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Carboxylate-assisted ruthenium(II)-catalyzed C–H activations of monodentate amides with conjugated alkenes†

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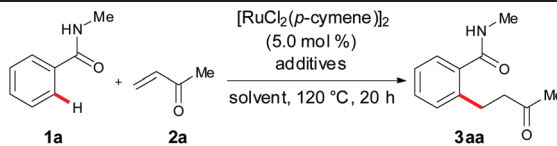
Carboxylate assistance enabled efficient and chemoselective ruthenium(II)-catalyzed hydroarylations of α,β -unsaturated ketones *via* C–H activation on monodentate benzamides. Furthermore, the versatile ruthenium(II) catalyst set the stage for oxidative C–H functionalization on acetanilides, furnishing diversely decorated quinolines in a step-economical fashion.

Transition metal-catalyzed C–H functionalizations have been recognized as increasingly viable tools for the step-economical formation of C–C bonds.¹ Particularly, metal-catalyzed hydroarylation reactions² *via* C–H activation are attractive because of their excellent atom-economy.³ Early findings by Lewis and Smith⁴ as well as Murai and co-workers^{5,6} indicated the considerable power of ruthenium(0) complexes as effective catalysts for hydroarylations through chelation-assisted C–H activation, which were proposed to proceed by oxidative addition of the C–H bond. Practical advances were achieved by Darses and Genet and co-workers through the *in situ* formation of $[\text{RuH}_2(\text{PPh}_3)_4]$ from $[\text{RuCl}_2(p\text{-cymene})]_2$, NaO_2CH and PPh_3 ,⁷ thus avoiding sensitive and expensive ruthenium(0) complexes, such as $[\text{Ru}_3(\text{CO})_{12}]$, $[\text{RuH}_2(\text{PPh}_3)_4]$, $[\text{Ru}(\text{CO})_2(\text{PPh}_3)_3]$, or $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$. As a part of our ongoing program on transition-metal-catalyzed C–H functionalizations,⁸ we recently developed ruthenium(II)-catalyzed hydroarylations *via* carboxylate-assisted C–H cleavages.⁹ Despite of these remarkable advances, the synthetically useful family of electron-deficient olefins,¹⁰ such as α,β -unsaturated ketones were thus far not viable substrates. While such transformations were accomplished with among others relatively expensive rhodium¹¹ or rhenium¹² catalysts, notable progress with ruthenium(II) complexes was very recently made by Chatani and co-workers highlighting that hydroarylations of α,β -unsaturated ketones could be realized, given that substrates displaying bidentate directing groups were employed.^{13,14} Herein, we report on an expedient access to β -aryl ketones and quinolines through ruthenium(II)-catalyzed hydroarylations and oxidative cascade annulations

with α,β -unsaturated ketones, respectively. It is noteworthy that the ruthenium(II)-catalyzed C–H activation strategy was realized with synthetically useful amides as atom-economical mono-dentate directing groups.

We initiated our studies by testing the feasibility of the envisioned ruthenium(II)-catalyzed C–H alkylation of benzamide **1a** with methyl vinyl ketone (**2a**) (Table 1). Interestingly, $\text{RuCl}_2(\text{PPh}_3)_3$, which was previously used for hydroarylations with bidentate directing groups,¹³ unfortunately, failed to deliver the desired product **3aa** with the assistance of the simple amide **1a** (entries 1 and 2). Similar trends were

Table 1 Optimization of ruthenium(II)-catalyzed C–H alkylation with benzamide **1a**^a

				
Entry	Additive A [mol%]	Additive B [equiv.]	Solvent	Yield ^b [%]
1	NaOAc (30)	—	PhMe	— ^c
2	NaOAc (30)	—	H ₂ O	— ^c
3	KPF ₆ (20)	—	H ₂ O	—
4	KPF ₆ (20)	NaOAc (2.00)	H ₂ O	—
5	PPh ₃ (15)	NaO ₂ CH (0.30)	PhMe	—
6	KOAc (30)	HOAc (1.00)	H ₂ O	64
7	KO ₂ CMe (30)	MesCO ₂ H (0.30)	H ₂ O	69
8	KO ₂ CMe (30)	MesCO ₂ H (1.00)	H ₂ O	80
9	KO ₂ CMe (30)	—	H ₂ O	51
10	KO ₂ CMe (30)	MesCO ₂ H (1.00)	H ₂ O	— ^d
11	—	MesCO ₂ H (1.00)	H ₂ O	29

^a General reaction conditions: **1a** (0.50 mmol), **2a** (1.00 mmol), $[\text{RuCl}_2(p\text{-cymene})]_2$ (5.0 mol%), KO₂CMe (30 mol%), MesCO₂H (1.00 equiv.), solvent (2.0 mL), under N₂, 120 °C, 20 h. ^b Isolated yield. ^c $\text{RuCl}_2(\text{PPh}_3)_3$ (10 mol%). ^d Without [Ru].

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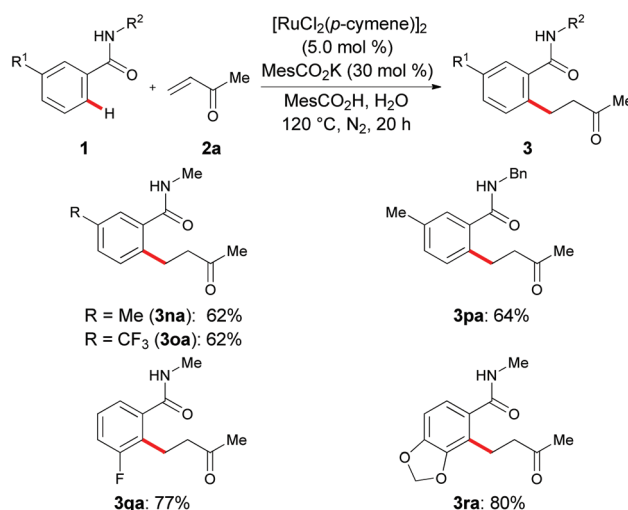
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5qo00167f



observed when employing $[\text{RuCl}_2(p\text{-cymene})]_2$ in combination with various additives (entries 3–5).

A significant improvement was realized using cocatalytic amounts of KOAc and stoichiometric amounts of HOAc as the additives with H_2O as inexpensive and nontoxic reaction medium^{15,16} (entry 6). Improved yields of the target compound **3aa** were obtained when employing the bulky MesCO_2K and MesCO_2H as the cocatalysts (entry 7). Here, the use of stoichiometric MesCO_2H provided the optimal results (entry 8). Furthermore, it is worth noting that the omission of either of the two additives resulted in significantly reduced yields of the alkylated benzamide **3aa** (entries 9–11).

With the optimized reaction conditions in hand, we tested its versatility in the C–H alkylation with weakly coordinating^{17,18} amides **1** (Scheme 1). Notably, in these chelation-assisted direct C–H alkylations, both electron-rich as well as electron-poor *para*-substituted benzamides **1a–1f** were identified as viable substrates. Moreover, a variation of the substitution pattern on the amide nitrogen with benzyl (**1g–i**), cyclohexyl (**1j**) or methoxyethyl (**1k**) groups, did not significantly alter the catalytic efficacy, while primary amides proved to be unsuitable substrates. More sterically hindered *ortho*-substituted benzamide **1l** was successfully alkylated as well, albeit the desired product **3la** was obtained in a slightly reduced yield. The widely applicable ruthenium(II) catalyst was not limited to aromatic benzamides **1**, but the reaction of hetero-



Scheme 2 Site-selective hydroarylations with *meta*-substituted arenes **1a**.

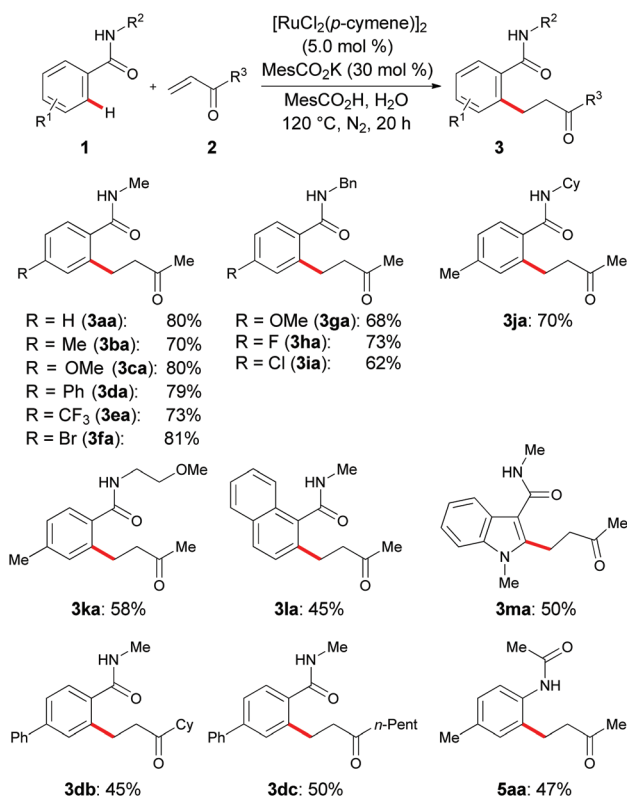
aromatic indole derivative **1m** also led to the site-selective C–H alkylation. In addition, among a representative set of α,β -unsaturated ketones, vinyl alkyl ketones **2b** and **2c** gave the alkylated products **3db** and **3dc**, respectively, in high yields. Interestingly, acetanilide **4a** was identified as a suitable substrate for hydroarylations likewise.

Intramolecular competition experiments with *meta*-methyl- or *meta*-trifluoromethyl-substituted arenes **1n–1p** were largely governed by steric interactions to site-selectively deliver the alkylated products **3na–3pa** at the sterically less hindered position (Scheme 2). In contrast, hydroarylations of the *meta*-substituted benzamides **1q** and **1r** featured a considerable *ortho*-orienting effect¹⁹ of the heteroatom substituent, thus leading to the site-selective formation of the sterically more hindered compounds **3qa** and **3ra**, respectively, as the sole products.

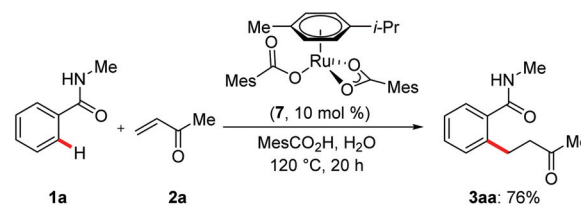
Remarkably, the well-defined, single-component $[\text{Ru}(\text{MesCO}_2)_2(p\text{-cymene})]$ ²⁰ catalyst **7** furnished the desired product, which illustrated the importance of carboxylate assistance (Scheme 3).²¹

An intermolecular competition experiment between arenes with different directing groups clearly highlighted that amides **1** are more powerful than ketone **8** in the chelation-assisted C–H alkylation (Scheme 4).

Given the unique reactivity of our carboxylate-assisted ruthenium(II) catalysis, we performed mechanistic studies to

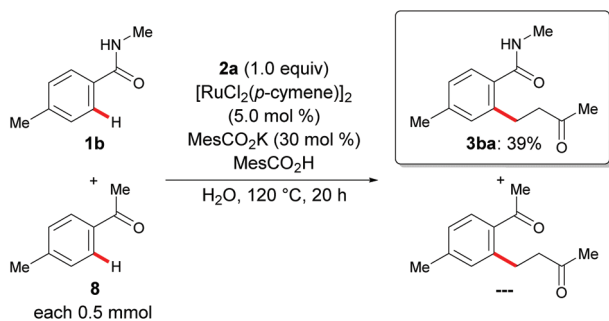


Scheme 1 Scope of the ruthenium(II)-catalyzed hydroarylation via C–H activation.



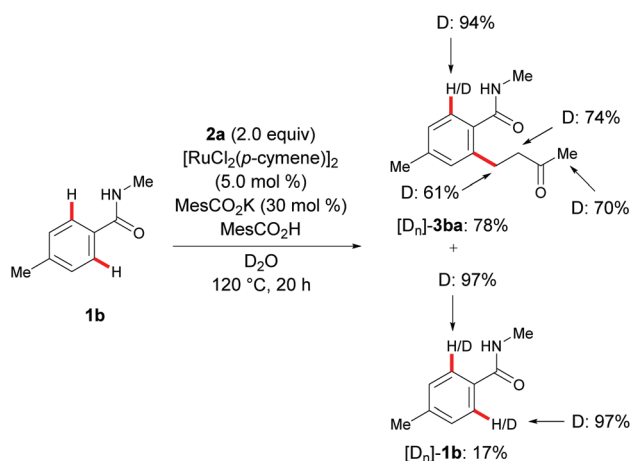
Scheme 3 C–H alkylation with single-component ruthenium(II) biscarboxylate catalyst **7**.



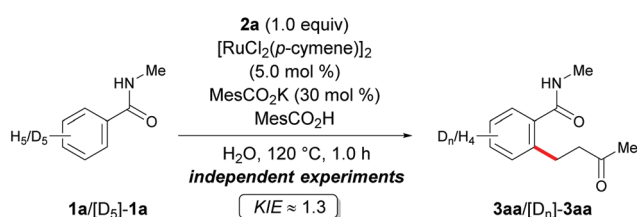
Scheme 4 Competition experiment between amide **1** and ketone **8**.

unravel its mode of action. To this end, strong evidence for a H/D exchange was gathered from C–H functionalization with starting material **1b** in the presence of the deuterated solvent D_2O (Scheme 5).^{9c} This observation can be rationalized in terms of a reversible C–H metalation step in the ruthenium(II)-catalyzed direct hydroarylation.

Moreover, the ruthenium-catalyzed C–H alkylation with isotopically labeled substrate $[\text{D}_5]$ -**1a** showed a negligible kinetic isotope effect (KIE) of $k_{\text{H}}/k_{\text{D}} \approx 1.3$ for the intermolecular KIE experiment (Scheme 6). This data again suggests the C–H bond metalation not to be the rate-determining step.



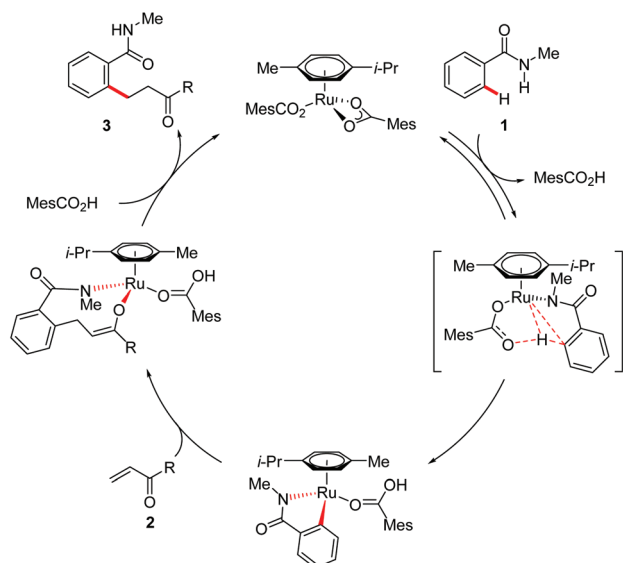
Scheme 5 H/D exchange experiment.



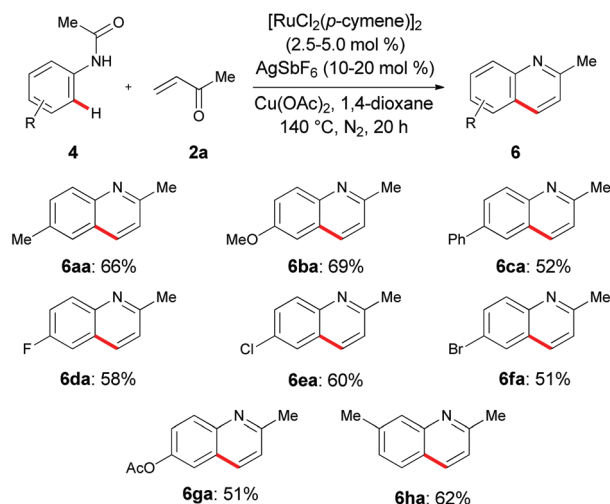
Scheme 6 Kinetic isotope effect (KIE) studies.

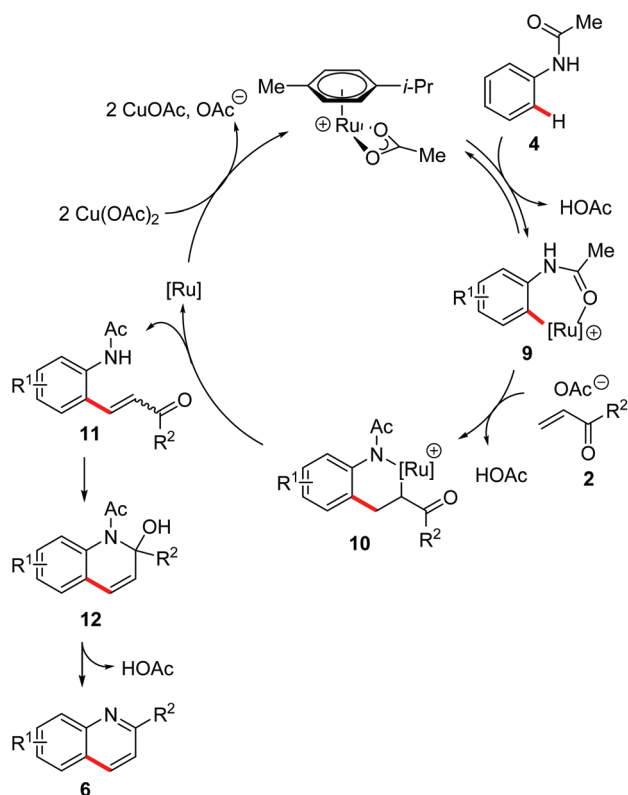
Based on these experimental findings and previous mechanistic insight, we propose a plausible catalytic cycle to involve an initial reversible C–H bond activation by carboxylate assistance, subsequent migratory insertion, and rate-determining reductive elimination (Scheme 7).

Inspired by our previous work on oxidative alkenylations,²² we subsequently probed the oxidative annulation of differently decorated acetanilides **4** with α,β -unsaturated ketone **2a** (Scheme 8). Importantly, the catalytic system was not limited to the use of electron-rich *N*-phenylacetamides **4a–4c**, but also allowed for the transformation of electron-poor substrates **4**. Valuable electrophilic functional groups, such as fluoro,



Scheme 7 Proposed catalytic cycle for carboxylate-assisted hydroarylation.

Scheme 8 Scope of the oxidative alkene annulations with substituted acetanilides **4**.



Scheme 9 Plausible catalytic cycle.

chloro, bromo and ester substituents, were well tolerated by the versatile ruthenium(II) catalyst. An intramolecular competition experiment with substrate **4h** bearing a *meta*-methyl substituent showed that the cyclization was governed by steric interactions to deliver the product **6ha** in high yield.

Based on our previous studies,²² we propose an initial C–H ruthenation to yield cycloruthenated complex **9** (Scheme 9). Thereafter, a migratory insertion of alkene **2** occurs to generate the intermediate **10**. Then, β -hydride-elimination furnishes the product of oxidative alkenylation **11**, while the catalytically active ruthenium(II) complex is regenerated by a sequence of reductive elimination and reoxidation. The desired quinoline **6** is obtained through an intramolecular nucleophilic attack of the anilide in intermediate **11**, followed by β -elimination of acetic acid to deliver the desired product **6**.

Conclusions

In summary, we have developed unprecedented ruthenium(II)-catalyzed hydroarylations and oxidative annulations on benzamides **1** and acetanilides **4** with α,β -unsaturated ketones **2** through C–H activation. The use of benzamides with monodentate directing groups renders our approach highly atom-economical, and the aqueous reaction conditions makes the process environmentally-benign. Detailed experimental mechanistic studies indicated a facile H/D-exchange. In

addition, a cascade oxidative annulation of α,β -unsaturated ketones **2a** with acetanilides **4** was developed to deliver decorated quinolines **6** in a highly step-economic fashion.

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