Structure and Reactivity of Aromatic Radical Cations Generated by $FeCl_3$

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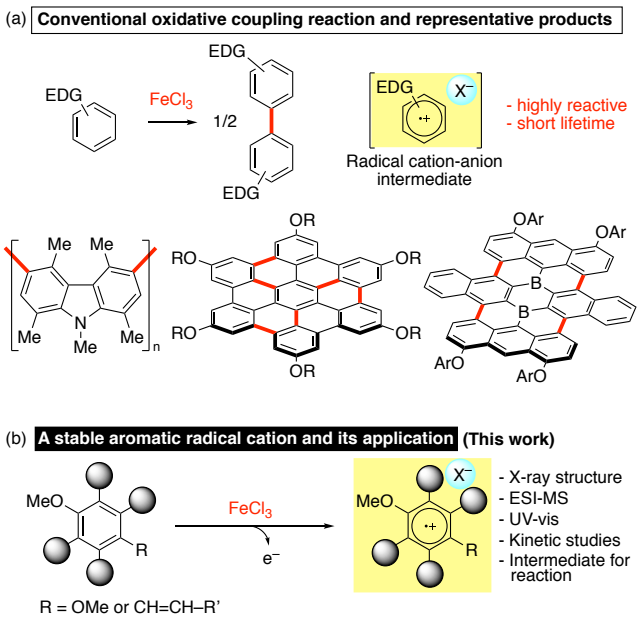
Supporting Information Placeholder

ABSTRACT: This paper describes the isolation and characterization of an aromatic radical cation generated by $FeCl_3$. X-ray crystallographic analysis and kinetic studies reveal the mechanism of the generation of aromatic radical cation. In the solid state, a tight ion-pair of a radical cation with $FeCl_4^-$ is observed. Leveraging the efficient generation of the radical cation–$FeCl_4^-$ ion pair, we explore a radical cation-induced cycloaddition of *trans*-anethole initiated by catalytic amount of $FeCl_3$. Both [4 + 2] cycloaddition and [2 + 2] cycloaddition with a broad substrate scope are also described. Moreover, a 100g-scale reaction is demonstrated with the use of 1 mol% of $FeCl_3$ as a simple and a highly active initiator.

Aromatic radical cations are open-shell reactive species that appear in various one-electron oxidation reactions.[1] Since radical cation-induced reactions exhibit reactivity and selectivity complementary to those in thermal reactions,[2] tremendous effort has been devoted to identifying radical cation-induced reactions. The explicit characterization of these key radical cation intermediates can serve as a basis for the discovery of further reactions. However, because of their high reactivities and short lifetimes, the structural characterization of radical cations has been challenging.[3] Within this catalytic regime, $FeCl_3$-promoted oxidation reactions are of particular interest.[4] For examples, $FeCl_3$ has been shown to promote oxidative coupling reactions[5,6] and the Scholl reaction,[7,8] which have been utilized for syntheses of polycyclic aromatic hydrocarbons for more than a century (Scheme 1a). Despite its wide application for material science,[9] the mechanism of the $FeCl_3$-promoted oxidation reaction has been scarcely studied. Whereas the oxidation reactions are believed to proceed through aromatic radical cations as a key intermediate,[6a–e,10] there have been no reports on the isolation of aromatic radical cations generated by $FeCl_3$. Major challenges include a highly reactive and labile aromatic radical cation, which decomposes or undergoes oxidation reaction immediately.[10,11] Therefore, the actual structure of aromatic radical cations remains unclear. In particular, the identity of counteranion (X^-) has remained elusive in key previous studies.

Here, we report the isolation and characterization of an aromatic radical cation–anion generated by $FeCl_3$ (Scheme 1b). Moreover, by means of the efficient generation of radical cation by $FeCl_3$, we have developed radical cation-induced [4 + 2] cycloaddition as well as [2 + 2] cycloaddition promoted by catalytic amounts of $FeCl_3$.

Scheme 1. $FeCl_3$-mediated Radical Cation Generation.



The isolation of an aromatic radical cation generated by $FeCl_3$ was approached empirically. Most of the electron-rich aromatics examined did not give isolable products. Fortunately, sterically congested arene **1** gave radical cation **2** in 84% yield in CH_2Cl_2/MeCN (Figure 1a). The X-ray crystal structure of **2** reveals an ion pair of $FeCl_4^-$ with $\mathbf{1}^{\bullet+}$ (Figure 1b). Additionally, $\mathbf{1}^{\bullet+}$ could be observed in solution by UV-vis spectroscopy (λ_{max} = 519 nm, 483 nm)[12] and ESI-MS analysis (m/z = 270.16) under ambient conditions (Figures 1c and 1d). To elucidate the mechanism for the generation of **2**, kinetic studies were conducted for $FeCl_3$ and **1**. First-order dependency for $FeCl_3$ and zero-order dependency for **1** were observed (Figure 1e), which suggested that the nuclearity of the iron species was un-

changed between the ground state and rate-determining transition state. Combined with the known structure **A** of $FeCl_3$ in MeCN,[13] we propose the overall mechanism for oxidation shown in Figure 1f. Namely, zero-order in **1** implies rate-limiting internal reorganization in the dimeric ground-state structure **A**, which we propose involves a ligand dissociation to afford $FeCl_4^-$ and $FeCl_2^+(MeCN)_3$ (**B**).[14] This oxidant **B** is immediately scavenged by **1** to give **2**, thus exhibiting zero-order behavior. Because the zero-order behavior suggests that **1** is an efficient scavenger of **B**, this observation suggests that less kinetically reducing arenes could also be oxidized by $FeCl_3$-promoted oxidation in MeCN.

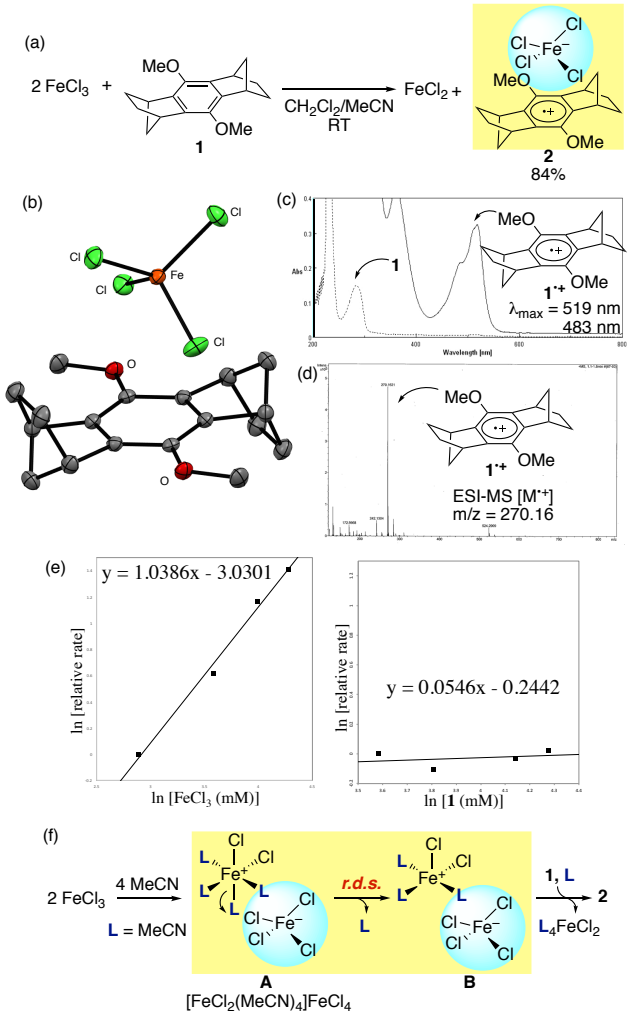
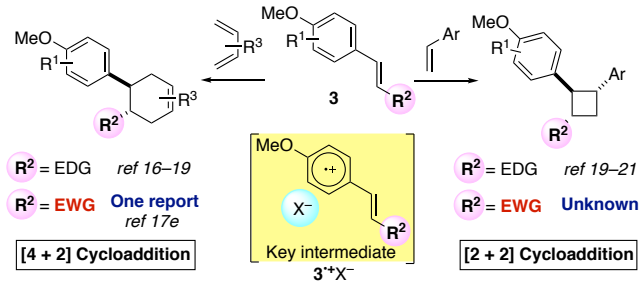


Figure 1. (a) The generation of radical cation **2** by $FeCl_3$. (b) Thermal-ellipsoid representation of **2** at the 50% probability level. Hydrogens have been omitted for clarity. (c) UV-vis spectrum of **2**. (d) ESI-MS spectrum for **2**. (e) Kinetic studies for $FeCl_3$ and **1**. (f) The proposed mechanism for the generation of **2**.

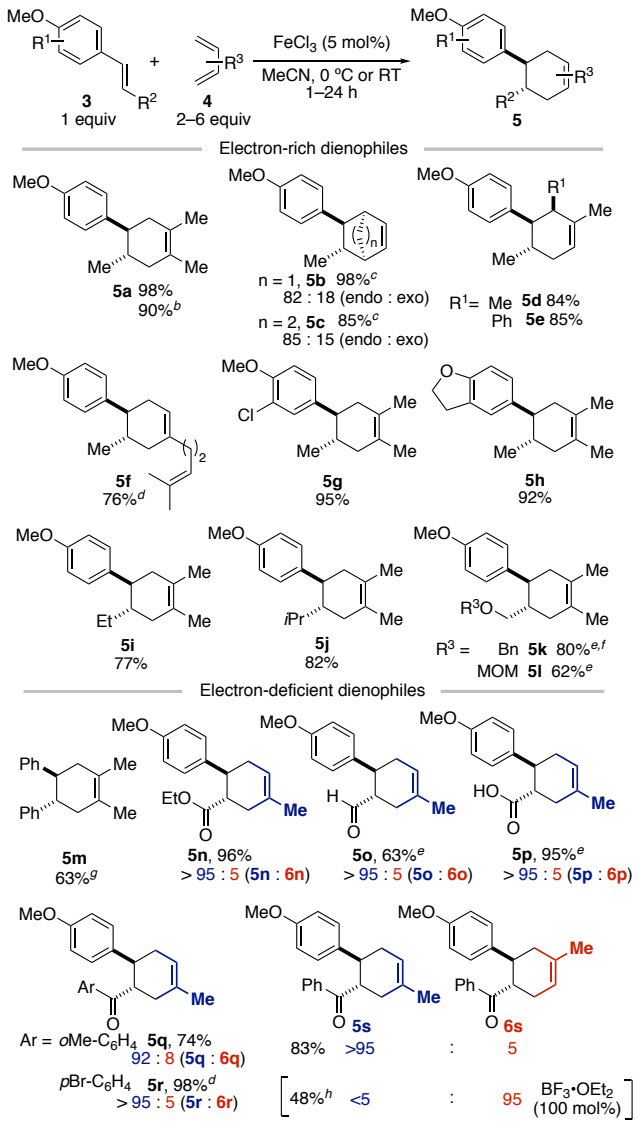
With the oxidant **B** identified, we applied $FeCl_3$-promoted oxidation for a radical cation-induced cycloaddition. We were intrigued by [4 + 2] cycloaddition and [2 + 2] cycloaddition of *trans*-anethole **3** (Scheme 2). The key intermediate is $\mathbf{3}^{\bullet+}$, which undergoes [4 + 2] cycloaddition with diene or [2 + 2] cycloaddition with styrene. To date, implementation of an initiator has been the primary strategy developed for the generation of $\mathbf{3}^{\bullet+}$.[15] Great progress has been made employing aminium radical cation,[16] photoredox catalysis,[17] electrochemical methods[18] and iron(III) catalysis[19] for [4 + 2] cycloaddition. With regard to cross [2 + 2] cycloaddition, photoredox catalysis,[20] hypervalent iodine initiator[21] and iron(III) catalysis[19] have been developed. Whereas a broad substrate scope of both cycloadditions has been achieved, electron-deficient *trans*-anetholes (**3**) are less explored. For examples, only one report of electron-deficient **3** for [4 + 2] cycloaddition has appeared recently from Ferreira's group.[17e] Regarding [2 + 2] cycloaddition, there have been no examples of electron-deficient **3**.[22] The generation of electron-deficient $\mathbf{3}^{\bullet+}$ is more difficult because of the high oxidation potential of such substrates. To achieve a wide substrate scope including electron-deficient **3**, *in-situ* formed **B** as a strong oxidant should be suitable.

Scheme 2. Previously Reported [4 + 2] Cycloaddition and [2 + 2] Cycloaddition.



Our studies in this area commenced with examination of $FeCl_3$-initiated [4 + 2] cycloaddition (Table 1). To our delight, 5 mol% of $FeCl_3$ gave the corresponding product in 98% yield when **3a** was used (see **5a**). Interestingly, 5 mol% of isolated **2** also promoted the cycloaddition to give **5a** in 90% yield. Both cyclic and acyclic dienes gave the corresponding products in high yields (see **5b**–**5f**). Various aromatic groups and substituents of β-position of **3** were well tolerated (see **5g**–**5l**). Remarkably, our oxidation system was also suitable for electron-deficient dienophiles (**3m**–**3s**). In some cases, 5 mol% of $Fe(OTf)_3$ in place of $FeCl_3$ was also effective (see **5k**–**5m**, **5o** and **5p**).[23] Presumably, higher oxidation potential of $Fe(OTf)_3$ facilitates the oxidation of such less-reducing substrates.[24] Whereas the conventional aminium radical cation give **5m** in only 30% yield,[25] iron(III) oxidation system afforded **5m** in an improved 63% yield. In the case of α,β-unsaturated carbonyls, such as esters, aldehydes, carboxylic acids and ketones (**3n**–**3s**), the corresponding products (**5n**–**5s**) were obtained in high yield with high regioselectivity in 2–24 h. As in previous examples of radical cation cycloaddition, the regioselectivity of the corresponding products (**5n**–**5s**) is complementary to that of thermal [4 + 2] cycloadducts (**6n**–**6s**). Indeed, the opposite isomer **6s** was mainly obtained from BF_3•OEt_2-promoted [4 + 2] cycloaddition of **3s**. These results suggest that $FeCl_3$ acts as a one-electron oxidant rather than a Lewis acid.

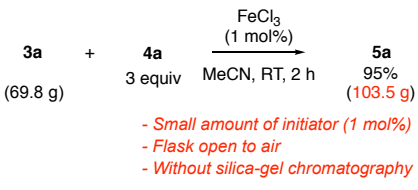
Table 1. Scope of Radical Cation-induced [4 + 2] Cycloaddition.[a]

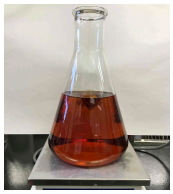


[a]The reaction was carried out with $FeCl_3$ (5 mol %), **3** (1 equiv) and **4** (2–6 equiv) in MeCN at 0 ºC or room temperature. [b]Using **2** (5 mol%) instead of $FeCl_3$. [c]CH_2Cl_2 was used as a solvent. [d]MeCN/CH_2Cl_2 were used as solvents. [e]Using $Fe(OTf)_3$ (5 mol%) instead of $FeCl_3$. [f]Using **4** (9 equiv). [g]Using $Fe(OTf)_3$ (10 mol%) instead of $FeCl_3$. [h]The reaction was carried out with BF_3•OEt_2 (100 mol %), **3** (1 equiv) and **4** (10 equiv) in Et_2O at room temperature.

To test the synthetic potential of our approach, a large-scale reaction was conducted (Scheme 3). When 69.8 g of **3a** was reacted in the presence of 1 mol% of $FeCl_3$, the crude product was obtained quantitatively in 2 h using a flask open to air. Moreover, removal of inorganic $FeCl_3$ by filtration through a short pad of silica-gel afforded pure **5a** in 95% yield (103.5 g), highlighting the operational simplicity of this methodology. Unlike photoredox catalysis, this method does not require specialized light-flux-maximizing flow apparatuses for large-scale reactions,[26] allowing $FeCl_3$-initiated [4 + 2] cycloaddition to be conducted on a 100g scale in standard glassware.

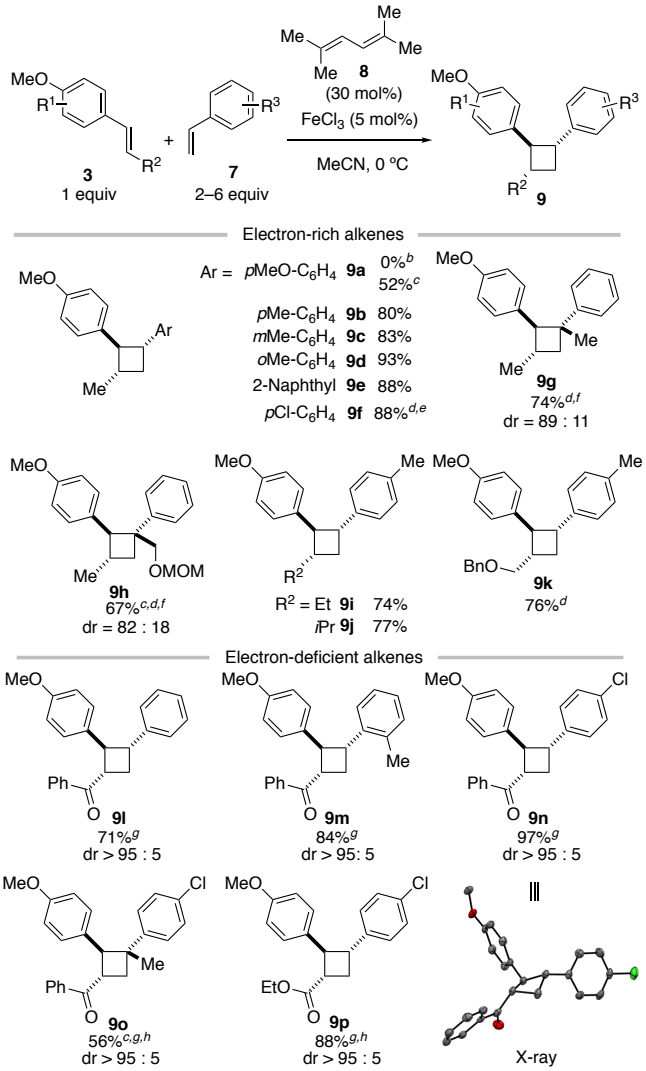
Scheme 3. 100-gram Scale Reaction.





Next, we turned our attention to the cross [2 + 2] cycloaddition of **3** with **7** (Table 2). Initial attempts using **3a** with **7a** gave unsatisfactory results. Namely, the desired **9a** was not obtained because of a polymerization of **7a** and a degradation of **9a**. Nicewicz and coworker have previously reported a [2 + 2] cycloaddition in which a redox-mediator is employed as an additive to putatively accelerate the chain-propagation step and subsequently minimize such side reactions.[27] In a similar manner, we sought a redox-mediator. After screening of additives, diene **8** was found to suppress side reactions. When 5 mol% of $FeCl_3$ was used with 30 mol% of diene **8**, various substituted styrenes (**7a**–**7f**), which having electron-withdrawing and electron-donating groups on aromatics, gave the corresponding products in high yields (see **9a**–**9f**). Whereas there are only two examples of the use of α-substituted styrenes in photoredox-initiated [2 + 2] cycloaddition,[20a] α-substituted styrenes (see **9g** and **9h**) were also suitable substrates under our conditions. With respect to **3**, both a sterically-congested substituents and an allylic ether group on the olefin were well tolerated (see **9i**–**9k**). As above, in some cases (**9e**, **9g**, **9h** and **9k**), $Fe(OTf)_3$ was more effective than $FeCl_3$.[23] To our delight, unprecedented electron-deficient **3** could be also used when $Fe(OTf)_3$ was employed. For examples, the corresponding products (**9l**–**9o**) were obtained in high yield with high diastereoselectivity when α,β-unsaturated ketones with various styrenes were used. The major diastereomer of **9n** was unambiguously analyzed by X-ray crystallography. It is worth noting that α-methyl substituted styrene also provided the corresponding **9o** in 56% yield with high diastereoselectivity. Moreover, α,β-unsaturated esters could be well tolerated without a decrease in yield (see **9p**). In summary, iron(III) salt-initiated [2 + 2] cycloaddition exhibits high reactivity with a broad substrate scope of both electron-rich and electron-deficient alkenes.

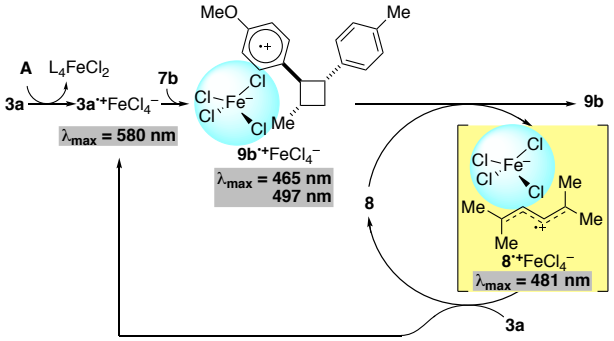
Table 2. Scope of Radical Cation-induced [2 + 2] Cycloaddition.[a]



[a]The reaction was carried out with $FeCl_3$ (5 mol %), **3** (1 equiv) and **7** (2–6 equiv) in MeCN at 0 ºC. [b]In the absence of **8**. [c]The yield was determined by ^1H NMR analysis using 1,3-dinitrobenzene as an internal standard. [d]Using $Fe(OTf)_3$ (5 mol%) instead of $FeCl_3$. [e]The reaction was carried out at room temperature. [f]The reaction was carried out at –20 ºC. [g]Using $Fe(OTf)_3$ (10 mol%) instead of $FeCl_3$. [h]Using **8** (10 mol%).

To elucidate the role of **8** in [2 + 2] cycloaddition, UV-vis analyses were conducted (Figure S9 and S10). Upon UV-vis monitoring of the reaction of $\mathbf{9b}^{\bullet+}$ with **8** (Figure S9), we observed the reduction of $\mathbf{9b}^{\bullet+}$ (λ_{max} = 465 nm, 497 nm) to give **9b** with concomitant formation of a new feature assigned to $\mathbf{8}^{\bullet+}$ (λ_{max} = 481 nm)[28]. Moreover, UV-vis observation of the reaction between $\mathbf{8}^{\bullet+}$ and **3a** showed the generation of $\mathbf{3a}^{\bullet+}$ (λ_{max} = 580 nm) along with **8** (Figure S10). These results suggest that **8** serves to promote the reduction of $\mathbf{9b}^{\bullet+}$ and the subsequent oxidation of **3a** as a redox-mediator. The summarized mechanistic proposal is shown in Scheme 4. After the generation of $\mathbf{3a}^{\bullet+}FeCl_4^-$ by $FeCl_3$, [2 + 2] cycloaddition of $\mathbf{3a}^{\bullet+}FeCl_4^-$ with **7b** affords $\mathbf{9b}^{\bullet+}FeCl_4^-$. The reduction of $\mathbf{9b}^{\bullet+}FeCl_4^-$ by **8** gives **9b** along with $\mathbf{8}^{\bullet+}FeCl_4^-$. Subsequent oxidation of **3a** by $\mathbf{8}^{\bullet+}FeCl_4^-$ regenerates $\mathbf{3a}^{\bullet+}FeCl_4^-$ and **8**. As a result of accelerating the chain propagation step, side reactions might be suppressed (Figure S11).

Scheme 4. A Plausible Role of 8.



In conclusion, the aromatic radical cation generated by $FeCl_3$ has been isolated and characterized for the first time. Moreover, by virtue of the generation of the radical cation–$FeCl_4^-$ as an ion pair, radical cation-induced [4 + 2] cycloaddition and [2 + 2] cycloaddition were developed, with the latter leveraging a novel diene redox-mediator as a co-catalyst. In addition to delivering a mild, inexpensive, straightforward, and easily scalable method for radical cation-induced cycloaddition chemistry, these results shed new light on iron(III)-promoted single-electron chemistry writ large.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.XXXXX.

Experimental procedure, characterization data, copies of ^1H NMR and ^{13}C NMR spectra of all new compounds (PDF)
X-ray data for **2** and **9n** (CIF)

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Notes

The authors declare no competing financial interest.

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(14) Dissociation of chloride from **A** is another possible rate-limiting step. To exclude this possibility, we conducted control experiments in the presence of chloride scavengers (see Table S1 in Supporting Information). However, chloride dissociation was not observed in these reactions. Therefore, dissociation of chloride and the generation of $FeCl^{2+}$ are less likely.

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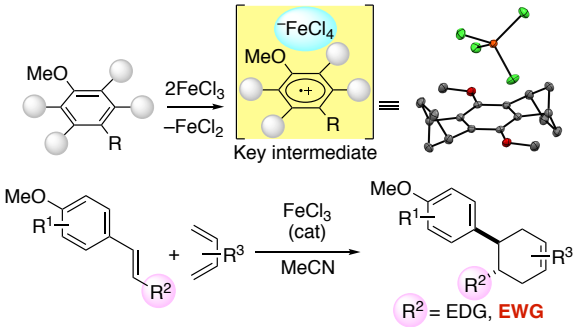
MeO
R
2FeCl3
–FeCl2
FeCl4
MeO
R
Key intermediate

MeO
R1
R2
+
R3
FeCl3
(cat)
MeCN
MeO
R1
R3
R2
R2 = EDG, EWG