Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 1995–2004

TETRAHEDRON: *ASYMMETRY*

Towards phase-transfer catalysts with a chiral anion: inducing asymmetry in the reactions of cations

Christabel Carter,[a] Sarah Fletcher[b] and Adam Nelson[a,*]

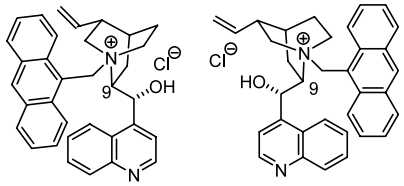
[a]*Department of Chemistry, University of Leeds, Leeds LS2 9JT, UK*
[b]*Syngenta, Leeds Road, Huddersfield HD2 1FF, UK*

Received 1 April 2003; accepted 2 May 2003

Abstract—The ability of chiral anions, for example bis[1,1′-bi-2-naphtholato]borate, to induce asymmetry in the reactions of prochiral cations was investigated. Ion-pairing of a borate anion with an aziridinium ion was demonstrated by NMR spectroscopy. The addition of *N*-methyl indole to an iminium ion (benzylidenedimethylammonium) and the ring-opening of an aziridinium ion (1,2-diphenyl-3-azonia-spiro[2.4]heptane) with benzylamine were studied. Low, but significant, (<15%) enantioselectivities were induced in the formation of the diamine benzyl-(1′,2′-diphenyl-2-pyrrolidin-1-yl-ethyl)-amine. The counterion of the additive was found to have a remarkable effect on the yield and the sense of enantioselectivity of these reactions.

1. Introduction

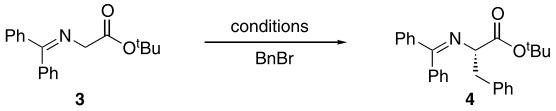
Asymmetric phase-transfer catalysis provides an extremely powerful and versatile means for inducing asymmetry in reactions of prochiral anions.[1] For example, cinchondinium (e.g. **1**) and cinchoninium (e.g. **2**) salts have been shown to induce high levels of enantioselectivity in a wide range of reactions including enolate alkylation,[2–4] Michael,[5] nucleophilic epoxidation,[6] cyclopropanation[7] and oxidative cyclisation reactions.[8] In this regard, the cinchona alkaloids may be considered to be 'charmed' templates for the design of effective phase-transfer catalysts.



1 **2**

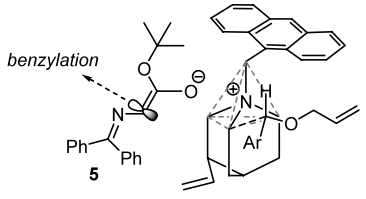
Asymmetric alkylations of the glycine derivative **3** have been widely studied (Scheme 1), and have been exploited in the synthesis of unnatural amino acid derivatives.[4,9] The enantioselectivity of this process can depend critically on the detailed substitution pattern of the phase-transfer catalyst. For example, cinchona alkaloid-derived catalysts induce the highest levels of enantioselectivity (up to 94% e.e.[2]) only when the bridgehead nitrogen is quaternised with a 9-anthracenylmethyl group.

Corey has proposed a model which explains the sense of the enantioselective alkylation of the enolate **5** (Fig. 1), and the importance of the size of the substituent on the quaternised nitrogen atom.[2] The enolate **5** is believed to be in close contact with the least hindered face of an imaginary tetrahedron formed by the four atoms surrounding the quaternary nitrogen atom.



3 **4**

Scheme 1.



5

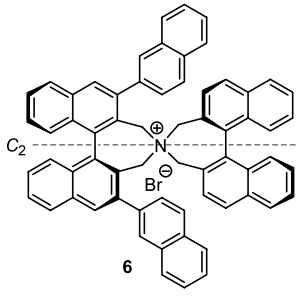
Figure 1.

* Corresponding author. E-mail: adamn@chem.leeds.ac.uk

0957-4166/$ - see front matter
doi:10.1016/S0957-4166(03)00367-7

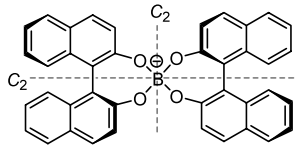
Three of the faces are blocked by the bicyclic quinuclidine framework, the allyloxymethyl group and the anthracene substituent. The enolate **5** contacts with the remaining, open face, and alkylation of its less hindered face leads to the observed enantiomer of the product **4**.

Ooi has exploited C_2 symmetry in the design of effective chiral phase-transfer catalysts, and the most exciting results were obtained with the rigid *spiro* quaternary ammonium salt **6**.[10] The rate and enantioselectivity of the benzylation of **3** was found to depend critically on the substitution pattern: with 1 mol% **6**, the reaction was complete within 30 min at 0°C, and gave the amino acid derivative (*R*)-**4** with 95% e.e.



6

In terms of Corey's model, the C_2 symmetry element of **6** means that the imaginary tetrahedron surrounding its nitrogen atom has two pairs of identical faces. The success of Ooi's catalyst may stem from its C_2 symmetry: only one design feature would be needed to block *two* faces of the imaginary tetrahedron. Close contact of the enolate **5** with either of the remaining faces, and asymmetric alkylation, would lead to the amino acid derivative **4**.



A third C_2 axis is perpendicular to the plane of the paper

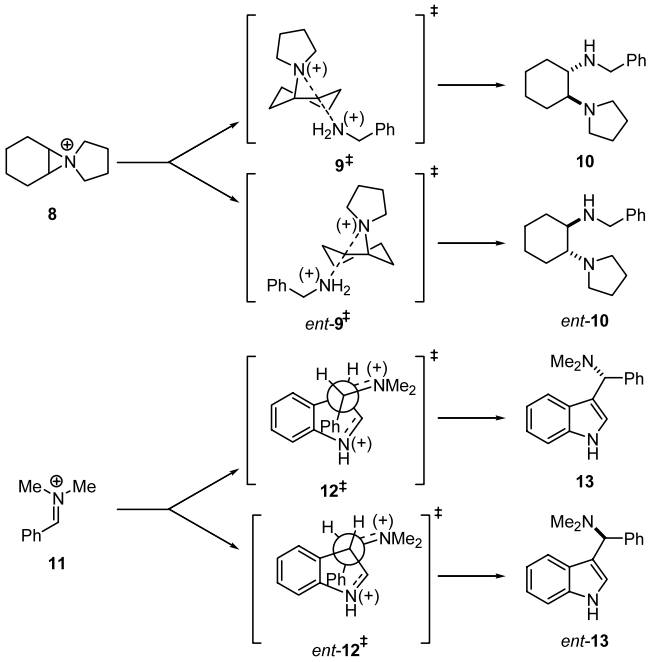
7

The aim of this research was to design chiral anions which would induce asymmetry in reactions involving prochiral, cationic intermediates. We felt that it might be possible to exploit some of the design features which have been found to underlie the success of the best cationic phase transfer catalysts. In particular, we chose to exploit symmetry in the design of chiral anions. The borate **7** is D_2 symmetric: it has three mutually perpendicular C_2 axes [the third C_2 axis is perpendicular to the plane of the paper (axis not shown)]. The faces of the imaginary tetrahedron surrounding the central boron atom are all identical, meaning that the same level of asymmetry would be induced if the reacting cation contacted any of its faces.

In addition, we chose to study the effect of D_3-symmetrical anions such as the hexacoordinate phosphate **17** in asymmetric reactions of cations. These anions are highly symmetrical and have been found to be highly effective chiral shift reagents for, for example, chiral cationic complexes[11] and phosphonium salts.[12] It was felt that these reagents might, therefore, be able to selectively stabilise one of an enantiomeric pair of transition states.

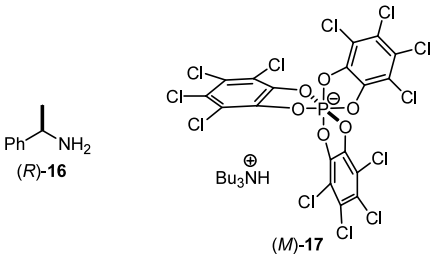
Herein, we describe our efforts to establish that stereochemical information could be transmitted between a chiral anion and a reacting cation. This goal would be the first step in the development of asymmetric phase-transfer catalysed processes. The success of some chiral quaternary ammonium salts as phase-transfer catalysts suggested that it should be possible to identify a similarly potent chiral anion.

We have investigated the possibility of inducing asymmetry in two classes of model reaction. Both of these reactions proceed under neutral conditions under which the D_2-symmetric borate **7** was expected to be chemically stable. Firstly, we have investigated ring-openings of prochiral aziridinium ions (such as **8**) with amine nucleophiles; in the case of the aziridinium **8**, ring-opening would be expected to occur *trans*-diaxially to give the *trans*-1,2-diamine **10**. Secondly, we have investigated the reaction of the iminium ion **11** with *N*-methylindole to give the tertiary amine **13**. In each case, selective stabilisation of one of the enantiomeric transition states (**9**‡/*ent*-**9**‡ or **12**‡/*ent*-**12**‡) by the chiral anion would give an enantiomerically enriched product.



2. Synthesis of salts with a chiral anion

The binaphthols (*R*)- and (*S*)-**14** were prepared by classical resolution[13] and were shown to have >99% e.e. by chiral analytical HPLC. Treatment of the binaphthols (*R*)- or (*S*)-**14** with boric acid and an amine in refluxing acetonitrile gave the borates (*R*,*R*)- or (*S*,*S*)-**15a**–**c** (Scheme 2 and Table 1).[14] Similarly, treatment with (*R*)- or (*S*)-**14** with sodium tetraborate and sodium hydroxide in THF–water[15] gave the borates (*R*,*R*)- or (*S*,*S*)-**15d**. The silver salts (*R*,*R*)- and (*S*,*S*)-**15e** were prepared by reaction of (*R*)- or (*S*)-**14** with monobromoborane methylsulfide complex in dichloromethane, evaporation, suspension in acetonitrile, and treatment with silver carbonate.[16] The tributylammonium TRISPHAT salt (*M*)-**17** was resolved classically by selective precipitation of the cinchonidinium (*P*) TRISPHAT salt.[11,17]



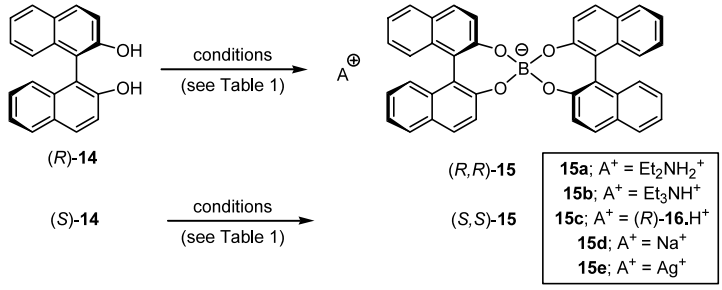
3. Synthesis of starting materials

The amino alcohols **18** and **23** were prepared by ring-opening of the corresponding *meso*-epoxides.[18] Treatment of the amino alcohols **18** and **23** with methanesulfonyl chloride and triethylamine gave the chloroamines **19** and **24** as single diastereoisomers with overall retention of configuration;[19] the *trans* configuration of **19** was established by measurement of the vicinal coupling constant between C*H*Cl and C*H*N ($^3J = 10.1$ Hz).

Treatment of the chloroamines **19** and **24** with benzylamine in a refluxing mixture of toluene and THF gave the diamines **20** and **25**, respectively.[20] The observation of overall retention of configuration for the transformations **19**→**20** and **24**→**25** confirmed the intermediacy of a *meso*-aziridinium ion in each case (**8** and **26**, respectively).[19,20] We preferred to synthesise the diamine **25** directly from the amino alcohol **23**: the diamine **25** was isolated in 78% yield over two steps for this one-pot[20] procedure (Scheme 3).

The aziridinium trifluoromethanesulfonate **21** was prepared either by treatment of the chloroamine **19** with silver trifluoromethanesulfonate, of by treatment of the amino alcohol **18** with trifluoromethanesulfonic anhydride and triethylamine. We were unable to prepare the trifluoromethanesulfonate salt of the aziridinium ion **26** using either of these methods, presumably reflecting its greater electrophilicity.

The 1,1-diamine **27**, prepared from benzaldehyde, was treated with acetyl chloride, and gave the iminium chloride[21] **28** in 85% yield, which was stored in the freezer until required. A racemic sample of the amine **13** was prepared in 82% yield by treatment of the iminium salt **28** with *N*-methyl indole (Scheme 4).[22]

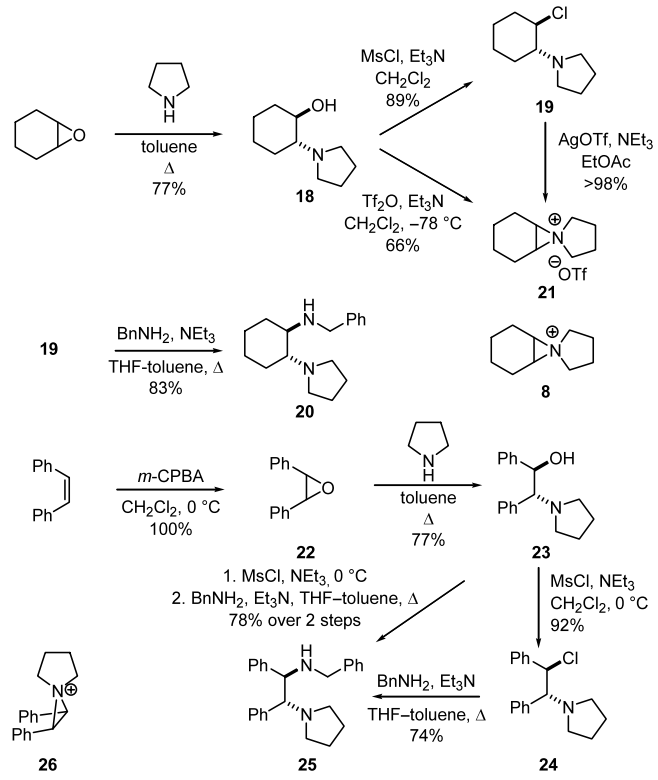


Scheme 2.

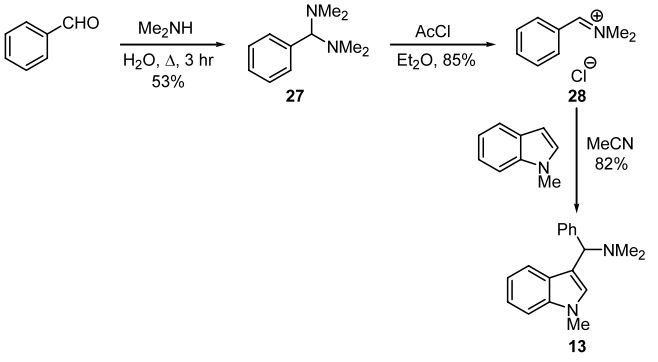
Table 1. Preparation of salts **15** with the chiral counterion **7**

Entry	Starting material	Conditions	Amine	Product	$[\alpha]_D^{20}$ (*c* in DMSO)	Yield (%)
1a	(*R*)-**14**	A	Et_2NH	(*R*,*R*)-**15a**	−265 (1.10)	88
1b	(*S*)-**14**	A	Et_2NH	(*S*,*S*)-**15a**	+271 (1.09)	84
2a	(*R*)-**14**	A	Et_3N	(*R*,*R*)-**15b**	−232 (1.01)	82
2b	(*S*)-**14**	A	Et_3N	(*S*,*S*)-**15b**	+249 (0.92)	85
3a	(*R*)-**14**	A	(*R*)-**16**	(*R*,*R*)-**15c**	−239 (1.06)	31
3b	(*S*)-**14**	A	(*R*)-**16**	(*S*,*S*)-**15c**	+321 (1.05)	37
4	(*R*)-**14**	B	–	(*R*,*R*)-**15d**	+174 (1.04)	42
5	(*R*)-**14**	C	–	(*R*,*R*)-**15e**	+136 (1.05)	15

A: $B(OH)_3$, amine, MeCN, Δ, 12 h; B: $Na_2B_4O_7{\cdot}10H_2O$, NaOH, THF–H_2O; C: 1. $BH_2Br{\cdot}Me_2S$, CH_2Cl_2; 2. Ag_2CO_3, MeCN.



Scheme 3.

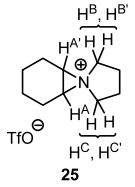


Scheme 4.

4. Investigation into ion-pairing between an aziridinium and a borate ion

The possibility of ion pairing between the aziridinium ion **8** and the borate anion **7** was investigated by NMR spectroscopy. A sample of the aziridinium salt **21** was dissolved in $CDCl_3$, and 0.1 equiv. of the salt (*R*,*R*)-**15c** were successively added until the solution was saturated; at each stage, the 300 MHz ^1H and the 75 MHz ^{13}C NMR spectra were recorded. The first indication that there was a favourable interaction was that the salt (*R*,*R*)-**15c** dissolved in the presence of the aziridinium salt **21**; previously the borate (*R*,*R*)-**15c** had been soluble only in DMSO-d_6.

The chemical shifts of the protons H^A, H^B and H^C and the carbons C^A and C^C were found to vary linearly with the amount of (*R*,*R*)-**15c** present (Figs. 2 and 3). This trend may indicate that the aziridinium ion **8** forms an ion pair with the borate anion **7**. However, there was no evidence for splitting of the enantiotopic pairs of protons $H^A/H^{A'}$, $H^B/H^{B'}$ and $H^C/H^{C'}$, suggesting that the enantiotopic sides of the aziridinium ion were not being effectively distinguished by the chiral anion. Previously, some chiral anions have been shown to ion pair diastereoselectively with chiral cations,[23] and to have value as chiral shift reagents.[11,12,24]



5. Effect of chiral additives on the reaction of *N*-methyl indole with an iminium ion

We adopted a screening approach to study the reaction of *N*-methyl indole with the iminium salt **28** (Scheme 5). The effect of solvent and 10 mol% of the chiral salt (*R*,*R*)-**15b** on the yield of the amine **13** was investigated (Table 2). Reactions were performed in parallel on a 0.076 mmol scale at 25°C in a Radley's carousel reaction station; in each case, the initial concentration of the iminium ion was 1.19 M, and the reaction time was 2 h. The products of the reactions were analysed, and the yields determined, by analytical HPLC.

In preliminary experiments, the solvent was found to have a profound effect on the yield of the amine **13**. In the absence of the additive (*R*,*R*)-**15b**, the yield of the amine **13** was significantly higher in the chlorinated solvents dichloromethane and chloroform than in acetonitrile, hexane or ethyl acetate. In none of these reactions were any by-products isolated; therefore, the yields of the products may give a reasonable guide to relative rates of each reaction. In the case of solvents with an intermediate dielectric constant, such as THF ($\varepsilon = 7.6$) and dichloromethane ($\varepsilon = 9.1$), the addition of 10 mol% (*R*,*R*)-**15b** increased the yield of **13**. This result suggests that the presence of the additive may reduce the activation energy of the reaction, presumably by selective stabilisation of its cationic transition state.

The reaction was investigated further in THF, chloroform and dichloromethane. In each case, the reactions were performed in parallel with 10 mol% of a chiral additive, and the yields were determined, by analytical HPLC. In general, the reactions were performed in duplicate using both (*R*,*R*) and (*S*,*S*) additives. For reactions which proceeded in >20% yield, the enantiomeric excesses were determined by chiral analytical HPLC by comparison with a racemic sample of the amine **13**.

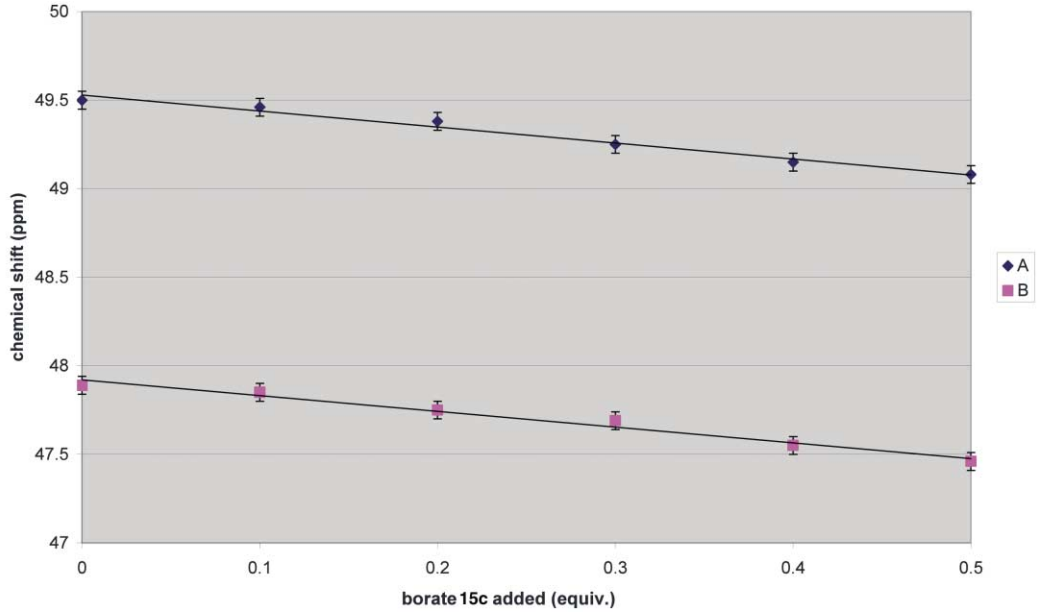


Figure 2.

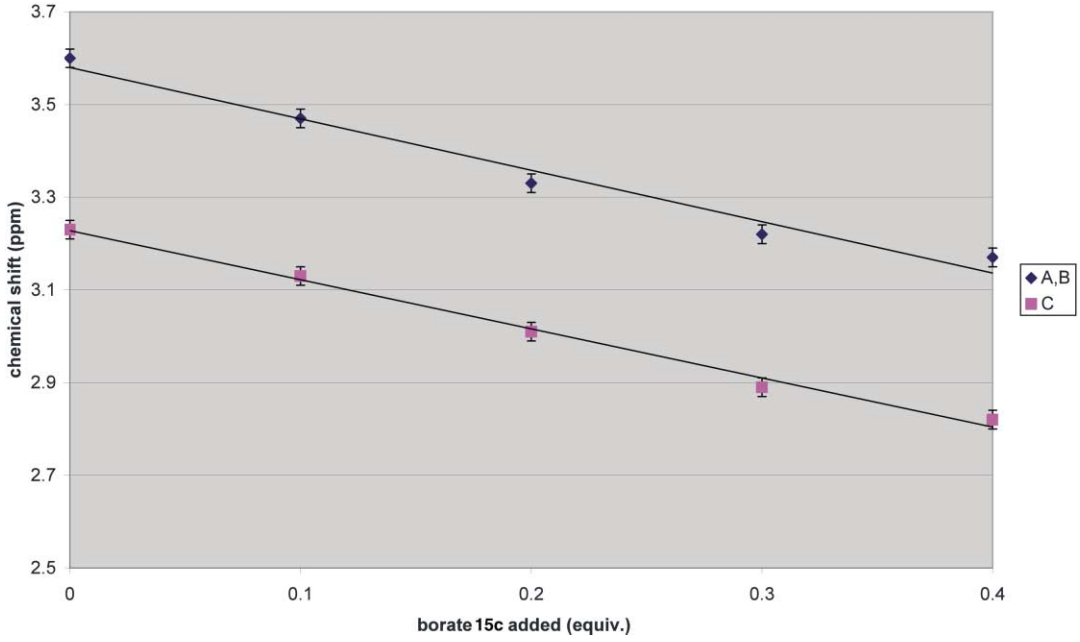
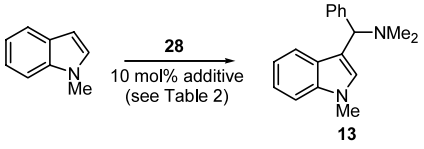


Figure 3.



Scheme 5.

The cationic counterion of the chiral additive had a remarkable effect on the yield of the product **13** (Table 2). Furthermore, the optimal counterion depended on the solvent which was used; in general, however, the salts with the more lipophilic ammonium ions—either the triethylammonium **15b** and (*R*)-α-methylbenzylammonium **15c** salts—gave the best yields of the amine **13**.

Table 2. Effect of solvent and additives on the yield and e.e. of the amine **13**

Solvent	THF		CH_2Cl_2		$CHCl_3$	
	Yield[a] (%)		Yield[a] (%)		Yield[a] (%)	
Additive	(*R*,*R*) additive [e.e. (%)][b]	(*S*,*S*) additive [e.e. (%)][b]	(*R*,*R*) additive [e.e. (%)][b]	(*S*,*S*) additive [e.e. (%)][b]	(*R*,*R*) additive [e.e. (%)][b]	(*S*,*S*) additive [e.e. (%)][b]
None	23		58		31	
15a	12[c]		22[c]		35[c]	
	[+3]	[−5]	[−6]	[−6]	[+3]	[−1]
15b	38[d]		62[d]		32[c]	
	[−3]	–	[−3]	–	[+1]	[+4]
15c	52[c]		28[c]		98[e]	
	[−10]	[−11]	[+8]	[+3]	–	[+3]
15d	22[d]		14[e]		0[c]	
	[+11]	–	–	[−8]	[f]	[f]
15e	3[e]		28[c]		20[e]	
	[f]	–	[−3]	–	[f]	–

[a] Determined by analytical HPLC.
[b] Determined by chiral analytical HPLC.
[c] Average yield for reactions with (*R*,*R*) and (*S*,*S*) additives.
[d] Yield for reactions with (*R*,*R*) additive.
[e] Yield for reactions with (*R*,*R*) additive.
[f] Enantiomeric excess not determined.

In each reaction, the iminium salt **28** was insoluble in the reaction mixture, and the reaction gradually became more homogeneous as the reaction proceeded.

The enantiomeric excesses of the product **13** were, however, extremely disappointing. Few of the products isolated had enantiomeric excesses which were significantly higher than the estimated experimental error (ca. ±5%). In order to recognise inherent systematic errors, the reactions were generally performed using both the (*R*,*R*) and the (*S*,*S*) additives. In the case of the additives **15a**–**b** and **15d**–**e**, the (*R*,*R*) and (*S*,*S*) additives were enantiomeric:[†] in these cases, the enantiomeric excesses measured were low, and were clearly close to the limits of experimental error since equal and opposite values were rarely observed. In view of the low enantiomeric excesses, the absolute configuration of the products was not determined.

6. Effect of chiral additives on the yield and enantioselectivity of ring-opening of an aziridinium ion

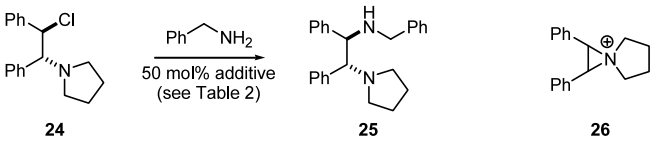
The influence of chiral additives on the yield and the enantioselectivity of ring-opening of prochiral aziridinium ions was also investigated. Preliminary experiments showed that the ring-opening of the aziridinium ion **8** was rather sluggish, particularly at low temperature, and efforts were, therefore, focused on the ring-opening of the aziridinium ion **26** with benzylamine (Scheme 6).

[†] The salts (*R*,*R*)- and (*S*,*S*)-**15c** are diastereoisomers. With these salts, equal and opposite enantiomeric excesses would not necessarily be expected, and were not, in fact, observed.

The reaction **24**→**26**→**25** was investigated in parallel in THF–toluene at four different temperatures, and the yield of each reaction was determined by analytical HPLC (see Table 3). The presence of 50 mol% of the chiral borates **15** generally increased the yield of the diamine **25**, particularly at elevated temperature (40–100°C). The effect of the counterion was rather less pronounced in this case, though the yields were better with the substituted alkylammonium **15a**–**c** and sodium **15d** salts. The tributylammonium TRISPHAT salt (*M*)-**17** improved the yield of the diamine **25**, particularly at higher temperatures (60 or 100°C).

The enantiomeric excesses (Fig. 4) were determined by chiral analytical HPLC for the reactions at 100°C which gave >20% yield of the diamine **25**. These reactions were, in general, performed with both enantiomeric additives in order to recognise systematic errors associated with each measurement. It is estimated that the random error associated with each enantiomeric excesses measurement was ±3%.

The chiral additives **15a**–**d** and (*M*)-**17** did have a significant effect on the enantioselectivity of the ring-opening of the aziridinium ion **26**. Although, the observed enantioselectivities were low (<ca. 15%), the enantiomeric excesses measured were generally higher than the inherent errors associated with each measurement. Furthermore, approximately equal levels of opposite senses of induction were observed for enantiomeric catalysts (*R*,*R*)- and (*S*,*S*)-**15a**–**b** and **15d**. Remarkably, the role of the substituted ammonium counterion in the additives is not simply as a bystander: the salts (*R*,*R*)-**15a** ($A^+ = Et_2NH_2^+$) and **15b** ($A^+ = Et_3NH^+$) induce opposite senses, although low levels, of asymmetry in the ring-opening of the aziridinium ion **26** (Fig. 4).



24 25 26

Scheme 6.

Table 3. Yields of the diamine **25** in THF–toluene as a function of temperature

Temperature	25°C	40°C	60°C	100°C
Additive	Yield[a] (%)	Yield[a] (%)	Yield[a] (%)	Yield[a] (%)
None	22	15	10	15
15a	21[b]	26[b]	12[b]	18[b]
15b	15[b]	28[b]	13[b]	25[b]
15c	15[b]	21[b]	16[b]	30[b]
15d	13	15[d]	17[d]	12[d]
15e	15[b]	28[c]	20[b]	27[b]
(*M*)-**17**	18	7	37	22

[a] Determined by analytical HPLC.
[b] Average yield for reactions with (*R*,*R*) and (*S*,*S*) additives.
[c] Yield for reactions with (*R*,*R*) additive.
[d] Yield for reactions with (*S*,*S*) additive.

7. Conclusion

The influence of chiral salts on reactions which involve cationic *meso* intermediates was investigated. Efforts were focused on two different classes of reaction: the addition of *N*-methyl indole to a prochiral iminium ion, and the ring-opening of a prochiral aziridium ion with an amine nucleophile. The addition of these chiral additives often had a very significant (beneficial or detrimental) effect. A surprising observation was that the cationic counterion of the chiral additive could have a very pronounced effect on the yield of the reaction.

Unfortunately, all of the observed enantioselectivities were low (<15% e.e.). However, in the case of the ring-opening of the aziridinium ion **26** with benzylamine, low, but significant, enantioselectivities were induced. Nonetheless, the levels of induction compare well the other studies in this area.[16,25] Remarkably, the chiral counterion was shown to have an effect on the sense, as well as the level, of the induction. The enantioselectivity may stem from selective stabilisation of one of the enantiomeric transition states by ion-pairing with the chiral anion present. ^{1}H NMR spectroscopy was used to show that the salt (*R*,*R*)-**15c** did interact with the aziridinium ion **8**; however, no evidence was obtained for enantioselective recognition of one of the enantiotopic sides of the ion **8**. The absence of enantioselective recognition in this case helps rationalise the low levels of enantioselectivities observed. The principles which have been used to design a 'first generation' of chiral anions may be applied in the future to help identify salts which are effective phase transfer catalysts for inducing asymmetry in reactions of cations.

8. Experimental

General experimental procedures have been described previously. The borates (*R*,*R*)-**15c**[14] and **15e**,[16] the TRIPHAT salt (*M*)-**17**,[11,17] the iminium chloride[21] **28**, the tertiary amine[22] **13** and the diamine[20] **20** were prepared as has been previously described. Analytical HPLC was conducted on a Gynkotek HPLC system with diode array detection; unless otherwise stated, the column oven was set at 24°C. A Chiracel OD column

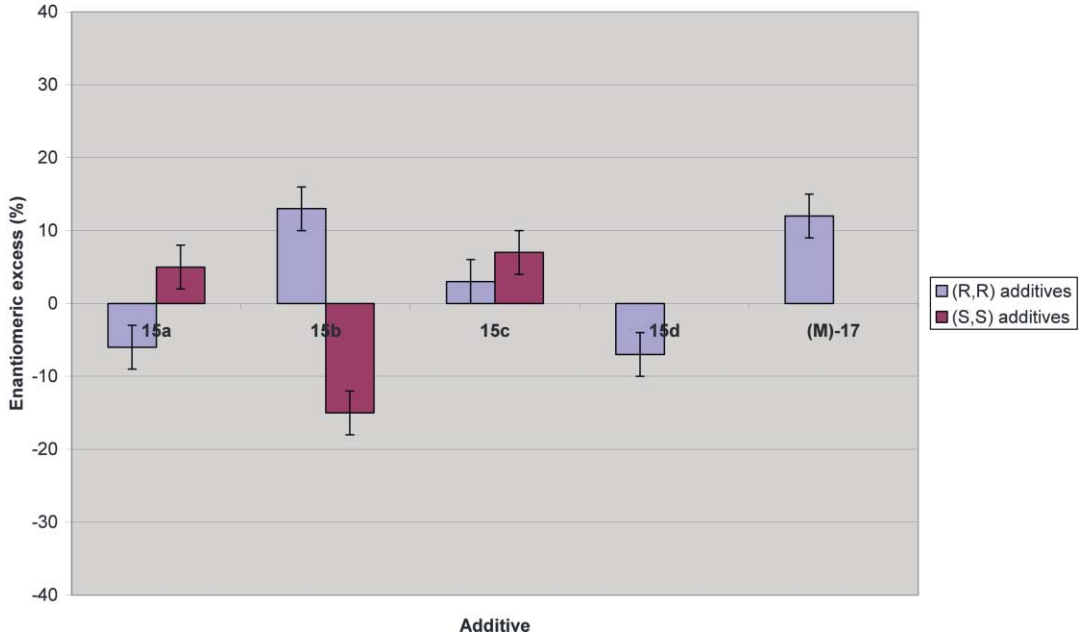


Figure 4. Enantiomeric excesses of the diamine **25** prepared at 100°C.

(4.6×250 mm) and a ChirobioticV (4.6×250 mm) column were used for chiral analytical HPLC and an XTerra C_{18} (5 μm, 4.6×50 mm) column for analytical HPLC; samples were calibrated against external standard samples.

8.1. Diethylammonium bis[(*R*)-1,1′-bi-2-naphtholato] borate (*R*,*R*)-15a

(*R*)-1,1′-Bi-2-naphthol (2.5 g, 8.73 mmol) was added to the stirred solution of boric acid (270 mg, 4.37 mmol) and diethylamine (1.35 ml, 13.1 mmol) in acetonitrile (18 ml). The reaction mixture was refluxed 16 h. The reaction mixture was cooled to rt then filtered. The precipitate was then dried under vacuum to leave the *borate salt* (*R*,*R*)-**15a** (5.01 g, 88%) as colourless plates, mp >300°C; $[\alpha]_D^{20}$ −265.3 (*c* 1.10, DMSO); (found: MH^+, 653.2815. $C_{44}H_{36}BNO_4$ requires *MH*, 653.2815); ν_{max}/cm^{-1} (Nujol mull) 1605, 1575, 1485, 1310, 1230, 800 and 730; δ_H (300 MHz; DMSO-d_6) 7.95 (8H, m, 3 and 4-H), 7.26–7.34 (8H, m, 5 and 8-H), 7.15 (8H, m, 6 and 7-H), 2.86 (4H, q, *J* 7.3, CH_2N), 1.10 (6H, t, *J* 7.3, 2×CH_3); δ_C (75 MHz; DMSO-d_6) 156.4, 133.1, 129.3, 128.5, 128.4, 126.1, 125.2, 124.9, 122.8, 122.2, 41.8 and 11.5; δ_B (250 MHz; DMSO-d_6) 8.96; *m*/*z* (FAB) 727.2 (100%, $MNH_2Et_2^+$), 653.1 (13, M^+) and 580 (82).

By the same method, (*S*)-1,1′-bi-2-naphthol **123** (2.5 g, 8.73 mmol) gave the *borate salt* (*S*,*S*)-**15a** (4.79 g, 84%) as colourless plates, $[\alpha]_D^{20}$ +271.0 (*c* 1.09, DMSO), spectroscopically identical to the enantiomeric salt obtained previously.

8.2. Triethylammonium bis[(*R*)-1,1′-bi-2-naphtholato] borate (*R*,*R*)-15b

By the same general method, (*R*)-1,1′-bi-2-naphthol (2.15g, 7.51 mmol) gave *borate salt* (*R*,*R*)-**15b** (4.19 g, 82%) as colourless crystals, $[\alpha]_D^{20}$ −232.4 (*c* 1.01, DMSO); (found MH^+, 682.3128. $C_{46}H_{40}BNO_4$ requires *MH*, 681.3128); ν_{max}/cm^{-1} (Nujol mull) 1463 (C=C), 1377 (C-O) and 1071 (C-O); δ_H (300 MHz; DMSO-d_6) 7.91 (4H, d, *J* 8.5, 3-H), 7.87 (4H, d, *J* 8.5, 4-H), 7.47 (4H, d, *J* 8.6, 5-H), 7.29 (4H, m, 6-H), 7.15 (4H, m, 7-H), 7.13 (4H, d, *J* 7.4, 8-H), 2.66 (6H, q, *J* 7.3 and 6.8, CH_2NH), 0.83 (9H, t, *J* 7.2, CH_2CH_3); δ_C (75 MHz; DMSO-d_6) 153.32, 133.2, 129.2, 128.9, 128.4, 126.2, 125.2, 124.9, 122.8, 122.2, 46.1 and 31.1; δ_B (250 MHz; DMSO-d_6) 8.98; *m*/*z* (FAB) 681 (40%, MH^+), 603 (100) and 580 (40).

By the same general method, (*S*)-(−)-1,1′-bi-2-naphthol 123 (2.5g, 8.73 mmol) gave the borate salt (*S*,*S*)-**15b** (5.06 g, 85%) as colourless crystals, $[\alpha]_D^{20}$ +249 (*c* 0.92, DMSO), spectroscopically identical to the enantiomeric salt obtained previously.

8.3. (*R*)-α-Methylbenzylamine bis[(*S*)-1,1′-bi-2-naphtholato] borate (*S*,*S*)-15c

By the same general method, (*S*)-1,1′-bi-2-naphthol (500 mg, 1.75 mmol) and (*R*)-(+)-α-methylbenzylamine (300 μl, 2.62 mmol) gave the *borate salt* (*S*,*S*)-**15c** (545 mg, 45%) as colourless plates, mp >300°C; $[\alpha]_D^{20}$ +320.9 (*c* 1.05, DMSO); ν_{max}/cm^{-1} (Nujol mull) 2920, 1463, 1377, 1247, 1070 and 1007; δ_H (300 MHz; DMSO-d_6) 7.7 (4H, d, *J* 8.5, 3-H), 7.46 (4H, d, *J* 8.5, 4-H), 7.22 (4H, t, *J* 6.9), 7.11–7.02 (8H, m), 6.89 (4H, m, 8-H), 3.48 (1H, q, *J* 6.6, C*H*-NH_3), 2.94 (3H, brs, NH_3), 0.74 (3H, d, *J* 6.6, CH_3-NH_3); δ_C (75 MHz; DMSO-d_6) 156.4, 153.4, 146.8, 133.2, 129.3, 128.6, 128.4, 127.1, 126.3, 126.2, 125.2, 124.8, 124.7, 122.8, 122.6, 122.2, 50.8 and 25.3; δ_B (250 MHz; DMSO-d_6) 9.01; *m*/*z* (FAB) 702.4 (23, MH^+), 580.1 (10), 286.1 (8), 122.0 (55) and 104.9 (100).

8.4. Sodium bis[(*R*)-1,1′-bi-2-naphtholato] borate (*R*,*R*)-15d

(*R*)-(−)-1,1′-Bi-2-naphthol (1 g, 3.5 mmol) in tetrahydrofuran (15 ml) was added to the stirred solution of sodium tetraborate (180 mg, 0.46 mmol) and sodium hydroxide (40 mg, 1 mmol) in water (4 ml). The reaction mixture was stirred at rt 16 h. The phases were separated and the organic layer was washed with saturated aqueous sodium chloride solution (2 ml) and the concentrated under reduced pressure to approx. 7 ml. The solution was cooled to 0°C and the precipitate was filtered to give the borate salt[26] (*R*,*R*)-**15d** (886 mg, 42%) as yellow plates, $[\alpha]_D^{20}$ +173.6 (*c* 1.04, DMSO).

8.5. General method for the screening methods for the synthesis of 13

N-Methylindole **13** (98 μl, 0.76 mmol) was added slowly to a stirred solution of the iminium salt **28** (160 mg, 0.91 mmol) and the additive in a solvent (640 μl). The reaction mixture was stirred at rt for 2 h. The precipitate formed was filtered off and washed with acetonitrile. The precipitate was redissolved in DCM (5 ml), 5% aqueous ammonia (3 ml) added and the layers separated. The organic layer was washed with water, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a crude product which was analysed by chiral HPLC (Chiralcel OD column; eluent: 99.99:0.001 hexane–triethylamine; retention times: **13**, 14.5 min; *ent*-**13**, 18.5 min; *N*-methylindole, 21.5 min).

8.6. 1,1-Pyrrolidinyl-2,3-cyclohexenylaziridinium trifluoromethanesulfonate 21

Triethylamine (2.2 ml, 15.2 mmol) was added dropwise to a stirred solution of the amino alcohol **18** (2.0 g, 11.8 mmol) in dichloromethane (210 ml). The reaction mixture was cooled to −78°C, trifluoromethanesulfonic anhydride (2.2 ml, 13.2 mmol), warmed slowly to 0°C over 90 min, saturated aqueous sodium hydrogen carbonate solution (150 ml) added and the layers separated. The aqueous layer was washed with dichloromethane (100 ml) and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give the *aziridinium salt* **21** (2.34 g, 66%) as brown needles, mp 29.1–30.7°C, R_f 0.79; ν_{max}/cm^{-1} 3436, 3076, 2943, 2866, 2252, 1453, 1361, 1279, 1224, 1163, 1081, 1030, 913, 732 and 689 (CF); δ_H (300 MHz; $CDCl_3$) 3.57 (4H, t, *J* 6.8, (C*H*)C*H*NCH_2), 3.23 (2H,

t, J 6.8, NCH_2), 2.25 (4H, t, J 7.3, CH_2CH_2), 2.12 (4H, q, J 7.3), 1.36 (4H, t, J 7.3); δ_C (75 MHz; $CDCl_3$) 123.0 (CF_3), 64.8, 49.3, 47.4, 25.0, 24.2, 18.9 and 18.0; m/z 301 (12%, M^+), 151 (26, $C_{10}H_{17}N$), 110 (31, $C_7H_{12}N$), 81 (49, C_6H_9), 69 (56, C_4H_7N), 43 (100, C_2H_5N).

8.7. 1,1-Pyrrolidinyl-2,3-cyclohexenylaziridinium trifluoromethanesulfonate 21

Silver trifluoromethanesulfonate (2.05 g, 7.99 mmol) was added to a stirred solution of the chloroamine **19** (1.5 g, 7.99 mmol) in ethyl acetate (75 ml). The reaction mixture was stirred for 1 h at rt, filtered and the filtrate was evaporated under reduced pressure to give the *aziridinium salt* **21** (2.41 g, 100%) as needles, spectroscopically identical to that previously obtained.

8.8. (*R**,*R**)-1,2-Diphenyl-2-pyrrolidin-1-yl-ethanol 23

Pyrrolidine (159 μl, 1.91 mmol) was added to the stirred solution of (*R**,*S**)-2,3-diphenyl oxirane[27] (250 mg, 1.27 mmol) in toluene (2 ml). The reaction mixture was refluxed for 24 h, cooled to rt, evaporated under reduced pressure to give a crude product which crystallised to give the *amino alcohol* **23** (326 mg, 96%), mp 88.5–89.4°C; R_f 0.18; (found: C, 80.6; H, 8.0; N, 5.2; $C_{18}H_{21}NO$ requires C, 80.9; H, 7.90; N, 5.2%); ν_{max}/cm^{-1} 3210, 1320, 1280, 1100 and 1060; δ_H (300 MHz; $CDCl_3$) 7.08–7.28 (10H, m, Ar-H), 5.29 (1H, br s, OH), 5.00 (1H, d, J 10.0, CH-OH), 3.82 (1H, d, J 10.0, CH-N), 2.64 (2H, m), 2.47 (2H, m), 1.62–1.78 (4H, m); δ_C (75 MHz; $CDCl_3$) 142.2, 130.6, 128.4, 128.2, 127.9, 127.7, 127.6, 72.3, 72.0, 48.4 and 23.1; m/z 268 (33%, MH^+), 267 (10, M^+), 266 (40), 160 (100), 105 (7) and 70 (15).

8.9. (*R**,*R**)-1-Chloro-1,2-diphenyl-2-pyrrolidin-1-yl-ethane 24

Methanesulfonyl chloride (650 μl, 8.4 mmol) and triethylamine (1.2 ml, 8.4 mmol) were added to the stirred solution of the amino alcohol **23** (1.5 g, 5.6 mmol) in dichloromethane (25 ml) at 0°C. The reaction mixture was slowly warmed to rt over 2 h, washed with saturated aqueous sodium bicarbonate solution (2×25 ml) and the organic layer dried (Na_2SO_4), filtered and evaporated under reduced pressure to leave the *chloroamine* 220 (1.6 g, 99%) as a brown oil; R_f 0.84; (found: MH^+, 286.1352. $C_{18}H_{20}NCl$ requires MH, 286.1363); ν_{max}/cm^{-1} 3025, 2950, 1610, 1480, 1445 and 710; δ_H (300 MHz; $CDCl_3$) 7.11 (8H, s, Ar-H), 6.96 (2H, m, Ar-H), 5.42 (1H, d, J 7.5, CH-Cl), 4.06 (1H, d, J 7.5, CH-N), 2.65 (2H, m, CH_a and CH_c), 2.56 (2H, m, CH_b and CH_d), 1.71 (4H, m, CH_2CH_2); δ_C (75 MHz; $CDCl_3$) 139.3, 136.6, 130.2, 128.7, 128.4, 128.2, 127.8, 127.5, 74.7, 64.6, 51.2 and 23.6; m/z (ES) 286.2 (100%, MH^+), 268.2 (83) and 250.2 (41).

8.10. (*R**,*R**)-Benzyl-(1′,2′-diphenyl-2-pyrrolidin-1-yl-ethyl)-amine 25

Benzylamine (287 μl, 2.62 mmol) and triethylamine (488 μl, 3.5 mmol) were added to the stirred solution of the chloroamine **24** (500 mg, 1.75 mmol) in toluene (5 ml) and THF (5 ml). The reaction mixture was refluxed for 24 h, cooled to rt, washed with saturated aqueous sodium bicarbonate solution (3×5 ml), dried (Na_2SO_4), filtered and evaporated to leave the crude product, which was purified by flash chromatography, eluting with 2:8 ethyl acetate–petrol, to give the *diamine* **25** (512 mg, 82%) as an orange oil, R_f 0.85; (found: MH^+, 357.2331. $C_{25}H_{28}N_2$ requires MH, 357.2331); ν_{max}/cm^{-1} 3299, 3061, 3027, 2821, 1602 and 1584; δ_H (300 MHz; $CDCl_3$) 7.32–7.39 (2H, m), 7.21–7.31 (5H, m), 7.03–7.17 (6H, m), 6.95 (2H, dt, J 6.2 and 1.8), 4.07 (1H, d, J 10.2, PhCH_aH$_b$), 4.00 (1H, d, J 10.2, PhCH$_a$$H_b$), 3.78 (1H, d, J 13.6, 1′- or 2′-H), 3.45 (1H, d, J 13.6, 2′- or 1′-H), 2.28–2.45 (4H, m) and 1.62 (4H, m); δ_C (75 MHz, $CDCl_3$) 141.4, 140.9, 140.8, 130.2, 128.9, 128.4, 128.3, 128.0, 127.8, 127.7, 127.3, 126.9, 70.1 (CH-NH), 61.9 (CH-N), 51.0 (CH_2-Ph), 47.7 (CH_2-N), 22.7 (CH_2); m/z (ES) 357 (100%, MH^+), 286 (77) and 250 (62).

8.11. General method for the screening methods for the synthesis of 25

Benzylamine (19 μl, 0.17 mmol) and triethylamine (24 μl, 0.17 mmol) were added to a stirred solution of the chloroamine **24** (25 mg, 0.09 mmol) in toluene (2 ml) and THF (2 ml). The reaction mixture was refluxed for 24 h, cooled to rt and washed with saturated aqueous sodium bicarbonate solution (2×2 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure to give the crude product which was analysed by analytical HPLC (Waters XTerra column; gradient elution: 0.1:0.1:19.8:80→ 0.1:0.1:99.8:0 triethylamine–acetic acid–methanol–water over 15 min; retention time: 8.72 min) and chiral HPLC (Waters XTerra column in series with Chirabiotic V column; gradient elution: 0.1:0.1:19.8:80→ 0.1:0.1:49.8:50 triethylamine–acetic acid–methanol–water over 8.75 min, followed by 0.1:0.1:99.8:0 triethylamine–acetic acid–methanol–water for 16.25 min; retention times: **25**, 19.4 min; *ent*-**25**; 21.3 min).

References

1. (a) Nelson, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1583; (b) Carter, C.; Nelson, A. In *Organic Synthesis Highlights V*; Schmaltz, H.-G.; Wirth, T., Eds.; Wiley: Weinheim, 2003.
2. Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.
3. (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353; (b) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595; (c) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000.
4. Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron* **2001**, *57*, 6447.
5. (a) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347; (b) Kim, D. Y.; Huh, S. C.; Kim, S. M. *Tetrahedron Lett.* **2001**, *42*, 6299.
6. (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1998**, *39*, 1599; (b) Alcaraz, L.; MacDonald, G.; Ragot, J.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron* **1999**, *55*, 3707; (c) Arai, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2145.
7. Arai, S.; Nakayama, K.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* **1999**, *40*, 4215.

8. Brown, R. C. D.; Kelly, J. F. *Angew. Chem., Int. Ed.* **2001**, *40*, 4496.
9. (a) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228; (b) Belokon, Y. N.; North, M.; Kublitski, V. S.; Ikonnikov, N. S.; Krasik, P. E.; Maleev, V. I. *Tetrahedron Lett.* **1999**, *40*, 6105; (c) Belokon, Y. N.; Davies, R. G.; North, M. *Tetrahedron Lett.* **2000**, *41*, 7245; (d) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, O. V.; Parmár, V. S.; Kumar, R.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 851.
10. Ooi, T.; Kameda, M.; Maruoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 6519.
11. Lacour, J.; Ginglinger, C.; Favarger, F.; Torche-Haldimann, S. *Chem. Commun.* **1997**, 2285.
12. Ginglinger, C.; Jeannerat, D.; Lacour, J.; Jugé, S.; Uziel, J. *Tetrahedron Lett.* **1998**, *39*, 7495.
13. Cai, D.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7991.
14. Perisamy, M.; Venkatraman, L.; Sivakumar, S.; Sampathkumar, N.; Ramanathan, C. R. *J. Org. Chem.* **1999**, *64*, 7643.
15. Matteson, D. S.; Ray, R.; Rocks, R. R.; Tsai, D. J. *Organometallics* **1983**, *2*, 1536.
16. Llewellyn, D. B.; Adamson, D.; Arndtsen, B. *Org. Lett.* **2000**, *2*, 4165.
17. Lacour, J.; Ginglinger, C.; Grivet, C.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **1997**, *36*, 609.
18. Shapiro, S. L.; Soloway, H.; Shapiro, H. J.; Freeman, L. *J. Am. Chem. Soc.* **1959**, *81*, 3993.
19. Anderson, S. R.; Ayers, J. T.; Vries, K. M.d.; Ito, F.; Mendenhall, D.; Vanderplas, B. C. *Tetrahedron: Asymmetry* **1999**, *10*, 2655.
20. O'Brien, P.; Poumellec, P. *Tetrahedron Lett.* **1996**, *37*, 5619.
21. Betschart, C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1999.
22. Grumbach, H. J.; Arend, M.; Risch, N. *Synthesis* **1996**, *7*, 883.
23. Lacour, J.; Jodry, J. J.; Ginglinger, C.; Torche-Haldimann, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 2379.
24. (a) Chen, Y.-X.; Metz, M. V.; Li, L.; Stern, S. L.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 6287; (b) Lacour, J.; Ginglinger, C.; Favarger, F. *Tetrahedron Lett.* **1998**, *39*, 4825.
25. Lacour, J.; Monchaud, D.; Marsol, C. *Tetrahedron: Asymmetry* **2002**, *43*, 8257.
26. Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem. Eur. J.* **1996**, *2*, 1368.
27. Lusinchi, X.; Hanquet, G. *Tetrahedron* **1997**, *53*, 13727.