

## Selective Reduction of Organic Compounds with *Al*-Fluorodiisobutylalane

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### Abstract

The new MPV-type reagent, *Al*-fluorodiisobutylalane (DIBAF), has been prepared and their reducing characteristics in the reduction of selected organic compounds containing representative functional groups have been examined in order to find out a new reducing system with unique applicability in organic synthesis. In general, the reagent is extremely mild, showing only reactivity toward aldehydes, ketones, and epoxides. The reagent achieves a clean 1,2-reduction of enals to the corresponding allylic alcohols in a 100% purity, but shows no reactivity toward enones. The reagent also shows an excellent regioselective cleavage of substituted epoxides. In addition, DIBAF produces the thermodynamically more stable alcohol epimer in high stereoselectivity in the reduction of cyclic ketones.

**Key words :** *Al*-Fluorodiisobutylalane, Selective reduction, Organic compounds

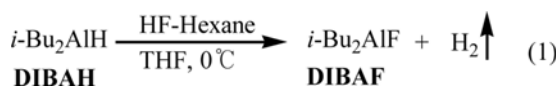
### 1. Introduction

In the previous communication<sup>[1]</sup>, we reported that *Al*-fluorodiisobutylalane (DIBAF), a new MPV type reagent, reacts readily with both aromatic and aliphatic epoxides to produce the corresponding alcohols in an essentially perfect regioselectivity. These results attracted us. It seems desirable to understand the reducing characteristics of the reagent in the reduction of organic functionalities. Accordingly, we examined the reduction pattern and reactivity of the reagent in the reduction of organic compounds containing representative functional groups in order to find out a new MPV type reducing system with unique applicability in organic synthesis.

### 2. Results and Discussion

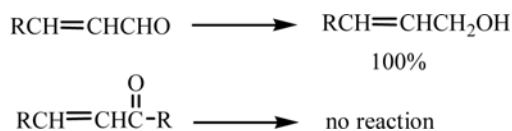
DIBAF can be prepared easily by a simple reaction of diisobutylaluminum hydride (DIBAH) with hydrogen fluoride in THF (Eq. 1).

The reactivity of DIBAF toward some representative aldehydes and ketones in Hexane-THF at 25°C was examined, and the results are summarized in Table 1.



As shown in the Table, DIBAF showed a very high reactivity toward a variety of aldehydes, but exhibited relatively lower reactivity toward ketones examined, showing a possibility for the chemoselective reduction between aldehydes and ketones.

A similar reactivity difference was also detected in the reaction of  $\alpha,\beta$ -unsaturated aldehydes and ketones as listed in Table 2. Thus, DIBAF readily reduced enals to the corresponding allylic alcohols but absolutely no reactivity toward enones examined. Furthermore, The reagent achieved a clean 1,2-reduction to show an essentially perfect selectivity; products are the corresponding allylic alcohols in 100% purity.



The most fascinating feature of the reagent seems to be the results obtained in the reaction of epoxides. As listed in Table 3, DIBAF reduced both aliphatic and aromatic epoxides examined in hexane-THF in 24 h at 25°C.

However, it is noteworthy that the reagent attacks

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**Table 1.** Reaction of Aldehydes and Ketones with *A*-Fluorodiisobutylalane (DIBAF) in Hexane-Tetrahydrofuran<sup>a,b</sup> at 25°C.

Compound	Time (h)	Yield of alcohol (%)
hexanal	0.5	95
	1	98
	3	99.9
benzaldehyde	0.5	96
	1	99
	3	100
<i>p</i> -tolualdehyde	0.5	94
	1	99.9
	3	99.9
<i>m</i> -tolualdehyde	0.5	97
	1	100
<i>p</i> -chlorobenzaldehyde	0.5	99.9
	1	100
2,6-dichlorobenzaldehyde	0.5	100
<i>p</i> -anisaldehyde	0.5	100
2-heptanone	24	68
	72	90
	120	94
	168	99
cyclohexanone	24	90
	72	98
	96	100
acetophenone	24	87
	72	94
	96	99
benzophenone	24	80
	120	92
	168	96
	240	100

<sup>a</sup>Determined by GC using a suitable internal standard. Concentration of each compound was 0.5 M.

<sup>b</sup>One equivalent of reagent was utilized.

aromatic epoxides more readily than aliphatic ones. **DIBAF** shows substituted alcohol is produced as a sole product by trapping of  $\beta$ -hydrogen from isobutyl group of the reagent at the site best able to accommodate a carbonium ion.

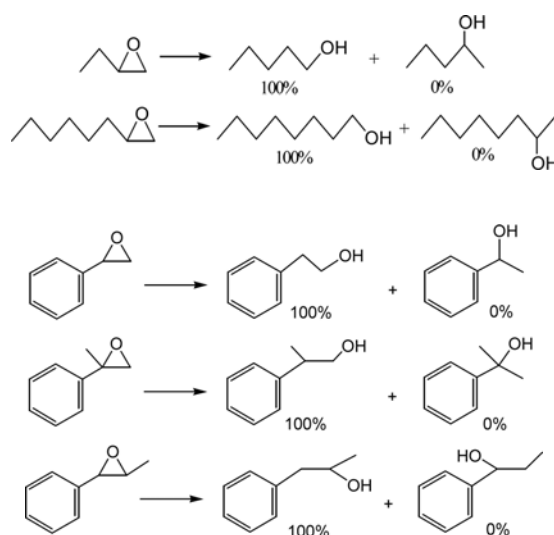
Furthermore, the most interesting example should be found in the reaction of *trans*- $\beta$ -methylstyrene oxide.

**Table 2.** Reaction of  $\alpha,\beta$ -Unsaturated Aldehydes (Enals) and Ketones (Enones) with DIBAF in Hexane-THF<sup>a,b</sup> at 25°C.

Compound	Time (h)	Yield of alcohol (%)
crotonaldehyde	1	88
	3	99.9
	6	99.9 <sup>c</sup>
2-hexenal	1	87
	6	94
	24	96
	120	100 <sup>c</sup>
cinnamaldehyde	6	88
	24	91
	72	96
3-penten-2-one	48	0
2-cyclohexen-1-one	48	0
isophorone	48	0
benzalacetone	48	0
chalcone	48	0

<sup>a,b</sup>See the corresponding footnotes in Table 1.

<sup>c</sup>One hundred % purity of the corresponding allylic alcohol.



Thus, the reaction yield 1-phenyl-2-propanol in a 100% selectivity. It is rather surprising that the reagent discriminates between the phenyl group- and the alkyl group- attacked carbon site.

Table 3. Reaction of Epoxide with DIBAF in Hexane-THF<sup>a</sup> at 25°C<sup>b</sup>.

Epoxides	Time (h)	Conversion (%) <sup>c</sup>	Product	Purity (%)
1,2-epoxybutane	6	87	1-butanol	100
	12	93	1-butanol	100
	24	100	1-butanol	100
1,2-epoxyoctane	6	78	1-octanol	100
	12	86	1-octanol	100
	24	96	1-octanol	100
	48	100	1-octanol	100
Styrene oxide	6	94	2-phenylethanol	100
	12	99	2-phenylethanol	100
	24	100 <sup>d</sup>	2-phenylethanol	100
$\alpha$ -methylstyrene oxide	6	98	2-phenyl-1-propanol	100
	12	100	2-phenyl-1-propanol	100
	24	100	2-phenyl-1-propanol	100
<i>trans</i> - $\beta$ -methylstyrene oxide	1	96	1-phenyl-2-propanol	100
	3	100	1-phenyl-2-propanol	100

<sup>a</sup>A mixture of hexane-THF (1:1).

<sup>b</sup>Ten % excess reagent utilized: 0.5 M concentration.

<sup>c</sup>Determined by GC using a suitable internal standard.

<sup>d</sup>Seventy six % of 2-phenylethanol was isolated from the 40 mmol scale of reaction mixture.

In the mechanistic point of view, the reaction of epoxides with DIBAF seems to involve the formation of a coordination complex, in which the aluminum atom bound to the epoxy oxygen, and followed by the hydride transfer *via* a cyclic transition state as in a usual reaction of carbonyl compounds with a MPV reagent.<sup>[2,3]</sup>

Such an anti-Markovnikov reductive opening of epoxides has previously been achieved with BH<sub>3</sub>-THF in the presence of BF<sub>3</sub>,<sup>[4]</sup> NaBH<sub>3</sub>CN in the presence of BF<sub>3</sub>,<sup>[5]</sup> KPh<sub>3</sub>BH in the presence of Ph<sub>3</sub>B<sup>[6]</sup>, and (PrO)<sub>3</sub>B.<sup>[7]</sup> However, each reagent possesses its own limitations of the reduction, such as a relatively low selectivity, requirement for drastic reaction conditions, an undesirable rearrangement product, etc.

The reactivity of the reagent toward other functional compounds was also examined and the results are summarized in Table 4. As Shown in the Table, DIBAF exhibited no reactivity toward acid chlorides, carboxylic acids, amides, nitriles and esters. Such a mild reducing characteristics of the reagent makes it possible the chemoselective reduction of aldehydes, ketones or epoxides in the presence of such inert compounds.

Finally, we applied DIBAF to the reduction of rep-

Table 4. Reaction of Other Organic Functional Groups with DIBAF in Hexane-THF<sup>a,b</sup> at 25°C.

Compound	Time (h)	Yield of reduction Product (%)
hexanoyl chloride	24	0
benzoyl chloride	24	1
benzoic acid	24	0
benzotrile	24	0
ethyl benzoate	24	0
benzamide	24	0

<sup>a,b</sup>See the corresponding footnotes in Table 1.

resentative cyclic ketones and examined its stereochemistry. As shown in Table 5, the reagent reduced cyclic ketones slowly both at 0 or 25°C except for 2-*t*-butylcyclohexanone and camphor. Particularly, the distinct rate difference between 2-methyl- and 2-*t*-butylcyclohexanone is remarkable: 2-methylcyclohexanone was readily reduced, but 2-*t*-butylcyclohexanone was quite slowly reduced. These results clearly indicate that the steric requirement around the coordination sphere is also an important factor upon the reduction rate. However, nevertheless the reactivity difference among cyclic

**Table 5.** Stereochemistry in the Reduction of Representative Cyclic Ketones with DIBALF in Hexane-THF<sup>a,b</sup>.

Compound	Temp (°C)	Time (h)	Yield of alcohol (%)	Ratio of more stable isomer (%) <sup>c</sup>
2-methylcyclohexanone	0	24	74	79
		120	92	92
		168	97	92 <sup>d</sup>
	25	24	96	89
		72	99	91
		120	100	92 <sup>d</sup>
3-methylcyclohexanone	0	24	91	89
		72	93	93
		120	97	94 <sup>e</sup>
	25	6	95	93
		24	100	95 <sup>e</sup>
		6	87	76
4-methylcyclohexanone	0	24	89	85
		72	97	89
		120	97	90 <sup>f</sup>
	25	6	90	93
		24	92	97
		72	100	99.8 <sup>f</sup>
3,3,5-trimethylcyclohexanone	0	6	68	81
		24	74	96
		72	78	99.9
	25	120	85	99.9 <sup>g</sup>
		6	80	93
		24	92	97
4- <i>t</i> -butylcyclohexanone	0	6	89	83
		24	93	90
		72	95	98
	25	120	97	99.9 <sup>h</sup>
		6	91	94
		24	96	96
2- <i>t</i> -butylcyclohexanone	0	72	99.9	99.9 <sup>h</sup>
		24	38	38

**Table 5.** Continued.

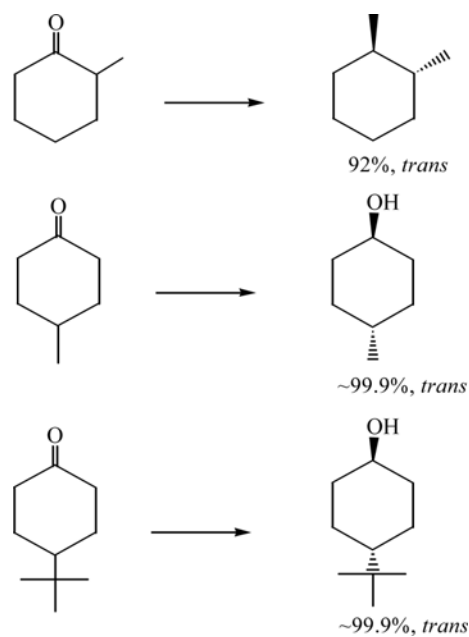
Compound	Temp (°C)	Time (h)	Yield of alcohol (%)	Ratio of more stable isomer (%) <sup>c</sup>
norcamphor	25	72	43	45 <sup>i</sup>
		24	60	99.9
		120	71	99.9 <sup>i</sup>
	0	24	66	57
		72	83	92
		120	94	92 <sup>j</sup>
camphor	25	24	84	95
		72	95	95
		120	99.9	95 <sup>j</sup>
	0	24	16	91
		120	31	92 <sup>k</sup>
		25	24	40
		120	72	91 <sup>k</sup>

<sup>a,b</sup>See the corresponding footnotes in Table 1.

<sup>c</sup>Normalized.

<sup>d</sup>*Trans* isomer. <sup>e</sup>*Cis* isomer. <sup>f</sup>*Trans* isomer. <sup>g</sup>*Cis* isomer.

<sup>h</sup>*Trans* isomer. <sup>i</sup>*Trans* isomer. <sup>j</sup>*Exo* isomer. <sup>k</sup>*Endo* isomer.



ketones, the stereochemistry of the product alcohols obtained in the reduction of all the cyclic ketones examined is consistently the thermodynamically more stable epimer.<sup>[8]</sup>

### 3. Conclusion

The reducing characteristics of the new **MPV** type reagent, DIBAF, are now fully understood. In general, the reagent is extremely mild, showing only reactivity toward aldehydes, ketones and epoxides. The reagent exhibits a unique reducing applicability in organic synthesis: the reagent achieved a clean 1,2- reduction of enals but showed no reactivity toward enones. The reagent also showed an excellent regioselective cleavage of phenyl- or alkyl- substituted epoxides. In addition, DIBAF produced the thermodynamically more stable alcohol epimer in high stereoselectivity from the reduction of alkyl- substituted cycloalkanones.

With organic research undertaking the synthesis of structures of increasing complexity, there was an evident and growing need for reagents possessing a high degree of selectivity. Therefore, this systematic study could have the organic chemist available a more complete spectrum of reagents for selective reductions.

### 4. Experimental Section

All glassware used in this study was predried at 140°C for at least 9 hours, assembled hot, and cooled under a stream of dry N<sub>2</sub> prior to use. All reactions were performed under a dry N<sub>2</sub> atmosphere. All chemicals used were commercial products of the highest purity available, which were further purified by standard methods before use. Et<sub>2</sub>O was distilled from sodium-benzophenone ketyl prior to use. Gas chromatographic analyses were carried out with a Varian 4400 chromatograph using DB-Wax and HP-FFAP capillary columns (30 m).

#### 4.1. Preparation of DIBAF

DIBAF in hexane was used as purchased from Aldrich, or prepared from the reaction of diisobutylaluminum hydride (DIBAH) and dry HF. HF was liquified at 0°C and reacted with an equivalent of DIBAH in THF.

#### 4.2. General Procedure for Reduction of Organic Compounds

The following procedure is illustrative. Into a 50 mL flask with a side-arm equipped with a downward-directed, water-cooled condenser leading to a mercury bubbler,<sup>7</sup> 0.60 g of styrene oxide (5 mmol), 5.5 mL of THF, tridecane (2 mmol) as an internal standard, and 5.5 mL of a 1.0 M solution of DIBAF (5.5 mmol) in hexane were injected.

#### 4.3. Reduction of Cyclic Ketones

The following procedure was used to explore the stereoselectivity of DIBAF. In the usual setup, the flask containing 5 mmol of ketone examined was reacted with 10 mmol of the reagent in THF (a total of 10 mL reaction mixture) at 25°C. At the appropriate time intervals, an aliquot was withdrawn and hydrolyzed with 3 *N* HCl. The aqueous layer was saturated with K<sub>2</sub>CO<sub>3</sub> and the organic layer was dried over anhydrous MgSO<sub>4</sub>. The organic layer was then subjected to gas chromatographic analysis.

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