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Ruthenium-Catalyzed Oxidative C−H Alkenylations of Anilides and Benzamides in Water

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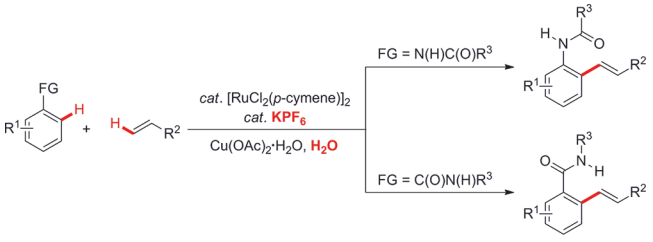
ABSTRACT



A cationic ruthenium(II) complex enabled efficient oxidative alkenylations of anilides in water as a green solvent and proved applicable to double C−H bond functionalizations of (hetero)aromatic amides with ample scope. Detailed studies provided strong support for a change of ruthenation mechanism in the two transformations, with an irreversible metalation as the key step in cross-dehydrogenative alkenylations of benzamides.

Direct oxidative alkenylations of (hetero)arenes *via* two-fold C−H bond cleavages are highly attractive tools for atom- and step-economical organic syntheses, because they avoid the preparation and use of prefunctionalized starting materials.[1] Based on early reports by Fujiwara and Moritani[2,3] a wealth of palladium- and rhodium-catalyzed oxidative alkenylations were developed.[4] Conversely, less expensive ruthenium complexes were as of yet underutilized for cross-dehydrogenative alkenylations of (hetero)arenes, with notable exceptions being accomplished only very recently.[5,6] Despite this significant recent progress, ruthenium-catalyzed direct oxidative alkenylations continue to be limited to (hetero)arenes bearing electron-withdrawing directing groups.[5,6] Given the importance of anilines as key intermediates for the preparation of bioactive

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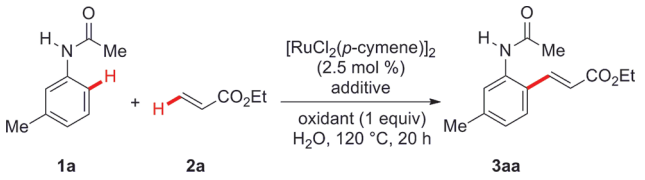
compounds and functional materials,[7] we hence set out to develop the first ruthenium-catalyzed cross-dehydrogenative alkenylations of anilines, on which we wish to report herein. Notably, the most efficient catalysis was achieved with a cationic[6c,e] ruthenium(II) complex in water[8,9] as a green solvent, which allowed for efficient cross-dehydrogenative alkenylations of benzamides[10] as well.

Table 1. Optimization of Alkenylation with Acetanilide **1a**[a]



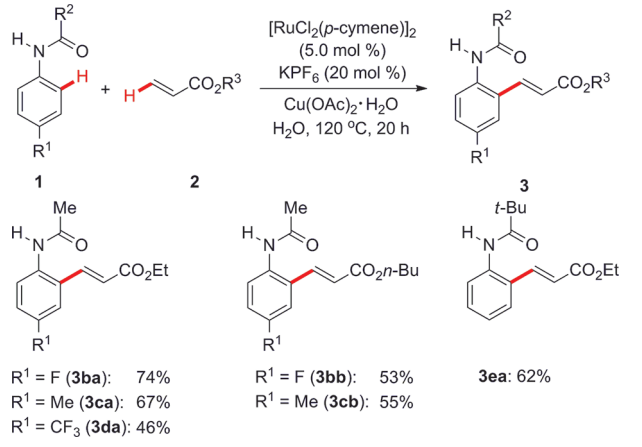
entry	oxidant	additive (mol %)	yield
1	$Cu(OAc)_2 \cdot H_2O$	KPF_6 (10)	–[b]
2	$Cu(OAc)_2 \cdot H_2O$	–	2%[c]
3	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$ (10)	54%
4	**$Cu(OAc)_2 \cdot H_2O$**	**KPF_6 (10)**	**87%**
5	$Cu(OAc)_2 \cdot H_2O$	KPF_6 (5.0)	80%
6	$Cu(OAc)_2 \cdot H_2O$	KPF_6 (10)	77%[d]
7	$Cu(OAc)_2 \cdot H_2O$	KPF_6 (10)	54%[e]
8	$Cu(OAc)_2 \cdot H_2O$ (10 mol %)	KPF_6 (10)	48%[c,d,f]
9	Ag_2CO_3	KPF_6 (10)	–
10	AgOAc	KPF_6 (10)	40%[c]

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), additive (10 mol %), oxidant (0.5 mmol), H_2O (2.0 mL), 120 °C, 20 h, under N_2, isolated yields. [b] Without $[RuCl_2(p\text{-cymene})]_2$. [c] GC conversion. [d] 100 °C. [e] *t*-AmOH (2.0 mL). [f] Under air.

At the outset of our studies, we optimized reaction conditions for the oxidative alkenylation of acetanilide **1a** with alkene **2a** (Table 1). In the absence of an additive, only trace amounts of the desired product **3aa** were formed (entries 1 and 2). Yet, high catalytic efficiency was ensured by a complex generated *in situ* from $[RuCl_2(p\text{-cymene})]_2$ and cocatalytic amounts of KPF_6 (entries 3–6), reaction conditions previously established for the generation of cationic ruthenium(II) complexes.[11] Water proved to be the solvent of choice (entries 4 and 7), and an aerobic oxidative alkenylation with cocatalytic amounts of $Cu(OAc)_2 \cdot H_2O$ was viable, albeit with reduced efficacy (entry 8). The use of silver(I) salts as terminal oxidants provided less satisfactory results but indicated a strong dependence of the catalyst's performance on the presence of acetates[12] (entries 9 and 10).

With an optimized catalytic system in hand, we explored its scope in the intermolecular oxidative alkenylation of anilides **1** (Scheme 1). Thus, the catalytic C–H bond functionalization in water allowed for the efficient conversion of *para*-substituted substrates **1b–d** and parent anilide **1e** *via* chemoselective monoalkenylations.

Scheme 1. Oxidative Alkenylations with Anilides **1**



Intramolecular competition experiments with *meta*-substituted anilides **1** site selectively delivered the products **3** through alkenylation in position C-6, likely due to steric interactions (Scheme 2). Notably, this reactivity pattern was not observed when using *meta*-fluoro-substituted anilide **1i**, as was previously noted for ruthenium-catalyzed C–H bond functionalization with organic electrophiles.[13]

Interestingly, intermolecular competition experiments revealed electron-rich anilides **1** to be preferentially functionalized (Scheme 3),[14] which is in good agreement with an electrophilic activation manifold.

Additionally, the cationic ruthenium(II) complex led to *ortho*-selective H/D exchange on anilide **1j**, when employing D_2O as the solvent (Scheme 4), thereby indicating a reversible cycloruthenation event.

However, the chemoselectivity was found to be significantly altered when using *N*-benzoyl anilines **1k** and **1l** as the substrates, solely leading to C–H bond alkenylation at the benzamide moiety (Scheme 5).

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(9) For examples of ruthenium-catalyzed C–H bond functionalizations with water: (a) Ackermann, L.; Hofmann, N.; Vicente, R. *Org. Lett.* **2011**, *13*, 1875–1877. (b) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 6629–6632. (c) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–3125. (d) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866–4877.

(10) For very recent examples of oxidative alkenylations with benzamides in *organic solvents*, see refs 6a,6e.

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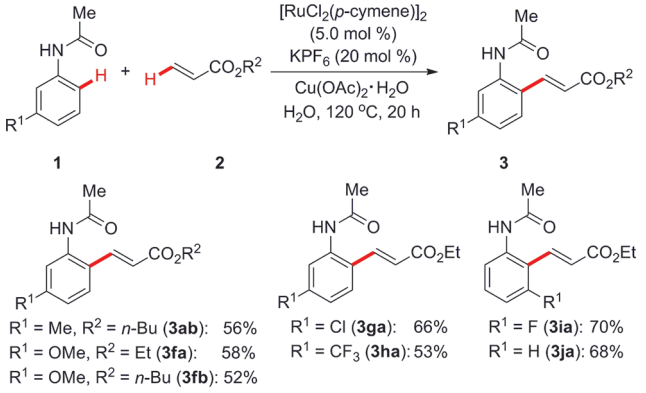
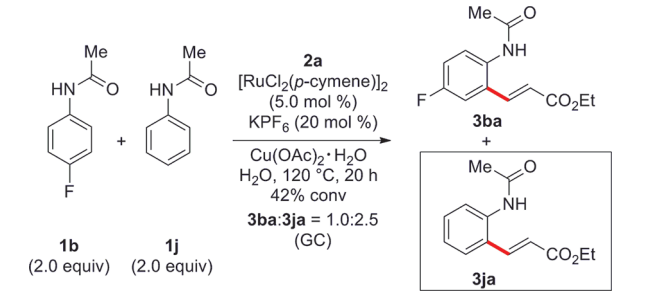
(14) For detailed information see the Supporting Information.

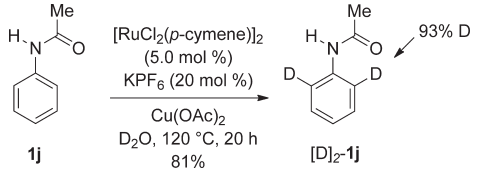
Scheme 2. Alkenylations with *Meta*-Substituted Substrates **1**



Scheme 3. Intermolecular Competition Experiment



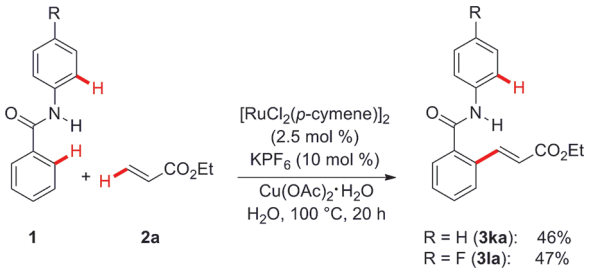
Scheme 4. Ruthenium-Catalyzed H/D Exchange in D_2O



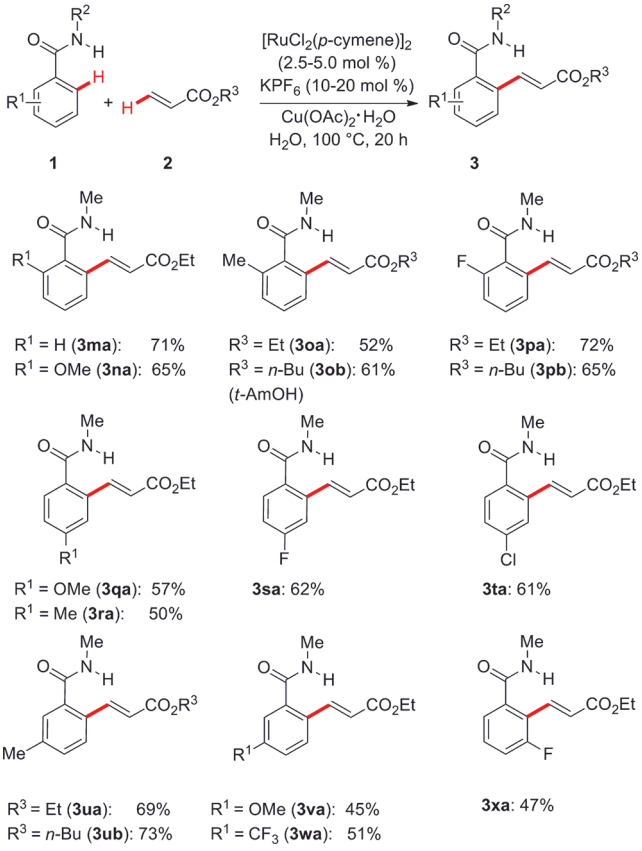
For the oxidative alkenylations of benzamides **1** the previously optimized reaction conditions (*vide supra*) were found to be superior as compared to numerous variations of the solvent (DMF, NMP, MeCN, *ortho*-xylene, *t*-AmOH), the oxidant ($CuBr_2$, Ag_2CO_3, AgOAc), or the cocatalytic additive (PPh_3, NH_4PF_6, $NaBF_4$, NH_4BF_4, $NaBPh_4$, BARF, NH_4OTf).[14]

Importantly, the cationic ruthenium(II) complex was broadly applicable and enabled the conversion of differently substituted benzamides **1** by chemoselective monoalkenylations (Scheme 6). The site selectivity within intramolecular competition experiments with *meta*-substituted benzamides **1u**–**1w** was largely governed by steric interactions. However, *meta*-fluoro-substituted arene **1x** was functionalized at its C-2 position. *N*-Pentafluorophenyl benzamide (**4**) was a viable substrate as well and delivered lactams **5** and **6** *via* a reaction sequence consisting of oxidative alkenylation and intramolecular aza-Michael addition (Scheme 7).

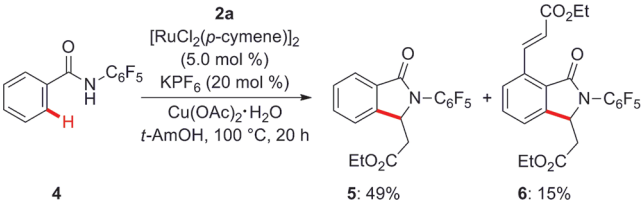
Scheme 5. Intramolecular Competition Experiment



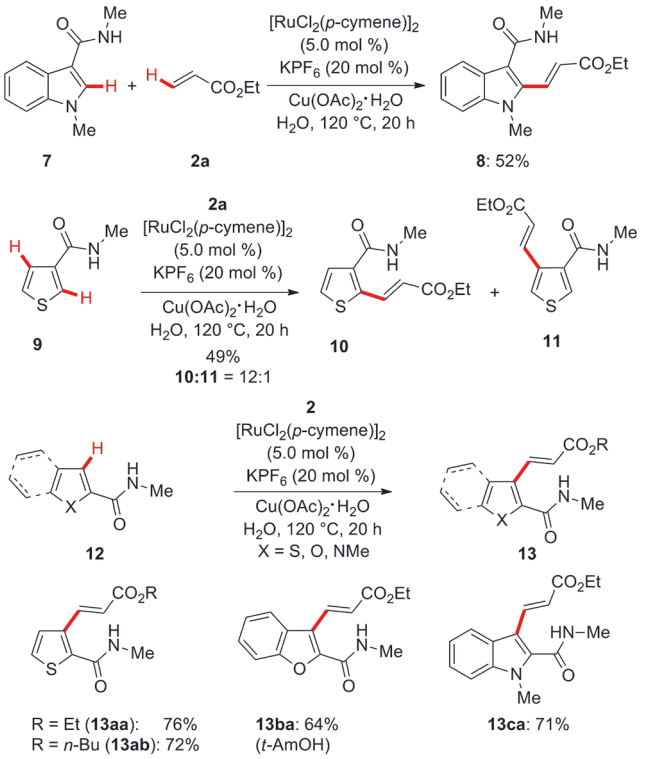
Scheme 6. Oxidative C–H Bond Alkenylation of Benzamides



Scheme 7. Oxidative Alkenylation of Benzamide **4**



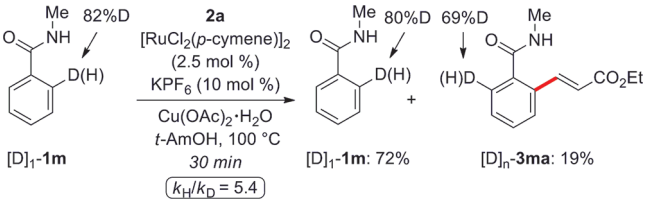
Scheme 8. Oxidative Alkenylation of Heteroaromatic Substrates



Further, direct C−H bond functionalization of heteroaromatic[15] amides **7**, **9**, and **12a**−**c** occurred with high catalytic efficacy and excellent site selectivity (Scheme 8).

As to the catalyst's working mode, intermolecular competition experiments indicated electron-deficient benzamides **1** to be converted with higher relative reaction rates.[14] Mechanistic studies with isotopically labeled substrate [D]$_1$-**1m** indicated the cycloruthenation to be irreversible, with an intramolecular kinetic isotope effect[16] of $k_H/k_D \approx 5.4$ (Scheme 9).

Scheme 9. Direct Alkenylation with Labeled Substrate [D]$_1$-**1m**



In summary, we have reported on the first ruthenium-catalyzed oxidative alkenylations of anilides. Detailed optimization studies revealed a cationic ruthenium(II) complex to be the catalyst of choice in water as a green solvent. The cationic catalyst also set the stage for efficient twofold C−H bond alkenylations with various benzamides. Mechanistically, the two transformations were found to display different rate-limiting steps, with an irreversible C−H bond metalation in cross-dehydrogenative alkenylations of benzamides. Further studies on ruthenium-catalyzed oxidative C−H bond functionalizations are ongoing in our laboratories and will be reported in due course.

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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.

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The authors declare no competing financial interest.