CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201301988

Ruthenium(II)-Catalyzed C−H Alkenylations of Phenols with Removable Directing Groups

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Abstract: Cationic ruthenium(II) complexes enabled oxidative alkenylations of phenols bearing easily cleavable directing groups. The optimized catalytic system allowed twofold C−H bond activations with excellent chemo-, site-, and diastereoselectivities. The double C−H functionalization process proceeded efficiently in an aerobic fashion under an atmosphere of ambient air. Detailed mechanistic studies were performed and provided strong support for an initial reversible C−H bond activation by the formation of six-membered ruthenacycles as the key intermediates.

Keywords: alkenylation • catalysis • C−H activation • cross-dehydrogenative coupling • reaction mechanisms • ruthenium

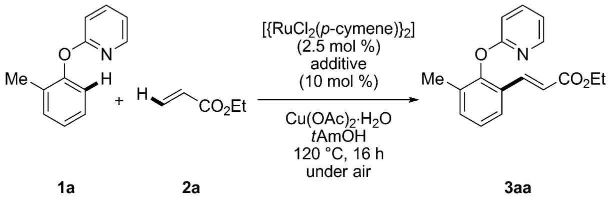
Introduction

Cross-dehydrogenative alkenylations of arenes by twofold C−H bond activation have emerged as increasingly viable tools for the atom- and step-economical preparation of styrene derivatives.[1] In particular, ruthenium(II) complexes[2] have very recently been identified as versatile catalysts for double C−H bond functionalizations with arenes bearing a diverse set of Lewis-basic directing groups.[3,4] However, despite these recent advances, ruthenium-catalyzed oxidative alkenylations of arenes arguably continue to be limited in that methods that exploit removable directing groups[5–7] are scarce. Given our recent success in the use of a removable directing group in the direct arylation with aryl halides as prefunctionalized arylating reagents,[8] we consequently became attracted to devising a novel ruthenium-catalyzed oxidative alkenylation of phenols displaying removable directing groups. As a result of our studies, we report herein on ruthenium-catalyzed twofold C−H functionalization with arenes and heteroarenes displaying easily cleavable directing groups. In contrast to the previously reported direct arylation catalyzed by neutral ruthenium-biscarboxylate complexes,[8] the new oxidative C−H bond functionalization was only accomplished with cationic ruthenium(II) catalysts.

Results and Discussion

Optimization studies: Given the broad synthetic utility of phenols and derivatives thereof,[9] at the outset of our studies we probed reaction conditions for the oxidative alkenylation of arene **1a** (Table 1). While carboxylate additives were found to be mandatory for ruthenium-catalyzed direct arylations with aryl halides,[8] they proved to be ineffective for the desired oxidative C−H bond functionalization (entries 1–4). In contrast, in-situ generated cationic ruthenium(II) complexes enabled the synthesis of desired product **3aa**, with $AgSbF_6$ giving optimal results (entries 5 and 6). The cationic catalyst thereby even allowed aerobic alkenyla-

Table 1. Optimization of oxidative alkenylation of arene **1a** with alkene **2a**.[a]



1a **2a** **3aa**

Entry	Additive	$Cu(OAc)_2\cdot H_2O$ [equiv]	Yield [%]
1	—	2.0	<5
2	KO_2CMes	2.0	<5
3	CsOAc	2.0	<5
4	AgOAc	2.0	<5
5	KPF_6	2.0	25
6	**$AgSbF_6$**	**2.0**	**83**
7	$AgSbF_6$	0.3	73
8	$AgSbF_6$	—	—
9	$AgSbF_6$	2.0	—[b]

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), $Cu(OAc)_2\cdot H_2O$ (1.0 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (2.5 mol%), *t*-AmOH (2.0 mL), $AgSbF_6$ (10 mol%), yields of isolated products. [b] Without [{$RuCl_2$(*p*-cymene)}$_2$].

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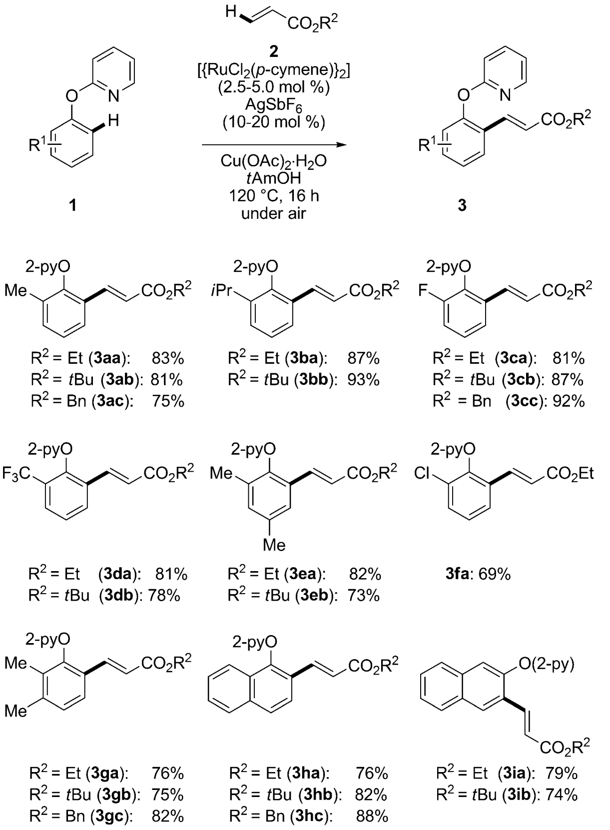
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201301988.

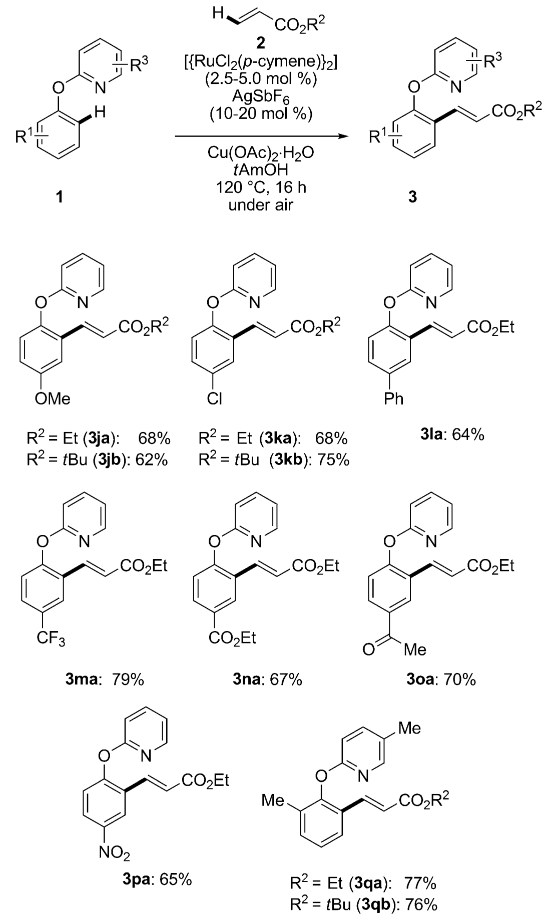
tions with cocatalytic amounts of $Cu(OAc)_2{\cdot}H_2O$ under an atmosphere of ambient air as the sacrificial oxidant (entry 7). Furthermore, additional experiments verified that the transformation did not proceed in the absence of $Cu(OAc)_2{\cdot}H_2O$ or the ruthenium catalyst (entries 8, and 9).

Reaction scope: The versatility of the catalytic system was subsequently probed in the oxidative alkenylation of differently substituted 2-aryloxypyridines **1** under an atmosphere of ambient air (Scheme 1). We were pleased to observe that the catalyst proved to be broadly applicable and, hence, furnished the desired products **3** in high yields. Notably, an *ortho*-C–Cl bond in substrate **1f** stayed intact, without any indication of its oxidative addition to the ruthenium catalyst. Furthermore, oxidative alkenylations with *α*- (**1h**) and *β*-naphthol derivatives (**1i**) delivered the products **3ha**–**3hc**, and **3ia** and **3ib**, respectively, with excellent site selectivities. Moreover, the catalytic C–H bond functionalizations occurred with excellent diastereoselectivities, delivering the *E* diastereomers as the sole products in all cases. However, attempted reactions with cyclohexene were as of yet not viable.



Scheme 1. Ruthenium-catalyzed oxidative direct alkenylation of arenes **1**.

The optimized ruthenium(II) catalyst was not limited to substrates bearing *ortho* substituents, but a variety of phenol derivatives **1** being devoid of *ortho* substitution provided the products of mono-alkenylation **3** with superb chemo- and site selectivities as well (Scheme 2). Notably, various important electrophilic functional groups, such as chloro, ester, ketone, or nitro substituents, were well tolerated by the catalytic system. Moreover, substrate **1q** with a substituted pyridyloxy group was converted with a comparable efficacy.

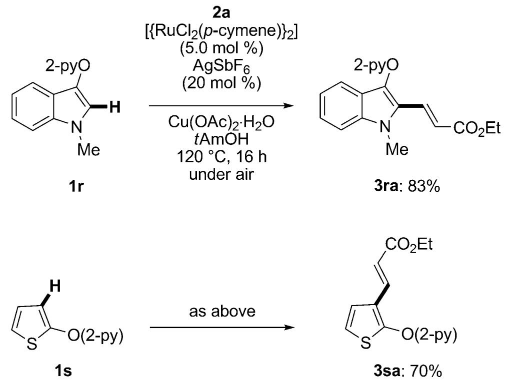


Scheme 2. Scope of oxidative twofold C–H bond functionalization with substituted substrates **1**.

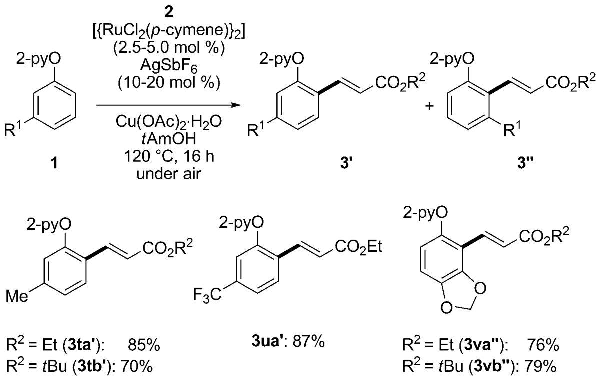
We were, furthermore, delighted to observe that heteroarenes proved to be suitable substrates as well, delivering the synthetically useful indole **3ra** and thiophene **3sa** (Scheme 3).

The site-selectivity of the oxidative C–H bond functionalization with *meta*-substituted phenol derivatives was largely controlled by steric interactions (**3ta′**–**3ua′**), whereas the oxygen of the acetal in arene **1v** exerted a notable secondary directing group effect (Scheme 4). It is important to note that the 2-pyridyloxy directing group was selectively cleaved to deliver the desired free phenol **4aa** (Scheme 5).

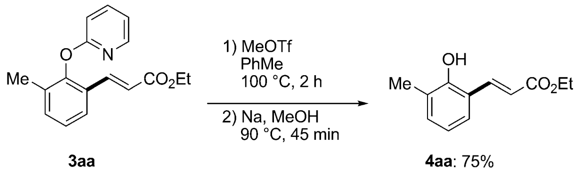
Mechanistic studies: Given the high catalytic efficacy of the optimized catalyst, we became intrigued by probing its mode of action. To this end, intermolecular competition experiments revealed electron-rich arenes to be preferentially converted (Scheme 6). This reactivity pattern contrasts previous observations that we made within direct arylations with aryl halides catalyzed by neutral ruthenium com-



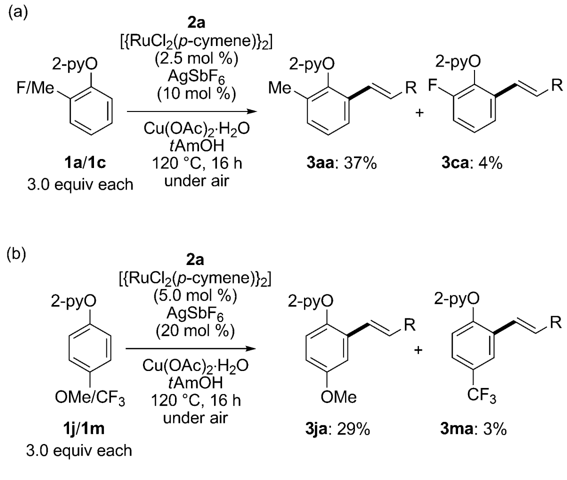
Scheme 3. Oxidative C–H bond functionalization with heterocyclic substrates **1r** and **1s**.



Scheme 4. Alkenylations with *meta*-substituted substrates **1t**-**v**.



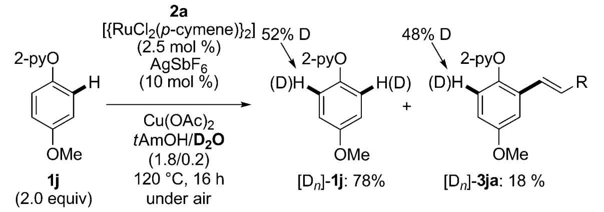
Scheme 5. Removal of the directing group.



Scheme 6. Intermolecular competition experiments ($R = CO_2Et$).

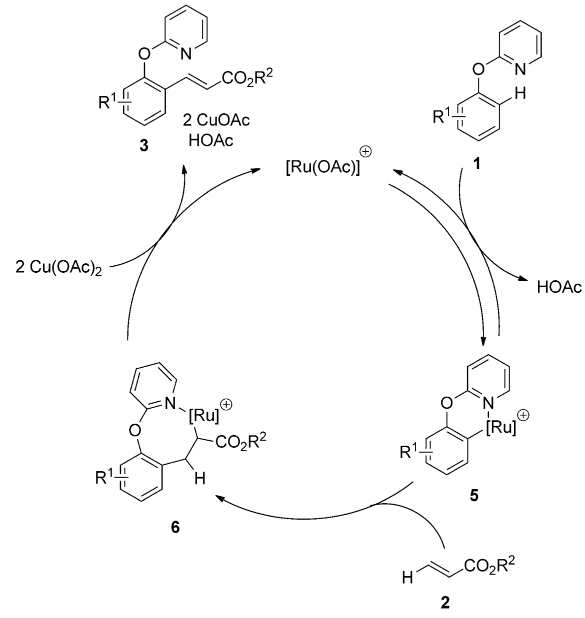
plexes.[8] In the present study, the inherently higher reactivity of phenols bearing electron-donating substituents can be rationalized in terms of an electrophilic-type C–H bond metalation event.

Further support for this mechanistic rationale was obtained from oxidative alkenylations with D_2O as an additive, which indicated a significant H/D scrambling in the *ortho*-positions of the reisolated substrate [D*n*]-**1j** and the product [D*n*]-**3ja** (Scheme 7).



Scheme 7. Oxidative alkenylation with D_2O as an additive ($R = CO_2Et$).

Based on these mechanistic studies, we propose the C–H bond activation to occur by a reversible electrophilic-type metalation event (Scheme 8), which in turn explains the unique activity of the cationic ruthenium(II) complexes. The thus-formed cycloruthenated complex **5** subsequently undergoes a migratory insertion with the alkene **2** to furnish the intermediate **6**. Finally, *β*-hydrid-elimination yields the desired product **3**, whereas reductive elimination and oxidation by $Cu(OAc)_2{\cdot}H_2O$ regenerate the catalytically active ruthenium(II) complex.



Scheme 8. Proposed catalytic cycle.

Conclusion

In summary, we have reported on the ruthenium-catalyzed oxidative alkenylations of arenes displaying removable directing groups. High catalytic efficacy in the twofold C–H bond functionalization process was achieved with a cationic ruthenium(II) complex, which even occurred in an aerobic fashion under an atmosphere of ambient air. The optimized catalyst allowed ruthenium-catalyzed C–H bond alkenylations of phenol derivatives with excellent chemo-, site-, and diastereoselectivities through the reversible formation of six-membered ruthenacycles as the key intermediates.

Experimental Section

Representative procedure: ruthenium-catalyzed oxidative alkenylation with substituted pyridines: A suspension of 2-(*o*-tolyloxy)pyridine (**1a**) (185.4 mg, 1.00 mmol), ethyl acrylate (**2a**) (52.0 mg, 0.52 mmol), [{RuCl$_2$(*p*-cymene)}$_2$] (7.6 mg, 2.5 mol%), AgSbF$_6$ (18.5 mg, 11 mol%) and Cu(OAc)$_2$·H$_2$O (200 mg, 1.00 mmol) in *t*AmOH (2.0 mL) was stirred at ambient temperature under N$_2$ for 5 min and then stirred at 120°C for 16 h under an ambient atmosphere of air. At ambient temperature, the reaction mixture was diluted with saturated aqueous NH$_4$Cl/NH$_3$ (1:1, 10 mL) and extracted with EtOAc (3×25 mL). The combined organic layers were dried over Na$_2$SO$_4$. After filtration and evaporation of the solvents in vacuo, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 15/1→10/1) to yield **3aa** (122 mg, 83%) as a colorless solid.

Acknowledgements

Support by the European Research Council under the European Community's Seventh Framework Program (FP7 2007–2013)/ERC Grant agreement no. 307535, and the Chinese Scholarship Council (fellowship to W.M.) is gratefully acknowledged. We further thank Mr. Carsten Rauch (Georg-August-Universität) for experimental support.

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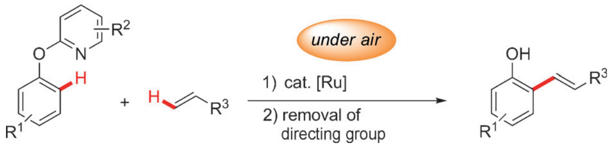
Received: May 23, 2013



Cationic ruthenium(II) complexes enabled oxidative alkenylations of phenols bearing cleavable directing groups with excellent site- and chemoselectivities. The twofold C–H functionalization efficiently proceeded in an aerobic fashion under ambient air.

C–H Activation

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Ruthenium(II)-Catalyzed C–H Alkenylations of Phenols with Removable Directing Groups