Asymmetric Reductions of Prochiral Ketones with Lithium [2-[2-(Benzyloxy)ethyl]-6,6-dimethylbicyclo[3.1.1]-3-nonyl]-9-boratabicyclo-[3.3.1]nonane (Lithium NB-Enantride) and Its Derivatives

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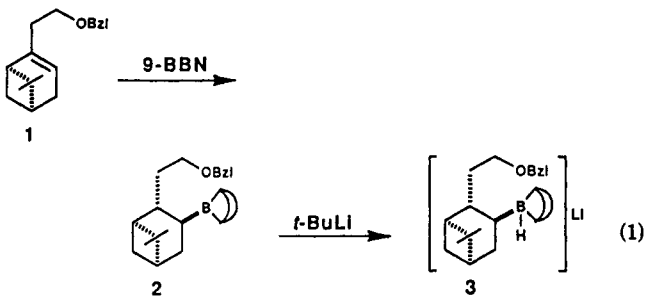
NB-Enantride, prepared by hydroboration of nopyl benzyl ether with 9-borabicyclo[3.3.1]nonane (9-BBN) followed by treatment with *tert*-butyllithium, is an effective asymmetric reducing agent. Especially noteworthy is the fact that it can reduce aliphatic ketones such as 2-octanone or 2-butanone in efficiencies approaching 80% enantiomeric excess. Several analogues have been tested in order to probe the structural features which contribute to making this reagent effective. The ether group evidently plays a role in obtaining high selectivity, since changing oxygen to nitrogen or sulfur causes a drop in selectivity. Moving the ether group by one atom in either direction or making it more hindered causes a drop in selectivity. However, replacing the $OCH_2C_6H_5$ group with a methyl group also results in an effective reducing agent and suggests that steric factors play an important role. The lithium cation was also found to be very important. Whereas the lithium compound reduced acetophenone within minutes at −78 °C, the potassium analogue gave no reduction over an extended period. At higher temperatures (−65 °C) reduction did slowly occur with the potassium compound, but the selectivity was greatly reduced in comparison to the lithium compound.

Introduction

One of the potentially easiest methods for the preparation of optically active alcohols is the asymmetric reduction of prochiral ketones. Among other methods[1] this transformation may be achieved by the use of metal hydrides in which chiral moieties are ligated to the metal. High asymmetric reductions have been reported in individual cases. Most of the effective reagents are derived from modifications of lithium aluminum hydrides.[2] The use of modified borohydrides has met with limited success with a few notable exceptions.[1,3] This lack of enantioselectivity contrasts the very high stereoselectivity obtained with trialkylborohydrides such as L-Selectride.[4,5]

We have observed that the lithium borohydride derived from hydroboration of nopyl benzyl ether (1) with 9-BBN and treatment with *tert*-butyllithium is a remarkably effective asymmetric reducing agent.[6] This reagent, NB-Enantride[4] (3) was found to be especially effective for aliphatic methyl ketones such as 2-butanone and 2-octanone. The results are especially surprising when one considers that the structurally very closely related Alpine-hydride[4] (derived from α-pinene) gives low enantiomeric purities.[7] Likewise the compound with one less carbon in the ether side chain (derived from myrtenyl benzyl ether) gave 1-phenyl ethanol of only 15% ee. In order to ascertain the structural features which contribute to the high selectivity with NB-Enantride, a number of analogues have been prepared. The results are presented herein.



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Results and Discussion

The reduction of a variety of ketones with NB-Enantride has been previously reported.[6] The results are summarized in Table I. In general, all reductions provide the *S* enantiomer except in the cases of α,α,α-trifluoroacetophenone and 4-heptyn-3-one in which the priorities of the large and small groups are reversed. The initial reductions were performed at −100 °C. At −78 °C there is a slight loss in selectivity.

One of the major drawbacks of most asymmetric reducing agents is that they are effective only for aromatic ketones. These results are to be expected in light of the proposed mechanism for asymmetric reductions which requires a dovetailing of large and small groups on the reducing agent and carbonyl.[8] Since a methyl and a straight-chain alkyl group have virtually the same steric size, the two faces of the carbonyl are not adequately distinguished. Furthermore, the electronic differences between an aromatic group and an alkyl group may play an important role. For example, the π-cloud of an acetylene group often makes an acetylene behave as an aromatic

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Table I. Asymmetric Reductions of Ketones with NB-Enantride and Alpine-Hydride[7]

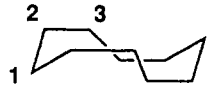
ketone	% ee[a]	ketone	% ee[a]
acetophenone	77 (*S*) (17)	3,3-dimethyl-2-butanone	2 (*S*) (3)
α,α,α-trifluoroacetophenone	50 (*R*)[b]	4-methyl-2-pentanone	30 (*S*) (16)
butyrophenone	54 (*S*)	3-methyl-2-butanone	68 (*S*) (36)
β-ionone	20 (*S*)	2-butanone	76 (*S*) (29)
4-heptyn-3-one	30 (*R*)	2-octanone	79 (*S*)
4-phenyl-3-butyn-2-one	10 (*S*)		

[a] Results for Alpine-Hydride are in parentheses and are based on rotations.[7] Results for NB-Enantride are detd. by NMR analysis using $Eu(dcm)_3$ or $Eu(hfc)_3$. The absolute configuration was detd. by comparison of the sign of rotation to literature values. All NB-Enantride redns. were run at −100 °C except for the acetophenone case (−78 °C). All Alpine-Hydride results are at −78 °C. [b] The enantiomeric excess was determined by HPLC using a Pirkle column: Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1981**, *46*, 2935.

group.[9] Surprisingly, NB-Enantride is effective for aliphatic ketones in which the two alkyl groups have rather similar sizes such as 2-butanone and 2-octanone. For example, 2-octanol is obtained in 79% ee, one of the highest obtained for a chemical reduction. However, it is ineffective when the alkyl groups are very different in size as in 3,3-dimethyl-2-butanone.

A working model for the asymmetric reduction of ketones with NB-Enantride must accommodate the fact that the side chain plays an important role in obtaining high efficiency. We chose to start with a 10-membered ring model which complexes the lithium cation between the oxygen of the benzyl ether side chain and the oxygen of the ketone functionality. Although it is unlikely that this model resembles the transition state (vide infra), it may at least be used as a mnemonic model for predicting the absolute configuration of the product.

Molecular mechanics calculations by Still established that the lowest energy conformation of cyclodecane is the boat–chair–boat (BCB) conformation and that the *A* value for a methyl group at the 1- or 3-position can be very high (6.6 and 9.2 kcal/mol).[10] Our own calculations on chair–chair–chair, chair–boat–chair and chair–chair–boat conformations confirms the observation that the 1- and 3-positions have a high bias for an equatorial substituent



In applying this information to the model for NB-Enantride, the ketone is placed in the 3-position of the cyclodecane ring. The pinane ring is essentially conformationally locked, and the ether side chain and borohydride substituent must be on opposite sides of the plane defined by the pinane ring (due to the stereochemistry of hydroboration). The ketone is oriented such that the largest group is placed in the lowest energy position, i.e. the equatorial position.

Probing the model of this reducing agent can be accomplished in several different ways. The model predicts that the complexing ability of the lithium cation is important in forming the 10-membered ring. Changing the metal atom of the cation to other metals with different complexing abilities should affect the transition state and observed selectivity. Along this line of reasoning, relocating or changing the benzyl ether oxygen atom to atoms with lower or no complexing abilities should also have drastic effects upon the reduction. The benzyl substituent of the ether group can also be changed to see if any effect upon selectivity is observed. Finally, disrupting the steric environment at the 11-position of the nopyl group should also have a large effect on reductions with this reagent.

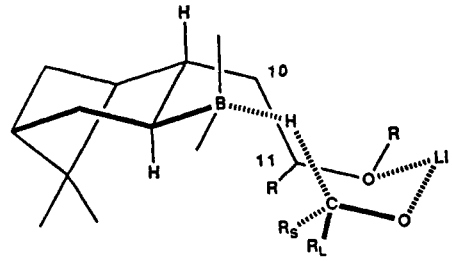


Figure 1. A predictive model for asymmetric reductions with NB-Enantride.

Cation Effects upon Rate and Selectivity of Reduction of Ketones with NB-Enantride. The metal cation can play an important role in hydride reductions. Early reports established a large difference between the reactivity of lithium borohydride and sodium borohydride. For example, sodium borohydride reduces esters very slowly, while lithium borohydride reduces esters much more readily.[11]

The cation is predicted to be a very important element in the proposed model for the reduction of ketones with NB-Enantride. In order to investigate this idea, a variety of reagents with various cations were prepared from the potassium borohydride reagent by exchange of the cation. The potassium (KNBE) reagent was readily prepared by treatment of the trialkylborane with potassium triisopropoxyborohydride.[12] Upon equilibration, no potassium triisopropoxyborohydride was present, as observed by ^{11}B NMR. Addition of metal salts to this solution resulted in the precipitation of potassium chloride and formation of the new metal borohydride as evidenced by the ^{11}B NMR.

Several cation derivatives of NB-Enantride were used to reduce acetophenone, and the extent of asymmetric reduction and relative rate of reduction were measured. For the lithium NB-Enantride reduction of acetophenone, a half-life of less than 60 s was observed at −78 °C. *On the other hand, no reduction of acetophenone was observed with potassium NB-Enantride (KNBE), even after 200 h.* The reaction of KNBE and acetophenone did not occur until the temperature was raised to −65 °C. At this temperature, the reaction still took over 20 h for completion. The half-life was observed to be 150 min. In addition to the decreased rate of reduction, KNBE was much less effective as an asymmetric reducing agent. The reagent was comparable to Alpine-hydride[7] in selectivity (21% ee at −65 °C).

The decreased rate and enantioselectivity observed with KNBE is also seen with other metal ions ($ZnCl_2$, 44% ee; $MgCl_2$, 19% ee; $Ti(Oi\text{-}Pr)_4$, 15% ee; $ZnCp_2Cl_2$, 11% ee). Though some were slightly higher than the potassium ion, all were within a close proximity of each other. Furthermore, none of the other metal borohydrides were observed to react with acetophenone below −65 °C.

This large selectivity and rate difference, caused solely by metal ion changes, has never been reported for tri-

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Table II. Reduction of Acetophenone with Ether Derivatives of NB-Enantride, at -78 °C

ether group	% ee[a]	ether group	% ee[a]
benzyl	77	THP	46
Me	72	CH_2OME	27
TBDMS	57		

[a] All products of *S* absolute configuration. Enantiomeric excess detd. using $Eu(hfc)_3$.

alkylborohydrides. All reports to date have shown only slightly changes in observed selectivity caused by changing the metal ion. In the case of L-Selectride, very little difference in selectivity is observed in the reduction of unsubstituted cyclohexanones.[5] Furthermore, no difference in rate of reduction is reported. Very similar results are observed with LS-Selectride[4] and KS-Selectride.[4,5]

Homologues of NB-Enantride. The structure of the side chain appears to be of critical importance in achieving high selectivity with NB-enantride. In the original disclosure of this reducing agent it was mentioned that the one carbon smaller homologue of NB-Enantride (prepared from myrtenol) reduced acetophenone in only 15% ee. In order to grasp a better understanding of the importance of the positioning of the oxygen atom, a homologue of NB-Enantride with one more carbon atom in the side chain (6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-(3′-propanol), homonopol) was synthesized. The homologue was prepared from nopol by conversion via the bromide to the Grignard and addition to formaldehyde, and subsequent transformation to the benzyl ether and then to the corresponding lithium trialkylborohydride.

A moderate enantioselectivity of 45% ee was observed in the reduction of acetophenone with this homologue of NB-Enantride. The product was of the same absolute stereochemistry, *S*, as that observed in the NB-Enantride reduction of this ketone. This result is intermediate between the one carbon smaller homologue synthesized from myrentol and NB-Enantride.

Effect of Oxygen Protecting Group. A variety of ether protecting groups can be accommodated in the reagent. The results of reduction of acetophenone with the corresponding trialkylborohydrides are presented in Table II. The results of the benzyl ether are included for comparison.

There appears to be very little correlation between the size of the ether group and the enantioselectivity. This can be seen if one compares the methyl-substituted ether to the *tert*-butyldimethylsilyl (TBDMS) ether. In general, all selectivities but the last entry in Table II are within a close proximity of one another. In the case of the last two entries, there are two possible sites for coordination of the lithium atom. The lower results with the last two entries are in agreement with potential complexation of lithium at the 13-position, as in the homologue derivative described above.

Heteroatom Analogues. With the above results indicating a large importance for the oxygen atom, the next step was to place a different atom in this position. The premise is based upon the fact that other heteroatoms should complex differently to the lithium atom and thus change the selectivity observed by the reagent.

The aza and thia analogues of NB-Enantride were synthesized from nopyl tosylate and hydroborated with 9-BBN. The hydroboration occurred with no remarkable differences from nopyl benzyl ether. The ^{11}B NMR chemical shifts of the trialkylboranes and borohydrides are summarized in Table III. The ^{11}B NMR spectrum of the phenylthia intermediate showed the trialkylborane at 77.7 ppm. This chemical shift is significant in that it shows slight, if any, upfield shifting, which would be caused by complexation of the sulfur atom to the boron. Likewise the pyrrolidine (81.0 ppm) and phenylethylamine (82.5 ppm) derivatives showed very slight upfield shifting. A typical trialkylborane, such as Alpine Borane, produces a signal at 82.0–86.0 ppm. Usual chemical shifts from strongly complexed trialkylboranes are in the region of 0.0 to -10.0 ppm (trimethylborane:methylamine -5.5 ppm[13]). Treatment of the trialkylborane with *tert*-butyllithium produced the corresponding trialkylborohydride. This again showed no chemical shift differences which could be attributed to heteroatom interaction with the boron atom.

Table III. Reduction of Acetophenone with 11-Heterosubstituted NB-Enantride Derivatives

substrate	^{11}B R_3B		^{11}B $Li[R_3BH]$	% ee of alcohol[a]
nopyl benzyl ether	86.0	-8.0	(d, J = 45 Hz)	77
benzyl nopyl sulfide	77.7	-5.56	(d, J = 58 Hz)	37
nopylphenylethylamine	82.51	-5.76	(d, J = 78 Hz)	54
N-nopylpyrrolidine	81.0	-5.98	(d, J = 69.9 Hz)	39

[a] All products are of the *S* absolute configuration. Enantiomeric excess determined using $Eu(hfc)_3$.

The results of the reduction of acetophenone with these derivatives are presented in Table III. In all cases, the reduction of acetophenone is slightly less selective than with NB-Enantride.

The ability of lithium to form complexes with oxygen, sulfur, and nitrogen has been reported in other systems.[14] In some instances, cyclic transition states containing the heteroatom and lithium cation have been envoked to explain the observed selectivity.[14] The strength of these complexes can be explained using hard–soft acid–base (HSAB) theory. The ability of lithium to complex to the ether, amine, and thioether bases decreases on going from oxygen and nitrogen to sulfur.[15]

The 11-Substituted Derivatives of NB-Enantride. The 11(*R*)-methylnopol 4 was prepared by reaction of (-)-β-pinene with acetaldehyde using a 50% excess of diethylaluminum chloride as catalyst.[16] A single diastereomer was formed according to HPLC and NMR analysis. The ene adduct was then converted to the benzyl ether and then to the lithium trialkylborohydride.

The 11(*S*)-methylnopol was prepared using a thermal ene reaction of (-)-β-pinene with chloral[17] to produce 11-(*R*)-(trichloromethyl)nopol. (Anhydrous chloral failed to give product until 1 mol % water was added.) The 11-(*R*)-(trichloromethyl)nopol was converted to the 11(*S*)-methylnopol by treatment with a 10-fold excess of lithium aluminum hydride. The product was an 81:19 mixture of diastereomers, in close agreement with the reported 83:17 diastereomeric mixture reported for the chloral reaction.[17] Stereochemical assignments are based on the X-ray structure of the chloral adduct.[17b]

The 11,11-dimethylnopol derivative was synthesized by a Lewis acid catalyzed ene reaction between (-)-β-pinene

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and acetone. The product was obtained in very high yields, which is contrary to the poor yields (15–20%) obtained in the intramolecular version of this reaction.[18] The product was then converted to the benzyl ether using conditions similar to the other methyl derivatives.

With these methyl derivatives of nopyl benzyl ether in hand, the next step was to accomplish the formation of the trialkylboranes and borohydrides. The 11(*R*)-methylnopyl benzyl ether was treated with 9-BBN, 0.5 M in THF, followed by reflux for 12 h. Analysis of the mixture at this point showed that complete hydroboration had occurred. Upon cooling to −78 °C, and treatment with *tert*-butyllithium, the trialkylborohydride was observed to be the only boron-containing species in the ^{11}B NMR. Thus, no difference in reactivity is observed between the formation of this reagent and NB-Enantride.

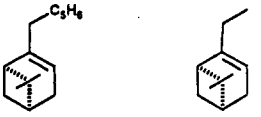
On the other hand, the 11(*S*)-methylnopyl benzyl ether showed a significant difference in reactivity. In order to accomplish complete hydroboration, it was necessary to reflux the alkene with 9-BBN for a period of 32 h. At this time complete hydroboration was observed, though decomposition products of 9-BBN were found during the ^{11}B NMR analysis. These amounted to 10% of the total boron-containing species. Reaction of this organoborane with *tert*-butyllithium was also observed to be somewhat slower than with NB-Enantrane.

With the 11,11-dimethylnopyl benzyl ether, a much greater difference in reactivity was observed. Upon treatment of this compound with 9-BBN, at reflux for up to 50 h, no hydroboration was observed. This was repeated several times to confirm the lack of reactivity. In all cases, the only boron-containing species observed by ^{11}B NMR was a dialkylborane (93%) identified as 9-BBN.

The difference in reactivity between the monomethyl derivatives was explored using PCMODEL[19] to model the transition state of the hydroboration reaction. These calculations suggest the 11*R* diastereomer should be more readily hydroborated with 9-BBN than the 11*S* diastereomer. In the transition state of the 11*R* diastereomer, one of the lowest energy conformers is one in which the hydrogen atom at the 11-position is pointing toward the incoming hydroboration reagent. The 11-methyl substituent is pointing away from both the incoming 9-BBN and the bridgehead of the pinene system. With the 11*S* diastereomer, one of the lowest energy conformers has the 11-methyl group pointing toward the bridgehead of the pinene system. The interaction of the methyl substituent with the bridgehead atoms raises the energy barrier of the transition state 0.6 kcal/mol higher than with the 11*R* diastereomer. Thus, a somewhat slower hydroboration reaction rate would be anticipated.

The 11(*R*)-methyl-NB-Enantride produced (*S*)-phenethyl alcohol in a 32% ee. The product is of the same absolute configuration as that observed with NB-Enantride, though much poorer selectivity is seen. With the 11(*S*)-methyl-NB-Enantride, an even lower selectivity of 11% ee is observed in the reduction of acetophenone. When corrected for the 17% of the 11(*R*)-methyl-NB-enentride present, the selectivity drops to about 7% ee. The reduced selectivity observed with the 11*S* and 11*R* derivatives may be accounted for by the fact that each contains a more hindered ether substituent. Steric factors could thus lead to lower selectivities.

Hydrocarbon Analogues. The above results indicate that the oxygen is important for high selectivity. This could be attributed to a complexation to the lithium or to a steric effect. In order to explore this idea, two hydrocarbon analogues of pinene, 2-benzylapopinene (**5**) and 2-ethylapopinene (**6**), were tested.[20] Hydroboration with



5 **6**

9-BBN and treatment with *t*-BuLi provided the corresponding lithium trialkylborohydride. The borohydride from **5** reduced acetophenone to 1-phenylethanol of 34% ee. The compound from **6** on the other hand gave 1-phenylethanol of 57% ee (**5**). Reduction of 2-octanone with this reagent provided (*S*)-2-octanol in 75% ee. The results are essentially the same as for NB-Enantride and suggest that the selectivity is due to a steric effect rather than a complexation of lithium to the ether oxygen. Similar results have been recently reported by Brown.[21]

Conclusions

During the course of the studies directed at grasping a better understanding of how NB-enantride achieves high enantioselectivity, several important facts have been learned. The first of these is that the lithium cation is vital to high selectivity and to enhance the rate of reduction. Changing the cation to any other species leads to a reagent which yields much poorer selectivity and a much slower reducing agent.

The size of the ether alkyl group of NB-Enantride appears to be modestly important in the selectivity observed with this reagent. Changing it to substituents with a variety of different steric environments does not sharply decrease the selectivity as was anticipated. If another coordination site is contained in the ether group, lower selectivity is observed.

The position of the oxygen atom in the side chain plays an important role in the selectivity observed during the course of a reduction. This selectivity is greatly diminished if the side chain is decreased by one carbon atom and is slightly diminished if the side chain is increased by one carbon. The heteroatom contained in the side chain is important in achieving high selectivity. When this atom is changed from oxygen to nitrogen or sulfur, a drop in enantioselectivity is observed. However, the hydrocarbon analogue derived from 2-ethylapopinene (**6**) is of essentially the same selectivity of NB-Enantride.

Substitution at the 11-position also drops the enantioselectivity of the reagent drastically. The product prepared from the 11*R* diastereomer does show an enhanced selectivity over the 11*S* diastereomer, but it is still much less selective than the parent reagent. The selectivity seems to be controlled by subtle changes in steric factors in the side chain rather than the ability of the oxygen to complex a metal since the hydrocarbon analog is also effective. It is highly unlikely that the transition state resembles the 10-membered ring depicted in Figure 1. However, this model may be used to predict the configuration of the product.

In conclusion, the exact nature of the mechanism which is responsible for the high selectivity observed with the asymmetric reducing agent NB-enantride is still unknown.

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We have gained some information, but some questions still remain. The side chain plays a very important role in achieving high enantioselectivity during the reduction. Lithium appears to be the cation of choice to achieve maximum selectivity and fast reaction rates. The absolute configuration of the product may be predicted using the mnemonic model in Figure 1.

Experimental Section

General Comments. All air- and moisture-sensitive materials were handled following standard procedures.[22] All reactions were carried out in a standard reaction vessel which consisted of an oven-dried, round-bottom, septum-capped, side-arm flask of the appropriate size containing a magnetic stirring bar, connected to a mercury bubbler and purged with argon. Tetrahydrofuran (THF) was freshly distilled from benzophenone–potassium ketyl. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX200 (200 MHz) in $CDCl_3$. ^{11}B NMR were recorded on Nicolet 300-MHz wide-bore NMR (at 96.272 923 MHz) with $BF_3{\cdot}Et_2O$ as external standard (0.00 ppm). Commercially available potassium triisopropoxyborohydride was purified as described in the literature.[23] Standardization of 9-BBN was accomplished using a 50:50 solution of methanol and THF at 35 °C. Standardization of *tert*-butyllithium was accomplished following the method of Watson and Eastham.[24] Enantiomeric excesses were determined using Eu(hfc)$_3$ or Eu(dcm)$_3$ as the chiral shift reagents following standard procedures.[25] Organic solutions were dried over anhydrous sodium sulfate unless indicated otherwise. Nopol (Aldrich) was distilled prior to use (bp 54–55 °C at 0.005 Torr, $[\alpha]^{25}_D$ −37.45° (neat, d = 0.96)). High purity nopol may be prepared by recrystallization of the (−)-α-methylbenzylamine salt of the half phthalate ester.[6] This results in slightly higher enantiomeric purities. Nopol benzyl ether was prepared by standard techniques.[6]

Preparation of a Stock Solution of Lithium NB-Enantride. To a 34.1-mL (15-mmol) aliquot of 0.44 M 9-BBN (freshly titrated) in THF was added 3.84 g (15 mmol) of nopyl benzyl ether via syringe. The mixture was stirred and heated at reflux for 12 h. An aliquot was transferred to an argon-purged NMR tube, analyzed by ^{11}B NMR (86.7 ppm, br s), and returned to the reaction vessel. The mixture was cooled to −78 °C (dry ice/acetone bath) while maintaining a positive argon pressure. Then, 5.77 mL of 2.6 M *tert*-butyllithium (15 mmol) was added dropwise while pausing for the yellow color to disappear between drops. The mixture was stirred for 0.5 h. An aliquot was analyzed by ^{11}B NMR (−8.0 ppm, d, J = 45 Hz). This solution was titrated for active hydride concentration using a 30% methanol solution in THF, and a value of 0.34 M was found (theory 0.357 M).

Lithium NB-Enantride Reduction of Acetophenone at −78 °C. At 14.6-mL (5-mmol) aliquot of lithium NB-Enantride stock solution was stirred and cooled at −78 °C (dry ice/acetone bath). A precooled (−78 °C) solution of 0.54 g (4.5 mmol) of acetophenone in 10.0 mL of THF was added dropwise over 1 min. Aliquots were analyzed by gas chromatography (GC) and ^1H NMR spectroscopy. Upon completion, the reaction mixture was quenched with 95% ethanol precooled to −78 °C. The solution was warmed to 35 °C. Oxidation was accomplished by the addition of 1.9 mL of 3 N sodium hydroxide solution followed by dropwise addition of an equal volume of 30% H_2O_2. The aqueous layer was saturated with K_2CO_3, and the organic layer was evaporated at aspirator pressure. The residue was triturated with hexane to precipitate the cyclooctanediol. The mixture was filtered by gravity, and the solvent was removed. The residue, weighing 2.1 g, was then bulb-to-bulb distilled at 0.025 Torr and 47–60 °C yielding 0.41 g, 75%, of 1-phenethyl alcohol, along with an unidentified minor (<5%) impurity. Final purification was accomplished by preparative GC on a 10 × $^1/_4$ in. 10% FFAP on Chromosorb W DCMS, at an oven temperature of 175 °C. Analysis of the purified material using Eu(hfc)$_3$ revealed a 77% enantiomeric excess of the (*S*)-alcohol.

Preparation of a Stock Solution of Potassium NB-Enantride. A solution of 5.13 g (20 mmol) of nopyl benzyl ether and 40.0 mL (20 mmol) of 0.5 M 9-BBN solution in THF was stirred and heated at reflux for 10 h. The mixture was then cooled to room temperature under argon and 20.0 mL of 1.0 M potassium triisopropoxyborohydride (20 mmol) was added; the mixture was stirred at room temperature for 1 h and was analyzed by ^{11}B NMR: −6.0 ppm, (d, J = 69.9 Hz). Titration for active hydride using 30% methanol in THF indicated a concentration of 0.30 M (theory 0.307 M).

Reduction of Acetophenone with Potassium NB-Enantride at −65 °C. A reaction vessel charged with 16.6 mL of 0.3 M potassium NB-Enantride stock solution (5.0 mmol) was cooled to −65 °C using a closed system refrigeration unit with an ethanol bath. After temperature equilibration, a 5.0-mL aliquot of 1.0 M acetophenone (5.0 mmol) in THF precooled to −65 °C was added dropwise over 60 s via syringe. Reaction progress was followed by GC analysis as previously described. Upon completion, the reaction mixture was quenched by addition of 2.0 mL of 30% ethanol in THF precooled to −65 °C and the product was isolated as in the lithium case. Analysis of the purified material using Eu(hfc)$_3$ revealed a 21% enantiomeric excess of the (*S*)-alcohol.

Preparation of Zinc NB-Enantride and Reduction of Acetophenone at −65 °C. A 16.5-mL (5 mmol) aliquot of the potassium NB-Enantride stock solution was cooled to 0 °C (ice bath) as 5.56 mL (5 mmol) of a 0.9 M solution of $ZnCl_2$ in THF was added. The mixture was cooled to −65 °C and stirred for 30 min. During this time a white precipitation (KCl) formed. Next, 5.0 mL (5 mmol) of a 1.0 M solution of acetophenone in THF, precooled to −65 °C, was added dropwise over a 60-s period. Aliquots were drawn and analyzed as previously described. Upon completion of reduction, the mixture was quenched by the addition of 30% ethanol in THF and the product isolated as previously described. Analysis of the purified material using Eu(hfc)$_3$ revealed a 44% enantiomeric excess of the (*S*)-alcohol.

11(*R*)-Methylnopol. A solution of 20.4 g (23.8 mL, 150 mmol) of (−)-β-pinene and 250 mL of anhydrous CH_2Cl_2 was stirred and cooled at 0 °C while 4.41 g (5.6 mL, 100 mmol) of acetaldehyde followed by 150 mL (150 mmol) of 1.0 M diethylaluminum chloride in hexane, were added dropwise via a syringe. During the addition, care was taken not to allow the reaction mixture temperature to rise above 0 °C. The reaction mixture was warmed to room temperature, stirred for 12 h, and cooled again to 0 °C. The mixture was quenched by cautious addition of 30.0 mL of pH 4.0 phosphate buffer solution. After gas evolution ceased, the organic layer was decanted from the solid aluminum salts, washed three times with 10 mL of water, and dried. The organic layer was filtered, and the solvent was removed by rotary evaporation at aspirator pressure. Evaporation and bulb-to-bulb distillation of the residue (19.2 g) at 53–55 °C (0.025 mm) gave 14.4 g (80%) of 11(*R*)-methylnopol. HPLC analysis of a silica column eluting with 5% EtOAc in hexane revealed that only one diastereomer was formed. $[\alpha]_D$ −41° (neat); ^1H NMR δ 0.84 (s, 3 H), 1.18 (d, J = 8 Hz, 3 H), 1.28 (s, 3 H), 1.8–2.5 (m, 8 H), 3.78 (m, 1 H), 5.35 (br s, 1 H); ^{13}C NMR δ 21.05, 23.85, 26.16, 30.17, 31.45, 37.83, 40.57, 45.62, 47.26, 64.12, 120.48, 145.47.

11(*R*)-Methylnopyl Benzyl Ether. A 2.74-g (68.5-mmol) portion of 60% sodium hydride/mineral oil dispersion was washed three times with hexanes followed by removal of the liquid layer and dried under a stream of nitrogen. The oil-free NaH was suspended in 50 mL of THF and stirred while 9.5 g (52.7 mmol) of 11(*R*)-methylnopol in 10 mL of THF was added. After gas evolution ceased, 9.07 g (6.3 mL 53 mmol) of benzyl bromide in 10 mL of THF was added dropwise. The reaction mixture was stirred and heated at reflux for 10 h after which 5.0 mL of 95% ethanol and 50 mL of water were added in succession. The organic layer was separated and washed three times with water and once with 10 mL of saturated NaCl. The organic layer was dried, filtered, and evaporated under aspirator pressure. Bulb-to-bulb distillation of the residue (9.4 g) at 87 °C (0.18 mm) gave 8.1 g (57%) of 11(*R*)-methylnopyl benzyl ether: $[\alpha]_D$ −54° (neat); ^1H NMR δ 0.83 (s, 3 H), 1.17 (d, J = 7 Hz, 2 H), 1.27 (s, 3 H), 1.7–2.3

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(m, 6 H), 3.50 (m, 1 H), 4.47 (s, 2 H), 5.23 (br s, 1 H), 7.33 (m, 5 H); ^{13}C NMR δ 19.64, 21.00, 26.25, 31.31, 31.70, 37.88, 40.65, 44.30, 45.96, 70.09, 73.64, 118.59, 127.11, 127.30, 128.08, 138.98, 145.15.

Preparation of 11(*R*)-(Trichloromethyl)nopol. To 29.48 g (19.65 mL, 200 mmol) of chloral was added (−)-β-pinene (27.29 g, 31.7 mL, 200 mmol), and the mixture was stirred while adding 0.01 mL of H_2O. The mixture was then heated for 4 h at reflux with stirring, cooled to room temperature, dissolved in 50 mL of diethyl ether, and washed three times with 10 mL of H_2O. The organic layer was dried and filtered, and the solvent was removed by rotary evaporation at aspirator pressure. The reside was bulb-to-bulb distilled at 65 °C and 0.02 Torr to yield 48.1 g (85%) of 11(*R*)-(trichloromethyl)nopol. ^{1}H and ^{13}C NMR are consistent with reported values:[26] $[\alpha]_D$ −4.6° (*c* 0.54, $CHCl_3$); exact mass calcd for $C_{12}H_{17}OCl_3$ 282.0344, found 282.0343.

Preparation of 11(*S*)-Methylnopol. A solution of 37.9 g (1000 mmol) of lithium aluminum hydride in 200 mL of THF was stirred and cooled with an ice bath, as the reaction vessel was purged with nitrogen and a 50:50 mixture of 28.3 g (100 mmol) of 11(*R*)-(trichloromethyl)nopyl in THF was added. When gas evolution ceased, the mixture was heated to reflux and stirred for 92 h. The mixture was then cooled to 0 °C, and the excess hydride was quenched by dropwise addition of 10 mL of ethyl acetate. Further quenching was accomplished by the addition of 20 mL of 50% ethanol in THF. The organic layer was filtered and washed three times with 30 mL of H_2O. The organic layer was then dried and filtered, and solvent was removed by rotary evaporation under aspirator pressure. The residue was bulb-to-bulb distilled at 50 °C and 0.02 Torr to yield 4.5 g (25%) of 11(*S*)-methylnopol. Analysis of this material by HPLC on a silica column eluting with 5% EtOAc in hexane revealed an 82:18 diastereomeric ratio, with the 11*S* isomer eluting before the 11*R* isomer: $[\alpha]_D$ −29.8° (neat); ^{1}H NMR (major isomer) δ 0.86, (s, 3 H), 1.15 (d, *J* = 6 Hz, 3 H), 1.28 (s, 3 H), 1.5–2.5 (m, 6 H), 3.76 (sextet, *J* = y Hz, 1 H), 5.31 (br s, 1 H); ^{13}C NMR δ 21.05, 22.63, 23.85, 26.16, 30.17, 31.21, 31.45, 31.87, 37.83, 40.57, 45.62, 47.26, 64.77, 119.8, 120.48, 145.47; exact mass calcd for $C_{12}H_{20}O$ 180.1514, found 180.1497.

Preparation of 11(*R*)- and 11(*S*)-Methyl-NB-Enantride and Reduction of Acetophenone. A solution of 1.35 g (5 mmol) of 11(*R*)- or 11(*S*)-methylnopyl benzyl ether in 10.0 mL (5 mmol) of 0.5 M 9-BBN in THF solution was stirred at reflux for a period of 12 h (32 h for the *S* isomer) to provide the trialkylborane (^{11}B NMR 86.0 ppm). The trialkylborohydride was prepared using the standard procedure (^{11}B NMR −7.9 ppm (d, *J* = 79.0 Hz) for the *R* isomer; −8.0 ppm (*J* = 72.0 Hz) for the *S* isomer). Acetophenone was then reduced using the standard procedure. Analysis of the purified material using Eu(hfc)$_3$ revealed a 32% enantiomeric excess of the (*S*)-alcohol from the *R* isomer and 11% ee from the *S* isomer.

Nopyl Tosylate. To a solution of 4.49 g (27 mmol) of nopol in 7.0 mL of dry pyridine was added 5.91 g (31 mmol) of *p*-toluenesulfonyl chloride. The flash was swirled and then stored in a refrigerator for 20 h. The resulting mixture was then poured into 20 mL of 50% HCl. This mixture was then extracted with diethyl ether and dried (K_2CO_3), and the solvent was removed by rotary evaporation, yielding 7.15 g (83%) of nopol tosylate: $[\alpha]^{25}_D$ −25.7° (*c* 5.25, $CHCl_3$); ^{1}H NMR δ 0.77 (s, 3 H), 1.07 (d, *J* = 9.0 Hz, 1 H), 1.23 (s, 3 H), 2.44 (s, 3 H), 4.03 (t, *J* = 7.0 Hz, 2 H), 5.24 (br s, 1 H), 7.34 (d, *J* = 8 Hz, 2 H), 7.78 (d, *J* = 8 Hz, 2 H); ^{13}C NMR δ 20.99, 21.54, 26.10, 31.21, 31.45, 36.01, 37.90, 40.51, 45.50, 68.48, 85.33, 119.56, 127.72, 129.66, 142.55, 144.56; exact mass calcd for $C_{18}H_{24}O_3S$ 320.1446, found 320.1446.

Preparation of Benzyl Nopyl Sulfide. Benzyl mercaptan (2.98 g, 24 mmol) was added to a vigorously stirred suspension of 1.35 g (24 mmol) of powdered KOH in 10 mL of dry dimethyl sulfoxide (DMSO). After being stirred for 0.5 h, the reaction mixture was transferred dropwise to a solution of 6.40 g (20 mmol) of noyl tosylate in 20 mL of dry DMSO. This solution was stirred for 24 h at room temperature. The reaction was quenched by pouring the mixture into 100 mL of cold water. This mixture was then extracted with three portions of 25 mL of diethyl ether. The ethereal layers were combined, followed by washing with 10 mL of 10% NaOH. The organic layer was dried (K_2CO_3) and filtered, and the solvent was removed by rotary evaporation under aspirator pressure. Vacuum distillation gave 4.2 g (77%) of benzyl nopyl sulfide (bp 130–132 °C at 0.025 mm): $[\alpha]^{25}_D$ −30.4° (*c* 5.14, $CHCl_3$); ^{1}H NMR δ 0.78 (s, 3 H), 1.13 (d, *J* = 9.0 Hz, 1 H), 1.24 (s, 3 H), 3.69 (s, 2 H), 5.18 (br s, 1 H), 7.27 (m, 5 H); ^{13}C NMR δ 20.99, 26.04, 29.02, 30.97, 31.39, 36.01, 36.44, 37.66, 40.51, 45.38, 116.95, 126.50, 128.08, 128.57, 138.29, 146.26; exact mass calcd for $C_{18}H_{24}S$ 272.1598, found 272.1591.

Preparation of Ethylnopylphenylamine. A solution of 6.40 g (20 mmol) of nopyl tosylate, 9.7 g (10 mL, 80 mmol) of *N*-ethylaniline, and 10 mL of THF was stirred and heated at reflux for 48 h. The THF was removed under reduced pressure. Next, 17 mL of a 1.5 M NaOH solution was added, and the mixture was stirred for 0.5 h. The mixture was extracted three times with 20 mL of diethyl ether. The combined ethereal layers were washed with 20 mL of 10% NaOH solution, 10 mL of water, and then 10 mL of a saturated NaCl solution. The organic layer was then dried and filtered, and the solvent was removed by rotary evaporation at aspirator pressure. The residue was distilled at 0.025 Torr, and the distillate was collected at 131–133 °C yielding 4.2 g (78%) of ethylphenylnopylamine: $[\alpha]^{25}_D$ −19.1° (*c* 4.99, $CHCl_3$); ^{1}H NMR δ 0.86 (s, 3 H), 1.13 (t, *J* = 7.0 Hz, 3 H), 1.18 (d, *J* = 8 Hz, 1 H), 1.29 (s, 3 H), 3.29 (m, 4 H), 5.28 (br s, 1 H), 6.65–7.19 (m, 5 H); ^{13}C NMR δ 12.42, 21.24, 26.28, 31.33, 31.70, 34.49, 37.96, 40.76, 44.59, 46.05, 48.85, 111.78, 115.37, 117.44, 129.12, 145.96, 147.66; exact mass calcd for $C_{19}H_{27}N$ 269.2143, found 269.2141.

Preparation of *N*-Nopylpyrrolidine. A solution of 8.9 g (28 mmol) of nopyl tosylate, 3.98 g (56 mmol) of freshly distilled pyrrolidine, and 30 mL of THF was stirred and heated at reflux for 10 h. All volatile compounds were then removed under vacuum. The residue was dissolved in diethyl ether, washed with 10 mL of water, and dried (K_2CO_3). The organic layer was evaporated at aspirator pressure. The residue was distilled at 0.025 Torr, and the distillate was collected from 70 to 72 °C to yield 5.35 g (87%) of *N*-nopylpyrrolidine: $[\alpha]^{25}_D$ −34.3° (*c* 4.82, $CHCl_3$); ^{1}H NMR δ 0.82 (s, 3 H), 1.15 (d, *J* = 8.0 Hz, 1 H), 1.26 (s, 3 H), 1.63–2.53 (m, 17 H), 5.22 (br s, 1 H); ^{13}C NMR δ 20.93, 23.18, 26.04, 31.03, 31.39, 36.44, 37.66, 40.51, 45.74, 53.83, 54.38, 116.41, 146.32; exact mass calcd for $C_{15}H_{25}N$ 219.1987, found 219.1995.

Preparation of Lithium Trialkylborohydrides from 11-Heterosubstituted NB-Enantrides and Reduction of Acetophenone (General Procedure). To 10.6 mL (5 mmol) of a 0.47 M 9-BBN solution in THF was added 5.5 mmol of the appropriate starting material in 5.0 mL of THF. The mixture was stirred while heating to reflux for 15–96 h. The mixture was cooled to −78 °C (dry ice/acetone slurry), and 2.80 mL (5 mmol) of *tert*-butyllithium, 1.8 M in pentane was added dropwise. This mixture was stirred at this temperature for 0.5 h. Next, 4.5 mL of a 1.0 M solution of acetophenone in THF, cooled to −78 °C, was added dropwise. The reaction mixture was stirred at this temperature until the reduction was complete (average of 2 h) and then quenched by the addition of 2.0 mL of 95% ethanol, precooled to −78 °C. After gas evolution ceased, the reaction mixture was warmed to room temperature, and the standard workup provided the 1-phenylethanol. Analysis of the purified material using Eu(hfc)$_3$ revealed the enantiomeric excesses of the (*S*)-alcohol.

Nopyl Bromide. To a suspension of 38.8 g (377 mmol) of NaBr in 150 mL of dry DMSO was added a solution of 40.8 g (127 mmol) of crude nopyl tosylate in 100 mL of DMSO, and the suspension was stirred for 5 h at 70 °C. The reaction was then quenched with water and extracted with hexane. The combined organic layers were washed with water and saturated NaCl andthen dried ($MgSO_4$). After evaporation of solvent the residue was distilled in vacuo to give 21.4 g (74%) of nopyl bromide (bp 51–51 °C at 0.25 mmHg): $[\alpha]^{25}_D$ −31.0° (*c* 4.98, $CHCl_3$); ^{1}H NMR δ 0.84 (s, 3 H), 1.17 (d, *J* = 8 Hz, 1 H), 1.27 (s, 3 H), 3.35 (t, *J* = 7 Hz, 2 H), 5.32 (br s, 1 H); ^{13}C NMR δ 21.12, 26.10, 30.36, 31.15, 31.51, 37.84, 40.27, 40.51, 45.32, 118.89, 144.99; exact mass calcd for $C_{11}H_{17}Br$ 228.0513, found 228.0502.

6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-(3′-propanol) (Homonopol). To a well-stirred mixture of 2.77 g (114 mmol) of

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magnesium turnings in 5 mL of THF was added a crystal of iodine together with a few drops of a neat nopyl bromide. After initiation of a reaction, an additional 15 mL of THF was added. Then a solution of 21.4 g (93.5 mmol) of nopyl bromide in 30 mL of THF was added dropwise, at a rate to maintain a mild reflux. The whole mixture was refluxed for 1 h and cooled, and a stream of gaseous formaldehyde formed from 8.4 g of paraformaldehyde was passed into the solution. Finally the reaction was quenched with about 11 mL of saturated NH_4Cl solution and left overnight. The organic layer was removed from a solid cake by filtration and dried ($MgSO_4$). After evaporation of solvent, the residue was distilled under reduced pressure to give 11.59 g (69%) of homonopol (bp 66-69 °C at 0.25 Torr): $[\alpha]^{25}_D$ -40.7° (c 5.135, $CHCl_3$); ^1H NMR δ 0.83 (s, 3 H), 1.27 (s, 3 H), 1.15 (d, J = 9 Hz, 1 H), 3.64 (t, J = 6 Hz, 2 H), 5.22 (br s, 1 H); ^{13}C NMR δ 20.94, 26.10, 29.93, 31.03, 31.39, 32.85, 37.66, 40.64, 45.56, 62.10, 115.74, 147.60; exact mass calcd for $C_{12}H_{20}O$ 180.1514, found 180.1511.

6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-(3′-propanol) Benzyl Ether. A solution of 5.34 g (29.6 mmol) of homonopol in 10 mL of THF was added dropwise to a vigorously stirred suspension of 1.185 g (39.5 mmol) of 80% NaH in 40 mL of dry THF. The mixture was then refluxed overnight, cooled to room temperature, treated with 6.32 g (37 mmol, 4.4 mL) of benzyl bromide, and refluxed for an additional 5 h. After cooling, the unreacted NaH was destroyed with 3 mL of methanol and the THF was removed under reduced pressure. The residue was diluted with water and extracted with ether. The combined organic extracts were washed with saturated NaCl solution and dried (K_2CO_3). After evaporation of ether, the residue was distilled in vacuo to give 3.55 g (44%) of homonopyl benzyl ether (bp 102-104 °C at 0.025 mmHg): $[\alpha]^{25}_D$ -26.3° (c 4.12, $CHCl_3$); ^1H NMR δ 0.81 (s, 3 H), 1.12 (d, J = 8 Hz, 1 H), 1.26 (s, 3 H), 3.46 (t, J = 7 Hz, 2 H), 4.49 (s, 2 H), 5.18 (br s, 1 H), 7.33 (m, 5 H); ^{13}C NMR δ 21.06, 26.22, 27.32, 31.15, 31.51, 33.22, 37.72, 40.76, 45.62, 69.95, 72.68, 115.92, 127.23, 127.35, 128.08, 138.54, 147.66; exact mass calcd for $C_{19}H_{26}O$ 270.1983, found 270.1991.

Reduction of Acetophenone with Homo-NB-Enantride. A solution of 1.688 g (6.24 mmol) of homonopyl benzyl ether was refluxed for 60 h with 11.2 mL (5.58 mmol) of 0.499 M 9-BBN solution in THF. Formation of the trialkylborohydride and workup followed the standard procedure.

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Carbon Acidity. 78. Extended Cesium Ion Pair Indicator Scale in Tetrahydrofuran

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A revised cesium ion pair acidity scale relative to fluorene at pK_a = 22.90 is presented. The range of the scale is extended 3 pK units by including more acidic indicators and now encompasses pK_as from 15.62 to 38.73. The accuracy of the scale has been improved by multiple equilibria among indicators. Uncertainties between close lying indicators is generally less than ±0.01 pK unit. Brønsted plots are constructed for series of fluorenyl and arylmethyl hydrocarbons. From these plots, the acidity value for toluene in THF was extrapolated (pK_a = 40.9). Comparisons are drawn to ionic acidities in dimethyl sulfoxide.

Introduction

We have recently presented a scale of cesium ion pair pKs in tetrahydrofuran (THF) for various indicators.[1] This scale was a revision of earlier scales[2] with updated values and with the reference system chosen as the pK of fluorene in dimethyl sulfoxide (DMSO).[3] This type of reference is required because absolute acidities in THF are not available. The cesium ion pair pKs of other compounds are defined by the equilibrium constant of eq 1, where R = 9-fluorenyl.

$$R^-Cs^+ + R'H \rightleftharpoons RH + R'^-Cs^+ \quad (1)$$

In the present work we have added new indicators to provide independent determinations of individual pKs and to fill large gaps in the previous scale. We have also improved methods for determining the content of any interfering impurities in the indicators. The lower end of the scale has been extended by 3 pK units.

Results and Discussion

Equilibrium Measurements. Several new indicators have been added to the scale at the lower pK_as and to fill in between adjacent indicators on the ion pair scale that have large differences in acidity. These new indicators are 7-phenyl-7*H*-benzo[*c*]fluorene (Ph-3,4-BF),[4,5] 9-*p*-biphenylylfluorene (9-BpFl),[6] 11-phenyl-11*H*-benzo[*a*]fluorene (Ph-1,2-BF),[7] 9-(*p*-(dimethylamino)phenyl)-fluorene (*p*-DMAPhFl),[5] 11-phenyl-11*H*-benzo[*b*]fluorene (Ph-2,3-BF), 9-isopropylidenefluorene (IPF),[8] 1,3-di-

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