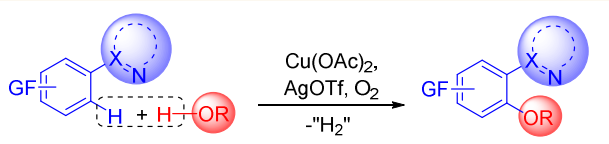


Dmitry Katayev, Sukalyan Bhadra, Wojciech I. Dzik, Christian Matheis and Lukas J. Gooßen*

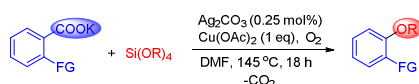
Fachbereich Chemie, TU Kaiserslautern, Erwin-Schrödinger-Straße 54, 67663 Kaiserslautern
Tel +49 631 205 2527, katayev@chemie.uni-kl.de

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. Owing to the abundance of the aryl ether moieties in biologically active molecules and functional materials, their synthesis via dehydrogenative coupling of arenes and free alcohols is highly desirable. We disclosed that a silver/copper catalyst allows the regiospecific dehydrogenative cross-coupling of donor-substituted arenes and alcohols. This finding constitutes an expedient synthetic entry to aryl and benzyl ethers.

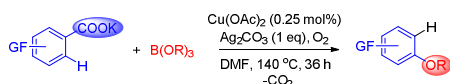


Introduction

The regioselective formation of C(sp²)-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 and the Chan-Evans-Lam coupling. As an alternative we have previously disclosed a decarboxylative variant of the Chan-Evans-Lam-type coupling [1].

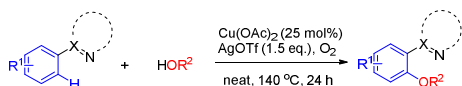


In the presence of a modified copper/silver bimetallic system, benzoates with a low tendency to extrude carbon dioxide undergo *ortho*-C-H-alkoxylation with concomitant loss of the carboxylate directing group in a protodecarboxylation step [2].

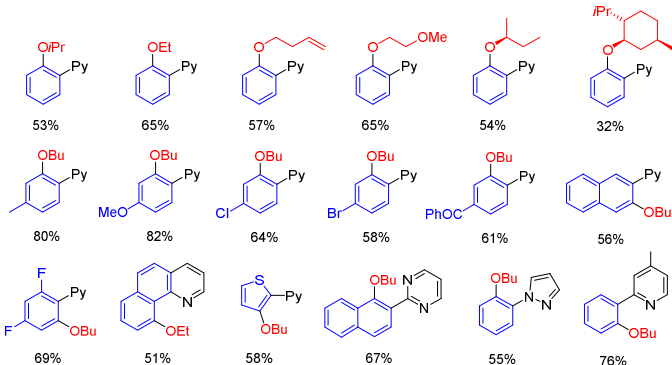


Based on Yu's Cu-catalyzed phenoxylation of arenes [3], the observation by Ribas and Stahl that a macrocyclic copper ligand was methoxylated by adding methanol [4], we reasoned that a copper catalyst might promote direct dehydrogenative cross-coupling between arenes and alcohols [5].

Scope of the Dehydrogenative Alkoxylation

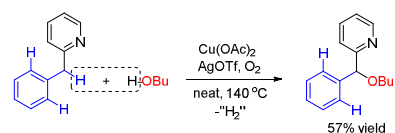


The bimetallic Cu(OAc)₂/AgOTf-based catalyst system allows dehydrogenative alkoxylation of a broad range of arylpyridines and alcohols under aerobic conditions. Alternative to 2-pyridyl, other *N*-chelating directing groups, e. g. pyrimidines, benzoquinoline and pyrazole can be used as well.



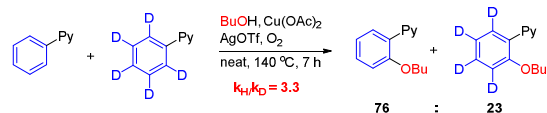
Dehydrogenative alkoxylation of an C(sp³)-H Bond

The reaction concept can be also applied for the alkoxylation of benzylic C-H groups, confirming that regioselective dehydrogenative alkoxylation are not limited to C(sp²)-H bonds.

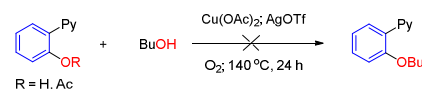


Mechanistic Studies

- The presence of radical quenchers such as TEMPO and *p*-benzoquinone completely suppressed product formation, suggesting that the reaction proceeds via a radical process.
- A high kinetic isotope effect of 3.3 was observed in the reaction between 2-phenylpyridine and 2-(phenyl-*d*₅)pyridine. When 2-phenylpyridine was ethoxylated with ethanol-*d*₁, no product scrambling in the starting material was detected. **Conclusion: the C-H activation of the arene is irreversible and is the rate-limiting step.**

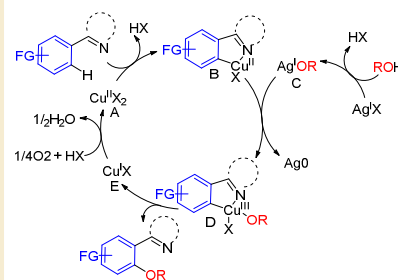


- Evidence against the formation of hydroxy arene intermediates, which can be possibly obtained from attack of (pre)oxo-copper species to the arene.



Proposed Mechanism for a Dehydrogenative Alkoxylation

Our proposed catalytic cycle is in agreement with all mechanistic investigations. The arene first undergoes chelation-assisted C-H activation in the presence of the Cu(II)-catalyst to form intermediate **B**. The alcohol is converted into silver alkoxide species **C** by reaction with AgOTf. In the redox process the alkoxy radical is transferred to the Cu(II)-arene species **C** to give the Cu(III)-intermediate **D** along with metallic silver. Reductive elimination of the alkoxyarene product furnishes a Cu(I)-species which is reoxidized in the presence of molecular oxygen to the initial Cu(II)-species **A**.



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

- [1] S. Bhadra, W. I. Dzik, L. J. Goossen, *J. Am. Chem. Soc.* **2012**, *134*, 9938-9941.
- [2] S. Bhadra, W. I. Dzik, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2013**, *52*, 2959-2962.
- [3] X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790-6791.
- [4] A. E. King, L. M. Huffman, A. Casitas, M. Costas, X. Ribas, S. S. Stahl, *J. Am. Chem. Soc.* **2010**, *132*, 12068-12073.
- [5] S. Bhadra, C. Matheis, D. Katayev, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2013**, DOI: 10.1002/anie.201303702.

We thank Saltigo GmbH, the DFG (SFB/TRR-88, "3MET"), BMBF and Swiss National Science Foundation for financial support.

DFG Deutsche Forschungsgemeinschaft

Bundesministerium für Bildung und Forschung

SFB/TRR 88 3MET.de

FN-SNF SWISS NATIONAL SCIENCE FOUNDATION