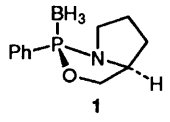
Synthesis of a New Class of Asymmetric Ketone Reduction Catalyst *via* a Diastereoselective Cyclisation Reaction: X-Ray Crystal Structure of $S_{(P)}R$-(−)-*N*-(*tert*-Butyldiphenylsilyl)dihydrobenzazaphosphole Oxide

Barry Burns,[a] Eric Merifield,[a] Mary F. Mahon,[b] Kieran C. Molloy[b] and Martin Wills*[,a]
[a] *School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK*
[b] *X-Ray Crystallographic Unit, School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK*

A stereoselective synthesis and X-ray crystal structure of dihydrobenzazaphosphole oxide $S_{(P)}R$-*trans*-**8**, a precursor of a new class of asymmetric ketone reduction catalyst, is described.

The reduction of non-symmetric ketones to chiral, non-racemic, alcohols using an asymmetric catalyst is a valuable transformation with potential application to a large number of synthetic processes.[1] One of the most successful catalysts for this application are the oxazaborolidine family of compounds reported by Itsuno and Corey.[2] Although impressive enantiomeric excesses may be achieved, the preparation of these catalysts requires great careful handling and rigorous exclusion of water.[2,3] One of the few asymmetric ketone reduction catalysts not based on the oxazaborolidine structure is the oxazaphospholidine–borane complex **1**, which was reported



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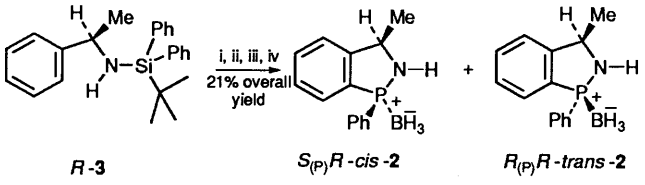
recently by Buono.[4] Although not as effective a catalyst in terms of enantiomeric inductions, this compound has the advantage of high stability and simple preparation. On the basis of this reported work and as part of a programme directed at the development of a general class of asymmetric phosphorus catalysts derived from α-methylbenzylamine we identified the dihydrobenzazaphosphole–borane complexes *cis*- and *trans*-**2** as potential asymmetric ketone reduction catalysts. Reduction catalysts of this class, to our knowledge, have not been previously reported. As well as being predicted to be chemically stable species,[5] they also have the potential advantage of ready availability in either antipodal form. They should also be 'tunable' for particular applications through variation of the group on the nitrogen atom and that at the phosphorus atom.

An enantiomerically pure phosphorus centre was considered essential if the catalyst was to be an effective one. Our approach to the synthesis of **2**, therefore, required a method that was short and efficient as well as capable of generating the target as a diastereomerically enriched or pure isomer. However, we envisaged that incomplete selectivity could be compensated for by chromatographic separation or crystallisation of diastereoisomers if necessary. Our method of choice, therefore, depended on the diastereoselective addition of a phosphorus dielectrophile to the dianion generated from appropriately protected α-methylbenzylamine, followed by trapping with borane.

Our choice of nitrogen protecting group was *tert*-butyldiphenylsilyl (TBDPS). This appeared to be an ideal candidate since it has been shown to be a valuable amine-protecting group,[6] most notably in the reported dilithiation and nucleophilic reactions of protected α-methylbenzylamine by Robinson.[7] Following some initial studies on the lithiation process, for which the use of butyllithium/tetramethylethylenediamine in ether was optimal,[8] the reaction of dilithio-*R*-**3**† with dichlorophenylphosphine followed by borane (dimethyl sulfide complex) resulted in the formation of an inseparable 1 : 1 mixture of diastereoisomeric adducts. Desilylation of this mixture was achieved by treatment with tetrabutylammonium fluoride to furnish a 1 : 1 mixture of $S_{(P)}R$-*cis*- and $R_{(P)}R$-*trans*-**2** (Scheme 1). The diastereoisomers of **2** are air-stable, highly

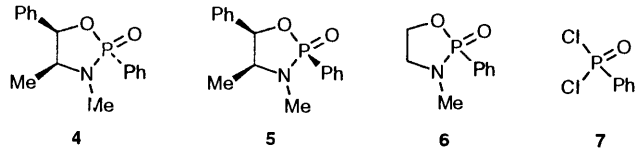


R-**3** $S_{(P)}R$-*cis*-**2** $R_{(P)}R$-*trans*-**2**

Scheme 1 *Reagents and conditions:* i, BuLi (2.2 equiv.), TMEDA (0.5 equiv), Et_2O, 0 °C, 16 h; ii, $PhPCl_2$, −78 °C, 1 h; room temp. 1.5 h; iii, BH_3·SMe_2 (1.2 equiv.) (2 mol dm^{-3} in THF), room temp., 2 h; iv, TBAF (1 mol dm^{-3} in THF; 1.1 equiv.), room temp., 3 h

crystalline materials which, unfortunately, proved to be only partially separable by flash chromatography. Although a practical synthesis of either diastereoisomer of **2** had not been achieved, the stability and crystalline properties represented an encouraging result. An alternative approach was, therefore, sought.

It is known that enantiomerically pure phosphine oxides may be reduced to phosphines with *inversion* of configuration using silyl trichloride and triethylamine.[9] We proposed that if a dihydrobenzazaphosphole **8**[10] could be prepared in diastereoisomerically pure form, this could be converted into **2** in a stereospecific fashion following the above protocol followed by trapping with borane.[11] Initial experiments involving the reaction between dilithio-*R*-**3** and dichlorophenylphosphine followed by oxidation proved fruitless, giving none of the expected products but only decomposition materials. In the expectation that the oxidising agents may have been causing decomposition we selected a series of electrophilic phosphorus(V) sources **4**–**7** for use in the cyclisation protocol.



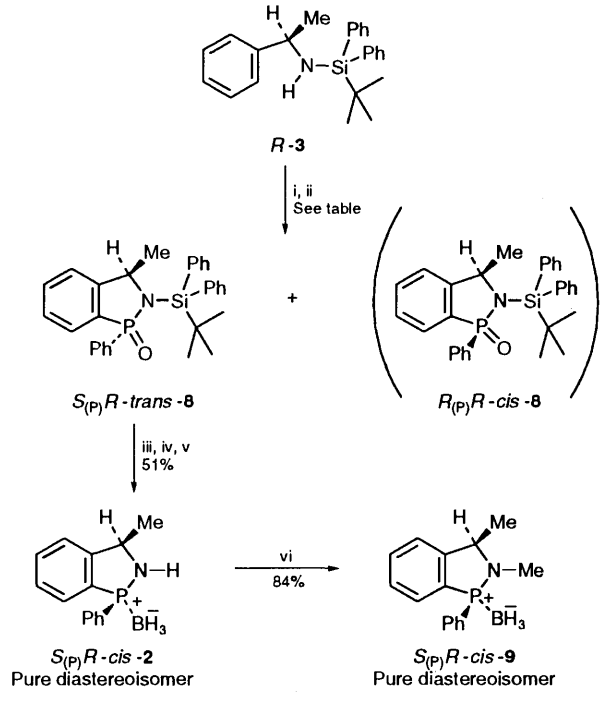
4 **5** **6** **7**

† Although readily available in either antipodal configuration, amine of *R*-configuration and derivatives thereof will be featured throughout this paper.

Table 1 Reactions of dilithiated **3** with electrophiles

Electrophile	Yield (%)	Ratio *trans*:*cis* **8**
4	20	>20:1
5	25	10:1
6	26	>20:1
7	43	>20:1

Compounds **4** and **5**,*[12] which are of a single configuration at phosphorus, were specifically chosen in an attempt to generate each diastereoisomer of **8** *via* sequential displacements of leaving groups at phosphorus in a stereoselective fashion.[13,14] To our surprise both **4** and **5** gave $S_{(P)}R$-*trans*-**8** as the major product (Scheme 2, Table 1). Indeed the racemic analogue **6** and the dichloride **7** also gave almost exclusively the same product in this sequence. In all cases the yields were low and the balance of material consisted of unchanged starting material *R*-**3**.† A single recrystallisation from dichloromethane–hexane furnished $S_{(P)}R$-*trans*-**8** as a single diastereoisomer. An X-ray crystallographic study of this novel heterocyclic material proved the relative stereochemistry of the product (Fig. 1).‡



Scheme 2 *Reagents and conditions:* i, BuLi (2.2 equiv.), TMEDA (0.5 equiv.), Et_2O, 0 °C, 16 h; ii, electrophile, −78 °C, 1 h; room temp. 1.5 h; iii, Et_3N (4.5 equiv.), $HSiCl_3$ (4 equiv.), toluene, 70 °C, 4 h; iv, BH_3·SMe (10 mol dm^{-3} in THF; 6 equiv.), room temp., 16 h; v, TBAF (1 mol dm^{-3} in THF; 1.1 equiv.), room temp., 3 h; vi, NaH (6 equiv.), MeI (2.5 equiv.), THF, room temp., 14 h

Reaction of $S_{(P)}R$-*trans*-**8** with trichlorosilane and triethylamine followed by addition of borane gave a complex product mixture. Treatment of the crude mixture with TBAF resulted in the formation of $S_{(P)}R$-*cis*-**2** as a single diastereoisomer. The stereochemistry in this product has been assigned on the basis of previous studies as that resulting from inversion of configuration at phosphorus. The remarkable stereoselective synthesis of $S_{(P)}R$-*trans*-**8** therefore, provided an efficient entry to a diastereoisomerically pure supply of the target borane complex $S_{(P)}R$-*cis*-**2**.

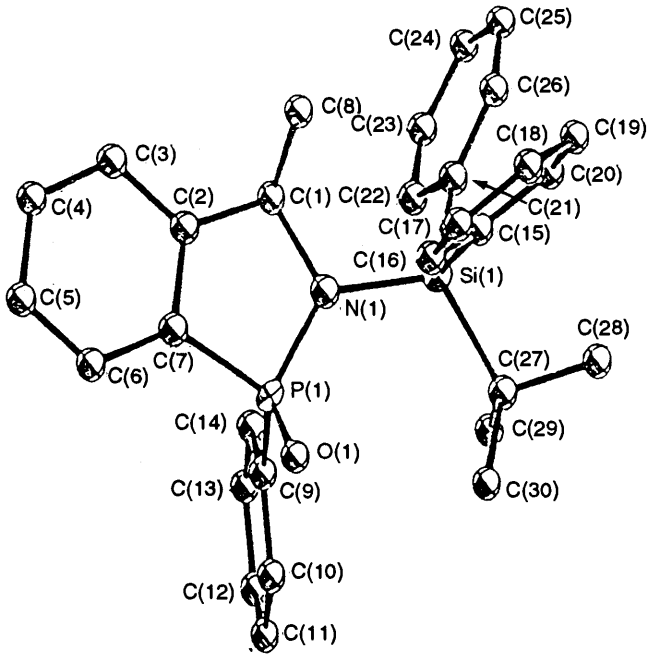
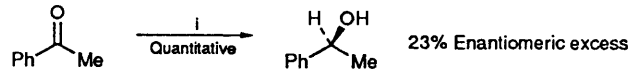


Fig. 1 X-Ray crystal structure of $S_{(P)}R$-*trans*-**8**

As predicted, $S_{(P)}R$-*cis*-**2** is an asymmetric catalyst for the reduction of ketones. In a preliminary experiment, the borane reduction of acetophenone in THF in the presence of 2 mol% of $S_{(P)}R$-*cis*-**2** gave phenethyl alcohol of 23% enantiomeric excess and of *S*-absolute configuration (Scheme 3).§ Unexpectedly, the methylated material $S_{(P)}R$-*cis*-**9** (Scheme 2) proved incapable of



Scheme 3 i, $S_{(P)}R$-*cis*-**2** (2 mol%), BH_3·SMe_2 (0.6 equiv.), THF, room temp.

* Compounds **4**–**6** were prepared by the reaction of **7** with the appropriate amino alcohol in the presence of triethylamine in dichloromethane.

† Reaction of dilithio-**3** generated in by the above method with benzaldehyde gave a 90% yield of product, suggesting that the *ortho*-anion is quenched during the reaction. This may be due to transmetallation with the phenyl ring in the electrophile: B. Burns and M. Wills, unpublished results.

‡ *X-Ray crystallographic data for* $S_{(P)}R$-*trans*-**8**: $C_{30}H_{32}NOPSi$, M = 481.61, orthorhombic, a = 10.099(4), b = 15.510(4), c = 16.560(4) Å, U = 2593.9 $Å^3$, space group $P2_12_12_1$, Z = 4, D_c = 1.23 g cm^{-3}, μ(Mo-Kα) = 1.35 cm^{-1}, $F(000)$ = 1024. Data were measured at room temperature on a Hilger and Watts Y290 four-circle diffractometer in the range $2 \leq \theta \leq 22°$. 1847 Reflections were collected of which 1275 were unique with $I > 3\sigma(I)$. Data were corrected for Lorentz and polarisation effects but not for absorption. The structure was solved by Direct methods and refined using the SHELX[15] suite of programs. In the final least squares cycles the silicon and phosphorus atoms were allowed to vibrate anisotropically. All other atoms were treated isotropically. Hydrogen atoms were included at calculated positions where appropriate. Final residuals after 10 cycles of least squares were $R = R_w = 0.0662$, for unit weights. Max. final shift/esd was 0.009. The max. and min. residual densities were 0.12 and −0.17 e $Å^{-3}$ respectively. The chiral integrity of the molecule as presented has a confidence level of greater than 95% over its mirror image based on the Hamilton test.[16]

§ The absolute configuration and enantiomeric purity of the phenethyl alcohol was initially measured by comparison of its optical rotation with the maximum published value; measured: $[\alpha]_D^{25}$ −10.5 (*c* 3.0, methanol), reported for the *S*-alcohol[17] $[\alpha]_D^{25}$ −45.5 (*c* 3.0, methanol). This was confirmed by conversion of our product to the *R*-methoxyphenyl(trifluoromethane)acetate derivatives[18] and comparison of the integrals of the resolved methoxy peaks in their 270 MHz ^1H NMR spectra.

catalysis of the same reduction reaction, from which racemic products were isolated. Further studies are currently underway on the development of these promising new asymmetric reduction catalysts and on the understanding of the distereoselective cyclisation reaction involved in the preparation of $S_{(P)}R$-*trans*-**8**.

Experimental

NMR coupling constants are recorded in Hz and [α] values as 10^{-1} deg cm^2 g^{-1}.

(R)-N-tert-*Butyldiphenylsilyl*-1-*phenylethylamine*[6] (R)-**3**.—*tert*-Butyldiphenylsilyl chloride (17.2 cm^3, 6.6 mmol) was added to a stirred solution of (*R*)-1-phenylethylamine (8.4 cm^3, 66 mmol) and triethylamine (18.4 cm^3, 132 mmol) in MeCN (200 cm^3). After the mixture had been stirred for 16 h at room temp. it was evaporated under reduced pressure and saturated aqueous ammonium chloride (150 cm^3) was added to the residue. The mixture was then extracted with ether (2 × 150 cm^3) and the combined extracts were washed with brine (100 cm^3), dried (Na_2SO_4), filtered and evaporated. Distillation of the residue at reduced pressure afforded (*R*)-**3** (20.3 g, 85%) as a viscous, colourless oil; b.p. 180 °C, 0.5 mmHg; δ_H 1.00 (9 H, s), 1.31 (3 H, d, *J* 6.5), 3.93 (2 H, br s, overlapping signals from CH and NH) and 7.13–7.75 (15 H, m); *m/z* (CI) 360 (M$^+$ + 1, 11%), 302 (M$^+$ − 57, 100), 282 (31) and 259 (21).

trans- *and* cis-**2**.—(*R*)-*N*-*tert*-Butyldiphenylsilyl-1-phenylethylamine (4.98 g, 13.9 mmol) in ether (20 cm^3) was bis-lithiated using butyllithium in hexanes (1.6 mol dm^{-3}; 18.2 cm^3, 29.2 mmol) and TMEDA (1.05 cm^3, 7.0 mmol) in ether (20 cm^3) for 20 h at room temp. The bis-anion solution was cooled to −70 °C, treated with dichlorophenylphosphine (2.25 cm^3, 16.6 mmol) and the residue stirred for 1 h at this temperature and then for 1.5 h at ambient temperature. After this, boron–dimethyl sulfide complex (BMS) in THF (2 mol dm^{-3}; 14 cm^3, 28 mmol) was added to it and stirring continued for 2 h at room temp.; at this point TLC analysis of the mixture indicated incomplete reaction. Additional BMS in THF (2 mol dm^{-3}; 7 cm^3, 14 mmol) was added to the mixture which was then stirred for a further 5 h at room temp. The solution was then diluted with ether and washed with saturated aqueous ammonium chloride and the aqueous phase was back-extracted with ether. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and evaporated. The resulting crude product in THF (55 cm^3) was treated with a solution of *tert*-butyl ammonium fluoride (TBAF) in THF (1 mol dm^{-3}; 16 cm^3, 16 mmol) and stirred at ambient temperature for 3 h. Saturated aqueous ammonium chloride was added to the mixture which was then extracted with ethyl acetate. The combined extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated. Purification of the residue by flash chromatography (eluent: petroleum–ethyl acetate, 10:1) afforded the heterocycle **2** (741 mg, 21%) as a viscous oil, a 1:1 mixture of diastereoisomers at P. This material could be crystallised from petroleum–ether: ν_{max}(thin film)/cm^{-1} 3377, 3057, 2970, 2925, 2866, 2368, 1436, 1107, 1056, 749, 693 and 607; δ_H 0.4–1.6 (3 H, br, *J* 45, BH_3), 1.57 (3 H, d, *J* 6, $CHCH_3$), 2.44 (0.5 H, d, *J* 14.0, NH), 2.70 (0.5 H, d, *J* 14.3, NH), 4.96 (1 H, m, $CHCH_3$) and 7.33–7.77 (9 H, m, aromatic H); *m/z* (CI) 277 (M$^+$ − BH_3, 73%), 212 (M$^+$ − BH_3 − Me, 43) and 150 (M$^+$ − BH_3 − Ph, 100).

Synthesis of trans-**8**.—A solution of (*R*)-**3** (5.0 g, 13.92 mmol) and tetramethylethylenediamine (1.05 cm^3, 6.95 mmol) in ether (2.5 cm^3) was treated with butyllithium (2.3 mol dm^{-3} solution in hexane; 15.14 cm^3, 34.8 mmol) at 0 °C. After being stirred for 90 min the yellow solution was cooled to −78 °C and phenylphosphonic dichloride (3.95 cm^3, 27.85 mmol) was added dropwise to it with shaking followed by an additional quantity of ether (20 cm^3). The solution was stirred overnight after which it was quenched by the addition of sat. aq. NH_4Cl (50 cm^3). The layers were separated and the aqueous phase extracted with dichloromethane (3 × 50 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure and the crude residue was purified by flash chromatography to give unchanged *R*-**3** (2.52 g, 51%) and $S_{(P)}R$-*trans*-**8** (2.80 g, 43%) which was purified by recrystallisation from dichloromethane–hexane; $[\alpha]_D^{25}$ −216.7 (*c* 0.95, methanol); δ_H 1.18 (9 H, s, CMe_3), 1.39 (3 H, d, *J* 6.6, $CHCH_3$), 5.04 (1 H, dq, *J* 6.7, 7.0, C*H*Me), 7.00 (2 H, m, aromatic H), 7.15–7.50 (10 H, m, aromatic H) and 8.05–8.09 (2 H, m, aromatic H); δ_C 18.26 (s), 25.92 (q), 27.67 (q), *ca.* 59.93 (dd, J_{PC} 6.6), 121.71 (dd, J_{PC} 11), 125.49 (d), 126.40 (dd, J_{PC} 13), 126.30 (d), 126.69 (s), 127.66 (d), 128.15 (d), 128.83 (s), 129.41 (d), 13.23 (d, J_{PC} 18, C_{ipso}), 134.64 (d), 135.61 (d), 147.69 (d, J_{PC} 20, C_{ipso}); *m/z* (CI) 482 (M$^+$, 100%) and 422 (M − Bu^t − 1$^+$, 60%) [Found: C, 74.6; H, 6.7; N, 2.8. $C_{30}H_{32}NOPSi$ requires C, 74.81; H, 6.70; N, 2.91%].

Synthesis of cis-**2** *by Reduction of* trans-**8**.—Triethylamine (0.09 cm^3, 0.65 mmol) was added to a stirred solution of trichlorosilane (0.06 cm^3, 0.59 mmol) in toluene (3.0 cm^3) at 0 °C over 10 min and the mixture was then heated to 70 °C. Phosphine oxide *trans*-**8** (70 mg, 0.15 mmol) was then added to it in one portion and heating continued for 4 h. The mixture was cooled to room temp. and partially evaporated (oil pump) and BMS (10 mol dm^{-3}; 0.1 cm^3, 1 mmol) was added to the residue. After a further 16 h at room temp. the reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate (10 cm^3) to the mixture which was then extracted with ether (2 × 20 cm^3). The combined extracts were washed with brine (10 cm^3), dried (Na_2SO_4), filtered and evaporated to give crude *N*-silylated *cis*-**2** as a colourless oil. Desilylation of this material using TBAF following the method given above for the diastereoisomeric mixture gave *cis*-**2** as a single diastereoisomer (18.2 mg, 0.075 mmol, 51%); $[\alpha]_D^{25}$ −62.7 (*c* 0.95, chloroform); δ_H 0.04–1.6 (3 H, br q, *J* 45, BH_3), 1.57 (3 H, d, *J* 6, $CHCH_3$), 2.70 (1 H, br d, *J* 14, NH), 4.98 (1 H, m, C*H*Me) and 7.33–7.77 (9 H, m, aromatic H); *m/z* 227 (M − $BH_3$$^+$, 73%), 212 (M − BH_3 − Me$^+$, 43%) and 150 (100%) (Found: C, 70.2; H, 7.3; N, 5.8. $C_{14}H_{17}BNP$ requires C, 69.75; H, 7.11; N, 5.81%).

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References

1 V. K. Singh, *Synthesis*, 1992, 605.
2 S. Wallbaum and J. Martens, *Tetrahedron: Asymmetry*, 1992, **3**, 1475.
3 D. J. Mathre, A. S. Thompson, A. W. Douglas, K. Hoogsteen, J. D. Carroll, E. G. Corley and E. J. J. Grabowski, *J. Org. Chem.*, 1993, **58**, 2880.
4 J.-M. Brunel, O. Pardigon, B. Faure and G. Buono, *J. Chem. Soc., Chem. Commun.*, 1992, 287.
5 Use of borane complexation for the stabilisation of phosphines, alkoxyphosphines and oxazaphospholidines: (*a*) T. Imamoto, T. Oshiki, T. Onozawa, T. Kusumoto and K. Sato, *J. Am. Chem. Soc.*, 1990, **112**, 5244; (*b*) T. Oshiki and T. Omamoto, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 3719; (*c*) S. Juge, M. Stephan, J. A. Laffitte and J. P. Genet, *Tetrahedron Lett.*, 1990, **31**, 6357.
6 L. E. Overman, M. E. Okazaki and P. Mishra, *Tetrahedron Lett.*, 1986, **27**, 4391.
7 (*a*) R. P. Robinson, K. M. Donahue and N. A. Saccomano, *Tetrahedron Lett.*, 1989, **30**, 5203; (*b*) R. Robinson, personal communication.
8 R. E. Ludt and C. R. Hauser, *J. Org. Chem.*, 1971, **36**, 1607.
9 (*a*) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman and D. J. Weinkauff, *J. Am. Chem. Soc.*, 1977, **99**, 5946.

10 M. J. P. Harger and P. A. Shimmin, *J. Chem. Soc., Chem. Commun.*, 1991, 1187.
11 U. Schmidt, B. Riedl, H. Griesser and C. Fitz, *Synthesis*, 1991, 657.
12 W. N. Setzer, B. G. Black, B. A. Hovanes and J. L. Hubbard, *J. Org. Chem.*, 1989, **54**, 1709.
13 J. M. Brown, J. V. Carey and M. J. H. Russell, *Tetrahedron*, 1990, **46**, 4877.
14 (*a*) O. Korpium, R. A. Lewis, J. Chickos and K. Mislow, *J. Am. Chem. Soc.*, 1968, **90**, 4842; (*b*) R. A. Lewis and K. Mislow, *J. Am. Chem. Soc.*, 1969, **91**, 7009.
15 G. M. Shedrick, SHELX86; SHELX76, a computer program for crystal structure determination, University of Gottingen, 1986; 1976.
16 W. C. Hamilton, *Acta. Crystallogr.*, 1965, **18**, 502.
17 J. V. B. Kanth and M. Periasamy, *J. Chem. Soc., Chem. Commun.*, 1990, 1145.
18 (*a*) J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543; (*b*) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, 1973, **95**, 512.

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