(s), 850 (s), 825 (s), 810 (s), 730 (s), 690 (s) cm^{-1}; mass spectrum, m/e (%) 252 (P, 3.4), 137 (4.3), 136 (13.9), 135 (100), 107 (6.9), 105 (7.7), 91 (5.1); mass spectrum, calcd for $C_{17}H_{20}Si$ 252.1334, found 252.1335.

3,7-Dimethyl-1-(trimethylsilyl)-2,6-octadiene (4). TLC R_f 0.70 (hexane); VPC (150 °C) R_t 2.8 min; ^1H NMR (200 MHz, $CDCl_3$) δ −0.03 (s, 9 H), 1.38 (d, J = 8.6 Hz, 2 H), 1.53 (s, 3 H), 1.59 (s, 3 H), 1.66 (s, 3 H), 1.9–2.1 (m, 4 H), 5.0–5.2 (m, 2 H); IR (liquid film) 2950 (s), 2920 (s), 1440 (m), 1380 (m), 1250 (s), 1155 (m), 850 (s) cm^{-1}.

Only the E isomer was obtained in this case, which was confirmed by comparison of NMR data of the product with those of an authentic sample (E/Z mixture).[7h]

3-Methyl-1-(trimethylsilyl)-2-nonene (5). E and Z isomers were characterized as a mixture: VPC (100 °C) Z isomer, R_t 8.8 min; E isomer, R_t 10.2 min; ^1H NMR (200 MHz, $CDCl_3$) δ −0.03 (s, 9 H), 0.75–0.95 (m, 3 H), 1.15–1.45 (m, 10 H), 1.52 (s, E isomer) and 1.65 (s, Z isomer) (65:35 total 3 H), 1.9–2.05 (m, 2 H), 5.0–5.2 (m, 1 H); IR (liquid film) 2950 (s), 2925 (s), 2850 (s), 1470 (m), 1380 (w), 1250 (s), 1155 (m), 850 (s) cm^{-1}.

Spectral data were identical with those of an authentic sample.[7h]

3-Chloro-1-(dimethylphenylsilyl)-2-butene (6a) and 3-Chloro-3-(dimethylphenylsilyl)-1-butene (6b). Allylsilanes **6a** (a mixture of E and Z isomers) and **6b** were characterized as a mixture. The spectral assignments were based on the relative intensity.

6a: ^1H NMR (200 MHz, $CDCl_3$) δ 0.33 and 0.36 (two s, total 6 H), 1.8–1.95 (m, 2 H), 2.10 (s with fine couplings, 3 H), 5.46 (t, J = 8.3 Hz with fine couplings) and 5.63 (t, J = 9.3 Hz with fine couplings) (total 2 H), 7.3–7.7 (m, 5 H).

6b: ^1H NMR (200 MHz, $CDCl_3$) δ 0.44 and 0.48 (two s, 6 H), 1.60 (s, 3 H), 5.0–5.2 (m, 2 H), 5.96 (dd, J = 10.6 and 16.9 Hz, 1 H), 7.3–7.7 (m, 5 H).

6a + 6b: IR (liquid film) 3060 (w), 3050 (w), 3000 (w), 2950 (m), 2920 (w), 1425 (s), 1250 (s), 1115 (s), 1060 (m), 830 (s), 695 (s) cm^{-1}; mass spectrum, calcd for $C_{12}H_{17}ClSi$ 224.0786, found 224.0775.

1-(4-Bromophenyl)-3-(trimethylsilyl)propene (7): ^1H NMR (60 MHz, $CDCl_3$) δ 0.06 (s, 9 H), 1.6–1.75 (m, 2 H), 6.1–6.3 (m, 2 H), 7.10 (d, J = 9 Hz, 2 H), 7.25 (d, J = 9 Hz, 2 H); IR (liquid film) 2940 (m), 1635 (m), 1480 (s), 1245 (s), 1140 (m), 1065 (m), 1000 (m), 955 (m), 855 (s) cm^{-1}; mass spectrum, calcd for $C_{12}H_{17}BrSi$ 268.0283, found 268.0285.

1-Bromo-4-(trimethylsilyl)benzene (12): VPC (150 °C) R_t 2.6 min; ^1H NMR (60 MHz, CCl_4) δ 0.27 (s, 9 H), 6.8–7.35 (m, 4 H); IR (liquid film) 3070 (w), 3035 (w), 3005 (w), 2950 (s), 2895 (w), 1575 (s), 1480 (s), 1380 (m), 1255 (s), 1105 (w), 1065 (s), 1010 (m), 1000 (m), 840 (s), 800 (s), 750 (s), 715 (s) cm^{-1}; mass spectrum, calcd for $C_9H_{13}BrSi$ 227.9969, found 227.9942.

4-(Trimethylsilyl)dibenzofuran (15): VPC (230 °C) R_t 3.4 min; ^1H NMR (60 MHz, CCl_4) δ 0.47 (s, 9 H), 7.05–7.6 (m, 5 H), 7.8–8.0 (m, 2 H); IR (liquid film) 3050 (w), 2950 (m), 2900 (w), 1580 (w), 1490 (w), 1470 (m), 1450 (s), 1390 (s), 1250 (s), 1180 (s), 880 (m), 830 (s), 750 (s) cm^{-1}; mass spectrum, m/e 242 (P+2, 1.7), 241 (P+1, 6.8), 2400 (P, 30.2), 227 (5.5), 226 (20.2), 225 (100), 195 (20.4), 165 (18.8), 113 (14.5); mass spectrum, calcd for $C_{15}H_{16}OSi$ 240.0969, found 240.0970. Anal. Calcd for $C_{15}H_{16}OSi$: C, 74.95; H, 6.71. Found: C, 75.22; H, 6.76.

3-(Trimethylsilyl)benzothiophene (16): VPC (200 °C) R_t 2.9 min; ^1H NMR (60 MHz, CCl_4) δ 0.41 (s, 9 H), 7.1–7.5 (m, 3 H), 7.7–7.95 (m, 2 H); IR (liquid film) 3050 (w), 2950 (m), 2880 (w), 1470 (m), 1450 (m), 1410 (s), 1250 (s), 1060 (m), 960 (s), 830 (s), 760 (s), 720 (s) cm^{-1}; mass spectrum, m/e (%) 197 (2.1), 196 (5.6), 194 (35.3), 177 (16.8), 173 (100); mass spectrum, calcd for $C_{11}H_{14}SSi$ 206.0585, found 206.0587. Anal. Calcd for $C_{11}H_{14}SSi$: C, 64.02; H, 6.84. Found: C, 64.17; H, 6.89.

Mixed Solvents Containing Methanol as Useful Reaction Media for Unique Chemoselective Reductions with Lithium Borohydride

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Received March 6, 1986

The reducing ability of lithium borohydride is greatly enhanced in mixed solvents containing methanol. Esters, lactones, and epoxides are reduced chemoselectively more rapidly with $LiBH_4$–MeOH(1 equiv added at the beginning)–ether than with $LiBH_4$–ether in the presence of other reducible groups such as carboxylic acid, chloro, nitro, and carbamoyl. On the other hand, nitro, nitrile, carboxyl, and primary and tertiary amide groups are reduced with $LiBH_4$–MeOH(4 equiv dropwise addition)–diglyme(or tetrahydrofuran). However, secondary amides derived from aliphatic amines and metal carboxylate are not reduced. Thus, unique chemoselective reductions of primary amide in the presence of secondary amide or metal carboxylate are achieved.

Metal hydrides and complex metal hydrides are widely used as reducing agents for organic compounds.[1] And much effort has been expended on developing a practical reducing system with novel functional group selectivities. In order to vary the reducing ability of complex metal borohydrides several methods have been applied:[1c,2] (1) varying the cation, (2) addition of metal salts, (3) varying the solvent, (4) use of catalysts. In spite of many efforts, the choice of solvent, especially the effects of mixed solvents, has not been fully studied.

This article reports the use of $LiBH_4$ and MeOH in ether solvents as selective reducing agents with significant synthetic potential.[3]

Lithium borohydride ($LiBH_4$) is commercially available and also easily prepared from sodium borohydride ($NaBH_4$)[4] and has been reported to be a selective reducing agent for esters,[2,5] although such reductions are relatively slow.

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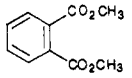
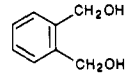
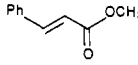
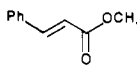
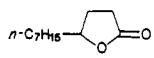
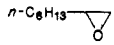
Table I. Reduction of Esters, Lactone, and Epoxides by $LiBH_4$–MeOH–Et_2O[a]

entry	substrate	molar ratio substrate:$LiBH_4$:MeOH	time, h	product	yield,[e,g] %
1	n-$C_9H_{19}CO_2CH_3$	1:1.5:1.5	0.25	n-$C_{10}H_{21}OH$	96 (58)
2	n-$C_9H_{19}CO_2CH_3$	1:2.0:2.5	0.25[b]	n-$C_{10}H_{21}OH$	94[f] (41)[f]
3	$(CH_3CH_2)_2CHCO_2CH_3$	1:1.5:1.5	0.50	$(C_2H_5)_2CHCH_2OH$	87
4	$(CH_3)_3CCO_2CH_3$	1:1.5:1.5	0.25	$(CH_3)_3CCH_2OH$	92
5	$PhCO_2CH_3$	1:1.5:1.5	0.50	$PhCH_2OH$	92 (41)
6	$PhCO_2CH_2CH_3$	1:1.5:1.5	0.75	$PhCH_2OH$	93[f] (22)[f]
7	$PhCO_2CH_2CH_3$	1:1.0:1.0	0.50	$PhCH_2OH$	70
8	$PhCO_2CH(CH_3)_2$	1:1.5:1.5	3.50	$PhCH_2OH$	49
9	$PhCO_2CH(CH_3)_2$	1:3.0:3.0	4.00	$PhCH_2OH$	74 (34)
10	$PhCO_2C(CH_3)_3$	1:3.0:3.0	5.00	$PhCH_2OH$	26 (6)
11		1:3.0:3.0	0.25		95
12		1:1.5:1.5	2.00	$PhCH{=}CHCH_2OH$ $PhCH_2CH_2CH_2OH$ $PhCH_2CH_2CO_2CH_3$	64[h] 24 4
13		1:6.0:18.0	6.30	$PhCH{=}CHCH_2OH$ $PhCH_2CH_2CH_2OH$ $PhCH_2CH_2CO_2CH_3$	71 22 2
14		1:1.5:1.5	0.25	n-$C_7H_{15}CH(OH)(CH_2)_3OH$	95
15		1:1.5:1.5	1.00	1- and 2-phenylethanols	99[c] (66)[d]
16		1:1.5:1.5	3.00	n-$C_6H_{13}CH(OH)CH_3$	73[f]

[a] Unless otherwise noted, reaction was carried out at reflux temperature. [b] Reaction was carried out at room temperature. [c] 1-Phenylethanol (64%) and 2-phenylethanol (35%). [d] 1-Phenylethanol (37%) and 2-phenylethanol (29%). [e] Isolated yield unless otherwise noted. [f] Yield was determined by GC. [g] Values in parentheses are the yields without using MeOH. [h] Methyl cinnamate was recovered in 4% yield.

Also, $LiBH_4$ displays much greater chemoselectivity than lithium aluminum hydride ($LiAlH_4$) and is more soluble in ether-type solvents than $NaBH_4$.[2]

During our continuing studies on chemoselective,[6] diastereoselective,[7,8] and enantioselective[9] reductions with complex borohydrides, we have found that the reducing power of $LiBH_4$ is greatly enhanced and unique chemoselectivities are achieved by employing ether-type solvents containing methanol (MeOH). Thus, reducing systems of $LiBH_4$–MeOH–Et_2O are effective for the rapid and selective reduction of esters. On the other hand, $LiBH_4$–MeOH–diglyme(or THF) is much more potent and enables the selective reduction of primary amides in the presence of secondary amides or carboxylic acid salts. To the best of our knowledge, the latter selective reduction by a conventional method has not been achieved. We report here in detail several chemoselective reducing system using $LiBH_4$ in ether-type solvents containing MeOH.

$LiBH_4$–MeOH–Et_2O Reducing System. The addition of an equimolar amount of MeOH to $LiBH_4$ strongly enhanced the reduction rates of esters, lactone, and epoxides by $LiBH_4$ in ether at room or refluxing temperatures. As shown in Table I, ethyl benzoate was reduced to benzyl alcohol in 93% yield by $LiBH_4$ in 0.75 h in ether containing MeOH (molar ratio MeOH/$LiBH_4$ = 1). On the other hand, without MeOH the yield of benzyl alcohol decreased to 22% yield (Table I, entry 6). The generality of the effect of MeOH was exemplified by the rapid reductions of aliphatic, aromatic, di- and α,β-unsaturated esters, epoxides, and lactone (Table I). In all cases examined, yields of the products increased significantly in the presence of MeOH. Furthermore, we examined the effect of the steric requirements of the ester alcohol group. The esters of sterically hindered carboxylic acids (pivalic acid and 2-ethylbutanoic acid) were rapidly reduced to the corresponding alcohols by the reducing system (entries 3 and 4). The difference in the steric hindrance in the acyl side of esters hardly affected the reducing rates (entries 1, 3, 4, and 5). On the other hand, the reduction of the esters derived from sterically hindered alcohols (secondary or tertiary alcohols) required longer reaction times than the esters of primary alcohols. Therefore, the leaving ability of the alkoxy group is more important than steric hindrance about the reaction site. Nevertheless, these latter reductions proceeded more rapidly than those without using MeOH (entries 5, 6, 8, 9, and 10, Table I). For example, *tert*-butyl benzoate was reduced in only 6% without using MeOH. However, benzyl alcohol was obtained in 26% in the presence of MeOH. On the other hand, 4-heptyl-4-butanolide (which is an intramolecular ester of a secondary alcohol) was reduced more rapidly than the corresponding isopropyl benzoate (entries 8, 9, and 14). In the reduction of epoxides the more substituted alcohol was produced predominantly. This 2-hexyloxirane

Table II. Reduction of Styrene Oxide

reducing system	total yield,[a] %	ratio of 1-phenylethanol:2-phenylethanol
$LiBH_4$–MeOH–Et_2O	99	65:35
$LiBH_4$–Et_2O	66	56:44

[a] Isolated as mixture of 1-phenylethanol and 2-phenylethanol. Ratio was determined by GC analysis.

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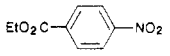
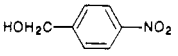
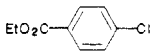
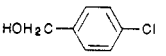
Table III. Chemoselective Reduction of Esters and Epoxide in the Presence of Nitro, Chloro, Carbamoyl, and Carboxyl Groups by $LiBH_4$–MeOH–Et_2O

$$A + B \xrightarrow[MeOH + Et_2O]{LiBH_4} C + B\ (recovery)$$

entry	substrate A	substrate B	time, h	product C	yield,[d] %	recovery,[d] % B
1[a]			0.5		90	
2[a]			0.5		91	
3[b]	$PhCO_2Et$	$PhCONH_2$	2.5	$PhCH_2OH$	100[e]	89
4[b]		$PhCONH_2$	1.5	phenylethanols	95	99
5[c]	$PhCO_2Me$	n-$C_9H_{19}CO_2H$	1.0	benzyl alcohol	92	98

[a] Molar ratio of substrate:$LiBH_4$:MeOH was 1:1.5:1.5. [b] Molar ratio of A:B:$LiBH_4$:MeOH was 1:1:3:3. [c] Molar ratio of A:B:$LiBH_4$:MeOH was 1:1:1.75:1.75. [d] Isolated yield unless otherwise noted. [e] Yield was determined by GC analysis.

was reduced selectively to 2-octanol (entry 16, Table I). Reduction of styrene oxide by $LiBH_4$–MeOH–Et_2O afforded 1-phenylethanol (64%) and 2-phenylethanol (35%) in 99% total yield (entry 15). On the other hand, without the use of MeOH, the total yield of 1- and 2-phenylethanols dropped to 66%.[10,11] Furthermore, the rapid and selective reductions of esters and epoxides in the presence of carboxylic acid, nitro, carbamoyl, or chloro groups were readily accomplished with $LiBH_4$–MeOH in ether. Results are shown in Table III. In all cases, esters were reduced selectively and rapidly. Such selective reductions can not be achieved by strong reducing agent such as $LiAlH_4$. For example, competitive reduction of methyl benzoate and decanoic acid with $LiBH_4$–MeOH in refluxing ether afforded benzyl alcohol in 92% yield, while decanoic acid was recovered in 98% yield (entry 5, Table III).

$LiBH_4$–MeOH–Diglyme(or THF) Reducing System. In changing to THF or diglyme as solvent, further enhancement of the reducing capabilities of $LiBH_4$ was observed.

Thus, nitro, nitrile, carboxylic acid, and primary amide groups, which are reported not to be reduced with $LiBH_4$ or to be reduced only sluggishly under the usual reaction conditions,[5] were reduced in high yields by $LiBH_4$ in DGM and MeOH. The powerful reducing ability of $LiBH_4$ in DGM–MeOH is clearly exemplified by the reduction of nitrobenzene (Table IV, entry 1). When nitrobenzene was reduced with $LiBH_4$ in refluxing DGM without MeOH, the yield of aniline was only 41%. However, the yield of aniline dramatically increased to 87% when nitrobenzene (1 mmol) was reduced by $LiBH_4$ (3 mmol) with dropwise addition of MeOH (11 mmol, molar ratio MeOH/$LiBH_4$ = about 4) during the reduction in refluxing DGM. It should be noted that reduction of nitrobenzene to aniline by complex metal hydride is usually difficult and the reduction stops at azo or azoxy stages.[12] The results of the

Table IV. Reduction of Various Kinds of Compounds by $LiBH_4$–MeOH–Diglyme

entry	substrate[a]	product	yield,[b,c] %
1	$PhNO_2$	$PhNH_2$	87 (41)
2	n-$C_8H_{17}NO_2$	n-$C_8H_{17}NH_2$	50
3	PhCN	$PhCH_2NH_2$	98 (70)
4	n-$C_7H_{15}CN$	n-$C_8H_{17}NH_2$	78
5	$PhCO_2H$	$PhCH_2OH$	89
6	n-$C_9H_{19}CO_2H$	n-$C_{10}H_{21}OH$	100 (83)
7	n-$C_9H_{19}CO_2H$	n-$C_{10}H_{21}OH$	85[d]
8	n-$C_9H_{19}CO_2H$	n-$C_{10}H_{21}OH$	39[e]
9	$PhCO_2Na$		[f]

[a] Unless otherwise noted, substrate (1 mmol), $LiBH_4$ (3 mmol), DGM (4 mL), and MeOH (0.45 mL) were used and reactions were carried out at reflux temperature. [b] Yield was determined by GC analysis. [c] The values in parentheses were yields without using MeOH. [d] Reaction was carried out at 140 °C. [e] Reaction was carried out at 100 °C. [f] Benzyl alcohol was not detected by GC analysis.

reductions of other groups with $LiBH_4$ in DGM–MeOH are summarized in Table IV. As shown, the presence of MeOH apparently increased the yields of the product of the reduction of benzonitrile to 98% (from 70% without MeOH, entry 3) and decanoic acid to 100% (from 83% without MeOH, entry 6). The effect of reaction temperature was also examined in the reduction of decanoic acid to 1-decanol (entry 6–8). At 100 °C the reaction mixture was a gel and the reaction was sluggish (39% yield). At reflux temperature, however, the reaction mixture became a clear solution and decanoic acid was reduced to 1-decanol in quantitative yield.

Reactivity to carbamoyl group by the above reducing system was also examined and the results are summarized in Table V. Aliphatic and aromatic primary amides were reduced to the corresponding primary amines in good to high yields (entries 1 and 2). The addition of MeOH gave an increased yield (71 → 92%). In the reduction of octanamide, octylamine was obtained in 77% yield together with 4% of heptyl cyanide. This result suggests that at least part of the reduction of primary amide may proceed via dehydration of the amide to the nitrile.[13] Unique

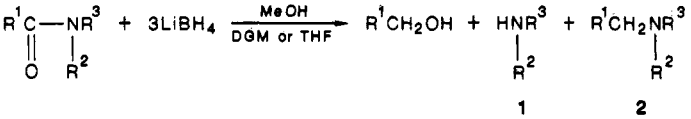
(10) For the reduction of epoxides with lithium triethylborohydride, see: Brown, H. C.; Narasimhan, S.; Somayaji, V. *J. Org. Chem.* **1983**, *48*, 3091.

(11) Professors Brown and Narasimhan recently reported that Lewis acids of boron such as *B*-methoxy-9-borabicyclo[3.3.1]nonane catalyze the reduction with $LiBH_4$. However, chemoselectivities between this method and the present discussing the $LiBH_4$–mixed solvent method are different. The degree of the acceleration of the reduction of esters by the present procedure using $LiBH_4$–MeOH–Et_2O was compared to that using *B*-methoxy-9-borabicyclo[3.3.1]nonane in the reduction of ethyl benzoate under similar reaction conditions (molar ratio of ester and $LiBH_4$, 1:1, temperature 35 °C, time 0.5 h, solvent Et_2O) except catalyst. The reduction of ethyl benzoate in the presence of MeOH afforded benzyl alcohol in 70% isolated yield, while 60% yield is claimed in the reduction using *B*-methoxy-9-borabicyclo[3.3.1]nonane. Removal of *B*-methoxy-9-borabicyclo[3.3.1]nonane requires base treatment of the reaction mixture. Brown, H. C.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 1604; **1984**, *49*, 3891.

(12) $LiBH_4$: Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1948**, 70, 3738. Borane–THF: Brown, H. C.; Heim, P.; Yoon, N. M. *Ibid.* **1970**, *92*, 1637. Aluminum hydride: Brown, H. C.; Yoon, N. M. *Ibid.* **1966**, *88*, 1464.

(13) The reaction of primary amide with $NaBH_4$ in refluxing diglyme affords nitrile. However, under the same reaction condition nitriles are not reduced by $NaBH_4$. Ellzey, S. E., Jr.; Mack, C. H.; Connick, W. J., Jr. *J. Org. Chem.* **1967**, *32*, 846. Part, if not all, of the $LiAlH_4$ reduction of primary amides proceeds via dehydration of amide to nitrile. Newman, M. S.; Fukunaga, T. *J. Am. Chem. Soc.* **1960**, *82*, 693.

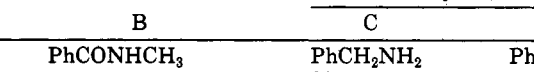
Table V. Reduction of Amides by $LiBH_4$–MeOH–Diglyme(or THF)[a]



entry	R^1	R^2	R^3	solvent	yield,[b,c] % alcohol	amine 1	amine 2
1	Ph	H	H	DGM			92 (71)
2	n-C_7H_{15}	H	H	DGM			77[e]
3	Ph	CH_3	H	DGM	4		15
4	n-C_7H_{15}	CH_3	H	DGM			16
5	Ph	Ph	H	DGM	19	28	65
6	CH_3	Ph	H	DGM		45	37
7[d]	Ph	CH_3	CH_3	THF	90		
8[d]	$PhCH_2$	CH_3	CH_3	THF	61		16

[a] Amide (1 mmol), $LiBH_4$ (3 mmol), DGM (or THF) (4 mL) and MeOH (0.45 mL). Reactions were carried out at reflux temperature. [b] Unless otherwise noted, yield was determined by GC analysis. [c] The value in parentheses is the yield without MeOH. [d] Isolated yield. [e] Heptyl cyanide was obtained in 4% yield.

Table VI. Chemoselective Reduction of Primary Amides in the Presence of Secondary Amide and Metal Carboxylate by $LiBH_4$–MeOH–Diglyme[a]



entry	A	B	yield,[b] % C	D	recovery,[c] % B
1	$PhCONH_2$	$PhCONHCH_3$	$PhCH_2NH_2$ 86	$PhCH_2NHCH_3$ 14	80
2	$PhCONH_2$	n-$C_7H_{15}CONHCH_3$	$PhCH_2NH_2$ 83	n-$C_8H_{17}NHCH_3$ 22	60
3	$PhCONH_2$	$PhCO_2Na$	$PhCH_2NH_2$ 92	$PhCH_2OH$ 5	77[d]
4	n-$C_7H_{15}CONH_2$	$PhCO_2Na$	n-$C_8H_{17}NH_2$ 90	$PhCH_2OH$ 38	60[d]

[a] A (1 mmol), B (1 mmol), $LiBH_4$ (3 mmol), DGM (4 mL), and MeOH (0.45 mL). [b] Determined by GC analysis. [c] Isolated yield. [d] Isolated as benzoic acid.

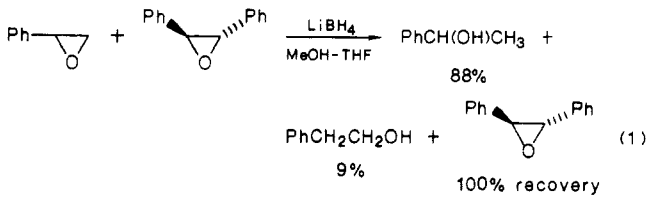
chemoselectivities with this reducing system were found in the reduction of secondary amides. Thus, secondary amides of aromatic amine were reduced in good yields (entries 5 and 6), while corresponding secondary amides of aliphatic amines were hardly affected (entries 3 and 4). The reactivity order of the primary and secondary amides by the present reducing system is unusual, because secondary amides are known to be reduced more rapidly than primary amides by borane or $LiAlH_4$.[14] Tertiary amides were reduced in THF–MeOH at reflux temperatures under milder condition than other primary and secondary amides. It is well-known that the reduction of amides proceed via carbon–nitrogen (C–N) or carbon–oxygen (C–O) bond fission of the carbamoyl group.[15] Reducing agents such as $LiAlH_4$ and borane usually afford amines via C–O bond fission. However, the reduction of tertiary amides with $LiBH_4$–MeOH–THF was found to afford alcohols predominantly via carbon–nitrogen bond fissions. The reduction of *N,N*-dimethylbenzamide by $LiBH_4$–MeOH–THF afforded benzyl alcohol selectively in 90% (entry 7), while without the MeOH a mixture of the benzyldimethylamine (33%, via C–O cleavage) resulted together with benzyl alcohol (58%).[16,17] Thus, the addition of MeOH not only increased the reducing power of $LiBH_4$ but also increased the selectivity in tertiary amide reductions.

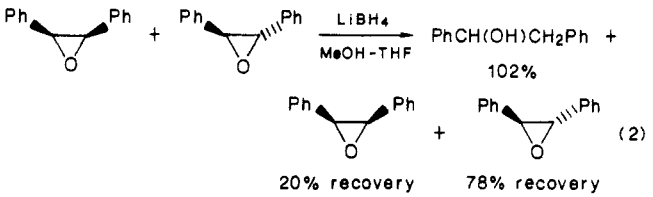
As described above, the $LiBH_4$–MeOH–DGM (or THF) reducing systems are powerful but do not reduce metal carboxylate and secondary amide derived from aliphatic amines.

In order to explore the synthetic scope of selective reductions available, competitive studies were conducted with groups normally difficult to distinguish reductively $LiBH_4$–MeOH–DGM (or THF). It had been reported that diborane reduces primary amides and does not reduce metal carboxylates.[18] However, a recent report revealed that metal carboxylates are reduced by diborane.[19] Therefore the selective reduction of primary amides by diborane in the presence of metal carboxylates should be difficult. Likewise, no report has appeared on the selective reduction of primary amides in the presence of secondary amides derived from primary aliphatic amines.[20] To take advantage of the present facile reduction of primary amides by the above-described $LiBH_4$–MeOH–DGM, we consequently carried out selective reductions of primary amides in the presence of metal carboxylate and secondary amide. The results of selective reductions by $LiBH_4$–MeOH–DGM are shown in Table VI. For example, a mixture of equimolar amounts of benzamide and sodium benzoate was reduced with three molar amounts of $LiBH_4$ in DGM and with dropwise addition of MeOH (entry 3). Benzamide was reduced selectively to afford benzylamine

(14) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons, Inc.: New York, 1967; p 588.
(15) Mičović, V. M.; Mihailović, M. L. *J. Org. Chem.* **1953**, *18*, 1190.
(16) Davis, M. *J. Chem. Soc.* **1956**, 3981.
(17) For the reduction of tertiary amides to alcohols with lithium triethylborohydride, see: Brown, H. C.; Kim, S. C. *Synthesis* **1977**, 635.
(18) Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1960**, *82*, 681.
(19) Yoon, N. M.; Cho, B. T. *Tetrahedron Lett.* **1982**, *23*, 2475.
(20) After the publication of our preliminary communication,[3] Hutchins et al. report that sodium (dimethylamino)borohydride reduces primary amide more rapidly than secondary amide. Hutchins, R. O.; Learn, K.; El-Telbany, F.; Stercho, Y. P. *J. Org. Chem.* **1984**, *49*, 2438.

in 92% yield. Sodium benzoate was recovered as benzoic acid in 77% isolated yield. Similarly, the reduction of the mixture of benzamide and *N*-methylbenzamide afforded benzylamine (86% yield) and benzylmethylamine (14% yield). The recovery of *N*-methylbenzamide was 80% (entry 1). Reductions of epoxides with $LiBH_4$–MeOH–THF also displayed structual selectivity. Thus, the selective reduction of styrene oxide in the presence of 2,3-diphenyloxirane was achieved (eq 1). Moreover, diastereomer-selective reduction of oxiranes was observed. Thus, reduction of an equimolar mixture of *cis*- and *trans*-2,3-diphenyloxirane with excess $LiBH_4$ (6 molar equiv) in THF in the presence of MeOH, the cis isomer was reduced more rapidly (ratio cis:trans reduction = 80:22).





Our main purpose of this study was to establish synthetic utility of mixed solvents containing MeOH in chemoselective reductions with $LiBH_4$. Therefore, it is not possible from the present study to conclude the definite mechanism involved. However, the following reductions were conducted in order to obtain some informations on the reduction mechanism. In the reduction of ethyl benzoate, the best yield (93%, Table I, entry 6) was attained when the molar ratio of MeOH to $LiBH_4$ was 1 (59% when the ratio was 0.5, and 27% when the ratio was 2). Surprisingly, aging effect was considerable. Thus, when an equimolar amounts of $LiBH_4$ and MeOH in Et_2O was allowed to stand at 0 °C for 2 h before the addition of the ester, the yield of benzyl alcohol dropped to 39% (93% comparative reduction under the same conditions without aging, Table I, entry 6). During the aging period, all the MeOH is considered to react with $LiBH_4$ to produce $LiBH_3(OMe)$ and/or various methoxy-substituted borohydrides as a result of the disproportionation. From the present study, it is not possible to define the exact structure of these species. As to the effect of alcohol, 2-propanol was found to be less effective than MeOH. Thus, in the comparative reduction of ethyl benzoate using 2-propanol instead of MeOH, the yield of benzyl alcohol dropped to 71% (93% with MeOH, Table I, entry 6).

We adopted two procedures of the addition of MeOH. One is the addition of an equimolar amount of MeOH to $LiBH_4$ at the beginning of the reduction of esters, the other is the dropwise addition of excess amount of MeOH during the reduction of the groups other than esters. Consequently capabilities of these two addition procedures were compared in the reduction of (dimethylamino)benzamide. Thus, a 3 molar amount of MeOH was added to a 3 molar amount of $LiBH_4$ in THF at the beginning of the reduction of a 1 molar amount of dimethylbenzamide. The benzyl alcohol obtained was only 44% yield (90% in comparative dropwise addition of excess MeOH, Table V, entry 7), and starting material was recovered in 55%. Apparently the dropwise addition of MeOH is more capable than the addition of MeOH at the beginning. This result suggests that the proton source required for the reduction is more effectively supplied in the dropwise addition than the addition at the beginning. It is known that a solvent such as 2-propanol is incorporated in the acyclic mechanism of the reduction of ketones with sodium borohydride in protic solvents. 2-Propanol donates a proton to the ketone oxygen atom.[21] The fact that, in the present reduction, MeOH affords a higher yield than 2-propanol may be due to the better hydrogen-bonding and proton-donating abilities of MeOH (pKa = 16–18) than 2-propanol (pKa = 18). This mechanism may be applicable to the present reducing system especially when MeOH is added dropwise to the reaction mixture. On the other hand, there is a possibility that methoxy-substituted lithium borohydrides formed in situ from the reaction with MeOH may be the actual reducing species. However, from the result of the aging effect, MeOH as proton source from the dropwise addition seems to be more important to increase the reducing capabilities.

As described, reducing system of $LiBH_4$–MeOH–Et_2O, DGM, or THF enabled various kinds of synthetically useful chemoselective reductions.

Experimental Section

Melting and boiling points were not corrected. IR spectra were recorded with a Hitachi 260-10 spectrophotometer. ^1H NMR spectra (60 MHz) were recorded by using either a Varian EM-360A NMR spectrometer or a JEOL JNM-PMX-60 NMR spectrometer. GC analyses were carried out with a Shimadzu gas chromatograph Model GC-4C. All of the reactions were run under an atmosphere of argon.

Materials. Methanol was stored over 3A molecular sieves. Diethyl ether, tetrahydrofuran and diglyme (DGM) were distilled from lithium aluminum hydride. Organic solutions were dried over anhydrous sodium sulfate.

Lithium borohydride ($LiBH_4$, Wako) was used without further purification and the hydride content determined as described.[22] Most of organic compounds utilized in this study were commercial products of high purities (Tokyo Kasei, Nakarai, Aldrich), but they were further purified by distillation when necessary. Secondary and tertiary amides were prepared by the Schotten–Baumann method using the corresponding acyl chloride and amine. Melting or boiling points of amides synthesized are as follows: *N*-methyloctanamide, mp 36–38 °C (lit.[23] mp 38.9 °C), *N*-methylbenzamide, mp 80–81 °C (lit.[24] mp 82 °C), *N,N*-dimethylphenylacetamide, bp 140 °C/3 mmHg (bath temperature) (lit.[25] bp 155 °C/10 mmHg), *N,N*-dimethylbenzamide, bp 155 °C/20 mmHg (bath temperature) (lit.[26] bp 139–140 °C/17 mmHg). Octanamide was synthesized from heptyl cyanide and hydrogen peroxide: mp 106–107 °C (lit.[27] mp 106 °C). 1-Nitrooctane was prepared by the method of Zubrick et al.[28] using 18-crown-6 as phase-transfer catalyst: bp 145–150 °C/25 mmHg (lit.[29] bp 72 °C/3 mmHg).

Determination of yields by GC analysis was performed by using internal standards. The analytical conditions (analyzed compound, internal standard and column temperature) are described below. The values in parentheses are retention times (min). A 25-m SE-30 capillary column and an FI detector were used: for 2-ethylbutanol (8.5), neopentyl alcohol (4.0), 45 °C; for 1-decanol (13.5), aniline (6.7), benzyl alcohol (8.4), octylamine (9.2), heptyl

(21) Wigfield, D. C.; Gowland, F. W. *J. Org. Chem.* **1977**, *42*, 1108.
(22) Brown, H. C. *Organic Syntheses via Boranes*; John Wiley and Sons, Inc.: New York, 1975.
(23) D'Alelio, G. F.; Reid, E. E. *J. Am. Chem. Soc.* **1937**, *59*, 109.
(24) Beilsteins 1926, 9, p 201.
(25) Reference 24, 9, p 437.
(26) Kikugawa, Y.; Ikegami, S.; Yamada, S. *Chem. Pharm. Bull.* **1969**, *17*, 98.
(27) Mitchell, J. A.; Reid, E. E. *J. Am. Chem. Soc.* **1931**, *53*, 1879.
(28) Zubrick, J. W.; Dunbar, B. I.; Durst, H. D. *Tetrahedron Lett.* **1975**, 71.
(29) Kornblum, N.; Taub, B.; Ungnade, H. E. *J. Am. Chem. Soc.* **1954**, *76*, 3209.

cyanide (10.4), benzylamine (6.8), and *N*-methylbenzylamine (10.0), naphthalene (26.0, standard), 80 °C; for *N*-methyloctylamine (9.8), naphthalene (14.3, standard), 90 °C.

Typical experimental procedures for each reducing system are shown below.

Reduction of Methyl Decanoate by $LiBH_4$–MeOH–Et_2O (Table I, Entry 1). A mixture of $LiBH_4$ (1.5 mmol), methyl decanoate (186 mg, 1 mmol), methanol (0.061 mL, 1.5 mmol), and Et_2O (4 mL) was refluxed for 15 min. The reaction was quenched with 1 N hydrochloric acid with ice-cooling. The mixture was diluted with water and was extracted with dichloromethane. The extract was dried and the solvent was evaporated under reduced pressure. Purification by silica gel TLC (dichloromethane/methanol = 30:1 as developing solvent) afforded 1-decanol (152 mg, 96%).

Selective Reduction of Methyl Benzoate in the Presence of Capric Acid by $LiBH_4$–MeOH–Et_2O (Table III, Entry 5). A mixture containing methyl benzoate (136 mg, 1 mmol), capric acid (172 mg, 1 mmol), $LiBH_4$ (1.75 mmol), methanol (0.071 mL, 1.75 mmol), and ether (4 mL) was refluxed for 1 h and was then cooled to room temperature. Water and 1 N hydrochloric acid were added to quench the reaction with ice-cooling; then the mixture was made basic to pH 11 with 1 N aqueous sodium hydroxide. The mixture was extracted with dichloromethane, the extract was dried, and the solvent was evaporated under reduced pressure. Purification by silica gel TLC (dichloromethane as developing solvent) afforded benzyl alcohol (99.8 mg, 92%) and methyl benzoate (3.7 mg, 3%). Meanwhile, aqueous phase was acidified to pH 1 with 3 N hydrochloric acid. The mixture was extracted with dichloromethane and dried over anhydrous sodium sulfate. Concentration and distillation by the bulb-to-bulb method (bath temperature 130 °C/3 mmHg) gave recovery of capric acid (168 mg, 98% recovery).

Reduction of Octanamide by $LiBH_4$–MeOH–DGM (Table V, Entry 2). Methanol (0.45 mL) was added dropwise to a mixture of octanamide (143 mg, 1 mmol), $LiBH_4$ (3 mmol), and DGM (4 mL) over a period of 2 h at reflux temperature. The mixture was refluxed for an additional 2 h and was cooled to room temperature. The reaction was quenched by adding methanol and water successively. After most of methanol was evaporated under reduced pressure, GC analysis showed the presence of *n*-octylamine (77%) and heptyl cyanide (4%).

Reduction of *N*,*N*-Dimethylbenzamide by $LiBH_4$–MeOH–THF (Table V, Entry 7). To a refluxing mixture of *N*,*N*-dimethylbenzamide (150 mg, 1 mmol), $LiBH_4$ (3 mmol), and THF (4 mL) was added methanol (0.45 mL) dropwise over a period of 2 h. After the mixture was cooled to room temperature, 1 N hydrochloric acid was added, and the mixture was alkalined to pH 11 with concentrated aqueous NaOH. The mixture was extracted with chloroform, the organic layer was dried, the solvent was evaporated under reduced pressure, and the residue was purified by preparative silica gel TLC (dichloromethane as developing solvent) to give benzyl alcohol (97 mg, 90%).

Selective Reduction of Benzamide in the Presence of Sodium Benzoate by $LiBH_4$–MeOH–DGM (Table VI, Entry 3). To a refluxing mixture of benzamide (121 mg, 1 mmol), sodium benzoate (144 mg, 1 mmol), $LiBH_4$ (3 mmol), and DGM (4 mL) was added methanol (0.45 mL) over a period of 2 h, and the mixture was refluxed for additional 2 h. After quenching the reaction by adding methanol and water, most of methanol was evaporated under reduced pressure. GC analysis showed the presence of benzyl alcohol (92%) and benzylamine (5%). The mixture was acidified with 6 N hydrochloric acid and was extracted with ether. The extract was dried and evaporated in vacuo. Most of DGM was removed by bulb-to-bulb distillation under reduced pressure. The residue was purified by preparative silica gel TLC (chloroform/methanol/acetic acid = 20:1:trace as developing solvent). Sodium benzoate was recovered as benzoic acid (94 mg) in 77%.

Selective Reduction of Styrene Oxide in the Presence of *trans*-2,3-Diphenyloxirane by $LiBH_4$–MeOH–THF. A mixture of styrene oxide (120 mg, 1 mmol), *trans*-2,3-diphenyloxirane (196 mg, 1 mmol), $LiBH_4$ (3 mmol), MeOH (0.25 mL), and THF (5 mL) was refluxed for 3 h. After cooling the mixture to room temperature, MeOH and water were added to quench the reaction. The mixture was extracted with dichloromethane which was dried and the solvent evaporated under reduced pressure. Purification by silica gel TLC (dichloromethane as developing solvent) afforded 1- and 2-phenylethanol (118 mg, 97%) and *trans*-2,3-diphenyloxirane (196 mg, 100% recovery). ^1H NMR analysis showed that the ratio of 1-phenylethanol and 2-phenylethanol was 91:9.

Diastereomer-Selective Reduction of *cis*-2,3-Diphenyloxirane in the Presence of *trans*-2,3-Diphenyloxirane by $LiBH_4$–MeOH–THF. A mixture containing *cis*-2,3-diphenyloxirane (196 mg, 1 mmol), *trans*-2,3-diphenyloxirane (196 mg, 1 mmol), $LiBH_4$ (6 mmol), THF (5 mL), and methanol (0.46 mL) was refluxed for 5 h. The reaction was quenched with MeOH and water. Most of methanol was evaporated under reduced pressure. The mixture was extracted with dichloromethane, the extract was dried, and solvent was evaporated under reduced pressure. Purification by silica gel TLC (dichloromethane as developing solvent) afforded 1,2-diphenylethanol (202 mg, 102%) and *cis*- and *trans*-2,3-diphenyloxirane (191 mg, 98%). ^1H NMR analysis showed that the recoveries of *cis*- and *trans*-2,3-diphenyloxirane were 20% and 78%, respectively.

Acknowledgment. We thank Mr. Hiroshi Hayashi for contribution in the early stage of this research and Mr. Koji Hiratsuka for technical assistance.

Registry No. $LiBH_4$, 16949-15-8; MeOH, 67-56-1; *n*-$C_9H_{19}CO_2CH_3$, 110-42-9; $(CH_3CH_2)_2CHCO_2CH_3$, 816-11-5; $(CH_3)_3CCO_2CH_3$, 598-98-1; $PhCO_2CH_3$, 93-58-3; $PhCO_2CH_2CH_3$, 93-89-0; $PhCO_2CH(CH_3)_2$, 939-48-0; $PhCO_2C(CH_3)_3$, 774-65-2; 2-$MeOCOC_6H_4CO_2Me$, 131-11-3; *n*-$C_{10}H_{21}OH$, 112-30-1; $(C_2H_5)_2CHCH_2OH$, 97-95-0; $(CH_3)_3CCH_2OH$, 75-84-3; $PhCH_2OH$, 100-51-6; 2-$HOCH_2C_6H_4CH_2OH$, 612-14-6; $PhCH{=}CHCO_2Me$, 103-26-4; $PhCH{=}CHCH_2OH$, 104-54-1; $PhCH_2CH_2CH_2OH$, 122-97-4; $PhCH_2CH_2CO_2Me$, 103-25-3; *n*-$C_7H_{15}CH(OH)(CH_2)_3OH$, 4272-02-0; $PhCH(OH)CH_3$, 98-85-1; $PhCH_2CH_2OH$, 60-12-8; *n*-$C_6H_{13}CH(OH)CH_3$, 123-96-6; 4-$O_2NC_6H_4CO_2Et$, 99-77-4; 4-$ClC_6H_4CO_2Et$, 7335-27-5; $PhCONH_2$, 55-21-0; 4-$O_2NC_6H_4CH_2OH$, 619-73-8; 4-$ClC_6H_4CH_2OH$, 873-76-7; *n*-$C_9H_{19}CO_2H$, 334-48-5; $PhNO_2$, 98-95-3; *n*-$C_8H_{17}NO_2$, 629-37-8; PhCN, 100-47-0; *n*-$C_7H_{15}CN$, 124-12-9; $PhCO_2H$, 65-85-0; $PhCO_2Na$, 532-32-1; *n*-$C_8H_{17}NH_2$, 111-86-4; $PhCH_2NH_2$, 100-46-9; *n*-$C_7H_{15}CONH_2$, 629-01-6; PhCONHMe, 613-93-4; *n*-$C_7H_{15}CONHMe$, 1119-57-9; PhCONHPh, 93-98-1; $CH_3CONHPh$, 103-84-4; *n*-$C_8H_{15}NH_2$, 111-86-4; $PhCH_2NHMe$, 103-67-3; *n*-$C_8H_{15}NHMe$, 2439-54-5; $PhNH_2$, 62-53-3; $PhCH_2NHPh$, 103-32-2; EtNHPh, 103-69-5; $PhCONMe_2$, 611-74-5; $PhCH_2CONMe_2$, 18925-69-4; Ph-$(CH_2)_2NMe_2$, 1126-71-2; *trans*-2,3-diphenyloxirane, 1439-07-2; *cis*-2,3-diphenyloxirane, 1689-71-0; 1,2-diphenylethanol, 614-29-9; dihydro-5-heptyl-2(3*H*)-furanone, 104-67-6; phenyloxirane, 96-09-3; hexyloxirane, 2984-50-1.