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Ruthenium(II)-Catalyzed Synthesis of Hydroxylated Arenes with Ester as an Effective Directing Group

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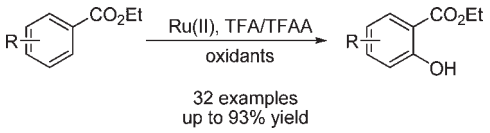
ABSTRACT



An unprecedented Ru(II) catalyzed *ortho*-hydroxylation has been developed for the facile synthesis of a variety of multifunctionalized arenes from easily accessible ethyl benzoates with ester as an efficient directing group. Both the TFA/TFAA cosolvent system and oxidants serve as the critical success factors in this transformation. The reaction demonstrates excellent reactivity, good functional group tolerance, and high yields.

Hydroxylated arenes are common structural scaffolds found in important pharmaceuticals, agrochemicals, polymers, and biologically active natural compounds,[1] which have also served as versatile intermediates in organic synthesis due to their rich reactivity.[2] Direct functionalization of C−H[3] bonds by transition metals emerged as a powerful method for generating new C−O[4] bonds in the past decade. More recently, two elegant methods toward *ortho*-acetoxylation and hydroxylation have been reported individually by the Sanford[5] and Yu[6] groups (Scheme 1). In both studies, $Pd(OAc)_2$ was employed as effective catalyst with either *N*-oxime ether or potassium carboxylate as the coordinating functional groups respectively.

Although significant advances to this field have been accomplished, many challenges remain. To date, most

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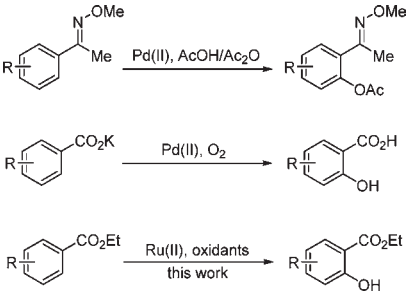
research have been focused on metals such as Pd,[7] Cu[8] or Fe,[9] etc. In contrast, other metals, like Ru[10] and Rh,[11] are rarely reported in this transformation. Furthermore, developing other appliable directing groups is still highly desired. The majority of studies so far reported had relied on using nitrogen-containing coordinating groups like pyridine,[12] amide,[13] oxime ether,[14] carbamate[15] or oxazoline,[16] etc. Lately, carboxylic acids[17] have also been successfully employed as efficient coordinating groups in many useful chemical transformations (Scheme 1).

In contrast, the application of an ester functionality as the feasible directing group in the transtion-metal-catalyzed *ortho*-aromatic C−H bond activation has been rarely reported,[18] especially considering that ester functional groups are not only readily available but also easily converted to alcohols, amides, and other carbonyl compounds. To the best of our knowledge, direct *ortho*-hydroxylation of arenes catalyzed by Ru(II) with ester as efficient directing group has not yet been achieved. Here, we report the first example of ruthenium(II) catalyzed *ortho*-hydroxylation of arenes assisted by ester functional groups (Scheme 1).

Scheme 1. Approaches for Hydroxylation of Arenes



In our continuous studies of preparing multifunctionalized arenes, we proposed that the ruthenium catalyst, under proper acidic conditions, allows C−H bond cleavage via an orthometalation process through chelation with carbonyl oxygen from aromatic esters. Consequently, a C−O bond formation is possible via the reductive elimination to afford corresponding hydroxylation or acetoxylation products. Herein, a model study was initiated with benzoate **1** in the presence of $[RuCl_2(p\text{-cymene})]_2$ in $AcOH/Ac_2O$ solvent system with $K_2S_2O_8$ as the terminal oxidant to test our hypothesis (Table 1). However, neither preferred hydroxylation nor acetoxylation reactions happened. After many fruitless attempts, we turned our attention to TFA. The hydroxylated product **2** was observed in less than 5% yield after the mixture was stirred for 6 h at 80 °C in TFA (Entry 4). Encouraged by this preliminary result, we started to optimize the reaction conditions. After a comprehensive screening, we found that TFA/TFAA cosolvent was superior over TFA with a notably higher level of efficiency. Further investigations revealed that the ratio of TFA/TFAA is critical for the reaction as well. For example, the conversion ratio of **2** from **1** was about 61% with TFA/TFAA (9:1/v:v), which could be further improved to 75% when using TFA/TFAA (7:3/v:v). A variety of other oxidants were also examined in the reaction, such as $PhI(OAc)_2$, KIO_4, $NaIO_4$,[19] HIO_3, Selectfluor, $Na_2S_2O_8$, and H_2O_2, etc. Among them, Selectfluor was noted to have a similar capability as $K_2S_2O_8$. It was observed that higher temperatures could speed up the reactions and improve the

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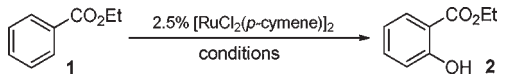
(19) Ethyl 3-iodobenzoate was major product when KIO_4 or $NaIO_4$ were used as oxidant.

yields. There is only slight differences with higher catalyst loadings in terms of reaction rates and conversion ratios. Generally, 0.025 equiv of $[RuCl_2(p\text{-cymene})]_2$ was enough to effectively promote the reaction. Attempts to use other ruthenium catalysts, such as $RuCl_2(PPh)_3$, $RuHCl(PPh)_3$, and $Ru_3(CO)_{12}$, were not very successful. Typically, the reaction will proceed to completion in TFA/TFAA within 11 h, in a clean manner, with 1.1 equiv of oxidant at 90 °C.

Table 1. Optimization of the Reaction Conditions



entry	oxidant (1.1 equiv)	conditions	yield[a] (%)
1	$K_2S_2O_8$	AcOH/Ac_2O/9:1, 80 °C, 7 h	0
2	$K_2S_2O_8$	AcOH/Ac_2O/6:4, 80 °C, 7 h	0
3	$K_2S_2O_8$	AcOH/Ac_2O/3:7, 80 °C, 7 h	0
4	$K_2S_2O_8$	TFA, 80 °C, 7 h	<5
5	$K_2S_2O_8$	TFA/TFAA/8:2, 80 °C,7 h	50
6	$K_2S_2O_8$	TFA/TFAA/7:3, 80 °C,7 h	44
7	$K_2S_2O_8$	TFA/TFAA/6:4, 80 °C,7 h	31
8	$K_2S_2O_8$	TFA/TFAA/9:1, 80 °C,7 h	61
9	$K_2S_2O_8$	TFA/TFAA/7:3, 80 °C, 11 h	75
10	KIO_4	TFA/TFAA/7:3, 80 °C,11 h	7
11	$NaIO_4$	TFA/TFAA/7:3, 80 °C, 11 h	trace
12	HIO_3	TFA/TFAA/7:3, 80 °C,11 h	20
13	$PhI(OAc)_2$	TFA/TFAA/7:3, B0 °C, 11 h	44
14	$Cu(OAc)_2$	TFA/TFAA/7:3, 80 °C, 11 h	0
15	H_2O_2	TFA/TFAA/7:3, 80 °C, 11 h	0
16	Selectfluor	TFA/TFAA/7:3, 80 °C,11 h	73[b]
17	Selectfluor	TFA/TFAA/6:4, 90 °C,4 h	41
18	Selectfluor	TFA/TFAA/6:4, 90 °C,6 h	53
19	Selectfluor	AcOH/Ac_2O/6:4, 90 °C, 8 h	0
20	Selectfluor	AcOH/Ac_2O/9:1, 90 °C, 8 h	0

[a] Conversion ratio. [b] Isolated yield.

Having identified these optimal conditions, we set out to explore the scope for this new reaction. As displayed in Figure 1, a variety of mono- and disubstituted ethyl benzoates were surveyed. The scope of the benzoate substituents was found to be very broad. Various benzoates was smoothly transformed into the corresponding *ortho*-hydroxylated products in moderate to excellent yields. The *ortho*-, *meta*-, and *para*-substituted aryl groups, as well as the electron-rich and electron-deficient aryl groups, were well tolerated. For instance, with iodic acid as the oxidant, satisfactory yields were also observed with substrates which contain strong electron-withdrawing groups, such as CF_3 and NO_2, etc. (**9**, **10**, **18**). Most *meta*-substituted substrates gave only one regioisomer, but in some cases, another regioisomeric product (compounds **19**, **22**, and **23**) was obtained albeit in minor amounts. Notably, heteroaromatic ethyl thiophene-2-carboxylate was also successfully employed to provide compound **21**. Besides ethyl benzoates, the feasibility of other alkyl benzoates in this transformation were tested as well, such as methyl, isopropyl, propyl, butyl, and benzyl. Among them, methyl benzoates were found to have the similar practicality to its ethyl counterparts to furnish hydroxylated products in good yields (**30**, **31**).

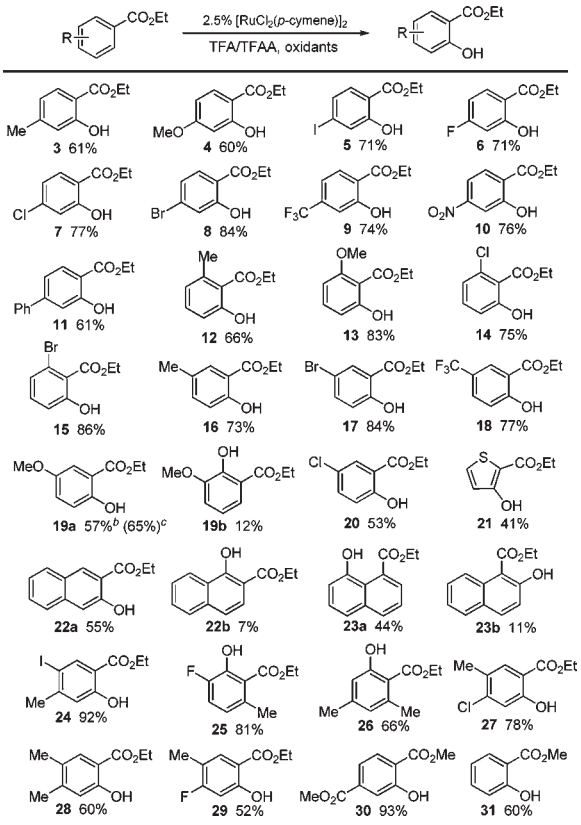
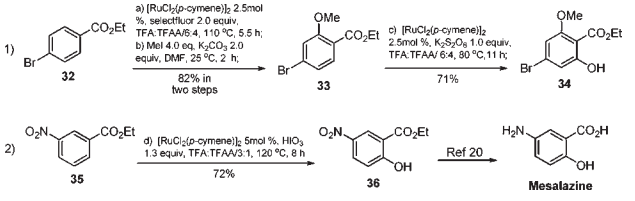


Figure 1. Substrate scope. (a) Isolated yield. (b) $K_2S_2O_8$ as oxidant. (c) Iodic acid as oxidant.

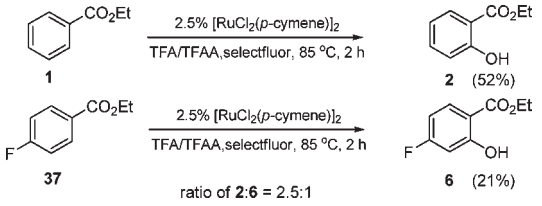
The applicability of this reaction was further demonstrated in an iterative *ortho*-hydroxylation of substrate **32**. The optimum reaction conditions proved to be successful to provide dihydroxylated compound **34** with a satisfactory yield. This new method also provides new opportunities for the construction of some biologically important molecules, which was exemplified in Scheme 2. Ethyl 3-nitrobenzoate was readily converted to hydroxylated compound **36**, which could be further transformed into Mesalazine, an anti-inflammatory drug, via a facile, sequential hydrolysis and reduction.[20]

Scheme 2. Iterative Hydroxylation and Application



As shown in Scheme 3, parallel competition experiments clearly show that the electron-rich aromatic ring reacts faster than its eletron-poor counterpart to furnish the ethyl 2-hydroxyl-5-methyl benzoate **2**. In addition, to probe the reaction mechanism, an intra- and an intermolecular isotope effect studies were conducted in parallel and a KIE value of 2.3 and 1.8[21] was obtained respectively (Scheme 4). While these results indicate that C−H activation might be involved in the rate-limiting step of this transformation, other possibilities could not be totally excluded at the current stage.[22]

Scheme 3. Separate Rate Constants Study



Although details about the mechanism still remain unclear, on the basis of these observations, it is possible that the catalytic pathway may go through a Ru(IV) intermediate C−Ru−O that reductively eliminates to afford the final product. The terminal oxidants could be involved in the reoxidation step of Ru(II). It should also be noted that a mechanism involving the common Ru(0)−Ru(II) catalytic cycle could not be completely ruled out.

In summary, an unprecedented Ru(II) catalyzed *ortho*-hydroxylation has been developed for the facile synthesis of multifunctionalized arenes from easily accessible starting materials. The TFA/TFAA cosolvent system serves as a critical success factor, and potassium persulfate, Selectfluor, or iodic acid is employed as a key oxidant in this

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(21) When the reaction was run in one flask, the corresponding KIE value was 4.0.

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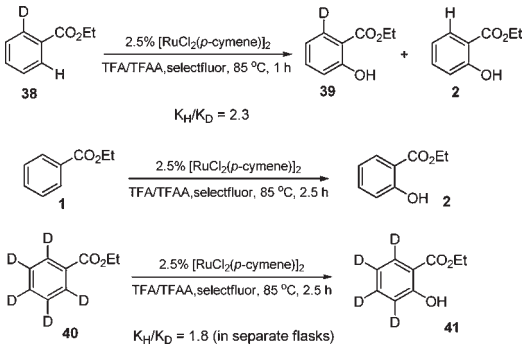
Scheme 4. Kinetic Isotope Effect



transformation. This method has been found to be generally useful for the preparation of *ortho*-hydroxylated ethyl benzoates, some of which are difficult to make via conventional approaches. The reaction demonstrates excellent reactivity, good functional group tolerance, and high yields, behavior that has been further exemplified in the synthetic applications. By employing a combination of $[RuCl_2(p\text{-cymene})]_2$, terminal oxidants, and a TFA/TFAA solvent system, we have discovered a highly efficient catalyst system for this unique C−O bond formation reaction. Further investigations into the mechanism and synthetic applications of this method are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.