Chemistry Europe
European Chemical Societies Publishing

C–H Activation

Insights into Ruthenium(II/IV)-Catalyzed Distal C–H Oxygenation by Weak Coordination

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Abstract: C–H hydroxylation of aryl acetamides and alkyl phenylacetyl esters was accomplished *via* challenging distal weak *O*-coordination by versatile ruthenium(II/IV) catalysis. The ruthenium(II)-catalyzed C–H oxygenation of aryl acetamides proceeded through C–H activation, ruthenium(II/IV) oxidation and reductive elimination, thus providing step-economical access to valuable phenols. The *p*-cymene-ruthenium(II/IV) manifold was established by detailed experimental and DFT-computational studies.

Introduction

Phenols are key structural motifs in various natural products and biologically relevant molecules.[1] In recent years, a number of methods for oxidative C–O bond formation on arenes has been developed.[2] Especially the catalytic hydroxylation of otherwise inert C–H bonds under transition metal catalysis represents an environmentally-benign as well as economically-attractive method towards an expedient access of substituted phenols.[3,4] The past few years have witnessed a considerable growth in the use of less expensive,[5] readily-accessible and versatile ruthenium(II) catalysts for C–H functionalization[6] as an alternative to commonly employed cost-intensive palladium and rhodium complexes.[7] To this end, considerable progress has been made in proximity-induced *ortho*-C–H transformations by employing ruthenium(II) complexes. In particular, carboxylate assistance has been recognized as a powerful tool for C–H activations through metal-ligand cooperation *via* a six-membered transition state.[8] Despite these undisputable advances, ruthenium-catalyzed C–H functionalization with distal, weakly coordinating directing groups, such as aryl acetamides, continues to be scarce,[9] mainly due to the formation of unfavorable six-membered metallacycle intermediates.[5f,10]

Within our program on ruthenium(II)-catalyzed atom- and step-economical C–H functionalization,[11] we developed the ruthenium-catalyzed C–H oxygenation of weakly *O*-coordinating aryl acetamides, on which we report herein (Figure 1). Significant features of our findings include a) an efficient strategy for the ruthenium(II/IV)-catalyzed C–H hydroxylations *via* distal weak *O*-coordination, b) ample substrate scope with synthetically useful amides and esters, c) use of mild hypervalent iodine reagents as the oxidant, and d) unprecedented experimental and computational mechanistic insights.

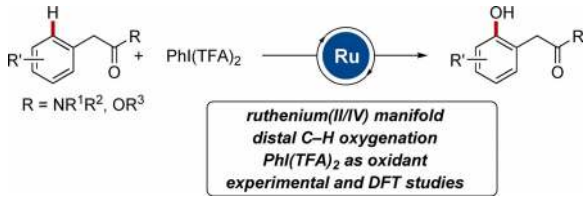

Figure 1. Ruthenium-catalyzed C–H oxygenation by distal weak coordination.

Results and Discussion

We commenced our studies by probing the envisioned C–H oxygenation of weakly *O*-coordinating amide **1a** with $[RuCl_2(p\text{-cymene})]_2$ as the catalyst and $PhI(TFA)_2$ as the oxygenation agent (Table 1). DCE was found to be the solvent of choice, whereas toluene, DMF, *m*-xylene and 1,4-dioxane gave inferior results (entries 1–6). Interestingly, TFA/TFAA turned out to be unsuitable for this reaction (entry 5). Control experiments confirmed the essential role of the ruthenium catalyst (entry 7). Notably, frequently employed palladium, nickel, cobalt, and rhodium catalysts fell short in providing the desired product **2a** (entries 8–11). The use of widely employed oxidants such as $K_2S_2O_8$ and $(NH_4)_2S_2O_4$ fell short in delivering the desired product **2a** under otherwise identical conditions (Table S1 in the Supporting Information).

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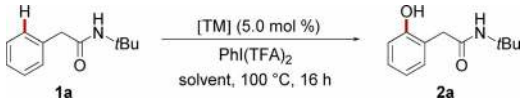
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/chem.202003062.

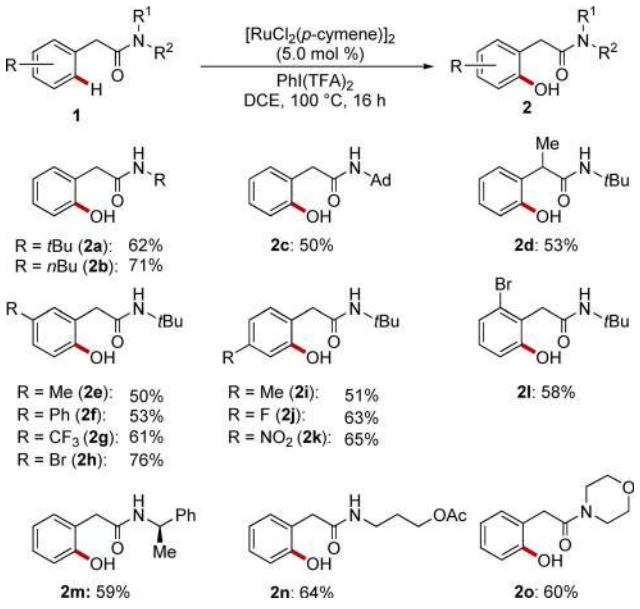
Table 1. Optimization of distal C–H oxygenation of acetamide **1a**.[a]



Entry	[TM]	Solvent	Yield (%)[b]
1	$[RuCl_2(p\text{-cymene})]_2$	1,4-dioxane	NR
2	$[RuCl_2(p\text{-cymene})]_2$	DMF	NR
3	$[RuCl_2(p\text{-cymene})]_2$	PhMe	15
4	$[RuCl_2(p\text{-cymene})]_2$	*m*-xylene	15
5	$[RuCl_2(p\text{-cymene})]_2$	TFA/TFAA[c]	NR
6	$[RuCl_2(p\text{-cymene})]_2$	DCE	62
7	–	DCE	NR
8	$Pd(OAc)_2$	DCE	42
9	$Ni(cod)_2$	DCE	NR
10	$[Cp^*Co(CO)I_2]$	DCE	NR
11	$[RhCp^*Cl_2]_2$	DCE	NR

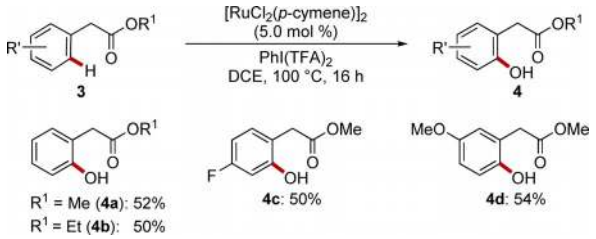
[a] Reaction conditions: **1a** (0.5 mmol), $PhI(TFA)_2$ (1.0 mmol), [TM] (5.0 mol %), solvent (2.0 mL), 16 h. [b] Yield of isolated products. [c] Ratio of TFA:TFAA: 1:1. Key: pentamethylcyclopentadiene (Cp*), 1,2-dichloroethane (DCE), *N*,*N*-dimethyl-formamide (DMF), 1,4-cyclooctadiene (cod), TFA/TFAA = trifluoroacetic acid/trifluoroacetic anhydride.

With the optimized reaction conditions in hand, we probed the versatility of the ruthenium(II)-catalyzed C–H oxygenation with differently decorated phenyl acetamides **1** (Scheme 1). Initially, we studied the effect exerted by the amide substitution pattern on the C–H oxygenation. Interestingly, sterically hindered amides such as **1a** and **1c** served as viable substrates and yielded the corresponding products **2**. The robustness of the ruthenium(II) catalysis was reflected by the excellent tolerance of valuable functional groups such as nitro, fluoro and bromo, thereby setting the stage for further late-stage diversifications. Electron-rich as well as electron-deficient amides were smoothly transformed into the corresponding monohydroxylated products **2** in moderate to good yield independent of the substitution pattern. *meta*-Bromo-substituted substrate **1h** gave the corresponding product **2h** as the sole product with excellent levels of regioselectivity and yield. Remarkably, no racemization of stereogenic center was observed in case of **2m**. Furthermore, the reaction proceeded well with tertiary amide, providing **2o**.



Scheme 1. Ruthenium-catalyzed C–H oxygenation of acetamides **1**.

It is noteworthy that the versatile ruthenium(II) catalyst was not limited to aryl acetamides. Indeed, we were pleased to identify more challenging, weakly-coordinating phenylacetyl esters as viable substrates (Scheme 2). To this end, excellent levels of site-selectivity was accomplished for the hydroxylation of electron-poor as well as electron-rich phenylacetyl esters providing the corresponding products **4c** and **4d**.

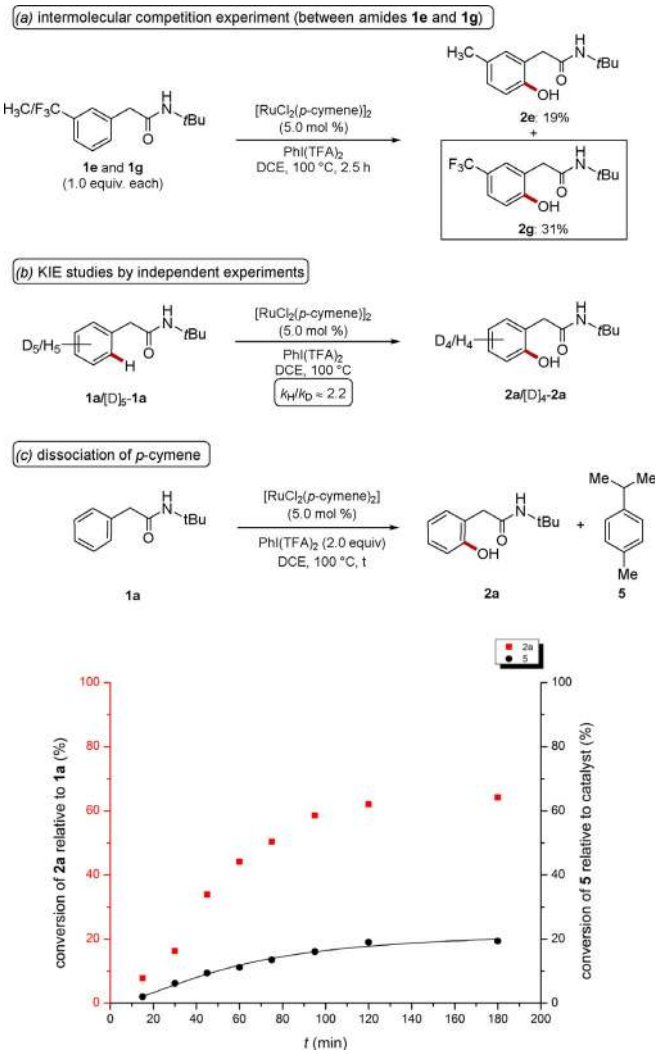


Scheme 2. Ruthenium-catalyzed C–H oxygenation of phenylacetyl esters **3**.

Given the excellent efficiency of the ruthenium(II)-catalyzed C–H oxygenation, we became interested in delineating its mode of action. To this end, an intermolecular competition experiment between differently substituted substrates **1** indicated electron-deficient arene **1g** to be inherently more reactive than electron-rich arene **1e**, which can be rationalized by a CMD-type mechanism (Scheme 3a).[12,13] Furthermore, kinetic isotope effect (KIE) studies by independent reactions suggested a kinetically relevant C–H metalation with a KIE of $k_H/k_D \approx 2.2$ (Scheme 3b). Thereafter, we investigated the possibility of *p*-cymene dissociation during the course of the reaction. A careful analysis of the final reaction mixture did not provide any evidence for the presence of significant amounts of free *p*-cymene (**5**) (Scheme 3c).[14]

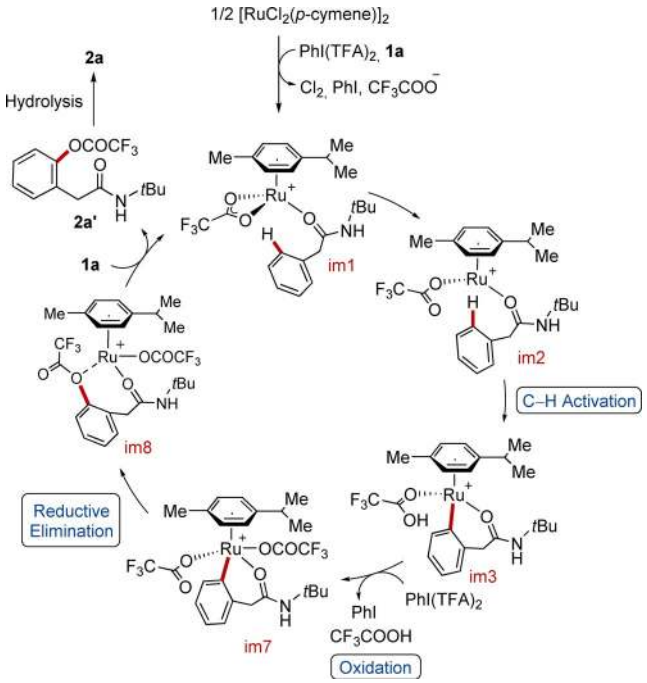
Based on our experimental studies, we propose a plausible catalytic cycle for ruthenium(II)-catalyzed C–H oxygenations to commence with a kinetically relevant C–H activation on acetamide **1a** by ruthenium(II) complex **im2** (Scheme 4). Thus generated ruthena(II)cycle **im3** will then undergo oxidation by the hypervalent iodine reagent $PhI(TFA)_2$, delivering ruthenium(IV) intermediate **im7**. Reductive elimination from **im7** leads to the formation of a new C–O bond, generating complex **im8**. Coordination of a trifluorocarboxylate anion to the metal center will liberate product **2a''** and regenerate the active catalyst **im1**. Alternatively, **2a''** will undergo hydrolysis to generate the final product **2a**.

In order to probe the catalyst's mode of action, we became interested in better understanding the mechanism of C–H oxygenation by density functional theory (DFT) studies (Figure 2). Geometry optimizations and frequency calculations were per-



Scheme 3. Key mechanistic findings.

formed at the B3LYP-D3(BJ)/6-31G*,def2-SVP(Ru,I) level of theory, while single point energies were calculated at the PBE0-D3(BJ)/6–311++G**,def2-TZVP(Ru,I)+SMD(DCE) level of theory.[15] Our findings unravel here that the initial C–H activation occurs from the intermediate **im2** facilitated by the acetate ligand *via* **TS2**. The thus formed ruthenacycle **im3** undergoes ligand exchange with $PhI(TFA)_2$ to generate **im4**. The oxidation process occurs from **im4** *via* two steps. The first step involves the cleavage of the I–O bond, along with the generation of Ru-I bond in a concerted fashion *via* **TS3**. The subsequent cleavage of the second I–O bond from **im5** *via* **TS4** leads to the formation of the intermediate **im6**. Upon release of iodobenzene, the trifluorocarboxylate anion coordinates to the metal center to form **im7**. Subsequently, facile reductive elimination occurs from **im6** *via* **TS5** involving a ruthenium(IV/II) process to generate the final product **im8**. The calculated energy barriers are overall in good agreement with the experimental data.



Scheme 4. Plausible catalytic cycle for ruthenium-catalyzed C–H oxygenation.

Conclusions

In summary, we have reported on ruthenium-catalyzed C–H oxygenations of weakly *O*-coordinating aryl acetamides proceeding through a challenging 6-membered ruthenacycle. This powerful strategy allowed for the rapid and site-selective installation of hydroxyl groups with ample scope, using mild and effective hypervalent iodine reagents. Furthermore, this versatile ruthenium(II) catalyst facilitates the direct C–H functionalization and tolerates challenging weakly-coordinating phenylacetyl esters. Mechanistic studies unraveled an oxidation induced reductive elimination manifold for distal acetamide-enabled C–H oxygenation.

Acknowledgements

Generous support by the DFG (SPP 1807 and Gottfried Wilhelm Leibniz prize) and the CSC (PhD fellowships to Q.B. and Z.S.) are gratefully acknowledged. Open access funding enabled and organized by Projekt DEAL.

Conflict of interest

The authors declare no conflict of interest.

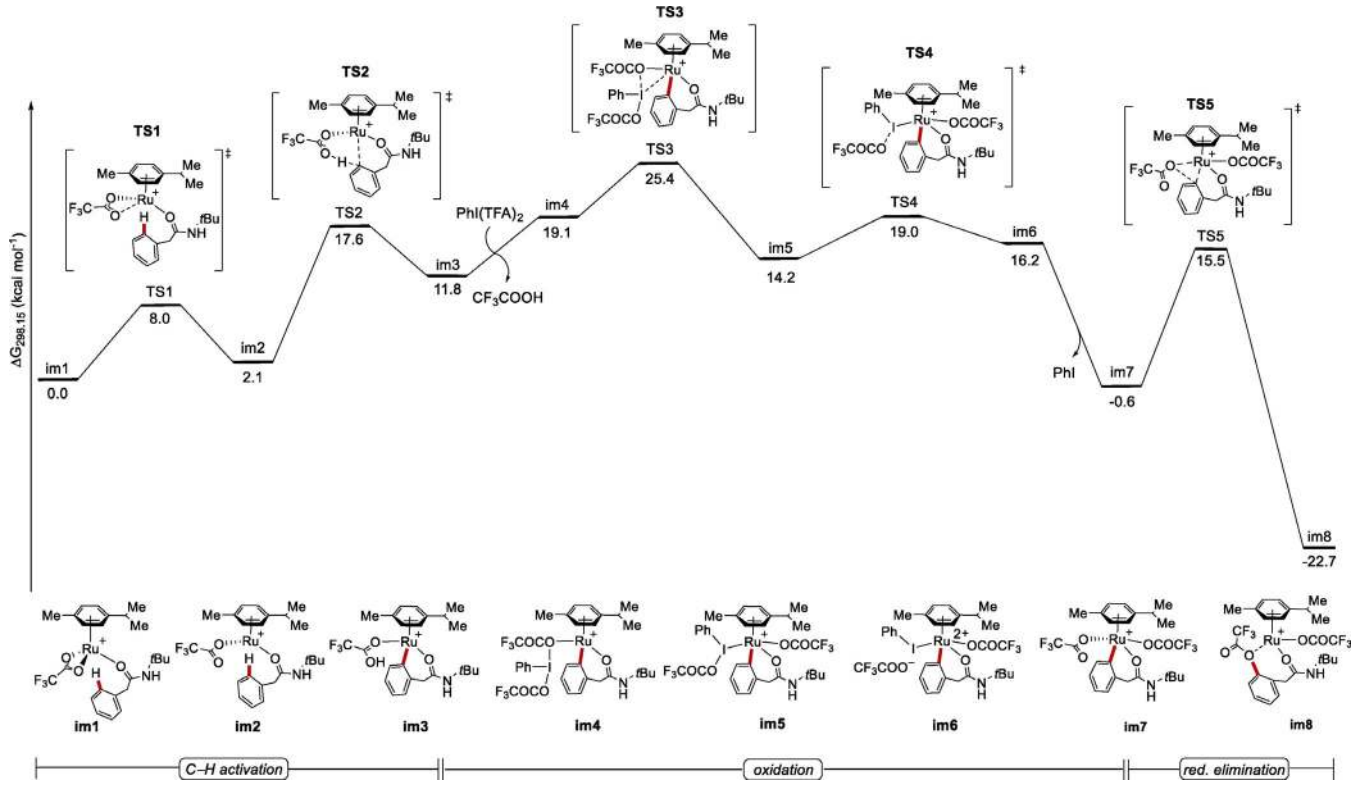


Figure 2. Computed relative Gibbs free energy in kcal mol^{-1} for the ruthenium-catalyzed C–H oxygenation reaction of **1a** at the PBE0-D3(BJ)/6–311++G**, def2-TZVP(Ru,I)+SMD(DCE)//B3LYP-D3(BJ)/6-31G*,def2-SVP(Ru,I) level of theory.

Keywords: amides · C–H activation · oxygenation · reaction mechanisms

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Manuscript received: June 26, 2020
Accepted manuscript online: June 29, 2020
Version of record online: October 29, 2020