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B-Chlorodiiso-2-ethylapopinocampheylborane – An Extremely Efficient Chiral Reducing Agent for the Reduction of Prochiral Ketones of Intermediate Steric Requirements

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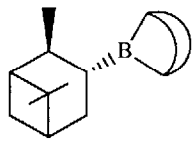
Abstract: *B*-Chlorodiiso-2-ethylapopinocampheylborane, Eap_2BCl, prepared from 2-ethylapopinene and chloroborane-methyl sulfide reduces prochiral ketones of intermediate steric requirements to the product alcohols in very high ee.

Asymmetric reduction of prochiral ketones is one of the best methods for obtaining optically pure *secondary* alcohols.[2] Recent chemical literature provides ample evidence for the fact that increasing numbers of organic chemists have undertaken the task of developing efficient chiral reducing agents. Our interest in chiral reducing agents spans more than a decade and we have had considerable success in the development of several excellent chiral reducing agents.[3] We classified ketones into different classes according to their type and reactivity and undertook a project to synthesize both enantiomers of a reagent that would reduce in high ee all classes of ketones to either enantiomer of the corresponding *secondary* alcohols.[3] The first successful demonstration of an efficient organoborane chiral reducing agent was achieved by Professor Mark Midland in the case of Alpine-Borane® (**1**) from α-pinene and 9-borabicyclo[3.3.1]nonane (9-BBN).[4] This reagent is very efficient in reducing highly reactive carbonyl groups, such as α-deuteroaldehydes, α,β-acetylenic ketones, α-keto esters, and α-halo ketones.[4,5] However, chiral reduction of slower reacting ketones, such as aralkyl and dialkyl ketones, was not successful probably because the dehydroboration of **1** in slow reductions is followed by an achiral reduction of the carbonyl group by 9-BBN produced in the dehydroboration stage.[6] By conducting the reductions under neat conditions it proved possible to suppress the dehydroboration and achieve high ee.[5] Midland also achieved this by conducting the reductions under very high hydrostatic pressures.[7] With a different approach, increasing the Lewis acidity of the boron atom in the reagent to provide for a stronger coordination of the carbonyl oxygen with the boron atom, we tested *B*-chlorodiisopinocampheylborane (Aldrich: DIP-Chloride®, **2**).[8] This proved to be an excellent reagent for the reduction of aralkyl ketones, achieving maximum chiral induction for most types of aralkyl ketones. α-Quaternary alkyl ketones are another class of ketones for which **2** is effective.[8c] The success achieved in the reduction of such ketones could probably be accounted for by a transition state in which the bulky α-quaternary alkyl group interacts sterically with the methyl group at the 2-position of the isopinocampheyl moiety.[8] When the steric interaction between the reagent and ketone is less, as in the reduction of 3-methyl-2-butanone (32% ee) and 2-butanone (4% ee), the chiral induction is poor.



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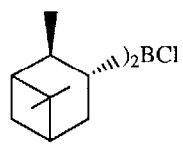

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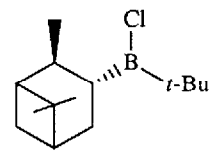

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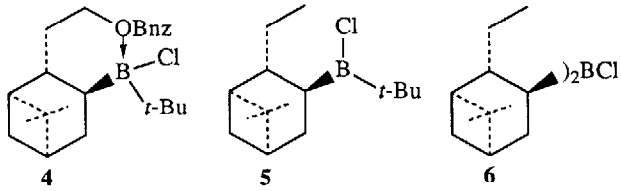
We then studied the effect of substituting one of the isopinocampheyl moieties in **2** with alkyl groups of increasing steric requirements such as Me, Et, *i*-Pr, *t*-Bu, etc. and found a correlation between steric requirements of the alkyl group R in the reagent IpcBRCl and the chiral induction realized in the reductions.[9] The reagent isopinocampheyl-*t*-butylchloroborane (**3**) gave results comparable to **2** though the rates of reductions were slightly slower. Our attention was then turned into increasing the steric bulk of the group at the 2-position of apopinene and we synthesized [iso-2-[2(benzyloxyethyl)apopinocampheyl]-*t*-butylchloroborane (**4**) from nopol benzyl ether and *t*-butylchloroborane.[10] Unfortunately, the rates of the reductions were extremely slow, presumably because of the internal coordination between the benzyl ether oxygen and the boron atom of the reagent. We sought to overcome this difficulty by removing the ether oxygen in the reagent, i.e. by preparing the reagent **5** from 2-ethylapopinene. This reagent **5** gave results comparable to **4** at a moderately faster rate than **4**.[10]

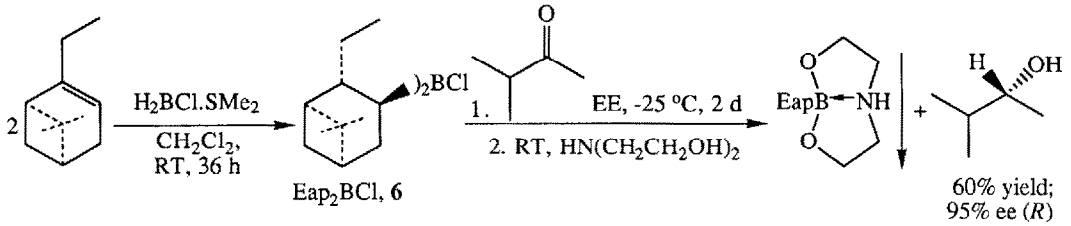


4 **5** **6**

The results realized thus far prompted us to synthesize *B*-chlorodiiso-2-ethylapopinocampheylborane (Eap$_2$BCl, **6**) from 2-ethylapopinene. We envisaged that the reaction rates with **6** will be faster than that for **5** and the chiral inductions should *at the least* be as good as that realized with **5**. One of the possible methods of preparation of **6** is using a procedure similar to the one used for the preparation of **2**. The rate and stoichiometry of the hydroboration of 2-ethylapopinene using borane-methyl sulfide complex has been studied in detail by us.[11] Unfortunately, the hydroboration does not provide the required dialkylborane, Eap$_2$BH, which could be easily converted to the required reagent **6**. Fortunately, hydroborations of olefins with $H_2BCl.EE$ and $H_2BCl.SMe_2$ are well studied[12] and we sought to prepare **6** *via* a direct hydroboration with these reagents. Hydroboration of 2-ethylapopinene with $H_2BCl.EE$ is complete in <1 h and the reagent is clean. But this procedure involves the preparation of chemically pure $H_2BCl.EE$ from $LiBH_4$ which increases the cost of the reagent. However, hydroboration of 2-ethylapopinene in dichloromethane using commercialy available $H_2BCl.SMe_2$ is complete in 36 h at rt. The initial product mixture showed two peaks in the ^{11}B NMR spectrum, a major peak at δ 74 ppm, corresponding to the desired reagent **6**, and a minor peak at δ 12 ppm, probably corresponding to the monohydroborated product EapBHCl.SMe$_2$. The solvent dichloromethane and dimethyl sulfide liberated during hydroboration were removed at aspirator vacuum and the residue was dissolved in pentane when a small amount of white precipitate was observed in the flask. Analysis of the ^{11}B NMR of the pentane solution showed that the peak at δ 12 had disappeared and the peak at δ 74 became more predominant with a very small (~2%) peak at δ 18 ppm, probably corresponding to EapBCl$_2$.SMe$_2$. The white precipitate dissolved in methanol and the ^{11}B NMR spectrum showed a sharp singlet at δ 18 ppm corresponding to a borate. This must have resulted from a redistribution reaction of the initially formed product.[13] We know from our experiences that the ~2% EapBCl$_2$ present in the reagent does not affect the chiral reduction.[14]

When we conducted the reduction of acetophenone in EE at –25 °C, with reagent **6** prepared as above, the reaction was complete in 24 h, as compared with the 5 h required by Ipc$_2$BCl. The steric bulk at the 2-position of apopinene, while it increases the enantiomeric excess of the product alcohols from reductions, decreases the rate of reduction.[10] When the reaction was complete (^{11}B NMR of a methanolysed aliquot at δ 32 ppm), the reaction mixture was warmed to rt and 2.2 equiv of diethanolamine was added. The precipitated diethanolamine complex was filtered, washed with pentane, and the filtrate concentrated. The liberated alcohol and 2-ethylapopinene were separated by column chromatography. The product alcohol was analyzed for the enantiomeric excess as its α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA)[15] derivative on a capillary gas chromatograph which showed it to be of ≥99% ee. This result is an improvement over the one provided by **2** (98% ee). But the effect of increasing the steric bulk from methyl to ethyl at the 2-position of apopinene in the

reagent was made clear by the reduction of those ketones which provides alcohols in poor ee with **2**. For example, 3-methyl-2-butanone was reduced by **2** to the corresponding alcohol in 32% ee whereas a reaction of the same ketone with **6** in EE at –25 °C within 48 h gave the corresponding alcohol in 95% ee! A similar effect was observed in the reduction of acetylcyclohexane when product alcohol of 97% ee was obtained with **6**, as compared to the 26% ee realized with **2**. 2-Cyclohexen-1-one was reduced to the corresponding alcohol in 74% ee as against the 36% ee provided by **2**. The results of reduction of the ten standard ketones[3] with **6** are summarized in Table 1. As can be seen from the table, reagent **6** reduces 5 out of the 10 classes of ketones to the alcohols in ≥95% ee. Three classes of ketones are reduced in the 70-80% ee range. Acetylenic ketones are reduced in 33% ee and β-keto ester protonolyzed Eap_2BCl.



To our knowledge this is the best result yet achieved for the reduction of aliphatic ketones with single branching α- to the carbonyl moiety. Though various reagents have been developed in the past, most of them handle aralkyl ketones, acetylenic ketones and/ or α-keto esters. DIP-Chloride handles nicely relatively hindered ketones, with the *t*-Bu moiety.[8c] Eap_2BCl extends asymmetric reduction to ketones of the 3-methyl-2-butanone type. Now we are searching for a new reagent which will handle the $-COCH_3$ and $-COCH_2CH_3$ moeities.

Table 1. Reduction of Prochiral Ketones With Eap_2BCl (6) in EE at –25 °C.

Class of ketone[3]	ketone	reactn time	% yield, isolated	%ee with **6**	config	%ee with **2**[8b]
1	3-methyl-2-butanone	2 d	65	95	(*R*)	32
1	acetylcyclohexane	3 d	65	97	(*R*)	26
2	2,2-dimethylcyclopentanone	24 h	68	≥99	(*R*)	98
3	acetophenone	24 h	80	≥99	(*R*)	98
4	acetylpyridine	7 d	60	≥99	(*R*)	92
5	2-chloroacetophenone	7 d	65	≥99	(*S*)	96
6	methyl benzoyl formate	1 h	78	70	(*S*)	50
7	ethyl benzoyl acetate	no reduction				
8	*trans*-4-phenyl-3-buten-2-one	14 d	60	82	(*R*)	81
9	2-cyclohexen-1-one	7 d	60	74	(*R*)	36
10	4-phenyl-3-butyn-2-one	5 h	82	33	(*S*)	21

In conclusion, we have developed a superior reagent which reduces many classes of ketones with essentially quantitative chirality transfer. Both enantiomers of the reagent can be synthesized at will from either enantiomer of 2-ethylapopinene, which can in turn be prepared from that enantiomer of α- or β-pinene which is readily available in high ee. The experimental conditions and work up are easy. These factors make the reagent very attractive.

A typical experimental procedure is as follows: All operations are carried out under nitrogen.[16] An oven-dried 100 mL round-bottomed flask equipped with a side-arm capped with a rubber septum, a magnetic stirring bar and a connecting tube attached to a mercury bubbler was flushed with nitrogen. The flask was immersed in an ice bath and 3.6 g (24 mmol) of (–)-2-ethylapopinene $[\alpha]_D^{24} = -46.4^o$ (neat) (≥99% ee) was dissolved in 10 mL of freshly distilled (over P_2O_5) dichloromethane. The solution was cooled at ice bath temperature for 15 min and 11 mmol of $BH_2Cl.SMe_2$ (Aldrich) was added dropwise. The reaction mixture was allowed to warm to rt and was left for 36 h when the hydroboration was complete. The ^{11}B NMR spectrum

showed a major peak at δ 74 ppm corresponding to the required reagent **6** and a minor peak at δ 11 ppm. Solvents were removed at aspirator vacuum. The residue was dissolved in dry pentane when a small amount of a white precipitate was observed. The supernatant liquid was decanted into another 100 mL flask. ^{11}B NMR spectrum of an aliquot at this stage showed a composition of >98% of the reagent **6** (δ 74 ppm) and <2% of an impurity at δ 18 ppm. Methanolysis of an aliquot showed corresponding amounts of iso-2-ethylapopinocampheylborinate and iso-2-ethylapopinocampheylboronate, respectively. Pentane was substituted with EE and the flask was cooled to –25 °C and 3-methyl-2-butanone (1.07 mL, 10 mmol) was added dropwise and stirring continued. Aliquots were methanolyzed at the reaction temperature at periodic intervals to monitor the reaction by ^{11}B NMR spectroscopy. On completion of the reaction (^{11}B: δ 32 ppm), the mixture was warmed to RT and diethanolamine (2.2 equiv) was added when the boron components precipitated out. Stirring was continued for 2 h and the precipitate was filtered off and washed with pentane. The filtrate was concentrated and chromatographed on silica gel. 2-Ethylapopinene was eluted with pentane, followed by 3-methyl-2-butanol with pentane-ether (80:20) mixture. Pentane and ether was removed by distillation and the alcohol was collected at 110-12 °C. Yield: 0.57g (65%). The menthyloxycarbonyl derivative[17] of the alcohol on analysis on a SPB-5 (30 m) capillary column showed 95% ee in the *R*-isomer of the alcohol.

The recovered 2-ethylapopinene showed physical properties identical to the starting material.

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13. $EapBCl_2.SMe_2$ can be produced by direct hydroboration of 2-ethylapopinene with $HBCl_2.SMe_2$ present (5-7%) in the commercial $H_2BCl.SMe_2$ (Aldrich). However, lower % of $EapBCl_2.SMe_2$ indicates that most of the $HBCl_2.SMe_2$ underwent redistribution during hydroboration. 2 $HBCl_2.SMe_2$ –> $H_2BCl.SMe_2 + BCl_3.SMe_2$. This also accounts for the $BCl_3.SMe_2$ observed in the reaction medium.
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