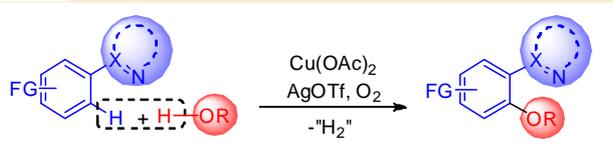


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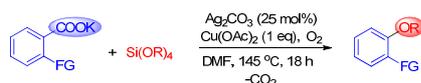
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**Abstract:** Dehydrogenative cross-couplings represent the most attractive strategy to introduce carbon- or heteroatom-based groups into organic molecules. Ideally, two different molecules are each selectively activated at one specific C-H or heteroatom-H group, and undergo regioselective cross-coupling with one another. The hydrogen formally produced is usually scavenged in an oxidative step, e.g. with the formation of water, which significantly contributes to the thermodynamic driving force of the reaction. The key advantage of this approach is the single step functionalization rather than a resource- and waste-intensive synthesis sequence of the prefunctionalization of substrates with leaving groups and traditional cross-couplings. We discovered a Cu(OAc)<sub>2</sub>/AgOTf catalyst system that allows a regioselective dehydrogenative cross-coupling of arenes substituted with directing groups and alcohols. This finding constitutes an expedient synthetic entry to aryl and benzyl ethers.

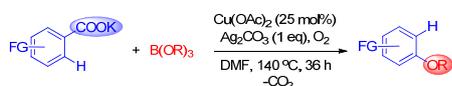


## Introduction

The regioselective formation of C(sp<sup>2</sup>)-O bonds is a synthetic transformation of fundamental importance, due to the presence of the aryl ether motif in many biologically active molecules and functional materials. The current state-of-the-art methods for their synthesis are Buchwald-Hartwig approach, Ullman reaction and the Chan-Evans-Lam coupling. As an alternative we have previously disclosed a decarboxylative variant of the Chan-Evans-Lam-type coupling.<sup>[1]</sup>

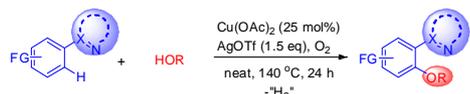


Furthermore we demonstrated that in the presence of a modified copper/silver bimetallic system, benzoates with a low tendency to extrude carbon dioxide undergo *ortho*-C-H-alkoxylation with concomitant loss of the carboxylate directing group in a protodecarboxylation step.<sup>[2]</sup>

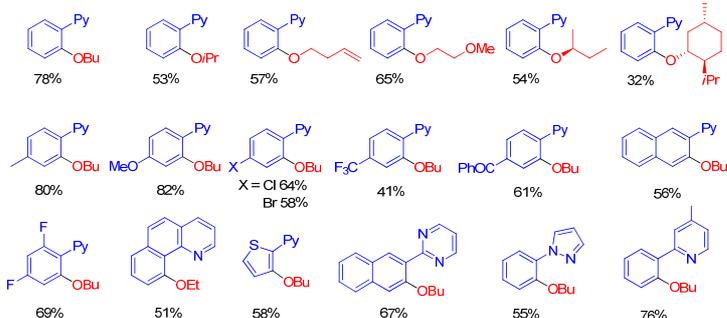


Based on Yu's Cu-catalyzed phenoxylation of arenes<sup>[3]</sup> and the observation by Ribas and Stahl that a macrocyclic copper ligand was methoxylated by adding methanol,<sup>[4]</sup> we reasoned that a copper catalyst might promote direct dehydrogenative cross-coupling between arenes and alcohols.<sup>[5]</sup>

## Dehydrogenative Alkoxylation

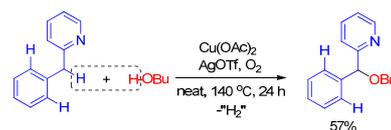


The bimetallic Cu(OAc)<sub>2</sub>/AgOTf-based catalyst system allows dehydrogenative alkoxylation of a broad range of arylpyridines and alcohols under aerobic conditions. As an alternative to 2-pyridyl, other *N*-chelating directing groups, e.g. pyrimidines, benzoquinoline and pyrazole can be used as well.



## Dehydrogenative Alkoxylation of a C(sp<sup>3</sup>)-H Bond

This strategy can also be used for the alkoxylation of benzylic C-H groups, confirming that regioselective dehydrogenative alkoxylation are not limited to C(sp<sup>2</sup>)-H bonds.



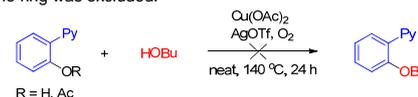
## Mechanistic Studies

The presence of radical quenchers, such as TEMPO and *p*-benzoquinone, completely suppressed product formation, suggesting that the reaction involves a radical step.

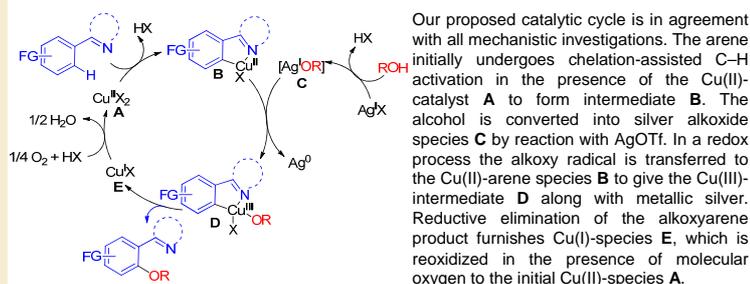
A high kinetic isotope effect of 3.3 was observed in the reaction between 2-phenylpyridine and 2-(phenyl-*d*<sub>5</sub>)pyridine. When 2-phenylpyridine was ethoxylated with ethanol-*d*<sub>1</sub>, no proton scrambling in the starting material was detected. **Conclusion:** The C-H activation of the arene is irreversible and the rate-determining step.



The intermediacy of a hydroxy- or acetoxyarene resulting from an attack of (pre)oxo-copper species to the arene ring was excluded.



## Proposed Mechanism for a Dehydrogenative Alkoxylation



## Literature and Further Reading (see also www.chemie.uni-kl.de/goossen)

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