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Iron-Catalyzed *ortho*-Selective Functionalization of Phenols: A Straightforward Strategy towards the 2′-Hydroxyphenyl-1,2-dione Skeleton

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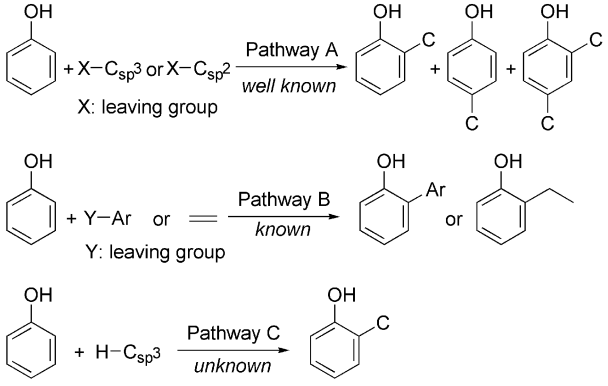
Keywords: Iron / C-H activation / Ketones / Fused-ring systems / Phenols

An iron-catalyzed *ortho*-functionalization of phenols was developed. The reactions of simple phenols with α-hydroxy ketones provide a novel and efficient method to construct 2′-hydroxyphenyl-1,2-dione derivatives.

Introduction

Direct functionalization of phenolic C–H bond has attracted much attention because phenols are one of the most important aromatic compounds in nature and industry.[1] The Friedel–Crafts reaction is one of the most well-known and powerful strategies for such a transformation.[2] However, usually it is difficult to control the regio- and/or monoselectivity if no directing group is present in the benzene ring (Scheme 1, pathway A). Although transition-metal-catalyzed selective aromatic C–H bond activation reactions, such as the Murai-type reaction,[3] have been studied extensively, simple phenols are not suitable substrates due to the formation of unfavorable four-membered metallacycles.[4] To achieve *ortho*-selectivity,[5] attractive complementary approaches include he application of an extra stoichiometric reagent,[6] a phosphinite co-catalyst,[7] or ligand.[8] In these cases, only sp^2-hybridized carbon atoms can be used (Scheme 1, pathway B). Although enolizable sp^3 C–H bonds reacted with indoles and pyrroles under the oxidative conditions,[9] there is no example for simple phenols (Scheme 1, pathway C).[10] Therefore, it is a great challenge to achieve the *ortho*-specific functionalization of simple phenols.

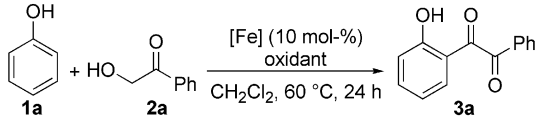


Scheme 1. Functionalization of phenol C–H bond.

Results and Discussion

The numerous advantages of iron make it highly attractive as a catalyst or reagent for chemical synthesis.[11] The challenge of selective functionalization of phenols prompted us to investigate the reaction of phenol (**1a**) and α-hydroxyphenylacetone (**2a**) in the presence of an iron catalyst (Table 1). $FeCl_3·6H_2O$ and $FeCl_3$ failed to give any oxidative coupling products (Table 1, Entries 1 and 2). A trace amount of 1,2-dione derivative **3a**[12] was found when $Fe(OAc)_2$ was used as the catalyst (Table 1, Entry 3). Inspi-

Table 1. Optimization of reaction conditions.[a]



1a **2a** **3a**

Entry	[Fe]	**1a** [equiv.]	Oxidant	Yield [%][b]
1	$FeCl_3·6H_2O$	1	$(tBuO)_2$	N.D.[c]
2	$FeCl_3$	1	$(tBuO)_2$	N.D.
3	$Fe(OAc)_2$	1	$(tBuO)_2$	trace
4	$FeCl_2$	1	$(tBuO)_2$	57
5	$FeBr_2$	1	$(tBuO)_2$	55
6	FeI_2	1	$(tBuO)_2$	N.D.
7	$FeCl_2$	3	$(tBuO)_2$	82
8	$FeCl_2$	3	*t*BuOOH	trace
9	$FeCl_2$	3	*m*-CPBA	trace
10	–	3	$(tBuO)_2$	N.D.
11	$FeCl_2$	3	–	N.D.
12[d]	$FeCl_2$	3	$(tBuO)_2$	trace

[a] Conditions: **2a** (0.5 mmol), [Fe] (0.05 mmol), oxidant (1.5 mmol), and CH_2Cl_2 (1.0 mL), 60 °C, 24 h. [b] Determined by ^1H NMR spectroscopy. [c] Not detected by ^1H NMR spectroscopy. [d] TEMPO (0.5 mmol) was added.

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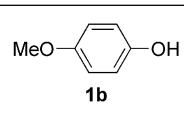
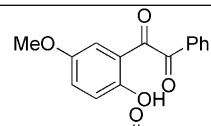
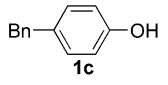
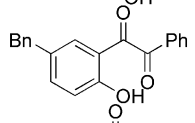
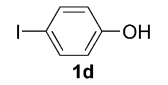
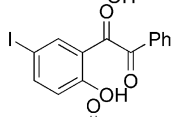
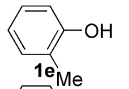
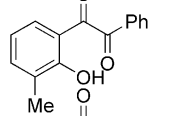
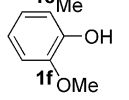
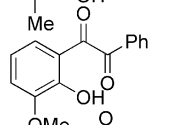
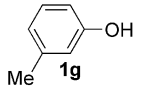
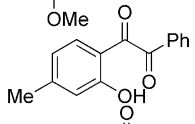
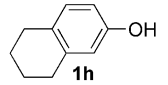
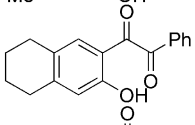
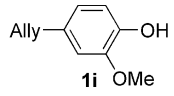
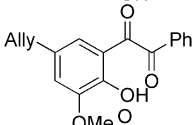
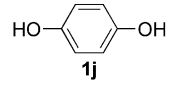
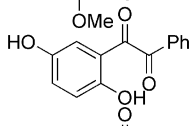
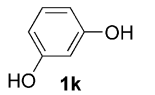
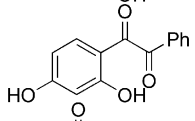
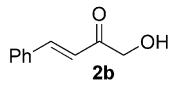
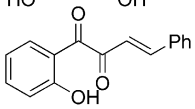
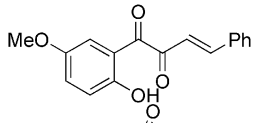
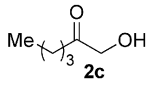
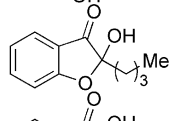
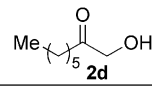
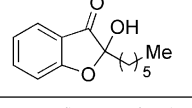
rationally, moderate yields of **3a** were obtained by the application of $FeCl_2$ and $FeBr_2$ (Table 1, Entries 4 and 5). However, FeI_2 did not promote this reaction (Table 1, Entry 6). We were pleased to find that an 82% yield of **3a** was achieved when 3 equiv. of phenol was used (Table 1, Entry 7). Other oxidants were not effective (Table 1, Entries 8 and 9). The control experiments suggested that both the iron catalyst and the oxidant are essential for the formation of **3a** (Table 1, Entries 10 and 11). TEMPO, a radical trapping reagent, prohibited the reaction (Table 1, Entry 12).

The generality of the reaction was investigated under the optimized conditions (Table 2). Phenols with *ortho*- and *para*-substituents were transformed smoothly into the corresponding products in good yields (Table 2, Entries 1–5). A halogen substituent such as iodine was tolerated under the reaction conditions, which facilitates further transformation (Table 2, Entry 3). *meta*-Substituted phenols provided the *completely* regioselective products **3g** and **3h** (Table 2, Entries 6 and 7). These results indicate that the regioselectivity of the reactions is dependent on the steric hindrance of phenols **1**. An allyl substituent was also tolerated (Table 2, Entry 8). Importantly, polyhydroxy phenols afforded the desired products smoothly (Table 2, Entries 9 and 10). These results suggest that the phenoxy radical is unlikely involved due to the radical quenching effect of polyhydroxy phenols. Vinyl and alkyl α-hydroxy ketones reacted with phenols to give the desired products in moderate to good yields (Table 2, Entries 11–14). It should be noted that benzofuranones were obtained for alkyl α-hydroxy ketone substrates (Table 2, Entries 13 and 14).[13] 2′-Hydroxyphenyl-1,2-dione derivatives are present in a variety of natural products and exhibit biological activity.[14] However, multistep procedures are generally required to construct the 2′-hydroxyphenyl-1,2-dione skeleton.[15] On the other hand, although regioselective acylation of phenols can be accomplished by other means, it would be very difficult to prepare acylation reagents for the synthesis of 2′-hydroxyphenyl-1,2-dione derivatives. Thus, we envisioned that the present method would provide an alternative strategy to build this unique skeleton.

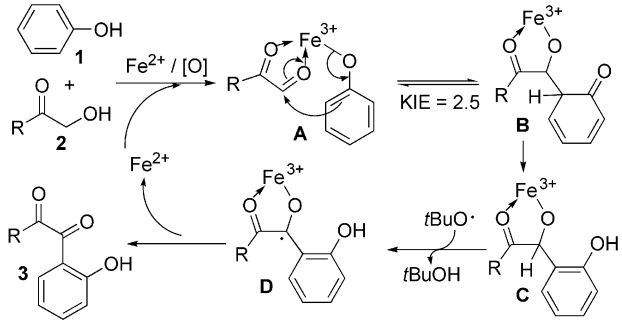
A tentative reaction pathway for the present transformation is proposed in Scheme 2. The *ortho*-selectivity of the reaction invokes iron-chelated intermediate **A**,[9e] which has one molecule of phenol attached. An intramolecular Friedel–Crafts reaction leads to *ortho*-specific intermediate **B**. This step is reversible because of the isotopic effect (KIE = 2.5) attributed to the ability of **B** to return to **A**[16] was observed in our study. The tautomerization of **B** would provide **C**. Subsequently, hydrogen abstraction affords radical intermediate **D**. Finally, ferric oxidation gives desired product **3** and regenerates the ferrous catalyst.

We did some preliminary studies of the reaction mechanism. The reaction of **1a** with 2-oxo-2-phenylacetaldehyde (**4**) was carried out under the standard reaction conditions [Equation (1)]. To our delight, desired product **3a** was formed in 77% yield, which is consistent with the result of Entry 7 in Table 1. In order to further verify this hypothesis, two control experiments were performed [Equations (2) and (3)]. The oxidation of **2a** was performed in the absence of phenols **1** [Equation (2)]. Although this reaction gave a complex mixture of products, aldehyde **4** was indeed observed by ^1H NMR spectroscopic analysis, combined with a trace amount of formal oxidative product **5**.[17] This result indicated that oxidation of **2a** to aldehyde **4** occurred in this

Table 2. Reactions of phenols **1** and α-hydroxy ketones **2**.[a]

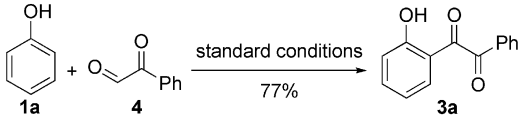
Entry	1	2	Product 3	Yield [%][b]
1	 **1b**	**2a**		**3b** 88
2	 **1c**	**2a**		**3c** 86
3	 **1d**	**2a**		**3d** 65
4	 **1e**	**2a**		**3e** 68
5	 **1f**	**2a**		**3f** 79
6	 **1g**	**2a**		**3g** 81
7	 **1h**	**2a**		**3h** 69
8	 **1i**	**2a**		**3i** 82
9	 **1j**	**2a**		**3j** 77
10	 **1k**	**2a**		**3k** 68
11	**1a**	 **2b**		**3l** 81
12	**1b**	**2b**		**3m** 65
13	**1a**	 **2c**		**3n** 51
14	**1a**	 **2d**		**3o** 56

[a] Conditions: **1** (1.5 mmol), **2** (0.5 mmol), $FeCl_2$ (0.05 mmol), $(tBuO)_2$ (1.5 mmol), and CH_2Cl_2 (1.0 mL), 60 °C, 24 h. [b] Isolated yield.

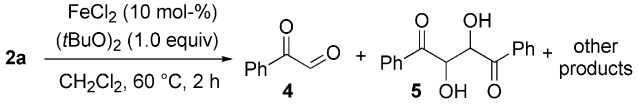


Scheme 2. A tentative mechanism for the formation of **3**.

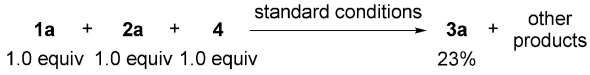
transformation. To our surprise, the reaction of **1a** with a 1:1 mixture of **2a** and **4** led to **3a** in only 23% yield [Equation (3)]. This result could not support free **4** as one intermediate, because the reactions of **2a** with **4** and/or themselves are much faster and lead to other byproducts rather than desired product **3a**. Thus, aldehyde **4** is most likely generated in situ through the coordination of **2a** to the iron catalyst (e.g. intermediate **A**).



(1)



(2)



(3)

Another possible reaction pathway is that a sequence of oxidative esterification[18] and Fries rearrangement could also provide the regioselective product. Accordingly, phenyl 2-oxo-2-phenylacetate (**6**) was synthesized and subjected to the reaction under the standard conditions [Equation (4)]. As **3a** was not observed, a Fries rearrangement of **6** is excluded. However, other reaction pathways still cannot be ruled out at the present stage. The details of the mechanisms need further investigation and will be reported in due time.

(4)

Conclusions

In summary, we have developed a novel *ortho*-selective functionalization of simple phenols, which allows the unique 2′-hydroxyphenyl-1,2-dione scaffold to be constructed. The mild reaction conditions, the generality of the substrates, and the application of an iron catalyst are also attractive merits for the present transformation. Further studies on the mechanism, scope, and synthetic applications of the reactions are in progress.

Experimental Section

Representative Procedure: To a mixture of phenol (**1a**; 1.5 mmol), α-hydroxyphenylacetone (**2a**; 0.5 mmol), and $FeCl_2$ (0.05 mmol) was added dichloromethane (1.0 mL) under a nitrogen atmosphere at room temperature. Then, di-*tert*-butyl peroxide (1.5 mmol) was slowly dropped into the mixture under a nitrogen atmosphere. The reaction temperature was raised to 60 °C for 24 h. The reaction solution was cooled to room temperature. The resulting reaction solution was quenched with saturated $NaHCO_3$ (2 mL) and extracted with dichloromethane (3 × 3 mL). The extract was washed with saturated $NaHCO_3$ (2 × 10 mL) and deionized water (10 mL). The extract was dried with $MgSO_4$. The solvent was evaporated in vacuo to afford the crude product. NMR yields were determined by ^{1}H NMR spectroscopy by using mesitylene as an internal standard. Solvent was evaporated, and the residue was purified by flash column chromatography (silica gel; ethyl acetate/petroleum ether, 1:100). The fraction with R_f = 0.6 (ethyl acetate/petroleum ether, 1:6) was collected to give desired product **3a**. ^{1}H NMR: δ = 11.39 (s, 1 H), 7.97 (d, J = 7.2 Hz, 2 H), 7.68 (t, J = 7.2 Hz, 1 H), 7.57–7.47 (m, 3 H), 7.46 (dd, J = 8.0, 1.6 Hz, 1 H), 7.07 (dd, J = 8.4, 0.8 Hz, 1 H), 6.87 (td, J = 8.0, 0.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 199.2, 191.9, 163.3, 138.0, 135.1, 132.6, 132.3, 129.9, 129.1, 119.7, 118.6, 116.8 ppm. FTIR (ATR): $\tilde{\nu}$ = 3064, 2987, 2315, 1726, 1680, 1620, 1579, 1481, 1452, 1385, 1311, 1228, 1157, 1028, 887, 758, 721 cm^{-1}. MS (EI): *m*/*z* (%) = 226 [M]$^+$, 121 (100), 105, 93, 77, 65, 63, 51, 39, 27. HRMS calcd. for $C_{14}H_{10}NaO_3$ 249.0522; found 249.0523.

Supporting Information (see footnote on the first page of this article): Representative experimental procedure and characterization of all new compounds.

Acknowledgments

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