PERKIN 1

Asymmetric α-substitution *versus* aza Diels–Alder reaction of electron deficient *N*-sulfonyl imines

Paul E. Morgan,[a] Ray McCague[b] and Andrew Whiting *[a]

[a] *Department of Chemistry, Faraday Building, U.M.I.S.T., P.O. Box 88, Manchester, UK M60 1QD*
[b] *ChiroTech Ltd., Cambridge Science Park, Milton Road, Cambridge, UK CB4 4WE*

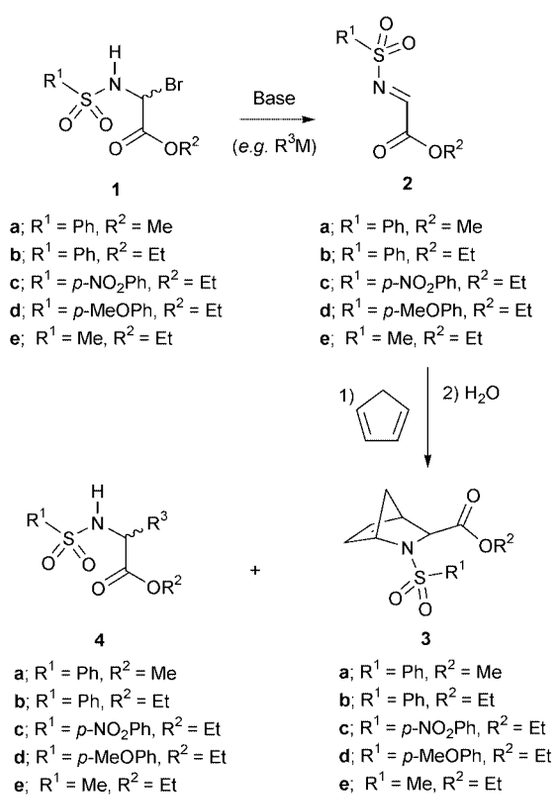
Received (in Cambridge, UK) 17th November 1999, Accepted 8th December 1999

Several *N*-arylsulfonylglycine esters have been brominated under photolytic conditions to provide the corresponding α-bromoglycine. These bromo esters can be treated with a range of bases to generate *N*-sulfonyl imino esters *in situ*; attempts to isolate the imines in a pure state were universally unsuccessful. Once generated, the imines can be trapped with cyclopentadiene to provide the corresponding aza Diels–Alder adducts in varying yields, depending upon the base used. In addition, if organometallic bases were employed (alkyllithiums and alkylaluminium reagents), not only were aza Diels–Alder adducts formed, but addition to the imine was also observed. In the case of organoaluminium reagents, imine addition was the major product. This process could be transformed into a stoichiometric asymmetric version, by generating a chiral aluminium reagent *in situ* to form a trialkyl (or trialkoxy) aluminium reagent, which when reacted with an *N*-sulfonyl bromoglycinate resulted in 19 to 62% enantiomeric excess of the corresponding substituted glycinate product.

Introduction

The asymmetric synthesis of α-amino acids has been the focus of considerable synthetic endeavour for many years and has relied upon methods such as an asymmetric Strecker reaction, asymmetric alkylation of glycinate derivatives, asymmetric amination of chiral enolates and asymmetric hydrogenation.[1] Amongst the various methods, the asymmetric addition of nucleophiles to an imine double bond[2] is important for accessing acyclic amino acid derivatives, while cyclic amino acid derivatives may also be derived from the cycloaddition of a diene to an imine, *i.e.* an aza Diels–Alder reaction.[3]

During studies related to the development of new methods for catalysing asymmetric aza Diels–Alder reactions to derive chiral synthons for the preparation of cyclic amino acid derivatives,[4] we examined the use of various methods for the generation of electron deficient imines, including imine **2**, which can be prepared *via* elimination of HBr from α-bromoglycinate **1**[5] (Scheme 1). Of many methods investigated for the efficient generation of imine **2**, organometallic reagents (RM, Scheme 1) were employed. However, not only were Diels–Alder adducts **3** isolated, but often α-substitution products **4** were also isolated.[6] In this paper, we discuss the full details of this investigation and its application to the asymmetric synthesis of *N*-sulfonyl α-amino acid derivatives.



Scheme 1

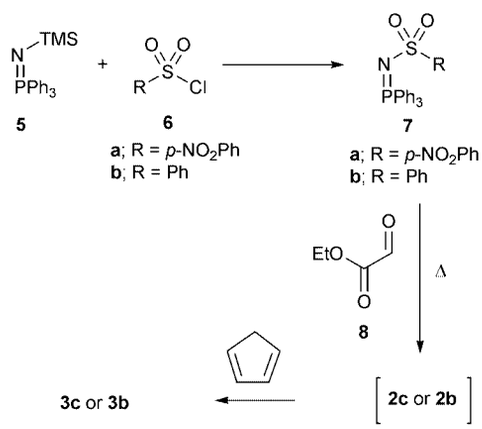
Results and discussion

In order to develop new asymmetric Lewis-acid catalysed entries to adducts of type **3**, we wished to generate imines of type **2** in a pure form and free from metal ligating by-products. We therefore extensively examined methods for the unambiguous formation of *N*-sulfonyl imines **2**. It has been reported that condensation of an aldehyde with a sulfonamide results in the formation of an *N*-sulfonyl imine,[7] however, we were unable to isolate the extremely moisture sensitive imine **2b** under the reported conditions. Additionally, attempted *in situ* trapping of the imine with cyclopentadiene to yield the cycloadduct **3b** resulted in low conversions (<23% yield). Similarly, using the isocyanate method of Holmes,[8] we were unable to cleanly isolate the sulfonyl imine **2d** in a pure state. An alternative solution to the clean generation of *N*-sulfonyl imines **2** was postulated using similar methods to those used by Jung and co-workers for the preparation of *N*-acyl imines, *i.e. via* an aza-Wittig reaction.[9] It was envisaged that use of a sulfonyl chloride **6** with ylide **5**, would provide the corresponding sulfonyl imine **2** (Scheme 2) after the aza-Wittig reaction.

Treatment of the *N*-trimethylsilylphosphinamide **5** with 4-nitrobenzenesulfonyl chloride **6a** gave the corresponding phosphorus ylide **7a** in high yield. In contrast, the reaction

DDOI: 10.1039/a909116e

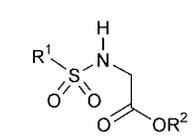
with benzenesulfonyl chloride **6b** gave very poor yields (<25%) of the corresponding phosphinamide **7b**, due to the lack of reactivity of the sulfonyl chloride. However, addition of sodium fluoride and a catalytic amount of 18-crown-6 to the reaction mixture in refluxing toluene effected clean generation of **7b** in 75% yield. The resulting *N*-sulfonylphosphinamides **7** were column stable and readily handled in air. The ensuing aza-Wittig reactions of ylides **7** proved less reactive than their acyl imine counterparts, reported by Jung and co-workers.[9] The reaction of either of the *N*-sulfonylphosphinamides **7** with ethyl glyoxylate **8** in refluxing toluene failed to yield the corresponding imines **2** in a quantitative manner (Scheme 2) and



Scheme 2

subsequent *in-situ* reaction with cyclopentadiene to yield the cycloadducts **3** resulted in low (*ca.* 5–25%) yields.

Having been unable to generate *N*-sulfonyl imines **2** in high yield and purity, an alternative method was examined based on work reported independently by Prato[5a] and Holmes,[5b] as summarised in Scheme 1, *i.e.* using a base mediated elimination of HBr from a bromoglycinate **1**. In order to probe the reactivity of *N*-sulfonyl imines generated by this method, a variety of *N*-sulfonyl glycine systems **9**[10] were prepared by reaction of the glycine ester with the corresponding sulfonyl chloride.[11] Subsequent photobromination of glycines **9** [eqn. (1)] produced the



a; R^1 = Ph, R^2 = Me
b; R^1 = Ph, R^2 = Et
c R^1 = *p*-NO_2Ph, R^2 = Et
d; R^1 = *p*-MeOPh, R^2 = Et
e; R^1 = Me, R^2 = Et
f; R^1 = Ph, R^2 = ^{t}Bu

Br_2, *hν*, Δ
CCl_4

1 (1)

a; R^1 = Ph, R^2 = Me 96 %
b; R^1 = Ph, R^2 = Et 95 %
c R^1 = *p*-NO_2Ph, R^2 = Et 92 %
d; R^1 = *p*-MeOPh, R^2 = Et 56 %
e; R^1 = Me, R^2 = Et 100 %

corresponding bromides **1** in reasonably pure form by direct crystallisation from the reaction mixture. The only exception being *tert*-butyl ester **9f**; exposure to the bromination conditions caused cleavage of the *tert*-butyl ester.

The highly hydrolytically unstable bromoglycinates **1** all appeared similar with respect to the sulfonamide and methine hydrogen resonances by ^{1}H NMR, with the exception of *p*-nitrophenylsulfonyl derivative **1c**, which exhibited a separation of 0.55 ppm between the NH and CH resonances. This compares with 0.05 ppm for the remaining bromine derivative **1**. Significantly, some batches of bromo compounds **1a**, **1b** and **1d**–**1e** showed coalescence of the NH and CH resonances, which strongly suggests proton exchange on the NMR time-scale, presumably catalysed by traces of HBr. This was not, however, observed for the 4-nitrophenylsulfonyl derivative **1c**, where the NH and CH signals were always distinct at δ 6.15 and 6.70.

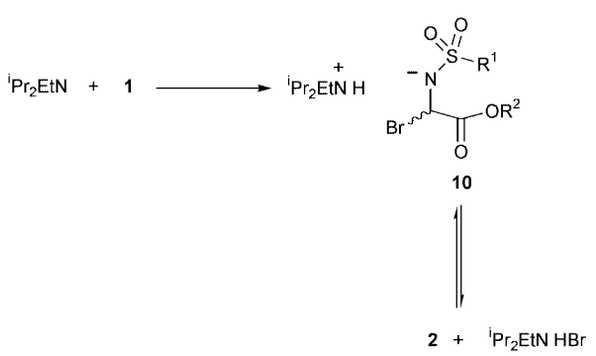
Having prepared a range of α-bromoglycinates **1**, suitable conditions for generation of the corresponding imines were examined. Of particular interest was the use of bases which would induce clean elimination of HBr without producing by-products which might inhibit the use of Lewis-acid catalysts. Consequently, metal alkyl-type bases were employed, since they offer the potential of producing a metal bromide and a neutral species, *e.g.* an alkane. Thus the α-bromoglycinates were screened against a variety of bases and solvents to determine the best conditions for generation of imines **2** (Scheme 1). Due to the hydrolytic sensitivity of imines **2**, the efficiency of the imine generation was determined by *in situ* trapping with cyclopentadiene as before. The results of this exercise are summarised in Table 1.

From observation of Table 1, it is apparent that the imines **2** were not generated in quantitative yields under most of the conditions examined. The most efficient production of aza Diels–Alder adduct **3** was obtained by using Hünig's base; use of lithium bases resulted in competing bromide substitution to provide the α-substituted products **4**, *via* imine generation and alkyllithium addition to the resulting C=N bond (Scheme 1). Additionally, different aryl substituents failed to have a profound effect on the generation of the imines **2**. Since the nitro group is a potent electron withdrawing group, it should cause an increase in the acidity of the sulfonyl NH of the bromoglycinate **1c** and should be more rapidly deprotonated under basic conditions. However, the resulting imine **2c** will be more electrophilic than unsubstituted systems and could result in increased α-substitution if the alkylating agent is still present in solution, rather than cycloaddition. Examination of the yields of the cycloadduct **3c** (Table 1) shows that there is little change in the ratio of α-substitution reaction *versus* cycloaddition. Thus the overall effect of the arylsulfonamide seems to be that despite increased acidity of the NH function by addition of an electron withdrawing group, the sensitivity of the resulting imine towards addition compensates, resulting in little change in product distribution. This point is reinforced by examination of different aryl substituents. Although the methoxy group of **1d**, being electron donating, should cause a decrease in the acidity of the NH, which by ^{1}H NMR shows its virtual coincidence with the α-CH, there is again no substantial change in product distribution. The degree of conversion of the bromoglycinate **1d** to the cycloadduct **3d** (Table 1) differs to a minor extent compared to the α-substituted product, with overall increased yields and a slight improvement in the ratio of the Diels–Alder cycloadduct to the α-substituted product. For final comparison, the effects of the arylsulfonyl substituent were compared with an *N*-methylsulfonyl substituent, *i.e.* **1e**. As before, the yield of the cycloadduct **3e** was again compromised by competing α-substitution products **4e** and the yields and product distribution were very similar to those obtained for the arylsulfonyl systems.

Since the amine bases efficiently produced the cycloadduct **3**, attempts were made to remove the ammonium hydrobromide salt from the reaction mixture by filtration of the precipitate from the reaction of bromide **1b** with Hünig's base (compare with entry 10, Table 1). However, subsequent addition of cyclopentadiene to the presumed intermediate imine **2b**, produced a fall in the yield of the subsequent Diels–Alder reaction to 56% from 95%. This may be attributed to the imine **2b** being insoluble and being removed with the amine hydrobromide salt, however, mass spectral data of the precipitate showed no evidence for this. Alternatively, the imine **2a** may exist in equilibrium with the ammonium sulfonamide salt **10** (Scheme 3) which is likely to be insoluble and hence be removed by filtration, thus lowering the yield of the subsequent Diels–Alder reaction.

Table 1 Conversion of bromides **1** to cycloadducts **3** *versus* addition products **4**

Entry	α-Bromo-glycinate	Base (equiv.)	Solvent	Temp./ °C	Time/ min	Yield **3** (%)	Yield **4** (%)
1	**1a**	Et_3N (1)	C_7H_8	RT	60	76	n/a
2	**1a**	$^iPr_2NEt$ (1)	C_7H_8	0	60	92	n/a
3	**1a**	DBU (1)	CH_2Cl_2	0	60	0	n/a
4	**1a**	^{n}BuLi (1)	C_7H_8	0	30	15	30
5	**1a**	^{n}BuLi (1)	C_7H_8	0	60	18	25
6	**1a**	MeLi (1)	C_7H_8	0	30	27	12
7	**1a**	MeLi (1)	C_7H_8	0	60	26	15
8	**1b**	Et_3N (3)	CH_2Cl_2	RT	10	22	n/a
9	**1b**	Et_3N (3)	C_7H_8	0	60	80	n/a
10	**1b**	$^iPr_2NEt$ (1)	C_7H_8	0	60	95	n/a
11	**1b**	DBU (1)	CH_2Cl_2	0	60	5	n/a
12	**1b**	^{n}BuLi (1)	C_7H_8	0	10	12	32
13	**1b**	^{n}BuLi (1)	C_7H_8	0	60	5	27
14	**1b**	^{n}BuLi (1)	C_7H_8	−78	60	5	47
15	**1b**	MeLi (1)	C_7H_8	0	30	38	12
16	**1b**	MeLi (1)	C_7H_8	0	60	42	13
17	**1b**	MeLi (1)	CH_2Cl_2	0	30	38	12
18	**1b**	LiHMDS (1)	C_7H_8	0	30	0	0
19	**1b**	^{t}BuLi (1)	C_7H_8	0	30	15	5
20	**1c**	Et_3N (1)	C_7H_8	0	60	72	n/a
21	**1c**	$^iPr_2NEt$ (1)	C_7H_8	0	60	96	n/a
22	**1c**	DBU (1)	CH_2Cl_2	0	60	0	n/a
23	**1c**	^{n}BuLi (1)	C_7H_8	0	30	20	27
24	**1c**	^{n}BuLi (1)	C_7H_8	0	60	17	25
25	**1c**	MeLi (1)	C_7H_8	−78	30	10	18
26	**1c**	MeLi (1)	C_7H_8	0	60	10	22
27	**1d**	Et_3N (1)	C_7H_8	RT	60	65	n/a
28	**1d**	$^iPr_2NEt$ (1)	C_7H_8	0	60	98	n/a
29	**1d**	DBU (1)	CH_2Cl_2	0	60	0	n/a
30	**1d**	^{n}BuLi (1)	C_7H_8	0	30	5	35
31	**1d**	^{n}BuLi (1)	C_7H_8	0	60	13	37
32	**1d**	MeLi (1)	C_7H_8	0	30	22	28
33	**1d**	MeLi (1)	C_7H_8	0	60	28	32
34	**1e**	Et_3N (1)	C_7H_8	RT	60	74	n/a
35	**1e**	$^iPr_2NEt$ (1)	C_7H_8	0	60	98	n/a
36	**1e**	DBU (1)	CH_2Cl_2	0	60	0	n/a
37	**1e**	^{n}BuLi (1)	C_7H_8	0	30	12	22
38	**1e**	^{n}BuLi (1)	C_7H_8	0	60	15	37
39	**1e**	MeLi (1)	C_7H_8	−78	30	23	22
40	**1e**	MeLi (1)	C_7H_8	0	60	29	12



Scheme 3

Having achieved minimal success with respect to generation of the imines **2** in a pure state, attempts were made to examine the reaction by ^{1}H NMR. Attempts to generate imines **2** with alkyllithium bases in the ^{1}H NMR tube failed to yield any significant results. However, when Hünig's base was used in dry, degassed d-chloroform, a difference in the spectrum was observed upon addition of the base. Acquisition of the ^{1}H NMR spectrum immediately after addition of the base to **1b** showed a complex set of signals, with peaks corresponding to the base, bromoglycinate **1b** and a rather broad peak at 8.20 ppm. However, acquisition of the spectrum some thirty minutes later saw a shift in the broad peak from 8.20 to 7.20 ppm, and the appearance of three sharp singlets at 8.15, 8.20 and 9.10 ppm, with an integration ratio of 1 : 2 : 2 respectively. The results of these ^{1}H NMR experiments may be explained by the mechanism shown in Scheme 3, *i.e.* after initial abstraction of the acidic NH, the ensuing ammonium glycinate sulfonamide appears as a broad singlet at 8.20 ppm. After thirty minutes, the imine **2b** is generated, together with the hydrogen bromide salt of the amine base. The HBr salt of Hünig's base appears as the broad singlet at 7.20 ppm at this concentration, with the remaining two singlets corresponding to the imino CH resonances for the *E*- and *Z*-imines. Obviously, the more thermodynamically stable *E*-imine would be expected to predominate over the *Z*-imine, which explains the observed resonance ratio. Finally, the peak at δ 9.10 may well correspond to some aldehyde derived from hydrolysis of the imine.

Having considered the fact that electronic alterations to the α-bromoglycinates **1** produced minimal difference with respect to generation of the imines **2**, it was decided that removing the possibility of α-substitution would be the logical answer to the problem of the α-substitution reaction, while avoiding amine bases. Therefore, the use of hydride based reagents was considered. The *N*-phenylsulfonyl derived α-bromoglycinate **1b** was therefore treated with a range of metal hydrides, to determine if generation of the imine could be achieved in a quantitative manner. The results of this exercise are shown in Table 2 (entries 1–6).

It can be clearly seen from Table 2 (entries 1–6) that the cycloadduct **3b** was produced in an almost quantitative manner (except for entry 2), presumably with the imine **2b** being generated by a deprotonation–elimination sequence by the addition of hydride reagents. However, a similar observation

Table 2 Hydride-induced conversion of **1b** to cycloadduct **3b**

Entry	α-Bromo-glycinate	Base	Lewis acid	Solvent	Temp./ °C	Time/ min	Yield of **3b** (%)	Ee of **3b** (%)
1	**1b**	NaH	n/a	THF	0	10	95	n/a
2	**1b**	NaH[a]	n/a	THF	0	10	56	n/a
3	**1b**	DIBAL-H	n/a	THF	−78	10	98	n/a
4	**1b**	DIBAL-H/(*R*)-Binaphthol	n/a	THF	−78	10	96	0
5	**1b**	K-Selectride	n/a	THF	−78	10	97	n/a
6	**1b**	NaH	n/a	THF	−100	10	89	n/a
7	**1b**	NaH	$TiCl_4$/(*R*)-Binaphthol	CH_2Cl_2	−100	15	86	0
8	**1b**	NaH	$Ti(O^iPr)_2Cl_2$/(*R*)-Binaphthol	CH_2Cl_2	−100	15	92	0
9	**1b**	NaH	Et_2AlCl/(*R*)-Binaphthol	CH_2Cl_2	−100	15	94	0
10	**1b**	NaH	$Ln(OTf)_3$	CH_2Cl_2	−100	15	75	n/a

[a] Precipitate filtered before addition of the diene.

Table 3 Aluminium complex-mediated conversion of **1b** to alkylated products **4b**

Entry	α-Bromo-glycinate	Reagent	Temp./ °C	Product 1 **4b**, R^3 (Yield [%])	Ee (configuration)	Product 2 **4b**, R^3 (Yield [%])
1	**1b**	Me_3Al	−78	Me (55)	n/a	n/a
2	**1b**	Et_3Al	−78	Et (95)	n/a	n/a
3	**1b**	$(EtO)_3Al$	0	EtO (76)	n/a	n/a
4	**1b**	$(^iPrO)_3Al$	0	^{i}PrO (97)	n/a	n/a
5	**1b**	Et_2AlCl, ^{n}BuLi	0	^{n}Bu (30)	n/a	Et (21)
6	**1b**	Et_2AlCl, ^{t}BuLi	0	^{t}Bu (0)	n/a	Et (18)
7	**1b**	Me_3Al, (*R*)-binaphthol	−78	Me (55)	52 (*S*)	n/a
8	**1b**	Et_3Al, (*R*)-binaphthol	−78	Et (90)	62 (*S*)	n/a
9	**1b**		RT	Et (95)	55 (*S*)	n/a
10	**1b**	$(EtO)_3Al$, (*R*)-binaphthol	−78	EtO (69)	19	n/a
11	**1b**	$(^iPrO)_3Al$, (*R*)-binaphthol	RT	^{i}PrO (97)	25	n/a
12	**1b**	Et_2AlCl, ^{n}BuLi, (*R*)-binaphthol	RT	^{n}Bu (35)	0	Et (12)

to that found for imine **2b** generation with amine bases was noted, *i.e.* filtration of the precipitate formed immediately after addition of the base (NaH), caused a decrease in the yield of the cycloadduct **3b** formed after reaction with cyclopentadiene (entry 2, Table 2). This reduction in the yield (to 56%) can be explained in an analogous manner to that described earlier, whereby the initial abstraction of the acidic NH yields the partially insoluble intermediate sodium sulfonamide salt, which in turn may be in equilibrium with the imine **2b**. Hence, removal of the precipitate led to the reduction in the overall yield of the imine **2b** and consequently the cycloadduct **3b**.

In the case of the DIBAL-H (entry 3 and 4, Table 2) induced elimination of hydrogen bromide, the by-product of imine **2b** generation would presumably be diisobutylaluminium bromide, which could in turn act as a Lewis acid for the resulting Diels–Alder reaction. As a result, attempts to generate a chiral aluminium Lewis acid, after addition of the hydride reagent, were undertaken. This was carried out by addition of a stoichiometric quantity of (*R*)-binaphthol, (Table 2, entry 4) to the imine **2b**–diisobutylaluminium bromide mixture, in the hope that this would lead to enantioselection in the subsequent Diels–Alder reaction. Only racemic Diels–Alder cycloadduct **3b** was isolated however, whether in the presence or absence of molecular sieves, though yields were high.

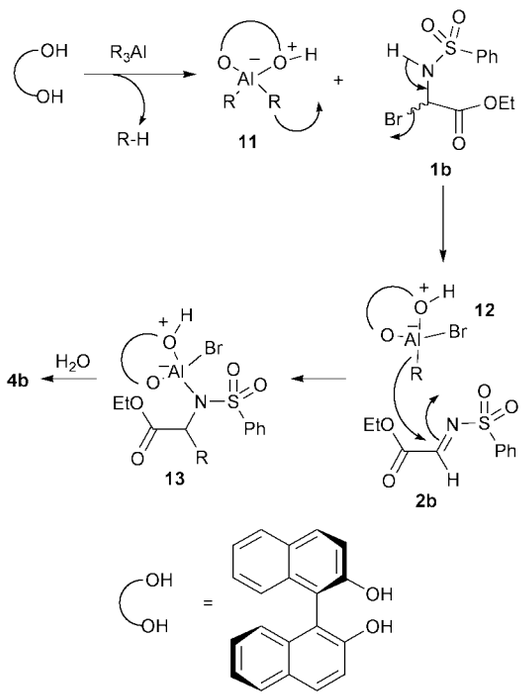
There is a fundamental question about whether it is actually possible to obtain asymmetric induction for the reaction of an imine of type **2** with cyclopentadiene to derive **3**. In order to probe the reactivity of imine **2b** in isolation, *i.e.* the thermal cycloaddition process, bromide **1b** was treated with sodium hydride at −100 °C (Table 2, entry 6) in the presence of cyclopentadiene. The reaction was complete in less than 10 minutes and produced an 89% yield of the cycloadduct **3b**. Clearly, this experiment shows the very high reactivity of imine **2b** under thermal conditions[12] and raises the likelihood that even if a chiral Lewis acid were added to the reaction, it may not result in sufficient imine activation to dominate the reaction outcome. Thus, asymmetric induction using the addition of an external Lewis acid catalyst to an imine **2** may be expected to be highly unlikely. Indeed, these conclusions seem to be supported by the results shown in Table 2, entries 7–9, where initial imine generation with sodium hydride was followed by complexation of the imine with a chiral Lewis acid, however, no asymmetric induction was obtained (chiral HPLC). In addition, using a lanthanide Lewis acid (Table 2, entry 10) after imine generation failed to produce identifiable differences in the thermal reaction.

A possible solution to this could be a slow generation of an imine **2**, using a Lewis acid to induce fragmentation of the bromide, followed by deprotonation. It would then be possible that the resulting Lewis acid complex, if closely associated with the imine **2**, may assist in producing asymmetric induction. We therefore began to examine the effect of adding aluminium-based Lewis acids to bromide **1b**, however it was immediately apparent from the first reaction attempted (Table 3, entry 2) that rather than obtaining the cycloadduct **3b**, only the α-substituted products **4b** were produced despite the presence of cyclopentadiene. Following an exploration of different achiral aluminium reagents (Table 3, entries 1–6), it was clear that such reagents produced efficient substitution products, except where attempts were made to generate *n*-butyl and *tert*-butyl aluminium reagents (entries 5 and 6). The asymmetric variant was therefore explored, whereby the trialkyl (or alkoxy) aluminium reagents were treated with (*R*)-binaphthol and subsequently added to the bromoglycinate **1b**. The results are shown in Table 3.

In order to generate an asymmetric version of the aluminium species, the trialkyl or trialkyloxy aluminium species was first treated with binaphthol. The resulting chiral reagent was then reacted with the bromide **1b**. In each case, the alkylaluminium complexes (*vide infra*) converted bromide **1b** through to the α-amino acid analogue **4b** with reasonable efficiency (Entries 7–9, Table 3) and with moderate enantioselectivity at −78 °C (52–62%). The ee was only marginally lowered by raising the tem-

perature to room temperature (entry 9, Table 3). Ee's for the alkoxy-derived reagents were much poorer (entries 10 and 11, Table 3), however, the fact that such compounds are highly hydrolytically sensitive means that any asymmetric induction is fortuitous. Finally, attempts to generate an asymmetric variant of the *n*-butylaluminium complex proved unrewarding, with only low yields of the ethyl derivative **4b** (R = Et) being obtained.

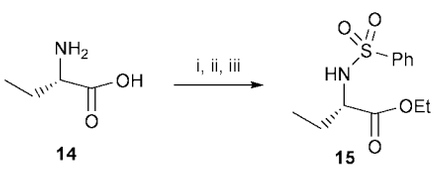
It is possible to propose a mechanism for the process which involves the initial formation of an aluminium complex **11** by reaction of the aluminium species with binaphthol (Scheme 4).



Scheme 4

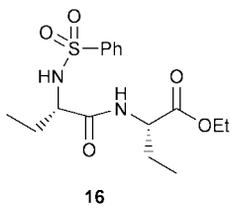
After formation of this aluminate, dehalogenation of **1b** could afford imine **2b** and the alkylaluminium bromide **12**, which in turn may act as a second Lewis acid. This complex may then deliver a second alkyl group to the imine **2b** to afford the α-substituted glycine derivative **4b**. Evidence for this mechanism has been obtained by treatment of the binaphthol with triethylaluminium, which produces only one molar equivalent of ethane gas. The resulting activated aluminium complex is therefore likely to be **11**. In order to derive the observed major enantiomeric products, attack of **12** [derived from (*R*)-binaphthol] on **2b** must occur from the *Si*-face. Examination of approximate molecular mechanics based models suggest that *Re*-face attack could be disfavoured due to steric repulsion between the sulfonyl oxygens of **2b** and the aluminium bromide function, whereas *Si*-face attack is less sterically congested.

In order to determine the ee of the products **4b**, chiral HPLC was used for the isopropoxy, ethoxy and ethyl derivatives. In the last case, the absolute configuration of the product was determined by comparison of the HPLC of the same derivative prepared from commercially available (*S*)-(+)-2-aminobutyric acid **14**, after a) formation of the acid chloride; b) esterification and c) subsequent sulfonylation (Scheme 5). Interestingly,

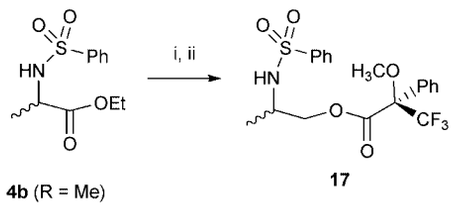


Scheme 5 i; $SOCl_2$, CH_2Cl_2. ii; EtOH. iii; $PhSO_2Cl$, CH_2Cl_2, Et_3N.

attempted formation of the ester using HCl–ethanol yielded predominately the amide **16** after sulfonylation.

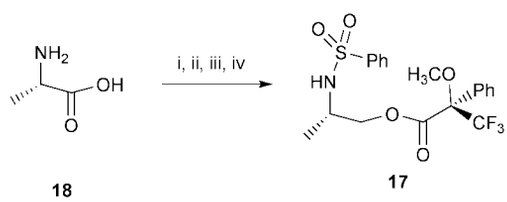


For the alanine analogue, *i.e.* **4b**, R = Me, (Table 3, entry 1), the ee was determined by reduction to the alcohol and conversion to the (+)-Mosher ester **17** (Scheme 6). The de was then



Scheme 6 i; $LiAlH_4$, Et_2O. ii; (+)-Mosher acid chloride, Et_3N.

determined by comparison of the methylene signals by ^1H NMR and was reinforced by ^{19}F NMR. The absolute configuration of this product was determined by the comparison with the ^1H NMR spectrum of the (+)-Mosher ester of the product derived from commercially available L-alanine, after esterification, sulfonylation, and reduction (Scheme 7) to the alcohol.



Scheme 7 i; HCl, EtOH, CH_2Cl_2. ii; $PhSO_2Cl$, Et_3N, CH_2Cl_2. iii; $LiAlH_4$, Et_2O. iv; (+)-Mosher acid chloride, Et_3N.

Summary

α-Bromoglycinates **1** are readily prepared by photobromination of the corresponding glycine. The ease of cycloaddition, *versus* nucleophilic addition, of the imine derivatives **2** depends entirely on the nucleophilicity *versus* basicity of the base system used. Imines of type **2** are highly electron deficient and are therefore difficult to isolate in a pure state using the bromoglycinate route, they can therefore react with dienes in the absence of other reactive nucleophiles. However, alkyl or alkyloxyaluminium based reagents are sufficiently nucleophilic to override cycloaddition processes and produce efficient α-substitution products **4b**. This process can be made asymmetric, but is stoichiometric in binaphthol and results in low to moderate asymmetric induction. Further developments of this work are underway to produce catalytic asymmetric variants of the imine substitution process.

Experimental

All reagents which were not prepared as detailed later were purchased from either Aldrich, Acrös Chimica, Avocado or Lancaster. Aryl- and alkyl-sulfonyl glycinates were prepared according to literature methods.[10,11] All commercial reagents were used without any further purification unless otherwise stated. Solvents were all distilled before use over either

benzophenone–sodium (THF) or calcium hydride (all remaining solvents) under an atmosphere of argon. TLC was performed on Merck plastic or aluminium sheets coated with silica gel 60 F_{254} (Art. 5735); the chromatograms were initially examined under UV light and then developed either with iodine vapour or a 10% ethanolic solution of molybdophosphoric acid and visualised by heating with a heat gun. Column chromatography was achieved under medium pressure, using Acrös Chimica silica gel, 0.035–0.07 nm (pore diameter: *ca*. 6 nm). All anhydrous, low temperature reactions were carried out in glassware which was dried prior to use by storage in a glass oven maintained at 140 °C and cooled under a stream of argon. Extractions were dried over magnesium sulfate. Evaporations were carried out using a Büchi rotary evaporator or Büchi cold-finger rotary evaporator, followed by drying *in vacuo*. Kugelröhr distillations were carried out using a Büchi GKR-51 Kugelröhr apparatus. Mps were determined using an Electrothermal melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 200 or 300 MHz on a Bruker AC200 or AC300 spectrometer. ^{13}C NMR spectra were recorded at 75.5 MHz on a Bruker AC300 spectrometer. ^{31}P NMR spectra were recorded at 81 MHz on a Bruker AC200 spectrometer. ^{1}H, ^{13}C and ^{31}P spectra were recorded using either $CDCl_3$ or DMSO as internal standards respectively. *J* Values are measured in Hz. IR spectra were recorded on a Perkin-Elmer 783 equipped with a PE600 data station or a Perkin-Elmer 1605 FT-IR, and UV spectra were recorded on a Perkin-Elmer l15 spectrometer. Electron impact (EI) (70 eV) and chemical ionisation (CI) spectra were recorded with a Kratos MS25. Fast atom bombardment (FAB) spectra were recorded on a Kratos MS50, using a *m*-nitrobenzylalcohol matrix and accurate mass determinations were carried out on a Kratos Concept IS spectrometer. Microanalyses were performed using a Carlo-Erba 1106 elemental analyser. Chiral HPLC was undertaken by the use of either a Chiralpak AD, OD or Chiracel OF chiral column with a Pye Unicam UV detector and pump. Optical rotations are given in 10^{-1} deg cm^2 g^{-1} and were performed on an Optical Activity AA-1000 polarimeter.

Preparation of triphenyl(*p*-nitrophenylsulfonylimino)-phosphorane 7a

p-Nitrobenzenesulfonyl chloride (0.634 g, 2.860 mmol) was added to a stirred slurry of triphenyl(trimethylsilylimino)phosphorane **5** (1.000 g, 2.860 mmol) in toluene (150 ml), heated to reflux under an atmosphere of argon. After heating for 24 h, the solution was evaporated to yield a brown solid (1.119 g). The solid was recrystallised from dichloromethane–hexane to yield **7a** as a pale brown solid (1.110 g, 90%): mp 147–149 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 1665 (s) N=P, 1527 (m) NO_2, 1377 (m) N–SO_2, 851 (w), 755 (w) and 722 (w); δ_H (300 MHz; $CDCl_3$) 7.41–7.80 (17H, m, ArH's), 8.05 (2H, d, *J* 10, ArH's); δ_C (300 MHz; $CDCl_3$) 123.4 (Ar), 127.2 (Ar, quat), 127.5 (Ar), 128.7 (Ar), 128.8 (Ar), 129.0 (Ar, quat), 132.0 (Ar), 132.9 (Ar, quat); δ_P (81 MHz; $CDCl_3$) 16.8; *m*/*z* (FAB) 463 (base peak, $M^+ + H$) [Found: *m*/*z* (FAB) 463.0882. Calc. for $C_{24}H_{20}N_2SO_4P$: *m*/*z,* 463.0881].

Preparation of triphenyl(phenylsulfonylimino)phosphorane 7b

Benzenesulfonyl chloride (0.505 g, 2.860 mmol) was added to a stirred slurry of triphenyl(trimethylsilylimino)phosphorane **5** (1.00 g, 2.86 mmol), sodium fluoride (0.120 g, 14.3 mmol) and 18-crown-6 (0.076 g, 0.286 mmol) in toluene (150 ml). The resulting solution was heated to reflux under argon. After heating for 24 h, the solution was evaporated to yield a brown solid (0.932 g). The solid was recrystallised from dichloromethane–hexane to yield **7b** as a pale brown solid (0.829 g, 75%): mp 137–139 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 1657 (s) N=P, 1362 (m) N–SO_2, 755 (w) and 723 (w); δ_H (300 MHz; $CDCl_3$) 7.39–7.78 (20H, m, ArH's); δ_C (75.5 MHz; $CDCl_3$) 123.4 (Ar), 125.7 (Ar, quat), 127.8 (Ar), 128.8 (Ar), 128.8 (Ar), 128.9 (Ar), 132.0 (Ar), 132.4 (Ar, quat); δ_P (81 MHz; $CDCl_3$) 16.7; *m*/*z* (FAB) 835 ($2M^+ + H$), 418 (base peak, $M^+ + H$) [Found: *m*/*z* (FAB) 418.1024. Calc. for $C_{24}H_{20}NSO_2P$: *m*/*z*, 418.1031].

Preparation of *N*,*N*-phthaloylglycine *tert*-butyl ester

A stirred mixture of toluene (150 ml), *tert*-butyl chloroacetate (24.39 g, 0.16 mol), potassium phthalimide (30.00 g, 0.16 mol) and hexadecyltributylphosphonium bromide (8.12 g, 16.00 mmol) was heated to reflux under argon. After 24 h, the cloudy solution was cooled, filtered and washed with diethyl ether. The combined organic filtrate was evaporated and chromatographed on silica gel (diethyl ether as eluant). The first fraction (1600 ml) was collected, washed with aqueous sodium hydroxide solution (1 M) and water, dried ($MgSO_4$) and evaporated to yield *N*,*N*-phthaloylglycine *tert*-butyl ester[11b] as a white solid (33.77 g, 81%): mp 90–92 °C (lit. 92–93 °C[11b]); ν_{max} (KBr disc)/cm^{-1} *inter alia* 1745 (s) C=O, 1710 (s) C=O, 1230 (m); δ_H (300 MHz; $CDCl_3$) 1.45 [9H, s, $C(CH_3)_3$], 4.30 (2H, s, CH_2), 7.70 (2H, m, ArH's), 7.90 (2H, m, ArH's); δ_C (75.5 MHz; $CDCl_3$) 27.8 [$C(CH_3)_3$], 39.5 (CH_2), 82.6 [$C(CH_3)_3$], 123.3 (Ar), 131.8 (Ar), 134.0 (Ar, quat), 166.1 and 167.4 (C=O, quat); *m*/*z* (FAB) 523 ($2M^+ + H$), 262 ($M^+ + H$), 206 (base peak, $M^+ - C_4H_7$) [Found: C, 64.1; H, 5.7; N, 5.1. Calc. for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.8; N, 5.4%].

Preparation of *N*-phenylsulfonylglycine *tert*-butyl ester 9f

Hydrazine monohydrate (2.30 g, 46.00 mmol) was added to a suspension of *N*,*N*-phthaloylglycine *tert*-butyl ester (12.00 g, 45.93 mmol) in ethanol (100 ml) with vigorous stirring. The solution was heated to reflux for 4 h, cooled and filtered. Benzenesulfonyl chloride (12.19 g, 69.00 mmol) was added to the resulting solution, followed by triethylamine (6.98 g, 69.00 mmol) in a dropwise manner. The mixture was stirred for 24 h before evaporation to yield a green solid. This solid was suspended in dichloromethane (100 ml), washed with water (100 ml), dried ($MgSO_4$) and evaporated. The residual solid was recrystallised from dichloromethane–hexane to yield the *N*-phenylsulfonylglycine *tert*-butyl ester[10c] **9f** as a white solid (11.78 g, 95%): mp 110–112 °C (lit. 117–117.5[10c]); ν_{max} (KBr disc)/cm^{-1} *inter alia* 3200 (m) NH, 2920 (m) CH_3, 1745 (s) C=O, 1240 (s) C–O, 760 and 690 (m); δ_H (300 MHz; $CDCl_3$) 1.45 [9H, s, $C(CH_3)_3$], 3.80 (2H, d, *J* 7.5, CH_2, collapses to a singlet upon addition of D_2O), 5.20 (1H, broad m, NH, disappears upon addition of D_2O), 7.65–7.69 (3H, m, ArH's), 8.00–8.05 (2H, m, ArH's); δ_C (75.5 MHz; $CDCl_3$) 27.9 [$C(CH_3)_3$], 44.9 (CH_2), 83.0 [$C(CH_3)_3$], 127.3 (Ar), 129.3 (Ar), 133.0 (Ar), 139.4 (Ar, quat), 167.9 (C=O, quat); *m*/*z* (FAB) 431 ($2M^+ - 2C_4H_7$), 272 ($M^+ + H$), 216 (base peak, $M^+ - C_4H_7$) [Found: C, 53.4; H, 6.1; N, 5.5; S, 12.2. Calc. for $C_{12}H_{17}NSO_4$: C, 53.1; H, 6.3; N, 5.2; S, 11.8%].

General procedure for bromination of *N*-sulfonylglycine esters 1

Bromine (1 eq.) was added to a slurry of the alkyl *N*-arylsulfonylglycinate **9** (1 eq.) in carbon tetrachloride under an atmosphere of argon. The mixture was irradiated with UV light (254 nm) while being heated under reflux for 2 h. After completion, the solvent was partially removed by distillation and the resulting suspended residue was cooled under a stream of argon to complete precipitation and left a brown suspended solid, which was filtered under argon and used without further purification. These solids could be stored *in vacuo* over phosphorus pentoxide for several months.

***N*-Phenylsulfonyl-α-bromoglycine methyl ester 1a.** Bromine (3.30 g, 41.00 mmol), *N*-phenylsulfonylglycine methyl ester **9a** (9.40 g, 41.00 mmol) and carbon tetrachloride (300 ml) according to the general procedure produced a brown solid **1a** (12.12 g, 96%): mp 79–81 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 3300 (s)

NH, 1740 (s) C=O, 1340 (s) C–O, 760 (m), 730 (m), 550 (m) C–Br; δ_H (300 MHz; $CDCl_3$) 4.19 (3H, s, OCH_3), 6.37 (2H, m, CH and NH), 7.61–7.81 (3H, m, ArH's), 8.07 (2H, d, *J* 10, ArH's); δ_C (75.5 MHz; $CDCl_3$) 53.5 (OCH_3), 53.8 (CHBr), 127.1 (Ar), 127.8 (Ar), 129.1 (Ar), 133.7 (Ar, quat), 165.9 (C=O, quat); *m*/*z* (FAB) 536 ($2M^+ - Br$), 228 (base peak, $M^+ - HBr$) [Found: C, 35.3; H, 3.9; N, 4.3; S, 10.1. Calc. for $C_9H_{10}NSO_4Br$: C, 35.1; H, 3.6; N, 4.6; S, 10.4%].

***N*-(*p*-Nitrophenylsulfonyl)-α-bromoglycine ethyl ester 1c.** Bromine (3.30 g, 41.00 mmol), *N*-*p*-nitrophenylsulfonylglycine ethyl ester **9c** (11.82 g, 41.00 mmol) and carbon tetrachloride (300 cm^3) according to the general procedure produced a brown solid **1c** (13.84 g, 92%): mp 89–91 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 3250 (m) NH, 2980 (m) CH_3, 1740 (s) C=O, 1330 (s) NO_2, 1240 (s) C–O, 850 (m) and 510 (m) C–Br; δ_H (300 MHz; $CDCl_3$) 1.30 (3H, t, *J* 7.5, C*H*$_3$CH$_2$O), 4.30 (2H, q, *J* 7.5, OC*H*$_2$CH$_3$), 6.15 (1H, d, *J* 10, CHBr), 6.70 (1H, d, *J* 10, NH), 8.15 (2H, d, *J* 10, ArH's), 8.40 (2H, d, *J* 10, ArH's); δ_C (75.5 MHz; $CDCl_3$) 13.9 (*C*H$_3$CH$_2$O), 53.3 (CHBr), 63.5 (CH$_3$*C*H$_2$O), 124.5 (Ar), 129.5 (Ar), 145.4 (Ar, quat), 150.4 (Ar, quat), 165.6 (C=O, quat); *m*/*z* (FAB) 573 ($2M^+ - Br$), 287 (base peak, $M^+ - Br$) [Found: C, 34.0; H, 3.2; N, 7.9; S, 8.8. Calc. for $C_{10}H_{11}N_2SO_6Br$: C, 32.7; H, 3.0; N, 7.6; S, 8.7%].

***N*-(*p*-Methoxyphenylsulfonyl)-α-bromoglycine ethyl ester 1d.** Bromine (3.30 g, 41.00 mmol), *N*-(*p*-methoxyphenylsulfonyl)-glycine ethyl ester **9d** (11.20 g, 41.00 mmol) and carbon tetrachloride (300 ml) according to the general procedure gave a yellow solid **1d** (8.10 g, 56%): mp 106–108 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 3220 (s) NH, 1740 (s) C=O, 1350 (m) C–O, 840 (m) and 490 (m) C–Br; δ_H (300 MHz; $CDCl_3$) 1.30 (3H, t, *J* 7.5, C*H*$_3$CH$_2$O), 3.85 (3H, s, OCH_3), 4.25 (2H, q, *J* 7.5, OC*H*$_2$CH$_3$), 6.15 (2H, m, NH and CH), 7.00 (2H, d, *J* 10, ArH's), 7.85 (2H, d, *J* 10, ArH's); δ_C (75.5 MHz; $CDCl_3$) 13.6 (*C*H$_3$CH$_2$O), 54.5 (CHBr), 55.5 (OCH_3), 63.2 (O*C*H$_2$CH$_3$), 114.0 (Ar), 114.2 (Ar), 114.3 (Ar), 129.2 (Ar), 129.7 (Ar, quat), 130.1 (Ar, quat), 163.7 (C=O, quat); *m*/*z* (FAB) 543 ($2M^+ - Br$), 272 ($M^+ - Br$), 171 (base peak, $M^+ - C_4H_6NO_2Br$) [Found: C, 37.8; H, 4.3; N, 4.3; S, 8.9. Calc. for $C_{11}H_{14}NSO_5Br$: C, 37.5; H, 4.0; N, 4.0; S, 9.1%].

***N*-Methylsulfonyl-α-bromoglycine ethyl ester 1e.** Bromine (3.30 g, 41.00 mmol), *N*-methylsulfonylglycine ethyl ester **9e** (7.43 g, 41.00 mmol) and carbon tetrachloride (300 ml) according to the general procedure gave a yellow solid **1e** (10.66 g, 100%): mp 108–110 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 3260 (m) NH, 1730 (s) C=O, 1340 (s) C–O and 500 (m) C–Br; δ_H (300 MHz; $CDCl_3$) 1.35 (3H, t, *J* 7.5, OCH$_2$C*H*$_3$), 3.15 (3H, s, SO_2CH_3), 4.30 (2H, q, *J* 7.5, OC*H*$_2$CH$_3$), 6.25 (2H, m, NH and CH); δ_C (75.5 MHz; $CDCl_3$) 13.6 (*C*H$_3$CH$_2$O), 41.9 (SO_2CH_3), 54.8 (CHBr), 63.3 (CH$_3$*C*H$_2$O), 165.5 (C=O, quat); *m*/*z* (FAB) 359 ($2M^+ - Br$), 180 ($M^+ - Br$) [Found: C, 24.4; H, 4.3; N, 6.2; S, 13.2. Calc. for $C_5H_{10}NSO_4Br$: C, 23.0; H, 3.9; N, 5.4; S, 12.3%].

General procedure for the preparation of cyclopentadiene cycloadducts 3 and α-substituted products 4

Base (1 eq.) was added to a stirred solution of the *N*-sulfonyl-α-bromoglycine **1** (1 eq.) in toluene (or other solvent as specified below) at 0 °C. After 30 min cyclopentadiene (2 eq.) was added and the mixture allowed to stir for 60 min. Water was added, the layers separated and the organic layer extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and evaporated to yield an orange oil. This oil was chromatographed on silica gel (ethyl acetate–hexanes (1 : 9) as eluant) to yield the cycloadducts **3**.

Cyclopentadiene cycloadduct 3a. Triethylamine (0.216 ml, 1.552 mmol), *N*-phenylsulfonyl-α-bromoglycine methyl ester **1a** (0.403 g, 1.552 mmol), toluene (40 ml) and cyclopentadiene (0.256 ml, 3.104 mmol) according to the general procedure gave a viscous orange oil (0.398 g) which was chromatographed to yield the cycloadduct **3a** (0.346 g, 76%) as a white solid: mp 64–65 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 1760 (m) C=O, 1220 (m) C–O, 745 and 692 (m) and 606 (s) C=C (*cis*); δ_H (300 MHz; $CDCl_3$) 1.73 (2H, ABq, *J* 9, septet, 115, CH_2), 3.31 (1H, s, COCHC*H*), 3.49 (1H, s, C*H*CO$_2$CH$_3$), 3.68 (3H, s, OCH_3), 4.56 (1H, s, NCH), 6.12–6.23 (2H, m, HC=CH), 7.44–7.55 (3H, m, ArH's), 7.82–7.87 (2H, m, ArH's); δ_C (75.5 MHz; $CDCl_3$) 46.3 (CH_2), 49.6 (COCH*C*H), 52.4 (CH_3), 59.7 (CO*C*H), 64.5 (NCH), 127.8 (Ar), 128.8 (Ar), 132.8 (Ar), 135.9 (Ar), 136.3 (HC=CH), 139.4 (Ar, quat), 171.2 (C=O, quat); *m*/*z* (FAB) 294 ($M^+ + H$), 234 ($M^+ - C_2O_2H_3$), 228 (base peak, $M^+ - C_6H_5$) [Found: C, 57.2; H, 5.2; N, 4.7; S, 10.5. Calc. for $C_{14}H_{15}NSO_4$: C, 57.3; H, 5.2; N, 4.8; S, 10.9%].

Cyclopentadiene cycloadduct 3b. (i) Diisopropylethylamine (0.282 ml, 1.62 mmol), *N*-phenylsulfonyl-α-bromoglycine ethyl ester **1b** (0.500 g, 1.620 mmol), toluene (40 ml) and cyclopentadiene (1.33 ml, 16.20 mmol) according to the general procedure gave an orange oil (0.510 g) which was chromatographed to yield the cycloadduct **3b** (0.473 g, 95%) as a white solid: mp 67–69 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 1750 (m) C=O, 1220 (m) C–O, 740 and 690 (m) and 610 (s) C=C (*cis*); δ_H (300 MHz; $CDCl_3$) 1.21 (3H, t, *J* 10, OCH$_2$C*H*$_3$), 1.72 (2H, ABq, *J* 10, septet, 127, CH_2), 3.32 (1H, s, COCHC*H*), 3.49 (1H, s, COCH), 4.12 (2H, q, *J* 7.5, OC*H*$_2$CH$_3$), 4.59 (1H, s, NCH), 6.04–6.21 (2H, m, HC=CH), 7.47 (3H, m, ArH's), 7.85 (2H, m, ArH's); δ_C (75.5 MHz; $CDCl_3$) 14.0 (*C*H$_3$CH$_2$O), 46.1 (CH_2), 49.5 (COCH*C*H), 59.7 (CO*C*H), 61.1 (CH$_3$*C*H$_2$O), 64.5 (NCH), 128.7 (Ar), 127.7 (Ar), 132.7 (Ar), 136.2 (Ar), 136.4 (Ar, quat), 139.4 (HC=CH), 170.6 (C=O, quat); *m*/*z* (CI) 325 ($M^+ + NH_4$), 308 ($M^+ + H$), 61 (base peak, $M^+ - C_{13}H_8SO_2$) [Found: C, 58.3; H, 5.8; N, 4.3; S, 10.3. Calc. for $C_{15}H_{17}NSO_4$: C, 58.6; H, 5.6; N, 4.6; S, 10.4%].

(ii) Sodium hydride (0.037 g, 1.552 mmol) was added to a stirred solution of *N*-phenylsulfonyl-α-bromoglycine ethyl ester **1b** (0.403 g, 1.552 mmol), dichloromethane (40 cm^3) and cyclopentadiene (0.256 ml, 3.104 mmol) and according to the general procedure gave a viscous orange oil (0.522 g), which was chromatographed to yield the cycloadduct **3b** (0.453 g, 95%) as a white solid and which was identical to that isolated in the previous procedure.

(iii) *n*-Butyllithium (0.648 ml of a 2.5 M solution in hexanes, 1.620 mmol), *N*-phenylsulfonyl-α-bromoglycine ethyl ester **1b** (0.500 g, 1.620 mmol), toluene (40 ml) and cyclopentadiene (1.334 ml, 16.20 mmol) according to the general procedure gave an orange oil (0.347 g) which was chromatographed to yield the cycloadduct **3b** (0.134 g, 27%) as a white solid, which was identical to that isolated from the previous procedure, together with the α-substituted glycine (0.024 g, 5%) **4b** (R = ^{n}Bu): mp 70 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 3279 (s) NH, 2959 (s) CH_3, 2873 (s) CH_2, 1724 (s) C=O, 1216 (s) C–O, 755 (s) and 689 (s); δ_H (300 MHz; $CDCl_3$) 0.79–0.89 (3H, m, CH$_2$CH$_2$C*H*$_3$), 1.10 (3H, t, *J* 7.5, OCH$_2$C*H*$_3$), 1.19–1.37 (4H, m, CH_2CH_2), 1.51–1.73 (2H, m, CHC*H*$_2$), 3.80–3.92 (3H, m, OC*H*$_2$CH$_3$ and C*H*NH), 5.25 (1H, d, *J* 10, NH), 7.47 (3H, m, ArH's), 7.85 (2H, m, ArH's); δ_C (75.5 MHz; $CDCl_3$) 14.0 (*C*H$_3$CH$_2$O), 14.0 (*C*H$_3$CH$_2$CH$_2$), 21.9 (CH$_3$*C*H$_2$CH$_2$), 25.4 (CH$_3$CH$_2$*C*H$_2$), 32.0 (*C*H$_2$CH), 55.7 (CHNH), 61.5 (OCH_2), 127.4 (Ar), 128.9 (Ar), 132.3 (Ar), 139.7 (Ar, quat), 171.7 (C=O, quat); *m*/*z* (FAB) 599 ($2M^+ + H$), 300 (base peak, $M^+ + H$) [Found: *m*/*z* (FAB), 300.1263. Calc. for $C_{14}H_{22}NSO_4$: *m*/*z*, 300.1270].

Cyclopentadiene cycloadduct 3c. Triethylamine (0.225 ml, 1.62 mmol), *N*-4-nitrophenylsulfonyl-α-bromoglycine ethyl ester **1c** (0.59 g, 1.62 mmol), toluene (40 ml) and cyclopentadiene (1.334 ml, 16.2 mmol) according to the general procedure gave an orange oil (0.467 g), which after chromatography gave

cycloadduct **3c** (0.410 g, 72%) as a white solid: mp 105–106 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 2920 (w) CH_3, 1730 (s) C=O, 1350 (s) NO_2, 1250 (m) C–O, 850 (s) and 620 (s); δ_H (300 MHz; $CDCl_3$) 1.24 (3H, t, *J* 7.5, OCH_2CH_3), 1.49–1.98 (2H, ABq, *J* 10, septet, 127.5, CH_2 bridgehead), 3.40 (1H, s, COCHC*H*), 3.62 (1H, s, COCH), 4.17 (2H, q, *J* 7.5, OCH_2CH_3), 4.58 (1H, s, NCH), 6.30–6.36 (2H, m, HC=CH), 8.08 (2H, d, *J* 10, ArH's), 8.33 (2H, d, *J* 10, ArH's); δ_C (75.5 MHz; $CDCl_3$) 13.9 (OCH_2CH_3), 46.1 (CH_2), 49.4 (COCHCH), 60.2 (COCH), 61.6 (OCH_2CH_3), 64.9 (NCH), 113.9 (Ar), 123.9 (Ar), 128.8 (Ar), 136.2 (Ar), 136.8 (Ar, quat), 145.6 (Ar, quat), 149.9 (HC=CH), 170.1 (C=O, quat); *m*/*z* (FAB) 706 ($2M^+ + H$), 353 ($M^+ + H$), 151 (base peak, $M^+ - C_6H_5N_2SO_4$) [Found: C, 50.9; H, 4.9; N, 7.8; S, 9.5. Calc. for $C_{15}H_{16}N_2SO_6$: C, 51.1; H, 4.6; N, 8.0; S, 9.1%].

Cyclopentadiene cycloadduct 3d. Triethylamine (0.225 ml, 1.62 mmol), *N*-4-methoxyphenylsulfonyl-α-bromoglycine ethyl ester **1d** (0.57 g, 1.62 mmol), toluene (40 ml) and cyclopentadiene (1.334 ml, 16.20 mmol) according to the general procedure gave an orange oil (0.402 g), which was chromatographed to yield the cycloadduct **3d** (0.356 g, 65%) as a white solid: mp 114–116 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 2990 (m) CH_3, 2870 (m) OCH_3, 1750 (s) C=O, 1260 (s) C–O, 850 (s) and 600 (s); δ_H (300 MHz; $CDCl_3$) 1.24 (3H, t, *J* 10, OCH_2CH_3), 1.39–2.05 (2H, ABq, *J* 10, septet, 110, CH_2 bridgehead), 3.28 (1H, s, COCHC*H*), 3.42 (1H, s, COCH), 4.15 (2H, q, *J* 7.5, OCH_2CH_3), 4.55 (1H, s, NCH), 6.01–6.21 (2H, m, HC=CH), 6.95 (2H, d, *J* 9.5, ArH's), 7.78 (2H, d, *J* 9.5, ArH's); δ_C (75.5 MHz; $CDCl_3$) 14.1 (OCH_2CH_3), 46.1 (CH_2), 49.6 (COCHCH), 55.5 (COCH), 55.7 (OCH_3), 61.4 (OCH_2CH_3), 64.3 (NCH), 113.9 (Ar), 130.0 (Ar), 131.0 (Ar), 131.9 (Ar), 135.9 (Ar, quat), 136.154 (Ar, quat), 162.9 (HC=CH), 170.8 (C=O, quat); *m*/*z* (FAB) 675 ($2M^+ + H$), 338 ($M^+ + H$), 171 (base peak, $M^+ - C_9H_{11}NO_2$) [Found: C, 57.0; H, 6.0; N, 4.3; S, 9.9. Calc. for $C_{16}H_{19}NSO_5$: C, 57.0; H, 5.7; N, 4.2; S, 9.5%].

Cyclopentadiene cycloadduct 3e. Triethylamine (0.225 ml, 1.6 mmol), *N*-methylsulfonyl-α-bromoglycine ethyl ester **1e** (0.500 g, 1.6 mmol), toluene (40 cm^3) and cyclopentadiene (1.334 ml, 16.200 mmol) according to the general procedure gave an orange oil (0.335 g), which was chromatographed to yield the cycloadduct **3e** (0.290 g, 74%): mp 99–101 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 2980 (m) CH_3, 1755 (s) C=O, 1330 (m) C–O, 695 (m); δ_H (300 MHz; $CDCl_3$) 1.30 (3H, t, *J* 7.5, OCH_2CH_3), 1.51–1.91 (2H, ABq, *J* 10, septet, 127.5, CH_2 bridgehead), 2.97 (3H, s, SO_2CH_3), 3.47 (1H, s, COCHC*H*), 3.62 (1H, s, COCH), 4.23 (2H, q, *J* 7.5, OCH_2CH_3), 4.63 (1H, s, NCH), 6.43–6.53 (2H, m, HC=CH); δ_C (75.5 MHz; $CDCl_3$) 14.3 (OCH_2CH_3), 41.6 (COCHCH), 46.7 (CH_2), 49.7 (COCH), 61.0 (NCH), 61.5 (OCH_2CH_3), 65.4 (SO_2CH_3), 137.0 (HC=CH), 171.0 (C=O, quat); *m*/*z* (FAB) 246 ($M^+ + H$), 151 (base peak, $M^+ - SO_2CH_2$) [Found: C, 49.2; H, 6.7; N, 5.5; S, 13.1. Calc. for $C_{10}H_{15}NSO_4$: C, 49.0; H, 6.2; N, 5.7; S, 13.1%].

Attempted asymmetric preparation of cyclopentadiene cycloadduct 3b

(i) DIBAL-H. DIBAL-H (0.220 cm^3 of a 1 M solution in toluene, 1.552 mmol) was added to a stirred solution of *N*-phenylsulfonyl-α-bromoglycine ethyl ester (0.403 g, 1.552 mmol) in dichloromethane (40 ml) cooled to −78 °C. The solution, with a slight colourless precipitate, was stirred for 30 min before the addition of (*R*)-binaphthol (0.444 g, 1.552 mmol). The turbid solution was stirred for a further 15 min before the addition of cyclopentadiene (0.256 ml, 3.104 mmol). After 10 mins, water (50 ml) was added, the mixture was extracted with dichloromethane (2 × 50 ml), the phases were separated, dried ($MgSO_4$) and evaporated to yield a viscous orange oil (0.482 g). This oil was chromatographed on silica gel [ethyl acetate–hexanes (1 : 9) as eluant] to yield the cycloadduct **3b** as a white solid (0.458 g, 96%) which was identical to that isolated above. The product was determined to be racemic by chiral HPLC using a Chiralpak AD column [propan-2-ol–hexane (20 : 80) as eluant], peaks at 582 and 534 s.

(ii) Diethylaluminium chloride. Diethylaluminium chloride (1.552 ml of a 1 M solution in hexanes, 1.552 mmol) was added to a stirred colourless solution of (*R*)-binaphthol (0.444 g, 1.552 mmol) cooled to −78 °C in dichloromethane (10 ml) and was allowed to stir for 30 min before cooling to −100 °C. This solution was then added *via* cannula to a stirred mixture of *N*-phenylsulfonyl-α-bromoglycine ethyl ester **1b** (0.403 g, 1.552 mmol) and sodium hydride (0.037 g, 1.552 mmol) cooled to −100 °C, which produced a pale yellow turbid solution. After 30 min, cyclopentadiene (0.256 ml, 3.104 mmol) was added and after a further 15 min, water (50 ml) was added. The mixture was extracted with dichloromethane (2 × 50 ml), separated, dried ($MgSO_4$) and evaporated to yield a viscous orange oil (0.905 g). Purification by silica gel chromatography [ethyl acetate–hexanes (1 : 9) as eluant] gave the cycloadduct **3b** (0.448 g, 94%) as a white solid, which was identical to that isolated above. The product was determined to be racemic by chiral HPLC as above.

Preparation of *N*-phenylsulfonyl-α-methylglycine ethyl ester 4b (R^3 = Me)[13]

Trimethylaluminium (0.776 ml of a 2 M solution in hexanes, 1.552 mmol) was introduced dropwise to a stirred solution of *N*-phenylsulfonyl-α-bromoglycine ethyl ester **1b** (0.500 g, 1.552 mmol) at −78 °C in dichloromethane (25 ml). The resulting pale yellow solution was stirred for 30 min, allowed to warm to RT and stirred for a further 8 h. Water (25 ml) was added, the layers were separated, extracted with dichloromethane (3 × 20 ml), dried ($MgSO_4$) and evaporated to yield the α-substituted product **4b** (R^3 = Me) as a white solid (0.225 g). Purification by silica gel chromatography [ethyl acetate–hexane (3 : 7) as eluant] gave the product **4b** (R^3 = Me)[13] as a white solid (0.220 g, 55%): mp 56–58 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 3300 (m) NH, 1735 (s) C=O, 1210 (w) C–O, 745 (m) and 690 (m); δ_H (300 MHz; $CDCl_3$) 1.11 (3H, t, *J* 7, OCH_2CH_3), 3.91–3.98 (3H, m, OCH_2CH_3 and NHC*H*, simplifies to a 2H, m upon addition of D_2O), 5.39 (1H, d, *J* 9, NH, disappears upon addition of D_2O), 7.46–7.59 (3H, m, ArH's), 7.84 (2H, m, ArH's); δ_C (75.5 MHz; $CDCl_3$) 13.9 (CH_3CH), 19.8 (OCH_2CH_3), 51.6 (CH_3CH_2CH), 61.8 (OCH_2CH_3), 127.2 (Ar), 129.1 (Ar), 132.5 (Ar), 139.8 (Ar, quat), 172.1 (C=O, quat); *m*/*z* (FAB) 258 (base peak, $M^+ + H$) [Found: C, 51.1; H, 5.7; N, 5.4; S, 12.6. Calc. C, 51.3; H, 5.9; N, 5.4; S, 12.5%].

Preparation of *N*-phenylsulfonyl-α-ethylglycine ethyl ester 4b (R^3 = Et)

Triethylaluminium (1.552 ml of a 1 M solution in hexanes, 1.552 mmol) was introduced dropwise to a stirred solution of *N*-phenylsulfonyl-α-bromoglycine ethyl ester **1b** (0.50 g, 1.552 mmol) at −78 °C in dichloromethane (25 ml). The resulting pale yellow solution was stirred for 30 min, allowed to warm to RT and stirred for a further 8 h. Water (25 ml) was added, the layers were separated, extracted with dichloromethane (3 × 20 ml), dried ($MgSO_4$) and evaporated to yield the α-substituted product **4b** (R^3 = Et) as a white solid (0.405 g). Purification by silica gel chromatography [ethyl acetate–hexane (3 : 7) as eluant] gave the product **4b** (R^3 = Et) as a white solid (0.400 g, 95%): mp 43–45 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 3280 (m) NH, 1735 (s) C=O, 1210 (w) C–O, 750 (m) and 690 (m); δ_H (300 MHz; $CDCl_3$) 0.90 (3H, t, *J* 7, CH_2CH_3), 1.06 (3H, t, *J* 7, OCH_2CH_3), 1.59–1.85 (2H, m, CH_3CH_2CH), 3.82–3.96 (3H, m, OCH_2CH_3 and NHC*H*, simplifies to a 2H, m upon addition of D_2O), 5.25 (1H, d, *J* 9, N*H*, disappears upon addition of D_2O), 7.45–

7.59 (3H, m, ArH's), 7.84 (2H, m, ArH's); δ_C (75.5 MHz; $CDCl_3$) 9.3 (CH_3CH_2), 13.9 (OCH_2CH_3), 26.7 (CH_3CH_2), 56.9 (CH_3CH_2CH), 61.6 (OCH_2CH_3), 127.5 (Ar), 129.0 (Ar), 132.7 (Ar), 139.8 (Ar, quat), 171.5 (C=O, quat); *m*/*z* (FAB) 543 ($2M^+ + H$), 272 ($M^+ + H$), 198 (base peak, $M^+ - C_3H_4O_2$) [Found: C, 53.1; H, 6.5; N, 5.3; S, 11.6. Calc. C, 53.1; H, 6.3; N, 5.2; S, 11.8%].

Preparation of *N*-phenylsulfonyl-α-ethoxyglycine ethyl ester 4b (R^3 = OEt)

Triethoxyaluminium (0.251 g, 1.552 mmol) was introduced to a stirred solution of *N*-phenylsulfonyl-α-bromoglycine ethyl ester **1b** (0.500 g, 1.552 mmol) at 0 °C in dichloromethane (25 ml). The resulting pale yellow solution was stirred for 30 min, allowed to warm to RT and stirred for a further 8 h. Water (25 ml) was added, the layers separated, extracted with dichloromethane (3 × 20 ml), dried ($MgSO_4$) and evaporated to yield the α-substituted product **4b** (R^3 = OEt) as a white solid (0.356 g). Purification by silica gel chromatography [ethyl acetate–hexane (3 : 7) as eluant] gave the product as a white solid (0.339 g, 76%): mp 52–55 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 3275 (m) NH, 1735 (s) C=O, 1210 (w) C–O, 750 (m) and 690 (m); δ_H (300 MHz; $CDCl_3$) 1.04 (3H, t, *J* 7, CH_2CH_3), 1.19 (3H, t, *J* 7, OCH_2CH_3), 3.42–3.72 (2H, m, CH_3CH_2OCH), 4.16 (2H, m, OCH_2CH_3), 5.06 (1H, d, *J* 9, CH, collapses to a singlet upon addition of D_2O), 5.93 (1H, d, *J* 9, NH, disappears upon addition of D_2O), 7.45–7.61 (3H, m, ArH's), 7.88 (2H, m, ArH's); δ_C (75.5 MHz; $CDCl_3$) 11.3 (CH_3CH_2), 14.2 (OCH_2CH_3), 63.6 (OCH_2CH_3), 69.0 (CH_3CH_2OCH), 69.4 (CH_3CH_2), 127.5 (Ar), 128.5 (Ar), 133.0 (Ar), 139.6 (Ar, quat), 171.2 (C=O, quat); *m*/*z* (FAB) 288 (base peak, $M^+ + H$) [Found: *m*/*z*, 288.3371. Calc. for $C_{12}H_{18}NSO_5$ *m*/*z*, 288.3379].

Preparation of *N*-phenylsulfonyl-α-isopropoxyglycine ethyl ester 4b (R^3 = O^iPr)

Triisopropoxyaluminium (0.317 g, 1.552 mmol) was introduced to a stirred solution of *N*-phenylsulfonyl-α-bromoglycine ethyl ester **1b** (0.500 g, 1.552 mmol) at 0 °C in dichloromethane (25 ml). After 30 min, the mixture was allowed to warm to RT and stirred for a further 8 h. Water (25 ml) was added, the layers separated, extracted with dichloromethane (3 × 20 ml), dried ($MgSO_4$) and evaporated to yield the α-substituted product **4b** (R^3 = O^iPr) as a colourless oil (0.502 g). Purification by silica gel chromatography [ethyl acetate–hexane (3 : 7) as eluant] gave the product **4b** (R^3 = O^iPr) as an oil (0.479 g, 97%): ν_{max} (KBr disc)/cm^{-1} *inter alia* 3280 (m) NH, 1750 (s) C=O, 1210 (w) C–O, 740 (m), 690 (m); δ_H (300 MHz; $CDCl_3$) 1.05 (3H, d, *J* 6, $CHCH_3$), 1.10 (3H, d, *J* 6, $CHCH_3$), 1.16 (3H, t, *J* 7, OCH_2CH_3), 3.92 (1H, septet, *J* 6, $HC(CH_3)_2$), 4.07 (2H, q, *J* 7, OCH_2CH_3), 5.07 (1H, d, *J* 9.5, NHC*H*, collapses to a singlet upon addition of D_2O), 5.77 (1H, d, *J* 9, N*H*, disappears upon addition of D_2O), 7.47–7.59 (3H, m, ArH's), 7.85 (2H, d, ArH's); δ_C (75.5 MHz; $CDCl_3$) 13.8 (CH_3CH_2), 21.5 ($CHCH_3$), 22.4 (CH_3CH), 62.2 (OCH_2CH_3), 70.1 (CHNH), 79.9 [$(CH_3)_2CH$], 126.8 (Ar), 129.0 (Ar), 132.8 (Ar), 140.9 (Ar, quat), 167.4 (C=O, quat); *m*/*z* (CI) 319 (base peak, $M^+ + NH_4$), 261 ($M^+ + NH_4 - C_3H_7O$) [Found: *m*/*z*, 319.1326. Calc. for $C_{13}H_{23}N_2SO_5$: *m*/*z*, 319.1328].

Preparation of *N*-phenylsulfonyl-α-*n*-butylglycine ethyl ester 4b (R^3 = ^{n}Bu)

Diethylaluminium chloride (1.552 ml of a 1 M solution in hexanes, 1.552 mmol) was added to a stirred solution of *n*-butyllithium (0.610 ml of a 2.5 M solution in hexanes, 1.552 mmol) in dichloromethane (5 ml) at 0 °C. After 30 min, this solution was added dropwise to a stirred solution of *N*-phenylsulfonyl-α-bromoglycine ethyl ester **1b** (0.500 g, 1.552 mmol) at 0 °C in dichloromethane (25 cm^3). The resulting pale yellow solution was stirred at this temperature for 30 min, allowed to warm to RT and stirred for a further 8 h. Water (25 cm^3) was added, the layers were separated, extracted with dichloromethane (3 × 20 cm^3), dried ($MgSO_4$) and evaporated to yield a mixture of α-substituted products **4b** (R^3 = Et) and **4b** (R^3 = ^{n}Bu) as an off white solid (0.267 g). The components were separated by silica gel chromatography [ethyl acetate–hexane (3 : 7) as eluant] and gave the α-ethyl derivative **4b** (R^3 = Et) (0.088 g, 21%) and the α-*n*-butyl derivative **4b** (R^3 = ^{n}Bu) (0.144 g, 31%), which were both identical to those products isolated above.

Attempted preparation of *N*-phenylsulfonyl-α-*tert*-butylglycine ethyl ester 4b (R^3 = ^{t}Bu)

Diethylaluminium chloride (1.552 ml of a 1 M solution in hexanes, 1.552 mmol) was added to a stirred solution of *tert*-butyllithium (0.913 ml of a 1.7 M solution in hexanes, 1.552 mmol) in dichloromethane (5 ml) at 0 °C. After 30 min, the solution was added dropwise to a stirred solution of *N*-phenylsulfonyl-α-bromoglycine ethyl ester **1b** (0.500 g, 1.552 mmol) at 0 °C in dichloromethane (25 ml). After 30 min, the mixture was allowed to warm to RT and stirred for a further 8 h. Water (25 ml) was added, the layers separated, extracted with dichloromethane (3 × 20 ml), dried ($MgSO_4$) and evaporated to yield the α-ethyl substituted product **4b** (R^3 = Et) as an off-white solid (0.225 g). Purification by silica gel chromatography [ethyl acetate–hexane (3 : 7) as eluant] gave the α-ethyl derivative **4b** (R^3 = Et) (0.075 g, 18%), which was identical to that isolated above.

Preparation of (*S*)-(+)-*N*-phenylsulfonyl-α-ethylglycine ethyl ester 15 from (*S*)-(+)-2-aminobutyric acid 14

(*S*)-2-Aminobutyric acid **14** (0.20 g, 1.93 mmol) was suspended in dichloromethane (5 ml) and treated with thionyl chloride (1.18 ml, 1.93 mmol). After 5 h, ethanol (10 ml) was added and the mixture was evaporated to yield a brown oil, which was resuspended in dichloromethane (5 ml) and treated with triethylamine (5.30 ml, 3.86 mmol) and phenylsulfonyl chloride (0.230 g, 1.93 mmol). The resulting solution was stirred overnight before the addition of water (15 ml). The organic phase was extracted with dichloromethane (3 × 15 ml), dried ($MgSO_4$) and evaporated to yield a white solid (0.299 g). Purification by column chromatography [ethyl acetate–hexane (3 : 7) as eluant] gave *N*-phenylsulfonamide ethyl ester **15** as a white solid (0.275 g, 53%): $[\alpha]_D^{20}$ +15 (*c* = 1, THF). This product was identical to that isolated above.

Preparation of amide 16

(*S*)-(+)-2-Aminobutyric acid **14** (0.050 g, 0.48 mol) was suspended in ethanol (5 ml) and saturated with hydrogen chloride gas. Evaporation gave a white solid which was suspended in dichloromethane (20 ml) and treated with triethylamine (1.99 ml, 1.45 mmol) and benzenesulfonyl chloride (0.084 g, 0.48 mmol). After 12 h, water (15 ml) was added, the layers separated, extracted with dichloromethane (3 × 10 ml), dried ($MgSO_4$) and evaporated to yield a pale brown oil (0.173 g). Purification by silica gel chromatography [ethyl acetate–hexane (1 : 1) as eluant] gave a colourless oil which was crystallised from dichloromethane–hexane to yield a white solid (0.065 g, 75%) identified as the amide **16**: $[\alpha]_D^{20}$ −9 (*c* = 1, THF); mp 127–129 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 3260 (m) and 3360 (m) NH, 1740 (s) C=O (ester), 1650 (s) C=O (amide), 1210 (m) and 1255 (m) C–O, 760 (w) and 690 (w); δ_H (300 MHz; $CDCl_3$) 0.75 (3H, t, *J* 7, CH_3CH_2CHNH), 0.85 (3H, t, *J* 7, CH_3CH_2CH), 1.27 (3H, t, *J* 7, CH_3CH_2O), 1.56–1.83 (4H, m, 2 × CH_3CH_2CH), 3.64–3.78 (1H, q, *J* 7, NHC*H*, collapses to a t upon addition of D_2O), 4.18 (2H, m, CH_3CH_2O), 4.34 (1H, q, *J* 7, COCH, collapses to a t upon addition of D_2O), 5.61 (1H, d, *J* 7, $NHSO_2$, disappears upon addition of D_2O), 6.45 (1H, d, *J* 7,

NHCO, disappears upon addition of D_2O), 7.41–7.59 (3H, m, ArH's), 7.85 (2H, d, *J* 7, ArH's); δ_C (75.5 MHz; $CDCl_3$) 9.2 (CH_3CH_2CHNH), 9.4 (CH_3CH_2CH), 14.1 (CH_3CH_2O), 25.3 (CH_3CH_2CHNH), 27.0 (CH_3CH_2CH), 53.3 (CH_3CH_2CH), 57.7 (NHCH), 61.6 (CH_3CH_2O), 126.3 (Ar), 129.0 (Ar), 132.8 (Ar), 139.7 (Ar, quat), 170.2 (NHC=O, quat), 171.8 (C=O, quat); *m*/*z* (FAB) 357 ($M^+ + H$), 283 ($M^+ - C_3H_5O_2$), 198 ($M^+ - C_7H_{12}NO_3$) [Found: *m*/*z*, 357.1489. Calc. for $C_{16}H_{25}N_2SO_5$: *m*/*z*, 357.1484].

Preparation of (−)-2-*N*-benzenesulfonamidopropanol[14]

Lithium aluminium hydride (0.389 mol of a 1 M solution in ether, 0.389 mmol) was added to a stirred solution of (−)-*N*-phenylsulfonyl-α-methylglycine ethyl ester **4b** (R^3 = Me) (0.10 g, 0.389 mmol) at −78 °C in THF (3 ml). The colourless solution was stirred overnight and heated at 60 °C for 1 h. Water (15 ml) was added, the layers separated, extracted with dichloromethane (3 × 10 cm^3), dried ($MgSO_4$) and evaporated to yield a yellow oil (0.075 g). The oil was purified by silica gel chromatography [ethyl acetate–hexanes (1:1) as eluant] to afford the alcohol[14] (0.052 g, 63%) as a colourless oil: $[\alpha]_D^{20}$ −20 (*c* = 1.4, THF); bp 121 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 3510 (m) OH, 3280 (m) NH, 705 (s) and 695 (s); δ_H (300 MHz; $CDCl_3$) 0.95 (3H, d, *J* 7, CH_3), 2.40 (1H, br s, OH, disappears upon addition of D_2O), 3.36 (2H, m, CH_2), 3.53 (1H, m, CH), 5.18 (1H, d, *J* 7, NH), 7.41–7.59 (3H, m ArH's), 7.81–7.86 (2H, m, ArH's); δ_C (75.5 MHz, $CDCl_3$) 17.6 (CH_3), 51.52 (CH), 66.1 (CH_2), 126.962 (Ar), 129.1 (Ar), 132.7 (Ar), 140.485 (Ar, quat); *m*/*z* (FAB) 216 (base peak, $M^+ + H$) [Found: *m*/*z*, 216.0688. Calc. for $C_9H_{14}NSO_3$: *m*/*z*, 216.0694].

Preparation of (+)-Mosher ester of 17

(−)-2-*N*-Benzenesulfonamidopropanol (0.050 g, 0.232 mmol) was dissolved in dichloromethane (2 ml) and treated with (+)-Mosher's acid chloride (0.059 g, 0.232 mmol), pyridine (0.474 ml, 0.464 mmol) and DMAP (0.010 g, 0.1 mmol). After 16 hours, the reaction was quenched with water (10 ml), extracted with dichloromethane (2 × 5 ml), dried ($MgSO_4$) and evaporated to yield a white solid (0.170 g). The solid was purified by silica gel chromatography [ethyl acetate–hexanes (4:6) as eluant] to yield the ester **17** as a white solid (0.020 g, 20%): mp 135–136 °C; ν_{max} (KBr disc)/cm^{-1} *inter alia* 3300 (m) NH, 1750 (m) C=O, 1250 (w), C–O, 690 (w) and 720 (w); δ_H (300 MHz; $CDCl_3$) 1.0 (3H, *J* 7, CH_3), 3.49 (3H, s, OCH_3), 3.65 (1H, m, CH), 4.10–4.29 (2H, m, CH_2), 4.62 (1H, d, *J* 7, NH, disappears upon addition of D_2O), 7.41–7.61 (8H, m, ArH's), 7.83–7.85 (2H, m, ArH's); δ_C (300 MHz; $CDCl_3$) 18.0 (CH_3), 48.3 (CH), 55.4 (OCH_3), 68.8 (CH_2), 126.82 (Ar), 127.3 (Ar), 128.6 (Ar), 129.2 (Ar), 132.8 (Ar, quat), 166.3 (C=O, quat); *m*/*z* (FAB) 432 ($M^+ + H$), 198 (base peak, $M^+ - C_{10}H_8O_3F_3$) [Found: *m*/*z*, 432.1097. Calc. for $C_{19}H_{20}NSO_5F_3$: *m*/*z*, 432.1092].

Preparation of *N*-phenylsulfonyl-α-methylglycine ethyl ester 4b (R^3 = Me) from L-alanine

L-Alanine (0.200 g, 2.24 mmol) was suspended in dichloromethane (25 ml) and saturated with hydrogen chloride gas until the solution became homogeneous. After 5 h, ethanol (10 ml) was added, the solvent evaporated and the resulting pale yellow oil was resuspended in dichloromethane (25 ml). This solution was treated with triethylamine (6.15 ml, 4.480 mmol) and benzenesulfonyl chloride (0.394 g, 2.24 mmol) and the resulting solution was stirred overnight before the addition of water (15 ml). Extraction with dichloromethane (3 × 15 ml), drying ($MgSO_4$) and evaporation gave a white solid (0.299 g). The solid was purified by silica gel chromatography [ethyl acetate–hexanes (3:7) as eluant] to afford the ester **4b** (R^3 = Me)[13] as a white solid (0.432 g, 75%): $[\alpha]_D^{20}$ −5 (*c* = 1, THF).

Asymmetric preparation of *N*-phenylsulfonyl-α-methylglycine ethyl ester 4b (R^3 = Me)

Trimethylaluminium (0.776 ml of a 2 M solution in hexanes, 1.552 mmol) was added dropwise at −78 °C under argon to a stirred solution of (*R*)-binaphthol (0.444 g, 1.552 mmol) in dichloromethane (10 ml). The resulting solution was stirred for 30 min before dropwise addition *via* cannula, to a stirred solution of *N*-phenylsulfonyl-α-bromoglycine ethyl ester **1b** (0.500 g, 1.552 mmol) at −78 °C in dichloromethane (25 ml). After 30 min, the mixture was allowed to warm to room temperature, left for a further 4 h, quenched with sat. ammonium chloride solution (25 ml), extracted with dichloromethane (3 × 20 ml), dried ($MgSO_4$) and evaporated to yield the α-substituted product **4b** (R^3 = Me)[13] and binaphthol as a white solid (0.665 g). The solid was purified by silica gel chromatography (ethyl acetate–hexanes (3:7) as eluant) to afford **4b** (R^3 = Me) as a white solid (0.220 g, 55%), which was identical to that isolated above. Binaphthol was also recovered (0.434 g, 98%). This product **4b** (R^3 = Me) was reduced and converted to the (+)-Mosher ester **17**, as outlined above and subsequent NMR analysis (by comparison of the methylene signals at δ 3.49 and 3.55 and reinforced by ^{19}F NMR of the CF_3 signals at δ 6.15 and 6.61) showed that the sample had a de of 52%.

Asymmetric preparation of *N*-phenylsulfonyl-α-ethylglycine ethyl ester 4b (R^3 = Et)

Triethylaluminium (1.552 ml of a 1 M solution in hexanes, 1.552 mmol) was added dropwise at −78 °C under argon to a stirred solution of (*R*)-binaphthol (0.444 g, 1.552 mmol) in dichloromethane (10 ml). The resulting solution was stirred for 30 min before dropwise addition *via* cannula, to a stirred solution of *N*-phenylsulfonyl-α-bromoglycine ethyl ester **1b** (0.500 g, 1.552 mmol) at −78 °C in dichloromethane (25 ml). After 30 min, the mixture was allowed to warm to room temperature, stirred for a further 4 h, quenched with sat. ammonium chloride solution (25 ml), extracted with dichloromethane (3 × 20 ml), dried ($MgSO_4$) and evaporated to yield the α-substituted product **4b** (R^3 = Et) and binaphthol as a white solid (0.902 g). The solid was purified by silica gel chromatography (ethyl acetate–hexanes (3:7) as eluant) to afford the product **4b** (R^3 = Et) as a white solid (0.378 g, 90%), which was identical to that reported above. Binaphthol was also recovered (0.427 g, 96%). The product **4b** (R^3 = Et) showed an ee of 62% by chiral HPLC using a Chiralpak AD column [propan-2-ol–hexane (20:80) as eluant] (peaks were observed at 11.14 and 12.56 min).

Asymmetric preparation of *N*-phenylsulfonyl-α-ethoxyglycine ethyl ester 4b (R^3 = OEt)

Triethoxyaluminium (0.251 g, 1.552 mmol) was added at −78 °C under argon to a stirred solution of (*R*)-binaphthol (0.444 g, 1.552 mmol) in dichloromethane (10 ml). The resulting solution was stirred for 30 min before dropwise addition *via* cannula, to a stirred solution of *N*-phenylsulfonyl-α-bromoglycine ethyl ester (0.500 g, 1.552 mmol) at −78 °C in dichloromethane (25 ml). The resulting pale yellow solution was stirred at this temperature for 30 min, allowed to warm to room temperature and stirred for a further 4 h. Sat. ammonium chloride solution (25 ml) was added, the layers separated, extracted with dichloromethane (3 × 20 ml) and the combined extracts dried ($MgSO_4$) and evaporated to yield the α-substituted product **4b** (R^3 = OEt) and binaphthol as a white solid (0.802 g). The solid was purified by silica gel chromatography using an eluant of ethyl acetate–hexanes (3:7) to afford the product **4b** (R^3 = OEt) as a white solid (0.307 g, 69%) and was found to be analytically identical to that isolated above. Binaphthol was also recovered (0.404 g, 90%). The product **4b** (R^3 = OEt) was determined to have an ee of 19% by chiral HPLC using a Chiralpak OD column with an eluant of propan-2-ol–hexane (30:70). Peaks were observed at 7.26 and 8.12 min.

Chiral catalysed preparation of *N*-phenylsulfonyl-α-isopropoxyglycine ethyl ester 4b ($R^3 = O^iPr$)

Triisopropoxyaluminium (0.317 g, 1.552 mmol) was added to a stirred solution of (*R*)-binaphthol (0.444 g, 1.552 mmol) in dichloromethane (10 ml), cooled to −78 °C. The resulting solution was stirred for 30 min before dropwise addition *via* cannula, to a stirred solution of *N*-phenylsulfonyl-α-bromoglycine ethyl ester **1b** (0.500 g, 1.552 mmol) at −78 °C in dichloromethane (25 ml). The resulting pale yellow solution was stirred at this temperature for 30 min; allowed to warm to room temperature and stirred for a further 4 h. Sat. ammonium chloride solution (25 ml) was added, the layers separated, extracted with dichloromethane (3 × 20 ml) and the combined extracts dried ($MgSO_4$) and evaporated to yield the α-substituted product **4b** ($R^3 = O^iPr$) and binaphthol as a white solid (0.905 g). The solid was purified by silica gel chromatography using an eluant of ethyl acetate–hexanes (3 : 7) to afford the product **4b** ($R^3 = O^iPr$) as a colourless oil (0.478 g, 97%) and was found to be analytically identical to that isolated above. Binaphthol was also recovered (0.424 g, 95%). The product **4b** ($R^3 = O^iPr$) was determined to have an ee of 25% by chiral HPLC using a Chiralpak OD column with an eluant of propan-2-ol–heptane (8 : 92). Peaks were observed at 8.33 and 12.65 min.

Chiral catalysed preparation of *N*-phenylsulfonyl-α-*n*-butylglycine 4b ($R^3 = {}^nBu$)

Diethylaluminium chloride (1.552 ml of a 1 M solution in hexanes, 1.552 mmol) was added dropwise to a stirred solution of *n*-butyllithium (0.608 ml of a 2.5 M solution in hexanes, 1.552 mmol) in dichloromethane (10 ml), cooled to −78 °C. The resulting solution was stirred for 30 min before the addition of (*R*)-binaphthol (0.444 g, 1.552 mmol). The solution was stirred for 30 min before the dropwise addition, *via* cannula, to a stirred solution of *N*-phenylsulfonyl-α-bromoglycine ethyl ester **1b** (0.500 g, 1.552 mmol) at −78 °C in dichloromethane (25 ml). The resulting pale yellow solution was stirred at this temperature for 30 min; allowed to warm to room temperature and stirred for a further 4 h. Saturated ammonium chloride solution (25 ml) was added, the layers separated, extracted with dichloromethane (3 × 20 ml) and the combined extracts dried ($MgSO_4$) and evaporated to yield a white solid (0.767 g). The solid was purified by silica gel chromatography using an eluant of ethyl acetate–hexanes (3 : 7) to afford the product **4b** ($R^3 = {}^nBu$) (0.161 g, 35%) and **4b** ($R^3 = Et$) (0.050 g, 12%), each as a white solid and were analytically identical to that isolated above. Binaphthol was also recovered (0.323 g, 73%). The product **4b** ($R^3 = {}^nBu$) was determined to be racemic by chiral HPLC using a Chirocel OF column with an eluant of propan-2-ol–heptane (10 : 90). Peaks were observed at 9.23 and 13.56 min.

Acknowledgements

We thank the EPSRC for a studentship (to P. E. M.) and Chiroscience for additional funding.

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Paper a909116e