

## Selective Reduction of Organic Compounds with Non-Free Hydride Reducing Agents

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Abstract

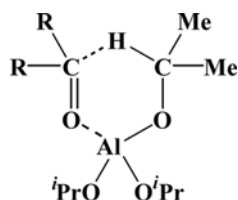
A series of non-free hydride reducing systems containing boron or aluminum atom, which possess no metal-hydride bond but an available hydrogen at a branched  $\beta$ -position, has been applied to the selective reduction (chemo-, regio-, and stereoselective reduction) of organic compounds. The systems, comprised of diisopinocampheylborane and diisobutylalane derivatives, exhibited almost perfect selectivities in the reduction of aldehydes and ketones. The characteristics features of this systems leading to a perfect transformation have been depicted in this report, especially in the 1) Reduction of  $\alpha,\beta$ -Unsaturated Carbonyl Compounds to Allylic Alcohols via 1,2-Reduction, 2) Chemoselective Reduction between Structurally Different Carbonyl Compounds, and 3) Stereoselective Reduction of Cyclic Ketones.

**Key words** : Chemoselective, Stereoselective, Reduction, Ketone, Aldehyde

### 1. Introduction

A series of non-free hydride reducing system, which possesses no metal-hydride bond but an available hydrogen at a branched  $\beta$ -position, has been applied to the selective reduction (chemo-, regio-, and stereoselective reduction) of organic compounds. The reaction of carbonyl compounds with these non-free hydride reducing agents proceeds a hydrogen transfer through the 6-membered cyclic transition state after coordination of carbonyl oxygen to the boron or aluminum atom of the reagents. Such unique characteristic feature of the reaction leads to a perfect selectivity in the reduction of aldehydes and ketones.

The advent of a reduction of carbonyl compounds with aluminum triisopropoxide, known as the Meerwein-Ponndorf-Verley (MPV) reduction,<sup>[1,2]</sup> dates back to 1925.



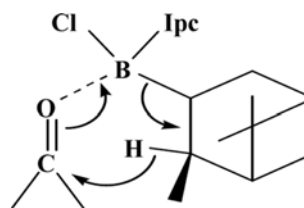
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Although its importance has declined due to the introduction of complex metal hydrides, there appear to be several instances where its application is preferable. Recently, we developed a new MPV type reduction using *Al*-chloro-, *Al*-alkoxy-, *Al*-dialkylamino-, and *Al*-pyrrolyldiisotutylalanes.<sup>[3-6]</sup>

In addition to that, chiral diisopinocampheylchloroborane ( $\text{Ipc}_2\text{BCl}$ ) has proven to be extremely efficient for the asymmetric reduction of a wide variety of ketones to obtain chiral alcohols in high enantiomeric excess.<sup>[7-9]</sup> The mechanism of the reduction also is explained *via* a cyclic boatlike transition state,



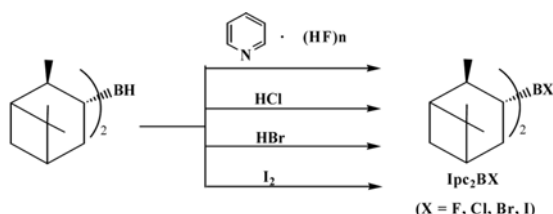
We found that  $\text{Ipc}_2\text{BCl}$  readily reduces  $\alpha,\beta$ -unsaturated carbonyl compounds to the corresponding allylic alcohols without any detectable 1,4-reduction product. In the course of extending this type of reaction, we developed a series of *B*-halodiisopinocampheylborane and *B*-alkoxydiisopinocampheyl-borane derivatives.<sup>[10-14]</sup>

All these non-free hydride reducing agents possess characteristic features of reduction :

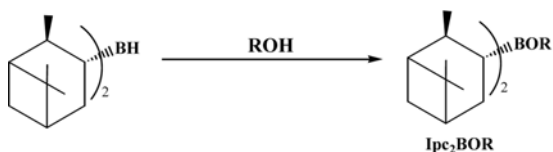
1) the key step in the reduction is the coordination of boron or aluminum atom to the carbonyl oxygen, 2) the hydride is transferred to the carbonyl carbon through the six-membered cyclic transition state. On the basis of this reaction mechanism, we have applied a series of these reducing systems to the selective reduction of organic compounds.

## 2. Preparation of Reagents.

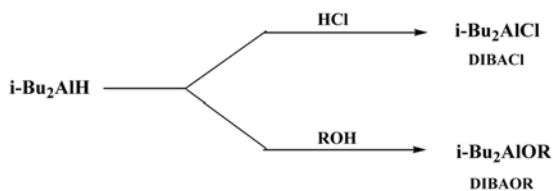
The diisopinocampheylhaloboranes were prepared by reaction of diisopinocampheylborane ( $\text{Ipc}_2\text{BH}$ ) and the corresponding halogenated reagents such as pyridinium poly(hydrogen fluoride), hydrogen chloride, hydrogen bromide and iodine, respectively.



The diisopinocampheylalkoxyboranes were also prepared by reaction with the corresponding alcohols.



The reaction of diisobutylaluminum hydride (DIBAH) with hydrogen chloride or alcohols provided the corresponding diisobutylaluminum derivatives.



### Reduction of $\alpha$ , $\beta$ -Unsaturated Carbonyl Compounds to Allylic Alcohols *via* 1,2-Reduction.

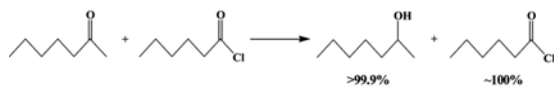
All the reagents converted  $\alpha$ ,  $\beta$ -unsaturated aldehydes and ketones to the corresponding allylic alcohols in a perfect selectivity. This outstanding outcome comes from the fact that the reduction can be occurred through

only the cyclic transition state.



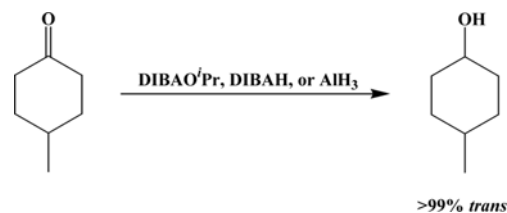
### Chemoselective Reduction between Structurally Different Carbonyl Compounds.

These reagents can also differentiate one carbonyl compound from the others. Some reagents even distinguish between aldehydes or between ketones. Most reagents can convert aldehydes and ketones even in the presence of acid chlorides. These results come from the fact that the reagent can coordinate selectively to the carbonyl oxygen.

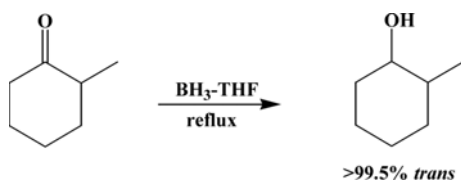


### Stereoselective Reduction of Cyclic Ketones.

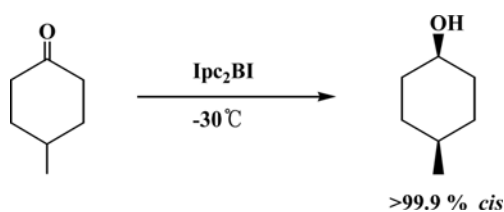
Sterically hindered alkylboron hydride reagents can convert cyclic ketones to the thermodynamically less stable alcohol epimers preferentially. However, generally acceptable synthetic method for the conversion of cyclic ketones to the more stable epimers have still been lacking. Recently, we found that diisobutylalane derivatives reveal an excellent stereoselectivity in such cyclic ketone reductions to provide the corresponding thermodynamically more stable alcohols. Furthermore, in the course of extending such exploration, we found that diisobutylaluminum hydride (DIBAH) and aluminum hydride ( $\text{AlH}_3$ ) itself can convert cyclic ketones to such epimers exclusively.<sup>[15-17]</sup>



Finally, in the course of reexamining the reducing characteristics of  $\text{BH}_3\text{-THF}$ , we also found that the reagent reveals an unexpectedly high stereoselectivity in such cyclic ketone reduction at higher temperatures in THF.<sup>[18]</sup>



On the other hand, the reaction of cyclic ketones with the diisopinocampheylhaloboranes showed a very interesting results, in which the stereoselectivity increases as the steric size of halogen atom increases and the alcohol products are mainly the thermodynamically less stable ones. Especially, the stereoselectivity achieved by the iodo derivative at  $-30^\circ\text{C}$  was essentially perfect to provide an almost pure less-stable alcohol epimer. Therefore, we can now obtain both isomer in a pure form by using MPV-type reagents.



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