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Dehydrative Direct Arylations of Arenes with Phenols via Ruthenium-Catalyzed C−H and C−OH Bond Functionalizations

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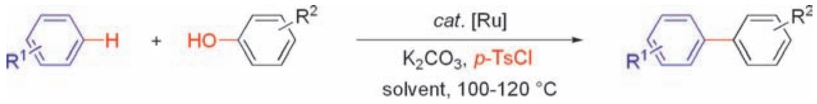
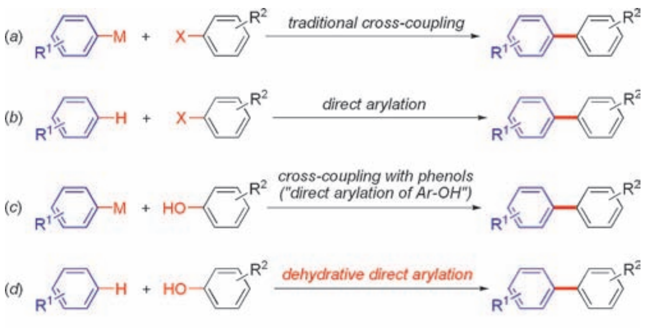
ABSTRACT



Phenols can be employed as proelectrophiles in operationally simple ruthenium-catalyzed dehydrative direct arylations, proceeding through chemo- and regioselective functionalizations of C−H *and* C−OH bonds.

Metal-catalyzed cross-coupling reactions have matured to being indispensable tools for C−C bond formations, which have proved particularly useful for the synthesis of diversely substituted biaryls. Traditionally, cross-coupling reactions rely on the use of preactivated substrates, namely organic (pseudo)halides and organometallic reagents as electrophiles and nucleophiles, respectively (Scheme 1, (a)).[1] Unfortunately, these activated starting materials lead to undesired waste from reagents, solvents, and additional purifications. Therefore, focus has shifted in recent years to the development of direct arylations employing unactivated arenes as pronucleophiles (Scheme 1, (b)).[2] While these C−H bond functionalization protocols have been recognized as ecologically benign and economically attractive alternatives to traditional cross-coupling strategies, the direct use of broadly available, yet inexpensive phenols as proelectrophilic reagents has remained largely unexplored. As a result, a first example of metal-catalyzed cross-couplings via C−OH bond functionalizations (Scheme 1, (c)) was disclosed only very recently. Thus, Fang and co-workers showed elegantly that phosphonium salts enabled an in situ activation of tautomerizable heterocycles, as well as their subsequent palladium-catalyzed cross-coupling using boronic acids as nucleophiles.[3] However, this methodology required a separate preformation of the corresponding heterocycle-phosphonium salt electrophile in the absence of the palladium catalyst.

Scheme 1. Strategies for Catalytic Biphenyl Syntheses



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Furthermore, the use of stoichiometric amounts of organometallic reagents in this cross-coupling reaction resulted, unfortunately, again in the generation of undesired byproduct (vide supra).[3]

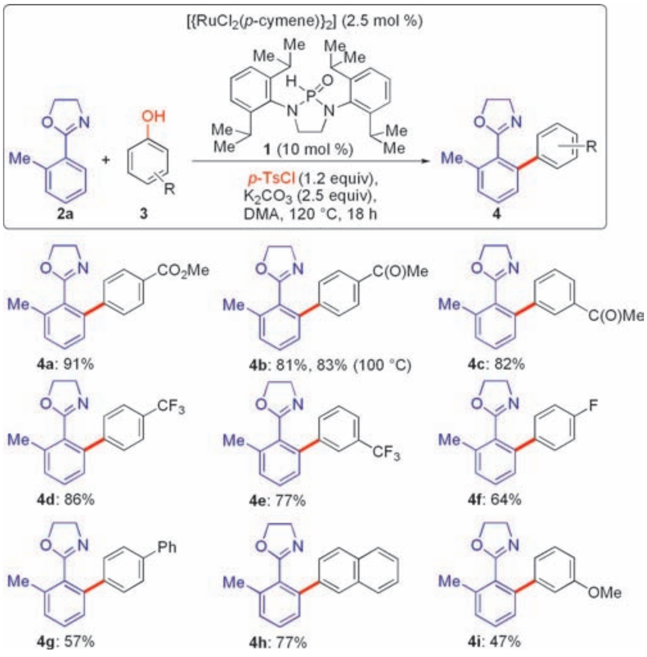
On the contrary, a significantly more sustainable approach would be represented by unprecedented direct arylations of arenes as pronucleophiles with phenols as proelectrophilic arylating reagents *via functionalizations of C−H and C−OH bonds (Scheme 1, (d))*. Herein, we present a first example of such a dehydrative coupling between simple arenes and inexpensive phenols,[4] which was accomplished with a highly chemo- and regioselective ruthenium[5] catalyst.

As part of our program directed toward the development of sustainable metal-catalyzed direct arylations,[6] we probed different transition metals, (pre)ligands, bases, and additives for the envisioned dehydrative direct arylation with phenols. Among a variety of reaction conditions, a system comprising ruthenium precursor [{RuCl$_2$(*p*-cymene)}$_2$] and HASPO[7] preligand **1**, along with K$_2$CO$_3$, *p*-toluenesulfonyl chloride (*p*-TsCl), and *N*,*N*-dimethylacetamide (DMA), was found to be superior (Tables S-1, and S-2 in the Supporting Information).

Thereby, an efficient and selective *in situ* activation of the phenolic starting material was accomplished. The methodology turned out to be operationally simple, since a successive addition of reagents for a preformation of the electrophile was not necessary. In addition to its chemical stability, the in situ generated catalyst displayed a remarkable chemo- and regioselectivity. Hence, undesired byproducts originating from nucleophilic reactivities of the phenols[8,9] or from desulfinylative coupling reactions[10] were not observed.[11]

With an optimized catalytic system in hand, we tested its scope in dehydrative direct arylations of oxazoline **2a** using differently substituted phenols (Scheme 2). These studies highlighted a broad functional group tolerance, which set the stage for the efficient conversion of electron-deficient (**4a−f**), as well as electron-rich (**4g−i**) phenols, bearing inter alia an ester, ketones, alkyl, and aryl fluorides, or an ether. Importantly, the high efficacy of the ruthenium catalyst allowed further for catalytic reactions to be performed at a reduced reaction temperature of 100 °C, as illustrated for the preparation of oxazoline **4b**.

Scheme 2. Dehydrative Direct Arylations of Oxazoline **2a**



Notably, dehydrative direct arylations were not restricted to oxazolines as pronucleophiles but could be employed for the direct functionalization of pyrazolyl-substituted arenes as well (Scheme 3). Hence, functionalized, electron-deficient, as well as electron-rich phenols **3** provided the desired biphenyls **6a−i** in high yields. Additionally, pyridyl-substituted pronucleophiles could be directly arylated, giving selectively the desired biphenyls **7a−c**.

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(6) Recent examples: (a) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081–3084. (b) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741–748. (c) Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Lett.* **2008**, *10*, 3409–3412. (d) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627–1629.

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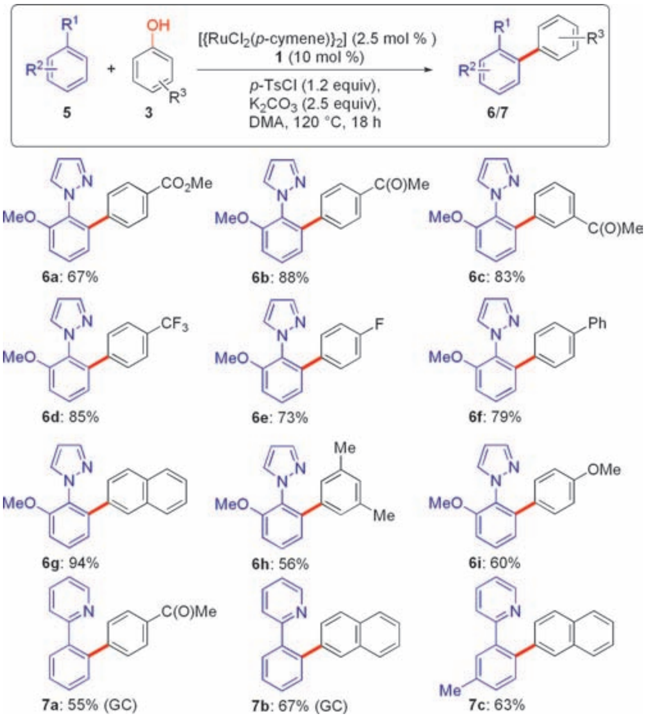
(9) For rhodium-catalyzed *ortho*-arylations of phenols, see: (a) Bedford, R. B.; Betham, M.; Caffyn, A. J. M.; Charmant, J. P. H.; Lewis-Alleyne, L. C.; Long, P. D.; Polo-Ceron, D.; Prashar, S. *Chem. Commun.* **2008**, 990–992. (b) Oi, S.; Watanabe, S.-I.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665–8668. (c) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112–114.

(10) Dubbaka, S. R.; Vogel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 7674–7684.

(11) Representative procedure, synthesis of product **4h**: A suspension of [{RuCl$_2$(*p*-cymene)}$_2$] (7.7 mg, 0.012 mmol, 2.50 mol %), oxazoline **2a** (80.9 mg, 0.502 mmol), preligand **1** (21.4 mg, 0.050 mmol, 10.0 mol %), K$_2$CO$_3$ (173 mg, 1.25 mmol), naphthalen-2-ol (**3h**) (86.5 mg, 0.600 mmol), and *p*-TsCl (114 mg, 0.600 mmol) in dry DMA (1.5 mL) was stirred for 5 min at ambient temperature and then for 18 h at 120 °C under N$_2$. At ambient temperature, EtOAc (70 mL) and H$_2$O (50 mL) were added to the reaction mixture, and the separated aqueous phase was extracted with EtOAc (2 × 70 mL). The combined organic layers were washed with brine (30 mL), dried over Na$_2$SO$_4$, and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 15/1 → 2/1) to yield **4h** (111 mg, 77%) as an off-white solid.

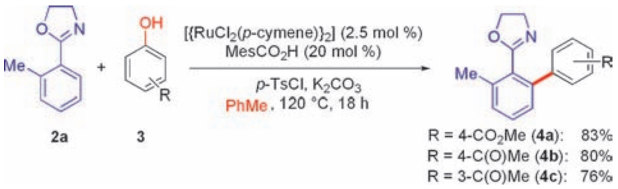
Scheme 3. Scope of Dehydrative Direct Arylations



When apolar toluene was used as solvent, a catalyst derived from carboxylic acid $MesCO_2H$[12] enabled most efficient direct arylations of oxazoline **2a**(Table S-2 in the Supporting Information) through a concerted metalation−deprotonation[12,13] mechanism (Scheme 4).

In summary, we report on the development of a first direct arylation between simple arenes as pronucleophiles and inexpensive, broadly available phenols as proelectrophiles. Notably, this operationally simple dehydrative arylation was achieved with a highly chemo- and regioselective ruthenium catalyst and proceeded through the functionalizations of both C−H as well as C−OH bonds.

Scheme 4. Dehydrative Direct Arylations in an Apolar Solvent



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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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