substrates while avoiding the formation of halide waste. As part of our interest in the field,[10] we present a user-friendly and operationally simple C−H hydroxylation using cheap Cu catalysts, thus becoming a powerful alternative for accessing functionalized arenes in a direct manner.

We started our investigations with **1a** as the model substrate, and the effect of metal precatalysts, oxidants, and solvents were systematically examined (Table 1). After some experimentation,[11] we found that $Pd(OAc)_2$ in combination with $K_2S_2O_8$ using TFA as solvent (entry 1) gave **2a** in 70% yield.[12,13] *These results are in sharp contrast with the known ability of Pd catalysts*

Scheme 1. Formal C−H Hydroxylation with Cu Catalysts

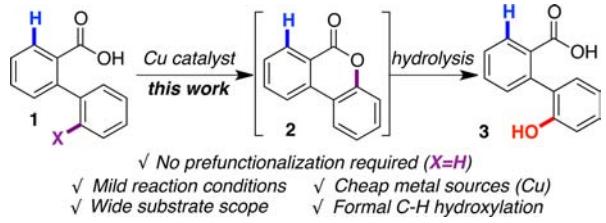
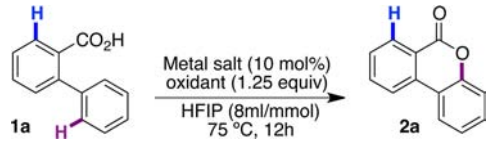


Table 1. Cu-Catalyzed C(sp^2)−H Functionalization[a]



entry	metal source	oxidant	additive (x mol %)	**4a** (%)[b]
1	$Pd(OAc)_2$	$K_2S_2O_8$	2-$FC_6H_4CO_2H$ (30)	70[c]
2	$Pd(OAc)_2$	BQ (1 equiv)	KOAc (200)	0[d]
3	$Cu(OAc)_2$	^{t}BuOOH	–	15
4	$Cu(OAc)_2$	^{t}BuOOBz	–	3
5	$Cu(OAc)_2$	$K_2S_2O_8$	–	3
6	$Cu(OAc)_2$	$[PhCO_2]_2$	–	95,88[e]
7	$Cu(OAc)_2$	$[PhCO_2]_2$	–	66,[f] 0[g]
8	$Cu(OTf)_2$	$[PhCO_2]_2$	–	21
9	$CuBr_2$	$[PhCO_2]_2$	–	79
10	CuOAc	$[PhCO_2]_2$	–	88
11	$Cu(OAc)_2$	$[PhCO_2]_2$	phen(10)[h]	58
12	–	$[PhCO_2]_2$	–	15
13	***$Cu(OAc)_2$***	***$[PhCO_2]_2$***	–	***97(95)***[i,j,k]

[a]**1a** (0.50 mmol), catalyst (10 mol %), oxidant (1.25 equiv), HFIP (8 mL/mmol) at 75 °C. [b]GC yield using decane as the internal standard. [c]Using TFA as solvent (4 mL/mmol) at rt. [d]Using Yu's conditions (ref 7b): $Pd(OAc)_2$ (10 mol %), KOAc (2.0 equiv), BQ (1.0 equiv), DMA at 1 atm of O_2. [e]Air instead of Ar. [f]O_2 (1 atm) instead of Ar. [g]Without $[PhCO_2]_2$ and O_2 (1 atm) instead of Ar. [h]Phen = 1,10-phenanthroline. [i]Using $Cu(OAc)_2$ (5 mol %). [j]Isolated yield. [k]No *ortho* C−H functionalization was observed when using these reaction conditions with 3-methylbenzoic acid as substrate.

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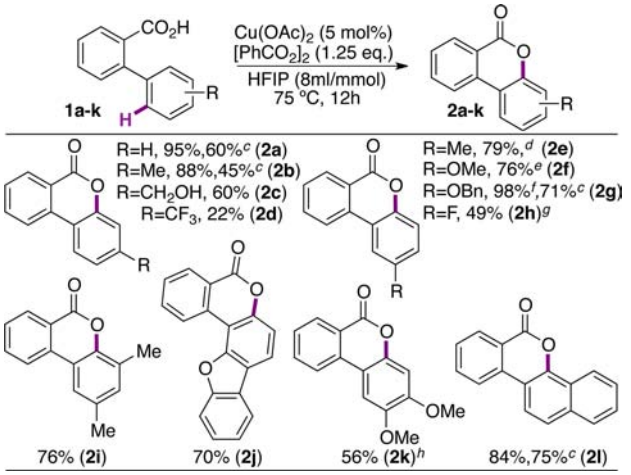
to promote ortho C−H hydroxylation of carbonyl-type compounds.[7b,14,15] To put this result into perspective, we found no reaction of **1a** under Yu's conditions (entry 2).[7b] However, the use of TFA as solvent makes the process not yet synthetically attractive, particularly when employing highly functionalized substrates. Therefore, we turned our attention to Cu-catalyzed processes, as these have become viable alternatives to the more widely utilized Pd-catalyzed reactions. Indeed, Cu-based methods are distinguished by their wide scope, high efficiency, and mild conditions.[16] We found that $Cu(OAc)_2$ as the catalyst with benzoyl peroxide provided excellent results at 75 °C (entry 6). Other oxidants (entries 3−5), Cu salts (entries 8−10), or additives (entry 11) did not improve the yield of **2a**.[17] As shown in entry 7, the presence of O_2 inhibited the reaction to some extent.[18] Control experiments showed that in the absence of $Cu(OAc)_2$ little conversion to **2a** occurred (entry 12). Importantly, we observed that the reaction operated equally well at lower catalyst loadings (entry 13). Quite illustratively, we found that the reaction of 3-methyl benzoic acid under our optimized conditions (entry 13) did not result in *ortho* C−H functionalization, showing the critical role of the pendent aryl ring.

With the optimized reaction conditions in hand, the scope of our Cu-catalyzed remote C−H functionalization was examined. As shown in Table 2, a host of benzoic acids could all be coupled with good to excellent yields.[13] While good results were found for electron-rich or -neutral arenes, low yields were obtained with electron-deficient rings (**2d**). Substituents in *ortho* position to the targeted C−H bond did not hinder the reaction, providing **2i** in good yields. As shown in Table 2, good regioselectivities could be obtained with unsymmetrical substrates; in all cases examined, the most accessible C−H bond was preferentially activated (**2e**, **2f**, **2g**, **2h**, and **2k**),[11] even in a relatively crowded environment (**2i**). As shown for **2l**, a single isomer was obtained with naphthalene backbones. Heterocycles could equally be accommodated under our optimized reaction protocol (**2j**). Particularly noteworthy was the tolerance of our method in the presence of benzyl alcohols (**2c**); under the limits of detection, no traces of aldehyde or carboxylic acid were found in the crude reaction mixtures. This is particularly important, as primary alcohols are susceptible toward oxidation in the presence of Cu catalysts and peroxides as oxidants.[19] Similarly, benzyl ethers were also tolerated as well (**2g**). As for Table 1 (entry 6), we found that the presence of O_2 (1 atm) had a deleterious effect on reactivity for selected substrates (**2a**, **2b**, **2g**, and **2l**); similarly, we found that the Pd-catalyzed conditions in Table 1 (entry 1) gave lower yields.[20]

Next, we studied the electronic and steric effects on the upper aryl ring (Table 3). Interestingly, both electron-donating and -deficient substituents gave the corresponding products in moderate to good yields. The chemoselectivity profile of our method was nicely illustrated by the fact that ethers (**2m**), sulfonates (**2n**), esters (**2o**), and ketones (**2s**) were all well tolerated, giving access to functionalized benzolactones in a straightforward fashion.[13] As shown for **2t**, **2n**, and **2o** the method also tolerated the presence of aryl halides and pseudohalides, thus leaving ample opportunities for further functionalization via conventional cross-coupling techniques. The methodology could be extended to nonaromatic carboxylic acids as well (**2q**), although in lower yields.[21] As for Table 2, we found that unprotected benzyl alcohols did not hinder the reaction, affording exclusively **2p** in high yields.

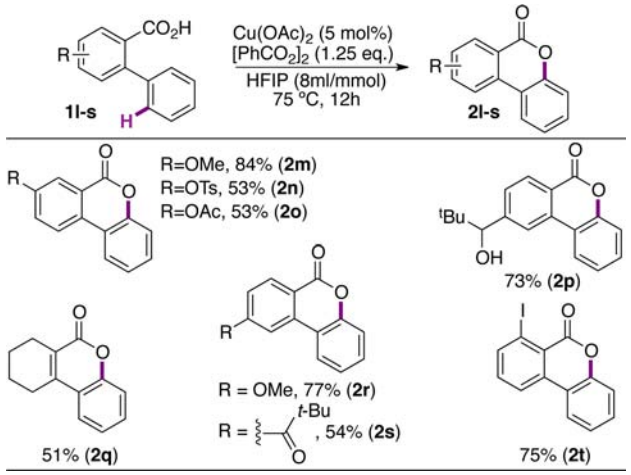
In light of the results shown in Tables 2−3, we anticipated that remote hydroxylated arenes could be within reach by a sequential hydrolysis event.[11] As shown in Table 4, this was indeed the case; the addition of LiOH at rt was found to be crucial, obtaining quantitative conversion to products **3a**−**3e**. The results compiled in Table 4 indicate that remote C−H hydroxylation of benzoic acids could be obtained in high overall yields in a sequential manner from available starting materials. Of particular importance is the successful preparation of **3f** since the corresponding product lacking the hydroxyl group has shown to be a promising candidate to prevent arteriosclerosis;[22,11] therefore, our protocol can be utilized as a platform for evaluating the biological activities of certain pharmacophores. On the basis of the results in Tables 2−4, we speculated that site selectivity could be achieved based on subtle electronic differences among different C−H bonds (Scheme 2). Interestingly, **3g** was obtained as the only isolated product in which the most electron-rich aromatic ring reacted

Table 2. Substituent Effects on the Bottom Ring[a,b]



[a]As for Table 1, entry 12. [b]Isolated yields, average of at least two runs. [c]O_2 atmosphere was used instead of Ar. [d]Isolated as a regioisomeric mixture (3:1). [e]Isolated as a regioisomeric mixture (5:1). [f]Isolated as a regioisomeric mixture (3:1). [g]Isolated as a regioisomeric mixture (4:1). [h]Isolated as a regioisomeric mixture (6:1).

Table 3. Substituent Effects on the Upper Ring[a,b]



[a]As for Table 1, entry 12. [b]Isolated yields, average of at least two runs.

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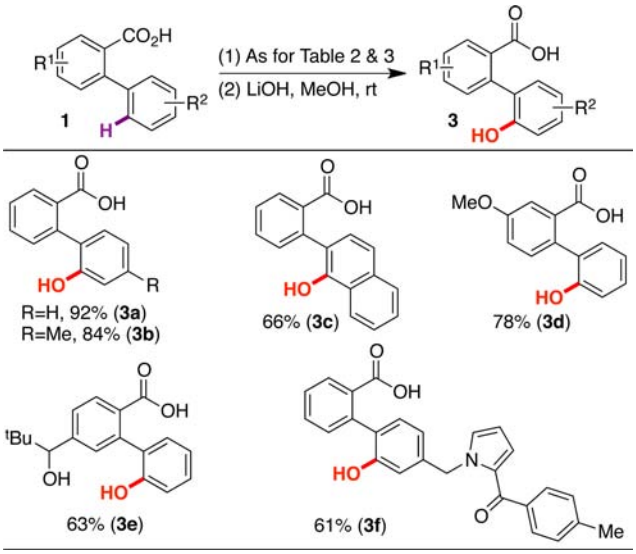
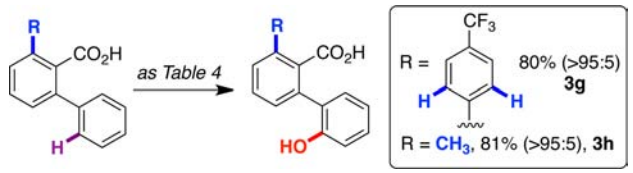
Table 4. Remote C−H Hydroxylation[a,b]



[a]As for Table 1, entry 12. [b]Overall yield (two steps).

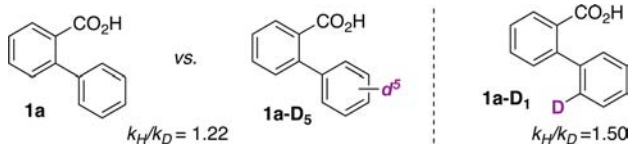
Scheme 2. Site-Selective among Different C−H Bonds



at a faster rate. Similarly, we obtained a high selectivity profile for **3h** suggesting that our protocol selectively activates C(sp^2)−H bonds in the presence of weak *ortho* benzylic C(sp^3)−H bonds.

To gain more insights into the mechanism, we studied the kinetic isotope effect[23] by comparing the initial rates of **1a** with **1a-D$_5$** (Scheme 3). We observed k_H/k_D = 1.22, suggesting that

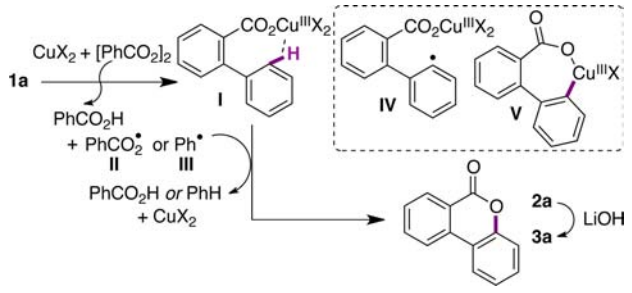
Scheme 3. Intermolecular and Intramolecular KIE



C−H bond cleavage was not involved in the rate-determining step.[11] This assumption was confirmed by the similar k_H/k_D obtained in the intramolecular kinetic isotope effect of **1a-D$_1$**.[11] In addition, we found that the reaction of **1a** under our optimized reaction conditions was significantly inhibited by the addition of radical scavengers such as TEMPO, BHT, or 1,1-diphenylethylene, among others.[11] While not yet conclusive, these experiments might suggest that single electron transfer processes come into play.

Although an in-depth discussion should await further investigations, at present we support a scenario that starts with the reaction of Cu(II) and [$PhCO_2$]$_2$ to give rise to a square-planar or square-pyramidal Cu(III) benzoate **I**[24] and a benzyloxy radical **II** that could undergo CO_2 extrusion (Scheme 4, **III**). Subsequently, **II** or **III** triggers a H-atom abstraction to afford **IV** that ultimately engages an intramolecular C−O bond-

Scheme 4. Mechanistic Hypothesis (X = OAc)



forming reaction (**2a**) while recovering the Cu(II) species.[25] At present, we hypothesize that the formation of **2a** from **IV** might be the rate-determining step of the reaction. Alternatively, we cannot rule out a different scenario via concerted metalation deprotonation (CMD)[26] from species **I** to **V** prior reductive elimination.[27]

In summary, we have described a direct and efficient hydroxylation via Cu-catalyzed C(sp^2)−H functionalization with weakly directing groups.[28,29] This protocol constitutes a user-friendly, operationally simple reaction for preparing hydroxylated arenes under mild reaction conditions with excellent chemoselectivity.[30] Further mechanistic studies and the extension to other substrates are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) We obtain the following results for a selection of substrates using Pd-catalyzed conditions (Table 1, entry 1): **2a** (70%), **2b** (55%), **2e** (44%; 5:1 regioisomeric mixture), **2l** (21%, 7:1 regioisomeric mixture). It is worth noting that, upon exposure of compounds **1a−k** to the conditions developed by Yu (ref 7b), no reaction took place.

(21) At present, we speculate this result suggests that coplanarity might be an important factor for success.

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