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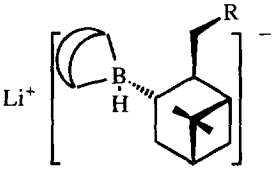
B-Iso-2-(2-diethylaminoethyl)apopinocampheyl-9-borabicyclo-[3.3.1]nonyl Hydride – An Improved Chiral Reducing Agent for Straight Chain Aliphatic Ketones

Steven A. Weissman[1] and P. Veeraraghavan Ramachandran*

H. C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University, West Lafayette, Indiana 47907-1393

Abstract: A series of chirally modified borohydrides of the type lithium B-iso-2-(alkyl)apopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride (**2-4** and **8-9**) were prepared to enable a strategic development of chiral reagents for the reduction of straight chain aliphatic ketones. Reagent **8** (alkyl = 2-diethylaminoethyl) reduces 2-octanone in 82% ee, significantly higher than that obtained with NB-Enantride (**7**) under identical conditions. An improved methodology for these reductions is also described.

The asymmetric reduction of prochiral ketones has become an important methodology for the synthesis of optically active secondary alcohols.[2] While superior reagents have been developed for the asymmetric reduction of several classes of ketones, such as aralkyl, α-acetylenic ketones, α-keto esters and α-branched aliphatic ketones, there has been a lack of success in achieving the asymmetric reduction of straight chain aliphatic ketones.[3] The use of metal hydride reagents incorporating a chiral auxiliary remains one of the most popular routes for the reduction of this elusive class of ketones.[4] Chirally modified aluminum reagents such as Noyori's Binal-H[5] and boron reagents, such as Alpine-Hydride™ (**1**)[6], Midland's NB-Enantride™ (**7**)[7] and Masamune's 2,5-dimethyl borolane[8] have been employed towards this end.



1 R = H
2 R = OMe
3 R = NEt_2
4 R = $N(i\text{-}Bu)_2$
5 R = CH_3
6 R = CH_2OMe
7 R = CH_2OBnz
8 R = CH_2NEt_2
9 R = $CH_2N(i\text{-}Bu)_2$

Midland and co-workers prepared a series of borohydride reagents derived from the analogs and homologs of nopol and carried out the reduction of acetophenone to understand the unexpected success achieved with **7**.[7b] Their strategies included replacing the oxygen with nitrogen or sulfur, moving the ether group by one atom in either direction or making it more hindered, and changing the metal ion from lithium to potassium, magnesium, titanium or zinc. All of these resulted in poorer induction.[7b] They have proposed a tentative 10-membered boat-chair-boat transition state model to predict the configuration of the product alcohols.[7b]

Recently, Brown and co-workers modified the α-pinene moiety of Alpine-Borane® (B-isopinocampheyl-9-borabicyclo[3.3.1]nonane), Alpine-Hydride™ (lithium B-isopinocampheyl-9-borabicyclo[3.3.1]nonyl hydride), and DIP-Chloride™ (B-chlorodiisopinocampheylborane) by placing an ethyl

group at the 2-position of the apopinene skeleton (2-ethylapopinene), in order to study the effect of increasing the steric requirement of the chiral auxiliary on the outcome of asymmetric ketone reductions.[9] Without exception, the enantiomeric excesses (ee's) obtained with these sterically modified organoborane reagents are significantly enhanced over those obtained with the α-pinene analogs. In order to substantiate this point and also to build on the success of NB-Enantride as a chiral reducing reagent for straight chain aliphatic ketones, a series of borohydride reagents of varying steric requirement at the 2-position of the apopinene skeleton were prepared and studied to examine their efficacy for the reduction of three representative classes of ketones: acetophenone (aralkyl), cyclohexyl methyl ketone (α-secondary aliphatic) and 2-octanone (straight chain aliphatic). For comparative purposes, the Alpine-Hydride reduction of acetophenone and the NB-Enantride reduction of all three ketones were repeated under identical conditions employing a standardized means of assaying the asymmetric induction (capillary GC analysis of the corresponding MTPA or MCF ester). The results of the study are summarized in the Table.

Table. Asymmetric Reduction of Representative Ketones with Chiral Lithium Trialkyl Borohydrides at −78 °C (−100 °C).[a,b,c]

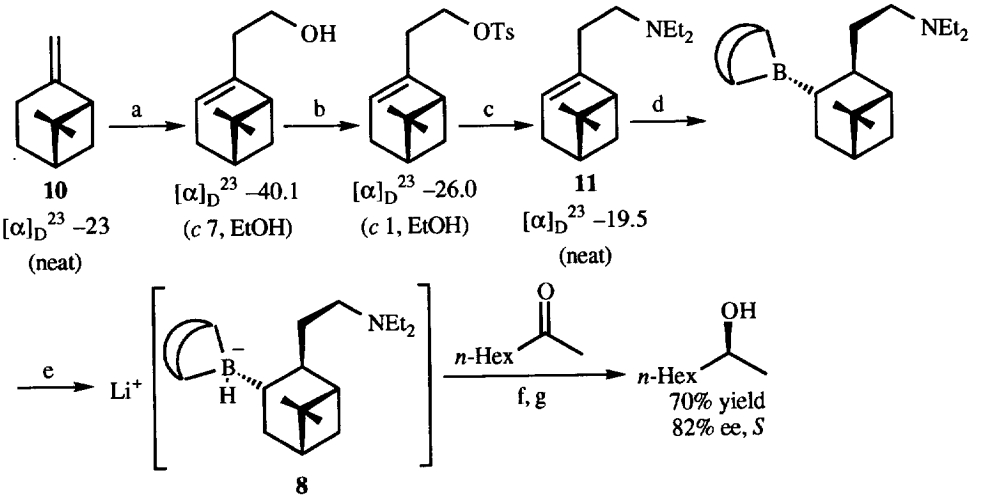
		% ee, Config.		
Reagent	R	acetophenone	acetylcyclohexane	2-octanone
1[d]	H	20, *R*	27, *R*	33, *R*
2	OMe	10, *S*	38, *S*	46, *S*
3	NEt_2	55, *S*	60, *S*	58, *S*
4	$N(i\text{-}Bu)_2$	23, *S*	17, *R*	14, *R*
5[e,f]	CH_3	56, *S*	70 (80), *S*	70 (77), *S*
6	CH_2OMe	60, *S*	75, *S*	67, *S*
7[e,f]	CH_2OBnz	63, *S*	65, *S*	67 (75)[g], *S*
8	CH_2NEt_2	59, *S*	66, *S*	77[f] (82)[f], *S*
9	$CH_2N(i\text{-}Bu)_2$	60, *S*	75, *S*	67, *S*

[a] Values corrected for 92% ee starting material. [b] All reactions were run on 3-8 mmole scale in THF/pentane (0.2 M) 2 h at −78 °C (% ee in parantheses for 3 h at −100 °C). Yields of the isolated alcohol were ≥70% in all cases (≥90% conversion). [c] Optical purities were determined by capillary GC analysis of the MTPA ester of product alcohol utilizing either a SPB™-5 or Supelcowax™ column. [d] Reagent derived from (+)-α-pinene and thus provided *R*-isomers. [e] From ref. 9b. [f] For ≥99% ee reagent. [g] Midland reports a value of 79% ee at −100 °C as determined by chiral lanthanide shift reagent (ref. 7).

The methyl ether analog (**6**) of NB-Enantride confirmed the lower value for the acetophenone reduction but showed improved induction in the acetylcyclohexane case. The identical ee's obtained for the 2-octanone reductions indicate that the benzyl group of **7** offers no advantage over reagent **6** for the reduction of straight chain ketones. The one carbon smaller homologue of reagent **6** displayed markedly lower chiral induction for all three classes of ketones. Changing the heteroatom from oxygen to nitrogen in the myrtenyl series showed mixed results depending on the *N*-alkyl groups. The diethylamino reagent (**3**) showed improved results vs oxygenated analog (**2**) whereas the diisobutylamino analog (**4**) was surprisingly a poor candidate overall. In fact, in the case of the two aliphatic ketones, a reversal of configuration of the product alcohols was observed. The difference in selectivity (a change of 36-39%) may not be due to the electronic environment since **4** is similar to **3** in all respects but for the steric requirements of the alkyl groups on the nitrogen atom. This points towards an optimum reagent from the myrtenylamine with appropriate alkyl groups on the nitrogen as the chiral auxiliary.

Still, none of the myrtanyl derivatives (**2-4**)[10] surpassed the previously reported results with reagent **5**, but they were better than those observed with Alpine-Hydride. This implied that the synthesis of an auxiliary in which a dialkylaminoethyl group was attached to the apopinene moiety might provide optimal results for the aliphatic ketone reductions. Accordingly, *N,N*-diethylnopylamine (**11**) was synthesized[11] from ß-pinene (**10**) of ≥99% ee[12] (Scheme). The reagent incorporating this auxiliary (**8**) provided 2-octanol in 77% ee (–78 °C) and 82% ee (–100 °C). Using optically pure nopyl benzyl ether ($[\alpha]_D^{23}$ –29.5 (*c* 10, $CHCl_3$), we prepared NB-Enantride and obtained 75% ee for the reduction of 2-octanone at –100 °C.[9b] Thus, the result of 82% ee for the reduction of 2-octanone is, to our knowledge, the highest for a non-enzymatic system.

Scheme



Reagents and Conditions: a) $(CH_2O)_n$/180 °C/4 h (80%)(ref. 13); b)TsCl, NEt_3 (93%); c) Et_2NH/THF/65 °C/16 h (83%); d) 9-BBN/neat/65 °C/6 h; e) t-BuLi/ –78° - 25 °C/THF/pentane; f) –100 °C, 3 h; g) H_2O_2/NaOH.

Reagent **9** with increased steric bulk of the amino alkyl groups provided no advantage over reagent **8** for the reduction of 2-octanone but showed some improvement for the reduction of acetylcyclohexane. Unlike reagent **4**, increasing the steric bulk of the alkyl group on the nitrogen atom from ethyl to *i*-butyl did not change the direction or the degree of selectivity. This shows that the change in ee occurs when the manipulation of the steric environment occurs closer to the 2-position of apopinene, supporting Brown's hypothesis.[9]

Determining **8** as the reagent of choice for the reduction of aliphatic straight-chain ketones, the reductions of 2-nonanone (69% ee) and 2-heptanone (65% ee) were performed at –78 °C to ensure the general utility of this reagent.

The original methodology[7] for the reductions employing NB-Enantride involved adding a dilute solution of the reagent (0.2 *M*) prechilled to –78 °C to a dilute solution (0.1 *M*) of the ketone stirred at –100 °C. While the majority of the reductions reported herein were performed using this technique,[14] we subsequently found that, in a representative case (reduction of 2-octanone at –78 °C with reagent **8**), the addition of neat ketone at ambient temperature to a 0.4 *M* solution[15] of the chilled reagent provides the alcohol of the same ee as using the original methodology. The modification makes these reagents more practical.

While we are not well versed as to the exact mode of action of these chiral lithium borohydrides, it is clear that the steric requirement of the organic groups at the 2-position of the apopinene skeleton plays a major role in the stereoselectivity of the reduction. It is noteworthy that these chiral auxiliaries are easily synthesized from inexpensive, commercially available starting materials.

We are continuing our studies of the reagents derived from *N, N, N*-myrtenyldialkylamines containing alkyl groups of varying steric requirements to develop the best reagent for the chiral reduction of straight chain aliphatic ketones.

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10. The pinene-based auxiliaries in reagents **2-4** were prepared from commercially available (–)-myrtenol (92% ee) as follows: myrtenyl methyl ether: with NaH and methyl iodide using the methodology described in ref. 7; myrtenyl amines: reaction of myrtenyl tosylate with the appropriate dialkylamine as noted in the Scheme of this manuscript.
11. Physical properties for compound **11**: bp 65 °C (0.1 mmHg); mp of HCl salt (THF) 141-142 °C. ^{13}C NMR of **11** ($CDCl_3$): 147.04 (C_2); 116.90 (C_1); 51.09 (C_{11}); 46.84 ($N\underline{C}H_2CH_3$); 46.07 (C_3); 40.81 (C_5); 37.93 (C_7); 34.17 (C_{10}); 31.65/31.27 (C_4 or C_6); 26.31 (C_8); 21.18 (C_9); 11.87 ($NCH_2\underline{C}H_3$).
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14. Improved methodology: 2-octanone (0.47 ml; 3.0 mmol) was added dropwise to a stirred solution of reagent **8** (11.0 ml; 0.40*M* in THF/pentane; 4.0 mmol) maintained at –78 °C. The resulting mixture was stirred at this temperature for 2 h at which time 0.3 ml of methanol was added dropwise to quench the reaction (Our work shows that methanol rapidly and quantitatively reacts with these borohydrides at –78 °C as measured by hydrogen evolution). The flask was warmed to 0 °C, carefully oxidized by the addition of 3 ml of 3N NaOH and then 1 ml of 30% H_2O_2 and then warmed to 50 °C for 1 h. The contents of the flask were saturated with K_2CO_3 and the organic layer decanted. The K_2CO_3 mass was triturated with ethyl ether and the organic layers combined, successively washed with 5% HCl, 10% $NaHCO_3$ and brine, and dried over magnesium sulfate. The volatiles were evaporated and the residue distilled to give 0.28 g of 2-octanol (71%). Capillary GC analysis (SPB™-5 column; 150 °C) of the Mosher ester indicates the presence of 88.5% (*S*)-isomer and 11.5% (*R*)-isomer (77% ee).
15. Approximate maximum solubility in THF/pentane at –78 °C.

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