



Cu-catalyzed Mild C(sp²)-H Functionalization Assisted by Carboxylic Acids En Route to Hydroxylated Arenes

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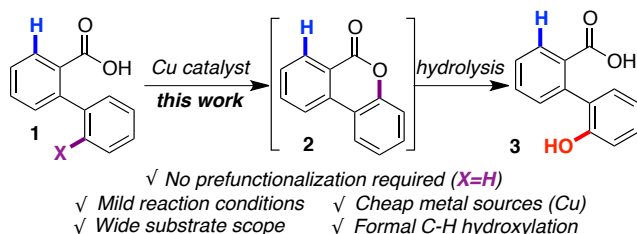
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INTRODUCTION

C-H functionalization protocols have emerged as a powerful tool for the synthesis of complex molecules¹ under the premises of atom, redox and step economy. Nevertheless, examples involving C-H functionalization/C-O bond formation are scarce in the literature, especially when using weakly coordinating directing groups (DG).² In 2011 we described the Pd-catalyzed direct functionalization of C(sp³)-H bonds using carboxylic acids as DG towards the synthesis of 5-membered benzolactones.³ This work describes a new Cu-catalyzed C(sp²)-H acetoxylation en route to valuable hydroxylated arenes.⁴

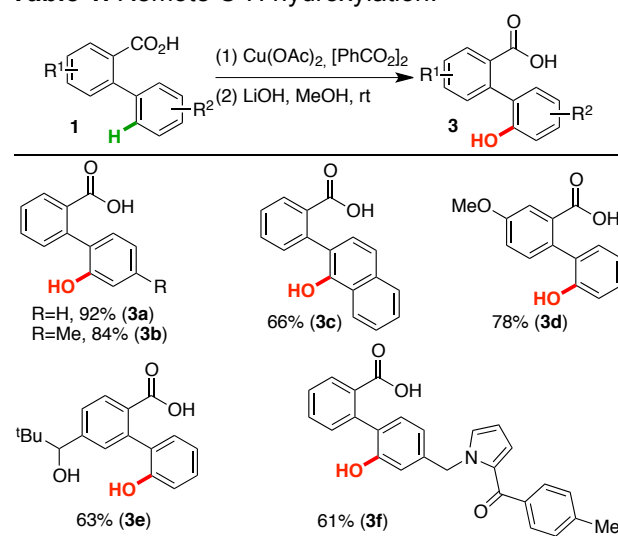
Figure 1. Formal C-H hydroxylation with Cu catalyst.



RESULTS AND DISCUSSION

This method is characterized by their wide substrate scope, including challenging substrate combinations with particularly sensitive functional groups and a diverse set of substitution patterns, both in the upper and bottom ring of the biaryl scaffold. Besides, we we anticipated that remote hydroxylated arenes could be within reach by a sequential hydrolysis event. Of particular importance is the successful preparation of **3f** (table 1) since the corresponding product lacking the hydroxyl group has shown to be a promising candidate to prevent arteriosclerosis. Initial mechanistic investigations suggest that C-H bond cleavage is not involved in the rate-determined step (Intramolecular $K_H/K_D=1.22$). In addition we found that the reaction was significantly inhibited by the addition of radical scavengers by TEMPO, BHT or 1,1-diphenylethylene. While not yet conclusive, these experiments may suggest that single electron transfer processes come into play.

Table 1. Remote C-H hydroxylation.



CONCLUSION

In summary, we have described a direct and efficient Cu-catalyzed C(sp²)-H functionalization using weakly coordinating DG's en route to hydroxylated arenes under mild reaction conditions and with excellent chemoselectivity profile.

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