A Highly Diastereoselective and Enantioselective Phase-Transfer Catalyzed Epoxidation of β-Trifluoromethyl-β,β-disubstituted Enones with H_2O_2

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ABSTRACT: *Trifluoromethylated organic compounds, especially chiral quaternary alcohols bearing trifluoromethyl group are of important intermediates in drugs, agrochemicals and etc. An efficient epoxidation of β-CF_3-β,β-disubstituted unsaturated ketones (**6**) has been developed with environmental benign hydrogen peroxide as the oxidant and F_5-substituted chiral quaternary ammonium salt (**1g** or **5**) derived from cinchona-alkaloid as the catalyst. Using 3 mol% of the catalyst, both enantiomers of (R,R) and (S,S) β-trifluoromethyl-α,β-epoxy ketones (**7**, **8**) were obtained in excellent diastereoselectivities (up to 100:1 d.r.) and enantioselectivities (up to 99.7% ee). The effects of catalyst structure, catalyst loading, substrate structure, the nature of oxidant, and reaction conditions on the catalyst capacities have been discussed in full length. The reaction mechanism was proposed to explain the origin of chiral induction. By subsequent reduction with zinc the epoxides are exhibited to be converted into trifluoromethylated quaternary alcohols without any loss in enantioselectivities. All new compounds are fully characterized by IR, NMR, elemental analysis and or high resolution mass spectrum.*

KEY WORDS: *Asymmetric catalysis, Epoxidation, Hydrogen peroxide, Phase transfer catalyst, Trifluoromethyl.*

INTRODUCTION

Trifluoromethylated organic compounds have recently emerged expansively as promising biologically active motifs for drug design due to the special properties of trifluoromethyl group [1]. As a consequence, many groups are committed to the introduction of trifluoromethyl group into organic compounds [2]. The construction of trifluoromethyl alcohol units exemplified by $CF_3C(OH)RR'$ is a particularly demanding task and a challenging topic in organic chemistry [3,4]. On the other hand, chemoselective reduction of α,β-epoxy ketones to β-hydroxy ketones has attracted much attention for several decades because the reduction products (β-hydroxy ketones) were very important intermediates in organic synthesis [5]. Obviously, the synthesis of β-trifluoromethyl-β-hydroxy ketones would be interesting. To the best of our knowledge, a general method for the direct catalytic asymmetric synthesis of β-trifluoromethyl-β-hydroxy ketones (Route A) is still lacking [6], probably because

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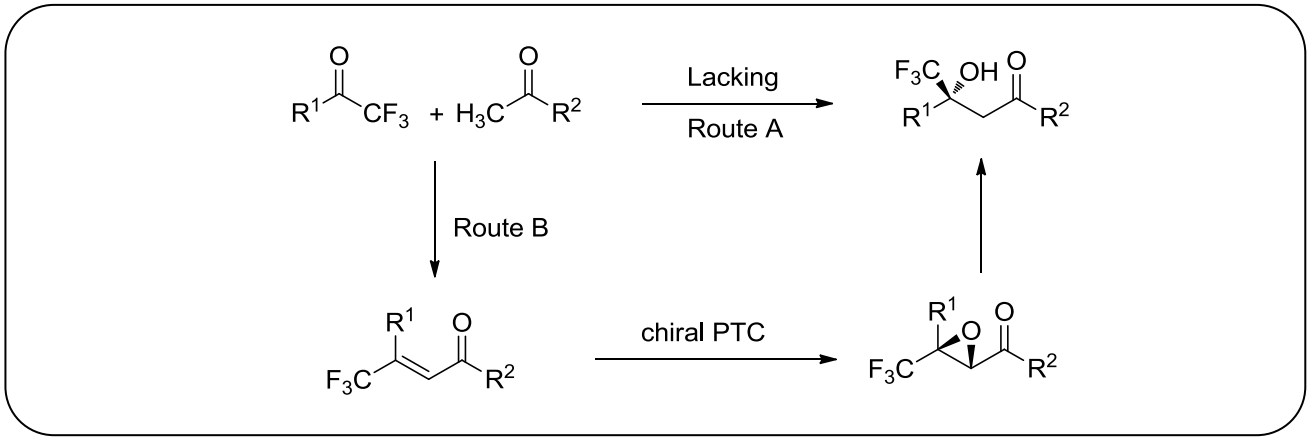


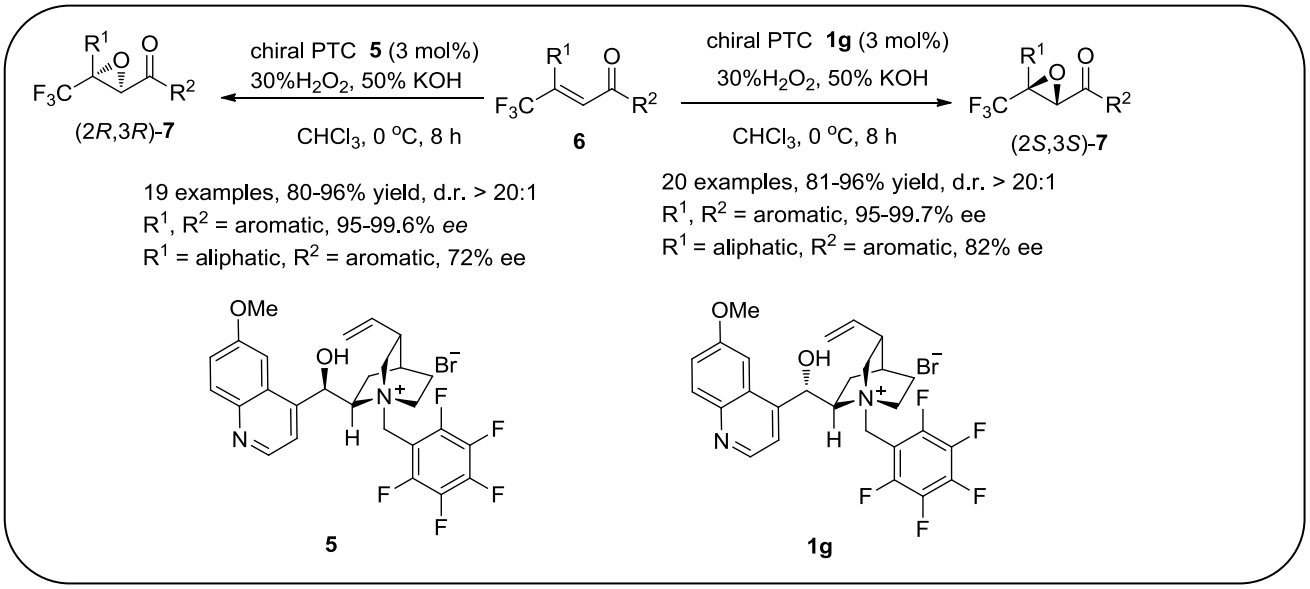
Scheme 1: Strategies for asymmetric synthesis of β-trifluoromethyl-β-hydroxy ketones.

of the special properties of trifluoromethyl group. The catalytic asymmetric epoxidation of β,β-disubstituted unsaturated ketones bearing a β-trifluoromethyl (Route B) is an ideal alternative for this purpose, and enantiomerically enriched trifluoromethylated epoxides with a quaternary carbon centers were obtained (Scheme 1).

Enantiomerically enriched α,β-epoxyketones are considered versatile chiral building blocks for access to several natural products and pharmaceuticals in asymmetric organic synthesis and medicinal chemistry [7]. Since the development of the asymmetric epoxidation of allylic alcohols by Sharpless in the early 1980s [8], considerable efforts were devoted to the development of an efficient catalytic system for asymmetric epoxidation of olefins in the last two decades [9]. Among them, the asymmetric epoxidation of electron-deficient olefins holds an indispensable position. In recent years, a variety of approaches available for asymmetric epoxidation of α,β-unsaturated ketones, have been surely elaborated [10]. As we all known, the most well-established methods used for this reaction include the use of chiral phase-transfer catalysts, chiral ligand-metal peroxides, polyamino acid, chiral hydroperoxides and chiral pyrrolidines [11]. Particularly, asymmetric phase-transfer catalysis has been extensively studied due to its many advantages [11c,12]. To date, cinchona alkaloid-derived PTCs (cinchona-PTCs) have been the most widely used PTCs by several groups including *Lygo* [13], *Arai* and *Shioiri* [14], *Corey* [15], *Park* [16], because PTC, e.g. quaternary ammonium salt, can be easily converted to the corresponding active species (ammonium hydroperoxide) with a mild and inexpensive oxidant such as H_2O_2. Although the asymmetric epoxidation of cyclic α,β-unsaturated ketones and acyclic β-unsaturated ketones has been competitively studied, a highly enantioselective epoxidation of acyclic β,β-disubstituted enones has to our knowledge less been described [17,18], especially for the β,β-disubstituted unsaturated ketones having a β-trifluoromethyl group. In 2011, *Yamamoto* reported the enantioselective epoxidation of acyclic β,β-disubstituted enones bearing a β-methyl group by $Fe(OTf)_2$ and phenanthroline giving the epoxide in 92% ee [18c]. However, β,β-disubstituted unsaturated ketones having a β-trifluoromethyl group were not explored. Recently, Shibata discovered an asymmetric aerobic epoxidation of β-trifluoromethyl-β,β-disubstituted enones induced by methylhydrazine, while it required use of equivalent of much flammable and toxic methylhydrazine [19].

Among the oxidants of the asymmetric epoxidation of α,β-unsaturated ketones, hydrogen peroxide is probably the best choice of terminal oxidant under the concept of green chemistry and the challenges of sustainable development demand for environmentally friendly and cost-effective approaches [20,21]. In addition, no universal phase-transfer catalyst is available for highly enantioselective epoxidation of all classes of different enone structures. Continuously exploring more effective and practical phase-transfer catalysis systems for asymmetric epoxidation of β,β-disubstituted unsaturated ketones bearing a β-trifluoromethyl group is still of great interest.

Previously, we communicated an enantioselective and diastereoselective epoxidation of acyclic β-CF3-β,β-disubstituted enones by H_2O_2 with pentafluorinated



Scheme 2: Catalytic asymmetric epoxidation of β,β-disubstituted enones bearing a β-trifluoromethyl group with hydrogen peroxide catalyzed by 1g and 5.

quinidine-derived phase transfer catalyst [22]. Herein, the effects of catalyst structure (**1a-g**, **2**, **3**, **4a-c**, **5**), reaction parameters, preparation of both (*S*,*S*) and (*R*,*R*) enantiomers in excellent yield (up to 96%), remarkable diastereoselectivity (up to 100:1 d.r.) and excellent enantioselectivity (up to 99% ee) (Scheme 2), and the plausible catalytic cycle are described in full length.

EXPERIMENTAL SECTION

The ^{1}H-NMR (400 MHz) spectra for solution in $CDCl_3$ and DMSO-d_6 were recorded on Bruker Avance 400 and Varian Mercury 400. Chemical shifts were reported in ppm from tetramethylsilane ($CDCl_3$, δ = 7.26; DMSO-d_6, δ = 2.50). Spectra were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration and assignment. ^{13}C NMR spectra were collected on Bruker Avance 400 and a Varian Mercury 400 (100 MHz) with complete proton decoupling. Chemical shifts were reported in ppm from the tetramethylsilane ($CDCl_3$, δ = 77.0; DMSO-d_6, δ = 39.5). The IR spectra were recorded on Thermo Scientific Nicolet iS10 with KBr pellets. Enantiomeric excesses were determined by HPLC on Shimadzu LC-20A apparatus with a Daicel Chiralpak OJ-H, AS-H, OD-H and AD-H. Optical rotations were measured on a Krüss P8000 polarimeter. HRMS was recorded on Bruker Apex IV FTMS. Mass spectra were performed on ZAB-HS mass spectrometer using ESI ionization. All melting points were determined on a XT4A melting point apparatus without correction. Analytical Thin Layer Chromatography (TLC) was performed using F254 pre-coated silica gel plate. Column chromatography was performed with silica gel (200–300 mesh). Petroleum ether (PE) used had a boiling point range of 60–90 °C. The β-CF_3-β,β-disubstituted enones (**6a-6t)** were prepared according to literature [22].

Procedure for the F_5-substituted quaternary ammonium salt catalyzed asymmetric epoxidation with hydrogen peroxide

Aqueous hydrogen peroxide (30%, 0.20 mL, 20.0 equiv) and 50% aqueous KOH (35μL, 3 equiv) were added to a mixture of β-trifluoromethyl β,β-disubstituted ketones **6a-t** (0.10 mmol), catalyst **1g** or **5** (1.8 mg, 0.003 mmol, 3 mol%), in $CHCl_3$ (0.1 mL), and the reaction mixture was stirred vigorously at 0 °C for 8 h. The reaction was quenched with water. Aqueous layer was extracted with EtOAc (15 mL x 3), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting mixture was purified by column chromatography with silica gel (PE/EtOAc = 50/1, v/v) to give the products (**7a-t, 8a-s**).

(2S,3S)-Phenyl(3-phenyl-3-(trifluoromethyl)oxiran-2-yl) methanone **(7a)**

Yield: 93%; white solid; m.p. 94–95 °C; $[\alpha]_D^{18}$ = –158.5 (*c* 0.13, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.05 (s, 0.01H), 4.75 (s, 1H), 7.21-7.30 (m, 0.95 × 3H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 59.0, 61.7 (q, *J* = 36.7 Hz), 121.6 (q, *J* = 278.6 Hz), 125.8, 127.1, 127.2, 127.3, 127.9, 128.9, 133.3, 133.8, 188.3; IR (KBr): 3031 , 1703, 1598, 1450, 1332, 1304, 1284, 1230, 1190, 1160, 1093, 1076, 1029, 1012, 960, 919, 884, 841, 764, 734, 689, 687, 669 cm^{-1}; MS (ESI): *m*/*z* = 315.0 (100) $[M + Na]^+$; The ee was determined by HPLC on Daicel Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 0.5 mL/min, 254 nm), $t_{(2S,3S)}$ = 12.9 min, $t_{(2R,3R)}$ = 31.5 min, 99% ee; d.r. = 50:1.

(2R,3R)-Phenyl(3-phenyl-3-(trifluoromethyl)oxiran-2-yl) methanone **(8a)**

Yield: 90%; $[\alpha]_D^{18}$ = +107.7 (*c* 0.13, CH_2Cl_2); The ee was determined by HPLC on Daicel Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 0.5 mL/min, 254 nm), $t_{(2S,3S)}$ = 12.9 min, $t_{(2R,3R)}$ = 31.4 min, 99.8% ee.

(2S,3S)- (4-Fluorophenyl)(3-phenyl -3- (trifluoromethyl) oxiran-2-yl)methanone **(7b)**

Yield: 84%; white solid; m.p. 50–53 °C; $[\alpha]_D^{18}$ = –155.0 (*c* 0.08, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.67 (s, 0.02H), 4.70 (s,1H), 7.11 (t, *J* = 6.4 Hz, 3H), 7.24-7.31 (m, 3H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.88-7.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 60.0 (d, *J* = 1.7 Hz), 62.6 (q, *J* = 37.0 Hz), 116.1, 116.3, 122.6 (q, *J* = 278.5 Hz), 126.7, 128.1, 128.4, 129.9, 131.0, 131.1, 131.2, 131.3, 165.0, 167.6, 188.2; IR (KBr): 3110, 3080, 2957, 2927, 1700, 1597, 1507, 1453, 1424, 1408, 1337, 1315, 1235, 1172, 1087, 1018, 964, 943, 883, 860, 844, 764, 730, 698, 609, 602 cm^{-1}; MS (ESI): *m*/*z* = 332.9 (100) $[M + Na]^+$; The ee was determined by HPLC on Daicel Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 11.9 min, $t_{(2R,3R)}$ = 17.3 min, 98% ee; d.r. = 50:1.

(2R,3R)-(4-Fluorophenyl)(3-phenyl-3-(trifluoromethyl) oxiran-2-yl)methanone **(8b)**

Yield: 81%; $[\alpha]_D^{18}$ = +205.0 (*c* 0.04, CH_2Cl_2); The ee was determined by HPLC on Daicel Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 11.9 min, $t_{(2R,3R)}$ = 17.3 min, 96% ee.

(2S,3S)- (4-Chlorophenyl) (3-phenyl-3-(trifluoromethyl) oxiran-2-yl)methanone **(7c)**

Yield: 82%; white solid; m.p. 90–91 °C; $[\alpha]_D^{18}$ = –132.1 (*c* 0.15, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.03 (s, 0.03H), 4.70 (s,1H), 7.24-7.33 (m, 3H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 60.0 (d, *J* = 1.7 Hz), 62.3 (q, *J* = 37.0 Hz), 122.5 (q, *J* = 278.6 Hz), 126.6, 128.0, 128.4, 129.2, 129.6, 130.0, 133.1, 140.9, 188.7; IR (KBr): 3067, 3014, 2924, 2850, 1698, 1588, 1572, 1487, 1450, 1424, 1399, 1336, 1315, 1298, 1285, 1233,1162, 1115, 1090,1021, 1008, 967, 946, 912, 882, 852, 831, 763, 748, 732, 718, 696, 640, 604, 531, 519 cm^{-1}; MS (ESI): *m*/*z* = 349.0 (100) $[M + Na]^+$; The ee was determined by HPLC on Daicel Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 7.2 min, $t_{(2R,3R)}$ = 13.6 min, 98% ee; d.r. = 50:1.

(2R,3R)- (4-Chlorophenyl) (3-phenyl-3-(trifluoromethyl) oxiran-2-yl)methanone **(8c)**

Yield: 80%; $[\alpha]_D^{18}$ = +285.0 (*c* 0.04, CH_2Cl_2); The ee was determined by HPLC on Daicel Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 7.4 min, $t_{(2R,3R)}$ = 14.0 min, 97% ee.

(2S,3S)- (4-Bromophenyl) (3-phenyl-3-(trifluoromethyl) oxiran-2-yl)methanone **(7d)**

Yield: 96%; white solid; m.p. 100–102 °C; $[\alpha]_D^{18}$ = –149.3 (*c* 0.13, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.02 (s, 0.02H), 4.69 (s, 1H), 7.24-7.26 (m, 2H), 7.29-7.33 (m, 1H), 7.37 (d, *J* = 7.2 Hz, 2H), 7.58-7.61 (dt, *J* = 1.8, 8.4 Hz, 2H), 7.70-7.73 (dt, *J* = 2.0, 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 59.9, 62.7 (q, *J* = 37.1 Hz), 122.5 (q, *J* = 278.6 Hz), 126.6, 128.0, 128.4, 129.7, 129.8, 130.0, 132.3, 133.5, 188.9; IR (KBr): 3051, 1700, 1592, 1472, 1390, 1201, 992, 901, 878, 847, 730, 699, 61 cm^{-1}; MS (ESI): *m*/*z* = 393.0 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 7.4 min, $t_{(2R,3R)}$ = 13.0 min, 95% ee; d.r. = 20:1.

(2R,3R)- (4-Bromophenyl) (3-phenyl-3-(trifluoromethyl) oxiran-2-yl)methanone **(8d)**

Yield: 85%; $[\alpha]_D^{18}$ = +156.1 (*c* 0.36, CH_2Cl_2); The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 6.9 min, $t_{(2R,3R)}$ = 12.3 min, 96% ee.

((2S,3S)-3-phenyl -3-(trifluoromethyl)oxiran-2-yl) (4-(trifluoromethyl)phenyl)methanone **(7e)**

Yield: 86%; white solid; m.p. 53–56 °C; $[\alpha]_D^{18}$ = –116.7 (*c* 0.12, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.67 (s, 0.05H), 4.73 (s, 1H), 7.23-7.32 (m, 3H), 7.36 (d, *J* = 7.2 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 60.1 (*J* = 1.7 Hz), 62.8 (q, *J* = 37.2 Hz), 122.4 (q, *J* = 278.4 Hz), 123.3 (q, *J* = 271.9 Hz), 125.9 (q, *J* = 3.7 Hz), 126.5, 128.1, 128.5, 128.6, 130.1, 135.4 (q, *J* = 32.9 Hz), 137.4, 189.5; IR (KBr): 3079, 3013, 2925, 1705, 1583, 1513, 1502, 1451, 1410, 1381, 1327, 1092, 1066, 1034, 1021, 1011, 970, 947, 913, 884, 837, 776, 764, 756, 729, 711, 696, 687, 641, 605, 520, 507 cm^{-1}; MS (ESI): *m*/*z* = 397.2 (100) $[M + K]^+$; The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 0.5 mL/min, 254 nm), $t_{(2S,3S)}$= 10.9 min, $t_{(2R,3R)}$ = 16.8 min, 98% ee; d.r. = 20:1.

((2R,3R) -3-phenyl -3-(trifluoromethyl)oxiran-2-yl) (4-(trifluoromethyl) phenyl)methanone **(8e)**

Yield: 82%; $[\alpha]_D^{18}$ = +86.2 (*c* 0.13, CH_2Cl_2); The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 0.5 mL/min, 254 nm), $t_{(2S,3S)}$ = 10.9 min, $t_{(2R,3R)}$ = 16.7 min, 96% ee.

(2S,3S)- Naphthalen-2- yl(3-phenyl-3-(trifluoromethyl) oxiran-2-yl)methanone **(7f)**

Yield: 87%; white solid; m.p. 76–79 °C; $[\alpha]_D^{18}$ = –386.0 (*c* 0.18, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.98 (s, 0.02H), 4.90 (s, 1H), 7.19-7.29 (m, 3H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.57-7.66 (m, 2H), 7.82-7.88 (m, 3H), 7.99 (d, *J* = 8.0 Hz, 1H), 8.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 60.2, 62.8 (q, *J* = 36.9 Hz), 122.7 (q, *J* = 278.5 Hz), 123.2, 126.9, 127.3, 127.9, 128.1, 128.4, 129.0, 129.3, 129.8, 129.9, 130.6, 132.2, 132.3, 136.0, 189.2; IR (KBr): 3066, 3005, 2917, 2849, 1693, 1628, 1468, 1452, 1352, 1334, 1302, 1275, 1269, 1224, 1188, 1125, 965, 946, 879, 826, 801, 764, 723, 698, 373 cm^{-1}; MS (ESI): *m*/*z* = 365.0 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 9.1 min, $t_{(2R,3R)}$ = 17.4 min, 98% ee; d.r. = 50:1.

(2R,3R)- Naphthalen-2- yl(3-phenyl-3-(trifluoromethyl) oxiran-2-yl)methanone **(8f)**

Yield: 81%; $[\alpha]_D^{18}$ = +329.3 (*c* 0.15, CH_2Cl_2); The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 9.0 min, $t_{(2R,3R)}$ = 17.3 min, 98% ee.

(2S,3S)- (1,1'-biphenyl)-4-yl-3-phenyl-3-(trifluoromethyl) oxiran-2-yl)methanone **(7g)**

Yield: 81%; white solid; m.p. 103–105 °C; $[\alpha]_D^{18}$ = –280.8 (*c* 0.25, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.09 (s, 0.01H), 4.79 (s, 1H), 7.24-7.323(m, 3H), 7.39-7.50 (m, 5H), 7.60-7.62 (m, 2H), 7.67-7.69 (m, 2H), 7.93-7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 60.1, 62.7 (q, *J* = 36.9 Hz), 122.7 (q, *J* = 278.6 Hz), 126.9, 127.3, 127.5, 128.1, 128.4, 128.6, 128.8, 129.0, 129.9, 133.4, 139.4, 147.0, 188.9; IR (KBr): 3071, 1697, 1678, 1604, 1582, 1452, 1404, 1336, 1288, 1240, 1172, 1087, 1025, 1006, 945, 917, 885, 852, 834, 778, 765, 750, 741, 730, 698, 648, 606, 522, 495 cm^{-1}; MS (ESI): *m*/*z* = 391.0 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, 0.5 mL/min, 254 nm), $t_{(2S,3S)}$ = 24.4 min, $t_{(2R,3R)}$ = 27.4 min, 99% ee; d.r. = 100:1.

(2R,3R) -(1,1'-biphenyl)-4-yl-3-phenyl-3-(trifluoromethyl) oxiran-2-yl)methanone **(8g)**

Yield: 84%; $[\alpha]_D^{18}$ =+330.0 (*c* 0.18, CH_2Cl_2); The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, 0.5 mL/min, 254 nm), $t_{(2S,3S)}$ = 24.7 min, $t_{(2R,3R)}$ = 27.3 min, 98% ee.

(2S,3S)-(3-Phenyl-3-(trifluoromethyl)oxiran-2-yl)(p-tolyl) methanone **(7h)**

Yield: 84%; white solid; m.p. 82–84 °C; $[\alpha]_D^{18}$ = –240.0 (*c* 0.24, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.41 (s, 3H), 4.05 (s, 0.04H), 4.75 (s, 1H), 7.22-7.30 (m, 5H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9, 60.0, 62.7 (q, *J* = 36.8 Hz), 122.7 (q, *J* = 278.5 Hz), 126.9, 128.1, 128.3, 128.4, 129.7, 129.9, 132.4, 188.7; IR (KBr): 3073, 3018, 2977, 1692, 1609, 1573, 1449, 1426, 1409, 1335, 1319, 1302, 1287, 1248, 1185, 1087, 1078, 1023, 1015, 1002, 969, 943, 913, 881, 852, 816, 785, 767, 729, 700, 642, 618, 611, 596, 521 cm^{-1}; MS (ESI): *m*/*z* = 329.1 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 5.8 min, $t_{(2R,3R)}$ = 17.7 min, 99% ee; d.r. = 25:1.

(2R,3R) -(3-Phenyl-3-(trifluoromethyl)oxiran-2-yl) (p-tolyl) methanone **(8h)**

Yield: 80%; $[\alpha]_D^{18}$ = +172.2 (*c* 0.18, CH_2Cl_2); The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 5.8 min, $t_{(2R,3R)}$ = 17.7 min, 99% ee.

(2S,3S)- (2-Methoxyphenyl) (3-phenyl-3-(trifluoromethyl) oxiran-2-yl)methanone **(7i)**

Yield: 94%; white solid; m.p. 72–83 °C; $[\alpha]_D^{18}$ = –295.0 (*c* 0.28, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.08 (s, 3H), 4.26 (s, 0.02H), 4.80 (s, 1H), 6.98 (t, *J* = 7.2, Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 7.25-7.31 (m, 3H), 7.45 (d, *J* = 6.8 Hz, 2H), 7.54-7.58 (m, 1H), 7.67 (dd, *J* = 1.6, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.6, 63.0 (q, *J* = 36.5 Hz), 63.4 (d, 1.9 Hz), 111.6, 121.3, 122.9 (q, *J* = 278.3 Hz), 127.8, 128.3, 128.5, 129.7, 131.1, 135.7, 159.7, 189.5; IR (KBr): 3057, 3023, 2950, 2842, 1680, 1597, 1580, 1485, 1467, 1451, 1438, 1214, 1185, 1150, 1117, 1018, 1008, 971, 946, 915, 877, 844, 782, 769, 728, 710, 699, 655, 640, 591 cm^{-1}; MS (ESI): *m*/*z* = 345.2 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 7.3 min, $t_{(2R,3R)}$ = 19.3 min, 99.7% ee; d.r. = 50:1.

(2R,3R)- (2-Methoxyphenyl)(3-phenyl-3-(trifluoromethyl) oxiran-2-yl)methanone **(8i)**

Yield: 81%; $[\alpha]_D^{18}$ = +296.0 (*c* 0.10, CH_2Cl_2); The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 7.3 min, $t_{(2R,3R)}$ = 19.3 min, 99.6% ee.

(2S,3S)- (3-Methoxyphenyl) (3-phenyl-3-(trifluoromethyl) oxiran-2-yl)methanone **(7j)**

Yield: 87%; white solid; m.p. 70–72 °C; $[\alpha]_D^{18}$ = –162.9 (*c* 0.14, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.81 (s, 3H), 4.00 (s, 0.02H), 4.77 (s, 1H), 7.15 (dd, *J* = 2.4, 8.0 Hz, 1H), 7.25-7.32 (m, 4H), 7.40 (t, *J* = 7.6 Hz, 3H), 7.52 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.5, 60.1 (d, *J* = 1.6 Hz), 62.8 (q, *J* = 36.9 Hz), 112.0, 120.8, 121.1, 122.6 (q, *J* = 278.7 Hz), 126.8, 128.1, 128.4, 129.9, 130.0, 136.1, 160.0, 189.1; IR(KBr): 3076, 3002, 2952, 1702, 1599, 1489, 1466, 1451, 1415, 1336, 1208, 1183, 966, 901, 890, 794, 779, 765, 741, 698, 684, 662, 646, 480 cm^{-1}; MS (ESI): *m*/*z* = 345.0 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 7.1 min, $t_{(2R,3R)}$ = 12.9 min, 99% ee; d.r. = 50:1.

(2R,3R)- (3-Methoxyphenyl) (3-phenyl-3-(trifluoromethyl) oxiran-2-yl) methanone **(8j)**

Yield: 81%; $[\alpha]_D^{18}$ = +147.7 (*c* 0.13, CH_2Cl_2); The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 7.2 min, $t_{(2R,3R)}$ = 13.0 min, 98% ee.

(2S,3S)- (4-Methoxyphenyl)(3-phenyl-3-(trifluoromethyl) oxiran-2-yl)methanone **(7k)**

Yield: 81%; white solid; m.p. 98–99 °C; $[\alpha]_D^{18}$ = –286.7 (*c* 0.12, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.87 (s, 3H), 4.05 (s, 0.01H), 4.72 (s, 1H), 6.92 (dt, *J* = 2.8, 8.8 Hz, 2H), 7.23-7.32 (m, 3H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.87 (dt, *J* = 2.8, 9.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.6, 60.0, 62.6 (qd, *J* = 2.7, 36.9 Hz), 114.2, 122.7 (q, *J* = 278.5 Hz), 127.0, 127.1, 128.1, 128.3, 129.8, 129.9, 130.6, 164.4, 187.6; IR (KBr): 2941, 1676, 1596, 1570, 1513, 1465, 1454, 1427, 1312, 1248, 1172, 1094, 1027, 1012, 969, 937, 878, 858, 845, 813, 765, 728, 706, 695, 644, 613, 596, 523cm^{-1}; MS (ESI): *m*/*z* = 345.1 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 7.8 min, $t_{(2R,3R)}$ = 10.8 min, 97% ee; d.r. = 100:1.

(2R,3R) -(4-Methoxyphenyl) (3-phenyl-3-(trifluoromethyl) oxiran-2-yl)methanone **(8k)**

Yield: 80%; $[\alpha]_D^{18}$ = +244.2 (*c* 0.10, CH_2Cl_2); The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 7.9 min, $t_{(2R,3R)}$ = 10.8 min, 97% ee.

(2S,3S)-(3-(4-Fluorophenyl)-3-(trifluoromethyl)oxiran-2-yl)(phenyl)methanone **(7l)**

Yield: 94%;colorless oil; $[\alpha]_D^{18}$ = –148.9 (*c* 0.85, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.66 (s, 0.02H), 4.77 (s,1H), 6.95 (t, *J* = 8.4 Hz, 2H), 7.38-7.41 (m, 2H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 60.1, 61.2 (q, *J* = 37.2 Hz), 115.6, 115.8, 122.5 (q, *J* = 278.5 Hz), 122.7, 122.8, 128.2, 129.0, 130.1, 130.2, 134.5,

134.7, 162.2, 164.7, 189.2; IR(KBr): 3062, 2926, 2360, 2341, 1703, 1680, 1666, 1609, 1599, 1582, 1515, 1451, 1426, 1413, 1322, 1299, 1285, 1267, 1233, 1180, 1101, 1075, 1015, 966, 954, 926, 883, 836, 816, 737, 705, 687, 669, 636, 603, 587, 571, 523 cm^{-1}; MS (ESI): *m*/*z* = 332.9 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 6.3 min, $t_{(2R,3R)}$ = 16.5 min, 98% ee; d.r. = 50:1.

(2R,3R)-(3-(4-Fluorophenyl)-3-(trifluoromethyl)oxiran-2-yl)(phenyl)methanone **(8l)**

Yield: 90%; $[\alpha]_D^{18}$ = +173.8 (*c* 0.48, CH_2Cl_2); The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 6.4 min, $t_{(2R,3R)}$ = 16.6 min, 97% ee.

(2S,3S)-(3-(4-Chlorophenyl)-3-(trifluoromethyl)oxiran-2-yl)(phenyl)methanone **(7m)**

Yield: 81%; white solid; m.p. 69–70 °C; $[\alpha]_D^{18}$ = –133.9 (*c* 1.30, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.03 (s, 0.03H), 4.70 (s, 1H), 7.24-7.33 (m, 3H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 60.0 (d, *J* = 1.5 Hz) , 62.3 (q, *J* = 37.2 Hz), 122.4 (q, *J* = 278.6 Hz), 125.4, 128.1, 128.8, 129.1, 129.5, 134.6, 134.7, 136.2, 189.0; IR (KBr): 3080, 3055, 3027, 2923, 1702, 1599, 1494, 1451, 1402, 1341, 1319, 1308, 1298, 1183, 1155, 1092, 1015, 967, 959, 941, 923, 882, 843, 828, 785, 750, 732, 709, 688, 668, 531 cm^{-1}; MS (ESI): *m*/*z* = 349.0(100) $[M+Na]^+$; The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 6.0 min, $t_{(2R,3R)}$ = 13.9 min, 98% ee; d.r. = 33:1.

(2R,3R)- (3-(4-Chlorophenyl)-3-(trifluoromethyl)oxiran-2-yl)(phenyl)methanone **(8m)**

Yield: 94%; $[\alpha]_D^{18}$ = +146.3 (*c* 1.05, CH_2Cl_2); The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 5.8 min, $t_{(2R,3R)}$ = 13.1 min, 97% ee.

(2S,3S)- (3-(4-Bromophenyl)-3-(trifluoromethyl)oxiran-2-yl)(phenyl)methanone **(7n)**

Yield: 96%; white solid; m.p. 77–79 °C; $[\alpha]_D^{18}$ = –223.2 (*c* 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.68 (s, 0.02H), 4.79 (s, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.40 -7.43 (m, 2H) 7.50 (t, *J* = 7.8 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 60.0, 61.3 (q, *J* = 37.2 Hz), 121.3 (q, *J* = 278.6 Hz), 123.5, 124.8, 127.1, 128.0, 128.7, 130.7, 133.5, 133.6, 187.9; IR (KBr): 3076, 3013, 2925, 2853, 2357, 2335, 1704, 1597, 1581, 1491, 1451, 1396, 1307, 1297, 1175, 1159, 1086,1071, 1011, 964, 940, 926, 844, 823, 785, 742, 724, 705, 687, 673, 604, 525 cm^{-1}; MS (ESI): *m*/*z* = 393.0 (100) $[M + Na]^+$; The ee was determined by HPLC on Daicel Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 6.0 min, $t_{(2R,3R)}$ = 13.7 min, 97% ee; d.r. = 50:1.

(2R,3R)-(3-(4-Bromophenyl)-3-(trifluoromethyl)oxiran-2-yl)(phenyl)methanone **(8n)**

Yield: 89%; $[\alpha]_D^{18}$ = +155.6 (*c* 0.90, CH_2Cl_2); The ee was determined by HPLC on Daicel Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 6.0 min, $t_{(2R,3R)}$ = 13.8 min, 96% ee.

(2S,3S)- (3-(4-Trifluorometnylphenyl)-3-(trifluoromethyl) oxiran-2-yl)(phenyl)methanone **(7o)**

Yield: 95%; colorless oil; $[\alpha]_D^{18}$ = –133.9 (*c* 0.23, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.06 (s, 0.04H), 4.82 (s, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.55 (t, *J* = 9.8 Hz, 4H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 60.0 , 62.4 (q, *J* = 37.3 Hz), 122.4 (q, *J* = 278.7 Hz), 123.5 (q, *J* = 271.5 Hz), 125.4 (q, *J* = 3.8 Hz), 128.2, 128.6, 129.1, 130.7, 132.1 (q, *J* = 32.7 Hz), 134.6, 134.7, 188.8; IR (KBr): 3063, 2915, 1703, 1679, 1599, 1582, 1451, 1412, 1267, 1232, 1171, 1132, 1068, 1022, 966, 945, 927, 884, 838, 775, 742, 688, 671, 639, 607, 523 cm^{-1}; MS (ESI): *m*/*z* = 383.0 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 4.7 min, $t_{(2R,3R)}$ = 8.9 min, 96% ee; d.r. = 25:1.

(2R,3R)-(3-(4-Trifluorometnylphenyl)-3-(trifluoromethyl) oxiran-2-yl)(phenyl)methanone **(8o)**

Yield: 96%; $[\alpha]_D^{18}$ = +191.3 (*c* 0.16, CH_2Cl_2); The ee was determined by HPLC on Chiralpak AS-H (*n*- hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 4.7 min, $t_{(2R,3R)}$ = 8.9 min, 95% ee.

(2S,3S)-Phenyl(3-(p-tolyl)-3-(trifluoromethyl)oxiran-2-yl) methanone **(7p)**

Yield: 86%; colorless oil; $[\alpha]_D^{18}$ = –149.1 (*c* 0.33, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 3H), 4.05 (s, 0.05H), 4.76 (s, 1H), 7.05 (d, *J* = 8.0, 2H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 60.0, 62.8 (q, *J* = 36.8 Hz), 122.7 (q, *J* = 278.6 Hz), 123.8, 127.9, 128.2, 128.9, 129.1, 134.3, 134.8, 139.9, 189.4; IR (KBr): 3373, 3042, 3001, 2928, 2855, 2351, 2337, 1697, 1614, 1597, 1580, 1518, 1450, 1403, 1381, 1334, 1233, 1171, 1085, 1074, 1031, 1017, 966, 955, 943, 928, 885, 823, 776, 685, 669, 602, 528 cm^{-1}; MS (ESI): *m*/*z* = 329.0 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 5.8 min, $t_{(2R,3R)}$ = 13.5 min, 99% ee; d.r. = 20:1.

(2R,3R)- Phenyl(3-(p-tolyl)-3-(trifluoromethyl)oxiran-2-yl)methanone **(8p)**

Yield: 83%; $[\alpha]_D^{18}$ = +173.3 (*c* 0.30, CH_2Cl_2); The ee was determined by HPLC on Chiralpak AS-H (*n*- hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 5.8 min, $t_{(2R,3R)}$ = 13.5 min, 98% ee.

(2S,3S)- Phenyl(-3-(thiophen-2-yl)-3-(trifluoromethyl) oxiran-2-yl)methanone **(7q)**

Yield: 90%; white solid; m.p. 58–60 °C; $[\alpha]_D^{18}$ = –100.0 (*c* 0.18, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.67 (s, 0.02H), 4.76 (s, 1H), 6.89 (dd, *J* = 4.0, 4.8 Hz, 1H), 7.15 (d, *J* = 3.2 Hz, 1H), 7.26-7.28 (m, 1H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.60-7.64 (m, 1H), 7.90 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 60.3 (q, *J* = 38.7 Hz), 61.4 (d, *J* = 1.5 Hz), 122.1 (q, *J* = 278.4 Hz), 127.0, 128.0, 128.1, 128.3, 129.0, 129.7, 134.5, 188.8; IR (KBr): 3136, 3092, 2925, 2363, 2335, 1698, 1598, 1581, 1451, 1439, 1356, 1323, 1232, 1197, 1086, 1071, 1054, 1013, 947, 909, 868, 851, 838, 774, 729, 692, 669, 594 cm^{-1}; MS (ESI): *m*/*z* = 321.1 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 7.8 min, $t_{(2R,3R)}$ = 23.0 min, 96% ee; d.r. = 50:1.

(2R,3R)- Phenyl(-3-(thiophen-2-yl)- 3-(trifluoromethyl) oxiran-2-yl)methanone (**8q**)

Yield: 83%; $[\alpha]_D^{18}$ = +155.7 (*c* 0.60, CH_2Cl_2); The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 7.7 min, $t_{(2R,3R)}$ = 22.5 min, 95% ee.

(2S,3S)-(4-bromo-3-methylphenyl)(3-(3,5-dichlorophenyl) - 3-(trifluoromethyl)oxiran-2-yl)methanone **(7r)**

Yield: 95%; white solid; m.p. 87-89 ºC; $[\alpha]_D^{18}$ = –171.3 (*c* 0.09, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.45 (s, 3H), 3.98 (s, 0.05H), 4.71 (s, 1H), 7.26-7.33 (m, 3H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1, 59.8, 61.8 (q, *J* = 37.5 Hz), 122.1 (q, *J* = 278.9 Hz), 125.7, 126.6, 126.8, 129.9, 130.1, 130.5, 132.7, 133.2, 133.5, 135.3, 139.4, 188.2; IR (KBr): 3037, 3011, 1700, 1601, 1496, 1181, 1021, 968, 870, 820, 729, 697, 600, 520 cm^{-1}; MS (ESI): *m*/*z* = 474.9 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 0.5 mL/min, 254 nm), $t_{(2S,3S)}$ = 12.9 min, $t_{(2R,3R)}$ = 31.5 min, 99% ee; d.r. = 25:1.

((2S, 3S)-3-ethyl-3-(trifluoromethyl)oxiran-2-yl) (phenyl)methanone **(7s)**

Yield: 88%; white solid; m.p. 53–55 °C; $[\alpha]_D^{25}$ = –38.6 (*c* 0.30, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03 (t, *J* = 7.8 Hz, 3H), 1.81 (q, *J* = 7.5 Hz, 2H), 3.68 (s, 0.01H), 4.50 (s, 1H), 7.56 (t, *J* = 8.0 Hz, 2H), 7.69 (t, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.8, 19.2, 59.0, 62.5 (q, *J* = 34.9 Hz), 123.3 (q, *J* = 278.8 Hz), 128.3, 129.1, 134.6, 134.9, 190.7; IR(KBr): 3026, 2987, 2954, 2893, 1697, 1647, 1450, 1345, 1228, 1159, 1149, 1102, 1084, 957, 842, 791, 713, 685, 666, 606 cm^{-1}; MS (ESI): *m*/*z* = 267.2 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 5.3 min, $t_{(2R,3R)}$ = 6.4 min, 82% ee; d.r. = 100:1.

((2R,3R)-3-ethyl-3-(trifluoromethyl)oxiran-2-yl)(phenyl) methanone **(8s)**

Yield: 85%; $[\alpha]_D^{25}$ = +35.1 (*c* 0.11, CH_2Cl_2); The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 4.6 min, $t_{(2R,3R)}$ = 5.6 min, 69% ee.

((2S, 3S)-3-benzyl-3-(trifluoromethyl)oxiran-2-yl)(phenyl)methanone **(7t)**

Yield: 90%; white solid; m.p. 76–78 °C; $[\alpha]_D^{25}$ = –89.1 (*c* 0.16, CH_2Cl_2);; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.04 (d, *J* = 15.0 Hz, 1H), 3.16 (d, *J* = 15.0 Hz, 1H),

3.97 (s, 0.01H), 4.56 (s,1H), 7.18-7.21 (m, 5H), 7.56 (t, J = 7.8 Hz, 2H), 7.70 (t, J = 7.2 Hz, 1H), 8.00 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.6, 58.9, 62.3 (q, J = 34.6 Hz), 123.0 (q, J = 279.2 Hz), 127.3, 128.3, 128.4, 129.1, 129.9, 133.1, 134.6, 135.1, 190.7; IR(KBr): 3064, 3035, 1686, 1596, 1496, 1454, 1431, 1347, 1315, 1186, 1156, 1077, 1000, 965, 860, 786, 734, 669, 633, 599 cm^{-1}; MS (ESI): m/z = 329.3 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane /*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 9.5 min, $t_{(2R,3R)}$ = 8.0 min, 81% ee; d.r. = 100:1.

((RS,3R)-3-benzyl-3-(trifluoromethyl)oxiran-2-yl)(phenyl) methanone **(8t)**

Yield: 87%; $[\alpha]_D^{25}$ = –76.3 (*c* 0.08, CH_2Cl_2);; The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), $t_{(2S,3S)}$ = 9.0 min, $t_{(2R,3R)}$ = 7.6 min, 72% ee.

Chemoselective reduction of β-trifluoromethyl-α,β-epoxy ketones

To a solution of **7** (0.10 mmol) in EtOH (1 mL), Zn (13.0 mg, 0.2 mmol, 2 equiv) and NH_4Cl (8.1 mg, 0.15 mmol, 1.5 equiv) were added. After the reaction mixture was stirred at 40 ºC for 2 h, it was quenched with water. Aqueous layer was extracted with EtOAc, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE/ethyl acetate = 20/1) on silica gel to give β-trifluoromethyl β-hydroxy ketone **9**.

(R)-4,4,4-trifluoro-3-hydroxy-1,3-diphenylbutan-1-one **(9a)**

Colorless oil, $[\alpha]_D^{18}$ = –97.6 (*c* 0.21, CH_2Cl_2) [lit. $[\alpha]_D^{20}$ = –85.9 (*c* 1.0, CH_2Cl_2, 90% ee)] [6d]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.64 (d, J = 17.6 Hz, 1H), 4.04 (d, J = 17.6 Hz, 1H), 5.68 (s, 1H), 7.32-7.39 (m, 3H), 7.49 (t, J = 8.0 Hz, 2H), 7.60-7.63 (m, 3H), 7.92-7.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.2, 76.5 (q, J = 28.9 Hz), 124.6 (q, J = 283.6 Hz), 126.3, 128.2, 128.5, 128.8, 130.0, 134.5, 136.3, 137.7, 199.7; IR (KBr): 3430, 3068, 2915, 2360, 2341, 1669, 1596, 1581, 1450, 1421, 1392, 1352, 1304, 1245, 1222, 1167, 1129, 1075, 1043, 1019, 1003, 954, 931, 913, 768, 758, 740, 710, 696, 685, 647, 621, 574, 539 cm^{-1}; MS (ESI): m/z = 317.1 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak AD-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), t_R = 10.0 min, t_S = 11.2 min, 99% ee.

(R)-1-(4-bromo-3-methylphenyl)-3-(3,5-dichlorophenyl)-4,4,4-trifluoro-3-hydroxybutan-1-one **(9b)**

Colorless oil, $[\alpha]_D^{18}$ = –83.9 (*c* 0.09, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.48 (s, 3H), 3.64 (d, J = 17.6 Hz, 1H), 3.80 (d, J = 17.2 Hz, 1H), 5.72 (s, 1H), 7.35 (t, J = 2.0 Hz, 1H), 7.48 (d, J = 0.08 Hz, 2H), 7.60 (dd, J = 2.0, 8.0 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.1, 51.5, 76.0 (q, J = 29.5 Hz), 125.1, 126.9, 126.9 (q, J = 284.1 Hz), 129.2, 130.2, 131.2, 132.9, 133.2, 134.8, 135.4, 139.3, 141.1, 198.4; IR (KBr): 3432, 3069, 2915, 1679, 1599, 1450, 1422, 1380, 1370, 1306, 1243, 1221, 1078, 1055, 1020, 998, 950, 928, 920, 761, 745, 712, 699 cm^{-1}; MS (ESI): m/z = 476.9 (100) $[M + Na]^+$; The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, 254 nm), t_R = 12.9 min, t_S = 31.5 min, 99% ee.

Ammonium bromides of cinchona alkaloids: General Procedure

To a flame-dried flask equipped with a magnetic stirring bar and a condenser was added with cinchona alkaloids (1 mmol), toluene (5 mL), and benzyl bromide derivatives (1.2 mmol, 1.2 equiv). The mixture was heated at 80 ºC until a TLC analysis showing that the starting material was completely consumed. Cooled to room temperature and poured onto Et_2O (30 mL) with stirring, the resulting suspension was stirred for another 1 h. Then the precipitate was purified by flash chromatography (MeOH/EtOAc = 1/10, v/v).

N-(3,5-Ditrifluoromethylbenzyl)quinidinium Bromide [11d] **(1a)**

Yield: 85%; white solid; m.p. 177 °C (decomp.); $[\alpha]_D^{28}$ +176.1 (*c* 0.19, CH_3OH); IR (KBr): 3394, 3201, 2954, 2664, 1622, 1509, 1473, 1432, 1374, 1281, 1214, 1226, 1178, 1135, 1027, 1005, 866, 905, 843, 828, 709, 682 cm^{-1}; ^{1}H NMR (400 MHz, DMSO–d_6): δ = 8.82 (d, J = 4.8 Hz, 1H), 8.56 (s, 2H), 8.38 (s, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.77 (d, J = 4.4 Hz, 1H), 7.53 (dd, J = 7.2, 2.4 Hz 1H),

7.44 (d, *J* = 2.4 Hz, 1H), 6.78 (d, *J* = 3.2 Hz, 1H), 6.48 (s, 1H), 6.04 (ddd, *J* = 17.4, 10.2, 7.2 Hz, 1H), 5.28 (d, *J* = 2.8 Hz, 1H), 5.22 (d, *J* = 12.4 Hz, 2H), 5.01 (d, *J* = 12.8 Hz, 1H), 4.34 (t, *J* = 10.0 Hz, 1H), 4.10–4.13 (m, 1H), 4.06 (s, 3H), 3.80 (t, *J* = 9.4 Hz, 1H), 3.48 (t, *J* = 11.4 Hz, 1H), 3.04 (q, *J* = 9.6 Hz, 1H), 2.62 (q, *J* =8.4 Hz, 1H), 2.42 (t, *J* = 11.6 Hz, 1H), 1.91 (s, 1H), 1.85–1.72 (m, 2H), 1.20–1.13 (m, 1H); ^{13}C NMR (100 MHz, DMSO–*d*$_6$): δ = 158.1, 147.9, 144.2, 143.7, 137.8, 135.1, 132.0, 131.7, 131.3 (q, *J* = 33.1 Hz), 130.1, 126.0, 125.0, 124.6 (q, *J* = 4.1 Hz), 123.7 (q, *J* = 271.3 Hz), 121.5, 120.9, 117.6, 103.1, 68.4, 65.2, 61.8, 56.3, 56.2, 54.7, 37.4, 26.9, 23.6, 21.1.

N-(4-Methylbenzyl)quinidinium Bromide [11d] **(1b)**

Yield: 80%; white solid; m.p. 240 °C (decomp.); $[\alpha]_D^{28}$ +154.3 (*c* 0.35, CH_3OH); IR (KBr): 3406, 3054, 1620, 1585, 1508, 1467, 1417, 1353, 1255, 1239, 1227, 1125, 1037, 1002, 928, 931, 816 cm^{-1}; ^{1}H NMR (400 MHz, DMSO–*d*$_6$): δ = 8.81 (d, *J* = 4.4 Hz, 1H), 8.02 (d, *J* = 5.2 Hz, 1H), 7.77 (d, *J* = 4.4 Hz, 1H), 7.60 (t, *J* = 3.8 Hz, 2H), 7.50 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.44 (s, 1H), 7.38 (d, *J* = 7.6 Hz, 2H), 6.84 (s, 1H), 6.53 (s, 1H), 6.03 (ddd, *J* = 17.6, 10.0, 7.2 Hz, 1H), 5.25 (s, 1H), 5.22 (d, *J* = 6.0 Hz, 1H), 5.00 (d, *J* = 12.8 Hz, 1H), 4.72 (d, *J* = 12.8 Hz, 1H), 4.23–4.19 (m, 1H), 4.07 (s, 3H), 3.96–3.94 (m, 1H), 3.85 (t, *J* = 9.2 Hz, 1H), 3.48 (t, *J* = 11.4 Hz, 1H), 2.90 (q, *J* = 9.6 Hz, 1H), 2.66 (q, *J* = 8.4 Hz, 1H), 2.39 (s, 4H), 1.89 (s, 1H), 1.76 (t, *J* = 8.8 Hz, 2H), 1.12–1.05 (m, 1H); ^{13}C NMR (100 MHz, DMSO–*d*$_6$): δ = 157.9, 147.9, 144.2, 144.0, 140.4, 137.7, 134.0, 131.9, 130.1, 125.9, 125.2, 121.9, 120.8, 117.5, 102.8, 67.7, 65.1, 63.6, 56.4, 56.1, 54.2, 37.2, 26.9, 23.6, 21.4, 21.1; HRMS calcd for $[C_{28}H_{33}N_2O_2]^+$: 429.2536, found 429.2540.

N-(4-Trifluoromethylbenzyl)quinidinium Bromide [11d] **(1c)**

Yield: 87%; white solid; m.p. 218 °C (decomp.); $[\alpha]_D^{28}$ +184.2 (*c* 0.15, CH_3OH); IR (KBr): 3398, 3209, 2954, 1621, 1589, 1509, 1373, 1427, 1325, 1227, 1241, 1170, 1125, 1068, 1021, 1003, 934, 864, 832 cm^{-1}; ^{1}H NMR (400 MHz, DMSO–*d*$_6$): δ = 8.82 (d, *J* = 4.4 Hz, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.97 (dd, *J* = 10.4, 9.2 Hz, 4H), 7.77 (d, *J* = 4.4 Hz, 1H), 7.51 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 6.84 (d, *J* = 3.6 Hz, 1H), 6.52 (s, 1H), 6.03 (ddd, *J* = 17.4, 10.5, 6.9 Hz, 1H), 5.25 (s, 1H), 5.10 (d, *J* = 8.4 Hz, 2H), 4.85 (d, *J* = 12.8 Hz, 1H), 4.28–4.22 (m, 1H), 4.06 (s, 3H), 4.02–4.00 (m, 1H), 3.86 (t, *J* = 9.4 Hz, 1H), 3.50 (t, *J* = 11.4 Hz, 1H), 3.00–2.90 (m, 1H), 2.69–2.63 (m, 1H), 2.40 (t, *J* = 11.4 Hz, 1H), 1.91 (s, 1H), 1.79–1.75 (m, 2H), 1.15–1.07 (m, 1H). ^{13}C NMR (100 MHz, DMSO–*d*$_6$): δ = 158.0, 147.9, 144.2, 143.8, 137.7, 135.1, 133.0, 131.9, 130.9 (q, *J* = 31.8 Hz), 126.4, 126.3, 125.9, 123.1, 121.7, 120.8, 117.5, 103.0, 68.1, 65.2, 62.9, 56.5, 56.2, 54.5, 37.2, 26.8, 23.6, 21.1.

N-(9-Anthrylmethyl)quinidinium Chloride [11d] **(1d)**

Yield: 80%; light yellow solid; m.p. 161 °C (decomp.) (lit.[26] mp 160 °C, decomp.); $[\alpha]_D^{28}$ +390.0 (*c* 0.12, CH_3OH); IR (KBr): 3394, 3183, 1621, 1508, 1458, 1473, 1431, 1258, 1362, 1240, 1227, 1029, 922, 864, 744 cm^{-1}; ^{1}H NMR (400 MHz, DMSO–*d*$_6$): δ = 8.98 (s, 1H), 8.86 (d, *J* = 4.4 Hz, 1H), 8.79 (d, *J* = 9.2 Hz, 1H), 8.70 (d, *J* = 9.2 Hz, 1H), 8.28 (dd, *J* = 8.2, 3.0 Hz, 2H), 8.05 (d, *J* = 9.2 Hz, 1H), 7.90 (d, *J* = 4.4 Hz, 1H), 7.82–7.74 (m, 3H), 7.69–7.64 (m, 3H), 7.53 (dd, *J* = 7.6, 2.4 Hz, 1H), 6.98 (s, 1H), 6.33 (d, *J* = 14.4 Hz, 1H), 6.03 (ddd, *J* = 17.2, 10.2, 7.2 Hz, 1H), 5.88 (d, *J* = 14.0 Hz, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 5.08 (d, *J* = 17.2 Hz, 1H), 4.46 (t, J = 9.2 Hz, 2H), 4.21 (s, 4H), 3.18 (t, *J* = 11.2 Hz, 1H), 2.62–2.54 (m, 1H), 2.46–2.35 (m,2H), 1.78 (s, 1H), 1.69 (d, *J* = 8.4 Hz, 1H), 1.56–1.53 (m, 1H), 1.10–1.04 (m, 1H); ^{13}C NMR (100 MHz, DMSO–*d*$_6$): δ = 157.9, 147.9, 144.3, 137.9, 133.5, 133.3, 132.5, 131.8, 131.7, 131.6, 130.2, 128.3, 128.0, 126.1, 126.0, 125.3, 125.0, 122.3, 121.0, 119.3, 117.5, 103.2, 67.9, 65.7, 56.5, 56.1, 55.8, 55.6, 37.7, 26.1, 24.2, 21.6.

N-(2-F-4-Br-benzyl)quinidinium Bromide [11d] **(1e)**

Yield: 79%; white solid; m.p. 174–176°C (decomp.); $[\alpha]_D^{28}$ +143.3 (*c* 0.14, CH_3OH); IR (KBr): 3387, 3198, 3006, 1621, 1520, 1473, 1460, 1431, 1338, 1259, 1241, 1205, 1113, 1026, 851, 828, 719 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 8.81 (d, *J* = 4.4 Hz, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.87–7.76 (m, 3H), 7.67 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.50 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 6.86 (d, *J* = 2.8 Hz, 1H), 6.51 (s, 1H), 6.03 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.25–5.23 (m, 2H), 5.06 (d, *J* = 12.4 Hz, 1H), 4.77 (d, *J* = 12.4 Hz, 1H), 4.19 (t, *J* = 9.6 Hz, 1H), 4.06 (s, 3H), 3.97–3.85 (m, 2H), 3.44 (t, *J* = 11.2 Hz, 1H), 3.12 (q, *J* = 10.0 Hz, 1H), 2.68–2.62 (m,1H), 2.36 (t, *J* = 11.2 Hz, 1H), 2.00 (s, 1H), 1.82–1.75

(m, 2H), 1.10–1.03 (m, 1H); ^{13}C NMR (100 MHz, DMSO–d_6): δ = 162.1 (d, J = 252.2 Hz), 157.9, 147.9, 144.2, 143.8, 137.6, 131.9, 129.0, 125.8, 125.5 (d, J = 10.1 Hz), 121.9, 120.7, 120.3 (d, J = 25.7 Hz), 117.5, 115.4 (d, J = 13.7 Hz), 102.8, 67.9, 65.3, 56.8, 56.1, 54.7, 37.4, 26.6, 23.7, 21.0; HRMS calcd for $[C_{33}H_{35}F_6N_2O_2]^+$: 511.1391, found 511.1398.

N-(2,4,5-Trifluorobenzyl)quinidinium Bromide [11d] **(1f)**

Yield: 69%; white solid; m.p. 182–185 °C (decomp.); $[\alpha]_D^{28}$ +194.8 (*c* 0.19, CH_3OH); IR (KBr): 3394, 3198, 3006, 1621, 1520, 1473, 1469, 1431, 1338, 1259, 1241, 1226, 1205, 1158, 1113, 1026, 851, 828, 719 cm^{-1}; ^{1}H NMR (400 MHz, DMSO–d_6): δ = 8.82 (d, J = 4.4 Hz, 1H), 8.16–8.10 (m, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.91–7.85 (m, 1H), 7.76 (d, J = 4.4 Hz, 1H), 7.50 (dd, J = 9.6, 2.8 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 2.8 Hz, 1H), 6.50 (s, 1H), 6.03 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H), 5.26–5.21 (m, 2H), 5.01 (d, J = 12.8 Hz, 1H), 4.77 (d, J = 13.6 Hz, 1H), 4.23–4.18 (m, 1H), 4.06 (s, 3H), 3.94–3.82 (m, 2H), 3.49 (t, J = 11.4 Hz, 1H), 3.22–3.15 (m, 1H), 2.67–2.60 (m, 1H), 2.36 (t, J = 11.8 Hz, 1H), 1.90 (s, 1H), 1.84–1.75 (m, 2H), 1.10–1.05 (m, 1H); ^{13}C NMR (100 MHz, DMSO–d_6): δ = 158.0 (ddd, J = 244.1, 9.9, 2.3 Hz), 157.9, 151.5 (dt, J = 251.2, 13.6 Hz), 147.9, 146.7 (ddd, J = 241.8, 12.6, 2.4 Hz), 144.2, 143.7, 137.7, 131.9, 125.9, 123.8 (dd, J = 19.1, 2.7 Hz), 122.0, 120.7, 117.6, 112.8 (dt, J = 17.0, 5.6 Hz), 107.5 (dd, J = 29.5, 21.4 Hz), 102.7, 68.0, 65.3, 56.4, 56.1, 56.0, 54.7, 37.5, 26.6, 23.7, 21.0; HRMS calcd for $[C_{27}H_{28}F_3N_2O_2]^+$: 469.2097, found 469.2098.

N-(2,3,4,5,6-pentafluorobenzyl)quinidinium Bromide [28] **(1g)**

Yield: 83 %; $[\alpha]_D^{18}$ = + 217.1 (*c* 0.11, CH_3OH); m.p. 190 °C (decomp.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 8.82 (d, J = 4.4 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.78 (d, J = 4.4 Hz, 1H), 7.51 (dd, J = 2.4, 9.2 Hz, 1H), 7.46 (d, J = 2.4 Hz, 1H), 6.98 (d, J = 2.8 Hz, 1H), 6.52 (s, 1H), 6.06 (ddd, J = 17.4, 10.2, 7.2 Hz, 1H), 5.26 (t, J = 10.4 Hz, 2H), 5.15 (d, J = 13.6 Hz, 1H), 4.91 (d, J = 13.6 Hz, 1H), 4.13 (m, 2H), 4.07 (s, 3H), 3.83 (t, J = 10.4 Hz, 1H), 3.61 (t, J = 11.2 Hz, 1H), 3.13 (d, J = 7.2 Hz, 1H), 3.11 (q, J = 7.2 Hz, 1H), 2.62 (q, J = 8.4 Hz, 1H), 2.35 (t, J = 11.4 Hz, 1H), 1.93 (s, 1H), 1.87–1.79 (m, 2H); ^{13}C NMR (100 MHz, DMSO–d_6): δ 157.8, 147.9, 144.2, 144.1, 138.3, 131.8, 125.8, 121.9, 120.8, 117.4, 103.1, 68.8, 65.4, 64.6, 59.7, 56.1, 52.2, 51.5, 46.1, 38.1, 26.1, 25.0, 20.9; IR (KBr): 3377, 3170, 2976, 2678, 1660, 1622, 1591, 1528, 1509, 1475, 1461, 1432, 1402, 1381, 1358, 1310, 1244, 1137, 1078, 1057, 1028, 964, 944, 917, 876, 832 cm^{-1}; HRMS calcd for $C_{27}H_{26}F_5N_2O_2$: 505.1909, found 505.1919.

1,3-Bis(quinidinium-N-methylene)benzene Dibromide [11d] **(2)**

A mixture of quinidine (324.4 mg, 1.0 mmol) with α,α′-dibromo-*m*-xylene (132.0 mg, 0.5 mmol) in a mixture of ethanol (1 mL), DMF (1.2 mL), and chloroform (0.4 mL) was stirred at 100 °C for 8 h. After cooling the reaction mixture to room temperature, the reaction mixture was diluted with methanol (40 mL) and then added to ether (200 mL) dropwise with stirring. The solid precipitated was filtered. The resulting precipitate was purified by flash chromatography (MeOH/EtOAc = 1/10, v/v). Yield: 75%; white solid; m.p. 218 °C (decomp.); $[\alpha]_D^{28}$ +197.2 (*c* 0.14, CH_3OH); IR (KBr): 3386, 2951, 2361, 1621, 1590, 1509, 1473, 1459, 1431, 1358, 1241, 1227, 1207, 1026, 1001, 934, 866, 828, 717, 855 cm^{-1}; ^{1}H NMR (400 MHz, DMSO–d_6): δ = 8.82 (d, J = 4.0 Hz, 2H), 8.07 (s, 1H), 8.03 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 7.6 Hz, 2H), 7.78 (d, J = 4.4 Hz, 2H), 7.74 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 2.0 Hz, 2H), 6.83 (d, J = 3.2 Hz, 2H), 6.56 (s, 2H), 6.03 (ddd, J = 16.8, 10.4, 6.8 Hz, 2H), 5.22–5.12 (m, 6H), 4.82 (d, J = 12.4 Hz, 2H), 4.24–4.19 (m, 2H), 4.09–3.99 (m, 8H), 3.85–3.80 (m, 2H), 3.53–3.47 (m, 2H), 3.27–3.22 (m, 2H), 2.77–2.70 (m, 2H), 2.42 (t, J = 11.4 Hz, 2H), 1.91 (s, 2H), 1.76–1.74 (m, 4H), 1.16–1.12 (m, 2H); ^{13}C NMR (100 MHz, DMSO–d_6): δ = 158.0, 147.9, 144.2, 143.9, 139.2, 137.7, 135.7, 131.9, 130.2, 129.0, 125.9, 121.8, 120.9, 117.5, 102.8, 68.0, 65.1, 63.3, 56.2, 54.1, 37.3, 26.9, 23.5, 21.1.

N-(3,3″,5,5″- tetrakis(trifluoromethyl) -1,1′:3′,1″-terbenzyl)quinidinium Bromide [11d] **(3)**

Yield: 71%; white solid; m.p. 186 °C (decomp.); $[\alpha]_D^{28}$ +129.5 (*c* 0.14, CH_3OH); IR (KBr): 3402, 3196, 2946, 1711, 1621, 1509, 1432, 1280, 1239, 1226, 1176, 1134, 1029, 1002, 900, 885, 844, 827, 718, 704, 683, 640 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, J = 4.4 Hz, 1H), 8.29 (s, 2H), 8.00 (s, 4H), 7.84 (s, 2H), 7.69 (d,

J = 6.0 Hz, 2H), 7.60 (s, 1H), 7.42 (s, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.71 (d, *J* = 5.6 Hz, 1H), 6.44 (s, 1H), 6.00 (s, 2H), 5.88 (ddd, *J* = 17.0, 10.2, 7.0 Hz, 1H), 5.23–5.17 (m, 2H), 4.66 (t, *J* = 10.0 Hz, 1H), 4.36 (t, *J* = 10.0 Hz, 1H),4.10 (t, *J* = 9.0 Hz, 1H), 3.77 (s, 3H), 3.34 (t, *J* = 11.2, 1H), 2.98 (q, *J* = 10.0 Hz, 1H), 2.28–2.43(m, 2H), 1.82 (s, 1H), 1.78 (d, *J* = 8.4 Hz, 2H), 0.90–0.83 (m, 1H); ^{13}C NMR (100 MHz, DMSO–d_6): δ = 157.8, 147.0, 143.9, 142.1, 139.8, 135.1, 133.1, 132.5 (q, *J* = 33.4 Hz), 131.5, 130.2, 127.3, 127.2, 127.1, 126.0, 123.1 (q, *J* = 272.0 Hz), 122.1 (q, *J* = 3.4 Hz), 120.4, 120.1, 118.4, 102.8, 68.2, 66.8, 61.5, 56.9, 56.3, 54.5, 38.1, 27.1, 24.0, 21.7.

N-(2,3,4,5,6- Pentafluorobenzyl-O(9) -2,3,4,5,6-pentafluorobenzyl)quinidinium Bromide **(4a)**

To a suspension of *N*-(2,3,4,5,6-pentafluorobenzyl)quinidinium bromide (292.7 mg, 0.5 mmol) in dichloromethane (2 mL) was added 2,3,4,5,6-pentafluorobenzyl bromide (652 mg, 2.5 mmol) and 50% aqueous KOH (280.0 µL, 2.5 mmol). The resulting mixture was stirred vigorously at room temperature for 4h. The mixture was diluted with water (3 mL) and was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude solid was purified by flash chromatography (MeOH/EtOAc = 1/10, v/v) to give a white solid (275.0 mg). Yield: 72%; $[\alpha]_D^{18}$ = +85.7 (*c* 0.10, CH_2Cl_2); m.p. 165 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, *J* = 4.4 Hz, 1H), 7.82 (d, *J* = 9.2 Hz, 1H), 7.60 (s, 1H), 7.50 (s, 1H), 7.35 (d, *J* = 4.4 Hz, 1H), 5.60 (d, *J* = 14.4 Hz, 1H), 5.51 (ddd, *J* = 17.2, 10.2, 6.8 Hz, 1H), 5.18 (d, *J* = 10.0 Hz, 1H), 4.92 (d, *J* = 10.4 Hz, 2H), 4.85 (d, *J* = 17.2 Hz, 1H), 4.22 (d, *J* = 10.4 Hz, 1H), 4.14 (s, 3H), 4.05 (m, 1H), 3.83 (m, 2H), 3.63 (t, *J* = 9.2 Hz, 1H), 3.43 (t, *J* = 10.4 Hz, 1H), 2.85 (m, 1H), 2.25 (t, *J* = 12.0 Hz, 1H), 2.04–1.88 (m, 2H), 1.85 (s, 1H), 1.71–1.63 (m, 1H), 1.00–0.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 146.9, 144.6, 137.8, 135.5, 131.6, 129.0, 128.2, 126.1, 125.3, 124.9, 124.8, 124.7, 123.1, 118.7, 117.2, 100.8, 73.43, 69.2, 57.3, 57.1, 57.0, 55.9, 55.5, 36.8, 26.2, 23.6, 21.3, 18.5; IR (KBr): 3409, 2939, 2739, 2677, 2492, 1659, 1621, 1525, 1509, 1477, 1433, 1398, 1382, 1358, 1309, 1262, 1229, 1241, 1133, 1060, 1038, 977, 962, 936, 869, 830 cm^{-1}; HRMS calcd for $C_{34}H_{27}F_{10}N_2O_2$: 685.1907, found 685.1897.

N-(2,3,4,5,6-Pentafluorobenzyl) -6´-hydroxyquinidinium Bromide **(4b)**

Thioethanol (2.30 mL, 30.8 mmol) was added under argon atmosphere to a stirred suspension of sodium hydride (370.0 mg, 15.4 mmol) in dry DMF (15 mL). Quinidine (500 mg, 1.5mmol) in dry DMF (7.5 mL) was added dropwise and the reaction mixture was stirred at 110 °C for 13 h. The solvent and excessive ethanethiol were removed under reduced pressure. Then pentafluorobenzyl bromide (574.2 mg, 2.2 mmol) was added in THF (9 mL). The reaction mixture was refluxed and monitored by TLC analysis. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (MeOH/EtOAc = 1/20, v/v). The product was obtained as pale white solid. Yield: 57%; $[\alpha]_D^{18}$ = +96.0 (*c* 0.10, CH_3OH); m.p. 170 °C (decomp.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 10.13 (s, 1H), 8.74 (d, *J* = 4.4 Hz, 1H), 7.94 (d, *J* = 9.2 Hz, 1H), 7.69 (d, *J* = 4.0 Hz, 2H), 7.40 (dd, *J* = 2.4, 9.2 Hz, 1H), 6.86 (d, *J* = 3.2 Hz, 1H), 6.33 (s, 1H), 6.03 (ddd, *J* = 17.2, 10.2, 7.2 Hz, 1H), 5.24 (d, *J* = 11.8 Hz, 2H), 5.18 (d, *J* = 5.2 Hz, 1H), 4.19–4.11 (m, 2H), 3.87 (t, *J* = 11.2 Hz, 1H), 3.61–3.51 (m, 2H), 2.63 (q, *J* = 8.4 Hz, 2H), 2.27(t, *J* = 11.6 Hz, 1H), 1.91–1.79 (m, 3H), 1.09–1.03 (m, 1H); ^{13}C NMR (100 MHz, DMSO–d_6): δ 156.5, 147.1, 143.3, 142.9, 137.5, 131.7, 126.2, 122.2, 120.5, 117.7, 105.3, 67.5, 65.7, 56.6, 54.6, 51.3, 37.7, 26.2, 23.8, 21.3; IR (KBr): 3193, 2975, 2940, 2739, 2677, 2491, 1620, 1528, 1509, 1467, 1433, 1398, 1309, 1220, 1135, 1035, 1011, 963, 947, 929 cm^{-1}; HRMS calcd for $C_{26}H_{24}F_5N_2O_2$: 491.1752, found 491.1758.

N-(2,3,4,5,6- Pentafluorobenzyl)-9 -O-benzyl-6'-hydroxyquinidinium Bromide **(4c)**

Sodium hydride (96.0 mg, 4.0 mmol) was added to a solution of quinidine (324.4 mg, 1.0 mmol) in dry DMF (5 mL). Benzyl chloride (173 µl, 1.5 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 20 h. The aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford yellowish oil**,** which was not isolated. Ethanethiol (434.0 µL, 5.8 mmol) was added to a stirred suspension of sodium hydride (139.3 mg, 5.8 mmol) in dry DMF (3 mL). The yellowish oil (300 mg) in dry DMF (3 mL) was added dropwise and the reaction

mixture was stirred at 110 °C for 15 h. The solvent and excess ethanethiol were removed under reduced pressure and the crude product was not isolated. Then the pentafluorobenzyl bromide (287.2 mg, 1.1 mmol) was added in THF (7 mL). The reaction mixture was refluxed and monitored by TLC analysis. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (MeOH/EtOAc = 1/20, v/v). The product was obtained as pale white solid. Yield: 41%; $[\alpha]_D^{18}$ = -32.0 (*c* 0.075, CH_3OH); m.p. 232 °C (decomp.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 9.63 (s, 1H), 8.80 (d, *J* = 4.0 Hz, 1H), 8.51 (s, 1H), 8.17–8.14 (m, 1H), 7.63 (s, 1H), 7.43–7.37 (m, 6H), 6.28 (s, 1H), 6.08 (d, *J* = 10.8 Hz, 1H), 5.70 (ddd, *J* = 17.4, 10.2, 6.4 Hz, 1H), 5.09 (d, *J* =8.4 Hz, 1H), 4.95 (d, *J* = 14.0 Hz, 1H), 4.78 (d, *J* = 10.8 Hz, 1H), 4.71–4.65 (m, 2H), 4.60–4.39 (m, 2H), 4.15 (t, *J* = 7.2 Hz, 1H), 3.75 (q, *J* = 7.2 Hz, 1H), 3.49–3.42 (m, 2H), 2.27 (t, *J* = 9.2 Hz, 1H), 2.03–1.92(m, 4H); ^{13}C NMR (100 MHz, DMSO–d_6): δ 166.8, 156.5, 145.5, 143.2, 135.8, 134.9, 134.0, 131.5, 131.0, 130.1, 129.0, 128.9, 128.6, 127.9, 125.0, 123.2, 122.9, 117.9, 103.9, 72.7, 71.1, 65.6, 64.7, 58.5, 55.3, 53.6, 36.8, 29.7, 26.2, 22.6, 20.8; IR (KBr): 3462, 2975, 2938, 2802, 2738, 2677, 2601, 2491, 1476, 1469, 1434, 1398, 1384, 1171, 1036 cm^{-1}; HRMS calcd for $C_{33}H_{30}F_5N_2O_2$:581.2222, found 581.2236.

N-(2,3,4,5,6-pentafluorobenzyl)quininium Bromide **(5)**

Yield: 74%; $[\alpha]_D^{18}$ = –195.8 (*c* 0.19, CH_3OH); m.p. 175 °C (decomp.); ^{1}H NMR (500 MHz, DMSO–d_6): δ 8.82 (d, *J* = 4.5 Hz, 1H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.78 (d, *J* = 4.5 Hz, 1H), 7.50 (dd, *J* = 2.0, 9.0 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 6.82 (d, *J* = 3.5 Hz, 1H), 6.58 (s, 1H), 5.78 (ddd, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.60 (d, *J* = 13.5 Hz, 1H), 5.10 (d, *J* = 17.0 Hz, 1H), 5.03 (d, *J* = 10.5 Hz, 1H), 4.75 (d, *J* = 13.5 Hz, 1H), 4.22–4.14 (m, 2H), 4.02 (s, 3H), 3.71 (t, *J* = 11.0 Hz, 1H), 3.65–3.62 (m, 1H), 3.49–3.45 (m, 1H), 2.66 (q, *J* = 8.0 Hz, 1H), 2.20 (m, 2H), 2.02 (d, *J* = 2.0 Hz, 1H), 1.82 (q, *J* = 10.0 Hz, 1H), 1.42 (q, *J* = 11.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO–d_6): δ 157.8, 147.9, 144.2, 144.1, 138.3, 131.8, 125.9, 121.9, 120.8, 117.3, 103.1, 68.8, 65.4, 64.6, 59.8, 56.1, 52.2, 51.5, 46.2, 38.1, 26.1, 25.0, 20.9; IR (KBr): 3380, 3195, 2987, 1618, 1600, 1520, 1465, 1431, 1356, 1312, 1240, 1202, 1052, 960, 942, 838 cm^{-1}; HRMS calcd for $C_{27}H_{26}F_5N_2O_2$: 505.1909, found 505.1911.

RESULTS AND DISCUSSION

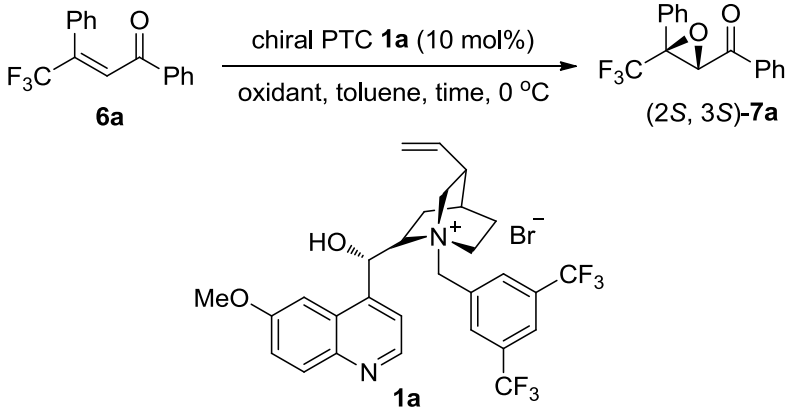
Effect of the oxidants

Firstly, a range of commercially available oxidants were screened in the epoxidation of (*E*)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-one (**6a**) in toluene at 0 °C. 30% H_2O_2 combined with 50% aqueous KOH affording the desired product **7a** in 51% ee albeit in good yield (Table 1, entry 1). 50% H_2O_2 led to the product with relative lower ee value (entry 2). Trichloroisocyanuic acid (TCCA) was successfully used in the enantioselective phase-transfer catalyzed epoxidation of enones [17b,17c], however, it was shown to be less effective when used in conjunction with 50% aqueous KOH (entry 3). When the *N*-chlorosuccinimide (NCS) was selected to promote the enantioselectivity, it promoted the reaction to give **2a** with 41% yield and 26% ee (entry 4). Subsequently, NaClO gave complicated and trace conversion (entry 5). Further decrease the dosage of the 30% H_2O_2 to 15 equivalents resulted in a deleterious effect on the reaction conversion, but without decrease of enantioselectivity. After screening common oxidants in the asymmetric epoxidation of enones, 30% H_2O_2-50% KOH was found with a relatively better ee value.

Effect of PTCs

Next, we turned our attention to the effects of chiral quaternary ammonium salt. Thus, a variety of quinidine-derived quaternary ammonium salts (**1a-g**, **2, 3**) were examined with different *N*-substituent at 10 mol% catalyst loading with results shown in Table 2. Dimeric catalyst **2** derived from quinidine gave a disappointing result of 43% yield and 59% ee (entry 2). Catalyst **3** led to the desired product with 46% ee (entry 3). *N*-(4-Methylbenzyl)ammonium bromide salt (**1b**) gave 39% ee albeit in good yield (entry 4). When **1c** containing a 4-trifluoromethyl benzyl group at the nitrogen atom of quinidine was employed, **7a** was formed in 85% yield and 44% ee (entry 5). It was noteworthy that **1d** bearing a bulky *N*-9-anthrylmethylene ring gave product with 74% ee value (entry 6). In the light of above results and structure of the catalyst, steric and electronic factors might greatly affect the enantioselectivity. It is known that fluorine is assigned the highest electronegativity value of all of the elements while the size of fluorine falls between that of hydrogen and oxygen [23]. Therefore, a series of F-substituted quinidine-derived ammonium salts were tested (entries 7-9). To our delight, electron-deficient

Table 1: The screening of the oxidants.[a]



Entry	Oxidant	Time (h)	Yield (%)[b]	ee (%)[c]
1[d]	30% H_2O_2	20	87	51
2[d]	50% H_2O_2	20	62	48
3[d]	TCCA	24	46	16
4[d]	NCS	24	41	26
5	NaClO	24	CP	ND
6[e]	30% H_2O_2	24	78	50

*a) Unless otherwise mentioned, all reactions were performed with **6a** (0.1 mmol), chiral ammonium salt **1a** (10 mol%), oxidant (20.0 equiv), in toluene (0.25 mol L^{-1}) at 0 °C. b) Isolated yield.*
c) Determined by chiral HPLC on Chiralpak AS-H. d) 50% aqueous KOH (35 μL, 3.0 equiv).
e) 30% H_2O_2 (15.0 equiv). TCCA = Trichloroisocyanuic acid. NCS = N-chlorosuccinimide.
CP = Complex mixture. ND = Not detected.

2,4,5-trifluorobenzyl ammonium salt **1f** increased the ee value to 79% (entry 8). Encouraged by this promising ee value, F_5-substituted catalyst **1g** was prepared and applied to this reaction affording excellent enantioselectivity (92% ee) and good yield (83%) (entry 9). This excellent enantioselectivity might result from F effect which was previously observed as a result of the formation of a tighter binding ion pair [24], which would lead to a more efficient chiral induction in the transition state.

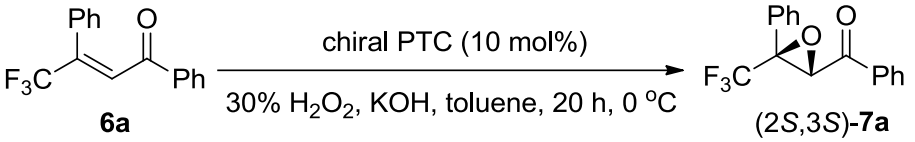
Effect of solvents

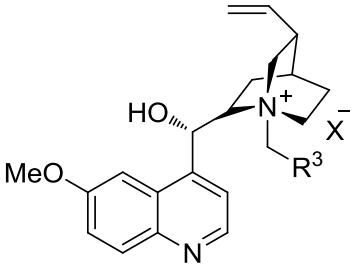
For optimization of the reaction conditions, the effect of solvents was screened. Solvents exhibited strong effect on the catalyst capability. As shown in Table 3, when toluene was used, the reaction was furnished with 92% ee (entry 1). *i*-Pr_2O gave similar result (entry 2). However, CH_2Cl_2 gave excellent yield (90%) and enantioselectivity (96%) (entry 4), while using $ClCH_2CH_2Cl$ led to a degraded enantioselectivity (94% ee) (entry 5). Compared with CH_2Cl_2, $CHCl_3$ gave better results (92% yield, 98% ee, entry 3). Consequently, the optimal appropriate solvent is $CHCl_3$.

Effects of catalyst loading and substrate concentration

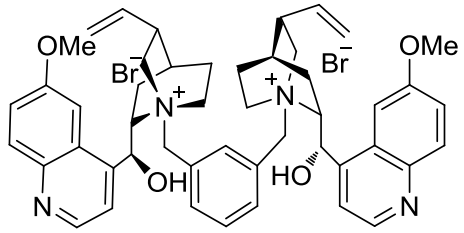
To obtain the optimum reaction condition, further optimization was focused on catalyst loading and substrate concentration (Table 4). Reasonably, as reducing the catalyst loading from 10 mol% to 5 mol%, the yields and ee value of product **7a** had no significant effect (entries 1 and 2). Further decrease of the catalyst loading to 3 mol% resulted in a deleterious effect on the reaction conversion even at longer reaction time, but without decrease of enantioselectivity (entry 3). To our delight, when the reaction was run at 1.0 mol/L concentration of **6a**, higher enantioselectivity 99% ee was obtained at 3 mol% of catalyst loading (entry 4).

Table 2: Effect of N-substituent of quinidine-derived quaternary ammonium salts on the enantioselectivity.[a]

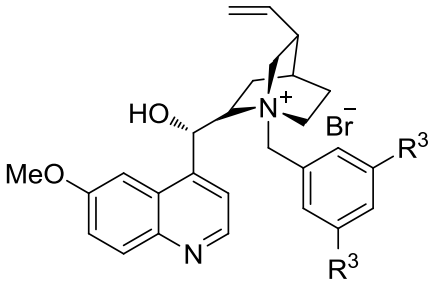




1a: R^3 = 3,5-$(CF_3)_2C_6H_3$, X = Br
1b: R^3 = 4-$CH_3C_6H_4$, X = Br
1c: R^3 = 4-$CF_3C_6H_4$, X = Br
1d: R^3 = 9-anthracenyl, X = Cl
1e: R^3 = 2-F-4-BrC_6H_3, X = Br
1f: R^3 = 2,4,5-$F_3C_6H_2$, X = Br
1g: R^3 = C_6F_5, X = Br



2

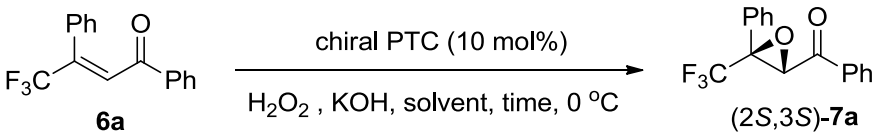


3: R^3 = 3,5-$(CF_3)_2$-C_6H_3

Entry	PTC (mol%)	Yield[b] (%)	ee[c] (%)
1	**1a**(10)	87	51
2	**2**(10)	43	59
3	**3**(10)	80	46
4	**1b**(10)	82	39
5	**1c**(10)	85	44
6	**1d**(10)	92	74
7	**1e**(10)	90	71
8	**1f**(10)	89	79
9	**1g**(10)	83	92

*a) Unless otherwise mentioned, all reactions were performed with **6a** (0.1 mmol), 30% H_2O_2 (0.2 mL, 20.0 equiv), chiral ammonium salt (10 mol%), 50% aqueous KOH (35 μL, 3.0 equiv.) in toluene (0.25 mol/L) at 0 °C.*
b) Isolated yield. c) Determined by chiral HPLC on Chiralpak AS-H.

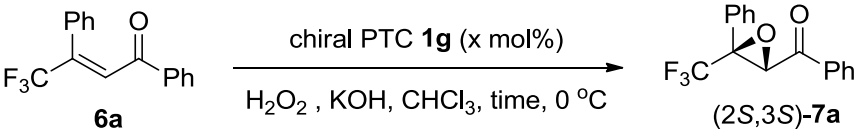
Table 3: Effect of solvent on the model reaction.[a]



Entry	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	toluene	20	83	92
2	*i*-Pr_2O	40	80	91
3	$CHCl_3$	6	92	98
4	CH_2Cl_2	6	90	96
5	$ClCH_2CH_2Cl$	8	76	94

*a) Unless otherwise mentioned, all reactions were performed with **6a** (0.1 mmol), 30% H_2O_2 (0.2 mL, 20.0 equiv), chiral ammonium salt **1g** (10 mol%), 50% aqueous KOH (35 μL, 3.0 equiv) in solvent (0.25 mol/L) at 0 °C.*
b) Isolated yield. c) Determined by chiral HPLC on Chiralpak AS-H.

Table 4: Effects of catalyst loading and concentration of 6a on the model reaction.[a]



Entry	PTC (mol%)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1g**(10)	6	92	98
2	**1g**(5)	8	88	98
3	**1g**(3)	8	80	98
4[d]	**1g**(3)	8	93	99
5[e]	**1g**(1)	12	75	98

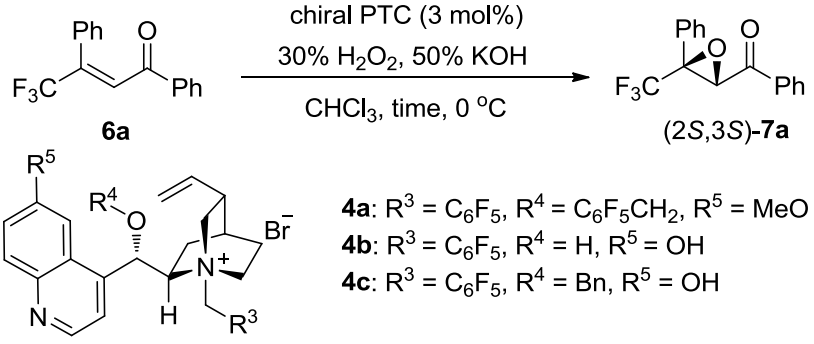
*a) Unless otherwise mentioned, all reactions were performed with **6a** (0.1 mmol), 30% H_2O_2 (0.2 mL, 20.0 equiv), chiral ammonium salt **1g** (x mol%), 50% aqueous KOH (35 μL, 3.0 equiv) in $CHCl_3$ (0.25 mol/L) at 0 °C.*
b) Isolated yield. C) Determined by chiral HPLC on Chiralpak AS-H.
*d) [**6a**] = 1.0 mol/L. e) [**6a**] = 2.0 mol/L.*

If 1 mol% of **1g** was used, it resulted in the retentive enantioselectivity (98% ee) and obviously eroded yield to 75% with concentrated reaction medium and a longer reaction time (entry 5).

Effect of hydrogen bonding

Hydrogen bond is believed playing important role in asymmetric epoxidation of α,β-unsaturated ketones [25]. As shown in Table 5, modification of the catalyst motif revealed that the C-9 hydroxyl group had to be unprotected to maintain good chiral inductive capability and conversion. Thus, C-9-protected **4a** led to a nearly racemic product 6% ee (entry 2), suggesting a live hydrogen bond and a possible π–π stacking between the benzyl moiety of catalyst and the aromatic portion of substrate as well [26]. Considering the indispensability of free hydroxyl group of the quinidine for achieving high enantiocontrol, deprotection of *O*-methyl yielded **4b**. However, the chiral inductive capability of **4b** was retained with bad conversion (entry 3), which indicated that one more free hydroxyl group at C-6 disturbed the hydrogen bond of C-9-OH and π–π stacking interactions. Furthermore, C-6-OH and C-9-*O*-benzylated catalyst **4c** gave trace conversion (entry 4).

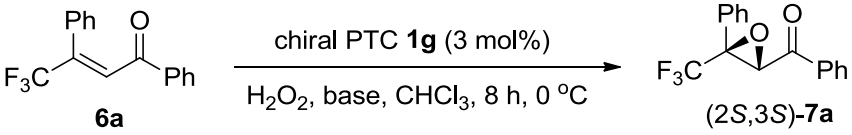
Table 5: Effect of hydroxyl groups at C-6 and C-9 on the enantioselectivity.[a]



Entry	PTC (mol%)	Time (h)	Yield[b] (%)	*ee*[c] (%)
1	**1g**(3)	8	93	99
2	**4a**(3)	16	23	6
3	**4b**(3)	16	18	90
4	**4c**(3)	16	trace	ND

*a) Reaction condition (unless otherwise mentioned): **6a** (0.1 mmol), 30% H_2O_2 (0.2 mL, 20.0 equiv), PTC (0.003 mmol, 3 mol%), 50% aqueous KOH (35 μL, 3.0 equiv) in $CHCl_3$ (0.10 mL) at 0 °C.*
b) Isolated yield. c) Determined by chiral HPLC on Chiralpak AS-H. ND = not detected.

Table 6: Effect of base on the enantioselectivity.[a]



Entry	Base	Yield[b] (%)	ee[c] (%)
1[d]	KOH (50%)	93	99
2[d]	KOH(2 mol/L)	85	98
3[d]	LiOH	89	98
4[e]	KOH (50%)	78	99

*a) Reaction condition (unless otherwise mentioned): **6a** (0.1 mmol), 30% H_2O_2 (0.2 mL, 20.0 equiv), PTC (0.003 mmol, 3 mol%), base (3.0 equiv) in $CHCl_3$ (0.10 mL) at 0 °C. b) Isolated yield.*
c) Determined by chiral HPLC on Chiralpak AS-H. d) 3 Equiv of KOH (50%) was used. e) 2 Equiv of KOH (50%) was used.

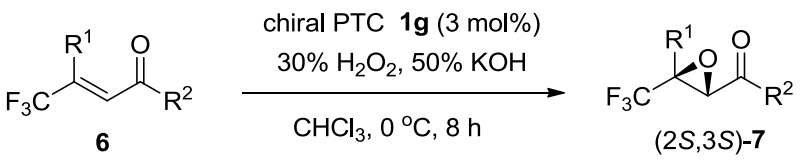
Effect of base

A subsequent survey revealed that base hardly affected this F_5-substituted cinchona phase transfer catalyzed asymmetric epoxidation of β,β-disubstituted unsaturated ketones bearing a β-trifluoromethyl group (Table 6, entries 1-3).

Substrate scope and limitation

With the optimized conditions in hand, the scope of substrate was evaluated with results listed in Table 7. A series of trifluoromethylated enone derivatives bearing fluoro, chloro, bromo, methyl, methoxy and phenyl groups on the aromatic rings (**6a-6u**) were selected to establish the generality of this process. All tested β-trifluoromethyl β,β-disubstituted α,β-unsaturated ketones were converted into corresponding epoxides with 3 mol% of catalyst **1g** with excellent diastereoselectivity and enantioselectivity. The combination of F_5-substituted cinchona phase transfer catalyst and hydrogen peroxide was proved greatly efficient. We are pleased to find

Table 7: Catalytic asymmetric epoxidation of various β,β-disubstituted unsaturated ketones 6 Using Catalyst 1g.[a]



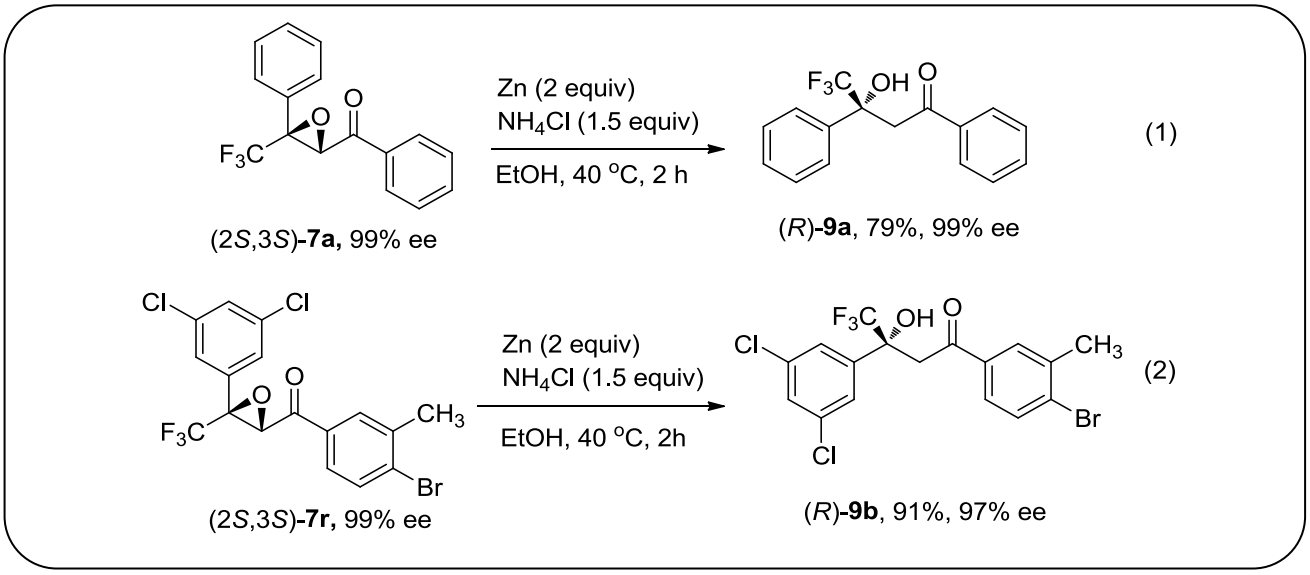
Entry	Product	R^1	R^2	Yield[b] (%)	d.r.[c]	ee[d] (%)
1	**7a**	Ph	Ph	93	50:1	99[e]
2	**7b**	Ph	4-FC_6H_4	84	50:1	98
3	**7c**	Ph	4-ClC_6H_4	82	50:1	98
4	**7d**	Ph	4-BrC_6H_4	96	20:1	95
5	**7e**	Ph	4-$CF_3C_6H_4$	86	20:1	98
6	**7f**	Ph	2-naphthyl	87	50:1	98
7	**7g**	Ph	4-PhC_6H_4	81	100:1	99
8	**7h**	Ph	4-MeC_6H_4	84	25:1	99
9	**7i**	Ph	2-$MeOC_6H_4$	94	50:1	99.7
10	**7j**	Ph	3-$MeOC_6H_4$	87	50:1	98.6
11	**7k**	Ph	4-$MeOC_6H_4$	81	33:1	97
12	**7l**	4-FC_6H_4	Ph	94	50:1	98
13	**7m**	4-ClC_6H_4	Ph	81	33:1	98
14	**7n**	4-BrC_6H_4	Ph	96	50:1	97
15	**7o**	4-$CF_3C_6H_4$	Ph	95	25:1	96
16	**7p**	4-MeC_6H_4	Ph	86	20:1	99
17	**7q**	2-thiophthyl	Ph	90	50:1	96
18	**7r**	3,5-$Cl_2C_6H_3$	4-Br-3-MeC_6H_3	95	20:1	99
19	**7s**	C_2H_5	Ph	88	100:1	82
20	**7t**	$C_6H_5CH_2$	Ph	90	100:1	81
21	**7u**	$C_6H_5CH_2$	*t*-Bu	CP	--	ND

*a) Unless otherwise mentioned, all reactions were performed with **6a** (0.1 mmol), 30% H_2O_2 (0.2 mL, 20.0 equiv), **1g** (1.8 mg, 0.003 mmol, 3 mol%), 50% aqueous KOH (35 μL, 3.0 equiv) in $CHCl_3$ (0.10 mL) at 0 °C.*

b) Isolated yield. c) Determined by ^1H NMR of the crude product.

*d) Determined by chiral HPLC. e) The absolute configuration of **7a** was determined to be (2S,3S) by comparing HPLC retention time and the sign of optical rotation of **9a** with that in literature Ref [6d].*

CP = Complex mixture. ND = Not detected.



Scheme 3: Chemoselective reduction of β-trifluoromethyl-α,β-epoxy ketones.

that the reaction can tolerated many kinds of functional groups on aromatic ring including electron-neutral, electron-withdrawing, electron-donating groups and thus accomplished with 95-99% ee and 20:1 to 100:1 d.r. (entries 1-17). Noteworthy, heterocyclic substrate **6q** was smoothly transferred into epoxide **7q** in excellent yield, diastereoselectivity and enantioselectivity (entry 17). In addition, β-CF_3-β-alkyl disubstituted substrates (**6s**, **6t**) were converted to the corresponding products in good ee and excellent yield (entries 19 and 20). However, the substrate possessing alkyl groups at both R^1 and R^2 sides gave complex mixtures (entry 21).

It is well-known that the *R* and *S* enantiomers commonly show very different biological activities. The facile access to both the *R* and *S* enantiomers of the products is of great importance in the asymmetric catalysis. To our delight, during the catalyst structure screening, both the (*R,R*) and (*S,S*) enantiomers of the products can be obtained in excellent yields and enantioselectivities with catalyst **1g** and **5**, respectively. The same substrate scope was explored in the presence of 3 mol% of catalyst **5** and the (*R,R*) enantiomers of the products **8a-s** were obtained in high to good high yields and comparable excellent enantioselectivities (Table 8).

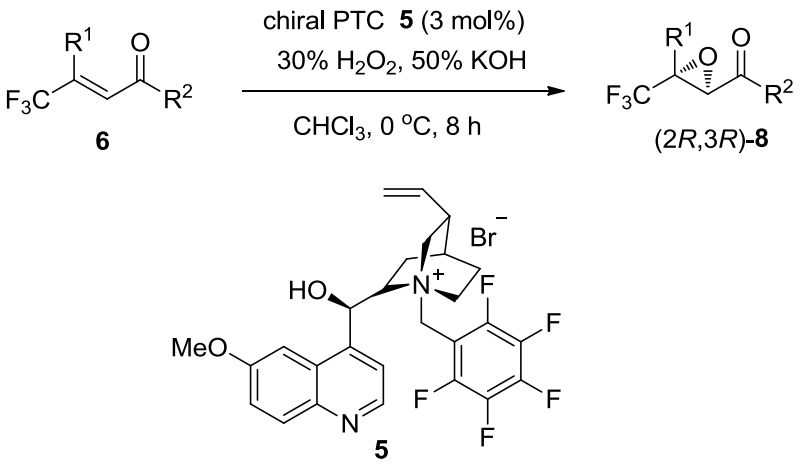
Since the difficulty to get optically pure trifluoromethylated organic compounds and the significant applications of these chemicals, the obtained β-CF_3-α,β-epoxyketones were used to prepare other trifluoromethyl-containing intermediates, such as β-trifluoromethyl-β-hydroxy ketones. Gratifyingly, direct one-step selective reduction of α,β-epoxy ketones (**7a**, **7r**) to β-hydroxy ketones (**9a**, **9b**) was completed smoothly without any loss of enantioselectivity (Scheme 3). Treatment of **7a** with Zn and NH_4Cl at mild conditions in EtOH for 2 hours gave (*R*)-**9a i**n 79% yield and 99% ee. β-Trifluoromethyl-β-hydroxy ketone **9b** is amongst an important class of compounds for new agrochemicals and veterinary medicines [26]. After similar process, β-trifluoromethyl-β-hydroxy ketone (*R*)-**9b** was synthesized in 91% yield with retained enantioselectivity.

It is noteworthy that excellent enantioselectivity for (2*R*,3*R*)-**7a** with the opposite stereochemistry was also achieved from (*Z*)-**6a** using catalyst **1g** (Scheme 4). This indicates that the peroxide adds as a nucleophile to the electrophilic β-carbon atom of the β-CF_3-β,β-disubstituted ketones forming the carbon–oxygen bond. Subsequently, the nucleophilic α-carbon atom attacks the electrophilic peroxygen atom to produce the desired β-trifluoromethyl-α,β-epoxy ketones [27].

Proposed mechanism

Based on the essential of the hydroxyl at C-9' of the quinidine-derived F_5-substituted quaternary ammonium salt and π–π stacking of the benzyl moiety and the aromatic portion of the substrate, the plausible catalytic cycle was proposed (Scheme 5). The active ammonium hydroperoxide intermediate **A** could be generated through metathesis of

Table 8: Catalytic asymmetric epoxidation of various β,β-disubstituted unsaturated ketones 6 using Catalyst 5.[a]

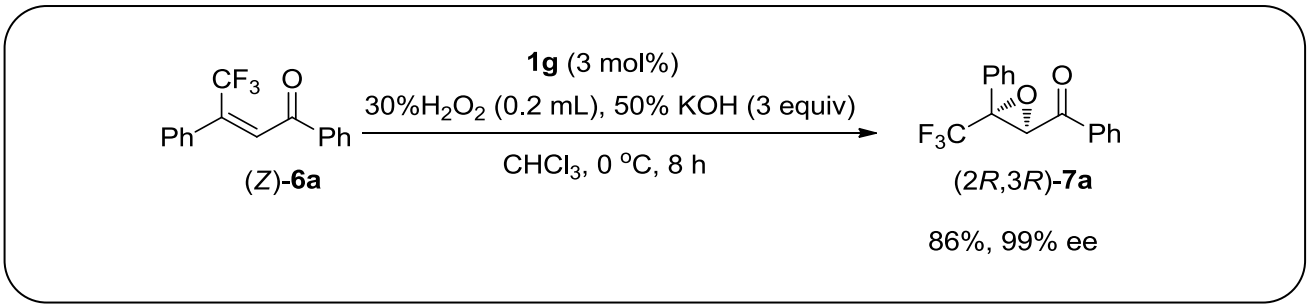


Entry	Product	R^1	R^2	Yield[b] (%)	d.r.[c]	ee[d] (%)
1	**8a**	Ph	Ph	90	33:1	99
2	**8b**	Ph	4-FC_6H_4	81	25:1	96
3	**8c**	Ph	4-ClC_6H_4	80	50:1	97
4	**8d**	Ph	4-BrC_6H_4	85	100:1	96
5	**8e**	Ph	4-$CF_3C_6H_4$	82	20:1	96
6	**8f**	Ph	2-naphthyl	81	100:1	98
7	**8g**	Ph	4-PhC_6H_4	84	100:1	98
8	**8h**	Ph	4-MeC_6H_4	80	33:1	99
9	**8i**	Ph	2-$MeOC_6H_4$	81	50:1	99.6
10	**8j**	Ph	3-$MeOC_6H_4$	81	50:1	98
11	**8k**	Ph	4-$MeOC_6H_4$	80	20:1	97
12	**8l**	4-FC_6H_4	Ph	90	33:1	97
13	**8m**	4-ClC_6H_4	Ph	94	50:1	97
14	**8n**	4-BrC_6H_4	Ph	89	33:1	96
15	**8o**	4-$CF_3C_6H_4$	Ph	96	50:1	95
16	**8p**	4-MeC_6H_4	Ph	83	50:1	98
17	**8q**	2-thiophthyl	Ph	83	100:1	95
18	**8r**	C_2H_5	Ph	85	33:1	70
19	**8s**	$C_6H_5CH_2$	Ph	87	50:1	72

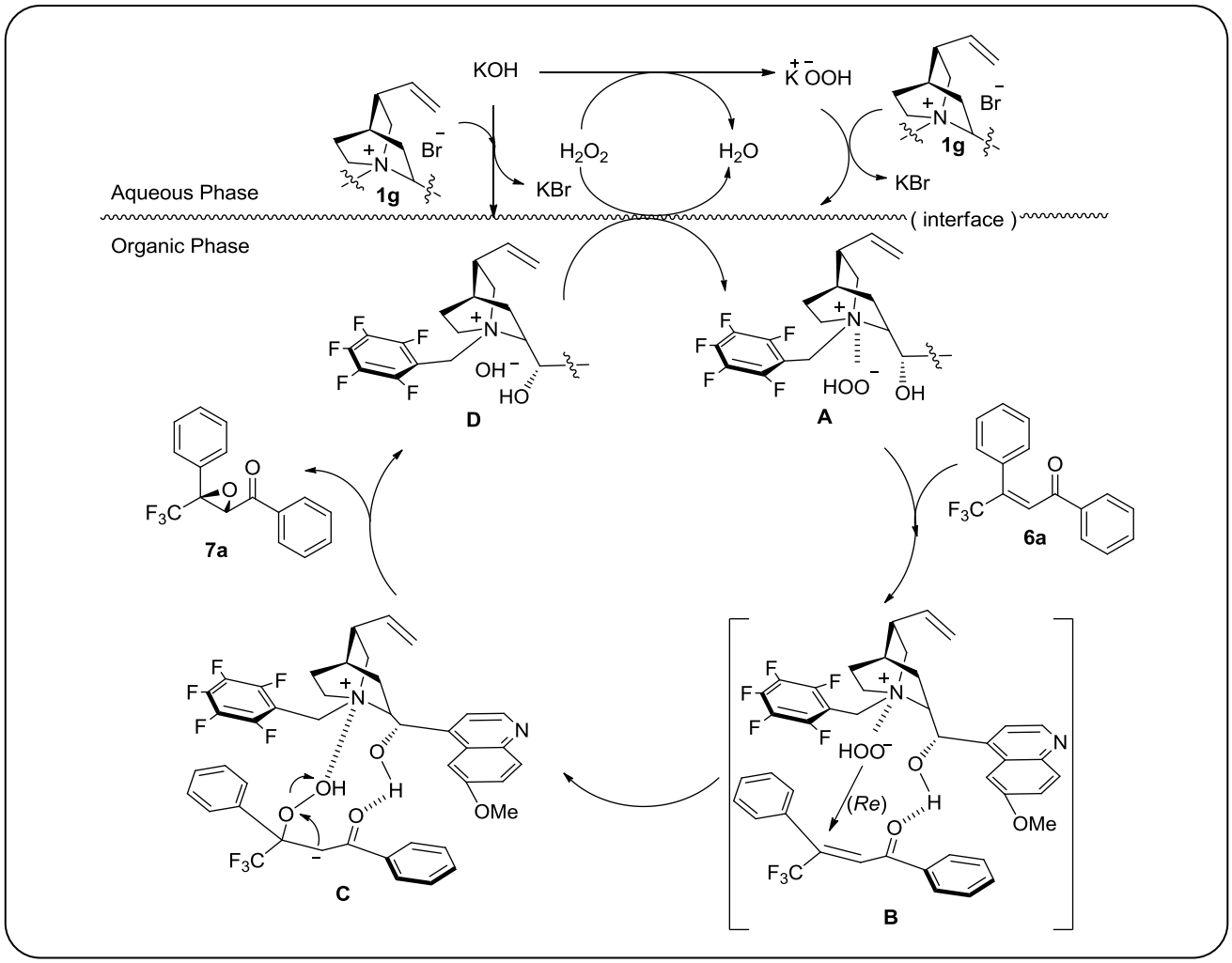
*a) Unless otherwise mentioned, all reactions were performed with **6** (0.1 mmol), 30% H_2O_2 (0.2 mL, 20.0 equiv), **5** (1.8 mg, 0.003 mmol, 3 mol%), 50% aqueous KOH (35 μL, 3.0 equiv) in $CHCl_3$ (0.10 mL) at 0 °C.*

b) Isolated yield. c) Determined by ^1H NMR of the crude product.

d) Determined by chiral HPLC.



Scheme 4: Asymmetric epoxidation of (Z)-6a.



Scheme 5: Proposed catalytic cycle

either ammonium hydroxide intermediate **D** or ammonium bromide (**1g**) itself. Subsequently, the hydroperoxide anion captures enone **6a** through an intermolecular hydrogen-bond with the carbonyl oxygen atom of the substrate, together with a possible π–π stacking between the fluorinated benzyl moiety and the aromatic ring of the substrate. Then the reaction goes through the transition state **B** and the following attack of hydroperoxide to the β-carbon from *Re* face forming the intermediate **C**. Finally, it follows an intramolecular cyclization and leads to the formation of the epoxide product **7a** and generation of **D** simultaneously. The catalytic cycle is completed with the generation of the ammonium hydroperoxide **A**.

CONCLUSIONS

In summary, a general asymmetric epoxidation of β-trifluoromethyl-β,β-disubstituted ketones using F_5-substituted quaternary ammonium salt and hydrogen peroxide as well as the plausible catalytic cycle have been developed. The methodology is featured in the followings: (i) a wide scope of β-CF_3-β-alkyl disubstituted substrates are tolerated in both excellent enantioselectivity (up to 99.7% ee) and diastereoselectivity (up to 100:1) and excellent yield (up to 96%) at 3 mol% of catalyst loading; and (ii) aqueous hydrogen peroxide, a mild, inexpensive, and environmentally benign oxidant, can be used under mild reaction conditions for β, β-disubstituted enones; (iii) remarkably, both (*R*,*R*) and (*S*,*S*) enantiomers were easily obtained in excellent yields and excellent enantioselectivities using catalysts **1g** and **5** respectively; (iv) some optically pure and medicinally important trifluoromethylated intermediates, e.g. β-trifluoromethyl-β-hydroxy ketones, were readily prepared by selective reduction of the expoxide products.

SUPPLEMENTARY MATERIALS

Supplementary materials are available (59 Pages):

1- General information

2- Chiral HPLC spectra **7a-7t** and **8a-8t**

3- NMR spectra

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