Asymmetric reduction of prochiral cycloalkenones. The influence of exocyclic alkene geometry

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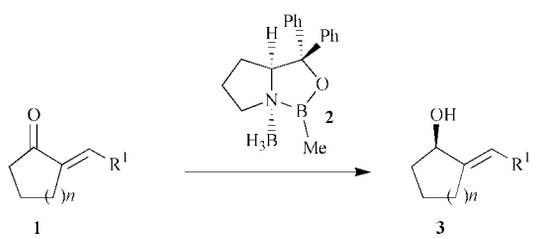
The asymmetric reduction of a series of prochiral enones of general structure **1** using the Corey oxazaborolidine **2**, leading to enantiomerically enriched allylic cycloalkanols **3** is described. The influence of alkene geometry on both the sense (*R vs. S*) and efficiency (% ee) of the asymmetric reduction process has been probed for two systems, (*E*)- and (*Z*)-**4** and (*E*)- and (*Z*)-**7**, based on cyclohexanone and cyclopentanone respectively. The absolute stereochemistry of the cyclopentyl derivative (*E*)-**8** has been established by X-ray crystallographic analysis of carbamate **10**. The ability to assign an absolute configuration to allylic alcohols **3**, based on the NMR methods described earlier by Riguera, has been evaluated.

The combination of oxazaborolidines and borane to mediate the asymmetric reduction of prochiral ketones represents a highly efficient process that has become one of the benchmarks of contemporary asymmetric synthesis.[1,2] Over recent years, extensive efforts have been applied towards identifying more efficient oxazaborolidine catalysts[3] and, following a series of detailed studies, a number of the critical features associated with the catalytic cycle and the influence of additives have also been elucidated.[4,5]

Understanding the basic mechanism of an asymmetric process is important, particularly because this information can be applied towards developing a model capable of predicting both the sense and also (though more difficult) the level of asymmetric induction that might be anticipated. Several different models[6–10] have been proposed to explain the course of oxazaborolidine-mediated reductions and, in addition, electronic factors associated with the ketone substituents have also been shown to be important in determining the stereochemical outcome.[11] The latter, while clearly of significance, is more a difficult property to incorporate within a computational model. There are some broader issues to be considered since in a practical sense, an ability to define the types of ketones that represent viable substrates for particular reagents is key to exploiting the potential associated with individual asymmetric reductants. Most work in this area has, however, focussed on the "reagent" rather than "substrate" side of the problem.

As part of a broader synthetic project, we have examined the capability of the Corey oxazaborolidine–borane complex **2**[2a,12] to mediate the asymmetric reduction of a cyclic ketone **1**, where prochirality is due to the location of an adjacent *exocyclic* C=C associated with the enone.[13] It is interesting to note that enones based on general structure **1**, although readily prepared, have attracted little attention as substrates for asymmetric reduction despite the synthetic potential inherent in the corresponding allylic alcohols **3**.†

A series of prochiral enones have been evaluated as substrates for this asymmetric reduction, which is outlined in Scheme 1, and our preliminary results have been reported.[13b] ‡ A



Scheme 1

number of specific examples that are relevant to this discussion, as well as results obtained for several new substrates using our optimised reaction conditions, are shown in Table 1. This work did, however, raise two issues. Firstly, defining the stereochemical outcome of the reduction step by establishing the absolute configuration of the product allylic alcohol was considered important; the value of most mechanistic models is as a predictive tool and any such predictions must, at some point, be validated. A second and potentially more intriging aspect of these molecules, which we did not examine in our initial work, is the variable associated with enones **1** *i.e.* (*E*)- *vs.* (*Z*)-alkene geometry, and the impact that this makes on the stereochemical outcome of the reduction: (1*R*) *vs.* (1*S*) allylic alcohol. We considered this latter feature unusual given that most "standard" prochiral ketones, which find use as test substrates for asymmetric reductions, do not incorporate such stereochemical "complications", and it was therefore of interest to establish the role, if any, that exocyclic

† The bioreduction process reported by Fuganti and co-workers[16a–c] provides an alternative entry into cyclic allylic alcohols related to **3**. A more lengthy procedure to one example of an allylic alcohol of this type has been described by Warren and Harmat.[16d]

‡ We have also evaluated the use of catalytic (20 mol%) amounts of **2** (using $BH_3{\cdot}SMe_2$ as the stoichiometric reductant), and the results of this study have already been described.[13b] In this present work, we used one equivalent of **2** in order to minimize the impact made by competing pathways that have been shown to participate under catalytic reduction conditions.[5d,12]

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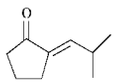
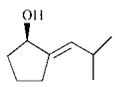
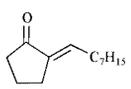
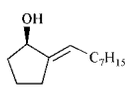
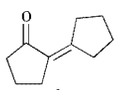
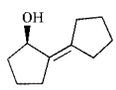
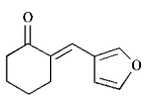
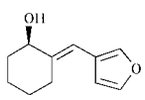
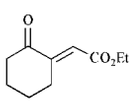
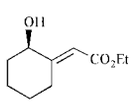
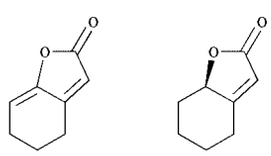
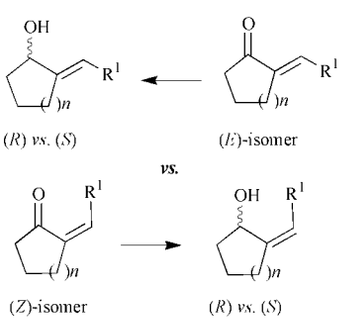
Table 1 Asymmetric reduction of prochiral enones using (*S*)-**2**

Enone **1**	Allylic alcohol **3**	Yield (%)	ee (%)[a]
 **1a**	 **3a**	84	88[b]
 **1b**	 **3b**	89	94[b]
 **1c**	 **3c**	98	88[b]
 **1d**	 **3d**	81	87
 **1e**	 **3e**	98	> 95[b,c]

[a] For optimised reaction conditions using stoichiometric **2**, see Experimental. The % ee of alcohols **3a**–**3e** were determined *via* the corresponding Moshers ester derivative. [b] Absolute stereochemistry has not been established in these cases. In the case of **3d**, see text. [c] Reduction of the (*Z*)-isomer of **1e** gave the corresponding α,β-unsaturated lactone in 36% ee, but this reaction did not go to completion. The (*Z*)-isomer of **1e** was prone toward enolisation–cyclisation to give **i**.[15a] Asymmetric reduction of the (*Z*)-isomer of **1e** led to the known unsaturated lactone **ii**,[15b] and the enantiomeric excess obtained (36% ee, absolute configuration unknown) was determined by a chiral shift NMR experiment using Eu[(+)-hfc]$_3$ [hfc = (heptafluoropropylhydroxymethylene)camphorate]. This reaction was, however, slow and did not reach completion.



i **ii**



(*R*) *vs.* (*S*) (*E*)-isomer

vs.

(*Z*)-isomer (*R*) *vs.* (*S*)

alkene geometry plays in determining both the sense and level of asymmetric induction.§

Our study has concentrated on (*E*)- and (*Z*)-exocyclic enones derived from cyclohexanone (and PhCHO) and cyclopentanone (and PhCHO), (*E*)-**4** and (*Z*)-**4**, and (*E*)-**7** and (*Z*)-**7** respectively.

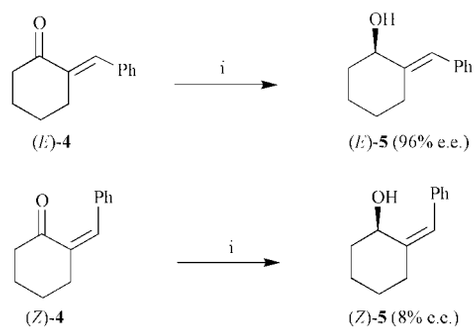
§ A number of acyclic enones have been used as substrates for oxazaborolidine-mediated reductions, and the presence of α and α′ substituents does influence the sense of asymmetric induction.[14] These substrates were the subject of a parallel computational study, but this used the s-*trans* enone arrangement, a conformational option that is not available to enones **1**.

In this paper we provide evidence to support the assignment of absolute configuration to allylic alcohols **3** based on X-ray crystallographic analysis and ^{1}H NMR. In addition, the influence of alkene geometry on the asymmetric reduction of representative cyclopentyl and cyclohexyl enone variants has been established.

Results and discussion

Asymmetric reduction of (*E*)-4 and (*Z*)-4

The reduction of (*E*)-**4** and (*Z*)-**4** was carried out using a stoichiometric amount of oxazaborolidine-borane complex **2** under our optimised conditions (addition of the enone substrate to the reductant at −20 °C over 35 min) and the enantiomeric excess of the allylic alcohol products (*E*)-**5** (isolated in 96% ee) and (*Z*)-**5** (isolated in 8% ee) was determined by chiral phase HPLC (Scheme 2). The corresponding racemic alcohols



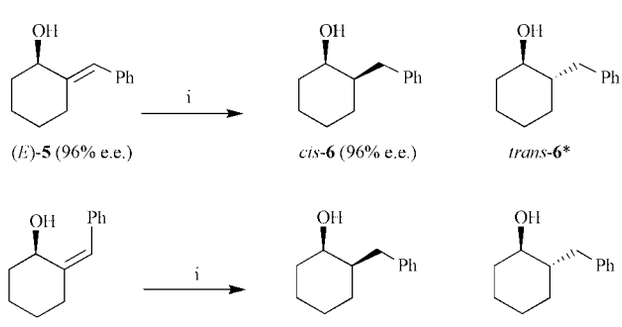
(*E*)-**4** (*E*)-**5** (96% e.e.)

(*Z*)-**4** (*Z*)-**5** (8% e.e.)

Scheme 2 *Reagents and conditions*: i, **2**, CH_2Cl_2, −20 °C.

served as analytical standards and were prepared by direct reduction of the corresponding enone with $NaBH_4$.

The key stereochemical issue to be established was whether alkene geometry influenced the sense (*R vs. S*) of asymmetric induction, and clearly alkene geometry does make a significant impact on the level of asymmetric induction (96 *vs.* 8% ee). We have correlated the structures of (*E*)-**5** and (*Z*)-**5** using the sequence shown in Scheme 3. Hydrogenation of (*E*)-**5** gave a



(*E*)-**5** (96% e.e.) *cis*-**6** (96% e.e.) *trans*-**6***

(*Z*)-**5** (8% e.e.) *cis*-**6** (10% e.e.) *trans*-**6***

Scheme 3 *Reagents and conditions*: i, H_2, 10% Pd on C, EtOH (*% ee not determined).

mixture of the 2-benzylcyclohexanols *cis*-**6** and *trans*-**6** which were separable by chromatography, and chiral phase HPLC of *cis*-**6** confirmed that no significant loss of enantiomeric purity had occurred. Once again, the racemic variants were available using the same reduction process and provided the corresponding racemic analytical standards.¶

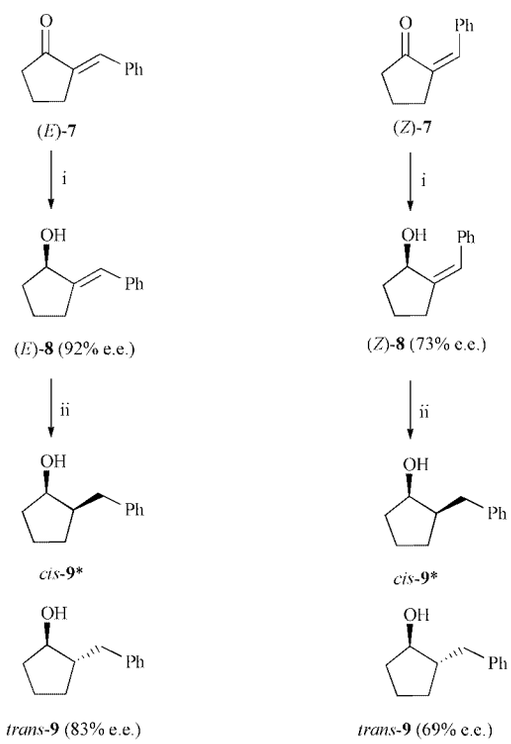
A similar result was obtained when hydrogenation of (*Z*)-**5** was carried out to give a mixture of *cis*- and *trans*-**6**. Again, no

¶ *cis*- and *trans* **6** and *cis*- and *trans*- **9** have been reported by Fuganti.[16a–c] We have not carried out an independent assignment of relative stereochemistry since the precise structure of the isomer involved (*cis vs. trans*) was not relevant to the correlations that we have drawn.

significant erosion of enantiomeric purity was observed during the reduction step and chiral HPLC confirmed that *cis*-**6** derived from (*E*)-**5** (96% ee) has the same absolute configuration (*R*) as *cis*-**6** derived from (*Z*)-**5** (10% ee); the absolute configuration of *cis*-**6** is based on the earlier work of Fuganti *et al* (see below).[16a–c] In other words, within the cyclohexyl series based on (*E*)- and (*Z*)-**4**, the exocyclic alkene geometry does not have a direct impact on the sense of asymmetric induction available from oxazolidinone reduction. However, while the (*E*)-isomer is reduced with a high degree of asymmetric induction, the corresponding (*Z*)-isomer is a very poor substrate for the oxazaborolidine–borane reagent **2**.

Asymmetric reduction of (*E*)-7 and (*Z*)-7

Asymmetric reduction of the cyclopentyl based enones (*E*)-**7** and (*Z*)-**7** was also carried out and, once again, we were able to correlate the resulting allylic alcohols (*E*)-**8** (isolated in 92% ee) and (*Z*)-**8** (isolated in 73% ee) following alkene hydrogenation (Scheme 4).



Scheme 4 *Reagents and conditions*: i, **2**, CH_2Cl_2, −20 °C; ii, H_2, 10% Pd on C, EtOH (* *cis* isomer was obtained in trace amounts and % ee was not determined).

We have carried out hydrogenation of both (*E*)- and (*Z*)-**8**, and in both cases, alkene reduction led to the *trans* diastereomer *trans*-**9** as the predominate product; *cis*-**9** was only detected in trace amounts. Analysis of *trans*-**9** (by chiral phase HPLC) demonstrated that alkene geometry did not alter the sense of asymmetric induction and (1*R*)-*trans*-2-benzylcyclopentan-1-ol **9** was produced from both (*E*)-**8** and (*Z*)-**8**; the absolute configuration of *trans*-**9** has also been established (see below). In this cyclopentyl series, the level of asymmetric induction is influenced to a lesser extent by alkene geometry, although it is interesting that some loss of enantiomeric integrity was detected during the conversion of both (*E*)-**8** and (*Z*)-**8** to *trans*-**9**.

Assignment of absolute configuration

In the cyclohexyl series, the *R* absolute configuration of (*E*)-**5** can be assigned based on the earlier work of Fuganti *et al.* who have prepared the corresponding (*S*)-enantiomer. In the case of the cyclopentyl derivative *trans*-**9**, we were able to prepare the corresponding (*S*)-α-methylbenzylcarbamate **10** (Scheme 5), the structure of which was determined by X-ray crystallographic analysis (Fig. 1).‖ This established the absolute stereochemistry of (*E*)- and (*Z*)-**8** (and *cis*- and *trans*-**9**) as (1*R*).

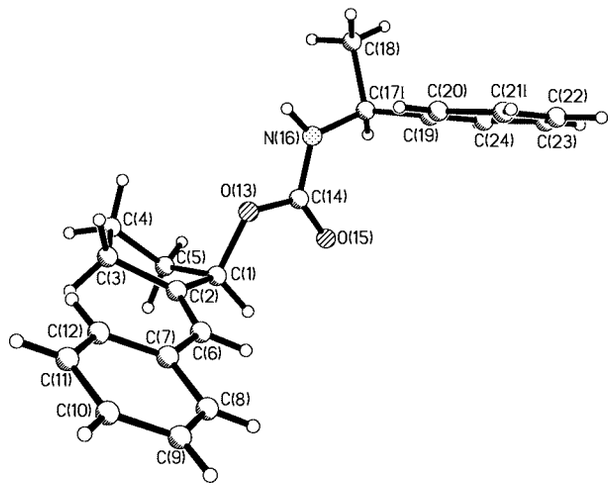
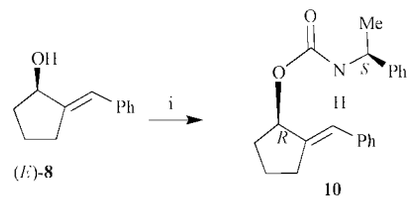


Fig. 1 Crystal structure of carbamate **10**.



Scheme 5 *Reagents and conditions*: i, (*S*)-α-methylbenzyl isocyanate, DMAP, CH_2Cl_2 (96%).

Application of NMR methods for the determination of absolute configuration

A major challenge within asymmetric synthesis is the determination of absolute configuration. The use of X-ray crystallographic analysis, while often a very secure means of assigning configuration, is a hit-or-miss affair since obtaining a suitable crystalline derivative can be time consuming. Spectroscopic methods based on NMR approaches have gained in popularity as a convenient and rapid means of analysis that are also well suited to microscale methodologies.[17] Recently, Riguera and coworkers have reported a simplified method for the determination of absolute configuration of secondary alcohols based on use of esters derived from either (*R*)- or (*S*)-α-methoxyphenylacetic acid (MPA).[18] Until recently, this was achieved by preparation of both diastereomeric esters, using the alcohol and (*R*)- and (*S*)-MPA, followed by comparison of the two products by NMR. Riguera has now demonstrated that it is possible to elucidate an absolute configuration using only one diastereo-

‖ X-Ray diffraction measurements were determined on a Siemens SMART area detector diffractometer, using graphite monochromated Mo-Kα radiation. No absorption correction was applied. The structure was solved by direct-methods (SHELXS) and full-matrix least squares refinement carried out using SHELXL-93 (SHELXTL version 5.03, Siemens Analytical X-ray, Madison WI, 1994). Absolute configuration was assigned by using the known stereochemistry of the (*S*)-α-methylbenzyl moiety incorporated within carbamate **10**. $C_{21}H_{23}NO_2$, $M = 321.40$, orthorhombic, $a = 5.1199(13)$, $b = 13.998(4)$, $c = 24.286(6)$ Å, $U = 1740.6(8)$ Å^3, $T = 173$ K, space group $P2_12_12_1$ (no. 19), $Z = 4$, μ(Mo-Kα) = 0.078 mm^{-1}, 18250 reflections measured, 3980 unique, ($R_{int} = 0.0765$) reflections used in all calculations, $wR2 = 10.3\%$ (all data), $R_1 = 5.0\%$ [2526 $I > 4\sigma(I)$ data]. CCDC reference number 207/459. See http://www.rsc.org/suppdata/p1/b0/b004540n for crystallographic files in .cif format.

Table 2 Variable temperature ^{1}H NMR data[a] for the (*R*)-MPA ester of (*E*)-**3d**

Temperature/°C	δ H(1)	δ H_{vinyl}	δ H(3)	δ H(3)[b]
22	5.32	5.67	2.35	2.18
−40	5.26	5.32	2.42	2.05
−60	5.24	5.13	2.46	1.97
−80	5.22	4.93	2.53	1.90

H_{vinyl} undergoes an upfield shift of 0.76 ppm on cooling from 22 to −80 °C. One of the C(3) methylene protons undergoes an upfield shift (by 0.28 ppm) and the other C(3) proton shifted downfield (by 0.18 ppm). Small upfield and downfield shifts associated with H(5) and H(6) were observed, but these signals were overlapping and unambiguous assignments were not possible. [a] 400 MHz, CD_2Cl_2. [b] Assignment based on a COSY analysis. The C(3) methylene appears as two separate multiplets, but these have not been individually assigned.

Table 3 Variable temperature ^{1}H NMR data[a] for the (*R*)-MPA ester of (*E*)-**5**

Temperature/°C	δ H(1)	δ H_{vinyl}	δ H(3)	δ H(3)[b]
22	5.32	6.04	2.33	2.15
−40	5.32	5.73	2.38	1.98
−60	5.32	5.57	2.43	1.93
−80	5.32	5.32	[c]	1.94

H_{vinyl} undergoes an upfield shift of 0.72 ppm on cooling from 22 to −80 °C. One of the C(3) methylene protons undergoes an upfield shift (by 0.21 ppm) and the other proton shifts downfield (by ≤0.1 ppm). [a] 400 MHz, CD_2Cl_2. [b] Assignment is based on a COSY analysis. The C(3) methylene appears as two separate multiplets (not individually assigned). [c] The lower field signal was very broad at this temperature.

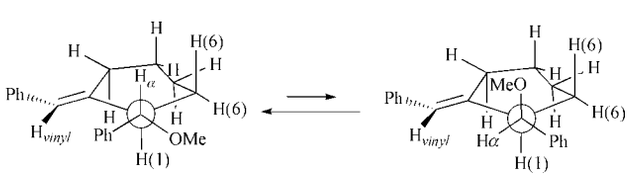


Fig. 2 *sp* and *ap* Conformations corresponding to the (*R*)-MPA ester of (1*R*,*E*)-**5** (see ref. 18).

mer, thereby obviating the need to prepare and compare two derivatives.[18b]

Since this method has not yet been applied to allylic alcohols of the type described in this paper, and given that we have firm experimental data available, it was of interest to apply the simplified Riguera protocol within this context. The process relies on the thermodynamic preference for the *sp* rather than *ap* conformation associated with MPA esters (Fig. 2). At low temperatures the population of the *sp* conformer is increased resulting in either a downfield shift (for those protons not shielded by the aryl ring) or an upfield shift (for those protons which are shielded) relative to the observed shift of the same proton(s) at room temperature. By acquiring ^{1}H NMR data at various temperatures, the direction of shift can be used to deduce the absolute configuration of the secondary alcohol.

In Tables 2–5 we have shown data for three MPA esters derived from allylic alcohols (*E*)-**3d**, (*E*)-**5** and (*E*)-**8**. In the case of (*E*)-**8** (for which we have X-ray crystallographic data as the basis of our assignment of the (*R*)-configuration), esters derived from both (*R*)- and (*S*)-MPA were prepared and evaluated. ^{1}H NMR studies were carried out in CD_2Cl_2 solution and on cooling from +22 to −80 °C, H_{vinyl} showed very significant upfield shifts (between 0.41 and 0.76 ppm), which is fully consistent with Riguera's model. The individual methylene protons at C(3) of these three derivatives shifted in different directions to one another, but here one cannot exclude an influence associated with the anisotropic influence of the aryl substituent

Table 4 Variable temperature ^{1}H NMR data[a] for the (*R*)-MPA ester of (*E*)-**8**

Temperature/°C	δ H(1)	δ H_{vinyl}
22	5.65	6.18
−40	5.59	5.97
−60	5.58	5.88
−80	5.55	5.77

H_{vinyl} undergoes an upfield shift of 0.41 ppm on cooling from 22 to −80 °C. Small changes were observed for some of the methylene signals between δ 1.60 and 2.63, but we have been unable to assign the (overlapping) signals involved. [a] 400 MHz, CD_2Cl_2.

Table 5 Variable temperature ^{1}H NMR data[a] for the (*S*)-MPA ester of (*E*)-**8**

Temperature/°C	δ H(1)	δ H_{vinyl}	δ H(6)[b]
22	5.67	6.56	1.59
−40	5.62	6.55	1.50
−60	5.59	6.55	1.48
−80	5.57	6.55	1.45

One signal associated with the C(6) methylene undergoes an upfield shift of 0.14 ppm on cooling from 22 to −80 °C. H_{vinyl} also shifts upfield by 0.01 ppm. [a] 400 MHz, CD_2Cl_2. [b] This assignment is based on a COSY analysis but we cannot assign the stereochemistry of the H(6) proton involved.

on the alkene. The shifts associated with H(6) (H(5) in the case of (*E*)-**8**) were both less marked and less clear cut. The difficulty here was that the ring methylene protons overlapped and it was not possible to track and assign individual signals with confidence at the different temperatures used. Shifts associated with H(1) are included in Tables 2–5, but these do not appear to have a diagnostic value.

In the case of the other diastereomeric series, the (*S*)-MPA ester of (*E*)-**8**, then much smaller shifts (≤0.15 ppm) were observed for all protons. Interestingly, when (*R*)- and (*S*)-indan-1-ol was used as a test substrate by Riguera, the "mismatched" diastereomer combination (in Riguera's work this was the (*R*)-MPA ester of (*S*)-indan-1-ol) showed only small (<0.05 ppm) shift changes. The "matched" diastereomer—the (*S*)-MPA ester of (*S*)-indan-1-ol—displayed somewhat larger (0.05 to 0.1 ppm) shift changes, with H(7) (which we can compare to H_{vinyl} in MPA derivatives of (*E*)-**8**) showing a significant upfield shift. With the (*S*)-MPA ester of (*R*,*E*)-**8**, H(6) moved to higher field (as expected), but a very small (insignificant?) upfield shift (0.01 ppm) was also associated with the H_{vinyl} signal.

Generally, the shift associated with H_{vinyl} in the "mismatched" (*S*, *R*) diastereomer was much less pronounced than in the "matched" (*R*, *R*) combination, and this signal appears to be the most diagnostic when applying the simplified version of the Riguera procedure to allylic alcohols of this type. Using the data shown in Tables 2–5, we can confirm the absolute configuration of both (*E*)-**5** and (*E*)-**8** as (1*R*) and assign the configuration of (*E*)-**3d** as (1*R*).

In summary, by using prochiral exocyclic enones we have determined a series of potentially important factors associated with oxazaborolidine-mediated asymmetric reduction. We must acknowledge that the stereochemical outcome described for enones **4** and **7** is predicted by existing transition state models[6–10] (based on a large *vs*. small substituent effect), but these models do not recognise the subtleties associated with enone geometry and ring size. Three key points can be made.

1. For the limited range of substrates we have studied, alkene geometry does not alter (*i.e*. reverse) the sense of asymmetric induction, although (*E*)-alkenes are reduced with a higher degree of asymmetric induction than is observed with the corresponding (*Z*)-isomers.

2. Alkene geometry is more influential in the cyclohexyl series than in the corresponding five-membered ring: while (*E*)-**4** is a good substrate, (*Z*)-**4** gives the corresponding allylic alcohol in very low% ee.

3. Clearly, when predicting the level of asymmetric induction, one cannot consider only alkene geometry and ignore ring size (6- *vs*. 5-ring). We had anticipated that there might be a significant decrease in% ee associated with presence of a (*Z*)-alkene, given that this would place the alkenyl substituent in close proximity to ketone carbonyl which itself provides a co-ordination site for the reductant. While this is true in the cyclohexyl series, this argument does not hold to the same degree in the case of the cyclopentyl substrate. In this latter case, alkene geometry makes a less significant impact, which may reflect the modified (more accessible) environment associated with the carbonyl residue in the five-membered ring.

That alkene geometry can influence the stereochemical outcome of the oxazaborolidine reduction process is clear. However, while it is tempting to speculate on the reasons behind this, any attempt to apply current predictive models would also involve assuming that other key mechanistic features of the reaction remained the same. Alkene geometry will influence the environment around the carbonyl residue, which may, in turn, have an impact on co-ordination and/or hydride delivery. Significant structural variations within the ketone substrate may also have a bearing on the stability of the intermediates involved; it is known that oxazaborolidine **2** is not the only reductant present in the reaction mixture.[5d] We would hope that future work directed towards modelling the process of hydride transfer involved in this important asymmetric process would take account of and benefit from the results described in this paper.

Experimental

General

Infrared spectra (ν_{max}) were recorded using a Perkin-Elmer 1715 FTIR spectrometer, in the range of 4000–600 cm^{-1} either as a neat film on NaCl plates or as a solution in CH_2Cl_2. Mass spectra *m*/*z* (EI, CI, FAB) were obtained using a Fisons/VG Analytical Autospec System. Nuclear magnetic resonance (NMR) spectra were recorded at the field strength and in $CDCl_3$, unless otherwise indicated using standard pulse sequences on an Alpha 500, JEOL GX400 or a Lambda 300 spectrometer, with proton and carbon assignments made using a combination of $^1H/^1H$ and $^1H/^{13}C$ correlation spectra. Coupling constants are reported in hertz (Hz).

(*S*)-Oxazaborolidine–borane complex (*S*)-**2** (as well as the corresponding (*R*)-enantiomer) were kindly provided by Dr David Mathre (Merck).

Enones **1a**,[19] **1b**,[19] **1c**[20,21] and **1e**[15,22,23] were prepared using literature procedures.

2-(3-Furylmethylidene)cyclohexanone (1d)

To a solution of sodium hydroxide (6.52 g) in water (1500 cm^3) was added cyclohexanone (33.8 cm^3, 326 mmol). After stirring for 5 min at room temperature, 3-furaldehyde (9.75 cm^3, 112 mmol) was added and the solution stirred for a further 72 hours. The reaction mixture was then quenched with acetic acid to pH 7 and extracted with toluene (4 × 40 cm^3). The organic extracts were washed with brine (3 × 300 cm^3), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an orange oil which was purified by distillation under reduced pressure to yield a yellow oil, bp 138–140 °C/2 mmHg which crystallised on cooling. Recrystallisation gave the *title compound* (10.9 g, 55%) as a pale yellow solid, mp 51–52 °C (from petroleum ether) (Found: C, 75.1; H, 6.7; $C_{13}H_{16}O$ requires C, 75.0; H, 6.9%. Found: M^+, 176.0835. $C_{11}H_{12}O_2$ requires 176.0837); ν_{max} (Nujol mull)/cm^{-1} 1719 (C=O); δ_H (400 MHz; $CDCl_3$) 1.87 (4 H, m, 2 × CH_2), 2.51 (2 H, t, *J* 7, 6-H_2), 2.73 (2 H, td, *J* 7 and 2, 3-H_2), 6.59 (1H, d, *J* 1, 4′-H), 7.42 (1 H, m, C=C*H*Ar), 7.46 (1 H, m, 5′-H) and 7.66 (1 H, m, 2′-H); δ_C (75.5 MHz; $CDCl_3$) 22.9 (CH_2), 23.3 (CH_2), 28.8 (CH_2), 38.8 (CH_2), 111.3 (CH), 121.9 (C), 126.9 (CH), 134.3 (C), 143.4 (CH), 144.72 (CH) and 200.5 (C=O); *m*/*z* (EI) 176 (M^+, 71%), 148 (20), 91 (45).

(*Z*)-2-Benzylidenecyclohexanone (*Z*)-4.[24] Benzylidenecyclohexanone (*Z*)-**4** was prepared in 18% yield by photoisomerisation of (*E*)-2-benzylidene cyclohexanone (*E*)-**4** as described previously.[24] δ_H (270 MHz; $CDCl_3$) 1.87–2.03 (4 H, m, 2 × CH_2), 2.55 (2 H, t, *J* 7, CH_2), 2.63 (2 H, t, *J* 7, CH_2), 6.39 (1 H, s, C=C*H*Ar) and 7.20–7.35 (5 H, m, Ar).

(*Z*)-2-Benzylidenecyclopentanone (*Z*)-7.[25] Benzylidenecyclopentanone (*Z*)-**7** was prepared in 18% yield by photoisomerisation of (*E*)-2-benzylidenecyclopentanone (*E*)-**7** as described previously.[25] δ_H (270 MHz; $CDCl_3$) 1.98 (2 H, quintet, *J* 7.5, 4-H_2), 2.42 (2 H, t, *J* 7.5, 5-H_2), 2.83 (2 H, d t, *J* 7.5 and 2, 3-H_2), 6.73 (1 H, t, *J* 2, C=C*H*Ar), 7.28–7.43 (3 H, m, 3 × Ar*H*) and 7.80–7.90 (2 H, m, 2 × Ar*H*).

General procedure for reduction of exocyclic enones with $NaBH_4$

To a solution of the enone (1 mmol) in MeOH (2 cm^3) was added $NaBH_4$ (1 mmol) and the mixture was stirred at room temperature until the reaction was judged complete by TLC. The reaction was then quenched with H_2O (5 cm^3) and the aqueous phase extracted with EtOAc (3 × 5 cm^3). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resultant residue was purified by flash column chromatography (petroleum ether–EtOAc) to afford the corresponding racemic allylic alcohol. ^1H NMR data for individual compounds are provided below and the racemates were all resolved using the analytical chiral phase HPLC conditions described below.

General procedure for asymmetric reduction of enones

To a solution of (*S*)-oxazaborolidine–borane complex (*S*)-**2** (58 mg, 0.2 mmol) in dry CH_2Cl_2 (0.3 cm^3) at −20 °C was added a solution of the enone (0.2 mmol) in CH_2Cl_2 (0.6 cm^3) over a period of 35 min. After the reaction was complete, as judged by TLC, cold (0 °C) MeOH (3 cm^3) was carefully added, and the cooling bath was removed and stirring continued for 1 h. Removal of solvents *in vacuo* and purification of the residue by flash column chromatography (petroleum ether–EtOAc) yielded the allylic alcohol product. The enantiomeric excess of the product was then determined either (i) by preparation and ^1H NMR analysis of the Mosher ester derivative **3a**–**e**, see below) or (ii) by chiral phase HPLC (used for products derived from **4** and **7**). The latter required use of a Chiracel OD column [250 mm length, 4.6 mm internal diameter, with a sample size of 0.01 cm^3 (substrate concentration of 1 mg cm^{-3}) through a loop of 0.02 cm^3 with detection at 254 nm] eluting with 90% hexane–10% propan-2-ol (unless otherwise stated) at a flow rate of 1 cm^3 min^{-1}. Retention times are quoted in minutes.

General procedure for preparation of Mosher ester derivatives

To a solution of the allylic alcohol (0.09 mmol) in dry CH_2Cl_2 (1 cm^3) was added DMAP (*ca*. 6 mg), Et_3N (0.039 cm^3) and (*R*)-(MTPA) chloride (0.14 mmol) and the mixture stirred at room temperature until the reaction was complete, as judged by TLC. The solution was then filtered through a short pad of silica and the residue washed with 50 : 50 petroleum ether–EtOAc. The filtrate was concentrated *in vacuo* to give the Mosher ester derivative which was not purified further, and in each case, the Mosher ester of the racemic alcohol was prepared and used an analytical standard. Analysis was carried out by ^1H NMR but the Mosher ester derivatives were not characterized further.

(±)- (*E*)-2-Isobutylidenecyclopentan-1-ol (*E*)-3a[26]

Using the general procedure, reduction of **1a** gave the *title compound* as a colourless syrup in 72% yield; δ_H (270 MHz; $CDCl_3$) 0.97 (6 H, dd, *J* 7 and 1.5, 2 × Me), 1.51–1.92 (5 H, m), 2.13–2.45 (3 H, m), 4.36 (1 H, br t, *J* 5, 1-H) and 5.36 (1 H, dq, *J* 9 and 1.5, C=C*H*CHMe$_2$).

(1*R,*E*)-2-Isobutylidenecyclopentan-1-ol (1*R**,*E*)-3a**

Using the general procedure, reduction of (*E*)-**1a** gave the *title compound* as a colourless oil in 84% chemical yield and 88% ee. The enantiomeric excess was determined by ^{1}H NMR spectroscopy by conversion to the Mosher's ester using the method described above. δ_H (270 MHz; $CDCl_3$) 5.55 (0.94 H, m, C=C*H*-CHMe$_2$) and 5.63 (0.06 H, m, C=C*H*CHMe$_2$).

(±)-(*E*)-2-Octylidenecyclopentan-1-ol (±)-(*E*)-3b

Using the general procedure, reduction of **1b** gave the *title compound* in quantitative yield as a colourless oil (Found: M + H$^+$, 197.1901. $C_{13}H_{24}O$ requires *M*, 197.1905); ν_{max} (liquid film)/cm^{-1} 3382, 1651; δ_H (270 MHz; $CDCl_3$) 0.86–0.91 (3 H, m, C*H*$_3$), 1.12–2.40 (19 H, m), 4.38 (1 H, m, 1-H) and 5.53 (1 H, m, C=C*H*C$_7$H$_{15}$); *m*/*z* (CI) 197 (M + H$^+$).

(1*R,*E*)-2-Octylidenecyclopentan-1-ol (1*R**,*E*)-3b**

Using the general procedure, reduction of (*E*)-**1b** gave the *title compound* as a colourless solid in 89% chemical yield and 94% ee. The enantiomeric excess was determined by ^{1}H NMR spectroscopy by conversion to the Mosher's ester using the method described above. δ_H (270 MHz; C_6D_6) 3.15 (2.91 H, m, OMe) and 3.21 (0.09 H, m, OMe).

(±)-2-Cyclopentylidenecyclopentan-1-ol (±)-3c[27]

Using the general procedure, reduction of **1c** gave the *title compound* as a colourless crystalline solid in 91% yield, mp 58–59 °C (from petroleum ether) (lit.,[27] 57–59 °C); δ_H (270 MHz; $CDCl_3$) 1.25–2.36 (15 H, m) and 4.57 (1 H, br s, 1-H).

(1*R)-2-Cyclopentylidenecyclopentan-1-ol (1*R**)-3c**

Using the general procedure, reduction of (*E*)-**1c** gave the *title compound* as a colourless solid in 98% chemical yield and 88% ee. The enantiomeric excess was determined by ^{1}H NMR spectroscopy by conversion to the Mosher's ester using the method described above. δ_H (270 MHz; $CDCl_3$) 5.75 (0.94 H, m, 1-H) and 5.82 (0.06 H, m, 1-H).

(±)-2-(3-Furylmethylidene)cyclohexan-1-ol (±)-3d

Using the general procedure, reduction of **1d** gave the *title compound* as a colourless syrup in 94% yield (Found: M$^+$, 178.0990. $C_{11}H_{14}O_2$ requires 178.0994); ν_{max} (liquid film)/cm^{-1} 3385; δ_H (400 MHz; $CDCl_3$) 1.45–1.66 (5 H, m), 1.80–1.99 (2 H, m), 2.18 (1 H, M), 2.74 (1 H, m), 4.21 (1 H, m, C*H*OH), 6.21 (1 H, s, C=C*H*Ar), 6.42 (1 H, s, 3′-H) and 7.38–7.41 (2 H, m, 2′-H and 5′-H); δ_C (75.5 MHz; $CDCl_3$) 23.0 (CH_2), 27.0 (CH_2), 27.5 (CH_2), 36.4 (CH_2), 73.7 (CH), 110.8 (CH), 111.2 (CH), 121.8 (CH), 140.6 (CH), 142.6 (CH) and 143.9 (CH).

(1*R*)-2-(3-Furylmethylidene)cyclohexan-1-ol (1*R*)-3d

Using the general procedure, reduction of (*E*)-**1d** gave the *title compound* as a colourless oil in 81% chemical yield and 87% ee. The enantiomeric excess was determined by ^{1}H NMR spectroscopy by conversion to the Mosher's ester using the method described above. δ_H (270 MHz; $CDCl_3$) 6.12 (0.94 H, s, C=C*H*Ar), 6.25 (0.06 H, s, C=C*H*Ar), 6.36 (0.93 H, m, 4′-H) and 6.42 (0.07 H, m, 4′-H).

(±)-2-[(Ethoxycarbonyl)methylidene]cyclohexan-1-ol (1*R*)-3e[28]

Using the general procedure, reduction of **1e** gave the *title compound* as a colourless oil in 57% yield; δ_H (270 MHz; $CDCl_3$) 1.20 (3 H, t, *J* 7) and 1.42–2.20 (8 H, m), 3.65 (1 H, m), 4.15 (4 H, m) and 5.95 (1 H, br s, 1-H).

(1*R)-2-[(Ethoxycarbonyl)methylidene]cyclohexan-1-ol (1*R**)-(*E*)-3e**

Using the general procedure, reduction of (*E*)-**1e** gave the *title compound* as a colourless oil in 76% chemical yield and >95% ee. The enantiomeric excess was determined by ^{1}H NMR spectroscopy by conversion to the Mosher's ester using the method described above. δ_H (270 MHz; $CDCl_3$) 5.80 (1 H, s, C=C*H*CO$_2$Et) (the signal associated with the other enantiomer of **3e** appeared at 5.60 ppm but was not detected).

(1*R*,*E*)-2-Benzylidenecyclohexan-1-ol (1*R*,*E*)-5

Using the general procedure, reduction of (*E*)-**4** gave the *title compound* as a colourless crystalline solid in 76% chemical yield and in 96% ee. (*E*)-**5** $[\alpha]_D^{22}$ +35.8 (*c* 1.2, $CHCl_3$), (1*S*)-isomer lit.,[16a] $[\alpha]_D^{22}$ −35.2 (*c* 1.2, $CHCl_3$). Retention times: major enantiomer 5.93 min (98.2% area); minor enantiomer 7.45 min (1.8% area); δ_H (270 MHz; $CDCl_3$) 1.40–2.16 (8 H, m, 4 × CH_2), 2.71 (1 H, m, OH), 4.23 (1 H, m, 1-H), 6.52 (1 H, s, C=C*H*Ar) and 7.17–7.34 (5 H, m, Ar).

(1*R*,*Z*)-2-Benzylidenecyclohexan-1-ol (1*R*,*Z*)-5

Using the general procedure, reduction of (*Z*)-**4** gave the *title compound* as a colourless crystalline solid in 71% yield and in 8% ee. Retention times: minor enantiomer 5.71 min (45.7% area); major enantiomer 6.91 min (53.4% area); δ_H (270 MHz; $CDCl_3$) 1.36–1.57 (4 H, m), 1.78–1.95 (3 H, m), 2.18 (1 H, m), 2.61 (1 H, tdd, *J* 16, 6 and 2), 4.83 (1 H, s, C*H*OH), 6.35 (1 H, s, C=C*H*Ar) and 7.20–7.35 (5 H, m, Ar). The racemic alcohol has been described and is prepared by photoisomerisation of (*E*)-**5**.[29]

(1*R*,*E*)-2-Benzylidenecyclopentan-1-ol (1*R*,*E*)-8

Using the general procedure, reduction of (*E*)-**7** gave the *title compound* as a colourless crystalline solid in 67% yield and 92% ee. Retention times (95% hexane–5% propan-2-ol): major enantiomer 13.01 min (95.8% area); minor enantiomer 14.63 min (4.2% area); δ_H (270 MHz; $CDCl_3$) 1.58–2.04 (5 H, m), 2.50–2.80 (2 H, m), 4.58 (1 H, m, 1-H), 6.57 (1 H, q, *J* 2.5, C=C*H*Ar) and 7.15–7.40 (5 H, m, Ar). The racemic alcohol has been described.[30]

(1*R*,*Z*)-2-Benzylidenecyclopentan-1-ol (1*R*,*Z*)-8

Using the general procedure, reduction of (*Z*)-**7** gave the *title compound* as a pale yellow oil in 72% yield and 73% ee. Retention times (95% hexane–5% propan-2-ol): major enantiomer 8.25 min (86.7% area); minor enantiomer 9.11 min (13.3% area); δ_H (270 MHz; $CDCl_3$) 1.58–2.0 (5 H, m), 2.37–2.76 (2 H, m), 4.87 (1 H, m, C*H*OH), 6.49 (1 H, s, C=C*H*Ar) and 7.20–7.50 (5 H, m, Ar). The racemic alcohol has been described.[31]

General procedure for hydrogenation of allylic alcohols

To a solution of the allylic alcohol (0.15 mmol) in EtOH (5 cm^3) was added a catalytic amount of 10% palladium on carbon and the reaction vessel was evacuated and purged with hydrogen (balloon) several times. After stirring for 18 h under an atmosphere of hydrogen, the reaction mixture was filtered through a short pad of Celite and the residue washed with EtOH (5 × 10 cm^3). The filtrate was concentrated *in vacuo* and purified by flash column chromatography (petroleum ether–EtOAc) to afford the reduced secondary alcohol.

cis- and *trans*-(±)-2-Benzylcyclohexanol (±)-6

Method A. Reduction of (±)-(*E*)-2-benzylidenecyclohexan-1-ol **5** using the general procedure, followed by flash column chromatography (hexane–EtOAc) gave (i) (±)-*cis*-2-benzylcyclohexan-1-ol *cis*-**6** in 36% yield as a colourless crystalline solid, mp 68–69 °C (from hexane) (lit.,[16b] 67–70 °C). Retention times for the enantiomers (Chiralcel OD, 95%, hexane–55% propan-2-ol) 6.28 min and 8.71 min; δ_H (270 MHz; $CDCl_3$) 1.15–1.80 (10 H, m, 4 × CH_2, OH and 2-H), 2.55 (1 H, dd, *J* 12.5 and 7.5, C*H*Ar), 2.70 (1 H, d d, *J* 12.5 and 7.5, C*H*Ar), 3.8 (1 H, br s, C*H*OH) and 7.16–7.32 (5 H, m, Ar).

Continued elution gave (ii) (±)-*trans*-2-benzylcyclohexan-1-ol *trans*-**6** in 25% yield as a colourless crystalline solid, mp 45–47 °C (from hexane) (lit.,[16b] 46–48 °C); δ_H (270 MHz; $CDCl_3$) 0.85–2.02 (10 H, m, 4 × CH_2, OH and 2-H), 2.35 (1 H, dd, *J* 14 and 8, C*H*Ar), 3.18 (1 H, dd, *J* 14 and 4, C*H*Ar), 3.30 (1 H, m, C*H*OH) and 7.15–7.33 (5 H, m, Ar).

Method B. Reduction of (±)-(*Z*)-2-benzylidenecyclohexan-1-ol (±)-(*Z*)-**5** using the general procedure, followed by flash column chromatography gave: (i) *cis*-(±)-2-benzylcyclohexan-1-ol *cis*-**6** in 28% yield and (ii) *trans*-(±)-2-benzylcyclohexan-1-ol *trans*-**6** in 26% yield. Both compounds were identical (^{1}H NMR and HPLC characteristics) to that obtained from the (*E*)-isomer.

Reduction of (1*R*,*E*)-2-benzylidenecyclohexan-1-ol (1*R*,*E*)-5

Reduction of (1*R*,*E*)-2-benzylidenecyclohexan-1-ol (1*R*,*E*)-**5** (with 96% ee) was carried out using the general procedure. Following isolation of the *cis*-isomer, HPLC analysis demonstrated that the *cis*-**6** was obtained in 96% ee.

Reduction of (1*R*,*Z*)-2-benzylidenecyclohexan-1-ol (1*R*,*Z*)-5

Reduction of (1*R*,*Z*)-2-benzylidenecyclohexan-1-ol (1*R*,*Z*)-**5** (with 8% ee) was carried out using the general procedure. Following isolation of the *cis*-isomer, HPLC analysis demonstrated that the *cis*-**6** was obtained in 10% ee.

cis- and *trans*-(±)-2-Benzylcyclopentanol (±)-9[16b]

Method A. Reduction of (±)-(*E*)-2-benzylidenecyclopentan-1-ol (±)-(*E*)-**8** using the general procedure, followed by flash column chromatography (petroleum ether–EtOAc) gave (i) *cis*-(±)-2-benzylcyclopentan-1-ol *cis*-**9** in <5% yield as a colourless oil. δ_H (270 MHz; $CDCl_3$) 1.22–2.1 (8 H, m, 3 × CH_2, OH and 2-H), 2.55 (1 H, dd, *J* 10 and 6, C*H*Ar), 2.76 (1 H, dd, *J* 10 and 6, C*H*Ar), 3.91 (1 H, m, C*H*OH) and 7.18–7.32 (5 H, m, Ar).

Continued elution gave (ii) *trans*-(±)-2-benzylcyclopentan-1-ol *trans*-**9** in 20% yield as a colourless oil. Retention times for both enantiomers (Chiralcel OD, 95% hexane–5% propan-2-ol) 6.07 min and 9.81 min; δ_H (270 MHz; $CDCl_3$) 1.2–2.1 (8 H, m, 3 × CH_2, OH and 2-H), 2.68 (1 H, dd, *J* 14 and 8, C*H*Ar), 2.85 (1 H, dd, *J* 14 and 8, C*H*Ar), 4.08 (1 H, m, C*H*OH) and 7.15–7.35 (5 H, m, Ar).

Method B. Reduction of (±)-(*Z*)-2-benzylidenecyclopentan-1-ol (±)-(*Z*)-**8** using the general procedure, followed by flash column chromatography gave (i) *cis*-(±)-2-benzylcyclopentan-1-ol *cis*-**9** in < 5% yield and (ii) *trans*-(±)-2-benzylcyclopentan-1-ol *trans*-**9** in 40% yield which was identical (^{1}H NMR and HPLC characteristics) to that obtained from the (*E*)-isomer.

Reduction of (1*R*,*E*)-2-benzylidenecyclopentan-1-ol (1*R*,*E*)-8

Reduction of (1*R*,*E*)-2-benzylidenecyclopentan-1-ol (*E*)-**8** (with 92% ee) was carried out using the general procedure. Following isolation of *trans*-**9**, HPLC analysis demonstrated that the *trans* compound was obtained in 83% ee.

Reduction of (1*R*,*Z*)-2-benzylidenecyclopentan-1-ol (1*R*,*Z*)-8

Reduction of (1*R*,*Z*)-2-benzylidenecyclopentan-1-ol (*Z*)-**8** (with 73% ee) was carried out using the general procedure. Following isolation of the *trans*-**9**, HPLC analysis demonstrated that the *trans* compound was obtained in 69% ee.

(1*R*,*E*)-(2-Benzylidenecyclopentan-1-yl) *N*-[(*S*)-1-(phenylethyl)]-carbamate 10

A solution of alcohol (*E*)-**8** (50 mg, 0.29 mmol, 92% ee) in CH_2Cl_2 (1 cm^3) was treated with DMAP (a few crystals) followed by (*S*)-α-methylbenzyl isocyanate (45 mm^3, 0.32 mmol). The solution was allowed to stand for 20 h, and water (10 cm^3) was added. The mixture was extracted with CH_2Cl_2 (3 × 10 cm^3) and the combined extracts were washed with water, followed by brine and then dried (Na_2SO_4). Removal of solvent followed by chromatography (EtOAc–hexanes) gave *carbamate* **10** (90 mg, 96%) as a colourless solid (Found: *M* 321.1730. $C_{21}H_{23}NO_2$ requires *M*, 321.1728); ν_{max} ($CHCl_3$)/cm^{-1} 3440, 1717; δ_H (300 MHz; $CDCl_3$) 1.48 (3 H, d, *J* 7), 1.51–2.10 (4 H, m), 2.50–2.75 (2 H, m), 4.87 (1 H, m), 4.98 (1 H, br s), 5.55 (1 H, m), 6.58 (1 H, br s) and 7.20–7.40 (10 H, m) (broadening/poor resolution of most signals was observed); δ_C (75.5 MHz; $CDCl_3$) 22.6 (CH_3)*, 23.3 (CH_2), 29.6 (CH_2), 32.5 (CH_2), 51.0 (CH)*, 79.8 (CH)*, 126.0 (CH), 126.1 (CH), 126.8 (CH), 127.3 (CH), 128.3 (CH), 128.6 (CH), 128.7 (CH), 137.7 (C), 143.3 (C), 143.6 (C)* and 155.8 (C) (* these signals were broadened).

Crystals suitable for X-ray crystallographic analysis were obtained by recrystallisation from MeOH–H_2O.

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