

Selective Reduction of Organic Compounds with *Al*-Methanesulfonyldiisobutylalane

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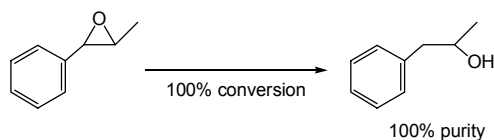
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The new **MPV** type reagent, *Al*-methanesulfonyldiisobutylalane (DIBAO₃SCH₃), has been prepared and its reducing characteristics in the reduction of selected organic compounds containing representative functional groups have been examined in order to find out a new reducing system with high selectivity in organic synthesis. 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. Thus, the reagent can achieve a clean 1,2-reduction of α,β -unsaturated aldehydes and ketones to produce the corresponding allylic alcohols in 100% purity. In addition, the reagent shows an excellent regioselectivity in the ring-opening reaction of epoxides. Finally, DIBAO₃SCH₃ shows a high stereo-selectivity in the reduction of cyclic ketones to produce the thermodynamically more stable epimers exclusively.

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

Introduction

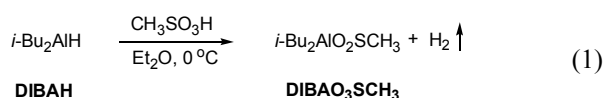
In the previous paper,¹ we reported that *Al*-methanesulfonyldiisobutylalane (DIBAO₃SCH₃), a new Meerwein-Ponndorf-Verley (**MPV**) type reagent,² achieves a perfect regioselectivity in the reduction of alkyl- or/and phenyl-substituted epoxides at a satisfactory rate. For example, the reagent can discriminate between the phenyl group- and the alkyl group- substituted carbon sites in the reaction of *trans*- β -methylstyrene oxide.



These results attracted us. It seems desirable to characterize the reducing characteristics of the reagent in order to find out its applicability in organic synthesis. Accordingly, we decided to undertake a systematic investigation of general reduction pattern of DIBAO₃SCH₃ under standardized reaction conditions (Et₂O, 25 °C).

Results and Discussion

DIBAO₃SCH₃ can be prepared easily by a simple reaction of diisobutylaluminum hydride (DIBAH) with an equivalent of methanesulfonic acid in Et₂O (Eq. 1).



The reactivity of DIBAO₃SCH₃ toward some simple aldehydes and ketones in Et₂O at 25 °C was examined, and the results are summarized in Table 1. As shown in the Table, the reagent showed a relatively high reactivity toward aldehydes

to be completely reduced within 24 h, but relatively lower reactivity toward ketones. A similar pattern was also observed in the reduction of α,β -unsaturated aldehydes and ketones. Thus, for example, cinnamaldehyde is readily reduced by 10% excess reagent within 24 h at 25 °C, but isophorone requires a long period of reaction time. However, excess reagent (2 equiv)

Table 1. Reaction of simple aldehydes and ketones with *Al*-methanesulfonyldiisobutylalane (DIBAO₃SCH₃) in ethyl ether^a at 25 °C

Compound	Time (h)	Yield of alcohol (%) ^a
hexanal	0.5	93
	1	94
	3	96
	6	98
	24	100
benzaldehyde	0.5	60
	1	77
	3	88
	6	92
	24	99.9, 75 ^c
2-heptanone	1	69
	3	71
	6	75
	24	86
	72	89
	120	95
acetophenone	1	72
	3	76
	6	80
	24	86
	72	90
benzophenone	120	97
	1	27
	6	51
	72	64
	120	78

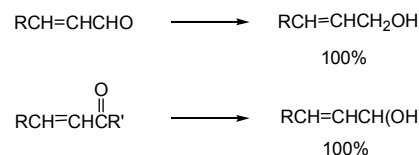
^a10% excess reagent utilized; 0.5 M concentration. ^bAnalyzed by GC using a suitable internal standard. ^cIsolated yield on distillation.

Table 2. Reaction of α,β -unsaturated aldehydes and ketones with $\text{DIBAO}_3\text{SCH}_3$ in Et_2O^a at 25 °C

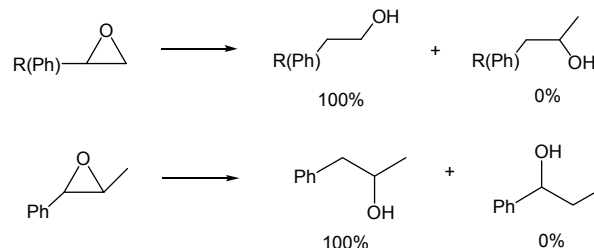
Compound	Reagent/ Compd	Time (h)	Conversion (%) ^b	Purity of allylic alcohol (%) ^b
crotonaldehyde	1.1	1	61	100
		3	91	100
		6	97	100
		24	100	100
	2.0	1	95	100
		3	98	100
cinnamaldehyde	1.1	1	50	100
		3	89	100
		6	94	100
		24	99	100
	2.0	1	89	100
		3	93	100
isophorone	1.1	6	98	100
		24	98	100
		72	98	100
		120	99	100
	2.0	1	89	100
		3	93	100
chalcone	1.1	6	68	100
		24	79	100
		72	95	100
		120	99	100
	2.0	1	89	100
		3	93	100

^aConcentration of each compound was 0.5 M. ^bPurity of all allylic alcohol products are absolutely 100%, determined by GC using a suitable internal standard. ^cIsolated yield on distillation.

reduced both aldehydes and ketones at a satisfactory rate. In addition, especially noteworthy is the chemoselectivity appeared in these reactions. The reagent achieved a clean 1,2-reduction to show a perfect selectivity: products are the corresponding allylic alcohols in 100% purity.



The most outstanding feature of the reagent comes from the results obtained in the reaction of epoxides.¹ $\text{DIBAO}_3\text{SCH}_3$ reduced both aliphatic and aromatic epoxides examined in Et_2O at 25 °C to produce the substituted alcohol in 100% purity by trapping β -hydrogen from isobutyl group of the reagent at the site best able to accommodate a carbocation, as summarized in Table 3. Furthermore, the reagent discriminates between the phenyl group- and alkyl group- attached carbon site in the reaction of *trans*- β -methylstyrene oxide: The selectivity reaches 100% to produce only 2-phenyl-2-propanol as a sole product.


Table 3. Reaction of epoxides with $\text{DIBAO}_3\text{SCH}_3$ in Et_2O^a at 25 °C

Epoxides	Time (h)	Conversion (%) ^b	Product	Purity (%) ^b
1,2-epoxybutane	6	79	1-butanol	100
	24	92		100
	48	99		100
1,2-epoxyoctane	6	75	1-octanol	100
	24	90		100
	48	100		100
2,3-epoxy-2-methylbutane	6	72	3-methyl-2-butanol	100
	24	88		100
	72	95		100
	120	98		100
styrene oxide	6	95	2-phenylethanol	100
	24	100 ^c		100
α -methylstyrene oxide	3	93	2-phenyl-1-propanol	100
	6	98		100
	24	100		100
<i>trans</i> - β -methylstyrene oxide	3	89	2-phenyl-2-propanol	100
	6	100		100

^a10% excess reagent utilized; 0.5 M concentration. ^bDetermined by GC using a suitable internal standard. ^c74% of 2-phenylethanol was isolated on distillation.

Table 4. Reaction of other functional compounds with DIBAO₃SCH₃ in Et₂O^a at 25 °C

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

^aTwo equiv of reagent utilized; concentration of each compound was 0.5 M.^bAnalyzed by GC using a suitable internal standard. ^cDimethyl sulfide formed.

Such an *anti*-Markovnikov reductive ring-opening of epoxides by MPV type reagents has previously been exemplified with (PrO₃)₃B,³ *Al*-fluorodiisobutylalane (DIBAF)⁴ and *Al*-acetoxydiisobutylalane (DIBAOAc).⁵ Such reagents also showed an excellent regioselectivity, but each reagent possesses its own limitations in the reduction procedure, such as relatively lower reactivity, requirement of sophisticated experimental technique for preparing reagent, *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, 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.

Finally, we applied the reagent to the reduction of representative cyclic ketones and examined its stereochemistry. As shown in Table 5, 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-

Table 5. Stereochemistry in the reduction of cyclic ketones with DIBAO₃SCH₃ in Et₂O^a at 25 °C

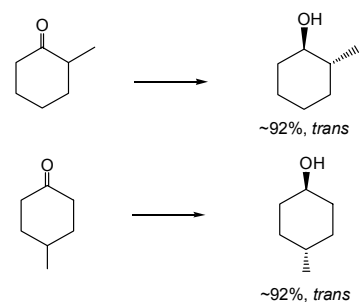
Ketones	Reagent/Compd	Time (h)	Yield of alcohol (%) ^b	Ratio of more stable alcohol (%) ^c
2-methylcyclohexanone	1.1	1	69	39 ^d
		3	99	43
		24	99	86
		72	99	90
		120	99	92
	2.0	1	83	39
		3	99.9	40
		24	99.9	41
		72	99.9	89
3-methylcyclohexanone	1.1	1	88	60 ^e
		3	99.9	72
		6	99.9	82
		24	99.9	89
		72	99.9	92
		120	99.9	92
	2.0	1	96	53
		3	99.5	55
		6	99.9	58
		24	99.9	62
		72	99.9	90
4-methylcyclohexanone	1.1	1	94	56 ^f
		3	99	59
		6	99.9	66
		24	100	86
		72	100	90
		120	100	92
	2.0	1	99.9	53
		3	99.9	58
		6	99.9	62
		24	100	66
		72	100	89

Table 5. continued

Ketones	Reagent/Compd	Time (h)	Yield of alcohol (%) ^b	Ratio of more stable alcohol (%) ^c
2- <i>t</i> -butylcyclohexanone	1.1	3	12	23 ^g
		24	20	23
		72	20	26
	2.0	3	31	25
		24	42	27
		72	45	28
		240	46	27
	4- <i>t</i> -butylcyclohexanone	1.1	1	96
3			98	69
6			99	71
24			99	88
72			99	94
2.0		1	98	61
		3	99.5	62
		6	99.9	63
		24	99.9	64
		72	99.9	87
3,3,5-trimethylcyclohexanone	1.1	1	78	15 ⁱ
		3	95	23
		6	98	35
		24	99.9	93
		72	99.9	98
	2.0	1	94	15
		3	99	16
		6	99.9	17
		24	100	21
		72	100	88
norcamphor	1.1	1	51	3 ^j
		3	73	5
		6	87	6
		24	95	14
		72	95	69
		168	95	76
		240	95	80
	2.0	3	86	4
		6	97	4
		24	98	5
72		99.5	67	
camphor	1.1	24	6	44 ^k
		120	7	45
	2.0	24	14	43
		72	15	51

^aConcentration of each compound examined was 0.5 M. ^bDetermined by GC. ^cNormalized. ^d*Trans* isomer. ^e*Cis* isomer. ^f*Trans* isomer. ^g*Trans* isomer. ^h*Trans* isomer. ⁱ*Cis* isomer. ^j*Exo* isomer. ^k*Endo* isomer.

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 epimers exclusively.⁶



Conclusion

The reducing characteristics of the new **MPV** type reagent, $\text{DIBAO}_3\text{SCH}_3$, is 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. Thus, the reagent achieved a clean 1,2-reduction of α,β -unsaturated aldehydes and ketones to produce the corresponding allylic alcohols in 100% purity. In addition, the reagent showed an excellent regioselectivity in the ring-cleavage reaction of epoxides. Finally, the reagent showed a high stereoselectivity in the reduction of cyclic ketones to produce the thermodynamically more stable epimers exclusively.

With organic research undertaking the synthesis of structures of increasing complexity, there has been an evident and growing need for reagents possessing a higher degree of selectivity. Therefore, this systematic exploration could provide an additional information available for selective reduction of organic function.

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_2 prior to use. All reactions were performed under a dry N_2 atmosphere. All chemicals used were commercial products of the highest purity available, which were further purified by standard methods before use. Et_2O 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*-methanesulfonyldiisobutylalane ($\text{DIBAO}_3\text{SCH}_3$) in Et_2O . Into an oven-dried, 100 mL flask with a sidearm 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 Et_2O to be 2.0 M. The flask was inserted into a water-circulating bath and maintained at 25 °C. To this solution was added 15 mL of a 5.0 M solution of methanesulfonic acid (75 mmol) in Et_2O dropwise. After the complete evolution of hydrogen gas, the solution was diluted with Et_2O to be 1.5 M. The ^{27}Al NMR spectra of the solution showed a broad singlet centered at δ -23.7 ppm relative to $\text{Al}(\text{H}_2\text{O})_6^{3+}$.

General procedure for reduction of organic compounds. The reaction of benzaldehyde with 1.1 equiv of $\text{DIBAO}_3\text{SCH}_3$ 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), 4.5 mL of Et_2O and tri-decane as an internal standard. The solution was maintained in a circulating bath at 25 °C. To this was added 3.7 mL of a stock solution of $\text{DIBAO}_3\text{SCH}_3$ (5.5 mmol) in Et_2O with stirring. At the appropriate time interval (i.e., 0.5, 1, 3, 6 and 24 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 K_2CO_3 and the organic layer was dried over anhydrous MgSO_4 . The organic layer was then subjected to gas chromatographic analysis to yield 88% of benzyl alcohol at 3 h and 99.9% at 24 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 16 mL of Et_2O and the solution was maintained in a circulating bath at 25 °C. Into the solution was injected 22 mL of a stock solution of $\text{DIBAO}_3\text{SCH}_3$ (33 mmol) in Et_2O 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 MgSO_4 . The solvent was distilled out under reduced pressure and a careful fractional distillation gave 2.43 g (75% yield) of essentially pure benzyl alcohol.

Reduction of cyclic ketones. The following procedure was used to explore the stereoselectivity of $\text{DIBAO}_3\text{SCH}_3$. In the usual setup, the flask containing 5 mmol of ketone examined was reacted with 10 mmol of the reagent in Et_2O (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_2CO_3 and the organic layer was dried over anhydrous MgSO_4 . The organic layer was then subjected to gas chromatographic analysis.

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