

C–H Activation

Carboxylate-Assisted Ruthenium(II)-Catalyzed Hydroarylations of Unactivated Alkenes through C–H Cleavage**

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Metal-catalyzed functionalizations of unactivated C–H bonds have in recent years emerged as increasingly viable methods for the step-economical formation of C–C bonds.^[1] Particularly, direct additions of arenes onto C–C multiple bonds are highly attractive because of their perfect atom-economy.^[2,3] Based on pioneering studies by Murai, Kakiuchi, and Chatani,^[4,5] ruthenium complexes were identified as arguably the most versatile catalysts for hydroarylations through cleavages of unactivated C–H bonds.^[6] Thus far, the highest catalytic activities were achieved with low-valent ruthenium catalysts, such as $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$, $[\text{RuH}_2(\text{PPh}_3)_4]$, $[\text{Ru}(\text{CO})_2(\text{PPh}_3)_3]$, $[\text{Ru}_3(\text{CO})_{12}]$, or $[\text{RuH}_2(\text{H}_2)_2(\text{PCy}_3)_2]$, which are unfortunately often rather unstable or relatively expensive. A significant practical progress was, however, recently achieved by Darses, Genet et al. through the elegant in situ formation of $[\text{RuH}_2(\text{PPh}_3)_4]$ from $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$, sodium formate, and PPh_3 .^[7] Whereas this catalytic system displayed a remarkably high catalytic activity, it proved as of yet restricted to activated alkenes, namely vinyl silanes and styrenes. In recent years, carboxylate assistance was found to be the key to success for versatile ruthenium-catalyzed direct C–H bond arylations and alkylations as well as oxidative C–H bond transformations.^[8,9] Despite these notable advances, metal carboxylates^[10] were as of yet not exploited as cocatalytic additives for ruthenium-catalyzed hydroarylations. Within our research program on atom-economical hydroarylations,^[11] we unraveled highly efficient and broadly applicable ruthenium(II)biscarboxylate catalysts for additions of C–H bonds onto unactivated alkenes, on which we report herein.

We commenced our studies by exploring the effect of representative cocatalytic additives for the ruthenium-catalyzed hydroarylation of the challenging unactivated alkene **2a** (Table 1). Not surprisingly, simple $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ did

Table 1: Optimization of ruthenium-catalyzed hydroarylation.^[a]

Entry	Additive	Solvent	T [°C]	Yield [%]
1	–	PhMe	120	–
2	NaPF_6 ^[c]	PhMe	100	–
3	KPF_6 ^[c]	PhMe	100	–
4	AgOTf	PhMe	100	13 ^[b]
5	AgOAc	PhMe	100	27 ^[b]
6	KOAc	1,4-dioxane	120	48 ^[b]
7	KOPiv	1,4-dioxane	120	56 ^[b]
8	KO_2CAd	1,4-dioxane	120	80, ^[b] 71
9	KO_2CMes	1,4-dioxane	120	85, ^[b] 72
10	KO_2CMes	PhMe	120	95, ^[b] 79
11	KO_2CMes	H_2O	120	> 99, ^[b] 74
12	KO_2CMes	PhMe	80	90, ^[b] 75
13	KO_2CMes ^[c,d]	PhMe	100	95, ^[b] 82
14	KOAc ^[c,d]	PhMe	100	66, ^[b] 54
15	PPh_3 ^[c] HCO_2Na	PhMe	120	6 ^[b]

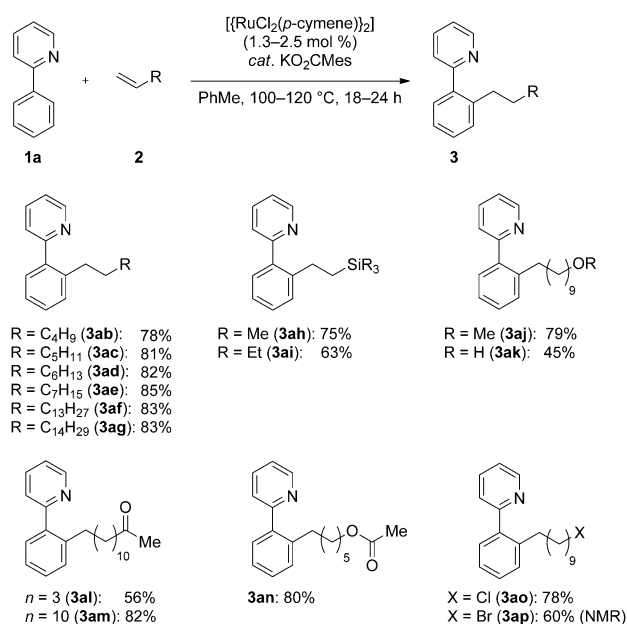
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (2.5 mol %), additive (30 mol %), solvent (3.0 mL), yields of isolated products. Ad = adamantyl; Mes = 2,4,6-trimethylphenyl; Piv = pivaloyl; Tf = trifluoromethanesulfonyl. [b] Conversion determined by GC using *n*-tridecane as internal standard. [c] Additive (15 mol %). [d] **2a** (2.0 mmol), $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ (1.25 mol %).

not affect the desired C–H bond functionalization in the absence of an additive (entry 1). Likewise, the use of cationic complexes derived in situ from among others KPF_6 or AgOTf led only to unsatisfactorily low yields (entries 2–5). On the contrary, more promising results were achieved when utilizing metal carboxylates as additives, with sterically demanding KO_2CMes providing optimal yields of the desired mono-*n*-alkylated product **3aa** (entries 6–9). Among a set of representative solvents, most efficient catalysis was accomplished in toluene (entries 9–13). However, the excellent chemoselectivity also allowed the use of water as environmentally benign, nontoxic, and inexpensive reaction medium (entry 11), and enabled efficient catalysis at lower reaction temperatures, thereby again illustrating the beneficial features of the KO_2CMes -derived catalyst (entries 12–14). Notably, the carboxylate-derived ruthenium(II) complex was found to be superior in the hydroarylation of unactivated alkene **2a** when compared to reported^[7] ruthenium catalysts (entry 15).

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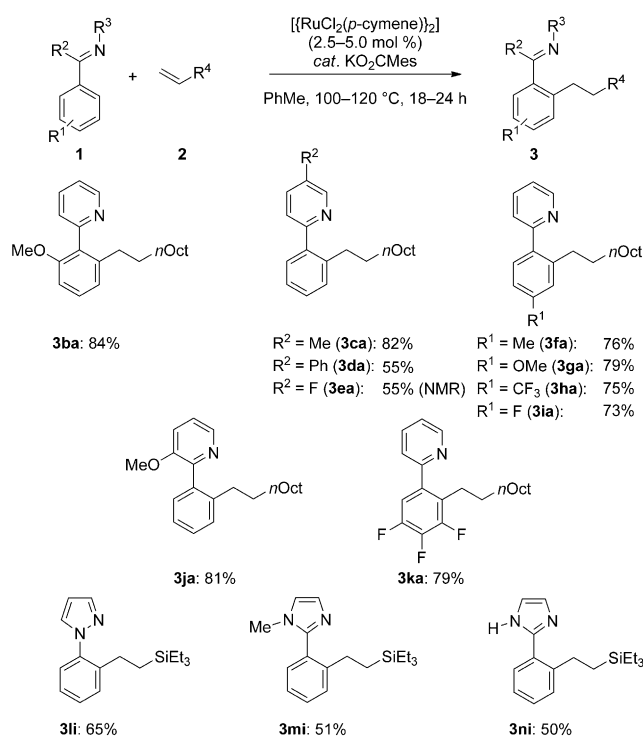
Scheme 1. Scope of hydroarylations of alkenes **2**.

With an optimized catalytic system in hand, we next explored its versatility by employing a variety of unactivated alkenes **2** (Scheme 1). Differently substituted unactivated alkenes furnished the corresponding products **3** in high yields. The catalytic system proved to be tolerant of valuable functional groups, such as ether, ketone, hydroxy, or ester substituents. Intriguingly, competition experiments with haloalkenes **2o** and **2p** highlighted the excellent chemoselectivity of the carboxylate-assisted hydroarylations, in that products stemming from direct C–H bond alkylations with alkyl halide moieties^[12] were not observed. This selectivity pattern is likely due to the absence of stoichiometric amounts of a carbonate base.

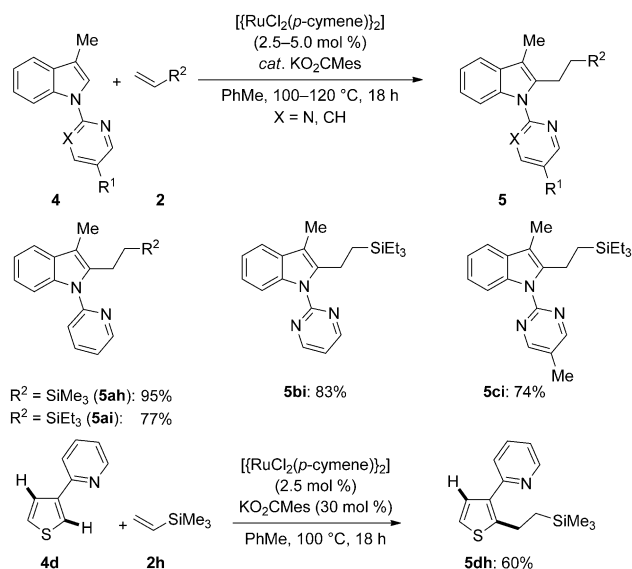
Carboxylate-assisted ruthenium(II)-catalyzed hydroarylation further set the stage for the high-yielding conversion of *ortho*-, *meta*-, and *para*-substituted arenes, thereby selectively delivering the monosubstituted products **3ba–3ka** (Scheme 2). Notably, the optimized catalyst was not restricted to pyridine derivatives. Indeed, the C–H bond functionalization also occurred site-selectively on pyrazolyl and imidazolyl-substituted arenes (**3li–3ni**), even when being N-unprotected (**3ni**).

In consideration of the crucial importance of heteroarenes as the key structural motifs in various bioactive molecules, we were delighted to observe that hydroarylations with indole and thiophene derivatives **4a–4d** proceeded in a site-selective manner as well (Scheme 3). The use of 2-pyrimidyl directing groups on the indole nitrogen atom^[13] (**4b**, and **4c**) could furthermore be utilized for a strategy employing removable directing groups.

Given the high catalytic activity and remarkably broad scope of the carboxylate-assisted ruthenium-catalyzed hydroarylation, we became attracted by probing its mode of action. To this end, intramolecular competition experiments with *meta*-substituted arenes **1o** and **1p** revealed that steric



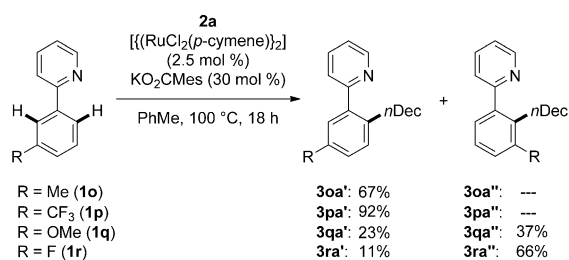
Scheme 2. Carboxylate-assisted hydroarylations with arenes **1**.



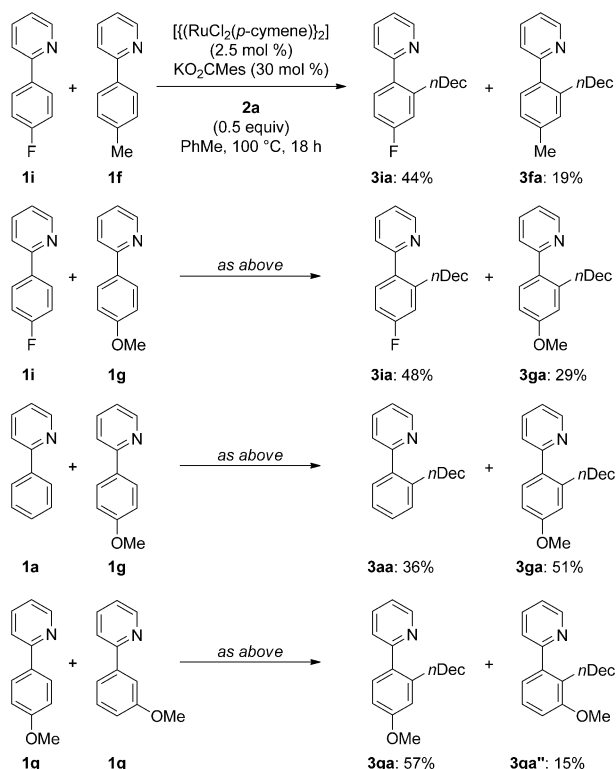
Scheme 3. Carboxylate-assisted hydroarylations with heteroarenes **4**.

interactions were largely influencing the site selectivity (Scheme 4). However, heteroatom substituents in substrates **1q** and **1r** led to the predominant functionalization at the sterically more congested C2 positions.

Intermolecular competition experiments with substituted starting materials highlighted that the nucleophilicity of the arenes did not influence their relative reactivities (Scheme 5 and the Supporting Information), thus rendering an electrophilic reaction mechanism unlikely to be operative. Contra-



Scheme 4. Hydroarylations with *meta*-substituted arenes **1o–r**.

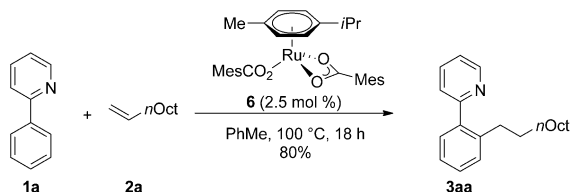


Scheme 5. Intermolecular competition experiments.

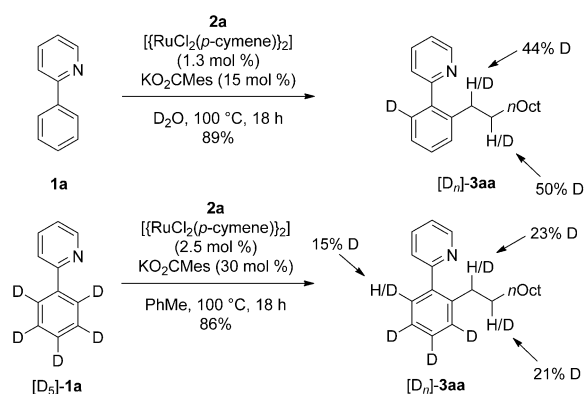
rially, the inductive effect of the heteroatom substituent was found to be of key importance.

As to the working mode of the catalyst, it is further noteworthy that well-defined biscalboxylate complex **6**^[12a,14] led to isolation of product **3aa** in a yield comparable to the one obtained with the in situ generated catalytic system (Scheme 6).

Ruthenium-catalyzed hydroarylations with D_2O or isotopically labeled substrate $[\text{D}_5]$ -**1a** indicated the C–H bond metalation to be reversible in nature (Scheme 7).

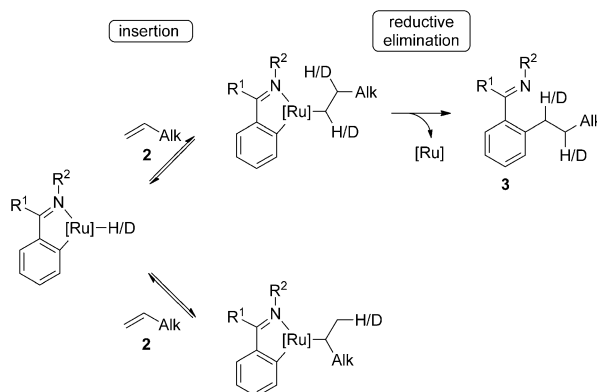


Scheme 6. Ruthenium(II) biscalboxylate catalyst **6**.



Scheme 7. Hydroarylations with isotopically labeled compounds.

Based on these experimental findings, our competition experiments, and previous mechanistic insight,^[6] we propose the reductive elimination to be the rate-determining step (Scheme 8).



Scheme 8. Proposed reaction mechanism. Alk = alkyl.

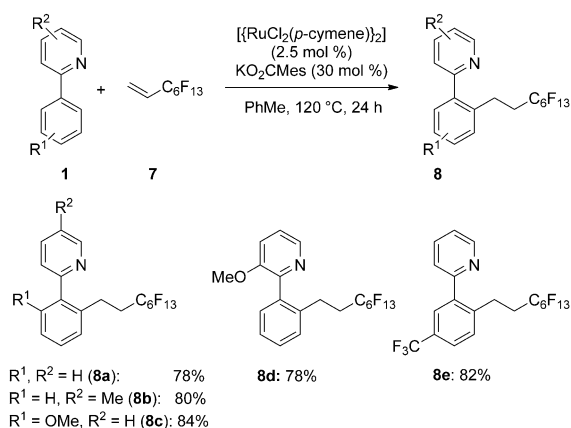
In recent years, the preparation of fluorinated compounds has attracted significant interest, since fluorine uniquely affects the properties of organic molecules and thus enhances solubility, bioavailability, and metabolic stability compared to nonfluorinated analogues.^[15,16] Therefore, we were pleased to observe an outstanding catalytic efficacy in challenging hydroarylations with highly fluorinated alkene **7** through carboxylate-assisted C–H bond functionalization (Scheme 9).

In summary, we have reported on carboxylate-assisted ruthenium-catalyzed hydroarylations of unactivated alkenes employing various (hetero)arenes with ample scope. Thus, ruthenium(II)biscalboxylate complexes enabled versatile atom- and step-economical additions of C–H bonds onto unactivated alkenes, and allowed for the synthesis of highly fluorinated alkylated arenes.

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Scheme 9. Hydroarylations of fluorinated alkene **7**.

Keywords: alkenes · arenes · C–H functionalization · homogeneous catalysis · ruthenium

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