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Well-Defined Ruthenium(II) Carboxylate as Catalyst for Direct C−H/C−O Bond Arylations with Phenols in Water

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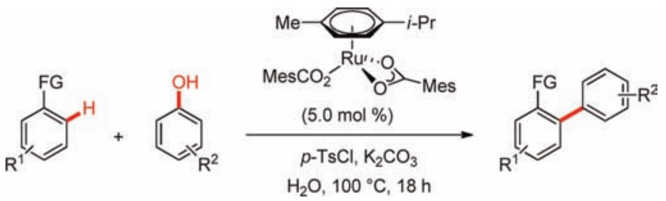
ABSTRACT



The ruthenium(II) carboxylate complex [Ru(O_2CMes)$_2$(*p*-cymene)] enabled efficient direct arylations of unactivated C−H bonds with easily available, inexpensive phenols. Extraordinary chemoselectivity of the well-defined ruthenium catalyst set the stage for challenging C−H/C−O bond functionalizations to occur under solvent-free conditions as well as in water, and allowed first direct C−H bond arylations with user-friendly diaryl sulfates as electrophiles.

Transition-metal-catalyzed cross-coupling reactions between nucleophilic organometallic reagents and electrophilic organic halides are arguably the most versatile tools for the assembly of biaryls (Scheme 1a), key structural motifs in medicinal chemistry or material sciences.[1] While these methods have matured to be highly reliable and versatile, considerable recent efforts were directed toward the development of more sustainable processes for biaryl syntheses. Particularly, catalyzed arylations *via* C−O bond cleavages bear great potential,[2,3] since the corresponding electrophiles are readily accessible from inexpensive phenols and can easily be implemented in site-selective arene functionalizations.[4] This approach gained a noteworthy recent impetus through the use of fluorine-free phenol derivatives, such as aryl carbamates, phosphates, or sulfamates as arylating reagents (Scheme 1b).[5] Despite this remarkable progress in catalyzed C−O bond activation these protocols require stoichiometrically functionalized organometallic nucleophiles, whereas significantly more atom- and step-economical methods involved the direct use of ubiquitous C−H bonds[6] as latent functional groups (Scheme 1c).[7] Unfortunately, all of these strategies

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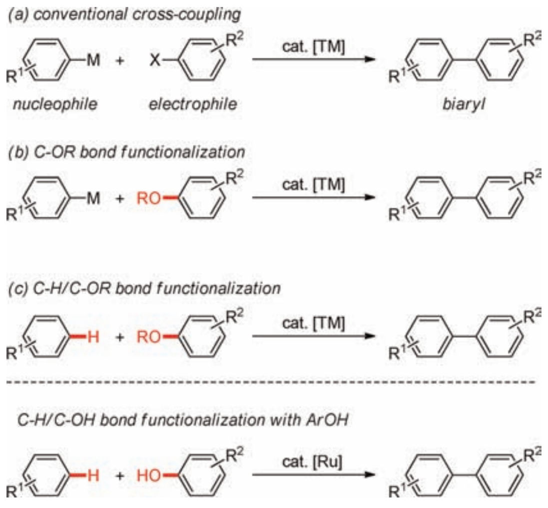
(Scheme 1b and c) strongly rely on a separate derivatization step for the activation of the phenolic starting material. This additional operation not only is time-consuming but also generates additional undesired waste during the formation and isolation of the electrophile. Indeed, a considerable improvement of step economy would be constituted by the direct use of phenols without a separate functionalization step. To this end, we devised ruthenium-catalyzed[8,9] direct C−H[10] bond arylations with phenols *via* C−H/C−OH bond functionalizations in a nonsequential fashion.[11] Unfortunately, these challenging arylations could thus far solely be achieved with *in situ* generated ruthenium complexes predominantly derived from a secondary phosphine oxide[12] as a preligand using aprotic DMA as the solvent.[11]

Scheme 1. Recent Strategies for Sustainable Biaryl Syntheses



During studies on the working mode of ruthenium-catalyzed C−H bond functionalizations we recently unraveled carboxylate assistance[13] as the key to success for efficient direct arylations and identified ruthenium(II) carboxylates as powerful catalysts for direct arylations with aryl halides.[14,15] Given our interest in employing water as sustainable solvent for ruthenium-catalyzed[16] C−H bond transformations,[17,18] we consequently became attracted by probing well-defined ruthenium(II) complexes in the challenging direct arylation with phenols in water, on which we wish to report herein. Notable features of the optimized catalyst include a significantly reduced cocatalyst loading as compared to the *in situ* generated catalyst as well as the use of widely available diaryl sulfates[19] for direct C−H bond arylations.

We initiated our studies by testing well-defined complex $[\mathrm{Ru(O_2CMes)_2}(p\text{-cymene})]$ (**1**) in the direct arylation of

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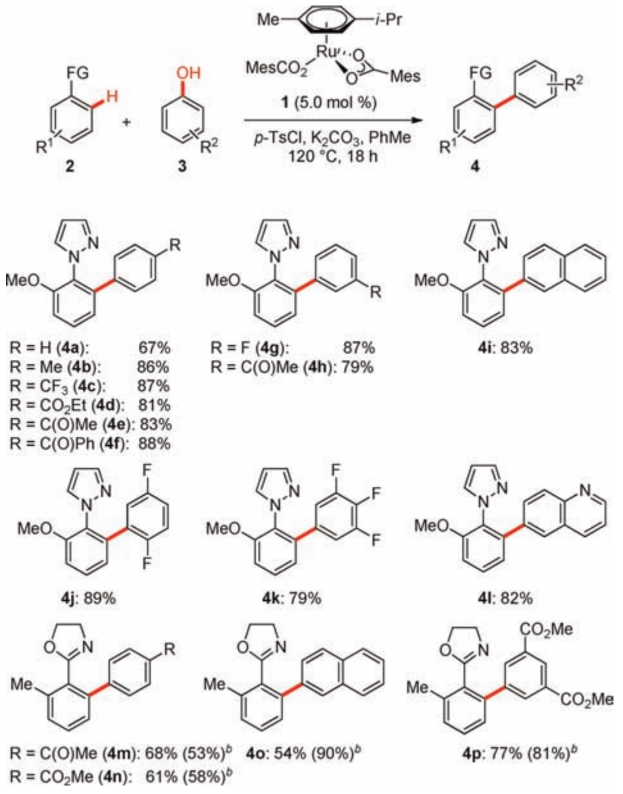
unactivated C–H bonds on pyrazolyl- and oxazolinyl-substituted arenes **2**, directly employing inexpensive phenols **3** in toluene as the solvent (Scheme 2). Gratifyingly, both electron-rich and -deficient proelectrophiles **3** could be employed, bearing important functional groups, such as ester, keto, or fluoro substituents. Furthermore, a heteroaromatic hydroxyquinoline chemoselectively furnished the corresponding biaryl **4l** as well.

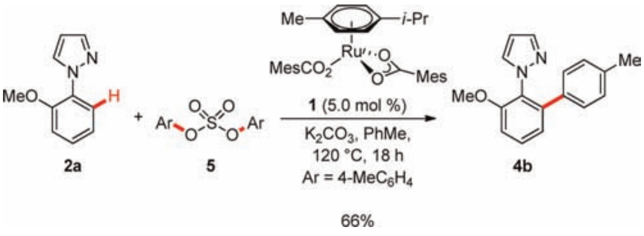
Scheme 2. Scope of Direct C–H/C–OH Bond Arylation with Complex **1**[a]



[a] Yields of isolated products. [b] In parentheses: Isolated yields for reactions with preformed aryl tosylates.

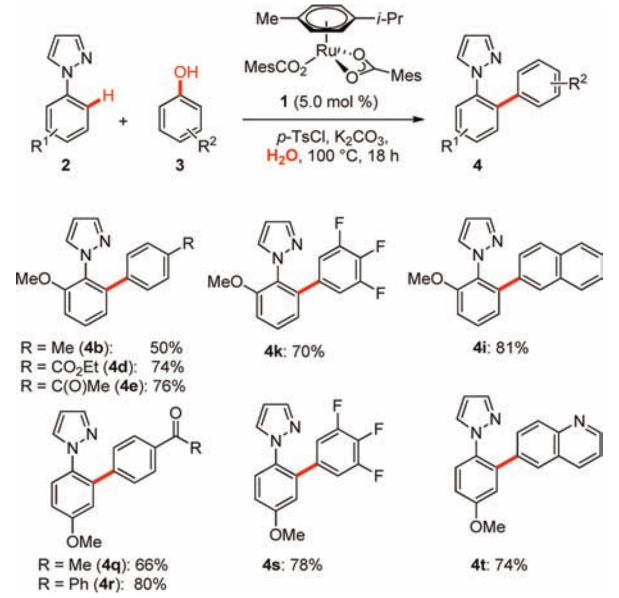
Diaryl sulfates **5** are easily accessible, inexpensive electrophiles, which have thus far not been utilized for transition-metal-catalyzed C–H bond functionalizations.[6] Yet, catalyst **1** allowed for the unprecedented direct arylation of arene **2a** with di(*p*-tolyl) sulfate **5**, thereby providing the desired product **4b** in a high yield (Scheme 3).

Scheme 3. Direct Arylation Using Diaryl Sulfate **5**



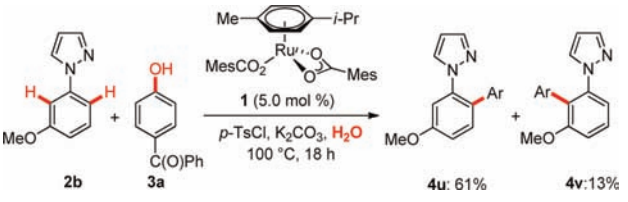
To our delight, the extraordinary chemoselectivity of well-defined ruthenium complex **1** further allowed first direct C–H/C–OH bond arylations to be performed in water as a green solvent (Scheme 4). Notably, the protocol proved tolerant of a wide diversity of functional groups, and chemoselectively delivered the monoarylated products **4** not only when employing *ortho*-substituted arenes but also with *para*-substituted substrates **2**.

Scheme 4. Formal Dehydrative Direct Arylations with Water as Sustainable Solvent



An intramolecular competition experiment with *meta*-substituted arene **2b** in water as the solvent led to the direct arylation predominantly occurring at the less sterically congested C–H bond (Scheme 5).

Scheme 5. Intramolecular Competition Experiment with Catalyst **1** in Water (Ar = 4-$C_6H_4C(O)Ph$)



Finally, we probed the direct arylation of arene **2a** in the absence of solvent,[20] which fortunately also gave rise

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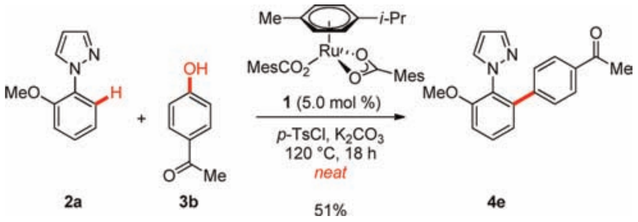
to the chemoselective formation of desired product **4e** (Scheme 6).

Scheme 6. Direct Arylation under Solvent-Free Reaction Conditions



In summary, we have reported on the first use of a well-defined ruthenium(II) biscarboxylate complex for highly efficient direct arylations of unactivated C–H bonds using inexpensive phenols. The highly step-economical C–H/C–OH bond functionalization process was characterized by a wide substrate scope and an outstanding chemoselectivity, which allowed for direct arylations to be performed in water as a sustainable solvent as well as under solvent-free reaction conditions. The high catalytic efficacy of [Ru(O_2CMes)$_2$(*p*-cymene)] (**1**) was further reflected by the unprecedented direct C–H bond arylation with user-friendly diaryl sulfates as arylating reagents.

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

The authors declare no competing financial interest.