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Ruthenium-Catalyzed Oxidative C−H Bond Alkenylations in Water: Expedient Synthesis of Annulated Lactones

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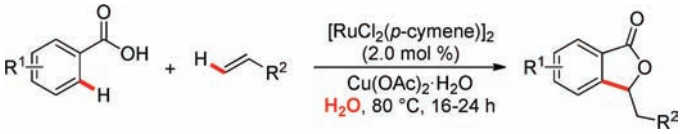
ABSTRACT



Ruthenium-catalyzed cross-dehydrogenative C−H bond alkenylations occurred efficiently in environmentally benign water, which was exploited for an oxidative phthalide synthesis with ample scope. Mechanistic studies provided strong evidence for the oxidative alkenylation to proceed by an irreversible C−H bond metalation *via* acetate assistance.

Cross-dehydrogenative C−H bond functionalizations[1] have attracted significant recent attention, because these methods avoid the tedious, multistep preparation of pre-functionalized starting materials and, hence, enable a streamlining of organic synthesis.[2] Particularly, pioneering studies by Fujiwara and Moritani[3] as well as Matsumoto[4] have set the stage for a plethora of oxidative palladium- and rhodium-catalyzed alkenylations, respectively.[1,2] Yet, less expensive ruthenium catalysts have thus far been underutilized for cross-dehydrogenative C−H bond alkenylations,[5,6] with notable exceptions being represented by elegant contributions from Milstein[5a] as well as Miura and Satoh.[5b]

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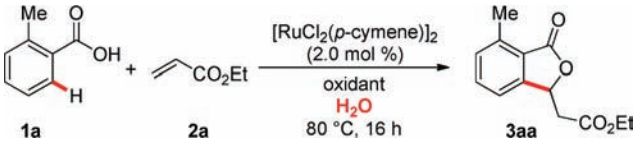
Remarkable practical progress in catalyzed functionalizations of unreactive C−H bonds was recently accomplished by the use of water as an environmentally benign, nonflammable, and nontoxic reaction medium.[7,8] Based on recent studies directed toward the ruthenium-catalyzed oxidative annulations of alkynes[9] we developed first ruthenium-catalyzed oxidative C−H bond alkenylations in water,[10] on which we wish to report herein. Specifically, benzoic acids[11] underwent a reaction sequence comprising an intermolecular oxidative alkenylation and a subsequent oxa-Michael reaction. Thereby, diversely substituted phthalides were obtained, which constitute valuable intermediates in organic synthesis and indispensable structural motifs of bioactive molecules.[12] It is noteworthy that related palladium- or rhodium-catalyzed cascade reactions have thus far only been realized in organic solvents.[13]

At the outset of our studies, we probed the effect of representative oxidants, additives, and solvents on the ruthenium-catalyzed cross-dehydrogenative alkenylation of benzoic acid **1a** employing olefin **2a** (Table 1). Notably, the desired product **3aa** was not formed in the absence of a sacrificial oxidant (entry 1). Yet, particularly $Cu(OAc)_2$ proved to be effective among various terminal oxidants (entries 2−10). Interestingly, $CuBr_2$ could be employed as well, provided that superstoichiometric amounts of an acetate salt were present (entries 6−8), thus indicating carboxylate assistance.[14,15] Among representative solvents, H_2O turned out to be the most suitable (entries 9−13). With respect to the reaction mechanism, it is notable that TEMPO as an additive did not inhibit the catalytic activity (entry 14).[16]

Table 1. Optimization of Ruthenium-Catalyzed Oxidative Alkenylations[a]



1a 2a 3aa

entry	oxidant	additive	solvent	yield
1	---	---	H_2O	---
2	$PhI(OAc)_2$	---	H_2O	---
3	benzoquinone	---	H_2O	25%
4	$AgNO_3$	---	H_2O	---
5	AgOAc	---	H_2O	<5%
6	$CuBr_2$	---	H_2O	---
7	$CuBr_2$	LiOAc (3.0 equiv)	H_2O	66%
8	$CuBr_2$	NaOAc (3.0 equiv)	H_2O	86%
9	$Cu(OAc)_2$	---	H_2O	95%
10	$Cu(OAc)_2$	---	H_2O	90%[b]
11	$Cu(OAc)_2$	---	MeOH	28%
12	$Cu(OAc)_2$	---	*t*-AmOH	34%
13	$Cu(OAc)_2$	---	*m*-xylene	---
14	$Cu(OAc)_2$	TEMPO (20 mol %)	H_2O	95%

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %), oxidant (2.0 equiv), H_2O (5.0 mL), 80 °C, 16 h; isolated yields. [b] $[RuCl_2(p\text{-cymene})]_2$ (1.0 mol %).

Subsequently, we explored the scope of the ruthenium-catalyzed oxidative phthalide synthesis in water (Scheme 1). We were delighted to observe that differently substituted benzoic acids **1** were converted with high efficacy. For instance, the catalytic system tolerated valuable electrophilic functional groups, such as fluoro or bromo substituents. Further, sterically hindered *ortho*-substituted acids **1a**−**1h** proved to be viable

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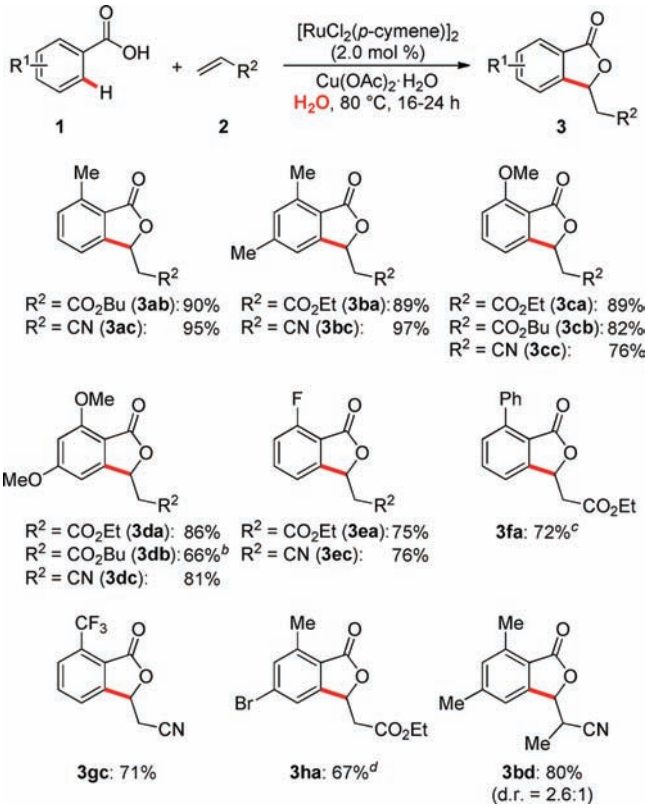
(16) Reactions in the presence of 3 wt % of surfactant PTS/H_2O (polyoxyethanyl α-tocopheryl sebacate) did not provide improved yields in a set of representative transformations.

Scheme 1. Scope of Ruthenium-Catalyzed Oxidative C−H Bond Functionalization in Water[a]



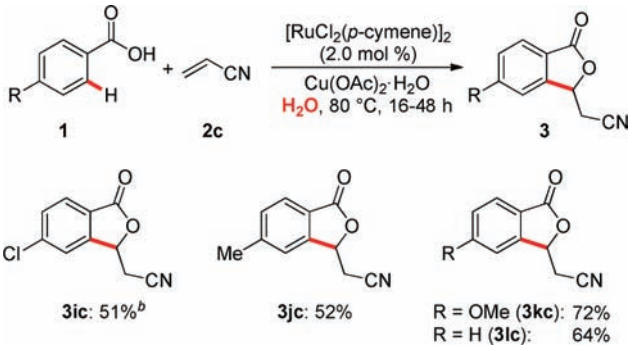
[a] Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %), $Cu(OAc)_2 \bullet H_2O$ (2.0 mmol), H_2O (5.0 mL), 80 °C, 16–24 h; isolated yields. [b] 3,5-Dimethoxyphenylacrylic acid butyl ester (**4db**) was also isolated in 29% yield. [c] $[RuCl_2(p\text{-cymene})]_2$ (4.0 mol %). [d] 48 h.

starting materials. The protocol was not restricted to acrylic acid esters **2** as olefinic substrates, but also allowed for the conversion of acrylonitrile **2c**. Notably, more sterically demanding α-substituted alkene **2d** furnished desired product **3bd** in a comparably high isolated yield. Interestingly, the cross-dehydrogenative reaction between benzoic acid **1d** and alkene **2b** delivered desired lactone **3db**, along with significant amounts of product **4db** through a direct alkenylation/decarboxylation cascade reaction.

The ruthenium catalyst turned out to be broadly applicable, and thus also enabled the selective conversion of benzoic acids **1i**−**1l** not bearing an *ortho*-substituent (Scheme 2).

Considering the remarkably broad scope and high chemoselectivity of the ruthenium catalysis in water, we thereafter probed its working mode through the use of isotopically labeled substrates. Hence, reactions with starting material **1l**-$[D_5]$ highlighted that a reversible H/D exchange was not operative (Scheme 3a). Moreover, an intermolecular competition experiment was indicative of an irreversible ruthenation event with a kinetic isotope effect (KIE) of $k_H/k_D \approx 3.6$ (Scheme 3b).

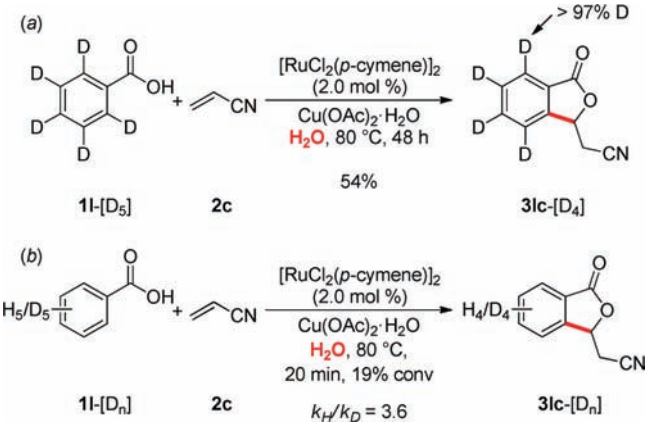
Scheme 2. Oxidative C−H Bond Functionalization with *para*-Substituted Acids **1** in Water[a]



[a] Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.0 mol %), $Cu(OAc)_2 \bullet H_2O$ (2.0 mmol), H_2O (5.0 mL), 80 °C, 16–24 h; isolated yields. [b] 48 h.

In summary, we have disclosed the first ruthenium-catalyzed oxidative C−H bond alkenylation with water as an environmentally benign, nontoxic reaction medium. Thus, a highly chemoselective ruthenium catalyst enabled a versatile phthalide synthesis with ample scope through a reaction sequence consisting of cross-dehydrogenative alkenylation and subsequent intramolecular oxa-Michael reaction. Experimental mechanistic studies were suggestive of a kinetically relevant, irreversible C−H bond ruthenation through acetate assistance.

Scheme 3. Oxidative C−H Bond Functionalizations with Substrate **1l**-$[D_5]$



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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.