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Iron(III) Chloride Catalyzed Oxidative Coupling of Aromatic Nuclei

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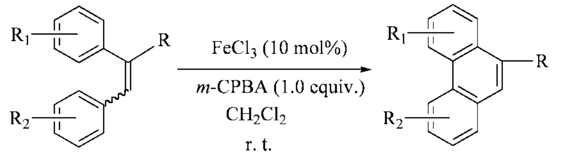

Easily available and nontoxic FeCl$_3$ catalyzes intramolecular oxidative coupling for the direct construction of the phenanthrene ring using *meta*-chloroperbenzoic acid as sole oxidant at room temperature in excellent yields. The mechanistic investigations show that FeCl$_3$-catalyzed coupling proceeds through the heterolytic coupling ($A^+ + B$). The catalytic approach has been applied to intermolecular biaryl coupling of 2-naphthols and phenol ether.

Phenanthrene ring and biaryl linkages are extensively presented in natural products, pharmaceuticals, materials, and many other important organic molecules,[1–3] especially phenanthroindolizidine and phenanthroquinolizidine alkaloids and 1,1′-binaphthalene derivatives. Phenanthroindolizidine and phenanthroquinolizidine alkaloids exhibit interesting pharmacological properties, among which antitumor activity is most notable.[3,4] The synthesis of the phenanthrene ring is the key step in the preparation of these alkaloids.[5] Metal-based intramolecular oxidative coupling to yield the phenanthrene ring by using thallium(III) trifluoroacetate (TTFA),[6] lead(IV) tetraacetate (Pb(OAc)$_4$),[7] and vanadium oxytrifluoride (VOF$_3$) or vanadium oxytrichloride (VOCl$_3$)[8] have been developed. However, these coupling reactions require large excess amount of metal salts, at least stoichiometric, extensive application of these reagents has been limited by high toxicity, severe conditions, and low yields. The most common method for biaryl C−C bond construction is metal-catalyzed cross-coupling between two functionalized starting materials.[9–11] However, a most attractive approach to the phenanthrene ring and biaryls would be the direct oxidative coupling of two unfunctionalized arenes.[12] In such a transformation, both starting materials could be used directly without prior functionalization, and the sole byproduct would be 2 equiv of H$^+$. Therefore, the development of catalytic oxidative coupling for the construction of a C−C bond starting directly from arenes is highly desirable.

Iron(III) chloride (FeCl$_3$) which can act as an oxidant is extensively used in organic synthesis.[13] Recently, we synthesized polymethoxy-substituted phenanthrene-9-carboxylic acid via intramolecular oxidative coupling using 3.5 equiv of FeCl$_3$.[14] This methodology suffers from difficulty in separation of organic and inorganic products. However, FeCl$_3$-catalyzed intramolecular oxidative coupling is virtually unknown.

Herein, we report FeCl$_3$-catalyzed intramolecular oxidative coupling reaction using *meta*-chloroperbenzoic acid (*m*-CPBA) as the oxidant. Furthermore, we investigate the reaction mechanism of the present intramolecular oxidative coupling reaction in detail. Meanwhile, the FeCl$_3$/*m*-CPBA oxidation system was also applied to intermolecular oxidative coupling of 2-naphthols and phenol ether.

As a starting point, we chose (*E*)-methyl-2,3-bis(3,4-dimethoxyphenyl)acrylate (**1a**) as the standard substrate to investigate suitable reaction conditions for the desired intramolecular oxidative coupling reaction. The results are summarized in Table 1.

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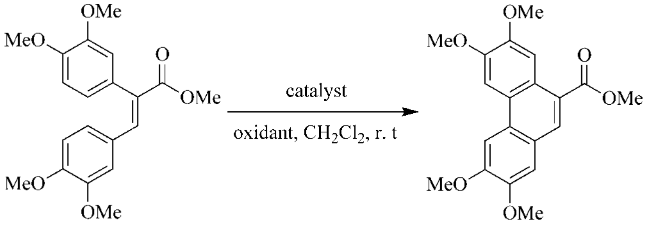
TABLE 1. Oxidative Coupling of 1a[a]



1a **1b**

entry	catalyst (mol %)	oxidant (equiv)	time [h]	conv. [b] [%]	yield[b] [%]
1	none	DTBP [c] (1)	48	3	2
2	$FeCl_3$ (40)	DTBP (1)	40	92	91
3	none	*m*-CPBA[d] (1)	29	16	0
4	$FeCl_3$ (40)	*m*-CPBA (1)	0.5	100	99
5	$FeCl_3$ (20)	*m*-CPBA (1)	0.5	100	97
6	$FeCl_3$ (10)	*m*-CPBA (1)	1.5	99	99
7	$FeCl_3$ (5)	*m*-CPBA (1)	11	96	94
8	$FeCl_3$ (2)	*m*-CPBA (1)	9	90	88
9	$FeCl_3$ (2)	*m*-CPBA (1)	11	91	78
10	$FeCl_3$ (2)	*m*-CPBA (1)	48	97	85
11	$FeCl_3$ (10)	none	24	16	15
12[e]	$FeCl_2$ (20)	DTBP (2)	6	4	4
13	$FeCl_2$ (10)	*m*-CPBA (1)	12	84	82

[a] Conditions: **1a** (179 mg, 0.5 mmol), CH_2Cl_2 (50 mL). [b] Conversion and yield were determined by HPLC. [c] DTBP = di-*tert*-butylperoxide. [d] *m*-CPBA = *meta*-chloroperbenzoic acid. [e] Reaction temperature: 38 °C.

TABLE 2. Effect of Various Solvents on Coupling of 1a[a]

entry	solvent	time [h]	conv.[b] [%]	yield[b] [%]
1	CH_3CN	6	22	4
2	THF	6	12	0
3	CH_2Cl_2	1.5	99	99
4	$CHCl_3$	1	98	98
5	DCE[c]	1	100	99
6	CH_3OH	10	18	8
7	acetone	6	8	3

[a] Conditions: **1a** (179 mg, 0.5 mmol), $FeCl_3$ (10 mol %), *m*-CPBA (1.0 equiv), solvent (50 mL), room temperature. [b] Conversion and yield were determined by HPLC. [c] DCE = $ClCH_2CH_2Cl$.

TABLE 3. Effect of Temperature and Concentration on Coupling of 1a[a]

entry	conc. (mol/L)	temp [°C]	time [h]	conv.[b] [%]	yield[b] [%]
1	0.01	15	1.5	99	99
2	0.01	40	1	99	99
3	0.01	−10	2	100	98
4	0.05	rt	1	99	99
5	0.1	rt	18.5	99	99

[a] Conditions: substrate **1a** (179 mg, 0.5 mmol), $FeCl_3$ (10 mol %), *m*-CPBA (1.0 equiv). [b] Conversion and yield were determined by HPLC.

The desired coupling product **1b** was obtained in 91% yield with $FeCl_3$ (40 mol %) as the catalyst and di-*tert*-butylperoxide (DTBP) as the oxidant (Table 1, entry 2). With the use of DTBP as an oxidant alone, the reaction gave trace coupling product (Table 1, entry 1). Compared with DTBP, *m*-CPBA demonstrates a higher oxidative ability. Further investigations showed that *m*-CPBA alone was not effective for the oxidative coupling of **1a** (Table 1, entry 3), but nearly quantitive yield of **1b** was obtained when $FeCl_3$ (40, 20, and 10 mol %) was used as the catalyst and *m*-CPBA (1.0 equiv) was used as the oxidant (Table 1, entries 4−6), showing that $FeCl_3$ is an active species for the coupling reaction. The yield of **1b** decreased gradually when 5 and 2 mol % of $FeCl_3$ was used as catalyst (Table 1, entries 7 and 8), but the reaction remained highly efficient even using 2 mol % of $FeCl_3$ as the catalyst (Table 1, entry 8). In the absence of oxidant, use of 10 mol % $FeCl_3$ only gave the coupling product in 15% yield (Table 1, entry 9). $FeCl_2$ showed moderate catalytic activity when *m*-CPBA was used as oxidant (Table 1, entry 11). The $FeCl_2$/DTBP system was less effective than the $FeCl_2$/*m*-CPBA system, probably because DTBP was not effective in oxidizing Fe^{2+} to Fe^{3+} as compared to *m*-CPBA (Table 1, entry 10).

A survey of solvents indicated that this new reaction was sensitive to the solvent medium (Table 2), and almost quantitative conversion and yield could obtained in halogenated alkane solvents such as CH_2Cl_2, $ClCH_2CH_2Cl$, and $CHCl_3$.

Temperature and concentration effects on the coupling reaction are shown in Table 3, which shows that the reaction can be performed in a wide range of temperature and concentration with excellent yields. However, considering operational simplicity and large-scale preparation, the reactions were carried out at room temperature and 0.05 mol/L.

Consequently, the optimized reaction conditions were as follows: 10 mol % of $FeCl_3$, 1.0 equiv of *m*-CPBA, the concentration of the substrate was 0.05 mol/L, at room temperature, dichloromethane as solvent.

Various compounds were tested as substrates for the intramolecular oxidative coupling reaction under the above optimized conditions (Table 4).

Substrate (*E*)-**2a**, which also has an electron-withdrawing group (−COOH) on the double bond, was found to react smoothly under these conditions and gave the desired product **2b** in 96% yield (Table 4, entry 2). In addition, a larger-scale reaction (100-fold scaled up) showed the same result as for the small one.

Intramolecular oxidative coupling of (*Z*)-**3a** and (*Z*)-**4a** catalyzed by $FeCl_3$ (10 mol %) also gave the corresponding coupling products **3b** and **4b** in almost quantitative yield, respectively (Table 4, entries 3 and 4), suggesting that configuration of the double bond has no effect to the oxidative reaction.

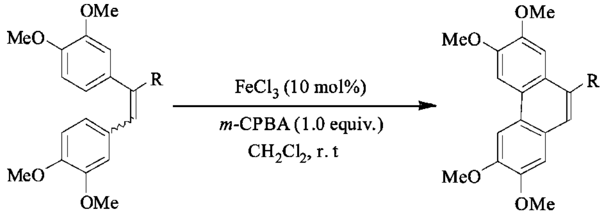
Subsequently, methoxyl group number and position effect on the coupling reaction are shown in Table 5.

Table 5 illustrates that at least three methoxy groups on two phenyls are necessary for the intramolecular oxidative coupling. When there are three or four methoxys on both phenyls, the reaction gave excellent yield (Tables 4 and 5, entries 1−4). When there are two methoxys (Table 5, entries 5 and 6) or no methoxy on both phenyls, the oxidative coupling did not work. In fact, most of phenanthroindolizidine and phenanthroquinolizidine alkaloids reported contained at least three methoxy groups, for example, tylophorine, antofine, and cryptopleurine. Hence, this facile and efficient protocol can be applicable to the synthesis of phenanthroindolizidine and phenanthroquinolizidine alkaloids.

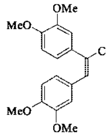
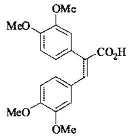
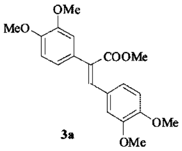
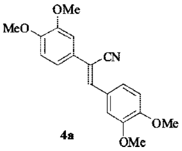
As far as we know, the reaction mechanism of intramolecular oxidative coupling has never been discussed so far. Herein, we investigate the reaction mechanism of the present oxidative coupling reaction in detail.

The nonstereospecificity of our coupling reaction (Table 4, entries 1−4) implied that the reaction go on via free radical species. This was the case because the addition of a radical-trapping compound, 2,2,6,6-tetramethylpiperidinyl-*N*-oxyl (TEMPO) (10 mol %), in the oxidative coupling of (*E*)-methyl-2,3-bis(3,4-

TABLE 4. Substrate Scope of Intramolecular Oxidative Coupling Reaction[a]

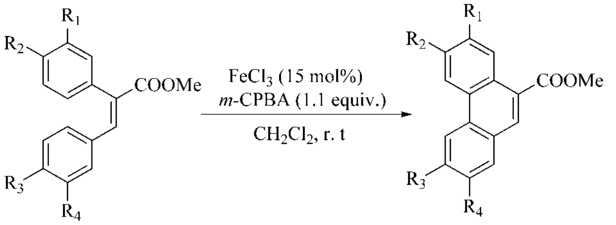


1a ~ 4a **1b ~ 4b**

Entry	Substrate	Time [h]	Conv.[b] [%]	Yield[b] [%]
1	 **1a**	1	99	99
2	 **2a**	0.5	100	96[c]
3	 **3a**	1	100	98
4	 **4a**	1	100	99

[a] Conditions: substrate **1a** (0.5 mmol). [b] Conversion and yield were determined by HPLC. [c] Yield corresponding to isolated product.

TABLE 5. Effect of Methoxy Number and Position on the Coupling Reaction



5a ~ 10a **5b ~ 10b**

entry	S[a]	R$_1$	R$_2$	R$_3$	R$_4$	P[b]	time [h]	GC conv. [%]	GC yield [%]
1	**5a**	H	CH$_3$O	CH$_3$O	CH$_3$O	**5b**	6	69	55
2	**6a**	CH$_3$O	CH$_3$O	CH$_3$O	H	**6b**	6	96	91
3	**7a**	CH$_3$O	H	CH$_3$O	CH$_3$O	**7b**	1	99	99
4	**8a**	CH$_3$O	CH$_3$O	H	CH$_3$O	**8b**	2	99	99
5	**9a**	CH$_3$O	CH$_3$O	H	H	**9b**	12	65	1[c]
6	**10a**	H	CH$_3$O	CH$_3$O	H	**10b**	11	70	0[d]

[a] S = substrate. [b] P = product. [c] 50% of **9a** was converted to halogenated product based on LC−MS. [d] 58% of **10a** was converted to epoxide.

dimethoxyphenyl)acrylate (**1a**) resulted in a significant decrease of the coupling yield (only 11%), compared to the quantitative yield attained under standard conditions (Table 4, entry 1).

We also test different redox potentials (E_{ox}) of **1a** (E_{ox} = 947 mV), **2a** (E_{ox} = 886 mV), **3a** (E_{ox} = 950 mV), and **4a** (E_{ox} = 996 mV). Because the E_{ox} value of **2a** is smaller than that of **1a**, **3a**, and **4a**, **2a** should be oxidized to form the cationic species more easily. The experiment results demonstrated that the oxidative coupling rate of **2a** is faster than that of **1a**, **3a**, and **4a** (Table 4).

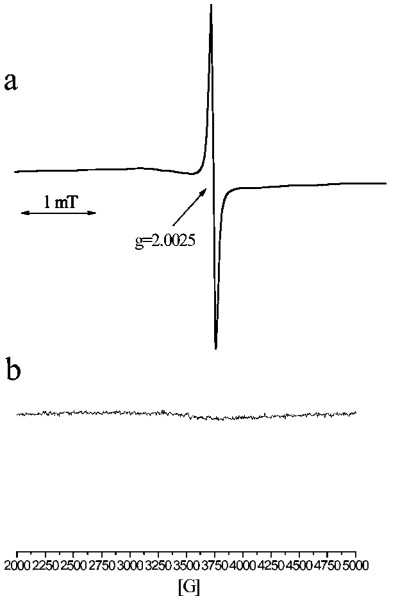


FIGURE 1. ESR spectra of FeCl$_3$-catalyzed oxidative coupling. (a) FeCl$_3$ (10 mol %)/m-CPBA (1.0 equiv) was treated with **1a** (0.5 mmol) in CH$_2$Cl$_2$. After 8 and 45 min, the spectrum was measured. (b) **1a** was dissolved in CH$_2$Cl$_2$, and the spectrum was measured.

To further clarify the mechanism of the present FeCl$_3$-catalyzed oxidative coupling, the ESR spectrum was then measured for the oxidative coupling of **1a**. As shown in Figure 1, a sharp signal at $g = 2.0025$ was observed (Figure 1a), which is assignable to a radical species derived from **1a**. The signal was not observed after the treatment of **1a** in CH$_2$Cl$_2$ (Figure 1b).

On the basis of the above experimental results, we propose the reaction mechanism for the present oxidative coupling (Scheme 1).

This reaction can be divided into three steps. The reaction proceeds with a typical radical mechanism via the one-electron transfer from substrate (*E*)- or (*Z*)-**1a** to FeCl$_3$ to give the reduced form (Fe^{2+}) and a radical cationic species (**2** or **4**) (step 1 in Scheme 1), which undergoes electrophilic attack to another rich electronic phenyl ring to form a C−C bond (see **3** and **6**; step 2 in Scheme 1). At last, **3** or **6** lost one electron and dehydro-aromatization to give the corresponding biaryl coupling product **1b** (step 3 in Scheme 1), and the reduced catalyst reacts with m-CPBA to regenerate the oxidized form (Fe^{3+}) with the formation of *meta*-chlorobenzoic acid and water. FeCl$_3$ and *meta*-chlorobenzoic acid can easily be removed by washing with water.

To our delight, we have applied the catalytic approach to intermolecular biaryl coupling of 2-naphthols and phenol ether (Table 6). Various kinds of 2-naphthols (**11a**−**13a**) were examined and gave the corresponding BINOLs (**11b**−**13b**) in moderate yields (Table 6, entries 1−3). 3,4-Dimethoxytoluene (**14a**) was also coupled by catalytic amount of FeCl$_3$, being driven by m-CPBA to give coupling product **14b** (Table 6, entry 4). All of the products were isolated and characterized by comparison of the physical data with the authentic samples data.

SCHEME 1. Tentative Mechanism for $FeCl_3$-Catalyzed Intramolecular Oxidative Coupling

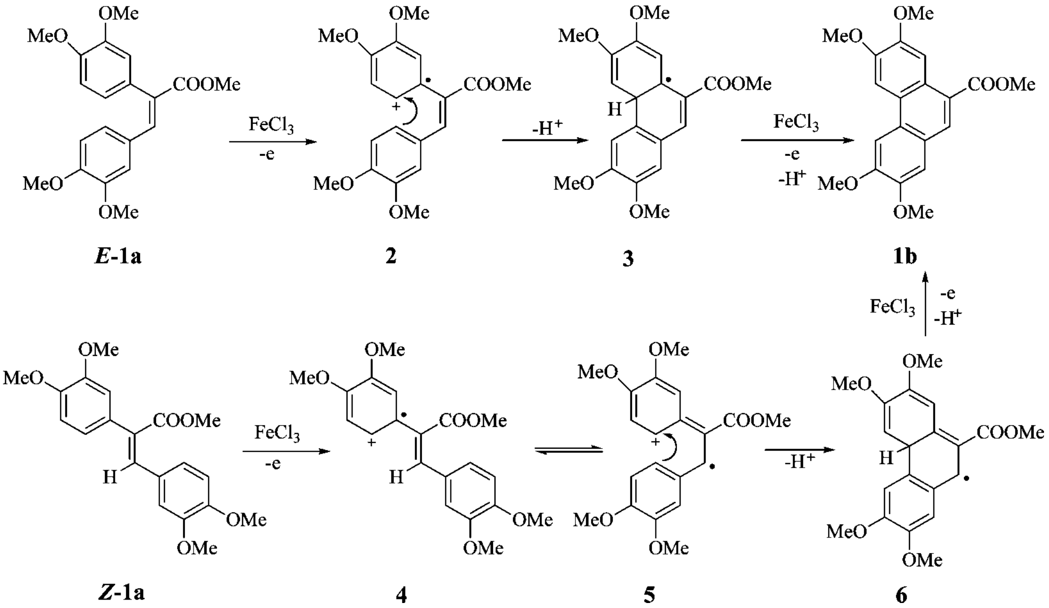
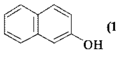
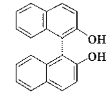
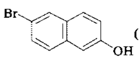
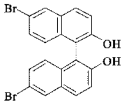
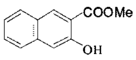
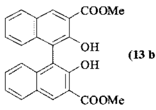
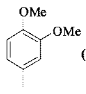
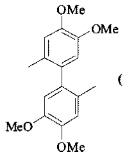


TABLE 6. Intermolecular Oxidative Coupling of 2-Naphthols and Phenol Ether Catalyzed by $FeCl_3$[a]

Entry	Substrate	Time [h]	Product	Conv.[b] [%]	Yield[b] [%]
1	 (11 a)	12	 (11 b)	99	76
2	 (12 a)	2	 (12 b)	100	58
3	 (13 a)	1	 (13 b)	93	47
4	 (14 a)	1	 (14 b)	100	58

[a] Conditions: substrate (2.5 mmol), $FeCl_3$ (10 mol %), *m*-CPBA (1.0 equiv), CH_2Cl_2 (50 mL), room temperature, under N_2 atmosphere. [b] Conversion and yield were determined by HPLC.

In summary, we have developed $FeCl_3$-catalyzed intramolecular oxidative coupling for the direct construction of the phenanthrene ring using *meta*-chloroperbenzoic acid (*m*-CPBA) as sole oxidant at room temperature in excellent yields. The mechanistic investigations show that the $FeCl_3$-catalyzed intramolecular oxidative coupling proceeds through the heterolytic coupling ($A^+ + B$) mechanism. The catalyst acts as a one-electron oxidant to form the reduced form. The reduced catalyst is reoxidized by *m*-CPBA. The catalytic approach has been applied to intermolecular biaryl coupling of 2-naphthols and phenol ether. The present system has the following significant advantages: (i) C−C bonds can be formed starting directly from arenes; (ii) the catalytic oxidative coupling reaction has been applied to both intramolecular and intermolecular coupling; (iii) simple workup procedures, mild conditions, and large-scale preparation; (iv) the use of easily available and nontoxic $FeCl_3$ as catalyst. Further studies on synthetic applications of this reaction are in progress.

Experimental Section

Typical Procedure for the Oxidative Coupling. To a solution of **1a** (179 mg, 0.5 mmol) in dry CH_2Cl_2 (50 mL) were added anhydrous $FeCl_3$ (8.1 mg, 0.05 mmol) and *m*-CPBA (86.3 mg, 0.5 mmol) under nitrogen. The reaction solution was stirred at room temperature for 1 h and then quenched with H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and evaporated in vacuo to yield a light yellow solid. The crude material was determined to be of 99% yield by HPLC analysis and purified by flash column chromatography on silica gel using a mixture of petroleum ether (60−90 °C) and ethyl acetate (v/v = 5:1) as the eluent to afford product **1b** as a white solid: mp 202−203 °C (lit.[15] mp 202−204 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.65 (s, 1H), 8.43 (s, 1H), 7.81 (s, 1H), 7.77 (s, 1H), 7.27 (s, 1H), 4.14 (s, 3H), 4.13 (s, 3H), 4.08 (s, 3H), 4.04 (s, 3H), 4.02 (s, 3H).

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Supporting Information Available: Spectroscopic data for **1a**−**10a**, **1b**−**8b**, and **11b**−**14b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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