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Ortho- and *Para*-Selective Ruthenium-Catalyzed C(sp^2)–H Oxygenations of Phenol Derivatives

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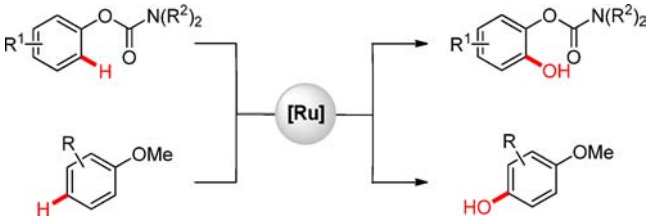
ABSTRACT



Versatile ruthenium catalysts allowed for efficient direct oxygenations of aryl carbamates under remarkably mild reaction conditions. In addition to chelation-assisted C–H activation, the optimized ruthenium catalyst proved amenable to *para*-selective hydroxylations of anisoles without Lewis basic directing groups.

The catalytic direct oxygenation of otherwise unreactive C(sp^2)–H bonds represents the most step-economical approach to substituted phenols.[1,2] While palladium complexes have proven to be useful catalysts for direct C–O bond formations,[3] a very recent success was accomplished with versatile ruthenium(II)[4] catalysts. Hence, arenes bearing weakly coordinating directing groups, such as amides, esters, or ketones, were efficiently converted into the corresponding phenol derivatives.[5] While these studies constituted notable progress in the direct oxygenation of electron-deficient substrates bearing electron-withdrawing directing groups, ruthenium(II)-catalyzed direct C–H bond oxygenations of phenol derivatives have as of yet proven elusive, despite the practical importance of phenols in medicinal chemistry, organic synthesis, material

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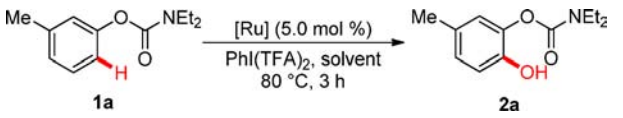
sciences, and crop protection.[6] Within our research program on sustainable C−H bond functionalizations for organic synthesis,[7] we now established first ruthenium-catalyzed hydroxylations of aryl carbamates, on which we report herein. Notably, the optimized catalytic system allowed for direct oxygenations under remarkably mild reaction conditions[8] and was not restricted to substrates displaying Lewis basic directing groups,[9] proving to be also applicable to direct *para*-selective[10] oxygenations with anisole derivatives.

Table 1. Optimization of C−H Oxygenation with Carbamate **1a**[a]



1a **2a**

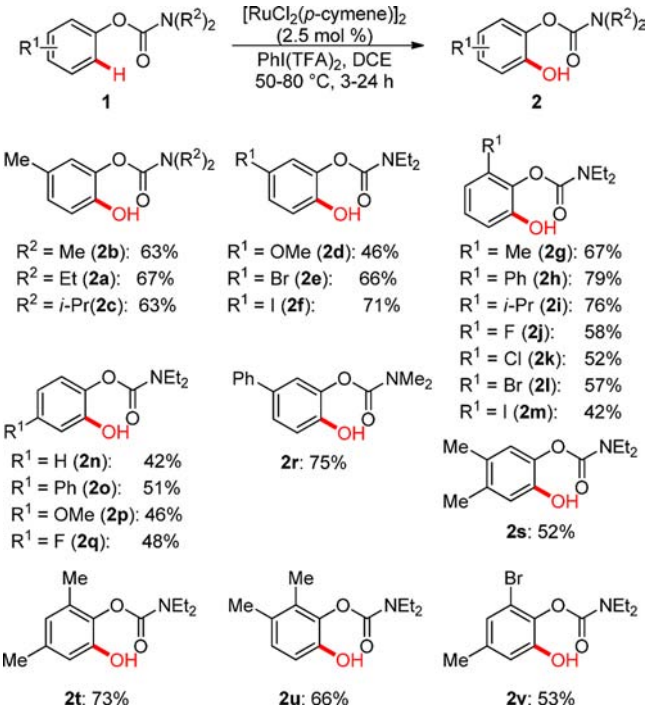
entry	[Ru]	solvent	yield (%)
1	–	DCE	–
2	$[Ru_3(CO)_{12}]$	DCE	39
3	$[Ru(O_2CMes)_2(p\text{-cymene})]$	DCE	46
4	$[RuCl_2(PPh_3)_3]$	DCE	53
5	$[RuCl_3(H_2O)_n]$	DCE	54
6	**$[RuCl_2(p\text{-cymene})]_2$**	**DCE**	**65**
7	$[RuCl_2(p\text{-cymene})]_2$	TFA/TFAA	30[b]
8	$[RuCl_2(p\text{-cymene})]_2$	1,4-dioxane	24[c]
9	$[RuCl_2(p\text{-cymene})]_2$	PhMe	57
10	**$[RuCl_2(p\text{-cymene})]_2$**	**DCE**	**67**[d]

[a] Reaction conditions: **1a** (0.5 mmol), $PhI(TFA)_2$ (1.0 mmol), solvent (2.0 mL), 80 °C, 3 h, isolated yield. [b] $K_2S_2O_8$ (2.0 equiv) instead of $PhI(FTA)_2$. [c] ^1H NMR conversion with CH_2Br_2 as the internal standard. [d] 50 °C, 24 h.

At the outset of our studies, we probed representative ruthenium precursors for the envisioned direct oxygenation of carbamate **1a** (Table 1). While the desired product **2a** was not formed in the absence of a ruthenium catalyst (entry 1), different ruthenium precursors enabled the desired transformation, with optimal results being obtained with $[RuCl_2(p\text{-cymene})]_2$ (entries 2−6). Furthermore, $PhI(TFA)_2$ and DCE were identified as the best oxidant and solvent, respectively (entries 6−9). Importantly, under the optimized conditions the ruthenium-catalyzed C−H bond oxygenation even proved viable at a rather low reaction temperature of 50 °C (entry 10).

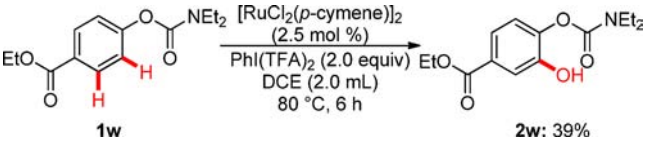
The versatility of the catalytic system was thereafter probed in the direct oxygenation of differently substituted carbamates **1** (Scheme 1). We were pleased to find that the catalyst was widely applicable and efficiently converted *para*-, *meta*-, and even more sterically hindered *ortho*-substituted aryl carbamates bearing various valuable electrophilic functional groups, such as chloro, bromo, or iodo substituents. It is noteworthy that the reactions generally proceeded with excellent chemo- and site-selectivities to deliver the mono-*ortho*-substituted products **2**.

Scheme 1. Scope of C−H Hydroxylation with Carbamates **1**



Given the high catalytic efficacy achieved within direct C−H bond oxygenations with aryl carbamates **1**, we became attracted by establishing the order of relative directing group abilities through competition experiments. Thus, an intramolecular competition experiment with bifunctional substrate **1w** clearly highlighted carbamates to be more potent directing groups as compared with esters (Scheme 2). This selectivity pattern is notable, since the C−H bond activation with aryl carbamates proceeds through the formation of less favorable six-membered ruthenacycles as the key intermediates.

Scheme 2. Intramolecular Competition Experiment



1w **2w:** 39%

In good agreement with this observation, intermolecular competition experiments between differently substituted

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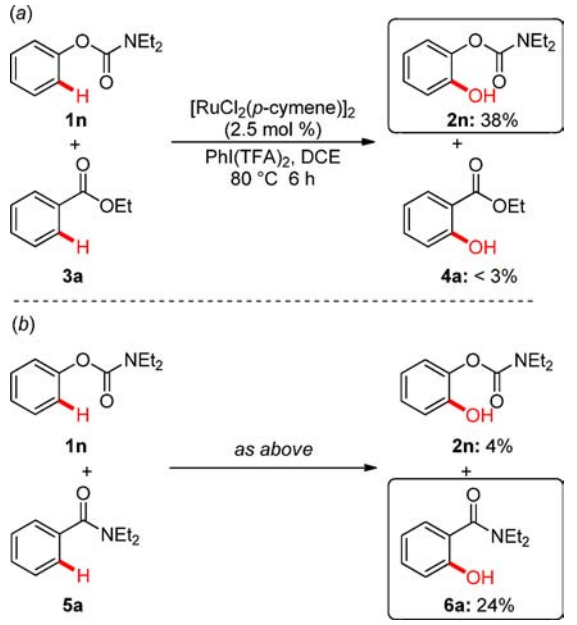
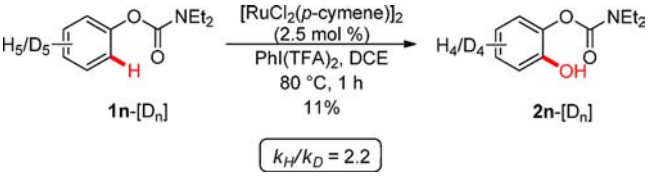
Scheme 3. Intermolecular Competition Experiments



Scheme 4. Kinetic Isotope Effect Study



arenes established the following order of directing group ability: amide > carbamate > ester (Scheme 3).

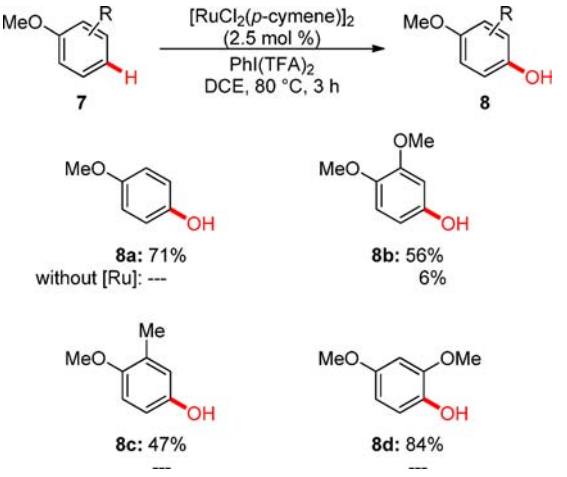
As to the C−H metalation step, studies with isotopically labeled substrate **1n-**[D_5] were suggestive of a kinetically relevant C−H activation with a KIE ≈ 2.2 (Scheme 4).

Thus far, ruthenium-catalyzed C(sp^2)−H bond oxygenations were to the best of our knowledge largely limited to substrates bearing Lewis basic directing groups,[4,5] consequently leading to *ortho*-substitution.[11] Thus, it is noteworthy that anisole derivatives **7** were also converted

(11) For recent ruthenium-catalyzed *meta*-selective C−H bond functionalizations, see: (a) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877–5884. (b) Saidi, O.; Marafie, J.; Ledger, A. E. W.; Liu, P. M.; Mahon, M. F.; Kociok-Kohn, G.; Whittlesey, M. K.; Frost, C. G. *J. Am. Chem. Soc.* **2011**, *133*, 19298–19301.

(12) Under otherwise identical reaction conditions the use of $AlCl_3$ or $FeCl_3$ as the catalyst led only to < 5% of product **8a**, as determined by GC analysis.

Scheme 5. *Para*-Selective C−H Oxygenation of Anisoles **7**



by the ruthenium(II) catalyst[12] to the corresponding hydroxylated phenols **8a**−**d**[10b] in a *para*-selective fashion (Scheme 5).

As to the reaction mechanism, oxygenations of anisole **7a** in the presence of catalytic (10 mol %) or stoichiometric (1 equiv) amounts of TEMPO furnished product **8a** in significantly reduced yields of 43% and 5%, respectively, which *inter alia* can be rationalized in terms of a single-electron-transfer oxidation. However, more detailed mechanistic studies are required to delineate the catalyst's exact mode of action.

In summary, we have reported on the first ruthenium-catalyzed C(sp^2)−H bond oxygenation of phenol derivatives. Thus, direct hydroxylations of aryl carbamates proceeded with high catalytic efficacy as well as excellent chemo- and *ortho*-selectivities. In contrast, the ruthenium(II) catalyst also allowed for the direct C−H bond functionalization on anisole derivatives, which occurred with *para*-selectivity.

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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.

The authors declare no competing financial interest.