Supplementary Material Available: Tables of atomic positions and thermal parameters and intramolecular bond lengths and angles and a full description of the data collection and structure solution and refinement (9 pages). Ordering information is given on any current masthead page.

Organoboron Compounds in Organic Synthesis. 2. Asymmetric Reduction of Dialkyl Ketones with (*R*,*R*)- or (*S*,*S*)-2,5-Dimethylborolane

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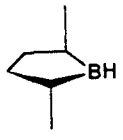
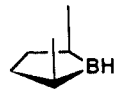
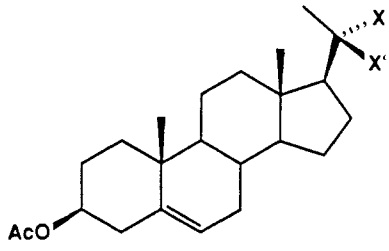
We wish to record herein the asymmetric reduction of two types of ketones $RCOR^1$ where R = Me, R^1 = alkyl (primary, secondary, and tertiary) for type I ketones and R = alkyl (primary), R^1 = alkyl (primary, secondary, and tertiary) for type II. The steric demands of R and R^1 being similar in both types of ketones, attainment of high enantiomeric excess in the reduction has been extremely challenging.[1] Successful examples are scarce and scattered (e.g., A–G in Table I) and there is no record of a reagent or reagents which meet the requirements set for the double-asymmetric strategy.[2] This difficult objective has been achieved in large measure through the use of (*R*,*R*)- or (*S*,*S*)-2,5-dimethylborolane (**1**).[3] The enantiomeric excess of hydroxyl compounds derived from type I ketones is 99–100% in most cases.



(R,R)-1

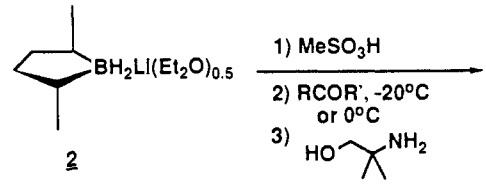


1a

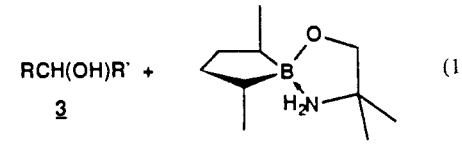


4 X,X'=O
a X=H; X'=OH
b X=OH; X'=H

Thus, treatment of the dihydridoborate **2** (1.2 equiv) in pentane[4] with 1.4 equiv of methanesulfonic acid (eq 1) provides reagent I which is comprised of 1.0 equiv of **1** and 0.2 equiv of 2,5-dimethylborolanyl mesylate.[5] Reagent I was used to reduce a set of dialkyl ketones (1 equiv).



2



3 (1)

Table I summarizes the results obtained with reagent I and compares them with those obtained earlier with the known chiral reagents A–G. While methyl, unbranched primary alkyl ketones (entries 1 and 2) are reduced with approximately 80% ee, branching at the β-position of the primary chain (in R^1) brings about near perfect asymmetric induction (entries 3–6). Therefore, it is not surprising that methyl, secondary and tertiary alkyl ketones are converted into the essentially enantiomerically pure hydroxyl compounds (entries 7–10). More remarkably, reduction of two type II ketones exhibits asymmetric inductions as high as 96% ee (entries 11, 12). Note the absolute configurations of the product alcohols that result from the reduction with (*R*,*R*)-**1** are all *R*.

Encouraged by the above results we have carried out several typical double-asymmetric reductions of chiral ketones under conditions identical with or similar to those used above.[6] Reduction of pregnenolone (**4**) is representative. With the aid of (achiral) reagent II, prepared from the dihydridoborate corresponding to achiral 2,5-*cis*-dimethylborolane (**1a**), the diastereofacial selectivity (**4a**/**4b**) of **4** is estimated to be 7.5. Preselection of a chiral reagent for matched and mismatched pairs can be readily made and reductions of **4** with (*R*,*R*)-**1** and (*S*,*S*)-**I** provide a mixture of the corresponding alcohols **4a** and **4b** in a ratio of 990:1 (matched) and 1:73 (mismatched), respectively. The demonstrated "reagent-controlled" diastereoselections are indeed remarkable and are predicted by the now-established rule of double-asymmetric synthesis.

While Reagent **I** constitutes a powerful synthetic tool, the mechanism of its asymmetric induction is not straightforward. 2,5-Dimethylborolanyl mesylate present in reagent I plays a catalytic role, and this intriguing feature is detailed in the following paper.[5]

Procedure for the Reduction of a Ketone. Compound (*R*,*R*)-**2** (20.38 mmol) in pentane (70 mL) was stirred with methanesulfonic acid (23.77 mmol) at room temperature for 2 h and the resulting mixture was cooled to −20 °C. 4-Methyl-2-pentanone (1.73 g, 16.98 mmol) was added and after the mixture was stirred 48 h at −20 °C precipitated $MeSO_3Li$ was removed by the filtration through a Celite bed and washed with pentane (2 × 5 mL). The combined mixture of the filtrate, washings, and a solution of 2-amino-2-methyl-1-propanol (20.37 mmol) in ether (10 mL) was vigorously stirred at room temperature for 1 h to precipitate the borolane–amino alcohol complex as a white solid. The mixture was filtered and the precipitate washed with a 1:4 ether/pentane mixture (3 × 10 mL). The filtrate and washings were combined and processed in the usual manner. Final distillation provided 1.41 g (81%) of 4-methyl-2-pentanol, bp 46–47 °C (17 torr).

The crude amino alcohol complex (3.6 g, 97%) was recrystallized from either isopropyl alcohol or 1,2-dimethoxyethane to provide crystals which consisted of 99.28% of *R*,*R*, 0.45% of *S*,*R*, and 0.27% of *S*,*S* isomer (99.01% ee).

(1) For recent reviews on asymmetric ketone reduction, see: (a) Morrison, J. D. *Asymmetric Synthesis*: Academic Press: New York, 1983; Vol. 2, Chapters 2–5. b) Brown, H. C. *Modern Synthetic Methods IV*; in press. (c) Hawkins, J. M. Ph.D. Dissertation, Massachusetts Institute of Technology, 1986.

(2) Masamune, S. Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(3) Masamune, S. Kim, B. M.; Petersen, J. S.; Sato, T.; Veenstra, S. J.; Imai, T. *J. Am. Chem. Soc.* **1985**, *107*, 4549.

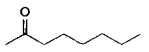
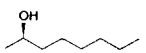
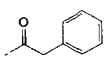
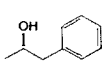
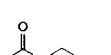
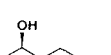
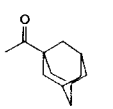
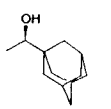
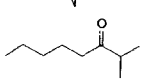
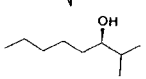
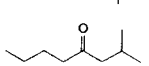
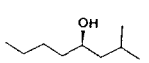
(4) Stored as a standard stock solution (see ref 3). The borohydride itself reduces dialkyl ketones with low percent ee (Sato, T.; Masamune, S., unpublished results).

(5) Masamune, S.; Kennedy, R. M.; Petersen, J. S.; Houk, K. N.; Wu, Y.-d., following paper in this issue.

(6) These results are summarized in the supplementary material.

0002-7863/86/1508-7402$01.50/0

Table 1. Asymmetric Reduction of Type I and II Ketones with Reagent 1 and Reagents A–G

		with (*R*,*R*)-**1** of 98.4% ee						% ee of **3** corrected for the enantiomeric purity of the chiral reagent (abs config)							
entry	ketone	reactn conditns[a]	alcohol **3**	isolated prod	isolated product, % yield	$[\alpha]^{25}_D$ of the isolated product	ee of **3**, %[b]	(*R*,*R*)-**1**	A[c]	B[d]	C[e]	D[f]	E[g]	F[h]	G[i]
1		A,C		**3a** (benzoate of **3**)	75	−36.7° (*c* 3.78, CCl_4)[j]	79.0[k]	80.3 (*R*)	76 (*S*)	43 (*S*)	4 ( )				
2		A,C		**3**	68	−8.24° (*c* 3.00, EtOH)[l]	80.0	81.3 (*R*)	79 (*S*)	48 (*S*), 63 (*S*)		58 (*R*)	29 (*R*)	61 (*R*)	24 (*R*)
3		A,C		**3a**	74	−38.7° (*c* 4.21, CCl_4)[m]	97.0	98.6 (*R*)	30 (*S*)			61 (*R*)			
4		B,C		**3**	81	−20.9° (*c* 11.1, EtOH)[m]	96.9								
5		A,C		**3**	76	−39.4° (*c* 2.25, EtOH)[n]	98.4	100 (*R*)							
6		A,C		**3**	69	−40.7° (*c* 2.45, C_6H_6)[n]	97.3	98.9 (*R*)						77 (*R*)	13 (*S*)
7		A,C		**3a**	69	−38.1° (*c* 3.23, CCl_4)[p]	98.4	100 (*R*)	68 (*S*)	62 (*S*), 90 (*S*)	32 ( )	60 (*R*)			
8		B,C		**3b** (acetate of **3**)	83	+10.6° (*c* 2.25, CCl_4)[q]	97.9	99.5 (*R*)					71 (*R*)		
9		B,D		**3a**	72	−43.0° (*c* 1.54, CCl_4)[r]	98.1	99.3 (*R*)	2 (*S*)	0.7 (*S*)	95 (*S*)	78 (*R*)			
10		A,D		**3b**	77	+18.1° (*c* 3.77, CCl_4)[s]	97.7	99.3 (*R*)					48 (*R*)		
11		A,D		**3**	74	+23.8° (*c* 3.00, EtOH)[t]	91.0	92.5 (*R*)							
12		A,D		**3**	72	−11.5° (*c* 3.00, EtOH)[u]	95.2	96.8 (*R*)							

[a] Reaction of 1.0 mmol of a ketone with reagent 1 prepared from 1.2 mmol of (*R*,*R*)-**2** and 1.4 mmol of $MeSO_3H$ (A) in hexane or (B) in pentane and (C) at −20 °C for 48 h or (D) at 0 °C for 24 h. [b] Estimated by capillary GC analysis of the (*R*)-MTPA ester of **3** unless otherwise noted. [c] Reagent A: NB enantride derived from (−)-nopol (Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2495). [d] Reagent B: alpine-borane derived from (+)-α-pinene (Midland, M. M.; McLoughlin, J. I. *J. Org. Chem.* **1984**, *49*, 1316; Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384) When two percent ee's are given for a ketone **3**, the higher one is recorded for the reduction under a high pressure of 6000 atom (Midland and McLoughlin). [e] Reagent C: diisopinocampheylchloroborane derived from (+)-α-pinene (Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5446). Also see ref 1b. [f] Reagent D: mixture of (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol and 2 equiv of borane (Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Org. Chem.* **1984**, *49*, 555; *J. Chem. Soc., Chem. Commun.* **1983**, 469). [g] Reagent E: mixture of *N*,*N*′-bis[(*S*)-α-methylbenzyl]sulfamide, benzylmethylamine, and 1 equiv of $LiAlH_4$ (hawkins, J. M.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3861). [h] Reagent F: mixture of diisobutylaluminum hydride, 1 equiv of $SnCl_2$, and 1 equiv of (*S*)-1-methyl-2-(piperidinomethyl)pyrrolidine (Oriyama, T.; Mukaiyama, T. *Chem. Lett.* **1984**, 2071). [i] Reagent G: Lithium aluminum hydride modified with equivalent molar amounts of (*S*)-2,2′-dihydroxy-1,1′-binaphthyl (BINAL-H) and ethanol (Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709, 6717). [j] Lit. $[\alpha]^{20}_D$ +39.23° (neat) for the (*S*)-benzoate (Kenyon, J.; Pickard, R. H. *J. Chem. Soc.* **1915**, 115). [k] Estimated by ^1H NMR of its MTPA ester, the CH_2CH_3 signals are compared. [l] Lit. $[\alpha]^{21}_D$ +10.1° (EtOH) for the *S* alcohol (Hill, R. K. *J. Am. Chem. Soc.* **1958**, *80*, 1611). [m] Lit. $[\alpha]^{27}_D$ +20.0° (neat) for the *S* alcohol (Mislow, K.; O'Brien, R. E.; Schaeffer, H. *J. Am. Chem. Soc.* **1962**, *84*, 1940). $[\alpha]_D$ not available for benzoate. [n] Lit. $[\alpha]^{27}_D$ +24.8° (neat) for the *S* alcohol.[m] [o] Lit. $[\alpha]_D$ +41.8° (C_6H_6) for the *S* alcohol (Pickard, R. H.; Kenyon, J. *J. Chem. Soc.* **1914**, 1115). (The optical rotation was measured "at the temperature of the laboratory".) [p] Lit. $[\alpha]^{26}_D$ +38.65° ($CHCl_3$) for the (*S*)-benzoate (Stevens, P. G. *J. Am. Chem. Soc.* **1933**, *55*, 4237) (calcd from 22.8% ee). [q] Measured at 28.5 °C, lit. $[\alpha]^{21}_D$ −10.6° (CCl_4) for the (*S*)-acetate.[3] [r] Measured at 28.5 °C, lit. $[\alpha]^{26}_D$ +41.84° ($CHCl_3$) for the (*S*)-benzoate[p] (calcd from 63.5% ee). [s] No data of $[\alpha]_D$ available for either **3** or its derivatives. [t] Lit. $[\alpha]_D$ +26.56° (EtOH) (Pickard, R. H.; Kenyon, J. *J. Chem. Soc.* **1913**, *103*, 1923). [u] Lit. $[\alpha]^{32}_D$ −9.48° (neat) (Levine, P. A.; Marker, R. E. *J. Biol. Chem.* **1931**, *90*, 669).

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Supplementary Material Available: Summary of the reduction of chiral ketones with *R,R* and *S,S* reagent I (2 pages). Ordering information is given on any current masthead page.

Organoboron Compounds in Organic Synthesis. 3. Mechanism of Asymmetric Reduction of Dialkyl Ketones with (*R,R*)-2,5-Dimethylborolane

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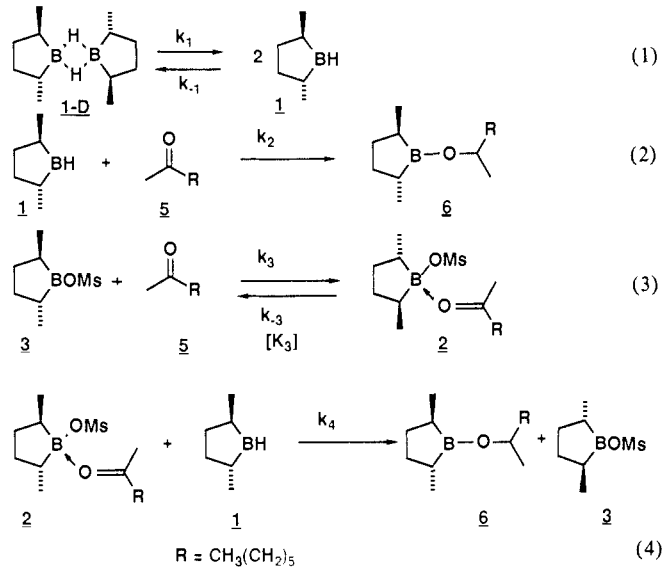
The preceding paper describes the asymmetric reductions of prochiral dialkyl ketones: Reagent I which contains dimeric (*R,R*)-2,5-dimethylborolane (**1**-D) (see Scheme I for the structures) provides the *R* alcohols of high enantiomeric purity.[1] These results surprised us, mainly because dialkyl ketones are isostructural with the corresponding terminal (type I) alkenes which, with **1**-D, undergo hydroboration with insignificant asymmetric induction.[2] No reasonable explanation for this apparent anomaly was immediately available. The accumulated evidence described below indicates, however, a rationalization for the observed high asymmetric induction. We propose the following mechanism for this reaction: A ketone forms the complex **2** with (*R,R*)-2,5-dimethylborolanyl mesylate (**3**) (Scheme I, eq 3) which is present in reagent I and subsequently complex **2** reacts with monomeric **1** (eq 1 and 4). The transition state of the last crucial step is also proposed and its geometry is evaluated with the aid of a combination of ab initio and MM2 computations.

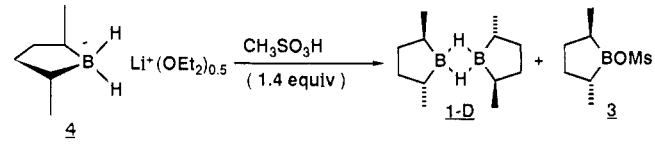
Experiment Set 1. Treatment of lithium dihydridoborate (**4**)[2] in hexane with dimethyl sulfate (1.2 equiv) provided **1**-D (^{11}B NMR δ 31.5) as the sole boron-containing species. Reduction of 2-octanone (**5**) with **1**-D, free from **3**, followed three-halves-order kinetics, first order in **5** and one-half order in **1**-D to provide (*S*)-2-octanol with 4% ee (cf. hydroboration of type I olefins).[2] The rate constant was $k_{3/2} = 7.0 \times 10^{-4}$ M$^{-1/2}$ at 29.9 °C.[3] Thus, this reduction (eq 1 and 2) proceeded in a manner expected from the reduction of **5** with dialkylboranes[4] and does not bring about high asymmetric induction (81% ee) observed in the reaction with reagent I.[1]

Set 2. Methanesulfonic acid (2 equiv) reacted with **4** to form mesylate **3** which was isolated and characterized (e.g., ^{11}B NMR δ 62.2). Thus, it was confirmed spectroscopically that reagent I prepared from **4** (1.2 equiv) and methanesulfonic acid (1.4 equiv)

Scheme I



Scheme II



contained **1**-D (1.0 equiv as monomer) and **3** (0.2 equiv) (Scheme II). Addition of ketone **5** (1 equiv) to **3** in hexane shifted its ^{11}B NMR signal to δ 44.5,[3] indicating **3**, a strong Lewis acid, formed complex **2** with **5**. Thus, at the initiation of the ketone reduction (1.0 equiv of **5** used), the solution contained **1**-D (1.0 equiv) and an equilibrium mixture of **2**, **3**, and **5** (eq 1 and 3).

Set 3. 2-Octanone was reduced at −10.0 °C with **1**-D in the presence of varying amounts of **3**. As the amount of **3** increased, the following trends were evident.[3] The reduction accelerated, the kinetic order changed from three-halves as observed in the absence of **3** to first order, and the percent ee of the product 2-octanol became higher. With 0.2 equiv of **3**, the first-order rate constant approximated $k_1 = 12.4 \times 10^{-4}$ s^{-1} and the ee of octanol was close to 80.4%, both being the highest values attainable at −10.0 °C.[3] With **1**-D (free from mesylate **3**) hydroboration of the highly reactive 1-decene and reduction of butyraldehyde (also highly reactive) proceeded with first-order rate constants of $k_1 = 12.1 \times 10^{-4}$ and 11.6×10^{-4} s^{-1} at −9.5 °C, respectively. These three values of k_1 agree well and should represent the rate constant of a step common to the three reactions (eq 1).

Proposed Mechanism and Transition State. Reduction of ketone **5** with **1**-D follows three-halves-order kinetics, typifying the behavior of a slow-reacting ketone toward a dialkylborane.[4] As shown in eq 1 and 2, an equilibrium dissociation of **1**-D is followed by a slow reaction of **1** with **5**. The change in kinetic order from three-halves to first order outlined in experiment set 3 demands the involvement of an "activated ketone" which reacts fast enough to render the dissociation of **1**-D into **1** rate-determining as observed in hydroboration and reduction of reactive substrates.[4] We propose this "activated ketone" is complex **2** in which the boron atom of **3** coordinates with the carbonyl group of **5** *syn to the (small) methyl group.*[5] With 0.2 equiv of **3**, **5** is no longer able to compete with **2** for monomeric **1**. The sum of eq 3 and 4 is equivalent to eq 2, thereby allowing **3** to play a catalytic role. Also note that the geometry of **2** is such that the incoming borolane **1** is oriented in the manner shown in **7**, reminiscent of the transition state involved in the highly enantioselective hydroboration of a trisubstituted alkene.[2]

(1) Imai, T.; Tamura, T.; Yamamuro, A.; Sato, T.; Wollmann, T. A.; Kennedy, R. M.; Masamune, S., preceding paper in this issue.
(2) Masamune, S.; Kim, B. M.; Petersen, J. S.; Sato, T.; Veenstra, S. J. *J. Am. Chem. Soc.* **1985**, *107*, 4549.
(3) Detailed in the supplementary material, the kinetic data were obtained with the aid of ^{11}B NMR spectrocopy (Varian XL-300).
(4) Brown, H. C.; Chandrasekharan, J.; Wang, K. K. *Pure Appl. Chem.* **1983**, *55*, 1387.
(5) Reetz, M. T.; Hullmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymann, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405.

0002-7863/86/1508-7404$01.50/0