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Recent Developments In Meerwein−Ponndorf−Verley and Related Reactions for the Reduction of Organic Functional Groups Using Aluminum, Boron, and Other Metal Reagents: A Review

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I. Introduction

The discovery of sodium borohydride[1] in 1942 and of lithium aluminum hydride[2] in 1945 brought about a revolutionary change in procedures for the reduction of functional groups in organic molecules.[3,4] Today, for instance, in dealing with the problem of reducing an aldehyde or ketone function, the synthetic organic chemist will rarely attempt to use such a conventional technique as the Meerwein−Ponndorf−Verley (**MPV**) reaction. Moreover, the advent of a variety of modified metal hydride reagents possessing a high degree of selectivity has made it possible to have a broad spectrum of reagents for selective reductions.[3]

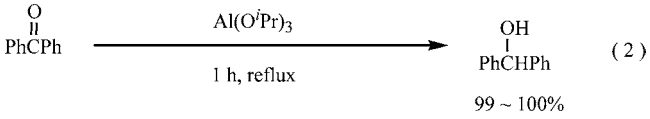
However, recent developments in the design of a new type of **MPV** reagent and in its application to the reduction of organic functional groups have led us to reassess its applicability and selectivity in organic synthesis. Consequently, it seems interesting to review the situation in which the newly developed **MPV** reactions can possibly be a complementary methodological option for such reductions. This review attempts to emphasize the distinct contrast in the reducing characteristics that exists between metal hydride reagents and **MPV** reagents. The purpose of this review is to illustrate the relationship of **MPV** type reduction to other methods of reduction and then to compare their usefulness in organic synthesis.

II. Origins of the MPV Reducing Agents

1. Discovery of Aluminum Compounds as MPV Reducing Agents. In 1925 it was found independently by Verley[5] and by Meerwein and Schmidt[6] that an aldehyde can be reduced to the corresponding carbinol with aluminum ethoxide in ethanol (eq 1).

$$\mathrm{RCHO} + \mathrm{CH_3CH_2OH} \overset{\mathrm{Al(OEt)_3}}{\rightleftharpoons} \mathrm{RCH_2OH} + \mathrm{CH_3CHO} \quad (1)$$

In 1926 Ponndorf found that by utilizing aluminum alkoxides of more readily oxidizable secondary alcohols, such as isopropyl alcohol, ketones as well as aldehydes could be reduced satisfactorily.[7] In 1937 Lund applied this method to a variety of aldehydes and ketones and explored the scope and applicability of the **MPV** reaction[8,9] (eq 2).



(2)

Meerwein also first utilized trialkylaluminum, such as triisobutylaluminum (**TIBA**),[10] for the reduction of aldehydes and ketones, which are readily reduced to the corresponding alcohols.[11]

2. Early Explorations for Boron Compounds as MPV Type Reducing Agents. The first report on trialkylborane as a reducing agent came from Meerwein in 1936,[10] in which heating a neat mixture of triethylborane and benzaldehyde eliminates ethylene with the formation of diethylboronic ester (eq 3).

$$\mathrm{Et_3B} + \mathrm{PhCHO} \xrightarrow[\text{neat}]{90-140\ ^\circ\mathrm{C}} \mathrm{CH_2{=}CH_2} + \mathrm{Et_2B{-}OCH_2Ph} \quad (3)$$

In this reaction benzaldehyde was reduced to the boronic ester of benzyl alcohol. About 30 years later, Mikhailov et al.[12] reexamined such a reaction with higher trialkylboranes in the presence of benzaldehyde at elevated temperatures (eq 4). They indicated that the rate of the elimination of an olefin (i.e., the reduction of benzaldehyde) from a trialkylborane

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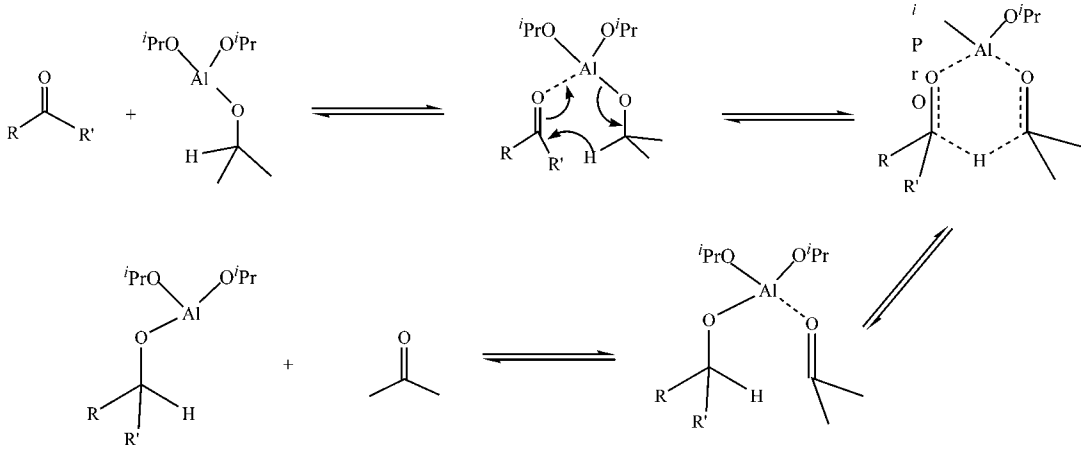
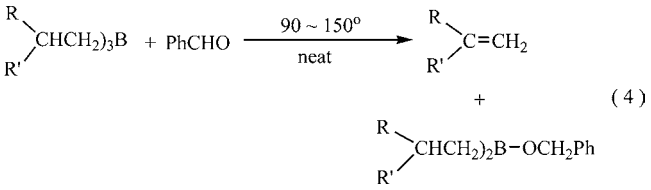
Scheme 1

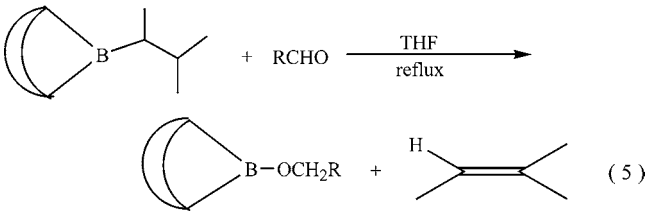


increases with an increase in the number of methyl groups on the β-carbon atom.



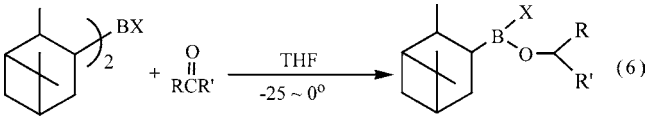
(4)

In late 1970 Midland initiated the improvement of such a sluggish reaction to a useful technique for the selective reduction of aldehydes using *B*-alkyl-9-borabicyclo[3.3.1]-nonane (*B*-R-9-**BBN**).[13] Especially, *B*-(3-methyl-2-butyl)-9-**BBN** (*B*-Siamyl-9-**BBN**) is an effective reagent for the reduction of a wide variety of aldehydes under mild conditions (i.e., 2 h in refluxing THF)[14] (eq 5).



(5)

Such *B*-R-9-**BBN** reagents show only a reactivity toward aldehydes: aldehydes are reduced rapidly, whereas ketones are reduced only very sluggishly. However, the situation changed when Professor Brown et al. developed diisopinocampheylhaloboranes(Ipc_2BX) in 1985.[15] These reagents can react with ketones at convenient rates even at −25 °C (eq 6).



(6)

3. Mechanistic Consideration of the MPV Reactions. A. Aluminum Reagents. As depicted in eq 1, the **MPV** reaction with aluminum ethoxide is reversible, but the equilibrium can be shifted to the point of complete reduction with the removal of the acetaldehyde with a stream of dry nitrogen. Similarly, the reaction of aluminum isopropoxide produces acetone, which can be removed from the equilibrium mixture by slow distillation.[5−9] The equilibrium proceeds by an oxidation−reduction reaction of a carbinol−carbonyl pair accelerated by aluminum alkoxide.[16,17]

The generally accepted mechanism for **MPV** reactions proceeds via a complex in which both the carbonyl compound and the reducing alcohol are bound to the metal ion, as shown in Scheme 1 for the reaction of aluminum isopropoxide. The carbonyl is then activated upon coordination to Al(III), followed by a hydride transfer from the alcoholate to the carbonyl group via a six-membered transition state.[18]

Likewise, the mechanism of the reaction of carbonyl compounds with triisobutylaluminum (**TIBA**) involves a hydride shift from the β-carbon atom and thus proves to be very similar to the **MPV** reduction process, which has been confirmed by mechanistic[19] and stereochemical[20] investigations (Scheme 2).

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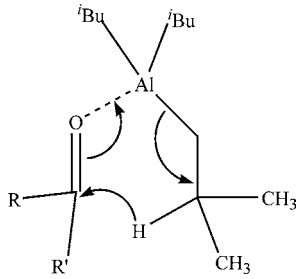
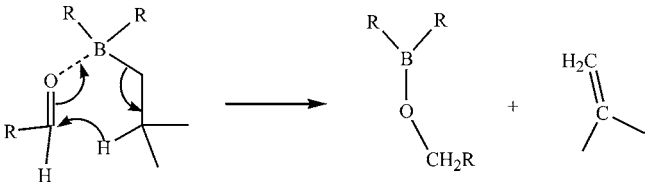
Scheme 2



Scheme 3



B. Boron Reagents. As in the report by Mikhailov[12] on the reaction of trialkylboranes with benzaldehyde at elevated temperatures, the rate of the elimination of an olefin from a trialkylborane increases with an increase in the number of methyl groups on the β-carbon atom, which indicates reaction with the elimination of a hydride ion via a cyclic electron ttransfer (Scheme 3).

Similarly, the kinetic study on the reduction of aldehydes with *B*-alkyl-9-**BBN** led to the conclusion that the reaction proceeds mainly by the cyclic process.[21]

C. Consideration on β-Hydrogen Source of Catalyst. The β-hydrogen sources in **MPV** reduction can be divided into two categories. As depicted in Scheme 1 for the classical **MPV** reduction, the β-hydrogen comes from an isopropoxy group of catalyst that, in turn, leads to the formation of acetone. On the other hand, as shown in Schemes 2 and 3, the β-hydrogen originates from an alkyl group of catalyst that, in turn, leads to the formation of alkene.

The formation of acetone causes the reaction to be reversible; therefore, we need to remove acetone in order to shift the equilibrium in the desired direction. However, the formation of alkene does not interfere in the reduction process.

III. Appearance of New MPV Type Reagents

We usually say that **MPV** reduction is performed with aluminum isopropoxide as a catalyst and isopropyl alcohol as a hydride source. From the mechanistic point of view as depicted in Scheme 1, however, there are two things to be considered. One is that the actual reduction takes place by virtue of the β-hydrogen transfer from an isopropoxy group attached to an Al atom of catalyst. This means that isopropyl alcohol does not participate at the key step of reduction: isopropyl alcohol acts as an isopropoxy group source which substantially provides a hydride. The other is that the **MPV** reaction is reversible: acetone formed accelerates the reversible reaction.

Practically, there is a problem involved in this reaction: the reduction usually proceeds sluggishly even with an excess of catalyst and requires the removal of acetone in order to shift the equilibrium in the desired direction.

Therefore, continuous efforts have been made to devise new catalysts and reagents to overcome such limitations.

1. Auminum-Containing Reagents. The classical **MPV** reaction with aluminum isopropoxide has been modified with the addition of trifluoroacetic acid (**TFA**) (**1**). Thus, the

$$\mathrm{Al(O^{i}Pr)_3}/\mathbf{TFA}$$

1

system **1** brings about the rapid reduction of aldehydes at room temperature in the absence of an external hydride source such as isopropyl alcohol.[22] Furthermore, the addition of small amounts of **TFA** improves the performance of aluminum isopropoxide: aluminum isopropoxide in catalytic amounts catalyses hydride transfer from isopropyl alcohol in **MPV** reduction.[23,24]

Efficient catalytic procedures for **MPV** reduction have been devised by employing various aluminum alkoxides, such as dimeric biphenoxyalkoxide $[(EDBP)Al(u\text{-}O^{i}Pr)]_2$[25] (**2**), sulfonylamioalkoxide[26] (**3**), and bidentate aluminum alkoxides[27] (**4**). Especially, **4** is able to capture both of the oxygen lone pairs simultaneously, enabling double electrophilic activation of carbonyls. Aluminum porphyrins,[28] such as 5,10,15,20-tetraphenylporphynatoaluminum chloride (**5**), also catalyse a novel hydrogen transfer process in the reduction of aldehydes and ketones with alcohols.

Recently, there have appeared a series of diisobutylaluminum derivatives, such as diisobutylhaloalanes[29] (**6**), diisobutylalkoxyalanes[30] (**7**), and diisobutylaminoalanes[31] (**8**), which were prepared by simple reaction of diisobutylaluminum hydride (**DIBAL-H**) with the corresponding hydrogen halides, alcohols, and amines, respectively (eqs 7−9).

$$\underset{\text{DIBAL}-\text{H}}{i\text{-Bu}_2\text{AlH}} + \text{HX} \rightarrow \underset{\mathbf{6}}{i\text{-Bu}_2\text{AlX}} \qquad (7)$$

$$i\text{-Bu}_2\text{AlH} + \text{ROH} \rightarrow \underset{\mathbf{7}}{i\text{-Bu}_2\text{AlOR}} \qquad (8)$$

$$i\text{-Bu}_2\text{AlH} + \text{R}_2\text{NH} \rightarrow \underset{\mathbf{8}}{i\text{-Bu}_2\text{AlNR}_2} \qquad (9)$$

These diisobutylaluminum derivatives have achieved a very

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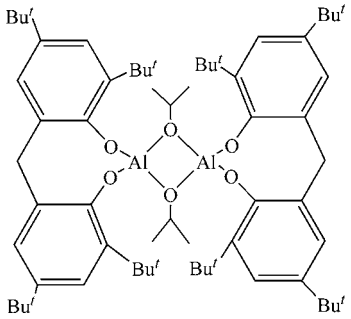

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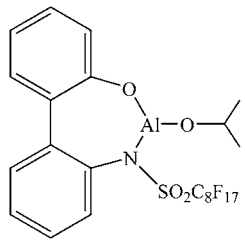

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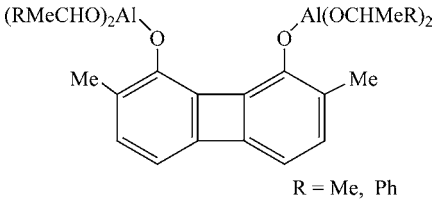

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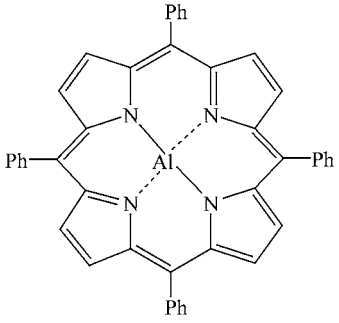

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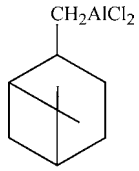
high chemo-, regio-, and stereoselectivity in the reduction of aldehydes and ketones.

In the 1950s and 1960s, the classical intermolecular asymmetric reduction of ketones using aluminum alkoxides of optically active alcohols was widely studied.[32] Since the 1980s the intramolecular asymmetric reduction of α,*β*-unsaturated ketones via tandem Michael addition−**MPV** reaction using aluminum alkoxide of optically active mercapto alcohol has been investigated.[33]

The chiral organodichloroaluminum reagent (**9**), derived from (−)-*β*-pinene, reduces a variety of aliphatic and aromatic ketones to chiral alcohols.[34]



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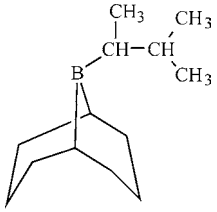
2. Boron-Containing Reagents. Generally, trialkylboranes are known to be tolerant to a wide variety of functional groups,[35] but a certain *B*-alkyl-9-**BBN**, especially *B*-Siamyl-9-**BBN** (**10**), is a mild chemoselective reducing agent for aldehydes.[13,14] Similarly, the asymmetric *B*-alkyl-9-**BBN**



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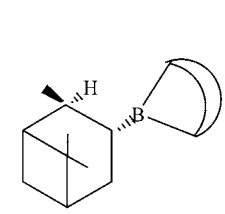
containing optically active terpenes,[36] such as (+)-α-pinene (**11**), (−)-*β*-pinene (**12**), (−)-camphene (**13**), and (+)-3-carene (**14**), can transfer a hydride from a chiral center of the alkyl group to a new chiral center of the carbonyl group of the deuterated aldehydes.



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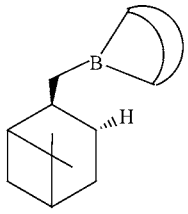

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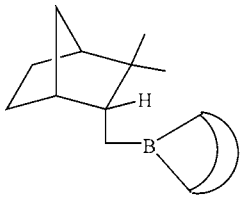

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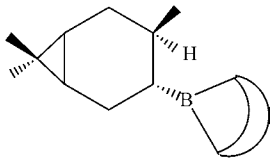

14

However, the first report on trialkylborane being capable of reducing both aldehydes and ketones under mild conditions appeared in 1985.[37] Professor Brown and his cowokers devised diisopinocampheylchloroborane (Ipc_2BCl) (**15**), which is the outcome of a strategic modification of the electronic and steric environments of the boron in trialkylboranes and can reduce a variety of ketones as well as aldehydes to the corresponding alcohols even at −25 °C. Soon after other mono- and diisopinocampheylhaloboranes (**16**−**20**) were also

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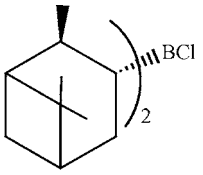
prepared.[38−42] Furthermore, hydroxy-, alkoxy-, acetoxy- and



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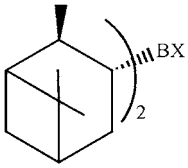

(X = F, Cl, Br, I)

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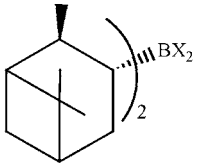

(X = F, Cl, Br)

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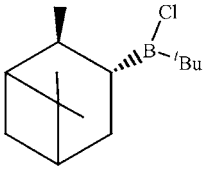

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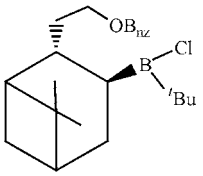

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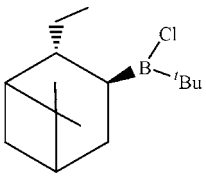

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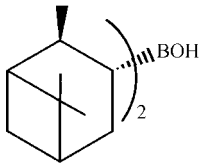
methanesulfonoxy-incorporated diisopinocampheylborane derivatives (**21**−**26**) were prepared, and their applicability in **MPV** type reduction was explored.[43−47]



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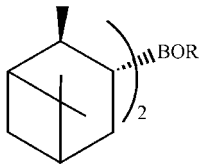

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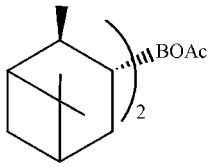
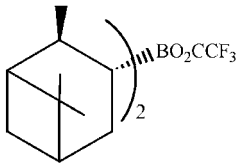


23



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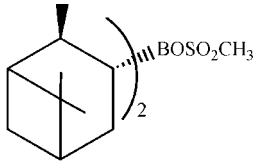

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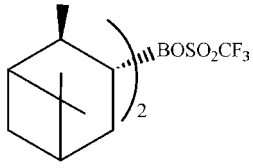

26

Boron isopropoxide, a counterpart of aluminum isopropoxide, also appears as a mild reducing agent, showing a high chemoselectivity in the reduction of aldehydes and ketones.[48]

3. Other Metal-Containing Reagents. Various lanthanide(III) iodoalkoxides were first utilized in **MPV** reduction by Kagan and co-workers in 1984.[49] Especially, *t*-BuOSmI$_2$ shows a promising catalytic activity in the reduction of a variety of aldehydes in the presence of isopropyl alcohol. They have also investigated the **MPV** reduction with lanthanide isopropoxides.[50] Among them, La(III) and Sm(III) appeared to be the most active in the reduction of 2-octanone.

The silica-anchored mononuclear isopropoxides of the elements of group IV, ≡SiOM(O^{i}Pr)$_3$, M = Zr, Hf, have been synthesized and shown to be efficient catalysts for the reduction of aldehydes and ketones in the presence of isopropyl alcohol.[51] Other zirconium alkoxides[52] and lithium alkoxides have also been introduced.[53] Group IV metallocene complexes such as bis(cyclopentadienyl)zirconium dihydrides (Cp_2ZrH_2) and hafnium dihydrides (Cp_2HfH_2) catalyze the **MPV** reduction of aldehydes and ketones in isopropyl alcohol.[54] The catalytic effect in the **MPV** reduction of ketones has also been observed in the presence of catalysts consisting of chelates of metals such as ruthenium,[55−57] iridium,[58−60] scandium,[61] yttrium,[61] tantalum,[62] and even rare earth elements such as samarium[63] and plutonium.[64]

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There have been reported a variety of acidic and basic heterogeneous catalysts which have been successfully used for the **MPV** reduction. Heterogeneous catalysts have advantages over homogeneous systems, so that workup is easy and catalyst recycling is possible. One of the widely used catalysts is magnesium oxide (MgO), a typical catalyst for a gas-phase transfer hydrogenation process.[66] Other metal oxides include alumina,[66g,67] silica,[66g] zirconia,[66g,68,69] and calcium oxide.[66i−j,70] A variety of mixtures of basic oxides prepared by calcination of Mg/Al, Mg/Ga, Mg/In, Ca/Al, Co/Al, and Cu/Al layered double hydroxides have also been examined as catalysts for the **MPV** reduction of aldehydes and ketones with isopropyl alcohol.[71]

Zeolites have appeared as recyclable heterogeneous catalysts to show various types of shape selectivity, because of their unique microporous structure.[72] Various types of zeolites such as zeolite A, X, and Y exchanged or impregnated with alkali and alkaline-earth cations possess unique catalytic activity in the **MPV** reductions, depending on the cationic site.[73] Zeolite beta (**BEA**), such as Sn-beta ([Sn]-**BEA**), Ti-beta ([Ti]-**BEA**), and Al-beta ([Al]-**BEA**), has also been applied to the stereoselective reduction of cyclohexanone derivatives.[74]

IV. Application for Organic Synthesis

The **MPV** reduction is a classical but still widely used metheod for organic synthesis, because of its high selectivity, relatively mild reaction conditions, simple and safe operations, and low cost. In general, **MPV** reduction is performed with various catalysts introduced in Section III and isopropyl alcohol as a hydride source; the mechanism can be described by the activation of the carbonyl group through its coordination to a Lewis acidic metal site followed by reversible hydride transfer from alcoholate to the carbonyl acceptor via a six-membered cyclic transition state, as shown in Schemes 1−3. From this mechanstic point of view, the key step of this reaction must be the coordination of carbonyl oxygen to the Lewis acidic metal site: without coordination of the substrate, no reduction takes place. Another characteristic feature of this reaction to be considered is the hydride-transfer pathway in which the reduction proceeds through the six-membered transition state. These combined characteristic features seem to play a major role in performing an excellent selectivity in the **MPV** reductions, such as the following chemo-, regio-, and stereoselective reductions of carbonyl and epoxy compounds.

1. General Reducing Characteristics of Diisobutylaluminum and Diisopinocampheylboron Derivatives toward Common Organic Functional Groups. Recently, the general reducing characteristics of diisobutylaluminum derivatives, such as *i*-Bu_2AlX (**6**), *i*-Bu_2AlOR (**7**), and *i*-Bu_2AlNR_2 (**8**), and diiopinocampheylboron derivatives, such as Ipc_2BX (**16**), Ipc_2BOR (**21**−**22**), Ipc_2BOAc (**23**), and $Ipc_2BO_2CCF_3$ (**24**), have been examined systematically. After a broad examination and comparison, some conclusions on the general reducing action of these derivatives toward organic functional groups have been drawn as follows:

(i) the relative reactivities of the Ipc_2BX series toward carbonyl compounds are in a sequence of $Ipc_2BCl > Ipc_2BF \gg Ipc_2BBr > Ipc_2BI$;

(ii) the reactivity of Ipc_2BOR (**22**) is much weaker than that of Ipc_2BX (**16**);

(iii) Ipc_2BOR (**22**) can reduce aldehydes but cannot attack ketones;

(iv) the relative reactivities of the *i*-Bu_2Al-series are *i*-Bu_2AlX > *i*-Bu_2AlOR> *i*-Bu_2AlNR_2;

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Table 1. **Comparison in reactivity of diisopinocampheylboron and diisobutylaluminum derivatives toward common organic functional groups[a]**

	organic functional groups					
reagent type	aldehyde	ketone	ester	acid chloride	nitrile	epoxide
Ipc_2BX	+++	++	−	−	+	+
Ipc_2BOR	++	−	−	−	−	−
$i\text{-}Bu_2AlX$	+++	+++	−	−	+	++
$i\text{-}Bu_2AlOR$	++	+	−	−	−	−
$i\text{-}Bu_2AlNR_2$	++	+	−	−	−	−

[a] + designates "reactive", whereas − designates "inert".

(v) the relative reactivities of the $i\text{-}Bu_2AlOR$ (**8**) series are $i\text{-}Bu_2AlOH > i\text{-}Bu_2AlOEt > i\text{-}Bu_2AlO^iPr > i\text{-}Bu_2AlO^t\text{-}Bu$;

(vi) the reactivity of $Ipc_2BO_2CCF_3$ (**24**), a fluorinated acetate derivative, is much higher than that of the acetate derivative itself, Ipc_2BOAc (**23**).

As a result, the reactivity depends on what kind of moiety is attached to diisobutylaluminum or diisopinocampheylboron. Such a reactivity difference may be attributed to the steric and electronic effects of the substituent.

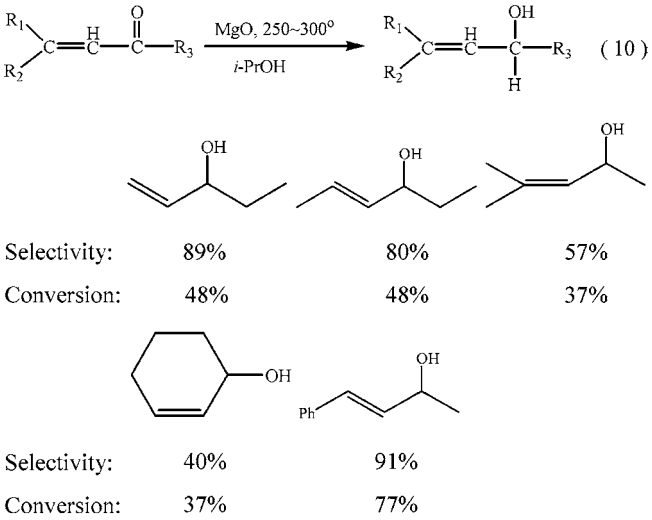
A relative reactivity toward organic functional groups is summarized in Table 1. Most derivatives are reactive toward aldehydes and ketones but quite inert to other functional groups including even acid chlorides. It is especially noteworthy that Ipc_2BOH appears to be the mildest among the derivatives, exhibiting absolutely no reactivity toward every organic functional group except aldehydes.

2. Conversion of α,β-Unsaturated Carbonyl Compounds to the Corresponding Allylic Alcohols. Reduction of α,β-unsaturated aldehydes and ketones with conventional reducing agents produces three possible products in a different ratio. Thus, reduction in a 1,2-addition fashion gives the corresponding unsaturated alcohol (allylic alcohol) (**27**). A conjugative addition (1,4-addition) affords the corresponding saturated carbonyl compound (**28**). And if the reduction proceeds in a 1,4-addition followed by 1,2-addition, a saturated carbinol (**29**) is produced (Scheme 4).

In particular, the selective conversion of α,β-unsaturated carbonyl compounds to the corresponding allylic alcohols (**27**) is the focus of attention, since it is often a key step in the preparation of various fine chemicals. Therefore, endless efforts have been made to develop reducing systems which effect such a regioselective conversion.[75−93]

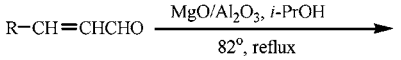
One of the most prominent potentials of the **MPV** process seems to be its capability of converting α,β-unsaturated carbonyl compounds to the corresponding allylic alcohols. However, only a few examples are found in the literature for such a selective reduction. In addition, even these examples have been designed for an industrial purpose using acid−base catalysts and isopropyl alcohol as a hydrogen donor.

MgO has been first utilized as a heterogeneous catalyst in a flow system for the reduction of α,β-unsaturated ketones.[66b] The conversion yields and selectivity do not appear to be high but seem to be good enough in an industrial sense (eq 10).



(10)

Magnesium−aluminum mixed oxide (MgO/Al_2O_3) has also been tested on the **MPV** reduction of various α,β-unsaturated aldehydes with isopropyl alcohol.[71j,k] A high ratio of convertibility and selectivity has been demonstrated in such a selective reduction (eq 11).



(11)

R=	Me	Et	*n*-Pr	Ph
Selectivity:	100%	98%	98%	93~97%
Conversion:	96~99%	98~100%	97~98%	71~95%

The mechanism, on which the hydrogen transfer from isopropyl alcohol to the carbonyl compound is based, involves the transfer of a hydride ion between both substrates via a six-link cyclic intermediate adsorbed on an acid−base pair in the catalyst (Scheme 5).[66g,71k] As mentioned above, diisobutylaluminum and diisopinocampheylboron derivatives (**6**−**8**, **16**, and **21**−**24**) have been applied to the regioselective reduction of α,β-unsaturated aldehydes and ketones, and the

(75) For a discussion on this subject, see: (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W.A. Benjamin: Menlo Park, California, 1972; pp 89−95. (b) Lane, C. F. *Aldrichimica Acta* **1976**, *9*, 31 and references therein.
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(77) Yoon, N. M.; Lee, H. J.; Kang, J.; Chung, J. S. *J. Korean Chem. Soc.* **1975**, *19*, 468.
(78) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 1197.
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(84) (a) Ashby, E. C.; Lin, J. J. *Tetrahedron Lett.* **1975**, 4453. (b) Ashby, E. C.; Lin, J. J.; Kovar, R. *J. Org. Chem.* **1976**, *41*, 1939.
(85) Cain, M. E. *J. Chem. Soc.* **1964**, 3532.
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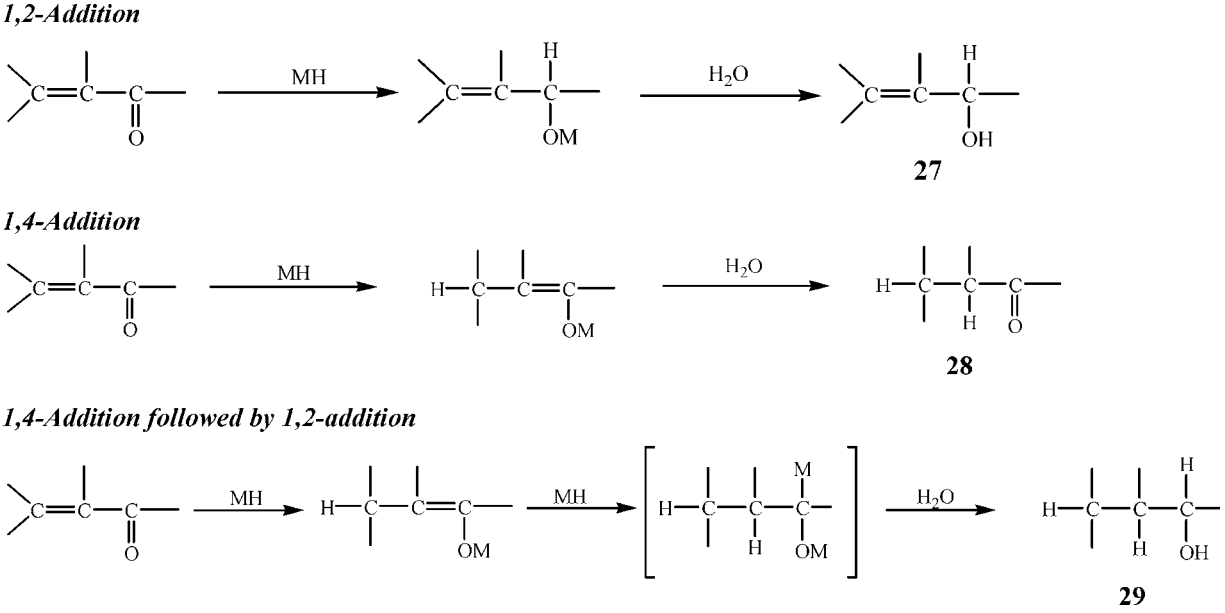
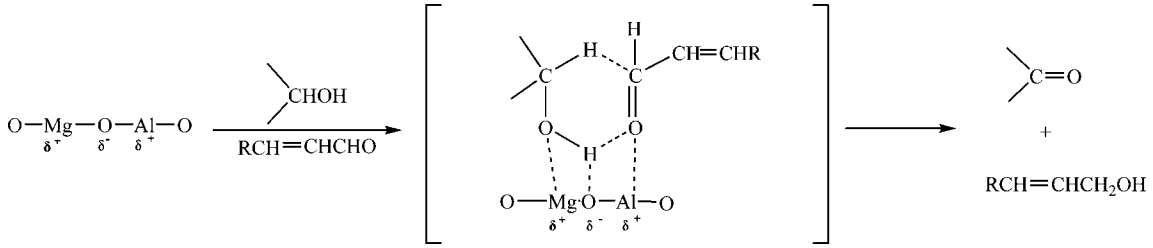
(90) (a) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1975**, *40*, 1864. (b) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 1197.
(91) Wilson, K. C.; Seidner, R. T.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1970**, 213.
(92) Ganem, B. *J. Org. Chem.* **1975**, *40*, 146.
(93) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194.

Scheme 4



Scheme 5



results are summarized in Table 2. All the derivatives examined can reduce a variety of α,*β*-unsaturated aldehydes and ketones to the corresponding allyic alcohols, except Ipc_2BOR[44−46,98] which can only reduce aldehydes but cannot attack ketones at all. Even though the reaction rates are different from each other, the selectivity appears to be essentially 100%. We can conjecture that such a selectivity may be attributed to the reaction mechanism as proposed in the **MPV** type reactions (Scheme 6). As in the mechanism, "*a-attack*" via a six-membered hydrogen transfer must be in a lower energy level than that of "*b-attack*" via an eight-membered hydrogen transfer.

In addition, it should be pointed out that the conversion yield to the corresponding alcohols reaches essentially 100% as well. It is not unusual that the classical **MPV** reaction using aluminum isopropoxide and the related **MPV** type reaction using other catalysts have been performed in the presence of isopropyl alcohol as a hydrogen donor, which, in turn, leads to the reaction mixture lying in equilibrium. Further, the resultant acetone formed in due reaction seems to make the reaction mixture more complicated. However, in such reactions with diisobutylaluminum or diisopinocampheylboron derivatives, no hydrogen donor has been added, and hence no equilibrium exists. The olefins formed, such as isobutylene or α-pinene, do not seem to interfere with these reactions.

It is noteworthy that some reagents can convert α,*β*-unsaturated ketones to the corresponding saturated ketones via a 1,4-addition fashion. Especially, LiCuH(*n*-C_4H_9),[105] NiCRA ($NaH-RONaNi(OAc)_2$) or NiCRA-$MgBr_2$, K*s*-Bu_3-BH,[92,93] $LiAlH_4-CuI$,[84] a $Cu/SiO_2/H_2$ system,[106] Li(alkynyl)-CuH,[107] $NaAlH_2(OCH_2CH_2OMe)$,[108] NaTeH,[109] and (*n*-$Bu)_2SnH$,[110] $NaHFe(CO)_8$,[111] and $K_3[Co(CN)_5H]$[112] have achieved such conversion in high yields.

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(95) Brown, H. C.; Krishnamurthy, S.; Yoon, N. M. *J. Org. Chem.* **1976**, *41*, 1778.
(96) Cha, J. S.; Nam, H. T.; Kwon, O. O. Unpublished results.
(97) Cha, J. S.; Kim, E. J.; Kwon, O. O.; Kim, J. M. *Bull. Korean Chem. Soc.* **1994**, *15*, 1033.
(98) Cha, J. S.; Nam, H. T.; Jang S. H.; Kwon, S. Y.; Park, S. J.; Kwon, O. O. *Bull. Korean Chem. Soc.* **2004**, *25*, 1948.
(99) Cha, J. S.; Park, S. J.; Kwon, O. O. Unpublished results.
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(102) Cha, J. S.; Kwon, O. O.; Kim, J. M.; Chun, J. H.; Lee, Y. S.; Lee, H. S.; Cho, S. D. *Bull. Korean Chem. Soc.* **1998**, *19*, 236.
(103) Cha, J. S.; Kwon, S. Y.; Kwon, O. O.; Kim, J. M.; Song, H. *Bull. Korean Chem. Soc.* **1996**, *17*, 900.
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(106) Ravasio, N.; Antenori, M.; Gargano, M.; Mastrorilli, P. *Tetrahedron Lett.* **1996**, *37*, 3529.
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(108) Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. *J. Org. Chem.* **1977**, *42*, 3180.
(109) Ramasamy, K.; Kalyanasundaram, S. K.; Shanmugam, P. *Synthesis* **1978**, 545.

Table 2. **Regioselective reduction of representative α,β-unsaturated carbonyl compounds with MPV type reagents[a]**

Compound	Reagent[b]	Rgt/ Cpd	Reaction temp. (℃)	Reaction time (h)	Yield (%)	Ref
$CH_3CH=CHCHO$	Ipc_2BF	1.1	0	24	100	96
	Ipc_2BCl	1.1	0	3	>99.9	41, 97
	Ipc_2BBr	2.0	0	48	95	41
	Ipc_2BI	2.0	25	24	98	41
	Ipc_2BOH	2.0	25	1	>99.9	45
	Ipc_2BOEt	2.0	25	1	100	45
	Ipc_2BO^iPr	2.0	25	1	100	45
	Ipc_2BO^tBu	2.0	25	1	100	44, 45
	Ipc_2BOC_{hex}	1.1	25	12	99	46, 98
	Ipc_2BOPh	1.1	25	6	100	98
	Ipc_2BOAc	1.1	25	6	99	104
	$Ipc_2BO_2CCF_3$	1.1	25	3	99.9	104
	$i\text{-}Bu_2AlF$	1.1	25	3	99.9	99
	$i\text{-}Bu_2AlCl$	1.1	25	3	>99.9	100
	$i\text{-}Bu_2AlOH$	2.0	25	3	>99.9	101
	$i\text{-}Bu_2AlOEt$	2.0	25	6	100	101
	$i\text{-}Bu_2AlO^iPr$	2.0	25	6	99	101
	$i\text{-}Bu_2AlO^tBu$	2.0	25	24	100	101, 102
	$i\text{-}Bu_2AlNEt_2$	2.0	25	12	>99.9	103
	$i\text{-}Bu_2AlN^iBu_2$	2.0	25	12	100	103
	$i\text{-}Bu_2AlNPh_2$	2.0	25	24	100	103
$CH_3CH_2CH_2CH=CHCHO$	Ipc_2BCl	1.1	0	3	100	41, 97
	Ipc_2BBr	2.0	0	48	90	41
	Ipc_2BI	2.0	25	48	95	41, 97
	Ipc_2BOH	2.0	25	3	100	45
	Ipc_2BOEt	2.0	25	3	100	45
	Ipc_2BO^iPr	2.0	25	3	100	45
	Ipc_2BO^tBu	2.0	25	3	100	45
	Ipc_2BOC_{hex}	1.1	25	12	100	45
	Ipc_2BOPh	1.1	25	3	100	44, 45
	Ipc_2BOAc	1.1	25	6	98	104
	$Ipc_2BO_2CCF_3$	1.1	25	3	100	104
	$i\text{-}Bu_2AlF$	1.1	25	6	94	99
	$i\text{-}Bu_2AlCl$	1.1	25	6	100	100
	$i\text{-}Bu_2AlOH$	2.0	25	6	100	101
	$i\text{-}Bu_2AlOEt$	2.0	25	24	100	101
	$i\text{-}Bu_2AlO^iPr$	2.0	25	24	100	101
	$i\text{-}Bu_2AlO^tBu$	2.0	25	72	100	101, 102
	$i\text{-}Bu_2AlNEt_2$	4.0	25	148	100	103
	$i\text{-}Bu_2AlN^iBu_2$	4.0	25	148	98	103
	$i\text{-}Bu_2AlNPh_2$	4.0	25	148	98	103
$PhCH=CHCHO$	Ipc_2BF	1.1	0	3	100	96
	Ipc_2BCl	1.1	0	12	100	41, 97
	Ipc_2BBr	1.1	0	48	95	41
	Ipc_2BI	1.1	25	144	100	41
	Ipc_2BOH	2.0	25	12	100	45
	Ipc_2BOEt	2.0	25	6	100	45
	Ipc_2BO^iPr	2.0	25	24	96	45
	Ipc_2BO^tBu	2.0	25	12	100	45
	Ipc_2BOC_{hex}	1.1	25	6	99	45
	Ipc_2BOPh	1.1	25	1	99	44, 45
	Ipc_2BOAc	1.1	25	3	99	104
	$Ipc_2BO_2CCF_3$	1.1	25	1	99.9	104
	$i\text{-}Bu_2AlF$	1.1	25	24	91	99
	$i\text{-}Bu_2AlCl$	1.1	25	24	100	100
	$i\text{-}Bu_2AlOH$	2.0	25	6	100	101
	$i\text{-}Bu_2AlOEt$	2.0	25	12	100	101
	$i\text{-}Bu_2AlO^iPr$	2.0	25	12	100	101
	$i\text{-}Bu_2AlO^tBu$	2.0	25	48	100	101, 102
	$i\text{-}Bu_2AlNEt_2$	2.0	25	24	100	103
	$i\text{-}Bu_2AlN^iBu_2$	2.0	25	24	99	103
	$i\text{-}Bu_2AlNPh_2$	2.0	25	72	97	103

Table 2 (Continued)

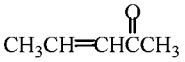
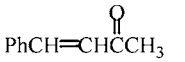
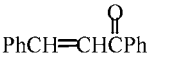
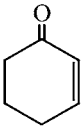
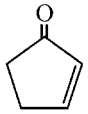
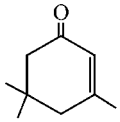
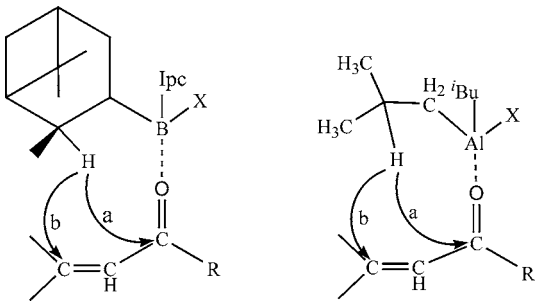
Compound	Reagent[b]	Rgt/ Cpd	Reaction temp. (°C)	Reaction time (h)	Yield (%)	Ref
	Ipc_2BCl	1.1	0	24	100	41, 97
	Ipc_2BBr	1.1	0	24	70	41
	Ipc_2BI	1.1	25	24	25	41
	Ipc_2BOH	2.0	25	24	0	45
	Ipc_2BOEt	2.0	25	24	0	45
	Ipc_2BOPh	2.0	25	24	0	45
	Ipc_2BOAc	1.1	25	24	5	104
	$Ipc_2BO_2CCF_3$	1.1	25	24	40	104
	i-Bu_2AlF	1.1	25	24	30	99
	i-Bu_2AlCl	1.1	25	6	100	100
	i-Bu_2AlOH	2.0	25	6	100	101
	i-Bu_2AlOEt	2.0	25	6	98	101
	i-Bu_2AlO^iPr	2.0	25	24	100	101
	i-Bu_2AlO^tBu	2.0	25	24	97	101, 102
	i-Bu_2AlNEt_2	2.0	25	12	100	103
	i-$Bu_2AlN^iBu_2$	2.0	25	12	100	103
	i-Bu_2AlNPh_2	2.0	25	24	100	103
	Ipc_2BF	1.1	0	24	60	96
	Ipc_2BCl	1.1	25	24	100	41, 97
	Ipc_2BBr	1.1	25	48	95	41
	Ipc_2BI	1.1	25	48	97	41
	Ipc_2BOH	2.0	25	24	0	45
	Ipc_2BOEt	2.0	25	24	0	45
	Ipc_2BOPh	2.0	25	24	0	45
	Ipc_2BOAc	1.1	25	24	15	104
	$Ipc_2BO_2CCF_3$	1.1	25	12	99	104
	i-Bu_2AlF	1.1	25	24	70	99
	i-Bu_2AlCl	1.1	25	24	100	100
	i-Bu_2AlOH	2.0	25	24	98	101
	i-Bu_2AlOEt	2.0	25	24	84	101
	i-Bu_2AlO^iPr	2.0	25	24	86	101
	i-Bu_2AlO^tBu	2.0	25	24	60	101, 102
	i-Bu_2AlNEt_2	4.0	25	148	100	103
	i-$Bu_2AlN^iBu_2$	4.0	25	148	98	103
	i-Bu_2AlNPh_2	4.0	25	148	98	103
	Ipc_2BCl	2.0	25	24	100	41, 97
	Ipc_2BBr	2.0	25	48	70	41
	Ipc_2BI	2.0	25	48	65	41
	Ipc_2BOH	2.0	25	24	0	45
	Ipc_2BOEt	2.0	25	24	0	45
	Ipc_2BOPh	2.0	25	24	0	45
	Ipc_2BOAc	1.1	25	6	11	104
	$Ipc_2BO_2CCF_3$	1.1	25	6	99	104
	i-Bu_2AlF	2.0	25	24	10	99
	i-Bu_2AlCl	2.0	25	72	99.9	100
	i-Bu_2AlOH	2.0	25	120	100	101
	i-Bu_2AlOEt	2.0	25	168	100	101
	i-Bu_2AlO^iPr	2.0	25	240	100	101
	i-Bu_2AlO^tBu	2.0	25	240	100	101
	i-Bu_2AlNEt_2	4.0	25	240	100	103
	i-$Bu_2AlN^iBu_2$	4.0	25	240	98	103
	i-Bu_2AlNPh_2	4.0	25	240	98	103
	Ipc_2BF	1.1	25	0.25	100	96
	Ipc_2BCl	1.1	0	3	>99.9	41, 97
	Ipc_2BBr	1.1	0	48	100	41
	Ipc_2BI	1.1	25	72	100	41
	Ipc_2BOH	1.1	25	3	0	45
	Ipc_2BO^tBu	1.1	25	48	0	45
	i-Bu_2AlCl	1.1	25	3	>99.9	100
	i-Bu_2AlOH	2.0	25	24	100	101
	i-Bu_2AlOEt	2.0	25	24	>99.9	101
	i-Bu_2AlO^iPr	2.0	25	72	100	101
	i-Bu_2AlO^tBu	2.0	25	72	96	101
	i-Bu_2AlNEt_2	2.0	25	24	100	103
	i-$Bu_2AlN^iBu_2$	2.0	25	24	100	103
	i-Bu_2AlNPh_2	2.0	25	24	100	103

Table 2. (Continued)

Compound	Reagent[b]	Rgt/ Cpd	Reaction temp. (℃)	Reaction time (h)	Yield (%)	Ref
	Ipc_2BCl	1.1	0	3	>99.9	41, 97
	Ipc_2BBr	1.1	0	48	100	41
	Ipc_2BI	1.1	25	72	100	41
	Ipc_2BOH	1.1	25	6	0	45
	Ipc_2BO^tBu	1.1	25	6	0	45
	i-Bu_2AlCl	1.1	25	12	100	100
	i-Bu_2AlOH	2.0	25	24	100	11
	i-Bu_2AlOEt	2.0	25	72	100	101
	i-Bu_2AlO^iPr	2.0	25	120	100	101
	i-Bu_2AlO^tBu	2.0	25	240	100	101
	i-Bu_2AlNEt_2	2.0	25	24	100	103
	i-$Bu_2AlN^iBu_2$	2.0	25	24	100	103
	i-Bu_2AlNPh_2	2.0	25	72	100	103
	Ipc_2BCl	1.1	0	12	100	41, 97
	Ipc_2BBr	1.1	0	48	95	41
	Ipc_2BI	1.1	25	24	90	41
	Ipc_2BOH	1.1	25	12	0	45
	Ipc_2BO^tBu	1.1	25	12	0	45
	Ipc_2BOAc	1.1	25	24	35	104
	$Ipc_2BO_2CCF_3$	1.1	25	12	99.9	104
	i-Bu_2AlF	1.1	25	6	0	99
	i-Bu_2AlCl	1.1	25	6	100	100
	i-Bu_2AlOH	2.0	25	72	100	101
	i-Bu_2AlOEt	2.0	25	72	100	101
	i-Bu_2AlO^iPr	2.0	25	120	>99.9	101
	i-Bu_2AlO^tBu	2.0	25	240	100	101
	i-Bu_2AlNEt_2	2.0	25	72	100	103
	i-$Bu_2AlN^iBu_2$	2.0	25	72	100	103
	i-Bu_2AlNPh_2	2.0	25	72	100	103

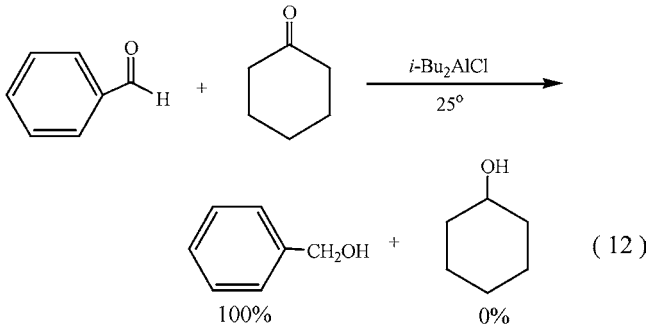
[a] Reaction mixtures contained reagent and compound in THF, Et_2O, or hexane. [b] Ipc = isopinocampheyl. [c] GC yields. [d] Purity of all alcohols obtained is essentially 100%.

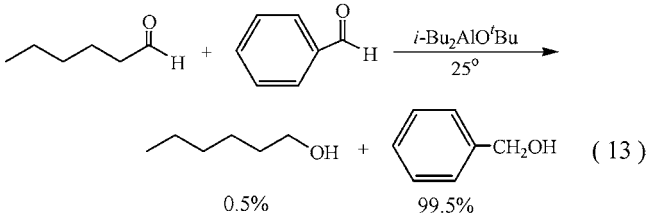
Scheme 6

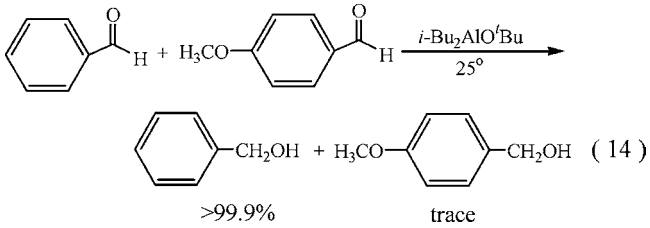


In addition, $[(Ph_3P)CuH]_6$[113] is generally effective for the selective conjugative hydride addition to α,β-unsaturated carbonyl compounds to produce the corresponding saturated carbonyl compounds cleanly.

3. Chemoselective Reduction between Structurally Different Carbonyl Compounds. Only a few examples for the selective reduction of aldehydes in the presence of ketones with the **MPV** type reagents appear in the literature. The first report for such conversion was performed with isopropyl alcohol on dehydrated alumina,[67] where the reduction rate for aldehydes is quite faster than that for ketones.







B-Siamyl-9-**BBN**[13,14] also shows a similar discrimination: a competition between bezaldehyde and acetophenone for a

(110) Brimage, D. R. G.; Davidson, R. S.; Lambeth, P. F. *J. Chem. Soc. C* **1971**, 1241.
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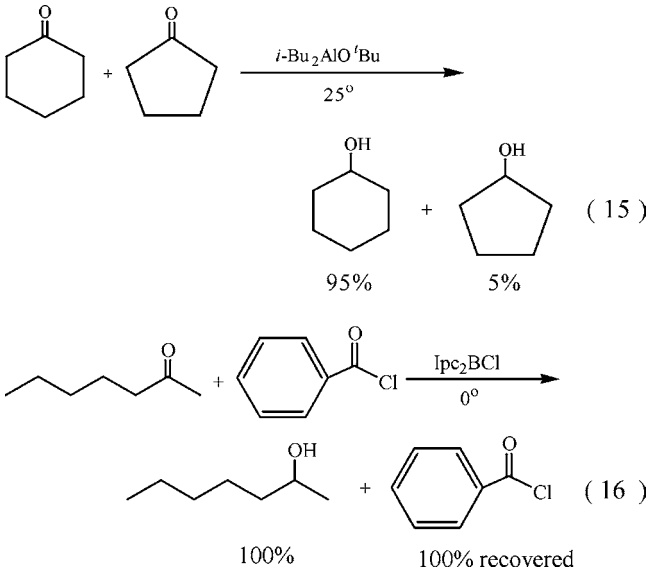
single equivalent of the reagent resulted in a >95% reduction of the aldehyde in 2 h at reflux with no detectable reduction of the ketone.

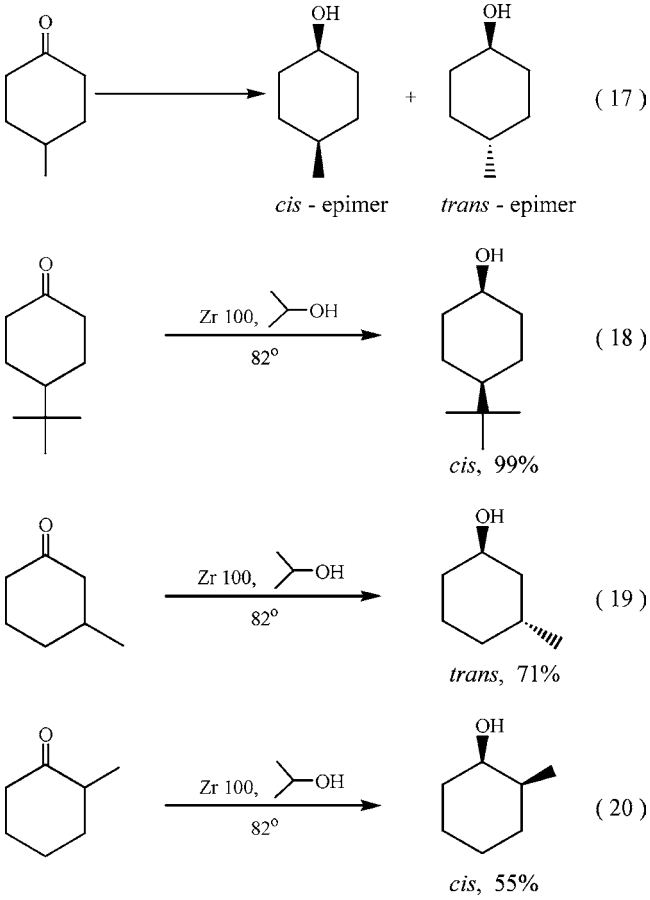
Recently, diisobutylaluminum and diisopinocampheylboron derivatives (**6**−**9** and **15**−**26**) have also been applied to the competitive reduction between structurally different carbonyl compounds with a standard list consisting of representative pairs of an aldehyde−an aldehyde, an aldehyde−a ketone, a ketone−a ketone, and a carbonyl compound−another reducible organic compound, as summarized in Table 3.

As is apparent from the table, both aliphatic and aromatic aldehydes are selectively reduced in the presence of quite a number of different ketones (eq 12). Even more remarkable is the chemoselective discrimination between aldehydes. Thus, benzaldehye can be selectively reduced in the presence of hexanal with *i*-Bu_2AlOR (eq 13). Butanal and hexanal are much more reactive than *p*-anisaldehyde toward *i*-Bu_2-AlOR (eq 14). Furthermore, various reagents can discriminate between structurally different ketones. Even cyclohexanone can be selectively reduced in the presence of cyclopentanone in an up to 95:5 selectivity with *i*-Bu_2AlO^tBu (eq 15). In addition, various functional groups, such as esters, nitriles, amides, and alkenes, are not affected by these reagents. Even acid chlorides are inert to the reagents (eq 16). Such an exceptional chemoselectivity is rather surprising. These results seem to arise from the selective coordination of the acidic reagent to one of the two carbonyl compounds.



Various reducing systems other than the **MPV** type reagents have also been applied efficiently for such chemoselective reductions.[114−127]

4. Stereoselective Reduction of Cycloalkanones. It has been desirable to have reagents that can reduce substituted cycloalkanones to the corresponding one of the two possible epimeric alcohols in 99% or better stereoselectivity. For example, in the reduction of 4-methylcyclohexanone one might expect to obtain *cis*-4-methylcyclohexanol, the thermodynamically less stable epimer, or *trans*-4-methylcyclohexanol, the thermodynamically more stable one (eq 17).



One of the exceptionally promising developments in the area of stereoselective reduction of cyclic ketones must be the advent of hindered trisubstituted borohydrides, such as lithium trisiamylborohydride ($LiSia_3BH$),[128] lithium tri-*s*-butylborohydride (Li^sBu_3BH),[129] potassium 9-*tert*-butyl-9-boratbicyclo[3.3.1]nonane (K9-^{t}Bu-9**BBN**H),[130] lithium (2,3-dimethyl-2-butyl)-*tert*-butoxy borohydride ($LiThx^tBuOBH_2$),[131] and so on.[132] These reagents reduce cyclic ketones with super stereoselectivity to produce the corresponding thermodynamically less stable alcohol epimer.

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Table 3. **Chemoselective reduction between structurally different carbonyl compounds with various MPV type reducing agents[a]**

starting mixture (A + B)	reagent	temp (°C)	time (h)	ratio of reduction products[b] from A and B (A′:B′)	ref
butanal + hexanal	*i*-Bu_2AlCl	25	1	95:5	29a
	i-Bu_2AlOH	25	3	57:43	30d
	i-Bu_2AlOEt	25	6	60:40	30d
	i-Bu_2AlO^iPr	25	6	65:35	30d
	i-Bu_2AlO^tBu	25	12	66:34	30d
	i-Bu_2AlNEt_2	25	3	80:20	103
	i-$Bu_2AlN^iBu_2$	25	3	82:18	103
	i-Bu_2AlNPh_2	25	6	70:30	103
butanal + benzaldehyde	*i*-Bu_2AlCl	25	0.5	95:5	29a
	i-Bu_2AlOH	25	3	20:80	30d
	i-Bu_2AlOEt	25	6	5:95	30d
	i-Bu_2AlO^iPr	25	6	4:96	30d
	i-Bu_2AlO^tBu	25	12	3:97	30d
	i-Bu_2AlNEt_2	25	1	30:70	103
	i-$Bu_2AlN^iBu_2$	25	1	27:73	103
	i-Bu_2AlNPh_2	25	3	25:75	103
hexanal + benzaldehyde	Ipc_2BCl	0	1	40:60	41
		−30	3	20:80	41
	i-Bu_2AlCl	25	0.5	3:97	29a
	i-Bu_2AlOH	25	3	20:80	30d
	i-Bu_2AlOEt	25	3	2:98	30d
	i-Bu_2AlO^iPr	25	3	1:99	30d
	i-Bu_2AlO^tBu	25	6	0.5:99.5	30d
	i-Bu_2AlNEt_2	25	1	25:75	103
	i-$Bu_2AlN^iBu_2$	25	1	25:75	103
	i-Bu_2AlNPh_2	25	3	30:70	103
hexanal + *p*-anisaldehyde	Ipc_2BCl	0	1	60:40	41
	i-Bu_2AlOH	25	3	83:17	30d
	i-Bu_2AlOEt	25	6	92:8	30d
	i-Bu_2AlO^iPr	25	6	93:7	30d
	i-Bu_2AlO^tBu	25	12	99:1	30d
	i-Bu_2AlNEt_2	25	3	80:20	103
	i-$Bu_2AlN^iBu_2$	25	3	85:15	103
	i-Bu_2AlNPh_2	25	6	70:30	103
benzaldehyde + *p*-anisaldehyde	Ipc_2BCl	0	1	60:40	41
	i-Bu_2AlOH	25	3	90:10	30d
	i-Bu_2AlOEt	25	3	99.5:0.5	30d
	i-Bu_2AlO^iPr	25	3	99.5:0.5	30d
	i-Bu_2AlO^tBu	25	6	>99.9:tr	30d
	i-Bu_2AlNEt_2	25	3	80:20	103
	i-$Bu_2AlN^iBu_2$	25	3	85:15	103
	i-Bu_2AlNPh_2	25	6	80:20	103
hexanal + cyclohexanone	Ipc_2BCl	0	3	70:30	41
		−30	3	100:0	41
	Ipc_2BOH	25	12	100:0	43, 45
	Ipc_2BOEt	25	12	100:0	45
	Ipc_2BO^iPr	25	12	100:0	45
	Ipc_2BO^tBu	25	6	100:0	44, 45
	i-Bu_2AlCl	25	1	97:3	29a
	i-Bu_2AlOH	25	3	85:15	30d
	i-Bu_2AlOEt	25	6	100:0	30d
	i-Bu_2AlO^iPr	25	6	98:2	30d
	i-Bu_2AlO^tBu	25	12	>99.9:tr	30d
	i-Bu_2AlNEt_2	25	3	70:30	103
	i-$Bu_2AlN^iBu_2$	25	3	80:20	103
	i-Bu_2AlNPh_2	25	6	70:30	103
hexanal + 2-heptanone	Ipc_2BCl	0	3	100:0	41
	Ipc_2BOH	25	12	100:0	43, 45
	Ipc_2BOEt	25	12	90:10	45
	Ipc_2BO^iPr	25	6	95:5	45
	Ipc_2BO^tBu	25	6	100:0	44, 45
	Ipc_2BOC_{hex}	25	24	100:0	46, 98
	Ipc_2BOPh	25	12	100:0	98
	Ipc_2BOAc	0	3	100:0	104
		25	1	100:0	104
	$Ipc_2BO_2CCF_3$	0	3	100:0	104
		25	1	99:1	104
	i-Bu_2AlCl	25	1	100:0	29a
	i-Bu_2AlOH	25	3	91:9	30d
	i-Bu_2AlOEt	25	6	100:0	30d
	i-Bu_2AlO^iPr	25	6	100:0	30d
	i-Bu_2AlO^tBu	25	12	100:0	30d
	i-Bu_2AlNEt_2	25	3	70:30	103
	i-$Bu_2AlN^iBu_2$	25	3	87:13	103
	i-Bu_2AlNPh_2	25	6	70:30	103

Table 3. (Continued)

starting mixture (A + B)	reagent	temp (°C)	time (h)	ratio of reduction products[b] from A and B (A′:B′)	ref
hexanal + acetophenone	Ipc_2BCl	0	3	100:0	41
	Ipc_2BOH	25	24	100:0	43, 45
	Ipc_2BOEt	25	6	>99.9:0	45
	Ipc_2BO^iPr	25	6	>99.9:0	45
	Ipc_2BO^tBu	25	24	100:0	44, 45
	Ipc_2BOC_{hex}	25	24	100:0	46, 98
	Ipc_2BOPh	25	12	100:0	98
	Ipc_2BOAc	25	3	100:0	104
	$Ipc_2BO_2CCF_3$	25	3	100:0	104
	i-Bu_2AlCl	25	1	100:0	29a
	i-Bu_2AlOH	25	3	90:10	30d
	i-Bu_2AlOEt	25	6	100:0	30d
	i-Bu_2AlO^iPr	25	6	99:1	30d
	i-Bu_2AlO^tBu	25	12	99.5:0.5	30d
	i-Bu_2AlNEt_2	25	3	90:10	103
	i-$Bu_2AlN^iBu_2$	25	3	92:8	103
	i-Bu_2AlNPh_2	25	6	70:30	103
hexanal + benzophenone	Ipc_2BCl	0	3	100:0	41
	Ipc_2BOH	25	24	100:0	43, 45
	Ipc_2BOEt	25	24	100:0	45
	Ipc_2BO^iPr	25	6	>99.9:0	45
	Ipc_2BO^tBu	25	6	100:0	44, 45
	Ipc_2BOC_{hex}	25	24	100:0	46, 98
	Ipc_2BOPh	25	12	100:0	98
	Ipc_2BOAc	0	3	100:0	104
	$Ipc_2BO_2CCF_3$	0	3	100:0	104
	i-Bu_2AlCl	25	1	100:0	29a
	i-Bu_2AlOH	25	3	95:5	30d
	i-Bu_2AlOEt	25	6	100:0	30d
	i-Bu_2AlO^iPr	25	6	100:0	30d
	i-Bu_2AlO^tBu	25	12	100:0	30d
	i-Bu_2AlNEt_2	25	3	92:8	103
	i-$Bu_2AlN^iBu_2$	25	3	95:5	103
	i-Bu_2AlNPh_2	25	6	90:10	103
cyclohexanone + cyclopentanone	Ipc_2BCl	0	1	65:35	41
		−30	3	80:20	41
	i-Bu_2AlCl	25	3	90:10	29a
	i-Bu_2AlOH	25	24	55:45	30d
	i-Bu_2AlOEt	25	24	90:10	30d
	i-Bu_2AlO^iPr	25	24	92:8	30d
	i-Bu_2AlO^tBu	25	48	95:5	30d
	i-Bu_2AlNEt_2	25	12	70:30	103
	i-$Bu_2AlN^iBu_2$	25	12	76:24	103
	i-Bu_2AlNPh_2	25	24	75:25	103
cyclohexanone + 2-heptanone	Ipc_2BCl	0	3	99.5:0.5	41
	i-Bu_2AlCl	25	3	99.9:0.1	29a
	i-Bu_2AlOH	25	24	60:40	30d
	i-Bu_2AlOEt	25	24	100:0	30d
	i-Bu_2AlO^iPr	25	24	100:0	30d
	i-Bu_2AlO^tBu	25	48	100:0	30d
	i-Bu_2AlNEt_2	25	12	75:25	103
	i-$Bu_2AlN^iBu_2$	25	12	80:20	103
	i-Bu_2AlNPh_2	25	24	60:40	103
cyclohexanone + acetophenone	Ipc_2BCl	0	3	95:5	41
		−30	12	100:0	41
	i-Bu_2AlCl	25	3	98:2	29a
	i-Bu_2AlOH	25	24	67:33	30d
	i-Bu_2AlOEt	25	24	95:5	30d
	i-Bu_2AlO^iPr	25	24	90:10	30d
	i-Bu_2AlO^tBu	25	48	90:10	30d
	i-Bu_2AlNEt_2	25	12	70:30	103
	i-$Bu_2AlN^iBu_2$	25	12	75:25	103
	i-Bu_2AlNPh_2	25	24	60:40	103
cyclohexanone + benzophenone	i-Bu_2AlCl	25	3	99.9:0.1	29a
	i-Bu_2AlOH	25	24	76:24	30d
	i-Bu_2AlOEt	25	24	100:0	30d
	i-Bu_2AlO^iPr	25	24	100:0	30d
	i-Bu_2AlO^tBu	25	48	100:0	30d
	i-Bu_2AlNEt_2	25	12	60:40	103
	i-$Bu_2AlN^iBu_2$	25	12	85:15	103
	i-Bu_2AlNPh_2	25	24	80:20	103
acetophenone + 2-heptanone	i-Bu_2AlCl	25	3	100:0	29a
	i-Bu_2AlOH	25	48	55:45	30d
	i-Bu_2AlOEt	25	48	100:0	30d
	i-Bu_2AlO^iPr	25	48	>99.9:tr	30d

Table 3. (Continued)

starting mixture (A + B)	reagent	temp (°C)	time (h)	ratio of reduction products[b] from A and B (A′:B′)	ref
	i-Bu_2AlO^tBu	25	72	96:4	30d
	i-Bu_2AlNEt_2	25	12	75:25	103
	i-$Bu_2AlN^iBu_2$	25	12	80:20	103
	i-Bu_2AlNPh_2	25	24	60:40	103
2-heptanone + benzophenone	*i*-Bu_2AlCl	25	12	91:9	29a
	i-Bu_2AlOH	25	96	53:47	30d
	i-Bu_2AlOEt	25	96	95:5	30d
	i-Bu_2AlO^iPr	25	96	94:6	30d
	i-Bu_2AlO^tBu	25	120	94:6	30d
	i-Bu_2AlNEt_2	25	12	75:25	103
	i-$Bu_2AlN^iBu_2$	25	12	79:21	103
	i-Bu_2AlNPh_2	25	24	80:20	103
acetophenone + benzophenone	Ipc_2BCl	0	3	99:1	41
	i-Bu_2AlCl	25	3	99.9:0.1	29a
	i-Bu_2AlOH	25	48	57:43	30d
	i-Bu_2AlOEt	25	48	100:0	30d
	i-Bu_2AlO^iPr	25	48	100:0	30d
	i-Bu_2AlO^tBu	25	72	96:4	30d
	i-Bu_2AlNEt_2	25	12	75:25	103
	i-$Bu_2AlN^iBu_2$	25	12	90:10	103
	i-Bu_2AlNPh_2	25	24	65:35	103
hexanal + hexanoyl chloride	Ipc_2BCl	0	3	99.9:0.1	41
	Ipc_2BOH	25	12	100:0	43, 45
	Ipc_2BOEt	25	12	100:0	45
	Ipc_2BO^iPr	25	6	100:0	45
	Ipc_2BO^tBu	25	6	100:0	44, 45
	Ipc_2BOC_{hex}	25	24	100:0	46, 98
	Ipc_2BOPh	25	12	100:0	98
	Ipc_2BOAc	25	1	100:0	104
	$Ipc_2BO_2CCF_3$	25	1	100:0	104
	i-Bu_2AlCl	25	1	100:0	29a
	i-Bu_2AlOH	25	3	100:0	30d
	i-Bu_2AlOEt	25	6	100:0	30d
	i-Bu_2AlO^iPr	25	6	100:0	30d
	i-Bu_2AlO^tBu	25	12	100:0	30d
hexanal + benzoyl chloride	Ipc_2BOH	25	12	100:0	43, 45
	Ipc_2BOEt	25	6	100:0	45
	Ipc_2BO^iPr	25	6	100:0	45
	Ipc_2BO^tBu	25	12	100:0	44, 45
	i-Bu_2AlOH	25	3	100:0	30d
	i-Bu_2AlOEt	25	6	100:0	30d
	i-Bu_2AlO^iPr	25	6	100:0	30d
	i-Bu_2AlO^tBu	25	12	100:0	30d
2-heptanone + benzoyl chloride	Ipc_2BCl	0	6	100:0	41
	i-Bu_2AlCl	25	12	100:0	29a
	i-Bu_2AlOH	25	24	98:2	30d
	i-Bu_2AlOEt	25	96	99:1	30d
	i-Bu_2AlO^iPr	25	96	100:0	30d
	i-Bu_2AlO^tBu	25	120	100:0	30d

[a] 1 equiv of reagent added to an equimolar mixture of starting compounds. [b] Total yields of product alcohols were ≥99%.

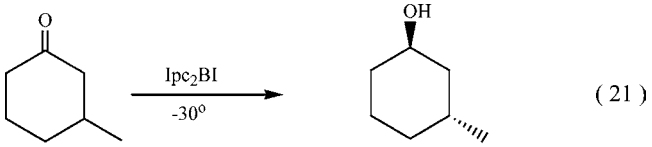
Recently, zeolite-catalyzed **MPV** reactions have been applied to the stereoselective reduction of 4-*tert*-butylcyclohexanone. Thus, zeolite beta (**BEA**) achieves such reduction to produce *cis*-4-*tert*-butylcyclohexanol, the thermodynamically less stable isomer, in a higher selectivity than 95%.[72,74a,b] Aluminum-free titanium beta([Ti]-**BEA**) zeolite also shows the same stereoselectivity of 98% to the *cis*-isomer.[72,74c] Various Na**BEA** zeolites with isopropyl alcohol can convert 4-*tert*-butylcyclohexanone to *cis*-4-*tert*-butylcyclohexanol in 96−99% selectivity with high conversion yields.[133] Another kind of zeolite such as Al-free Zr−Beta zeolite ([Zr]-**BEA**) can reduce 4-methyl- and 4-*tert*-butylcyclohexanone to the *cis*-isomer in a 99:1 ratio with high conversion yields, but the selectivity for reduction of 2-methyl- and 3-methylcyclohexanone does not reach that high[134] (eqs 18−20). In addition, a magnesium−aluminum oxide such as MgO−Al_2O_3[71i] and the supported zirconium 1-propoxide[52] have also been examined for such stereoselective reductions but showed somewhat lower selectivities than those achieved by the former zeolite beta catalysts.

(132) For other stereoselective reducing agents to produce the less stable alcohols and related reviews, see: (a) Corey, E. J.; Becker, K. B.; Varma, R. K. *J. Am. Chem. Soc.* **1972**, *94*, 8616. (b) Corey, E. J.; Albonico, S. M.; Koelliker, U.; Schaaf, T. K.; Varma, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 1491. (c) Corey, E. J.; Varma, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 7319. (d) Brown, H. C.; Kramer, G. W.; Hubbard, J. L.; Krishnamurthy, S. *J. Organomet. Chem.* **1980**, *188*, 1. (e) Cha, J. S.; Min, S. J.; Kim, J. M.; Kwon, O. O.; Jeoung, M. K. *Org. Prep. Proced. Int.* **1993**, *25*, 444. (f) Krishnamurthy, S. *Aldrichimica Acta* **1974**, *7*, 55. (g) Brown, C. A.; Krishnamurthy, S. *J. Organomet. Chem.* **1978**, *156*, 111. (h) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567.

(133) Copez, J.; Valente, J. S.; Clacens, J.-M.; Figueras, F. *J. Catal.* **2002**, *208*, 30.

(134) Zhu, Y.; Chuah, G.; Jaenicke, S. *J. Catal.* **2004**, *227*, 1.

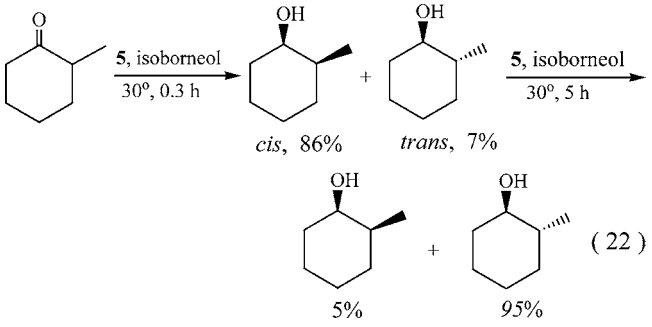
Very recently, diisopinocampheylhaloboranes such as Ipc_2BCl, Ipc_2BBr, and Ipc_2BI have been examined for their stereoselectivities in the reduction of typical cyclic ketones. The stereoselectivity for producing the thermodynamically less stable isomer increases dramatically with an increasing steric size of the halogen substituent. Especially the iodo derivative appears to be a really ideal stereoselective reducing agent, showing an essentially 100% selectivity in the reduction of representative cyclic ketones at −30 °C. However, Ipc_2BI has a drawback in producing alcohols, showing significantly low conversion yields[135] (eq 21).



(21)

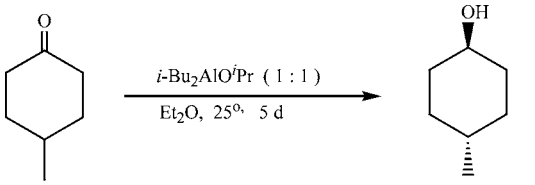
trans, 99% (45% conversion)

The other goal in the area of stereoselective reduction of cycloalkanones is to have reagents that can produce the thermodynamically more stable epimeric alcohols in high stereoselectivity. The observation that the alteration in the *cis*/*trans* selectivity might be possible was first reported by Jackman et al. They observed that in **MPV** reactions of substituted cycloalkanones the yield of the thermodynamically less stable isomer decreases gradually to reach the more stable isomer dominating as a result of the reversibility of the reaction after a prolonged reaction time. Konish et al. also observed that the ratio of *cis*/*trans* in the **MPV** reduction of 2-methylcyclohexanone with porphynatoaluminum chloride (**5**) as a catalyst and isoborneol as a reductant is time dependent owing to the concomitant epimerization of the reduced products. Thus, the initially formed *cis*/*trans* isomer ratio of 93:7 gradually changed with time to furnish a *cis*/*trans* ratio of 5:95 after 5 h (eq 22).



(22)

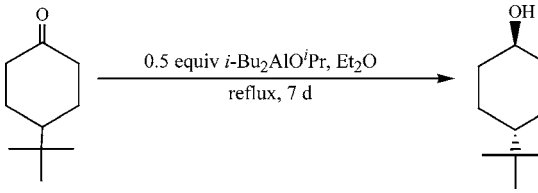
Recently, *i*-Bu_2AlO^iPr has been applied to the stereoselective reduction of representative monocyclic and bicyclic ketones.[136] Experiments were carried out under two different conditions: a mixture of ketone and reagent (1:1) at 25 °C in Et_2O or a mixture of ketone and reagent (2:1) in refluxing Et_2O.[136] In the experiment on an equimolar mixture of reagent and ketone at 25 °C, the stereochemistry of reduction appears apparently dependent on the reaction time. The stereoselectivity increases consistently with an increase of reaction time to afford the thermodynamically more stable isomer alcohols exclusively (eq 23), with the exception of camphor which is resistant to reduction under the reaction conditions. Further-



(23)

> 99%, *trans*

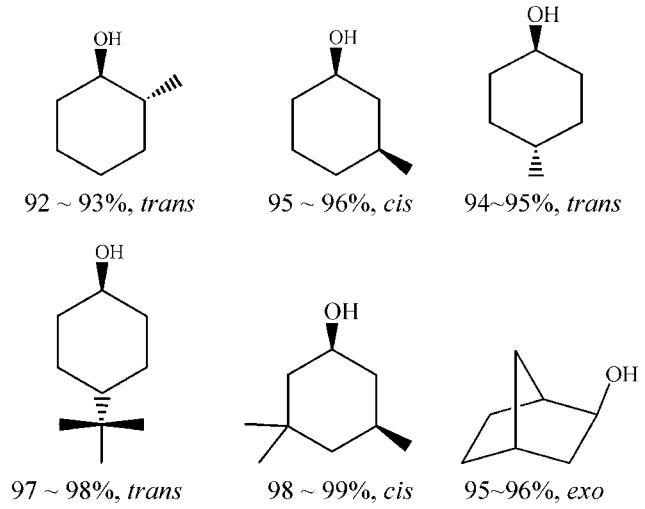
more, like triisobutylaluminum (**TIBA**), it has been found that the isobutyl group of *i*-Bu_2AlO^iPr is involved in this reduction.[136b] Therefore, 2 equiv of ketone are reduced with 1 equiv of the reagent in refluxing Et_2O, although the second ketone is reduced at a relatively slow rate (eq 24). This seems



(24)

98%, *trans*

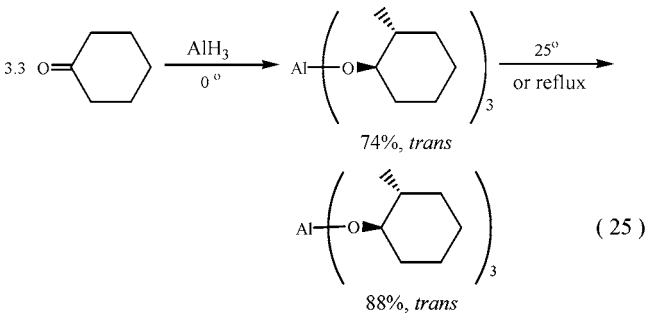
to be a phenomenon that must rise where the thermodynamically less stable alcohol isomer, one of the two isomers



produced by reduction with *i*-Bu_2AlO^iPr, is converted to the more stable one by thermodynamically controlled isomer equilibration via an **MPV** type reduction.[136a] Such a time dependence on the stereochemistry has also been found in the reduction of cyclic ketones with other aluminum derivatives such as **TIBA**[19,137] and 1-pyrrolyldiisobutylalane.[138]

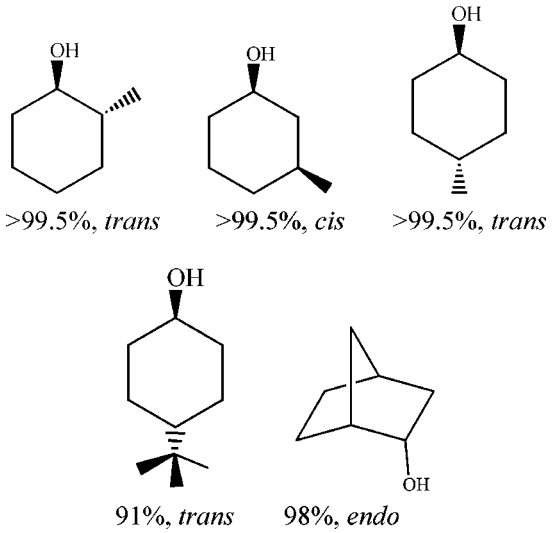
Such a mechanism involving thermodynamically controlled isomer equilibration can be extended to the utilization of diisobutylaluminum hydride (**DIBAL-H**) itself. When the reduction of excess cyclic ketone with **DIBAL-H** is carried

(135) Cha, J. S.; Kwon, O. O.; Lee, K. W.; Kim, J. M. *Bull. Korean Chem. Soc.* **2005**, *26*, 652.
(136) (a) Cha, J. S.; Kwon, O. O. *J. Org. Chem.* **1997**, *62*, 3019. (b) Cha, J. S.; Kwon, O. O. *Bull. Korean Chem. Soc.* **1997**, *18*, 689.
(137) (a) Heinsohn, G. E.; Ashby, E. C. *J. Org. Chem.* **1973**, *38*, 4232. (b) Winterfeldt, E. *Synthesis* **1975**, *617*.
(138) Kwon, O. O.; Cha, J. S. *Bull. Korean Chem. Soc.* **2000**, *21*, 659.

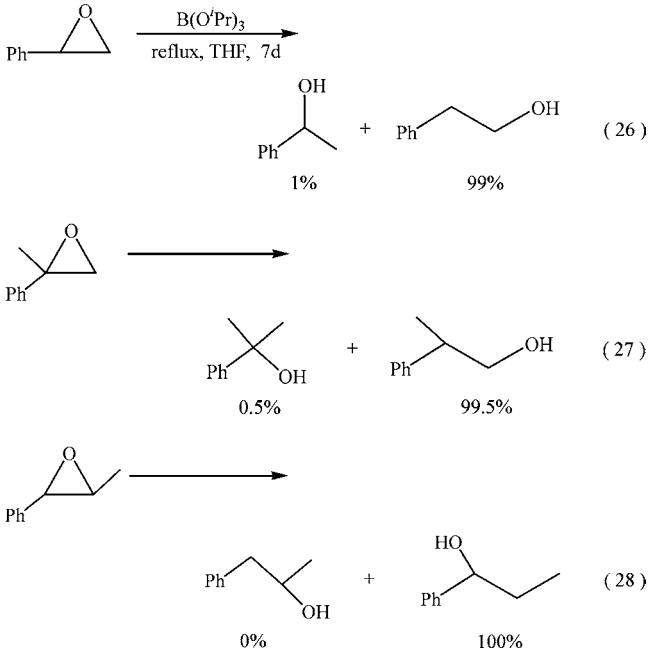


(25)

out at 0 °C, only the free hydride is involved and hence only



1 equiv of ketone is reduced to show low stereoselectivity.

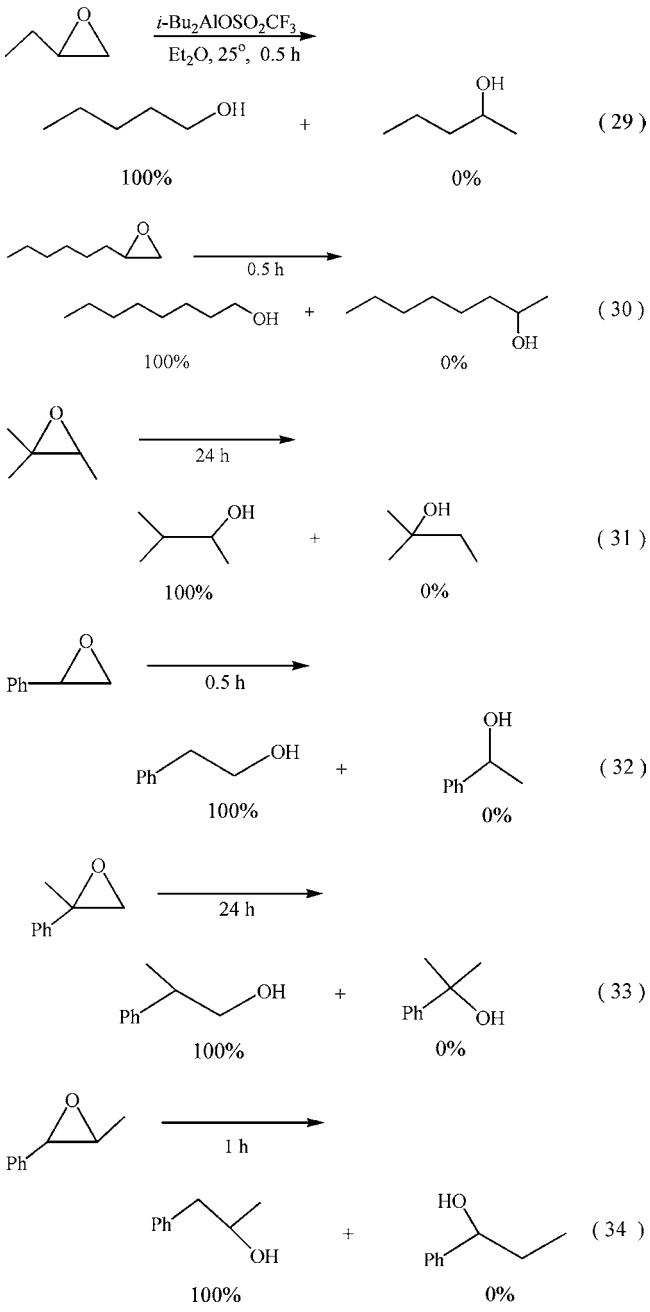


(26)

(27)

(28)

However, when the reduction is repeated at 25 °C or under reflux, one isobutyl group as well as the free hydride of **DIBAL-H** is also involved. And the system just follows the thermodynamically controlled isomer equilibration that is similar to the case of *i*-Bu_2AlO^iPr (Scheme 7).



(29)

(30)

(31)

(32)

(33)

(34)

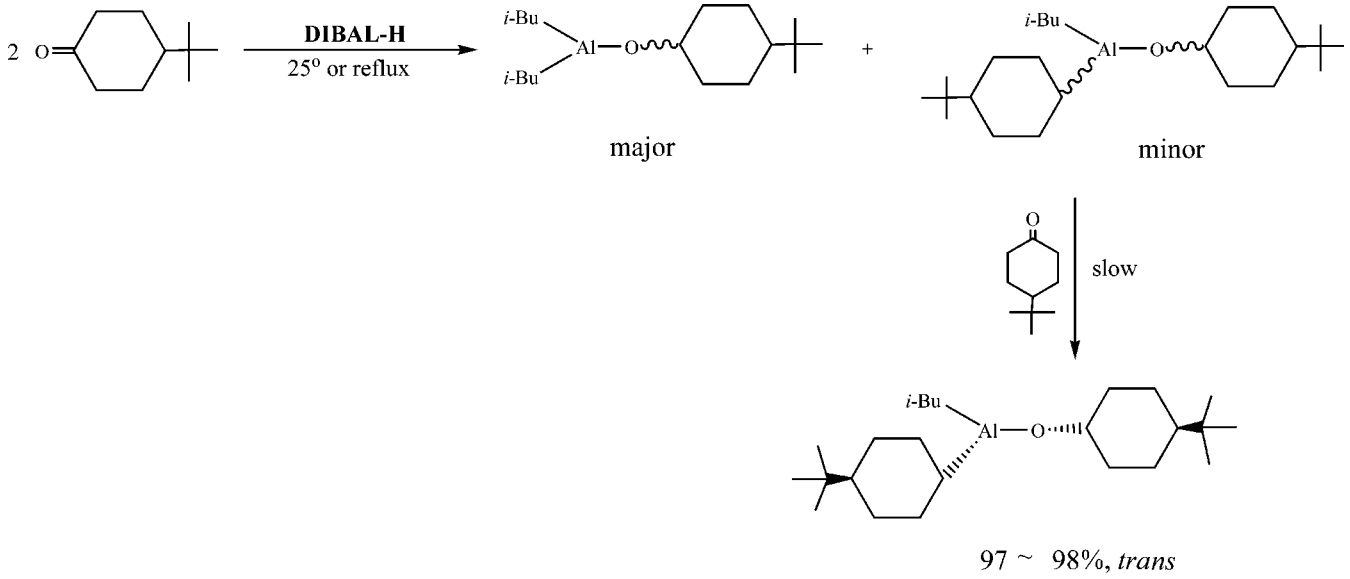
A similar trend has been observed in the reduction of cyclic ketones with AlH_3.[139] In this case, 3.3 equiv of ketone are needed. However, the stereoselectivity accomplished in this reduction appears somewhat lower than that achieved by diisobutylaluminum derivatives (eq 25).

A solution of BH_3-THF can also be applied to such stereoselective reductions.[140] Because of the relatively smaller size ofthe boron atom than that of the aluminum atom, the stereochemistry of reduction is dependent on the reaction time only under reflux, while the reactions at 0 °C and 25 °C show no such time dependence.

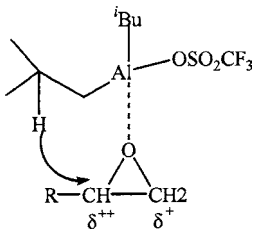
5. Regioselective Ring-Opening of Epoxides. The first report on the **MPV** type reduction of epoxides seems to be the communication which describes the reaction of epoxides

(139) Cha, J. S.; Moon, S. J.; Kwon, O. O.; Lee, Y. R. *Bull. Korean Chem. Soc.* **2000**, *21*, 128.
(140) Cha, J. S.; Moon, S. J.; Park, J. H. *J. Org. Chem.* **2001**, *66*, 7514.

Scheme 7



Scheme 8

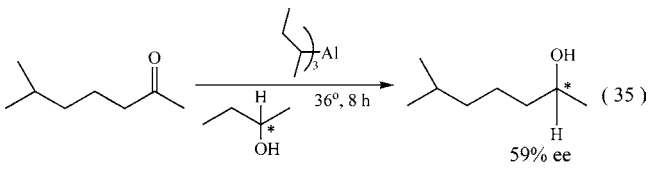


with boron isopropoxide.[141] The reagent is absolutely inert toward aliphatic epoxides such as 1,2-epoxybutane, 1,2-epoxyoctane, and 1,2-epoxycyclohexane even in refluxing THF for 7 days. On the other hand, the reaction of aromatic epoxides proceeds slowly in refluxing THF to produce exclusively the less substituted alcohols (eqs 26−28).

However, the newly devised *i*-$Bu_2AlOSO_2CF_3$ can reduce a variety of aliphatic and aromatic epoxides readily at 25 °C to the ring-opened alcohol products.[142] In this reaction, the less substituted alcohols are produced as the sole product (eqs 29−34).

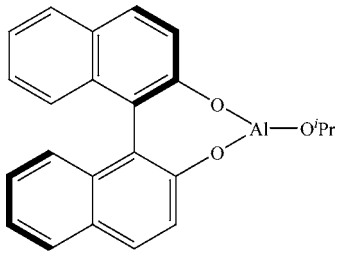
It may be concluded that the β-hydrogen transfer from reagent occurs only at the more positive carbon of the coordinated epoxy ring (Scheme 8).

5. Asymmetric Reduction. A. Intermolecular MPV Reduction. The asymmetric versions of the intermolecular **MPV** reduction of ketones employ optically active alcohols as chiral sources. The first experimental report on the asymmetric **MPV** reduction of ketones seems to be the publication by Doering and Young in 1949 of a preliminary communication describing reductions of ketones with optically active 2-butanol catalysed by aluminum alkoxide[32a] (eq 35). Such intermolecular **MPV** reduction has been continued



(35)

using a variety of optically active alcohols. However, only low or moderate enantioselectivity has been realized by this methodology.[32,144] Recently, the enantioselective, catalytic **MPV** reduction that utilizes isopropyl alcohol as a hydride source and is catalyzed by $AlMe_3$ and enantiopure 2,2′-dihydroxy-1,1′-biphenyl converts prochiral aromatic ketones to optically active alcohols in up to 83% ee.[145] The active catalyst was proposed as **30**.



30

Grignard reagents having an H atom on their β-carbon atom, derived from optically active alkyl halides, can also be applied to the asymmetric reduction of ketones.[146] The reduction of prochiral ketones by the optically active Grignard reagent from (+)-1-chloro-2-methylbutane afforded alcohols in low or moderate optical yields, but usually the chemical yields of the desired reduction products are quite low due to the competition with the addition reaction.[147] The enantioselectivity of these asymmetric reductions has been interpreted in terms of a six-membered cyclic transition state for the hydrogen transfer step [32a,147] (Scheme 9).

(141) Cha, J. S.; Park, J. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 1377.
(142) Cha, J. S.; Park, S. J. Manuscript in preparation.
(143) Doering, W. von E.; Aschner, T. C. *J. Am. Chem. Soc.* **1953**, *75*, 393.
(144) Campbell, E. J.; Zhou, H.; Ngugen, S. T. *Org. Lett.* **2001**, *3*, 2391.
(145) Campbell, E. J.; Zhou, H.; Ngugen, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1020.
(146) (a) Streitweiser, A., Jr.; Wolfe, J. R.; Schaeffer, W. D. *Tetrahedron* **1959**, *6*, 338. (b) Foley, W. M.; Welch, F. J.; La Combe, E. M.; Mosher, H. S. *J. Am. Chem. Soc.* **1959**, *81*, 2779. (c) MacLeod, R.; Welch, F. J.; Mosher, H. S. *J. Am. Chem. Soc.* **1960**, *82*, 876. (d) Burrows, E. P.; Welch, F. J.; Mosher, H. S. *J. Am. Chem. Soc.* **1960**, *82*, 880. (e) Birtwistle, J. S.; Lee, K.; Morrison, J. D.; Sanderson, W. A.; Mosher, H. S. *J. Org. Chem.* **1964**, *29*, 37.

Scheme 9

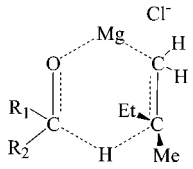
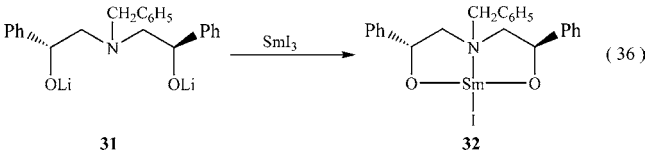


Table 4. Reduction of benzaldehyde-1-*d* with chiral *B*-alkyl-9-BBN reagents

reagent	ee, %	config
11	90	*S*
12	47	*S*
13	75	*R*
14	61	*S*

However, Evans and co-workers devised a catalytic, highly enantioselective **MPV** reduction using a chiral samarium catalyst.[148] The complex **32**, generated from the 1:1 chiral ligand **31**, and SmI_3 (eq 36), catalyzes the reduction of aromatic ketones by isopropyl alcohol to give optically active alcohols in up to 97% ee.



(36)

31 **32**

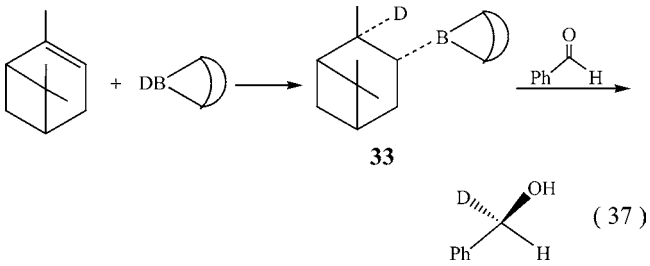
Very recently, a practical synthesis of ephedrine analogues with a high enantioselectivity by a highly diastereoselective **MPV** reduction of protected α-amino aromatic ketones using catalytic aluminum isopropoxide has been reported.[149] The high selectivity seems to arise from the chelation of the nitrogen atom to the aluminum (Scheme 10).

As described above, trialkylboranes are noted for their tolerance of a wide variety of functional groups.[3,5] However, Midland and co-workers demonstrated that certain *B*-alkyl-9-**BBN** reagents, like *B*-Siamyl-9-**BBN** (**10**), in contrast to many other trialkylboranes, can reduce aldehydes to the corresponding alcohols under exceptionally mild conditions,[150] because the presence of a tertiary *β*-hydrogen favors a fast reaction. In this reduction, the B-alkyl group is converted into the corresponding olefin (eq 5) via a six-membered cyclic transition state as depicted in Scheme 3. This observation has been brilliantly extended to the asymmetric reduction of benzaldehyde-1-*d* to optically active benzyl-α-*d*-alcohol using various chiral *B*-alkyl-9-**BBN** reagents [36a,b] (**11**−**14**). Among these reagents, **11** is the most effective chiral reducing agent (Table 4).

Table 5. Reduction of aldehydes with deuterated *B*-3-pinanyl-9-BBN (33)

aldehydes	alcohols	ee, %
$CH_3CH_2CH_2CHO$	$CH_3CH_2CH_2CHDOH$	101
$CH_3(CH_2)_4CHO$	$CH_3(CH_2)_4CHDOH$	89
$(CH_3)_3CCHO$	$(CH_3)_3CHDOH$	98
$(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCHO$	$(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCHDOH$	81
$C_6H_5CH{=}CHCHO$	$C_6H_5CH{=}CHCHDOH$	84
C_6H_5CHO	C_6H_5CHDOH	98
p-ClC_6H_4CHO	*p*-ClC_6H_4CHDOH	101
p-$O_2NC_6H_4CHO$	*p*-$O_2NC_6H_4CHDOH$	100
p-$CH_3C_6H_4CHO$	*p*-$CH_3C_6H_4CHDOH$	89
p-$CH_3OC_6H_4CHO$	*p*-$CH_3OC_6H_4CHDOH$	82
p-$(CH_3)_2NC_6H_4CHO$	*p*-$(CH_3)_2NC_6H_4CHDOH$	71

It has been observed that the *β*-hydrogen is actually utilized for the reduction. Therefore, that hydrogen added via the hydroboration process is the reducing hydrogen. In fact, the deuterated organoborane **33**, obtained by deuterioboration of α-pinene with 9-**BBN**-9-*d* quantitatively transfers deuterium to benzaldehyde (eq 37). The availability of the deuterated reagent (**33**) allows the asymmetric reduction of a variety of aldehydes (Table 5).

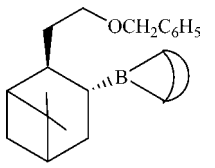


33

(37)

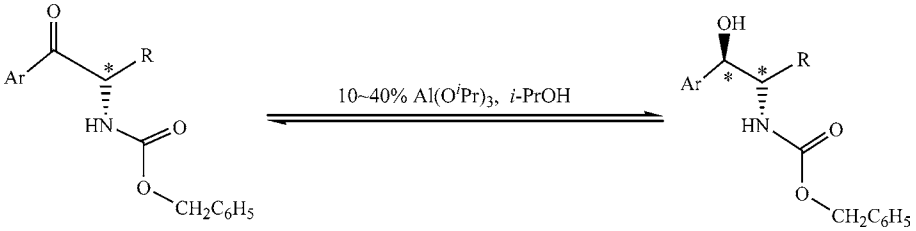
Soon after, several improved procedures to increase the rate of reaction and the enantiomeric efficiency by carrying out the reaction in more concentrated solution[151] or in highly pressurized neat compounds[152] have appeared. By these procedures most prochiral ketones are converted to the optically active alcohols in efficiencies approaching 100% ee.[36g,151,152]

In addition, the 9-**BBN** derivative of nopol benzyl ether, **NB**-Enantrane (**34**), has been successfully applied to the asymmetric reduction of α,*β*-acetylenic ketones to propargyl alcohols in 86−96% enantiomeric purity.[36f] *B*-(*cis*-10-pina-

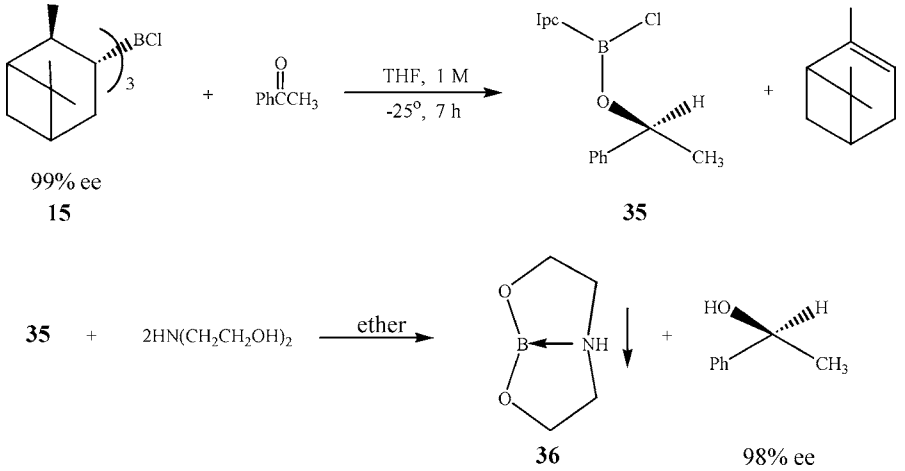


34

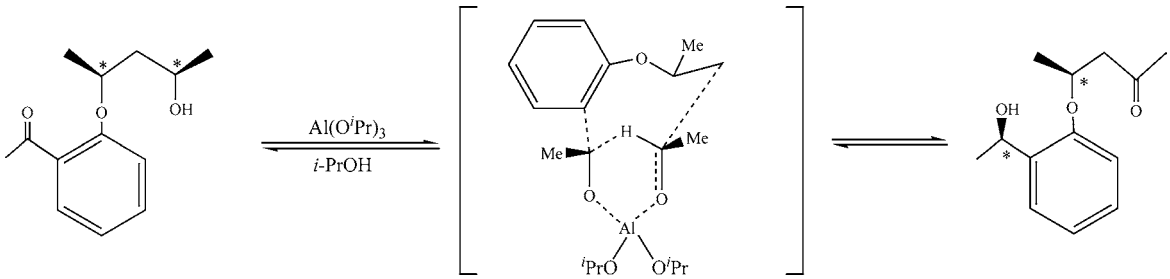
Scheme 10



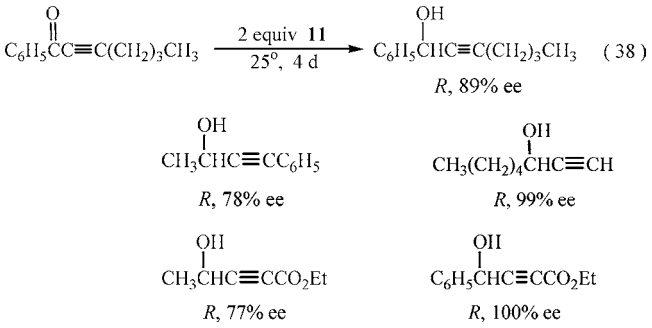
Scheme 11



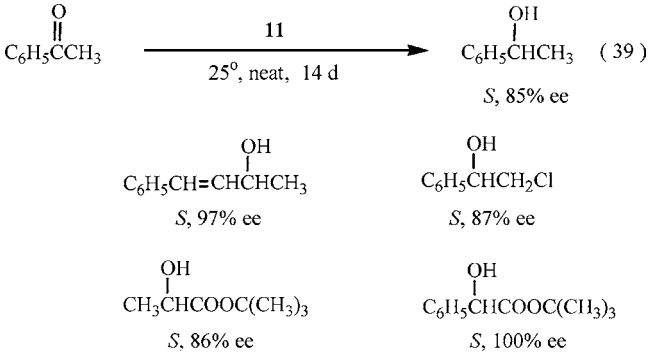
Scheme 12



nyl)-9-**BBN** (**12**) can also convert prochiral ketones to chiral alcohols in moderate enantioselectivity.[36i] Furthermore, 2 equiv of *B*-3-pinanyl-9-**BBN** (**11**) prepared from (+)-α-pinene reduces a variety of α,*β*-acetylenic ketones to the corresponding propargylic alcohols in exceptionally high enantiomeric purities, in the range of 73−100% ee (eq 38).[153]



Finally, Professor Brown and his co-worker have succeeded in reducing many simple, as well as functionalized, ketones with good to excellent asymmetric induction by carrying out the reaction with the neat reagent or highly concentrated (∼2 M to ∼5 M) solutions in THF[154] (eq 39).



Professor Brown and co-workers introduced a new asymmetric reducing agent, diisopinocampheylchloroborane (Ipc_2BCl, **15**), which is devised by a strategic modification.[155] Introducing a chlorine atom on the boron increases the Lewis acidity of the boron, thereby facilitating its reaction with the carbonyl group. **15**, derived from (+)-α-pinene, reacts with ketones at convenient rates even at −25 °C in THF (1 M), achieving the high chiral induction, and the reaction cleanly stops with elimination of 1 equiv of α-pinene. The isolation procedure involves a simple removal of the boron moiety by precipitation (**36**) with diethanolamine (Scheme 11). Results for the chiral reduction of ketones and a comparison

(147) (a) Mosher, H. S.; La Combe, E. M. *J. Am. Chem. Soc.* **1950**, *72*, 3994, 4991. (b) Mosher, H. S.; Parker, E. D. *J. Am. Chem. Soc.* **1956**, *78*, 4081. (c) Mosher, H. S.; Stevenot, J. E.; Kimble, D. O. *J. Am. Chem. Soc.* **1956**, *78*, 4374. (d) Mosher, H. S.; Loeffler, P. K. *J. Am. Chem. Soc*. **1957**, *79*, 903.

(148) Evans, D. A.; Nelson, S. G.; Gagné, M. R.; Muci, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 9800.

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(150) Midland, M. M.; Tramontano, A.; Zderic, A. *J. Organomet. Chem.* **1977**, *134*, C17.

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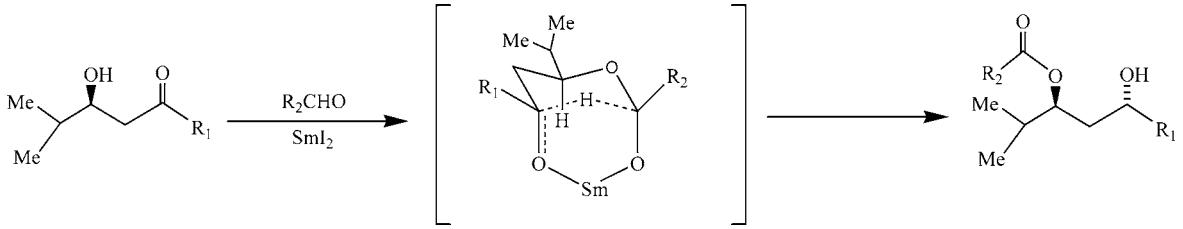
(153) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.

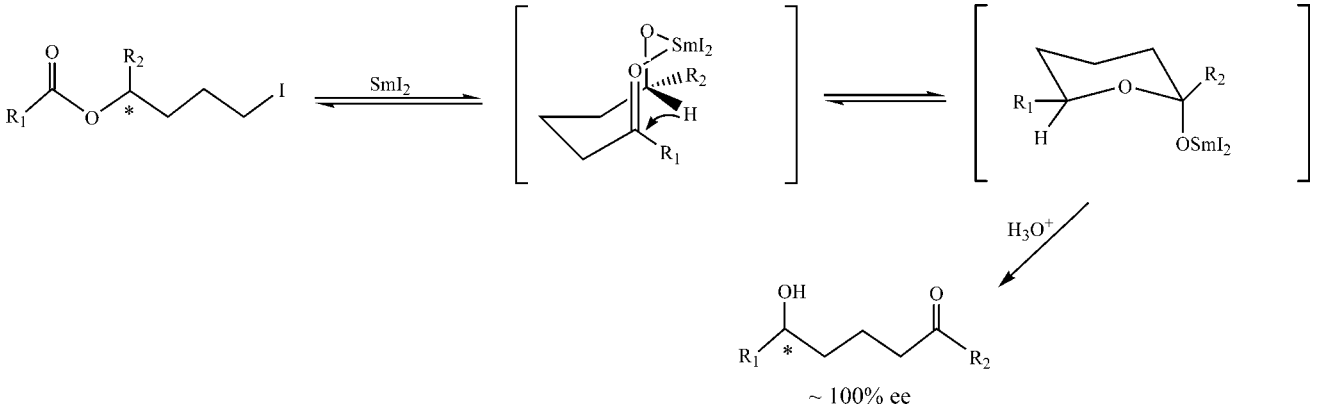
(154) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384.

(155) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5446.

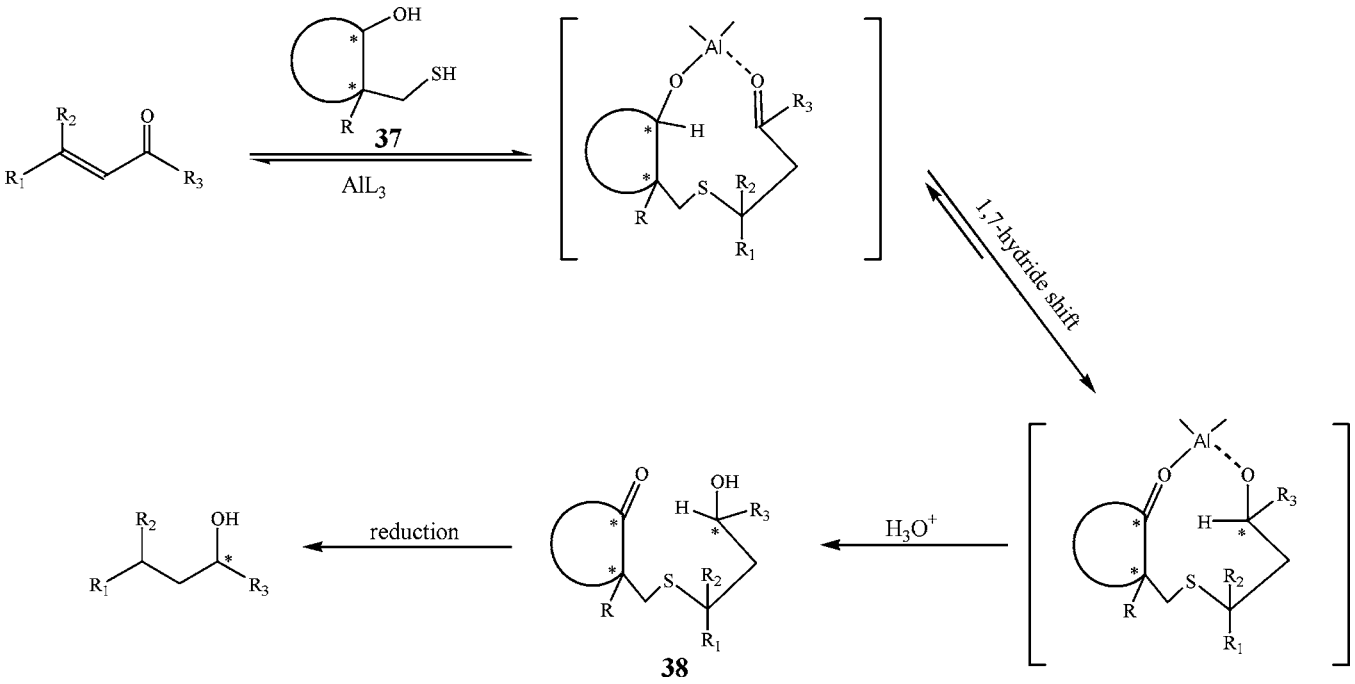
Scheme 13



Scheme 14



Scheme 15



of the data with these for some important reagents[157] are summarized in Tables 6 and 7.

They have also developed various chiral reducing agents (**16**−**20**) and applied them to the asymmetric reduction of ketones.[39,158]

B. Intramolecular MPV Reduction. The intramolecular asymmetric **MPV** reduction occurs in a molecule possessing

Table 6. **Comparison of chiral induction obtained by various reagents**

	% ee				
ketone	Ipc_2BCl (**15**) −25 °C	**11** 25 °C	**11** (high pressure)	Binal-H[156] −100 °C	**31** −100 °C
2-butanone	4	43			76
2-octanone			63	24	
3-methyl-2-butanone	32	62	90		68
3,3-dimethyl-2-butanone	95	0.6			2
acetophenone	98	85	100	95	70

(156) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.
(157) Brown, H. C.; Park, W. S.; Cho B. T.; Ramachandran, P. V. *J. Org. Chem.* **1987**, *52*, 5406.
(158) Brown, H. C.; Ramachandran, P. V.; Chandrasekharan, J. *Heteroatom Chem.* **1995**, *6*, 117.

Table 7. **Chiral reduction of aromatic ketones with 15 at −25 °C and a comparison with other reagents**

ketone	% ee	% ee by **11** neat condition	% ee by **11** high pressure	% ee by Binal-H[156] (−100 °C)
acetophenone	98	85	100	95
2′-acetonaphthone	98			
3-acetylpyridine	92	90	100	
2-acetylthiophenone	91			
butyrophenone	100			100
1-indanone	97			
isobutyrophenone	78			71
pivalophenone	79			44

a chiral alcohol moiety and involves 1,5- or 1,7-hydride shift via a six-membered cyclic transition state.[159] Generally the reduction proceeds with very high stereoselectivity (Scheme 12).

Samarium iodide also catalyses intramolecular Tishchenko reduction of β-hydroxy ketones towards *anti*-1,3-diol monoesters.[65] The mechanism proceeds via a hydride transfer as in the **MPV** reduction (Scheme 13).

Tandem intramolecular substitution or addition−**MPV** reduction provides an interesting synthetic tool for producing optically active compounds. Samarium(II) iodide induces sequential intramolecular **MPV** reduction to produce optically active β-hydroxy ketones[160] (Scheme 14). Other examples for such reactions are the synthesis of optically active secondary alcohols[161] and 1,3-mercapto alcohols[162] from α,β-unsaturated ketones via a tandem Michael addition−**MPV** reduction process. A chiral alcohol with a thiol moiety[34] associates with an α,β-unsaturated ketone by Michael addition of the thiol moiety with the assistance of a Lewis acid so that subsequent intramolecular **MPV** reduction gives an optically active saturated alcohol after reductive desulfuration, as depicted in Scheme 15. A variety of α,β-unsaturated ketones can be converted to the corresponding optically active secondary alcohols with up to 98% ee.

Optically active 1,3-mercapto alcohols have also been synthesized from α,β-unsaturated ketones via tandem Michael addition−**MPV** reduction utilizing chiral reagent **37**. The process is exactly depicted in Scheme 13, except the reductive desulfuration step of **38**. In this synthesis, a base-catalyzed elimination is involved to create two chiral carbons in *anti*-1,3-mercapto alcohols with up to 99% ee.

(159) Fujita, M.; Takarada, Y.; Sugimura, T.; Tai, A. *Chem. Commun.* **1997**, 1631.
(160) Molander, G. A.; McKie, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 5821.
(161) (a) Nishide, K.; Shigeta, Y.; Obata, K.; Node, M. *J. Am. Chem. Soc.* **1996**, *118*, 13103. (b) Node, M.; Nishide, K.; Shigeta, Y.; Shiraki, H.; Obata, K. *J. Am. Chem. Soc.* **2000**, *122*, 1927.
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V. Concluding Remarks

It is evident that the most desirable goal of the chemists working in the field of reduction of organic functional groups is to develop a full scope of selective reducing agents which can reduce selectively a particular functional group of concern while other functional groups are intact in a polyfuncionalized complex molecule.

There have appeared a variety of reducing systems, including reagents of "direct" and "indirect" hydride sources, which can possibly achieve a selective reduction of any organic functional group. However, it should be pointed out that despite their abundant choice in the literature one should consider carefully which reagent satisfies one's purpose, because each reagent possesses its own limitation. Besides, as the complexity of molecules with which chemists are concerned increases, it is necessary to develop new methods and reagents that will provide a very clean and selective reduction of a particular organic functional group.

Although most chemists seem to pay much less attention to the utilization of the **MPV** type reagents than to that of metal complex hydrides apparently due to their narrow diversity in reduction organic functional groups, the MPV reagents possess unique reducing characteristics. Because the **MPV** reduction takes place only after the coordination of the reagent to an oxygen atom of the compound, the reagents exhibit an exceptional selectivity. Furthermore, the recent achievements in catalytic **MPV** reduction using various homogeneous and heterogeneous catalysts promise well for future development. In this respect, it is hoped that the present review will provide some useful information to those chemists who are concerned with the selective reduction of organic functional groups.

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