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

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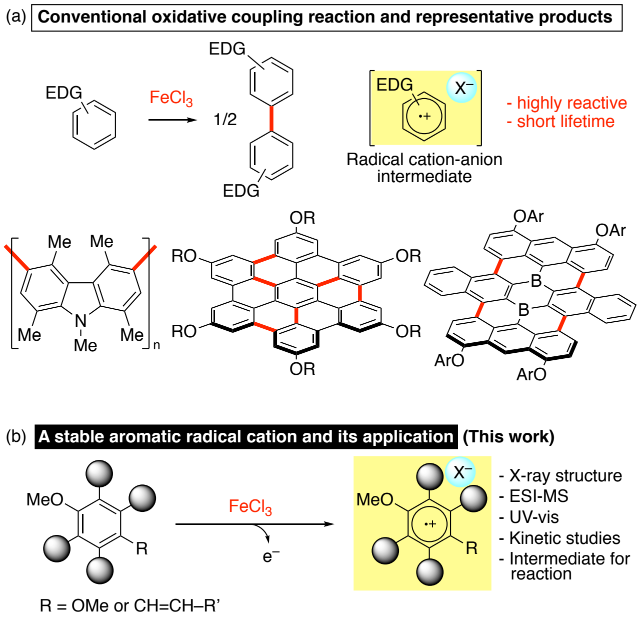
Supporting Information Placeholder

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 $1^{\bullet+}$ (Figure 1b). Additionally, $1^{\bullet+}$ 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 unchanged 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.

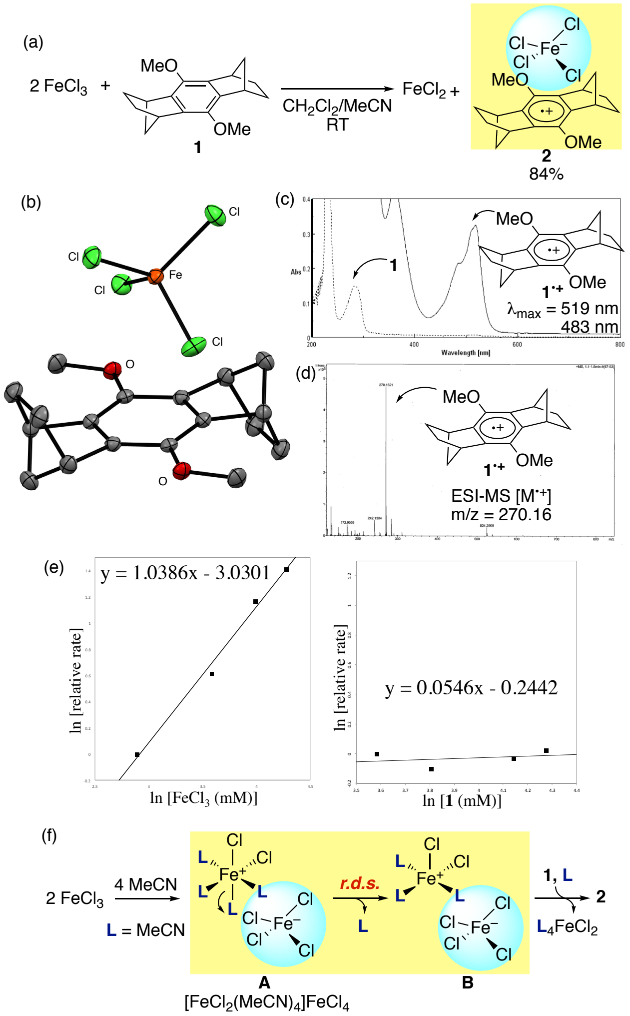
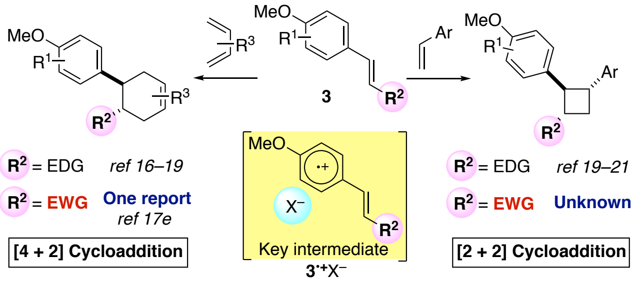


Figure 1. (a) The generation of radical cation **2** by FeCl$_3$. (b) Thermal-ellipsoid representation of **2** at the 50% probability level. Hydrogens have been omitted for clarity. (c) UV-vis spectrum of **2**. (d) ESI-MS spectrum for **2**. (e) Kinetic studies for FeCl$_3$ and **1**. (f) The proposed mechanism for the generation of **2**.

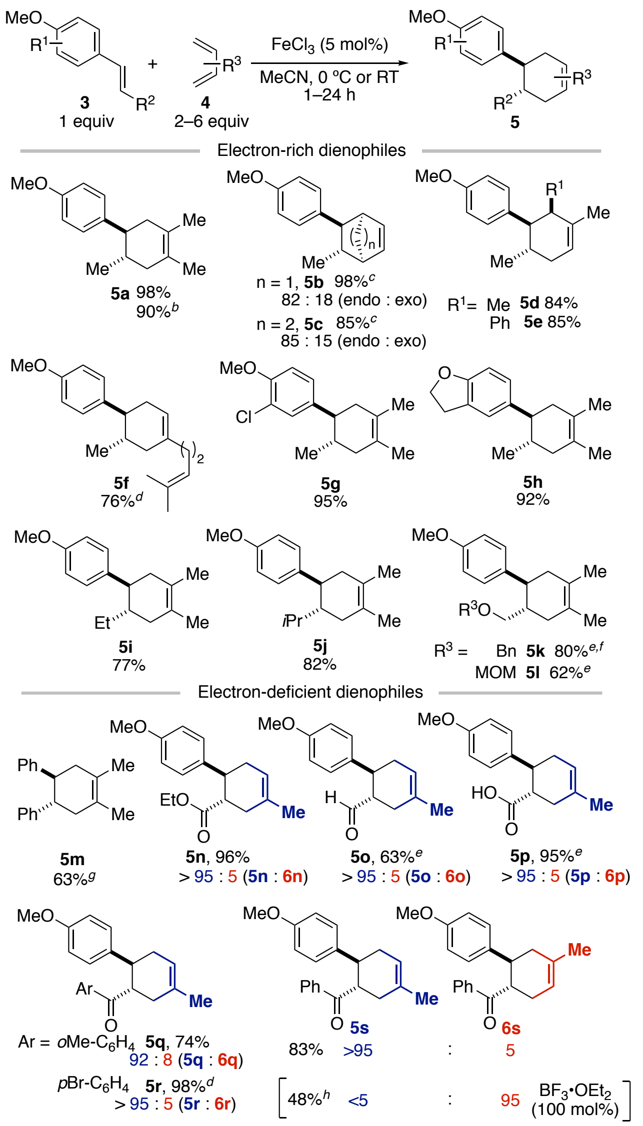
With the oxidant **B** identified, we applied FeCl$_3$-promoted oxidation for a radical cation-induced cycloaddition. We were intrigued by [4 + 2] cycloaddition and [2 + 2] cycloaddition of *trans*-anethole **3** (Scheme 2). The key intermediate is $\mathbf{3}^{\bullet+}$, which undergoes [4 + 2] cycloaddition 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.

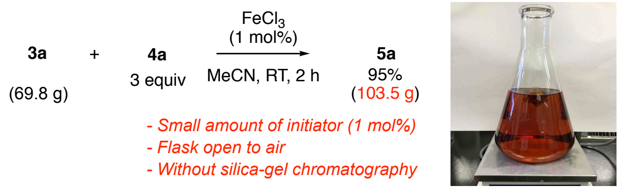
Table 1. Scope of Radical Cation-induced [4 + 2] Cycloaddition.[a]



[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.

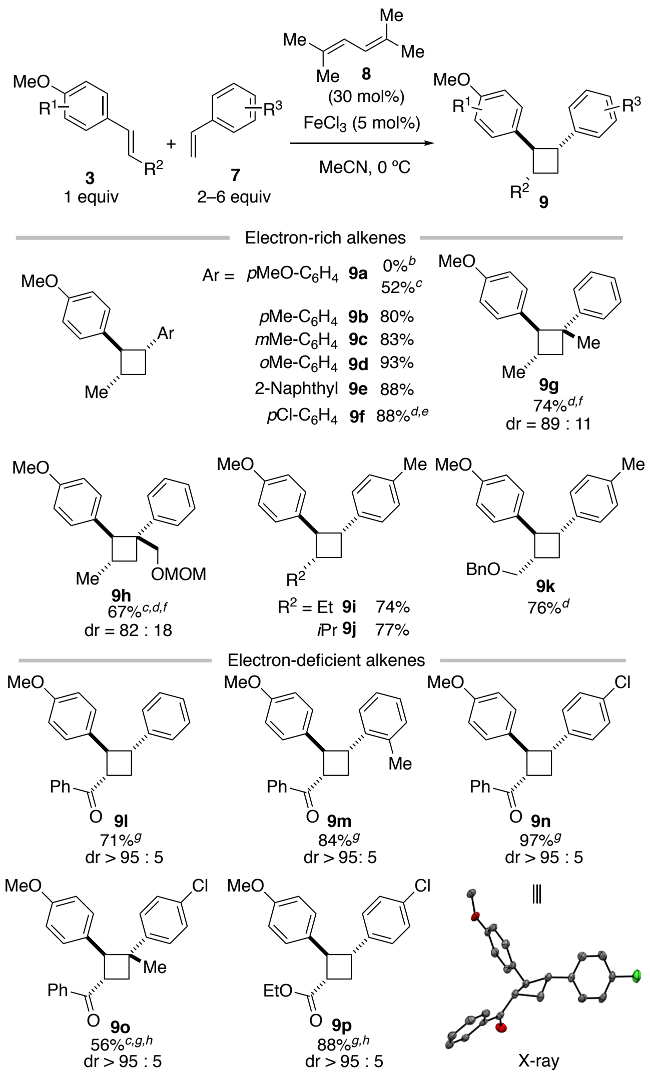
Scheme 3. 100-gram Scale Reaction.



- Small amount of initiator (1 mol%)
- Flask open to air
- Without silica-gel chromatography

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.

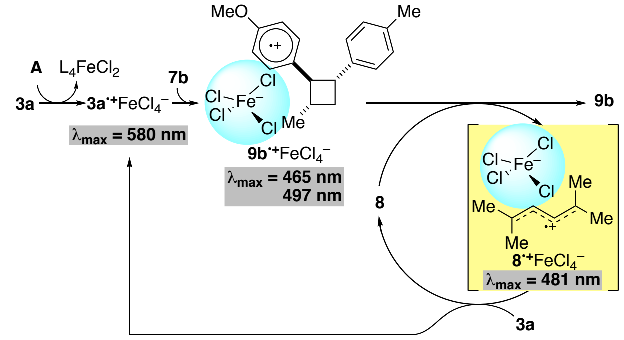
Table 2. Scope of Radical Cation-induced [2 + 2] Cycloaddition.[a]



[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 **9b**$^{•+}$ with **8** (Figure S9), we observed the reduction of **9b**$^{•+}$ (λ_{max} = 465 nm, 497 nm) to give **9b** with concomitant formation of a new feature assigned to **8**$^{•+}$ (λ_{max} = 481 nm)[28]. Moreover, UV-vis observation of the reaction between **8**$^{•+}$ and **3a** showed the generation of **3a**$^{•+}$ (λ_{max} = 580 nm) along with **8** (Figure S10). These results suggest that **8** serves to promote the reduction of **9b**$^{•+}$ and the subsequent oxidation of **3a** as a redox-mediator. The summarized mechanistic proposal is shown in Scheme 4. After the generation of **3a**$^{•+}FeCl_4^-$ by $FeCl_3$, [2 + 2] cycloaddition of **3a**$^{•+}FeCl_4^-$ with **7b** affords **9b**$^{•+}FeCl_4^-$. The reduction of **9b**$^{•+}FeCl_4^-$ by **8** gives **9b** along with **8**$^{•+}FeCl_4^-$. Subsequent oxidation of **3a** by **8**$^{•+}FeCl_4^-$ regenerates **3a**$^{•+}FeCl_4^-$ 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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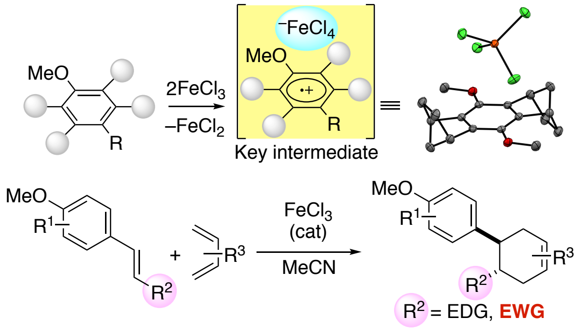
MeO
R
2FeCl3
–FeCl2
−FeCl4
MeO
•+
R
Key intermediate
MeO
R1
R2
+
R3
FeCl3
(cat)
MeCN
MeO
R1
R3
R2
R2 = EDG, EWG