2-Substituted-2,4-*endo*-dimethyl-8-oxabicyclo[3.2.1]octan-3-ones as catalysts for the asymmetric epoxidation of some alkenes with Oxone®

Solange Klein *† and Stanley M. Roberts

Department of Chemistry, Liverpool University, Liverpool, UK L69 7ZD

Received (in Cambridge, UK) 21st June 2002, Accepted 25th September 2002
First published as an Advance Article on the web 5th November 2002

A range of 2-substituted-2,4-dimethyl-8-oxabicyclo[3.2.1]octan-3-ones **13**–**18** are available in four steps and in states of high optical purity. The fluoroketone **18** was shown to be a catalyst for the asymmetric epoxidation of stilbene, (*E*)-methylstilbene, phenylstilbene and chalcone (59–68% ee at 24–67% conversion) using Oxone® as the primary oxidant.

Introduction

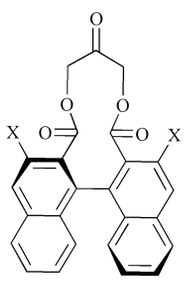
The formation of a dioxirane as an intermediate in an oxidation reaction was postulated first by Baeyer and Villiger during their study of the conversion of menthone into the corresponding lactone.[1] Much later Montgomery speculated, this time correctly, that a dioxirane was the active agent in some oxidation reactions employing Oxone® that were catalysed by selected ketones.[2] Labelling experiments subsequently confirmed the theory.[3]

In general, under well-defined pH conditions, excess Oxone® and a ketone can generate the corresponding dioxirane under biphasic conditions (*e.g.* dichloromethane–water mixture)[4] or monophasic conditions (acetonitrile–water).[5] The availability of *in situ* formation of dioxiranes prompted work directed at the utilisation of these powerful oxidants in organic synthesis. It was shown that dimethyldioxirane and methyl(trifluoromethyl)dioxirane both show an impressive propensity for the oxidation of alkenes, sulfides, amines and saturated hydrocarbons. More recently attention has been directed towards the use of chiral ketones for the preparation of the corresponding dioxiranes which may then serve to accomplish asymmetric oxidation reactions, particularly the stereoselective epoxidation of alkenes.[6]

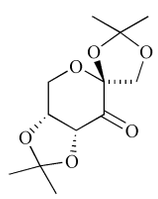
Following the observation that various electron-withdrawing substituents α to the carbonyl group of the influential ketone enhanced the rate of Oxone®-based reactions,[7] the bis(acyloxy)-ketone **1** was used to promote the asymmetric epoxidation of some (*E*)-alkenes; enantiomeric excesses (ee) up to 87% were observed for some *trans*-stilbene derivatives. Similar enantiomerically pure C_2-symmetric ketone catalysts derived from binaphthol were designed and used by Song and collaborators.[8]

The ability of non-C_2-symmetric ketones to promote highly enantioselective dioxirane-mediated epoxidation reactions was demonstrated by Shi *et al.*,[9] employing the ketone **2** (derived from D-fructose) and analogues.[10] A structurally related ketone derived from (−)–quinic acid has also shown good activity in the enantioselective epoxidation of a variety of alkenes.[11]

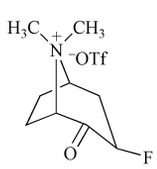
The activating effects of fluorine substitution adjacent to the ketone carbonyl moiety are apparent from studies on methyl(trifluoromethyl)dioxirane,[12] and the dioxiranes derived from 2-fluorocyclohexanones,[13] 2-fluoro-1-tetralones and 2-fluoroindan-1-ones.[14]



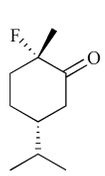
1



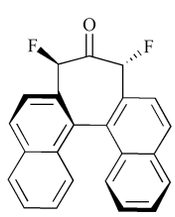
2



3

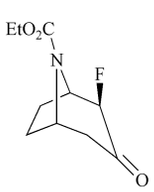


4

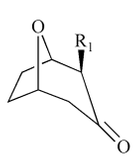


5

These data were influential in the design and subsequent use of oxidizing agents formed from the ketones **3**,[6] **4**[15] and more recently **5**.[16] Armstrong's important contributions to this field are noteworthy, particularly with regard to the new data presented in this paper. First, the Armstrong group rightly extolled the virtues of the α-fluoro-*N*-ethoxycarbonyltropinone **6** as an efficient catalyst for Oxone®-mediated epoxidation reactions. The same group subsequently prepared the oxabicycloalkanone **7** and various derivatives including the ester **8**. Oxidation of *trans*-stilbene using Oxone® and the enantiomerically enriched (80% ee) ketone **8** gave stilbene epoxide (74% ee).[17] Prompted by the recent disclosures from the London based group,[18] we report our studies, which are entirely complementary to those documented heretofore.



6



7:R^1=F
8:R^1=OAc

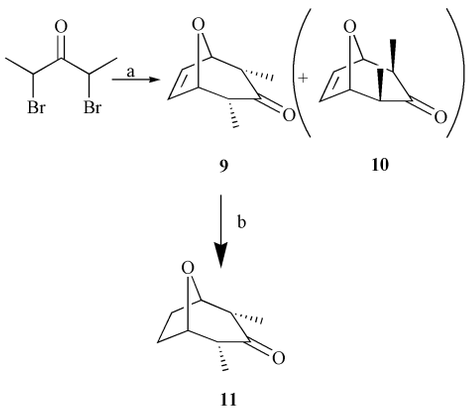
† *Present address*: Arrow Therapeutics, London, UK SE1 1DA. *E-mail*: sklein@arrowt.co.uk

 DOI: 10.1039/b205946k

Results and discussion

The early results reported by Armstrong's team using the azabicycloalkanone **6** attracted us to investigate the potential of chiral 8-oxabicyclo[3.2.1]octan-3-one derivatives for promoting asymmetric epoxidation reactions.

The ready availability of the 2,4-dimethyl-8-oxabicyclo[3.2.1]-octen-3-ones **9** and **10** by reaction of 2,4-dibromopentan-3-one with furan (82% yield)[19] stimulated us to use these materials as a starting point for our studies (Scheme 1). The 2,4-*endo*-



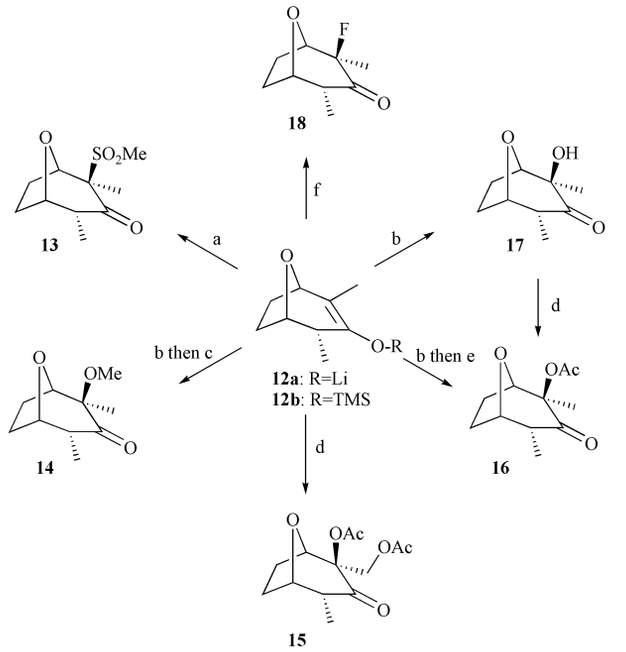
Scheme 1 *Reagents:* (a) NaI, Cu, furan, CH_3CN, 82%; (b) H_2, Pd–C (10%), EtOAc, quantitative.

dimethyl compound **9** is the major product and is efficiently separated from the diastereomer **10** by column chromatography or by crystallization from *n*-hexane (66% yield of **9** from 2,4-dibromopentan-3-one).

Hydrogenation of the alkene **9** over palladium on carbon furnished oxabicycle **11** in quantitative yield. Following the protocols invented by Simpkins and Majewski[20] the ketone **11** was treated with (*S*,*S*)-1,1′-dimethylbenzamide, *n*-butyllithium and lithium chloride in tetrahydrofuran (THF) at −78 °C. The resulting lithium enolate (**12a**) was quenched with a variety of electrophiles to give a range of derivatives **13**–**15** and **18**, or converted into the corresponding silyl enol ether (**12b**) to provide **16** and **17**. Each derivative was obtained in high stereochemical purity (90–98% ee) after recrystallization (Scheme 2).

The absolute configurations of the ketones **13** and **18** were confirmed by X-ray crystallography and circular dichroism respectively.[21] Such data are fundamentally important for validating mechanistic hypotheses correlating the stereochemistry of the catalyst and the outcome of the epoxidation reaction.

Initial epoxidation reactions were conducted on *trans*-β-methylstyrene and *trans*-stilbene. The protocol consisted of pre-stirring the substrate (1 equivalent) with the ketone (0.3 equivalents) in an acetonitrile–aqueous Na_2EDTA mixture,



Scheme 2 *Reagents and conditions:* (a) $MeSO_2Cl$, THF, 65%; (b) TMSCl, −78 °C, 95%; MCPBA, CH_2Cl_2 at −30 °C, TFA (aq), −25 °C, 45%; (c) $TMSCHN_2$, HBF_4 (aq), CH_2Cl_2, 26%; (d) PhSeCl, THF, −30 °C, 80%; H_2O_2, AcOH, THF, 0 °C, 90%; K_2OsO_4, NMO, acetone–H_2O; acetone, $CuSO_4$, H_2SO_4, rt, 27%; Ac_2O, TMSTf, 90%; (e) Ac_2O, TMSTf, CH_2Cl_2, 0 °C, 65%; (f) *N*-fluorobenzenesulfonimide, THF, 73%.

followed by addition of solid Oxone® (4 equivalents) and sodium hydrogencarbonate (12 equivalents). In the cases utilizing the ketones **13**–**16** racemic epoxide was obtained. However employment of the ketone **17** under standard conditions afforded optically active diphenyloxirane, albeit slowly and in modest optical purity (*ca.* 20% conversion, 37% ee). Unfortunately the ketone could not be recovered, seemingly undergoing reaction and/or decomposition under the oxidation conditions.

In contrast, the α-fluoroketone **18** displayed a much better ability to catalyse the asymmetric epoxidation of *trans*-stilbene. Under the standard conditions and using fluoroketone of high optical purity (98% ee) optically active diphenyloxirane was produced (68% ee at 67% conversion). The ketone could be recovered unchanged with no loss of optical purity.

The same ketone (**18**) was used to oxidise several other alkenes (Table 1). Reasonable enantiomeric excesses were obtained for the oxidation of methylstilbene, phenylstilbene and chalcone, though in the latter case the extent of conversion was low. *trans*-β-Methylstyrene, (*E*)-2-methyl-3-phenylpropenol and 1-phenyl-3,4-dihydronaphthalene were not good substrates.

Table 1 Epoxidation of selected alkenes using Oxone® and ketone **18**[a]

			Product	
Alkene	Time/h	Conversion (%)	ee (%)	Absolute configuration[b]
trans-β-Methylstyrene	8	55	34	*R*,*R*
(*E*)-Methylstilbene	8	43	59	*R*,*R*
	24	100	41	
Phenylstilbene	8	47	66	*R*
(*E*)-2-Methyl-3-phenylpropenol	8	100	7	—
Chalcone	8	24	67	2*S*,3*R*
1-Phenyl-3,4-dihydronaphthalene	8	80	17	1*S*,2*R*

[a] Reaction conditions: alkene, ketone (0.3 equiv.), Oxone® (4 equiv.), sodium hydrogencarbonate (12 equiv.), acetonitrile, Na_2 EDTA (aq.). [b] Assessed by comparison with literature data.

Summary and conclusions

A range of 2-substituted-2,4-dimethyl-8-oxabicyclo[3.2.1]octan-3-ones (**13**–**18**) are readily available in states of high optical purity. One member of this series (**18**) is a moderately effective catalyst for the asymmetric epoxidation of some acyclic electron-rich alkenes (Table 1). The catalyst may be recovered and recycled.

A direct comparison between the compounds **7** and **18** is available when (*E*)-stilbene is used as substrate for the epoxidation. Under similar reaction conditions the catalyst **7** (76% ee) gave epoxide (100% conversion, 63% ee) in less than 1 hour while catalyst **18** (98% ee) gave the same epoxide (67% conversion, 68% ee) over 8 hours. While the stereoselectivities of the oxidation catalysed by the two ketones are comparable, the dramatic difference in the observed rates of the reactions is quite clear. Although Oxone® can attack the ketone from both *endo*- and *exo*-faces, the presence of the two methyl groups flanking the carbonyl group greatly disfavours the attack of the dioxirane from the bottom face (remote from the electronegative halogen atom). It is reasonable to suggest that these structural attributes severely retard the approach of the olefin to the Criegee intermediate. Therefore decomposition of the dioxirane occurs and consequently diminishes the amount of epoxide formed.

The absolute configuration of the ketone **18** was firmly established and, using molecular models, the absolute configurations of catalyst and products were found to be consistent with the postulate that the oxidation occurs by transfer of the oxygen atom from the *exo*-face of the dioxirane *via* the electronically favoured "spiro"-transition state.[22]

Experimental

Elemental microanalyses were performed using a Carlo Erba elemental analyser. NMR spectra were recorded on a Brucker AMX 400 (^{1}H, 400 MHz; ^{13}C, 75 MHz) spectrometer. Chemical shifts are described in parts per million downfield shift from $SiMe_4$. Signals are reported as chemical shift (δ_H or δ_C), relative integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, and br = broad), coupling constant (*J*/Hz) and assignment (numbering according to the IUPAC nomenclature for the compound). ^{13}C spectra were referenced to $CDCl_3$ (δ 77.5). IR spectra were recorded in chloroform solutions using a Perkin-Elmer 881 infrared spectrometer and are recorded in reciprocal centimeters (cm^{-1}, wavenumbers). Mass spectra and accurate mass measurements were recorded on a VG 70-070E, or TRIO 1000 instrument. Major fragments are given as percentages of the base peak intensity (100%). Melting points were measured using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Specific optical rotations were measured at ambient temperature (24 ± 3 °C) from chloroform solutions using a 1 cm^3 cell with 0.1 dm path length, on an Optical Activity Ltd AA-1000 polarimeter operating at 589 nm, and are recorded in units of 10^{-1} deg cm^2 g^{-1}. Gas chromatographic analyses were performed with a Perkin-Elmer autosystem and a Shimadzu GC-14AH machine fitted with FID. Chiral GC separations were accomplished using Lipodex® E (25 m × 0.25 mm × 0.2 μm film thickness, Macherey-Nagel) and Chirasil® Dex CB (25 m × 0.25 mm × 0.25 μm film thickness, Chrompack) columns. The carrier gas was helium. High Performance Liquid Chromatographic analyses were performed with a Gilson 506 instrument or a Shimadzu 6A machine with UV detection at 254 nm. Chiral HPLC separations were carried out on Chiralpak® OD or AD columns (250 mm × 4.6 mm) from Daicel. Enantiomeric excess (ee) was determined by chiral GC or chiral HPLC and retention times (t_R) are quoted in minutes. Flash chromatography was performed using Merck 60 silica gel (40–63 μm). Analytical thin layer chromatography (TLC) was carried out on aluminium sheets coated with Merck 60 F_{254} silica gel and compounds were visualised either *via* treatment with cerium ammonium molybdate, *p*-anisaldehyde and/or UV lamp (254 nm). The solvents used were either distilled or of analytical reagent quality. THF was dried over sodium–benzophenone and distilled under nitrogen. Dichloromethane was distilled over calcium hydride.

2,4-*endo*,*cis*-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (9) and 2,4-*exo*,*cis*-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (10)

A two-necked flask (100 cm^3) was charged with furan (3.35 cm^3, 46 mmol), copper powder (10.2 g, 160 mmol), sodium iodide (45.38 g, 303 mmol) and dry acetonitrile (30 cm^3) under an atmosphere of argon. 2,4-Dibromopentan-3-one (6.6 cm^3, 48 mmol) was added dropwise to the resulting suspension over a period of 1 h. After 1.5 h, ethyl acetate (20 cm^3) and water (30 cm^3) were added to the reaction mixture. Copper salt was separated by filtration through a Büchner funnel and washed with ethyl acetate. The two phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with aqueous ammonia (25% w/v, 2 × 50 cm^3), followed by water until no blue color $[Cu(NH_3)_4(H_2O)_2]^{2+}$ was observed. The resulting organic solution was dried ($MgSO_4$) and concentrated under reduced pressure to afford a thick yellow oil (5.7 g, 82%) comprising a 4 : 1 diastereoisomeric mixture of cycloadducts **9** and **10** respectively (ratio determined by ^{1}H NMR). Flash column chromatography (SiO_2, using gradient elution of petroleum ether : ethyl acetate from 9 : 1 to 7 : 3) provided **9** (4.56 g, 66%) as a white solid. Mp 38–39 °C (from *n*-hexane) (Found: C, 71.3; H, 8.0. $C_9H_{12}O_2$ requires C, 71.0; H, 7.9%); ν_{max} (solution cell)/cm^{-1}: 1710 (C=O), 1048 (C–O); δ_H 0.96 (6H, d, *J* 7.6, H-9 and H-10), 2.81 (2H, qd, *J* 3 × 7.6 and 4.4, H-2 and H-4), 4.85 (2H, d, *J* 4.4, H-1 and H-5), 6.34 (2H, s, H-6 and H-7); δ_C 10.0 (C-9 and C-10), 50.4 (C-2 and C-4), 82.8 (C-1 and C-5), 133.6 (C-6 and C-7), 209.0 (C-3); MS (EI) *m*/*z* 152 $[M]^+$ 25%, 96 (46), 81 (100), followed by **10** (1.14 g, 16%) as a thick oil; ν_{max} (solution cell)/cm^{-1}: 1710 (C=O), 1048 (C–O); δ_H 1.36 (6H, d, *J* 7.7, H-9 and H-10), 2.26 (2H, m, H-2 and H-4), 4.65 (2H, s, H-1 and H-5), 6.26 (2H, s, H-6 and H-7); δ_C 17.8 (C-9 and C-10), 49.9 (C-2 and C-4), 82.1 (C-1 and C-5), 133.8 (C-6 and C-7), 213.6 (C-3); MS (EI) *m*/*z* 152 $[M]^+$ 21%, 96 (43), 81 (100).

2,4-*endo*,*cis*-Dimethyl-8-oxabicyclo[3.2.1]octan-3-one (11)

A solution of **9** (1 g, 6.6 mmol) in ethyl acetate (30 cm^3) was stirred under an atmosphere of hydrogen in the presence of palladium on carbon (0.1 g, 10%) for 3 h. The catalyst was removed by filtration through a pad of Celite® and the resultant solution concentrated to give **11** (1.1 g, 100%) as a thick colourless oil. ν_{max} (solution cell)/cm^{-1}: 1715 (C=O), 1050 (C–O); δ_H 0.95 (6H, d, *J* 7.0, H-9 and H-10), 1.62–1.85 (4H, m, H-6 and H-7), 2.81 (2H, m, H-2 and H-4), 4.48 (2H, m, H-1 and H-5); δ_C 9.6 (C-9 and C-10), 24.9 (C-6 and C-7), 50.4 (C-2 and C-4), 81.1 (C-1 and C-5), 210.3 (C-3); MS (EI) *m*/*z* 154 [M]+ 12%, 86 (100), 56 (94); HRMS (EI) found [M]+ 154.09904, $C_9H_{14}O_2$ requires 154.09938.

2,4-*endo*,*cis*-Dimethyl-3-trimethylsiloxy-8-oxabicyclo[3.2.1]oct-2-ene (12b)

Under an argon atmosphere, (*S*)-(−)-bis(α-methylbenzyl)amine (2.92 g, 12.97 mmol) dissolved in dry THF (10 cm^3) was cooled to −78 °C and *n*-butyllithium (5.17 cm^3 of a 2.5 M solution in hexane, 12.97 mmol) was added dropwise over 45 min. After addition the reaction mixture was allowed to reach −30 °C and then cooled at −78 °C. At this temperature lithium chloride (137 mg) was added followed by **11** (1 g, 6.48 mmol) in THF (10 cm^3) dropwise. The resultant solution was stirred at −78 °C

for 3 h. The enolate thus formed was treated with trimethylsilyl chloride (2.86 cm^3, 22.69 mmol) and triethylamine (3 cm^3), stirred for a further 30 min at the same temperature before being allowed to warm to room temperature. Ethyl acetate was added to the reaction mixture and the aqueous phase was further extracted with ethyl acetate. The combined organic phases were washed with a single portion of cold HCl (0.1 M), then with water and brine, dried ($MgSO_4$), and concentrated to yield **12b** (1.46 g, 98%) as a yellow oil. ν_{max} (solution cell)/cm^{-1}: 1679 (C=C), 1254 (C–OSi), 1049 (C–O); δ_H 0.17 (9H, s, $SiMe_3$), 0.91 (3H, d, *J* 7.1, H-10), 1.52 (3H, d, *J* 2.2, H-9), 1.65–2.01 (4H, m, H-6 and H-7), 2.82 (1H, m, H-4), 4.25 (1H, bs, H-1), 4.35 (1H, m, H-5); δ_C 0.4 ($SiMe_3$), 11.9 and 12.7 (C-9 and C-10), 23.0 and 33.0 (C-6 and C-7), 39.5 (C-4), 77.4 and 79.4 (C-1 and C-5), 115.7 (C-2), 143.5 (C-3); MS (FAB) *m*/*z* 227 $[M+H]^+$ 82%, 226 (100),197 (37), 209 (23); HRMS (FAB) found $[M+H]^+$ 227.14672, $C_{12}H_{23}O_2Si$ requires 227.14673.

2,4-*endo*,*cis*-Dimethyl-2-*exo*-methylsulfonyl-8-oxabicyclo[3.2.1]-octan-3-one (13)

Under an argon atmosphere, (*S*)-(−)-bis(α-methylbenzyl)amine (0.96 cm^3, 4.2 mmol) dissolved in dry THF (6 cm^3) was cooled to −78 °C and *n*-butyllithium (2.5 cm^3 of a 1.6 M solution in hexane, 4.0 mmol) was added dropwise over 45 min. After addition the reaction mixture was allowed to reach −30 °C and then cooled to −78 °C. At this temperature lithium chloride (50 mg) was added, followed by dropwise addition of ketone **11** (0.32 g, 2.1 mmol) in THF (5 cm^3). The resultant solution was stirred at −78 °C for 3 h. The enolate thus formed was treated with methanesulfonyl chloride (0.65 cm^3, 8.4 mmol) and stirred for 30 min at −78 °C before being allowed to warm to room temperature. Water was added to the reaction mixture and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with one portion of cold HCl (0.1 M) then with water and brine, dried ($MgSO_4$), and concentrated to yield a yellow solid. Flash column chromatography (SiO_2, eluent ethyl acetate : petroleum ether 3 : 7) provided **13** (0.32 g, 65%) as a white solid (Found: C, 51.7; H, 7.0. $C_{10}H_{16}O_4S$ requires C, 51.7; H, 6.9%); ν_{max} (solution cell)/cm^{-1}: 1710 (C=O), 1313, 1210 (SO_2); δ_H 1.03 (3H, d, *J* 6.9, H-10), 1.44 (3H, s, H-9), 1.57–2.16 (4H, m, H-6 and H-7), 2.93 (3H, s, CH_3), 3.42 (1H, qd, *J* 3 × 6.9 and 6.0, H-4), 4.62 (1H, t, *J* 2 × 6.0, H-5), 5.07 (1H, d, *J* 7.6, H-1); δ_C 10.2 (C-10), 15.1 (C-9), 24.9 and 26.1 (C-6 and C-7), 39.2 (CH_3), 49.8 (C-4), 76.6 (C-2), 78.3 and 80.4 (C-1 and C-5), 204.2 (C-3); MS (CI) *m*/*z* 250 $[M+NH_4]^+$ 100%, 170 (9), 153 (17); HRMS (CI) found $[M+NH_4]^+$ 250.11116, $C_{10}H_{20}NO_4S$ requires 250.11131. Slow recrystallisation in ethyl acetate increased the ee from 68% to 91%. The colourless crystals of **13** showed $[\alpha]_D^{24} = -270$ (*c* 0.1 in $CHCl_3$). Chiral GC: Lipodex® E; Injection 200 °C, program: 170 °C for 20 min, then 10 °C min^{-1} to 180 °C and left for 10 min, detection: FID 200 °C. t_R (−)-enantiomer 26.6 min, (+)-enantiomer 27.5 min.

2,4-*endo*,*cis*-Dimethyl-2-*exo*-methoxy-8-oxabicyclo[3.2.1]octan-3-one (14)

Trimethylsilyldiazomethane (2.0 M in hexane, 0.5 cm^3, 1 mmol) was added dropwise to a vigorously stirred mixture of the alcohol **17** (0.17 g, 1 mmol, 68% ee) and fluoroboric acid (50% aqueous, 0.175 g, 1 mmol) in dichloromethane (4 cm^3) at 0 °C. The stirring was continued at 0 °C and three further portions of trimethylsilyldiazomethane (0.5 mmol, 0.25 mmol, 0.25 mmol) were added dropwise at intervals of 20 min. The mixture was stirred at 0 °C for 30 min, poured into water and extracted with dichloromethane. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated to yield a yellow oil. Flash column chromatography (SiO_2, eluent ethyl acetate : petroleum ether 1 : 4) provided **14** (0. 063 g, 35%) as a white solid. ν_{max} (solution cell)/cm^{-1}: 1730 (C=O); δ_H 0.95 (3H, d, *J* 6.8, H-10), 1.15 (3H, s, H-9), 1.45–2.05 (4H, m, H-6 and H-7), 3.16 (4H, m, H-4 and CH_3), 4.36 (1H, d, *J* 7.7, H-1), 4.44 (1H, t, *J* 2 × 5.8, H-5); δ_C 9.4 (C-10), 13.1 (C-9), 24.0 and 24.7 (C-6 and C-7), (C-2)‡, 48.0 (C-4), 51.2 (CH_3), 80.9 and 82.9 (C-1 and C-5), 209.3 (C-3); MS (CI) *m*/*z* 202.3 $[M+NH_4]^+$ 100%, 185 (42), 170 (18); HRMS (CI) found $[M+H]^+$ 185.11840, $C_{10}H_{17}O_3$ requires 185.11777. Slow recrystallisation in ethyl acetate and *n*-hexane increased the ee from 68% to 95%. The colourless crystals of **14** showed $[\alpha]_D^{24} = -106$ (*c* 0.1 in $CHCl_3$). Chiral GC: Lipodex® E; Injection 200 °C, isotherm 140 °C, detection: FID 200 °C. t_R (−)-enantiomer 8.3 min, (+)-enantiomer 9.0 min.

2-*exo*-Acetoxy-2-*endo*-acetoxymethyl-4-*endo*-methyl-8-oxabicyclo[3.2.1]octan-3-one (15)

To a solution of **12** (0.41 g, 1.84 mmol) in THF (3 cm^3), under an atmosphere of argon, was added phenylselenyl chloride (0.42 g, 2.21 mmol) in THF (3 cm^3) at −30 °C dropwise. The mixture was stirred for 1 h at the same temperature and then warmed to room temperature. The reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (5 cm^3) and the product extracted into ethyl acetate. The combined extracts were washed with water and brine, dried ($MgSO_4$) and concentrated to yield an orange solid. Flash column chromatography (SiO_2, eluent ethyl acetate : petroleum ether 1 : 9) provided the bicyclic compound **15** (0.41 g, 72%) as a pale yellow solid. δ_H1.00 (3H, d, *J* 6.9, H-10), 1.08 (3H, s, H-9), 1.62–2 (4H, m, H-6 and H-7), 4.0 (1H, qd, *J* 3 × 6.9 and 6, H-4), 4.52 (1H, t, *J* 2 × 6.0, H-5), 4.59 (1H, d, *J* 7.0, H-1), 7.24–7.44 (5H, m, Ar); δ_C 9.9 (C-10), 18.2 (C-9), 23.9 and 26.3 (C-6 and C-7), 44.6 (C-4), 58.6 (C-2), 81.2 and 84.3 (C-1 and C-5), 127.6, 128.9, 129.2 and 137.5 (Ar), 207.2 (C-3). A solution of the adduct (0.28 g, 0.9 mmol) in THF (3 cm^3) containing glacial acetic acid (0.3 cm^3) was maintained at 0 °C (ice bath) during the addition of hydrogen peroxide (0.9 cm^3 of a 30% solution). The mixture was stirred at 0 °C for 1.5 h, prior to addition of saturated aqueous sodium hydrogencarbonate (6 cm^3). The product was extracted into ethyl acetate, and the combined extracts were washed with brine, dried ($MgSO_4$) and concentrated to yield an oil. Flash column chromatography (SiO_2, using ethyl acetate : petroleum ether 1 : 9) provided 2-methylene-4-*endo*-methyl-8-oxabicyclo[3.2.1]octan-3-one (0.15 g, 52%) as a clear oil. δ_H 1.08 (3H, d, *J* 7.1, H-10), 1.66–2.22 (4H, m, H-6 and H-7), 2.79 (1H, m, H-4), 4.52 (1H, m, H-5), 4.96 (1H, d, *J* 6.6, H-1), 5.12 (1H, s, exocyclic CH=), 5.82 (1H, s, exocyclic CH=); δ_C 10.3 (C-10), 24.3 and 32.15 (C-6 and C-7), 50.9 (C-4), 79.0 and 79.4 (C-1 and C-5), 117.3 (C-9), 146.7 (C-2), 201.0 (C-3). The enone (1.38 g, 8.96 mmol), *N*-methylmorpholine *N*-oxide monohydrate (2.10 g, 17.9 mmol), and potassium osmate dihydrate (0.659 g, 1.79 mmol) were stirred in acetone–water mixture (50–8 cm^3) at room temperature until TLC indicated that the reaction was complete. The reaction mixture was diluted with chloroform (400 cm^3) and HCl (16 cm^3, 5 M). The mixture was stirred for a further 15 min. The aqueous layer formed was removed prior to the addition of a saturated aqueous sodium metabisulfite solution (24 cm^3). The organic layer was then washed with water and brine, dried (Na_2SO_4) and concentrated to yield a white solid (1.087 g). The crude diol was dissolved in anhydrous acetone (15 cm^3) and was treated with dry copper sulfate (0.9 g) and sulfuric acid (20 drops, 98%) under an argon atmosphere. After 4 h, the residue was removed by filtration and the reaction mixture dissolved in dichloromethane and neutralised by addition of potassium carbonate. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated to yield a white solid. Flash column chromatography (SiO_2, eluent ethyl acetate : petroleum ether 1 : 4) provided spiro[3′,3′-dimethyl-2′,4′-

‡ Certainly under the $CDCl_3$ signal.

dioxacyclopentane]-1′,2-4-*endo*-methyl-8-oxabicyclo[3.2.1]-octan-3-one (0.55 g, 27% over two steps) as a white solid. Slow recrystallisation in *n*-hexane increased the ee of the product (90%) which was obtained as a colourless solid. $[a]_D^{24} = -28.4$ (*c* 1.9 in $CHCl_3$). Chiral GC: Chirasil® Dex CB; Injection 200 °C, program: 60 °C for 10 min, then 10 °C min^{-1} to 180 °C and left for 10 min, detection: FID 200 °C. t_R (−)-enantiomer 23.3 min, (+)-enantiomer 23.6 min. The title compound was synthesised by treatment of the bicyclic ketone (0.062 g, 2.7 mmol, 90% ee) with acetic anhydride (0.128 cm^3, 1.37 mmol) and trimethylsilyl trifluoromethanesulfonate (1 drop) at 0 °C. After 1 h the reaction was completed and quenched by addition of saturated aqueous sodium hydrogencarbonate. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated to yield an oil. Flash column chromatography (SiO_2, using ethyl acetate : petroleum ether 1 : 1) provided **15** (0. 040 g, 53%) as a white solid. $[a]_D^{24}$ −22.5 (*c* 0.8 in $CHCl_3$). Chiral GC: Chirasil® Dex CB; Injection 200 °C, isotherm 100 °C, detection: FID 200 °C. t_R (−)-enantiomer 29.6 min, (+)-enantiomer 30.1 min.

2-*exo*-Acetoxy-2,4-*endo*,*cis*-dimethyl-8-oxabicyclo[3.2.1]octan-3-one (16)

Ketone **17** (0.094 g, 0.5 mmol) dissolved in dichloromethane (3 cm^3) was treated with acetic anhydride (0.26 cm^3, 2.7 mmol) and trimethylsilyl trifluoromethanesulfonate (2 drops) at 0 °C. After 1 h the reaction was completed and quenched by addition of saturated aqueous sodium hydrogen carbonate. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated to yield an oil. Flash column chromatography (SiO_2, using ethyl acetate : petroleum ether 1 : 4) provided **16** (0. 092 g, 78%) as a white solid. ν_{max} (solution cell)/cm^{-1}: 1738 (C=O), 1259 (O–C=O); δ_H 0.95 (3H, d, *J* 6.6, H-10), 1.4 (3H, s, H-9), 1.35–2.00 (4H, m, H-6 and H-7), 2.12 (1H, s, CH_3), 3.07 (1H, m, H-4), 4.25 (1H, m, H-5), 4.58 (1H, d, *J* 7.8, H-1); δ_C 9.3 (C-10), 15.6 (C-9), 21.2 (CH_3), 23.9 and 24.2 (C-6 and C-7), 48.3 (C-4), 82.0 and 82.4 (C-1 and C-5), 85.8 (C-2), 169.9 (O(*C*)OCH_3), 204.2 (C-3); MS (CI) *m*/*z* 213 $[M+H]^+$ 100%, 230 (67), 170 (22); HRMS (CI) found $[M+H]^+$ 213.11258, $C_{11}H_{17}O_4$ requires 213.11268. Chiral GC: Chirasil® Dex CB; Injection 200 °C, isotherm 100 °C, detection: FID 200 °C. t_R (−)-enantiomer 17.9 min, (+)-enantiomer 18.2 min.

2,4-*endo*,*cis*-Dimethyl-2-*exo*-hydroxy-8-oxabicyclo[3.2.1]octan-3-one (17)

Silyl enol ether **12b** (0.61 g, 2.7 mmol) was dissolved in dichloromethane (8 cm^3), cooled to −35 °C and treated with MCPBA (0.56 g, 3.2 mmol). The temperature of the reaction was kept below −25 °C. After 1 h trifluoroacetic acid (0.20 cm^3, 2.7 mmol) was added. The mixture was warmed to 0 °C, diluted with dichloromethane and quenched with an aqueous solution of ammonium chloride (10 cm^3). The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated to yield an oil. Flash column chromatography (SiO_2, eluent ethyl acetate : petroleum ether 3 : 7) provided **17** (0.22 g, 48%) as a white solid (Found: C, 63.7; H, 8.3. $C_9H_{14}O_3$ requires C, 63.5; H, 8.3%); ν_{max} (solution cell)/cm^{-1}: 1724 (C=O), 1157 (OH); δ_H 0.97 (3H, d, *J* 6.6, H-10), 1.19 (3H, s, H-9), 1.45–2.05 (4H, m, H-6 and H-7), 3.23 (1H, m, H-4), 3.43 (1H, s, OH), 4.25 (1H, d, *J* 7.8, H-1), 4.43 (1H, dd, *J* 2 × 6.3, H-5); δ_C 9.4 (C-10), 16.6 (C-9), 23.8 (2 × CH_2, C-6 and C-7), 46.6 (C-4), 77.7 (C-2), 80.7 and 84.2 (C-1 and C-5), 208.1 (C-3); MS (EI) *m*/*z* 170 $[M]^+$ 29%, 81 (62), 55 (73), 43 (100). Slow recrystallisation in ethyl acetate and *n*-hexane increased the ee to 90%. The colourless crystals of **17** showed $[a]_D^{24} = -106$ (*c* 0.1 in $CHCl_3$). Chiral GC: Lipodex® E; Injection 200 °C, isotherm 140 °C, detection: FID 200 °C. t_R (−)-enantiomer 12.7 min, (+)-enantiomer 13.1 min.

2,4-*endo*,*cis*-Dimethyl-2-*exo*-fluoro-8-oxabicyclo[3.2.1]octan-3-one (18)

Under an argon atmosphere, (*S*)-(−)-bis(α-methylbenzyl)-amine (3.85 cm^3, 16.8 mmol) dissolved in dry THF (20 cm^3) was cooled to −78 °C and *n*-butyllithium (9.7 cm^3 of a 1.6 M solution in hexane, 15.6 mmol) was added dropwise over 1.5 h. After addition the reaction mixture was allowed to reach −30 °C and then cooled to −78 °C. At this temperature lithium chloride (150 mg) was added, followed by dropwise addition of ketone **11** (2 g, 12.9 mmol) in THF (10 cm^3). The resultant solution was stirred at −78 °C for 3 h. The enolate thus formed was treated with *N*-fluorobenzenesulfonimide (5.29 g, 16.8 mmol) and stirred for 30 min at −78 °C before being allowed to warm to room temperature. Water was added to the reaction mixture and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with one portion of cold HCl (0.1 M) then with water and brine, dried ($MgSO_4$), and concentrated to yield a yellow solid. Flash column chromatography (SiO_2, using ethyl acetate : petroleum ether 3 : 7) provided **18** (3.23 g, 69%) as a white solid (Found: C, 63.1; H, 7.6. $C_9H_{13}O_2F$ requires C, 62.8; H, 7.6%); ν_{max} (solution cell)/cm^{-1}: 1730 (C=O); δ_H 0.98 (3H, dd, *J* 6.9 and 0.8, H-9), 1.33 (3H, d, *J* 9.9, H-10), 1.45–2.10 (4H, m, H-6 and H-7), 3.27 (1H, m, H-4), 4.49 (2H, m, H-5 and H-1); δ_C 9.6 (C-10), 16.06 (d, *J* 24, C-9), 24.1 and 24.6 (C-6 and C-7), 49.1 (C-4), 81.1 (C-5), 82.6 (d, *J* 19.6, C-1), 96.3 (d, *J* 177.1, C-2), 204.8 (d, *J* 24, C-3); δ_F −148.1 (qd, *J* 22.5 and 3.7, FC-2); MS (EI) *m*/*z* 172 $[M]^+$ 23%, 124 (63), 104 (90), 69 (100); HRMS (EI) found $[M]^+$ 172.09010, $C_9H_{13}O_2F$ requires 172.08995. Two recrystallisations from *n*-hexane increased the ee of the product from 70% to > 98%. The colourless crystals of **18** showed $[a]_D^{24} = -10$ (*c* 1.4 in $CHCl_3$). Chiral GC: Lipodex® E; Injection 200 °C, column 120 °C, detection: FID 200 °C. t_R (−)-enantiomer 26.6 min, (+)-enantiomer 27.5 min.

Typical asymmetric epoxidation

Alkene (0.3 mmol) and the enantioenriched ketone (0.09 mmol) were dissolved in acetonitrile–aqueous Na_2EDTA (4×10^{-4} M, 6 cm^3/4 cm^3) and vigorously stirred. Sodium bicarbonate (0.038 g, 3.6 mmol) and Oxone® (0.092 g, 1.2 mmol) were added to the reaction mixture over a period of 5 min. Similarly at the beginning of each hour, the same portions of sodium bicarbonate and Oxone® were added to the reaction mixture. After 8 hours (or 24 hours) the reaction mixture was diluted with water (10 cm^3) and extracted with dichloromethane (4 × 15 cm^3), the combined extracts were washed, dried (Na_2SO_4) and concentrated. Conversion was estimated by analysing the crude mixture by NMR spectroscopy. Samples of pure epoxide (for analysis) were obtained using preparative TLC with *n*-hexane and a few drops of NEt_3 as eluent system.

Acknowledgements

We thank the Leverhulme Centre for Innovative Catalysis (LCIC) Forum "Catalysts for the Fine Chemical Industry" for a studentship (to SK).

References

1 A. Baeyer and V. Villiger, *Ber. Dtsch. Chem. Ges.*, 1899, **32**, 3625.
2 R. E. Montgomery, *J. Am. Chem. Soc.*, 1974, **96**, 7820.
3 (*a*) R. Curci, M. Fiorentino, L. Triosi, J. O. Edwards and R. H. Pater, *J. Org. Chem.*, 1980, **45**, 4758; (*b*) S. E. Denmark and Z. Wu, *J. Org. Chem.*, 1997, **62**, 8964.
4 A. R. Gallopo and J. O. Edwards, *J. Org. Chem.*, 1981, **46**, 1684.
5 D. Young, M. K. Wong and Y. C. Yip, *J. Org. Chem.*, 1995, **60**, 3887.
6 (*a*) S. E. Denmark and Z. Wu, *Synlett*, 1999, 847; (*b*) M. Frohn and Y. Shi, *Synthesis*, 2000, **14**, 1979.
7 (*a*) D. Yang, Y. C. Yip, M. W. Tang, M. K. Wong, J. H. Zheng and K. K. Cheung, *J. Am. Chem. Soc.*, 1996, **118**, 491; (*b*) D. Tang,

X. C. Wang, M. K. Wong, Y. C. Yip and M. W. Tang, *J. Am. Chem. Soc.*, 1996, **118**, 11311; (*c*) D. Yang, Y. C. Yip, M. W. Tang, J. H. Zheng and K. K. Cheung, *J. Am. Chem. Soc.*, 1998, **120**, 491.
8 C. E. Song, Y. H. Kim, K. C. Lee, S. Lee and B. W. Lin, *Tetrahedron: Asymmetry*, 1997, **8**, 2921.
9 (*a*) Y. Shi, Z. Wang, Y. Tu and M. Frohn, *J. Am. Chem. Soc.*, 1997, **119**, 11224; (*b*) Y. Shi, Z. Wang, Y. Tu and M. Frohn, *J. Org. Chem.*, 1997, **62**, 2328; (*c*) Z. X. Wang and Y. Shi, *J. Org. Chem.*, 1997, **62**, 8622; (*d*) Y. Shi, Y. Zhu, Y. Tu and H. Yu, *Tetrahedron Lett.*, 1998, **39**, 7819; (*e*) L. Shu and Y. Shi, *Tetrahedron Lett.*, 1999, **40**, 8721; (*f*) L. Shu and Y. Shi, *J. Org. Chem.*, 2000, **65**, 8807; (*g*) L. Shu and Y. Shi, *Tetrahedron*, 2001, **57**, 5213.
10 (*a*) H. Tian, X. She and Y. Shi, *Org. Lett.*, 2001, **3**, 715; (*b*) H. Tian, X. She, J. Xu and Y. Shi, *Org. Lett.*, 2001, **3**, 1929.
11 Z. X. Wang, S. Miller, O. P. Anderson and Y. Shi, *J. Org. Chem.*, 1999, **64**, 6443.
12 R. Mello, M. Fiorentino, C. Fusco and R. Curci, *J. Am. Chem. Soc.*, 1989, **111**, 6749.
13 S. E. Denmark, Z. Wu, C. M. Crudden and H. Matsuhashi, *J. Org. Chem.*, 1997, **62**, 8288.
14 D. S. Brown, B. A. Marples, P. Smith and L. Walton, *Tetrahedron*, 1995, **51**, 3587.
15 (*a*) see also A. Armstrong and B. R. Hayter, *Chem. Commun.*, 1998, 621; (*b*) A. Solladie-Cavallo and L. Bouerat, *Org. Lett.*, 2000, **2**, 3531.
16 C. J. Stearman and V. Behar, *Tetrahedron Lett.*, 2002, **43**, 1943.
17 A. Armstrong, B. R. Hayter, W. O. Moss, J. R. Reeves and J. S. Wailes, *Tetrahedron: Asymmetry*, 2000, **11**, 2057.
18 A. Armstrong, W. O. Moss and J. R. Reeves, *Tetrahedron: Asymmetry*, 2001, **12**, 2779.
19 A. M. Montana and D. Fernandez, *Tetrahedron Lett.*, 1999, **40**, 6499.
20 (*a*) M. Majewski, R. Lazny and P. Nowak, *Tetrahedron Lett.*, 1995, **31**, 5465; (*b*) B. J. Buns, N. S. Simpkins, Z. Spavold and M. J. Crimmin, *J. Chem. Soc., Perkin Trans. 1*, 1993, 3113.
21 The laevorotatory enantiomer displayed a positive Cotton effect.
22 (*a*) K. N. Houk, J. Lui, N. C. DeMello and K. R. Condroski, *J. Am. Chem. Soc.*, 1997, **119**, 10147; (*b*) see also A. Armstrong, I. Washington and K. N. Houk, *J. Am. Chem. Soc.*, 2000, **122**, 6297.