

Iron-Catalyzed Tandem Oxidative Coupling and Annulation: An Efficient Approach to Construct Polysubstituted Benzofurans

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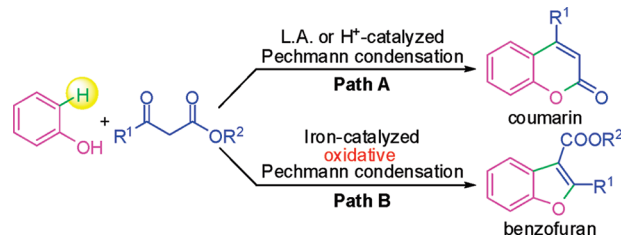
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Abstract: The combination of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and di-*tert*-butyl peroxide offers a novel and efficient method for the construction of polysubstituted benzofurans **3** from the reaction of simple phenols **1** and β -keto esters **2**, which are expected to give coumarins in the well-known Pechmann condensation. A variety of phenols reacted with β -keto esters to provide a range of benzofuran products in moderate to excellent yields. The regio-specific annulation was proven by the X-ray molecular structure of the product **3k**. Hydrate of FeCl_3 is essential for an achievement of the present transformation. The kinetic isotopic effect (KIE) experiments were carried out by competition experiments and displayed a $k_{\text{H}}/k_{\text{D}} = 1.0 \pm 0.1$. The kinetic isotopic effect indicated that aromatic C–H bond cleavage is not involved in the rate-determining steps of the present transformation. Moreover, the results clearly demonstrate that the dichotomous catalytic behavior of the iron catalyst, which is transition-metal catalyst in the oxidative coupling step and Lewis acid in the condensation step. The possible intermediate **5** was synthesized and converted into the desired benzofuran **3a** under the reaction conditions. A tentative mechanism of the formation of benzofurans **3** was proposed.

Introduction

Benzofuran is one of the important structural units and widely found in heterocyclic compounds of biological and medical importance. Many efforts have been made to achieve efficient synthesis of this motif.¹ The most powerful tool is undoubtedly the annulation reaction, in which prefunctionalized substrates, such as ortho-alkynyl or -halo phenol, were generally utilized;² however, to the best of our knowledge, simple phenols without halogen and alkyne substitutes have rarely been used as a starting material to directly construct those scaffolds.³ The Pechmann condensation is one of efficient reactions to synthesize coumarins by the reaction of phenols with β -keto esters in the presence of Lewis acid or protic acid (Scheme 1, Path A).⁴

Scheme 1. Coumarin Formation vs Benzofuran Formation



We reasoned that using iron catalysts could achieve an oxidative Pechmann condensation in the presence of an oxidant (Scheme 1, path B).

Transition-metal catalysts are widely and efficiently used in synthetic chemistry. The applications of inexpensive, easily available and nontoxic iron catalysts are attracting much attention in modern chemistry.⁵ A variety of iron-catalyzed Friedel–Crafts reactions,⁶ Aldol reactions,⁷ carbometalations,⁸ and cycloaddition reactions⁹ have been disclosed and developed successfully. Recently, many efforts were made to develop the

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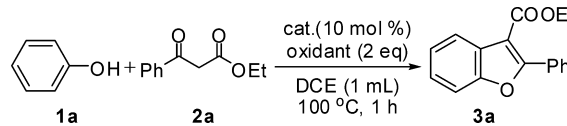
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redox processes involving iron catalysts in C–C bond formation reactions. Some significant works in iron-catalyzed cross-coupling reactions¹⁰ and selective C–H bond oxidations¹¹ have been documented in the literature. Importantly, Bolm recently reported iron-catalyzed Sonogashira reactions of terminal alkynes and aryl halides.¹² Nakamura disclosed for the first time iron-catalyzed biaryl syntheses via direct sp² C–H bond activation.¹³ We recently developed iron-catalyzed reactions of benzyl derivatives or heteroatom-containing molecules and 1,3-dicarbonyl compounds,^{14,15} which are formal oxidative coupling reactions of sp³ C–H bond and sp³ C–H bond.¹⁶ Our efforts in the field of C–H bond oxidation and C–C bond formation promoted us to investigate the present iron-catalyzed oxidative reaction, which involved the selective oxidative coupling of sp² C–H bond and sp³ C–H bond. Here we wish to report our efforts to realize a novel and practical synthesis of polysubstituted benzofurans using iron salt as a catalyst and organic peroxide as an oxidant (Scheme 1, path B).

Results and Discussion

Optimization of the Iron-Catalyzed Oxidative Reaction. The reaction of phenol **1a** and ethyl 3-oxo-3-phenylpropanoate **2a** was chosen as a model system to investigate the proposed transformation (Table 1). To our delight, substituted benzofuran **3a** was obtained in the presence of FeCl₂ and FeBr₂, albeit in low yields (Table 1, entries 1 and 2). **3a** was formed in 30% yield when FeCl₃ was used as a catalyst (Table 1, entry 3). Interestingly, the yield of **3a** was improved to 46% yield when

Table 1. Optimization of the Reaction Conditions^a



entry	catalyst	1a (equiv)	oxidant	yield (%) ^b
1	FeCl ₂	1	(<i>t</i> -BuO) ₂	8
2	FeBr ₂	1	(<i>t</i> -BuO) ₂	9
3	FeCl ₃	1	(<i>t</i> -BuO) ₂	30
4	FeCl ₃ ·6H ₂ O	1	(<i>t</i> -BuO) ₂	46
5	Fe(ClO ₄) ₃ ·xH ₂ O	1	(<i>t</i> -BuO) ₂	16
6	Fe(ClO ₄) ₂ ·xH ₂ O	1	(<i>t</i> -BuO) ₂	47
7	FeCl ₃ ·6H ₂ O	3	(<i>t</i> -BuO) ₂	75
8	FeCl ₃ ·6H ₂ O	3	(<i>t</i> -BuO) ₂	N.D. ^{c,d}
9	FeCl ₃ ·6H ₂ O	3	<i>t</i> -BuOOH	11
10	FeCl ₃ ·6H ₂ O	3	PhCOOO- <i>t</i> -Bu	8
11	—	3	(<i>t</i> -BuO) ₂	N.D.
12	FeCl ₃ ·6H ₂ O	3	—	22 ^e

^a Conditions: **2a** (0.5 mmol), FeCl₃ (0.05 mmol), peroxide (1.0 mmol) and DCE (1.0 mL), 100 °C, 1 h; unless otherwise noted; DCE = dichloroethane. ^b NMR yields are determined by ¹H NMR using mesitylene as an internal standard. ^c Not detected by ¹H NMR. ^d 4 Å molecular sieve (25 mg) was added. ^e FeCl₃·6H₂O (0.5 mmol) was used.

hydrated iron catalyst FeCl₃·6H₂O was employed (Table 1, entry 4). Although **3a** was obtained in 16% in the presence of Fe(ClO₄)₃·xH₂O, the yield of **3a** was raised to 47% when Fe(ClO₄)₂·xH₂O was used (Table 1, entries 5 and 6). Other iron salts, such as Fe₂(CO)₉, FeI₂, Fe(acac)₂, Fe(acac)₃, Fe(OAc)₂, Fe(dbm)₃, FeSO₄·9H₂O, Fe₂(SO₄)₃·xH₂O, FeF₃, FeF₃·3H₂O, Fe(NO₃)₃·3H₂O, were not effective for the benzofuran formation. In order to rationalize the role of the counterion, various additives such as KCl, NaCl, CaCl₂, KBr, etc. were added into the reactions together with inactive iron catalysts. However, the desired benzofuran **3a** was not observed in those experiments. In addition, **3a** was not observed in the presence of the copper catalysts such as CuBr, CuBr₂, CuCl, CuCl₂, CuI, Cu(acac)₂, Cu(OAc)₂, CuSO₄·5H₂O, CuF₂.¹⁷ Importantly, the yield of **3a** was further improved to 75% when 3 equiv of **1a** was used (Table 1, entry 7).¹⁸ The desired benzofuran **3a** was not observed when 4 Å molecular sieve was added into the reaction (Table 1, entry 8). This result indicated that a certain amount of water is essential for the present process. Other peroxides were much less efficient compared with di-*tert*-butyl peroxide (Table 1, entries 9 and 10). No desired products were formed in the absence of a catalyst (Table 1, entry 11). **3a** was obtained in 22% yield when a stoichiometric amount of FeCl₃·6H₂O was used in the absence of a peroxide (Table 1, entry 12). In this case, iron is proposed to act as both a catalyst and an oxidant in the reaction. Moreover, a variety of solvents were screened for the present reaction. Optimization revealed that the use of 1,2-dichloroethane (DCE) is very important, considering the

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- (18) *tert*-Butyl-substituted benzofuran **3c** was also obtained as a byproduct in ~8% for this case. By analyzing the reaction mixture, we found **1c** was generated in ~10%, which was formed by Friedel–Crafts alkylation of **1a**.

Table 2. Influence of Proton Sources^a

entry	H ⁺ source	NMR yield (%)
1	H ₂ O	72
2	MeOH	74
3	EtOH	70
4	<i>t</i> -BuOH	71
5	CH ₃ COOH	48
6	CF ₃ COOH	57
7	PhCOOH	30

^a Conditions: **1a** (1.5 mmol), **2a** (0.5 mmol), FeCl₃ (0.05 mmol), (*t*-BuO)₂ (1.0 mmol) and DCE (1.0 mL), 100 °C, 1 h; DCE = dichloroethane.

reactivity and selectivity of the present transformation.¹⁹ Other solvents were inferior to DCE with regard to the yield of the desired benzofuran **3a**, for example, MeNO₂ (53%), PhMe (29%), CHCl₃ (22%), hexane (20%), MeCN (6%). Nevertheless, the desired benzofuran **3a** was not observed when DMF, EtOH, or water was used as a solvent.²⁰

Proton Source in the Iron-Catalyzed Oxidative Reactions. The higher catalytic efficiency of FeCl₃·6H₂O compared with that of FeCl₃ prompted us to investigate the role of proton source in the present transformation. **3a** was obtained in 74% yield when a catalytic amount of H₂O together with 10 mol % FeCl₃ was used (Table 2, entry 1). We postulated that water might assist the proton transfer process involved in the reaction.²¹ Other proton sources were also examined for the present transformation. The control experiments showed that not only water but also various alcohols could accelerate the reactions, and the desired product was obtained with good yields (Table 2, entries 2–4). Furthermore, protic acids were added into the reaction mixtures, and the desired product **3a** was obtained with reasonable yields (Table 2, entries 5–7). These results indicated that the extra proton sources enhanced the catalytic efficiency of FeCl₃ in the present reactions. More studies on the influences of hydrate coordinated to iron are discussed in the section of Possible Pathways for Benzofuran Formation.

The Scope of the Substrates. With the optimal parameters established, we turned our attention to investigate the scope of the annulations reactions (Table 3). Both para-substituted phenols **1b–1e** and ortho-substituted phenols **1f–1h** were transformed into the corresponding products with good yields (Table 3, entries 1–7). Allyl substituent on the ortho-position of phenols is well tolerated, and the desired benzofuran **3f** was obtained in 74% yield (Table 3, entry 5). The reaction of tetrahydronaphthalen-2-ol **1i** and **2a** afforded two regioisomers with the ratio of 1:1 (Table 3, entry 8). β -Naphthalenol and its derivative were also transformed into the corresponding benzofurans smoothly (Table 3, entries 9 and 10). In contrast, phenol derivatives with strong electron-withdrawing groups, such as

Table 3. Reactions of Phenols **1** and α -Keto Esters **2**^a

Entry	1	2	Product 3	Yield (%) ^b
1				3b 78(70)
2		2a		3c (75)
3		2a		3d 85(71)
4		2a		3e 49(51) ^c
5		2a		3f 74(64)
6		2a		3g 75(58)
7		2a		3h (41)
8		2a		3i+3f 89 ^d
9		2a		3j (59)
10		2a		3k (65)
11				3l (63)
12		2b		3m (63)
13				3n (52) ^c
14				3o (20)
15				3p 63(48) ^c

^a Conditions: **1** (1.5 mmol), **2** (0.5 mmol), FeCl₃·6H₂O (0.05 mmol), (*t*-BuO)₂ (1.0 mmol) and DCE (1.0 mL), 100 °C, 1 h, unless otherwise noted; DCE = dichloroethane. ^b NMR yields are determined by ¹H NMR using mesitylene as an internal standard; isolated yields are given in parentheses. ^c 8 h. ^d The ratio of two isomers is 1:1.

-NO₂ and -Ac, did not react with β -keto esters under the standard reaction conditions. The regiospecific annulation was proven by the X-ray molecular structure of the product **3k** (Figure 1).²² Other aromatic β -keto esters **2b–2d** could also be used under the optimized reaction conditions (Table 3, entries 11–14). The low yield of **3o** was due to the low conversion of **2d** and the formation of some uncharacterized byproducts under the

(19) Recent studies from Nakamura's group indicated that 1,2-dihalide acted as an effective oxidant for the iron-catalyzed C–H bond activation, see reference 13.

(20) The efficiency of the present reactions appears to be dependent on the real concentration of the substrates during the reactions because the different types of condensation apparatus will affect the yields of the products. The related experiments are given in Supporting Information.

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(22) Crystal data for **3k**: C₂₁H₁₅BrO₃, MW = 395.24 g mol⁻¹, *T* = 293(2) K, Orthorhombic, space group *P*2(1)2(1)2(1), *a* = 4.1182(8) Å, *b* = 14.193(3) Å, *c* = 29.071(6) Å, α = 90°, β = 90°, γ = 90°, *V* = 1699.2(6) Å³, *Z* = 4, ρ_{calcd} = 1.545 Mg m⁻³, μ = 2.436 mm⁻¹, reflections collected: 14189, independent reflections: 2323 (*R*_{int} = 0.0987), Final *R* indices [*I* > 2 σ (*I*): *R*₁ = 0.0375, *wR*₂ = 0.0473, *R* indices (all data): *R*₁ = 0.1377, *wR*₂ = 0.0581.

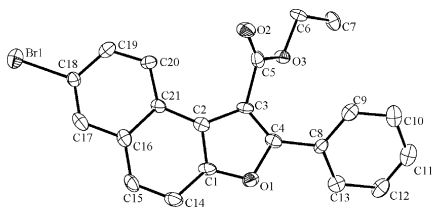
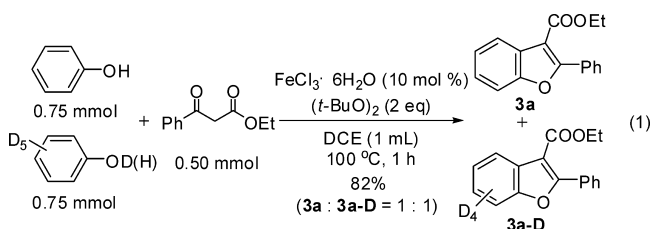


Figure 1. ORTEP drawing for product **3k**.

standard reaction conditions (Table 3, entry 14). The reaction of phenol **1a** with ethyl 3-oxobutanoate **2e** afforded the desired benzofuran **3p** in 63% yield; however, the prolonged reaction time was necessary in order to consume the starting materials (Table 3, entry 15). In this case, some byproducts were also observed, which could not be separated and characterized.

Competition Experiments between Phenol and Phenol-*d*₆. In order to assess whether the cleavage of phenolic C–H bond is involved in the rate-determining step, the isotopic effect experiments were carried out. First, the deuterated product **3a-D** was obtained in 78% yield when phenol-*d*₆ was used under the standard reaction conditions. Subsequently, the kinetic isotopic effect (KIE) experiments were carried out by competition experiments of a 1:1 mixture of phenol and phenol-*d*₆ or phenol-*d*₅ (eq 1). ¹H NMR analysis of the isolated benzofurans revealed a ratio of **3a** and **3a-D** (*k_H*/*k_D*) of 1.0 ± 0.1. The isotopic effect indicates that aromatic C–H bond cleavage is a fast step and thus not involved in the rate-determining steps of the present transformation.

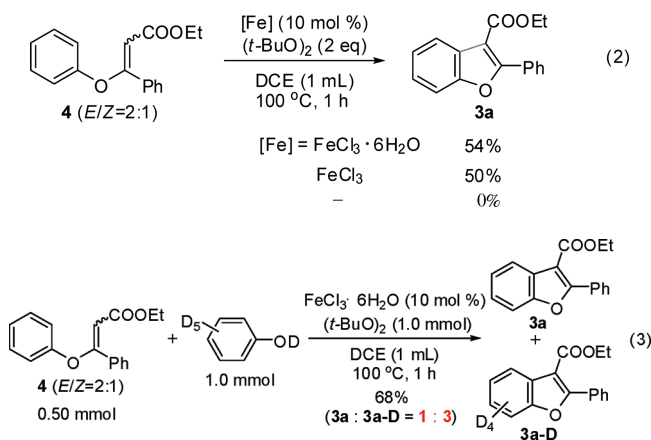


Possible Pathways for Benzofuran Formation. As mentioned above, the Pechmann reaction allows the synthesis of coumarins by the reactions of phenol with β -keto esters. Different mechanisms have been put forward to explain the possible pathways of the Pechmann reaction. In consideration of the whole process, one new C–C bond and one new C–O bond are formed. Accordingly, two possible pathways are summarized (Scheme 2): (1) transesterification of a β -keto ester followed by Friedel–Crafts cyclization of the ketone moiety affords coumarin (Pathway A);²³ (2) alternatively, coumarin is obtained in the sequence of Friedel–Crafts cyclization and transesterification (Pathway B).²⁴

In contrast to the classic Pechmann reaction, 5-membered annulation occurred in the presence of iron catalyst and organic peroxide. The initial mechanistic proposals were based on the sequential formation of C–C bond and C–O bond. Accordingly, two possible pathways were proposed for the benzofuran formation (Scheme 3). Pathway C presents an intermolecular condensation of **1** and **2** followed by oxidative coupling via intermediate **4**; alternatively, oxidative

coupling product **5** is formed and then transformed into the final benzofuran **3** via intramolecular condensation (Pathway D).

In an attempt to rationalize the possible pathways, ethyl 3-phenoxy-3-phenylacrylate (**4**) and ethyl 2-(2-hydroxyphenyl)-3-oxo-3-phenylpropanoate (**5**) were respectively synthesized. Benzofuran **3a** was obtained in 54% and 50% yields in the presence of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and FeCl_3 , respectively (eq 2). It should be noted that **3a** was not formed in the absence of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and/or di-*tert*-butyl peroxide. Recently, two excellent examples of Pd-catalyzed intramolecular oxidative coupling of *N*-aryl enamines to provide indoles were reported.²⁵ These results supported that transition-metal catalysts would promote 5-membered heteroaromatic ring formation via intramolecular oxidative coupling reactions. Because certain amounts of **1a** and **2a** were observed in the reaction mixtures when the reaction finished, we speculated that the decomposition of **4** led to the moderate yields of **3a** (eq 2). As we expected, when 2 equiv of phenol-*d*₆ was added, the desired benzofuran **3a** and the deuterated product **3a-D** were obtained in a combined yield of 68% (eq 3). Surprisingly, the ratio of **3a** and **3a-D** is 1:3, where 3:2 was expected if **3a** was formed from **4** and 50% of **4** was decomposed (eq 2). These results indicated that the product **3a** is formed mainly from the decomposition of **4** rather than direct intramolecular oxidative coupling of **4** (eq 2).

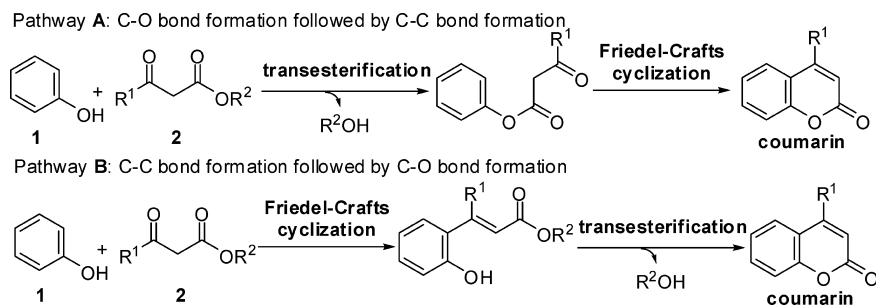
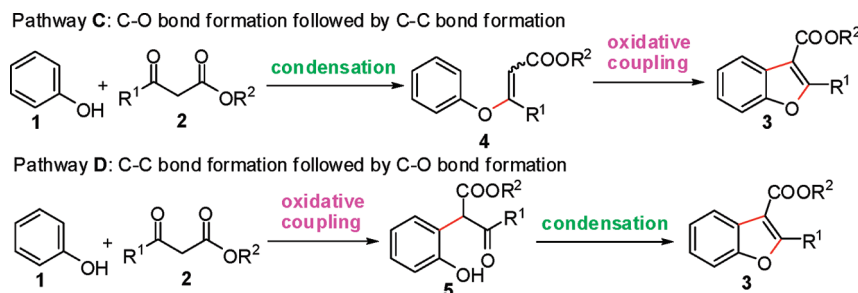
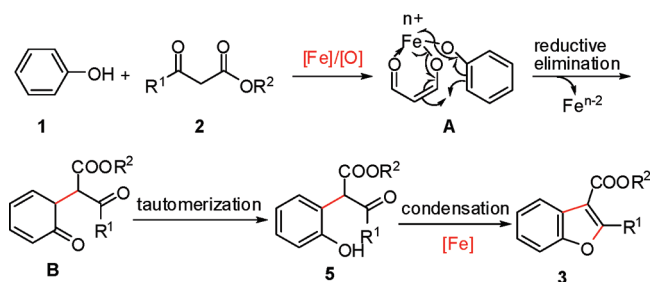


Inspirationally, **5** was also smoothly transformed into benzofuran **3a** in the presence of an iron catalyst at room temperature (eq 4). Although **3a** was formed in moderate yield using $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ as a catalyst, 89% isolated yield of **3a** was achieved in the presence of FeCl_3 at room temperature (eq 4). **3a** was not observed in the absence of a catalyst. These results suggested the following: (1) the condensation step is a faster step in Pathway D, Scheme 3; (2) the phenolic hydroxyl group most likely acts as a directing group in the oxidative coupling step because the oxidative coupling product at the para position of phenol was not observed in all cases; (3) hydrate coordinated to iron must play an important role in the oxidative coupling step because $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ retarded the efficiency of the condensation step; (4) the iron catalyst plays the dichotomous catalytic behavior in the present transformation, which is transition-metal

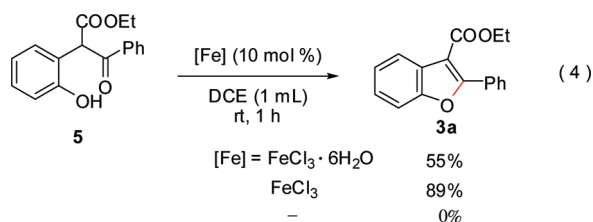
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Scheme 2. Possible Pathways of the Pechmann Reaction**Scheme 3.** Possible Pathways of Iron-Catalyzed Benzofuran Formation**Scheme 4.** Tentative Mechanism of Iron-Catalyzed Oxidative Reaction of **1** and **2**

catalyst in the oxidative coupling step and Lewis acid in the condensation step.



Accordingly, a tentative mechanism of the formation of benzofurans **3** is proposed in Scheme 4. An intermediate Fe^{n+} -chelated specie **A** may be formed *in situ*, and reductive elimination gave **B**. The tautomerization of **B** would provide **5**. Subsequently, the benzofuran **3** is formed by intramolecular condensation of **5** in the presence of iron catalyst. With regard to the possible mechanisms of the oxidative coupling step, both intermolecular radical coupling and intramolecular radical coupling chelated by transition metal were suggested by Barton²⁶ and Baran.²⁷ Because the present reactions showed the high

regioselectivity, a chelated radical-coupling mechanism is proposed for the formation of **5**. An important, but as yet unanswered, question is how hydrate coordinated to iron plays an important role in the oxidative coupling step. This challenge will stimulate our further studies to disclose the nature of the present transformation.

Conclusions and Outlook

In summary, we demonstrated an unprecedented and regioselective method to construct polysubstituted benzofurans. The combination of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and $(t\text{-BuO})_2$ is an effective system in the reactions of simple phenol derivatives and β -keto esters. The effect of water in the iron-catalyzed oxidative reaction is interesting. The control experiments showed that not only water but also various alcohols and protic acids could accelerate the reactions. The present oxidative reactions are chemospecific and regiospecific. The regioselectivity of the product **3k** was confirmed by X-ray diffraction. The kinetic isotopic effect (KIE) experiments showed a $k_{\text{H}}/k_{\text{D}} = 1.0 \pm 0.1$. The isotopic effect indicates that aromatic C-H bond cleavage is a fast step and not involved in the rate-determining steps in this transformation. In addition, two possible intermediates **4** and **5** were synthesized, which were transformed into the desired benzofuran **3a** under the standard reaction conditions. The results indicated that **5** is a possible intermediate in the present reactions. A tentative mechanism for the formation of benzofurans **3** was proposed.

The current process represents a novel oxidative Pechmann-type condensation, in which benzofuran is generated instead of coumarin. Iron catalysts together with organic peroxide have been proved to be very efficient in oxidative C-C bond formation. These results clearly demonstrate that the dichoto-

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mous catalytic behavior of the iron catalyst, which are transition-metal catalysts in the oxidative coupling step and Lewis acids in the condensation step. These findings should further encourage the development of iron chemistry as well as novel methodologies for organic synthesis. The utilization of the oxidative reactions for the synthesis of complex molecules should help to further elucidate the scope of the present transformation.

Experimental Section

General Information. NMR spectra were recorded on JEOL and Bruker NMR spectrometers. Mass spectra were determined with AEI-MS 50 for EI-MS. APEX II (Bruker Inc.) for HR-MS and ESI-MS. IR spectra were recorded by a Nicolet 5MX-S infrared spectrometer. Flash column chromatography was performed over silica gel 200–300. Recycling preparative HPLC, Japan Analytic Industry Co., Ltd., LC-9201 was applied. All reagents were weighed and handled in air and backfilled under N₂ at room temperature. All reactions were performed under a nitrogen atmosphere. 1,2-Dichloroethane (DCE) was freshly distilled with calcium hydride before use.

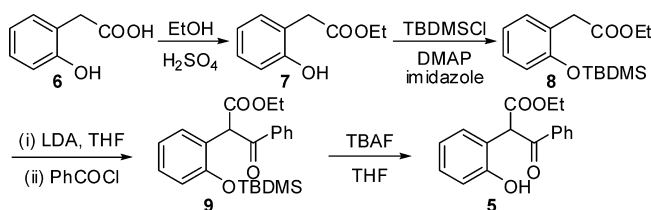
General Procedure for Products 3. To a mixture of ethyl benzoylacetate **2a** (0.5 mmol), phenol **1a** (1.5 mmol), and FeCl₃·6H₂O (0.05 mmol) was added 1,2-dichloroethane (DCE, 1.0 mL) under nitrogen at room temperature. Then di-*tert*-butyl peroxide (1.0 mmol) was dropped into the mixture under nitrogen. The reaction temperature was raised to 100 °C for 1 h. The temperature of the reaction was cooled to room temperature. The resulting reaction solution was quenched with 2 mL of saturated NaHCO₃ and extracted with 15 mL of ether four times. The extract was washed twice with 10 mL of saturated NaHCO₃ and two times with 10 mL of deionized water. The extract was dried over MgSO₄. The solvent was evaporated in vacuo to afford the crude products. NMR yields were determined by ¹H NMR using mesitylene as an internal standard. Solvent was evaporated, and the residue was purified by flash column chromatography on silica gel with ethyl acetate/petroleum ether (1:100) as an eluent. The fraction with a *R_f* = 0.6 (ethyl acetate/petroleum ether = 1:6) was collected to give the crude product. Then it was dissolved in 4 mL of CHCl₃ and purified by recycling preparative HPLC to afford the desired product **3a**. In some cases, the pure products **3** were obtained directly by flash column chromatography on silica gel with ethyl acetate/petroleum ether as an eluent.

Procedure for Intermediate 4. A stirred mixture of ethyl 3-phenylpropionate (1 mmol), phenol **1a** (1.1 mmol), anhydrous potassium carbonate (2 mmol), and dimethylformamide (DMF, 2 mL) was heated to 60 °C for 2 h. The temperature of reaction was cooled to room temperature. The resulting reaction solution was quenched with 20 mL of aqueous Na₂CO₃ (5%). The mixture was transferred to a separating funnel and extracted with 50 mL of ethyl acetate (EtOAc) four times. The extract was washed with 50 mL of aqueous sodium hydroxide (NaOH) solution (1%) and again with 50 mL of water. The organic phase was dried over MgSO₄, filtered, and concentrated in vacuo to afford 96% yield of intermediate **4**.

Procedure for Product 3a from 4. To a mixture of ethyl 3-phenoxy-3-phenylacrylate **4** (0.5 mmol) and FeCl₃·6H₂O (0.05 mmol) was added dichloroethane (DCE, 1.0 mL) under nitrogen at room temperature. Then di-*tert*-butyl peroxide (1 mmol) was dropped into the mixture under nitrogen. The reaction temperature was raised to 100 °C for 1 h. The temperature of reaction was cooled to room temperature. The resulting reaction solution was quenched with 2 mL of saturated NaHCO₃ and extracted with 15 mL of ether four times. The extract was washed two times with 10 mL of saturated NaHCO₃ and two times with 10 mL of deionized water. The extract was dried over MgSO₄. Solvent was evaporated, and the residue was purified by flash column chromatography on silica

gel with ethyl acetate/petroleum ether (1:100) as an eluent. The fraction with a *R_f* = 0.6 (ethyl acetate/petroleum ether = 1:6) was collected to give the product **3a**.

Procedures for Intermediate 5.²⁸



Step 1. H₂SO₄ (0.2 mL) was added to a solution of 2-(2-hydroxyphenyl)acetic acid **6** (10 mmol) in EtOH (20 mL). The reaction mixture was heated to reflux for 4 h. The reaction mixture was cooled to room temperature and then evaporated in vacuo to remove EtOH. The residue was solved in CH₂Cl₂ (20 mL). The resulting reaction mixture solution was washed with 20 mL of saturated NaHCO₃. The mixture was transferred to a separating funnel and washed two times with 20 mL of water. The extract was dried over MgSO₄. The solvent was evaporated in vacuo to afford ethyl 2-(2-hydroxyphenyl)acetate **7** (99%).

Step 2. To a mixture of ethyl 2-(2-hydroxyphenyl)acetate **7** (9.9 mmol), TBDMSCl (10 mmol), imidazole (15 mmol), and DMAP (1 mmol) was added dichloromethane (20 mL) under nitrogen at room temperature. The reaction mixture was stirred overnight at room temperature. The resulting reaction solution was filtrated and quenched with 20 mL of aqueous HCl (5%). The mixture was transferred to a separating funnel and washed two times with 20 mL of water. The extract was dried over MgSO₄. The solvent was evaporated in vacuo to afford ethyl 2-(2-(*tert*-butyldimethylsilyloxy)phenyl)acetate **8** (95%).

Step 3. To a solution of 2-(2-(*tert*-butyldimethylsilyloxy)phenyl)acetate **8** (9.5 mmol) in dry THF (5 mL) was slowly added a solution of LDA (20 mmol) in THF (20 mL) under nitrogen at –78 °C. The light-yellow solution was stirred for 30 min at –78 °C and then was allowed to warm to 0 °C. A solution of benzoyl chloride (10 mmol) in THF (5 mL) was added slowly at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The resulting reaction solution was quenched with 5% aqueous HCl (20 mL) and extracted three times with 20 mL of ethyl acetate. The combined extracts were washed with water (50 mL) and dried over MgSO₄. Solvent was evaporated, and the residue was purified by flash column chromatography on silica gel with ethyl acetate/petroleum ether (1:20) as an eluent to afford ethyl 2-(2-(*tert*-butyldimethylsilyloxy)phenyl)-3-oxo-3-phenylpropanoate **9** (53%).

Step 4. To a solution of **9** (5.0 mmol) in dry THF (10 mL) was slowly added TBAF (10 mmol, 1 M in THF) under nitrogen at room temperature. The reaction mixture was stirred at room temperature for 15 min. The resulting reaction solution was quenched with water (20 mL) and extracted three times with 20 mL of ethyl acetate. The combined extracts were dried over MgSO₄. Solvent was evaporated, and the residue was purified by flash column chromatography on silica gel with ethyl acetate/petroleum ether (1:5) as an eluent. The fraction with a *R_f* = 0.5 (ethyl acetate/petroleum ether = 1:2) was collected and to give ethyl 2-(2-hydroxyphenyl)-3-oxo-3-phenylpropanoate **5** (90%, 45% yield for 4 steps).

Procedure for Product 3a from 5. To a mixture of **5** (0.5 mmol) and FeCl₃·6H₂O or FeCl₃ (0.05 mmol), was added dichloroethane (DCE, 1.0 mL) under nitrogen at room temperature. The reaction mixture was stirred at room temperature for 1 h. Solvent was evaporated, and the residue was purified by flash column chromatography on silica gel with ethyl acetate/petroleum ether (1:100)

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as an eluent. The fraction with a $R_f = 0.6$ (ethyl acetate/petroleum ether = 1:6) was collected to give the desired product **3a**.

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Supporting Information Available: Representative experimental procedures, characterization of all compounds, and X-ray crystallography data for **3k**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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