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Oxidative Alkenylation of Aromatic Esters by Ruthenium-Catalyzed Twofold C–H Bond Cleavages

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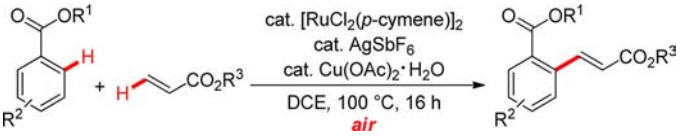
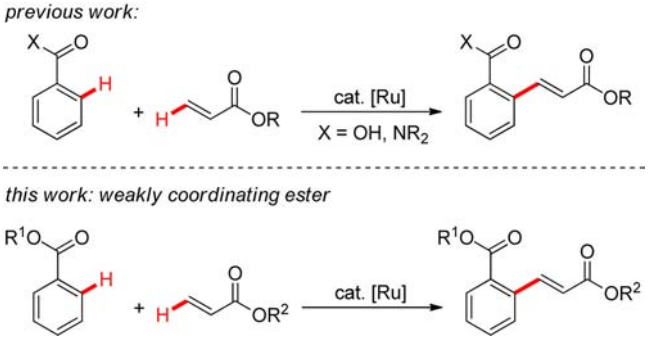
ABSTRACT



Cationic ruthenium(II) complexes enabled catalytic twofold C–H bond functionalizations with weakly coordinating aromatic esters in a highly chemo-, site- and diastereo-selective as well as site selective fashion. The oxidative Fujiwara–Moritani-type alkenylation provided step-economical access to diversely substituted styrenes and proved viable in an aerobic manner. Mechanistic studies were indicative of a reversible acetate-assisted cycloruthenation step.

Styrene derivatives are useful intermediates in synthetic organic chemistry, and one of their most atom- and step-economical syntheses exploits catalyzed C–H bond functionalizations.[1] While early studies revealed palladium complexes as effective catalysts,[2] important recent progress was achieved by inter alia Miura and Satoh, Yu, Li, and Glorius with the development of versatile protocols for selective palladium- and rhodium-catalyzed cross-dehydrogenative alkenylations.[3] In contrast, rather inexpensive ruthenium complexes have only recently been exploited as catalysts for oxidative C–H bond alkenylations on arenes.[4,5] While these chelation-assisted reactions were site selectively accomplished utilizing benzamides or benzoic acids, ruthenium-catalyzed[6] oxidative[7] alkenylations with readily available, yet only weakly coordinating esters have thus far proven elusive (Scheme 1).

Scheme 1. Ruthenium-Catalyzed Double C–H Bond Functionalizations



Within our research program on the use of C–H bonds as latent functional groups in organic synthesis,[8] we thus became attracted by cross-dehydrogenative alkenylations of aromatic esters and, particularly, by devising challenging intermolecular twofold C–H bond functionalizations

(1) Illustrative reviews on C–H bond functionalizations: (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292. (b) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740–4761. (c) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503–4513. (d) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57–84. (e) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677–685. (f) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1119–1126. (g) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (h) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820–5831. (i) Ackermann, L.; Vicente, R; Kapdi, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826 and references cited therein.

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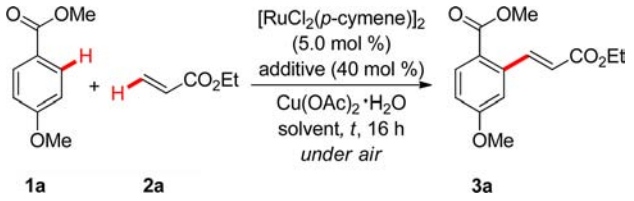
between two different esters in a chemoselective fashion. Herein, we wish to disclose our[9] findings on the development of versatile ruthenium-catalyzed oxidative alkenylations of easily modifiable (hetero)aromatic esters, which were even achieved in an aerobic manner. Furthermore, we present the first detailed mechanistic studies, providing strong support for a reversible C−H bond ruthenation step.

We commenced our studies by probing a variety of cocatalytic additives and solvents for the envisioned twofold C−H bond functionalization between aromatic ester **1a** and alkenylic ester **2a**, employing $Cu(OAc)_2 \cdot H_2O$ as the oxidant under an atmosphere of ambient air (Table 1). While different metal carboxylates as well as KPF_6 as the additives gave only unsatisfactory yields (entries 1−4), more promising results were accomplished using silver(I) salts, with $AgSbF_6$ proving to be optimal (entries 5−8).[10] Notably, the use of $CuBr_2$ as the oxidant did not deliver the desired product **3a** (entry 9), thereby indicating carboxylate assistance to be of relevance.[11] Among a variety of solvents, DCE was found to allow the most efficient catalysis (entries 8−14). It is furthermore noteworthy that the catalyzed double C−H bond functionalization could also be performed in the absence of a solvent (entry 15), while AcOH as the (co)solvent did not improve the yield (entries 16−17).

Table 1. Optimization of C−H Bond Alkenylation of Ester **1a**[a]



entry	additive	solvent	t (°C)	yield (%)
1	–	DCE	100	–
2	NaOAc	DCE	100	–
3	CsOAc	DCE	100	–
4	KPF_6	DCE	100	–
5	AgOAc	DCE	100	–
6	$AgBF_4$	DCE	100	30[b]
7	AgO_3SCF_3	DCE	100	48
8	**$AgSbF_6$**	**DCE**	**100**	**62**
9	$AgSbF_6$	DCE	100	–[c]
10	$AgSbF_6$	H_2O	120	–
11	$AgSbF_6$	DMF	120	–
12	$AgSbF_6$	*o*-xylene	120	–
13	$AgSbF_6$	1,4-dioxane	100	27[b]
14	$AgSbF_6$	*t*-AmOH	120	13
15	$AgSbF_6$	–	100	40
16	$AgSbF_6$	DCE/AcOH (1.8/0.2)	100	19
17	$AgSbF_6$	AcOH	100	8[b]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), solvent (2.0 mL); isolated yields, under air. [b] GC conversion. [c] $CuBr_2$ (1.0 mmol) as the oxidant.

With an optimized catalytic system in hand, we subsequently explored its scope in the oxidative alkenylation of diversely decorated esters **1** (Scheme 2). Notably, the cationic ruthenium(II) catalyst efficiently converted *para*- and more sterically congested *ortho*-substituted esters **1**, thereby chemoselectively delivering the mono-*ortho*-alkenylated arenes **3a**−**3g** and **3h**−**3m** as the sole products, respectively. Likewise, a more hindered ester group could be present

(3) Selected recent examples: (a) Baxter, R. D.; Sale, D.; Engle, K. M.; Yu, J.-Q.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 4600–4606. (b) Patureau, F. W.; Nimphius, C.; Glorius, F. *Org. Lett.* **2011**, *13*, 6346–6349. (c) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350–2353. (d) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1064–1067. (e) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 3024–3033. (f) Li, X.; Gong, X.; Zhao, M.; Song, G.; Deng, J.; Li, X. *Org. Lett.* **2011**, *13*, 5808–5811. (g) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982–9983. (h) Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916–5921. (i) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, 1407–1409. (j) Dams, M.; De Vos, D. E.; Celen, S.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3512–3515. (k) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587. Recent reviews: (l) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788–802. (m) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651–3678. (n) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212–11222 and references cited therein.

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(5) For examples of related oxidative annulations of alkynes, see: (a) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379–6382. (b) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Org. Lett.* **2011**, *13*, 3278–3281. (c) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548–6551. (d) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.* **2012**, *14*, 930–933. (e) Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2012**, *3*, 177–180. (f) Chinnagolla, R. K.; Jeganmohan, M. *Chem. Commun.* **2012**, *48*, 2030–2032. (g) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764–767. (h) Parthasarathy, K.; Senthilkumar, N.; Jayakumar, J.; Cheng, C.-H. *Org. Lett.* **2012**, *14*, 3478–3481. (i) Thirunavukkarasu, V. S.; Donati, M.; Ackermann, L. *Org. Lett.* **2012**, *14*, 3416–3419.

(6) An elegant rhodium-catalyzed olefination of arene esters was reported by Chang and coworkers: Park, S. H.; Kim, J. Y.; Chang, S. *Org. Lett.* **2011**, *13*, 2372–2375.

(7) For examples of ruthenium-catalyzed hydroarylations with aromatic esters, see: (a) Kakiuchi, F.; Ohtaki, H.; Sonoda, M.; Chatani, N.; Murai, S. *Chem. Lett.* **2001**, 918–919. (b) Neisius, N. M.; Plietker, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5752–5755 and references cited therein.

(8) Recent reviews: (a) Ackermann, L. *Pure Appl. Chem.* **2010**, *82*, 1403–1413. (b) Ackermann, L. *Isr. J. Chem.* **2010**, *50*, 652–663.

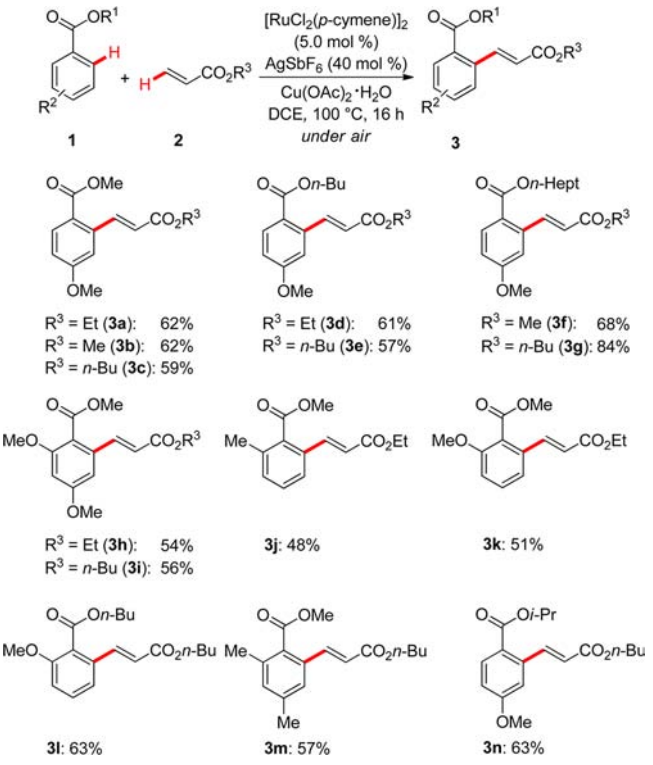
(9) During the preparation of our manuscript a related independent study was disclosed: Padala, K.; Pimparkar, S.; Madasamy, P.; Jeganmohan, M. *Chem. Commun.* **2012**, *48*, 7140–7142.

(10) The desired product **3a** was not formed when using $[RuCl_2(PPh_3)_3]$ as the catalyst.

(11) Recent examples of carboxylate-assisted ruthenium-catalyzed C−H bond activations: (a) Ackermann, L.; Pospech, J.; Potukuchi, H. K. *Org. Lett.* **2012**, *14*, 2146–2149. (b) Ackermann, L.; Diers, E.; Manvar, A. *Org. Lett.* **2012**, *14*, 1154–1157. (c) Ackermann, L.; Lygin, A. *Org. Lett.* **2011**, *13*, 3332–3335. (d) Ouellet, S. G.; Roy, A.; Molinaro, C.; Angelaud, R.; Marcoux, J.-F.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem.* **2011**, *76*, 1436–1439. (e) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032–5035. (f) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045–6048 and references cited therein.

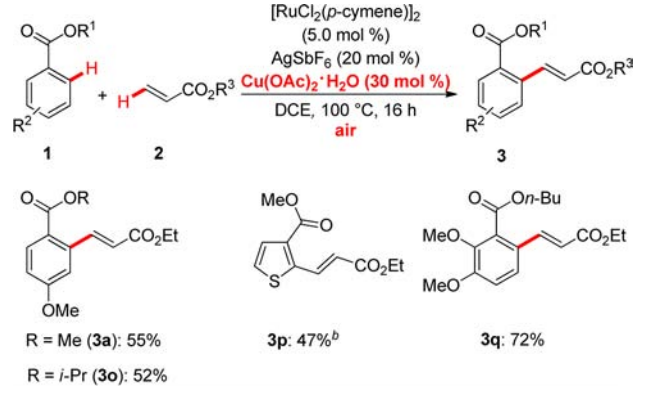
within the twofold C−H bond functionalization strategy to furnish the desired product of cross-dehydrogenative alkenylation (**3n**).[12]

Scheme 2. Scope of Oxidative Alkenylation with Esters **1**



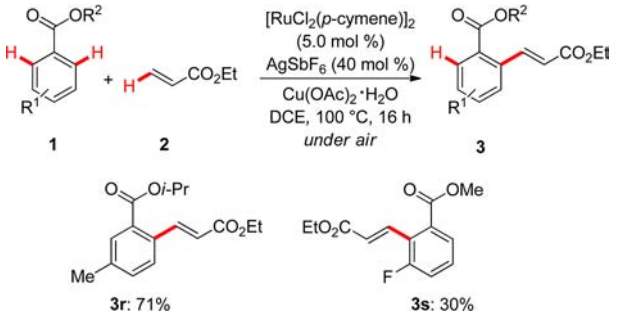
Importantly, the oxidative C−H bond functionalization was also viable in an aerobic fashion, using cocatalytic amounts of $Cu(OAc)_2 \cdot H_2O$ under an atmosphere of ambient air (Scheme 3). The aerobic oxidative alkenylation site selectively occurred on arenes as well as heteroarenes **2** with high catalytic efficacy.

Scheme 3. Aerobic Oxidative Alkenylation with Esters **1**[a]

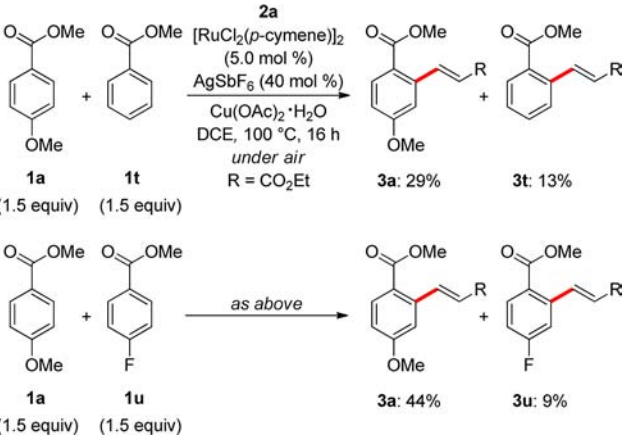


[a] Isolated yields. [b] The corresponding hydroarylation product was formed in 8% yield (by ^{1}H NMR).

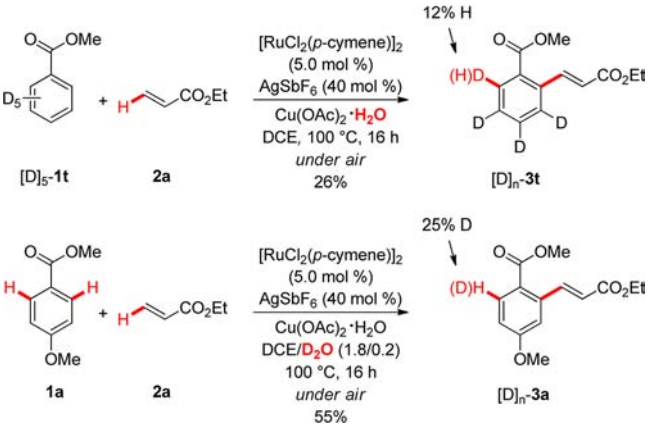
Scheme 4. Intramolecular Competition Experiments



Scheme 5. Intermolecular Competition Experiments



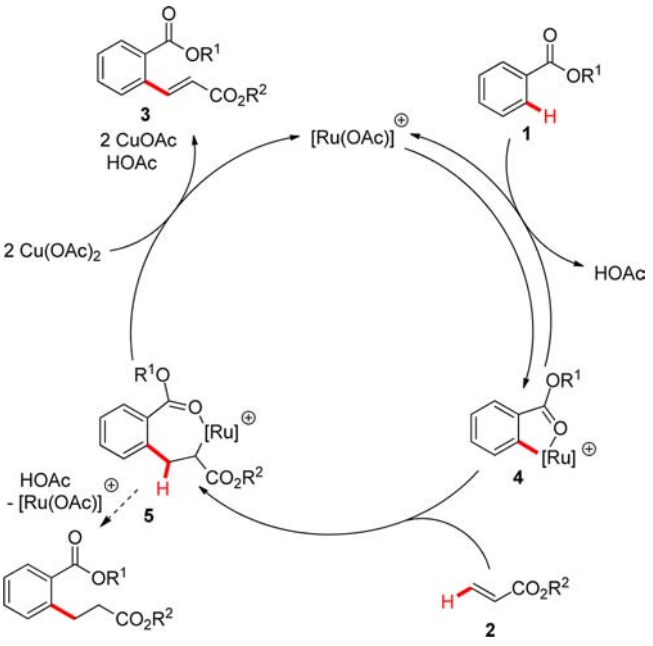
Scheme 6. Oxidative Alkenylation with Isotopically Labeled Substrate or Cosolvent



Given the remarkable catalytic activity of the cationic ruthenium(II) complex, we initiated mechanistic studies to

(12) The use of *para*-bromo- or *para*-amino-substituted benzoic acid esters provided thus far only unsatisfactory low conversions.

Scheme 7. Proposed Catalytic Cycle



unravel its mode of action. To this end, we performed intramolecular competition experiments, which showed that the selectivity of the conversion with arene **1r** was largely influenced by steric interactions. On the contrary, *meta*-fluoro-substituted substrate **1s** exclusively led to the functionalization at the position C-2 (Scheme 4).

Moreover, intermolecular competition experiments between differently substituted arenes **1** revealed electron-rich esters to be preferentially converted (Scheme 5).

Mechanistic studies with isotopically labeled substrate $[D]_5$-**1t** or in the presence of the cosolvent D_2O highlighted a H/D scrambling, thus indicating the C−H bond ruthenation step to be reversible in nature (Scheme 6).

Based on these mechanistic studies we propose the catalytic cycle to involve an initial reversible acetate-assisted[13] cycloruthenation to form complex **4** (Scheme 7). Subsequent migratory insertion of alkene **2** and β-hydride elimination furnish desired product **3**, while reductive elimination and reoxidation by $Cu(OAc)_2$ regenerate the catalytically active cationic species.

In summary, we have reported on site-selective ruthenium-catalyzed oxidative alkenylations of arenes bearing weakly coordinating esters. Importantly, cationic ruthenium(II) complexes served as efficient catalysts for cross-dehydrogenative C−H bond functionalizations between aryl- and alkenyl-substituted esters in a highly chemo-/diastereoselective as well as site selective fashion. The optimized catalyst proved to be broadly applicable and also allowed for aerobic oxidative alkenylations with cocatalytic amounts of $Cu(OAc)_2 \cdot H_2O$, utilizing air as an inexpensive terminal oxidant. Detailed mechanistic studies were suggestive of a reversible cycloruthenation step through acetate assistance. Further studies on ruthenium-catalyzed oxidative C−H bond functionalizations are currently ongoing in our laboratories and will be reported in due course.

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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.

(13) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345.

The authors declare no competing financial interest.