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

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INTRODUCTION

C-H functionalization protocols have emerged as a powerful tool for the synthesis of complex molecules 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). 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. This work describes a new Cu-catalyzed C(sp³)-H acetoxylation en route to valuable hydroxylated arenes.

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

![Cu catalyst](image)

1. No prefunctionalization required (X=H)
2. Mild reaction conditions
3. Wide substrate scope
4. Cheap metal sources (Cu)
5. Formal C-H hydroxylation

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 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 Kd/Ko=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.

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BuO</td>
<td>MeO</td>
<td>H</td>
<td>63% (3e)</td>
</tr>
<tr>
<td>HO</td>
<td>MeO</td>
<td>H</td>
<td>61% (3f)</td>
</tr>
</tbody>
</table>

CONCLUSION

In summary, we have described a direct and efficient Cu-catalyzed C(sp³)-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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