JOC*Article*

Enantioselective Epoxidation of Alkenes Catalyzed by 2-Fluoro-*N*-Carbethoxytropinone and Related Tropinone Derivatives

Alan Armstrong,*[,†,‡] Ghafoor Ahmed,[†] Belen Dominguez-Fernandez,[‡] Barry R. Hayter,[†] and J. Steven Wailes[†]

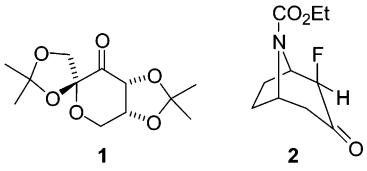
School of Chemistry, University of Nottingham, Nottingham NG7 2RD, U.K., and Department of Chemistry, Imperial College, London SW7 2AY, U.K.

a.armstrong@ic.ac.uk

Received August 15, 2002

Several α-substituted *N*-carbethoxytropinones have been evaluated as catalysts for asymmetric epoxidation of alkenes with Oxone, via a dioxirane intermediate. α-Fluoro-*N*-carbethoxytropinone (**2**) has been studied in detail and is an efficient catalyst which does not suffer from Baeyer−Villiger decomposition and can be used in relatively low loadings. This ketone was prepared in enantiomerically pure form using chiral base desymmetrization of *N*-carbethoxytropinone. Asymmetric epoxidation catalyzed by **2** affords epoxides with up to 83% ee. Among other derivatives tested, the α-acetoxy derivative **7** affords the highest enantioselectivities.

Asymmetric epoxidation of alkenes is an extremely valuable synthetic transformation,[1] particularly because the epoxide products can be opened with a wide range of nucleophiles. The Sharpless asymmetric epoxidation reaction represented a major advance, but it is limited to allylic alcohols as substrates. The development of catalytic systems for the asymmetric epoxidation of "unfunctionalized" alkenes—those lacking coordinating functionality to allow temporary anchoring between reagent and substrate—is a more challenging goal. An important development came in the early 1990s with the independent report of chiral manganese salen complexes by the groups of Jacobsen and Katsuki. These systems often give high enantioselectivities for certain alkene substitution patterns but generally give poor results for epoxidation of, for example, trans-disubstituted and terminal alkenes.[1] Our own interests[2−6] have focused on the use of nonmetal catalysts[7] for the epoxidation of alkenes. Ketones have been known for some time to promote alkene epoxidation by Oxone, via a dioxirane intermediate.[8] Early studies of this system utilized a two-phase water/organic solvent system in which the solubility properties of the ketone and alkene substrate were a crucial consideration,[9] and the first examples of chiral-ketone-mediated dioxirane epoxidation gave low enantioselectivities.[10] An important development was the discovery by Yang[11] of a homogeneous CH_3CN/H_2O solvent system which for the first time allowed the catalytic activity and enantioselectivity of a wide range of ketones to be evaluated.[12−14] Since this time, several chiral ketones have been reported that afford good to excellent enantioselectivities,[15−17] with the fructose-derived ketone **1** discovered by Shi and co-workers offering excellent



1 **2**

results for trans- and trisubstituted alkenes.[18] However,

* To whom correspondence should be addressed at Imperial College.
† University of Nottingham.
‡ Imperial College.

(1) Bonini, C.; Righi, G. *Tetrahedron* **2002**, *58*, 4981.
(2) Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K.; Wailes, J. S. *Tetrahedron* **1999**, *55*, 2341. Armstrong, A.; Draffan, A. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2861.
(3) Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621.
(4) Armstrong, A.; Hayter, B. R. *Tetrahedron* **1999**, *55*, 11119.
(5) Armstrong, A.; Hayter, B. R.; Moss, W. O.; Reeves, J. R.; Wailes, J. S. *Tetrahedron: Asymmetry* **2000**, *11*, 2057.
(6) Armstrong, A.; Moss, W. O.; Reeves, J. R. *Tetrahedron: Asymmetry* **2001**, *12*, 2779.
(7) Adam, W.; Saha-Moller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499. Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.
(8) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187.
(9) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; Depue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391.
(10) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155. Curci, R.; Daccolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831. Brown, D. S.; Marples, B. A.; Smith, P.; Walton, L. *Tetrahedron* **1995**, *51*, 3587.
(11) Yang, D.; Wong, M. K.; Yip, Y. C. *J. Org. Chem.* **1995**, *60*, 3887.
(12) Yang, D.; Wong, M. K.; Yip, Y. C.; Wang, X. C.; Tang, M. W.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1998**, *120*, 5943.
(13) Yang, D.; Yip, Y. C.; Chen, J.; Cheung, K. K. *J. Am. Chem. Soc.* **1998**, *120*, 7659.
(14) Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491. Yang, D.; Wang, X. C.; Wong, M. K.; Yip, Y. C.; Tang, M. W. *J. Am. Chem. Soc.* **1996**, *118*, 11311.
(15) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979.
(16) Adam, W.; Zhao, C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995. Song, C. E.; Kim, Y. H.; Lee, K. C.; Lee, S.; Jin, B. W. *Tetrahedron: Asymmetry* **1997**, *8*, 2921. Adam, W.; Saha-Moller, C. R.; Zhao, C. G. *Tetrahedron: Asymmetry* **1999**, *10*, 2749. Kim, Y. H.; Lee, K. C.; Chi, D. Y.; Lee, S. G.; Song, C. E. *Bull. Kor. Chem. Soc.* **1999**, *20*, 831. Matsumoto, K.; Tomioka, K. *Heterocycles* **2001**, *54*, 615. Matsumoto, K.; Tomioka, K. *Chem. Pharm. Bull.* **2001**, *49*, 1653. Matsumoto, K.; Tomioka, K. *Tetrahedron Lett.* **2002**, *43*, 631.
(17) Bortolini, O.; Fogagnolo, M.; Fantin, G.; Maietti, S.; Medici, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1113.
(18) Wang, Z. X.; Tu, Y.; Frohn, M.; Zhang, J. R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.

10.1021/jo026322y CCC: $22.00
Published on Web 11/08/2002

this ketone undergoes decomposition by Baeyer−Villiger decomposition under the reaction conditions, necessitating its use in relatively high loading, although higher pH reaction conditions offer better catalytic efficiency.[19] Shi has reported more robust catalysts[20] and new ketones offering complementary substrate selectivity[21] which generally require more lengthy syntheses than **1**.

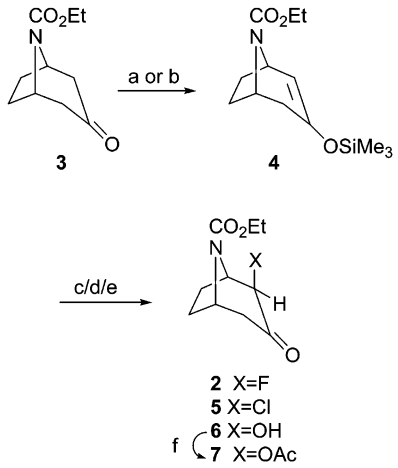
Our own early studies also identified the prevention of the Baeyer−Villiger reaction as a major issue,[4] and in 1998 we reported α-fluoro-*N*-carbethoxytropinone (**2**) as a stable and recyclable catalyst.[3] Here we report in full our studies on the use of **2** as an epoxidation catalyst, including substrate scope and the influence of reaction conditions on enantioselectivity. The effect of replacement of the fluorine atom with alternative α-substituents is also discussed.[5] While our early studies on **2** were underway, Denmark reported some pioneering work on the use of α-fluoro ketones as promoters of alkene epoxidation by Oxone, including a fluorotropinium salt.[22,23] More recently, other groups,[24] including Solladie-Cavallo's,[25,26] have reported further studies on asymmetric epoxidation using chiral fluoro ketones.

Results and Discussion

From our early studies on the reactivity of ketones as epoxidation promoters,[4] we recognized the need for an efficient ketone catalyst to be activated electronically. Since we desired a conformationally well-defined system to aid in prediction and rationalization of asymmetric induction, we were attracted to commercially available *N*-carbethoxytropinone (**3**). As well as the activating inductive effect of the bridgehead nitrogen, we reasoned that the rigid bicyclic nature of this catalyst should have two important consequences. First, it should be possible to introduce a range of activating substituents on the α-carbon via enolate chemistry, with introduction of the electrophile occurring on the less hindered exo face. Second, in the derived dioxirane intermediates, the two oxygens should be differentiated effectively by the same steric effect: i.e., the alkene should approach predominantly the less hindered *exo*-dioxirane oxygen. Ketone **3** itself showed low epoxidation activity: under the Yang CH_3CN/H_2O conditions, 10 equiv of **3** was required for complete epoxidation of (*E*)-stilbene within 3 h. Importantly, however, there was no evidence for decomposition of **3** under these conditions, suggesting that the azabicyclo-[3.2.1]octanone framework was worthy of investigation. As a first example of an electron-withdrawing α-substituent, we prepared the α-fluoro derivative **2** from **3** by treatment of the derived trimethylsilyl enol ether **4** with a Selectfluor reagent[27,41] (Scheme 1). The best reproducibility was obtained using 2 equiv of Selecfluor that had been dried over high vacuum for 24 h. The relative stereochemistry of **2** was initially assigned on the basis of the assumption that the fluorination would occur on the less hindered exo face, in line with precedent for similar reactions, and this assignment was later confirmed by X-ray crystallography, which clearly showed the fluorine to occupy an axial orientation on the exo face.[42] Racemic **2** proved to be an excellent catalyst for the epoxidation of (*E*)-stilbene (Table 1): using 10 mol % **2**, reaction was complete in less than 2 h (entry 4), while reasonable conversions were possible at the 1 mol % level over longer time periods (entry 6). This catalytic activity compares well with that of other ketone catalysts reported in the area. Importantly, there was no evidence for Baeyer−Villiger reaction by ^{1}H NMR, and the catalyst could be recovered (≥70% yield) by column chromatography.

In view of the extremely promising catalytic activity of **2**, we then required a method for its synthesis in enantiomerically pure form. For this purpose, we were

SCHEME 1[a]



[a] Legend: (a) LDA, TMSCl, THF, −78 °C; (b) **8**, 2 equiv of *n*BuLi, LiCl, TMSCl, THF, −100 °C; (c) 2 equiv of Selectfluor, CH_3CN, 63% from **3** for (±)-**2**, 55% for (+)-**2**; (d) NCS, NaOAc, acetone/H_2O, 56% from **3** for (±)-**5**, 45% for (+)-**5**; (e) dimethyldioxirane, acetone, CH_2Cl_2, 60% from **3** for (±)-**6**, 55% for (+)-**6**; (f) Ac_2O, catalytic $Sc(OTf)_3$, 74%.

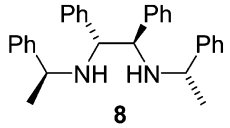
TABLE 1. Oxone Epoxidation of (*E*)-Stilbene Catalyzed by Ketone 2[a]

entry	(±)-**2** (mol %)[b]	conversn (%)[c]	*t* (h)
1	100	100	<0.25
2	50	100	<0.25
3	25	100	<0.5
4	10	100	2
5	5	100	≤20
6	1	62[d]	24

[a] Conditions: alkene (0.1 mmol), Oxone (1.0 mmol of $KHSO_5$), $NaHCO_3$ (1.55 mmol), CH_3CN (1.5 mL), aqueous Na_2EDTA (1 mL of 0.4 mM solution), room temperature. [b] Relative to alkene. [c] By TLC analysis. [d] Measured by ^{1}H NMR spectroscopy.

(19) Wang, Z. X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099.
(20) Tian, H. Q.; She, X. G.; Shi, Y. *Org. Lett.* **2001**, *3*, 715.
(21) Tian, H. Q.; She, X. G.; Xu, J. X.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929. Tian, H. Q.; She, X. G.; Yu, H. W.; Shu, L. H.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435. Tian, H. Q.; She, X. G.; Shu, L. H.; Yu, H. W.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551.
(22) Denmark, S. E.; Wu, Z. C.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288. Denmark, S. E.; Wu, Z. C. *Synlett* **1999**, 847.
(23) Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002**, *67*, 3479.
(24) Legros, J.; Crousse, B.; Bourdon, J.; Bonnet-Delpon, D.; Begue, J. P. *Tetrahedron Lett.* **2001**, *42*, 4463. Legros, J.; Crousse, B.; Bonnet-Delpon, D.; Begue, J. P. *Tetrahedron* **2002**, *58*, 3993. Stearman, C. J.; Behar, V. *Tetrahedron Lett.* **2002**, *43*, 1943.
(25) Solladie-Cavallo, A.; Bouerat, L. *Org. Lett.* **2000**, *2*, 3531.
(26) Solladie-Cavallo, A.; Bouerat, L.; Jierry, L. *Eur. J. Org. Chem.* **2001**, 4557. Solladie-Cavallo, A.; Jierry, L.; Bouerat, L.; Taillasson, P. *Tetrahedron: Asymmetry* **2001**, *12*, 883. Solladie-Cavallo, A.; Jierry, L.; Bouerat, L.; Schmitt, M. *Tetrahedron* **2002**, *58*, 4195.
(27) Banks, R. E. *J. Fluorine Chem.* **1998**, *87*, 1. Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737.

attracted to the pioneering work of the Simpkins group on desymmetrization of tropinones using chiral lithium amide bases.[28] Treatment of **3** with the lithium amide base derived from **8**[29] (1 equiv) and *n*BuLi (2 equiv) in

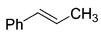
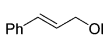
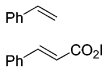
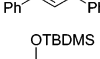


8

the presence of Me_3SiCl (5 equiv) and LiCl (1 equiv) gave the crude silyl enol ether **4**, which was reacted without purification with the Selectfluor reagent. The resulting sample of **2**, ca. 60% ee, was recrystallized once from ether−petrol and then once from CH_2Cl_2−petrol to provide ketone **2** of >98% ee according to chiral HPLC analysis. The absolute stereochemistry was assigned on the basis of the precedent of Simpkins, who converted essentially the same intermediate silyl enol ether as ***ent*-4** (NCO_2Me in place of NCO_2Et), prepared using ***ent*-8**, into the natural product (−)-anatoxin-a.[28] The other enantiomer, ***ent*-2**, was also prepared by using the other enantiomer of the chiral base **8**.

Enantiomerically enriched **2** was then used as an asymmetric epoxidation catalyst. The first substrate investigated was (*E*)-stilbene (Table 2, entries 1 and 2), which was epoxidized with an encouraging 76% ee at room temperature with 10 mol % **2**. As expected, the other catalyst enantiomer ***ent*-2** afforded an enantiomeric product (entry 2). Replacement of either or both of the aromatic substitutents resulted in lowering of epoxidation enantioselectivity. Thus, β-methylstyrene was epoxidized with 56% ee (entry 3), while 1,2-*trans*-dialkyl-substituted alkenes afforded 40−44% ee (entries 5−7). An allylic hydroxyl substituent appeared to offer no benefit over the corresponding acetate (entries 5 and 6). Trisubstituted aromatic alkenes (entries 8−10) proved to be the best substrates. Phenylstilbene was epoxidized in 83% ee (entry 8, 9); replacement of one or more of the phenyl substituents with an aliphatic group resulted in lower enantioselectivity (entries 10 and 11). In common with many dioxirane systems, cis-1,2-disubstituted, 1,1-disubstituted, and monosubstituted alkenes gave poor results (entries 12−15). Dioxiranes are generally regarded as electrophilic oxidants; therefore, there are few examples of their use for the epoxidation of electron poor alkenes.[17,25,30] The results for the epoxidation of (*E*)-ethyl cinnamate and (*E*)-chalcone were therefore promising (entries 16 and 17), although requiring higher catalyst loading. Shi[31] and Adam[32] have shown that the fructose-derived ketone **1** can give excellent enantioselectivities in the epoxidation of trisubstituted silyl enol ethers and, in particular, enol benzoates. However, these substrates gave very poor results with catalyst **2** (entries 18−20), even using the Shi higher pH reaction conditions (entry 20).

TABLE 2. Catalytic Asymmetric Epoxidation of Alkenes Using Fluoroketone 2[a]

Entry	Substrate	Catalyst	*t* (h)	Yield (%)	ee	Product Configuration[k]
1		**2**	< 3	88	76[f]	(*R, R*)
2		***ent*-2**	3	92	75[f]	(*S, S*)
3		***ent*-2**	1	45	56[g]	(*S, S*)
4		***ent*-2**	24	71	68[g]	(*S, S*)
5		***ent*-2**	4	79	41[g,h]	(*S, S*)
6		***ent*-2**	6	63	40[g]	(*S, S*)
7		***ent*-2**	2	83	44[g,i]	(*S, S*)
8		**2**	< 4	100	83[g]	(*R*)
9		***ent*-2**	3	94	83[g]	(*S*)
10		**2**	< 4	100	73[g]	(*R, R*)
11		**2**	< 6	97	69[g]	(*R, R*)
12		***ent*-2**	1	96	18[g]	(*1S, 2R*)
13		***ent*-2**	3	80	22[f]	(*S*)
14		**2**	< 2	33	29[g]	(*R*)
15		***ent*-2**	4	92	30[g]	(*S*)
16		***ent*-2**[b]	24	51	64[j]	(*2R, 3S*)
17		***ent*-2**[b]	20	94	54[f]	nd[l]
18		**2**[c]	2	73[e]	14[f]	*(R)*[e]
19		**2**[c]	2.5	100	20[f]	*(R)*
20		**2**[c, d]	2.5	74	18[f]	*(R)*

[a] Conditions: alkene (0.1 mmol), Oxone (1.0 mmol of $KHSO_5$), $NaHCO_3$ (1.55 mmol), CH_3CN (1.5 mL), aqueous Na_2EDTA (1 mL of 0.4 mM solution), **2** (10 mol %), room temperature. [b] 25 mol % **2** used. [c] Reaction carried out at 0 °C. [d] Reaction performed using Shi pH 10 conditions: alkene (0.1 mmol), **2** (10 mol %), CH_3CN (1.5 mL), catalytic Bu_4NHSO_4, Oxone (0.28 mmol), $Na_2B_4O_7{\cdot}10H_2O$ (0.05 M in 0.04 mM aqueous Na_2EDTA, 1 mL), K_2CO_3 (0.58 mmol), H_2O (0.65 mL), 0 °C. [e] Yield and ee of 2-hydroxypropiophenone, following desilylation (TBAF) of initial product. [f] Measured by chiral HPLC (Chiralcel OD). [g] Measured by ^1H NMR in the presence of Eu(hfc)$_3$ as chiral shift reagent. [h] Converted to acetate prior to ee measurement. [i] Epoxide opened with NaOMe and converted to acetate prior to ee measurement. [j] Measured by chiral HPLC (Chiralcel OJ). [k] Absolute configurations were determined by comparison to literature data (see Supporting Information). [l] Absolute configuration not assigned.

Optimization of Reaction Conditions for Epoxidation using 2. Having ascertained the substrate scope of epoxidation catalyzed by **2**, we selected the reaction with (*E*)-stilbene for more detailed study to ascertain the prospects of improving enantioselectivity through opti-

(28) Newcombe, N. J.; Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1995**, 831.
(29) Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391.
(30) Wu, X.-Y.; She, X. G.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792.

TABLE 3. Variation of Solvent and pH for Epoxidation of (*E*)-Stilbene Catalyzed by *ent*-2

entry	conditions	temp, °C	ee[d]
1	Yang[a]	room temp	75
2	Yang[a]	0	79
3	Shi[b]	room temp	77
4	Shi[b]	0	81
5	Yang (1/2 CH_3CN/DMM)[a,c]	room temp	74

[a] Conditions; alkene (0.1 mmol), Oxone (1.0 mmol of $KHSO_5$), $NaHCO_3$ (1.55 mmol), CH_3CN (1.5 mL), aqueous Na_2EDTA (1 mL of 0.4 mM solution), **2** (10 mol %). [b] Conditions: alkene (0.1 mmol), **2** (10 mol %), CH_3CN (1.5 mL), catalytic Bu_4NHSO_4, Oxone (0.28 mmol), $Na_2B_4O_7{\cdot}10H_2O$ (0.05 M in 0.04 mM aqueous Na_2EDTA, 1 mL), K_2CO_3 (0.58 mmol), H_2O (0.65 mL). [c] 1/2 $CH_3CN/(CH_3O)_2CH_2$ used in place of CH_3CN. [d] Measured by chiral HPLC (Chiralcel OD). *S*,*S* product obtained in all cases.

TABLE 4. Variation of Quantity of Oxone in Epoxidation of (*E*)-Stilbene Catalyzed by 2[a]

entry	amt of $KHSO_5$ (equiv)	*t* (h)	conversn (%)	ee[d]
1	10	<2	100[b]	76
2	5	4	100[b]	77
3	2.5	6	100[b]	76
4	1.5	24	87[c]	75

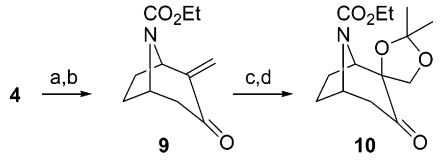
[a] Conditions: alkene (1 equiv), Oxone, $NaHCO_3$ (15.5 equiv), 3/2 CH_3CN/aqueous Na_2EDTA (0.4 mM), **2** (10 mol %). [b] Determined by TLC analysis. [c] Measured by ^1H NMR. [d] Measured by chiral HPLC (Chiralcel OD). *R*,*R* product obtained in all cases.

mization of reaction parameters such as temperature and solvent. Shi has shown that reaction solvent and pH can have a significant effect with catalyst **1**.[18,33] The results of our studies are shown in Table 3. Under the Yang conditions, lowering the reaction temperature to 0 °C resulted in a small increase in product ee (entries 1 and 2). Use of the Shi higher pH conditions at 0 °C afforded the highest ee (81%; entry 4), but $CH_3CN/(CH_3O)_2CH_2$ as solvent[18,33] did not offer any improvement. While we have not attempted optimization of reaction conditions for other substrates in Table 2, the results in Table 3 suggest that control of pH and temperature offer modest improvements.

The Yang oxidation system employed in Tables 1 and 2 employs a large excess of Oxone (5 equiv; 10 equiv of the active oxidant, $KHSO_5$). An important question is whether the amount of co-oxidant employed could be reduced without detriment to conversion or enantioselectivity. The results in Table 4 indicate that the amount of $KHSO_5$ can be reduced to 2.5 equiv (entry 3) without affecting the product ee, and with complete conversion in a reasonable time period (6 h).

Replacement of Fluorine with Alternative α-Substituents. The strategy used for the synthesis of **2** could readily be used to prepare ketones bearing alternative α-substituents to allow their effect on reactivity and asymmetric induction to be assessed. We prepared the α-chloro (**5**), α-hydroxy (**6**), and α-acetoxy (**7**) derivatives as shown in Scheme 1. In line with precedent, reaction of the electrophile was assumed in all cases to have occurred on the less hindered exo face, leading to the axially substituted product (as for the fluoro ketone **2**). The highly enantioselective Shi catalyst **1** utilizes a spiro-fused acetonide motif in the α-position, and incorporation of this feature in our own bicyclic ketone system could potentially retain the enantioselectivity while offering increased stability toward the Baeyer–Villiger reaction relative to the Shi ketone **1**. This derivative **10** was prepared as shown in Scheme 2, via dihydroxylation of the exocyclic enone **9**. Ketones **5**–**7** and **10** were prepared and tested initially in racemic form for the epoxidation of (*E*)-stilbene (Table 5). Chloride **5** was markedly poorer than **2** (entries 1 and 2), in line with the lower electronegativity of the α-substituent. Acetonide **10**, disappointingly, appeared to undergo decomposition by the Baeyer–Villiger reaction, leading to low epoxidation efficiency (entry 3). Alcohol **6** also underwent decomposition under the reaction conditions, leading to low levels of epoxidation (entry 4). The corresponding acetate **7** showed more promising results (entries 5–7): although less active than **2**, it appeared to be stable. Chloride **5** and acetate **7** were prepared in nonracemic form by use of nonracemic **4** prepared using chiral base desymmetrization as previously. Unlike **2**, however, neither **5** nor **7** could be reliably recrystallized to enantiomeric purity; therefore, they were tested in the asymmetric epoxidation of (*E*)-stilbene with samples of ca. 76% ee. Assumption of a linear relationship between catalyst ee and product ee[34] allowed calculation of an ee_{max} value, the expected enantiomeric excess with enantiomerically pure catalyst (Table 6). Chloro ketone **5** showed lower enantioselectivity than **2** (entry 2), but acetate **7** afforded a higher ee_{max} value (entry 3), albeit requiring higher catalyst loading due to its lower reactivity. The α-acetoxy substituent is therefore a promising lead for new catalyst families.[6]

SCHEME 2[a]



[a] Legend: (a) Et_2Zn/CH_2I_2, Et_2O, room temperature, 18 h, 42% from **4**; (b) $SnCl_4$, DMSO, CH_2Cl_2, room temperature, 24 h, 80%; (c) $K_2OsO_4{\cdot}2H_2O$, NMO, quinuclidine, acetone/H_2O, room temperature, 16.5 h, 82%; (d) 2,2-Dimethoxypropane, $HClO_4$, acetone, 0 °C, 3 h, 70%.

TABLE 5. Epoxidation of (*E*)-Stilbene Catalyzed by Racemic Ketones 2, 5–7, and 10[a]

entry	ketone	amt of ketone (mol %)	*t* (h)	conversn (%)[b]
1	**2**	10	2	100
2	**5**	100	24	21
3	**10**	100	24	13
4	**6**	100	24	8
5	**7**	100	<1	100
6	**7**	50	<1	100
7	**7**	10	24	44

[a] Conditions; alkene (0.1 mmol), Oxone (1.0 mmol of $KHSO_5$), $NaHCO_3$ (1.55 mmol), CH_3CN (1.5 mL), aqueous Na_2EDTA (1 mL of 0.4 mM solution). [b] Estimated by integration of the ^1H NMR spectrum of the crude product.

(31) Zhu, Y. M.; Tu, Y.; Yu, H. W.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819. Zhu, Y. M.; Shu, L. H.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818.

(32) Adam, W.; Fell, R. T.; Saha-Moller, C. R.; Zhao, C. G. *Tetrahedron: Asymmetry* **1998**, *9*, 397.

(33) Wang, Z. X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328.

(34) This linear relationship has been proven for a related 8-oxabicyclo[3.2.1]octan-3-one catalyst.[6]

TABLE 6. Epoxidation of (*E*)-Stilbene Catalyzed by Nonracemic Ketones 2, 5, and 7[a]

entry	ketone	amt of ketone (mol %)	*t* (h)	conversn (%)[b]	ketone ee[c]	product ee[d]	ee_{max}[e]
1	**2**	10	2	100	100	76	76
2	**5**	100	24	21	76	41	54
3	**7**	20	3	100	76	66	86

[a] Conditions: alkene (0.1 mmol), Oxone (1.0 mmol of $KHSO_5$), $NaHCO_3$ (1.55 mmol), CH_3CN (1.5 mL), aqueous Na_2EDTA (1 mL of 0.4 mM solution). [b] Estimated by integration of the ^1H NMR spectrum of the crude product. [c] Determined by chiral HPLC analysis. [d] Measured by chiral HPLC (Chiralcel OD). *R*,*R* product obtained in each case. [e] 100((product ee)/(ketone ee)).

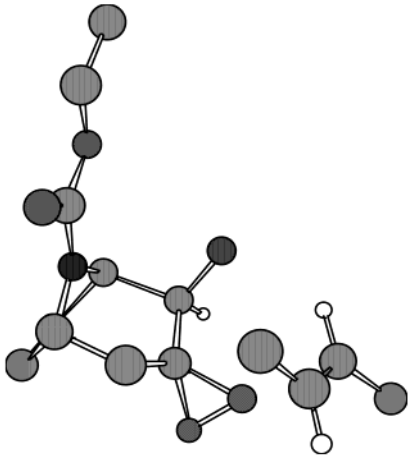
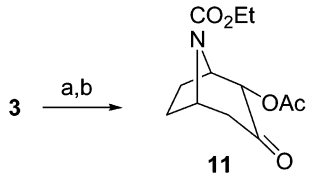


FIGURE 1. TS model for approach of *trans*-alkene to ketone **2**.

Transition State Model. One of the most attractive features of the dioxirane system—particularly compared to transition-metal-catalyzed oxidation procedures—is its well-defined nature, allowing speculation on the mode of asymmetric induction. The configuration of the major epoxide enantiomer obtained in the results in Tables 1 and 6 fit the simple transition state model in Figure 1. Here, the alkene approaches the less hindered *exo*-dioxirane oxygen in a spiro orientation. This preference for a spiro mode of approach is by now well precedented, being consistent with the selectivities observed by catalysts reported by several groups,[12,18] as well as with computational studies.[35] A hydrogen substituent on the alkene occupies the fluorine region of the catalyst. In accord with this model, low enantioselectivities are obtained for terminal alkenes, which can present either enantiotopic face to the dioxirane while fulfilling the requirements of this TS model. For all alkenes, the minor epoxide enantiomer could arise (a) from alkene approach with a non-hydrogen substituent in the fluorine region of the catalyst, (b) from approach on the "achiral" endo face, or (c) from a competing planar transition state.

The levels of asymmetric induction obtained (up to 83% ee) are remarkable, given the small steric size of the fluorine substituent. The fact that selectivity drops when aryl rings are replaced with aliphatic substituents suggests that n$-\pi$ repulsive interactions[13] may be responsible in part for disfavoring modes of approach where aromatic substituents are placed in the fluorine region of the catalyst. We recently reported a computational study of the reaction between fluorinated dioxiranes and alkenes.[36] This study suggested a possible attractive interaction between an olefinic hydrogen, which bears a partial positive charge in the TS, and the partial negative charge on the fluorine. While we have no firm evidence that this interaction has a significant role in the observed asymmetric induction, it does provide a possible explanation for the surprisingly low levels of enantioselectivity observed in the epoxidation of silyl enol ethers and enol benzoates relative to other trisubstituted alkenes (Table 2, entries 18−20). These substrates would be expected to have diminished partial positive charge on the alkene hydrogen due to the resonance effect of the oxygen substituent, resulting in smaller attraction to the fluorine in the TS leading to the major enantiomer and, hence, lower selectivity. Alternatively, epoxidation of these reactive, electron-rich alkenes may proceed via an early TS where interaction between substrate and fluorine is reduced.

SCHEME 3[a]



[a] Legend: (a) $PhI(OAc)_2$, KOH, MeOH, room temperature, 24 h, 70%. (b) Ac_2O, catalytic $Sc(OTf)_3$, CH_3CN, room temperature, 20 h, 63%.

Denmark has described studies of the reactivity of 4-*tert*-butyl-2-fluorocyclohexanones and noted an interesting stereoelectronic effect: the axial fluoro isomer is a far less efficient catalyst than the equatorial one.[22] However, the two isomers undergo Baeyer−Villiger decomposition[37] and hydrate formation at different rates. It would be of interest to know whether in our bicyclo[3.2.1]octanones, which do not appear to participate in these side reactions, the greater epoxidation efficiency of equatorial isomers still holds. To date, we have not been able to prepare the equatorial fluoro analogue of **2**. However, we have made the equatorial analogue **11** of acetate **7** (Scheme 3). The key step in the synthesis of **11** was the reaction of ketone **3** with $PhI(OAc)_2$. Moriarty[38] has shown that reaction of tropan-3-one under these conditions affords the equatorial α-hydroxy dimethyl ketal, presumably via initial reaction of the electrophilic iodine species on the less hindered exo face of the enolate followed by addition of methanol to the exo face of the ketone and internal displacement of the iodine leaving group by the hydroxyl group of the resulting hemiketal. Qualitatively, we have observed that the equatorial acetate **11** is less reactive than the axial isomer **7** (Table 7); neither appears to undergo decom-

(35) Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147. Bach, R. D.; Glukhovtsev, M. N.; Gonzalez, C.; Marquez, M.; Estevez, C. M.; Baboul, A. G.; Schlegel, H. B. *J. Phys. Chem. A* **1997**, *101*, 6092.

(36) Armstrong, A.; Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 6297.

(37) Crudden, C. M.; Chen, A. C.; Calhoun, L. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2851.

(38) Moriarty, R. M.; Prakash, O.; Vavilikolanu, P. R.; Vaid, R. K.; Freeman, W. A. *J. Org. Chem.* **1989**, *54*, 4008.

TABLE 7. Epoxidation of (*E*)-Stilbene Catalyzed by Racemic Ketones 7 and 11[a]

entry	ketone	amt of ketone (mol %)	*t* (h)	conversn (%)
1	**7**	20	3	100[b]
2	**11**	100	24	54[c]

[a] Conditions: alkene (0.1 mmol), Oxone (1.0 mmol of $KHSO_5$), $NaHCO_3$ (1.55 mmol), CH_3CN (1.5 mL), aqueous Na_2EDTA (1 mL of 0.4 mM solution). [b] Assessed by TLC analysis. [c] Estimated by integration of the ^1H NMR spectrum of the crude product.

position under the reaction conditions. This higher reactivity of the axial isomer could reflect faster dioxirane formation or faster oxygen transfer to the olefin. Our aforementioned computational study of epoxidation by fluorinated dioxiranes[36] suggests that the oxygen transfer step should indeed have a lower activation energy for the axial fluoro isomer, and so it is reasonable to suggest that the apparent greater reactivity of the axial acetate **7** may also indicate faster oxygen transfer. Solladie-Cavallo's recent results also suggest higher reactivity for axially halogenated ketones.[25]

Conclusions

In conclusion, we have found that α-fluoro-*N*-carbethoxytropinone (**2**) is an efficient catalyst for the epoxidation of alkenes by Oxone; it can be used in low loadings and recovered and recycled. When it is prepared in enantiomerically pure form, it affords high enantioselectivity for alkene epoxidation (up to 83% ee for trisubstituted aromatic alkenes). Variation of the α-substituent has been investigated, and the α-acetoxy derivative **7** has shown promising results. Synthesis and testing of more complex substitution patterns, as well as other alterations to the bicyclo[3.2.1]octanone framework, are under investigation.

Experimental Section

General experimental procedures are similar to those reported previously[39] and are provided in the Supporting Information.

Preparation of Racemic Silyl Enol Ether 4. To a solution of diisopropylamine (1.2 mL, 9.1 mmol) in THF (60 mL) at −78 °C was added *n*BuLi (as a 2 M solution in hexanes, 4.56 mL, 9.12 mmol). The solution was warmed to 0 °C, stirred for 20 min, and cooled again to −78 °C. The ketone **3** (1.50 g, 7.61 mmol) in THF (15 mL) was added dropwise. After 30 min chlorotrimethylsilane (1.4 mL, 11 mmol) was added and the solution warmed to −20 °C. Saturated aqueous sodium hydrogen carbonate solution (25 mL) was added and the mixture extracted into petrol (3 × 75 mL). The combined organics were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a pale yellow oil. Flash column chromatography (50% ether−50% petrol) gave the silyl enol ether **4** (1.94 g, 95%) as a pale yellow oil appearing as a mixture of rotamers in the ^{13}C NMR spectrum and giving a broadened ^1H NMR spectrum: IR (film) 1704, 1651 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.16 (br d, *J* 2.5, 1H), 4.36 (m, 2H), 4.10 (q, *J* 7.0, 2H), 2.74 (m, 1H), 2.13 (m, 1H), 2.00−1.60 (m, 4H), 1.24 (t, *J* 7.0, 3H), 0.16 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 154.6, 149.1; 148.5, 109.7, 61.0, 52.1, 39.5, 38.8, 35.8; 35.1, 30.1, 29.2, 14.8, 0.2; MS *m*/*z* (EI) 269 (M^+, 6%), 240 (M − Et, 100%); HRMS calcd for $C_{13}H_{23}O_3NSi$ (M^+) 269.1436, found 269.1447.

Preparation of Enantiomerically Enriched Silyl Enol Ether 4. To a solution of chiral diamine **8**[29] (2.14 g, 5.07 mmol) in THF (20 mL) at −90 °C was added *n*BuLi (as 2.5 M in hexanes, 4.10 mL, 10.3 mmol). The solution was warmed to room temperature over 20 min and then cooled to −70 °C, and a solution of LiCl (previously fused under vacuum, 215 mg, 5.12 mmol) in THF (15 mL) was added. The solution was warmed again to room temperature over 15 min before cooling to −100 °C. Chlorotrimethylsilane (3.25 mL, 25.6 mmol) was added, followed by ketone **3** (1.00 g, 5.07 mmol) in THF (20 mL) dropwise. During this addition the internal temperature of the reaction was carefully monitored and the speed of addition carefully adjusted in order to keep the temperature close to −100 °C. The reaction mixture was then warmed to −20 °C. Saturated aqueous sodium hydrogen carbonate solution (50 mL) was added and the mixture extracted into petrol (3 × 100 mL). The combined organics were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a pale yellow oil which was used without further purification. ^1H NMR data were as for the racemic compound.

(1*R,2*R**,5*S**)-2-Fluoro-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylic Acid Ethyl Ester (2).** To a stirred solution of the racemic silyl enol ether **4** (1.36 g, 5.0 mmol) in dry CH_3CN (40 mL) under nitrogen was added in a single portion Selectfluor (3.54 g, 10.0 mmol). The reaction mixture was stirred at room temperature for 1 h and then poured into EtOAc (250 mL) and washed with H_2O (3 × 50 mL). The organic phase was dried over $MgSO_4$ and evaporated to dryness under reduced pressure to give a yellow oil (1.41 g). Flash chromatography over silica using 50% ether/50% petrol as eluent gave the fluoro ketone **2** (681 mg, 63%) as a colorless oil: UV λ_{max} 198 nm (0.693), 224 (0.963); IR (film) 1731, 1698 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.74 (br s, 1H), 4.62 (br s, 1H), 4.40 (d, $^2J_{HF}$ = 49.0 Hz, 1H), 4.24−4.08 (m, 2H), 3.03 (m, 1H), 2.36 (d, *J* 15.0, 1H), 2.15−1.95 (m, 2H), 1.65−1.35 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$; 2:1 mixture of rotamers) δ 202.0 (C, d, $^2J_{CF}$ = 19 Hz), 154.1 (C), 92.8 (d, $^1J_{CF}$ = 186 Hz, *C*HF), 61.5 (CH_2), 56.4 (CH, d, $^2J_{CF}$ = 19 Hz), 53.1 (CH), 46.7 (CH_2), 27.3 (CH_2), 22.6 (CH_2), 14.6 (CH_3 major rotamer), 14.5 (CH_3 minor rotamer); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ 219.6 (d, $^2J_{HF}$ = 49.0 Hz, major rotamer), 219.3 (d, $^2J_{HF}$ = 48.5 Hz, minor rotamer); MS *m*/*z* (FAB^+) 216 (MH^+, 80%); HRMS calcd for $C_{10}H_{15}FO_3N$ (MH^+) 216.1036, found 216.1034. Anal. Calcd for $C_{10}H_{14}FO_3N$: C, 55.8; H; 6.55; N, 6.50. Found: C, 55.9; H, 6.70; N, 6.70.

(1*R*,2*R*,5*S*)-(+)-2-Fluoro-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylic Acid Ethyl Ester (2). This compound was prepared by the same procedure as for racemic **2**, but starting from enantiomerically enriched **4**. Purification twice by flash column chromatography (20−100% ether in petrol followed by 1% methanol in dichloromethane) gave the ketone **(+)-2** (55%) as a pale yellow oil, which on standing crystallized to plates, shown by chiral HPLC (Chiralcel OD, 1:100 ^{i}PrOH:hexane with 0.1% TFA added as eluent, flow rate 1 mL/min, detection at 224 nm) with elution times 27 min (minor, 1*S*,2*S*,5*R* enantiomer) and 29.3 min (major, 1*R*,2*R*,5*S* enantiomer) to be of 60% ee, spectroscopically identical with the racemic sample previously prepared. Recrystallization from ether/petrol and then from dichloromethane/petrol gave colorless needles of >98% ee: mp 57.5 °C; $[\alpha]^{27}_D$ = +7.3 (*c* 1.16, CH_2Cl_2).

The enantiomeric catalyst ***ent*-2** was prepared by using ***ent*-8** in the reaction with **3**, proceeding via the silyl enol ether ***ent*-4**.

(1*R,2*R**,5*S**)-(±)-2-Chloro-3-oxo-8-azabicyclo[3.2.1]-octane-8-carboxylic Acid Ethyl Ester (5).** To a stirred solution of sodium acetate (0.37 g, 4.53 mmol) and *N*-chlorosuccinimide (0.37 g, 2.79 mmol) in acetone (8 mL) and H_2O (2 mL) at 0 °C was added a solution of racemic silyl enol ether **4** (500 mg, 1.86 mmol) in acetone (3 mL). The reaction mixture was warmed, with stirring, to room temperature over 17 h and then quenched by addition of 20% aqueous sodium metabisulfite solution (10 mL) and brine (25 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL), and then the

(39) Armstrong, A.; Barsanti, P. A.; Jones, L. H.; Ahmed, G. *J. Org. Chem.* **2000**, *65*, 7020.

combined organic extracts were washed with saturated sodium hydrogen carbonate solution (50 mL), dried over $MgSO_4$, and evaporated to dryness under reduced pressure to give a yellow oil (456 mg). Flash chromatography over silica using 50% ether−50% petrol as eluent gave the chloro ketone **5** (241 mg, 56%) as a colorless oil: IR (film) 1724, 1698 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.82−4.57 (m, 2H), 4.20 (m, 2H), 3.96 (s, 1H), 3.18 (br d, J = 15.5 Hz, 1H), 2.29 (d, J = 15.5 Hz, 1H), 2.25−1.95 (m, 2H), 1.75−1.55 (m, 2H), 1.29 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1 (C), 154.0 (C), 62.1 (CH), 61.6 (CH_2), 58.1 (CH), 53.0 (CH), 44.6 (CH_2), 27.5 (br CH_2), 27.1 (br CH_2), 14.5 (CH_3); MS m/z (FAB+) 232 (MH^+, ^{35}Cl, 35%); HRMS calcd for $C_{10}H_{15}{}^{35}ClO_3N$ (MH^+) 232.0740, found 232.0735.

(1*R*,2*R*,5*S*)-(+)-2-Chloro-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylic Acid Ethyl Ester (5). The above procedure using nonracemic **4** followed by flash chromatography twice over silica using first 40% ether/60% petrol and then 0.5% MeOH/99.5% CH_2Cl_2 as eluent gave nonracemic **5** (45%) as a yellow solid, shown by chiral HPLC (Chiralcel OJ, 1/100 ^{i}PrOH/hexane with 0.1% TFA added as eluent, flow rate 1 mL/min, detection at 221 nm) to be of 78% ee, with elution times of 24.4 min (minor enantiomer) and 28.4 min (major enantiomer), which were spectroscopically identical with those of the racemic sample prepared previously. A single recrystallization from petrol gave pale brown needles of >98% ee: mp 52.0−53.0 °C; $[\alpha]^{25}_D$ = +152 (*c* 1.11, $CHCl_3$). Anal. Calcd for $C_{10}H_{14}NO_3Cl$: C, 51.84; H, 6.06; N, 6.05. Found: C, 51.84; H, 6.03; N, 6.06.

(1*R,2*R**,5*S**)-(±)-2-Hydroxy-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylic Acid Ethyl Ester (6).** To a stirred solution of the racemic silyl enol ether **4** (0.402 g, 1.5 mmol) in dry CH_2Cl_2 (20 mL) at room temperature under nitrogen was added dimethyldioxirane[40] (30 mL of a 0.075 M solution in acetone, 2.25 mmol). The reaction mixture was stirred at room temperature for 2 h, and then the solvent was removed under reduced pressure to give a colorless oil (375 mg). Flash chromatography over silica using 50% ether/50% petrol and then 100% ether as eluent yielded the alcohol **6** (196 mg, 63%) as a colorless oil: IR ($CHCl_3$) 3550, 2982, 1724, 1683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.62−4.58 (m, 2H), 4.22 (q, J = 7 Hz, 2H), 3.84 (s, 1H), 3.06 (d, J = 15 Hz, 1H), 2.26 (d, J = 15 Hz, 1H), 2.12−2.02 (m, 2H), 2.00 (br, 1H), 1.65−1.52 (m, 2H), 1.30 (t, J = 7 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) 206.5 (C), 155.4 (C), 79.3 (CH), 62.3 (CH_2), 58.7 (CH), 53.8 (CH), 46.3 (CH_2), 28.1 (CH_2), 24.4 (CH_2), 15.1 (CH_3); MS m/z (EI) 213 (M^+, 27%), 140 ($M - CO_2Et$, 100%); HRMS calcd for $C_{10}H_{15}NO_4$ (M^+) 213.1001, found 213.0991.

(1*R*,2*R*,5*S*)-(+)-2-Hydroxy-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylic Acid Ethyl Ester (6). The above procedure using nonracemic silyl enol ether **4**, followed by flash chromatography on silica using 10% EtOAc/90% petrol to 100% EtOAc as eluent gave nonracemic **6** (55%) as a colorless oil, $[\alpha]^{25}_D$ = +20.4 (*c* 0.83, $CHCl_3$), at 80% ee (shown by subsequent chiral HPLC analysis of the derived acetate). NMR data agreed with those of the previously prepared racemic sample.

(1*R,2*R**,5*S**)-(±)-2-Acetoxy-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylic Acid Ethyl Ester (7).** To a stirred solution of alcohol **6** (196 mg, 0.92 mmol), in dry CH_3CN (10 mL) under nitrogen, were added acetic anhydride (347 μL, 3.7 mmol) and a solution of $Sc(OTf)_3$ (5 mg, 0.01 mmol) in dry CH_3CN (100 μL). The reaction mixture was stirred at room temperature for 1 h, quenched by addition of saturated sodium hydrogen carbonate solution (10 mL), and extracted into ether (4 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness under reduced pressure to give a pale yellow oil (260 mg). Flash chromatography over silica using 50% ether/50% petrol as eluent gave the acetate **7** (174 mg, 74%) as a colorless oil, which crystallized on storage: mp 53−54 °C (Et_2O/petrol); IR ($CHCl_3$) 1748, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.82−4.57 (m, 3H), 4.27−4.11 (m, 2H), 3.01 (br, 1H), 2.37 (1H, d, J = 15 Hz), 2.14−2.00 (m, 2H), 2.06 (s, 3H), 1.66−1.61 (m, 2H), 1.29 (m, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 202.8 (C), 169.2 (C), 154.0 (C), 78.3 (CH), 61.3 (CH_2), 55.1 (CH), 52.8 (CH), 46.7 (CH), 27.3 (CH_2), 24.3 (CH_2), 20.5 (CH_3), 14.5 (CH_3); MS m/z (EI) 255 (M^+, 1%), 213 ($MH - OAc$, 8%); HRMS calcd for $C_{12}H_{17}NO_5$ (M^+) 255.1107, found 255.1115. Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.70; H, 6.65; N, 5.40.

(1*R*,2*R*,5*S*)-(+)-2-Acetoxy-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylic Acid Ethyl Ester (7). This compound was prepared as described above for the racemate, starting from nonracemic **4**, giving material spectroscopically identical with the racemic sample. The material was shown by chiral HPLC (Chiralcel OD, 1/100 iPrOH/hexane, 1 mL/min flow rate, detection at 221 nm) to be of 80% ee, with retention times of 27.4 min (minor enantiomer) and 30.0 min (major enantiomer). Additional data; $[\alpha]^{24}_D$ = +48.4 (*c* 1.00, $CHCl_3$) at 80% ee.

(1*R,5*S**)-2-Methylene-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylic Acid Ethyl Ester (9). (a) Cyclopropanation of Silyl Enol Ether 4.** To a stirred solution of the silyl enol ether **4** (683 mg, 2.55 mmol) in dry ether (15 mL) at 0 °C under nitrogen was added dropwise Et_2Zn (2.55 mL of a 1.0 M solution in hexanes, 2.55 mmol) followed by CH_2I_2 (248 μL, 3.06 mmol). The reaction mixture was stirred at room temperature for 20 h, quenched with saturated ammonium chloride solution (25 mL), and diluted with ether (50 mL), and the phases were separated. The organic phase was washed with saturated sodium hydrogen carbonate solution (25 mL) and H_2O (25 mL). The organic phase was dried over $MgSO_4$ and evaporated to dryness under reduced pressure to give a pale yellow oil (718 mg). Flash chromatography over silica (previously washed with 1% Et_3N/99% eluent) using 25% ether/75% petrol as eluent gave the cyclopropane (300 mg, 42%) as a colorless oil: IR ($CHCl_3$) 1681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29 (br, 1H), 4.10−4.07 (m, 3H), 2.51 (br, 1H), 2.09−2.04 (m, 1H), 1.97−1.92 (m, 1H), 1.85−1.74 (m, 3H), 1.25−1.21 (m, 3H), 1.14 (br, 1H), 0.87 (br, 1H), 0.23 (br, 1H), 0.11 (s, 9H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 154.0 (C), 60.8 (CH_2), 51.9 (CH), 51.6 (C), 49.3 (CH), 41.6 (br, CH_2), 30.0 (br, CH_2), 28.8 (br, CH_2), 26.0 (CH), 17.9 (CH_2), 14.7 (CH_3), 1.3 (3 × CH_3); MS m/z (EI) 283 (M^+, 6%). HRMS calcd for $C_{14}H_{25}NO_3Si$ (M^+) 283.1604, found 283.1611.

(b) Formation of Enone 9. To a stirred solution of the cyclopropane silyl ether (300 mg, 1.06 mmol) in dry CH_2Cl_2 (15 mL) under nitrogen was added dropwise $SnCl_4$ (127 μL, 1.1 mmol). The reaction mixture was stirred at room temperature for 2 h and then the solvent removed under reduced pressure to give the crude stannane as an oily yellow solid. The crude stannane was redissolved in dry CH_2Cl_2 (15 mL), dry DMSO (270 μL, 3.18 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 20 h. The resultant white precipitate was removed by filtration and washed with CH_2Cl_2 (10 mL). The combined filtrate and washings were washed with saturated ammonium chloride solution (2 × 30 mL), dried over $MgSO_4$, and evaporated to dryness under reduced pressure to give a colorless oil (314 mg). Flash chromatography over silica using 50% ether/50% petrol as eluent yielded the enone **9** (177 mg, 80%) as a colorless oil: IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.92 (s, 1H), 5.24 (s, 1H), 4.90 (br, 1H), 4.57 (br, 1H), 4.16 (q, J = 7 Hz, 2H), 2.77 (br, 1H), 2.46 (d, J = 17 Hz, 1H), 2.29−2.17 (m, 2H), 1.81−1.66 (m, 2H), 1.26 (t, J = 7 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 198.3 (C), 153.8 (C), 146.1 (C), 119.4 (br, CH_2), 61.4 (CH_2), 58.2 (CH), 52.4 (CH), 47.5 (CH_2), 31.2 (br, CH_2), 28.8 (br, CH_2), 14.6 (CH_3); MS m/z (EI) 209 (M^+, 11%), 181 ($MH^+ - Et$, 100%); HRMS calcd for $C_{11}H_{15}NO_3$ (M^+) 209.1052, found 209.1057.

(40) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

(41) 1-(Chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).

(42) Details of this X-ray crystal structure are given in the Supporting Information.

Acetonide (±)-10. To a stirred suspension of $K_2OsO_4 \cdot 2H_2O$ (0.90 mg, 2.44 μmol), quinunclidine (1.3 mg, 12 μmol), and *N*-methylmorpholine *N*-oxide (56 mg, 0.48 mmol) in H_2O (106 μL) was added a solution of the enone **9** (50 mg, 0.24 mmol) in acetone (0.56 mL). The reaction mixture was stirred vigorously at room temperature for 5 days, and then solid sodium metabisulfite (∼0.5 g) was added and vigorous stirring continued for a further 1 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and the solid was removed by filtration through a pad of Celite and washed with CH_2Cl_2 (10 mL). The combined filtrate and washings were evaporated to dryness under reduced pressure to give a yellow oil which was azeotroped twice with toluene to yield the crude diol (48 mg, 82%) as a pale yellow oil: IR ($CHCl_3$) 3535, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 (br, 1H), 4.52 (br, 1H), 4.26−4.18 (m, 2H), 4.05 (d, *J* = 12 Hz, 1H), 3.62 (d, *J* = 12 Hz, 1H), 3.15 (d, *J* = 15 Hz, 1H), 2.72 (br, 1H), 2.21 (d, *J* = 15 Hz, 1H), 2.03−2.01 (m, 2H), 1.87 (br, 1H), 1.63−1.54 (m, 2H), 1.30 (t, *J* = 7 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 208.4 (C), 155.4 (C), 90.1 (C), 62.7 (CH_2), 61.8 (CH_2), 59.1 (CH), 53.6 (CH), 45.9 (CH_2), 27.8 (CH_2), 23.5 (CH_2), 14.6 (CH_3); MS *m*/*z* (EI) 243 (M^+, 12%), 140 (M − CO_2Et − CH_3OH, 100%); HRMS calcd for $C_{11}H_{17}NO_5$ (M^+) 243.1107, found 243.1111.

To a stirred solution of the diol (20 mg, 82 μmol) in acetone (0.3 mL) and 2,2-dimethoxypropane (6 μL) at 0 °C under nitrogen was added perchloric acid (3.5 μL of a 70% aqueous solution). The reaction mixture was stirred at 0 °C for 3 h and then the pH adjusted to 7−8 with concentrated ammonia solution. The reaction mixture was stirred for 5 min and then the solvent removed under reduced pressure to give a white solid. Flash chromatography over silica using 75% ether/25% petrol as eluent yielded the acetonide **10** as a white solid (16 mg, 70%): mp 112−113 °C; IR ($CHCl_3$) 1723 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.65 (br, 1H), 4.61 (br, 1H), 4.45 (br, 1H), 4.28−4.15 (m, 2H), 3.66 (d, *J* = 9 Hz, 1H), 3.11 (br, 1H), 2.36 (d, *J* = 15 Hz, 1H), 2.09−1.97 (m, 2H), 1.61−1.44 (m, 2H), 1.48 (s, 3H), 1.31 (t, *J* = 7 Hz, 3H), 1.26 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 204.7 (C), 154.5 (C), 111.6 (C), 86.1 (C), 65.5 (CH_2), 61.2 (CH_2), 60.3 (CH), 53.4 (CH), 46.7 (CH_2), 27.6 (CH_2), 26.6 (CH_3), 25.5 (CH_3), 24.3 (CH_2), 14.6 (CH_3); MS *m*/*z* (EI) 283 (M^+, 9%), 268 (M − Me, 3%); HRMS calcd for $C_{14}H_{21}NO_5$ (M^+) 283.1420, found 283.1408.

(1*R,2*S**,5*S**)-(±)-2-Acetoxy-3-oxo-8-azabicyclo[3.2.1]-octane-8-carboxylic Acid Ethyl Ester (11).** To a stirred solution of potassium hydroxide (850 mg, 15.2 mmol) in dry MeOH (12 mL) at 0 °C under nitrogen was added a solution of *N*-carbethoxytropinone **3** (700 mg, 3.5 mmol) in dry MeOH (6 mL) dropwise over 10 min. The reaction mixture was stirred at 0 °C for a further 10 min, and $PhI(OAc)_2$ (1.83 g, 5.5 mmol) was added portionwise over 10 min. The reaction mixture was warmed to room temperature, with stirring, overnight. Most of the solvent was removed under reduced pressure and H_2O (25 mL) added. The reaction mixture was saturated with solid NH_4Cl and then extracted with CH_2Cl_2 (6 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness under reduced pressure to give a yellow oil (2.16 g). Flash chromatography over silica using 40% ether/60% petrol as eluent yielded the α-hydroxy dimethyl ketal (635 mg, 70%) as a colorless oil: IR (liquid film) 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.15 (br, 1H), 4.11 (q, *J* = 7 Hz, 2H), 3.82 (br, 1H), 3.28 (s, 3H), 3.26 (s, 3H), 3.20−3.11 (m, 2H), 2.09 (dd, *J* = 15 Hz, 2, 1H), 2.03−1.58 (m, 5H), 1.23 (t, *J* = 7 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 153.6 (C), 98.3 (C), 73.1 (CH), 60.9 (CH_2), 57.0 (CH), 52.0 (CH_3), 50.8 (CH), 48.4 (CH_3), 35.4 (CH_2), 26.5 (br, CH_2), 23.1 (br, CH_2), 14.5 (CH_3); MS *m*/*z* (EI) 259 (M^+, 4%), 227 (M − OMe, 8%), 199 (M − OMe − Et, 20%); HRMS calcd for $C_{12}H_{21}NO_5$ (M^+) 259.1420, found 259.1423.

To a stirred solution of the dimethyl ketal (50 mg, 0.193 mmol) in dry CH_3CN (1 mL) at room temperature under nitrogen was added acetic anhydride (273 μL, 0.29 mmol), followed by dropwise addition of a solution of $Sc(OTf)_3$ (5 mg, 0.01 mmol) in dry CH_3CN (100 μL). The reaction mixture was stirred at room temperature for 20 h, during which a color change from colorless to yellow was observed. The reaction mixture was quenched by addition of saturated sodium bicarbonate solution (5 mL), diluted with H_2O (5 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness under reduced pressure to give a pale yellow oil (52 mg). Flash chromatography of the crude product over silica using 50% ether/50% petrol as eluent gave the acetate **11** (31 mg, 63%) as a colorless crystalline solid: mp 83−85 °C; IR ($CHCl_3$) 1753, 1728, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.24 (br s, 1H), 4.65−4.50 (m, 2H), 4.26−4.20 (m, 2H), 2.80 (br, 1H), 2.45 (d, *J* = 15 Hz, 1H), 2.19 (s, 3H), 2.15−1.95 (m, 2H), 1.95−1.85 (m, 1H), 1.70−1.60 (m, 1H), 1.31 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5 (C), 169.5 (C), 153.7 (C), 76.6 (CH), 61.9 (CH_2), 56.5 (CH), 53.8 (CH), 48.0 (CH_2), 28.5 (br, CH_2), 24.4 (br, CH_2), 20.6 (CH_3), 14.6 (CH_3); MS *m*/*z* (EI) 255 (M^+, 1%), 212 (M − OAc, 10%), 210 (M − OEt, 8%), 195 (MH^+ − OAc, 32%); HRMS calcd for $C_{12}H_{17}NO_5$ (M^+) 255.1107, found 255.1105. Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.49; H, 6.61; N, 5.41.

One-Phase Epoxidation System: Yang pH 7.5. To a solution of ketone and alkene (0.1 mmol) in CH_3CN (1.5 mL) was added Na_2EDTA (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 30 min. The reaction mixture was stirred vigorously until completion (by TLC analysis) or for 24 h and then diluted with H_2O (10 mL) and extracted into ether (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness under reduced pressure. Flash chromatography over silica (previously washed with 1% Et_3N/99% eluent) yielded the relevant epoxide.

One-Phase Epoxidation System: Shi pH 10. To a solution of ketone and alkene (0.1 mmol) in CH_3CN (1.5 mL) was added tetrabutylammonium hydrogensulfate (2.0 mg, 5.9 μmol) and $Na_2B_4O_7$ (1.0 mL of a 0.05 M solution in 0.4 mM aqueous Na_2EDTA solution). After the mixture was cooled to 0 °C, solutions of Oxone (85 mg, 0.14 mmol of $KHSO_5$) in 0.4 mM aqueous Na_2EDTA solution (0.65 mL) and K_2CO_3 (80 mg, 0.58 mmol) in H_2O (0.65 mL) were added simultaneously by syringe pump over $1^1/_2$ h. The reaction mixture was stirred vigorously until completion (by TLC analysis) or for 24 h and then diluted with H_2O (10 mL) and extracted into ether (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness under reduced pressure. Flash chromatography over silica (previously washed with 1% Et_3N/99% eluent) yielded the desired epoxide.

Acknowledgment. We thank the EPSRC, the DTI, and a consortium of companies for funding this work through the LINK Asymmetric Synthesis Second Core Program and the EPSRC for a project grant (No. GR/M84534). We are grateful to Pfizer, Merck Sharp and Dohme, AstraZeneca, and Bristol-Myers Squibb for unrestricted support of our research programs.

Supporting Information Available: References to characterization data for epoxide products and methods for determination of epoxide enantiomeric excesses, X-ray structural data of ketone **2**, and ^1H NMR spectra of ketones **2**, **6**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026322Y