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# Broadening the catalyst and reaction scope of regio- and chemoselective C–H oxygenation: a convenient and scalable approach to 2-acylphenols by intriguing Rh(II) and Ru(II) catalysis†

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A unique Rh(II) and Ru(II) catalyzed C–H oxygenation of aryl ketones and other arenes has been developed for the facile synthesis of diverse functionalized phenols. The reaction demonstrates excellent reactivity, regio- and chemoselectivity, good functional group compatibility and high yields. The practicality of this method has been proved by gram-scale synthesis of a few different 2-acylphenols. Its utility has been well exemplified in further applications in heterocycle synthesis and direct modifications of drug Fenofibrate.



## Introduction

Hydroxylated arenes are highly valuable chemicals related to pharmaceuticals, agrochemicals and polymers in industry.[1] In the last decade, direct functionalization of $SP^2$ C–H bonds by transition-metal[2] emerged as a powerful method for generating new C–O[3] bonds. Although significant progress has been made in this field, there are still many difficulties and challenges for the direct C–H oxygenation in terms of catalyst scope, reaction scope, regio- and chemoselectivity and practicality of prevalent protocols. To date, the vast majority of research have been focused on the employment of transition metal Pd[4] catalysts. In contrast, other metals, like Ru[5] and Rh,[6] are barely documented in this type of transformation. Compared with palladium, ruthenium complexes are significantly less expensive and rhodium catalysts often show its distinct selectivity and efficiency in different types of transformations.

Recently, our group have reported the first example of Ru(II) catalyzed *ortho*-hydroxylation of benzoates.[7,8] In our continuous studies of developing new general tools for functionalized phenol synthesis, we try to further expand both substrate and catalyst scopes for this C–H oxygenation reaction, which would greatly boost and improve the practicality and generality of this chemistry. Therefore, the following two queries arose for us: (1) Is the ruthenium-catalyzed C–H oxygenation reaction is applicable for different types of aryl ketones?[9] The answer to this question has a multi-fold meaning. Firstly, although the use of a ketone group as the directing group by Ru catalysts is well known, the reaction only afforded the C–C coupling products.[10] By contrast, ketone directed C–O bond formation by ruthenium is unknown. Secondly, the potential C–O coupling reaction of aryl ketones will afford 2-acylphenols which are an important structural motif of a diversity of drugs and natural products. Besides serving as useful synthetic intermediates for preparation of a number of heterocycles, such as benzofuranone, benzoxazole and dibenzoxazepine, *etc.*, 2-acylphenols were also utilized as key building blocks for therapeutic agents like Propafenone and Celiprolol. Thirdly, as aromatic ketones are frequent scaffolds in drugs and synthetic intermediates for pharmaceuticals and natural products, this method potentially can provide a rapid access to hydroxylated analogues of a broad range of substrates for early drug discovery. (2) Besides ruthenium, we were curious if rhodium could efficiently promote this reaction as well. As rhodium has never been reported in this type of C–H oxygenation reaction, we are particularly interested in the possible new catalytic activity of rhodium catalysts and its substrate scope. Moreover, expanding the catalyst and reaction scope will provide more choice and better control for its synthetic applications.

Accordingly, based on our experience and understanding of this chemistry, we envisioned that ruthenium and rhodium catalysts, under certain acidic conditions, could promote C–H bond activation *via* an orthometalation process through weak

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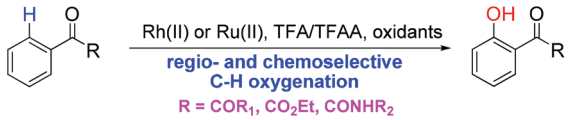



**Scheme 1** Developing a new approach for C–H oxygenation of diverse arenes with Rh and Ru catalysts.

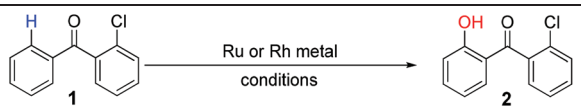
coordination with carbonyl oxygen of aryl ketones. Subsequently, a C–O bond formation is possible *via* the reductive elimination to afford corresponding phenols with suitable acids and oxidants[11] (Scheme 1). Herein, we report a novel of Rh(II) and Ru(II) catalyzed regio- and chemoselective C–H oxygenation of various arenes including aryl ketones, benzoates and benzamides, and its convenient applications in heterocycle synthesis and direct modification of drugs.

## Results and discussion

To test our hypothesis, a model study was initiated with aromatic ketone **1** in the presence of various ruthenium catalysts in TFA/TFAA solvent system with commercially available $K_2S_2O_8$[12] as the terminal oxidant. To our delight, the formation of phenol product **2** was observed in 57% yield with $K_2S_2O_8$ in the presence of $[RuCl_2(p\text{-cymene})]_2$ after stirring for 2 h at 80 °C (entry 1). A variety of other oxidants were also examined in the reaction, such as $PhI(OAc)_2$, $KIO_4$, $NaIO_4$, selectfluor[13] and $Na_2S_2O_8$, *etc.* Among them, selectfluor and $PhI(OAc)_2$ was noted to have a similar capability as $K_2S_2O_8$ (entries 2 and 9). Other Ru(II) catalysts were attempted in the reaction as well, such as $RuCl_2(PPh)_3$ and $Ru(CO)HCl(PPh)_3$, which showed similar catalytic efficiency as $[RuCl_2(p\text{-cymene})]_2$. In contrast, either none or only trace amount of product were formed, if $RuCl_3$ and $RuO_2$ were employed under the same conditions. In parallel, various rhodium metals were also applied to probe their potential catalytic activities. Surprisingly and intriguingly, when $Rh(OAc)_2$ was applied to the reaction, desired phenol **2** was obtained with a yield of 53% (entry 14). However, no reaction occurred at all with Rh(III) and Rh(I) catalysts (entries 16 and 17), even with elongated reaction times. This initial result suggests that Ru(II) and Rh(II) catalyzed C–H oxygenation with the carbonyl oxygen of aryl ketones as effective coordinating group could occur under proper acidic conditions. Encouraged by the preliminary results, we set out to optimize the reaction conditions. After extensive testing, we found that the ratio of TFA–TFAA around 7 : 3 is most suitable for the reaction. There are only slight differences with the addition of ligands such as pyridine in terms of reaction rates and conversion ratios. In general, the reaction will proceed to completion with 2.5% equiv. of $[RuCl_2(p\text{-cymene})]_2$ or $Rh(OAc)_2$ and 2.0 equiv. of oxidants ($K_2S_2O_8$ or $PhI(OAc)_2$) in the presence of TFA–TFAA (7 : 3/v : v) within 3–4 hours at 80 °C (Table 1).

With the optimized conditions in hand, we next began to survey this new reaction scope with both Ru(II) and Rh(II) catalysts. As showed in Table 2, a variety of aromatic ketone substrates were efficiently transformed into the desired phenol products not only in moderate to excellent yields, but also with excellent regio- and chemoselectivity. Compared to $Rh(OAc)_2$, the overall catalytic activity of $[RuCl_2(p\text{-cymene})]_2$ is better in terms of efficiency and both catalysts share a similar selectivity. [Yields of substrates with $Rh(OAc)_2$ are shown in brackets.] We found that the scope of the substituents was very broad.

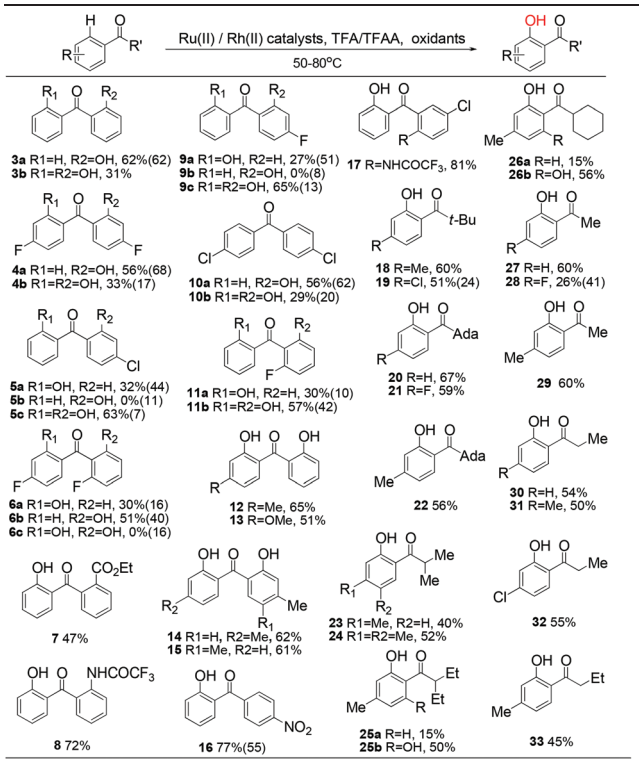
**Table 1** Optimization of the reaction conditions




| Entry | Catalyst | Oxidant[c] | Conditions | Yield[a] (%) |
|---|---|---|---|---|
| 1 | $[RuCl_2(p\text{-cymene})]_2$ | $K_2S_2O_8$ | TFA/TFAA (1.4 : 0.6), 80 °C, 2 h | 57% |
| 2 | $[RuCl_2(p\text{-cymene})]_2$ | Selectfluor | TFA/TFAA (1.4 : 0.6), 80 °C, 2 h | 41% |
| 3 | $RuCl_3$ | $PhI(OAc)_2$ | TFA/TFAA (1.4 : 0.6), 80 °C, 3 h | 3% |
| 4 | $RuO_2$ | $PhI(OAc)_2$ | TFA/TFAA (1.4 : 0.6), 80 °C, 3 h | NR |
| 5 | $Ru_3(CO)_{12}$ | $PhI(OAc)_2$ | TFA/TFAA (1.4 : 0.6), 80 °C, 3 h | 5% |
| 6 | Dichlorotris(1,10-phenanthroline)ruthenium(II) hydrate | $PhI(OAc)_2$ | TFA/TFAA (1.4 : 0.6), 80 °C, 3 h | NR |
| 7 | $Ru(CO)ClH(PPh_3)_3$ | $PhI(OAc)_2$ | TFA/TFAA (1.4 : 0.6), 80 °C, 3 h | 38% |
| 8 | $RuCl_2(PPh_3)_3$ | $PhI(OAc)_2$ | TFA/TFAA (1.4 : 0.6), 80 °C, 3 h | 40% |
| 9 | $[RuCl_2(p\text{-cymene})]_2$ | $PhI(OAc)_2$ | TFA/TFAA (2.0 : 0), 80 °C, 2 h | 51% |
| 10 | $[RuCl_2(p\text{-cymene})]_2$ | $PhI(OAc)_2$ | TFA/TFAA (1.4 : 0.6), 80 °C, 3 h | 72%[b] |
| 11 | $[RuCl_2(p\text{-cymene})]_2$ | $PhI(OAc)_2$ | TFA/TFAA(1.0 : 1.0), 80 °C, 2 h | 46% |
| 12 | $[RuCl_2(p\text{-cymene})]_2$ | $PhI(OAc)_2$ | TFA/TFAA (0.5 : 1.5), 80 °C, 2 h | 35% |
| 13 | $[RuCl_2(p\text{-cymene})]_2$ | $PhI(OAc)_2$ | TFA/TFAA (0 : 2.0), 80 °C, 2 h | 34% |
| 14 | $Rh(OAc)_2$ | $K_2S_2O_8$ | TFA/TFAA (1.8 : 0.2), 80 °C, 17 h | 53%[b] |
| 15 | $Rh(OAc)_2$ | Selectfluor[d] | TFA/TFAA (1.8 : 0.2), 80 °C, 17 h | 26% |
| 16 | $RhCl(PPh_3)_3$ | Selectfluor | TFA/TFAA (1.8 : 0.2), 80 °C, 17 h | NR |
| 17 | $[(RhCp^*Cl_2)_2]$ | Selectfluor | TFA/TFAA (1.8 : 0.2), 80 °C, 17 h | NR |

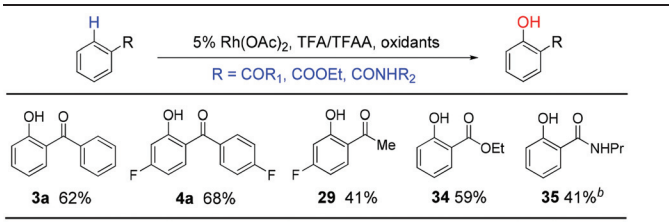
[a] Conversion ratio. [b] Isolated yield. [c] 2.0 equiv. [d] 1.5 equiv.

**Table 2** Ruthenium and rhodium catalyzed regio- and chemoselective C–H oxygenation of aryl ketones[a,b]

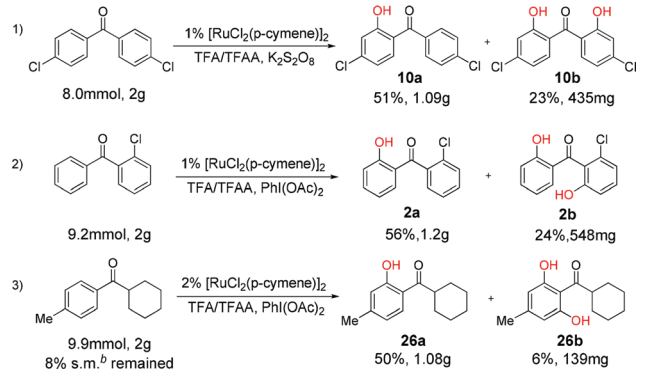



[a] Isolated yield. [b] Ada: 1-adamantyl; *t*-Bu: *tert*-butyl.

**Table 3** Representative ketone, benzoate and benzamide as substrates under rhodium(II) catalysis[a]




[a] Isolated yield. [b] Unoptimized.



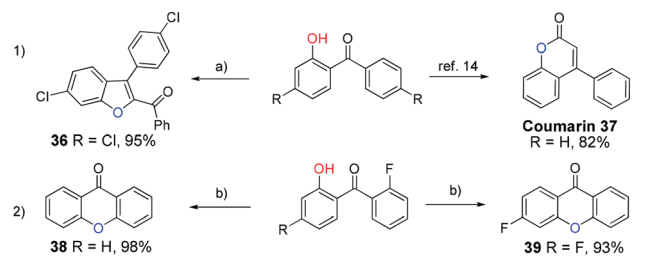

**Scheme 2** Gram-scale synthesis of 2-acylphenols under ruthenium(II) catalysis. [a]Isolated yield. [b]Starting material.

The strong electron withdrawing and electron donating functional groups (nitro, halides, ester, amide, methoxyl and alkyl *etc*.), as well as various *ortho*, *meta* and *para*-substituted aryl groups were well tolerated. It was noticed that the more electron-rich parts of unsymmetrical diaryl ketones were hydroxylated prior to less electron-rich parts (**7**, **9**, **16**). Quite impressively, in a few cases, synthetically challenging dihydroxylated products (**5**, **9**, **11**, **25**, **26**) can be obtained as major products. Additionally, to our delight, remarkable chemo- and regioselectivity can be achieved with aryl ketone substrates (**23**–**33**), which contain reactive alpha-protons. It is notable because these phenols are difficult-to-prepare products or usually need tedious steps to prepare using known methods. It is noteworthy that this protocol was conducted without the need for air- or moisture-proof conditions.

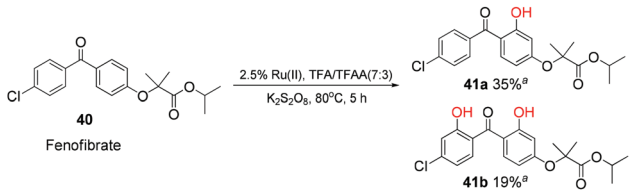
Subsequently, the reaction conditions with $Rh(OAc)_2$ as the catalyst were applied to other substrates including benzoates, benzamides and phenylacetates. As displayed in Table 3, we are very pleased to find that these three types of molecules were successfully transformed into the corresponding phenol products in modest to good yields. To the best of our knowledge, this represents the first example of Rh(II) catalyzed regio- and chemoselective C–H oxygenation of these substrates.

To further prove both practicality and effectiveness of this method in the synthesis, we prepared 2-acylphenol **2**, **10** and **26** on a gram scale under the optimized conditions with only 1% $[RuCl_2(p\text{-cymene})]_2$ catalyst loading (Scheme 2). Interestingly, besides the mono-hydroxylation product, a considerable amount of the di-hydroxylation product, **10b**, **2b** and **26b**, was formed as well, which could be readily transformed into 1-hydroxyxanthone or 1-chloroxanthone under different conditions. In comparison with conventional approaches requiring air-/moisture-proof conditions, the current method is advantageous for rapid access to these types of molecules because of its operational simplicity and broad availability of starting materials.

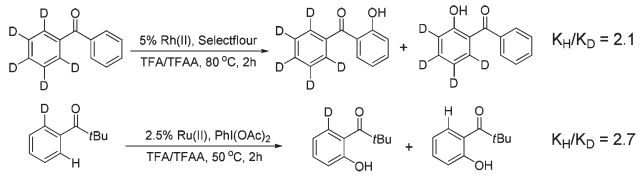
As shown in Scheme 3, to demonstrate the synthetic utility of this C–H oxygenation reaction, a variety of biologically important *O*-containing heterocyclic compounds were prepared from 2-acylphenols. Not only benzofuran **36** and coumarin **37**,[14] but also demanding xanthone derivative **39** can be




**Scheme 3** Synthetic applicability of 2-acylphenols. *Conditions*: (a) 2-bromo acetophenone, $K_2CO_3$, MeCN, reflux, 16 h, 95%; (b) $K_2CO_3$, acetone, reflux, 4 h.




**Scheme 4** Direct C–H oxygenation of drug Fenofibrate. [a]Isolated yield.




**Scheme 5** Kinetic isotope effect studies.

readily obtained from corresponding the 2-acylphenols using known transformations.

Direct modification of drugs or drug candidates *via* C–H activation is a particularly attractive approach for modern drug discovery, which highly depends on the practicality of such chemical processes. Therefore, in Scheme 4, we show the feasibility of our new reaction by performing direct C–H oxygenation of Fenofibrate, a prescription drug commonly used to treat unhealthy triglyceride and cholesterol levels. Pleasingly, both mono- and di-hydroxylated products (**41a**, **41b**) were found in a total yield of 54%. This method can provide a new approach to prepare novel analogues of a broad range of drugs which contain aromatic ketone scaffolds.

Further investigations were performed to gain some insight of the reaction mechanism, which is illustrated in Scheme 5. The consistent and significant KIE values were observed from both Rh(II)-catalyzed ($k_H/k_D$ = 2.1) and Ru(II)-catalyzed ($k_H/k_D$ = 2.7) isotope effect studies, which indicated that the C–H bond cleavage step might be involved in the rate-limiting step of this transformation.

Although details about the mechanism remain unclear, on the basis of our studies, a plausible mechanism for this reaction is demonstrated as followings. Step (i) involves chelation of Rh(II)/Ru(II) to carbonyl oxygen atom from the ketone substrates and the following chelate-directed C–H activation of the substrate could afford a five-membered cyclometalate(II) intermediate. In the second step (ii), Rh(II)/Ru(II) was oxidized into possible Rh(IV)/Ru(IV) intermediate. The final step (iii) involves carbon–oxygen bond-forming reductive elimination to afford the trifluoroacetated product and turned Rh(IV)/Ru(IV) back into Ru(II)/Rh(II). The trifluoroacetated product was converted to hydroxylated ketones after the later aqueous workup.[15]

## Conclusions

In summary, a novel Rh(II) and Ru(II) catalyzed regio- and chemoselective phenol synthesis has been developed for the synthesis of a variety of functionalized phenols from easily accessible arenes. The reaction demonstrates excellent reactivity, *ortho*-selectivity, good functional group tolerance and high yields. The practicality of this new method was tested by a few gram-scale syntheses of 2-acylphenols. Its utility has been well exemplified in further applications in heterocycle synthesis and direct modification of drug Fenofibrate. By employing a combination of Rh(II) and Ru(II) catalysts, oxidants and TFA/TFAA, we have discovered a highly efficient catalyst system for this unique regio- and chemoselective C–H oxygenation reaction. Further studies into the scope and the mechanism of this reaction are in progress in our laboratory.

## Acknowledgements

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