The diastereoselective and enantioselective substitution reactions of an isoindoline–borane complex

Azhar Ariffin,[a] Alexander J. Blake,[a] Mark R. Ebden,[a] Wan-Sheung Li,[a] Nigel S. Simpkins *[a] and David N. A. Fox[b]

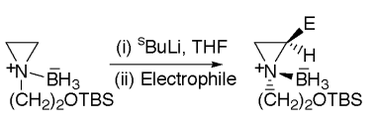
[a] *School of Chemistry, University of Nottingham, University Park, Nottingham, UK NG7 2RD*
[b] *Department of Discovery Chemistry, Pfizer Central Research, Sandwich, Kent, UK CT13 9NJ*

Received (in Cambridge) 15th June 1999, Accepted 13th July 1999

The alkylation of *N*-methylisoindoline–borane complex, using ^{n}BuLi in THF is diastereoselective, the substitution occurring predominantly *syn* to the borane group. Use of the ^{s}BuLi–sparteine reagent mixture in Et_2O changes the diastereoselectivity observed and enables the reaction to be conducted enantioselectively, giving the chiral isoindoline–borane complexes in up to 89% ee. The relative and absolute configurations of the chiral products were established by X-ray structure determinations and NMR studies. The new asymmetric process is shown to be an enantioselective deprotonation reaction, and the intermediate organolithium is shown to be epimerisable.

Over the past few years several research groups have described the use of Lewis acid activators, such as BF_3 or BH_3, to facilitate the α-metallation of a range of tertiary amines, including benzylic, allylic and even saturated types, by either lithium tetramethylpiperidide (LTMP) or ^{s}BuLi.[1] We recently described our own results in this area, in which the use of borane activation allowed interesting regiocontrol in the metallation and electrophilic substitution of certain tertiary amines.[2] Following this first phase of our work, it became clear that the use of such borane activation could also have implications for controlling the stereochemistry of amine substitution reactions.

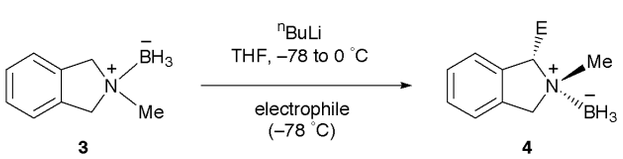
Firstly, a paper by Vedejs and Kendall showed that the borane activation technique is applicable to aziridines, and that the alkylation chemistry of such systems is highly diastereocontrolled, both the metallation and electrophilic quench occurring *syn* to the BH_3 group, *e.g.* the conversion of amine–borane complex **1** into substituted derivative **2**, Scheme 1.[3]



1 **2**

Scheme 1

Our own preliminary report in this area described the stereocontrolled alkylation of the amine–borane complex **3** derived from *N*-methylisoindoline, for example the simple alkylation reactions which furnished diastereomeric mixtures of products in which **4** was the major component, Scheme 2.[4]

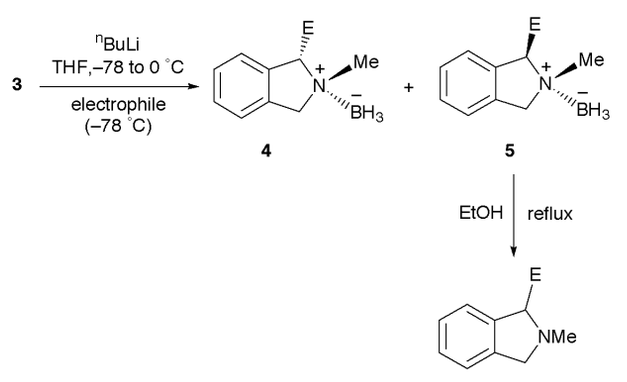


3 **4**

Scheme 2

An enantioselective variant of this reaction was also described, which allowed the isolation of product complexes in good levels of enantiomeric excess.[4] Herein we describe further details of this research, which has sought to probe the scope of the reaction and the origins of the diastereo- and enantiocontrol, which were not clear from our preliminary findings.

Table 1 Diastereoselective alkylation of **3**



Electrophile	Product	**3**→**4**–**5** (%)	Dr **4**:**5**	**4**–**5**→**6** (%)
Bu_3SnCl	**4**–**5a**	95	5:1	—
Me_3SiCl	**4**–**5b**	77	4:1	—
AllylBr	**4**–**5c**	84	6:1	87
BnBr	**4**–**5d**	99	3:1	83
Me_2CO	**4**–**5e**	—	—	62
Ph_2CO	**4**–**5f**	—	—	78
$ArCH_2Br$[a]	**4**–**5g**	66	2:1	94
EtI	**4**–**5h**	93	6:1	71
MeI	**4**–**5i**	75	5:1	63

[a] Ar = 2-naphthyl.

(i) Diastereoselective substitution of 3 using BuLi in THF

Treatment of the readily accessible *N*-methylisoindoline–borane complex **3** with ^{n}BuLi in THF, followed by addition of an electrophile, gave the anticipated substituted complexes as mixtures of diastereomers, Table 1. The results require some detailed comment, but the overall observation is that alkylation or addition to carbonyl compounds is possible in high yield and that the reactions occur to give mainly diastereomer **4**, in which the new substituent is incorporated *syn* to the BH_3 group on nitrogen. Many of the product yields shown are somewhat improved compared to the initial report, but it should be noted that the very high diastereomeric ratio quoted in the original communication for quenching with Bu_3SnCl proved not to be reproducible under these standard conditions. In the case of silylated or stannylated intermediates **4**–**5a** and **4**–**5b** decomplexation was not possible without decomposition, whereas in the case of carbonyl addition products **4**–**5f** and **4**–**5g** the

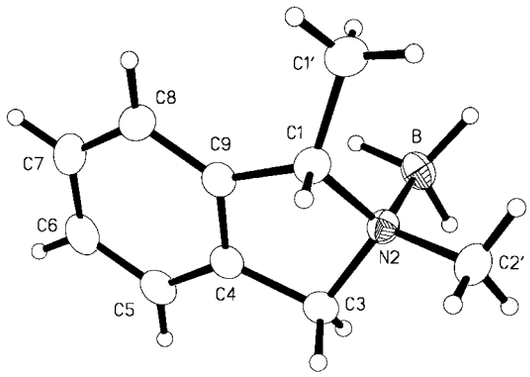
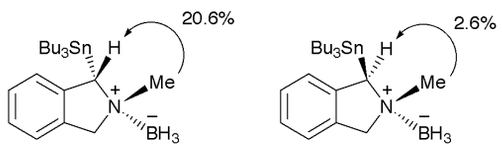


Fig. 1 X-Ray crystal structure of borane complex **4i**.



4a **5a**

Fig. 2 Diagnostic NOE enhancements in borane complexes **4a** and **5a**.

borane complexes were unstable and only the free amine was isolated.

The relative stereochemistry of the major product in each of the reactions described in Table 1 was initially based entirely on the X-ray structure determination carried out for the major product, **4i**, obtained from the methylation reaction, Fig. 1. The X-ray structure of **4i** reveals that the N2–B bond [1.629(2) Å] is considerably longer than the N2–C2′ bond [1.485(2) Å], allowing the two nitrogen substituents to be clearly distinguished. Moreover, the BH_3 group may be slightly larger than the N–CH_3 group, judging from the B–H bond length [1.13(2) Å] compared to the C–H (0.96 Å, idealised) bond length. It is difficult to see how such minor differences could lead to the observed levels of diastereocontrol, based on steric arguments, and later results point to alternative controlling factors (*vide infra*).

Additional NMR experiments were carried out on other products in order to lend credence to our previous assumption that all of the major products **4** belonged to the same diastereomeric series. In particular, detailed NOE experiments were possible on either the stannylated (**4**–**5a**) or silylated (**4**–**5b**) compounds, since in these cases the diastereomers could be separated, Fig. 2.

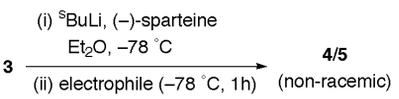
As can be seen from Fig. 2 the results for **4a** and **5a** support our assignments, the NOE enhancement seen for the methine CH on irradiating the NMe being *ca.* eight fold greater for one isomer than the other. Analogous results were seen for **4b** and **5b**, and similar experiments were performed on the benzylated and ethylated series—although these were done on the (in these cases inseparable) mixtures of isomers.

At this stage our results seem to mirror quite closely the findings of Vedejs and Kendall in terms of the preferred mode of reaction being *syn* to the BH_3 group.[3] However, the variations in diastereomer ratios seen on changing the nature of the electrophilic quench seemed to point to a stereochemically labile intermediate organometallic, a contrasting situation compared to that found with the aziridines.[5]

(ii) Enantioselective substitution of 3 using ^{s}BuLi–sparteine in diethyl ether

An asymmetric variant of the substitution reactions of complex **3**, presented in Table 1 was achieved simply by employing ^{s}BuLi–(−)-sparteine as the base, which resulted in the formation of the desired products in diastereo- and enantiocontrolled fashion, Table 2.[6]

Table 2 Enantioselective alkylation of **3**



Electrophile	Product	**3**→**4**–**5** (%)	Dr **4**:**5**	Ee (%)[c]
Bu_3SnCl	**4**–**5a**	95	1:20	89
Me_3SiCl	**4**–**5b**	84	1:14	85
AllylBr	**4**–**5c**	65	1:3	87
BnBr	**4**–**5d**	53	1:5	83
Ph_2CO	**4**–**5f**	(62)[b]	—	—[d]
$ArCH_2Br$[a]	**4**–**5g**	58	1:5	—[d]
EtI	**4**–**5h**	71	10:1	75
MeI	**4**–**5i**	70	1:2	83
$^nC_5H_{11}Br$	**4**–**5j**	65	20:1	56

[a] Ar = 2-naphthyl. [b] Yield of free amine. [c] Ee of major diastereomer in each case. [d] Not determined.

In general the yields of products are very good and the levels of enantiomeric excess are similar for most of the electrophiles, being of the order of 85%. In the cases of iodoethane and bromopentane as electrophiles, warming of the reaction mixture was required in order to achieve satisfactory reaction, which may explain the apparent erosion of enantiomeric excess. However, perhaps the most striking aspect of the results is the dramatic change in diastereoselectivity for most of the electrophiles used, compared to the outcome of the corresponding reactions using ^{n}BuLi in THF. This aspect of the results was not apparent when we submitted our initial communication because only a few such asymmetric reactions had been attempted. Now, with a broader range of results available compared to our earlier report, and further NMR and X-ray data (*vide infra*) which secure stereochemical assignments, our earlier interpretation of the results requires slight reassessment.[7]

In the cases of series **4**–**5c**, **d**, **f** and **g** were carried out decomplexation of the mixtures of diastereomeric borane complexes to give the corresponding non-racemic amines **6** in good yields (although we did not assay for the ee of these products). The likely stereochemistry of these compounds was deduced following further experiments described in the next section.

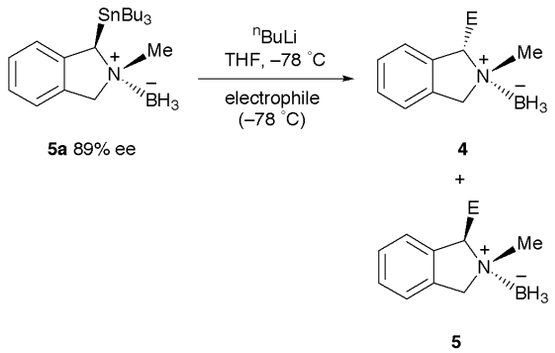
(iii) Origins of the diastereo- and enantioselectivity

The swap in diastereoselectivity from **4** to **5** as the major product (for most electrophiles used) when changing from ^{n}BuLi–THF to ^{s}BuLi–sparteine–ether could clearly be a result of the change in alkyllithium or the solvent, or could be due to the chiral diamine ligand. Several explanations could also be proposed for the observed enantioselectivity, depending upon whether the intermediate organolithium was stereochemically labile, and whether the initial deprotonation event was the principal determinant of the asymmetric induction. Further experiments were designed in order to probe the origins of both the diastereoselectivity and enantioselectivity of the substitution reactions.

In order to probe solvent effects we carried out the metallation of **3** with ^{s}BuLi in either Et_2O or THF, Scheme 3. As can be seen, the stereochemical results for the two solvents are highly complementary, with Et_2O resulting in substitution *anti* to the borane group to give **5**, whilst the reaction in THF furnishes **4**, the product of substitution *syn* to boron.

This result indicated the powerful effect of the solvent on the stereochemical outcome, although at this point it was not possible to reach a conclusion about which of the metallation or electrophilic quenching steps was responsible for the results. Certainly, the fact that rather variable ratios of **4**:**5** were obtained under either set of conditions (Tables 1 and 2) pointed to a stereochemically labile organolithium intermediate. However, an alternative explanation might be that the solvent

Table 3 Transmetallation–substitution of **5a**



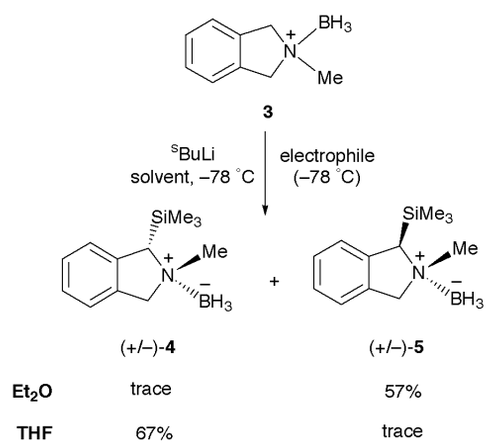
5a 89% ee

4

+

5

Electrophile	**5a**→**4**–**5** (%)	Dr **4**:**5**	Ee (%)
MeI	83	6:1	78
EtI	80	5:1	80
AllylBr	70	9:1	79
Me_3SiCl_3	81	10:1	71

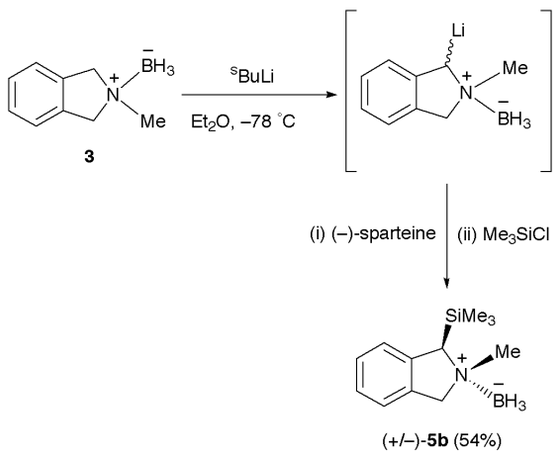


Scheme 3

altered the diastereoselectivity in the initial metallation, giving configurationally stable intermediates, which then reacted with the different electrophiles with a variable degree of retention/inversion. In order to further probe these possibilities we carried out a range of transmetallation reactions employing diastereomerically pure stannylated derivative **5a** of 89% ee, Table 3.

The reactions are seen to occur with overall inversion, *i.e.* the tin substrate is pure **5**, whilst the products are mainly diastereomer **4**, this result conforming to our expectation that the solvent effect from THF would exert a powerful influence. This result, taken in combination with the solvent effects in Scheme 3 provide compelling evidence that the intermediate organolithium is stereochemically labile. Since in THF the reaction in Scheme 3 is highly selective for **4** then, if this was the result of a configurationally stable intermediate, we would expect the transmetallation sequence from **5a** to give mainly product diastereomer **5**. This is clearly not the case and so the intermediate must be stereochemically labile.[8]

Table 3 also shows that the transmetallation–substitution process starting with material of 89% ee yields products which are still highly enantiomerically enriched, although some erosion of ee is evident depending upon the electrophile employed. This shows that the intermediate organolithium is reasonably configurationally stable with respect to racemisation, despite the apparent ease of epimerisation at the lithiated centre. This is because both of the possible diastereomeric organolithiums resulting from **5a** (or **3**) have a fixed configuration at the chiral nitrogen centre, which acts as a kind of stereochemical "anchor". This last feature suggested to us that the observed asymmetric induction in the ^{s}BuLi–sparteine reactions is due to an initial asymmetric deprotonation step, which fixes the configuration at nitrogen (although not the stereochemistry at carbon). One further reaction was carried out in order to fully discount an alternative mechanism, which would involve an asymmetric substitution mechanism, in which the dominant feature responsible for the induction would be association of the (racemic) organometallic with sparteine, Scheme 4.



Scheme 4

The borane complex **3** was metallated in Et_2O in the usual way, and then sparteine was added to the mixture at −78 °C, followed by Me_3SiCl. The expected product **5b** was isolated as a single diastereomer, but was found to be almost racemic (ee ≤ 5%), this result being in accord with our proposed asymmetric deprotonation mechanism.

In order to further clarify the mode of asymmetric induction we re-examined one of the results in Table 2 in much more detail. Firstly, for the product of electrophilic quenching with Me_3SiCl (**4**–**5b**), it was found that the enantiomers of both diastereomers could be separated by HPLC. In fact, all four possible stereoisomers could be analysed simultaneously, making determination of dr and ee values very straightforward. Furthermore, since both the enantiomerically enriched samples were crystalline, we were able to determine the absolute and relative stereochemistry for the major constituents of **4b** and **5b** by recrystallisation and determination of the structures by X-ray crystallography. The obtained structures are shown in Figs. 3 and 4, and the overall picture for the asymmetric deprotonation of **3** which emerges from the data is shown in Scheme 5.

The figures shown for each component lead to the observed (measured) dr and ee values, and the absolute configurations can be assigned with certainty from the X-ray data. Therefore it is possible to conclude that the principle origin of the asymmetric induction is a deprotonation in which the chiral base selects for the arrowed position to the extent of 92.6:7.4—*i.e.* the initial ratio of A:B is about 9:1. This approximate ratio can also be extracted from the HPLC data for other electrophiles, although in these cases X-ray structural data on the intermediate borane complexes is lacking. It is also clear from the above data that decomplexation of the two diastereomeric, enantiomerically enriched, borane complexes should give amines of *opposite* absolute configuration. This conclusion differs from our initial assignment, which was made tentatively, based on preliminary polarimetric results.[9]

Although all of the data in Table 2 can be accommodated by the above explanation, the switch in diastereoselectivity seen for the electrophiles EtI and $^{n}C_5H_{11}Br$, compared to the other examples is perplexing. In these two cases only, the alkylation

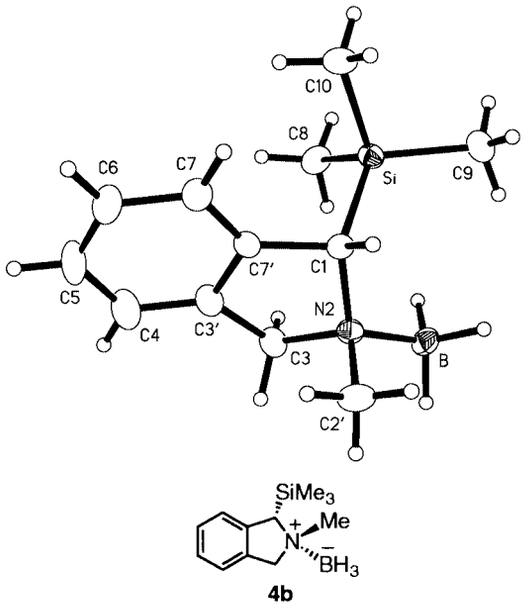


Fig. 3 X-Ray crystal structure of borane complex **4b**.

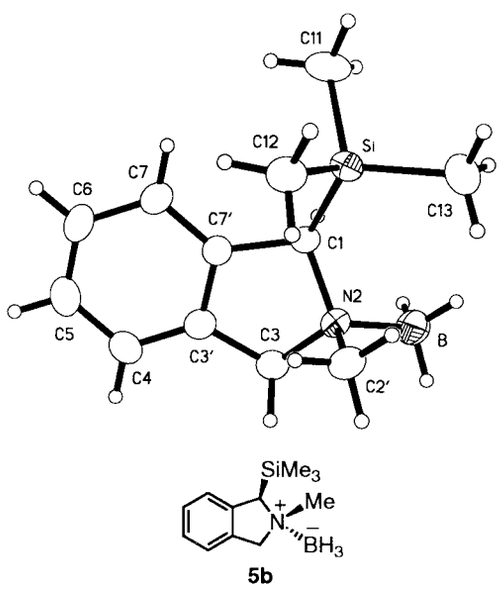


Fig. 4 X-Ray crystal structure of borane complex **5b**.

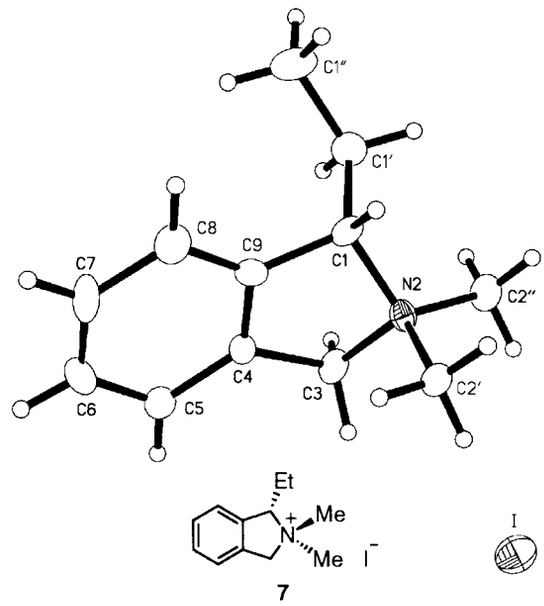
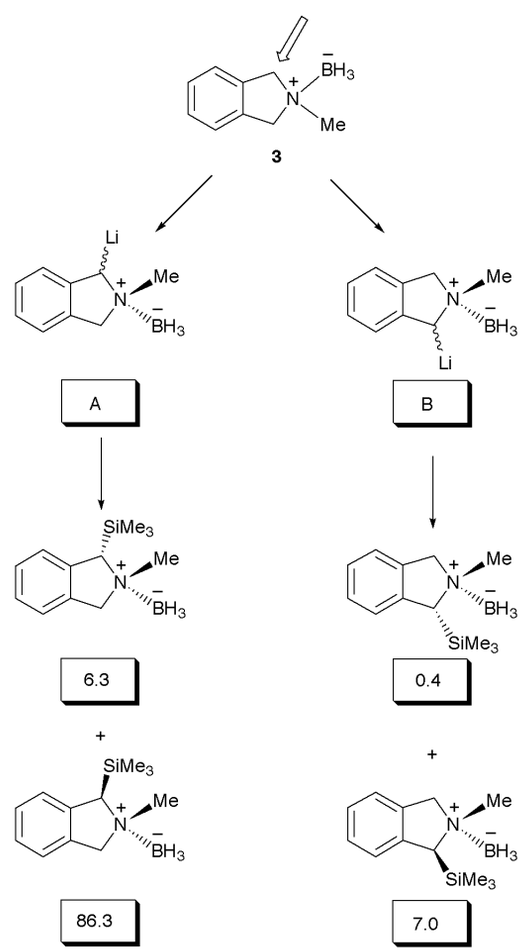


Fig. 5 X-Ray crystal structure of ammonium salt **7**.



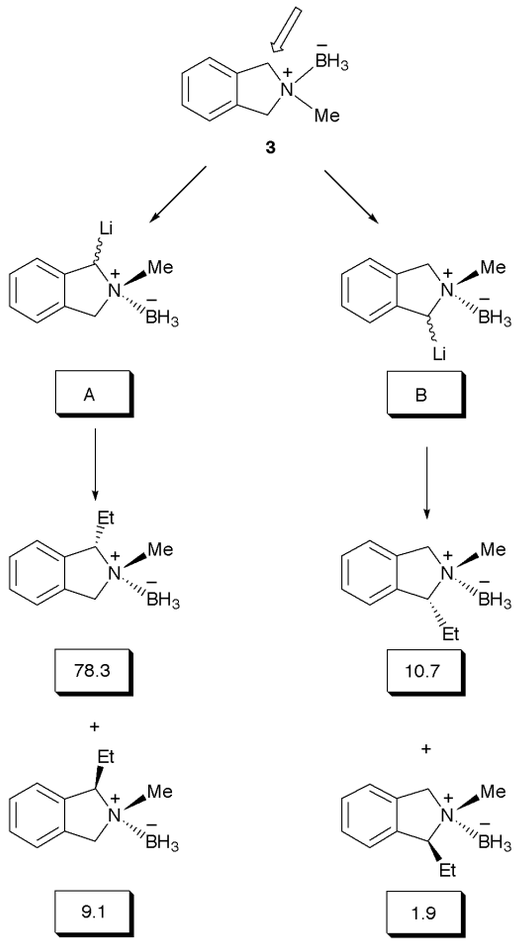
Scheme 5

reactions were sluggish enough to require slow warming, and this may account for the different sense of diastereoselectivity seen. In the case of reaction with EtI a more detailed analysis can tentatively be made since we were able to establish the configuration at the newly formed stereocentre in the major isomer by obtaining an X-ray structure for the ammonium iodide **7**, Fig. 5.

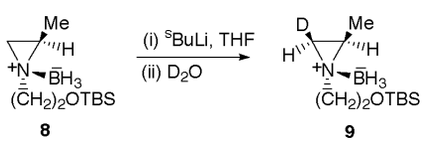
This compound was obtained by treating the *mixture* of optically active borane complexes **4**–**5h** with 6 M HCl, followed by MeI, and then recrystallising from hexane–CH_2Cl_2. If we assume that the resulting structure originates from the major enantiomer present in the intermediate non-racemic amine, then the result can be seen to be in accord with HPLC data for this reaction, Scheme 6.

From the above analysis we can predict the stereochemistry of the free amines **6** resulting from the asymmetric metallation process. In the case of EtI and $^nC_5H_{11}Br$ they should have the (1*S*)-configuration analogous to the ammonium salt **7**, whereas for the other electrophiles the opposite (1*R*)-configuration should predominate.

Even though the above study has uncovered the key aspects of this novel type of asymmetric deprotonation reaction, it remains difficult to do more than speculate as to the detailed origins of the diastereoselectivity and enantioselectivity. In the former regard, the solvent plays a key role, but the striking differences in diastereoselectivity seen on changing from diethyl ether to THF could well be due to changes in aggregation state of the intermediate organolithium. Likewise, it is impossible to rationalise in detail the sense of asymmetric induction seen with sparteine, simply because the usual steric arguments cannot be applied with much confidence. In their study,[3] Vedejs and



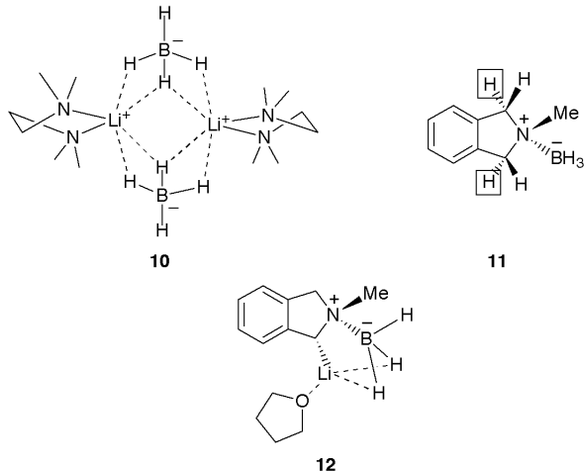
Scheme 6



Scheme 7

Kendall identified a distinct tendency for metallation *syn* to the BH_3 subunit, for example the transformation of **8** into **9**, Scheme 7. This result was attributed to a combination of steric and electrostatic effects. Since the N–B bond is longer than the corresponding exocyclic N–C bond it was considered that the BH_3 unit might be more tolerant of 1,2-eclipsing interactions with an approaching alkyllithium than the *N*-methylene unit. In addition there could be an electrostatic interaction between the lithium ion of the base and the BH_3 unit. Such interactions have been observed in the solid state, and are illustrated by the X-ray structure of TMEDA–$LiBH_4$, which can be represented as shown for **10**.[10]

In the asymmetric deprotonation of our isoindoline system such an attractive effect, involving the borane group and the approaching lithium base, might be crucial to the asymmetric induction by reducing the number of metallation pathways. For example, it is possible that the key asymmetric step involves chiral base selection between only one set of enantiotopic hydrogens, which are oriented *syn* to the borane group, as highlighted in **11**. It is even possible that such interactions might play a part in determining the diastereoselectivity of the subsequent electrophilic quench by offering some stabilisation to the intermediate organometallic in which the lithium is *syn* with respect to the borane, as suggested by structure **12**.



Conclusion

A new type of asymmetric deprotonation reaction has been investigated, using the ^{s}BuLi–sparteine reagent, which gives interesting amine–borane complexes in synthetically useful levels of enantiomeric excess. The mechanism of the reaction has been demonstrated to involve an enantioselective deprotonation to give a non-racemic organolithium which is configurationally stable at nitrogen but stereochemically labile with respect to the C–Li bond. Dramatic solvent effects on the diastereoselectivity of electrophilic quenching are observed, which are not easily rationalised.

The types of products prepared by this chemistry have previously been prepared in racemic and non-racemic form using Meyers' formamidine methodology.[11] The initial adducts could be further alkylated to give *trans*-1,3-dialkylated isoindolines, which have potential applications as C_2-symmetric chiral auxiliaries.[12] Although we have not carried out further work on the chiral borane complexes **4** and **5**, the chemistry described herein could provide a complementary approach to such auxiliaries.

Experimental

General details

The general procedures and the experimental details for preparation of complexes **3**, **4i**, **5i** and **6i** were as described previously.[2]

Diastereoselective reactions in Table 1

Typical procedure: synthesis of 4a–5a using ^{n}BuLi in THF. A solution of ^{n}BuLi (0.84 ml of a 1.60 M solution in hexanes, 1.35 mmol) was added dropwise to a solution of complex **3** (100 mg, 0.68 mmol) in THF (10 ml) at −78 °C under an atmosphere of nitrogen. The reaction mixture was then warmed to 0 °C and stirred for 1 h at this temperature, before recooling to −78 °C. Tributyltin chloride (0.55 ml, 2.0 mmol) was added in one portion and the mixture stirred at −78 °C for 1 h before saturated aqueous $NaHCO_3$ (1 ml) was added with subsequent warming to room temperature. After addition of EtOAc (10 ml), the organic layer was separated, washed with saturated $NaHCO_3$ (5 ml), brine (2 × 5 ml), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The resulting light brown oil was purified by flash column chromatography on silica gel (2% EtOAc–light petroleum) to give firstly **4a** as a colourless oil (230 mg, 78%), ν_{max} ($CHCl_3$)/cm^{-1} 3155, 2956, 2923, 2871, 2363 (B–H), 2320 (B–H) and 2253 (B–H); δ_H (400 MHz, $CDCl_3$) 0.86 [9H, t, *J* 7, $Sn(CH_2)_3CH_3$], 0.97 [6H, m, $Sn(CH_2)_3CH_3$], 1.26 [6H, m, $Sn(CH_2)_3CH_3$], 1.44 [6H, m, $Sn(CH_2)_3CH_3$], 1.50–2.50 (3H, v br, BH_3), 2.76 (3H, s, NCH_3), 3.95 (1H, d, J_{AB} 15, NCHH), 4.26 (1H, s, NCHSn), 4.40 (1H, d, J_{AB} 15, NCHH), 7.00 (1H, d, *J* 7, ArH), 7.11 (1H, dd, *J* 7 and 7, ArH) and 7.19

(2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 12.1 (*C*H_2), 13.7 (*C*H_3), 27.5 (*C*H_2), 29.0 (*C*H_2), 53.3 (*C*H_3), 68.1 (*C*H_2), 73.3 (*C*H), 120.4 (Ar*C*H), 122.9 (Ar*C*H), 125.6 (Ar*C*H), 127.8 (Ar*C*H), 134.2 (Ar*C*) and 143.5 (Ar*C*); *m*/*z* (FAB) 436 [$(M - H)^+$, 24%] (HRMS: found $[M - H]^+$, 436.2157. Requires [*M* − *H*], 436.2197) followed by **5a** as a low melting point white solid (50 mg, 17%, 95% overall) (Found: C, 57.80; H, 9.31; N, 3.27. $C_{21}H_{40}BNSn$ requires C, 57.84; H, 9.25; N, 3.21%); ν_{max} ($CHCl_3$)/cm^{-1} 2957, 2924, 2854, 2416 (B–H), 2373 (B–H), 2314 (B–H) and 1460; δ_H (400 MHz, $CDCl_3$) 0.90 [9H, t, *J* 7, $Sn(CH_2)_3CH_3$], 1.08 [6H, m, $Sn(CH_2)_3CH_3$], 1.34 [6H, m, $Sn(CH_2)_3CH_3$], 1.49 [6H, m, $Sn(CH_2)_3CH_3$], 1.50–2.50 (3H, v br, B*H*$_3$), 2.78 (3H, s, NC*H*$_3$), 4.02 (1H, d, J_{AB} 15, NC*H*H), 4.54 (1H, d, J_{AB} 15, NCH*H*), 4.76 (1H, s, NC*H*Sn), 7.01 (1H, d, *J* 7, Ar*H*) and 7.19 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 11.1 (*C*H_2), 13.6 (*C*H_3), 27.3 (*C*H_2), 28.9 (*C*H_2), 53.1 (*C*H_3), 69.5 (*C*H_2), 71.5 (*C*H), 120.9 (Ar*C*H), 122.5 (Ar*C*H), 126.0 (Ar*C*H), 127.6 (Ar*C*H), 135.6 (Ar*C*) and 143.1 (Ar*C*); *m*/*z* (FAB) 436 [$(M - H)^+$, 0.1%] (HRMS: found $[M - H]^+$, 436.2210. Requires [*M* − *H*], 436.2200).

Synthesis of 4b–5b using ^{n}BuLi in THF. The above typical procedure was followed using **3** (100 mg, 0.68 mmol), and the resulting light brown oil was purified by flash column chromatography on silica gel (3% Et_2O–light petroleum) to give firstly **4b** as a colourless oil (91 mg, 61%), ν_{max} ($CHCl_3$)/cm^{-1} 2949, 2902, 2364, 2329, 2277, 1603 and 1461; δ_H (400 MHz, $CDCl_3$) 0.23 (9H, s, Si*Me*$_3$), 1.1–2.7 (3H, v br, B*H*$_3$), 2.76 (3H, s, NC*H*$_3$), 3.75 (1H, s, NC*H*Si), 3.90 (1H, d, J_{AB} 15, NC*H*H), 4.50 (1H, d, J_{AB} 15, NCH*H*), 7.14 (1H, m, Ar*H*) and 7.21–7.25 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) −0.5 [Si(*C*H_3)$_3$], 54.7 (N*C*H_3), 68.5 (*C*H_2), 73.2 (*C*H), 123.0 (Ar*C*H), 123.4 (Ar*C*H), 126.7 (Ar*C*H), 127.4 (Ar*C*H), 135.7 (Ar*C*) and 141.0 (Ar*C*); *m*/*z* (FAB) 218 [$(M - H)^+$, 2%], 204 [$(M - CH_3)^+$, 4] (HRMS: found $[M - H]^+$, 218.1544. Requires [*M* − *H*], 218.1536) followed by **5b** as a colourless oil (24 mg, 16%, 77% overall), ν_{max} ($CHCl_3$)/cm^{-1} 2952, 2901, 2360, 2330, 2272 and 1460; δ_H (400 MHz, $CDCl_3$) 0.28 (9H, s, Si*Me*$_3$), 0.8–2.4 (3H, v br, B*H*$_3$), 2.84 (3H, s, NC*H*$_3$), 4.03 (1H, d, J_{AB} 14, NC*H*H), 4.30 (1H, s, NC*H*Si), 4.52 (1H, d, J_{AB} 14, NCH*H*), 7.15 (1H, m, Ar*H*) and 7.21–7.25 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) −0.3 [Si(*C*H_3)$_3$], 50.0 (N*C*H_3), 70.0 (*C*H_2), 70.7 (*C*H), 122.6 (Ar*C*H), 122.9 (Ar*C*H), 126.8 (Ar*C*H), 127.6 (Ar*C*H), 136.5 (Ar*C*) and 140.8 (Ar*C*); *m*/*z* (FAB) 218 [$(M - H)^+$, 8%], 204 [$(M - CH_3)^+$, 22].

Synthesis of 6c using ^{n}BuLi in THF. The above typical procedure was followed using complex **3** (100 mg, 0.68 mmol), and the resulting light brown oil was purified by flash column chromatography on silica gel (10% EtOAc–light petroleum) to give an inseparable mixture of diastereomers (**4c**–**5c**) (106 mg, 84%). The diastereomeric mixture was dissolved in EtOH (10 ml) and refluxed for 16 h. After cooling to room temperature, the solvent was removed under reduced pressure and the resulting oil was purified by Kugelrohr distillation to give **6c** as a colourless oil (85 mg, 87%), bp 55 °C/0.5 mbar; ν_{max} ($CHCl_3$)/cm^{-1} 3081, 2945, 2846, 2783, 1738, 1640, 1461, 1358; δ_H (400 MHz, $CDCl_3$) 2.60 (3H, s, N-C*H*$_3$), 2.65 (2H, m, NCHC*H*$_2$), 3.66 (1H, dd, J_{AB} 13 and 3, NCH*H*), 3.75 (1H, m, NC*H*), 4.28 (1H, dd, J_{AB} 13 and 2, NC*H*H), 5.10 (1H, dd, *J* 10 and 2, CH=CH*H*), 5.19 (1H, dd, *J* 17 and 2, CH=C*H*H), 5.90 (1H, ddt, *J* 17, 10 and 7, C*H*=CHH) and 7.21–7.25 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 37.5 (*C*H_2), 40.8 (N-*C*H_3), 60.8 (*C*H_2), 69.5 (*C*H), 116.8 (CH=*C*H_2), 122.1 (Ar*C*H), 122.2 (Ar*C*H), 126.6 (Ar*C*H), 126.8 (ArCH), 135.5 (*C*H=CH$_2$), 139.9 (Ar*C*) and 143.4 (Ar*C*); *m*/*z* (FAB) 174 [$(M + H)^+$, 21%] (HRMS: found $[M + H]^+$, 174.1276. Requires [*M* + *H*], 174.1283).

Synthesis of 6d using ^{n}BuLi in THF. The above typical procedure was followed using complex **3** (100 mg, 0.68 mmol), and the resulting light brown oil was purified by flash column chromatography on silica gel (10% EtOAc–light petroleum) to give an inseparable mixture of diastereomers (**4d**–**5d**) (159 mg, 99%) in a ratio of 3:1. The diastereomeric mixture was dissolved in EtOH (10 ml) and refluxed for 5 h. After cooling to room temperature the solvent was removed under reduced pressure to give **6d** as a light brown oil (125 mg, 83%), ν_{max} ($CHCl_3$)/cm^{-1} 3165, 2893, 2846 and 1359; δ_H (400 MHz, $CDCl_3$) 2.45 (3H, s, N-C*H*$_3$), 3.02 (1H, dd, J_{AB} 14 and 7, NCHCH*H*), 3.11 (1H, dd, J_{AB} 14 and 6, NCHC*H*H), 3.64 (1H, dd, J_{AB} 13 and 2, NC*H*H), 3.99 (1H, m, NC*H*CH$_2$), 4.26 (1H, dd, J_{AB} 13 and 2, NCH*H*), 6.87 (1H, dd, *J* 7 and 1, Ar*H*), 7.09 (1H, m, Ar*H*), 7.15 (2H, m, Ar*H*), 7.20 (1H, m, Ar*H*) and 7.28 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 41.2 (NCH*C*H$_2$), 41.3 (N-*C*H$_3$), 60.9 (N*C*H$_2$), 71.4 (N*C*HCH$_2$), {(122.1, 122.6, 126.2, 126.6, 126.9, 128.3, 129.6), Ar*C*H}, 139.3 (Ar*C*), 139.6 (Ar*C*) and 143.6 (Ar*C*); *m*/*z* (EI) 221 [$(M - 2H)^+$, 24%] (HRMS: found $[M - H]^+$, 222.1250. Requires [*M* − *H*], 222.1283).

Synthesis of 6e using ^{n}BuLi in THF. The above typical procedure was followed using complex **3** (100 mg, 0.68 mmol), and the resulting dark brown oil was purified by Kugelrohr distillation to give **6e** as a colourless oil (80 mg, 62%), bp 70 °C/0.3 mbar; ν_{max} ($CHCl_3$)/cm^{-1} 3459, 2973, 2946, 2853, 2794, 1687, 1458 and 1374; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, s, C*H*$_3$), 1.32 (3H, s, C*H*$_3$), 2.59 (3H, s, N-C*H*$_3$), 3.68 (1H, d, *J* 15, NCH*H*), 3.76 (1H, s, NC*H*C), 4.43 (1H, d, *J* 15, NC*H*H) and 7.19–7.30 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 24.9 (*C*H$_3$), 26.0 (*C*H$_3$), 47.5 (N-*C*H$_3$), 62.1 (N*C*H$_2$), 73.5 [$CH_3C(OH)CH_3$], 82.4 (N*C*HC), 122.7 (Ar*C*H), 124.1 (Ar*C*H), 126.7 (Ar*C*H), 127.4 (Ar*C*H), 139.7 (Ar*C*) and 140.6 (Ar*C*) (HRMS: found M^+, 191.1309. Requires *M*, 191.1310).

Synthesis of 6f using ^{n}BuLi in THF. A solution of ^{n}BuLi (0.91 ml of a 1.49 M solution in hexanes, 1.35 mmol) was added dropwise to a solution of complex **3** (100 mg, 0.68 mmol) in THF (10 ml) at −78 °C under an atmosphere of nitrogen. The solution was then warmed to 0 °C and stirred for 1 h, before recooling to −78 °C. Benzophenone (0.250 g, 1.37 mmol) in THF (1 ml) was added in one portion and the mixture stirred at −78 °C for 1 h before MeOH (1 ml) was added with subsequent warming to room temperature. Solvent was evaporated under reduced pressure and the residue was dissolved in EtOH (10 ml) and stirred at room temperature for 12 h. After evaporation of the solvent, the residue was purified by flash column chromatography on silica gel (30% EtOAc–light petroleum) to give **6f** as a colourless oil (167 mg, 78%), ν_{max} ($CHCl_3$)/cm^{-1} 3382 (OH), 2953, 2856, 2796, 1461 and 1354; δ_H (400 MHz, $CDCl_3$) 2.20 (3H, s, NC*H*$_3$), 3.71 (1H, d, J_{AB} 14, NC*H*H), 4.32 (1H, d, J_{AB} 14, NCH*H*), 4.75 (1H, br, D_2O exchange, O*H*), 5.05 (1H, s, NC*H*C), 5.88 (1H, d, *J* 8, Ar*H*), 6.84 (1H, m, Ar*H*), 7.11 (2H, m, Ar*H*), 7.22–7.37 (6H, m, Ar*H*), 7.54 (2H, m, Ar*H*) and 7.76 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 44.3 (*C*H$_3$), 62.2 (*C*H$_2$), 78.7 (*C*H), 121.8 (ArCH), 125.0 (ArCH), {(126.3, 126.6, 126.8, 126.8, 127.5, 128.0, 128.2), Ar*C*H}, {(139.0, 140.7, 144.2, 146.9), Ar*C*}; *m*/*z* (FAB) 316 [$(M + H)^+$, 23%] (HRMS: found $[M + H]^+$, 316.1695. Requires [*M* + *H*], 316.1701).

Synthesis of 6g using ^{n}BuLi in THF. The above typical procedure was followed using complex **3** (100 mg, 0.68 mmol), and the resulting light brown solid was purified by flash column chromatography on silica gel (5% EtOAc–light petroleum) to give an inseparable mixture of diastereomers (128 mg, 66%). The diastereomeric mixture was dissolved in EtOH (10 ml) and refluxed for 5 h. After cooling to room temperature the solvent was removed under reduced pressure to give **6g** as a white solid (115 mg, 94%), mp 98 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2944, 2847, 2786, 1601, 1461 and 1358; δ_H (400 MHz, $CDCl_3$) 2.47 (3H, s, NC*H*$_3$), 3.20 (1H, dd, J_{AB} 14 and 7, NCHCH*H*), 3.27 (1H, dd, J_{AB} 14 and 7, NCHC*H*H), 3.68 (1H, dd, J_{AB} 13 and 2, NCH*H*), 4.12

(1H, m, NC*H*CH_2), 4.29 (1H, dd, J_{AB} 13 and 2, NC*H*H), 6.89 (1H, d, *J* 7, ArH), 7.08 (1H, m, Ar*H*), 7.17 (2H, m, Ar*H*), 7.45 (3H, m, Ar*H*) and 7.81 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 41.5 (NCH*C*H_2, NCH_3), 61.0 (N*C*H_2), 71.3 (N*C*HCH_2), {(122.1, 122.6, 125.4, 126.0, 126.7, 127.0, 127.7, 127.7, 127.9, 128.1), Ar*C*H}, {(132.3, 133.7, 137.0, 139.7, 143.7), Ar*C*}; *m*/*z* (EI) 272 [$(M - H)^+$, 2%] (HRMS: found $[M - H]^+$, 272.1452. Requires [*M* − *H*], 272.1439).

Synthesis of 6h using ^{n}BuLi in THF. The above typical procedure was followed using complex **3** (100 mg, 0.68 mmol), and the resulting light brown oil was purified by flash column chromatography on silica gel (10% EtOAc–light petroleum) to give **4h**–**5h** as an inseparable mixture of diastereomers (110 mg, 93%). The diastereomeric mixture (90 mg, 0.51 mmol) was dissolved in EtOH (10 ml) and refluxed for 16 h. After cooling to room temperature the solvent was removed under reduced pressure to give **6h** as a brown oil (64 mg, 71%), ν_{max} ($CHCl_3$)/cm^{-1} 2877, 2844, 2780, 1484, 1460 and 1360; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7, CH_2CH_3), 1.61 (2H, m, CH_2CH_3), 2.54 (3H, s, NCH_3), 3.64 [2H, m, (NC*H*H + NC*H*CH_2CH_3)], 4.25 (1H, d, *J* 11, NCH*H*) and 7.19 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 9.2 (*C*H_3), 24.9 (*C*H_2), 41.0 (*C*H_3), 61.0 (*C*H_2), 71.1 (*C*H), 122.0 (Ar*C*H), 122.1 (Ar*C*H), 126.6 (Ar*C*H), 126.7 (Ar*C*H), 140.2 (Ar*C*) and 143.5 (Ar*C*); *m*/*z* (CI) 162 [$(M + H)^+$, 15%] (HRMS: found $[M + H]^+$, 162.11287. Requires [*M* + *H*], 162.1283).

Enantioselective reactions in Table 2

Typical procedure: synthesis of (1*S*,2*S*)-4a and (1*R*,2*S*)-5a mediated by ^{s}BuLi–(−)-sparteine. A solution of (−)-sparteine (3.4 ml, 14.87 mmol) and ^{s}BuLi (10.4 ml of a 1.3 M solution in cyclohexane, 13.51 mmol) in Et_2O (20 ml) was stirred at −20 °C for 20 min prior to cannula addition to a suspension of **3** (1.00 g, 6.76 mmol) in Et_2O (50 ml) at <−78 °C. The suspension was stirred at this temperature for 1 h and tributyltin chloride (9.0 ml, 33.8 mmol) was added in one portion. Stirring was maintained at −78 °C for a further 1 h before saturated aqueous $NaHCO_3$ (10 ml) was added with subsequent warming to room temperature. After addition of EtOAc (40 ml), the organic layer was separated, washed with saturated brine (2 × 20 ml) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure. The resulting yellow residue was subjected to short column chromatography (neat light petroleum then 5% EtOAc–light petroleum) to remove tributyltin chloride. Further purification by flash column chromatography on silica gel (1% EtOAc–light petroleum) gave **4a** as a colourless oil (0.15 g, 5%), $[\alpha]_D^{20}$ −32 (*c* 1.24 in $CHCl_3$) followed by a low melting point solid **5a** (2.66 g, 90%), $[\alpha]_D^{20}$ −9 (*c* 1.0 in $CHCl_3$). Spectroscopic details for both complexes were in accordance with those for the racemic samples described above. HPLC analysis using a Chiralcel OD column [0.1% isopropyl alcohol (IPA) in hexane as eluent] indicated that the product mixture contained **5a** as the major diastereomer [89% ee, retention time 10.3 min (minor) and 11.6 min (major)] and **4a** as the minor diastereomer [45% ee, retention time 6.5 min (major) and 8.3 min (minor)].

Synthesis of (1*S*,2*S*)-4b and (1*R*,2*S*)-5b mediated by ^{s}BuLi–(−)-sparteine. The above typical procedure was followed using **3** (500 mg, 3.40 mmol) and chlorotrimethylsilane (2.16 ml, 17.0 mmol), and the resulting yellow residue was purified by flash column chromatography on silica gel (4% EtOAc–light petroleum) to give **4b** as a white solid (36 mg, 5%), $[\alpha]_D^{21}$ 32 (*c* 0.17 in $CHCl_3$) followed by **5b** as a colourless oil (586 mg, 79%, 84% overall), $[\alpha]_D^{21}$ 0.9 (*c* 0.71 in $CHCl_3$). Spectroscopic details for both complexes were in accordance with those for the racemic samples described above. HPLC analysis using a Chiralcel OD column (0.5% IPA in hexane as eluent) indicated that the product mixture contained **4b** as the major diastereomer [85% ee, retention time 13.2 min (minor) and 14.5 min (major)] and **5b** as the minor diastereomer [89% ee, retention time 12.8 min (minor) and 20.6 min (major)].

Recrystallisation of **4b** from hexane gave colourless crystals suitable for X-ray analysis. Storage of **5b** in a freezer for two days caused the oil to solidify, and subsequent recrystallisation from hexane gave colourless crystals (mp 59 °C) suitable for X-ray analysis.

Synthesis of (1*R*)-6c mediated by ^{s}BuLi–(−)-sparteine. The above typical procedure was followed using **3** (100 mg, 0.68 mmol) and allyl bromide (0.29 ml, 3.38 mmol), and the resulting brown residue was purified by flash column chromatography on silica gel (5% EtOAc–light petroleum) to give an inseparable mixture of diastereomers (83 mg, 65%). HPLC analysis using a Chiralcel OD column (1.5% IPA in hexane as eluent) indicated that the product mixture contained **5c** as the major diastereomer [87% ee, retention time 11.0 min (minor) and 12.3 min (major)] and **4c** as the minor diastereomer [88% ee, retention time 16.6 min (minor) and 18.7 min (major)].

The diastereomeric mixture (83 mg, 0.44 mmol) was then dissolved in EtOH (5 ml) and heated at reflux for 12 h. After removal of the solvent, the resulting oil was purified by Kugelrohr distillation to give **6c** as a colourless oil (60 mg, 79%), $[\alpha]_D^{20}$ −115 (*c* 0.03 in $CHCl_3$). Spectroscopic details were in accordance with those for the racemic sample described above.

Synthesis of (1*R*)-6d mediated by ^{s}BuLi–(−)-sparteine. The above typical procedure was followed using **3** (100 mg, 0.68 mmol) and benzyl bromide (0.24 ml, 2.0 mmol), and the resulting residue was purified by flash column chromatography on silica gel (5% EtOAc–light petroleum) to give an inseparable mixture of diastereomers (85 mg, 53%). HPLC analysis using a Chiralcel OD column (2% IPA in hexane as eluent) indicated that the product mixture contained **5d** as the major diastereomer [83% ee, retention time 12.9 min (major) and 14.7 min (minor)] and **4d** as an undetermined mixture of enantiomers.

The diastereomeric mixture (85 mg, 0.36 mmol) was then dissolved in EtOH (5 ml) and refluxed for 12 h. After cooling to room temperature the solvent was evaporated under reduced pressure to give **6d** as a yellow oil (70 mg, 87%), $[\alpha]_D^{20}$ −34 (*c* 0.75 in $CHCl_3$). Spectroscopic details were in accordance with those for the racemic sample described above.

Synthesis of (1*R*)-6f mediated by ^{s}BuLi–(−)-sparteine. The above typical procedure was followed using **3** (100 mg, 0.68 mmol) and benzophenone (0.250 g, 1.35 mmol). The solvent was evaporated from the crude product under reduced pressure and (−)-sparteine was removed by flash column chromatography on silica gel (20% EtOAc–light petroleum). The crude sample was dissolved in EtOH (5 ml) and stirred at room temperature for 12 h. After removal of the solvent, the residue was purified by flash column chromatography on silica gel (20% EtOAc–light petroleum) to give **6f** as a colourless oil (132 mg, 62%), $[\alpha]_D^{20}$ +78 (*c* 0.61 in $CHCl_3$). Spectroscopic details were in accordance with those for the racemic sample described above.

Synthesis of (1*R*)-6g mediated by ^{s}BuLi–(−)-sparteine. The above typical procedure was followed using **3** (100 mg, 0.68 mmol) and 2-(bromomethyl)naphthalene (2-ArCH_2Br) (0.30 g, 1.35 mmol), to give a crude product, which was purified by flash column chromatography on silica gel (5% EtOAc–light petroleum) to give an inseparable mixture of diastereomers (113 mg, 58%). The diastereomeric mixture (113 mg, 0.39 mmol) was then dissolved in EtOH (5 ml) and refluxed for 12 h. After cooling to room temperature, the solvent was removed under reduced pressure to give **6g** as a white solid (100 mg, 93%), $[\alpha]_D^{20}$ −53 (*c* 0.59 in $CHCl_3$). Spectroscopic details were in accordance with those for the racemic sample described above.

Synthesis of (1*S*,2*S*)-4h and (1*R*,2*S*)-5h mediated by ^{s}BuLi–(−)-sparteine. The above typical procedure was followed using **3** (100 mg, 0.68 mmol) and iodoethane (0.27 ml, 3.4 mmol), except that alkylation was facilitated by warming slowly (*ca.* 12 h) to room temperature. Work-up as before, followed by flash column chromatography on silica gel (5% EtOAc–light petroleum) gave an inseparable mixture of diastereomers (84 mg, 71%). HPLC analysis using a Chiralcel OD column (5% IPA in hexane as eluent) indicated that the product mixture contained **4h** as the major diastereomer [75% ee, retention time 11.4 min (minor) and 12.8 min (major)] and **5h** as the minor diastereomer [65% ee, retention time 8.4 min (minor) and 10.0 min (major)].

Synthesis of (1*S*,2*S*)-4i and (1*R*,2*S*)-5i mediated by ^{s}BuLi–(−)-sparteine. The above typical procedure was followed using **3** (74 mg, 0.5 mmol) and iodomethane (0.16 ml, 2.5 mmol), and the residue purified by flash column chromatography on silica gel (3% then 5% EtOAc–light petroleum) gave **4i** (21 mg, 26%), $[\alpha]_D^{25}$ +15.1 (*c* 1.07 in $CHCl_3$), followed by **5i** (35.4 mg, 44%, 70% overall), $[\alpha]_D^{25}$ +8.5 (*c* 1.77 in $CHCl_3$) spectroscopic details for both compounds were in accordance with those for the racemic samples described above. HPLC analysis using a Chiralcel OD column (10% IPA in hexane as eluent) indicated that the product mixture contained **5i** as the major diastereomer [83% ee, retention time 7.4 min (minor) and 10.1 min (major)] and **4i** as an undetermined mixture of enantiomers.

Synthesis of (1*S*,2*S*)-4j and (1*R*,2*S*)-5j mediated by ^{s}BuLi–(−)-sparteine. The above typical procedure was followed using **3** (74 mg, 0.5 mmol) and 1-bromopentane (0.31 ml, 2.5 mmol), except that alkylation was facilitated by warming slowly (*ca.* 12 h) to room temperature. Work-up as before, followed by flash column chromatography on silica gel (5% EtOAc–light petroleum) to give a trace amount of **5j** followed by **4j** (70 mg, 65%), $[\alpha]_D^{21}$ +52 (*c* 3.09 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2959, 2861, 2384, 2277 and 1463; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7, CH_2CH_3), 1.0–2.2 (3H, v br, B*H*$_3$), 1.63 (1H, m), 2.74 (3H, s, NC*H*$_3$), 3.90 (1H, dd, *J* 10 and 4, NC*H*), 3.96 (1H, d, *J* 15, ArCHH), 4.53 (1H, d, *J* 15, ArCHH) and 7.24–7.32 (4H, m, Ar*H*); δ_C (68 MHz, $CDCl_3$) 13.9 (CH_3), 22.4 (CH_2), 25.8 (CH_2), 31.5 (CH_2), 31.6 (CH_2), 52.9 (NCH_3), 66.8 (NCH_2), 76.7 (*C*H), 123.0 (Ar*C*H), 123.8 (Ar*C*H), 127.5 (Ar*C*H), 127.9 (ArCH), 135.8 (Ar*C*) and 141.1 (Ar*C*); *m*/*z* (EI) 216 ($M^+ - 1$, 2%) and 144 (11) (HRMS: found $M^+ - 1$, 216.1927. Requires *M* − *1*, 216.1924). HPLC analysis using a Chiralcel OD column (2% IPA in hexane as eluent) indicated that the product mixture contained **4j** as the major diastereomer [56% ee, retention time 9.3 min (minor) and 10.6 min (major)] and **5j** as an undetermined mixture of enantiomers.

Solvent effect: metallation of 3 using ^{s}BuLi in different solvent systems. A solution of ^{s}BuLi (1.04 ml of a 1.3 M solution in hexanes, 1.35 mmol) was added dropwise to a solution of complex **3** (100 mg, 0.68 mmol) in solvent (either Et_2O or THF, 10 ml) at −78 °C under an atmosphere of nitrogen. The reaction mixture was stirred for 1 h at −78 °C. Chlorotrimethylsilane (0.43 ml, 3.4 mmol) was added in one portion and the mixture stirred at −78 °C for 1 h before saturated aqueous $NaHCO_3$ (1 ml) was added with subsequent warming to room temperature. After addition of EtOAc (10 ml), the organic layer was separated, washed with saturated aqueous $NaHCO_3$ (5 ml), brine (2 × 5 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting light brown oil was purified by flash column chromatography on silica gel (3% Et_2O–light petroleum) to give either **4b** or **5b** as the major product depending on the solvent used (see text). The product was identified by ^{1}H NMR, which was identical to the authentic sample.

Transmetallation-substitution of 5a in THF solution. In a typical transmetallation reaction: a solution of ^{n}BuLi (87 μl of a 1.57 M solution in hexanes, 0.14 mmol) was added dropwise to a solution of **5a** (50 mg, 0.11 mmol) in THF (5 ml) at −78 °C under an atmosphere of nitrogen. The reaction mixture was stirred at this temperature for 1 h before the electrophile (0.57 mmol) was added in one portion. Stirring was maintained at this temperature for a further 1 h before saturated aqueous $NaHCO_3$ (3 ml) was added with subsequent warming to room temperature. After addition of EtOAc (5 ml), the organic layer was separated, washed with brine (2 × 5 ml) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel (2–5% EtOAc–light petroleum) to give a mixture of diastereomers. The products were identified by ^{1}H NMR, and were identical to the authentic samples described above. HPLC analysis using a Chiralcel OD (0.5–5% IPA in hexane as eluent) indicated that the product mixture contained products **4** and **5** as indicated in Table 3.

Data for crystal structure determinations

Crystal structure determination of 4i. A crystal was mounted on a glass fibre and transferred into the cold stream of the low temperature device of the diffractometer.

Crystal data. $C_{10}H_{16}BN$, *M* = 161.05, monoclinic, *a* = 10.061(3), *b* = 9.145(3), *c* = 11.597(5) Å, *β* = 114.76(3)°, *U* = 968.9(4) Å^3, *T* = 150(2) K, space group $P2_1/n$ (No. 14), *Z* = 4, D_c = 1.104 g cm^{-3}, *μ*(Mo-K*α*) = 0.062 mm^{-1}, 2457 reflections measured, 1699 unique (R_{int} 0.011), 1698 used in all calculations. Final R_1 [$1425F > 4\sigma(F)$] = 0.0425 and *wR*(all F^2) was 0.104.

Crystal structure determination of 4b. A crystal was mounted on a multi-filament glass fibre and transferred into the cold stream of the low temperature device of the diffractometer.

Crystal data. $C_{12}H_{22}BNSi$, *M* = 219.21, orthorhombic, *a* = 8.201(2), *b* = 9.792(3), *c* = 16.905(6) Å, *U* = 1357.5(7) Å^3, *T* = 150(2) K, space group $P2_12_12_1$ (No. 19), *Z* = 4, D_c = 1.073 g cm^{-3}, *μ*(Mo-K*α*) = 0.144 mm^{-1}, 5373 reflections measured (including Friedel opposites), 2630 unique (R_{int} 0.029), 2630 used in all calculations. Final R_1 [$2464F > 4\sigma(F)$] = 0.0361 and *wR*(all F^2) was 0.0860. The Flack enantiopole parameter refined to 0.00(14).[13]

Crystal structure determination of 5b. A crystal was mounted on a dual-stage glass fibre and transferred into the cold stream of the low temperature device of the diffractometer.

Crystal data. $C_{12}H_{22}BNSi$, *M* = 219.21, orthorhombic, *a* = 9.877(4), *b* = 10.076(5), *c* = 13.669(9) Å, *U* = 1360.3(12) Å^3, *T* = 150(2) K, space group $P2_12_12_1$ (No. 19), *Z* = 4, D_c = 1.070 g cm^{-3}, *μ*(Mo-K*α*) = 0.143 mm^{-1}, 3156 reflections measured (including Friedel opposites), 2647 unique (R_{int} 0.021), 2647 used in all calculations. Final R_1 [$2362F > 4\sigma(F)$] = 0.0563 and *wR*(all F^2) was 0.143. The Flack enantiopole parameter refined to 0.0(2).[13]

Crystal structure determination of 7. A crystal was mounted on a dual-stage glass fibre and transferred into the cold stream of the low temperature device of the diffractometer.

Crystal data. $C_{12}H_{18}IN$, *M* = 303.17, monoclinic, *a* = 8.639(3), *b* = 7.619(4), *c* = 9.731(4) Å, *β* = 97.22(3)°, *U* = 635.5(3) Å^3, *T* = 150(2) K, space group $P2_1$ (No. 4), *Z* = 2, D_c = 1.585 g cm^{-3}, *μ*(Mo-K*α*) = 2.486 mm^{-1}, 3969 absorption-corrected reflections measured (including Friedel opposites), 2227 unique (R_{int} 0.014) used in all calculations. Final R_1 [$2207F > 4\sigma(F)$] = 0.0125 and *wR*(all F^2) was 0.0318. The Flack enantiopole parameter refined to 0.15(3).[13]

CCDC reference number (for **4i**, **4b**, **5b** and **7**) 207/352. See http://www.rsc.org/suppdata/p1/1999/2439 for crystallographic files in .cif format.

Acknowledgements

We are grateful to Pfizer Central Research, Sandwich, UK, and to the Royal Society of Chemistry for a Hickinbottom Fellowship, which provided the funding to support M. R. E. We are also grateful to the University of Malaya (Lembah Pantai, 59100 Kuala Lumpur, Malaysia) for financial support of A. A. through the SLAB scheme. We also acknowledge the Engineering and Physical Sciences Research Council (EPSRC) for funding for a diffractometer and for a postdoctoral award to W.-S. L.

References

1 For reviews, see (*a*) S. V. Kessar and P. Singh, *Chem. Rev.*, 1997, **97**, 721; (*b*) B. Carboni and L. Monnier, *Tetrahedron*, 1999, **55**, 1197.
2 M. R. Ebden, N. S. Simpkins and D. N. A. Fox, *Tetrahedron*, 1998, **54**, 12923.
3 E. Vedejs and J. T. Kendall, *J. Am. Chem. Soc.*, 1997, **119**, 6941.
4 A. J. Blake, M. R. Ebden, D. N. A. Fox, W.-S. Li and N. S. Simpkins, *Synlett*, 1998, 189.
5 Lithiated *N*-formamidine tetrahydroisoquinoline derivatives are similarly configurationally unstable, see for example (*a*) A. I. Meyers, J. Guiles, J. S. Warmus and M. A. Gonzalez, *Tetrahedron Lett.*, 1991, **32**, 5505; see also (*b*) R. E. Gawley and Q. Zhang, *Tetrahedron*, 1994, **50**, 6077; (*c*) T. R. Elworthy and A. I. Meyers, *Tetrahedron*, 1994, **50**, 6089.
6 Sparteine is a very important ligand for asymmetric metallation, see for reviews (*a*) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park and S. Thayumanavan, *Acc. Chem. Res.*, 1996, **29**, 552; (*b*) D. Hoppe and T. Hense, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2282.
7 In our original communication diastereomer **4** was mistakenly reported as the major product from quenching with Me_3SiCl.
8 This argument relies on the transmetallation reaction of **5a** proceeding with initial retention of configuration, which can usually be assumed, see for example P. Beak and A. I. Meyers, *Acc. Chem. Res.*, 1986, **19**, 356.
9 The very small quantities of the minor isomer **4b** available in non-racemic form, combined with the small values of the apparent specific rotations resulted in the misassignment.
10 (*a*) D. R. Armstrong, W. Clegg, H. M. Colquhoun, J. A. Daniels, R. E. Mulvey, I. R. Stephenson and K. Wade, *J. Chem. Soc., Chem. Commun.*, 1987, 630; (*b*) see also H. Nöth, S. Thomas and M. Schmidt, *Chem. Ber.*, 1996, **129**, 451.
11 (*a*) L. J. Beeley and C. J. M. Rockell, *Tetrahedron Lett.*, 1990, **31**, 417; (*b*) A. I. Meyers and B. Santiago, *Tetrahedron Lett.*, 1995, **36**, 5877; (*c*) R. E. Gawley, S. R. Chemburkar, A. L. Smith and T. V. Anklekar, *J. Org. Chem.*, 1988, **53**, 5381.
12 J. K. Whitesell, *Chem. Rev.*, 1989, **89**, 1581.
13 H. D. Flack, *Acta Crystallogr., Sect. A*, 1983, **39**, 876.

Paper 9/04788C