Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), www.mdpi.org/ecsoc-4.htm, September 1-30, 2000

[A0094]

Studies Towards New Reagents for Asymmetric Hydroboration: Synthesis of Racemic *Trans*-2,5-diisopropylborolane

Kevin J. Hodgetts,* Gerhard Lascober and Massimo Zorzi

Department of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

Current Address for Correspondence:
K.J. Hodgetts, Neurogen Corporation, 35 Northeast Industrial Road,
Branford, CT 06405, USA.
E-mail: khodgetts@nrgn.com

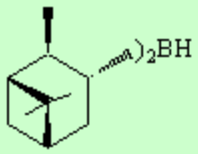
Received: 17 August 2000 / Uploaded: 20 August

Abstract

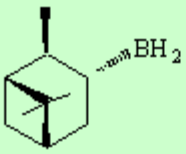
The cyclic hydroboration of 2,7-dimethyl-2,6-octadiene was studied. It was found that the stereochemical outcome of the reaction was dependent upon the solvent, temperature, time, and the nature of the borane reagent. Monobromoborane in carbon tetrachloride at 76 ^{o}C gave after 8 hr a 4:1 mixture of *trans:cis*-2,5-diisopropylborolane. Pure racemic *trans*-2,5-diisopropyl borolane was isolated following selective complexation of the *cis*-2,5-diisopropylborolane with 1-(2-hydroxyethyl)-pyrrolidine.

Introduction

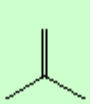
In 1961, Brown described the first synthesis of a chiral hydroborating reagent, diisopinocampheylborane Ipc_2BH **1**, a reagent that has been shown to hydroborate sterically less demanding prochiral *cis*-alkenes in high e.e.[1] Unfortunately, the size of Ipc_2BH **1** causes sluggish additions to trisubstituted and sterically hindered alkenes resulting in lower e.e. To improve upon this problem monoalkylboranes such as monoisopinocampheylborane $IpcBH_2$ **2** were developed.[2] The reduced steric requirements of $IpcBH_2$ **2** facilitates the hydroboration of trisubstituted and *trans*-alkenes in good to excellent e.e. Although neither reagent provides high e.e. for the hydroboration of type I alkenes, the correct choice of reagent can give good results with alkenes types II, III and IV. Indeed the availability of a-pinene and relative ease of synthesis[3] of **1** and **2** has made them the most widely used asymmetric hydroboration systems.[4]



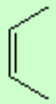
Ipc_2BH **1**



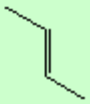
$IpcBH_2$ **2**



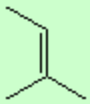
Type I



Type II

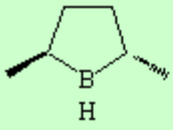


Type III

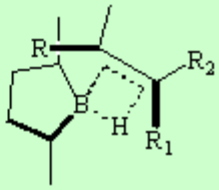


Type VI

In 1985, Masamune[5] introduced the C_2 symmetric *trans*-2,5-dimethylborolane **3**[6] as a rationally designed hydroboration reagent that gave very high e.e.'s for type II, III and IV alkenes; type I alkenes again gave poor results. The extent and directionality of the asymmetric induction observed with **3** is consistent with the proposed four-membered transition state model **4** shown below. For type II, III and IV alkenes (R=alkyl) the borolane methyl substituent clearly differentiates between the alkyl and hydrogen at the alkene terminus to give excellent asymmetric induction. For type I alkenes (R=H) the borolane methyl substituent is relatively ineffective in differentiating between the two faces of the alkene, resulting in poor asymmetric induction.



3

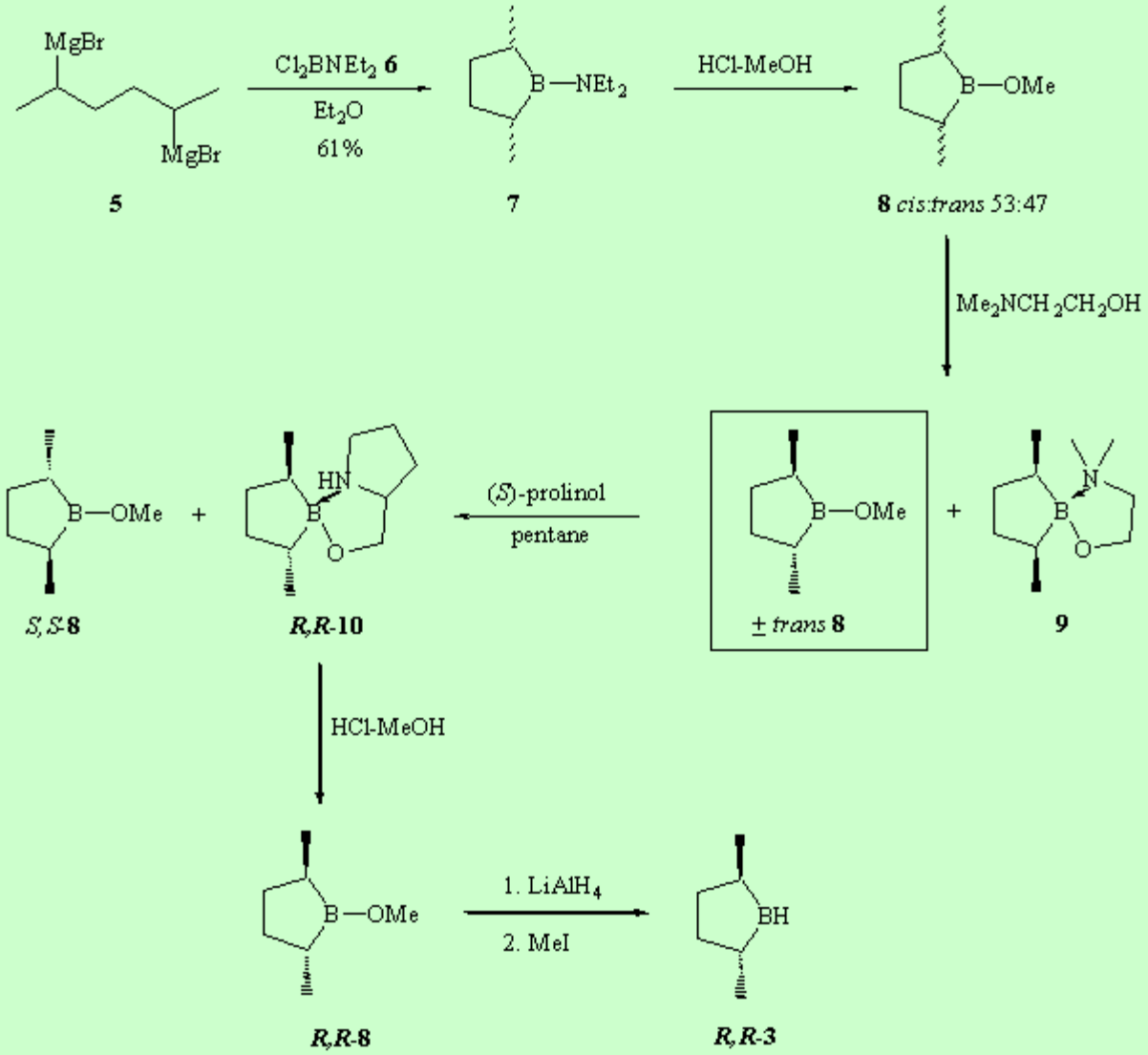


4

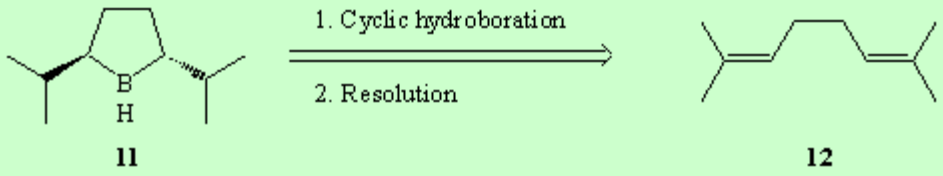
Typical % enantiomeric excesses, following oxidation, for the asymmetric hydroboration of prochiral alkenes with the reagents **1**, **2** and **3** are given below.[3,4,5]

Reagent	Type I	Type II	Type III	Type IV
1	5-30	60-99	<25	25-75
2	<5	<25	73-92	52-82
3	<5	95-96	96-99	93-97

The results would suggest Masamune's C_2 symmetric *trans*-2,5-dimethylborolane **3** to be the reagent of choice for asymmetric hydroboration, however, **3** has found almost no use as a reagent for asymmetric hydroboration. This is presumably because of the rather lengthy and tedious sequence of reactions and separations required for its preparation. The synthesis of **3** is outlined below. Potentially troublesome features include: preparation of the 'double' Grignard **5**, preparation of diethylaminodichloroborane **6**, the formation of approximately 50% of the unwanted *cis*-dimethyl borolane **7** in the cyclization step, and the subsequent need to remove this unwanted material by selective complexation.



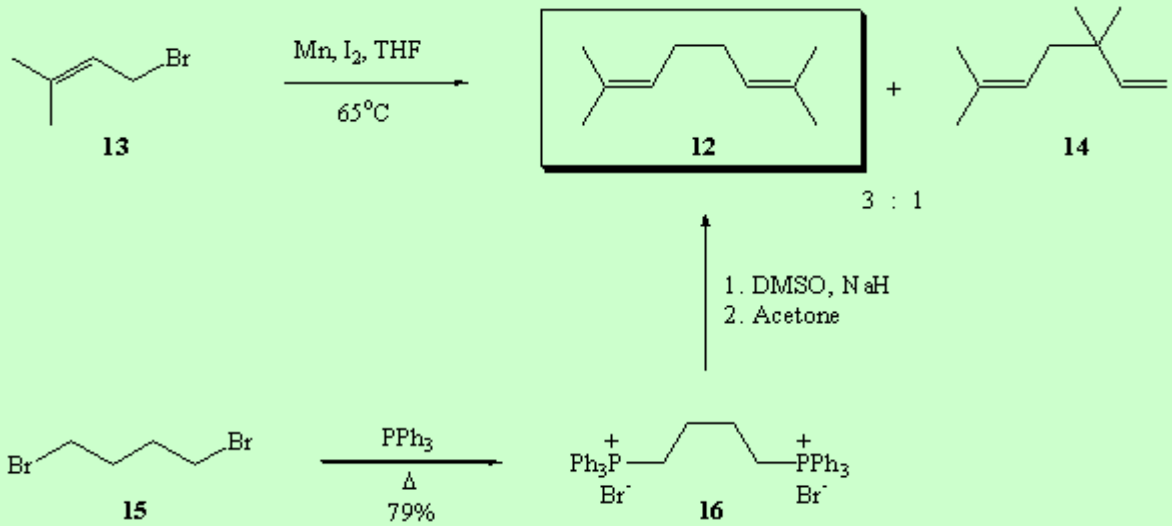
We wished to prepare new reagents for asymmetric hydroboration that retained the structural features of Masamune's C_2 symmetric *trans*-2,5-dimethylborolane **3** but were easier and more practical to prepare. Potentially these new reagents might give better asymmetric induction for type I alkenes as well as types II, III and IV. *Trans*-2,5-diisopropyllborolane **11**, having a greater steric demand than its methyl predecessor, was proposed as our target. We envisioned that the *trans*-borolane ring system might be selectively formed *via* the cyclic hydroboration[7] of 2,7-dimethyl-2,6-octadiene **12** and a resolution similar to that employed by Masamune would quickly give the pure enantiomers of *trans*-2,5-diisopropyllborolane **11**.



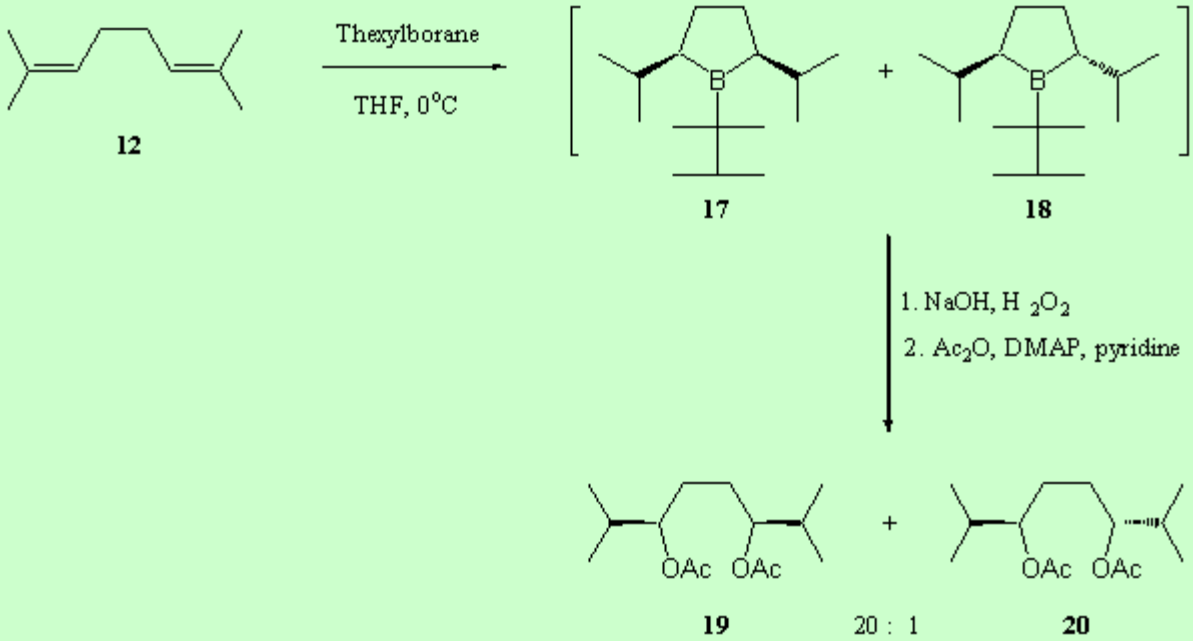
Results

2,7-Dimethyl-2,6-octadiene **12** was conveniently prepared in large scale by two alternate methods as shown below. 4-Bromo-2-methyl-2-butene **13** was dimerized with manganese powder and iodine in refluxing THF to give a 75% yield of a 3:1 mixture of the desired 2,7-dimethyl-2,6-octadiene **12** and the isomeric 3,3,6-trimethyl-1,5-heptadiene **14**. The diene **12** was isolated in pure form following careful distillation in 39% yield. Alternatively **12** was prepared *via* a *bis*-Wittig reaction. Butane-1,4-bis(triphenylphosphonium) dibromide **16** was prepared in 79% yield by refluxing 1,4-dibromobutane **15** with triphenyl phosphine. The phosphonium salt was converted to its ylide and treated with an

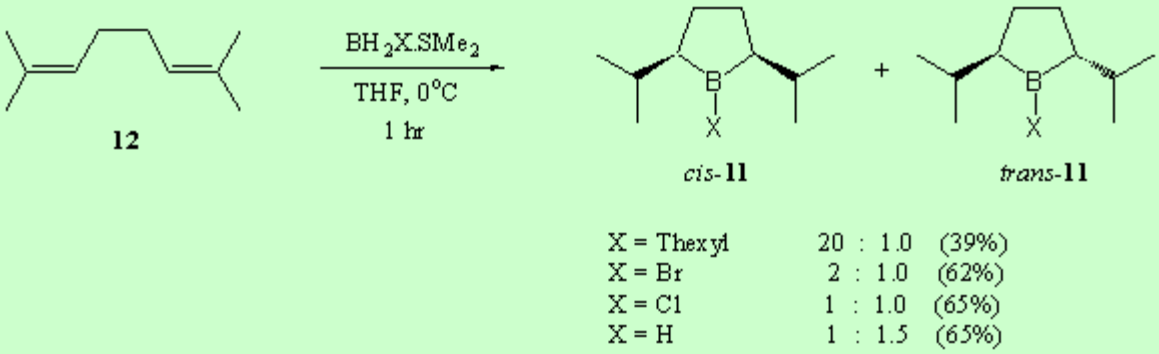
excess of acetone to give following distillation the pure diene **12** in 54% yield.

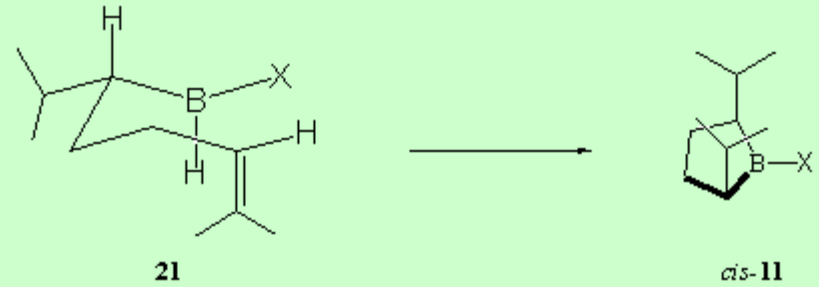


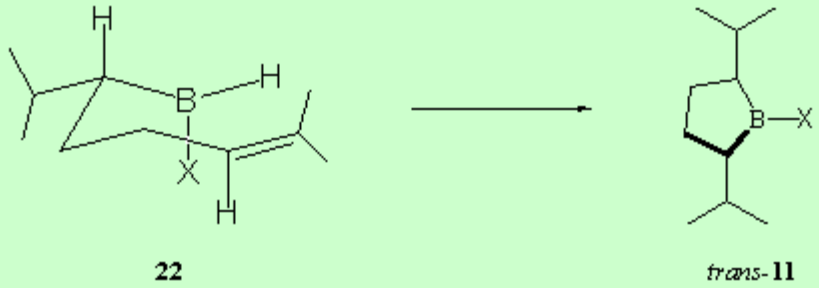
With a large quantity of 2,7-dimethyl-2,6-octadiene **12** in hand we were in position to examine its cyclic hydroboration. Still has previously reported that hydroboration of **12** with thexylborane and oxidative work up gave predominantly *meso*-2,7-dimethyl-3,6-octanediol.[8] Repetition of this reaction and conversion of the diols to their diacetates **19** and **20** gave compounds that were easily separable by capillary column GC, which would become our method of analysis for cyclic hydroboration studies.



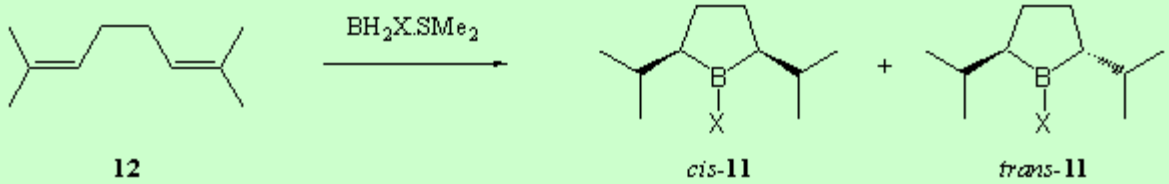
We anticipated that replacement of the bulky thexyl group of the hydroboration reagent with a smaller group would lead to greater selectivity for the desired *trans*-2,5-diisopropyllborolane **11**. Indeed, monobromoborane gave a 2:1 ratio of the *cis*:*trans*-borolanes in THF at 0°C. Under the same conditions monochloroborane gave a 1:1 ratio and borane itself gave a ratio slightly in favor of the desired *trans*-borolane. The preference of cyclic hydroboration for the *cis*- or *trans*-borolane can be explained by considering the intermediates **21** and **22** in which the isopropyl group is in an equatorial position. To produce the *cis*-borolane **11**, hydroboration must proceed across the axial double bond with the X group occupying an equatorial position as depicted in **21**. To produce the *trans*-borolane **11** hydroboration proceeds across the equatorial double bond with the X group occupying an axial position as depicted in **22**. These intermediates are consistent with the results observed. For thexylborane the large thexyl group adopts the equatorial position and therefore gives the *cis*-borolane **11** *via* intermediate **21**. As the X group decreases in size (thexyl>Br>Cl>H) the intermediate **22** becomes more important and more of the *trans*-borolane **11** is produced under the conditions studied.







Although there is a trend towards the desired *trans*-borolane the ratios are not much better than those obtained by Masamune's 'double' Grignard reaction in his synthesis of *trans*-2,5-dimethylborolane **3**. Since hydroboration is a reversible reaction we postulated that under equilibration conditions the *trans*-borolane **11** might be the more favored product. We therefore studied the cyclic hydroboration of **12** at the refluxing temperature of several solvents with monobromo- and monochloroborane.[9] The results of which are shown below.

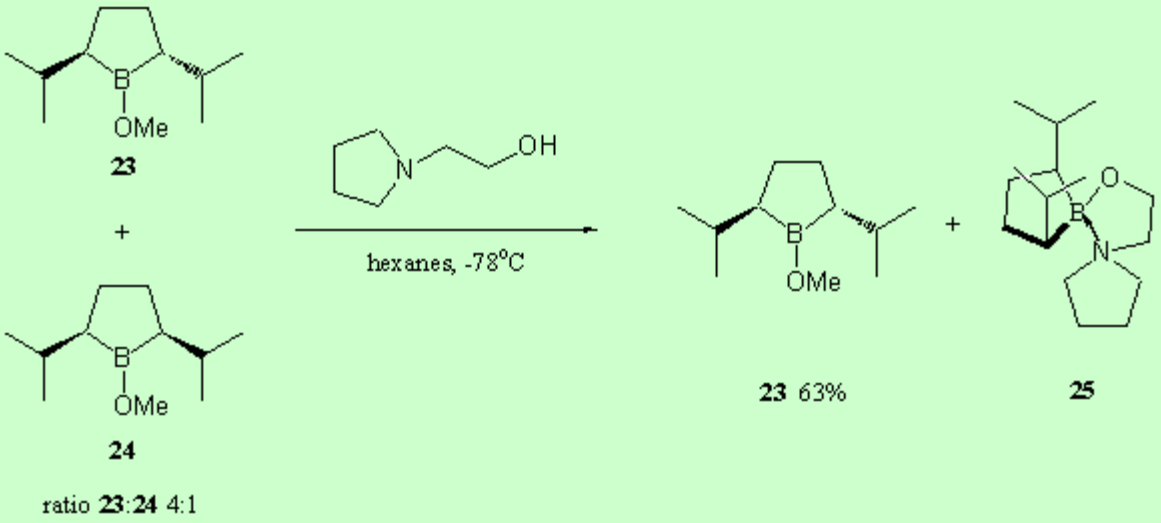


Entry	Borane	Solvent	Temp. (°C)	Time (hr.)	Yield (%)	*Trans: Cis*
1	$H_2BBr.SMe_2$	THF	0	1	63	1.0:2
2	$H_2BBr.SMe_2$	THF	0	8	59	1.0:2
3	$H_2BBr.SMe_2$	THF	65	1	57	1.0:1
4	$H_2BBr.SMe_2$	THF	65	8	55	1.5:1

5	$H_2BBr.SMe_2$	Et_2O	34	8	69	2.5:1
6	$H_2BBr.SMe_2$	CH_2Cl_2	40	8	67	3.0:1
7	$H_2BBr.SMe_2$	PhMe	110	8	49	2.7:1
8	$H_2BBr.SMe_2$	CCl_4	76	8	70	4.0:1
9	$H_2BCl.SMe_2$	THF	65	8	62	1.0:2
10	$H_2BCl.SMe_2$	THF	65	8	57	1.0:1
11	$H_2BCl.SMe_2$	CCl_4	76	8	62	2.8:1

The hydroboration of **12** with monobromoborane in THF at 0^oC for 1 hr gave as reported earlier a *trans:cis* ratio of 1:2. Increasing the reaction time to 8 hr at 0^oC gave the same product ratio. However, increasing the reaction temperature to 65^oC gave a 1:1 product ratio after 1 hr and after 8 hr the ratio was 1.5:1 in favor of the desired *trans*-borolane. Changing the solvent to ether, dichloromethane or toluene gave, after 8 hr at the refluxing temperature of the solvent, *trans:cis* ratios of 2.5-3.0:1. The best *trans:cis* ratio of 4.0:1 was found when the reaction was carried out in refluxing carbon tetrachloride for 8 hr. Similar product ratios were obtained when monochloroborane was used as the hydroboration reagent. Frustratingly, increasing the reaction times further or carrying out the reaction in sealed tubes at higher temperatures failed to improve the *trans:cis* ratios and generally resulted in extensive decomposition of the products. Nevertheless the *trans:cis* ratio of 4:1 from the carbon tetrachloride reaction was a significant improvement and we next investigated the resolution of the borolane isomers.

In Masamune's work the *cis*-dimethylborolane was removed by complexation with *N,N*-dimethylaminoethanol and the *trans*-dimethylborolanes **8** then resolved by complexation with (*S*)-prolinol and (*S*)-valinol respectively. Initially we tried to directly resolve our 4 : 1 mixture by complexation with the appropriate amount of (*S*)-prolinol, however, the small amount of complex formed was identified as the *cis*-borolane complex. Attempted resolution with various other amino alcohols also failed to precipitate the *trans*-borolane. It therefore appears to be necessary to remove the offending 20% of the *cis*-borolane **24** first. Replication of Masamune's work with *N,N*-dimethylaminoethanol failed to produce a separable complex. Various primary, secondary and tertiary amino-alcohols were screened in the complexation process. Gratifyingly the use of pyrrolidinoethanol in hexane at low temperatures gave a precipitate of the *cis*-complex **25**. Storage of the mixture at –78 ^oC for 4 hr and removal of the solution *via* cannula left behind essentially pure *cis*-complex **25**. The decanted solution was concentrated and distilled at reduced pressure to give the racemic *trans*-borolane **23** in >95% purity and 63% yield.



Conclusion

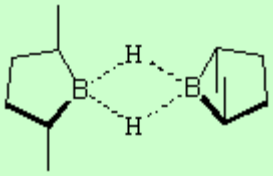
Pure racemic *trans*-2,5-diisopropyl borolane **23** was isolated following cyclic hydroboration of the readily available diene **12** and selective complexation of the *cis*-2,5-diisopropylborolane **24** with 1-(2-hydroxyethyl)-pyrrolidine. The resolution of **23** and application of the derived chiral borolanes in asymmetric synthesis will be described in due course.

Acknowledgments

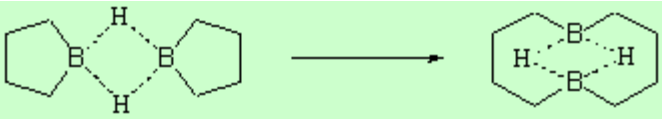
KJH wishes to thank University College Dublin and Schering Plough (Avondale) for the funding of this research under the Newman Fellowship program and the Department of Chemistry at the University College Dublin for the use of facilities during this research. GL and MZ wish to thank University College Dublin under the erasmus student exchange program. Dr Mike Casey is warmly thanked for his disclosure of unpublished results and his help throughout the course of this work.

References and notes

1. Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.*, 1961, **83**, 486.
2. Brown, H.C.; Yoon, N.M. *J. Am. Chem. Soc.*, 1977, **99**, 5514.
3. Brown, H.C.; Mandal, A.K.; Yoon, N.M.; Singaram, B.; J.R. Schwier, Jadhav, P.K. *J. Org. Chem.*, 1982, **47**, 5069; Brown, H.C.; Jadhav, P.K.; Mandal, A.K. *J. Org. Chem.*, 1982, **47**, 5074.
4. Burgess, K.; Van Der Donk, W.A. in Advanced Asymmetric Synthesis, Stephenson, G.R. (ed) 1996, Chapman and Hall.
5. Masamune, S.; Kim, B-M.; Petersen, J.S.; Sato, T.; Veenstra, S.J. *J. Am. Chem. Soc.*, 1985, **107**, 4549.
6. The dialkylborolanes described probably exist in the dimeric form shown below but are drawn in the text as the monomer for simplicity.



7. For a review on cyclic hydroboration see Brown, H.C.; Negishi, E. *Tetrahedron*, 1977, **33**, 2331.
8. Still, W.C.; Darst, K.P. *J. Am. Chem. Soc.*, 1980, **102**, 7385.
9. Borane itself was not used because the parent borolane is known to be thermally unstable and to isomerize easily to the 1,6-diboracyclodecane. [10]



10. Brown, H.C.; Negishi, E. *J. Am. Chem. Soc.*, 1971, **93**, 6682.

All comments on this poster should be sent by e-mail to (mailto:ecsoc@listserv.arizona.edu) ecsoc@listserv.arizona.edu with **A0094** as the message subject of your e-mail.
