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Oxidative Radical Coupling

Iron-Catalyzed Oxidative Radical Cross-Coupling/Cyclization between Phenols and Olefins**

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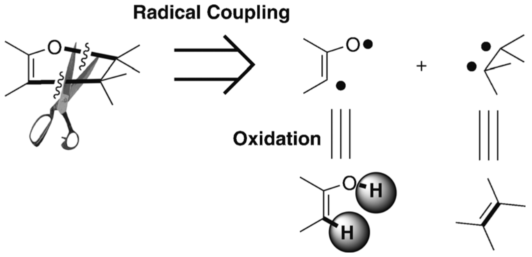
Dedicated to Professor Irina Petrovna Beletskaya

Oxidative cross-coupling involving two nucleophiles has recently showed its powerful potential in constructing carbon–carbon and carbon–heteroatom bonds.[1] Theoretically, for an oxidative cross-coupling reaction, not only activated nucleophiles such as organometallic reagents RM could be employed, but also R−H (C−H) could be directly applied as the nucleophiles.[2] Undoubtedly, if those RH or RXH reagents could be directly utilized as reactants for the formation of molecules, ideal syntheses will be successfully achieved. In recent years, a variety of RH reagents, such as *ortho*-directed Ar−H, terminal alkynes, alkenes, and specific C_{sp^3}−H, have been oxidatively functionalized.[3] Seeking different RH or RXH as nucleophiles and applying them in valuable organic molecules syntheses still remains a challenge.

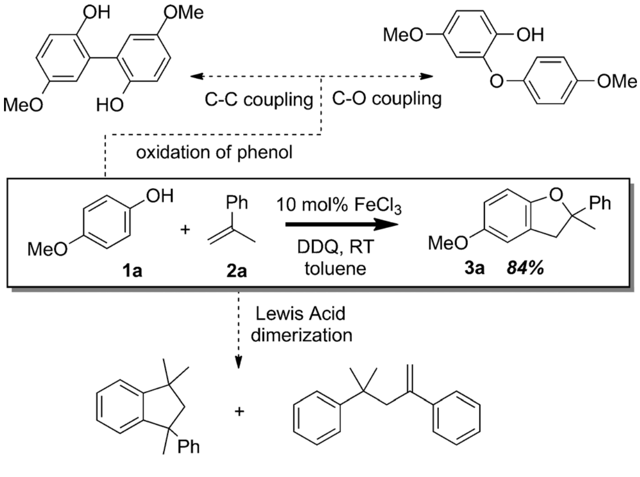
Phenols are one of the most readily available chemicals, and they are versatile synthetic building blocks.[4] Since the 1920s, oxidative phenol coupling has received considerable attention owing both to its extensive applications in the formation of dimeric products and its proposed involvement in the biosynthesis of a number of natural products.[5] It has been known that phenols and naphthols could be readily oxidized in the presence of various chemical or biological oxidants.[6] However, when simple phenols are employed in oxidative cross-couplings, the desired product is often concomitant by the formation of homocoupling by-products.[7] Moreover, the formation of higher-molecular-weight polymer products or C,O-connected phenol portions, for example quinol ethers, might also occur depending on the oxidant and the experimental conditions.[8] Thus, utilizing phenols as nucleophiles in oxidative cross-coupling still remains problematic, and selectivity is particularly challenging. Herein, we present an iron-catalyzed oxidative radical cross-coupling/cyclization between phenol and olefin towards the synthesis of dihydrobenzofuran[9] at room temperature in a highly selective manner.

Generally, it has been accepted that phenol derivatives usually undergo single electron transfer, which leads to a phenoxyl radical.[6] We therefore propose an oxidative radical cross-coupling idea (Scheme 1). The phenol derivatives could act as bis-nucleophiles (the C−H and O−H) in the proposed reaction, and the olefins are imported as a link for a quick syntheses of dihydrobenzofurans from readily available phenol and olefins. In this regard, the transition-metal-catalyzed oxidative radical cross-coupling of 4-methoxyphenol **1a** and α-methylstyrene **2a** was initially examined.



Scheme 1. Proposal for oxidative radical cross-coupling.

In principle, by employing **1a** and **2a** as the substrates in the presence of an oxidant, many possible reactions might take place as mentioned above, such as oxidation of phenol to afford the homo C−C coupling or C−O coupling, as well as the dimerization of olefin (Scheme 2).[10] However, when $FeCl_3$ was utilized as the catalyst and 2,3-dichloro-5,6-dicyano-1,4-benzoqinone (DDQ) as the oxidant, a highly selective oxidative cross-coupling/cyclization of **1a** with **2a**



Scheme 2. Reactions between phenols and olefins.

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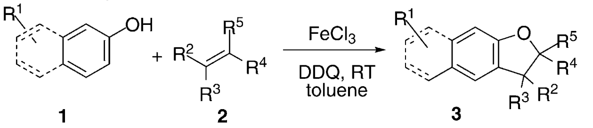
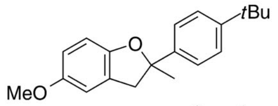
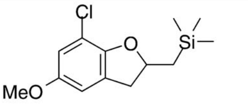
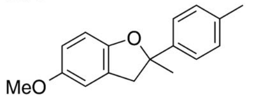
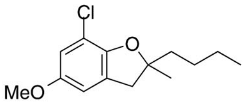
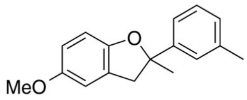
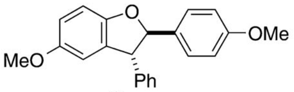
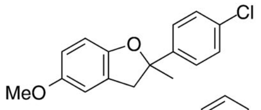
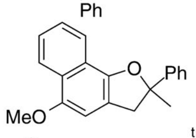
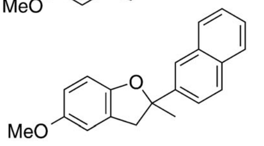
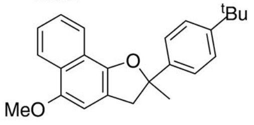
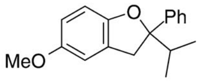
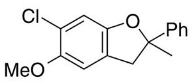
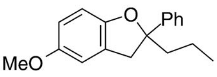
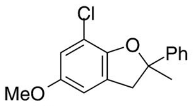
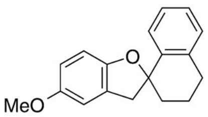
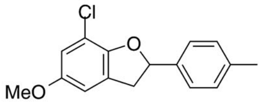
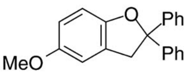
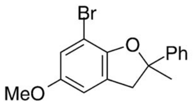
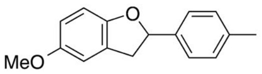
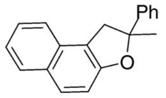
occurred, affording dihydrobenzofuran **3a** in an excellent yield of isolated product of up to 84% (Scheme 2).[11] Other reaction parameters, such as oxidants and solvents were also explored, whereby worse selectivity was observed (Supporting Information, Table S1). To date, iron salts have been rarely utilized in the formation of dihydrobenzofurans.[12] With respect to this, Fe-catalyzed highly selective oxidative cross-coupling/cyclization of phenols with olefins to construct polysubstituted 2,3-dihydrobenzofuran at room temperature was particularly important, which encouraged us to do further examinations.

With the optimized conditions in hand, we further explored the scope of this $FeCl_3$-catalyzed oxidative cross-coupling/cyclization. As shown in Table 1, various α-alkylstyrenes were tested. We were pleased to find that α-methylstyrenes bearing electron-donating groups, such as *tert*-butyl and methyl, could be suitable substrates to afford the corresponding polysubstituted 2,3-dihydrobenzofurans in good yields (Table 1; **3b**, **3c**, and **3d**). An electron-withdrawing group, such as Cl, was also tolerated in this transformation, affording the desired product **3e** in 50% yield. A naphthalene-substituted olefin was also compatible, with an excellent yield (**3f**). Both α-isopropylstyrene and α-propylstyrene could react with **1a** smoothly to afford the desired products **3g** and **3h** in 51% and 87% yields, respectively. 1,2,3,4-tetrahydro-1-methylenenaphthalene and 1,1-diphenyl-

Table 1: Iron-catalyzed oxidative cyclization between phenols and olefins.[a]



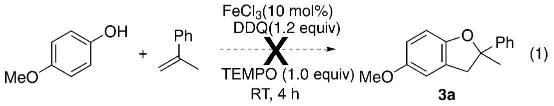
Entry	3	Product	Yield[b]	Entry	3	Product	Yield[b]
1	**3b**		*86%*	11	**3l**		*74%*
2	**3c**		*86%*	12	**3m**		*81%*
3	**3d**		*83%*	13	**3n**		*38%*[c] *52%*[d]
4	**3e**		*50%*	14	**3o**		*49%*
5	**3f**		*97%*	15	**3p**		*65%*
6	**3g**		*51%*	16	**3q**[e]		*82%*
7	**3h**		*87%*	17	**3r**[e]		*86%*
8	**3i**		*77%*	18	**3s**[e]		*93%*
9	**3j**		*79%*	19	**3t**[e]		*87%*
10	**3k**		*77%*	20	**3u**[f]		*62%*

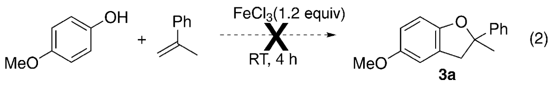
[a] Reaction conditions: except where otherwise noted, all of the reactions were performed with **1** (0.3 mmol), **2** (0.6 mmol), $FeCl_3$ (10 mol%), and 2,3-dichloro-5,6-dicyano-1,4-benzoqinone (DDQ; 0.36 mmol) in toluene (3 mL) at 25 °C for 4 h under N_2. [b] Yield of isolated product. [c] **2** ((*Z*)-1-methoxy-4-styrylbenzene). [d] **2** ((*E*)-1-methoxy-4-styrylbenzene). [e] **2** (0.3 mmol). [f] **2** (0.9 mmol).

ethylene were also allowed to react with **1a** to produce the polysubstituted 2,3-dihydrobenzofurans **3i** and **3j** in 77 % and 79 % yields. Furthermore, *para*-methylstyrene could produce the expected product **3k** in 77 % yield. Alkyl-based olefins, like allyltrimethylsilane and 2-methylhex-1-ene, could be suitable substrates to afford the corresponding polysubstituted 2,3-dihydrobenzofurans **3l** and **3m** in 74 % and 81 % yields. To our delight, (*E*)-1-methoxy-4-styrylbenzene and (*Z*)-1-methoxy-4-styrylbenzene were also allowed to react with **1a** to afford the product **3n** in 38 % and 52 % yields, respectively.

We further tested oxidative cyclization of various phenol derivatives. When α-naphthol was employed, the desired dihydrobenzofurans **3o** and **3p** could be afforded in 49 % and 65 % yields, respectively. It was noteworthy that 4-methoxylphenol with halogen substituents, such as chloride and bromide, could be suitable substrates to produce the corresponding polysubstituted 2,3-dihydrobenzofurans (**3q**, **3r**, **3s**, **and 3t**) in good yields, which enable a potential application in further functionalizations. Moreover, β-naphthol reacted smoothly, and the desired dihydrobenzofurans **3u** could be obtained in 62 % yield.

As we proposed above, this iron-catalyzed oxidative cross coupling/cyclization might undergo radical process. To gain preliminary mechanistic information about this transformation, some experiments were performed. First, a radical-trapping experiment was carried out. In the presence of one equiv of TEMPO, no product **3a** was obtained under the optimized conditions [Eq. (1)].[13] Then, the reaction between **1a** and **2a** in the presence of 1.2 equiv of $FeCl_3$ without DDQ was conducted. However, no desired product **3a** was obtained, even after 4 h at room temperature [Eq. (2)].





Furthermore, by employing the oxidative coupling between 2-chloro-4-methoxyphenol (**1b**) and 4-methylstyrene (**2b**) as a model, electron paramagnetic resonance (EPR) experiments were then performed. As shown in Figure 1 A, a mixture of $FeCl_3$ and **1b** or DDQ was detected by EPR spectroscopy, and no new signal was observed compared to the authentic sample of $FeCl_3$, **1b**, and DDQ. However, when phenol **1b** was mixed with DDQ, a strong signal with a g-factor of 2.004 was clearly detected (Figure 1 B, gray line). This result showed that DDQ reacted with phenol to produce a radical. To assign this signal, phenol **1a** was subsequently examined to react with DDQ instead of **1b** through EPR. A strong signal was also observed (Figure 1 B, black line), for which the g-factor is also 2.004. If this radical originated from phenol, different g-factors should be detected when employing different phenols. However, the identical g-factor of both signals suggested that it probably be assigned to HDDQ radical.[14]

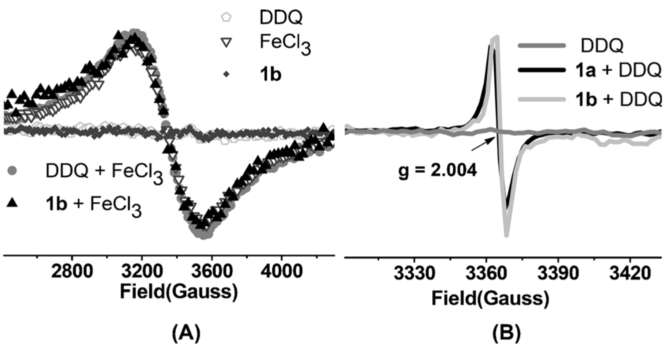


Figure 1. A) EPR spectra from the reaction between $FeCl_3$ and **1b** or DDQ in toluene at room temperature. B) EPR spectra of a DDQ and phenol mixture in toluene at room temperature.

The $FeCl_3$-catalyzed oxidative radical cross-coupling of **1b** and **2b** was then monitored by EPR spectroscopy (Figure 2 A). First, **1b**, **2b**, and DDQ were mixed in toluene at room temperature, and the same signal was also observed. When a catalytic amount of $FeCl_3$ was added, the signal gradually disappeared. Meanwhile, the operando IR experiment of the same reaction was also performed. As shown in Figure 2 B, when DDQ was added to **1b**, the concentration of **1b** and DDQ decreased slowly,[15] even after the addition of **2b**. However, tallying with the previous EPR phenomenon, all of the substrates were consumed quickly as soon as $FeCl_3$ was added, accompanying the accumulation of the HDDQH and the desired product.

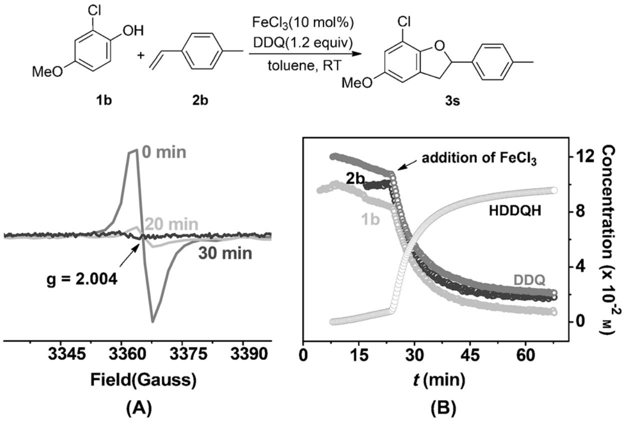
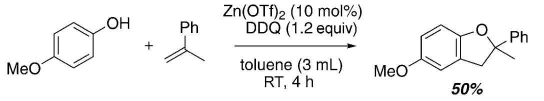


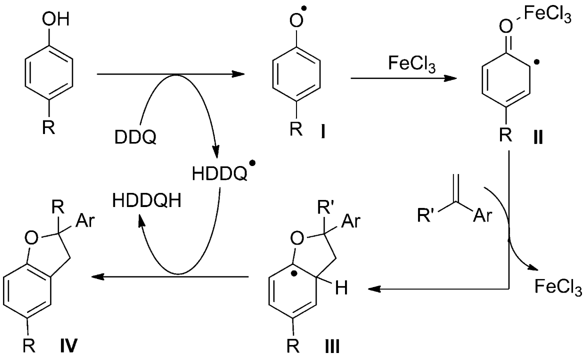
Figure 2. A) EPR spectra acquired during the oxidative cross-coupling reaction time course between **1b** and **2b**. B) Profile of the reaction between **1b** (0.1 M) and **2b** (0.1 M) in toluene at room temperature monitored by in situ IR spectroscopy.

The above EPR and operando IR study revealed that $FeCl_3$ plays a key role in this oxidative radical coupling. We envisioned that $FeCl_3$ might be indispensable as the Lewis acid. To testify this assumption, other Lewis acids were employed in this transformation. The results showed that an appreciable amount of the desired product could be afforded by utilizing other Lewis acids as the catalysts. When using catalytic amount of $Zn(OTf)_2$, **3a** was afforded in 50 % yield [Eq. (3)]. This result revealed that $FeCl_3$ might act as a Lewis acid in the overall transformation.



(3)

Based on the above results, a putative mechanism was proposed (Scheme 3). First, DDQ oxidizes phenol, producing an HDDQ radical and phenol radical **I**.[16] By stabilizing the resonance structure of the phenol radical, $FeCl_3$ as a Lewis acid might promote the radical transfer from an O-radical to C-radical, which could subsequently lead to radical addition with alkenes to produce the intermediate **III**.[17] Finally, a hydrogen radical from **III** was trapped by an HDDQ radical, and dihydrobenzofuran was released. In this transformation, the oxidative cross-product **IV** has been obtained in high selectivity, which we believe to be due to $FeCl_3$. As a Lewis acid, $FeCl_3$ is more likely to coordinate with the O-atom to stabilize the C-radical and increase the activity of radical **II** to react with alkenes. If $FeCl_3$ was absent, the O-radical **I** could directly attack alkenes to produce the isomerized product of **IV**, which is actually not observed in the whole process.



Scheme 3. Proposed mechanism.

In conclusion, a highly efficient and selective Fe-catalyzed oxidative radical cross-coupling/cyclization to prepare dihydrobenzofurans under mild conditions has been established by directly utilizing phenols and olefins as nucleophiles. Preliminary mechanistic studies revealed that a radical was involved in the overall process: DDQ was vital in the initiating step. Furthermore, $FeCl_3$ might act as a Lewis acid to promote this transformation. This procedure provided an atom-economic, environmentally friendly, and practical approach to complement the oxidative coupling reaction of phenols for the construction of carbon–carbon and carbon–heteroatom bonds. The detailed mechanism is currently under investigation in our laboratory and will be reported in due course.

Experimental Section

General procedure: DDQ (0.36 mmol) and $FeCl_3$ (0.03 mmol, in the glovebox) were added to an oven-dried Schlenk tube equipped with a stir-bar. The reaction tube was then evacuated and purged with nitrogen three times. Phenol (0.3 mmol), toluene (3 mL), and olefin (0.6 mmol) were added simultaneously under nitrogen, or the phenol was added finally. The Schlenk tube was allowed to stir at room temperature for 4 h. After the crude mixture was concentrated under vacuum, the pure product was obtained by flash chromatography on silica gel with petroleum ether/ethyl acetate (100/1).

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