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FULL PAPER

Unprecedented Asymmetric Epoxidation of Isolated Carbon–Carbon Double Bonds by a Chiral Fluorous Fe(III) Salen Complex: Exploiting Fluorophilic Effect for Catalyst Design

Yuki Kobayashi,[a] Riho Obayashi,[a] Yuki Watanabe,[a] Hiroki Miyazaki,[a] Issei Miyata,[a] Yuta Suzuki,[a] Yukihiro Yoshida,[b] Takayuki Shioiri,[a] and Masato Matsugi*[a]

Dedicate to Prof. Masatomo Nojima on the occasion of his 77th birthday.

Abstract: The first asymmetric epoxidation of isolated carbon–carbon double bonds by a chiral salen complex using ubiquitous Fe(III) as a center-metal is described. By simultaneously introducing fluorous tags and ^{t}butyl groups into the ligand of the salen complex, asymmetric epoxidation is achieved. The fluorous tags act as both the electron-withdrawing groups to improve the catalytic activity for oxidation and the driving force to form a unique asymmetric stereo environment. Crystallographic analysis of the complex revealed that the catalyst has a distinctive umbrella structure based on intramolecular fluorophilic effect. This is the first example of asymmetric catalytic space construction that exploits fluorous space-interaction of neighboring fluorous tags.

Introduction

Optically pure chiral salen complexes[1] are known as effective asymmetric epoxidation catalysts for isolated carbon–carbon double bonds that do not have coordinating functional groups at adjacent positions. This field has been primarily developed through the excellent pioneering studies conducted by Jacobsen et al.[2] and Katsuki et al.,[3] and has since been extended to other useful asymmetric reactions. Several interesting salen catalysts, including a reusable complex, and related reactions have been reported.[4] However, Mn, Ru, or V are generally required as the metal center of the salen complex to achieve high reactivity in asymmetric epoxidation.[5] In this study, we report the first asymmetric epoxidation of isolated double bonds using a fluorous Fe(III) salen complex as the catalyst. This catalyst has several interesting characteristics owing to the electron-withdrawing nature and fluorophilicity[6] of the fluorous tags. We also demonstrate that immobilization by fluorous stacking between neighboring fluorous tags endows the catalyst with an unusual strained asymmetric structure.

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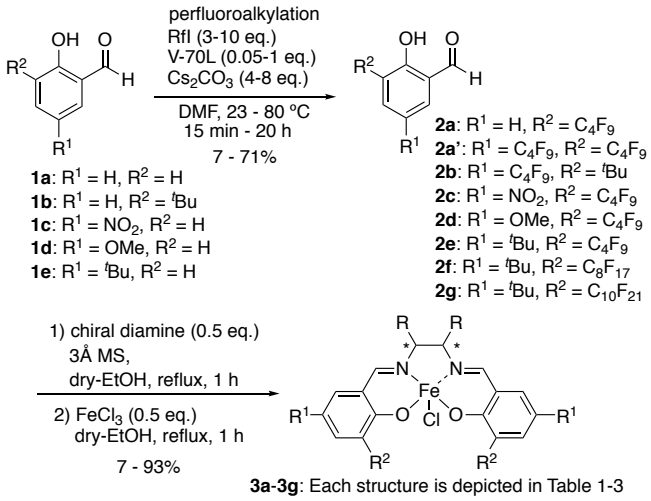
Iron is a ubiquitous metal and is non-toxic to humans. Therefore, the use of the iron in catalysts is preferable in terms of sustainability and safety.[7] Further, various chiral iron catalysts for asymmetric synthesis have been known,[8] and asymmetric oxidations using various P450-mimic iron complexes and various other complexes have been reported to date.[9] However, to the best of our knowledge, the asymmetric epoxidation of isolated double bonds using optically pure chiral salen complexes containing iron has not been reported. This is most likely because epoxidation of isolated double bonds using iron salen complexes[10] is difficult due to the low oxidation activity of iron. The introduction of plural electron-withdrawing groups to the achiral iron salen ligands has been reported as an effective means of increasing the oxidation activity of the catalyst in terms of the oxidation–reduction potential in aerobic oxidation systems. However, the reactions reported were not asymmetric epoxidations.[11] The only successful example of an asymmetric oxidation using a chiral and optically pure iron salen complex is the oxidation of prochiral sulfur,[12] which is more easily oxidized than carbon–carbon double bonds.

Herein, we report the first asymmetric epoxidation of isolated double bonds using a fluorous Fe(III) salen complex as the catalyst. This catalyst has several interesting characteristics owing to the electron-withdrawing nature and fluorophilicity of the fluorous tags. We also demonstrate that immobilization by fluorous stacking between neighboring fluorous tags endows the catalyst with an unusual strained asymmetric structure.

Results and Discussion

Through our previous study, we know that the introduction of fluorous tags to the 3' and 5' position on Jacobsen-type Mn(III) salen ligands increases the oxidation activity of the catalyst for isolated double bonds.[13] Therefore, we attempted to activate Fe(III) salen complexes by introducing fluorous tags onto the ligands.[14]

The novel fluorous Fe(III) salen complexes (**3a**–**3g)**, which have fluorous tags on the 3,3' positions, were prepared *via* ligand exchange of $FeCl_3$, with each fluorous salen ligand as shown in Scheme 1. These fluorous salen ligands were prepared from salicylaldehyde derivatives (**1a**–**1e**) *via* a perfluoroalkylation protocol that we have previously reported.[15] For comparison, we also synthesized a non-fluorous-iron salen complex (**3h**) bearing an n-butyl chain on the 3,3' position instead of a perfluoroalkyl chain and compound **3i** bearing ^{t}butyl groups on the 3,3' position.



Scheme 1. Synthesis of fluorous Fe(III) salen complexes.

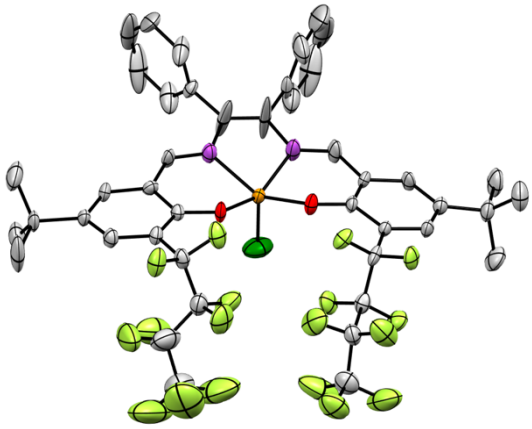


Figure 1. ORTEP representation of the molecular structure of the fluorous Fe(III) salen complex **3e** (grey: C, green: Cl, lime green: F, orange: Fe, purple: N, red: O). Hydrogen atoms are omitted for clarity.

Molecular structures of the representative fluorous salen Fe(III) complex **3e**, determined by X-ray diffraction measurements at 100 K, are shown in Figures 1 and 2.[16] This complex has a unique crystal structure in which intramolecular stacking of the fluorous tags (C_4F_9 groups) occurs. The shortest distance between fluorine atoms on the tags is 2.91 Å, which is shorter than the sum of the *van der* Waals radii (2.94 Å).[17] It should be noted that an eclipse conformation is adopted by the asymmetric source moiety (1,2-diphenylethylenediamine), forming an umbrella conformation that was hitherto unknown in salen complex chemistry. Although salen complexes have been known to exhibit C_2 symmetrical stepped conformations[4a] with the asymmetric sources in the gauche form, our fluorous salen complex is quite different from the usual salen complex. The asymmetric environment is transmitted from the asymmetric source to the terminal fluorous tags along the salen skeleton, such as a neuronal network, and the complex itself exhibits asymmetric distortion (Figure 2). There are some reports that perfluoroalkyl chains interact with each other *via* fluorophilic effect through space.[18] However, the use of this interaction for the conformational design of catalysts has not been reported to date.

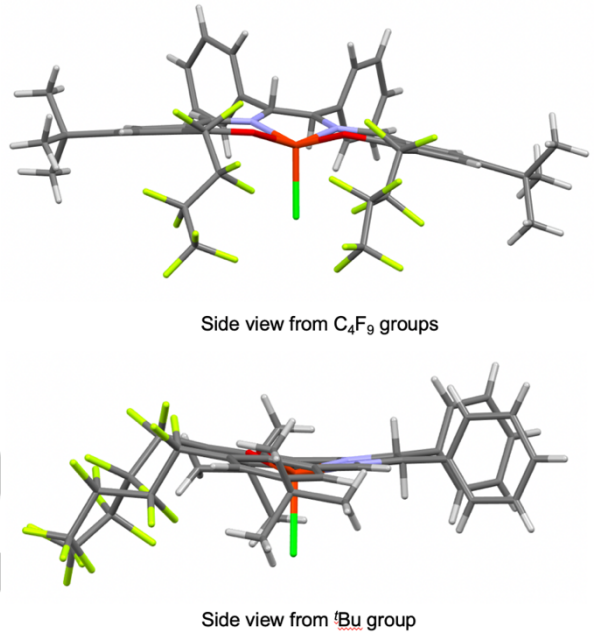


Figure 2. Molecular structure of the fluorous Fe(III) salen complex **3e**, determined by X-ray structural analysis.

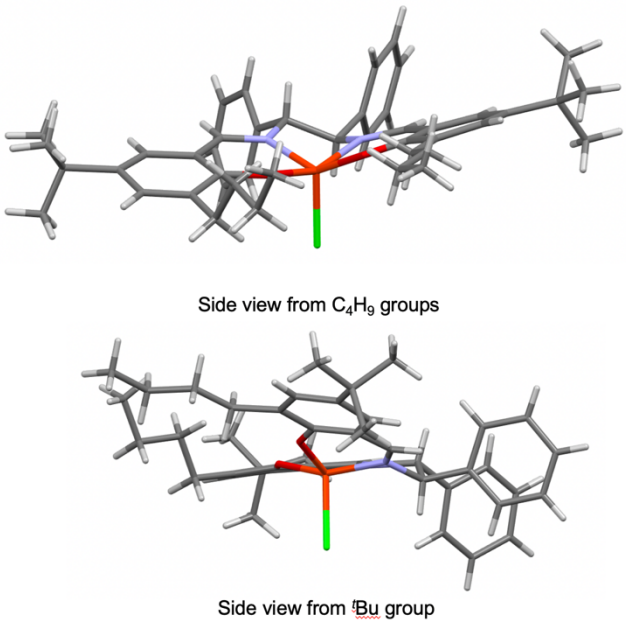
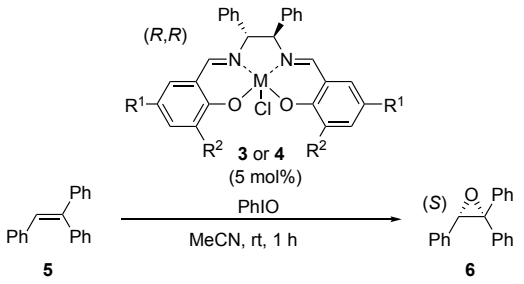


Figure 3. Molecular structure of the non-fluorous Fe(III) salen complex **3h** determined by X-ray structural analysis. Only one orientation of each disordered *n*butyl group is shown.

Figure 3 shows the X-ray structure of the non-fluorous version of the Fe(III) salen complex (**3h**).[19] In this case, the C_4H_9 groups do not stack, rather, they adopt the usual C_2 symmetrical stepped conformation[4a] with asymmetric sources adopting the gauche form. This demonstrates that the fluorophilicity between the adjacent fluorous tags changes the asymmetric spatial structure of the complex, leading to the possibility of imparting reactivities and stereoselectivities that are different from those of typical salen catalysts.

Table 1. Asymmetric epoxidation of triphenylethylene **5** using Fe(III) salen complexes.



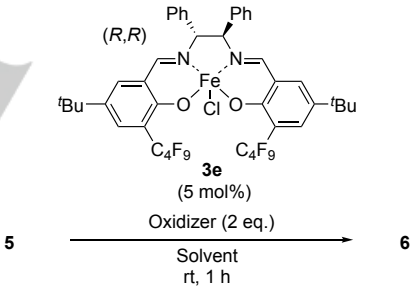
Entry	Cat.	M	R^1	R^2	Conv.(%)[a]	*Ee*(%)[b]
1	**4**	Mn	^{t}Bu	^{t}Bu	100	73
2	**3i**	Fe	^{t}Bu	^{t}Bu	no reaction	-
3	**3a'**	Fe	C_4F_9	C_4F_9	trace	-
4	**3c**	Fe	NO_2	C_4F_9	no reaction	-
5	**3e**	Fe	^{t}Bu	C_4F_9	63	80
6	**3h**	Fe	^{t}Bu	C_4H_9	10	42
7	**3f**	Fe	^{t}Bu	C_8F_{17}	56	81
8	**3g**	Fe	^{t}Bu	$C_{10}F_{21}$	33	71
9	**3b**	Fe	C_4F_9	^{t}Bu	16	45
10	**3a**	Fe	C_4F_9	H	26	62
11	**3d**	Fe	OMe	C_4F_9	46	34
12	**3j**	Fe	H	H	29	24

[a] Determined via ^{1}H NMR. [b] Determined *via* HPLC (DAICEL chiral column, OD-3, hexane: ^{i}PrOH = 9:1, flow rate 0.4 mL/min).

The epoxidation of triphenylethylene in acetonitrile in the presence of iodosobenzene was conducted as a model reaction to confirm the suitability of the catalyst for the epoxidation of isolated double bonds (Table 1). Epoxidation using the Jacobsen-type[1b] Mn(III) salen complex **4**, performed as a control experiment, afforded the corresponding epoxide in 100% conversion with 73% *ee* (Entry 1). When the corresponding Fe(III) version of the same complex was used, the reaction did not proceed at all (Entry 2). No effective epoxidation occurred, even when we introduced electron-withdrawing groups to both the 3' and 5' positions on the Fe(III) salen skeleton to improve the redox potential of Fe (Entries 3 and 4). Surprisingly, the reaction proceeded successfully with moderate yield and selectivity (63% conversion, 80% *ee*) when the Fe(III) complex with one fluorous tag on the 3' position and a ^{t}butyl group on the 5' position was used (Entry 5). Furthermore, the reaction proceeded quantitatively with the same stereoselectivity upon extending the reaction time to 3 h. Notably, the stereoselectivity here is slightly higher than that achieved with the known Mn(III) complex **4** under these conditions.

The epoxidation also progressed using the non-fluorous catalyst **3h**, which bears an ^{n}butyl group on the 3' position instead of a ^{t}butyl group (Entry 6). However, a drastic decrease in reactivity and selectivity was observed in this case (Entry 6). The use of catalysts with longer fluorous tags (**3f**, **3g**) had a slight influence on reactivity and enantioselectivity, with the reactivity decreasing with increasing chain length (Entries 7 and 8). The reaction was observed to progress when complexes bearing both an electron-withdrawing fluorous tag and an electron-donating ^{t}butyl group on the 3' and 5' positions, respectively, were used. However, although the reaction also proceeded with other combinations of substituents (Entries 9–12), **3e** was found to be the superior catalyst in terms of reactivity and stereoselectivity.

Table 2. Influence of oxidizer and solvent for epoxidation of **5** using **3e**.

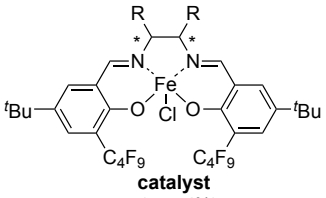


Entry	Solvent	Oxidizer	Conv.(%)[a]	*Ee*(%)[b]
1[c]	MeCN	PhIO	63	80
2	MeCN	TBHP	62	11
3	MeCN	mCPBA	92	17
4	MeCN	^{t}BuCHO/O_2	16	4
5	MeCN	NaOCl $5H_2O$	no reaction	-
6	MeCN	30% H_2O_2	no reaction	-
7	CH_2Cl_2	PhIO	77	75
8	$CHCl_3$	PhIO	69	60
9	THF	PhIO	9	29
10	$PhCF_3$	PhIO	48	54
11	HFIP	PhIO	no reaction	-

[a] Determined by ^{1}H NMR. [b] Determined *via* HPLC (DAICEL chiral column, OD-3, hexane: ^{i}PrOH = 9 :1, flow rate 0.4 mL/min). [c] Same data as Entry 5 of Table 1.

Next, we identified a suitable oxidant for epoxidation using the Fe(III) salen complex **3e** (Table 2). We found that iodosobenzene was the most suitable oxidant in acetonitrile (Entry 1). Although the reaction proceeded when a hydroperoxide (*t*butyl hydroperoxide: TBHP) or peracid (mCPBA) was used, lower stereoselectivity was observed in each case (Entries 2 and 3). Although the reaction also proceeded under aerobic oxidation conditions in the presence of pivalaldehyde,[20] the stereoselectivity was extremely low (Entry 4). The use of sodium hypochlorite pentahydrate or hydrogen peroxide as the oxidizing agent was found to be unsuitable in terms of reactivity (Entries 5 and 6). We concluded that non-halogenated acetonitrile is the most suitable of the assayed solvents (Entries 7–11).

Table 3. Influence of the asymmetric source in the epoxidation of **5**.



catalyst (5 mol%)

5 → PhIO (2 eq.), MeCN, rt, 1 h → (*S*)-**6** or (*R*)-**6**

Entry	Cat.	R	Conv.(%)[a]	*Ee*(%)[b]	Config.
1	**3e**	(*R,R*)-Ph	63	80	*S*
2	**3k**	(*R,R*)-$(CH_2)_4$-	26	82	*S*
3	**3l**	(*S,S*)-1-naphthyl	71	68	*R*
4	**3m**	(*S,S*)-3,5-dimethylphenyl	63	78	*R*
5	**3n**	(*S,S*)-2,4,6-trimethylphenyl	55	46	*R*
6	**3o**	(*S,S*)-2,4,6-trimethoxyphenyl	95	82	*R*
7	**3p**	(*S,S*)-4-methoxyphenyl	41	86	*R*
8	**3q**	(*S,S*)-4-nitrophenyl	85	75	*R*
9	**3r**	(*S,S*)-4-fluorophenyl	65	81	*R*
10	**3s**	(*S,S*)-4-dimethylaminophenyl	90	21	*R*
11	**3t**	(*S,S*)-2-chlorophenyl	44	70	*R*
12	**3u**	(*S,S*)-2-hydroxyphenyl	94	39	*R*
13	**3v**	(*R*)-propane-1,2-diamine	80	7	*S*
14	**3w**	(*S*)-2,3-diaminopropanoic acid	96	51	*R*
15	**3x**	(*S*)-1,1'-binaphtyl-2,2'-diamine	No reaction	-	-

[a] Determined via ^{1}H NMR. [b] Determined *via* HPLC (DAICEL chiral column, OD-3, hexane: ^{i}PrOH = 9:1, flow rate 0.4 mL/min).

Then, we investigated the effect of other ligands upon stereoselectivity using various Fe(III) salen complexes bearing a different commercially available chiral diamine moiety as the asymmetric source (Table 3). The structure of the asymmetric source affected not only stereoselectivity but also oxidation activity. Although the Fe(III) complex derived from 1,2-bis(4-methoxyphenyl)ethane-1,2-diamine exhibited the highest stereoselectivity of these complexes, the catalytic activity for the epoxidation was only moderate (Entry 7). Thus, we concluded that catalyst **3o** derived from 1,2-bis(2,4,6-trimethoxyphenyl)ethane-1,2-diamine presents the optimal balance of both oxidation activity and stereoselectivity in these catalysts (Entry 6). However, little difference in stereoselectivity between **3e** and **3o** was observed; furthermore, the asymmetric source in **3e** is significantly less expensive than that in **3o**. Therefore, catalyst **3e** is the most suitable Fe(III) salen complex in terms of practicality and cost among the catalysts prepared in the current study.

Table 4. Asymmetric epoxidations using the Fe(III) salen complex **3e**.

Substrate → **3e** (5 mol%), PhIO (2 eq.), MeCN, rt → Epoxide

Entry	Substrate	Time (h)	Conv. (%)[a]	*Ee* (%)[b]
1	triphenylethylene (**5**)	3	100	80
2	*trans-stilbene (**7**)*	12	58	36
3[c]	(*Z*)-β-methylstyrene (**8**)	4	100	66[d]
4	(*E*)-β-methylstyrene (**9**)	12	32	36[e]
5	α-methylstyrene (**10**)	12	83	48[f]
6	1-phenylcyclohexene (**11**)	12	100	55[e]
7	1-(4-methoxyphenyl)-2,2-diphenylethene (**12**)	3	100	60[g]
8	(*E*)-1-fluoro-4-styrylbenzene (**13**)	12	56	38

[a] Determined via ^{1}H NMR. [b] Determined *via* HPLC (DAICEL chiral column, OD-3, hexane: ^{i}PrOH = 9:1, flow rate 0.4 mL/min). [c] PhIO of 4 equiv. was used. [d] Determined via HPLC (DAICEL chiral column, OD-3, hexane, flow rate 0.4 mL/min). [e] Determined via HPLC (DAICEL chiral column, OD-3, hexane, flow rate 0.5 mL/min). [f] Determined via GC (Agilent Cyclodex-β, oven temp. 75 °C, hexane, carrier gas: He). [g] Determined via HPLC (DAICEL chiral column, OD-3, hexane: ^{i}PrOH = 99:1, flow rate 0.4 mL/min).

Next, the substrate scope of the protocol using **3e** was investigated (Table 4). We identified an interesting characteristic of this epoxidation protocol: the oxidation of *trans*-olefins is more effective than that of *cis*-olefins in terms of stereoselectivity. This observation is significant because currently known salen Mn(III) complexes are typically more effective for *cis*-olefins.[5c] For example, when the epoxidation of substrate **7** is conducted using

a Mn(III) complex **4** under PhIO conditions, the obtained enantiomeric excess is 1% *ee*.[13] However, the fluorous Fe(III) version exhibited a stereoselectivity that exceeds 36% *ee* under the same conditions (Entry 2).[21] In the comparison between the (*Z*) and the (*E*)-methylstyrene, the (*Z*)-form exhibited higher stereoselectivity. However, the selectivity did not disappear in the (*E*)-form unlike the known Mn salen complex (Entry 3 *vs.* 4). Although the use of electron rich olefins as the substrate tended to provide higher reactivity, the tendency was hard to declare with respect to the enantioselectivity (Entries 5-8).

To investigate whether the reaction proceeds *via* radical species or a concerted mechanism, a radical clock experiment[22] using cyclopropane compound **14**[23] and catalyst **3e** was conducted (Figure 4). This experiment revealed that the reaction proceeds *via* a radical mechanism if the cyclopropane-ring-opened product **18** is obtained. In our experiment, no cyclopropane-ring-opened product was observed. Therefore, we conclude that this reaction does not proceed via radical species. It is most likely that the epoxidation proceeds through a concerted mechanism or a cation-intermediate process[24] in the umbrella-type asymmetric space of the active hypervalent iodine Fe(III) complex, which remains in trivalent state, as shown in Figure 5. A similar hypervalent iodide Mn(III) salen complex was isolated by Fujii *et al*. in their pioneering work.[25] During oxidizing reagent screening (Table 2), aerobic oxidation conditions afforded a dramatically lower stereoselectivity than hypervalent iodine conditions (Entry 4 *vs.* Entry 1). This result suggests that the active species of the catalyst is not an oxo-Fe-type complex.

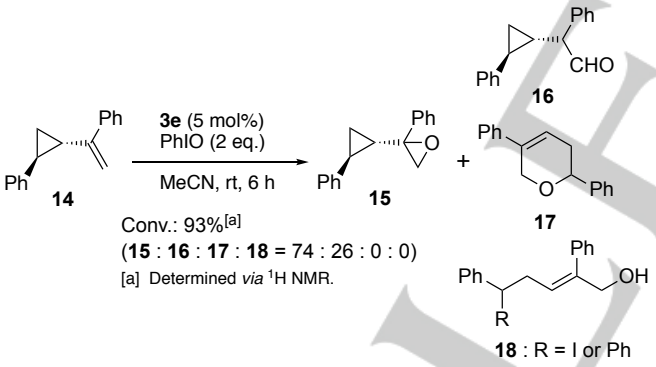


Figure 4. Radical clock experiment.[23]

Conclusions

In summary, we have achieved the first asymmetric epoxidation of isolated double bonds using a fluorous Fe(III) salen complex. This complex has an uncommon umbrella structure owing to intramolecular fluorous through-space interactions, resulting in different epoxidation characteristics and preferable substrates to those of the corresponding Mn(III) complexes. We believe that the formation of airspace utilizing the intramolecular fluorophilic effect between fluorous tags on the ligands is an effective strategy for the designing of unique catalyst reaction spaces, and may be extended to the design of novel catalysts for other reactions.

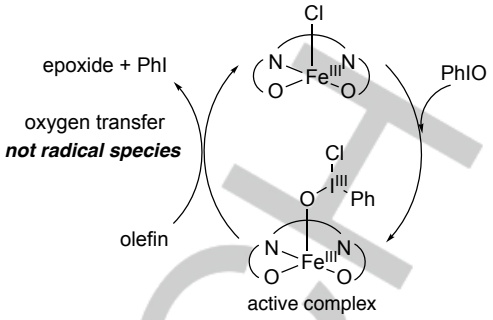


Figure 5. A plausible catalytic cycle for the current epoxidation.

Experimental Section

General Information: All the laboratory chemicals were purchased from Tokyo Chemical Industry Co., Ltd., Wako Pure Chemical Industries, Ltd., Sigma-Aldrich Co. LLC, and Kanto Chemical Co., Inc. used without further purification unless otherwise stated. Solvents were removed by rotary evaporation under reduced pressure using a 40-50 ºC water bath. Non-volatile compounds were dried in vacuo at 0.01 mbar. All reactions were stirred magnetically and reaction was monitored by thin layer chromatography (TLC) using silica gel plates. Purification by chromatography was performed on silica gel 60 N (spherical, neutral, 63–210 µm, Kanto Chemical Co., Inc.). Melting points were determined in open-ended capillaries using a Bibby Scientific Ltd. Stuart® SMP-30 instrument and are uncorrected. All nuclear magnetic resonance (NMR) spectra were recorded with JEOL JNM-EX270 (^{1}H: 270 MHz, ^{13}C: 67.8 MHz) and JEOL ECA-500 (^{13}C: 124.5 MHz, ^{19}F: 466 MHz) spectrometers. Chemical shifts (δ) are given in units of ppm, and coupling constants (*J*) are given in Hz. Abbreviations for multiplicity are as follows: *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *m* (multiplet), *br* (broad). High-performance liquid Chromatography (HPLC) analyses were performed by Daicel OD-3 columns with UV Detector L2400. GC analysis was performed on a GC-4000 Plus with Agilent Cyclodex-ß columns. High-resolution mass spectra (HRMS) was performed by FAB (JEOL JMS HX-110) using a magnetic sector analyzer. The spectra were calibrated with PEG 200, PEG 400, PEG 600 and Ultramark 1621® prior to data acquisition.

Typical procedure for epoxidation of olefin: To a solution of olefin in MeCN (0.9 mL) were added catalyst (0.05 eq.) and PhIO (2 eq.). The reaction mixture was then stirred at room temperature for 1-12 h. The reaction mixture was quenched with aq. sodium sulfite. After the addition of ethyl acetate, the organic phase was separated, dried over Na_2SO_4, filtered, and evaporated. Conversion was evaluated from the ^{1}H NMR spectra by integration of olefin and epoxide signals. Enantiomeric excesses (*ee*) of each epoxide was determined *via* HPLC.

2,2,3-Triphenyloxirane (6)[13] : Conv. 100%, 80% *ee* [The *ee* was determined by HPLC analysis (DAICEL CHIRALCEL OD-3 column; hexane/^{i}PrOH = 9 : 1, flow rate 0.4 mL min, t_R = 7.05 min (major), t_R = 12.29 min (minor)]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.33 (s, 1 H), 7.02–7.39 (m, 15 H).

2,3-Diphenyloxirane (epoxide of **7)**[13] **:** Conv. 58%, 36% *ee* [The *ee* was determined by HPLC analysis (DAICEL CHIRALCEL OD-3 column; hexane/^{i}PrOH = 9 : 1, flow rate 0.4 mL min, t_R = 10.09 min (major), t_R =

16.03 min (minor)]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.87 (s, 2 H), 7.34–7.39 (m, 10 H).

(*Z*)-2-Methyl-3-phenyloxirane (epoxide of **8)**[26] **:** Conv. 100%, 66% *ee* [The *ee* was determined by HPLC analysis (DAICEL CHIRALCEL OD-3 column; hexane, flow rate 0.4 mL min, t_R = 10.04 min (major), t_R = 11.38 min (minor)]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.09 (d, *J* = 5.94 Hz, 3 H), 3.31-3.38 (m, 1 H), 4.07 (d, *J* = 4.59 Hz, 1 H), 7.29–7.38 (m, 5 H).

(*E*)-2-Methyl-3-phenyloxirane (epoxide of **9)**[27] **:** Conv. 32%, 36% *ee* [The *ee* was determined by HPLC analysis (DAICEL CHIRALCEL OD-3 column; hexane, flow rate 0.5 mL min, t_R = 41.34 min (major), t_R = 45.79 min (minor)]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.09 (d, *J* = 5.94 Hz, 3 H), 3.31-3.38 (m, 1 H), 4.07 (d, *J* = 4.59 Hz, 1 H), 7.29–7.38 (m, 5 H).

2-Methyl-2-phenyloxirane (epoxide of **10)**[27] **:** Conv. 83%, 48% *ee* [The *ee* was determined by GC analysis (Agilent Cyclodex-ß, oven temp. 75 °C, carrier gas; He), t_R = 12.08 min (major), t_R = 12.86 min (minor)]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.72 (s, 3 H), 2.81 (d, *J* = 5.13 Hz, 1 H), 2.98 (d, *J* = 5.40 Hz, 1 H), 7.20–7.39 (m, 5 H).

1-Phenylcyclohexene oxide (epoxide of **11)**[27] **:** Conv. 100%, 55% *ee* [The *ee* was determined by HPLC analysis (DAICEL CHIRALCEL OD-3 column; hexane, flow rate 0.5 mL min, t_R = 26.95 min (major), t_R = 31.65 min (minor)]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.44-1.68 (m, 4 H), 1.94 (s, 2 H), 2.09 (s, 1 H), 2.29 (s, 1 H), 3.08 (s, 1 H), 7.31–7.39 (m, 5 H).

3-(4-Methoxyphenyl)-2,2-diphenyloxirane (epoxide of **12)**[28] **:** Conv. 100%, 60% *ee* [The *ee* was determined by HPLC analysis (DAICEL CHIRALCEL OD-3 column; hexane/^{i}PrOH = 99 : 1, flow rate 0.4 mL min, t_R = 14.01 min (major), t_R = 21.02 min (minor)]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.73 (s, 3 H), 4.26 (s, 1 H), 6.68 (d, *J* = 8.64 Hz, 2 H), 6.93 (d, *J* = 8.64 Hz, 2 H), 7.26–7.35 (m, 10 H).

2-(4-Fluorophenyl)-3-phenyloxirane (epoxide of **13)**[29] **:** Conv. 56%, 38% *ee* [The *ee* was determined by HPLC analysis (DAICEL CHIRALCEL OD-3 column; hexane/^{i}PrOH = 9 : 1, flow rate 0.4 mL min, t_R = 9.79 min (major), t_R = 11.93 min (minor)]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.84 (dd, *J* = 1.62, 7.02 Hz, 2 H), 7.06–7.35 (m, 9 H).

Typical procedure for perfluoroalkylation of salicylaldehyde: To a suspension of salicylaldehyde and cesium carbonate (4-8 eq.) in DMF (10 mL) was added perfluorobutyl iodide (3-10 eq.). The mixture was stirred for 15 min - 20 h at 23 - 80 °C in oil bath. The mixture was quenched with 1 M aq. HCl. After the addition of diethyl ether, the organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel to give perfluoroalkylated compound.

2-Hydroxy-3-(perfluorobutyl)benzaldehyde (2a): (130.6 mg, 9%); yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$): δ 11.86 (s, 1 H), 9.96 (s, 1 H), 7.79 (t, *J* = 7.02 Hz, 1 H), 7.16 (t, *J* = 7.56 Hz, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 196.4, 160.8, 138.1, 136.4, 136.3, 121.4, 119.4, 117.0-120.7 (m, C_4F_9); ^{19}F NMR (466 MHz, $CDCl_3$): δ -80.8, -109.0, -122.1, -125.7; HRMS [FAB+] *m/z* calcd for $C_{11}H_6F_9O_2$: 341.0224, found: 341.0239.

2-Hydroxy-3,5-bis(perfluorobutyl)benzaldehyde (2a'): (34.0 mg, 20%); yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$): δ 12.21 (s, 1 H), 10.03 (s, 1 H), 8.03 (s, 1 H), 7.94 (s, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 195.6, 163.2, 136.6, 134.5, 134.4, 121.2, 120.5, 120.1-110.5 (m, C_4F_9); ^{19}F NMR (466 MHz, $CDCl_3$): δ -80.8, -109.4, -110.7, -122.1, -122.5, -125.4, -125.8; HRMS [FAB+] *m/z* calcd for $C_{15}H_5F_{18}O_2$: 559.0002, found: 559.0014.

3-(*tert*-Butyl)-2-hydroxy-5-(perfluorobutyl)benzaldehyde (2b): (156.6 mg, 7%); yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$): δ 12.14 (s, 1 H) , 9.94 (s, 1 H), 7.67 (s, 2 H), 1.44 (s, 9 H); ^{13}C NMR (124.5 MHz, $CDCl_3$): δ 195.6, 162.8, 138.9, 130.6, 130.0, 119.2, 118.8, 118.8-105.8 (m, C_4F_9), 34.2, 27.9; ^{19}F NMR (466 MHz, $CDCl_3$): δ -81.0, -110.3, -122.6, -125.5; HRMS [FAB+] *m/z* calcd for $C_{15}H_{14}F_9O_2$: 396.0772, found: 396.0781.

2-Hydroxy-5-nitro-3-(perfluorobutyl)benzaldehyde (2c): (23 mg, 20%); yellow solid; mp 96 ºC; ^{1}H NMR (270 MHz, $CDCl_3$): δ 12.47 (br, 1 H), 10.06 (s, 1 H), 8.76 (d, *J* = 2.7 Hz, 1 H), 8.68 (d, *J* = 2.7 Hz, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 195.3, 164.9, 139.9, 133.0, 131.5, 131.4, 120.5, 118.7-111.0 (m, C_4F_9); ^{19}F NMR (466 MHz, $CDCl_3$): δ -80.8, -109.2, -121.8, -125.7; HRMS [FAB+]: *m/z* calcd for $C_{11}H_5F_9NO_4$: 386.0075, found: 386.0045.

2-Hydroxy-5-methoxy-3-(perfluorobutyl)benzaldehyde (2d): (163.3 mg, 23%); yellow solid; mp 51 ºC; ^{1}H NMR (270 MHz, $CDCl_3$): δ 11.35 (s, 1 H), 9.91 (s, 1 H), 7.34 (d, *J* = 3.24 Hz, 1 H), 7.26 (d, *J* = 3.24 Hz, 1 H), 3.86 (s, 3 H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 195.9, 154.8, 152.0, 123.6, 123.5, 121.3, 121.0, 117.7-109.3 (m. C_4F_9), 56.2; ^{19}F NMR (466 MHz, $CDCl_3$): δ -80.8, -108.9, -122.1, -125.8; HRMS [FAB+]: *m/z* calcd for $C_{12}H_8F_9O_3$: 371.0330, found: 371.0332.

5-(*tert*-Butyl)-2-hydroxy-3-(perfluorobutyl)benzaldehyde (2e): (156.6 mg, 71%); yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$): δ 11.64 (s, 1 H), 9.95 (s, 1 H), 7.75 (q, *J* = 4.05 Hz, 2 H), 1.36 (s, 9 H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 196.6, 158.6, 142.6, 134.6, 133.7, 133.6, 121.0, 118.7-108.9 (m, C_4F_9), 34.3, 31.1; ^{19}F NMR (466 MHz, $CDCl_3$): δ -80.8, -108.9, -122.3, -125.8; HRMS [FAB+]: *m/z* calcd for $C_{15}H_{13}O_2F_9$: 397.0850, found: 397.0862.

5-(*tert*-Butyl)-2-hydroxy-3-(perfluorooctyl)benzaldehyde (2f): (182.0 mg, 57%); yellow solid; mp 48 ºC; ^{1}H NMR (270 MHz, $CDCl_3$): δ 11.65 (s, 1 H), 9.95 (s, 1 H), 7.75 (q, *J* = 4.59 Hz, 2 H), 1.36 (s, 9 H); ^{13}C NMR (124.5 MHz, $CDCl_3$): δ 196.7, 158.7, 142.7, 134.6, 133.8, 133.7, 121.1, 118.4-106.2 (m, C_4F_9), 34.4, 31.1; ^{19}F NMR (466 MHz, $CDCl_3$): δ -80.6, -108.7, -

121.3, -121.4, -121.6, -121.8, -122.5, -126.0; HRMS [FAB+]: *m/z* calcd for $C_{19}H_{14}O_2F_{17}$: 597.0722, found: 597.0730.

5-(*tert*-Butyl)-2-hydroxy-3-(perfluorodecyl)benzaldehyde (2g): (44.8 mg, 37%); yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$): δ 11.65 (s, 1 H), 9.95 (s, 1 H), 7.76 (q, *J* = 4.86 Hz, 1 H), 1.36 (s, 1 H); ^{13}C NMR (124.5 MHz, $CDCl_3$): δ 196.7, 158.7, 142.7, 134.6, 133.8, 133.7, 121.1, 118.4-106.2 (m, $C_{10}F_{21}$), 34.4, 31.1; ^{19}F NMR (466 MHz, $CDCl_3$); δ -80.6, -108.7, -121.3, -121.4 -121.6, -121.7, -122.5, -125.9; HRMS [FAB+]: *m/z* calcd for $C_{21}H_{14}O_2F_{21}$: 697.0658, found: 697.0637.

Preparation of 5-(*tert*-butyl)-3-butyl-2-(methoxymethoxy)benzaldehyde: Under N_2 atmosphere, a solution of 1-(*tert*-butyl)-4-(methoxymethoxy)benzene (100 mg, 0.5 mmol) in dry THF was cooled at 0 ºC in ice bath. ^{n}BuLi (1.6 M in hexane, 1.8 ml, 3.0 mmol) was slowly added to this solution. The reaction mixture was stirred for 15 min and then was stirred at room temperature for 15 min. To the reaction mixture was added butyl iodide (553.6 mg, 3 mmol) at 0 ºC. The mixture was stirred for 30 min. The excess of ^{n}BuLi was quenched with sat. NH_4Cl aq.. After the addition of diethyl ether, the organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated. Under N_2 atmosphere, the residue was dissolved in dry diethyl ether and cooled at 0 ºC in ice bath. To the reaction mixture were added TMEDA (348.6 mg, 3 mmol) and ^{n}BuLi (1.6 M in hexane, 1.8 ml, 3.0 mmol). The resulting mixture was stirred for 15 min at 0 ºC and then was stirred at room temperature for 15 min. To the reaction mixture was added dry DMF (220 mg, 3 mmol) at 0 ºC. The mixture was stirred for 30 min. The excess of ^{n}BuLi was quenched with sat. NH_4Cl aq.. After the addition of diethyl ether, the organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was dissolved in CH_2Cl_2 (1 ml) and cooled at 0 ºC in ice bath. To the reaction mixture was added TFA (1 ml). The resulting mixture was stirred for 1 h. The excess of TFA was quenched with sat. aq. $NaHCO_3$. After the addition of ethyl acetate, the organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 20 : 1) to afford 3-butyl-5-*tert*-butyl-2-hydroxybenzaldehyde. (40 mg, 34%, 3 steps); color less oil; ^{1}H NMR (270 MHz, $CDCl_3$): δ 11.11 (s, 1 H), 9.87 (s, 1 H), 7.43 (d, *J* =1.9 Hz, 1 H), 7.35 (d, *J* = 2.7 Hz, 1 H), 2.66 (t, *J* = 8.1 Hz, 2 H), 1.66-1.54 (m, 2 H), 1.41 (q, *J* = 7.83 Hz, 2 H), 1.33 (s, 9 H), 0.95 (t, *J* = 7.29 Hz, 3 H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 197.0, 157.7, 142.1, 135.0, 130.9, 127.4, 119.6, 34.0, 31.8, 31.3, 29.2, 22.6, 14.0; HRMS [FAB+]: *m/z* calcd for $C_{15}H_{23}O_2$: 235.1698, found: 235.1720.

Typical procedure for preparation of fluorous Fe(III) salen complex: Under N_2 atmosphere, to a suspension of fluorous salicylaldehyde and 3Å M.S. in dry EtOH (11 mL) was added ethylenediamine (0.5 eq). The mixture was stirred at reflux in oil bath for 1 h. A solution of $FeCl_3$ (0.5 eq) in dry EtOH (5 mL) was syringed into the reaction mixture. The resulting mixture was stirred for 1 h. 3Å M.S. was removed by filtration through a pad of Celite and washed with dichloromethane. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on silica gel to afford fluorous salen complex.

Fluorous Fe(III) salen complex (3a): (101.6 mg, 28%); black crystal; mp 221 ºC (dec); HRMS [FAB+]: *m/z* calcd for $C_{44}H_{55}FeN_2O_2$: 911.0667, found: 911.0662.

Fluorous Fe(III) salen complex (3a'): (17.4 mg, 20%); black crystal; mp 300 ºC (dec); HRMS [FAB+]: *m/z* calcd for $C_{44}H_{19}F_{36}FeN_2O_2$: 1347.0223, found: 1347.0255.

Fluorous Fe(III) salen complex (3b): (177.2 mg, 22%); black crystal; mp 189 ºC (dec); HRMS [FAB+]: *m/z* calcd for $C_{44}H_{37}F_{18}FeN_2O_2$: 1023.1919, found: 1023.1874.

Fluorous Fe(III) salen complex (3c): (16.7 mg, 54%); orange solid; mp 151 °C (dec); HRMS [FAB+]: *m/z* calcd for $C_{36}H_{19}F_{18}FeN_4O_6$: 1001.0367, found: 1001.0367.

Fluorous Fe(III) salen complex (3d): (4.7 mg, 8%); brown solid; mp 218 ºC; HRMS [FAB+]: *m/z* calcd for $C_{38}H_{25}F_{18}FeN_2O_4$: 971.0876, found: 971.0907.

Fluorous Fe(III) salen complex (3e): (190.3 mg, 86%); brown solid; mp 130 ºC (dec); HRMS [FAB+]: *m/z* calcd for $C_{44}H_{37}F_{18}FeN_2O_2$: 1023.1917, found: 1023.1948.

Fluorous Fe(III) salen complex (3f): (40.6 mg, 37%); brown solid; mp 193 ºC; HRMS [FAB+]: *m/z* calcd for $C_{52}H_{37}F_{34}FeN_2O_2$: 1423.1662, found: 1423.1660.

Fluorous Fe(III) salen complex (3g): (50.9 mg, 44%); brown solid; mp 199 ºC; HRMS [FAB+]: *m/z* calcd for $C_{56}H_{37}F_{42}MN_2O_2$: 1623.1534, found: 1623.1554.

Non-fluorous Fe(III) salen complex (3h): (34.7 mg, 63%); black crystal; mp 194 ºC (dec); HRMS [FAB+]: *m/z* calcd for $C_{44}H_{55}FeN_2O_2$: 699.3613, found: 699.3606.

Non-fluorous Fe(III) salen complex (3i): (105.5 mg, 21%); black crystal; mp >300 ºC (dec); HRMS [FAB+]: *m/z* calcd for $C_{44}H_{55}FeN_2O_2$: 699.3615, found: 699.3657.

Non-fluorous Fe(III) salen complex (3j): (120.7 mg, 29%); black crystal; mp 300 ºC (dec); HRMS [FAB+]: *m/z* calcd for $C_{28}H_{23}FeN_2O_2$: 475.1111, found: 475.1143.

Fluorous Fe(III) salen complex (3k): (56.5 mg, 67%); black crystal; mp 220 ºC (dec); HRMS [FAB+]: *m/z* calcd for $C_{36}H_{35}F_{18}FeN_2O_2$: 925.1761, found: 925.1746.

Fluorous Fe(III) salen complex (3l): (45.1 mg, 81%); black crystal; mp 163 ºC (dec); HRMS [FAB+]: *m/z* calcd for $C_{52}H_{41}F_{18}FeN_2O_2$: 1123.2230, found: 1123.2224.

Fluorous Fe(III) salen complex (3m): (33.5 mg, 62%); brown solid; mp 100-110 ºC; HRMS [FAB+]: *m/z* calcd for $C_{48}H_{45}F_{18}FeN_2O_2$: 1079.2543, found: 1079.2543.

Fluorous Fe(III) salen complex (3n): (34.0 mg, 77%); brown solid; mp 110-120 ºC; HRMS [FAB+]: *m/z* calcd for $C_{50}H_{49}F_{18}FeN_2O_2$: 1107.2856, found: 1107.2877.

Fluorous Fe(III) salen complex (3o): (21.5 mg, 45%); brown solid; mp 135 ºC (dec); HRMS [FAB+]: *m/z* calcd for $C_{50}H_{49}F_{18}FeN_2O_4$: 1203.2551, found: 1203.2557.

Fluorous Fe(III) salen complex (3p): (10.3 mg, 21%); brown solid; mp 179 ºC; HRMS [FAB+]: *m/z* calcd for $C_{44}H_{35}F_{18}FeN_4O_6$: 1113.1619, found: 1113.1637.

Fluorous Fe(III) salen complex (3q): (5.2 mg, 11%); brown solid; mp 194 ºC (dec); HRMS [FAB+]: *m/z* calcd for $C_{44}H_{35}F_{18}FeN_4O_6$: 1113.1619, found: 1113.1637.

Fluorous Fe(III) salen complex (3r): (12.3 mg, 24%); brown solid; mp 206 ºC (dec); HRMS [FAB+]: *m/z* calcd for $C_{44}H_{35}F_{20}FeN_2O_2$: 1059.1729, found: 1059.1708.

Fluorous Fe(III) salen complex (3s): (7.8 mg, 20%); brown solid; mp >300 ºC; HRMS [FAB+]: *m/z* calcd for $C_{44}H_{35}F_{20}FeN_2O_2$: 1109.2761, found: 1109.2734.

Fluorous Fe(III) salen complex (3t): (15.3 mg, 32%); brown solid; mp 212 ºC; HRMS [FAB+]: *m/z* calcd for $C_{36}H_{35}Cl_2F_{18}FeN_2O_2$: 1091.1138, found: 1091.1151.

Fluorous Fe(III) salen complex (3u): (27.1 mg, 40%); brown solid; mp 187 ºC (dec); HRMS [FAB+]: *m/z* calcd for $C_{44}H_{37}F_{18}FeN_2O_4$: 1055.1815, found: 1055.1814.

Fluorous Fe(III) salen complex (3v): (5.2 mg, 8%); brown solid; mp 152 ºC; HRMS [FAB+]: *m/z* calcd for $C_{33}H_{31}F_{18}FeN_2O_2$: 885.1448, found: 885.1471.

Fluorous Fe(III) salen complex (3w): (5.1 mg, 7%); brown solid; mp >300 ºC; HRMS [FAB+]: *m/z* calcd for $C_{33}H_{29}F_{18}FeN_2O_4$: 915.1189, found: 915.1178.

Fluorous Fe(III) salen complex (3x): (55.8 mg, 93%); brown solid; mp 97 ºC; HRMS [FAB+]: *m/z* calcd for $C_{50}H_{37}F_{18}FeN_2O_2$: 1095.1917, found: 1095.1924.

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Conflict of interest

The authors declare no conflict of interest.

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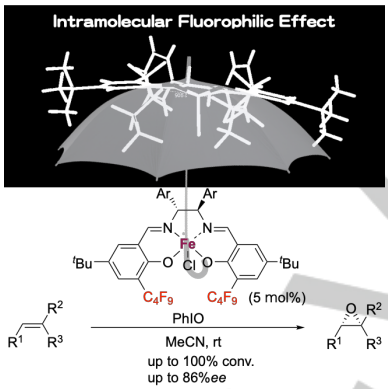
FULL PAPER

The first asymmetric epoxidation of isolated carbon–carbon double bonds using an Fe(III)-centered chiral salen complex is described. This is the first example of novel asymmetric space construction for a catalyst that exploits the intramolecular fluorophilic effect of fluorous tags.



Asymmetric Epoxidation *

*Yuki Kobayashi, Riho Ohbayashi, Yuki Watanabe, Hiroki Miyazaki, Issei Miyata, Yuta Suzuki, Yukihiro Yoshida, Takayuki Shioiri, Masato Matsugi**

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Unprecedented Asymmetric Epoxidation of Isolated Carbon–Carbon Double Bonds by a Chiral Fluorous Fe(III) Salen Complex: Exploiting Fluorophilic Effect for Catalyst Design

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