Hydroboration/Intramolecular Reduction of Allyl Ketones with (Diisopinocampheyl)borane: A Convenient Synthesis of Enantiomerically Enriched 1,4-Diols

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Summary: The hydroboration of a variety of allyl ketones with (−)-(diisopinocampheyl)borane precedes a highly stereoselective intramolecular reduction of the ketone, providing a convenient procedure for the preparation of enantiomerically enriched alcohols.

We recently reported a procedure for the preparation of enantiomerically enriched secondary alcohols using keto boronate ester substrates.[2] That procedure allowed the construction of nonracemic alcohols from ketone precursors in which there was little steric or electronic differentiation between the alkyl substituents flanking the carbonyl functional group. Enantiomerically pure (4-ketoalkyl)boronates were used as substrates, and it was hypothesized that these formed kinetically active cyclic complexes that underwent stereoelectronically controlled, intermolecular attack by a reducing agent, providing the desired products. While the mechanistic interpretation agreed with the experimental results obtained in that study, it was not possible to detect the postulated boronate/ketone intramolecular complex spectroscopically.[3] In order to increase the likelihood of observing an intramolecular Lewis acid/Lewis base complex of this type, replacement of the boronate ester by a stronger Lewis acid, such as a trialkylborane, was contemplated. Switching to a stronger Lewis acid component could not only provide greater opportunities for detection of intramolecular complexes, but could furnish substantial synthetic advantages as well. For example, use of a stronger Lewis acid could provide enhanced activation of the carbonyl, thereby permitting use of less reactive nucleophiles in the carbonyl addition reaction. Furthermore, a stronger B–O interaction was anticipated to "tighten" the transition structure leading to product. This would have the effect of magnifying important steric effects in the transition state, thereby enhancing stereoselectivity. Of particular interest in this regard was the possibility that readily available, nonracemic organoboranes could be utilized as an entry to enantiomerically enriched alcohols.

With these goals in mind, 1-nonen-4-one (**1a**) was treated with 1 equiv of (−)-diisopinocampheylborane [(−)-$(IPC)_2$BH, prepared from (1*R*,5*R*)-(+)-α-pinene] in THF at 0 °C.[4] The solvent was removed after an appropriate amount of time, and an IR spectrum was taken to determine the nature of the intermediate generated. Somewhat surprisingly, the resulting clear oil did not exhibit an IR signal in the region typical of a carbonyl stretch. The ^{11}B NMR spectrum of this oil indicated the complete disappearance of the starting dialkylborane and the formation of a new compound with a ^{11}B peak centered at 57 ppm, a typical ^{11}B resonance for a borinate ester (R_2BOR).[5] The ^{13}C NMR spectrum of this oil (C_6D_6) revealed the presence of a methine carbon atom (CH, determined by APT) attached to an oxygen (δ 75.49). When this oil was subjected to sodium perborate oxidation[6] followed by flash chromatography, (*R*)-1,4-nonanediol was isolated in 98% yield and 96% ee.[7] This unexpected result prompted an examination of the rate of disappearance of the ketone during the hydroboration process. By doing this, it was determined that (+)-α-pinene was formed at approximately the same rate as the ketone disappeared.

That the enantioselectivity is not a result of an initial reduction of the carbonyl by (−)-$(IPC)_2$BH is clear from at least two lines of evidence. First, both IPC_2BH and $IPCBH_2$ (which, in principle, could be present in the reaction mixture) reduce ketones with only low levels of enantioselectivity (9–46% ee's).[8] Secondly, we[9] and others[10] have observed that hydroboration of unhindered olefins takes place much more rapidly than carbonyl reduction. Thus, both monoalkylboranes and dialkylboranes can be utilized to hydroborate a terminal olefin selectively in the presence of a ketone.

Even though it seemed evident that hydroboration was occurring first, there were still at least two means by which the ketone could be reduced intramolecularly to provide the observed product. At this point the preferred mechanism is an intramolecular version of the trialkylborane (Midland) reduction, wherein a concerted reduction of the carbonyl takes place with release of (+)-α-pinene (Scheme 1).[11] This mechanism is also analogous to intramolecular versions of the Meerwein–Ponndorf–Verley reaction.[12] That the trialkylborane initially generated could take part in such a facile (0 °C, THF solution, ambient pressure, 1.5 h) intramolecular reduction is at first somewhat surprising. By comparison, the bimolecular reaction of neat Alpine-Borane with various ketones typically requires at least 7 days at room temperature to proceed to completion, and even at 6000 atmospheres of pressure reaction times are typically at least 1 day.[11] Entropic factors associated with the intramolecularity of

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(3) The lack of direct physical evidence for the existence of a boronate/ketone complex is not unique. For additional reports of high stereochemical control via postulated (but unobserved) boronate complexes see: (a) Chen, K. M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923. (b) Matteson, D. S.; Michnick, T. J.; Willett, R. D.; Patterson, C. D. *Organometallics* **1989**, *8*, 726. (c) Hoffmann, R. W.; Wolff, J. *Chem. Ber.* **1991**, *124*, 563, and references therein. (d) Molander, G. A.; Bobbitt, K. L. *J. Am. Chem. Soc.* **1992**, *114*, 2759.

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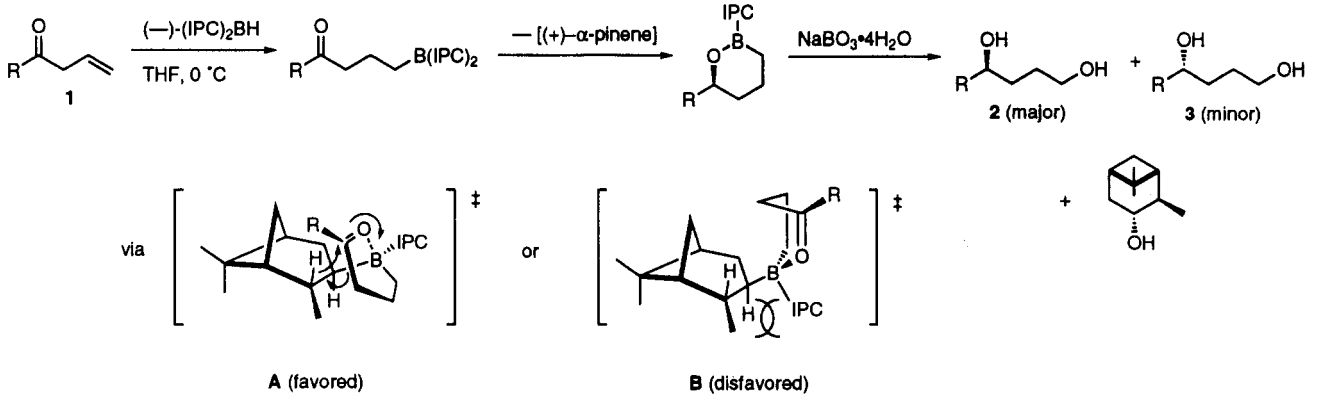
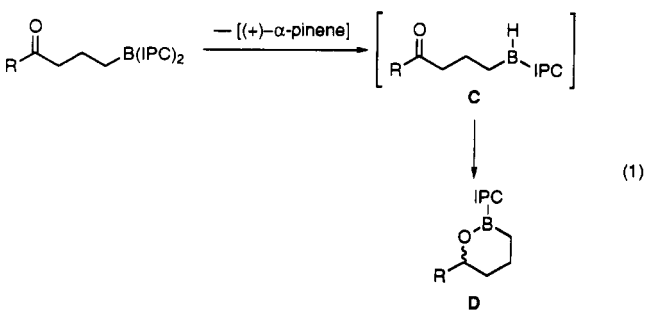
Scheme 1



the current process might explain the dramatic increase in reaction rates relative to the intermolecular version of the reaction. Midland and co-workers have determined that in related intermolecular reactions the entropies of activation for reductions using *B-n*-octyl-9-BBN were about −45 cal deg^{-1} mol^{-1}.[13] The entropic advantages inherent in the current intramolecular reactions would not only favor the formation of a tight Lewis acid/Lewis base complex but in addition would provide a high effective concentration of this activated complex positioned ideally for the concerted, intramolecular reduction reaction.

Interestingly, this mechanism implies that, to a dramatic degree, only one of two limiting diastereomeric transition structures is involved. Thus, if the trialkylborane (IPC_2BR) intramolecularly complexes with the carbonyl (generating a tetrahedral boron), the two isopinocampheyl groups are no longer equivalent, but are in fact diastereotopic. Although the precise factors involved in the stereoselection are difficult to pin down, the favored transition structure (**A**) appears to minimize steric interactions and also provides close approach of the hydride to the carbonyl center. The alternative transition structure (**B**) likely incorporates steric interactions between the "dummy" isopinocampheyl group and the methyl substituent on the "active" isopinocampheyl group. This trialkylborane model thus appears to rationalize the high selectivity observed in these reactions.

A second mechanism cannot be completely ruled out, however. Thus, the initially generated trialkylborane could release (+)-α-pinene in a dehydroboration reaction, generating a dialkylborane. Rapid intramolecular reduction would provide the observed product (eq 1). Although



(1)

hindered alkyl(diisopinocampheyl)boranes are known to undergo dehydroborations,[8a,14] there is apparently no direct evidence for the rate of dehydroboration in trialkylboranes derived from terminal alkenes and IPC_2BH.[15]

However, on the basis of analogous trialkylboranes this process would appear to be too slow for the overall process described herein. Furthermore, we have examined the reaction of (monoisopinocampheyl)borane ($IPCBH_2$)[16] with substrate **1a** (eq 2).[9] After oxidation and conversion

(2)

to the (bis) Mosher ester, it was determined that in fact **3a** was the major enantiomer generated (only 11% ee). If, as anticipated, the hydroboration process occurred chemoselectively, then the same intermediate (**C**) would be involved in this process as that depicted in eq 1. The fact that **3a** was the major enantiomer generated when using $IPCBH_2$ for the hydroboration/reduction process thus implies that **C** cannot be involved in reactions involving IPC_2BH reductions. In spite of these arguments, further mechanistic studies appear warranted.

By whatever mechanism it takes place, this process represents a substantial simplification of the enantioselective boronate ester reduction process previously developed.[2,3d] Consequently, the reaction conditions were optimized and a preliminary study was carried out to determine the scope of the reaction.[17] A number of

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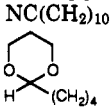
(17) Representative reduction procedure: In a 10-mL round-bottomed flask equipped with a magnetic stir bar and an argon inlet/outlet was placed 0.42 g (1.5 mmol) of (−)-diisopinocampheylborane [(−)-$(IPC)_2BH$ prepared from (1*R*,5*R*)-(+)-α-pinene] and 1 mL of THF. This heterogeneous mixture was placed in a 0 °C ice bath and stirred for 5 min, and then 0.14 g of 1-nonen-4-one (**1a**) (1.0 mmol) was added directly via a microsyringe. During the next 10 min, the colorless precipitate of (−)-$(IPC)_2BH$ slowly began to disappear, and the solution typically became homogeneous 30 min after the addition of the allyl ketone. The reaction was maintained at 0 °C for a total of 1.5 h at which time a TLC analysis indicated that the ketone had completely reacted. While the 0 °C reaction temperature was maintained, 1 mL of water and 0.77 g of sodium perborate tetrahydrate (5.0 mmol) were added to the THF solution. After this mixture was stirred for 30 min, the entire contents of the flask were transferred to a separatory flask with the aid of 25 mL of ether. Approximately 5 mL of water was added to the separatory funnel, and solid potassium carbonate was added until the aqueous layer became a thick paste. The organic layer was separated, the thick white aqueous paste was washed an additional five times with ethyl acetate, the organic layers were combined, dried over $MgSO_4$, and filtered, and the solvents were removed *in vacuo*. The resulting clear oil containing pinene, isopinocampheol, and the desired diol was subjected to flash column chromatography (60% ethyl acetate/hexane). Solvent removal followed by Kügelrohr distillation provided (*R*)-1,4-nonanediol (**2a**) in 98% isolated yield.

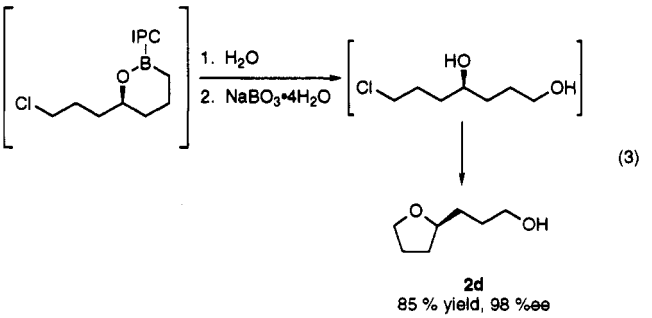
Table 1. Results of the Stereoselective Hydroboration/ Reduction of β,γ-Unsaturated Ketones 1a–1g with (−)-(IPC)$_2$BH

substrate	R	% isolated yield (2 + 3)[a]	enantioselectivity (% ee)[b]
1a	n-C_5H_{11}	98	96
1b	C_6H_{11}	91	87[c]
1c	C_6H_5	86	94
1d	$Cl(CH_2)_3$	85	98[a,d]
1e	$NC(CH_2)_{10}$	98	75
1f		88	86
1g	$CH_3O_2C(CH_2)_4$	94	88

[a] Refers to the yields of purified diol, except for 1d (see eq 2). All new compounds have been fully characterized spectroscopically (^{1}H, NMR, ^{13}C NMR, IR), and elemental composition has been established by combustion analysis and/or high-resolution mass spectrometry. [b] Determined by ^{19}F NMR of the crude Mosher diester unless otherwise specified. In all cases, the ^{19}F NMR spectra of the racemic and enantiomeric Mosher diesters have been measured to ensure adequate resolution in the ^{19}F NMR spectra. [c] Determined by 500-MHz ^{1}H NMR of the multiplet corresponding to the methylene protons adjacent to the primary ester (4.15–4.36 ppm). [d] Determined by capillary GC analysis of the menthyl carbonate derived from (−)-menthyl chloroformate.

polyfunctional substrates were tested to determine the compatibility of various functional groups to this reductive procedure. As can be concluded from the results outlined in Table 1, this procedure has been successfully applied to a number of diverse β,γ-unsaturated ketones. After oxidation of the cyclic borinate intermediates, diol products possessing high degrees of enantiomeric enrichment were isolated.

In addition to diverse reactions that might be carried out on the cyclic borinate ester intermediate (e.g., protonation, Suzuki-type coupling,[18] Matteson homologation,[19] and other processes[20]) the compatibility of functional groups on the β,γ-unsaturated ketones may provide direct routes to nitrogen heterocycles, cyclic hemiacetals, and lactones. For example, the basic oxidation procedure directly converts the cyclic borinate ester derived from substrate 1d into the tetrahydrofuran derivative (eq 3).



(3)

2d
85 % yield, 98 %ee

The present procedure emphasizes several important features of organoborane chemistry. It clearly indicates that olefins react with dialkylboranes much faster than with ketones. Although precedented, few general procedures have taken advantage of this selectivity.[10] Secondly, it accents the dramatic effect that intramolecularity has on the Midland reduction process and provides a means by which one can take advantage of this for the enantioselective synthesis of simple ketones. Finally, this procedure represents a substantial improvement in the synthesis of enantiomerically enriched 1,4-diols from readily available (both enantiomers) and inexpensive starting materials. Future investigations will be directed toward the greater understanding and further development of this simple, yet highly versatile, transformation.

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Supplementary Material Available: Complete experimental details and spectral data for the synthesis of compounds **1a–g** and **2a–g** (**3a–g**) (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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