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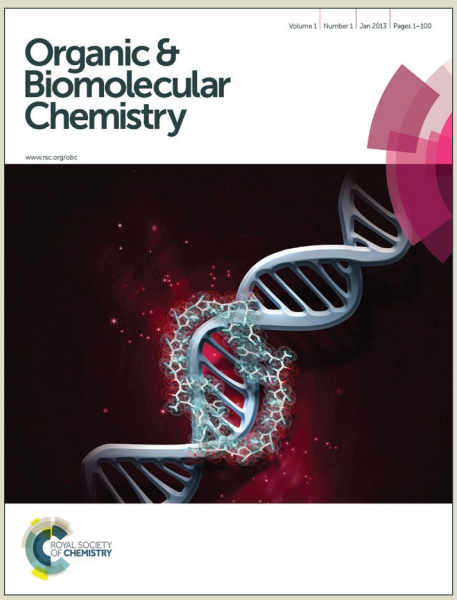





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# Enantioselective organocatalytic oxidation of ketimine

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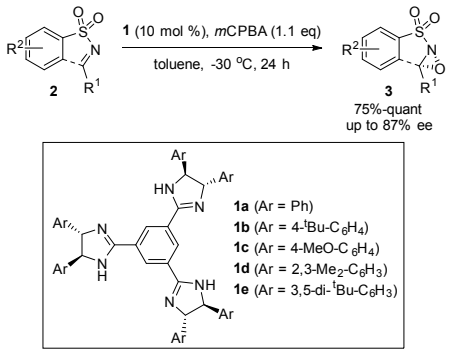
$C_3$-symmetric chiral trisimidazolines with *m*-chloroperbenzoic acid promoted the organocatalytic oxidation of *N*-sulfonyl ketimine. The present imidazoline catalysis produced oxaziridines bearing a tetrasubstituted carbon stereogenic center in high yields with up to 87% ee.

## Introduction

Oxaziridines are three-membered heterocycles that consist of oxygen, nitrogen and carbon atoms. These strained small heterocycles function as purely organic, non-acidic agents for the electrophilic transfer of oxygen and/or nitrogen to alkenes, enolates, and heteroatoms.[1] Among existing oxaziridines, those with a sulfonyl group on the nitrogen atom are the most widely used as Davis' reagents because of their easy handling.[2] In 2011, Jørgensen reported the first catalytic and enantioselective synthesis of oxaziridines from *N*-tosyl aldimines using the cinchona alkaloid-derived organocatalyst with *m*-chloroperbenzoic acid (*m*CPBA).[3a] Following this success, a catalytic enantioselective oxidation of *N*-sulfonyl aldimines has been recognized as one of the most straightforward methods to construct chiral oxaziridines.[4]

**Scheme 1** Enantioselective organocatalytic oxidation of ketimines **2** using $C_3$-symmetric chiral trisimidazolines **1** with *m*CPBA




To date, the synthetic utility of chiral oxaziridine derivatives has been markedly enhanced,[1,5] although few reports on the catalytic and enantioselective oxidation of ketimines have been published. As a solitary example, in 2012, Yamamoto reported that a chiral hafnium(IV) complex facilitated oxygen–atom transfer from cumene hydroperoxide to *N*-tosyl ketimine to give the corresponding oxaziridine with a chiral tetrasubstituted carbon stereogenic center in 38% yield with 98% ee.[6] The development of an efficient method for constructing chiral oxaziridines from ketimines has been a challenge in recent asymmetric chemistry. Here, we report the enantioselective organocatalytic oxidation of ketimines **2** using $C_3$-symmetric chiral trisimidazolines **1** with *m*CPBA. The present imidazoline catalysis afforded the corresponding oxaziridines **3** bearing a chiral tetrasubstituted carbon stereogenic center in high yields with up to 87% ee (Scheme 1).

## Results and discussion

Our group previously reported the enantioselective organocatalytic Michael reaction, bromolactonization, and Friedel–Crafts-type reactions involving $C_3$-symmetric chiral trisimidazoline **1**.[7] In the imidazoline catalysis, a synergistic activation by the imidazolines can lead to specific control of the transition–state structure, leading to products with high enantioselectivity.

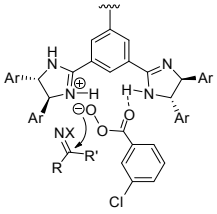


**Fig. 1** A plausible key intermediate for the oxidation reaction of ketimines with *m*CPBA

We assumed that in the trisimidazoline-catalyzed oxidation of ketimine with *m*CPBA, one imidazoline could function as a Brønsted base and another could act as a Brønsted acid, resulting in the *in situ* formation of a chiral peroxide that could transfer oxygen to the

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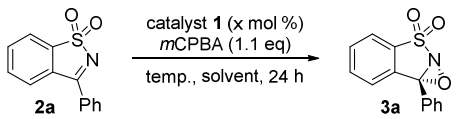
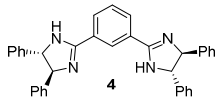
ketimine, thereby furnishing the desired oxaziridine with high enantiocontrol (Fig. 1).

**Table 1** Oxidation of ketimine **2a** catalyzed by chiral imidazolines



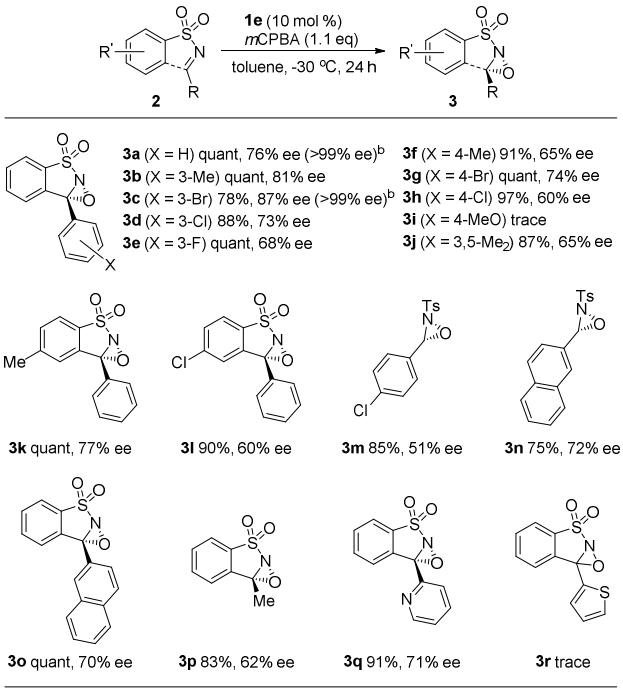

| Entry | Catalyst (mol %) | Temp. (°C) | Solvent | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | **1a** (10) | –20 | toluene | quant | 48 |
| 2 | **1a** (10) | –30 | toluene | quant | 52 |
| 3 | **1a** (10) | –40 | toluene | quant | 51 |
| 4 | **1a** (10) | –50 | toluene | 53 | 45 |
| 5 | **1a** (10) | –30 | $EtC_6H_5$ | quant | 42 |
| 6 | **1a** (10) | –30 | $ClC_6H_5$ | quant | 48 |
| 7 | **1a** (10) | –30 | *o*-xylene | quant | 45 |
| 8 | **1a** (10) | –30 | *m*-xylene | 73 | 32 |
| 9 | **1a** (10) | –30 | *n*-hexane | 12 | 11 |
| 10 | **1a** (10) | –30 | $CH_2Cl_2$ | 58 | 42 |
| 11 | **1a** (10) | –30 | $CHCl_3$ | 51 | 35 |
| 12[c] | **1a** (10) | –30 | toluene | quant | 52 |
| 13 | **1a** (5) | –30 | toluene | 90 | 47 |
| 14 | **1a** (1) | –30 | toluene | 66 | 25 |
| 15 | **4** (15) | –30 | toluene | quant | 12 |
| 16 | **1b** (10) | –30 | toluene | quant | 20 |
| 17 | **1c** (10) | –30 | toluene | quant | 50 |
| 18 | **1d** (10) | –30 | toluene | quant | 46 |
| 19 | **1e** (10) | –30 | toluene | quant | 76 |
| 20 | None | –30 | toluene | trace | - |

[a]Isolated yield. [b]Determined by HPLC (Daicel Chiralpak IA). [c]*m*-Cl-$C_6H_4CO_2H$ (40 mol %) was added.




As the first step in the development of the oxaziridination, the oxidation of ketimine **2a** with *m*CPBA (1.1 eq) was attempted using 10 mol % of chiral trisimidazoline **1a**[7a-7d] (Table 1). A screening of the reaction conditions with catalyst **1a** (Entries 1–11) revealed that the process in toluene at –30 °C gave the desired oxaziridine **3a** in quantitative yield and with 52% ee (Entry 2). In the oxidation of **2a** with **1a** and *m*CPBA, *m*-chlorobenzoic acid (*m*CBA) was also formed as a side product. In the presence of *m*CBA (40 mol %), the reaction produced **3a** in 52% ee quantitatively (Entry 12). Because *m*CBA is insoluble in toluene at –30 °C, the acid did not affect the reaction. When a catalyst loading of 1 mol % was applied to the reaction, the product's yield and ee decreased (Entry 14). Since a lower enantioselectivity was observed when using bisimidazoline **4** (Entry 15), the three chiral imidazoline units on catalyst **1a** were essential. Next, to establish high asymmetric induction to substrate **2a**, we tested chiral catalysts **1** with various substituents on their imidazoline rings (Entries 16–19). The catalysts bearing 4-$^t$Bu-$C_6H_4$ (**1b**),[7e] 4-MeO-$C_6H_4$ (**1c**),[7f] and 2,3-$Me_2$-$C_6H_3$ (**1d**)[7g] did not improve the stereoselectivity (Entries 16–18). The use of the newly designed trisimidazoline **1e**, which was derived from (1*S*,2*S*)-1,2-bis(3,5-di-*tert*-butyl phenyl)ethane-1,2-diamine,[8] improved ee of **3a** (76% ee, Entry 19) while maintaining the high chemical yield. In the absence of catalyst, no background reaction was observed under the optimized conditions (Entry 20). Hydrogen peroxide, sodium hypochlorite, or peracetic acid was tested as a co-oxidant in the reaction and did not give successful results.

**Scheme 2** Substrate scope[a]




[a]Yield values were based on the isolated products. The ee values were determined by HPLC (Daicel Chiralpak IA for **3a, 3b, 3k** and **3l**; Chiralpak ID for **3c, 3d, 3e, 3f, 3g, 3h, 3p** and **3q**; Daicel Chiralcel OD-H for **3j, 3n** and **3o**; Daicel Chiralcel OJ for **3m**). [b]After a single recrystallization.

The organocatalyst **1e** with *m*CPBA efficiently promoted the oxidation of various substituted ketimines **2** to afford the corresponding oxaziridines **3** bearing a tetrasubstituted carbon stereogenic center (Scheme 2). The oxaziridination of ketimines **2b–2h**, and **2j–2l** with electron-withdrawing or electron-donating groups on their aromatic rings afforded products **3b–3h**, and **3j–3l** in 78% to quantitative yields with 60–87% ees. The oxidation of aldimines **2m** and **2n** readily afforded their corresponding oxaziridines **3m** and **3n** in good yields and enantioselectivities. Although the introduction of a 2-naphthyl, methyl or 2-pyridyl group onto the ketimine (**2o–2q**) was tolerated, 4-methoxyphenyl and 2-thiophenyl ketimines (**2i** and **2r**) were decomposed under the optimized conditions. Optically pure **3a** and **3c** were obtained after a single recrystallization of the product from hexane/$CH_2Cl_2$. The absolute configuration of **3a** was assigned as the (*R*)-form by comparison with optical rotation data reported in the literature.[3a,4d-4e,6,9]

To investigate how the substrates interacted with imidazoline catalyst **1**, we conducted $^1$H-NMR experiments using catalyst **1a**, ketimine **2j** and *m*CPBA (Fig. 2). When ketimine **2j** and catalyst **1a** were mixed, no signal shift was observed (See ESI). In contrast, the mixing of catalyst **1a** and *m*CPBA resulted in a shift of the proton signal of catalyst **1a** (aromatic protons on the core benzene ring: from δ = 8.97 ppm to 10.49 ppm; benzylic protons on the imidazoline rings: from δ = 4.88 ppm to 5.12 ppm, Figs. 2a and 2c, also see ESI) and of the signal of the peracid proton of *m*CPBA from δ = 11.17 ppm to 6.60-7.60 ppm (Figs. 2b and 2c). Additionally, a 2D-NOESY NMR spectrum also showed the interaction between the catalyst **1a** and *m*CPBA (Fig. 3 and also see ESI). These observations

suggest that an ion pair formed between the catalyst and *m*CPBA. This association was implied by $^1$H-NMR measurements of a 1:3 mixture of catalyst **1a** and *m*CPBA, inducing a characteristic downfield shift of the signal for the protons of catalyst **1a** and *m*CPBA.[7,10]

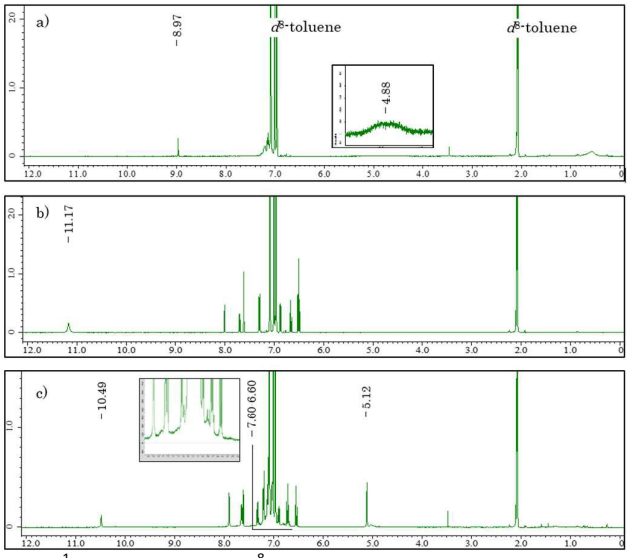



**Fig. 2** $^1$H-NMR spectra in $d^8$-toluene : a) catalyst **1a**, b) *m*CPBA, c) catalyst **1a** + *m*CPBA

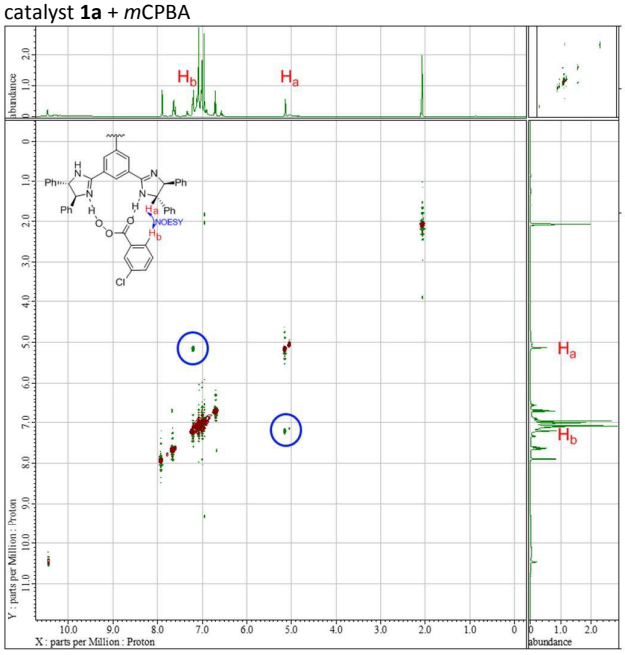
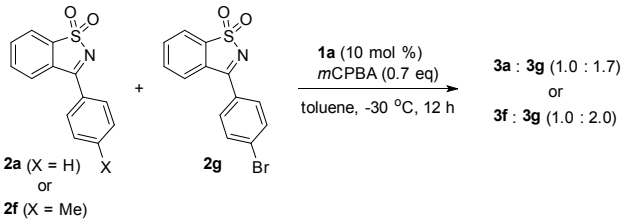



**Fig. 3** 2D-NOESY NMR spectrum of catalyst **1a** and *m*CPBA in $d^8$-toluene

A competition experiment between phenyl-substituted ketimine **2a** and 4-bromophenyl-substituted ketimine **2g** showed that the **3a**/**3g** product ratio was 1.0/1.7. In a similar competition study, oxaziridine **2f** having a 4-methylphenyl group was obtained in a 1.0/2.0 ratio against **3g** (Scheme 3).

In the present process, an electron deficient group tends to accelerate the reaction rate. These obtained results are in agreement with the oxidation mechanism shown in Figs. 1 and 4. Initially, one imidazoline nitrogen atom in catalyst **1e** is protonated by *m*CPBA, whereas the other imidazoline group coordinates to the oxygen atom of the peroxy carbonyl group, leading to tight-ion-pair aggregation. Next, attack of the generated chiral oxidant to ketimine **2** forms oxaziridine **3** through an α-aminoperoxy intermediate.[3] After the oxaziridination, *m*CBA was released from imidazoline **1e** because *m*CBA is insoluble under the optimized conditions. The chiral peracid species was regenerated from imidazoline **1e** with *m*CPBA.

**Scheme 3** Comparison of reactivity




The oxidation of ketimine **2** mediated by the chiral peracid occurred *via* an intermediate conformation with the least steric hindrance between the *tert*-butyl moieties of the catalyst and the fused aromatic ring of the substrate. Therefore the reaction using (*S*)-**1e** would favor the generation of the (*R*)-configuration products **3a**–**3h** and **3j**–**3p** or the (*S*)-configuration product **3q**.

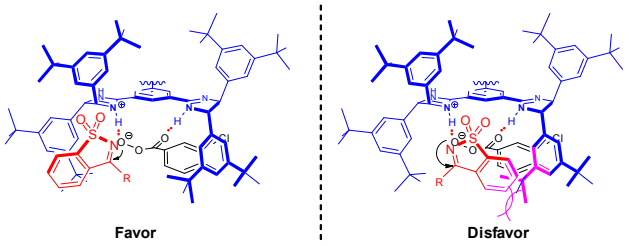



**Fig. 4** Possible mode of enantioselection

## Conclusions

We have demonstrated the first imidazoline-mediated enantioselective organocatalytic oxidation of ketimine. Various ketimine substrates bearing either electron-withdrawing or electron-donating groups were successfully oxidized in the presence of 10 mol % of $C_3$-symmetric chiral trisimidazolines **1** with *m*CPBA (1.1 eq). An investigation into the detailed reaction mechanism and an improvement of the asymmetric induction ability of catalyst **1** as well as a synthetic utility of the chiral oxaziridines **3** is currently underway.

## Experimental section

### General information

All reactions were performed with standard Schlenk technique under $N_2$ atmosphere. $^1$H-, $^{13}$C- and $^{19}$F-NMR spectra were recorded with JEOL JMN LA-400 FT NMR or JNM ECA600 FT NMR ($^1$H-NMR 600 or 400 MHz, $^{13}$C-NMR 150 or 100 MHz). $^1$H-NMR spectra are reported in ppm (δ) relative to the chemical shift of

tetramethylsilane. Multiplicity (s = singlet, d = doublet, q = quartet, t = triplet, m = multiplet). $^{13}$C-NMR spectra reported in ppm (δ) relative to the central line of triplet for $CDCl_3$ at 77.00 ppm. $CF_3CO_2H$ used as external standards for $^{19}$F-NMR. Mass spectra were obtained on JMS-T100LC-JEOL (ESI), JMS-700-JEOL (FAB) and Shimadzu AXIMA-TOF (MALDI) spectrometers. Optical rotations were measured with JASCO P-1030 polarimeter. HPLC analyses were performed on a JASCO HPLC system (JASCO PU 980 pump and UV-975 UV/Vis detector) using a mixture of hexane and 2-propanol eluents. FT-IR spectra were recorded on a JASCO FT-IR system (FT/IR4100). Melting point was measured with SHIMADZU DSC-60. Column chromatography on $SiO_2$ was performed with Kanto Silica Gel 60 (40-100 µm). Commercially available organic and inorganic compounds were used without further purification. The solvents were purified and dried by the standard procedures. Cyclic ketimines **2a-g** and **2i-l**, aldimine **2m** were prepared following the reported procedures.[11]

**Preparation of trisimidazoline 1e**

Trimethyl benzene-1,3,5-tris(carboxylimidate)[7e] (0.124 mmol, 31.0 mg) and (1*S*,2*S*)-1,2-bis (3,5-di-*tert*-butyl phenyl) ethane-1,2-diamine[8] (0.435 mmol, 190 mg) were dissolved in mixture of EtOH and pyridine (4.4 mL, 10:1) under $N_2$. The resulting solution was heated at 80 °C for 24 h. After cooling to room temperature, the solvent was removed *in vacuo* and the remaining residues were purified by $SiO_2$ column chromatography (Hexane:AcOEt = 5:1) to give **1e** (160 mg, 91 %). Colorless solid; m.p. > 300 °C; $^1$H-NMR ($CDCl_3$) δ 8.70 (s, 3H), 7.35 (dd, 6H, *J* = 1.8, 1.8 Hz), 7.18 (d, 6H, *J* = 1.8 Hz), 7. 13 (d, 6H, *J* = 1.8 Hz), 5.64 (brs., 3H), 5.15 (d, 3H, *J* = 7.8 Hz), 4.90 (d, 3H, *J* = 7.8 Hz), 1.30 (s, 54H), 1.29 (s, 54H); $^{13}$C NMR ($CDCl_3$) δ 161.2, 151.2, 150.8, 142.8, 142.4, 131.1, 128.2, 121.8, 121.6, 121.2, 120.2, 80.7, 69.9, 34.88, 34.86, 31.52, 31.47; HRMS (MALDI-TOF): calcd for $C_{99}H_{139}N_6$, m/z = 1412.1056 [(M+H)$^+$], found m/z = 1412.1016; $[\alpha]_D^{25}$ = –85.1 (*c* 1.39 , $CHCl_3$); IR (KBr): ν 3374, 2963, 2904, 2868, 1624, 1599, 1581, 1477, 1362 cm$^{-1}$.

**Preparation of ketimine 2j**

To a mixture of Mg turnings (2 eq., 5.46 mmol, 130 mg) and iodine (one crystal) in THF (dry, degassed), 5-bromo-*m*-xylene (2 eq., 5.46 mmol, 1.00 g, 0.73 mL) was added dropwisely at room temperature under $N_2$. After stirring for 30 min, the resulting Grignard reagent was transferred by using syringe under $N_2$, and then added dropwisely to other flask containing saccharin (2.73 mmol, 0.50 g) dissolved in 5.5 mL THF. The reaction was stirred overnight at room temperature followed by quenching using sat. $NH_4Cl_{aq.}$ solution. The reaction mixture was extracted by using dichloromethane followed by washing using brine, drying by $Na_2SO_4$ and finally the solvent was removed *in vacuo*. The remaining residues was dissolved in dry toluene (14 mL) followed by adding of tosyl acid (2.2 mmol, 0.38 g). Then the reaction was heated under reflux using Dean-Stark system overnight. After cooling to room temperature, the solvent was removed using rotavap followed by the addition of sat. $NH_4Cl_{aq.}$ solution (20 mL). The resulting mixture was extracted by dichloromethane and subsequently dried using sodium sulfate. After removing of the solvent under vaccum, the remaining solid was chromatographed over silica gel (Hexane:Ethyl acetate = 2:1) to give the product **2j** (394 mg, 53 %). Pale yellow solid; m.p. 189-190 °C; $^1$H-NMR ($CDCl_3$) δ 8.02-8.00 (m, 1H, ArH), 7.90-7.90 (m, 1H, ArH), 7.79-7.74 (m, 2H, ArH), 7.58-7.57 (m, 2H, ArH), 7.33-7.32 (m, 1H, ArH), 2.44 (s, 6H, 2×$CH_3$); $^{13}$C-NMR ($CDCl_3$) δ 171.4, 141.0, 139.1 (2×C), 135.2, 133.6, 133.3, 130.7, 130.3, 127.2 (2×C), 126.7, 123.0, 21.3 (2×C); HRMS (ESI) calcd for $C_{15}H_{13}NNaO_2S$, m/z = 294.0559 [(M+Na)$^+$], found m/z = 294.0552; IR (KBr): ν 3062, 3008, 2921, 1602, 1530, 1458, 1382, 1237 cm$^{-1}$.

**General procedure for enantioselective organocatalytic oxidation of ketimine**

A mixture of ketimine **2** (0.0145 mmol) and trisimidazoline **1e** (10 mol%, 1.45 µmol, 2 mg) was dissolved in 0.15 mL toluene and then cooled to –30 °C. After that *m*-chloroperbenzoic acid (1.1 eq., 0.0158 mmol, 3.9 mg) was added one time at the same temperature and then the reaction was stirred for 24h under $N_2$. The final oxaziridine product **3** was purified by PTLC ($SiO_2$, Hexane : Ethyl acetate = 2:1).

**3a**: Analytical data were well matched with the reported literature.[12] White solid (quant); $^1$H-NMR ($CDCl_3$) δ 7.88 (dd, 1H, ArH, *J* = 2.0, 7.60 Hz), 7.80-7.70 (m, 2H, ArH), 7.65-7.49 (m, 6H, ArH); enantiomeric excess: 76 %, determined by HPLC (Chiralpak IA, hexane/2-propanol = 9/1, flow rate = 1 mL/min, 25°C, 214 nm) minor peak: $t_R$ = 12.5 min, major peak: $t_R$ = 11.4 min; $[\alpha]_D^{26}$ = +81.3 (*c* 0.92, $CHCl_3$).

**3b**: White solid (quant); m.p. 110-111 °C; $^1$H-NMR ($CDCl_3$) δ 7.89-7.87 (m, 1H, ArH), 7.79-7.71 (m, 2H, ArH), 7.65-7.62 (m, 1H, ArH), 7.41-7.36 (m, 4H, ArH), 2.42 (s, 3H, $CH_3$); $^{13}$C-NMR ($CDCl_3$) δ 139.1, 134.8, 134.5, 133.8, 132.7, 132.1, 128.9, 128.5, 128.1, 127.8, 125.2, 124.1, 85.4, 21.4; HRMS (ESI) calcd for $C_{14}H_{11}NNaO_3S$, m/z = 296.0352 [(M+Na)$^+$], found m/z = 296.0346; enantiomeric excess: 81 %, determined by HPLC (Chiralpak IA, hexane/2-propanol = 9/1, flow rate = 1 mL/min, 25°C, 214 nm) minor peak: $t_R$ = 10.7 min, major peak: $t_R$ = 8.8 min; $[\alpha]_D^{23}$ = +174.0 (*c* 0.92, $CHCl_3$). IR (KBr): ν 2924, 2852, 1454, 1363, 1334, 1236, 1185, 1132, 1094 cm$^{-1}$.

**3c**: White solid (78%); m.p. 130-131 °C; $^1$H-NMR ($CDCl_3$) δ 7.90 (d, 1H, ArH, *J* = 7.20 Hz), 7.83-7.70 (m, 4H, ArH), 7.63 (d, 1H, ArH, *J* = 7.20 Hz), 7.55 (d, 1H, ArH, *J* = 7.80 Hz), 7.41 (t, 1H, ArH, *J* = 7.80 Hz); $^{13}$C-NMR ($CDCl_3$) δ 134.5, 134.4, 134.0, 133.8, 133.1, 131.0, 130.6, 130.2, 127.8, 126.8, 124.3, 123.1, 84.3 (Oxaziridine C); HRMS (ESI) calcd for $C_{13}H_8BrNNaO_3S$, m/z = 359.9300 [(M+Na)$^+$], found m/z = 359.9299; enantiomeric excess: 87%, determined by HPLC (Chiralpak ID, hexane/2-propanol = 9/1, flow rate = 0.5 mL/min, 25°C, 214 nm) minor peak: $t_R$ = 62.6 min, major peak: $t_R$ = 54.6 min; $[\alpha]_D^{22}$ = +116.0 (*c* 0.20, $CHCl_3$); IR (KBr): ν 3094, 3076, 2230, 1364, 1325, 1157, 1126, 1112 cm$^{-1}$.

**3d**: White solid (88 %); m.p. 125-126 °C; $^1$H-NMR ($CDCl_3$) δ 7.91-7.88 (m, 1H, ArH), 7.82-7.74 (m, 2H, ArH), 7.64-7.60 (m, 2H, ArH), 7.56 (dt, 1H, ArH, *J* = 2.00, 7.20 Hz), 7.52-7.45 (m, 2H, ArH); $^{13}$C-NMR ($CDCl_3$) δ 135.3, 134.5, 134.0, 133.9, 133.0, 131.6, 130.4, 130.0, 128.2, 127.9, 126.3, 124.3, 84.4 (Oxaziridine C); HRMS (ESI) calcd for $C_{13}H_8ClNNaO_3S$, m/z = 315.9806 [(M+Na)$^+$], found m/z = 315.9800; enantiomeric excess: 73 %, determined by HPLC (Chiralpak ID, hexane/2-propanol = 9/1, flow rate = 1 mL/min, 25°C, 214 nm) minor peak: $t_R$ = 24.4 min, major peak: $t_R$ = 14.5 min; $[\alpha]_D^{18}$ = +245.0 (*c* 0.44, $CHCl_3$); IR (KBr): ν 3063, 1463, 1363, 1320, 1182, 1166 cm$^{-1}$.

**3e**: White solid (quant); m.p. 132-133 °C; $^1$H-NMR ($CDCl_3$) δ 7.90-7.88 (m, 1H, ArH), 7.82-7.74 (m, 2H, ArH), 7.66-7.64 (m, 1H, ArH), 7.54-7.49 (m, 1H, ArH), 7.42-7.40 (m, 1H, ArH), 7.34-7.26 (m, 2H, ArH); $^{13}$C-NMR ($CDCl_3$) δ 162.8 (d, $^1J_{C\text{-}F}$ = 247.9 Hz), 134.4, 134.0, 133.8, 133.0, 130.9 (d, $^3J_{C\text{-}F}$ = 7.7 Hz), 130.3 (d, $^3J_{C\text{-}F}$ = 7.6 Hz), 127.9,

124.3, 124.0, 118.6 (d, $^2J_{C-F}$ = 21.0 Hz), 115.3 (d, $^2J_{C-F}$ = 23.8 Hz), 84.4 (Oxaziridine C); $^{19}$F-NMR ($CDCl_3$): δ -110.2; HRMS (ESI) calcd for $C_{13}H_8FNNaO_3S$, m/z = 300.0101 [(M+Na)$^+$], found m/z = 300.0096; enantiomeric excess: 68 %, determined by HPLC (Chiralpak ID, hexane/2-propanol = 9/1, flow rate = 1 mL/min, 25°C, 214 nm) minor peak: $t_R$ = 24.4 min, major peak: $t_R$ = 15.8 min; $[\alpha]_D^{20}$ = +26.8 (*c* 1.40, $CHCl_3$); IR (KBr): ν 3096, 3074, 1594, 1449, 1366, 1326, 1180, 1165 cm$^{-1}$.

**3f**: White solid (91 %); m.p. 106-107 °C; $^1$H-NMR ($CDCl_3$) δ 7.99 (dd, 1H, ArH, *J* = 1.20, 6.60 Hz), 7.79-7.69 (m, 2H, ArH), 7.64 (dd, 1H, ArH *J* = 1.20, 6.60 Hz), 7.49 (d, 2H, ArH, *J* = 7.60 Hz), 7.32 (d, 2H, ArH, *J* = 8.40 Hz), 2.44 (s, 3H, $CH_3$); $^{13}$C-NMR ($CDCl_3$) δ 141.7, 134.8, 134.6, 133.8, 132.7, 129.7, 128.0 (2×C), 124.9, 124.1, 85.4 (Oxaziridine C), 21.5; HRMS (ESI) calcd for $C_{14}H_{11}NNaO_3S$, m/z = 296.0352 [(M+Na)$^+$], found m/z = 296.0352; enantiomeric excess: 65 %, determined by HPLC (Chiralpak ID, hexane/2-propanol = 9/1, flow rate = 1 mL/min, 25°C, 237 nm) minor peak: $t_R$ = 23.4 min, major peak: $t_R$ = 18.9 min; $[\alpha]_D^{23}$ = +137.0 (*c* 0.87, $CHCl_3$); IR (KBr): ν 3035, 1611, 1359, 1328, 1179, 1101, 944 cm$^{-1}$.

**3g**: White solid (quant); m.p. 133-134 °C; $^1$H-NMR ($CDCl_3$) δ 7.90-7.88 (m, 1H, ArH), 7.81-7.73 (m, 2H, ArH), 7.69-7.65 (m, 2H, ArH), 7.62-7.60 (m, 1H, ArH), 7.89 (dd, 1H, ArH, *J* = 1.60, 6.80 Hz); $^{13}$C-NMR ($CDCl_3$) δ 134.6, 134.1, 133.2, 132.5 (3×C or 2×C), 129.9 (2×C or 3×C), 128.0, 127.1, 126.3, 124.5, 84.9 (Oxaziridine C); HRMS (ESI) calcd for $C_{13}H_8BrNNaO_3S$, m/z = 359.9300 [(M+Na)$^+$], found m/z = 359.9292; enantiomeric excess: 74 %, determined by HPLC (Chiralpak ID, hexane/2-propanol = 9/1, flow rate = 1 mL/min, 25°C, 214 nm) minor peak: $t_R$ = 23.3 min, major peak: $t_R$ = 26.8 min; $[\alpha]_D^{25}$ = +70.6 (*c* 1.33, $CHCl_3$); IR (KBr): ν 3068, 1595, 1399, 1359, 1327, 1188, 1166, 1129 cm$^{-1}$.

**3h**: White solid (97 %); m.p. 144-145 °C; $^1$H-NMR ($CDCl_3$) δ 7.89 (dd, 1H, ArH, *J* = 1.20, 6.80 Hz), 7.82-7.75 (m, 2H, ArH), 7.62 (dd, 1H, ArH, *J* = 0.80, 6.80 Hz), 7.57-7.50 (m, 4H, ArH); $^{13}$C-NMR ($CDCl_3$) δ 137.8, 134,5, 134.02, 133.95, 133.0, 129.5 (2×C), 129.4 (2×C), 127.8, 126.4, 124.3, 84.7 (Oxaziridine C); HRMS (ESI) calcd for $C_{13}H_8ClNNaO_3S$, m/z = 315.9806 [(M+Na)$^+$], found m/z = 315.9806; enantiomeric excess: 60 %, determined by HPLC (Chiralpak ID, hexane/2-propanol = 9/1, flow rate = 1 mL/min, 25°C, 254 nm) minor peak: $t_R$ = 20.9 min, major peak: $t_R$ = 18.0 min; $[\alpha]_D^{22}$ = +161 (*c* 1.03, $CHCl_3$); IR (KBr): ν 3096, 3080, 2926, 1598, 1494, 1454, 1405, 1358, 1188, 1131, 1091, 944, 813, 768, 572 cm$^{-1}$.

**3j**: White solid (87 %); m.p. 103-104 °C; $^1$H-NMR ($CDCl_3$) δ 7.88-7.86 (m, 1H, ArH), 7.78-7.70 (m, 2H, ArH), 7.64-7.62 (m, 1H, ArH), 7.19 (brs, 3H, ArH), 2.37 (s, 6H, 2×$CH_3$); $^{13}$C-NMR ($CDCl_3$) δ 138.9 (2×C), 134.9, 134.4, 133.8, 132.9, 132.7, 128.1, 127.7, 125.6 (2×C), 124.0, 85.5 (Oxaziridine C), 21.3 (2×C); HRMS (ESI) calcd for $C_{15}H_{13}NNaO_3S$, m/z = 310.0508 [(M+Na)$^+$], found m/z = 310.0500; enantiomeric excess: 65 %, determined by HPLC (Chiralpak ID, hexane/2-propanol = 9/1, flow rate = 1 mL/min, 25°C, 214 nm) minor peak: $t_R$ = 8.7 min, major peak: $t_R$ = 12.4 min; $[\alpha]_D^{21}$ = +148.0 (*c* 0.63, $CHCl_3$); IR (KBr): ν 3062, 3008, 2921, 1602, 1530, 1458, 1382, 1333, 1237 cm$^{-1}$.

**3k**: White solid (quant); m.p. 174-175 °C; $^1$H-NMR ($CDCl_3$) δ 7.87 (dd, 1H, ArH, *J* = 0.80, 6.40 Hz), 7.78-7.70 (m, 2H, ArH), 7.64 (dd, 1H, ArH, *J* = 0.80, 7.60 Hz), 7.50-7.47 (m, 2H, ArH), 7.32 (d, 2H, ArH, *J* = 8.40 Hz), 2.44 (s, 3H, $CH_3$); $^{13}$C-NMR ($CDCl_3$) δ 141.7, 134.8, 134.6, 133.8, 132.7, 129.7 (3×C), 128.0 (2×C), 124.9, 124.1, 85.4, 21.5; HRMS (ESI) calcd for $C_{14}H_{11}NNaO_3S$, m/z = 296.0352 [(M+Na)$^+$], found m/z = 296.0347; enantiomeric excess: 77 %, determined by HPLC (Chiralpak IA, hexane/2-propanol = 9/1, flow rate = 1 mL/min, 25°C, 214 nm) minor peak: $t_R$ = 10.3 min, major peak: $t_R$ = 8.4 min; $[\alpha]_D^{20}$ = +160.0 (*c* 0.95, $CHCl_3$); IR (KBr): ν 3446, 1598, 1451, 1361, 1330, 1184, 1147, 1123 cm$^{-1}$.

**3l**: White solid (90 %); m.p. 127-128 °C; $^1$H-NMR ($CDCl_3$) δ 7.81 (d, 1H, ArH, *J* = 8.00 Hz), 7.73 (dd, 1H, ArH, *J* = 1.60, 8.00 Hz), 7.63-7.52 (m, 6H, ArH); $^{13}$C-NMR ($CDCl_3$) δ 140.7, 136.8, 133.4, 132.9, 131.8, 129.4 (2×C), 128.4, 128.1 (2×C), 127.4, 125.5, 84.8; HRMS (ESI) calcd for $C_{13}H_8ClNNaO_3S$, m/z = 315.9806 [(M+Na)$^+$], found m/z = 315.9806; enantiomeric excess: 60 %, determined by HPLC (Chiralpak IA, hexane/2-propanol = 20/1, flow rate = 0.5 mL/min, 25°C, 212 nm) minor peak: $t_R$ = 23.5 min, major peak: $t_R$ = 20.1 min; $[\alpha]_D^{24}$ = +11.4 (*c* 1.27, $CHCl_3$); IR (KBr): ν 3090, 1587, 1454, 1363, 1330, 1184, 1085, 960 cm$^{-1}$.

**3m**: Analytical data were well matched with the reported literature.[3a] White solid (85 %); $^1$H-NMR ($CDCl_3$) δ 7.92 (d, 2H, ArH, *J* = 8.40 Hz), 7.43 (d, 2H, ArH, *J* = 8.40 Hz), 7.38 (s, 4H, ArH), 5.43 (s, 1H, oxaziridine H), 2.49 (s, 3H, $CH_3$). enantiomeric excess: 51 %, determined by HPLC (Chiralcel OJ, hexane/2-propanol = 9/1, flow rate = 1 mL/min, 25°C, 254 nm) minor peak: $t_R$ = 20.7 min, major peak: $t_R$ = 25.9 min.

**3n**: Analytical data were well matched with the reported literature.[3a] White solid (75 %); $^1$H-NMR ($CDCl_3$) δ 8.03 (br s, 1H, ArH), 7.96 (d, 2H, ArH, *J* = 8.0), 7.90-7.80 (m, 3H, ArH), 7.60-7.50 (m, 2H, ArH), 7.44 (d, 2H, ArH, *J* = 8.0 Hz), 7.40 (dd, 1H, ArH, *J* = 1.60, 8.80 Hz), 5.62 (s, 1H, oxaziridine H), 2.51 (s, 3H, $CH_3$). enantiomeric excess: 72 %, determined by HPLC (Chiralcel OD-H, hexane/2-propanol = 9/1, flow rate = 1 mL/min, 25°C, 230 nm) minor peak: $t_R$ = 9.7 min, major peak: $t_R$ = 8.6 min.

**3o**: White solid (quant); m.p. 110-111 °C; $^1$H-NMR ($CDCl_3$) δ 8.15 (d, 1H, ArH, *J* = 1.60 Hz), 7.98 (d, 1H, ArH, *J* = 8.00 Hz), 7.94-7.90 (m, 3H, ArH), 7.80 (td, 1H, ArH, *J* = 1.20, 7.60 Hz), 7.45 (td, 1H, ArH, *J* = 1.60, 8.00 Hz), 7.69-7.57 (m, 4H, ArH); $^{13}$C-NMR ($CDCl_3$) δ 134.7, 134.5, 134.4, 133.9, 132.8, 132.6, 129.1, 128.9, 128.5, 128.1, 128.0, 127.9, 127.2, 125.2, 124.2, 123.8, 85.5; HRMS (ESI) calcd for $C_{17}H_{11}NNaO_3S$, m/z = 332.0352 [(M+Na)$^+$], found m/z = 332.0344; enantiomeric excess: 70 %, determined by HPLC (Chiralpak ID, hexane/2-propanol = 9/1, flow rate = 1 mL/min, 25°C, 214 nm) minor peak: $t_R$ = 29.5 min, major peak: $t_R$ = 23.0 min; $[\alpha]_D^{20}$ = +193.0 (*c* 0.73, $CHCl_3$); IR (KBr): ν 3058, 1452, 1369, 1185, 1165cm$^{-1}$.

**3p**: Analytical data were well matched with the reported literature.[12] White solid (83 %); $^1$H-NMR ($CDCl_3$) δ 7.82-7.68 (m, 4H, ArH), 2.14 (s, 3H, $CH_3$); enantiomeric excess: 62 %, determined by HPLC (Chiralpak ID, hexane/2-propanol = 9/1, flow rate = 1 mL/min, 25°C, 214 nm) minor peak: $t_R$ = 27.4 min, major peak: $t_R$ = 25.1 min; $[\alpha]_D^{17}$ = +13.4 (*c* 0.38, $CHCl_3$).

**3q**: White solid (91 %); m.p. 144-145 °C; $^1$H-NMR ($CDCl_3$) δ 8.73 (d, 1H, ArH, *J* = 4.00 Hz), 8.19-8.15 (m, 1H, ArH), 7.90 (td, 1H, ArH, *J* = 1.60, 8.00 Hz), 7.86-7.82 (m, 1H, ArH), 7.79-7.73 (m, 2H, ArH), 7.71 (d, 1H, ArH), 7.50 (ddd, 1H, ArH, *J* = 0.80, 4.40, 7.20 Hz); $^{13}$C-NMR ($CDCl_3$) δ 149.4, 149.1, 137.6, 134.3, 133.7, 133.4, 132.5, 130.0, 125.7, 123.7, 123.3, 83.1 (Oxaziridine C); HRMS (ESI) calcd for $C_{12}H_8N_2NaO_3S$, m/z = 283.0148 [(M+Na)$^+$], found m/z = 283.0143;

enantiomeric excess: 71 %, determined by HPLC (Chiralpak ID, hexane/2-propanol = 9/1, flow rate = 1 mL/min, 25°C, 214 nm) minor peak: $t_R$ = 28.8 min, major peak: $t_R$ = 24.7 min; $[\alpha]_D^{20}$ = +134.0 (*c* 0.60, $CHCl_3$); IR (KBr): ν 3096, 3068, 1454, 1373, 1336, 1186, 1165 $cm^{-1}$.

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## Notes and references

1 For recent reviews, see: (*a*) K. S. Williamson, D. J. Michaelis and T. P. Yoon, *Chem. Rev.,* 2014, **114**, 8016; (*b*) G. D. Sala and A. Lattanzi, *ACS Catal.*, 2014, **4**, 1234.

2 (*a*) F. A. Davis and A. C. Sheppard, *Tetrahedron,* 1989, **45**, 5703. (*b*) F. A. Davis and B.-C. Chen, *Chem. Rev.,* 1992, **92**, 919; (*c*) V. A. Petrov and G. Resnati, *Chem. Rev.,* 1996, **96**, 1809.

3 (*a*) L. Lykke, C. Rodríguez-Escrich and K. A. Jørgensen, *J. Am. Chem. Soc.,* 2011, **133**, 14932; (*b*) L. Lykke, K. S. Halskov, B. D. Carlsen, V. X. Chen and K. A. Jørgensen, *J. Am. Chem. Soc.,* 2013, **135**, 4692.

4 (*a*) D. Uraguchi, R. Tsutsumi and T. Ooi, *J. Am. Chem. Soc.*, 2013, **135**, 8161; (*b*) T. Zhang, W. He, X. Zhao and Y. Jin, *Tetrahedron*, 2013, **69**, 7416; (*c*) Y. Jin, T. Zhang, W. Zhang, S. Chang and B. Feng, *Chirality*, 2014, **26**, 150; (*d*) R. Tsutsumi, S. Kim, D. Uraguchi and T. Ooi, *Synthesis*, 2014, **46**, 871; (*e*) D. Uraguchi, R. Tsutsumi and T. Ooi, *Tetrahedron*, 2014, **70**, 1691.

5 For recent examples of transformations of *N*-sulfonyl oxiaziridines, see: (*a*) S. Dong, X. Lui, Y. Zhu, P. He, L. Lin and X. Feng, *J. Am. Che. Soc.*, 2013, **135**, 10026; (*b*) K. S. Williamson, J. W. Sawicki and T. P. Yoon, *Chem. Sci*., 2014, **5**, 3524, see also references therein.

6 J. L. Olivares-Romero, Z. Li and H. Yamamoto, *J. Am. Chem. Soc.*, 2012, **134**, 5440.

7 (*a*) K. Murai, S. Fukushima, S. Hayashi, Y. Takahara and H. Fujioka, *Org. Lett*., 2010, **12**, 964; (*b*) K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura and H. Fujioka, *Angew. Chem. Int. Ed*., 2010, **49**, 9174; (*c*) K. Murai, S. Fukushima, A. Nakamura, M. Shimura and H. Fujioka, *Tetrahedron,* 2011, **67**, 4862; (*d*) K. Murai, A. Nakamura, T. Matsushita, M. Shimura and H. Fujioka, *Chem. Eur. J.,* 2012, **18**, 8448; (*e*) K. Murai, T. Matsushita, A. Nakamura, N. Hyogo, J. Nakajima and H. Fujioka, *Org. Lett*., 2013, **15**, 2526; (*f*) S. Takizawa, S. Hirata, K. Murai, H. Fujioka and H Sasai, *Org. Biomol. Chem*., 2014, **12**, 5827; (*g*) K. Murai, N. Shimizu and H. Fujioka, *Chem. Commun.,* 2014, **50**, 12530; (*h*) K. Murai, J. Nakajima, A. Nakamura, N. Hyogo and H. Fujioka, *Chem. Asian. J.*, 2014, **9**, 3511.

8 J. H. Barnard, C. Wang, N. G. Berry and J. Xiao, *Chem. Sci.*, 2013, **4**, 1234.

9 T. Fukuzumi and J. W. Bode, *J. Am. Chem. Soc*., 2009, **131**, 3864.

10 (*a*) A. Kraft and R. Fröhlich, *Chem. Commun*., 1998, 1085; (*b*) A. Kraft, F. Osterod and R. Fröhlich, *J. Org. Chem*., 1999, **64**, 6425.

11 (*a*) K. Y. Lee, C. G. Lee and J. N. Kim, *Tetrahedron Lett.*, 2003, **44**, 1231; (*b*) M. Rommel, T. Fukuzumi and J. W. Bode, *J. Am. Chem. Soc*., 2008, **130**, 17266; (*c*) T. Nishimura, A. Noishiki, G. C. Tsui and T. Hayashi, *J. Am. Chem. Soc*., 2012, **134**, 5056; (*d*) A. G. Kravina, J. Mahatthananchai and J. W. Bode, *Angew. Chem. Int. Ed*., 2012, **51**, 9433; (*e*) T. Nishimura, Y. Ebe and T. Hayashi, *J. Am. Chem. Soc*., 2013, **135**, 2092; (*f*) S. Takizawa, F. A. Arteaga, Y. Yoshida, M. Suzuki and H. Sasai, *Asian J. Org. Chem*., 2014, **3**, 412.

12 F. A. Davis, J. C. Towson, D. B. Vashi, R. ThimmaReddy, J. P. McCauley., M. E. Harakal and D. J. Gosciniak, *J. Org. Chem.*, 1990, **55**, 1254.