Chart II

15 R = CH=CH$_2$
16 R = CHO
17 R = CH=CHCO$_2$Et

18 X = OMe, R = Et
24 X = H, R = tBu

19 X = OH, R = CH(OCH$_2$CH$_2$O)
20 X = N⟨⟩, R = CH(OCH$_2$CH$_2$O)

21 R = CH(OCH$_2$CH$_2$O)
22 R = CHO
23 R = CH=CHCO$_2$tBu

cyclization of **23** gave a 7:1 mixture of diasteromeric perhydroindans (93%) with **24** as the major stereoisomer.[9,17,22]

In summary, reductive alkylation of benzoic acid derivatives followed by iodolactonization and free radical cyclization affords an efficient new route to perhydroindans. The radical cyclizations proceed with modest to excellent steroselectivity, a major concern with using free radical carbon–carbon bond-forming reactions in the synthesis of complex molecules. Applications of this protocol to synthesis of carbocyclic natural products as well as studies directed toward understanding features that govern exo–endo partitioning of radicals of type **4** are currently being addressed.[23]

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Registry No. **1**, 99-04-7; **2**, 85585-43-9; **3**, 85585-44-0; **5**, 85585-45-1; **6**, 85585-46-2; **7**, 85647-17-2; **8**, 85585-47-3; **9**, 85585-48-4; **10**, 85585-49-5; **11**, 35000-38-5; **12**, 85585-50-8; **13**, 85585-51-9; 7β-**13**, 85612-02-8; **14**, 85585-52-0; **15**, 85585-53-1; **16**, 85585-54-2; **17**, 85585-55-3; **18**, 85585-56-4; 7β-**18**, 85647-18-3; **19**, 85585-57-5; **20**, 85585-58-6; **21**, 85585-59-7; **22**, 85585-60-0; **23**, 85585-61-1; **24**, 85585-62-2; 7β-**24**, 85647-19-4; 4-bromo-1-butene, 5162-44-7; 1-bromo-3,3-dimethoxypropane, 36255-44-4; 1-(3,3-dimethoxypropyl)-3-methylcyclohexa-2,5-dienoic acid, 85585-63-3; *m*-anisic acid, 586-38-9; benzoic acid, 65-85-0; 2-(2-bromoethyl)-1,3-dioxolane, 18742-02-4.

Supplementary Material Available: Procedures for the preparation of **9**, **10**, **12**, and **13** (3 pages). Ordering information is given on any current masthead page.

(22) Lactone **24** was converted to demethyl-**14** (72%; mp 111–112 °C) via the same reaction sequence used to convert **13** to **14**.

(23) Preliminary experiments have shown that the radicals derived from **15** and *rel*-(1*S*,5*S*,8*S*)-1-(3-buten-1-yl)-8-iodo-6-oxabicyclo[3.2.1]-oct-2-en-7-one display endo–exo partitioning similar to that observed for **4**.

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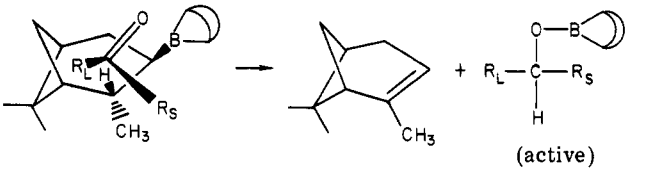
Asymmetric Reduction of Prochiral α-Halo Ketones with *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane

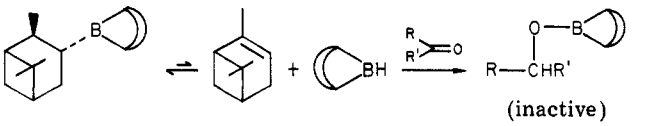
Summary: *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane reduces aryl α-haloalkyl ketones to the corresponding halohydrins in nearly quantitative chemical yield and high optical induction. This reagent yields somewhat lower optical induction in the case of the aliphatic analogue, 1-bromo-3-methyl-2-butanone. The halohydrins can be converted to the corresponding chiral epoxides or dehalogenated to the parent alcohol with retention of optical activity.

Sir: In the last couple of years, *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (**1**, Midland's reagent) has emerged as an exceptionally valuable reagent for the asymmetric reduction of various carbonyl compounds.[1-3] The reagent embodies attractive features such as ready availability[4] in both *d* and *l* forms, a mild and simple experimental procedure, and enzyme-like selectivity in many instances. Whereas the reduction proceeds rapidly with aldehydes and acetylenic ketones, the reaction time is often inconveniently long for other cases such as simple ketones. We discovered that the use of neat reagents or concentrated solutions overcomes this difficulty in many cases, making the Midland procedure more general.[3]

Midland and co-workers have shown that electron-withdrawing substituents on the carbonyl compound increase the rate of reduction.[1,5] We have also observed that ester[3,6] or cyano[7] groups attached directly to the carbonyl function bring about a major increase in the rate of reduction. Although not necessarily true in all cases, usually an enhanced reduction rate also increases the optical induction since it favors the cyclic mechanism (eq 1) over



(active) (1)



(inactive) (2)

the dissociation mechanism (eq 2). We reasoned that an electron-withdrawing substituent such as halogen substituted α to the carbonyl group should also provide a similar rate increase and improved asymmetric induction. Moreover, the reduction products in this case would be halohydrins, readily converted to the valuable optically active epoxides or to the parent optically active alcohols.

Our expectation was realized in the reduction of α-bromoacetophenone (**2**). The reduction, using 100% excess

(1) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352.
(2) Midland, M. M.; McDowell, D. D.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.
(3) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1982**, *47*, 1606.
(4) Now commercially available from Aldrich Chemical Co. under the name Alpine-borane.
(5) Midland, M. M.; Zderic, S. A. *J. Am. Chem. Soc.* **1982**, *104*, 525.
(6) Midland and co-workers have observed similar effect in the reduction of methyl benzoylformate. Private communication from Dr. Midland.
(7) Unpublished results. Experiment in progress.

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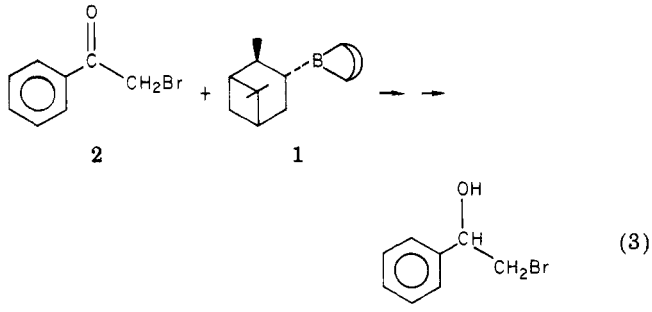
Table I. Reduction of α-Halo Ketones with Neat *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane at 25 °C Using 100% Excess Reagent

ketone	time, days	yield,[c] %	% optical induction: obsd	% optical induction: corr to 100% ee α-pinene	abs config
α-chloroacetophenone	6-8	91	88.5[d]	96.2	*R*
α-bromoacetophenone	4	95	86[e]	93	*R*
α-iodoacetophenone	2	60	86[e]	93	*R*
α,*p*-dibromoacetophenone[a]	3	95	88[f]	96	*R*[i]
α-bromo-*p*-cyanoacetophenone[a]	2-3	60	88[f]	96	*R*[i]
α-bromo-2′-acetonaphthone[a]	3-4	90	83[g]	90	*R*
α,α,α-trifluoroacetophenone	45[b]	57	32[d,h]	35	*R*
1-bromo-3-methyl-2-butanone	14	60	61[f]	66	*R*[i]
3-bromo-3-methyl-2-butanone	nr				

[a] Reaction carried out in ~5 M THF solution. [b] Reaction went to 90% completion. [c] Isolated yield of >96% pure material. [d] By comparison of specific rotation with literature value.[14] [e] By conversion to styrene oxide and comparison of its specific rotation with literature value.[12] [f] By the ^{19}F NMR analysis of MTPA esters.[15] [g] By debromination and comparison of the rotation of alcohol with literature value.[16] [h] Reference 17. [i] Absolute configuration not known but probably *R*. [j] No reaction.

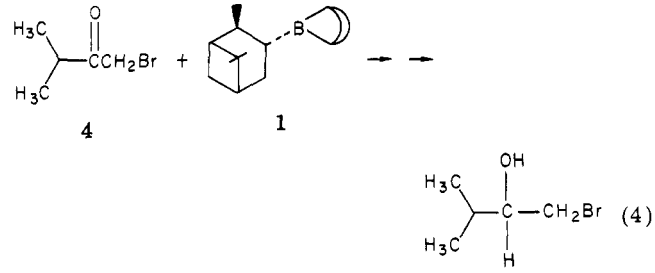
reagent (derived from 92% ee (+)-α-pinene), without any solvent, went to completion in 4 days (eq 3). The bromohydrin **3** was isolated in 95% yield and 86% ee by the simple ethanolamine procedure for the removal of the 9-BBN moiety.[8] The optical purity and configuration of the bromohydrin **3** were established from known literature values and also by conversion to (*R*)-styrene oxide (3 M NaOH, ether–pentane–water, 15 min at 25 °C), as well as to (*S*)-1-phenylethanol (lithium triethylborohydride, 24 h at 25 °C). In order to determine which halogen had the most suitable characteristics as the activating group, we studied the reduction of α-chloro- and α-iodoacetophenones. Due to poor solubility of the former in the neat reagent, the reaction took about 6 days for completion. Nevertheless, the chlorohydrin was obtained in 91% yield and 88.5% ee. α-Iodoacetophenone, on the other hand, was more soluble in the reagent and the reduction required only 2 days. The reaction, unfortunately, was accompanied by some deiodonation, and the yield of iodohydrin was only 60% (86% ee). In every case, treatment of the halohydrins with alkali gave (*R*)-styrene oxide. Since *R* halohydrins give *R* epoxides, this establishes the configuration of the starting halohydrins as *R*. One might notice that the cyclic mechanism of reduction (eq 1), proposed by Midland,[1] correctly predicts this configuration (the bulky phenyl group comes over the α-pinene ring).



2 1 3 (95% yield, 86% ee, *R*) (3)

The reduction of some other ketones such as α,*p*-dibromoacetophenone (Table I) did not proceed in neat reagent because they were almost completely insoluble. In such cases the reaction was carried out in highly concentrated (~5 M) partially heterogeneous THF solutions. Judging from the results, this modified procedure was not detrimental and the corresponding bromohydrins were obtained in excellent optical purity (88% ee in this case).

The results proved less satisfactory in other cases. Thus, the reduction of 1-bromo-3-methyl-2-butanone (**4**) under neat conditions required almost 14 days, and the corresponding bromohydrin **5** was obtained in only 61% ee (eq 4). The other isomer of **4**, 3-bromo-3-methyl-2-butanone, failed to react. Similarly, the reduction of α,α,α-trifluoroacetophenone was extremely slow, requiring almost 45 days to achieve ~90% completion. The product exhibited a disappointing 32% optical induction. The slow reaction may be either due to the steric bulk of the trifluoromethyl group or its powerful electron-withdrawing capacity. The former might make it difficult for the reagent to approach the substrate while the latter might prevent the complexation between the reagent and the ketone by depleting the electron density at the oxygen atom of the carbonyl group.



4 1 5 (61% ee) (4)

Lastly, we carried out the reduction of α-bromoacetophenone with the Midland reagent derived from both (+)- and (−)-α-pinene of nearly 100% optical purity.[9] The results showed that one can indeed extrapolate the results obtained with the 92% ee α-pinene to calculate the optical induction values that can be realized with reagent of 100% ee.

The bromohydrin **3** is a convenient intermediate for the preparation of various β-dialkylamino alcohols via styrene oxide. By a slight modification of the procedure reported in the literature[10] for the synthesis of racemic Ubine, we converted our styrene oxide to (−)-*N*,*N*-dimethyl-β-hydroxy-β-phenethylamine (**6**, Ubine, eq 5). The alkaloid had an optical purity of 88.9% ee (93% chemical yield) with a configuration corresponding to the natural product.

In conclusion, our studies extend the application of the Midland reagent to yet another class of carbonyl com-

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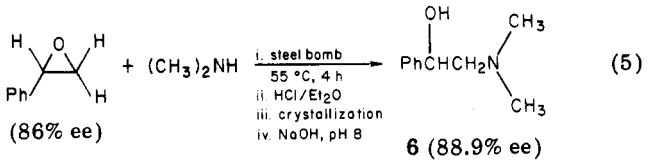

(5)

pounds. The halohydrins so formed constitute valuable synthons, as demonstrated by the synthesis of the natural product, Ubine, in high optical purity.

The following experimental procedure is typical.

An oven-dried 50-mL round-bottom flask, equipped with a side arm, magnetic stirring bar, and connecting tube, was cooled to room temperature in a stream of nitrogen. The flask was charged with 2.44 g of solid 9-BBN (20 mmol), and 3.5 mL of (+)-α-pinene ($[\alpha]^{23}_D$ 47.3°, 92% ee) was injected. The flask was heated at 65 °C for 5 h to complete the hydroboration. The flask was cooled to 25 °C, and 1.99 g of α-bromoacetophenone (10 mmol) was added to it under a stream of nitrogen. The reaction mixture was initially heterogeneous but became homogeneous as the reaction progressed. The reaction was followed by ^{1}H NMR by monitoring the disappearance of the -C(O)CH_2Br proton and the appearance of α-pinene and the >B—OCHCH_2Br protons. After 4 days, acetaldehyde was added to destroy excess reagent, and the liberated α-pinene was pumped off at 40 °C (0.01 mm). Anhydrous ether (25 mL) was added to the flask, it was cooled to 0 °C, and 1.32 mL of ethanolamine (22 mmol) was added. After 15 min, the ethanolamine adduct was removed by filtration through a sintered-glass funnel. The precipitate was washed twice with cold ether. The combined filtrate was washed with brine and dried over magnesium sulfate, and the ether was removed on a rotary evaporator. The oil so obtained was distilled by using a Kügelrohr oven at 100 °C (0.01 mm): yield, 1.9 g (94.5%); GC analysis showed it to be >96% pure; ^{1}H NMR (CCl_4) δ 3.1–3.6 (complex, 3 H; one proton exchanges with D_2O), 4.6–4.9 (dd, 1 H), 7.1 (br, 5 H). A part of the compound was purified further by MPLC and distilled: $[\alpha]^{25}_D$ −33.54° (c 5, $CHCl_3$), 86%[11] ee (93% ee for 100% α-pinene).

The bromohydrin was converted to styrene oxide in quantitative yield by treating with an equimolar amount of 3 M aqueous sodium hydroxide in a two-phase system containing ether and pentane. It was further purified by MPLC and distilled: $[\alpha]^{23}_D$ 40.2° (c, 1.05, benzene); 86% ee, R.[12]

The bromohydrin was converted to 1-phenylethanol by treatment with 3 molar equiv of lithium triethylborohydride in THF. The alcohol was purified by preparative GC on an SE-30 column: $[\alpha]^{23}_D$ −36.3° (neat, l = 0.5 dm), 84.6% ee, S.[13]

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Registry No. 1, 64106-79-2; 2, 70-11-1; 3, 73908-23-3; 4, 19967-55-6; 5, 1438-12-6; 6, 34469-09-5; 9-BBN, 280-64-8; α-chloroacetophenone, 532-27-4; α-iodoacetophenone, 4636-16-2; α,p-dibromoacetophenone, 99-73-0; α-bromo-p-cyanoacetophenone, 20099-89-2; α-bromo-2′-acetonaphthone, 613-54-7; α,α,α-trifluoroacetophenone, 434-45-7; 3-bromo-3-methyl-2-butanone, 2648-71-7; α-(chloromethyl)benzenemethanol, 56751-12-3; α-(iodomethyl)benzenemethanol, 85611-59-2; p-bromo-α-(bromomethyl)benzenemethanol, 58777-84-7; p-cyano-α-(bromomethyl)benzenemethanol, 85554-13-8; α-(bromomethyl)-2-naphthalene, 85554-14-9; α-(trifluoromethyl)benzenemethanol, 10531-50-7; (R)-styrene oxide, 20780-53-4; (S)-1-phenylethanol, 1445-91-6; (+)-α-pinene, 7785-70-8.

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