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Radical-Cation-Induced Crossed [2 + 2] Cycloaddition of Electron-Deficient Anetholes Initiated by Iron(III) Salt

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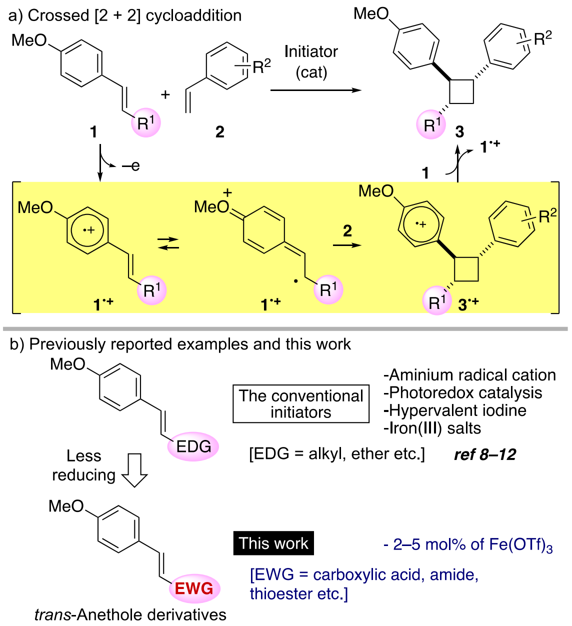
Abstract. Radical cation-induced crossed [2 + 2] cycloaddition of electron-deficient anetholes was developed with the use of Fe(OTf)$_3$ as an initiator. Various 1,2-diarylcyclobutanes can be synthesized in high yields with high diastereoselectivity from electron-deficient anetholes, which have been less explored using conventional methods. This practical reaction system can be used for a decagram-scale reaction (12 gram), in which the resulting product can be transformed to 1,2-dicarbonyl compounds.

Keywords: Radical cation; Iron(III) salt; [2 + 2] Cycloaddition; Electron-deficient anethole; Styrene

Because cyclobutane derivatives are present in various natural products and pharmaceuticals,[1] tremendous effort has been devoted to their synthesis.[2–4] Among them, radical cation-induced crossed [2 + 2] cycloaddition of anetholes with styrenes is of particular interest because it is one of the most straightforward methods to synthesize 1,2-diarylcyclobutanes **3** (Scheme 1a).[5] Thus far, various one-electron oxidants have been developed as initiators for the crossed [2 + 2] cycloaddition of anetholes. In general, an initiator oxidizes anethole **1** to give a key radical cation $\mathbf{1}^{\bullet+}$.[6,7] The resulting $\mathbf{1}^{\bullet+}$ reacts with styrenes **2** to give $\mathbf{3}^{\bullet+}$. The final step is reduction of $\mathbf{3}^{\bullet+}$ by **1** as chain propagation. Regarding generation of the key intermediate $\mathbf{1}^{\bullet+}$ of crossed [2 + 2] cycloaddition, great progress has been made using aminium radical cation,[8] photoredox catalysis,[9] hypervalent iodine[10] and iron(III) initiators.[11,12] Whereas electron-rich anetholes can be used for these conventional methods, electron-deficient anetholes has been less explored for crossed [2 + 2] cycloaddition (Scheme 1b).[12,13] Because electron-deficient anetholes are less-reducing substrates, the generation of anethole radical cation $\mathbf{1}^{\bullet+}$ is less likely.[14]

In our previous study, we developed FeCl$_3$-initiated crossed [2 + 2] cycloaddition of various electron-rich anetholes.[12] When FeCl$_3$ initiator is used in the presence of 2,5-dimethyl-2,4-hexadiene as a redox mediator, electron-rich anetholes can be used for crossed [2 + 2] cycloaddition. Besides, pairs of electron-deficient anetholes can be also used. However, the substrate scope has been still limited to α,β-unsaturated ketones and esters. To expand the scope of electron-deficient anetholes, we were intrigued by optimizing the iron(III) salt initiator and the reaction conditions. We anticipated that cationic iron(III) salt, having a less-coordinating counter anion, would improve its oxidation potential. If the proper iron(III) salt oxidizing electron-deficient anetholes is used, generation of the key $\mathbf{1}^{\bullet+}$ and subsequent cycloaddition should be possible. Therefore, we began to explore iron(III) salts that could oxidize a variety of electron-deficient anetholes.

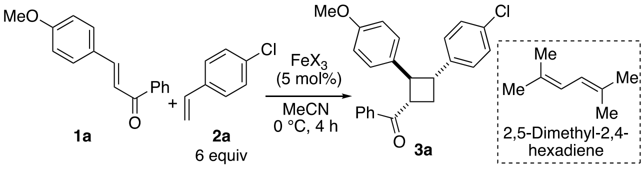


Scheme 1. Radical cation-induced crossed [2 + 2] cycloaddition.

To identify a highly active initiator, our initial attempt was focused on the screening of iron(III) salts for crossed [2 + 2] cycloaddition of 4-

methoxychalcone **1a** with styrene **2a** (Table 1). When 10 mol% of iron(III) salt [$Fe(acac)_3$, $Fe(OAc)_3$, $Fe(OCOCF_3)_3$ or $Fe(OTs)_3$] was used as an initiator, the corresponding product **3a** was not obtained (entries 1–4). When $FeCl_3$ was used, the corresponding product **3a** was obtained in 53% yield (entry 5). In contrast, iron(III) salts having less-coordinating anion were efficient. For example, the corresponding product was obtained quantitatively when $Fe(ClO_4)_3$ or $Fe(OTf)_3$ was used (entries 6 and 7). Notably, the corresponding product was obtained with high diastereoselectivity [dr > 95:5] in contrast to those with relatively low diastereoselectivity in triplet-sensitized crossed [2 + 2] cycloadditions.[13] The amount of initiator [$Fe(ClO_4)_3$ or $Fe(OTf)_3$] could be reduced to 5 mol% without decreasing the yield (entries 8 and 9). The best result was obtained when 5 mol% of $Fe(OTf)_3$ was used as an initiator (entry 9). 2,5-Dimethyl-2,4-hexadiene, which efficiently suppressed the degradation of electron-rich *trans*-anethole in our previous study,[12] did not improve the yield (entry 10). Presumably, electron-deficient *trans*-anethole **1a** is more stable than electron-rich *trans*-anethole. The degradation and dimerization of **1a** are less likely in comparison with electron-rich *trans*-anethole (see Scheme S1 in Supporting Information for details). Therefore, 2,5-dimethyl-2,4-hexadiene was not required as a redox mediator for crossed [2 + 2] cycloaddition of electron-deficient anetholes.

Table 1. Screening of Iron(III) Salt.[a]

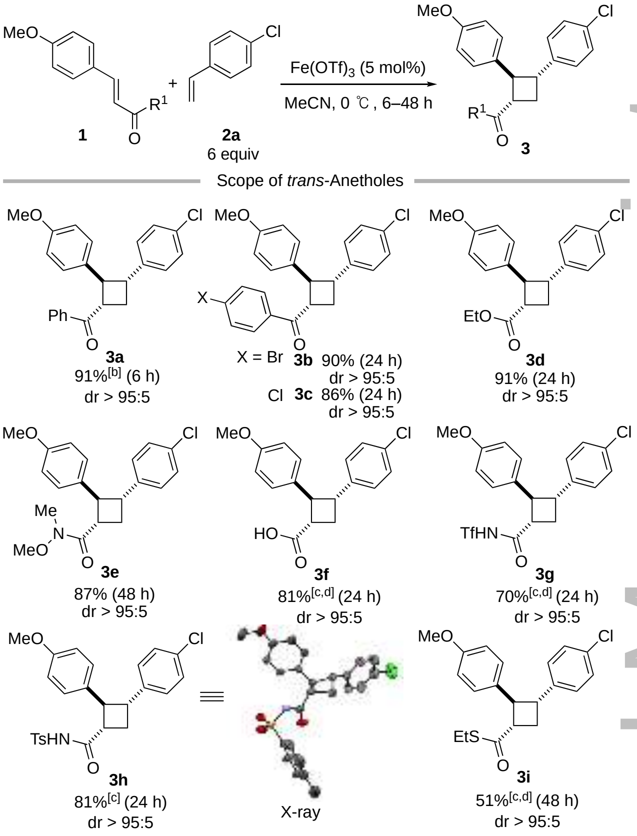


entry	FeX_3 [mol%]	Yield[b] [%]	dr
1	$Fe(acac)_3$ 10	0	–
2	$Fe(OAc)_3$ 10	0	–
3	$Fe(OCOCF_3)_3$ 10	0	–
4	$Fe(OTs)_3$ 10	0	–
5	$FeCl_3$ 10	53	>95:5
6	$Fe(ClO_4)_3$ 10	96	>95:5
7	$Fe(OTf)_3$ 10	98	>95:5
8	$Fe(ClO_4)_3$ 5	90[c]	>95:5
9	$Fe(OTf)_3$ 5	94[c,d]	>95:5
10	$Fe(OTf)_3$ 5	72[e]	>95:5

[a] The reaction was carried out with FeX_3 (5.0 mol%, 0.00925 mmol), diene (0–15 mol %, 0–0.0278 mmol), **1a** (1.0 equiv, 0.185 mmol) and **2** (6.0 equiv, 1.11 mmol) in MeCN at 0 ºC. [b] The yield was determined by ^1H NMR analysis using 1,3-dinitrobenzene as an internal standard. [c] 1.5 h. [d] Isolated yield. [e] 15 mol% of 2,5-dimethyl-2,4-hexadiene was used.

With the optimized conditions in hand, we examined the scope of substrate (Table 2). Regarding α,β-unsaturated carbonyl compounds, various carbonyl compounds were well-tolerated. Simple carbonyl groups, such as ketones, ester and amide were suitable functional groups under the reaction conditions (see **3a**–**3e**). In the case of **1a**, the amount of $Fe(OTf)_3$ could be reduced to 2 mol% without decreasing the yield of the corresponding **3a**. Moreover, carboxylic acid **1f** and sulfonyl acetamides **1g** and **1h**, which have an acidic proton, were also suitable carbonyl groups, although 10 mol% of $Fe(OTf)_3$ was required. Notably, relatively labile thioester **1i** was tolerated under the reaction conditions to afford the corresponding product, although the yield was moderate.

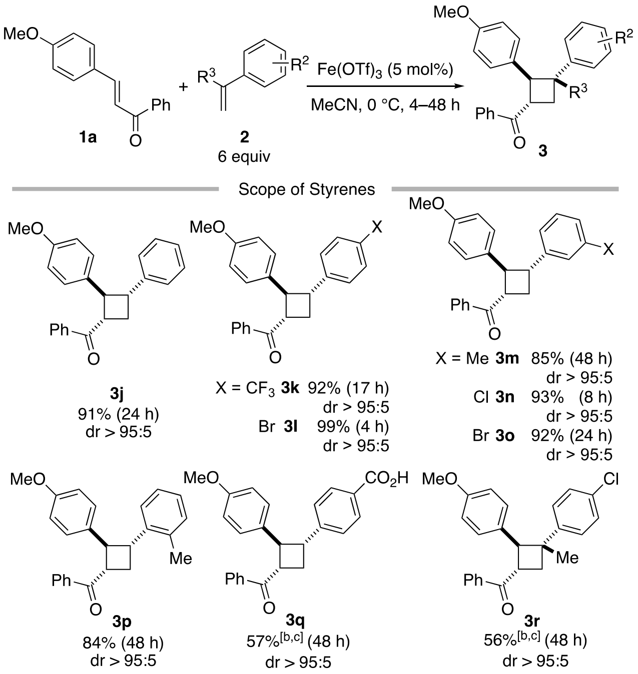
Table 2. Scope of *trans*-Anetholes.[a]



[a] The reaction was carried out with $Fe(OTf)_3$ (5.0 mol%, 0.00925 mmol), **1** (1.0 equiv, 0.185 mmol) and **2** (6.0 equiv, 1.11 mmol) in MeCN at 0 ºC. [b] $Fe(OTf)_3$ (2.0 mol%, 0.00370 mmol). [c] $Fe(OTf)_3$ (10 mol%, 0.0185 mmol). [d] The yield was determined by ^1H NMR analysis using 1,3-dinitrobenzene as an internal standard.

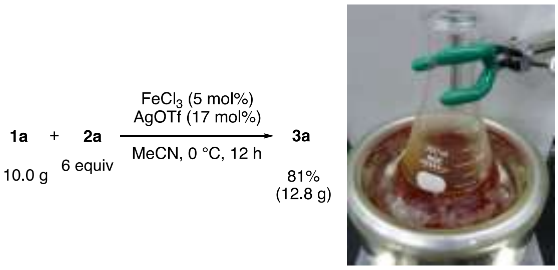
Regarding styrene, a variety of electron-donating and -withdrawing substituents of the aromatic group could be used (Table 3). For example, *ortho*-, *meta* and *para*-substituents of the aromatic group of styrene (**2j**–**2p**) did not decrease the yield. Styrene **2q** having a carboxylic acid provided the corresponding product in high yield in the presence of 10 mol% of $Fe(OTf)_3$. Moreover, α-methyl-substituted styrene provided the corresponding **3r**, although the yield was somewhat moderate. In short, various electron-deficient anetholes and styrenes can be used in iron(III) salt-initiated crossed [2 + 2] cycloaddition in comparison with conventional methods.[12]

Table 3. Scope of styrene.[a]



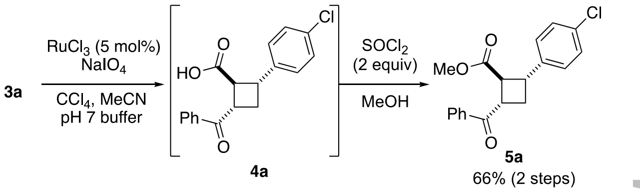
[a]The reaction was carried out with $Fe(OTf)_3$ (5 mol%, 0.00925 mmol), **1** (1.0 equiv, 0.185 mmol) and **2** (6.0 equiv, 1.11 mmol) in MeCN at 0 ºC. [b]$Fe(OTf)_3$ (10 mol%, 0.0185 mmol). [c]The yield was determined by ^1H NMR analysis using 1,3-dinitrobenzene as an internal standard.

To test the synthetic potential of our approach, a large-scale reaction was conducted (Scheme 2). When 10 g of **1a** was used in the presence of 5 mol% of $Fe(OTf)_3$ prepared from $FeCl_3$ and AgOTf, the crude product was obtained quantitatively in 12 hours using a flask open to air. Concentration and distillation to remove the solvent and **2a** under reduced pressure gave a crude mixture, which was purified by flash chromatography to provide pure **3a** in 81% yield (12.8 g). Since $Fe(OTf)_3$ is one of the simplest and strongest inorganic iron(III) oxidants,[15] a decagram-scale reaction in standard glassware (300 mL Erlenmeyer flask) could be successfully conducted.



Scheme 2. Decagram-scale reaction.

Finally, we performed a transformation of **3a** to demonstrate the utility of the [2 + 2] cycloadduct (Scheme 3). Oxidative cleavage of the 4-(MeO)C_6H_4 group of **3a** afforded 1,4-dicarbonyl compound **4a**.[16] After esterification under acidic conditions, 1,4-ketoester **5a** was obtained in 66% yield. Cyclobutanes with a 1,4-dicarbonyl moiety are present in potential pharmaceuticals.[17] Construction of the cyclobutane by crossed [2 + 2] cycloaddition of electron-deficient anetholes can be used to synthesize these compounds.



Scheme 3. Transformation of the product **3a**.

In summary, $Fe(OTf)_3$ has been developed as an initiator for the crossed [2 + 2] cycloaddition of electron-deficient anetholes. A cationic iron(III) salt has strong oxidation potential, which is sufficient for oxidizing less-reducing anetholes. With the optimal iron(III) salt identified, a wide substrate scope of electron-deficient anetholes and styrenes has been achieved. As a simple yet efficient one-electron oxidant, $Fe(OTf)_3$ is a suitable initiator even for decagram-scale reactions (12 gram-scale). We believe that this study provides a powerful method for the synthesis of 1,2-diaryl cyclobutanes, and also provides further insight into the oxidation properties of iron(III) salts for other relevant one-electron oxidation reactions.

Experimental Section

General procedure for crossed [2 + 2] cycloaddition: A one dram vial equipped with a magnetic stir bar was charged with $Fe(OTf)_3$ (0.05 equiv, 0.00925 mmol) and MeCN (600 μL) at ambient conditions. After being stirred for 5 min at 0 ºC, styrene (6.0 equiv, 1.11 mmol) and α,β-unsaturated carbonyl compound (1.0 equiv, 0.185 mmol) were added to the mixture. The resulting mixture was stirred at 0 ºC and monitored periodically by TLC. Upon consumption of α,β-unsaturated carbonyl compound, the reaction mixture was directly subjected to silica gel chromatography (hexane/ethyl acetate) to give the desired product.

CCDC-1952076 contains the supplementary crystallographic data for **3h**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac. uk/data_request/cif.

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