Selective Reduction of Carbonyl and Epoxy Compounds Using Aluminum, Boron and Other Metal Reagents. Comparison of Reducing Characteristics between the Meerwein-Ponndorf-Verley Type Reduction and Metal Complex Hydrides Reduction: A Review†

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Received June 28, 2007

The newly-developed Meerwein-Ponndorf-Verley (**MVP**) type reagents using aluminum, boron and other metals for reduction of organic functional groups such as carbonyl and epoxy compounds have been surveyed. highlighted and reviewed in this account are the appearance of new **MPV** type reagents and their application to the selective reduction of organic functions. Finally, this account emphasizes the distinct contrast in the reducing characteristics existed between metal hydride reagents and **MPV** reagents, and compares their usefulness in organic synthesis.

Key Words : Metal complex hydrides, MPV reactions, Reduction, Carbonyl and epoxy compounds, Aluminum and boron reagents

Introduction

The Meerwein-Ponndorf-Verley (**MPV**) reaction has been known as a mild and specific method of reducing carbonyl compounds since 1925. However, 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 undertake to use such a conventional technique. 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 new type of **MPV** reagent and in its application for the reduction of organic functional groups such as carbonyl and epoxy compounds led us to reassess its applicability and selectivity in organic synthesis. Consequently, it appears of interest to review recent situation where the newly-developed **MPV** reactions are possibly the complementary methods of choice for such reductions. This review has attempted to emphasize the distinct contrast in the reducing characteristics existed between metal hydride reagents and **MPV** reagents. It is the purpose of this review to illustrate the relationship of **MPV** type reduction to other methods of reduction and then to compare their usefulness in organic synthesis.

Origins of the MPV Reducing Agents

1. Discovery of Aluminum Compounds as MPV Reducing Agents. In the year 1925 it was discovered 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 (Eqn. 1).

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

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] (Eqn. 2).

$$\underset{\underset{\|}{O}}{PhCPh} \xrightarrow[1\ h,\ reflux]{Al(O^iPr)_3} \underset{|}{PhCHPh}\ (OH) \qquad (2)$$

99 ~ 100%

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

† This paper is dedicated to Professor Sang Chul Shim on the occasion of his honorable retirement.

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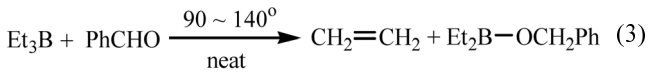
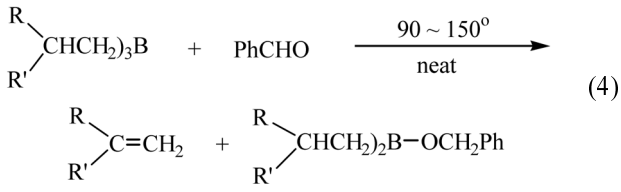
a reducing agent originated from Meerwein in 1936,[10] in which heating a neat mixture of triethylborane and benzaldehyde eliminates ethylene with formation of diethylboronic ester (Eqn. 3). In this reaction benzaldehyde was



(3)

reduced to the boronic ester of benzyl alcohol. About thirty years later, Mikhailov *et al*.[12] reexamined such a reaction with higher trialkylboranes in the presence of benzaldehyde at elevated temperatures (Eqn. 4). They indicate that the rate of the elimination of an olefin (*i.e.* the reduction of benzaldehyde) from a trialkylborane increases with increase in the number of methyl groups on the β-carbon atom.



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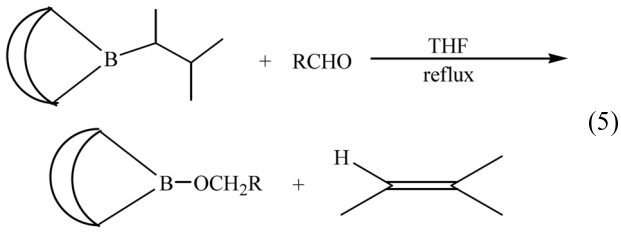
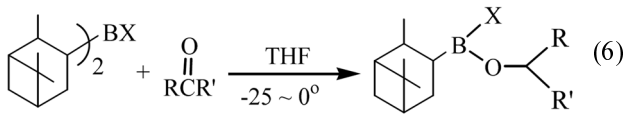
In late 1970 Midland initiated to improve such a sluggish reaction to a useful technique for the selective reduction of aldehydes using *B*-alkyl-9-borabicyclo[3.3.1]nonane (*B*-R-9-**BBN**).[13] Especially, *B*-(3-methyl-2-butyl)-9-**BBN** (*B*-Siamyl-9-**BBN**) is an effective reagent for the reduction of a wide variety of aldehydes under mild conditions (*i.e.*, 2 h in refluxing THF)[14] (Eqn. 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 has been 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 (Eqn. 6).



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3. Mechanistic Consideration of the MPV Reactions.

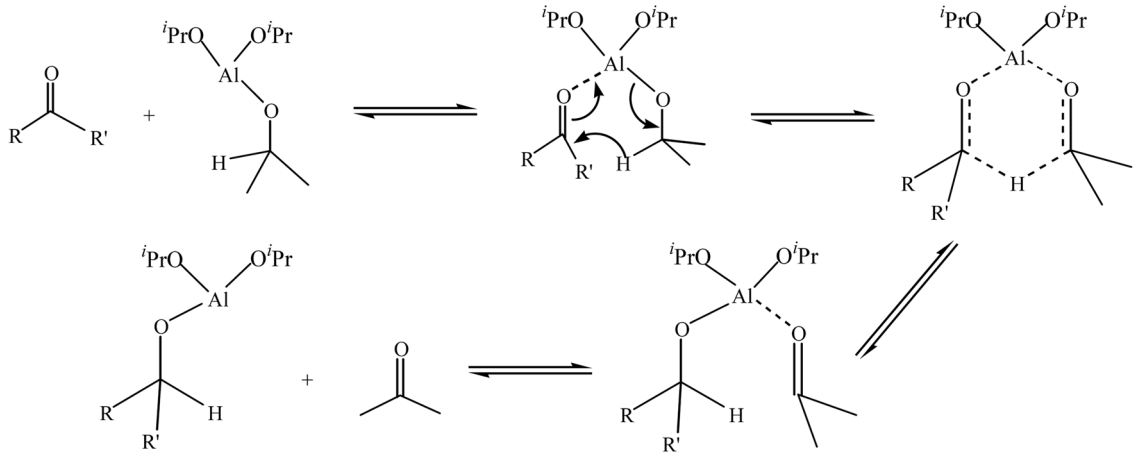
***A. Aluminum reagents*:** As depicted in Eqn. (1), the **MPV** reaction with aluminum ethoxide is reversible, but the equilibrium can be shifted to the point of complete reduction by removal of the acetaldehyde with a stream of dry nitrogen. Similarly, the reaction of aluminum isopropoxide produces 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 hydride shift from the β-carbon atom and thus proves to be very similar to the **MPV** reduction process, has been confirmed by mechanistic[19] and stereochemical[20] investigations (Scheme 2).

***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 increase in the number of methyl groups on the β-carbon atom, which indicates reaction with elimination of a hydride ion *via* a cyclic electron



Scheme 1

transfer (Scheme 3).

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

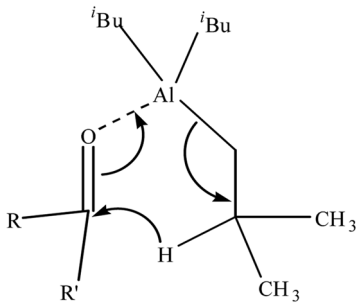
***C. Consideration on β-hydrogen source of catalyst*:** The *β*-hydrogen sources in **MPV** reduction can be divided into two categories. As depicted in Scheme 1 for the classical **MPV** reduction, the *β*-hydrogen comes from isopropoxy group of catalyst that, in turn, leads to the formation of acetone.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

The formation of acetone causes the reaction being 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.

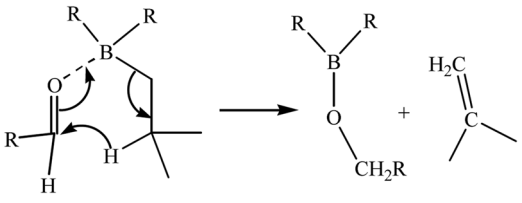
Appearance of New MPV Type Reagents

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 points to be considered. One is that the actual reduction takes place by virtue of the *β*-hydrogen transfer from isopropoxy group attached to 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 **MPV** reaction is reversible: acetone formed accelerates the reversible reaction.

Practically, there have encountered some problems in this reaction: the reduction usually proceeds sluggishly even with an excess catalyst and requires the removal of acetone in order to shift the equilibrium in the desired direction.



Scheme 2



Scheme 3

Therefore, efforts to devise new catalysts and reagents to overcome such limitations have been continuously devoted.

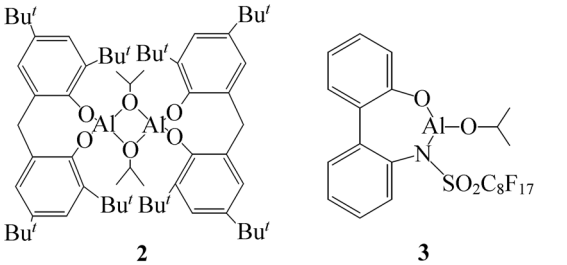
1. Auminum-Containing Reagents. The classical **MPV** reaction with aluminum isopropoxide has been modified by addition of trifluoroacetic acid (**TFA**) (**1**). Thus, the system **1**

$$Al(O^iPr)_3 / \mathbf{TFA}$$

1

brings about rapid reduction of aldehydes at room temperature in the absence of 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 $[(EDBP)Al(u\text{-}O^iPr)]_2$[25] (**2**), sulfonylamioalkoxide[26] (**3**), and bidentate aluminum alkoxides[27] (**4**). Especially, **4** is able to capture both of the oxgen lone pairs simultaneously, enabling double electrophilic activation of carbonyls. Aluminum porphyrins,[28] such as 5,10,15,20-tetraphenylporphynatoaluminum chloride (**5**), also catalyses a novel hydrogen transfer process in the reduction of aldehydes and ketones with alcohols.



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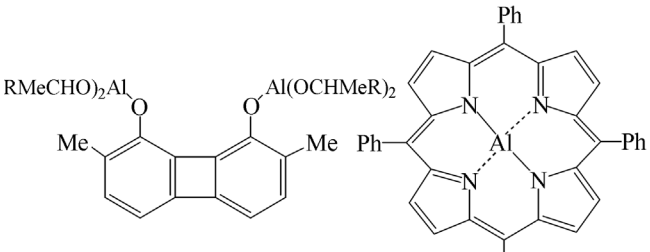


4 **5**

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 (Eqn. (7-9)). These diisobutylaluminum derivatives have achieved a very high chemo-, regio- and stereoselectivity in the reduction of aldehydes and ketones.

$$\underset{\text{(DIBAL—H)}}{i\text{-}Bu_2AlH} + HX \longrightarrow \underset{\mathbf{6}}{i\text{-}Bu_2AlX} \qquad (7)$$

$$i\text{-}Bu_2AlH + ROH \longrightarrow i\text{-}Bu_2AlOR \quad (8)$$

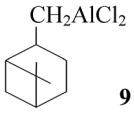
7

$$i\text{-}Bu_2AlH + R_2NH \longrightarrow i\text{-}Bu_2AlNR_2 \quad (9)$$

8

In the 1950s and 1960s, the classical intermolecular asymmetric reduction of ketones using aluminum alkoxides of optically active alcohols was widely studied.[32] After then from 1980s 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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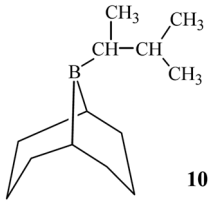
2. Boron-Containing Reagents. Generally, trialkylboranes are known to be tolerant to a wide variety of functional groups,[35] but certain *B*-alkyl-9-**BBN**, especially *B*-Siamyl-9-**BBN** (**10**) is a mild chemoselective reducing agent for aldehydes.[13,14] Similarly, the asymmetric *B*-alkyl-9-**BBN** containing optically active terpenes,[36] such as (+)-α-pinene (**11**), (−)-β-pinene (**12**), (−)-camphene (**13**), and (+)-3-carene



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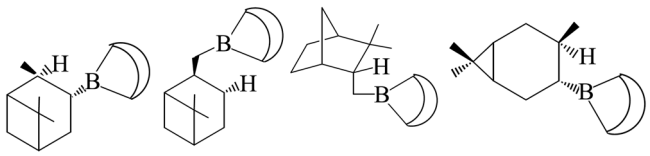
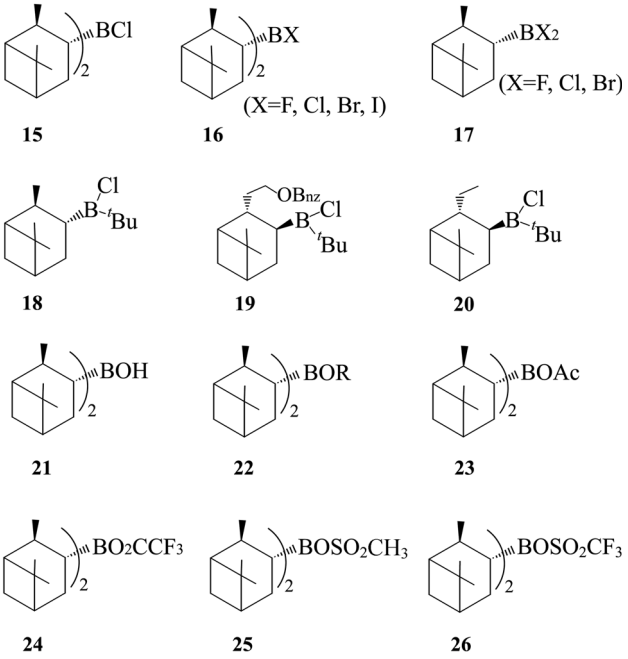
(**14**), can transfer a hydride from a chiral center of the alkyl group to a new chiral center of the carbonyl group of the deuterated aldehydes.



11 **12** **13** **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 from a strategic modification of the electronic and steric environments of the boron in trialkylboranes can reduce a variety of ketones as well as aldehydes to the corresponding alcohols even at −25 °C. Soon other mono- and diisopinocampheylhaloboranes (**16-20**), were also prepared.[38-42] Furthermore, hydroxy-, alkoxy-, acetoxy- and methanesulfonoxy-incorporated diisopinocampheylborane derivatives (**21-26**) were prepared and their applicability in **MPV** type reduction was explored.[43-47]



15 **16** **17**

18 **19** **20**

21 **22** **23**

24 **25** **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) iodo alkoxides were first utilized in **MPV** reduction by Kagan and coworkers 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, $\equiv SiOM(O\,^iPr)_3$, M = Zr, Hf, have been synthesized and shown to be efficient catalysts for 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 ($Cp_2H_fH_2$) 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] or tantalum,[62] or even rare earth elements such as samarium[63] and plutonium.[64]

There have been reported a variety of acidic and basic heterogeneous catalysts which have been successfully used for the **MPV** reduction. Heterogeneous catalysts have as advantages over homogeneous systems that work-up is easy and catalyst recycling is possible. One of the widely used catalysts is magnesium oxide (MgO), a typical catalyst for 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]

Application for Organic Synthesis

The **MPV** reduction is a classical but still widely used metheod for organic synthesis, because of high selectivity, relatively mild reaction conditions, simple and safe operations, and the low cost. In general, **MPV** reduction is performed with various catalyst 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 Lewis acidic metal site followed by reversible hydride transfer from alcoholate to the carbonyl acceptor *via* six-membered cyclic transition state as shown in Scheme 1 to 3. In this mechanstic point of view, the key step of this reaction must be the coordination of carbonyl oxygen to 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 performing an excellent selectivity in the **MPV** reductions, such as the following chemo-, regio-, and stereoselective reductions of carbonyl and epoxy compounds.

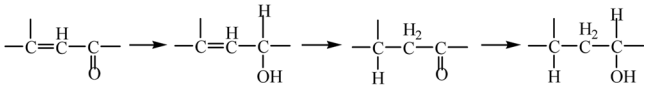
1. General Reducing Characteristics of Diisobutylaluminum and Diisopinocampheylboron Derivatives toward Common Organic Functional Groups. Recently, the general reducing characteristics of diisobutylaluminum derivatives, such as *i*-Bu_2AlX (**6**), *i*-Bu_2AlOR (**7**) and *i*-Bu_2AlNR_2 (**8**), and 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 comparsion, some conclusions on the general reducing action of these derivatives toward organic functional groups have been drawn as follows:

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

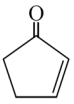
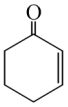
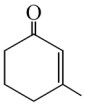
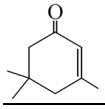
(ii) the reactivity of Ipc_2BOR (**22**) is much weaker than Ipc_2BX (**16**);

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

Table 1. Regioselective Reduction of Representative α,β-Unsaturated Carbonyl Compounds with Metal Hydrides



27 **28** **29**

Compound	Reagent	Ratio (%)			Ref
		27	28	29	
CH_2=CHCHO	$NaBH_4$	85	0	15	76
	$LiBH_4$	96	–	2	76
	$Zn(BH_4)_2$	100	0	0	77
CH_3CH=CHCHO	$NaBH_4$	92	0	8	76
	$LiBH_4$	100	0	0	76
	$Zn(BH_4)_2$	100	0	0	77
	9-BBN	98	–	–	78
PhCH=CHCHO	$NaBH_4$	100	0	0	76
	$LiAlH_4$	0	0	100	81
	$LiAlH_4$	100	0	0	79
	$NaBH_3CN$	80	–	–	80
	Li *n*-$BuBH_3$	100	0	0	82
	$Zn(BH_4)_2$	100	–	–	77
	9-BBN	99	–	–	78
	$NaHFe(CO)_8$	0	90	0	83
CH_2=$CHCOCH_3$	$NaBH_4$	57	0	43	76
	$LiAlH_4$	83	0	7	76
	$Zn(BH_4)_2$	91	0	9	77
CH_3CH=$CHCOCH_3$	$NaBH_4$	65	0	35	76
	$LiAlH_4$	98	–	1	76
	$LiAlH_4$-CuI	0	97	0	84
	9-BBN	99	0	0	78
$(CH_3)_2C$=$CHCOCH_3$	$NaBH_4$	92-100	0	0-8	76, 85
	$LiAlH_4$	100	0	0	76, 85
PhCH=CHCOCH$_3$	Li *n*-$BuBH_3$	100	0	0	82
PhCH=CHCOPh	$NaBH_4$	18	0	82	86
	$LiAlH_4$	100	0	0	87
	$LiAlH_4$-CuI	0	100	0	84
	$NaBH_4$	0	100	0	88
	$NaBH_4$, LiCl	1	0	99	89
	$NaBH_4$, $CeCl_3$	93	7	0	89
	9-BBN	100	–	–	90
	AlH_3	90	6	4	88, 90
	i-Bu_2AlH	99	0	0.5	90, 91
	$Zn(BH_4)_2$	96	0	4	77
	$NaBH_4$, $CeCl_3$	97	3	0	89
	Li *n*-$BuBH_3$	92	8	0	82
	K-Selectride	0	95	0	92, 93
	9-BBN	100	0	0	78
	$LiAlH_4$	94	–	2	76
	$NaHFe(CO)_8$	0	100	0	83
	$NaBH_4$	70	0	30	76
	$LiAlH_4$	100	0	0	76
	$Zn(BH_4)_2$	97.5	0	2.5	77
	9-BBN	100	0	0	90
	Li *n*-$BuBH_3$	100	0	0	82

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

(v) the relative reactivities of *i*-Bu_2AlOR (**8**) series are *i*-Bu_2AlOH > *i*-Bu_2AlOEt > *i*-Bu_2AlO^iPr > *i*-Bu_2AlO^tBu;

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

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

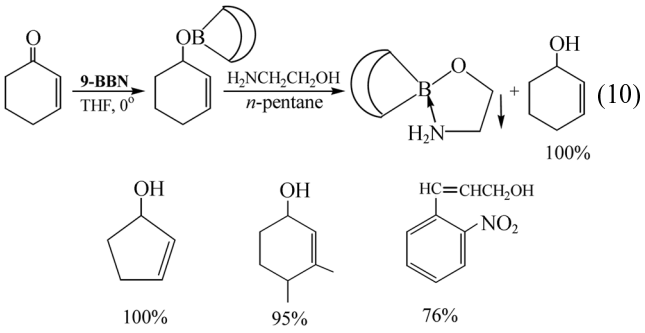
A relative reactivity toward organic functional groups is summarized in Table 1. Most derivatives are reactive toward aldehydes and ketones, but quite inert to other functional groups including even acid chlorides. Especially noteworthy is that Ipc_2BOH appears the mildest one among the derivatives, exhibiting absolutely no reactivity toward every organic functional groups 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 the 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 special interest since this is often a key step in the preparation of various fine chemicals. Therefore, endless efforts have been undertaken to develop reducing systems which effect such a regioselective conversion.[75-93]

In Table 1, some common metal hydrides capable of converting α,β-unsaturated carbonyl compounds to the corresponding allylic alcohols in a 1,2-reduction fashion or to the corresponding saturated carbonyl compounds in a 1,4-reduction fashion are collected. However, it should be kept in mind that the ratio of products achieved by any particular reagent might be varied by changing the nature of solvent, reaction temperature, addition mode of reagent and substrate, amount of reagent utilized, reaction period, and others.

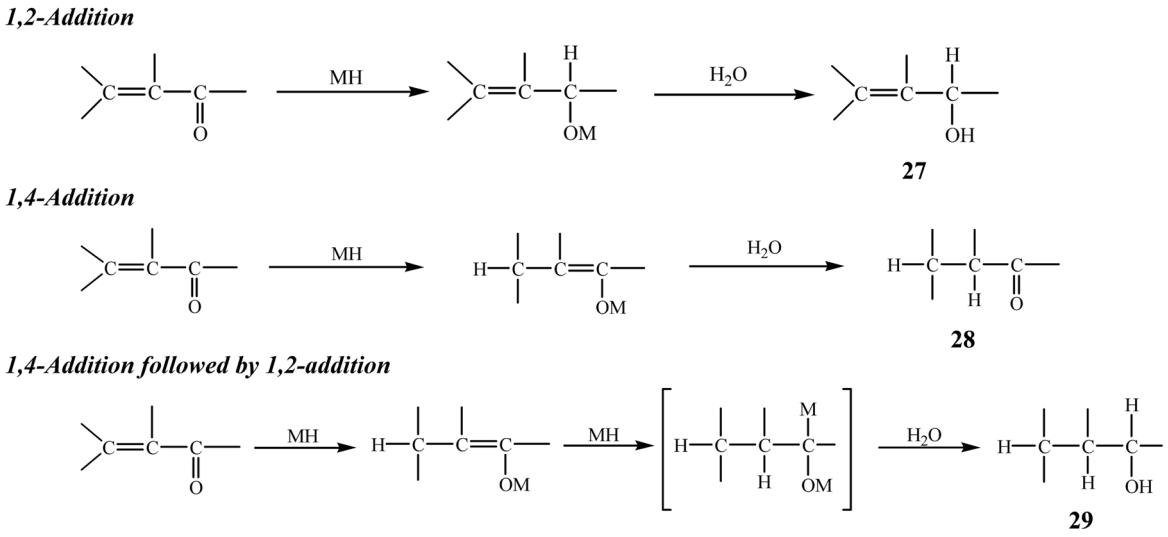
As shown in the Table, 9-**BBN**,[78] Li *n*-$BuBH_3$[82] and *i*-Bu_2AlH[90,91,94] show a high selectivity in the reduction of such unsaturated carbonyl compounds. Especially, 9-**BBN** is a reagent of choice because of its mildness. Unlike the conventional reagent, the reagent permits the presence of almost any other functional group except the isolated carbon-carbon multiple bonds.[95] Furthermore, the development of a unique non-aqueous work-up procedure renders possible the isolation of the alcohols in excellent yields[90] (Eqn. 10).



(10)

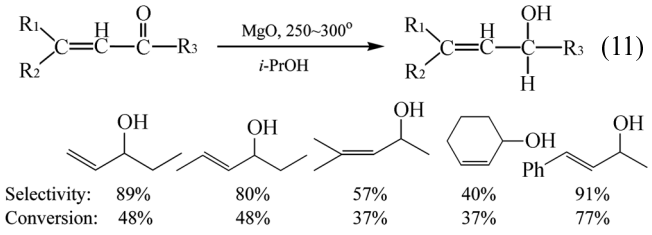
One of the most prominent potentials of the **MPV** process seems to be capable of converting α,β-unsaturated carbonyl compounds to the corresponding allylic alcohols. However, only a few examples are shown in literature for such selective reduction. In addition, even these examples have been designed for an industrial purpose using acid-basic 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 appear to be not high, but seem to be good enough in an industrial

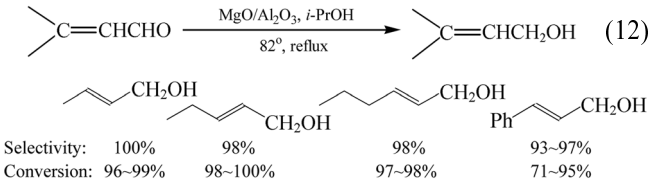


Scheme 4

sense (Eqn. 11).



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 (Eqn. 12).



The mechanism, based on which the hydrogen transfer from isopropyl alcohol to the carbonyl compound 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 earlier, 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 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 not attack ketones at all. Even though the reaction rate is different each other, the selectivity appears to be an essentially 100%. We can envision 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* a 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 usual 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 being lied in equilibrium. Further, the resultant acetone formed in due reaction seems to make the reaction mixture more complicated.

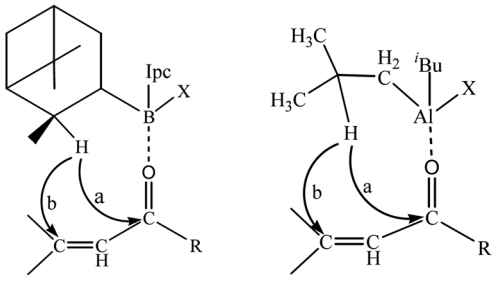
Table 2. Comparison in Reactivity of Diisopinocampheylboron and Diisobutylaluminum Derivatives toward Common Organic Functional Groups[a]

Reagent type	Organic functional groups					
	Aldehyde	Ketone	Ester	Acid chloride	Nitrile	Epoxide
Ipc_2BX	+++	++	–	–	+	+
Ipc_2BOR	++	–	–	–	–	–
i-Bu_2AlX	+++	+++	–	–	+	++
i-Bu_2AlOR	++	+	–	–	–	–
i-Bu_2AlNR_2	++	+	–	–	–	–

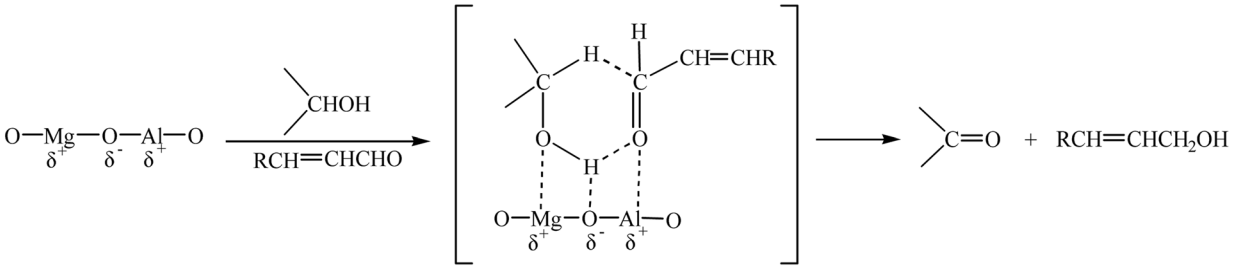
[a]+ Designates 'reactive', whereas designates 'inert'.

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 seem not to interfere with these reactions.

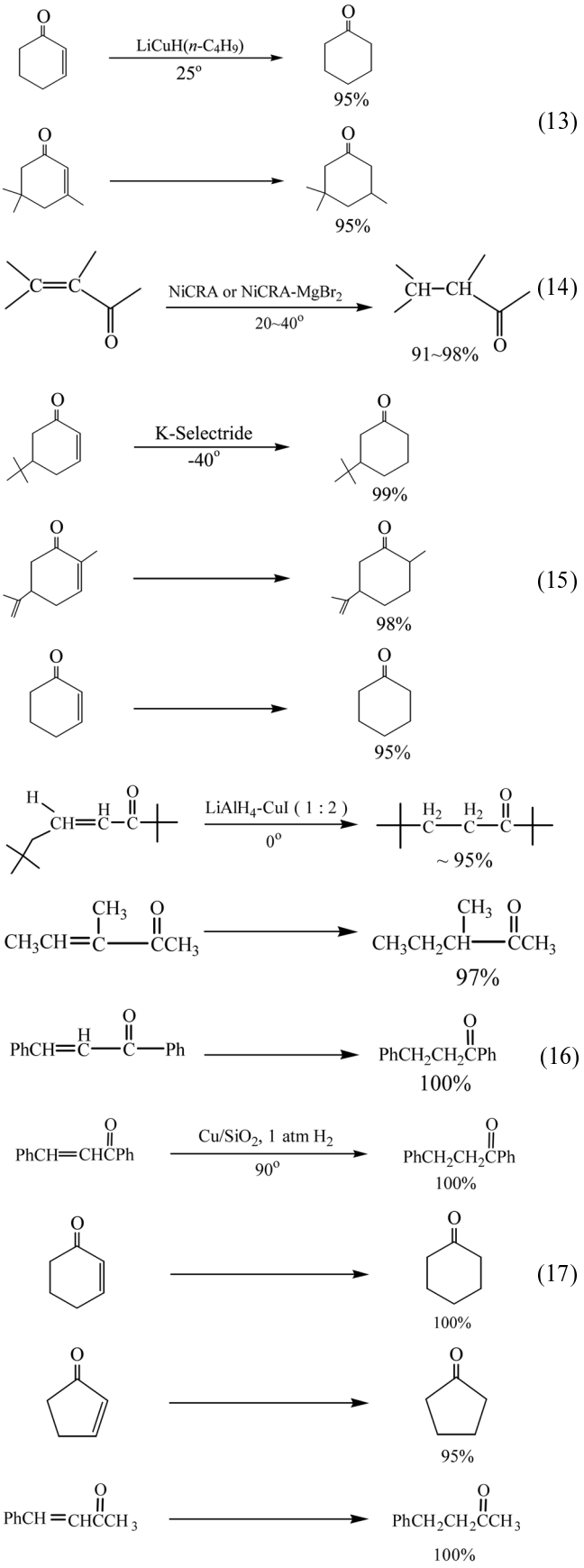
It is noteworthy that some reagents can convert α,β-unsaturated ketones to the corresponding saturated ketones *via* a 1,4-addition fashion. Especially, LiCuH(*n*-C_4H_9)[105] (Eqn. 13), NiCRA (NaH-RONaNi(OAc)$_2$) or NiCRA-$MgBr_2$ (Eqn. 14), K*s*-Bu_3BH[92,93] (Eqn. 15), $LiAlH_4$-CuI[84] (Eqn. 16), $Cu/SiO_2/H_2$ system[106] (Eqn. 17), Li(alkynyl)CuH,[107] $NaAlH_2(OCH_2CH_2OMe)$,[108] NaTeH,[109] and (n-Bu)$_2$SnH,[110] NaHFe(CO)$_8$,[111] $K_3[Co(CN)_5H]$[112] have achieved such conversion in high yields.



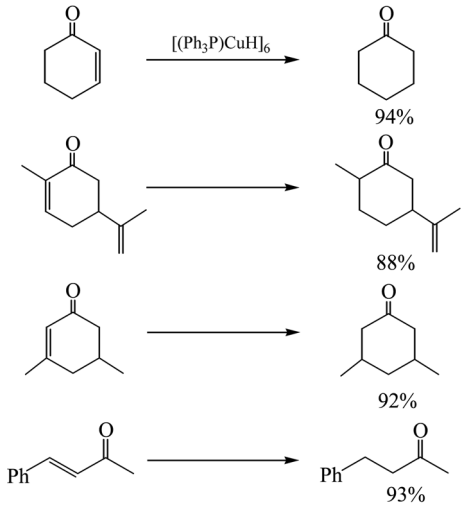
Scheme 6



Scheme 5



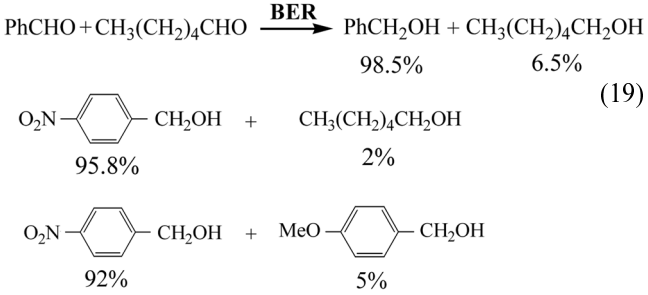
In addition, $[(Ph_3P)CuH]_6$[113] is generally effective for the selective conjugative hydride addition to α,β-unsaturated carbonyl compounds to produce the corresponding saturated carbonyl compounds cleanly (Eqn. 18).



3. Chemoselective Reduction between Structurally Different Carbonyl Compounds. As growing the complexity of molecules which chemists are concerning, new methods and new reagents which offer a very clean and selective reduction of one carbonyl group in the presence of another or in the presence of other functional groups have been constantly being sought.

There have appeared several efficient chemoselective reducing agents and systems in literature. It would be better to compare the selectivity of reagents capable of discriminating between a pair of functional groups.

A. Selective reduction of conjugated aldehyde in the presence of non-conjugated aldehyde with reducing systems other than the MPV type reagents: $NaBH_4$-$ErCl_3$ seems to be the reagent for the selective reduction of conjugated aldehyde in the presence of non-conjugated aldehyde[114] (Table 4). **BER** (Borohydride Exchange Resin) shows also a high selectivity for such purpose, but only a few examples were reported[115] (Eqn. 19). This reagent can also discriminate *p*-nitrobenzaldehyde from *p*-methoxybenzaldehyde in a ratio of 92:5.



B. Selective reduction of aldehyde in the presence of ketone with reducing systems other than the MPV type reagents: Tetrabutylammonium cyanoborohydride in acidic media was reported to show a possibility for the selective reduction of aldehyde in the presence of ketone.[115] Sodium triacetoxyborohydride[117] can discriminate benzaldehyde from acetophenone in a portion of 92:8. Lithium di-*n*-butyl-

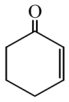
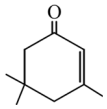
Table 3. Regioselective Reduction of Representative α,β-Unsaturated Carbonyl Compounds with MPV Type Reagents[a]

Compound	Reagent[b]	Rgt/Cpd	Reaction temp. (°C)	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-Bu_2AlF	1.1	25	3	99.9	99
	i-Bu_2AlCl	1.1	25	3	>99.9	100
	i-Bu_2AlOH	2.0	25	3	>99.9	101
	i-Bu_2AlOEt	2.0	25	6	100	101
	i-Bu_2AlO^iPr	2.0	25	6	99	101
	i-Bu_2AlO^tBu	2.0	25	24	100	101, 102
	i-Bu_2AlNEt_2	2.0	25	12	>99.9	103
	i-$Bu_2AlN^iBu_2$	2.0	25	12	100	103
	i-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-Bu_2AlF	1.1	25	6	94	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	24	100	101
	i-Bu_2AlO^iPr	2.0	25	24	100	101
	i-Bu_2AlO^tBu	2.0	25	72	100	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
$PhCH=CHCHO$	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-Bu_2AlF	1.1	25	24	91	99
	i-Bu_2AlCl	1.1	25	24	100	100
	i-Bu_2AlOH	2.0	25	6	100	101
	i-Bu_2AlOEt	2.0	25	12	100	101
	i-Bu_2AlO^iPr	2.0	25	12	100	101

Table 3. Continued

Compound	Reagent[b]	Rgt/Cpd	Reaction temp. (°C)	Reaction time (h)	Yield (%)	Ref
	i-Bu_2AlO^tBu	2.0	25	48	100	101, 102
	i-Bu_2AlNEt_2	2.0	25	24	100	103
	i-$Bu_2AlN^iBu_2$	2.0	25	24	99	103
	i-Bu_2AlNPh_2	2.0	25	72	97	103
$CH_3CH{=}CHC(=O)CH_3$	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
$PhCH{=}CHC(=O)CH_3$	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
$PhCH{=}CHC(=O)Ph$	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

Table 3. Continued

Compound	Reagent[b]	Rgt/Cpd	Reaction temp. (°C)	Reaction time (h)	Yield (%)	Ref
	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
	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%.

9-**BBN** "ate" complex[118] (**30**) can also reduce heptanal in the presence of 2-heptanone (95:5). Amine-borane such as *t*-$BuNH_2{\cdot}BH_3$[119] differentiates between benzaldehyde and acetophenone in a ratio of 98:2. Tributyltin hydride can also reduce aldehydes in the presence of ketones in a good selectivity.[120]

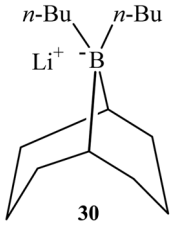


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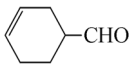
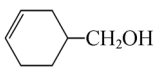
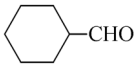
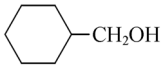
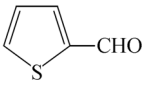
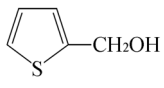
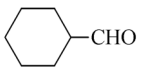
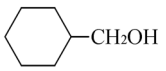
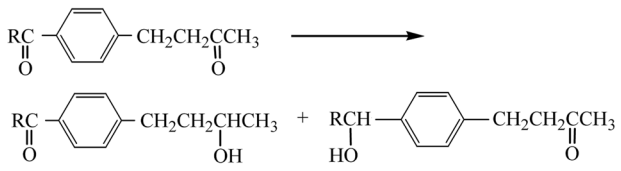
Table 4. Selective Reduction of Conjugated Aldehyde in the Presence of Non-Conjugated Aldehyde with $NaBH_4$-$ErCl_3$ in Aqueous Ethanol at −15 °C

Pair of compounds	Ratio of products	
$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCHO$	$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2OH$	100
+	+	
$(CH_3)_2C=CHCH_2CH_2CH(CH_3)CH_2CHO$	$(CH_3)_2C=CHCH_2CH_2CH(CH_3)CH_2CH_2OH$	13
$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCHO$	$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2OH$	80
+	+	
$CH_3(CH_2)_4CHO$	$CH_3(CH_2)_4CH_2OH$	13
PhCHO	$PhCH_2OH$	93
+	+	
$CH_3(CH_2)_4CHO$	$CH_3(CH_2)_4CH_2OH$	12
PhCHO	$PhCH_2OH$	93
+	+	
		11
PhCHO	$PhCH_2OH$	85
+	+	
		0
		85
+	+	
		0

In Table 5, the selectivities of lithium tris(3-ethyl-3-pentyl)oxyaluminum hydride (**LTEPA**),[121] **BER**,[115] 9-**BBN**-Pyridine[122] and BH_3-LiCl (1:0.1) system[123] in competitive reaction between aldehyde and ketone are compared. All the reagents are very good for such chemoselective reduction.

In addition, the selectivities between aldehydes and ketones by lithium tri-*tert*-alkoxyaluminumhydrides,[121] such as Li(*t*-BuO)$_3$AlH (**LTBA**), Li(*t*-AmO)$_3$AlH (**LTAA**), Li(Et_2MeCO)$_3$AlH (**LTMPA**) and Li(Et_3CO)$_3$AlH (**LTEPA**), are summarized in Table 6. **LTEPA**, the most sterically crowded one among them, shows the best selectivity.

C. Selective reduction between ketones with reducing systems other than the MPV type reagents: The selective reduction between structurally different ketones has been performed by various reducing systems: di-*n*-butyl-9-**BBN** "ate" complex[118] (**30**) can discriminate between the regioisomers of ketones such as 2-heptanone and 4-heptanone in a ratio of 91:9. Translation of these intermolecular results to an intramolecular situation has been demonstrated as following (Eqn. 20):



R = Ph	~100%	0%	(20)
i-Pr	>99%	< 1%	
n-Pr	97%	3%	
Et	90%	10%	

Table 5. Relative Reactivities of Aldehydes and Ketones toward Some Reducing Systems

RCHO/R_1R_2CO	Temp. (°C)	Ratio of RCH_2OH / R_1R_2CHOH			
		LTEPA	**BER**	9-**BBN**-Py	BH_3-LiCl (1 : 0.1)
hexanal/2-octanone	0	99.6 : 0.4			
	−78	100 : 0			
hexanal/acetophenone	0		99.5 : 4.7		
hexanal/cyclohexanone	0	93.6 : 6.4			
	−78	99.6 : 0.4			
benzaldehyde/cyclohexanone	0	92.5 : 7.5		93 : 1.5	
	−78	97.7 : 2.3			
benzaldehyde/2-heptanone	0		100 : 0		99.5 : 0
benzaldehyde/acetophenone	0	99.5 : 0.5	99 : 1	94 : 2	100 : 0

Table 6. Relative Reactivities of Aldehydes and Ketones toward Lithium Tri-*tert*-alkoxyaluminum Hydrides in THF

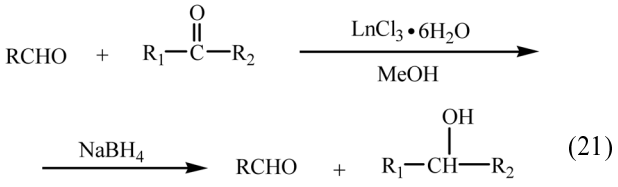
$RCHO/R_1R_2CO$	Temp. (°C)	Ratio of RCH_2OH / R_1R_2CHOH			
		LTBA	**LTAA**	**LTMPA**	**LTEPA**
hexanal/2-heptanone	0	99:1	99.5:0.5	99:1	99.6:0.4
	−78	99.5:0.5		99.8:0.2	100:0
benzaldehyde/acetophenone	0	99:1	99:1	99:1	99.5:0.5
hexanal/cyclohexanone	0	87:13	92:8	92.2:7.8	93.6:6.4
	−78	91.5:8.5	96:4	95.1:4.9	99.6:0.4
benzaldehyde/cyclohexanone	0	66.7:33.3		84.5:15.5	92.5:7.5
	−78	73:27	77:23	88:12	97.7:2.3

Table 7. Chemoselective Reduction of Ketone in the Presence of Aldehyde with $NaBH_4$-$LnCl_3$ Systems

$RCHO/R_1R_2CO$	Ketalization catalyst	Ratio of RCH_2OH/R_1R_2CHOH
cyclohexanecarboxaldehyde + cyclododecanone	$NdCl_3$	30:92
benzaldehyde + cycloheptanone	$ErCl_3$	7:83
benzaldehyde + 5-nonanone	$CeCl_3$	17:84
benzaldehyde + 2-cyclohexenone	$ErCl_3$	5:82
hexanal + cyclohexanone	$CeCl_3$	2:100
hexanal + 2-octanone	$CeCl_3$	13:96
cyclohexanecarboxaldehyde + cyclohexanone	$CeCl_3$	15:100

$NaBH_4$-lanthanoid chloride system showes a possibility for the selective reduction between ketones, but the selectivity appears not high.[124] *t*-$BuNH_2{\cdot}BH_3$ has also been tested for the selective reduction between cyclohexanone and other ketones.[112] KPh_3BH can reduce 2-heptanone selectively in the presence of 4-heptanone in a ratio of 94:6.[125]

D. Selective reduction of ketone in the presence of aldehyde with reducing systems other than the MPV type reagents: There have appeared some ingenious methods for selectively reducing a ketone in the presence of an aldehyde. Usually, this transformation necessitates a three-step process: protection of the aldehyde, reduction of the ketone, and finally liberation of the aldehyde. Such chemoselective reduction was first reported using $NaBH_4$-lanthanoid chloride system.[124,126] This method involves the protection of aldehyde *via* ketalization. Among the lanthanoid chlorides examined $CeCl_3$ appears the best[126] (Eqn. 21), and the results are summarized in Table 7.



(21)

Li(*t*-BuO)$_3$AlH-*t*-$BuNH_2$ system has utilized another protecting method for aldehyde as an imine formation.[127] This system can also be applied for the selective reduction of ketones in the presence of conjugated aldehydes which $NaBH_4$-$CeCl_3$ system[126] fails to discriminate (Table 8).

E. Chemoselective reduction between carbonyl compounds with the MPV type reagents: Only a few examples for the selective reduction of aldehydes in the presence of ketones with the **MPV** type reagents have appeared in literature. The first report for such conversion was performed by isopropyl alcohol on dehydrated alumina,[67] where the reduction rate for aldehydes in quite faster than that for ketones. *B*-Siamyl-9-**BBN**[13,14] also shows similar discrimation: a competition between bezaldehyde and acetophenone for a 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.

Table 8. Chemoselective Reduction of Ketone in the Presence of Aldehyde with Li(*t*-BuO)$_3$AlH-*t*-$BuNH_2$ System

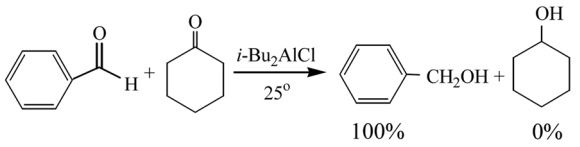
$RCHO/R_1R_2CO$	Ratio of RCH_2OH/R_1R_2CHOH
octanal/2-heptanone	1:100
octanal/cyclohexanone	2:100
cyclohexanecarboxaldehyde/2-heptanone	1:100
cyclohexanecarboxaldehyde/cyclohexanone	<1:99
benzaldehyde/2-heptanone	<1:100
benzaldehyde/acetophenone	2:100
geranial/acetophenone	<1:99

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 9.

As is apparent from the Table, both aliphatic and aromatic aldehydes are selectively reduced in the presence of quite a number of different ketones (Eqn. 22). Even more remarkable is the chemoselective discrimination between aldehydes. Thus, benzaldehye can be selectively reduced in the presence of hexanal with *i*-Bu_2AlOR (Eqn. 23). Butanal and hexanal are much more reactive than *p*-anisaldehyde toward *i*-Bu_2AlOR (Eqn. 24). Furthermore, various reagents can

discriminate between structurally different ketones. Even cyclohexanone can be selectively reduced in the presence of cyclopentanone in a up to 95:5 selectivity with *i*-Bu_2AlO^tBu (Eqn. 25). 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 (Eqn. 26).

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



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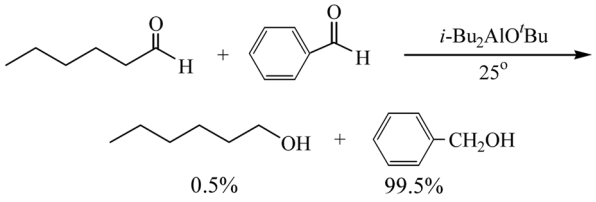

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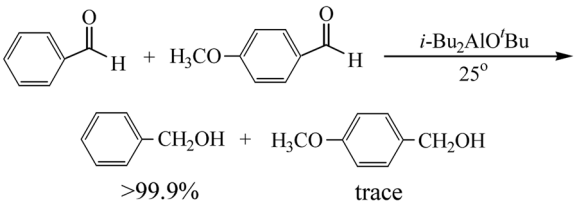

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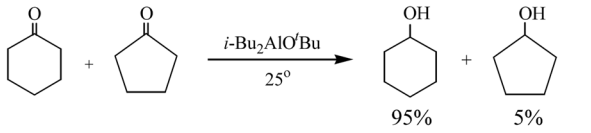

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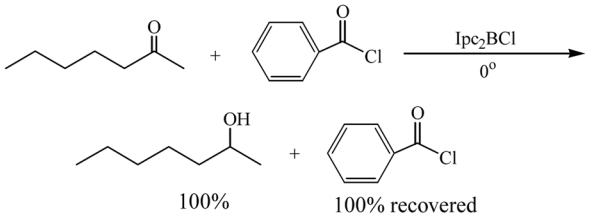
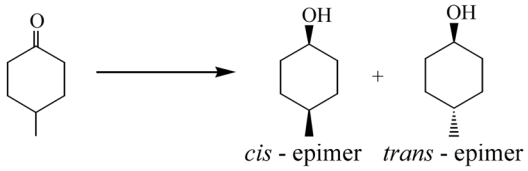


(26)

4. Stereoselective Reduction of Cycloalkanones. It has been desirable to have reagents that could reduce substituted cycloalkanones to the corresponding one of 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 (Eqn. 27).



(27)

Table 9. Chemoselective Reduction between Structurally Different Carbonyl Compounds with Various MPV Type Reducing Agent[a]

Starting mixture	Reagent	Temp. (°C)	Time (h)	Ratio of reduction products[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

Table 9. Continued

Starting mixture	Reagent	Temp. (°C)	Time (h)	Ratio of reduction products[b]	Ref
	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
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

Table 9. Continued

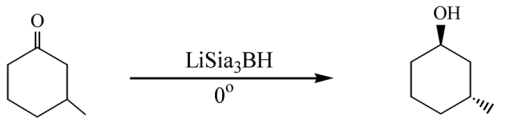
Starting mixture	Reagent	Temp. (°C)	Time (h)	Ratio of reduction products[b]	Ref
	i-Bu_2AlOEt	25	6	100 : 0	30d
	i-Bu_2AlO^iPr	25	6	99 : 1	30d
	i-Bu_2AlO^tBu	25	12	99.5 : 0.5	30d
	i-Bu_2AlNEt_2	25	3	90 : 10	103
	i-$Bu_2AlN^iBu_2$	25	3	92 : 8	103
	i-Bu_2AlNPh_2	25	6	70 : 30	103
hexanal + benzophenone	Ipc_2BCl	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

Table 9. Continued

Starting mixture	Reagent	Temp. (°C)	Time (h)	Ratio of reduction products[b]	Ref
	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
	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

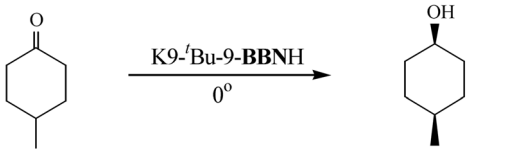
[a]One equivalent of reagent added to an equimolar mixture of starting compounds. [b]Total yields of product alcohols were ≥99%.

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-*t*-butyl-9-boratbicyclo[3.3.1]nonane (K9-^{t}Bu-9**BBN**H),[130] lithium (2,3-dimethyl-2-butyl)-*t*-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 (Eqn. 28 and 29), as summarized in Table 10.



(28)

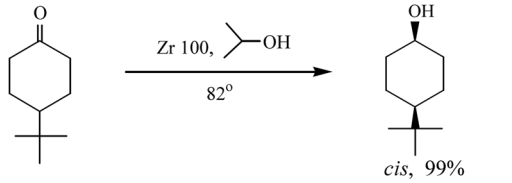
trans, 98%



(29)

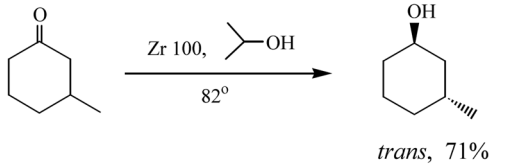
cis, 94%

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 4-*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-methy and 4-*tert*-butylcyclohexanone to the *cis*-isomer in a 99:1 ratio with high conversion yields, but the selectivity for reduction 2-methyl and 3-methylcyclohexanone reaches not high[134] (Eqn. 30-32). In addition, a magnesiumaluminum 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.



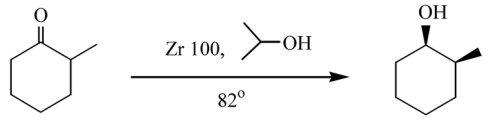
(30)

cis, 99%



(31)

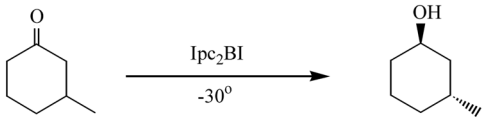
trans, 71%



(32)

cis, 55%

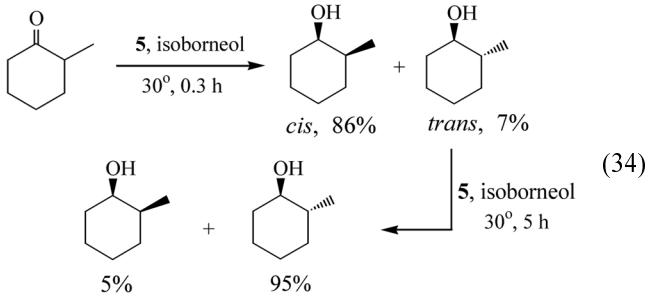
Very recently, diisopinocampheylhaloboranes such as Ipc_2BCl, Ipc_2BBr and Ipc_2BI have been examined for their stereoselectivities in the reduction of typical cyclic ketones. The stereoselectivity for producing the thermodynamically less stable isomer increases dramatically with increasing steric size 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 possesses a drawback in producing alcohols, showing significantly low conversion yields[135] (Eqn. 33).



(33)

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 have observed that in **MPV** reaction 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 prolonged reaction times. Konish *et al*. have 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 (Eqn. 34).



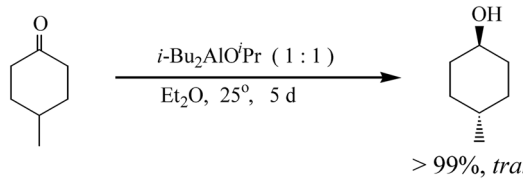
(34)

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

Table 10. Stereoselectivity in the Reduction of Cyclic Ketones with Representative Reagents at 0 °C

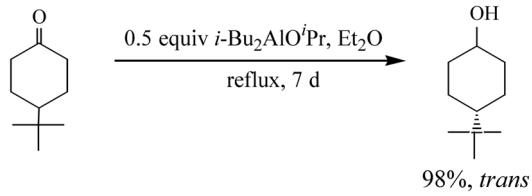
Ketone	Reagent	Selectivity in less stable epimer (%)
2-methylcyclohexanone	LiThx^{t}BuOBH$_2$	>99.5
	K9-OThx-9-**BBN**H	98.5
	Li^{s}Bu$_3$BH	99.3
	LiSia$_3$BH	99.4
	K9-^{t}Bu-9-**BBN**H	99.5
	LiThx^{t}BuOBH	>99.5
3-methylcyclohexanone	LiThx^{t}BuOBH$_2$	96
	K9-OThx-9-**BBN**H	90
	Li^{s}Bu$_3$BH	85
	LiSia$_3$BH	98
	K9-^{t}Bu-9-**BBN**H	96
	LiThx^{t}BuOBH	96
4-methylcyclohexanone	LiThx^{t}BuOBH$_2$	92
	K9-OThx-9-**BBN**H	85.5
	Li^{s}Bu$_3$BH	80.5
	LiSia$_3$BH	93
	K9-^{t}Bu-9-**BBN**H	94
	LiThx^{t}BuOBH	92
4-*t*-butylcyclohexanone	LiThx^{t}BuOBH$_2$	95
	K9-OThx-9-**BBN**H	87
	Li^{s}Bu$_3$BH	87.5
	LiSia$_3$BH	96.5
	K9-^{t}Bu-9-**BBN**H	98.5
	LiThx^{t}BuOBH	95
3,3,5-trimethyl-cyclohexanone	LiThx^{t}BuOBH$_2$	>99.5
	K9-OThx-9-**BBN**H	>99.9
	Li^{s}Bu$_3$BH	99.8
	LiSia$_3$BH	99
	K9-^{t}Bu-9-**BBN**H	99
	LiThx^{t}BuOBH	>99.5
norcamphor	LiThx^{t}BuOBH$_2$	98
	K9-OThx-9-**BBN**H	95
	Li^{s}Bu$_3$BH	99.6
	LiSia$_3$BH	99
	K9-^{t}Bu-9-**BBN**H	95.5
	LiThx^{t}BuOBH	98
camphor	LiThx^{t}BuOBH$_2$	>99.5
	K9-OThx-9-**BBN**H	97.5
	Li^{s}Bu$_3$BH	99.6
	LiSia$_3$BH	>99.9
	K9-^{t}Bu-9-**BBN**H	99.9
	LiThx^{t}BuOBH	>99.5

reagent and ketone at 25 °C, the stereochemistry of reduction appears apparently dependent on the reaction time. The stereoselectivity increases consistently with increase of reaction time to afford the thermodynamically more stable isomer alcohols exclusively (Eqn. 35), with exception of camphor which is resistant to reduction under the reaction conditions. Furthermore, like triisobutylaluminum (**TIBA**), it has been found that the isobutyl group of *i*-Bu$_2$AlO^{i}Pr is involved



(35)

in this reduction.[136b] Therefore, two equivalents of ketone are reduced with one equivalent of the reagent in refluxing Et$_2$O, although the second ketone is reduced in a relatively slow rate (Eqn. 36). This seems to be a phenomenon that must rise

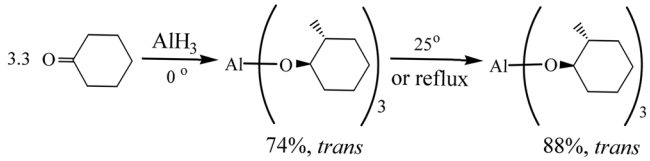


(36)

where the thermodynamically less stable alcohol isomer, one of the two isomer produced by reduction with *i*-Bu$_2$AlO^{i}Pr, is converted to the more stable one by thermodynamically controlled isomer equilibration *via* a **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]

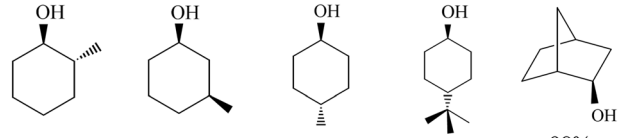
Such a mechanism involving thermodynamically controlled isomer equilibration can be extended to utilization of diisobutylaluminum hydride (**DIBAL-H**) itself. When the reduction of excess cyclic ketone with **DIBAL-H** is carried out at 0 °C, only the free hydride is involved and hence only one equivalent of ketone is reduced to show a low stereoselectivity. 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 in similar to the case of *i*-Bu$_2$AlO^{i}Pr (Scheme 6).

A similar trend has also been observed in the reduction of cyclic ketones with AlH$_3$.[139] In this case 3.3 equiv of ketone is needed. However, the stereoselectivity accomplished in this reduction appears somewhat lower than that achieved by diisobutylaluminum derivatives (Eqn. 37).

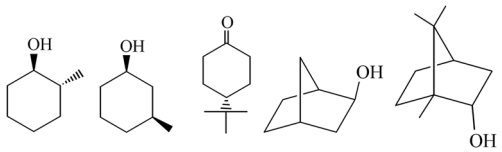


(37)

A solution of BH$_3$-THF can also be applied to such stereoselective reductions.[140] Because of the relatively smaller size of boron atom than that of 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 a time dependence.

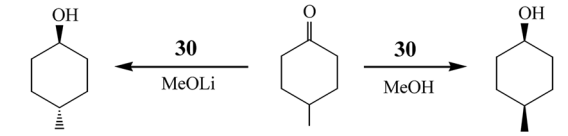


It is noteworthy to point out that the reductions of cyclohexanones with lithium-NH_3-ROH.[141] and with sodium dithionite[142] afford nearly exclusive formation of the equatorial alcohols, however the selectivity in the reduction of bicyclic ketones is relatively low.



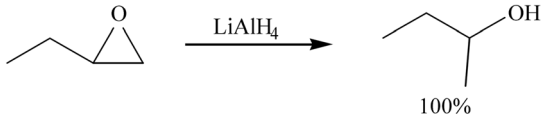
Li–NH_3–ROH:	99%, *trans*	94%, *cis*	99%, *trans*	15%, *exo*	90%, *endo*
$Na_2S_2O_4$:	71%, *trans*		87%, *trans*	15%, *exo*	65%, *endo*

It is quite interesting that 9-**BBN** "ate" complex (**30**) can reduce cycloalkanones to both *cis*- and *trans*-cycloalkanols in reasonably high isomeric purity with a mere change in additive such as MeOLi and MeOH[118] (Eqn. 38).

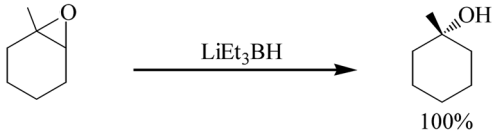


(38)

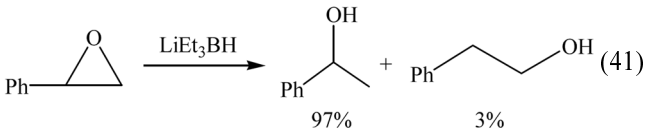
5. Regioselective Ring-Opening of Epoxides. As expected for S_N2 processes, nucleophilic hydride transferring reagents, such as $LiAlH_4$[143] and $LiEt_3BH$,[144] attack epoxides at the less substituted site to afford the more highly substituted alcohol (Eqn. 39-41).



(39)

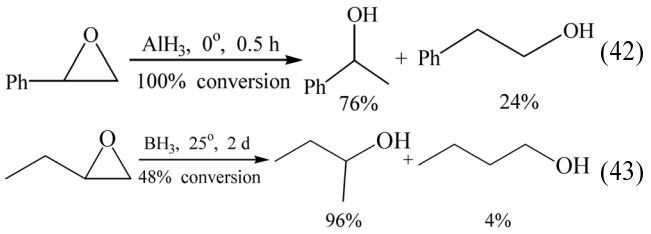


(40)



(41)

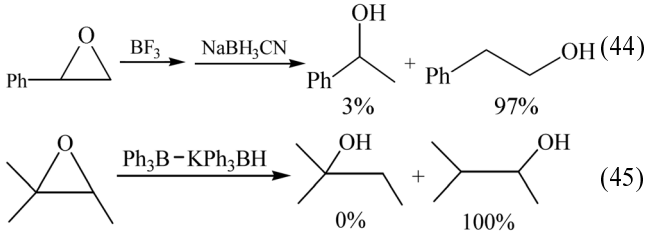
On the other hand, with electrophilic hydride reagents such as BH_3[145] and AlH_3[146] reverse opening is often observed to produce the less substituted alcohol, but mixtures usually result (Eqn. 42-43).



(42)

(43)

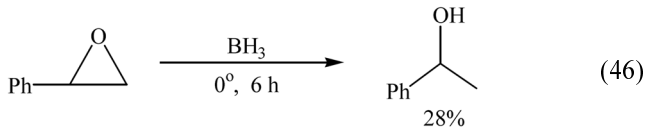
However, activation of epoxide by complexation with a Lewis acid, and followed by nucleophilic attack with conventional mild metal hydrides has been demonstrated to be the most convenient and reliable process for producing predominately the less substituted alcohols.[147,148] The addition of a Lewis acid not only accelerates the rate but also changes the products drastically. BF_3 and Ph_3B are utilized as an efficient Lewis acid for such activation (Eqn. 41-45).



(44)

(45)

The BF_3 effect on the rate enhancement and hence the clean product formation has also been observed in the reduction of epoxides with BH_3.[149] Thus, the reduction of styrene oxide with BH_3 alone provides only 28% of the expected 2-phenylethanol at 0 °C in 6 h.[145] However, the presence of BF_3 completely reduces styrene oxide at 0 °C in less than 0.5 h to give a clean product (Eqn. 46-47).



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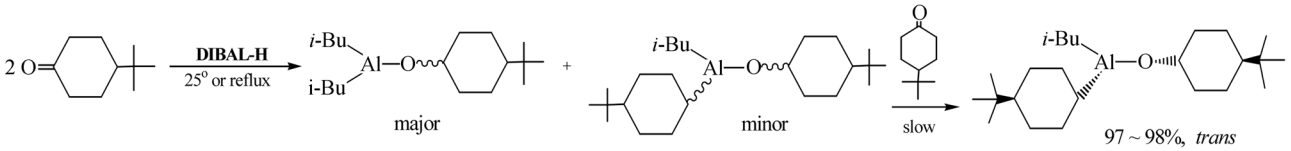
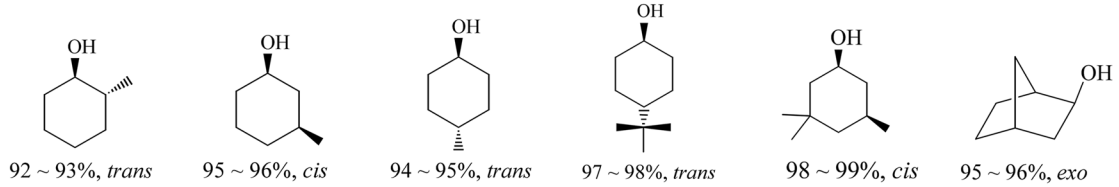
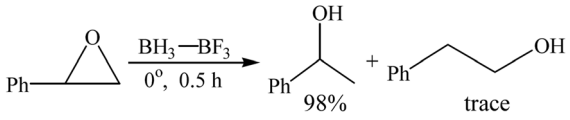


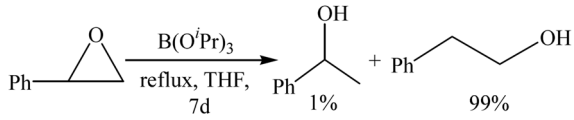


Scheme 7



(47)

The first report on the **MPV** type reduction of epoxides seems to be the communication which describes the reaction of epoxides with boron isopropoxide.[150] 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 (Eqn. 48-50).



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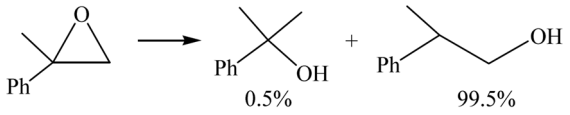

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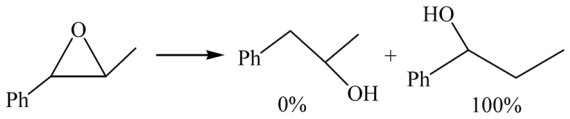
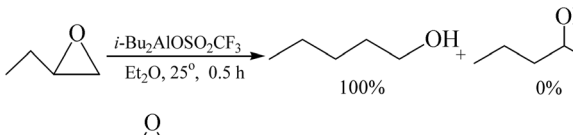


(50)

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.[151] In this reaction, the less substituted alcohols are produced as a sole product (Eqn. 51-56).



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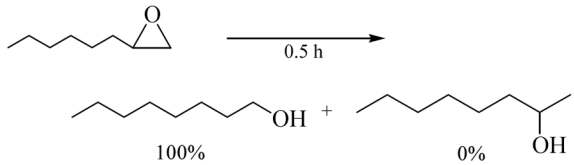

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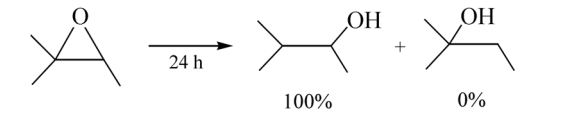

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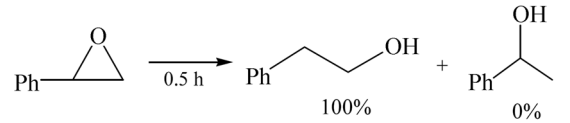

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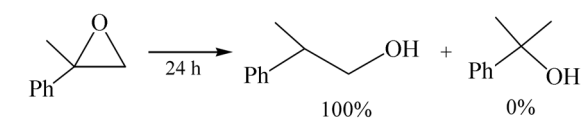

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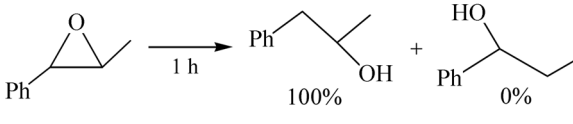

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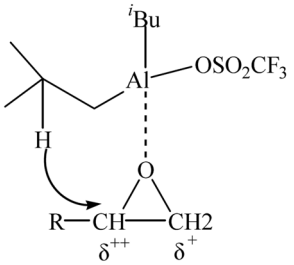
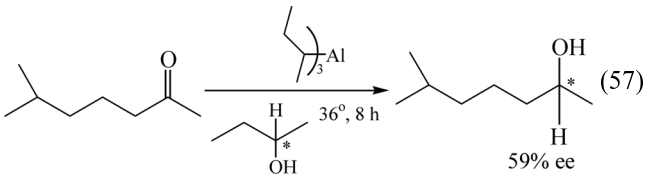


Scheme 8

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

6. Asymmetric Reduction.

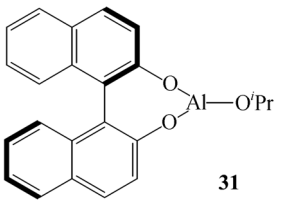
A. Intermolecular MPV reduction: The asymmetric versions of the intermolecular **MPV** reduction of ketones employ optically active alcohols as chiral sources. The first experimental report on the asymmetric **MPV** reduction of ketones seems to be the publication by Doering and Young in 1949 of a preliminary communication describing reductions of ketones with optically active 2-butanol catalysed by aluminum alkoxide[32a] (Eqn. 57).



(57)

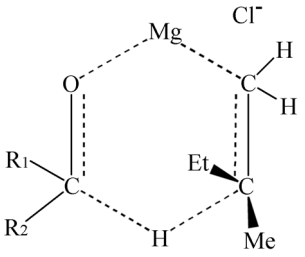
Such intermolecular **MPV** reduction have been continued using a variety of optically active alcohols.

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 **31**.



31

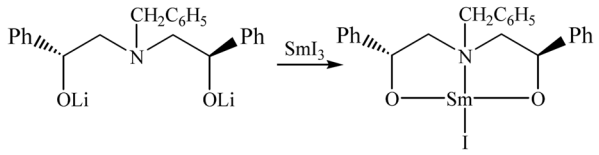
Grignard reagents having **H** atom on their *β*-carbon atom, derived from optically active alkyl halides, can also be applied to asymmetric reduction of ketones.[146] The reduction of prochiral ketones by the optically active Grignard reagent from (+)-1-chloro-2-methylbutane afforded alcohols in low 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



Scheme 9

terms of a six-membered cyclic transition state for the hydrogen transfer step[32a,147] (Scheme 9).

However, Evans and coworkers devised a catalytic, highly enantioselective **MPV** reduction using a chiral samarium catalyst.[148] The complex **33**, generated from the 1:1 chiral ligand **32**, and S_mI_3 (Eqn. 36), catalyzes the reduction of aromatic ketones by isopropyl alcohol to give optically active alcohols in up to 97% ee.

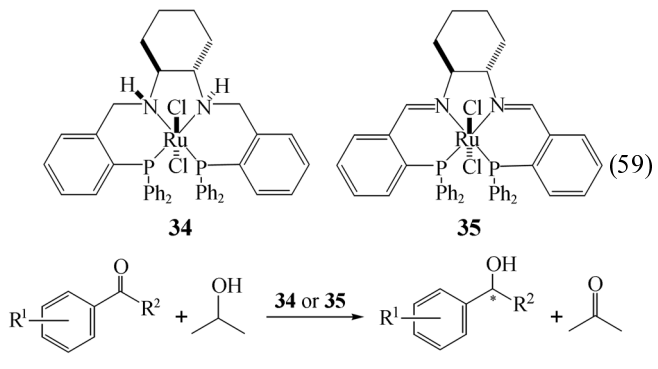


(58)

32 **33**

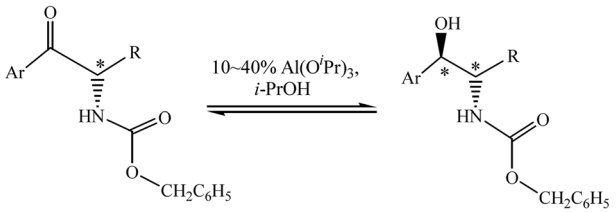
Very recently, a practical synthesis of ephedrine analogues with a high enantioselectivity by a highly diastereoselective **MPV** reduction of protected α-amino aromatic ketones using catalytic aluminum isopropoxide has been reported.[149] The high selectivity seems to arise from the chelation of the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

Furthermore, the asymmetric transfer hydrogenation of a variety of ketones using a late transition metal chiral rhodium, ruthenium or iridium catalyst is extremely promising.[56,158,159] Especially, Ru complexes having a tetradentate diphosphine/diamine ligand (**34**) or diphosphine/diimine ligand (**35**) in isopropyl alcohol convert various substituted aromatic ketones to 1-phenylethanols in high yields and with up to 97% ee[160] (Eqn. 59). And a chiral Ru complex formulated as **36** acts as an efficient catalyst for asymmetric transfer hydrogenation of aromatic ketone in isopropyl alcohol or formic acid, showing enantioselectivity of up to 99% ee.[160]

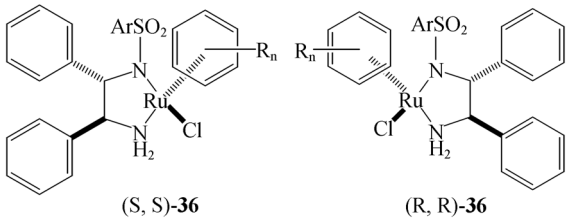


(59)

34 **35**



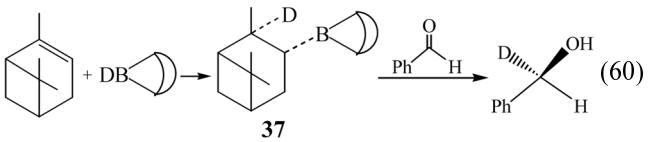
Scheme 10



(S, S)-**36** (R, R)-**36**

As described before, trialkylboranes are noted for their tolerance of a wide variety of functional groups.[3,5] However, Midland and coworkers demonstrated that certain *B*-alkyl-9-**BBN**, 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 (Eqn. 5) *via* six-membered cyclic transition state depicted in Seheme 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 12).

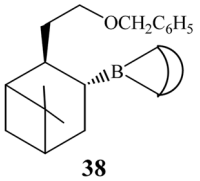
It has been observed that the β-hydrogen is actually utilized for the reduction. Therefore, that hydrogen added *via* the hydroboration process is the reducing hydrogen. In fact, the deuterated organoborane **37**, obtained by deuterioboration of α-pinene with 9-**BBN**-9-*d* quantitatively transfers deuterium to benzaldehyde (Eqn. 60). The availability of the deuterated reagent (**37**) allows the asymmetric reduction of a variety of aldehydes (Table 13).



(60)

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.[151,152,36g]



38

Table 11. Stereoselective Reduction of Cyclic Ketones with *i*-Bu_2AlO^iPr in Et_2O

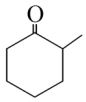
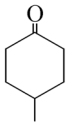
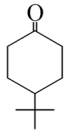
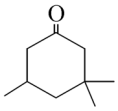
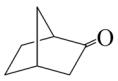
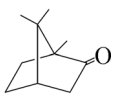
Ketone	Reaction time (h)	Ketone:Reagent = 1:1 (25 °C)		Ketone:Reagent = 2:1 (reflux)	
		Ratio of more stable isomer (%)	Yield of alcohol (%)	Ratio of more stable isomer (%)	Yield of alcohol (%)
	3	49	51		
	6	67	71		
	24	85	92	87	76
	72	91	98	89.5	87
	120	95	>99.9	90	92
	168	96	100		
	360			93.5	99
	6	91	98		
	24	93	99	91	81
	72	93	>99.9	92	92
	96	94	100		
	120	95	100	92	97
	240			94	>99.9
	3	89	94		
	24	92	99	92	87
	72	94	>99.9	93.5	94
	96	97	100		
	120	>99.9	100	94	97
	240			97	100
	6	91	98		
	24	95	>99.9	91	82
	72	97	100	94.5	94
	96	98	100		
	120			97	97
	240			98	100
	12	97	89		
	24	98	94	93	78.5
	72	>99.9	99	94	89
	120			94.5	90
	168			96	97
	6	85	43		
	24	90	76	68	58
	72	93	96	81	73
	120	97	100	86	80
	240			91.5	98
	24	31	7	35	2.5
	120	36	14	49	6
	168	37	23		
	360			69	20

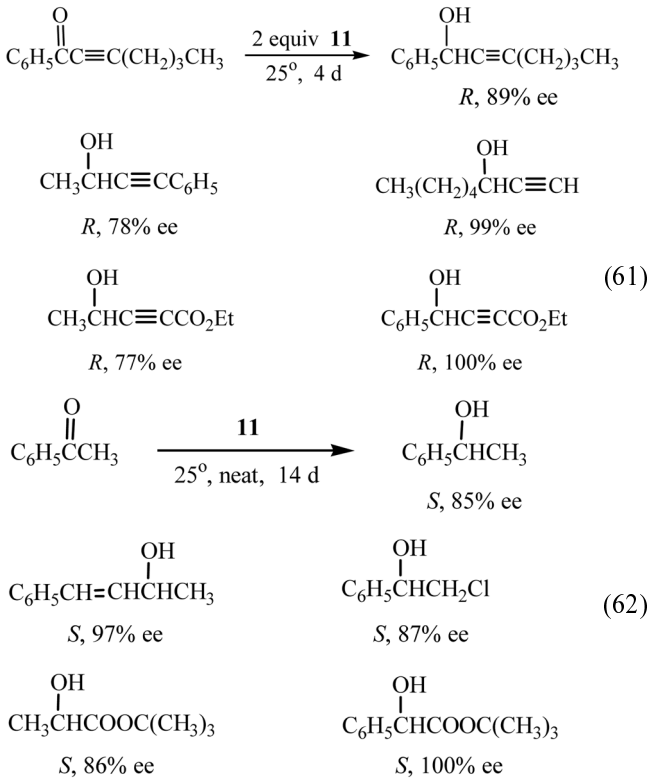
Table 12. Reduction of Benzaldehyde-1-*d* with Chiral *B*-Alkyl-9-**BBN** Reagents

Reagent	ee, %	Config.
11	90	S
12	47	S
13	75	R
14	61	S

In addition, the 9-**BBN** derivative of nopol benzyl ether, **NB**-Enantrane (**38**) 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-pinanyl)-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 (Eqn. 61).[153] Finally, Professor Brown and coworker 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] (Eqn. 62).

Table 13. Reduction of Aldehydes with Deuterated *B*-3-Pinanyl-9-**BBN** (**30**)

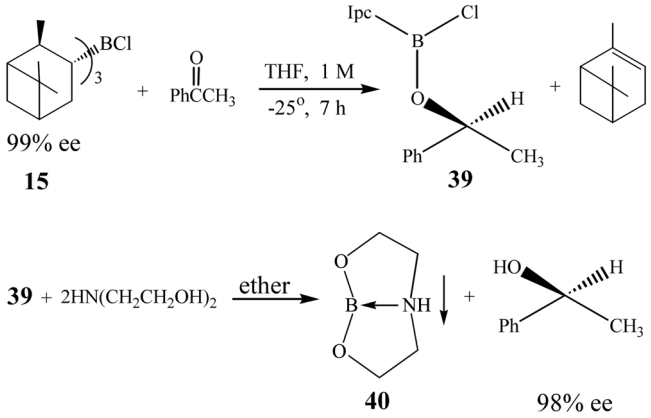
Aldehydes	Alcohols	ee, %
$CH_3CH_2CH_2CHO$	$CH_3CH_2CH_2CHDOH$	101
$CH_3(CH_2)_4CHO$	$CH_3(CH_2)_4CHDOH$	89
$(CH_3)_3CCHO$	$(CH_3)_3CHDOH$	98
$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCHO$	$(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCHDOH$	81
$C_6H_5CH=CHCHO$	$C_6H_5CH=CHCHDOH$	84
C_6H_5CHO	C_6H_5CHDOH	98
p-ClC_6H_4CHO	*p*-ClC_6H_4CHDOH	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



Professor Brown and coworkers 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 (**40**) with diethanolamine (Scheme 11). Results for the chiral reduction of ketones and a comparison of the data with these for some important reagents[157] are summarized in Table 6 and 7.

They have also developed various chiral reducing agents



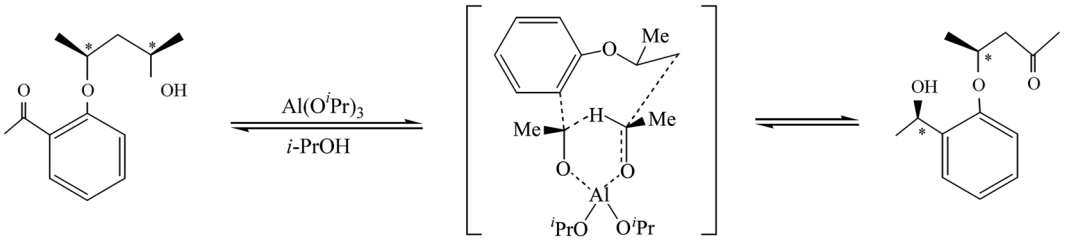
Scheme 11

(**16**-**20**) and applied to the asymmetric reduction of ketones.[39,158]

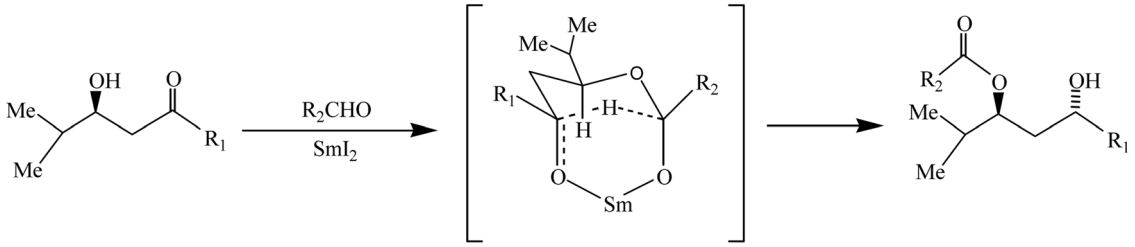
B. Intramolecular MPV reduction: The intramolecular asymmetric **MPV** reduction occurs in a molecule possessing a chiral alcohol moiety and involves 1,5- or 1,7-hydride shift *via* six-membered cyclic transition state.[159] Generally the reduction proceeds with very high stereoselectivity (Scheme 12).

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).

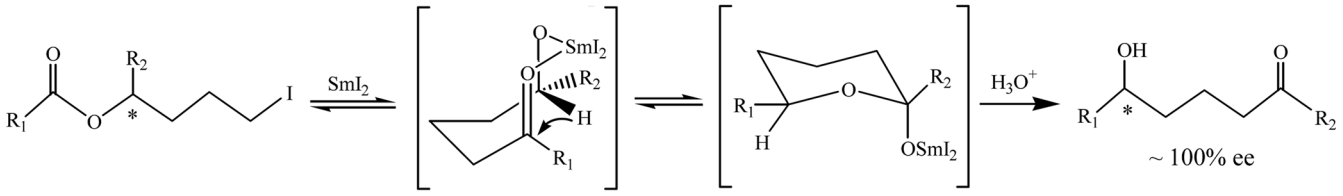
Tandem intramolecular substitution or addition – **MPV** reduction provides an interesting synthetic tool for producing optically active compounds. Samarium (II) iodide induces sequential intramolecular **MPV** reduction to produce optically active β-hydroxy ketones[160] (Scheme 14). Other examples for such reactions are the synthesis of optically active secondary alcohols[161] and 1,3-mercapto alcohols[162] from α,β-unsaturated ketones *via* 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 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



Scheme 12



Scheme 13



Scheme 14

Table 14. Comparison of Chiral Induction Obtained by Various Reagents

Ketone	% ee				
	Ipc_2BCl (**15**) −25°	**11** 25°	**11** (high pressure)	Binal-H[167] −100°	**31** −100°
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

Table 15. Chiral Reduction of Aromatic Ketones with **15** at −25 °C and a Comparison with Other Reagents

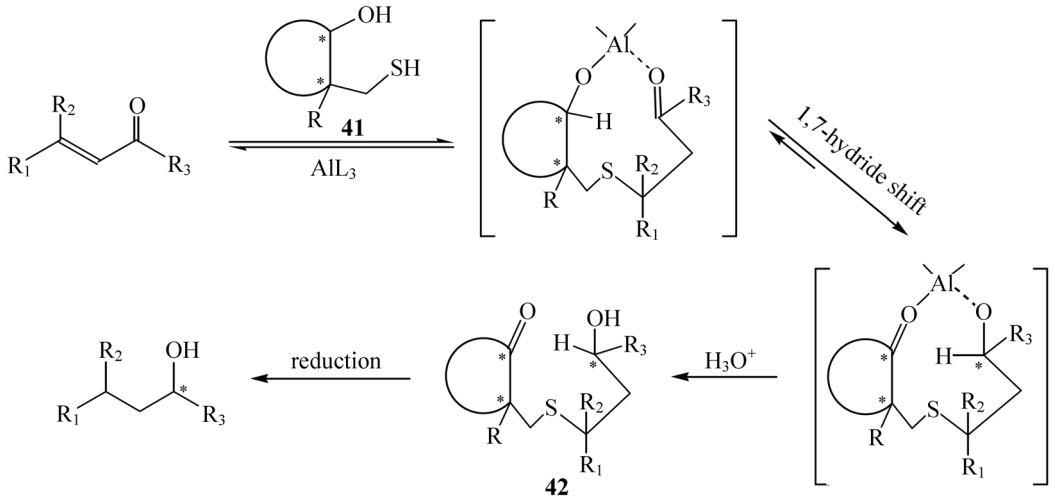
Ketone	% ee	% ee by **11**		% ee by Binal-H[167] (−100°)
		neat condition	high pressure	
acetophenone	98	85	100	95
2'-acetonaphthone	98			
3-acetylpyridine	92	90	100	
2-acetylthiophenone	91			
butyrophenone	100			100
1-indanone	97			
isobutyrophenone	78			71
pivalophenone	79			44

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 **41**. The process is exactly same as depicted in Scheme 13, except the reductive desulfuration step of **42**. 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.

Concluding Remarks

It is evident that the most desirable goal of the chemists



Scheme 15

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 being 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 in spite of their abundant choice in literature one should consider carefully which reagent satisfies one's purpose, because each reagent possesses its own limitation.

Besides, as growing the complexity of molecules which chemists are concerning, continuous efforts to develop new methods and new reagents providing a very clean and selective reduction of particular orgnic functional group are demanding.

Although most chemists seem to pay much less attention to utilize the **MPV** type reagents than metal complex hydrides apparently due to their narrow diversity in reduction toward organic functional groups, the MPV reagents possess unique reducing characteristics. Because the **MPV** reduction takes place only after coordination of the reagent to oxygen atom of the compound, the reagents exhibit an exceptional selectivity. Furthermore, the recent achievement in catalytic MPV reduction using various homogeneous and heterogeneous catalyst is promising. Therefore, this review might provide some useful informations to chemists who are concerning about the selective reduction of organic functional groups.

Acknowledgment. Part of references published by the author and coworkers was made possible by the financial support of the Korea Research Foundation Grant (R05-2004-000-10252-0) and the Advanced Research Center in Yeungnam University (214001). This review is dedicated to the memory of Professor Sang Chul Shim, an outstanding scientist in the field of organometallic chemistry, who retired from Kyungpook National University in February, 2008. The author keeps in mind his warm-hearted friendship given to the author.

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