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Bicyclo[3.2.1]octanone catalysts for asymmetric alkene epoxidation: the effect of disubstitution

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Abstract—A series of 2-fluoro-8-oxabicyclo[3.2.1]octan-3-ones are prepared and tested as catalysts for alkene epoxidation with Oxone®. These catalysts provide *trans*-stilbene oxide with up to 83% ee, but the highest ee value is obtained with the monofluorinated ketone **2**: both 2,2- and 2,4-disubstituted catalysts afford epoxide of lower ee.

1. Introduction

Catalytic asymmetric epoxidation of alkenes is an exceptionally valuable synthetic transformation.[1] The development of efficient methods for asymmetric epoxidation of simple, 'unfunctionalised' alkenes is a particular challenge, and some of the most spectacular progress in recent years has come from the use of small organic molecules to promote oxygen transfer by Oxone®.[2] While iminium salts are starting to provide promising levels of enantioselectivity,[3] chiral dioxiranes derived from chiral ketones have already given excellent results for trans- and trisubstituted alkenes.[4–7] An especially noteworthy feature of these dioxirane systems is that they have allowed greatly improved understanding of the mechanisms of asymmetric induction through synthetic and computational studies.[8] A further understanding of dioxirane–substrate interactions is especially important for further progress with the challenging terminal alkene class: despite highly encouraging results with styrenes,[9] these substrates generally still do not reach practical levels of enantioselectivity. In our own contributions to the chiral dioxirane area, we have reported that the bicyclo[3.2.1]octanone system provides a conformationally well-defined framework, which is relatively resistant to Baeyer–Villiger decomposition. The prototype fluoroketone **1** afforded *E*-stilbene oxide with 76% ee at 10 mol % catalyst loading, and, due to its stability, could be recycled.[10,11] This feature allowed preparation of a silica-supported variant.[12] In exploring the effects of structural modifications, we discovered the more enantioselective oxabicyclic ester **3**.[13,14] For both catalysts, the major observed enantiomer in the epoxidation of *E*-alkenes fits a spiro-TS (cf. Fig. 1) in which

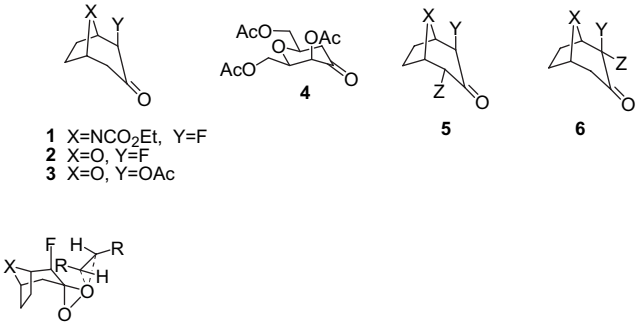

Figure 1.

an olefinic hydrogen substituent sits in the catalyst region occupied by the axial α-substituent. Computational studies[15] on fluorinated cyclohexanone dioxiranes suggest that the axial α heteroatom in catalysts such as **1**–**3** serve to make the equatorial dioxirane oxygen more reactive than the axial one; in line with this idea, we recently reported[16] that monocyclic ketones **4**, lacking the steric effect of the two-carbon bridge in the bicyclic systems, afford only slightly lowered enantioselectivities.

All of the catalysts we have reported to date have a single substituent α to the ketone carbonyl group. In this paper, we report the first studies of the effect of two electronegative substituents, with the successful synthesis and testing of catalysts of general structure **5** and **6**.[17]

2. Results and discussion

2.1. Ketone synthesis

Our first synthetic targets were ketones of type **5** with an equatorial α′-substituent in addition to the usual axial

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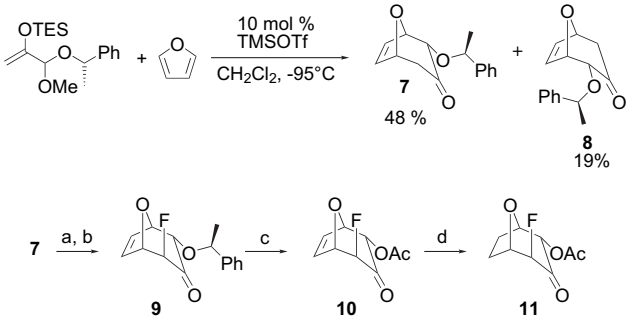
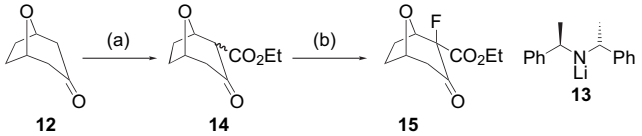
α-group. We reasoned that the 'pseudo-C_2-symmetry' of this catalyst class would mean that any approach of the alkene to the *endo*-oxygen of the dioxirane intermediate, would be expected on simple steric expectations to lead to formation of the same product enantiomer as attack on the *exo*-oxygen. Since reaction of enolate derivatives of these bicyclic ketones with electrophiles generally proceeds on the *exo*-face, we introduced the required *endo*-substituent by starting our synthesis with the diastereoselective furan [4+3]-cycloaddition process of Hoffmann,[18] which provides separable diastereomers **7** and **8** (Scheme 1). The major isomer **7** was converted to the corresponding triethylsilyl enol ether, electrophilic fluorination of which with Selectfluor™ (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate)) provided **9**. Simultaneous removal of the α-methylbenzyl auxiliary and acetylation, followed by hydrogenation of the alkene, afforded the desired α,α′-disubstituted catalyst **11** (Scheme 1). The axial orientation of the fluorine substituent, expected based on the strong precedent for electrophilic attack on the less hindered, *exo*-face of the intermediate silyl enol ether, was confirmed by the analysis of ^{1}H NMR coupling constants. In particular, the hydrogen α to fluorine displayed a 2.1 Hz coupling to the bridgehead proton. Additionally the proton α to the acetoxy group exhibited a 5.5 Hz coupling to the fluorine, consistent with the expected 1,3-diaxial relationship between these two atoms.



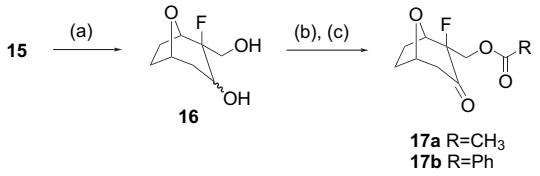
Scheme 1. Reagents and conditions: (a) LDA, Et_3SiCl, THF, −78 °C (96%); (b) 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate) (Selectfluor™), CH_3CN, rt (45%); (c) CH_3COCl (3 equiv), $FeCl_3$ (3 equiv), rt, 15 s (72%); (d) H_2, Pd/C, EtOH (100%).

We next targeted the 2,2-disubstituted catalyst series **6**. Initial attempts to prepare catalysts of this type by further functionalisation of **7** were thwarted by difficulties in effecting enolisation on the side of the ketone bearing the oxygen substituent. We therefore reverted to our earlier strategy in which desymmetrisation of the parent ketone **12** with chiral base **13**[19] was followed by reaction with Mander's reagent to afford the β-ketoester **14** in 76% yield as a mixture of diastereomers and keto-enol tautomers, which underwent electrophilic fluorination with Selecfluor™ in the absence of added base, leading to **15** (Scheme 2). Chiral GC analysis indicated 98.5% de and 80% ee for **15**.



Scheme 2. Reagents and conditions: (a) **13**, THF, −78 °C, DMPU then $NCCO_2Et$ (76%); (b) 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis-(tetrafluoroborate) (Selectfluor™), CH_3CN, rt (54%).

The synthesis of further interesting 2,2-disubstituted derivatives was planned by conversion of the ester group present in compound **15** to the alcohol oxidation level, which would allow preparation of a wide range of diverse ester derivatives. Thus, a straightforward sequence (Scheme 3) of $LiAlH_4$ reduction, selective esterification of the primary alcohol and TPAP oxidation[20] allowed access to acetate **17a** and benzoate **17b**, the latter being prepared in order to probe for aromatic–aromatic interactions between catalyst and substrate. The ee of these two ketones was determined by chiral GC and was found to be 80%.

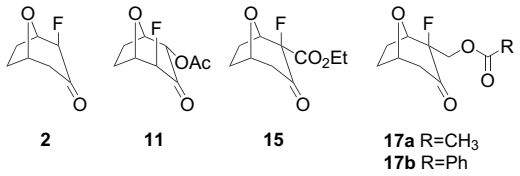


Scheme 3. Reagents and conditions: (a) $LiAlH_4$, THF (70%); (b) Ac_2O, pyridine (51%) or PhCOCl, Et_3N, CH_2Cl_2 (60%); (c) TPAP, NMO, CH_2Cl_2 (87% for **17a**, 100% for **17b**).

2.2. Epoxidation results

The results using ketones **2**, **11**, **15**, **17a** and **17b** as catalysts for alkene epoxidation with Oxone® are shown in Table 1. Where the catalysts were not enantiomerically pure, the observed epoxide enantiomeric excess has been converted to ee_{max}, the ee expected assuming a linear relationship

Table 1. Ketone-catalysed Oxone® epoxidation of alkenes[a]



Entry	Ketone	Alkene	Conversion[b] (%)	ee (%)[c]
1[d]	**2**	*E*-Stilbene	100	83 (*R*,*R*)
2[e]	**11**	—	100	64 (*S*,*S*)
3	**15**	—	92	77 (*R*,*R*)
4	**17a**	—	84	68 (*R*,*R*)
5	**17b**	—	80	63 (*R*,*R*)
6[e]	**11**	Styrene	100	2 (*S*)
7[f]	**15**	—	100	14 (*R*)
8	**17a**	—	100	29 (*R*)
9	**17b**	—	79	25 (*R*)
10[e]	**11**	α-Methylstyrene	100	8 (*S*)
11[f]	**15**	—	100	8 (*S*)
12	**17a**	—	61	2 (*S*)
13	**17b**	—	100	3 (*S*)

[a] Reaction conditions: alkene (1 equiv), ketone (20 mol %), Oxone® (10 equiv of $KHSO_5$), $NaHCO_3$ (15.5 equiv), CH_3CN/aq Na_2EDTA (0.4 mmol/dm^3 solution) (3:2, 25 mL/mmol), 24 h, rt.

[b] Estimated by integration of the ^{1}H NMR spectrum of the crude reaction mixture.

[c] Measured by chiral HPLC or GC (see Section 4). Catalyst **2** was of 76% ee; catalysts **15**, **17a** and **17b** were of 80% ee. For these catalysts, the quoted ee is ee_{max}=100×epoxide ee/ketone ee.

[d] Taken from Ref. 13.

[e] 10 mol % ketone employed.

[f] 100 mol % ketone employed.

between catalyst ee and product ee, which we have shown to be the case for **1** and **3**.[14,21] Since we have found in the past that performance in the epoxidation of *E*-stilbene is a good general indicator of catalyst selectivity with *trans*-alkenes,[10] we selected this as our test substrate for this olefin class (entries 1–5). All catalysts proved to be reasonably efficient, but the 2,2-disubstituted ketones **17** were less reactive than the other catalysts. In all the cases for *E*-stilbene epoxidation, the major product enantiomer is consistent with predominant reaction via spiro-approach on the *exo*-dioxirane oxygen with the olefinic hydrogen occupying the catalyst quadrant containing the axial fluorine atom (as in Fig. 1). Interestingly, all of the disubstituted catalysts afforded lower epoxide ee than did **2**. Ketone **11** gave the opposite epoxide enantiomer, as expected, but the markedly lower level of selectivity was surprising given the 'pseudo-C_2 symmetry' of this system mentioned earlier, and given that in the established spiro-TS-model, only an olefinic hydrogen occupies the quadrant of the catalyst occupied by the acetoxy group. One possible explanation for the low selectivity with **11** comes from our earlier computational studies,[15] which indicated that the TS for epoxidation of ethene with equatorial-fluoro-cyclohexanedioxirane is highly asynchronous, with the developing C–O bond to the end of the olefin closest to the equatorial fluorine being markedly shorter than the other. If this phenomenon was also produced by the equatorial acetoxy group in **11**, it would have the effect of moving the other end of the olefin away from the stereocontrolling axial fluorine substituent, thus lowering epoxidation enantioselectivity. While this explanation is speculative, it is noteworthy that Singleton has recently demonstrated by measuring kinetic isotope effects as well as B3LYP studies that TS-asynchronicity is indeed an important consideration in determining levels of stereocontrol,[8] suggesting that further mechanistic studies on **11** would be informative. In practical terms, however, the 2,2-disubstituted catalysts **15** and **17** were also less enantioselective than **2**. For the highly challenging terminal alkenes, styrene and α-methylstyrene, again all of the disubstituted catalysts gave disappointing results (entries 6–13). While we did not test catalyst **2** with these substrates, the previously reported results[10] using similar catalyst **1** are 29% ee (*R*) for styrene, and 22% ee (*S*) for α-methylstyrene. Thus for styrene epoxidation, 2,4-disubstitution as in catalyst **11** appears to lower enantioselectivity markedly (entry 6), while the incorporation of the ester unit on the same carbon as the fluorine (catalyst 15, entry 7) is also deleterious. However, both catalysts **17** appear to give very similar results to the monosubstituted systems (entries 8 and 9). All of the disubstituted catalysts gave very poor results with the challenging 1,1-disubstituted alkene, α-methylstyrene (entries 10–13).

These results suggest that these particular disubstitution motifs are not productive designs for enantioselective ketone catalysts. It is interesting to compare these results, however, with the successful ketone catalysts developed by Shi and co-workers.[5] Their polysubstituted ketone catalysts generally contain a spirocentre α to the ketone (either as an acetonide or as an oxazolidinone), suggesting that polysubstitution in itself is not disadvantageous and that incorporation of spirocentres adjacent to the ketone in our own catalysts is well worth investigating.

3. Conclusions

In conclusion, we have successfully devised synthetic routes to novel bicyclo[3.2.1]octanones bearing two electron-withdrawing substituents α to the ketone. These are effective catalysts for alkene epoxidation using Oxone®, but afford lower enantioselectivities than their monosubstituted counterparts. These observations are interesting when compared to the success of polysubstituted ketones containing a spirocentre adjacent to the ketone, developed by Shi and co-workers.[5] Future studies will therefore examine the effect of incorporation of spirocyclic substitution α to the ketone in our oxabicyclo[3.2.1]octanone framework.

4. Experimental

General experimental details have been described previously.[16]

4.1. Ketone synthesis

4.1.1. (1*S*,2*S*,4*S*,5*R*)-2-Fluoro-4-((*S*)-1-phenylethoxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one 9. To a solution of diisopropylamine (0.36 mL, 2.59 mmol) in THF (4.4 mL) was added 2.5 M ^{n}BuLi (1.03 mL, 2.59 mmol) dropwise at −78 °C. After 5 min, the reaction was allowed to warm to room temperature and then cooled to −78 °C. Triethylsilyl chloride (0.50 mL, 2.98 mmol), a solution of oxabicyclic ketone (−)-**7**[18] (0.486 g, 1.99 mmol) in THF and triethylamine (1.25 mL, 8.95 mmol) were then added. After 24 h, the reaction mixture was quenched by the addition of saturated sodium bicarbonate solution (20 mL) at room temperature and the aqueous layer was extracted with diethyl ether (3×100 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (100% petroleum ether) to yield the silyl enol ether (685 mg, 96%) as a colourless oil; $[\alpha]_D^{22}$ −181.2 (*c* 1.06, $CHCl_3$); ν_{max}/cm^{-1} 3026, 2957, 2876, 1637, 1384, 1211, 1093; δ_H (250 MHz, $CDCl_3$) 7.40–7.25 (5H, m, Ph), 6.66 (1H, dd, *J* 6.1, 1.8 Hz, H6), 6.06 (1H, dd, *J* 6.1, 1.8 Hz, H7), 5.31 (1H, d, *J* 4.9 Hz, H4), 4.75 (1H, q, *J* 6.4 Hz, OC*H*Ph), 4.64 (1H, dd, *J* 4.6, 1.8 Hz, H5), 4.58 (1H, dd, *J* 6.1, 1.8 Hz, H1), 3.99 (1H, d, *J* 6.1 Hz, H2), 1.43 (3H, d, *J* 6.4 Hz, CHCH_3), 1.02 (9H, t, *J* 8.0 Hz, CH_2CH_3), 0.74 (6H, q, *J* 8.0 Hz, CH_2CH_3); δ_C (62.5 MHz, $CDCl_3$) 149.5, 144.4, 141.0, 128.5, 127.8, 127.5, 126.5, 108.4, 79.9, 76.5, 73.4, 24.1, 6.7, 5.1. These spectroscopic data agreed with the literature values.[18]

To a stirred solution of the silyl enol ether (179 mg, 0.502 mmol) in acetonitrile (5 mL) at room temperature under a nitrogen atmosphere, Selectfluor™ (178 mg, 0.502 mmol) was added and the mixture stirred for 24 h at room temperature. Tetra-*n*-butylammonium fluoride (0.5 mL, 1 M in THF, 0.50 mmol) was then added to the reaction mixture. After stirring for 0.5 h at room temperature, water (20 mL) and diethyl ether (20 mL) were added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3×25 mL) and the combined organic extracts were dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced

pressure and purified by flash column chromatography (9:1 petroleum ether/diethyl ether) to afford **9** (59.0 mg, 45%) as a white solid; mp 123–124 °C; $[\alpha]_D^{22}$ −140.0 (*c* 1.10, $CHCl_3$); R_f 0.34 (9:1 petroleum ether/diethyl ether); ν_{max}/cm^{-1} 3057, 2986, 1739, 1603, 1266, 1114; δ_H (400 MHz, $CDCl_3$) 7.40–7.29 (5H, m, Ph), 6.60–6.53 (1H, m, H6), 6.16 (1H, dd, *J* 6.0, 1.5 Hz, H7), 5.01 (1H, d, *J* 9.2 Hz, H1), 4.80 (1H, q, *J* 6.4 Hz, OC*H*Ph), 4.70 (1H, dd, *J* 5.0, 1.6 Hz, H5), 4.40 (1H, dd, *J* 49.1, 1.4 Hz, H2), 4.26 (1H, dd, *J* 5.1, 1.6 Hz, H4), 1.50 (3H, d, *J* 6.4 Hz, $CHCH_3$); δ_C (100 MHz, $CDCl_3$, DEPT, hmqc) 200.9 (C, $^2J_{C-F}$ 18.4 Hz, C_3), 142.8 (C, Ar-C), 137.1 (CH, $^4J_{C-F}$ 2.8 Hz, C6), 128.7 (CH, Ar-H), 128.7 (CH, C7), 128.1 (CH, Ar-H), 126.4 (CH, Ar-H), 90.5 (CH, $^1J_{C-F}$ 192.2 Hz, C2), 81.6 (CH, C4), 80.9 (CH, $^2J_{C-F}$ 20.5 Hz, C1), 80.4 (CH, C5), 79.4 (CH, O*C*HPh), 24.0 (CH_3, CH_3); MS (CI–NH_3): *m/z* (%) 280 (100, M+NH_4^+); Found: M+NH_4^+, 280.1350. $C_{15}H_{19}NO_3F$ requires 280.1349.

4.1.2. (1*S*,2*S*,4*S*,5*R*)-2-Fluoro-4-acetoxy-8-oxabicyclo[3.2.1]oct-6-en-3-one 10. To a solution of oxabicyclic ketone **9** (59 mg, 0.225 mmol) in dry CH_2Cl_2 (10 mL) at room temperature under a nitrogen atmosphere, anhydrous $FeCl_3$ (100 mg, 0.617 mmol) and acetyl chloride (48.0 μL, 0.675 mmol) were added and the reaction mixture was stirred for 15 s at room temperature under nitrogen. Water (20 mL) and diethyl ether (20 mL) were added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3×25 mL) and the combined organic extracts were dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and purified by flash column chromatography (8:2 petroleum ether/ethyl acetate) to afford **10** (32.6 mg, 72%) as a pale yellow oil; $[\alpha]_D^{22}$ +24.5 (*c* 1.31, $CHCl_3$); R_f 0.20 (8:2 petroleum ether/ethyl acetate); ν_{max}/cm^{-1} 3100, 2977, 2941, 1759, 1745, 1228, 1079; δ_H (250 MHz, $CDCl_3$) 6.55–6.49 (1H, m, H6), 6.25 (1H, dd, *J* 6.1, 1.8 Hz, H7), 5.74 (1H, dd, *J* 5.1, 1.2 Hz, H4), 5.15 (1H, d, *J* 9.1 Hz, H1), 5.02 (1H, dd, *J* 5.1, 1.5 Hz, H5), 4.50 (1H, dd, *J* 48.8, 1.5 Hz, H2), 2.16 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$, hmqc) 195.0 ($^2J_{C-F}$ 18.9 Hz, C3), 169.1 (*C*=OCH_3), 136.0 (C6), 129.7 (C7), 90.1 ($^1J_{C-F}$ 193.4 Hz, C2), 81.2 ($^2J_{C-F}$ 20.5 Hz, C1), 79.0 (C5), 76.4 (C4), 20.4 (C=O*C*H_3); MS (CI–NH_3): *m/z* (%) 218 (100, M+NH_4^+); Found: M+H^+, 201.0564. $C_9H_{10}FO_4$ requires 201.0563.

4.1.3. (1*S*,2*S*,4*S*,5*R*)-2-Fluoro-4-acetoxy-8-oxabicyclo[3.2.1]oct-3-one 11. To a stirred solution of oxabicyclic ketone **9** (19.7 mg, 0.0984 mmol) in dry ethanol (4 mL), Pd/C (20 mg, 10% Pd on C) was added. The reaction vessel was then flushed with hydrogen gas and the reaction mixture was stirred for 24 h at room temperature under a positive hydrogen pressure. The reaction mixture was filtered through Celite, with diethyl ether as an eluent, and the filtrate was concentrated under reduced pressure and purified by flash column chromatography (1:9 petroleum ether/ether) to obtain the title compound (20.8 mg, 100%) as a colourless oil; $[\alpha]_D^{22}$ −30.2 (*c* 1.13, $CHCl_3$); R_f 0.83 (diethyl ether); ν_{max}/cm^{-1} 2962, 2929, 2863, 1757, 1743, 1468, 1376, 1230, 1082; δ_H (250 MHz, $CDCl_3$) 5.62 (1H, ddd, *J* 5.5, 3.7, 0.9 Hz, H5), 4.78 (1H, m, H1), 4.69 (1H, apparent t, *J* 5.5 Hz, H4), 4.52 (1H, dd, *J* 49.1, 2.1 Hz, H2), 2.18 (3H, s, CH_3), 2.14 (1H, m, H7), 2.02–1.90 (1H, m, H6), 1.90–1.80 (1H, m, H6), 1.60–1.46 (1H, m, H7); δ_C (100 MHz, $CDCl_3$, DEPT, hmqc) 196.5 (C, $^2J_{C-F}$ 20.5 Hz, C3), 169.0 (C, *C*=OCH_3), 93.7 (CH, $^1J_{C-F}$ 187.0 Hz, C2), 78.2 (CH, $^2J_{C-F}$ 19.0 Hz, C1), 77.5 (CH, C4), 76.1 (CH, C5), 23.8 (CH_2, C6), 23.1 (CH_2, $^3J_{C-F}$ 4.6 Hz, C7), 20.5 (CH_3, C=O*C*H_3); MS (CI–NH_3): *m/z* (%) 220 (100, M+NH_4^+); Found: M+NH_4^+, 220.0990. $C_9H_{15}NFO_4$ requires 220.0985.

4.1.4. (1*R*,2*R*,5*S*)-2-Fluoro-3-oxo-8-oxabicyclo[3.2.1]oct-2-carboxylic acid ethyl ester 15. To a solution of the chiral base **13** (4.44 g, 17.00 mmol) in THF (68 mL) at −78 °C was slowly added 2.70 M *n*BuLi (12.7 mL, 34.44 mmol). After 15 min, the solution was allowed to warm to −10 °C and then cooled again to −78 °C. The starting ketone **12** (2 g, 15.87 mmol) dissolved in THF (16 mL) was slowly added and the mixture was stirred at this temperature for 30 min followed by slow addition of DMPU (1.9 mL, 15.87 mmol) and ethylcyanoformate (2 mL, 19.04 mmol). Formation of a precipitate was observed before the complete addition of the acylating agent, which dissolves allowing the solution to warm to −45 °C once all the $NCCO_2Et$ has been added. The mixture was further stirred at this temperature for 30 min and then allowed to warm up to 0 °C. After 3 h of reaction, the solution was poured into cold water (100 mL). The expected product was extracted into Et_2O (3×150 mL), and some products were extracted into EtOAc (3×120 mL). The combined organic extracts were dried, filtered and the volatiles evaporated under reduced pressure to give a crude oil. Purification by flash chromatography on silica gel (CH_2Cl_2) afforded the ketoester **14** (2.4 g, 76%) as a colourless oil, as a mixture of diastereomers and tautomers by ^1H NMR analysis; ν_{max}/cm^{-1} 3500, 2978, 1737, 1720, 1657, 1383, 1299, 1200, 1060, 825; *m/z* (CI) MH^+ 199; Found: MH^+, 199.0969. $C_{10}H_{15}O_4$ requires 199.0970.

To a solution of non-racemic **14** (1.50 g, 7.57 mmol) in CH_3CN (90 mL) was added Selectfluor™ (2.67 g, 7.57 mmol). The mixture was stirred for 18 h, concentrated to half volume and the residue partitioned between H_2O and CH_2Cl_2 1:2 (95 mL). The organic extracts were washed with water (20 mL) and the organic layer was dried ($MgSO_4$), filtered and the volatiles evaporated under reduced pressure to give a crude product, which was purified by flash chromatography on silica gel (CH_2Cl_2) to give the fluorinated ketone **15** (1.40 g, 54%) as a colourless oil together with unreacted starting material **14** (608 mg, 41%).

*Data for **15***: $[\alpha]_D^{22}$ −6.5 (*c* 0.15, CH_2Cl_2) at 80% ee; ν_{max}/cm^{-1} 2964, 2929, 1752, 1729, 1470, 1370, 1290, 1260, 1091, 1061, 1030; δ_H (300 MHz, $CDCl_3$) 4.80 (1H, t, *J* 5.5 Hz, H-5), 4.73 (1H, t, *J* 8.3 Hz, H-1), 4.38–4.31 (2H, m, O*C*H_2CH_3), 3.15 (1H, dt, *J* 15.0, 4.0 Hz, H-4_{ax}), 2.41 (1H, d, *J* 15.0 Hz, H-4_{eq}), 2.20–2.05 (3H, m, 2 H-7&H-6), 1.80–1.72 (1H, m, H-6), 1.35 (3H, t, *J* 7.0 Hz, CH_3); δ_C (75.6 MHz, $CDCl_3$) 197.7 (C=O ketone, d, J_{C-F} 22.5 Hz), 165.3 (C=O ester, d, J_{C-F} 23.7 Hz), 95.0 (CF, d, J_{C-F} 197.5 Hz), 79.1 (CH, d, J_{C-F} 19.0 Hz), 75.85 (CH), 62.4 (CH_2), 47.3 (CH_2), 28.2 (CH_2), 24.3 (CH_2), 14.0 (CH_3); *m/z* (GC–MS) (CI); Found: $(M+NH_4)^+$, 234.1141. $C_{10}H_{17}NO_4F$ requires 234.1142. λ_{max} 234.8 nm.

GC conditions: G-TA column (γ-cyclodextrin, trifluoroacetyl), 20 m×0.25 mm; carrier gas: helium; thermalchiral

method: ee 80%, de 98.5%, major diastereoisomer: t_R 15.9 and 16.7, minor diastereoisomer: t_R 16.2 and 16.4.

*Diol **16***: To a solution of **15** (3.0 g, 13.8 mmol) in THF (130 mL) at 0 °C was slowly added $LiAlH_4$ (1 g, 26.3 mmol) and the mixture was allowed to warm to room temperature. After 2 h, $Na_2SO_4 \cdot 10H_2O$ was slowly added at 0 °C and further stirred at room temperature for 1 h. The mixture was filtered over $MgSO_4$ and further washed with EtOAc (300 mL). Evaporation of the volatiles gave a crude oil, which was purified by flash chromatography on silica gel (Et_2O to EtOAc) to give **16** (1.70 g, 70%) as 1.7:1 mixture of two diastereoisomers, ν_{max}/cm^{-1} 3392, 2957, 1459, 1260, 1075, 1027, 862; *m/z* (CI); Found: $(M+NH_4)^+$, 194.1189. $C_8H_{17}NO_3F$ requires 194.1192. The two isomers could be separated for analytical purposes: less polar isomer, mp 72–73 °C; δ_H (250 MHz, $CDCl_3$) 4.44 (1H, br t), 4.22 (1H, br t), 4.13–4.04 (1H, m, H-1), 3.91–3.73 (2H, m, H-3,5), 2.37–2.25 (1H, m, H-4), 2.23–2.11 (3H, m, 2OH, H-4), 2.01–1.90 (3H, m, 7, H6), 1.64 (1H, d, *J* 15.0 Hz, H-6); δ_C (75.5 MHz, $CDCl_3$) (less polar) 95.4 (C, J_{C-F} 172.6 Hz), 75.9 (CH, J_{C-F} 18.1 Hz), 73.4 (CH), 66.0 (CH, J_{C-F} 35.0 Hz), 63.9 (CH_2, J_{C-F} 21.3 Hz), 35.5 (CH_2), 27.7 (CH_2), 24.9 (CH_2, J_{C-F} 6.0 Hz).

More polar isomer, mp 102–103 °C; δ_H (250 MHz, $CDCl_3$) 4.54–4.48 (2H, m, C*H*$_2$–OH), 4.08 (1H, dd, *J* 17.0, 12.8 Hz), 3.80–3.65 (2H, m, H-3,5), 2.35–2.29 (2H, br s, 2OH), 2.04–1.96 (2H, m, 2H-4), 1.91–1.66 (4H, m, 2H-6, 2H-7); δ_C (75.6 MHz, $CDCl_3$) 95.9 (C, J_{C-F} 180.7 Hz), 76.3 (CH, J_{C-F} 18.3 Hz), 73.9 (CH), 64.9 (CH, J_{C-F} 20.5 Hz), 63.9 (CH_2, J_{C-F} 24.4 Hz), 37.9 (CH_2), 27.3 (CH_2), 25.3 (CH_2, J_{C-F} 5.0 Hz).

4.1.5. (1*R*,2*R*,5*S*)-2-Fluoro-2-methyleneacetoxy-8-oxabicyclo[3.2.1]octan-3-one 17a. A mixture of diastereoisomers **16** (885 mg, 5.2 mmol) was dissolved in pyridine (5 mL) and treated with Ac_2O (0.65 mL, 5.7 mmol) at −10 °C. After 2 h, the solution was quenched by the addition of H_2O (11 mL) and extracted into EtOAc (35×3 mL). The combined organic layers were dried, filtered and the volatiles evaporated under reduced pressure to give a crude product, which was purified by flash chromatography (4:1 CH_2Cl_2/Et_2O) to give a mixture of diastereoisomers (565 mg, 51%), ν_{max}/cm^{-1} 3454, 2959, 1746, 1374, 1239, 1065, 1033, 969; *m/z* (CI); Found: $(M+NH_4)^+$, 236.1299. $C_{10}H_{19}NO_4F$ requires 236.1298. The diastereomers could be separated for analytical purposes; less polar isomer, white solid, mp 82–83 °C; δ_H (300 MHz, $CDCl_3$) 4.64–4.46 (3H, m, C*H*HOAc, H-1,3), 4.23 (1H, dd, *J* 13.0, 28.8 Hz, CH*H*OAc), 3.77–3.65 (1H, m, H-5), 2.13 (3H, s, CH_3), 2.07–1.77 (5H, m, OH, 2H-4, 2H-7), 1.71–1.67 (2H, m, 2H-6); δ_C (75.5 MHz, $CDCl_3$) 170.0 (C=O), 92.8 (C, J_{C-F} 180.0 Hz), 76.1 (CH, J_{C-F} 18.4 Hz), 73.9 (CH, J_{C-F} 12.1 Hz), 65.8 (CH), 63.6 (CH_2, J_{C-F} 24.7 Hz), 38.1 (CH_2), 27.2 (CH_2), 25.2 (CH_2, *J* 5.4), 20.7 (CH_3).

More polar isomer, colourless oil, δ_H (300 MHz, $CDCl_3$) 4.56 (1H, dd, *J* 27.6, 12.6 Hz, C*H*HOAc), 4.49–4.39 (1H, m, H-1), 4.26–4.14 (2H, m, H-3, C*H*HOAc), 3.98–3.83 (1H, m, H-5), 2.57 (1H, br s, OH), 2.33–2.18 (1H, m, H-4), 2.16–2.04 (2H, m, H-4, H-7), 2.15 (3H, s, CH_3), 1.98–1.80 (2H, m, H-7, H-6), 1.63 (1H, d, *J* 14.5 Hz, H-6); δ_C (75.5 MHz, $CDCl_3$) 171.6 (C=O), 92.8 (C, J_{C-F} 180.0 Hz), 76.1 (CH, J_{C-F} 17.7 Hz), 73.4 (CH), 66.0 (CH, J_{C-F} 34.5 Hz), 64.5 (CH_2, J_{C-F} 18.9 Hz), 35.5 (CH_2), 27.7 (CH_2), 24.8 (CH_2, J_{C-F} 5.3 Hz), 20.8 (CH_3).

To a solution of the mixture of diastereoisomeric acetates (430 mg, 1.97 mmol) in CH_2Cl_2 (50 mL) was added molecular sieves 4 Å (1.15 g), 4-NMO (406 mg, 3.5 mmol) followed by a catalytic amount of TPAP. The mixture was stirred at room temperature and after 45 min filtered through a silica path and rinsed with EtOAc (75 mL). The volatiles were evaporated under reduced pressure and the crude product was purified by flash chromatography (petroleum ether/Et_2O 3:2) to give **17a** (370 mg, 87%) as a white solid, mp 58–59 °C; $[\alpha]_D^{20}$ +20.6 (*c* 0.34, CH_2Cl_2) at 80% ee; ν_{max}/cm^{-1} 2986, 2969, 1747, 1729, 1233, 1053, 1055; δ_H (250 MHz, $CDCl_3$) 4.80–4.69 (2H, m, H-1,5), 4.53 (1H, dd, *J* 15.0, 13.7 Hz, C*H*HOAc), 4.37 (1H, dd, *J* 31.8, 13.7 Hz, C*H*HOAc), 3.15 (1H, dt, *J* 14.6, 4.3 Hz, H-4$_{ax}$), 2.33 (1H, d, *J* 14.6 Hz, H-4$_{eq}$), 2.13 (3H, s, CH_3), 2.09–2.03 (2H, m, H-6,7), 1.86–1.59 (2H, m, H-6,7); δ_C (75.5 MHz, $CDCl_3$) 201.1 (C=O, *J* 24.1 Hz), 170.3 (C=O), 94.4 (C, *J* 187.4 Hz), 78.0 (CH, *J* 20.1 Hz), 77.2 (CH), 61.3 (CH_2, *J* 21.4 Hz), 47.6 (CH_2, *J* 1.3 Hz), 28.0 (CH_2), 23.7 (CH_2, *J* 4.0 Hz), 20.7 (CH_3); *m/z* (CI); Found: $(M+NH_4)^+$, 234.1137. $C_{10}H_{17}NO_4F$ requires 234.1142.

GC conditions: G-TA column (γ-cyclodextrin, trifluoroacetyl), 20 m×0.25 mm; carrier gas: helium; Isotherm3 method 130 °C (40 min); ee 80%, de 98.5%, major diastereoisomer: t_R 19.5 and 21.2, minor diastereoisomer: t_R 23.0 and 24.0.

4.1.6. (1*R*,2*R*,5*S*)-2-Fluoro-2-methylenebenzoate-8-oxabicyclo[3.2.1]octan-3-one 17b. To a solution of **16** (major diastereomer) (50 mg, 0.28 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (43 μL, 0.28 mmol). The mixture was cooled to −40 °C and benzoyl chloride (36 μL, 0.31 mmol) was added slowly. After 2 h, the mixture was allowed to warm to room temperature and quenched by the addition of a saturated solution of $NaHCO_3$ (aq) and extracted into Et_2O (5×3 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the volatiles evaporated to give a crude residue purified by flash chromatography on silica gel (1:1 CH_2Cl_2/Et_2O) to give the benzoate (47 mg, 60%) as a white solid, mp 110–111 °C; ν_{max}/cm^{-1} 3410, 2960, 2928, 1722, 1250, 1050; δ_H (300 MHz, $CDCl_3$) 8.10–8.07 (2H, m, 2H$_{ar}$), 7.64–7.57 (1H, m, 1H$_{ar}$), 7.51–7.44 (2H, m, 2H$_{ar}$), 4.85–4.75 (1H, m), 4.63–4.57 (1H, m), 4.53–4.49 (2H, m), 3.91–3.69 (1H, m, H-5), 2.11–1.88 (6H, m), 1.84–1.70 (2H, m); δ_C (75.6 MHz, $CDCl_3$) 166.15 (C=O), 133.5 (CH, J_{C-F} 21.9 Hz), 130.0 (CH, J_{C-F} 31.9 Hz), 129.5 (C), 128.6 (CH, J_{C-F} 4.3 Hz), 93.2 (C, J_{C-F} 181.0 Hz), 76.3 (CH, J_{C-F} 18.7 Hz), 74.0 (CH), 64.5 (CH, *J* 20.4 Hz), 64.1 (CH_2, J_{C-F} 25.1 Hz), 38.2 (CH_2), 27.2 (CH_2), 25.2 (CH_2, J_{C-F} 5.0 Hz); *m/z* (CI); Found: $(M+NH_4)^+$, 298.1453. $C_{15}H_{21}NO_4F$ requires 298.1455.

To a solution of the benzoate (45 mg, 0.16 mmol) in CH_2Cl_2 (6 mL) was added activated MS 4 Å (120 mg), followed by 4-NMO (41 mg, 0.35 mmol) and tetra-*n*-propylammonium perruthenate (TPAP) (3 mg, 5 mol %). After 1 h, the solution

was filtered through a silica gel path and rinsed with Et_2O (25 mL). The volatiles were evaporated under reduced pressure to give **17b** (44 mg, 100%) as a white solid, mp 84–85 °C; $[\alpha]_D^{24}$ +12.8 (*c* 0.39, Et_2O); ν_{max}/cm^{-1} 2985, 1729, 1286, 1074, 1002; δ_H (300 MHz, $CDCl_3$) 8.08 (2H, dd, *J* 8.2, 1.3 Hz, $2H_{ar}$), 7.62 (1H, dd, *J* 7.9, 1.1 Hz, $1H_{ar}$), 7.47 (2H, dd, *J* 7.7, 0.8 Hz, $2H_{ar}$), 4.88–4.81 (2H, m, *H*HC–CF, H-1), 4.77 (1H, s, H-5), 4.69 (1H, dd, *J* 21.7, 13.7 Hz, H*H*C–CF), 3.21 (1H, dt, *J* 14.7, 4.4 Hz, H-4_{ax}), 2.38 (1H, d, *J* 14.7 Hz, H-4_{eq}), 2.19–2.04 (2H, m, H-6,7_{endo}), 1.74 (2H, d, *J* 8.5 Hz, H-6,7_{exo}); δ_C (75.6 MHz, $CDCl_3$) 201.1 (C=O, J_{C-F} 22 Hz), 165.9 (C=O), 133.4 (CH), 129.8 (CH), 129.4 (C), 128.5 (CH), 94.7 (C, J_{C-F} 186.4 Hz), 78.0 (CH, J_{C-F} 19.6 Hz), 75.7 (CH), 61.9 (CH_2, J_{C-F} 21.6 Hz), 47.6 (CH_2, J_{C-F} 2.0 Hz), 28.1 (CH_2), 23.8 (CH_2, J_{C-F} 4.0 Hz); *m/z* (CI); Found: $(M+NH_4)^+$, 296.1290. $C_{15}H_{19}NO_4F$ requires $(M+NH_4)^+$ 296.1298.

GC conditions: G-TA column (γ-cyclodextrin, trifluoroacetyl), 20 m×0.25 mm; carrier gas: helium; thermalchiral method: $T_{init.}$: 50 °C (3 min), 10 °C/min to T_{final}: 180 °C (15 min); 80% ee; R_t 25.5 (minor) and 26.7 (major).

4.2. Epoxidation procedure

To a solution of ketone and alkene (0.1 mmol) in acetonitrile (1.5 mL) was added aqueous Na_2EDTA solution (1.0 mL of a 0.4 mM aqueous solution). Oxone® (307 mg, 1.0 mmol $KHSO_5$) and $NaHCO_3$ (130 mg, 1.55 mmol) were added in portions simultaneously over 60 min. The reaction mixture was stirred vigorously at room temperature until completion (monitored by TLC) and for 24 h, and then diluted with water (10 mL) and the reaction mixture extracted into petrol ether or diethyl ether as appropriate (3×25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Flash column chromatography on silica, previously washed with 2% Et_3N in petroleum ether, eluting with appropriate proportion of petroleum ether and diethyl ether afforded the relevant epoxide.

4.3. Determination of epoxide enantiomeric purity in Table 1

E-Stilbene oxide: chiral HPLC on Chiracel OD (Diacel Chemical Industries Ltd., Catalogue Number: 14025), 20% *i*-PrOH/hexane, 1.0 mL/min at 30 °C in oven detecting at 254 nm, as detailed by Shi.[22] Absolute configuration determined by comparison to Shi's results.

Styrene oxide: chiral GC on Chiraldex G-TA (Advanced Separation Technologies Ltd., Catalogue Number: 71020), helium head pressure 13 psi at 75 °C in oven, injection temperature 200 °C, detection by FID at 250 °C, as detailed by Shi.[22] Absolute configuration was determined by comparison to Shi's results.

α-Methylstyrene oxide: chiral HPLC on Chiracel OD (Diacel Chemical Industries Ltd., Catalogue Number: 14025), 5% *i*-PrOH/hexane, 0.8 mL/min at 30 °C in oven detecting at 254 nm, as detailed by Shi.[22] Absolute configuration determined by comparison to Shi's results.

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References and notes

1. Xia, Q. H.; Ge, H. Q.; Ye, C. P.; Liu, Z. M.; Su, K. X. *Chem. Rev.* **2005**, *105*, 1603–1662.
2. Armstrong, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1460–1462.
3. Page, P. C. B.; Buckley, B. R.; Heaney, H.; Blacker, A. J. *Org. Lett.* **2005**, *7*, 375–377; Page, P. C. B.; Buckley, B. R.; Blacker, A. J. *Org. Lett.* **2004**, *6*, 1543–1546; Page, P. C. B.; Rassias, G. A.; Barros, D.; Bethell, D.; Schilling, M. B. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3325–3334.
4. Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497–505.
5. Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488–496.
6. Recent examples: Shing, T. K. M.; Leung, G. Y. C.; Yeung, K. W. *Tetrahedron Lett.* **2003**, *44*, 9225–9228; Shing, T. K. M.; Leung, Y. C.; Yeung, K. W. *Tetrahedron* **2003**, *59*, 2159–2168; Crane, Z.; Goeddel, D.; Gan, Y. H.; Shi, Y. *Tetrahedron* **2005**, *61*, 6409–6417.
7. For other examples of epoxidation catalysis with fluorocyclohexanones, see: Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002**, *67*, 3479–3486; Denmark, S. E.; Wu, Z. C. *Synlett* **1999**, 847–859; Denmark, S. E.; Wu, Z. C.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288–8289; Denmark, S. E.; Wu, Z. C. *J. Org. Chem.* **1998**, *63*, 2810–2811; Solladie-Cavallo, A.; Roje, M.; Giraud-Roux, M.; Chen, Y.; Berova, N.; Sunjic, V. *Chirality* **2004**, *16*, 196–203; Solladie-Cavallo, A.; Bouerat, L. *Org. Lett.* **2000**, *2*, 3531–3534; Solladie-Cavallo, A.; Bouerat, L.; Jierry, L. *Eur. J. Org. Chem.* **2001**, 4557–4560; Solladie-Cavallo, A.; Jierry, L.; Bouerat, L.; Taillasson, P. *Tetrahedron: Asymmetry* **2001**, *12*, 883–891; Solladie-Cavallo, A.; Jierry, L.; Bouerat, L.; Schmitt, M. *Tetrahedron* **2002**, *58*, 4195–4199; Solladie-Cavallo, A.; Jierry, L.; Klein, A. *C. R. Chim.* **2003**, *6*, 603–606; Solladie-Cavallo, A.; Lupattelli, P.; Jierry, L.; Bovicelli, P.; Angeli, F.; Antonioletti, R.; Klein, A. *Tetrahedron Lett.* **2003**, *44*, 6523–6526; Solladie-Cavallo, A.; Jerry, L.; Klein, A.; Schmitt, M.; Welter, R. *Tetrahedron: Asymmetry* **2004**, *15*, 3891–3898; Solladie-Cavallo, A.; Jierry, L.; Lupattelli, P.; Bovicelli, P.; Antonioletti, R. *Tetrahedron* **2004**, *60*, 11375–11381; Solladie-Cavallo, A.; Jierry, L.; Norouzi-Arasi, H.; Tahmassebi, D. *J. Fluorine Chem.* **2004**, *125*, 1371–1377; Freedman, T. B.; Cao, X.; Nafie, L. A.; Solladie-Cavallo, A.; Jierry, L.; Bouerat, L. *Chirality* **2004**, *16*, 467–474.
8. Singleton, D. A.; Wang, Z. H. *J. Am. Chem. Soc.* **2005**, *127*, 6679–6685.
9. Shu, L. H.; Wang, P. Z.; Gan, Y. H.; Shi, Y. *Org. Lett.* **2003**, *5*, 293–296; Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5794–5798; Tian, H. Q.; She, X. G.; Xu, J. X.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929–1931.
10. Armstrong, A.; Ahmed, G.; Dominguez-Fernandez, B.; Hayter, B. R.; Wailes, J. S. *J. Org. Chem.* **2002**, *67*, 8610–8617.
11. Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621–622.
12. Sartori, G.; Armstrong, A.; Maggi, R.; Mazzacani, A.; Sartorio, R.; Bigi, F.; Dominguez-Fernandez, B. *J. Org. Chem.* **2003**, *68*, 3232–3237.
13. Armstrong, A.; Hayter, B. R.; Moss, W. O.; Reeves, J. R.; Wailes, J. S. *Tetrahedron: Asymmetry* **2000**, *11*, 2057–2061.

14. Armstrong, A.; Moss, W. O.; Reeves, J. R. *Tetrahedron: Asymmetry* **2001**, *12*, 2779–2781.
15. Armstrong, A.; Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 6297–6298.
16. Armstrong, A.; Tsuchiya, T. *Tetrahedron* **2006**, *62*, 257–263.
17. Subsequent to our first report (Ref. 13) on the use of 8-oxabicyclo[3.2.1]octanones, some related ketone catalysts with additional alkyl substituents were described: Klein, S.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2686–2691.
18. Stark, C. B. W.; Pierau, S.; Wartchow, R.; Hoffmann, H. M. R. *Chem.—Eur. J.* **2000**, *6*, 684–691; Misske, A. M.; Hoffmann, H. M. R. *Chem.—Eur. J.* **2000**, *6*, 3313–3320.
19. Bunn, B. J.; Cox, P. J.; Simpkins, N. S. *Tetrahedron* **1993**, *49*, 207–218.
20. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.
21. Reeves, J. R. PhD thesis, University of London, 2002.
22. Tu, Y.; Wang, Z. X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807.