20 21

-78 °C for 20 min produced an approximate 1:1 mixture of **20** and cyclopropane **21**[10a].

Elaboration of lactone **4** to verrucarol is under current investigation and will be reported upon in due course.

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Registry No. **4**, 79410-03-0; **7a**, 79410-04-1; **7b**, 79410-05-2; **8**, 79410-06-3; **9**, 79410-07-4; **10a**, 79410-08-5; **10b**, 79464-62-3; **11**, 79420-95-4; **12**, 79410-09-6; **13**, 79410-10-9; **14**, 79410-11-0; **15**, 79410-12-1; **15a**, 79410-13-2; **16**, 79410-14-3; **17**, 79410-15-4; **18**, 79410-16-5; **19**, 79410-17-6; **20**, 79410-18-7; **21**, 79410-19-8.

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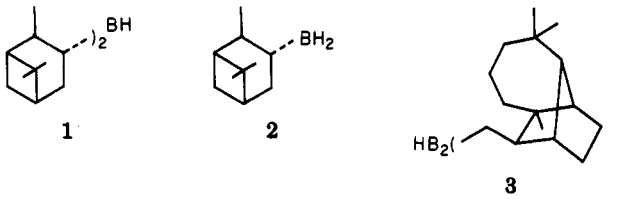
High Asymmetric Induction in the Chiral Hydroboration of Trans Alkenes with Isopinocampheylborane. Evidence for a Strong Steric Dependence in Such Asymmetric Hydroborations

Summary: Isopinocampheylborane, $IpcBH_2$ (**2**), achieves asymmetric hydroboration of trans-disubstituted alkenes with exceptionally high asymmetric induction. The product alcohols, obtained after oxidation of the intermediate organoboranes, exhibit enantiomeric purities in the range of 70–92% ee. The enantiomeric purities of the products increase with the increasing steric requirement of the alkyl substituent in the trans-disubstituted alkene.

Sir: Diisopinocampheylborane, Ipc_2BH (**1**), is a chiral hydroborating agent with very large steric requirements.[1] It hydroborates prochiral olefins with very low steric requirements such as 2-methyl-1-alkenes to provide optically active products in the range of 5–30% ee.[2] It is exceptionally effective with cis-disubstituted alkenes with considerably higher steric requirements,[3] achieving asymmetric synthesis as high as 98.4% for *cis*-2-butene.[4] Unfortunately, it fails with olefins of still higher steric requirements such as trans-disubstituted alkenes[5] and trisubstituted alkenes.[5]

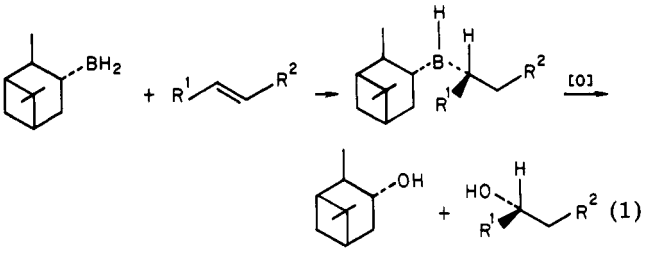
We recently discovered that trisubstituted alkenes are handled satisfactorily by chiral hydroborating agents of lower steric requirements, isopinocampheylborane, $IpcBH_2$ (**2**),[6,7] and dilongifolylborane, Lgf_2BH (**3**).[8]



1 2 3

With these reagents, appropriate trisubstituted alkenes could be converted into optically active products in the range of 52–100% ee. Only the large class of trans-disubstituted alkenes has not yet been successfully transformed into optically active products by asymmetric hydroboration.

An attempt to apply dilongifolylborane to *trans*-2-butene was unsatisfactory, yielding 2-butanol, after oxidation, of only 26% ee.[9] However, $IpcBH_2$ was far more favorable, yielding 2-butanol of 73% ee (eq 1; $R^1 = R^2 = CH_3$).



(1)

This experiment encouraged us to explore the application of $IpcBH_2$ to a number of representative trans-disubstituted alkenes: *trans*-3-hexene (eq 1; $R^1 = R^2 = C_2H_5$), *trans*-2,2,5,5-tetramethyl-3-hexene (*trans*-di-*tert*-butylethylene; eq 1; $R^1 = R^2 = C(CH_3)_3$), *trans*-2-pentene (eq 1; $R^1 = CH_3$, $R^2 = C_2H_5$), and *trans*-1-phenyl-1-propene (eq 1; $R^1 = Ph$, $R^2 = CH_3$). In all cases the asymmetric hydroboration proved satisfactory. Oxidation produced the corresponding alcohols with optical activities in the range of 70–92% ee. The results are summarized in Table I.

The reagent, $IpcBH_2$, preferentially attacks from the bottom enantiotopic face of the *trans*-alkene (eq 1) to provide product alcohols of the same absolute configuration. It should be noted that (+)-2,2,5,5-tetramethyl-3-hexanol and (+)-1-phenyl-1-propanol have an *R* notation because of the change in priority of the substituents on the chiral carbon atom. However, these products have an absolute configuration related to that of the other alcohols listed in Table I.

The importance of the steric factor is indicated by the increase in the optical purity of the product in proceeding from *trans*-2-butene ($R = CH_3$) or *trans*-3-hexene ($R = C_2H_5$) to *trans*-di-*tert*-butylethylene ($R = C(CH_3)_3$).

It is also of interest to note the range in the effectiveness of diisopinocampheylborane, a hydroborating agent of large steric requirements, and isopinocampheylborane, a hydroborating agent of low steric requirements (Table II).

The experimental procedure follows. All operations were carried out under nitrogen. TMED·2$IpcBH_2$ was prepared by following the reported procedure.[10] A 0.6 M solution of TMED·2$IpcBH_2$ was made in THF. To 53.3 mL (32 mmol) of this solution was added 7.9 mL (64 mmol) of boron trifluoride etherate at 25 °C. The reaction mixture was stirred at 25 °C for 1.25 h. The solution containing

(1) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486.
(2) Zweifel, G.; Ayyangar, N. R.; Brown, H. C. *J. Am. Chem. Soc.* **1964**, *86*, 1076.
(3) Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *J. Am. Chem. Soc.* **1964**, *86*, 397.
(4) Brown, H. C.; Yoon, N. M. *Isr. J. Chem.* **1977**, *15*, 12.
(5) Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *J. Am. Chem. Soc.* **1964**, *86*, 1071.
(6) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 5514.
(7) Mandal, A. K.; Jadhav, P. K.; Brown, H. C. *J. Org. Chem.* **1980**, *45*, 3543.
(8) Jadhav, P. K.; Brown, H. C. *J. Org. Chem.* **1981**, *46*, 2988.
(9) Jadhav, P. K.; Brown, H. C., to be submitted for publication.
(10) Brown, H. C.; Schwier, J. R.; Singaram, B. *J. Org. Chem.* **1978**, *43*, 4395.

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Table I. Asymmetric Hydroboration of Representative Trans-Disubstituted Olefins with Isopinocampheylborane ($IpcBH_2$)[a] in 1:1 Ratio[b]

olefin	product alcohols				
	alcohol	yield, % (isolated)	$[\alpha]^{23}_D$, deg	% ee	config
trans-2-butene	2-butanol	73	+9.8 (neat)	73[c]	*S*
trans-3-hexene	3-hexanol	83	+5.3 (neat)	75[d]	*S*
trans-2,2,5,5-tetramethyl-3-hexene	2,2,5,5-tetramethyl-3-hexanol	61	+34.8 (*c* 5, EtOH)	92[e]	*R*[h,i]
trans-2-pentene	2-pentanol (47%), 3-pentanol (53%)	78	+12.95 (*c* 7.39, Et_2O)	70[f]	*S*
trans-β-methylstyrene	1-phenyl-1-propanol	72	+20.6 (neat)	75[g]	*R*[i]

[a] The reagent is prepared from (+)-α-pinene: $[\alpha]^{23}_D$ +48.3°; 94.4% ee. [b] The reactions were carried out on a 50-mmol scale. [c] Based on maximum rotation $[\alpha]^{25}_D$ -13.5° (neat): Leroux, P. J.; Lucas, H. J. *J. Am. Chem. Soc.* **1951**, *73*, 41. [d] Based on maximum rotation $[\alpha]^{18}_D$ -7.13° (neat): Kenyon, J.; Poplett, R. *J. Chem. Soc.* **1945**, 273. [e] As determined by 90-MHz NMR with the chiral lanthanide shift reagent tris[[(heptafluoroprop-1-yl)hydroxymethylene]-*d*-camphorato]-europium(III) [Eu(hfc)$_3$]. [f] Based on maximum rotation $[\alpha]^{20}_D$ +18.5° (*c* 7.39, Et_2O): Levene, P. A.; Mikeska, L. A. *J. Biol. Chem.* **1927**, *75*, 587. [g] Based on maximum rotation $[\alpha]^{17}_D$ -27.35° (neat): Pickard, R. H.; Kenyon, J. *J. Chem. Soc.* **1911**, *99*, 45. [h] The absolute configuration of 2,2,5,5-tetramethyl-3-hexanol has not been established. We predict that the (+) isomer is probably *R*. [i] *R* notation arises for the related absolute configuration of the other products, designated *S*, because of a change in the priorities of the substituents attached to the chiral carbon atom.

Table II. Summary of the Asymmetric Hydroboration Results of Various Classes of Alkenes with Diisopinocampheylborane and Isopinocampheylborane

class of alkene	Ipc_2BH ee, %	$IpcBH_2$ ee, %
2-methyl-1-alkenes	5-30	1.5[a,b]
cis-alkenes	76-98.4	20-24
trans-alkenes	13[a,c]	70-92
trisubstituted alkenes	14-22	52-100

[a] Only one example. [b] 2-Methyl-1-butene. [c] *trans*-2-Butene.

free $IpcBH_2$ was then removed from the slurry of TMED·$2BF_3$ by filtration under nitrogen through a filter chamber.[11] The solid TMED·$2BF_3$ was washed with three 9-mL portions of THF. The solution of $IpcBH_2$ in THF thus obtained was found to be 0.8 M by hydride estimation. $IpcBH_2$ (62.5 mL, 50 mmol) in THF was cooled to -25 °C. The flask was then charged with 2.7 mL of THF (to make the solution of 0.7 M in $IpcBH_2$) followed by dropwise addition of 6.2 mL (50 mmol) of *trans*-3-hexene over a period of 5 min. The dialkylborane precipitates out of the solution after 10 min. The contents of the flask were further stirred at -25 °C for 9 h to ensure completion of the reaction. The reaction mixture was carefully (H_2 evolution!) treated with 4 mL (100 mmol) of methanol at -25 °C and slowly warmed up to 25 °C. It was then treated with 18.4 mL of 3 M NaOH followed by 15 mL of 30% aqueous hydrogen peroxide dropwise, with the temperature of the reaction mixture maintained below 40 °C. After an additional hour at 50 °C, the reaction mixture was cooled, and the alcohol products were extracted into ether and dried. Fractional distillation provided 4.25 g of (*S*)-(+)-3-hexanol: bp 130–133 °C (745 mm); 83% yield (>97% GLC pure). The alcohol was further purified by preparative GLC (10% Carbowax) to obtain >99.9% GLC-pure material: n^{20}_D 1.4145; $[\alpha]^{25}_D$ +5.3° (neat); 75% ee.

This development makes it possible to realize high optical purities in the hydroboration of three of the four major classes of alkenes. Only the less steric demanding group, the 2-methyl-1-alkenes, do not yield optically active products in the desirable range.

With increasing knowledge of the steric requirements of different chiral hydroborating agents, it may be possible to tailor-make reagents which will improve the already promising results.

Registry No. 2, 64065-15-2; *trans*-2-butene, 624-64-6; *trans*-3-hexene, 13269-52-8; *trans*-2,2,5,5-tetramethyl-3-hexene, 692-48-8; *trans*-2-pentene, 646-04-8; *trans*-β-methylstyrene, 873-66-5; (*S*)-2-butanol, 4221-99-2; (*S*)-3-hexanol, 6210-51-1; (*R*)-2,2,5,5-tetramethyl-3-hexanol, 79449-64-2; (*S*)-2-pentanol, 26184-62-3; (*S*)-3-pentanol, 79449-65-3; (*R*)-1-phenyl-1-propanol, 1565-74-8.

(11) For a description of the filtration chamber, see: Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M., Eds.; "Organic Syntheses via Organoboranes"; Wiley-Interscience: New York, 1975; p 191.

(12) Postdoctoral research associate on Grant 2 R01 GM 10937-19 from the National Institutes of Health.

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On the Mechanism of Graham's Reaction

Summary: The oxidative cyclization of amidines to 3-chloro-3-substituted diazirines with aqueous sodium hypochlorite proceeds through *N*-chloro- and *N,N'*-dichloroamidines; the latter are isolable in certain cases.

Sir: In 1965, Graham reported the direct preparation of (3-alkyl-, 3-aryl-, and 3-alkoxy-3-halodiazirines by the action of aqueous NaOCl (or NaOBr) on various alkyl- or arylamidines and isoureas in aqueous dimethyl sulfoxide (Me_2SO) solution.[2] Despite the importance of this conversion for the generation of numerous halocarbene precursors,[3,4] its mechanism remains obscure. Graham's original suggestions are summarized in Scheme I.[2]

Successive N-halogenations of amidine **1** produce *N*-haloamidine **2** and then *N,N'*-dihaloamidine **3**. The latter is converted to *N*-halodiazirine **6**, either by internal displacement of X^- within anion **4** or by cyclization of a subsequent iminonitrene, **5**. Intermediate **6** is finally converted to 3-halodiazirine **8** by an addition–elimination reaction with X^- or by ionization to diazirinium ion **7**,

(1) (a) Rutgers University. (b) Merck Institute.
(2) W. H. Graham, *J. Am. Chem. Soc.*, 87, 4396 (1965).
(3) "Science Citation Index" (Institute for Scientific Information, Philadelphia, PA) reveals 58 citations of ref 2 between 1965 and 1980.
(4) For a brief review, see K. MacKenzie in "The Chemistry of the Hydrazo, Azo, and Azoxy Groups", S. Patai, Ed., Wiley, New York, 1975, Part 1, pp 329 ff. see especially pp 333, 334, 342, 343.

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