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Asymmetric Epoxidation of Fluoroolefins by Chiral Dioxirane. Fluorine Effect on Enantioselectivity

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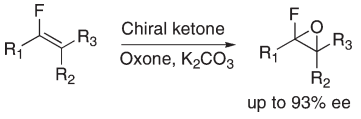

The asymmetric epoxidation of various fluoroolefins has been studied using chiral ketone catalyst, and up to 93% ee was achieved with fructose-derived ketone **1**.

Chiral ketones represent an important class of organic catalysts for asymmetric epoxidation.[1] Our previous studies have shown that ketones **1** and **2** are highly effective for the epoxidation of *trans*- and trisubstituted olefins,[2,3] and ketones **3** are highly effective for the epoxidation of *cis*- and related olefins (Figure 1).[4] The electronic and steric properties of substituents on an olefin have an important impact on the enantioselectivity for the epoxidation. The epoxidation with ketones **1** and **2** proceeds mainly via spiro transition state **A**, which is favored over spiro **B** due to the steric effect and favored over planar **C** due to the stabilizing secondary orbital interaction between the oxygen nonbonding orbital of the dioxirane and the π^* orbital of the olefin in the spiro transition state (Figure 2).[2,3,5] The stereodifferentiation for the epoxidation with ketones **3** likely results from electronic interactions.[4] It appears that there exists an attraction between the π substituent of the olefin and the oxazolidinone moiety of the catalyst (spiro **D** is favored over spiro **E**) (Figure 3).[4]

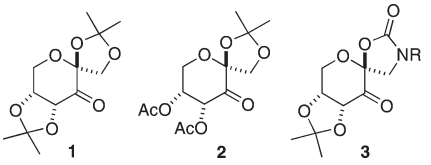

FIGURE 1. Ketones **1**−**3**.

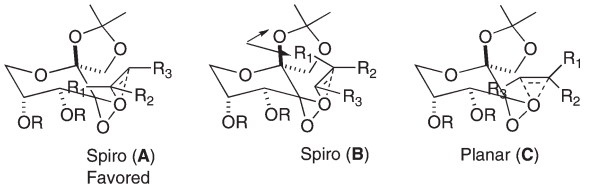

FIGURE 2. Proposed transition states for the epoxidation with ketones **1** and **2**.

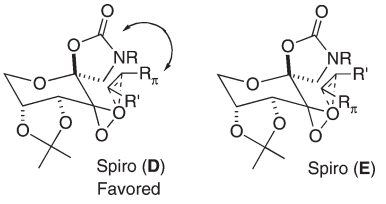

FIGURE 3. Proposed transition states for the epoxidation with ketones **3**.

Fluorine has unique steric and electronic properties and is widely used to alter the properties of organic molecules.[6,7] It is foreseeable that fluorinated olefins may display different steric and electronic properties for the epoxidation with chiral ketones as compared to their nonfluorinated counterparts. We decided to investigate the asymmetric epoxidation of monofluorinated olefins using ketones **1**−**3** to explore the effect of fluorine on reactivity and enantioselectivity. Herein, we wish to report our studies on this subject.[8−12]

The syntheses of various fluoroolefins are outlined in Schemes 1−4. Fluoroolefins **4**, **5**, **8**, **9**, and **11** were

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(2) For leading references on ketone **1**, see: (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328. (c) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (d) Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213.

(3) For leading references on ketone **2**, see: (a) Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792. (b) Wang, B.; Wu, X.-Y.; Wong, O. A.; Nettles, B.; Zhao, M.-X.; Chen, D.; Shi, Y. *J. Org. Chem.* **2009**, *74*, 3986.

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(5) For leading references on theoretic studies on transition states for the dioxirane epoxidation, see: (a) Bach, R. D.; Andrés, J. L.; Owensby, A. L.; Schlegel, H. B.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1992**, *114*, 7207. (b) Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147. (c) Jenson, C.; Liu, J.; Houk, K. N.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 12982. (d) Deubel, D. V. *J. Org. Chem.* **2001**, *66*, 3790. (e) Singleton, D. A.; Wang, Z. *J. Am. Chem. Soc.* **2005**, *127*, 6679.

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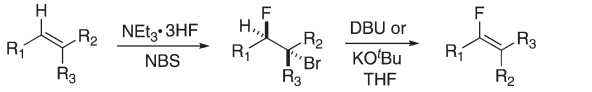
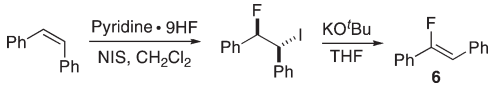
SCHEME 1



4, R_1 = Ph, R_2 = H, R_3 = Me
5, R_1 = Ph, R_2 = Me, R_3 = H
8, R_1 = *n*-Bu, R_2 = H, R_3 = *n*-Bu
9, R_1 = *n*-Bu, R_2 = *n*-Bu, R_3 = H
11, R_1 = Ph, R_2 = R_3 = H

SCHEME 2



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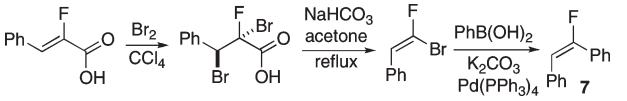
SCHEME 3



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synthesized by fluorobromination[13] followed by HBr elimination using DBU[14] or KO^{t}Bu[15] (Scheme 1). (*Z*)-Fluorostilbene (**6**) was synthesized by iodofluorination of *cis*-stilbene[16] followed by the elimination of HI with KO^{t}Bu (Scheme 2), and (*E*)-fluorostilbene (**7**) was synthesized via Suzuki coupling of phenylboronic acid and the corresponding bromide[17] (Scheme 3). (1-Fluoro-2-methylprop-1-enyl)-benzene (**10**) was synthesized in three steps from diethyl phosphite via the fluorination of diethyl α-hydroxybenzylphosphonate with DAST (Scheme 4).[18]

The epoxidations of fluoroolefins **4**−**11** were carried out with 28−30 mol % of ketones **1**, **2**, and **3a** (R = *p*-EtPh) in MeCN/DMM (2:1 v/v) at 0 °C for 8 h (Table 1). Good to high ee's (74−93%) were obtained for the epoxidation of olefins **4** and **5** with ketones **1** and **2** (Table 1, entries 1−2, 4−5). Modest ee (41%) was obtained for the epoxidation of olefin **5** with ketone **3a** (Table 1, entry 6) and the configuration of the resulting epoxide is opposite to that of epoxides resulting from ketones **1** and **2**. The epoxidation of olefins **6-9**

SCHEME 4

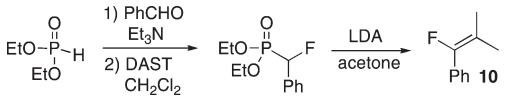

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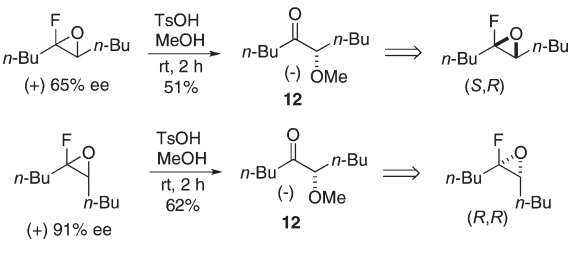
TABLE 1. Asymmetric Epoxidation of Fluoroolefins with Ketones 1−3a[a]

entry	substrate	ketone	yield[b] (%)	ee[c] (%)	config.[d]
1		**1**	70	93	(+)
2		**2**	60	90	(+)
3	**4**	**3a**	71	30	(+)
4		**1**	63	74	(-)-(*R*,*R*)
5		**2**	68	92	(-)-(*R*,*R*)
6	**5**	**3a**	67	41	(+)-(*S*,*S*)
7		**1**	39	91	(+)
8		**2**	67	85	(+)
9	**6**	**3a**	88	85	(+)
10		**1**	56	83	(-)
11		**2**	86	91	(-)
12	**7**	**3a**	60	56	(-)
13		**1**	83	77	(+)
14		**2**	83	65	(+)
15	**8**	**3a**	71	46	(+)
16		**1**	83	80	(+)-(*R*,*R*)
17		**2**	77	91	(+)-(*R*,*R*)
18	**9**	**3a**	80	6	(+)-(*R*,*R*)
19		**1**	42	43	(+)
20		**2**	70	33	(+)
21	**10**	**3a**	79	62	(+)
22		**1**	64	27	(-)
23		**2**	75	39	(-)
24	**11**	**3a**	68	32	(+)

[a]All reactions were carried out with olefin (0.20 mmol), ketone **1**, or **3a** (0.06 mmol) or hydrate of ketone **2** (0.056 mmol), Oxone (0.27−0.53 mmol), K_2CO_3 (0.81−2.12 mmol), and Bu_4NHSO_4 (0.012 mmol) in MeCN/DMM (2:1 v/v) and buffer at 0 °C (bath temperature) for 8 h. [b]Isolated yield. [c]The ee's were determined by chiral GC (Chiraldex B-DM), except for entries 7−9 which were determined by chiral HPLC (Chiralcel OD). [d]The absolute configurations of entries 4−6 and 16−18 were determined using the VCD spectra by BioTools.

SCHEME 5



(9) For additional examples of asymmetric epoxidation of fluoroolefins, see: Bortolini, O.; Fogagnolo, M.; Fantin, G.; Maietti, S.; Medici, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1113.

(10) For examples of epoxidation of fluoroolefins, see: (a) Elkik, E.; Le Blanc, M. *Bull. Soc. Chim. Fr.* **1971**, *38*, 870. (b) Camps, F.; Messeguer, A.; Sánchez, F.-J. *Tetrahedron* **1988**, *44*, 5161. (c) Dubuffet, T.; Sauvêtre, R.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 5923. (d) Lluch, A.-M.; Sánchez-Baeza, F.; Messeguer, A.; Fusco, C.; Curci, R. *Tetrahedron* **1993**, *49*, 6299. (e) Kornilov, A. M.; Sorochinsky, A. E.; Kukhar, V. P. *Tetrahedron: Asymmetry* **1994**, *5*, 1015. (f) Michel, D.; Schlosser, M. *Tetrahedron* **1996**, *52*, 2429. (g) Tranel, F.; Haufe, G. *J. Fluorine Chem* **2004**, *125*, 1593.

(11) For examples of fluorinated epoxide synthesis by ring closure of halogenated alcohols, see: (a) Kirrmann, A.; Nouri-Bimorghi, R. *Bull. Soc. Chim. Fr.* **1972**, *6*, 2328. (b) Duhamel, P.; Leblond, B.; Poirier, J.-M. *J. Chem. Soc., Chem. Commun.* **1993**, 476. (c) Duhamel, P.; Leblond, B.; Bidois-Séry, L.; Poirier, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2265. (d) Shimizu, M.; Takebe, Y.; Kuroboshi, M.; Hiyama, T. *Tetrahedron Lett.* **1996**, *37*, 7387. (e) Hollenstein, H.; Luckhaus, D.; Pochert, J.; Quack, M.; Seyfang, G. *Angew. Chem.* **1997**, *109*, 136. (f) Shimizu, M.; Yamada, N.; Takebe, Y.; Hata, T.; Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2903.

(12) For an example of fluorinated epoxide synthesis by halogen substitution of chlorinated or brominated epoxides, see: Leroy, J.; Bensoam, J.; Humiliere, M.; Wakselman, C.; Mathey, F. *Tetrahedron* **1980**, *36*, 1931.

(13) Haufe, G.; Alvernhe, G.; Laurent, A.; Ernet, T.; Goj, O. *Org. Synth.* **1999**, *76*, 159.

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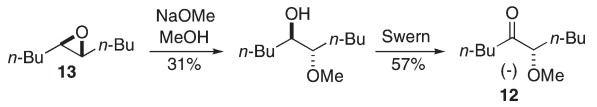
(17) (a) Eddarir, S.; Francesch, C.; Mestdagh, H.; Rolando, C. *Bull. Soc. Chim. Fr.* **1997**, *134*, 741. (b) Chen, C.; Wilcoxen, K.; Huang, C. Q.; Strack, N.; McCarthy, J. R. *J. Fluorine Chem.* **2000**, *101*, 285.

(18) (a) Taylor, W. P.; Zhang, Z.-Y.; Widlanski, T. S. *Bioorg. Med. Chem.* **1996**, *4*, 1515. (b) Tsai, H.-J.; Lin, K.-W.; Ting, T.-h.; Burton, D. J. *Helv. Chem. Acta.* **1999**, *82*, 2231.

SCHEME 6



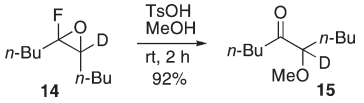
generally gave good to high ee's (65−91%) with ketones **1** and **2** (Table 1, entries 7−8, 10−11, 13−14, 16−17). However, the ee's obtained for these olefins with ketone **3a** are generally low (6−56% ee) (Table 1, entries 12, 15, 18) except in the case of olefin **6** (85% ee) (Table 1, entry 9). The ee's for the epoxidation of (1-fluoro-2-methylprop-1-enyl)benzene (**10**) and α-fluorostyrene (**11**) are generally modest (27−62% ee) as these are not effective substrates for the ketones tested (Table 1, entries 19−24).[19]

In order to determine the absolute configuration of the fluorinated epoxides, the epoxides obtained from olefins **8** and **9** with ketone **2** (Table 1, entries 14 and 17) were treated with anhydrous TsOH−MeOH at rt for 2 h, giving (−)-(*S*)-6-methoxydecan-5-one (**12**) in both cases (Scheme 5).[20] The absolute configuration of 6-methoxydecan-5-one was determined by comparing the absolute configuration of the methoxy ketone synthesized from the epoxide (**13**) with known configuration (Scheme 6).[2c] When the deuterated (*E*)-5-fluorodec-5-ene oxide (**14**) was treated with anhydrous TsOH−MeOH at rt for 2 h, deuterated 6-methoxydecan-5-one (**15**) was obtained, suggesting that MeOH attacks on the nonfluorinated carbon to form the corresponding ketone (Scheme 7). The absolute configuration determined by the above reaction sequence confirmed the absolute configuration obtained with the VCD data from BioTools (Table 1, entry 17).

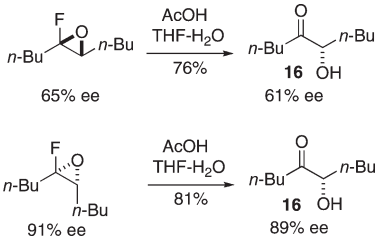
When the epoxide obtained from olefins **8** and **9** was treated with acetic acid in THF−H_2O at 60 °C for 20 h, (*S*)-6-hydroxydecan-5-one (**16**) was obtained with only a slight loss of ee (Scheme 8).[21] When deuterated epoxide **17** was subjected to the same conditions (acetic acid in THF−H_2O at 60 °C for 20 h), (*S*)-deuterated-6-hydroxydecan-5-one (**18**) was obtained in 89% ee, which further supports that nucleophilic attack occurs on the nonfluorinated carbon (Scheme 9).

High enantioselectivities were obtained for *Z*-olefins **4** and **6** with ketones **1** and **2** (Table 1, entries 1−2, 7−8), suggesting that spiro **F** is favored over spiro **G** due to steric interaction between the phenyl ring on the olefin and the spiro ketal group of the catalyst (Figure 4). The lower ee's obtained for *E*-olefins **5** and **7** with ketone **1** as compared to that of olefins **4** and **6** (Table 1, entry 4 vs 1 and 10 vs 7) indicate that fluorine is not as effective in disfavoring spiro **I** as phenyl group in disfavoring spiro **G** (Figures 4 and 5, R = CMe_2). Higher ee's obtained for the epoxidation of olefins **5** and **7** with ketone **2** compared to that of ketone **1** (Table 1, entry 5 vs 4 and 11 vs 10) could be due to additional beneficial interactions between the F and/or Ph group of the olefin and the acetate group of the catalyst in

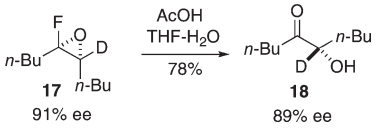
SCHEME 7



SCHEME 8



SCHEME 9



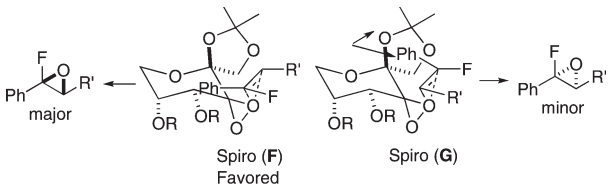


FIGURE 4. Proposed transition states for the epoxidation of olefins **4** and **6** with ketones **1** and **2**.

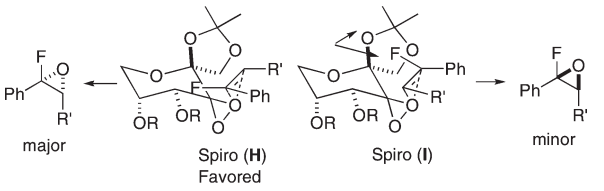


FIGURE 5. Proposed transition states for the epoxidation of olefins **5** and **7** with ketones **1** and **2**.

transition state spiro **H** (R = Ac), thus increasing the ee's (Figure 5).[3b]

The higher ee's obtained for the epoxidation of olefin **9** than that of olefin **8** with ketones **1** and **2** suggest that the fluorine atom may be more effective in disfavoring spiro **M** than the *n*-butyl group is in disfavoring spiro **K** (Figure 6). High ee (91%) obtained for olefin **9** with ketone **2** again suggests that there may be beneficial interactions between the fluorine of the olefin and the OAc group of the catalyst in transition state spiro **L** (R = Ac) as in the case of spiro **H** (Figure 5), thus increasing the ee.

Lower ee obtained for the epoxidation of olefin **8** with ketone **1** (Table 1, entry 13) as compared to its nonfluorinated counterpart (77% ee for **8** vs 91% ee (*E*)-dec-5-ene with ketone **1**[2c]) could be due to the fact that the lone pair of the fluorine substituent raises the π^* orbital of the olefin causing the weakening of the secondary orbital interaction between the π^* orbital of the olefin and the nonbonding

(19) The fluoroepoxides are reasonably stable except the epoxide from olefin **7**, which readily decomposes on silica gel. The epoxides from olefins **4**, **5**, and **11** are extremely volatile.

(20) The determination of the ee of compound **12** was attempted, but with no success.

(21) The absolute configuration of 6-hydroxydecan-5-one is reported in: Curci, R.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Rosa, A. *Tetrahedron Lett.* **1996**, *37*, 115.

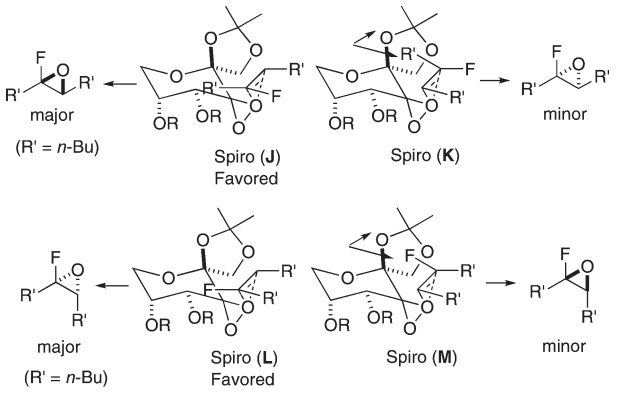


FIGURE 6. Proposed transition states for the epoxidation of olefins **8** and **9** with ketones **1** and **2**.

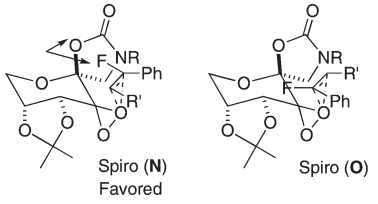


FIGURE 7. Proposed transition states for the epoxidation of olefins **5** and **11** with ketone **3a**.

orbital of the dioxirane in spiro **J**, thus leading to more competition from planar **C**-like transition state and decreasing the ee.

The fluorine atom did not show a beneficial effect on the epoxidation with ketone **3a**. In fact, in most cases, lower ee's were obtained for fluorinated olefins than nonfluorinated olefins (Table 1).[4] For example, only 41% and 32% ee were obtained, respectively, for olefins **5** and **11** with ketone **3a** (Table 1, entries 6 and 24). Compared to spiro **D** (Figure 3), spiro **N** (Figure 7) is disfavored by the fluorine possibly via steric[22] and/or electronic repulsion.

In conclusion, a series of fluoroolefins were epoxidized with ketones **1**−**3a**, and up to 93% ee was obtained. In some cases, the fluorine can act as an effective directing group via its steric and/or electronic interactions with ketone catalysts. In other cases, however, the fluorine is detrimental to the enantioselectivity for the epoxidation. These results provide us better understanding of the effect of the olefin substituent on the chiral ketone-catalyzed epoxidation.

Experimental Section

Representative Asymmetric Epoxidation Procedure with Ketone 1 (Table 1, Entry 16). To a solution of olefin **9** (0.20 mmol, 0.032 g), ketone **1** (0.06 mmol, 0.015 g), and TBAHS (0.012 mmol, 0.004 g) in MeCN/DMM (2:1, v/v) (3.0 mL) was added buffer (0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4×10^{-4} M aq Na_2EDTA, pH 9.3) (2.0 mL) with stirring. Upon cooling to 0 °C, a solution of Oxone (0.27 mmol, 0.21 M in 4×10^{-4} M aq Na_2EDTA, 1.30 mL) and a solution of K_2CO_3 (1.16 mmol, 0.89 M in 4×10^{-4} M aq EDTA, 1.30 mL) were added dropwise separately and simultaneously via syringe pump over 8 h. The reaction was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (pentane to pentane−Et_2O, 40:1, v/v) to give the epoxide as a colorless oil (0.029 g, 83% yield, 80% ee): IR (film) 2960, 1468 cm^{-1}; $[\alpha]^{20}_D = +12.8$ (*c* 0.86, $CHCl_3$, 80% ee); ^1H NMR (300 MHz, $CDCl_3$) δ 3.23−3.20 (m, 1H), 1.91−1.73 (m, 2H), 1.67−1.26 (m, 10H), 0.96−0.85 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 100.3, 96.9, 62.9, 62.6, 29.6, 29.2, 28.2, 28.0, 25.8, 22.7, 22.6, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −129.2 (t, J = 19.9 Hz). Anal. Calcd for $C_{10}H_{19}FO$: C, 68.93; H, 10.99. Found: C, 68.69; H, 10.87.

Representative Asymmetric Epoxidation Procedure with Ketone 2 (Table 1, Entry 17). To a solution of olefin **9** (0.20 mmol, 0.032 g), hydrate of ketone **2** (0.056 mmol, 0.018 g), and TBAHS (0.012 mmol, 0.004 g) in MeCN/DMM (2:1, v/v) (3.6 mL) was added buffer (0.05 M aq Na_2HPO_4−0.05 M aq KH_2PO_4, pH 7.0) (1.2 mL) with stirring. Upon cooling to 0 °C, a solution of Oxone (0.40 mmol, 0.21 M in 4×10^{-4} M aq EDTA, 1.92 mL) and a solution of K_2CO_3 (0.81 mmol, 0.42 M in 4×10^{-4} M aq EDTA, 1.92 mL) were added dropwise separately and simultaneously via syringe pump over 8 h. The reaction was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (pentane to pentane−Et_2O, 40:1, v/v) to give the epoxide as a colorless oil (0.027 g, 77% yield, 91% ee).

Representative Asymmetric Epoxidation Procedure with Ketone 3 (Table 1, entry 18). To a solution of olefin **9** (0.20 mmol, 0.032 g), ketone **3a** (0.06 mmol, 0.021 g), and TBAHS (0.012 mmol, 0.004 g) in MeCN/DMM (2:1, v/v) (3.0 mL) was added buffer (0.1 M K_2CO_3−AcOH in 4×10^{-4} M aq Na_2EDTA, pH 9.3) (2.0 mL) with stirring. Upon cooling to 0 °C, a solution of Oxone (0.53 mmol, 0.21 M in 4×10^{-4} M aq EDTA, 2.52 mL) and a solution of K_2CO_3 (2.12 mmol, 0.84 M in 4×10^{-4} M aq EDTA, 2.52 mL) were added dropwise separately and simultaneously via syringe pump over 8 h. The reaction was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (pentane to pentane−Et_2O, 40:1, v/v) to give the epoxide as a colorless oil (0.028 g, 80% yield, 6% ee).

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Supporting Information Available: The synthesis and characterization of olefins and epoxides along with the data for the determination of the enantiomeric excess of the epoxides and the VCD data. This material is available free of charge via the Internet at http://pubs.acs.org.

(22) The van der Waals' radii of fluorine is larger than hydrogen (1.47 vs 1.20 Å) (see ref 7).