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Highly Efficient Asymmetric Epoxidation of Electron-Deficient α,β-Enones and Related Applications to Organic Synthesis

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Abstract: The asymmetric epoxidation of electron-deficient olefins has been achieved using inexpensive and readily available prolinols as catalysts with good to excellent yields and enantioselectivities. The utility of the resulting chiral epoxides was illustrated by elaboration to several synthetically useful compounds featuring a concise synthesis of (−)-(5*R*,6*S*)-balasubramide.

Keywords: asymmetric catalysis; enones; epoxidation; stereoselectivity; synthesis

Introduction

The catalytic enantioselective epoxidation of olefins is one of the most widely studied reactions in asymmetric catalysis due to the extensive presence of the resulting chiral epoxide structures in biologically active compounds as well as their great utility in organic synthesis.[1] As an important type of functionalized olefins, acyclic α,β-unsaturated ketones have been among the most investigated targets in this field and numerous catalysts such as metal complexes,[2] phase-transfer catalysts (PTC),[3] chiral *N*-oxides[4] and polypeptides[5] have been applied to the asymmetric epoxidation of these compounds with varied degrees of success. Recently, the asymmetric organocatalytic epoxidation of α,β-unsaturated aldehydes or ketones has emerged as a promising area,[6] which is highlighted with several advantages such as mild reaction conditions, simple experimental manipulations, inexpensive and readily available catalysts. Our group has also developed several new catalysts for this transformation.[7] Despite these advances, the present system principally suffers from a narrow substrate scope restricted mostly to chalcones, which are not easily convertible to other useful structures for practical uses in organic synthesis.[6,7] In addition, the reaction generally requires long reaction times (4–6 days) due to the low reactivity of these substrates. Therefore, it is still desirable to delve into this reaction to address these problems.

In our previous studies,[7] we have observed a moderate rate-accelerating effect arising from the presence of electron-withdrawing groups on the phenyl ring of R^2 (R^2 = substituted phenyl groups) (Figure 1). We envisioned that when the R^2 groups were more electron-withdrawing groups such as CF_3, CCl_3 and CO_2R rather than the previously used aryl groups or alkyl groups, the reactivity of the double bond in the Michael-type addition step in the transition state may be further increased and, more importantly, the use of these groups would give rise to products allowing facile further conversions to various synthetically useful structures. Herein, we report the details of this research.

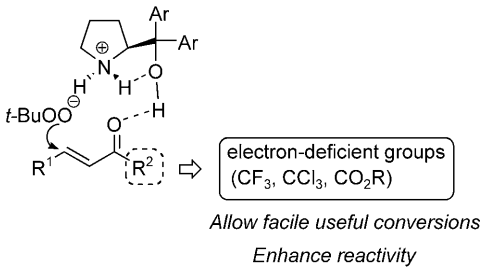


Figure 1. Proposed transition state for the prolinol-catalyzed epoxidation of α,β-unsaturated ketones.

Results and Discussion

To begin with, a series of 4-substituted prolinols was synthesized as catalysts for evaluation in this research (Figure 2).[7b,8] Firstly, the epoxidation of α-keto esters **1** was investigated and methyl 2-oxo-4-phenylbut-(*E*)-3-enoate **1a** was selected as the probe substrate for catalyst evaluation (Table 1). As expected, in comparison with the reactions of chalcones under similar reaction conditions,[6,7] the reaction times were significantly reduced for the epoxidation of **1a** with moderate to excellent yields in the presence of 15 mol% of the catalysts **7a–7g** and **7i** using *n*-hexane as the solvent at room temperature (Table 1, entries 1–11). Particularly, with the optimal catalyst **7f**, the reaction could proceed to completion within 4 h affording the desired product **2a** in 94% yield and 90% *ee* (Table 1, entry 6). Furthermore, high enantioselectivity (91% *ee*) could still be achieved when the loading of **7f** was lowered from 15 mol% to 10 mol%, albeit with a drop in the yield (Table 1, entry 12). Finally, the highest enantioselctivity was obtained (96% *ee*) with 83% yield when the reaction was conducted with 10 mol% of **7f** at −10 °C (Table 1, entry 14) and this condition was adopted for our subsequent study of the substrate scope.

The results of the epoxidation of a selected spectrum of α-keto esters under the above optimized reaction conditions are shown in Table 2. In general, most of the examined substrates with different substituents in both the ester moiety and phenyl ring could afford the desired products in good yields and with excellent enantioselectivities in 9–15 h, irrespective of the electronic nature or the steric hindrance of the substituents. It seemed that both the reaction rate and yield were greatly influenced by the solubility of the substrate α-keto esters in *n*-hexane. For instance, the ep-

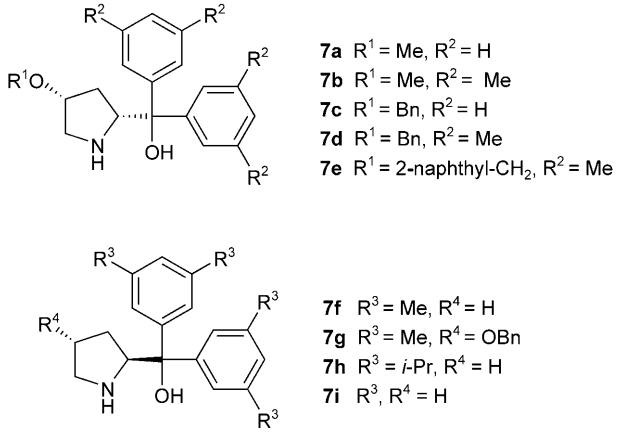
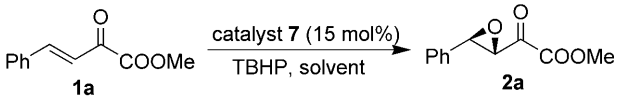


Figure 2. Catalysts evaluated in this study.

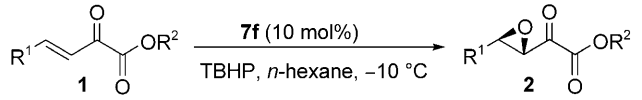
Table 1. Screening of catalysts and solvents for the enantioselective epoxidation of α-keto ester **1a**.[a]



Entry	Catalyst	Solvent	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	**7a**	hexane	20	30	53	−80
2	**7b**	hexane	20	30	74	−85
3	**7c**	hexane	20	30	79	−75
4	**7d**	hexane	20	18	95	−85
5	**7e**	hexane	20	30	89	−83
6	**7f**	hexane	20	4	94	90
7	**7g**	hexane	20	30	75	46
8	**7i**	hexane	20	14	53	47
9	**7f**	CCl_4	20	30	73	88
10	**7f**	toluene	20	30	47	88
11	**7f**	THF	20	30	trace	–[d]
12[e]	**7f**	hexane	20	5	79	91
13[e]	**7f**	hexane	0	7	94	95
14[e]	**7f**	hexane	−10	11	83	96

[a] Unless otherwise specified, the reaction was carried out with 2.0 equiv of TBHP in the presence of 15 mol% of **7** at 20 °C.
[b] Isolated yields after flash column chromatography.
[c] Enantiomeric excess was determined by HPLC analysis using a chiral column.
[d] Not determined.
[e] 10 mol% of **7f** was employed.

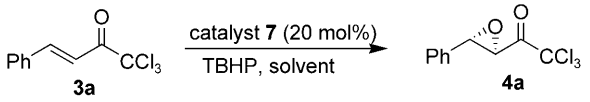
Table 2. Asymmetric epoxidation of β,γ-unsaturated α-keto esters catalyzed by **7f**.[a]



Entry	R^1, R^2	Time [h]	Product	Yield [%][b]	*ee* [%][c]
1	Ph, Me (**1a**)	11	**2a**	83	96
2	Ph, Et (**1b**)	11	**2b**	90	95
3	Ph, Allyl (**1c**)	11	**2c**	91	94
4	Ph, *i*-Pr (**1d**)	11	**2d**	91	94
5	Ph, *t*-Bu (**1e**)	9	**2e**	92	96
6	Ph, Bn (**1f**)	14	**2f**	96	94
7	*p*-F-C_6H_4, Me (**1g**)	9	**2g**	90	96
8	*p*-Cl-C_6H_4, Me (**1h**)	15	**2h**	87	98
9	*p*-Br-C_6H_4, Me (**1i**)	15	**2i**	89	98
10	*o*-Br-C_6H_4, Me (**1j**)	15	**2j**	88	94
11	*m*-Cl-C_6H_4, Me (**1k**)	10	**2k**	87	97
12[d]	*p*-NO_2-C_6H_4, Me (**1l**)	12	**2l**	60	94
13[d]	*p*-Me-C_6H_4, Me (**1m**)	24	**2m**	52	92

[a] Unless otherwise specified, the reaction was carried out with 2.0 equiv of TBHP in the presence of 10 mol% of **7f** at −10 °C.
[b] Isolated yield after flash column chromatography.
[c] Determined by HPLC analysis using chiral columns. The absolute configuration of **2** was determined to be 2*S*,3*R*.
[d] The reaction was carried out at room temperature.

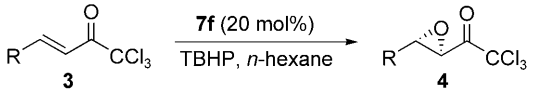
Table 3. Screening of catalysts and solvents for the enantioselective epoxidation of α, β-unsaturated trichloromethyl ketones **3**.[a]



Entry	Catalyst	Solvent	Temp. [°]	Time [h]	Yield [%][b]	*ee* [%][c]
1	**7a**	hexane	20	48	trace	–[d]
2	**7b**	hexane	20	15	62	–61
3	**7c**	hexane	20	48	trace	–[d]
4	**7d**	hexane	20	15	35	–67
5	**7f**	hexane	20	15	77	86
6	**7h**	hexane	20	20	54	81
7	**7i**	hexane	20	48	trace	–[d]
8	**7f**	CCl_4	20	48	trace	–[d]
9	**7f**	toluene	20	48	trace	–[d]
10	**7f**	hexane	0	48	62	85
11[e]	**7f**	hexane	0	48	57	85

[a] Unless otherwise specified, the reaction was carried out with 2.0 equiv. of TBHP in the presence of 20 mol% of **7** at 20 °C.
[b] Isolated yields after flash column chromatography.
[c] Enantiomeric excess was determined by HPLC analysis using a chiral column.
[d] Not determined.
[e] 15 mol% of **7f** was employed.

Table 4. Asymmetric epoxidation of α,β-unsaturated trichloromethyl ketones.[a]



Entry	R	Time [h]	Product	Yield [%][b]	*ee* [%][c]
1	Ph (**3a**)	15	**4a**	77	86
2	*p*-F-C_6H_4 (**3b**)	10	**4b**	82	81
3	*p*-Cl-C_6H_4 (**3c**)	10	**4c**	93	86
4	*p*-Br-C_6H_4 (**3d**)	7	**4d**	81	86
5	*m*-Cl-C_6H_4 (**3e**)	10	**4e**	83	84
6	*o*-Cl-C_6H_4 (**3f**)	24	**4f**	36	56
7	*p*-NO_2-C_6H_4 (**3g**)	15	**4g**	84	76
8	PhCH=CH (**3h**)	36	**4h**	50	99
9	Me (**3i**)	36	**4i**	43	75

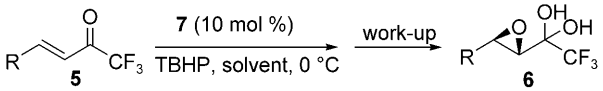
[a] Unless otherwise specified, the reaction was carried out with 2.0 equiv. of TBHP in the presence of 20 mol% of **7f** at 20 °C.
[b] Isolated yield by flash column chromatography.
[c] Converting **4** to corresponding α-epoxy esters followed by HPLC analysis. The absolute configuration of **4** was determined to be 2*R*, 3*S*.

oxidation of substrates **1l** and **1m**, which are poorly soluble in *n*-hexane, only provided the desired products in moderate yields after 12 and 24 h, respectively, even at elevated temperatures (Table 2, entries 12 and 13).

Subsequently, the epoxidations of another useful type of α,β-enones, namely the α,β-unsaturated trichloromethyl ketones **3** were investigated (Table 3 and Table 4). It seemed that the sterically more demanding trichloromethyl group was inferior to the adjacent ester group in α-keto esters **1** for the present transformation: under the similar reaction conditions as above, the desired epoxides were generally obtained with diminished yields and enantioselectivities even with a slightly larger amount of the catalyst **7f** (Table 3, entries 1–7). However, accelerations in the reaction rates were still observed as expected and the reactions could go to completion within 7–36 h (Table 4). When the reaction was conducted at a lower temperature, no improvement in the enantioselectivity was observed (Table 3, entries 10 and 11). Moreover, steric factors seemed to play a large role in this system since substrate **3f** bearing a substituent at the 2-position of the phenyl ring gave rise to the desired epoxide with both apparently lower yield and enantioselectivity (Table 4, entry 6). Notably, aliphatic ketone **3i** could also undergo the epoxidation to deliver the desired product with moderate enantioselectivity and acceptable yield (Table 4, entry 9).

The efficient catalyst system was also extended to the epoxidation of α,β-unsaturated trifluoromethyl ketones (Table 5). Preliminary investigations showed that the reaction was best performed with catalyst **7d** at 0 °C in *n*-hexane (Table 5, entries 1–8). We speculated that a less effective catalyst for the epoxidation of **1** and **3** was nevertheless advantageous for the epoxidation of the α,β-unsaturated trifluoromethyl ketone with respect to its more electron-withdrawing nature than trichloromethyl or ester group. The same effect was also observed in the catalyst loadings. Increasing the catalyst loading promoted the reaction rate, however, the observed enantioselectivities were compromised (Table 5, entries 4 and 5). Using **7d** as the catalyst, the products were generally obtained in good yields within 12–28 h. *para*-Substituted substrates gave rise to the epoxides with high enantioselectivities except for the ethyl group-substituted **5f**, which was probably due to its enhanced electron-donating nature (Table 5, entries 9–13). Substrates **5g** and **5i** with substituents at the 2-position were found to be less reactive, affording the corresponding products in lower yields and enantioselectivities, which was similar to the observations in the epoxidation of α, β-unsaturated trichloromethyl ketones (Table 5, entries 14 and 16). Notably, the resulting epoxides were quickly transformed to their hydrated forms in the process of work-up.[9]

Table 5. Epoxidation of α,β-unsaturated trifluoromethyl ketones catalyzed by **7**.[a]

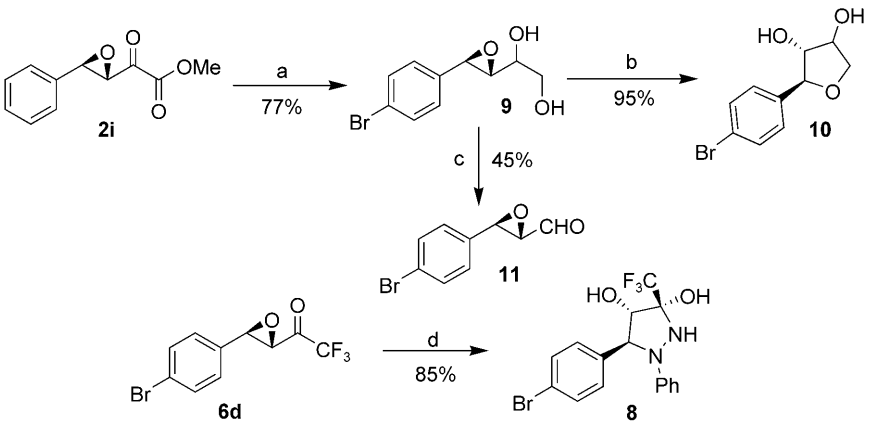


Entry	Catalyst	Solvent	R	Temp. [°C]	Time [h]	Product	Yield [%][b]	*ee* [%][c]
1	**7d**	*n*-hexane	Ph (**5a**)	20	10	**6a**	78	72
2	**7e**	*n*-hexane	Ph (**5a**)	20	18	**6a**	72	51
3	**7f**	*n*-hexane	Ph (**5a**)	20	8	**6a**	80	-52
4	**7d**[d]	*n*-hexane	Ph (**5a**)	20	8	**6a**	76	64
5	**7d**[e]	*n*-hexane	Ph (**5a**)	20	8	**6a**	82	60
6	**7d**	*n*-hexane	Ph (**5a**)	0	18	**6a**	76	96
7	**7d**	CCl_4	Ph (**5a**)	20	8	**6a**	85	66
8	**7d**	toluene	Ph (**5a**)	20	8	**6a**	52	21
9	**7d**	*n*-hexane	*p*-F-C_6H_4 (**5b**)	0	12	**6b**	88	90
10	**7d**	*n*-hexane	*p*-Cl-C_6H_4 (**5c**)	0	12	**6c**	84	90
11	**7d**	*n*-hexane	*p*-Br-C_6H_4 (**5d**)	0	12	**6d**	82	95
12	**7d**	*n*-hexane	*p*-CH_3-C_6H_4 (**5e**)	0	18	**6e**	80	95
13	**7d**	*n*-hexane	*p*-Et-C_6H_4 (**5f**)	0	18	**6f**	81	78
14	**7d**	*n*-hexane	*o*-Cl-C_6H_4 (**5g**)	0	28	**6g**	65	52
15	**7d**	*n*-hexane	*m*-Cl-C_6H_4 (**5h**)	0	18	**6h**	79	89
16	**7d**	*n*-hexane	*o*,*p*-di-Cl-C_6H_3 (**5i**)	0	28	**6i**	70	53

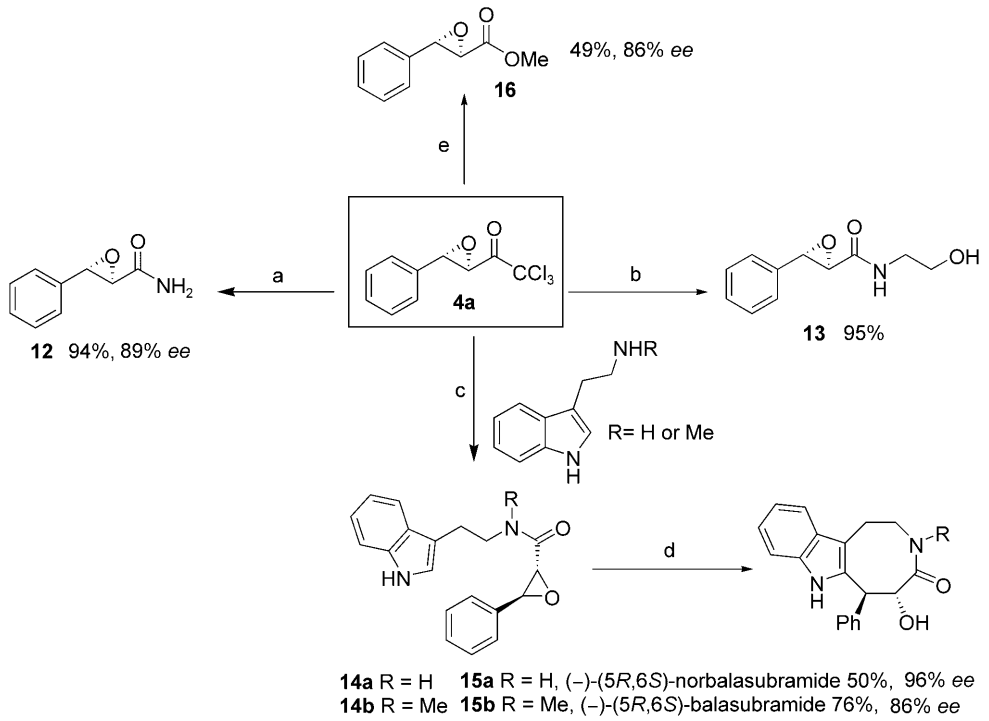
[a] Unless otherwise specified, the reaction was carried out with 2.0 equiv. of TBHP in the presence of 10 mol% of catalyst **7**.
[b] Isolated yields by flash column chromatography.
[c] Determined by HPLC analysis using the chiral column Daicel Chiralcel AS-H. Configuration (2*S*,3*R*) for **6a** obtained by **7d**, **7e** and (2*R*,3*S*) by **7f**.
[d] 20 mol% of **7d** was used as the catalyst.
[e] 30 mol% of **7d** was used as the catalyst.

In an effort to realize our goal of generating synthetically useful structures, efficient further transformations of the α-epoxy ketones obtained above were then investigated (Scheme 1). First, hydrazinolysis of the trifluoromethyl epoxide **6d** with phenylhydrazine afforded the heterocyclic compound **8** with a trifluoromethyl-substituted quaternary carbon centre in 85% yield.[10] These types of heterocyclic compounds are useful intermediates in the preparation of biologically interesting compouds.[11]

Reduction of the β-epoxy-α-keto esters **2** with sodium borohydride in the presence of anhydrous calcium chloride furnished the chiral diol **9** in excellent yield.[12] This compound could then be easily transformed to dihydroxytetrahydrofuran **10**, a structure that can be seen in many natural products,[13] by refluxing in water for three hours.[14] Alternatively, compound **9** could also be converted to another useful synthon, the epoxy aldehyde **11**.



Scheme 1. Synthetic transformations of the chiral epoxides **2i** and **6d**: a) $NaBH_4$, $CaCl_2$, MeOH, 0 °C, *dr* = 2:1, 1.5 h; b) Water, reflux, 3 h; c) $NaIO_4$, CH_2Cl_2, room temperature, 1 h; d) $PhNHNH_2$, EtOH, −15 °C, 3 h.



Scheme 2. Synthetic transformations of the chiral epoxide **4a**: a) $NH_3{\cdot}H_2O$, CH_3CN, room temperature, 1 h; b) ethanolamine, CH_3CN, room temperature, 10 h; c) CH_3CN, room temperature, 10 h; d) $Yb(OTf)_3$, CH_3CN, room temperature, 10 h; e) $NaHCO_3$, MeOH, 30 °C, 0.5 h.

Conversions of the α,β-epoxy trichloromethyl ketones were more facile due to the good reactivity of the trichloromethyl group as a leaving group (Scheme 2). The amides **12**–**14** could be easily obtained in high yields by the reactions of **4a** with the corresponding amines in acetonitrile without any catalyst.[15] The products **12** and **13** thus obtained are important intermediates in organic synthesis.[16] Furthermore, using an $Yb(OTf)_3$-catalyzed intramolecular ring-opening reaction of the epoxide structure, a straightforward synthesis of chiral (−)-(5*R*,6*S*)-balasubramide **15b** was achieved with good yield in two steps from **4a**. This may be the most efficient method for the synthesis of this compound up to date.[16b,17] By heating in methanol in basic conditions for 0.5 hour, the product **4a** could be easily transformed to α-epoxy ester **16**. The absolute configuration of the epoxide **4a** was determined to be 2*R*,3*S* by comparison of the optical rotation value of the product **16** with that reported.[18]

Conclusions

In conclusion, we have achieved the highly efficient and enantioselective epoxidation of three types of electron-deficient α,β-unsaturated ketones in synthetically useful yields. This reaction largely expands the method for the synthesis of epoxides useful in a synthetic context. In addition, we have demonstrated the synthetic utility of our epoxide substrates, leading to the efficient synthesis of (−)-(5*R*,6*S*)-norbalasubramide and (−)-(5*R*,6*S*)-balasubramide in good yields over three steps. Studies on the further applications of these epoxidations in organic synthesis are in progress.

Experimental Section

General Procedure for the Asymmetric Epoxidation of α,β-Unsaturated Ketones

To a solution of ketone **1a** (0.1 mmol) and catalyst **7** (0.005–0.02 mmol) in hexane (1.0 mL) was added TBHP (0.2 mmol, 6.35 M in toluene, 30 μL) at the appropriate temperature, and the resulting mixture was stirred for the specified time (Table 1, Table 2, Table 3, and Table 4). After completion as indicated by TLC, the crude mixture was concentrated on a rotary evaporator. The residue was directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 10:1) to give the pure epoxide **2a** as a white solid; yield: 80%; mp 70 °C; $[\alpha]_D^{27.3}$: −139.9 (*c* 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.39$ (m, 3H), 7.33 (m, 2H), 4.20 (dd, $J = 1.5$ Hz, 13.5 Hz, 2H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 187.94$, 160.75, 134.50, 129.37, 128.77, 125.88, 60.72, 60.11, 53.23; IR (film): $\nu = 3222$, 1755, 1693, 1364, 1288, 1133, 1023, 701 cm^{-1}; EI-MS: *m*/*z* (abundance) = 206 (M^+, 3.10), 91 (100), 121 (67.25), 90 (22.85), 65 (22.19), 89 (19.09), 77 (17.69), 51 (15.29), 119 (13.82); anal. calcd. for

$C_{11}H_{10}O_4$: C 64.07, H 4.89; found: C 64.34, H 5.10; HPLC (separation conditions: Chiralcel AS-H, 20 °C, 254 nm, 90:10 hexane/*i*-PrOH, 1.00 mL min^{-1}): t_{major} = 19.1 min, t_{minor} = 13.9 min.

2,2,2-Trichloro-1-[(2*R*,3*S*)-3-phenyloxiran-2-yl]ethanone (4a): Jelly; yield: 77%; $[\alpha]_D^{26}$: −127.1 (*c* 1.00, $CHCl_3$); IR (neat): ν = 2925, 1756, 1599, 1454, 1069 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.42 (m, 5H), 4.29 (d, *J* = 0.9 Hz, 1H), 4.15 (d, *J* = 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.16, 134.12, 129.51, 128.87, 125.79, 96.89, 61.33, 57.19; EI-MS: *m*/*z* (abundance) = 229 (M^+−Cl, 6.95), 91 (100.00), 105 (37.03), 131 (34.48), 77 (22.87), 103 (20.52), 89 (14.67), 51 (13.69) 65 (10.37); HR-MS: *m*/*z* = 228.9820, calcd. for $C_{10}H_7Cl_3O_2$: 228.9823; HPLC (separation conditions: Chiralcel OD-H, 20 °C, 220 nm, 90:10 hexane/*i*-PrOH, 1.00 mL min^{-1}): t_{major} = 18.9 min, t_{minor} = 25.2 min.

2,2,2-Trifluoro-1-[(2*S*,3*R*)-3-phenyloxiran-2-yl]ethane-1,1-diol (6a): White solid; yield: 76%; mp 139–140 °C; $[\alpha]_D^{22.9}$: 51.5 (*c* 0.75, $CHCl_3$); IR (film): ν = 3422, 1465, 1189, 721 cm^{-1}; ^{19}F NMR (282 MHz, $CDCl_3$): δ = −84.3 (s, 3 F); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.40 (s, 1H), 3.95 (s, 1H), 7.18–7.31 (m, 5H); MS (EI): *m*/*z* = 216 (M^+−H_2O); HPLC (separation conditions: Chiralcel AS-H, 20 °C, 254 nm, 90:10 hexane/*i*-PrOH, 1.00 mL min^{-1}): t_{major} = 18.6 min, t_{minor} = 22.6 min.

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