ORGANIC CHEMISTRY
FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2015, **2**, 1035

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

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Received 22nd May 2015,
Accepted 17th June 2015

DOI: 10.1039/c5qo00167f

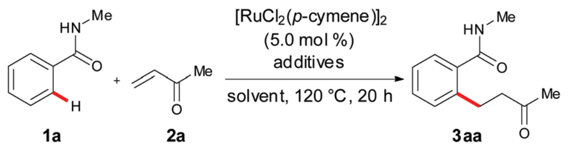
rsc.li/frontiers-organic

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 reactions[2] *via* C–H activation are attractive because of their excellent atom-economy.[3] Early findings by Lewis and Smith[4] 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 $[RuH_2(PPh_3)_4]$ from $[RuCl_2(p\text{-cymene})]_2$, NaO_2CH and PPh_3,[7] thus avoiding sensitive and expensive ruthenium(0) complexes, such as $[Ru_3(CO)_{12}]$, $[RuH_2(PPh_3)_4]$, $[Ru(CO)_2(PPh_3)_3]$, or $[RuH_2(CO)(PPh_3)_3]$. 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 rhodium[11] or rhenium[12] 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, $RuCl_2(PPh_3)_3$, 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_2O	—[c]
3	KPF_6 (20)	—	H_2O	—
4	KPF_6 (20)	NaOAc (2.00)	H_2O	—
5	PPh_3 (15)	NaO_2CH (0.30)	PhMe	—
6	KOAc (30)	HOAc (1.00)	H_2O	64
7	KO_2CMes (30)	$MesCO_2H$ (0.30)	H_2O	69
8	**KO_2CMes (30)**	**$MesCO_2H$ (1.00)**	**H_2O**	**80**
9	KO_2CMes (30)	—	H_2O	51
10	KO_2CMes (30)	$MesCO_2H$ (1.00)	H_2O	—[d]
11	—	$MesCO_2H$ (1.00)	H_2O	29

[a] General reaction conditions: **1a** (0.50 mmol), **2a** (1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol%), KO_2CMes (30 mol%), $MesCO_2H$ (1.00 equiv.), solvent (2.0 mL), under N_2, 120 °C, 20 h. [b] Isolated yield. [c] $RuCl_2(PPh_3)_3$ (10 mol%). [d] Without [Ru].

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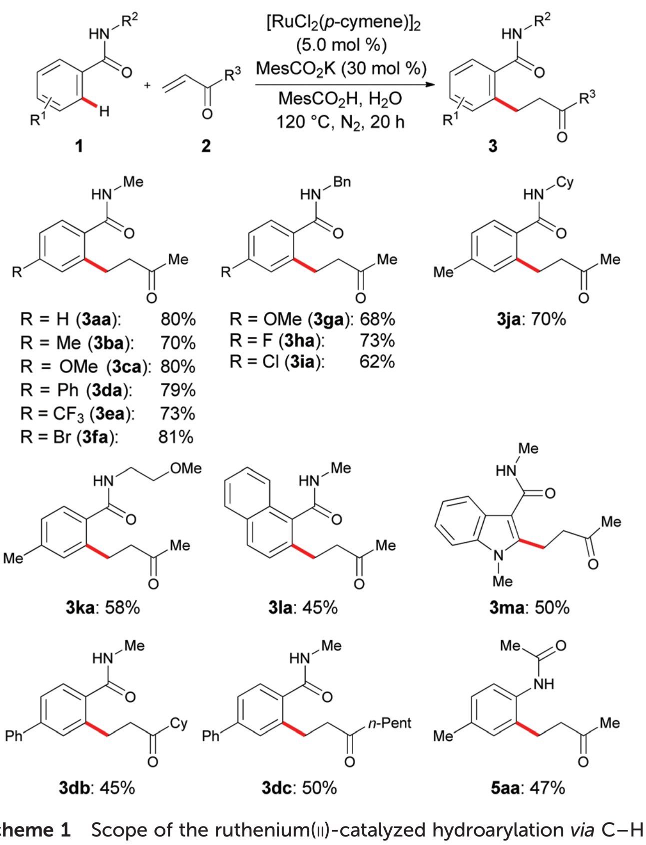
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5qo00167f

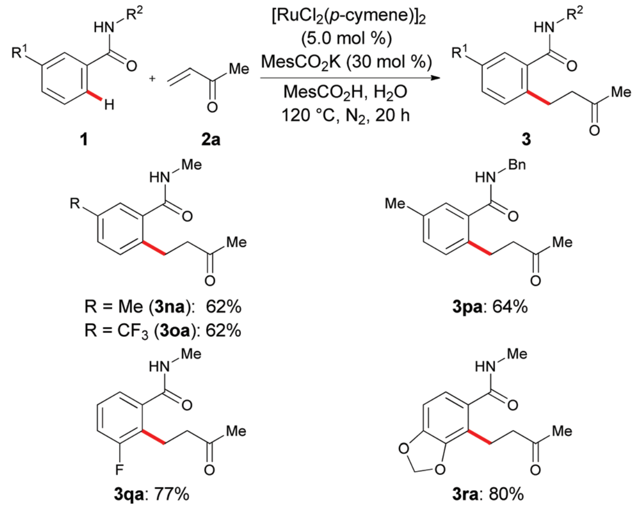
observed when employing $[RuCl_2(p\text{-cymene})]_2$ in combination with various additives (entries 3–5).

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 heteroaromatic 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.



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



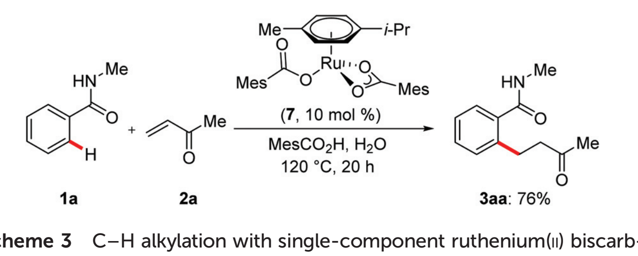
Scheme 2 Site-selective hydroarylations with *meta*-substituted arenes **1a**.

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 effect[19] 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.

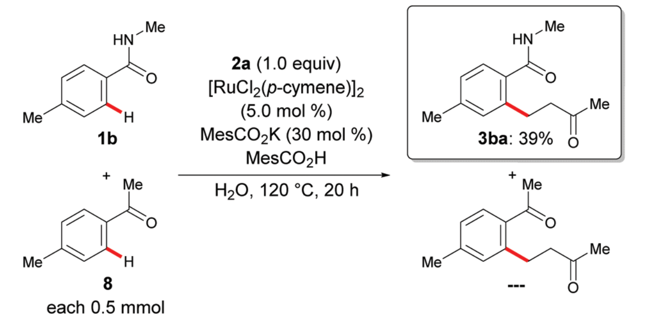
Remarkably, the well-defined, single-component $[Ru(MesCO_2)_2(p\text{-cymene})]$[20] catalyst **7** furnished the desired product, which illustrated the importance of carboxylate assistance (Scheme 3).[21]

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



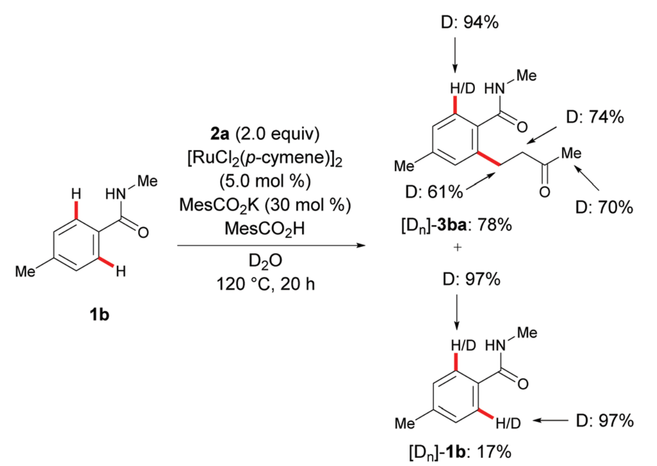
Scheme 3 C–H alkylation with single-component ruthenium(II) biscarboxylate catalyst **7**.



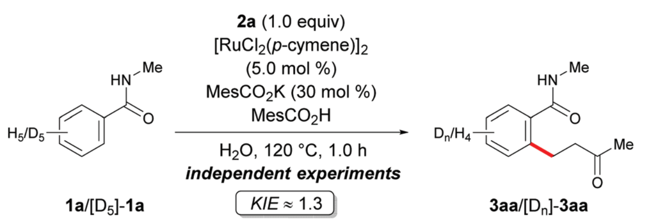
Scheme 4 Competition experiment between amide **1** and ketone **8**.

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 [D_5]-**1a** showed a negligible kinetic isotope effect (KIE) of $k_H/k_D \approx 1.3$ for the intermolecular KIE experiment (Scheme 6). This data again suggests the C–H bond metalation not to be the rate-determining step.



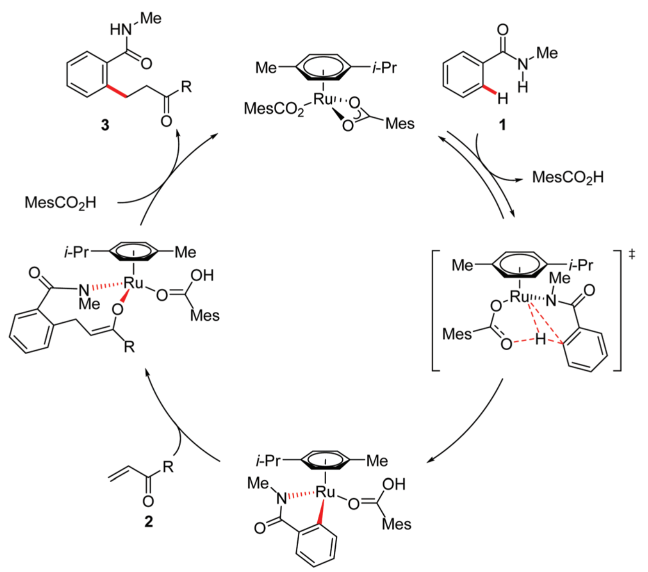
Scheme 5 H/D exchange experiment.



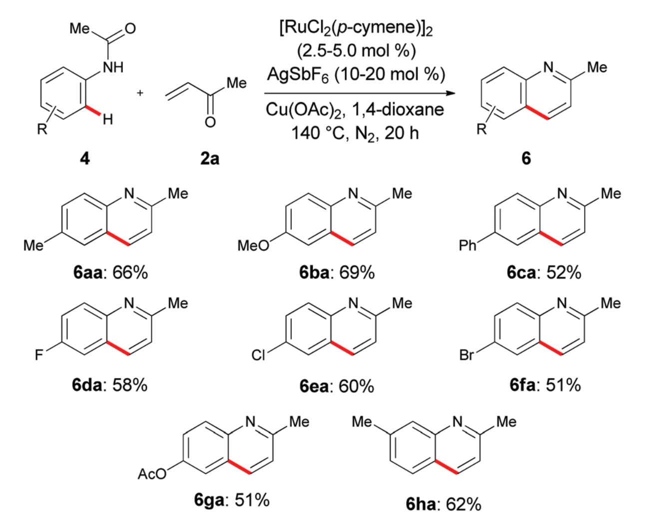
Scheme 6 Kinetic isotope effect (KIE) studies.

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).

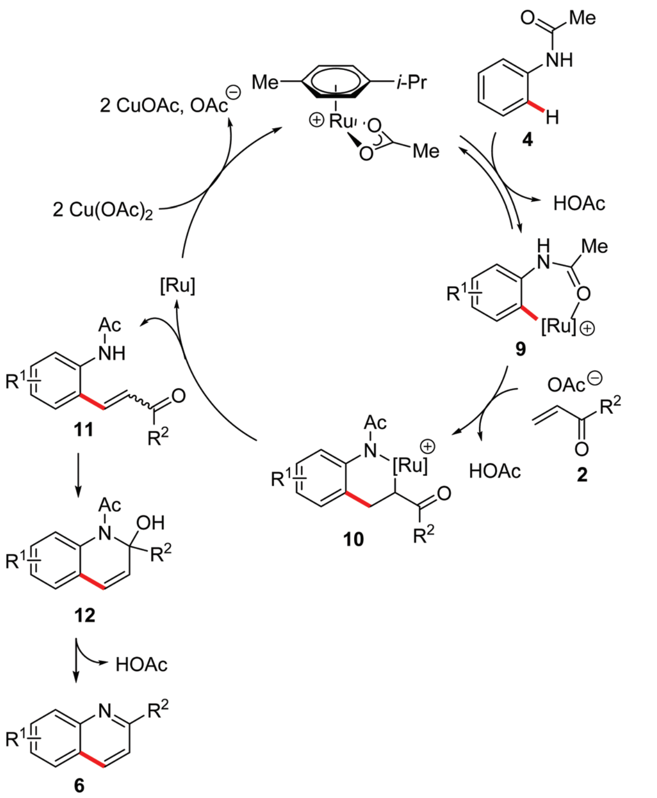
Inspired by our previous work on oxidative alkenylations,[22] we subsequently probed the oxidative annulation of differently decorated acetanilides **4** with α,β-unsaturated ketone **2a** (Scheme 8). Importantly, the catalytic system was not limited to the use of electron-rich *N*-phenylacetamides **4a–4c**, 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.

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 J.L.) is gratefully acknowledged.

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