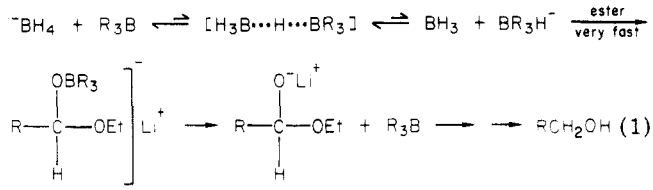

rate would be retarded, as observed (Table I).

This procedure offers a simple mild conversion of esters to alcohols. The selective reduction of the ester group in the presence of reducible groups appears to be readily achieved. Consequently, this development markedly enhances the utility of the reagent, $LiBH_4$, for the convenient reduction of esters and their selective reduction in the presence of many reducible functional groups. The full scope of such selective reductions is currently under investigation.

Acknowledgment. We thank the U.S. Army Research Office (ARO DAAG-29-79-C-0027) for financial support of this study.

Registry No. $LiBH_4$, 16949-15-8; LiH-9-BBH, 76448-08-3; $LiEt_3BH$, 22560-16-3; $LiB(OMe)_2$-9-BBN, 81095-46-7; $LiEt_3BOMe$, 81130-65-6; B-OMe-9-BBN, 38050-71-4; BF_3·OEt_2, 109-63-7; BH_3·THF, 14044-65-6; Bu_3B, 122-56-5; $OctB(OMe)_2$, 81044-43-1; $(MeO)_3B$, 121-43-7; $(PhO)_3B$, 1095-03-0; $(DodO)_3B$, 2467-15-4; ethyl caproate, 123-66-0; ethyl benzoate, 93-89-0; ethyl pivalate, 3938-95-2; methyl stearate, 112-61-8; ethyl cyclohexanecarboxylate, 3289-28-9; ethyl 1-adamantanecarboxylate, 2094-73-7; ethyl 4-chlorobenzoate, 7335-27-5; ethyl 3-chloropropionate, 3938-95-2; ethyl 4-nitrobenzoate, 99-77-4.

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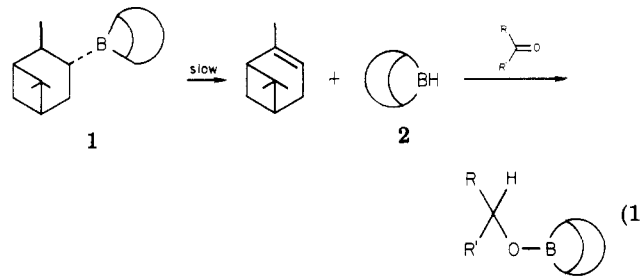
Improved Procedure for the Asymmetric Reduction of Prochiral Ketones by *B*-(3-Pinanyl)-9-borabicyclo[3.3.1]nonane

Summary: An improved experimental procedure gives good optical induction in the reduction of nonacetylenic prochiral ketones, using the chiral trialkylborane *B*-(3-pinanyl)-9-borabicyclo[3.3.1]nonane (Midland's reagent).

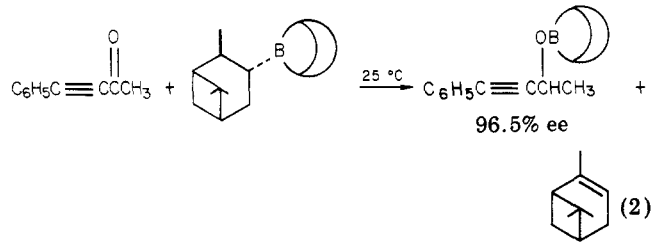
Sir: Recently, *B*-(3-pinanyl)-9-borabicyclo[3.3.1]nonane (1) was shown to be a very useful chiral reducing agent for the reduction of aldehydes and acetylenic ketones.[1] In addition to giving excellent chemical yields and optical induction, the reagent has several advantages in being readily available in both *d* and *l* forms, requiring mild reaction conditions and simple workup procedures, while exhibiting high chemoselectivity (many other readily reducible functionalities are tolerated).

However, the reagent is not useful for the reduction of simple, nonacetylenic ketones, possibly of even greater interest. The difficulty in this case apparently arises from the very slow reaction at room temperature under such conditions. The usual reduction by a cyclic mechanism is replaced by an alternate mechanism involving a prior dissociation of the reagent (eq 1). Reduction of the ketone



by the dissociation product, 9-borabicyclo[3.3.1]nonane (9-BBN, 2), produces inactive product. Increasing the temperature as a means of enhancing the rate of reaction is self-defeating, since it leads to enhanced dissociation of the reagent.[2]

It occurred to us that it should be possible to increase the rate of reaction as well as to minimize the undesirable dissociation by carrying out the reaction in more concentrated solutions. Accordingly, we carried out the reduction of 4-phenyl-3-butyn-2-one (3, eq 2) in a 2 M THF solution



(the original workers had used a 0.5 M solution of 9-BBN in THF to prepare the reagent and slightly more dilute solutions for the actual reductions). The reaction went to completion in ~20 h (as against 48 h in the original procedure) and the alcohol obtained had a specific rotation of +69.6°, substantially higher than the value of +51.8° achieved by Midland and co-workers in their original procedure.[1] This specific rotation of the alcohol represents an optical purity of 96.5% on the basis of Midland's value of 51.8° for 72% ee. Since we had started with α-pinene of 92% ee, this value appears to be a little high. This discrepancy may be due to the fact that Midland and co-workers used NMR shift reagents to determine optical purity and the rotation reported by them may be a little low. Encouraged, we then tried the neat reagent. In this case, the reaction went to completion in ~8–12 h, using only 40% excess reagent, and the alcohol obtained had the same optical purity as the one from the 2 M THF reaction.

Encouraged by this result, we applied this procedure (neat conditions) to the reduction of acetophenone and other representative aliphatic ketones (eq 3–5). In most cases, using 100% excess reagent, the reaction went to completion in 7–10 days at room temperature. Moderate to good optical induction was realized (all results reported are for reagent from 92% ee α-pinene). Thus, acetophenone was reduced to α-methylbenzyl alcohol in an enantiomeric excess of 78%. In the aliphatic series, 2-

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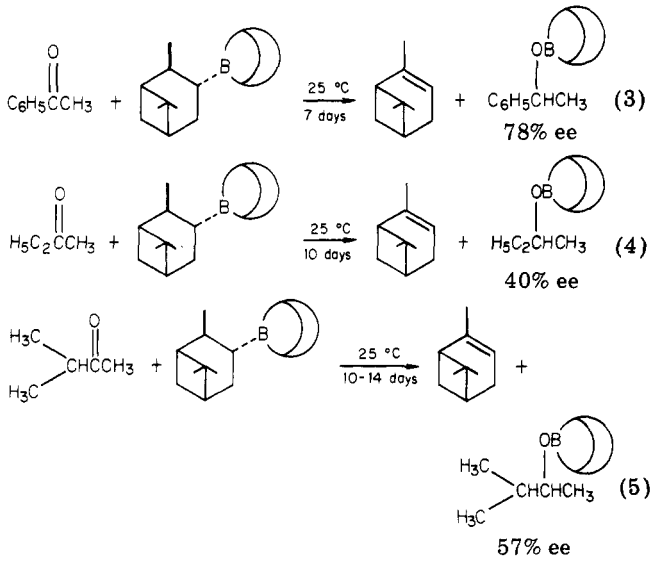
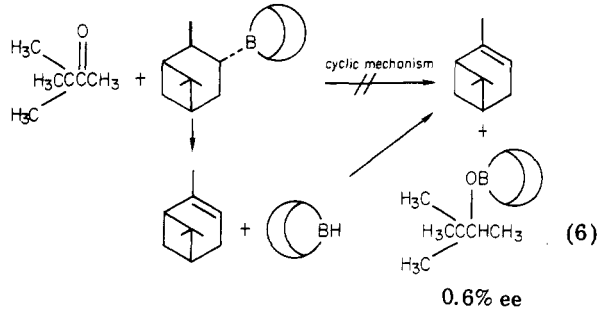
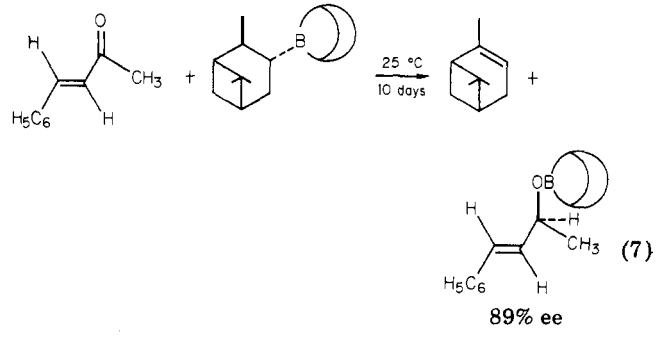


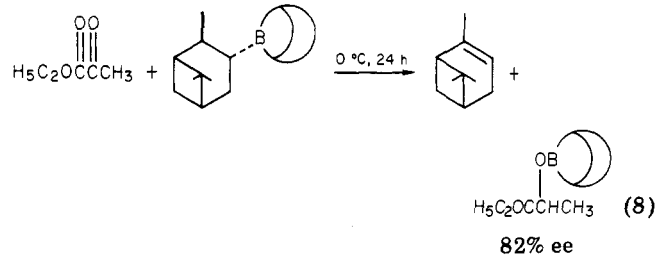
butanone and 2-octanone are reduced to the corresponding alcohols in 40% ee and 44% ee, respectively. Increasing the steric inequality of the alkyl groups attached to the carbonyl group, as in 3-methyl-2-butanone (eq 5), increases the optical induction to 57% ee. However, a further differentiation suddenly reverses this trend, so that with 3,3-dimethyl-2-butanone, only 0.6% optical induction is realized. The reduction proceeds very slowly in this case (60% reaction in 40 days at 25 °C). Presumably, the major portion of the reaction goes via the dissociation mechanism (eq 6).



Next, we tried our method for the chiral reduction of α,β-unsaturated ketones. In comparison to acetylenic ketones, these are reduced relatively slowly. Nevertheless, excellent optical induction was realized in the reduction of *trans*-4-phenyl-3-buten-2-one (eq 7). Somewhat lower enantiomeric excess was achieved for 1-acetyl-1-cyclohexene, 59% ee.



Lastly, the reagent seems to offer good prospects for the chiral reduction of α-keto esters. Thus, ethyl pyruvate is reduced rapidly at 25 °C to ethyl lactate in 76% optical yield. The rate was sufficiently rapid as to make it practical to carry out the reaction at 0 °C, achieving a further improvement in optical yield (eq 8). These experimental results are summarized in Table I.



The following experimental procedure is typical. An oven-dried, 50-mL, round-bottom flask equipped with a septum-capped side arm, magnetic stirring bar, reflux condenser, and stopcock adaptor was cooled to room temperature in a stream of nitrogen. The flask was charged with 2.5 g of solid 9-BBN (20 mmol) and 3.5 mL (22 mmol) of (+)-α-pinene ($[\alpha]^{25}_D$ +47.3°, 92% ee, distilled from $LiAlH_4$) was added to the flask. The flask was heated in an oil bath to 65 °C for 5 h. A ^{11}B NMR at the end of this period revealed only the R_3B peak (+80 ppm). The flask was cooled to room temperature and 1.17 mL of acetophenone (10 mmol) was injected into the flask. The contents of the flask were stirred at room temperature. The reaction was followed by low-temperature GC analysis on a 6 ft × 0.25 in. DC-710 on Chromosorb W column. Comparison of the amount of α-pinene formed and acetophenone remaining gave a good idea of the progress of reaction. After 7 days, the flask was cooled to 0 °C and 1 mL of acetaldehyde was added to destroy the excess reagent. Liberated α-pinene was pumped off at 40 °C (0.01 mm) and the residue dissolved in 10 mL of ether. The solution was cooled to 0 °C and 1.32 mL (22 mmol) of ethanolamine was added to remove the 9-BBN moiety. The white solid was separated by filtration and washed twice with cold ether. The combined filtrate and washings were washed twice with brine and dried over sodium sulfate, and the ether was evaporated with a rotary evaporator. The oil so obtained was distilled with a short-path condenser to give 0.85 g of an oil. GC analysis (6 ft × 0.25 in., 10% Carbowax 20M on Chromosorb W-AW-DMCS) showed that it was >98% pure. It was further purified by preparative gas chromatography and the rotation taken: $[\alpha]^{25}_D$ −35.6° (*c* 5.19, methanol). This represents an optical purity of 78%. The alcohol gave ^1H NMR and IR spectra identical with those for an authentic sample. *B*-(3-pinanyl)-9-BBN is now available from the Aldrich Chemical Co. as the product "Alpine Borane".

We believe that the chemical yields approach 100% with losses primarily involved in the isolations. In a number of the preparations we made, no attempt to maximize the chemical yields reported in Table I.

In conclusion, our modified procedure retains all of the advantages of the original method while extending the scope and utility of the Midland reagent to the chiral reduction of a broad spectrum of carbonyl compounds other than aldehydes and acetylenic ketones.

Acknowledgment. The financial support of the National Institutes of Health, GM 10937-19, during the course of this work is gratefully acknowledged.

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Table I. Reduction of Prochiral Ketones with Neat *B*-(3-Pinanyl)-9-borabicyclo[3.3.1]nonane (92% ee α-Pinene)

ketone	reaction condition: reagent, molar equiv	temp, °C	time	optically active alcohol: % yield	$[\alpha]_D$, deg	% ee: obsd, %	% ee: cor %	abs config[o]
3-butyn-2-one	1.4	25	4 h	80[a]	+37.7 (c 2.3, dioxane)	73[d]	79	
4-phenyl-3-butyn-2-one	1.4	25	4 h	95[b]	+69.9 (neat)	96.5[e]	105	
4-methyl-1-pentyn-3-one	1.4	25	8-12 h	87[a]	+14.6 (c 2, dioxane)	91[f]	99	
trans-4-phenyl-3-buten-3-one	1.4	25	10 days	80[b]	−22.3 (c 5.2, $CHCl_3$)	89[g]	97	*S*
1-acetyl-1-cyclohexene	1.4	25	12 days	90[a]	−7.47 (c 4.15, $CHCl_3$)	59[h]	64	*S*
acetophenone	2	25	7 days	68[b]	−33.4 (neat)	78[i]	85	*S*
2-butanone	2	25	10 days	90[a]	−5.4 (neat)	40[j]	43	*S*
3-methyl-2-butanone	2	25	14 days	100,[a] 78[b]	+3.06 (neat)	57[k]	62	*S*
3,3-dimethyl-2-butanone	2	25	40 days	40[b,c]	+0.050 (neat)	0.6[l]	0.7	*S*
2-octanone	2	25	7 days	65[b]	+4.12 (neat)	44[m]	48	*S*
ethyl pyruvate	1.4	25	4 h	50[b]	−8.83 (neat)	76[n]	83	*S*
ethyl pyruvate	1.4	0	24 h	50[b]	−9.43 (neat)	82[n]	89	*S*

[a] GC yield. [b] Isolated yield. [c] Reaction was only 70% complete. [d] Based on calculated $[\alpha]_D$ (max) 52° (c 2.3, dioxane).[3] [e] Based on calculated $[\alpha]_D$ (max) 71.9° (neat). [f] Based on calculated $[\alpha]_D$ (max) 16° (c 2, dioxane).[3] [g] Based on calculated $[\alpha]_D$ (max) 25° (c 5.16, $CHCl_3$).[4] [h] Based on calculated $[\alpha]_D$ (max) 12.6° (c 4.15, $CHCl_3$).[4] [i] Based on $[\alpha]_D$ 42.85° (neat).[5] [j] Based on $[\alpha]_D$ 13.5° (neat).[6] [k] Based on $[\alpha]_D$ 5.34° (neat).[7] [l] Based on $[\alpha]_D$ 8.1° (neat).[8] [m] Based on $[\alpha]_D$ 9.57° (neat). [n] Based on $[\alpha]_D$ 11.5° (neat). [o] Based on the literature cited and W. Klyne and J. Buckingham, "Atlas of Stereochemistry", Oxford University Press: New York, 1974.

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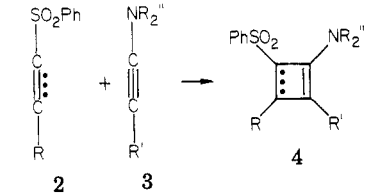
[2 + 2] Cycloadditions of Ynamines with α,β-Unsaturated Sulfones: Approach to Versatile Four-Membered Carbocyclic Intermediates[1]

Summary: The interaction of ynamines with various α,β-unsaturated sulfones, such as 1-alkenyl, 1-alkynyl, or 1,3-alkadienyl sulfones, leads to the ready formation of the vicinally amino- and sulfonyl-substituted cyclobuta ring in a regiospecific manner. The resulting cyclobutenamines can be hydrolyzed to the corresponding α-sulfonylcyclobutanones, which can, in turn, be alkylated or desulfonylated to yield substituted cyclobutanones.

Sir: Vinylic sulfones have been recognized recently as versatile synthons, both for the construction of three- and six-membered carbocycles[2,3] and for the generation of (α-sulfonylvinyl)lithium[4] and (α-sulfonylalkyl)lithium[5] reagents. As a dienophile in [4 + 2] cycloadditions, phenyl vinyl sulfone has been shown to an excellent ethylene equivalent. The resulting cyclohexenyl sulfones can be sequentially alkylated and desulfonylated to provide 4-alkyl-1-cyclohexenes selectively and in high yield.[3]

In our further studies on the utility of vinylic sulfones in synthesis,[1] we have now found that a wide variety of α,β-unsaturated sulfones undergo [2 + 2] cycloaddition reactions with ynamines to form four-membered carbocycles readily. Although thiete 1,1-dioxide (**1**) had previously been reported to undergo [4 + 2] and [2 + 2] cycloadditions with enamines and ynamines,[6] we have found that such [2 + 2] cycloadditions are not restricted to strained vinylic sulfones, such as **1**, but are general for vinylic, acetylenic, and 1,3-dienylic sulfones (eq 1). As



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vinylic sulfone participants, phenyl vinyl sulfone (**2a**), phenyl (*E*)-β-styryl sulfone (**2b**), (*E*)-(methoxycarbonyl)-ethenyl phenyl sulfone (**2c**), benzothiophene 1,1-dioxide (**2d**), and 2-sulfolene (**2e**) reacted readily with the ynamines **3**, *N*,*N*-diethyl-1-propynylamine (**3a**) and *N*-ethynylmorpholine (**3b**). Depending on the specific sulfone, the cycloaddition proceeded between 25 and 80 °C, either in methylene chloride solution or without solvent. The acetylenic sulfones, phenyl 1-propynyl sulfone (**2f**) and phenyl phenylethynyl sulfone (**2g**), reacted with **3a** even more readily than their vinylic counterparts. Finally, it is noteworthy that 1,3-butadien-1-yl phenyl sulfone (**5**)

(1) Part 4 of the series "Sulfone Reagents in Organic Synthesis"; for previous parts, see *J. Org. Chem.* **1979**, *44*, 3277, 3279; **1980**, *45*, 4534.
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