

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

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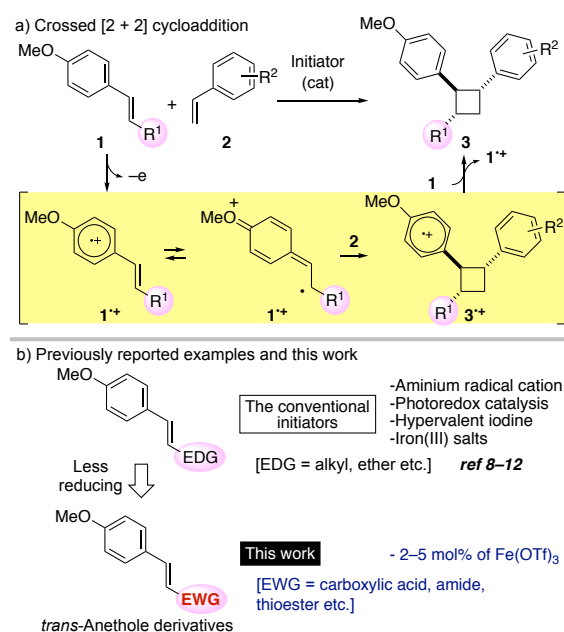
Abstract. Radical cation-induced crossed [2 + 2] cycloaddition of electron-deficient anetholes is developed with the use of Fe(OTf)₃ as an initiator. Various 1,2-diarylcyclobutanes can be synthesized in high yields with high diastereoselectivity from electron-deficient anetholes, which have been less explored using conventional methods. This practical reaction system can be used for a deca-gram-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 **1^{•+}**.^[6,7] The resulting **1^{•+}** reacts with styrenes **2** to give **3^{•+}**. The final step is reduction of **3^{•+}** by **1** as chain propagation. Regarding generation of the key intermediate **1^{•+}** 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 **1^{•+}** is less likely.^[14]

In our previous study, we developed FeCl₃-initiated crossed [2 + 2] cycloaddition of various electron-rich anetholes.^[12] When FeCl₃ 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 **1^{•+}** and subsequent cycloaddition should be possible. Therefore, we began to explore iron(III) salts that could oxidize a variety of electron-deficient anetholes.

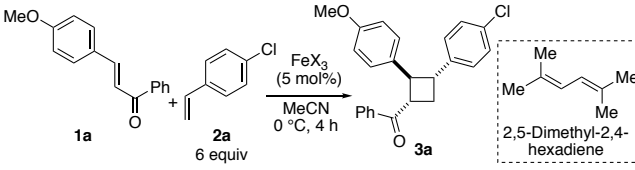


Scheme 1. Radical cation-induced crossed [2 + 2] cycloaddition.

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(OCOCF₃)₃ or Fe(OTf)₃] was used as an initiator, the corresponding product **3a** was not obtained (entries 1–4). When FeCl₃ 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(ClO₄)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(ClO₄)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]



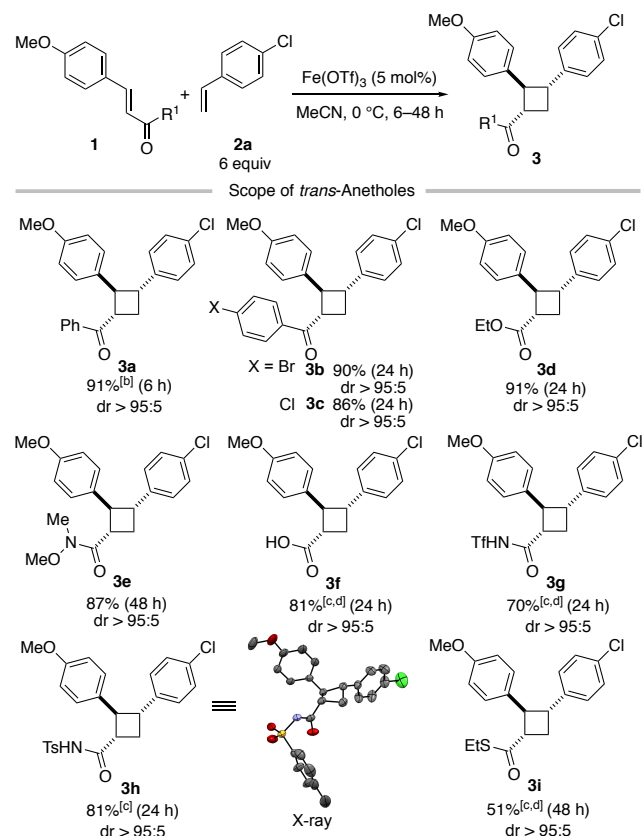
entry	FeX ₃ [mol%]	Yield ^[b] [%]	dr
1	Fe(acac) ₃ 10	0	—
2	Fe(OAc) ₃ 10	0	—
3	Fe(OCOCF ₃) ₃ 10	0	—
4	Fe(OTf) ₃ 10	0	—
5	FeCl ₃ 10	53	>95:5
6	Fe(ClO ₄) ₃ 10	96	>95:5
7	Fe(OTf) ₃ 10	98	>95:5
8	Fe(ClO ₄) ₃ 5	90 ^[c]	>95:5
9	Fe(OTf) ₃ 5	94 ^[c,d]	>95:5
10	Fe(OTf) ₃ 5	72 ^[e]	>95:5

^[a]The reaction was carried out with FeX₃ (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 °C. ^[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.

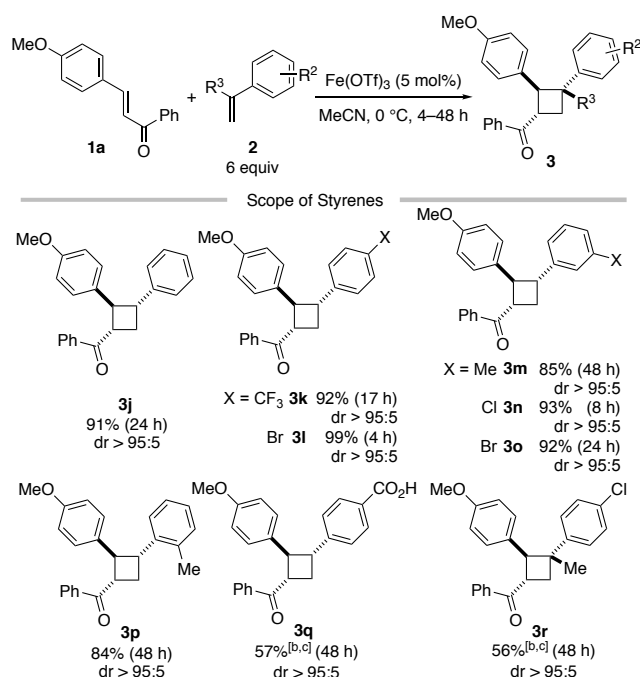
Table 2. Scope of *trans*-Anetholes.^[a]



^[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 °C. ^[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.

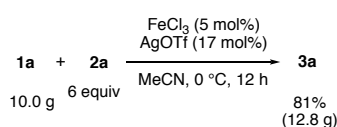
Regarding styrene, a variety of electron-donating and -withdrawing substituents of the aromatic group could be used (Table 3). For example, *ortho*-, *meta*- and *para*-substituents of the aromatic group of styrene (**2j–2p**) did not decrease the yield. Styrene **2q** having a carboxylic acid provided 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 $\text{Fe}(\text{OTf})_3$ (5 mol%, 0.00925 mmol), **1** (1.0 equiv, 0.185 mmol) and **2** (6.0 equiv, 1.11 mmol) in MeCN at 0 °C. ^[b] $\text{Fe}(\text{OTf})_3$ (10 mol%, 0.0185 mmol). ^[c]The yield was determined by ¹H NMR analysis using 1,3-dinitrobenzene as an internal standard.

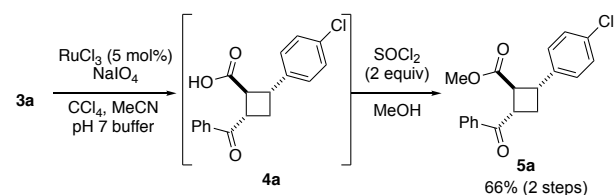
To test the synthetic potential of our approach, a large-scale reaction was conducted (Scheme 2). When 10 g of **1a** was used in the presence of 5 mol% of $\text{Fe}(\text{OTf})_3$ prepared from FeCl_3 and AgOTf , the crude product was obtained quantitatively in 12 hours using a flask open to air. Concentration 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 $\text{Fe}(\text{OTf})_3$ is one of the simplest and strongest inorganic iron(III) oxidants,^[15] a deca-gram-scale reaction in standard glassware (300 mL Erlenmeyer flask) could be successfully conducted.



Scheme 2. Deca-gram-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)C₆H₄ 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, $\text{Fe}(\text{OTf})_3$ 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, $\text{Fe}(\text{OTf})_3$ is a suitable initiator even for deca-gram-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 $\text{Fe}(\text{OTf})_3$ (0.05 equiv, 0.00925 mmol) and MeCN (600 μL) at ambient conditions. After being stirred for 5 min at 0 °C, 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 °C 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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References

- [1] a) T. V. Hansen, Y. Stenström, Naturally Occurring Cyclobutanes, in *Organic Synthesis: Theory and Applications*, ed. Hudlicky, T., Elsevier, Oxford, UK, **2001**, vol. 5, pp. 1–38; b) V. M. Dembitsky, *J. Nat. Med.*, **2008**, 62, 1–33; c) A. Sergeiko, V. V. Proikov, L. O. Hanus, V. M. Dembitsky, *Open Med. Chem. J.* **2008**, 2, 26–37.
- [2] a) E. Lee-Ruff, G. Mladenova, *Chem. Rev.* **2003**, 103, 1449–1483; b) E. Lee-Ruff, Synthesis of Cyclobutanes, in *The Chemistry of Cyclobutanes*, (Eds.: Z. Rappoport, J. F. Liebman), Wiley, **2005**, pp. 281–355; c) S. Poplata, A. Tröster, Y.-Q. Zou, T. Bach, *Chem. Rev.* **2016**, 116, 9748–9815.
- [3] For selected reviews of photochemical [2 + 2] cycloadditions, see: a) M. T. Crimmins, *Chem. Rev.* **1988**, 88, 1453–1473; b) M. Demuth, G. Mikhail, *Synthesis* **1989**, 145–162; c) D. I. Schuster, G. Lem, N. A. Kaprinidis, *Chem. Rev.* **1993**, 93, 3–22; d) J. Iriondo-Alberdi, M. F. Greaney, *Eur. J. Org. Chem.* **2007**, 4801–4815; e) T. Bach, J. P. Hehn, *Angew. Chem. Int. Ed.* **2011**, 50, 1000–1045.
- [4] For selected electrochemical methods for [2 + 2] cycloaddition, see: a) Y. Okada, R. Akaba, K. Chiba, *Org. Lett.* **2009**, 11, 1033–1035; b) Y. Okada, A. Nishimoto, R. Akaba, K. Chiba, *J. Org. Chem.* **2011**, 76, 3470–3476.
- [5] For selected homo [2 + 2] cycloaddition of anetholes, see: a) F. A. Bell, R. A. Crellin, H. Fujii, A. Ledwith, *J. Chem. Soc. D.* **1969**, 1969, 251–252; b) A. Ledwith, *Acc. Chem. Res.* **1972**, 5, 133–139; c) H. Ohara, T. Itoh, M. Nakamura, E. Nakamura, *Chem. Lett.* **2001**, 30, 624–625; d) C. A. Marquez, H. Wang, F. Fabbretti, J. O. Metzger, *J. Am. Chem. Soc.* **2008**, 130, 17208–17209. e) M. Riener, D. A. Nicewicz, *Chem. Sci.* **2013**, 4, 2625–2629.
- [6] Y. Okada, K. Chiba, *Chem. Rev.* **2018**, 118, 4592–4630.
- [7] For related cyclizations leveraging the generation of *trans*-anethole radical cation, see: a) D. J. Bellville, N. L. Bauld, R. Pabon, S. A. Gardner, *J. Am. Chem. Soc.* **1983**, 105, 3584–3588; b) R. A. Pabon, D. J. Bellville, N. L. Bauld, *J. Am. Chem. Soc.* **1983**, 105, 5158–5159; c) D. W. Reynolds, N. L. Bauld, *Tetrahedron* **1986**, 42, 6189–6194; d) S. Lin, M. A. Ischay, C. G. Fry, T. P. Yoon, *J. Am. Chem. Soc.* **2011**, 133, 19350–19353; e) S. M. Stevenson, M. P. Shores, E. M. Ferreira, *Angew. Chem. Int. Ed.* **2015**, 54, 6506–6510; f) R. F. Higgins, S. M. Fatur, S. G. Shepard, S. M. Stevenson, D. J. Boston, E. M. Ferreira, N. H. Damrauer, A. K. Rappé, M. P. Shores, *J. Am. Chem. Soc.* **2016**, 138, 5451–5464; g) Y. Zhao, M. Antonietti, *Angew. Chem. Int. Ed.* **2017**, 56, 9336–9340; h) P. D. Morse, T. M. Nguyen, C. L. Cruz, D. A. Nicewicz, *Tetrahedron* **2018**, 74, 3266–3272; i) Y. Okada, Y. Yamaguchi, A. Ozaki, K. Chiba, *Chem. Sci.* **2016**, 7, 6387–6395.
- [8] a) N. L. Bauld, R. Pabon, *J. Am. Chem. Soc.* **1983**, 105, 633–634; b) N. L. Bauld, *Tetrahedron* **1989**, 45, 5307–5367.
- [9] a) M. A. Ischay, M. S. Ament, T. P. Yoon, *Chem. Sci.* **2012**, 3, 2807–2811; b) R. Li, B. C. Ma, W. Huang, L. Wang, D. Wang, H. Lu, K. Landfester, K. A. I. Zhang, *ACS Catal.* **2017**, 7, 3097–3101.
- [10] a) I. Colomer, R. C. Barcelos, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2016**, 55, 4748–4752; b) I. Colomer, C. Batchelor-McAuley, B. Odell, T. J. Donohoe, R. G. Compton, *J. Am. Chem. Soc.* **2016**, 138, 8855–8861.
- [11] a) Y. Yu, Y. Fu, F. Zhong, *Green Chem.* **2018**, 20, 1743–1747; b) J. H. Shin, E. Y. Seong, H. J. Mun, Y. J. Jang, E. J. Kang, *Org. Lett.* **2018**, 20, 5872–5876.
- [12] T. Horibe, S. Ohmura, K. Ishihara, *J. Am. Chem. Soc.* **2019**, 141, 1877–1881.
- [13] Triplet-sensitized crossed [2 + 2] cycloadditions of α,β -unsaturated carbonyls were recently reported. A variety of α,β -unsaturated carbonyls can be used despite the low diastereoselectivity of the product. a) Z. D. Miller, B. J. Lee, T. P. Yoon, *Angew. Chem. Int. Ed.* **2017**, 56, 11891–11895; b) T. Lei, C. Zhou, M.-Y. Huang, L.-M. Zhao, B. Yang, C. Ye, H. Xiao, Q.-Y. Meng, V. Ramamurthy, C.-H. Tung, L.-Z. Wu, *Angew. Chem. Int. Ed.* **2017**, 56, 15407–15410.
- [14] For the generation of electron-deficient anethole radical cation for [4 + 2] cycloaddition, see: S. M. Stevenson, R. F. Higgins, M. P. Shores, E. M. Ferreira, *Chem. Sci.* **2017**, 8, 654–660.
- [15] J. R. Cabrero-Antonino, A. Leyva-Pérez, A. Corma, *Chem. Eur. J.* **2013**, 19, 8627–8633.
- [16] P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, 46, 3936–3938.
- [17] K. Raha, K. M. Merz, *J. Med. Chem.* **2005**, 48, 4558–4575.

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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