resentative. The procedure was actually the same as in procedure B, except for the reaction temperature. Thus, the mixture was heated to 90–95 °C for 1 h with stirring. The solid disappeared. The mixture was cooled to room temperature and saturated with magnesium sulfate heptahydrate. The organic layer was separated and dried, and on removal of the solvent, almost pure stearaldehyde (12.35 g, 92%) was obtained: mp 37–38 °C (lit.[33] mp 38 °C). The ^{1}H NMR spectrum agreed with that of an authentic sample.

Procedure D. This is a procedure that can be used when no solid bisulfite adduct is formed. 5-Carbethoxy-1-pentanal was regenerated by this procedure. To the separated aqueous sodium bisulfite adduct layer following washing with diethyl ether was added 50 mL of a 37% formaldehyde solution. Then magnesium sulfate heptahydrate was added until saturation had been achieved. A 50-mL portion of pentane was added, and the mixture was stirred for 1 h. The pentane layer was separated and dried, and on evaporation of all solvent, an 81% yield of almost pure aldehyde (n^{20}_D 1.4269) was obtained. The further purification by distillation gave pure 5-carbethoxy-1-pentanal (5.70 g, 72%): bp 117–118 °C (13 mm); n^{20}_D 1.4268; ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 3 H, CH_3), 1.6 (m, 4 H, CH_2), 2–2.6 (m, 4 H, CH_2), 4.1 (q, 2 H, CH_2O), 10 (m, 1 H, CHO). Anal. Calcd: C, 60.74; H, 8.92. Found: C, 60.35; H, 9.21.

Isolation of Aldehydes by Distillation. Isolation of stearaldehyde is illustrative. In the usual setup, 30 mmol of stearic acid was reduced with 66 mmol of the reagent in methylene chloride at room temperature for 15 min, the same as the procedure described previously. The reaction mixture was transferred with a double-ended needle to the flask containing 40 mL of cold water in an ice water bath and hydrolyzed with vigorous stirring for 1 h at room temperature. The acidic solution was neutralized with 20 mL of 3 N aqueous sodium hydroxide solution, followed by adding a small quantity of sodium bicarbonate powder. The mixture with water was then subjected to distillation directly. The distillation was continued until the total 95 mL of distillate was collected. Almost all of the thexylboronic acid was distilled out, along with water. A 30-mL portion of pentane was added to the residue, and the organic layer was separated and dried. On removal of solvent, the crude product was obtained in a yield of 102%: mp 34 °C (lit.[33] mp 38 °C). The ^{11}B NMR spectrum of the crude product indicated the presence of some thexylboronic acid. The product was further purified by passing through an alumina column with diethyl ether as an eluent, providing pure stearaldehyde (7.65 g, 95%): mp 38 °C (lit.[33] mp 38 °C). The ^{1}H NMR spectrum agreed with that of an authentic sample.

Selective Reduction of Aliphatic Carboxylic Acid in the Presence of Benzoic Acid. The competitive reaction between hexanoic acid and benzoic acid is representative. In the usual setup, a 100-mL flask was charged with 0.61 g of benzoic acid (5 mmol), 0.93 g of hexanoic acid (5 mmol), and 3 mL of methylene chloride. The mixture was cooled to 0 °C. To this stirred mixture was then added 5.17 mL of 3.0 M thexylchloroborane in methylene chloride (15.5 mmol) dropwise. After the hydrogen evolution was complete, the mixture was brought to room temperature and stirred for 1 h. The reaction was then quenched with 5 mL of water, and *n*-nonane was added as an internal standard. GC analysis of the organic layer indicated a 92% yield of hexanal and 6% yield of benzaldehyde.

In the larger scale reaction (50 mmol of each carboxylic acid), a 74% yield of hexanal was isolated by using the sodium bisulfite method in the usual manner, and a 90% yield of benzoic acid was recovered by using the potassium carbonate extraction.

Registry No. 1, 75067-06-0; benzoic acid, 65-85-0; benzaldehyde, 100-52-7; α-naphthoic acid, 86-55-5; α-naphthaldehyde, 66-77-3; *p*-methoxybenzoic acid, 100-09-4; *p*-methoxybenzaldehyde, 123-11-5; *p*-nitrobenzoic acid, 62-23-7; *p*-nitrobenzaldehyde, 555-16-8; *m*-cyanobenzoic acid, 1877-72-1; *m*-cyanobenzaldehyde, 24964-64-5; terephthalic acid, 100-21-0; terephthalaldehyde, 623-27-8; hexanoic acid, 142-62-1; hexanal, 66-25-1; decanoic acid, 334-48-5; decanal, 112-31-2; stearic acid, 77-92-9; stearaldehyde, 638-66-4; neopentanoic acid, 75-98-9; trimethylacetaldehyde, 630-19-3; diphenylacetic acid, 117-34-0; diphenylacetaldehyde, 947-91-1; cyclohexanecarboxylic acid, 98-89-5; cyclohexanecarboxaldehyde, 2043-61-0; 1,10-decanedicarboxylic acid, 693-23-2; 1,10-decanedicarboxaldehyde, 38279-34-4; 6-bromohexanoic acid, 4224-70-8; 6-bromohexanal, 57978-00-4; adipic acid monoethyl ester, 626-86-8; 5-carbethoxy-1-pentanal, 27983-42-2.

Selective Reductions. 40. A Critical Examination of the Relative Effectiveness of Various Reducing Agents for the Asymmetric Reduction of Different Classes of Ketones

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Among a wide variety of highly promising asymmetric reducing agents recently reported in the literature, 20 promising reagents were selected for critical examination. All of the data for the asymmetric reductions of prochiral ketones by these 20 reagents were compiled. The various ketones were organized into 10 distinct classes. However, direct comparison of the relative effectiveness of these 20 reagents for individual classes of ketones proved not possible because of the wide variation in the individual ketones used to test each reagent. In the hope of making possible such comparison, we selected one representative ketone for each of the 10 different classes of ketones. Then, six of the most promising reagents were selected: *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane, *B*-Ipc-9-BBN (neat); diisopinocampheylchloroborane, Ipc_2BCl; a mixed reagent of 2 equiv of BH_3 with (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol, BH_3–AMDPB (2:1); NB-Enantride; K-Glucoride; and Binal-H. These six reagents were applied to the 10 selected standard ketones. On the basis of results obtained for the six reagents and the 10 selected ketones, preferred reagents are suggested for the asymmetric reduction of individual classes of ketones.

Chiral modifications of complex metal hydride reagents with a wide variety of chiral auxiliaries for the asymmetric reduction of carbonyl compounds have been studied actively during the last 2 decades. However, asymmetric

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reducing agents developed in the early stage of this program commonly provided only low optical inductions in the asymmetric reduction of prochiral ketones.[2] Recently considerably better success has been realized in developing promising asymmetric reducing agents achieving excellent optical inductions in the asymmetric reduction of various prochiral ketones.[3] Thus, a wide variety of highly promising asymmetric reducing agents has now become available for such application.

The very success of this program has created a problem. No one particular reagent is effective for all of the different classes of ketones. Regretably, no systematic comparison between different reagents for certain classes of functionalized ketones is available. Such systematic comparison among reagents for the asymmetric reduction of various classes of ketones would greatly assist synthetic organic chemists in selecting an appropriate reagent for a desired transformation.

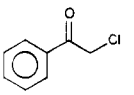
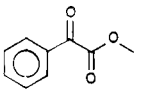
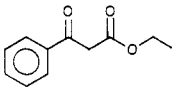
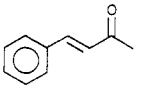
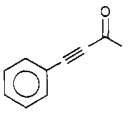
Accordingly, we decided to undertake such a systematic comparative study by assembling all of the results for the asymmetric reduction of various classes of prochiral ketones reported for 20 promising reagents. The ketones were subdivided into 10 different classes. Unfortunately, we discovered that each author had selected different test ketones. Consequently, a direct comparison of results with the same ketones was not possible. In examining the crude data, it appeared that six reagents were more promising. We decided to select 10 representative ketones, one for each class, and undertake to provide complete data for these six reagents.

Consequently, the present paper reports results for the asymmetric reduction of 10 selected representative ketones with the six more promising reagents. Examination of the results permits selection of preferred reagents for the reduction of individual classes of ketones.

Results and Discussion

As pointed out earlier, we first collected all of the asymmetric reduction data available in the literature[4] for the 20 promising reagents selected, namely, *B*-Ipc-9-BBN (Alpine-borane), THF (A);[5] *B*-Ipc-9-BBN, neat (B);[6] *B*-Ipc-9-BBN, 6 kbar (C);[7] NB-Enantrane (D);[8] Ipc_2BCl (E);[9] BH_3–AMDPB (2:1) (F);[10] (*R,R*)-2,5-dimethylborolane (G);[11] NB-Enantride (H);[12] $LiBH_4$–DBC–*t*-BuOH (I);[13] $NaBH_4$–IBA–DIPGF (J);[14] K-Glucoride (K);[15] $LiAlH_4$–

Chart I. Representatives of Various Classes of Ketones

	class	ketone
I.	acyclic	
II.	cyclic	
III.	aralkyl	
IV.	heterocyclic	
V.	α-halo	
VI.	α-keto esters	
VII.	β-keto esters	
VIII.	acyclic conjugated enones	
IX.	cyclic conjugated enones	
X.	conjugated ynones	

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(2) For a review of earlier work, see: (a) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice Hall: Englewood Cliffs, NJ, 1971. (b) Valentine, D., Jr.; Scott, J. W. *Synthesis* **1978**, 329. (c) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 175. (d) ApSimon, J. W.; Seguin, R. P. *Tetrahedron* **1979**, *35*, 2797.

(3) For a review of recent work, see: (a) Midland, M. M. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, Chapter 2. (b) Grandbois, E. R.; Howard, S. I.; Morrison, J. D. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, Chapter 3. (c) Haubenstock, H. *Top. Stereochem.* **1983**, *14*, 231. (d) ApSimon, J. W.; Lee Collier, T. *Tetrahedron* **1986**, *42*, 5157.

(4) The collection of asymmetric reduction data is available upon request to the author.

(5) Reagent A, *B*-Ipc-9-BBN, THF: This reagent is available from Aldrich Chemical Co. as Alpine-borane. (a) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352. (b) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371. (c) Tramontano, A. Ph.D. Thesis, University of California, Riverside, Aug 1980.

(6) Reagent B, *B*-Ipc-9-BBN, neat: (a) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1982**, *47*, 1606. (b) Brown, H. C.; Pai, G. G. *Ibid.* **1983**, *48*, 1784. (c) Brown, H. C.; Pai, G. G.; Jadhav, P. K. *J. Am. Chem. Soc.* **1984**, *106*, 1531. (d) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384.

(7) Reagent C, *B*-Ipc-9-BBN, 6 kbar: Midland, M. M.; McLoughlin, J. I. *J. Org. Chem.* **1984**, *49*, 1316.

(8) Reagent D, NB-Enantrane: NB-Enantrane is a registered trademark of Aldrich Chemical Co. Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2814.

(9) Reagent E, Ipc_2BCl: Available from Aldrich Chemical Co. (a) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5446. (b) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *Ibid.* **1986**, *51*, 3394.

(10) Reagent F, BH_3–AMDPB (2:1), AMDPB = (*S*)-(−)-2-amino-1,1-diphenylbutan-1-ol: (a) Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Chem. Commun.* **1981**, 315. (b) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *Ibid.* **1983**, 469. (c) Itsuno, S.; Hirao, A.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1673. (d) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Org. Chem.* **1984**, *49*, 555. (e) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039.

(11) Reagent, G, (*R,R*)-2,5-Dimethylborolane: Imai, T.; Tamura, T.; Yamamuro, A.; Sato, T.; Wollman, T. A.; Kennedy, R. M.; Masamune, S. *J. Am. Chem. Soc.* **1986**, *108*, 7402.

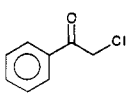
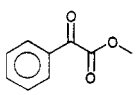
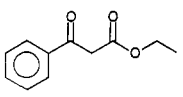
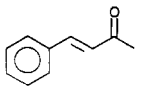
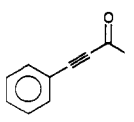
(12) Reagent H, NB-Enantride: NB-Enantride is a registered trademark of Aldrich Chemical Co. Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2495.

(13) Reagent I, $LiBH_4$–DBC–*t*-BuOH: (a) Soai, K.; Oyamada, H.; Yamanoi, T. *J. Chem. Soc., Chem. Commun.* **1984**, 413. (b) Soai, K.; Yamanoi, T.; Hikima, H.; Oyamada, H. *Ibid.* **1985**, 138.

(14) Reagent J, $NaBH_4$–IBA–DIPGF, IBA = isobutyric acid, DIPGF = 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose: (a) Hirao, A.; Itsuno, S.; Owa, M.; Nagami, S.; Mochizuki, H.; Zoorov, H. H. A.; Niakahama, S.; Yamazaki, N. *J. Chem. Soc., Perkin Trans. 1* **1981**, 900. (b) Morrison, J. D.; Grandbois, E. R.; Howard, S. I. *J. Org. Chem.* **1980**, *45*, 4229.

(15) Reagent K, K-Glucoride, potassium 9-*O*-(1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane: (a) Brown, H. C.; Park, W. S.; Cho, B. T. *J. Org. Chem.* **1986**, *51*, 1934. (b) Brown, H. C.; Park, W. S.; Cho, B. T. *Ibid.* 3278. (c) Brown, H. C.; Cho, B. T.; Park, W. S. *Ibid.* 3396.

Table I. Asymmetric Reduction of Representative Ketones

	ketone	% ee of alcohol products[a]																		
		A[b]	B[c]	C[d]	D[e]	E[f]	F[g]	G[h]	H[i]	I[j]	J[k]	K[l]	L[m]	M[n]	N[o]	O[p]	P[q]	Q[r]	R[s]	S[t]	T[u]
1			62	[90]		32	60	(100)	68			(39)									(86)
2						(98)						(84)									
3		7	87	[100]		(98)	94		70		78	(78)	(75)	84	95	51	95	97			
4				[100]		(92)															
5			96				96[v]										95[w]				
6			90				25[v]														
7										(84)											
8			56[x] 97	 [71]						(76) 101		 60[x]				 (72)			61[x] (98)		
9																(100)	*y*			(98)	
10		[78]	106.5		[86]					(10)											

[a] Values represent % ee determined by rotation of product alcohols or their derivatives. Values in brackets represent % ee determined by shift reagent NMR technique. Values in parentheses represent % ee determined by diastereomeric derivatization (MTPA, MCF, etc.), followed by analysis by HPLC, GC, ^{19}F NMR, or ^{1}H NMR. [b] Reagent A: *B*-Ipc-9-BBN, THF, ref 5. [c] Reagent B: *B*-Ipc-9-BBN, neat, ref 6. [d] Reagent C: *B*-Ipc-9-BBN, 6 kbar, ref 7. [e] Reagent D: NB-Enantrane, ref 8. [f] Reagent E: Ipc_2BCl, ref 9. [g] Reagent F: BH_3–AMDPB (2:1), ref 10. [h] Reagent G: (*R,R*)-2,5-dimethylborolane, ref 11. [i] Reagent H: NB-Enantride, ref 12. [j] Reagent I: $LiBH_4$–DBC–*t*-BuOH, ref 13. [k] Reagent J: $NaBH_4$–IBA–DIPGF, ref 14. [l] Reagent K: K-Glucoride, ref 15. [m] Reagent L: $LiAlH_4$–Darvon Alc, ref 16. [n] Reagent M: $LiAlH_4$–MEP–ArOH, ref 17. [o] Reagent N: LiAlH–diamine, ref 18. [p] Reagent O: $LiAlH_4$–aminobutanol, ref 19. [q] Reagent P: Binal-H, ref 20. [r] Reagent Q: $LiAlH_4$–DBP–EtOH, ref 21. [s] Reagent R: $LiAlH_4$–MEP–NEA, ref 22. [t] Reagent S: $LiAlH_4$–MEP–EAP, ref 23. [u] Reagent T: TBADH, ref 24. [v] Using a similar reagent, BH_3–AMDPP (2:1), AMDPP = (2*S*,3*R*)-(−)-2-amino-3-methyl-1,1-diphenylpentanol, ref 10e. [w] For α-bromoacetophenone. [x] Based on calculated $[\alpha]^{20}_D$ 39.6° (*c* 5.26, $CHCl_3$): Kawasaki, M.; Suzuki, Y.; Terashima, S. *Chem. Lett.* **1984**, 239. [y] Mainly cyclohexanol at 25 °C.

Darvon Alc (L);[16] $LiAlH_4$–MEP–ArOH (M);[17] $LiAlH_4$–diamine (N);[18] $LiAlH_4$–aminobutanol (O);[19] Binal-H (P);[20] $LiAlH_4$–DBP–EtOH (Q);[21] $LiAlH_4$–MEP–NEA (R);[22] $LiAlH_4$–MEP–EAP (S)[23] and TBADH (T).[24] The ketones used for asymmetric reductions were divided into 10 distinct classes, and one representative ketone for each class was then selected (Chart I). Then we assembled the available data for the representative ketones with respect to these 20 selected reagents (Table I). Table I reveals that comparison between those reagents for asymmetric reduction of a particular class is not possible because, with the exception of acetophenone, a significant portion of the

(16) Reagent L, $LiAlH_4$–Darvon Alc, Darvon Alc = [2*S*,3*R*]-(+)-4-(dimethylamino)-3-methyl-1,2-diphenyl-2-butanol: (a) Yamaguchi, S.; Mosher, H.; Pohland, A. *J. Am. Chem. Soc.* **1972**, *94*, 9254. (b) Yamaguchi, S.; Mosher, H. *J. Org. Chem.* **1973**, *38*, 1870. (c) Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339. (d) Cohen, N.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1980**, *45*, 582.

(17) Reagent M, $LiAlH_4$–MEP–ArOH, MEP = *N*-methylephedrine, ArOH = 3,5-dimethylphenol: Vigneron, J. P.; Jacquet, I. *Tetrahedron* **1976**, *32*, 939. Vigneron, J. P.; Bloy, V. *Tetrahedron Lett.* **1979**, 2683.

(18) Reagent N, $LiAlH_4$–diamine, diamine = (*S*)-2-(2,6-xylidinomethyl)pyrrolidine: Asami, M.; Mukaiyama, T. *Heterocycles* **1979**, *12*, 499.

(19) Reagent O, $LiAlH_4$–aminobutanol, aminobutanol = (*S*)-4-anilino-3-(methylamino)-1-butanol: (a) Sato, T.; Goto, Y.; Fujisawa, T. *Tetrahedron Lett.* **1982**, *23*, 4111. (b) Sato, T.; Gotoh, Y.; Wakabayashi, Y.; Fujisawa, T. *Ibid.* **1983**, *24*, 4123.

(20) Reagent P, Binal-H: (a) Noyori, R.; Tomino, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129. (b) Nishizawa, M.; Yamada, M.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 247. (c) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709. (d) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *Ibid.* 6717.

(21) Reagent Q, $LiAlH_4$–DBP–EtOH, DBP = (*S*)-(−)-10,10′-dihydroxy-9,9′-biphenanthryl: Yamamoto, K.; Fukushima, H.; Nakazaki, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1490.

(22) Reagent R, $LiAlH_4$–MEP–NEA, MEP = *N*-methylephedrine, NEA = *N*-ethylaniline: Terashima, S.; Tanno, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1980**, 1026.

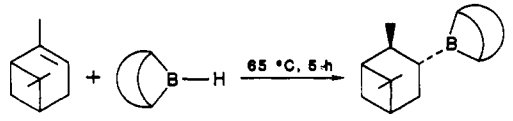
(23) Reagent S, $LiAlH_4$–MEP–EAP, MEP = *N*-methylephedrine, EAP = 2-(ethylamino)pyridine: Kawasaki, M.; Suzuki, Y.; Terashima, S. *Chem. Lett.* **1984**, 239.

(24) Reagent T, TBADH, *thermoanaerobium brockii* alcohol dehydrogenase: Keinan, E.; Hafeli, E. K.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 162.

corresponding data was not available for most of the representative ketones.

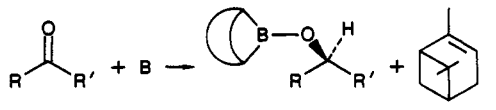
Consequently, we selected six of the more promising reagents, namely, reagents B, E, F, H, K, and P, and undertook to achieve a complete profile study for the 10 selected representative ketones (**1**–**10**) for each of these six reagents. Asymmetric reductions of representative ketones with these six reagents, in cases where the data were not available, were carried out carefully following the published procedures. The optical yields of the alcoholic products were analyzed either by measuring the rotation of the isolated material (where the rotation for 100% material appeared well established) or by capillary GC analysis of the corresponding (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA)[25] or, also commonly, the (−)-menthylchloroformate (MCF) derivatives.[26] On the basis of both our results and available data from the literature, preferred reagents are suggested for each class of ketones.

Asymmetric Reductions of Representative Ketones with the Six Reagents. Reagent B, *B*-Ipc-9-BBN, neat, represents the reagent prepared by the neat hydroboration of (+)- or (−)-α-pinene with 9-borabicyclo[3.3.1]nonane (9-BBN) (eq 1). The reagent utilizes its β-hydrogen for



(1)

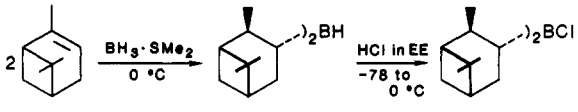
the asymmetric reduction, liberating 1 equiv of α-pinene (eq 2). For reagent B, the asymmetric reduction of ke-



(2)

tones **1**, **3**, **5**, **6**, **8**, and **10** were available. Consequently, we carried out the asymmetric reductions of **2**, **4**, **7**, and **9** to complete the series. Originally the reagent was reported to be highly effective in the reductions of **5**, **6**, and **10** (96%, 90% and 106.5% ee, respectively). (The earlier 106.5% ee value has been corrected by a capillary GC analysis of the MTPA esters.) The present work revealed that the reagent is also highly effective for the reduction of acetylpyridine, **4**, providing 93% ee of the corresponding alcoholic product.

Reagent E, Ipc_2BCl, represents the reagent prepared by the treatment of diisopinocampheylborane, Ipc_2BH (99% ee), with dry hydrogen chloride in ethyl ether (EE) (eq 3).

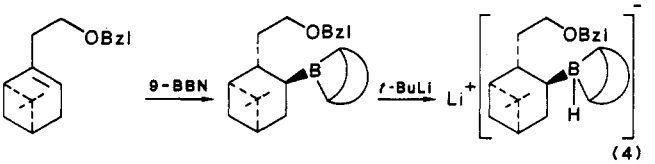


(3)

The reagent also reduces ketones via a β-hydrogen transfer, liberating 1 equiv of α-pinene. The reagent was originally described as one of the best reagents for the asymmetric reduction of arylalkyl ketones[9a] and α-tertiary alkyl ketones.[9b] The present work revealed that the reagent is also effective for the asymmetric reduction of **5**, an α-halo ketone (95% ee).

Reagent F, BH_3–AMDPB (2:1), represents the mixed reagent of uncertain structure prepared from 2 equiv of borane and (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol.[10] Asymmetric reductions of ketones **1**, **3**, **5**, and **6** were available in the literature. We carried out the asymmetric reductions of **2**, **4**, and **7**–**10**. The asymmetric reduction of acetophenone **3** with reagent F was confirmed (94% ee). However, the asymmetric reductions of **8**–**10** required the use of "dried reagent"[10c] prepared by the evaporation of all of the volatile components of the reagent, followed by redissolution in THF.[27] Reagent F was originally reported to be effective for the asymmetric reduction of **3**. A similar reagent with (*S*)-(−)-2-amino-3-methyl-1,1-diphenylpentan-1-ol (AMDPP) (see footnote *l* in Table II) was reported to be highly effective for the reductions of **5** (96% ee) and pinacolone[10e] (96% ee). The present work revealed that reagent F is also highly effective in the reduction of **2**, providing 96% ee of the corresponding alcohol product.

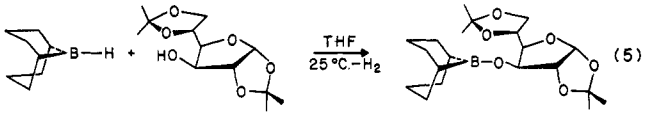
Reagent H, NB-Enantride, is the reagent prepared by hydroboration of nopol benzyl ether with 9-BBN, followed by hydridation of the corresponding trialkylborane using *t*-BuLi (eq 4). We carried out those reductions for ketones



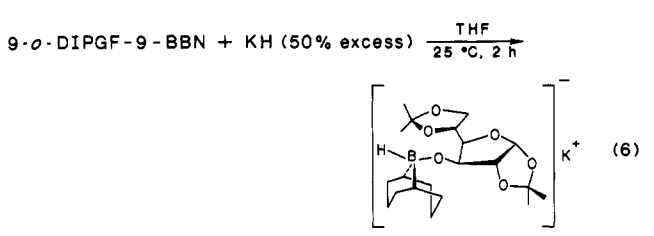
(4)

not available from the original literature (**2**, **4**, **5**, **6**, **8**, and **9**) by using a commercial reagent (Aldrich, nopol $[\alpha]^{23}D$ −36.08°, neat) at −78 °C. The commercial reagent reduced acetophenone **3** at −78 °C, providing 57% ee of the product alcohol, whereas the literature value, 70% ee, was obtained by using the reagent prepared from purified nopol ($[\alpha]^{23}D$ −39.96°, neat) at −100 °C. The reagent was reported to be effective in the reduction of acyclic aliphatic ketones, such as **1** (68% ee). Reagent H provided no other promising result among the other representative ketones.

Reagent K, K-Glucoride, is the reagent prepared by the treatment of 9-BBN with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (DIPGF), followed by the conversion of the corresponding borinic ester into the corresponding borohydride with excess potassium hydride in THF (eq 5 and 6). The reagent was reported to be effective in the



(5)



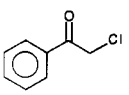
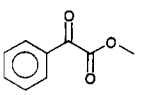
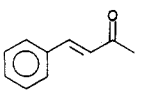
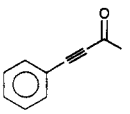
(6)

reductions of cyclic aliphatic ketones, such as **2**, and aralkyl ketones, such as **3** (84% ee and 78% ee, respectively).[15a] The reductions of hindered aralkyl ketones provided highly encouraging results, such as 87% ee for isobutyrophenone and 97–100% ee for pivalophenone.[15a] Additionally, the present work revealed that the reagent provides generally good optical yields (>60%) for various classes of ketones,

(25) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(26) (a) Westley, J. W.; Halpern, B. *J. Org. Chem.* **1968**, *33*, 3978. (b) Pirkle, W. H.; Hanske, J. R. *Ibid.* **1977**, *42*, 2436.

(27) The original reagent, BH_3-AMDPB (2:1), exhibited the presence of a significant amount of unreacted BH_3·THF in the ^{11}B NMR spectrum, thereby causing concurrent hydroboration in the reduction of unsaturated carbonyl compounds, such as **8**, **9**, and **10**.

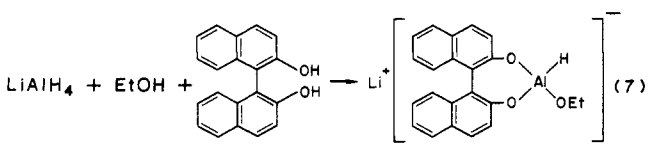
Table II. Asymmetric Reduction of Representative Ketones

ketone	% ee of alcohol products[a]					
	B[b]	E[c]	F[d]	H[e]	K[f]	P[g]
	62	32	60	68	36	(78)[h]
	(19.6)[i]	(98)	(96)[i]	(1)[i]	(84)	11[h]
	87	(98)	94 (94)[i]	70 (57)[i,j]	(78)	95
	(93)[i]	(92)	(73)[i]	(8)[i,j]	70[i]	
	96	95	96[l]	41[i,j]	77[i]	95[k]
	90	70[i,m]	25[l]	(33)[i,j]	(92)[i]	24[h]
	56[n]	12[i,n]	6[i,o]	13[i,j,n]	60[n]	70[h,n]
	(30.4)[i]	(36)[i]	(35)[i,o]	*i,j,p*	*i,p*	*q*
	(83)[i,r]	(21)[i]	(7)[i,o]	(10)	(61)[i]	(89)[h]

[a] See corresponding footnote in Table I. [b-g] See footnotes *c*, *e*, *f*, *h*, *k*, and *p* in Table I, respectively. [h] Present work contributed by Professor R. Noyori and his student, A. Yanagisawa. [i] Present work. [j] By using commercial NB-Enantride (Aldrich, nopol $[\alpha]^{23}_D$ -36.08, neat) and reduction at -78 °C in THF. [k] α-Bromoacetophenone. [l] Chiral auxillary used is AMDPP = (2*S*,3*R*)-(-)-2-amino-3-methyl-1,1-diphenylpentanol. [m] For the product from crystalline intermediate. Product from filtrate exhibited 50% ee. [n] Based on calculated maximum value, $[\alpha]^{20}_D$ 39.6° (*c* 5.26, $CHCl_3$), determined by NMR shift reagent technique. Kawasaki, M.; Suzuki, Y.; Terashima, S. *Chem. Lett.* **1984**, 239. A similar value was reported by ^1H NMR analysis of the MTPA derivatives. Sato, T.; Gotoh, Y.; Wakabayashi, Y.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 4123. [o] The original reagent prepared following literature procedure exhibited concurrent hydroboration. "Dried reagent" obtained by evaporation of volatiles, followed by redissolution in THF, provided the desired reduction. [p] Mainly 1,4-reduction. [q] Mainly cyclohexanol at 25 °C. [r] Uncorrected value of 76.7% ee by capillary GC analysis of MTPA esters, α^{22}_D 68.88° (neat). Originally reported as 106.5% ee after correction for the optical purity of α-pinene used (92% ee) on the basis of the calculated maximum rotation $[\alpha]_D$ 71.94° (neat) from the literature: Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.

except in one refractory case, **1**. More importantly, the reagent K reduced methyl benzoylformate (**6**) with an optical yield of 92% ee. Exploration of this lead led us to the discovery that K-Glucoride, K, appears to be the best available reagent for the asymmetric reduction of α-keto esters to the corresponding α-hydroxy esters[15c] with optical purities approaching 100% ee.

Reagent P, Binal-H, represents the reagent prepared by chiral modification of $LiAlH_4$ with (*R*)- or (*S*)-binaphthol and 1 equiv of EtOH[20] (eq 7). Pertinent data were only



(7)

available for **3**, **5**, and **9**. The reagent was originally reported as one of the most effective reagents for asymmetric reduction of aralkyl ketones, such as **3** (95% ee). It was also effective for the reduction of an α-halo ketone, **5** (95% ee), conjugated enones, such as β-ionones (100% ee), and conjugated ynones, such as 1-undecyn-3-one (96% ee). The present work reveals that reagent P also provides good optical yields in the reduction of **1**, **8**, and **10** (78%, 70% and 89% ee, respectively).

Selection of Preferred Reagents. On the basis of the completed Table II, pertinent data from Table I, and other data in our compilation collected from the original literature, we selected preferred asymmetric reducing agents for the various structurally different classes of ketones (Table III).

Recently Masamune and co-workers achieved excellent optical yields of hydroxyl compounds (92.5% ee–100% ee) by the asymmetric reduction of acyclic ketones with (*R*,*R*)- or (*S*,*S*)-2,5-dimethylborolane, G.[11] Despite the major drawback of a rather lengthy synthesis, reagent G, prepared by treatment of the corresponding dihydroborate with 1.4 equiv of methanesulfonic acid, provides the best available results for the asymmetric reduction of either unhindered or hindered acyclic ketones, thus being selected for both classes. *B*-Ipc-9-BBN, 6 kbar (C), an enzyme TBADH (T) (TBADH = *thermoanaerobium brockii* alcohol dehydrogenase), and NB-Entantride (M) were selected as the next preferred reagents for the class of unhindered acyclic ketones on the basis of the results of reduction of **1** in Table I and other substrates in our full

Table III. Preferred Asymmetric Reducing Agents

classes of ketones		preferred reagents (in order of effectiveness)
I. acyclic	a. unhindered	G, 2,5-dimethylborolane
		C, *B*-Ipc-9-BBN, 6 kbar
		T, TBADH enzyme
		H, NB-Enantride
	b. hindered	G, 2,5-dimethylborolane
		E, Ipc_2BCl
		F, BH_3–AMDPB (2:1)
II. cyclic		E, Ipc_2BCl
		F, BH_3–AMDPB (2:1)
		K, K-Glucoride
III. aralkyl	a. unhindered	C, *B*-Ipc-9-BBN, 6 kbar
		E, Ipc_2BCl
		Q, $LiAlH_4$–DBP–EtOH
		P, Binal-H
		N, $LiAlH_4$–diamine
		F, BH_3–AMDPB (2:1)
	b. hindered	K, K-Glucoride
		N, $LiAlH_4$–diamine
		E, Ipc_2BCl
IV. heterocyclic		C, *B*-Ipc-9-BBN, 6 kbar
		B, *B*-Ipc-9-BBN, neat
		E, Ipc_2BCl
V. α-halo		B, *B*-Ipc-9-BBN, neat
		F, BH_3-AMDPB (2:1)
		E, Ipc_2BCl
		P, Binal-H
VI. α-keto esters		K, K-Glucoride
		B, *B*-Ipc-9-BBN, neat
VII. β-keto esters		I, $LiBH_4$–DBC–*t*-BuOH
		E, Ipc_2BCl
VIII. acyclic conjugated enones		P, Binal-H
		R, $LiAlH_4$–MEP–NEA
		I, $LiBH_4$–DBC–*t*-BuOH
		O, $LiAlH_4$–aminobutanol
IX. cyclic conjugated enones		O, $LiAlH_4$–aminobutanol
		S, $LiAlH_4$–MEP–EAP
X. conjugated ynones		P, Binal-H
		D, NB-Enantrane
		M, $LiAlH_4$–MEP–ArOH
		A, *B*-Ipc-9-BBN, THF

compilation (2-butanone, 2-octanone, etc.). Ipc_2BCl (E) and BH_3–AMDPB (2:1) (F) were selected as the next two preferred reagents for hindered acyclic ketones on the basis of the reduction of pinacolone (E, 95% ee; F, 96% ee with AMDPP as a chiral auxiliary) and other α-tertiary alkyl ketones in our compilation.

Similary, reagents Ipc_2BCl (E), BH_3–AMDPB (2:1) (F), and K-Glucoride (K) were selected for cyclic ketones on the basis of the reduction of **2** (98%, 96% and 84% ee, respectively, Table II) and other substrates in the compilation, such as 2,2-dimethylcyclohexanone and spiro-[4.4]-nonan-1-one.

Several reagents were highly effective for the reduction of unhindered aralkyl ketones such as found for acetophenone (**3**): B-Ipc-9-BBN, 6 kbar, (C), 100% ee; Ipc_2BCl (E), 98% ee; $LiAlH_4$–DBP–EtOH (Q), 97% ee (DBP = (*S*)-(–)-10,10′-dihydroxy-9,9′-biphenanthryl); Binal-H (P), 95% ee; $LiAlH_4$–diamine (N), 95% ee (diamine = (*S*)-2-(2,6-xylidinomethyl)pyrrolidine); and BH_3–AMDPB (2:1) (F), 94% ee. For the hindered arylalkyl ketones, K-Glucoride (K) was selected as the preferred reagent on the basis of the fact that reagent K provides 97–100% ee of reduction product from pivalophenone and 87% ee from isobutyrophenone. $LiAlH_4$–diamine (N) and Ipc_2BCl (E) were reported to give 89% ee and 78% ee for isobutyrophenone reduction, leading to their selection as the next preferred reagents.

For heterocyclic ketones, represented by 3-acetylpyridine, *B*-Ipc-9-BBN, 6 kbar (C), was selected first and *B*-Ipc-9-BBN, neat (B), and Ipc_2BCl (E) were also selected on the basis of results of the present study (100%, 93%, and 92% ee, respectively).

For the α-halo ketones, represented by α-chloroacetophenone, *B*-Ipc-9-BBN, neat (B), BH_3–AMDPB (2:1) (F), Ipc_2BCl (E), and Binal-H (P) were selected as the preferred reagents providing high optical yields of the corresponding alcohol products (96%, 96%, 95%, and 95% ee, respectively).

The class of α-keto esters, represented by methyl benzoylformate, (**6**) is reduced most effectively by K-Glucoride (K) and B-Ipc-9-BBN, neat (B) (92% and 90% ee, respectively).

For the asymmetric reduction of β-keto esters represented by ethyl benzoylacetate (7) Soai's $LiBH_4$ reagent modified with (*R,R′*)-*N,N′*-dibenzoylcystine (DBC) and *t*-BuOH was reported to provide consistently high optical yields in several examples (84–92% ee), thus being selected as the preferred reagent for this class. All of the six selected reagents failed to provide the desired product in the reduction of **7**. Evidently, the acidic methylene hydrogen atoms interfere with the reduction. However, Ipc_2BCl (E) was reported to reduce ethyl 2,2-dimethylacetoacetate and methyl 1-methyl-2-oxo-cyclopentanecarboxylate with 84% and 96% ee, respectively.[9b] In these β-keto esters, there is no active hydrogen to interfere with the reagent.

For acyclic conjugated enones, two reagents, Binal-H (P) and $LiAlH_4$ modified with *N*-methylephedrine (MEP) and *N*-ethylaniline (NEA)[22] (R) were reported to provide high optical yields for several different examples of the class. With reagent P, β-ionone, (*E*)-1-cyclopentyl-1-octen-3-one, (*E*)-5-dodecen-7-one, and (*E*)-3-octen-2-one were reduced to give 100%, 92%, 91%, and 79% ee, respectively.[20d] With reagent R, a series of acyclic conjugated enones were reduced, providing good optical yields in the range of 61–92% ee.[22] $LiBH_4$–DBC–*t*-BuOH (I) and $LiAlH_4$–aminobutanol (O) (aminobutanol = (*S*)-4-anilino-3-(methylamino)-1-butanol) were selected as the next preferable reagents on the basis of the results of the reduction of **8** (76% and 72%, respectively, Table I).

The six reagents we selected failed to achieve high optical inductions or failed to provide clean 1,2-reduction product in the reduction of cyclic conjugated enones, represented by cyclohexenone. However, recently two new reagents were reported to provide excellent optical yields in the reduction of a series of cyclic conjugated enones, namely, $LiAlH_4$–aminobutanol (O)[19] and $LiAlH_4$–MEP–EAP (S)[23]. Thus, reagent O reduces **9**, with 100% ee (Table I), and reagent S reduces **9**, 2-methylcyclohexenone, 3-methylcyclohexenone, and cycloheptenone in 98%, 96%, 90%, and 73% ee, respectively.[23]

The asymmetric reduction of 4-phenyl-3-butyn-2-one (**11**), representing the class of conjugated ynones, was best achieved by using Binal-H (P) (89% ee, Table II). However, NB-Enantrane (D) is also highly effective for the reduction of a variety of conjugated ynones[8] (86–96% ee). Reagent $LiAlH_4$–MEP–ArOH (M),[17] ArOH = 3,5-dimethylphenol, and *B*-Ipc-9-BBN, THF (A)[5] were also selected for the class on the basis of available data from the literature.

Conclusion

A rational selection of the preferred asymmetric reducing agents is suggested for the asymmetric reduction of various classes of ketones. The selection was made on the basis of a compilation of all of the results for the asymmetric reduction of various classes of prochiral ketones reported for the 20 more promising reagents and the far more complete results obtained in the present study for the asymmetric reduction of 10 representative ketones, each

representing a class of ketone, with the six most promising reagents.

We hope that this critical examination of the data will be helpful to synthetic organic chemists in facilitating the selection of appropriate reagents to achieve their desired transformations. We also propose that any new promising reagents proposed should be examined, as a minimum, against the same 10 representative ketones to facilitate comparison of the relative effectiveness of the different reagents.

Experimental Section

Materials and General Procedures. All operations were carried out under a nitrogen atomosphere with oven-dried glassware. Experimental techniques of handling air-sensitive materials are described elsewhere.[28] Tetrahydrofuran was dried over 4-Å molecular sieves and distilled from sodium benzophenone ketyl prior to use. Anhydrous diethyl ether from Mallinckrodt was used without further purification. (*S*)-(−)-2-Amino-3-methyl-1,1-diphenylbutan-1-ol was prepared from (*S*)-valine hydrochloride reacting with excess PhMgCl. NB-Enantride was purchased from Aldrich Chemical Co. and used after determining hydride concentration and investigation of ^{11}B NMR spectrum. All substrate ketones were obtained from commercial sources: 3-methyl-2-butanone, acetophenone, 3-acetylpyridine, α-chloroacetophenone, methyl benzoylformate, ethyl benzoylacetate, *trans*-4-phenyl-3-buten-2-one, cyclohexenone, and 4-phenyl-3-butyn-2-one from Aldrich and 2,2-dimethylcyclopentanone from Wiley Organics. (*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) and (−)-menthyl chloroformate (MCF) were purchased from Aldrich. MTPA was used for diastereomeric derivatization after being converted into the corresponding acid chloride (MTPA-Cl). The optical purities (% ee) of the alcohol products obtained by the reduction of 3-methyl-2-butanone, acetophenone, 3-acetylpyridine, methyl benzoylformate, cyclohexenone, and 4-phenyl-3-buten-2-one were determined by capillary GC analysis of the corresponding MTPA ester derivatives and 2,2-dimethylcyclopentanol as a MCF derivative. The % ee of product 2-chloro-1-phenylethyl alcohol was determined by the rotation of the corresponding styrene oxide, and the % ee of 4-phenylbuten-2-ol was determined by the rotation of the isolated material. GC analyses were performed on a Hewlett-Packard 5750 chromatograph equipped with a Hewlett-Packard 3390A integrator/plotter with capillary columns (15 m Supelcowax and 50 m methylsilicone). Rotations were measured on a Rudolph Polarimeter Autopol III.

Asymmetric Reductions of Ketones. Reductions using *B*-Ipc-9-BBN, neat (B), Ipc_2BCl (E), K-Glucoride (K), and Binal-H (P) were carried out following the procedures described in the original literature (ref 6, 9, 15, and 20, respectively). NB-Enantride (H) was used for reductions of representative ketones in THF at −78 °C, whereas the original procedure utilized the reagent prepared from purified nopol benzyl ether and −100 °C.[12] With reagent F, BH_3–AMDPB (2:1), the reduction of ketones containing unsaturated double or triple bonds, such as 4-phenyl-3-butene-2-one, cyclohexenone, and 4-phenyl-3-butyn-2-one required the use of "dried reagent". With the regular reagent of F, those reductions were complicated by the concurrent hydroboration. The "dried reagent" was prepared by treatment of 2 equiv of borane in THF with a solution of (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (AMDPB) at −78 °C and stirring at 0 °C for 8 h, followed by evaporation of volatile components (water aspirator) and redissolution of the residue in fresh THF.

Analysis of the α-hydroxy ester obtained in the reduction of methyl benzoylformate with K-Glucoride in representative for the % ee determination of the alcohol products. A distilled sample of methyl mandelate obtained by the reduction with K-Glucoride according to the procedure in the literature[15c] and an authentic *dl*-methyl mandelate sample were derivatized with MTPA-Cl following the Mosher procedure.[25] Capillary GC analysis (Supelcowax, 15 m) of MTPA esters derived from *dl*-methyl mandelate revealed base-line separation of two peaks of equal intensity. A similar analysis of MTPA esters derived from the reduction product revealed a composition of 4% *S* and 96% *R* (i.e., 92% ee) of the product methyl mandelate.

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Registry No. **1**, 563-80-4; **1** (alcohol), 598-75-4; **2**, 4541-32-6; **2** (alcohol), 37617-33-7; **3**, 98-86-2; **3** (alcohol), 98-85-1; **4**, 350-03-8; **4** (alcohol), 4754-27-2; **5**, 532-27-4; **5** (alcohol), 1674-30-2; **6**, 15206-55-0; **6** (alcohol), 110661-51-3; **7**, 122-57-6; **7** (alcohol), 36004-04-3; **9**, 930-68-7; **9** (alcohol), 822-67-3; **10**, 1817-57-8; **10** (alcohol), 5876-76-6; B, 64106-79-2; E, 85116-37-6; AMDPB, 110661-52-4; H, 81572-37-4; K, 101696-41-7; P, 86502-90-1; BH_3, 13283-31-3.

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