Asymmetric Reductions with Organoborane Reagents

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Received March 2, 1989 (Revised Manuscript Received June 12, 1989)

Contents

M. Mark Midland was born in Fort Dodge, IA, on Jan 1, 1946. His interest in chemistry was stimulated by high school teachers in Spirit Lake and Marshalltown, IA. He received a B.S. degree in chemistry from Iowa State University in 1968. In 1972, he received his Ph.D. degree from Purdue University under the direction of H. C. Brown. He received an NSF Fellowship during his graduate studies. After graduation he stayed on at Purdue as Professor Brown's Research Assistant. In 1975, he joined the faculty in the Chemistry Department at the University of California, Riverside. He has been awarded a Sloan Fellowship. His research interests include the development and application of new methods for the synthesis of optically active compounds.

I. Introduction

Stereochemistry often plays an important role in the biological activity of molecules. Often the wrong enantiomer of a compound has no biological activity. In some cases the wrong enantiomer may elicit an undesirable response or inhibit response. For example, as little as 1% of the enantiomer of the opposite configuration of the Japanese beetle pheromone ((*R*,*Z*)-5-(1-decenyl)dihydro-2(3*H*)-furanone) will decrease the number of beetles caught in a trap by 50%. Material containing 10% of the wrong enantiomer is essentially inactive.[1] The development of synthetic methods for achieving high enantiomeric purity has thus been an important area.

The synthesis of optically active molecules has traditionally fallen into three categories: stereoselective transformations of optically active starting materials, resolution of racemic mixtures, and asymmetric synthesis from prochiral substrates. Each of these methods has its particular advantages and disadvantages that must be weighed in a synthesis.[2]

One of the more useful of the asymmetric reactions is the reduction of a prochiral ketone to an optically active alcohol.[3] The alcohols produced by such a process may serve as chiral building blocks at the beginning of a synthesis, or they may serve as desired end products directly. In either case, the proper selection of the asymmetric reducing agent is critical, and several factors may influence which reagent one chooses.

In choosing an asymmetric reducing agent, one often seeks to mimic the action of enzymes. That is, one would like to use reagents that are catalytic, are selective, yield products of high enantiomeric purity, and behave predictably with other functional groups. In addition to the selectivities often associated with enzymes, it is also desirable to employ reagents that are inexpensive, are easy to handle, are tolerant of a "typical" organic solvents and functional groups, are effective on a wide range of substrates, allow for the easy isolation of the products, and are available in both enantiomeric forms. Clearly, no one reagent can be expected to provide all the desirable traits one would like in a reducing agent. Thus, much effort has been aimed at producing reagents that provide useful compromises.

An asymmetric reducing agent need not be catalytic if it can be easily obtained and is inexpensive. The cost factor may be further reduced if the chiral ligand can be recycled. Yet the most critical factor to the synthetic chemist is often the degree of asymmetry introduced into the substrate system.

Trialkylboranes embody many desirable features as reducing agents. Organoboranes are readily prepared[4] and are tolerant of many functional groups. They do not possess an active hydrogen on boron. Before this study was undertaken, they were generally thought to

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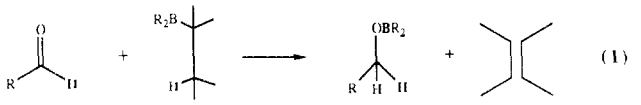
be inert toward ketones, aldehydes, and many other carbonyl groups. However, under forcing conditions (150 °C), aldehydes could be reduced to alcohols by a process reminiscent of the Meerwein–Ponndorf–Verley reduction.[5]



(1)

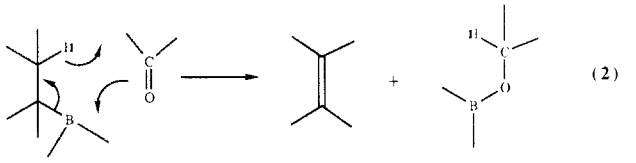
Because of the rather harsh conditions, this reaction was unattractive to synthetic chemists. If one could perform the reaction at moderate temperatures and at a reasonable rate, then the process could be synthetically valuable since the nature of the reducing agent could be changed through the hydroboration of various olefins.

This review will concentrate on reagents in which the "active" hydride is derived from the alkyl group of the organoborane.[6] In general, the reductions will involve a Meerwein–Ponndorf–Verley type of process as depicted in eq 1. A number of other very effective borohydride reagents have also been developed. These include the C_2 axis based reagents,[7] the aminoborane reagents,[8] and the sugar-modified borohydrides.[9]

II. Mechanism of Reduction

A. Bimolecular Reaction versus Dehydroboration–Reduction

The reduction of ketones by trialkylboranes may follow one of two mechanistic pathways. The first involves a bimolecular six-centered transition state in which the hydrogen β to the boron is transferred to the carbonyl carbon.



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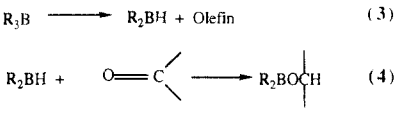
Alternatively, the reaction could proceed by a two-step process involving a dehydroboration–reduction pathway.

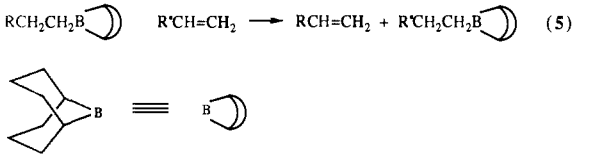


(3)

(4)

Presumably the first step (eq 3) would be the rate-determining step and the rate would be independent of the carbonyl concentration or structure in this two-step process. Kinetic studies have indicated that the reduction of aldehydes is bimolecular.[10] In agreement with the bimolecular reaction, the rate is changed by changes in the carbonyl component. Electron-withdrawing para substituents increase the rate of benzaldehyde reduction. This result is consistent with addition of a hydride to the carbonyl carbon. Finally, the reaction can proceed rapidly under very mild conditions (room temperature) while the dehydroboration process usually requires much stronger conditions.

With more hindered carbonyl compounds such as acetophenone or 3,3-dimethyl-2-butanone, the rate becomes independent of the ketone conconcentration and structure. The mechanism switches to the dehydroboration–reduction pathway. In order to understand the dehydroboration process more fully, the exchange reaction of *B*-alkyl-9-borabicyclo[3.3.1]nonane (9-BBN) compounds with olefin was studied.[11]



(5)

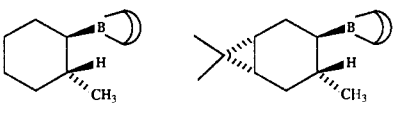
Mikhailov proposed that this reaction proceeded through a cyclic, concerted process similar to eq 2.[12] We have shown that the reaction proceeds through a first-order dehydroboration process similar to eq 3 and 4. In general, the dehydroboration reaction has a half-life of 4000–6000 min in refluxing tetrahydrofuran. However, *B*-3-pinanyl-9-BBN (Alpine-Borane[13]) undergoes the dehydroboration reaction at an unusually fast rate. The half-life for the process is only 500 min in refluxing tetrahydrofuran. This unexpectedly facile dehydroboration process has important implications for asymmetric reduction. The liberated 9-BBN will rapidly reduce carbonyl compounds to racemic product.

B. Structure–Activity Relationships

The reaction reported by Mikhailov required vigorous conditions. A possible explanation seemed to be that the tri-*n*-butylborane used by Mikhailov was sterically congested and/or not electronically suited for β-hydride transfer to the carbonyl carbon. The less sterically congested alkyl-9-BBN compounds[14] were thus studied. The *n*-butyl compound was only slightly more reactive than tri-*n*-butylborane. However, increased substitution at the β position greatly increases the rate of reduction of benzaldehyde.[15]

The reaction is remarkly selective in the transfer of hydrogen from the more substituted β position of the alkyl group. Thus, 2-butyl-9-BBN gives only *cis*- and *trans*-2-butene and no 1-butene. Likewise, 2,3-dimethyl-2-butyl-9-BBN (thexyl-9-BBN) gives only 2,3-dimethyl-2-butene and no 2,3-dimethyl-1-butene despite the fact that there are six methyl hydrogens β to boron. Remarkably, the cyclooctyl portion of 9-BBN does not transfer a hydrogen.

The rate of reduction is further increased if the alkyl group can form a favorable syn-planar B–C–C–H conformation. Thus, *trans*-2-methylcyclopentyl-9-BBN rapidly reduces benzaldehyde while *trans*-2-methylcyclohexyl-9-BBN does not. In the latter case, the cyclohexyl ring must adopt a boat conformation in order to achieve the eclipsed B–C–C–H conformation.



slow fast

The cyclopropyl group of 3-caranyl-9-BBN forces the B–C–C–H bond to be eclipsed and thus this reagent reduces benzaldehyde very rapidly.

The syn arrangement of the B–C–C–H bonds presumably leads to favorable orbital interactions in the developing π system of the liberated olefin. The cyclooctyl portion of 9-BBN is locked into a six-membered

ring. The β hydrogens are therefore constrained to a 60° dihedral angle with boron and cannot develop an favorable overlapping arrangement. Thus, only the *B*-alkyl group is eliminated.

III. Chemoselectivity

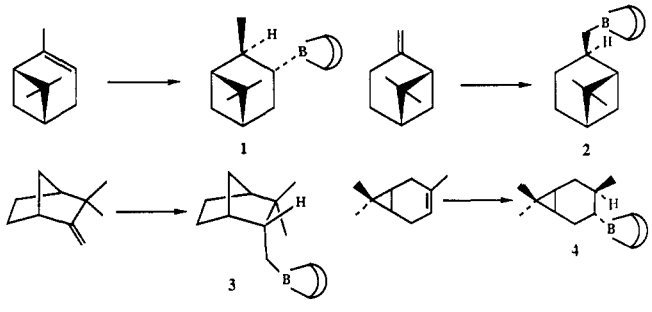
Organoboranes are generally considered to be inert to most functional groups, including aldehydes and ketones. However, with the proper alkyl group, *B*-alkyl-9-BBN compounds will rapidly reduce aldehydes. Most other functional groups such as olefins, acetylenes, esters, acid chlorides, pyridines, alkyl halides, and ethers are untouched by the organoborane reagent. Under forcing conditions (refluxing tetrahydrofuran) the dehydroboration process (eq 3) may become important. The liberated 9-BBN will then reduce some functional groups.[16]

The *B*-alkyl-9-BBN compounds exhibit a remarkable degree of chemoselectivity. For example, aldehydes are completely reduced while even unhindered ketones are untouched.[17] The acetylenic ketone of 2-nonyne-4,8-dione is selectively reduced without reduction of the methyl ketone.[18]

(6)

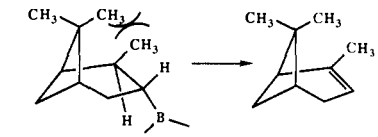
IV. Reagents

The ability to create the reducing agent by hydroboration of an olefin allows one to incorporate a number of structural and electronic features into the reducing agent. Furthermore, because of the very high stereo- and regiospecificity achieved in hydroborations with 9-BBN, the resulting reagent is often structurally well defined. For example, optically active terpenes such as α-pinene, β-pinene, camphene, and 3-carene can be transformed into the optically active reducing agents 1–4.



Several organoborane asymmetric reducing agents have now been evaluated. Each has advantages for certain classes of carbonyl compounds. The first effective reagent was derived from hydroboration of α-pinene. Since both (+)- and (−)-α-pinene are available, both enantiomers of the reagent can be prepared. The reagent is now available from Aldrich under the trade name Alpine-Borane. Alpine-Borane is particularly effective for reduction of aldehydes and acetylenic ketones.

Alpine-Borane reduces benzaldehyde with exception ease.[19] The reactivity of this reagent may be due to its ability to form a favorable coplanar B–C–C–H arrangement. In addition, there is a buildup of steric strain in the reagent caused by the *cis*-1-methyl group being forced into the *gem*-dimethyl groups on the four-membered ring (eq 7). This strain is like a compressed spring and is relieved upon going to the α-pinene product.



(7)

Normally, the α-pinene is approximately 92% ee, and this is often the limiting factor in determining the purity of the optically active alcohol. Highly enriched α-pinene (99% ee) can be prepared[18] or obtained from Aldrich Chemical Co.

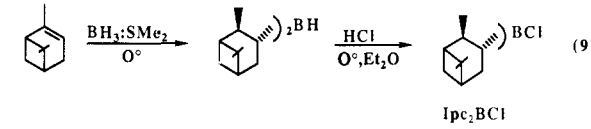
A related borane may be prepared by hydroboration of the ethers of nopol.[20]

(8)

This borane behaves like Alpine-Borane prepared from (−)-α-pinene, but it is somewhat more selective. The benzyl ether derivative is available from Aldrich under the trade name NB-Enantrane.

Other terpenes such as 3-carene, camphene, and β-pinene have also been examined. Only the reagent from β-pinene (*cis*-myrtanyl-9-BBN (**2**)) has been extensively studied.[21] The β-pinene is commercially available in only the (−) form. However, methods exist for preparing high-purity β-pinene in either the (+) or (−) form.[22] *cis*-Myrtanyl-9-BBN is effective for hindered acetylenic ketones.

The use of dialkylchloroboranes provides reagents of increased Lewis acidity and reactivity. Brown has prepared a series of these reagents[23] and found that diisopinocampheylchloroborane (Ipc_2BCl, eq 9) is an



(9)

Ipc_2BCl

excellent reducing agent.[24] This reagent is readily prepared in two steps by hydroboration of 92% ee α-pinene with borane–methyl sulfide followed by treatment with dry hydrogen chloride. The intermediate Ipc_2BH crystallizes from solution, and the major enantiomer of α-pinene is concentrated on boron. The final borane is thus enriched to 99% ee. The Ipc_2BCl can be recrystallized from pentane, and an X-ray structure of this material has been published.[24] The reagent is especially effective for reduction of aromatic–aliphatic ketones and hindered aliphatic ketones.

V. Aldehydes

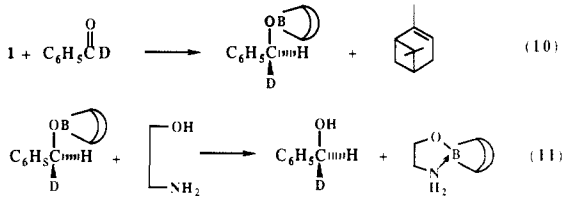
All of the reagents produced from terpenes and 9-BBN (1–4) reduce benzaldehyde with ease at room temperature. In order to ascertain the asymmetric induction attainable with these reagents, [1-^{2}H]benzaldehyde was reduced to [α-^{2}H]benzyl alcohol. Among these reagents, *B*-3-pinanyl-9-BBN proved to be exceptionally selective in transferring the β hydride to one of the prochiral faces of the labeled aldehyde (eq 10). When optically pure α-pinene was used, none of the

TABLE I. Reduction of Aldehydes with Deuterated Alpine-Borane

aldehyde	% ee[a]	aldehyde	% ee[a]
butanal	100	*p*-chlorobenzaldehyde	100
2,2-dimethylpropanal	98	*p*-nitrobenzaldehyde	100
cinnamaldehyde	84	*p*-methoxybenzaldehyde	87
benzaldehyde	98		

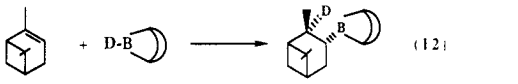
[a] Corrected for α-pinene purity and amount of deuterium incorporation.

minor enantiomer of the reduction product could be observed with an optically active NMR shift reagent.[19]



These reductions are readily amenable to large-scale reactions. In the case of acetylenic ketones, we have performed reductions on a 2.5-mol scale without difficulty. It is advisable to cool the large-scale reactions since the reduction may become exothermic. Excess Alpine-Borane is destroyed by addition of a low-boiling aldehyde such as acetaldehyde. This helps prevent contamination of the desired product with isopinocampheol. The borane component may be removed by precipitation as the ethanolamine complex (eq 11) or by the usual oxidative workup using hydrogen peroxide and base.

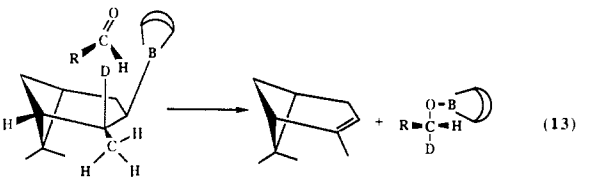
An alternative method for obtaining the labeled primary alcohols is to reduce the unlabeled aldehyde with deuterio-Alpine-Borane. This reagent is readily prepared from deuterio-9-BBN.[25]



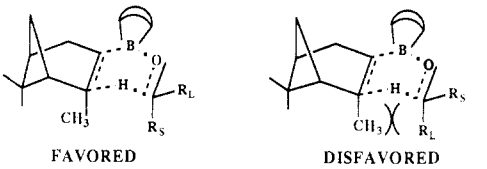
The availability of a deuterated reagent provides easy access to a variety of labeled alcohols. Results from representative aldehydes are provided in Table I. Aliphatic and aromatic aldehydes are reduced with equal facility. Electron-withdrawing groups on benzaldehyde provide faster rates of reduction. Electron-donating groups slow down the reaction and tend to give lower enantiomeric purities. The lower purities presumably come from the competing dehydroboration–reduction process. This competing pathway could be eliminated by running the reaction neat[26] but this has not been tested. The use of tritiated aldehydes leads to enantiomerically enriched radiolabeled alcohols.[27]

VI. A Predictive Transition-State Model for Reductions

In all cases, the deuterated Alpine-Borane prepare from (+)-α-pinene leads to the *R* enantiomer. The reaction mechanism is similar to reductions with Grignard and Meerwein–Ponndorf–Verley reagents. For these reagents, it is postulated that there is a dovetailing of the small group on the carbonyl compound with a large group on the reducing agent.[28] This seems to minimize interactions by keeping the large groups away from one another. Applying this model to the Alpine-Borane reagent predicts the wrong product. Instead, the larger group of the aldehyde seems to approach over the pinanyl ring as depicted in eq 13.



Although this "wrong" model can be used in a predictive sense, it seems unlikely that the two large groups approach one another as depicted. An alternative explanation is that the transition state resembles more a boat-like cyclohexane structure. The major product arises from the model in which the large group is in an equatorial-like position. This model places the large group as far away from the pinanyl group as is possible.



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The boat-like transition state also fits the observation that a syn-planar B–C–C–H arrangement leads to a faster rate of reduction. Calculations suggest that the transition state is distorted from a boat. The B–C–C–H is slightly twisted from a 0° dihedral angle and the transferring hydrogen becomes more collinear with the two carbons.[29]

Regardless of the precise structure of the transition state, the simple model depicted above predicts the correct absolute configuration for reductions with Alpine-Borane. In all cases to date, the smaller group assumes the "axial" position.

VII. Acetylenic Ketones

The trialkylboranes are exceedingly chemoselective reducing agents. Initial attempts to reduce acetophenone with Alpine-Borane required refluxing in tetrahydrofuran for 2 days. Under these conditions, product of only 10% enantiomeric purity was obtained. Presumably, a major portion of the product resulted from the dehydroboration–reduction pathway. The sluggishness of the reaction could be explained by examination of the simple transition-state models. In the case of aldehydes, the hydrogen occupies the "axial" position. In the case of ketones, an alkyl group must occupy this position. The steric interaction with the methyl of the pinanyl group becomes severe enough to retard the reaction. In order to reduce ketones, the alkyl group of the ketone had to be smaller than a methyl group! The Alpine-Borane reduction of less congested acetylenic ketones was investigated.

A. Alpine-Borane

Acetylenic ketones are somewhat more hindered than aldehydes and require slightly longer reaction times.[30] Terminal acetylenic ketones and acetylenic keto esters are completely reduced after 8 h at room temperature in 0.5 M tetrahydrofuran. Internal acetylenic ketones require 1–4 days under these conditions but the process

TABLE II. Reduction of Alkynyl Ketones with Alpine-Borane

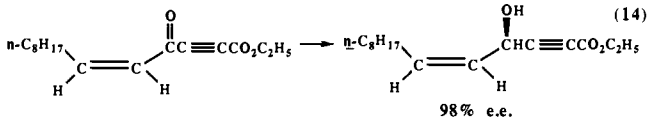
ketone RCOC≡CR′			
R	R′	% yield[a]	% ee[b]
C_6H_5	n-C_4H_9	72	89[c]
CH_3	C_6H_5	98	78
CH_3	C_6H_5	95	108[d,e]
n-C_3H_7	n-C_6H_{13}	68	77[c]
n-C_5H_{11}	n-C_4H_9	66	85
CH_3	H	80	79[d]
n-C_5H_{11}	H	70	92[c]
$CH(CH_3)_2$	H	78	99
$CH(CH_3)_2$	H	87	99[d]
$CH_3O_2CCH_2CH_2$	n-C_8H_{17}	75	98
CH_3	$CO_2C_2H_5$	59	77
CH_3CH_2	$CO_2C_2H_5$	58	96
n-C_5H_{11}	$CO_2C_2H_5$	72	92
C_6H_5	$CO_2C_2H_5$	64	100
(Z)-$C_5H_{11}CH$=$CHCH_2$	$CO_2C_2H_5$	73	90[c]
(Z)-$C_8H_{17}CH$=CH	$CO_2C_2H_5$	62	98[c]
CH_3	$C(CH_3)_3$	62	73[c]

[a] Isolated yield based on starting ketone. [b] Determined by analysis of the Eu(dcm)$_3$-shifted NMR spectrum. The numbers are corrected for 92% ee α-pinene. [c] 100% optically pure (+)-α-pinene was used. [d] Using neat conditions. [e] By rotation.

may be accelerated by running the reaction neat.[26] Warming should be avoided since this leads to the competing dehydroboration–reduction process.

The reaction is applicable to a number of ketones (Table II). In general, methyl ketones give the lowest selectivity as would be expected on the basis of steric effects. If the group next to the ketone is a branched alkyl group or phenyl group, then the purity of the α-pinene is the limiting factor in obtaining high enantiomeric purities.

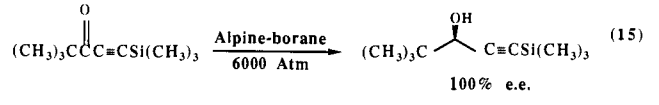
The reagent easily discriminates the acetylenic group from other unsaturated groups. For example, a vinyl acetylenic ketone was reduced to the alcohol with 98% enantiomeric efficiency (eq 14). This ketone is ex-



(14)

tremely sensitive to acid- or base-catalyzed isomerization of the cis double bond. No isomerization occurred during the reduction.

The only ketone that failed to undergo reduction contained a *tert*-butyl group adjacent to the carbonyl group. Reduction presumably occurs by the dehydroboration–reduction pathway. The use of high pressure (6000 atm) circumvents this problem.



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B. Chiral Acetylenic Ketones

Since the reagent shows very high steric effects, the reduction of chiral acetylenic ketones was investigated. A β substituent as in chromanyl substrate **5** showed

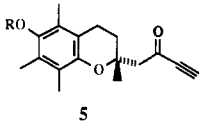

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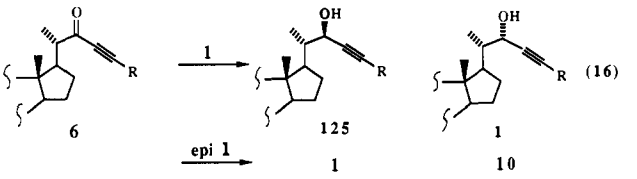
TABLE III. Reduction of α,β-Acetylenic Ketones with NB-Enantrane

ketone RCOC≡CR′			
R	R′	% yield[a]	% ee[b]
n-C_5H_{11}	H	74	95
n-C_5H_{11}	CH_3	79	91
n-C_5H_{11}	$Si(CH_3)_3$	81	96
C_2H_5	C_2H_5	77	94
cyclohexyl	n-C_5H_{11}	84	96
CH_3	C_6H_5	87	86
n-C_5H_{11}	$CO_2C_2H_5$	74	91

[a] Isolated yield. [b] Determined by analysis of the Eu(hfc)$_3$-shifted NMR spectrum.

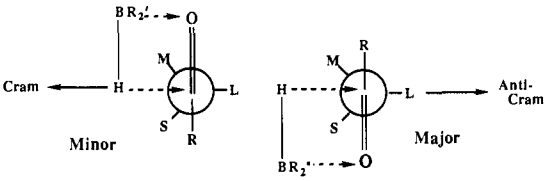
little or no effect. Moving the center closer, as in the steroid ketone **6** (eq 16), did show the effect of double asymmetric induction.[31] Reduction with Alpine-Borane



(16)

prepared from 92% (+)-α-pinene (96:4 (+):(−)) provided a 125:1 mixture of alcohols. The reagent from (−)-α-pinene (also 96:4) gave a 1:10 mixture of alcohols. Furthermore, the latter reaction was very slow and did not reach completion.

The effect of the stereocenter in the ketone is to induce an "anti"-Cram addition to the ketone. With the reagent from (+)-α-pinene, this induction works cooperatively with the induction from the organoborane and a >96:4 ratio of product is obtained. This anti-Cram selectivity hass been observed for hydroboration of chiral olefins and R_2BH reduction of chiral ketones.[32] The stereochemistry of these additions is the opposite of that predicted for nucleophilic additions using the Felkin–Anh model.[33] A modified model can be used to predict the stereochemistry of these reactions.



In this model, the large group is placed perpendicular to the carbonyl and opposite to the approaching hydride. The reagent then approaches the carbonyl in a conformation that minimizes interaction with the medium alkyl group.

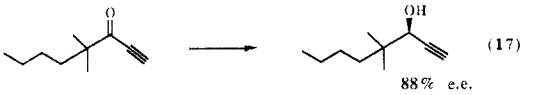
C. NB-Enantrane

The reduction of ketones can be improved by using the reagent prepared from nopol benzyl ether, NB-Enantrane[20] (eq 8, Table III). Reductions with NB-Enantrane are somewhat slower than with Alpine-Borane, presumably because of the very subtle steric change between the two reagents. Usually the reductions are complete in 24–48 h when the reactions are run in the absence of solvent. The slight increase in steric requirements provides somewhat better asymmetry inductions with NB-Enantrane, particularly with

methyl acetylenic ketones.

D. Myrtanyl-9-BBN

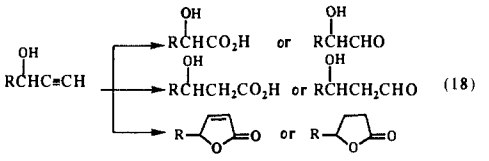
Myrtanyl-9-BBN is able to accommodate ketones with bulky aryl groups. Thus, 2,2-dimethyl-4-nonyn-3-one, which requires high pressure with Alpine-Borane, is easily reduced at atmospheric pressure to the *R* alcohol in 86% ee. These reductions require about 2 days to reach completion and are generally applicable to hindered acetylenic ketones. For example, 4,4-dimethyl-1-octyn-3-one, a useful intermediate in prostaglandin synthesis, gives the *R* product in 88% ee.



(17)

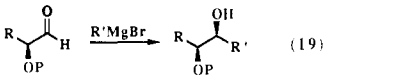
E. Uses of Acetylenic Alcohols

The reduction of acetylenic ketones provides products that are valuable since the acetylenic unit provides a convenient handle for further transformations. For example, the acetylene may be converted into other functional groups such as α-hydroxy or β-hydroxy aldehydes and acids,[34] butenolides, or lactones.[35]



(18)

The α-alkoxy group of aldehydes may be used to direct stereoselective additions to the carbonyl through a chelation-controlled process (eq 19 and 20).[36]



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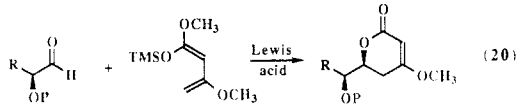
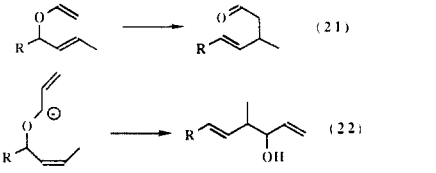


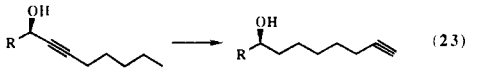
(20)

Reduction of the acetylene can product optically active *cis*- or *trans*-allylic alcohols or saturated alcohols which are not readily available by asymmetric reduction. The allylic alcohols may then be used to stereoselectively construct carbon–carbon bonds through sigmatropic rearrangements.[37]



(21)
(22)

The acetylene handle may be moved through a series of methylene units to a terminal position using potassium 3-aminopropylamide (KAPA) without affecting the enantiomeric purity of the alcohol.[38]



(23)

TABLE IV. Reduction of Ketones with Alpine-Borane

ketone	time, days	press., atm	% yield	% ee[a]
2-octanone	7	1	65	48
	1	6000	63	63
3-methyl-2-butanone	14	1	78	62
	1	6000	47	90
3,3-dimethyl-2-butanone	40	1	40	0.7
	9	6000	0	0
acetophenone	7	1	68	85
	1	6000	80	100
α,α,α-trifluoroacetophenone	45	1	57	35
	3	6000	46	54
α-chloroacetophenone	6–8	1	91	96
tetralone	3	6000	43	89
3-buten-2-one	5	1	30	65
	11 h	6000	67	49
trans-4-phenyl-3-buten-2-one	10	1	80	97 (58)[b]
	23 h	6000	90	71

[a] Using 100% ee α-pinene or correcting for α-pinene enantiomeric purity. [b] Value of 97% determined by rotation and value of 58% determined by using NMR shift reagent.

The terminal acetylene can then be oxidized to an acid or alkylated to a new internal acetylene.

VIII. Ketones

A. Alpine-Borane

As previously mentioned, the trialkylboranes are exceptionally chemoselective reducing agents, capable of reducing aldehydes in the presence of essentially any ketone. In fact, ketones are not reduced at all under conditions that reduce aldehydes or most acetylenic ketones.[17] Attempts to reduce ketones under more forcing conditions, such as refluxing tetrahydrofuran, lead to high yields of product but low asymmetric inductions. Mechanistic studies revealed that the reduction was probably occurring by the dehydroboration–reduction pathway.

The desired pathway (eq 2) involves a bimolecular process while the undesired pathway (eq 3 and 4) is unimolecular. By running the reaction in the absence of solvent, Brown was able to increase the rate of the bimolecular process and minimize competitive reduction by 9-BBN.[26] In general, these reactions are performed at room temperature using 40–100% excess Alpine-Borane. Excess reagent is destroyed by the addition of acetaldehyde. This liberates α-pinene and limits contamination of the product by isopinocampheol. The liberated α-pinene may be removed under vacuum and recycled. Under these conditions typical ketones are reduced in 7–14 days.

An alternative approach for increasing the rate of reduction with Alpine-Borane involves the use of high pressure. Because the desired process is bimolecular and involves a decrease in volume in the transition state, increased pressure should increase the rate. The dehydroboration–reduction process, on the other hand, involves a dissociative process and increase in volume in the rate-determining step. High pressure should decrease the rate of this reaction.

Equipment for achieving pressures of 2000 atm is readily constructed[39] and equipment for higher pressures is commercially available. Even at 2000 atm the reaction is accelerated and the dehydroboration step is eliminated. Acetophenone is reduced with essentially

100% enantiomeric efficiency.[40]

A variety of ketones have been reduced by these two methods (Table IV). Simple ketones such as acetophenone and 2-octanone are reduced in 7–14 days under the neat conditions or in 1 day at 6000 atm. The extent of asymmetric induction is dependent on the difference in steric size of the two groups flanking the carbonyl and the extent of dehydroboration during the reduction period. Alpine-Borane undergoes about 2–3% dehydroboration per day so that at 1 atm there is a decrease of about 2–3% ee for each day that the reaction requires.

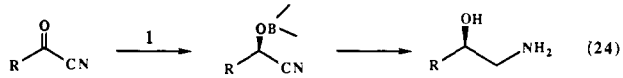
Aromatic ketones such as acetophenone and 3-acetylpyridine are reduced in essentially 100% efficiency. Even aliphatic ketones are reduced with high efficiency. For example, 3-methyl-2-butanone gives the alcohol in 90% enantiomeric efficiency. However, increasing the size of the alkyl group as in 3,3-dimethyl-2-butanone completely changes the course of the reaction. This substrate is reduced to essentially racemic products at 1 atm over a 40-day period and is not reduced at all at 6000 atm over a 9-day period.

The reduction of α,β-unsaturated compounds is highly dependent upon the substrate. The induction again is dependent upon the difference in size of the two groups. For example, 1-acetyl-1-cyclohexane gives good results while 3-methyl-2-cyclohexenone does not. *trans*-4-Phenyl-3-buten-2-one gives excellent results at 1 atm (where the purity was measured by rotation), but lower results at 6000 atm (where the purity was measured by using NMR shift reagents). The difference in results may reflect the analytical methods used.

Electron-withdrawing groups generally accelerate the rate of reduction.[10] Thus, α-bromoacetophenone is reduced about twice as fast as acetophenone.[41] However, α,α,α-trifluoroacetophenone is reduced at a much slower rate and lower % ee (18% at 1 atm, 54% at 6000 atm). The trifluoromethyl group is slightly larger than a methyl group and this may account for the slower rate. Some of the halogenated ketones are insoluble in neat Alpine-Borane and thus give lower rates. In these cases, addition of a small amount of tetrahydrofuran helps to dissolve the substrate and speed the process.

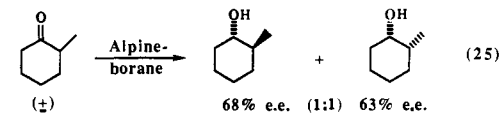
Use of an α-keto ester also causes rate acceleration.[42] The reduction of methyl pyruvate proceeds rapidly at room temperature (4 h) and in high efficiency (86% ee). The use of a larger ester such as *tert*-butyl pyruvate leads to even better induction (100% ee). Similar results are obtained with a wide variety of α-keto esters.

Cyano ketones are rapidly reduced to optically active cyanohydrins.[43] These are reduced in situ to the 1,2-amino alcohols of high enantiomeric purity.



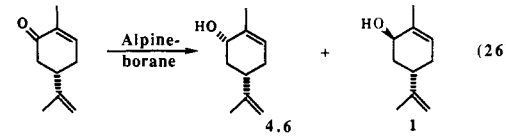
(24)

The reduction of chiral ketones indicates that if the stereocenter is on the large side of the ketone, then there is little effect on the asymmetric induction.[40] If it is on the small side, then the rate can be changed dramatically. For example, both enantiomers of 2-methylcyclohexanone (stereocenter on the large side) are reduced at the same rate and in the same sense. Although the reaction is fairly enantioselective, it is not stereoselective in the usual sense. A 1:1 mixture of the cis and trans isomers is formed.



(25)

In the case of carvone (eq 26 and 27) the isopropylidene group is on the small side. *d*-Carvone is reduced at 6000 atm within 3 days. The two epimeric alcohols are formed in a 4.6:1 ratio. The reduction of *l*-carvone showed no progress after 5 days at 6000 atm.



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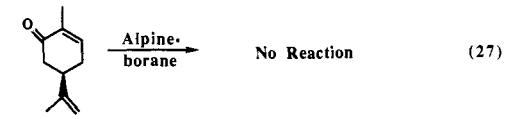


(27)

B. Myrtanyl-9-BBN

Myrtanyl-9-BBN is a less sterically congested reducing agent and is therefore able to accommodate more hindered ketones than Alpine-Borane.[21] Although 3,3-dimethyl-2-butanone is not reduced by Alpine-Borane, it is reduced by myrtanyl-9-BBN at atmospheric pressure within 10 days to a product of 23% ee. The dehydroboration pathway is, however, a major problem. Myrtanyl-9-BBN undergoes dehydroboration about twice as fast as Alpine-Borane. Performing the reduction at 5000 atm provides product of 64% ee (*S* configuration) within 2 days.

Less hindered ketones are reduced within 2–3 days at atmospheric pressure. Acetophenone gives product of 33% ee while α-tetralone gives product of 66% ee. In both cases the *S* alcohol is obtained.

Two very similar reagents have been reported by Giacomelli. These have the same myrtanyl structure but replace the boron component with either aluminum dichloride[44] or beryllium chloride.[45] The aluminum reagent gives approximately the same percentage of enantiomeric excess as the boron compound. However, both the aluminum and beryllium compounds give alcohols of the *opposite* configuration from that derived with the boron reagent.

C. Dialkylchloroboranes

A benefit of using organoborane reducing agents is that the electronic and steric requirements of the reagent may be widely varied. Brown has investigated the dialkylchloroboranes with the assumption that the halogen might increase the Lewis acidity of boron and thus enhance the reactivity.[23] The dialkylchloroboranes do indeed provide an increased reactivity.

Reaction with benzaldehyde occurs in <1 min in many cases. The reduction process has other characteristics that are similar to those of the *B*-alkyl-9-BBN compounds. Thus, bis(*trans*-2-methylcyclohexyl)-chloroborane reacts slowly while the 2-methylcyclopentyl analogue reacts rapidly. The pinanyl compound, however, is exceptional in its reactivity. Not only is the first equivalent of pinene eliminated in <1 min but the second pinanyl group can also be eliminated in <1 min.

Typical ketones, such as acetophenone, are reduced within 5 h at −25 °C with diisopinocampheylchloro-

TABLE V. **Reduction of Ketones with Diisopinocampheylchloroborane**

ketone	time, h	alcohol yield,[a] %	% ee[b]
acetophenone	5	72	98 (97.4)
propiophenone	5	62	98.3 (97.3)
butyrophenone	5	77	100 (98.2)
decanophenone	5	75	(95)
isobutyrophenone	24	68	90
pivalophenone	12 days[c]	*d*	79.3
1-indanone	15	62	97 (97.4)
α-tetralone	50	70	85.6 (87.4)
2′-acetonaphthone	7	90	98.1
3-acetylpyridine	15[d]	67	91.7 (92.4)
2-acetylthiophene	15[d]	85	(91.3)
2′,5′-dimethoxypropiophenone	1	80	(96)
3,3-dimethyl-2-butanone	12 days	50	93 (95)
ethyl 2,2-dimethylacetoacetate	12 days	69	(84)
2,2-dimethylcyclopenanone	12	71	(98)
2,2-dimethylcyclohexanone	12	60	(91)
spiro[4.4]nonan-1-one	12	65	100 (95)
methyl benzoylformate	10		(70)
trans-4-phenyl-3-buten-2-one	10	65	81
4-phenyl-3-butyn-2-one	2	78	(21)

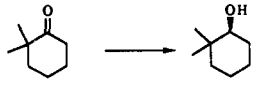
[a] Isolated yield. [b] Determined by rotation. Values in parentheses determined by capillary GC via MTPA or MCF derivative. [c] Reaction was 60% complete in 12 days. [d] A 2-equiv portion of the reagent was use.

borane (Ipc_2BCl)[24] compared to 7–14 days at room temperature with Alpine-Borane. The reagent is particularly effective for aryl *n*-alkyl ketones and α-*tert*-alkyl ketones (Table V). For example, acetophenone and other *n*-alkyl phenyl ketones are reduced in 98% ee. Increasing the size of the alkyl group decreases the rate of reduction as well as the % ee, but the results are still very good. Aromatic cyclic ketones such as 1-indanone or α-tetralone are also reduced with very high efficiency.

(28)

97% e.e.

Purely aliphatic ketones such as 2-butanone give unsatisfactory results. If, however, the aliphatic ketone contains an α-tertiary group, then the results are excellent. Ketones such as 3,3-dimethyl-2-butanone require 12 days at room temperature but cyclic ketones such as 2,2-dimethylcyclohexanone only require 12 h.

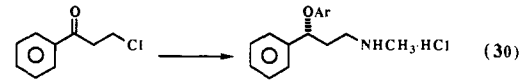


(29)

91% e.e.

The Ipc_2BCl reagent is able to accommodate α-keto esters such as methyl ethylpyruvate (45% ee) and methyl benzoylformate (50–70% ee). However, β-keto esters gave complex mixtures. α,β-Unsaturated ketones give generally good results. 2-Cyclohexenone gives 36% ee, but 4-phenyl-3-buten-2-one gives 81% ee. The prostaglandin intermediate 1-iodo-*trans*-1-octen-3-one gives a very good 85% ee.

α-Haloacetophenones are reduced to the corresponding halohydrin in high efficiency. The chloride gives the best results (96% ee versus 67% ee for the iodide). A more remote halide has no unusual effect. 3-Chloropropiophenone gives 97% ee, essentially the same result as propiophenone. The halo alcohols are versatile intermediates in organic synthesis. They may be converted into epoxides, substituted tetrahydrofurans, or amines. For example, Brown has prepared a series of antidepressant drugs in both enantiomeric forms.[46]



(30)

The major product of reductions with Ipc_2BCl may be predicted by using the model put forth for Alpine-Borane. The only exception is 2-octanone, which gives the *R* configuration instead of the predicted *S*. However, reduction gives only 7% ee and rationalization of the major product in cases where the enantiomeric excess is so low is tenuous at best.

Brown has investigated a series of isopinocampheylalkylchloroboranes (IpcBRCl) in which the steric requirement of the alkyl group was varied.[47] The size of the R group plays an important role in determining the effectiveness of the reagent as well as controlling the absolute configuration of the product. Small alkyl groups (methyl or ethyl) on IpcBRCl resulted in low asymmetric induction upon reduction of acetophenone (15–33% ee). As the alkyl group becomes larger, the reagent becomes more effective (isopropyl, 81% ee; cyclopentyl, 84% ee; isopinocampheyl, 98% ee). In each case the *S* alcohol is obtained in accord with the simple model.

The *tert*-butyl derivative proved to be highly selective, acetophenone giving product of 96% ee. However, the product was enriched in the *R* isomer. This reversal in absolute configuration from that obtained with Alpine-Borane or Ipc_2BCl was observed for a number of ketones. However, 3-methyl-2-butanone gives the *S* enantiomer as expected from the simple model. The cause of this unusual reversal in absolute configuration has not been explained.

IX. Conclusions

The asymmetric reduction of ketones has progressed to the point where these reagents can be reliably used in a synthetic scheme. A simple model based on steric size can be used to predict the absolute configuration of the product. In general, best results for aldehydes and acetylenic ketones are obtained with Alpine-Borane. More hindered ketones give the best results with Ipc_2BCl. Both reagents are available in either enantiomeric form and in a high degree of purity.

X. Acknowledgments

I thank the National Institutes of Health for support of this research. None of the research could have been accomplished without an excellent group of students working on the project. Their names are listed in the references.

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