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Efficient General Synthesis of 1,2- and 1,3-Diols in High Enantiomeric Excess via the Intramolecular Asymmetric Reduction of the Corresponding Ketoalkyl Diisopinocampheylborinate Intermediates[1]

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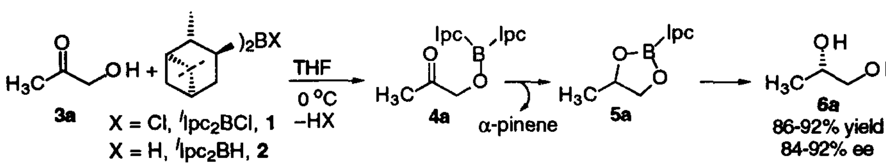
Abstract: The first successful asymmetric reduction of unhindered aliphatic ketones with *B*-chlorodiisopinocampheylborane is reported. In contrast to the reduction in high ee of aralkyl ketones, such as acetophenone, with the reagent, the reduction of unhindered dialkyl ketones, such as 3-methyl-2-butanone, provides only poor ee. However, treatment of α- and β-hydroxyketones with one equiv of diisopinocampheylborane or *B*-chlorodiisopinocampheylborane rapidly produces the corresponding ketoalkyl diisopinocampheylborinate intermediates, which then undergo facile intramolecular reduction. This reaction sequence, followed by oxidative workup, provides a general synthesis of 1,2- and 1,3-diols in 84-≥99% enantiomeric excess.

The unique structural features of α-pinene contribute to its facile elimination from *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane®) and make possible Midland's successful application of this trialkylborane for the asymmetric reduction of aldehydes and acetylenic ketones,[3] although the reduction of the carbonyl groups by trialkylboranes typically require relatively extreme conditions.[4] Reasoning from the probable reaction mechanism that an increase in the Lewis acidity of the boron atom might be beneficial, we tested (–)- and (+)-*B*-chlorodiisopinocampheylboranes (^{d} and ^{l}Ipc_2BCl, (–)- and (+)-DIP-Chloride™, **1**) and established them as successful reagents for the reduction of a variety of representative prochiral ketones.[5] During a systematic study of the compatibility of **1** with the presence of representative functional groups in the aromatic ring of acetophenone, we observed that *ortho*-hydroxyl and -carboxyl groups provide the corresponding reduction products in the opposite optical isomer as compared to the product from acetophenone.[6,7] These were attributed to the intramolecular nature of these reductions.

The relatively rapid reduction of *o*-hydroxylic and -carboxylic acetophenones suggested an examination of the applicability of **1** for a similar intramolecular reduction of aliphatic hydroxy ketones, notwithstanding the fact that an intermolecular reduction of ketones with *B*-methoxydiisopinocampheylborane fails under these conditions. A possible mechanism for the reduction of such systems involves coordination of the carbonyl oxygen to the boron atom as the operating factor. Our optimism, even with the decreased Lewis acidity of the boron atom due to the attached alkoxy oxygen atom, was also supported by a recent report by Molander[8] that a keto group in the position γ to the boron atom, in *B*-alkyldiisopinocampheylborane, is rapidly (3 h) reduced via an intramolecular path, although Alpine-Borane reductions of unactivated ketones are normally complete at room temperature (rt) under neat conditions only within 7-15 days.[9]

The treatment of hydroxyacetone (acetol, **3a**) with (+)-**1** (from (–)-α-pinene), at 0 °C, liberates one equiv of HCl to form the corresponding borinate (**4a**) with a singlet in the ^{11}B NMR spectrum at δ 52 revealing that, unlike the behavior of the borinate intermediate from the *o*-hydroxyacetophenones (^{11}B NMR δ 13)[6], the oxygen atom of the carbonyl group is not coordinated to the boron atom. This intermediate then undergoes an intramolecular reduction within 12 h, eliminating one molar equiv of α-pinene to form the boronate (**5a**, ^{11}B NMR: δ 32). The usual diethanolamine workup[5] provides a mixture of the expected diol (**6a**) and α-pinene, readily separated by column chromatography on silica gel. Analysis of the diol as the bis-trifluoroacetate (bis-TFA) on a gas chromatograph (GC) fitted with a Chiraldex-GTA capillary column established the diol produced to be of 84% enantiomeric excess (ee). Comparison of the optical rotation, $[\alpha]_D^{25}$ –13.9 (neat), with that reported in the literature ($[\alpha]_D^{20}$ –15) reveals it to be the *S*-isomer.[10] The yield and purity of the product are not satisfactory using either the diethanolamine or the alkaline hydrogen peroxide (oxidative) workup. Fortunately the perborate oxidation[11] provides the pure product in 86-92% yields in 84-92% ee (eq 1).



(1)

This is the first successful reduction of an unhindered aliphatic ketone in such high ee with **1**. In contrast to the reduction in high ee of aralkyl ketones, such as acetophenone (98% ee) by **1**, the reagent provides only poor ee for the reduction of unhindered dialkyl ketones, such as 3-methyl-2-butanone (32% ee) and 2-butanone (4%).[5]

The utilization of 2 equiv of the reagent, rather than 1, provides the diol in only 16% ee, containing the opposite (*R*) isomer preferentially, presumably the result of a competing intermolecular reduction. Indeed, we have obtained opposite configurations for the products from inter- and intramolecular reductions of structurally similar substrates with **1**.[6,7] Since the reaction is intramolecular, the reaction temperature had little effect on the enantioselectivity. A reaction temperature of 0 °C is optimal for this reduction (Table).

The generality of this intramolecular reaction was demonstrated by reducing several representative α-hydroxyketones (**3b-e**, Table). In all of the cases studied, the product 1,2-diols are obtained in as high as 84-≥99% ee. The stereochemistry of the product is the same for all of the hydroxy ketones reduced thus far. Unlike the course of the intermolecular reduction[5] with **1**, where the configurations of the products are primarily controlled by the steric interaction of the large groups on one side of the carbonyl moiety with the methyl group at the 2-position of the apopinene structure, the approach of the carbonyl group to the boron atom is hindered in the intramolecular reduction (Scheme). The controlling factor may still be the methyl group at the 2-position in α-pinene. However, the flexibility is limited and the hydride is probably delivered from the side that minimizes the interaction between the 2-methyl group of pinene and the R group of the ketone. Apparently, substitution at the α-position affects neither the stereochemistry nor the % ee.[12]

Scheme

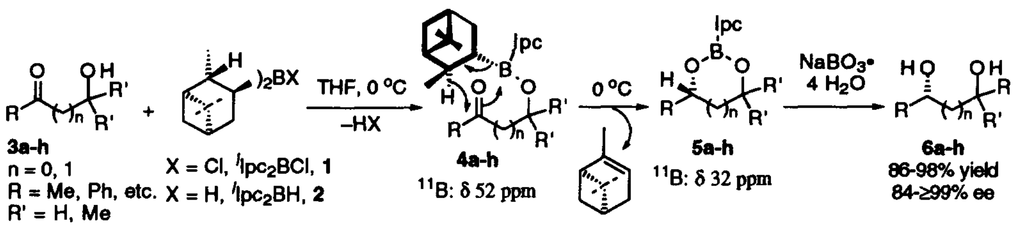


Table. Intramolecular Asymmetric Reduction of Representative 1- and 2-Hydroxy Ketones $RCO(CH_2)_nC(R')_2OH$ with (+)-Ipc_2BX in THF

entry	ketone No.	R	n	R'	reagent Ipc_2BX X	reactn. condn. temp. °C	time[a] h	product diol isol. yield, %	ee[b] %	config.[c]
1	**3a**	Me	0	H	Cl	0	12	86	84	*S*
2[d]	**3a**	Me	0	H	Cl	0	12	89	84	*R*
3[e]	**3a**	Me	0	H	Cl	0	4	90	16	*R*
4	**3a**	Me	0	H	Cl	–25	45	85	81	*S*
5	**3a**	Me	0	H	Cl	–78	48[f]			
6	**3a**	Me	0	H	H	0	12	92	92	*S*
7	**3b**	Et	0	H	Cl	0	12	90	92	*S*[g]
8	**3b**	Et	0	H	Cl	–25	48	92	94	*S*[g]
9	**3b**	Et	0	H	H	0	12	86	≥99	*S*[g]
10	**3c**	Ph	0	H	Cl	0	5	98	85	*S*
11	**3d**	Ph	0	Me	Cl	0	11	91	95	*S*[g]
12	**3e**	Furyl	0	H	Cl	0	22	90	94[h]	*R*
13	**3f**	Me	1	H	Cl	0	36	87	91	*S*
14	**3g**	*i*-Bu	1	Me	Cl	0	2	88	93	*S*[g]
15	**3h**	Ph	1	Me	Cl	0	2	95	≥99	*R*[g]

[a]Determined by ^{11}B NMR spectroscopy. [b]Determined as the bis-trifluoroacetate on a Chiraldex-GTA capillary column unless otherwise stated. [c]Determined by comparing the sign of optical rotation with that reported in the literature unless otherwise stated. [d]For a reaction with (–)-**1**. [e]For a reaction with two equiv of the reagent. [f]Only 5% conversion was observed by ^{11}B NMR spectroscopy. [g]By analogy with other diols of known configuration. [h]% ee determined by comparing $[\alpha]_D^{25}$ 35.5 (*c* 2.4, $CHCl_3$) with $[\alpha]_D^{25}$ 38.0 (*c* 3.3, $CHCl_3$) reported in the literature.[13]

The intramolecular nature of the reduction persuaded us to examine diisopinocampheylborane (Ipc_2BH, **2**) to produce the reducing intermediate. Although, **2** is not a good reducing agent itself,[14] it serves efficiently in intramolecular reductions of *o*-hydroxy and *o*-carboxylacetophenones.[6,7] Accordingly, treatment of acetol with one equiv of **2** liberates one molar equiv of hydrogen within 5 min forming the same intermediate as in the reaction with **1**. The liberation of one equiv of hydrogen and the high ee of the product diol shows that the carbonyl group is not reduced by the borane reagent, prior to the formation of the borinate. This intermediate then undergoes the intramolecular reduction providing, after workup, the diol in a yield of 85%. The analysis as above reveals the product to be 92% ee. This modified procedure may be of special value for the reduction of hydroxy ketones sensitive to HCl.

This reaction could be extended to the β-hydroxy ketones as well (Table), although the reaction rate is somewhat slower (**3f**). Substitution of the β-hydrogens with methyl groups, however, accelerates the reduction considerably (**3g,h**). It is probable that the intramolecular reduction cannot be extended beyond β-hydroxy ketones under these conditions. The reduction of 1-hydroxy-4-pentanone at 0 °C is too slow to be of any practical use.

In conclusion, we have reported the first successful asymmetric reduction of unhindered aliphatic ketones with DIP-Chloride. We have demonstrated an efficient preparation of 1,2- and 1,3-diols in very high ee via an intramolecular reduction involving diisopinocampheylborinate intermediates. The ready synthesis of 1,2- and 1,3-hydroxy ketones using standard procedures, coupled with this convenient reduction[15] provides a simple general synthesis of the corresponding diols in high ee. The important transformations of these types of diol intermediates should now be facilitated by the ready availability of both isomers of α-pinene and the commercial availability of **1**. This *neighboring group effect* for asymmetric reduction appears capable of broad applicability and we are exploring its utility.

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