

Selective Reduction of Organic Compounds with *Al*-Trifluoromethanesulfonyldiisobutylalane. Comparison of Its Reactivity with *Al*-Methanesulfonyldiisobutylalane

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The new **MPV** type reagent, *Al*-trifluoromethanesulfonyldiisobutylalane (DIBAO₃SCF₃), has been prepared and its reducing characteristics in the reduction of selected organic compounds containing representative functional groups have been examined, and compared its reactivity with that of *Al*-methanesulfonyldiisobutylalane (DIBAO₃SCH₃) in order to understand the fluorine-substituent effect on its reactivity. In general, the reactivity of DIBAO₃SCF₃ appears to be much higher than that of DIBAO₃SCH₃, apparently due to the acidity increase by the electron-withdrawing fluorine-substituent. The reagent reduced aldehydes and ketones readily, but showed a perfect selectivity in the reduction of α,β -unsaturated aldehydes and ketones to produce the corresponding allylic alcohols in an absolutely 100% purity. In addition, the reagent achieved the regioselective cleavage of phenyl- or/and alkyl-substituted epoxides to the less substituted alcohols in a perfect regioselectivity. Moreover, the reagent also showed an high stereoselectivity in the reduction of substituted cycloalkanones to produce the thermodynamically more stable alcohol epimers exclusively.

Key Words: *Al*-Trifluoromethanesulfonyldiisobutylalane, Selective reduction, Organic functional groups, **MPV** type reduction

Introduction

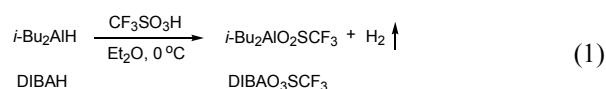
As described in the previous article,¹ the introduction of acetoxy or trifluoroacetoxy group to diisobutylaluminum hydride (DIBAH) provides a new class of Meerwein-Ponndorf-Verley (**MPV**) type reagents, *Al*-acetoxydiisobutylalane (DIBAOAc) and *Al*-trifluoroacetoxydiisobutylalane (DIBAO₃CCF₃), which possess unique reducing characteristics of an excellent selectivity in the reduction of carbonyl compounds and epoxides. Especially noteworthy is that the introduction of the electron-withdrawing fluorine-substituent into acetoxy group increases its reactivity effectively. This phenomenon clearly indicates that the Lewis acidity plays a role in part in the reactivity of **MPV** type reagents.

In the successive reports,²⁻⁴ we introduced a new class of **MPV** type reagents, the methanesulfonyl group-incorporated diisobutylalane derivatives such as *Al*-methanesulfonyldiisobutylalane (DIBAO₃SCH₃) and *Al*-trifluoromethanesulfonyldiisobutylalane (DIBAO₃SCF₃). Such reagents appeared to be extremely mild, but exhibited a remarkable reactivity toward epoxides to produce the regioselectively ring-opened products. Especially noteworthy is that the fluorinated derivative, DIBAO₃SCF₃ is much higher in reactivity than DIBAO₃SCH₃ itself. Thus, the ring-opening reaction of simple epoxides by DIBAO₃SCF₃ is completed within 0.5 h at 25 °C, whereas DIBAO₃SCH₃ requires 24 - 48 h under the same reaction conditions.

These results intrigued us. It seems desirable to understand the full-scope of the reducing characteristics of DIBAO₃SCF₃ and compare its reactivity with that of DIBAO₃SCH₃ in order to find out their applicability in the selective reduction of organic compounds. This article described such a systematic study on the reducing pattern of DIBAO₃SCF₃.

Results and Discussion

DIBAO₃SCF₃ can be prepared easily by a simple reaction of diisobutylaluminum hydride (DIBAH) with trifluoromethanesulfonic acid in Et₂O at 0 °C (Eq. 1).



The reactivity of DIBAO₃SCF₃ toward some representative aldehydes and ketones in Et₂O at 25 °C was examined and compared with that of DIBAO₃SCH₃, and the results are summarized in Table 1. As compared in the Table, the reactivity of DIBAO₃SCF₃ toward carbonyl compounds appears to be much higher than that of DIBAO₃SCH₃. Thus, for example 10% excess DIBAO₃SCF₃ reduced simple aldehydes examined to the corresponding alcohol within 6 h at 25 °C, whereas DIBAO₃SCH₃ required at least 24 h for complete reduction under the same reaction conditions.

A similar reactivity difference was also observed in the reaction of α,β -unsaturated aldehydes and ketones, as summarized in Table 2. Thus, for example, excess DIBAO₃SCF₃ (2 equiv) reduced cinnamaldehyde to cinnamyl alcohol within 1 h at 25 °C, whereas DIBAO₃SCH₃ required 6 h for complete reduction. In addition, especially noteworthy is that both reagents even of excess amount achieved a clean 1,2-reduction to show a perfect chemoselectivity: products are the corresponding allylic alcohols in 100% purity.

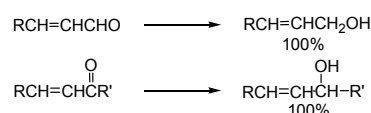
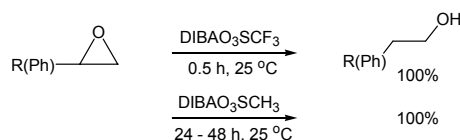


Table 1. Reaction of simple aldehydes and ketones with *Al*-trifluoromethanesulfonyldiisobutylalane (DIBAO₃SCF₃) in diethyl ether^a at 25 °C

Compound	Time (h)	Yield of alcohol (%) ^b	
		DIBAO ₃ SCF ₃	DIBAO ₃ SCH ₃ ^c
hexanol	0.5	100	93
	1	100	94
	3		96
	6		98
	24		100
benzaldehyde	0.5	87	60
	1	94	77
	3	99.5	88
	6	100, 74 ^d	92
	24		99.9, 75 ^d
2-heptanone	0.5	77	
	1	85	69
	3	90	71
	6	92	75
	24	96	86
	48	98	
	72		89
	120		95
acetophenone	0.5	81	
	1	88	72
	3	95	76
	6	97	80
	24	98	86
	72	98	90
benzophenone	120		97
	3	65, 72 ^e	
	6	75, 93 ^e	51
	24	82, 98 ^e	
	48	85, 98 ^e	
72		64	
120		78	

^aTen % excess reagent utilized; concentration of each compound was 0.5 M. ^bDetermined by GC using a suitable internal standard. ^cData taken from ref. ^dIsolated yield on distillation. ^eTwo equivalent of reagent utilized.

The most fascinating feature of the reagent seems to be the results obtained in the reaction of epoxides, as summarized in Table 3. DIBAO₃SCF₃ readily reduced a variety of alkyl- or/and phenyl-substituted epoxides examined to the ring-opened products in 0.5 - 6 h at 25 °C. The reactivity of the reagent appeared much higher than that of DIBAO₃SCH₃.¹ These results clearly indicate that the strong electron-withdrawing fluorine substituent in methanesulfonyl group increases the acidity of the reagent, that leads to a stronger coordination of the reagent to epoxy oxygen and in turn an easier attack on epoxy carbon to produce a ring-opened product.

**Table 2.** Reaction of α,β -unsaturated aldehydes and ketones with DIBAO₃SCF₃ in Et₂O^a at 25 °C

Compound	Reagent/ Compd	Time (h)	Yield of alcohol (%) ^b		Purity (%) ^d
			DIBAO ₃ SCF ₃	DIBAO ₃ SCH ₃ ^c	
crotonaldehyde	1.1	0.5	83		100
		1	86	61	100
		3	96	91	100
		6	99.5	97	100
		24	99.5	100	100
	2	0.5	99.5		100
		1	99.5, 72 ^e	95	100
		3		98	100
		6		100, 73 ^e	100
cinnamaldehyde	1.1	0.5	62	41	100
		1	83	50	100
		3	99	89	100
		6	99	98	100
		24		98	100
	2	0.5	98	74	100
		1	99	89	100
		3		93	100
		6		98	100
		24		98	100
isophorone	1.1	6	85	50	100
		24	98	75	100
	2	6	96	74	100
		24	99	82	100
		72		98	100
chalcone	1.1	6	82	45	100
		24	94	70	100
		48	99	78	100
	2	6	92	68	100
		24	100	79	100
		72		95	100
120		99	100		

^{a-c}See the corresponding footnote in Table 1. ^dPurity of all allylic alcohol products are absolutely 100%. ^eIsolated yield on distillation.

More interestingly, in spite of such high reactivity the regioselectivity achieved by reagent in the reduction of epoxides was rather surprising. For example, the reaction of one alkyl- or phenyl-substituted epoxides such as 1,2-epoxyoctane and styrene oxide provided only the corresponding primary alcohol as a sole product. These results clearly indicate that the reaction proceeds through trapping of β -hydrogen from isobutyl group of the reagent at the site best able to accommodate a carbocation.

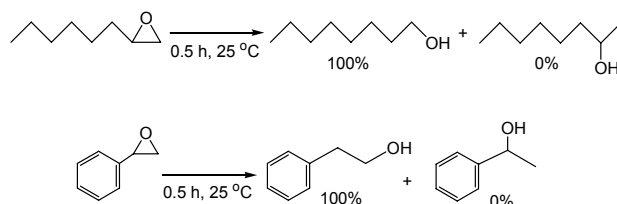
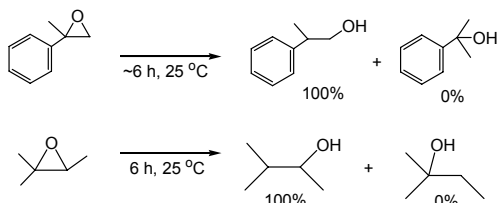


Table 3. Reaction of epoxides with DIBAO₃SCF₃ in Et₂O^a at 25 °C

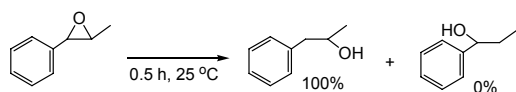
Epoxides	Time (h)	DIBAO ₃ SCF ₃	DIBAO ₃ SCH ₃ ^a	Product	Purity (%) ^b
		Conversion(%) ^b	Conversion(%) ^b		
1,2-epoxybutane	0.5	100		1-butanol	100
	6		79		100
	24		92		100
	48		99		100
1,2-epoxyoctane	0.5	100		1-octanol	100
	6		75		100
	24		90		100
	48		100		100
2,3-epoxy-2-methylbutane	0.5	94		3-methyl-2-butanol	100
	3	97			100
	6	100	72		100
	24		88		100
	72		95		100
styrene oxide	0.5	100 ^c		2-phenylethanol	100
	6		95		100
	24		100		100
<i>α</i> -methylstyrene oxide	0.5	90		2-phenyl-1-propanol	100
	3	95	93		100
	6	99	98		100
	12	100			100
	24		100		100
<i>trans</i> - <i>β</i> -methylstyrene oxide	0.5	100		2-phenyl-2-propanol	100
	3		89		100
	6		100		100

^aTen % excess reagent utilized; 0.5 M concentration. ^bDetermined by GC using a suitable internal standard. ^cSeventy four % of 2-phenylethanol was isolated from the 40 mmol scale reaction.

Such phenomenon was further verified by the results obtained from the reaction of alkyl-substituted or alkyl- and phenyl-substituted more epoxides such as 2,3-epoxy-2-methylbutane and *α*-methylstyrene oxide: the products were 3-methyl-2-butanol and 2-phenyl-1-propanol, respectively, and the selectivity was also 100%.



More interestingly, the reaction of *trans*-*β*-methylstyrene oxide yielded only 1-phenyl-2-propanol as a sole product within 0.5 h at 25 °C, showing 100% selectivity. This reagent can discriminate between the phenyl-group and the alkyl-group substituted carbon sites.



Such an *anti*-Markovnikov reductive ring-opening of epoxides has previously been achieved with BH₃-THF in the presence of BF₃,⁵ NaBH₃CN in the presence of BF₃,⁶ KPh₃BH in

the presence of Ph₃B,⁷ (iPrO₃)B,⁸ *Al*-fluorodiisobutylalane (DIBAF),⁹ and *Al*-methanesulfonyldiisobutylalane (DIBAO₃SCH₃).¹ However, each reagent possesses its own limitations of the reduction, such as a relatively low regioselectivity require-

Table 4. Reaction of other functional compounds with DIBAO₃SCF₃ in Et₂O^a at 25 °C

Compound	Time (h)	Yield of alcohol (%) ^b	
		DIBAO ₃ SCF ₃	DIBAO ₃ SCH ₃ ^c
caproic acid	72	0	0
benzoic acid	72	0	0
ethyl caproate	72	0	0
ethyl benzoate	72	0	0
phenyl acetate	72	0	0
hexanoyl chloride	24	0	5
benzoyl chloride	24	0	0
caproamide	72	0	0
benzamide	72	0	0
<i>N,N</i> -dimethylbenzamide	72	0	0
hexanenitrile	72	0	0
benzonitrile	72	0	0
phenyl disulfide	72	0	0
phenyl sulfone	72	0	0
dimethyl sulfoxide	0.5	100	100

^aTwo equiv of reagent utilized; concentration of each compound was 0.5 M.

^bAnalyzed by GC using a suitable internal standard. ^cData taken from ref.

^dDimethyl sulfide formed.

Table 5. Stereochemistry in the reduction of representative cyclic ketones with DIBAO₃SCF₃ in Et₂O^{a,b} at 25 °C

Ketone	Reagent/Compd	Time (h)	DIBAO ₃ SCF ₃		DIBAO ₃ SCH ₃ ^c		
			Yield of alcohol (%)	Ratio of stable isomer (%) ^c	Yield of alcohol (%)	Ratio of stable isomer (%) ^c	
2-methylcyclohexanone	1.1	1	94	91 ^d	69	39 ^d	
		3	95	92	99	43	
		6	97	93			
		24	98	93	99	86	
		72	98	93	99	90	
		120			99	92	
	2	0.5	98	95			
		1	99	94	83	39	
		3	99	94	99.9	40	
		24			99.9	41	
		72			99.9	89	
	3-methylcyclohexanone	1.1	1	92	95 ^e	88	60 ^e
			3	99	95	99.9	72
6			99	96	99.9	82	
24			99	96	99.9	89	
72					99.9	92	
120					99.9	92	
2		0.5	98	90			
		1	98	90	96	53	
		6	99	90	99.9	58	
		24	99	91	99.9	62	
		72	99	90	99.9	90	
4-methylcyclohexanone		1.1	1	98	93 ^f	94	56 ^f
			3	100	93	99	59
	6		100	93	99.9	66	
	72		100	94	100	89	
	2	1	91	90	99.9	53	
		3	99	90	99.9	58	
		72	99	91	100	89	
2- <i>t</i> -butylcyclohexanone	1.1	3	28	26 ^g	12	23	
		24	64	32	20	23 ^g	
		72	65	43	20	26	
	2	3	40	27	31	25	
		24	81	38	42	27	
		72	86	44	45	28	
		240	88	52	46	27	
	4- <i>t</i> -butylcyclohexanone	1.1	0.5	94	99 ^h		
			1	98	99	96	66 ^h
3			99.5	99	98	69	
6			99.5	99	99	71	
24					99	88	
72					99	94	
2		0.5	99	98			
		1	99	98	98	62	
		3			99.5	62	
		6			99.9	63	
		24			99.9	64	
		72			99.9	87	
3,3,5-trimethylcyclohexanone	1.1	1	96	86 ⁱ	78	15 ⁱ	
		3	99	89	95	23	
		6	99.6	92	98	35	
		24	99.8	95	99.9	93	
		72	99.8	98	99.9	98	

Table 5. Continued.

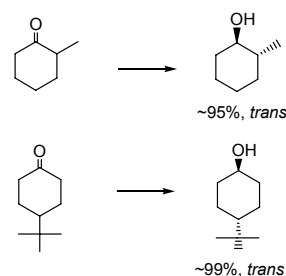
Ketone	Reagent/Compd	Time (h)	DIBAO ₃ SCF ₃		DIBAO ₃ SCH ₃ ^c	
			Yield of alcohol (%)	Ratio of stable isomer (%) ^c	Yield of alcohol (%)	Ratio of stable isomer (%) ^c
	2	0.5	99	84		
		1	99.4	85	94	15
		3	99.6	85	99	16
		6	99.6	85	99.9	17
		24	99.6	85	100	21
		72			100	88
norcamphor	1.1	1	75	81 ^j	51	3 ^j
		3	89	84	73	5
		6	94	84	87	6
		24	99.5	85	95	14
		72	99.5	87	95	69
		240			95	80
camphor	1.1	24	13	51 ^k	6	44 ^k
		72	16	53		
		120	19	54	7	45
	2	24	49	62	14	43
		72	52	64	15	51

^aconcentration of each compound was 0.5 M. ^bDetermined by GC. ^cNormalized. ^dTrans isomer. ^eCis isomer. ^fCis isomer. ^gTrans isomer. ^hTrans isomer. ⁱCis isomer. ^jExo isomer. ^kEndo isomer.

ment for drastic reaction conditions, as undesirable rearrangement product, a relatively low chemoselectivity, *etc.*¹⁰

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, the reagent exhibited absolutely no reactivity toward carboxylic acids, esters, acid chlorides, amides, nitriles, and sulfur compounds only except for sulfoxide. Dimethyl sulfoxide was readily reduced to dimethyl sulfide. Such a unique reducing characteristics of the reagent makes it possible the chemoselective reduction of aldehydes, ketones or epoxides in the presence of such inert compounds. The reactivity of reagent toward these organic functional groups appears exactly same as that of DIBAO₃SCH₃, as compared in Table 4.

Finally, we applied the reagent to the reduction of representative cyclic ketones and examined its stereochemistry. As shown in Table 5, the reactivity difference between DIBAO₃SCF₃ and DIBAO₃SCH₃ was also detected in this cycloalkanone reduction: DIBAO₃SCF₃ is much stronger than DIBAO₃SCH₃. The reagent readily reduced all the cyclic ketones examined at 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 inert to the reagent. These results clearly indicate that the steric requirement around the coordination sphere, where the aluminum atom of the reagent is coordinated to carbonyl oxygen, is also an important factor upon the reduction rate. However, nevertheless the reactivity difference among cyclic ketones examined, the reaction proceeds via the thermodynamically controlled isomer equilibration to produce the thermodynamically more stable exclusively.⁶



Conclusion

The reducing characteristics of a new MPV type reagent, DIBAO₃SCF₃ are now fully understood, and compared with those of DIBAO₃SCH₃. Generally, the reactivity of DIBAO₃SCF₃ appears to be much higher than that of DIBAO₃SCH₃, apparently due to the Lewis acidity increase by the strong electron-withdrawing fluorine-substituent. Such an intended modification of reactivity induces a reagent possessing a particularly unique applicability in organic synthesis. The reagent achieved a clean 1,2-reduction of α,β -unsaturated aldehydes and ketones to produce the corresponding allylic alcohols in 100% purity. Furthermore, the reagent performed a perfect regioselective cleavage of phenyl- or/and alkyl-substituted epoxides at a fast rate. In addition, the reagent produced the thermodynamically more stable alcohol epimer in high stereoselectivity in the reduction of alkyl-substituted cycloalkanones. Particularly noteworthy is that, despite of its relatively high reactivity toward carbonyl compounds and epoxides, DIBAO₃SCF₃, appears to be extremely mild and absolutely inert to other organic functional groups examined. Consequently, the reagent can find a

useful application in the selective reduction of organic functionalities.

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 N₂ prior to use. All reactions were performed under a dry N₂ atmosphere. All chemicals used were commercial products of the highest purity available, which were further purified by standard methods before use. Et₂O 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).

Preparation of *Al*-Trifluoromethanesulfonyldiisobutylalane (DIBAO₃SCF₃). Into an oven-dried, 100 mL flask with a side-arm equipped with a downward-directed, water-cooled condenser leading to a mercury bubbler, 11 g of diisobutylaluminum hydride (DIBAH, 75 mmol) was injected using a double-ended needle and diluted with Et₂O to be 2.0 M. The flask was inserted into a water-circulating bath and maintained at 0 °C. To this solution was added 15 mL of a 5.0 M solution of trifluoromethanesulfonic acid (75 mmol) in Et₂O dropwise. After the complete evolution of hydrogen gas, the solution was diluted with Et₂O to be 1.5 M. The ²⁷Al NMR spectra of the solution showed a broad singlet centered at δ-18 ppm relative to Al(H₂O)₆³⁺.

General Procedure for Reduction of Organic Compounds. The reaction of benzaldehyde with 1.1 equiv of DIBAO₃SCF₃ is illustrative. An oven-dried, 50 mL flask, fitted with a sidearm and a bent adapter connected to a mercury bubbler, was charged with 0.53 g of benzaldehyde (5 mmol), 5.5 mL of Et₂O and tridecane as an internal standard. The solution was maintained in a circulating bath at 25. To this was added 3.7 mL of a stock solution of DIBAO₃SCF₃ (5.5 mmol) in Et₂O with stirring. At the appropriate time interval (*i.e.*, 0.5, 1, 3 and 6 h), an aliquot (*ca.* 1 mL) was withdrawn, and the mixture was hydrolyzed with 3 N HCl for 2 hrs. The aqueous layer was saturated with K₂CO₃ and the organic layer was dried over anhydrous MgSO₄. The organic layer was then subjected to gas chromatographic

analysis to yield 99.5% of benzyl alcohol at 3 h and 100% at 6 h.

Isolation of Reduction Products. The following procedure is representative for isolation of reduction products on distillation. In the assembly previously described was placed 3.18 g of benzaldehyde (30 mmol) in 22 mL of Et₂O and the solution was maintained in a circulating bath at 25 °C. Into the solution was injected 40 mL of a stock solution of DIBAO₃SCF₃ (33 mmol) in Et₂O with stirring and the reaction mixture was stirred for 6 hrs. The mixture was then quenched with 3 N HCl. The aqueous layer was saturated with NaCl. The separated organic layer was dried over anhydrous MgSO₄. The solvent was distilled out under reduced pressure and a careful fractional distillation gave 2.40 g (74% yield) of essentially pure benzyl alcohol.

Reduction of Cyclic Ketones. The following procedure was used to explore the stereoselectivity of DIBAO₃SCF₃. In the usual setup, the flask containing 5 mmol of ketone examined was reacted with 5.5 mmol of the reagent in Et₂O (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 K₂CO₃ and the organic layer was dried over anhydrous MgSO₄. The organic layer was then subjected to gas chromatographic analysis.

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