Ate Complex from Diisobutylaluminum Hydride and n-Butyllithium as a Powerful and Selective Reducing Agent for the Reduction of Selected Organic Compounds Containing Various Functional Groups

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The "ate" complex generated from diisobutylaluminum hydride and *n*-butyllithium in an equimolar ratio either in tetrahydrofuran–hexane or in toluene–hexane was reacted with a series of selected organic compounds containing various functional groups in order to explore the reducing properties and to determine the synthetic utility of the reagent. The reagent is very effective for selective 1,2-reduction of both acyclic and cyclic enones. The reagent in tetrahydrofuran–hexane gives slightly better 1,2-selectivity than in toluene–hexane in the reduction of some acyclic enones, whereas the reagent in toluene–hexane gives better 1,2-selectivity in the reduction of conjugated cyclohexenones. Esters and lactones are completely reduced to the corresponding alcohols at room temperature, whereas they are reduced to the corresponding alcohols and aldehydes at −78 °C even with an excess amount of the reagent. Partial reduction of the esters and the lactones to the corresponding aldehydes has not been observed. Acid chlorides are rapidly reduced to the corresponding alcohols with an excess amount of the reagent at −78 °C, whereas they are reduced to a mixture of the alcohol, the aldehyde, and the unreacted acid chloride with a stoichiometric amount of the reagent at −78 °C. Acid anhydrides are rapidly and quantitatively reduced to an equimolar mixture of the acid and the alcohol at −78 °C. Carboxylic acids and primary and secondary amides are inert to the reagent at room temperature and are recovered unchanged. Tertiary amides are cleanly reduced to the aldehydes with a stoichiometric amount of the reagent either at 0 °C or at room temperature, whereas they are inert to the reagent at −78 °C, which permits the selective reduction of other reducible functional groups in the presence of the tertiary amide group at the latter temperature. The reagent rapidly reduces simple primary alkyl, benzyl, and allyl bromides but slowly primary alkyl chlorides and secondary alkyl bromides. Tertiary alkyl and aryl halides are essentially inert to the reagent, whereas trityl bromide and vinyl bromide are reduced at a reasonable rate. Epoxides are cleanly reduced to the corresponding alcohols. The opening of the epoxide ring with this reagent proceeds with excellent isomeric purity, yielding the more highly substituted alcohol almost exclusively. Nitriles are resistant to reduction and are only slowly converted to the corresponding aldehydes at room temperature. Disulfides are rapidly and quantitatively reduced to the corresponding thiols. Sulfoxides and sulfones are inert to the reagent and are recovered unchanged. Selective reductions of an ester in the presence of other reducible groups such as a bromide, a tertiary amide, and a nitrile are achieved with the reagent at −78 °C by using a modified procedure. Furthermore, the reagent is capable of reducing selectively a ketone in the presence of an ester.

The development of hydride reducing agents, capable of achieving stereo- and chemoselective reductions, has attracted a great deal of recent attention.[1] Such selective reductions have been accomplished by modifying the steric and electronic effects of the substituents on the boron atom or the aluminum atom. For instance, lithium aluminum hydride is well-known to be an exceedingly powerful reducing agent, capable of reducing many functional groups, and is thus of little value for selective reductions. However, lithium tri-*tert*-butoxyaluminum hydride is a very mild reducing agent, and it resembles sodium borohydride in terms of its selectivity for functional groups.

Although the reducing properties of alkali metal trialkylborohydrides have been intensively studied,[2] there are only several reports in the literature on the reducing properties of alkali metal trialkylaluminum hydrides.[3] The ate complex from diisobutylaluminum hydride (Dibah) and methyllithium was originally utilized for the facile trans hydroalumination of disubstituted alkynes by Zweifel,[4] but its reducing property has been unexplored. Studies directed toward stereoselective reduction with the ate complexes from Dibah and various alkyllithiums were briefly described by Kovacs.[5] Recently, we have reported that the use of the ate complex from Dibah and *tert*-butyllithium provides a convenient method for conversion of hindered cyclic ketones and bicyclic ketones to the corresponding thermodynamically less stable alcohols.[6] Furthermore, these ate complexes were utilized successfully to achieve stereo- and chemoselective reductions in several instances by Trost.[7]

The lack of systematic investigations of the reducing properties of these ate complexes prompted a detailed study of the reduction of a series of selected organic compounds containing various functional groups with the ate complex from Dibah and *n*-butyllithium in tetrahydrofuran–hexane and/or toluene–hexane. This article describes the results of these investigations.

Results and Discussion

Preparation of the Ate Complex from Dibah and n-Butyllithium in Tetrahydrofuran–Hexane or in

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(2) (a) Krishnamurthy, S. *Aldrichimica Acta* **1974**, *7*, 55 and references cited therein. (b) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.

(3) Although the ate complexes from Dibah and alkyllithiums have been previously described as lithium trialkylaluminum hydrides in several occasions (ref 4, 5a, 6, and 7b), the formation of lithium trialkylaluminum hydrides has not been fully determined by spectroscopic methods. Since the exact nature of the reducing agent is not known at the present time, we have described the reducing agent as the ate complex from Dibah and *n*-butyllithium rather than lithium diisobutyl-*n*-butylaluminum hydride. See also ref 28.

(4) Zweifel, G.; Steele, R. *J. Am. Chem. Soc.* **1967**, *89*, 5085.

(5) (a) Kovacs, G.; Galambos, G.; Juvancz, Z. *Synthesis* **1977**, 171. (b) Zakharkin, L. I.; Grandberg, N. V. *Izv. Akad. Nauk. USSR, Ser. Khim.* **1976**, *11*, 2612; *Chem. Abstr.* **1977**, *86*, 120831.

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(7) (a) Trost, B. M.; Nishimura, Y.; Yamamoto, K.; McElvain, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 1328. (b) Trost, B. M.; Jungheim, L. N. *Ibid.* **1980**, *102*, 7910. (c) Trost, B. M.; Rivers, G. T.; Gold, J. M. *J. Org. Chem.* **1980**, *45*, 1835. (d) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, 4929.

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Toluene–Hexane. A solution of the ate complex generated from Dibah and *n*-butyllithium in tetrahydrofuran–hexane was prepared by the dropwise addition of equimolar amounts of *n*-butyllithium in hexane to the solution of Dibah in hexane diluted with tetrahydrofuran at 0 °C under nitrogen. A suspension of the ate complex generated from Dibah and *n*-butyllithium in toluene–hexane was prepared in the same way by substituting toluene for tetrahydrofuran. The hydride concentration was ascertained by GLC analysis of reduction products from reduction of 4-*tert*-butylcyclohexanone with the reagent. The reagent showed no sign of decomposition when kept at 0 °C under nitrogen for one week.

Reduction of Selected Organic Compounds. In order to establish the synthetic utility of this reagent, we studied the reductions of a series of selected organic compounds containing various functional groups.

Although the amount of the reagent employed depends upon the nature of the reaction, in general, 1.5 or 3.0 equiv of the reagent was utilized for most functional groups to ensure complete reduction, whereas 1 equiv of the reagent was used for partial reductions. Reductions of all functional groups except enones[9] were carried out in tetrahydrofuran–hexane at −78 and 0 °C and/or room temperature, depending upon the nature of the reaction. For the reductions, the ratio of tetrahydrofuran (or toluene) to hexane was adjusted to approximately 4:1.

Enones. Selective 1,2-reduction of enones is an important reaction in organic synthesis and considerable progress has been made in the development of various hydride reducing agents for this purpose.[10] Reduction of enones to the corresponding allylic alcohols with hydride reducing agents often occurs with varying amounts of concomitant reduction of the double bonds leading to saturated alcohols and/or saturated ketones due to competing 1,2- vs. 1,4-attack by hydride.[11] Since it has been demonstrated that the mode of attack depends critically on several factors, such as the hydride reducing agents used, the structure of enones, and solvents,[11,12] predictions concerning 1,2- vs. 1,4-attack for a particular enone are difficult. For instance, although Dibah[13] is well-known to be the most effective and widely used reagent for selective 1,2-reduction of enones, certain limitations in the reduction of acyclic enones have been noted by Ashby.[14] Although the ate complex generated from Dibah and *n*-butyllithium in tetrahydrofuran–hexane has been recently utilized for the selective 1,2-reduction of enones,[7b,15] it seems to be of considerable interest to explore the synthetic effectiveness of this reagent by examining the scope and limitations and to reexamine the synthetic effectiveness of Dibah. Thus, we undertook a detailed study of the reduction of a variety of structurally different enones with both reagents in two media, tetrahydrofuran–hexane and toluene–hexane. Reductions were carried out at −78 °C for 3 h by using enones and the reagent in a 1:1.5 molar ratio.

A systematic study was performed on acyclic enones. From the reduction results as seen in Table I, it is evident that this reagent is more effective than Dibah in terms of 1,2-selectivity. The reagent reduced acyclic enones to the corresponding allylic alcohols with greater than 90% 1,2-selectivity. Reduction of **2** with the reagent proceeded with 100% 1,2-selectivity, demonstrating the superior 1,2-selectivity over Dibah. Although the reagent in tetrahydrofuran–hexane gave slightly better 1,2-selectivity for **1** and **4**, the ratio of 1,2- vs. 1,4-reduction appears to be relatively solvent independent. However, Dibah gave better 1,2-selectivity in toluene–hexane than in tetrahydrofuran–hexane and the ratio of 1,2- vs. 1,4-reduction appears to be solvent sensitive for certain enones such as **2** and **4**. Such sensitivity has been reported previously.[16]

Several noteworthy features were observed from the reduction results of conjugated cyclohexenones such as **5**, **6**, and **7**. First, although the reagent is still effective for the selective 1,2-reduction, Dibah gave slightly better 1,2-selectivity compared to this reagent unlike the reduction of acyclic enones. Second, the ratio of 1,2- vs. 1,4-reduction by the reagent appears to be solvent sensitive and better 1,2-selectivity is obtained in toluene–hexane. Reduction of conjugated cyclohexenones with this reagent in toluene–hexane gave the corresponding allylic alcohols as a major product with greater than 94% 1,2-selectivity. Third, the ratio of 1,2- vs. 1,4-reduction by Dibah appears to be relatively solvent independent, although notable solvent dependence has been observed in the reduction of **5**. Furthermore, it is noteworthy that the reduction of β-unsubstituted cyclohexenones such as **5** and **6** by both reagents proceeded with excellent 1,2-selectivity unlike exclusive 1,4-reduction by K-Selectride (Aldrich).[12a]

In the reduction of 2-cyclopentenone, this reagent and Dibah were equally effective for selective 1,2-reduction and the reduction in toluene–hexane was slightly more prone toward 1,2-reduction than in tetrahydrofuran–hexane.

Table I summarizes the reduction results for enones chosen to determine the synthetic effectiveness of this reagent and Dibah both in tetrahydrofuran–hexane and in toluene–hexane.

Esters and Lactones. Reduction of methyl caprylate with 3 equiv of the reagent at −78 °C for 6 h afforded a 63:32 mixture of capryl aldehyde and capryl alcohol. This result indicates that the initial reduction product, the tetrahedral intermediate, forms rapidly but breaks down rather slowly under the reaction condition employed. However, with 3 equiv of the reagent at room temperature esters such as methyl caprylate and methyl benzoate were cleanly reduced to corresponding alcohols within 30 min.

In order to achieve complete and selective reduction of the ester in the presence of other reducible functional groups, a modified procedure was developed (discussed later). For methyl caprylate, 2 equiv of the reagent was added to the compound at −78 °C and maintained there.

(8) Attempts to prepare the reagent in pure THF were unsuccessful. Removal of solvents (THF–hexane) in vacuo and subsequent addition of THF resulted in the decomposition of the hydride to some extent (20–30%). Thus, we chose mixed solvent systems in remaining reductions.

(9) We have demonstrated the effectiveness of toluene–hexane as a solvent in the selective 1,2-reduction of enones. Thus, reductions of enones were carried out in two media, toluene–hexane and tetrahydrofuran–hexane. Kim, S.; Moon, Y. C.; Ahn, K. H. *J. Org. Chem.* **1982**, *47*, 3311.

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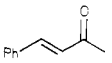
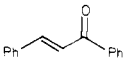
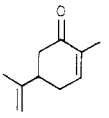
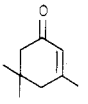
(15) According to ref 7b, the reagent appears to give better yields than Dibah in a number of reactions.

(16) According to ref 14, reduction of **1**, **2**, and **4** with Dibah in THF at 0 °C gives a 1,2/1,4 ratio of 81:18, 6:90, and 35:50, respectively.

Table I. Reduction of Enones with the Ate Complex from Dibah and *n*-BuLi in Toluene-Hexane and THF-Hexane at −78 °C for 3 h[a]

enone	no.	reagent	solvent[b]	product ratio[c] allylic alcohol	saturated alcohol	saturated ketone	isolated yield,[d] %
	1	$LiAlH(i\text{-}Bu)_2(n\text{-}Bu)$[e]	toluene	93	7	0	(95)
			THF	94	6	0	(94)
		$(i\text{-}Bu)_2AlH$	toluene	93	7	0	(97)
			THF	94	6	0	(98)
	2	$LiAlH(i\text{-}Bu)_2(n\text{-}Bu)$	toluene	100	0	0	99
			THF	100	0	0	98
		$(i\text{-}Bu)_2AlH$	toluene	83	0	17	97
			THF	42	0	58	98
	3	$LiAlH(i\text{-}Bu)_2(n\text{-}Bu)$	toluene	100	0	0	98
			THF	100	0	0	97
		$(i\text{-}Bu)_2AlH$	toluene	100	0	0	99
			THF	98	1	1	98
	4	$LiAlH(i\text{-}Bu)_2(n\text{-}Bu)$	toluene	90	0	10	99
			THF	99	0	1	99
		$(i\text{-}Bu)_2AlH$	toluene	87	3	10	98
			THF	45	0	55	99
	5	$LiAlH(i\text{-}Bu)_2(n\text{-}Bu)$	toluene	94	3	3	(96)
			THF	58	10	32	85
		$(i\text{-}Bu)_2AlH$	toluene	98	1	1	(94)
			THF	87	6	7	82
	6	$LiAlH(i\text{-}Bu)_2(n\text{-}Bu)$	toluene	94	0	6	93
			THF	85	0	15	98
		$(i\text{-}Bu)_2AlH$	toluene	100	0	0	94
			THF	96	0	4	96
	7	$LiAlH(i\text{-}Bu)_2(n\text{-}Bu)$	toluene	96	0	4	90
			THF	77	2	21	97
		$(i\text{-}Bu)_2AlH$	toluene	99	0	1	92
			THF	98	0	2	96
	8	$LiAlH(i\text{-}Bu)_2(n\text{-}Bu)$	toluene	99	1	0	(83)
			THF	96	2	2	(82)
		$(i\text{-}Bu)_2AlH$	toluene	98	1	1	(81)
			THF	87	6	7	(80)

[a] Molar ratio of H^-/enone was 1.5. [b] Toluene and THF refer to toluene-hexane (4:1) and THF-hexane (4:1), respectively. [c] Product ratio in reduction of 3 and 4 were determined by silica gel column chromatographic separation. Otherwise, product ratio were determined by GLC. [d] The numbers in parentheses indicate GLC yield. Increase of molecular weight (+2), resulting from further reduction of saturated ketones to saturated alcohols, was neglected in the isolated yields. [e] The formulation $LiAlH(i\text{-}Bu)_2(n\text{-}Bu)$ is meant to indicate only the stoichiometry based on a acid-base reaction.

After 1 h, the reaction mixture was treated with an excess amount of ethanolic sodium borohydride and allowed to warm to room temperature over 1 h. Capryl alcohol was isolated in 95% yield without the contamination of capryl aldehyde after usual workup.

Since the possibility of partial reduction of an ester to the corresponding aldehyde[17] was indicated by the reduction result for the reaction of methyl caprylate with 3 equiv of the reagent at −78 °C, reductions using 1 equiv of the reagent at −78 °C were performed. Contrary to our expectation, reduction of methyl caprylate with 1 equiv of the reagent at −78 °C for 1 h afforded a mixture of 43% of capryl aldehyde, 29% of capryl alcohol, and 28% of the unreacted ester. Similar results were realized with methyl benzoate under the same reaction condition.

Reduction of thiol esters was briefly examined. Reduction of *S-sec*-butyl benzothioate with 3 equiv of the reagent at room temperature for 30 min afforded benzyl alcohol in 94% yield. Partial reduction of a thiol ester did not give good results, yielding a mixture of the corresponding alcohol, the aldehyde, and the unreacted thiol ester as observed in the partial reduction of an ester.

With 3 equiv of the reagent at room temperature lactones were rapidly reduced to the diols. Lactones such as ϵ-caprolactone and phthalide were reduced to 1,6-hexanediol and 1,2-benzenedimethanol in the yields of 80% and 87%, respectively. Unlike Dibah,[18] the reagent failed to reduce lactones to lactols. Thus, ϵ-caprolactone was reduced to a mixture of 23% of 1,6-hexanediol, 45% of 5-hydroxyhexanal, and 30% of the unreacted lactone by 1 equiv of the reagent at −78 °C for 1 h.

The experimental results for the reduction of esters and lactones are summarized in Table II.

Carboxylic Acids, Acid Chlorides, and Acid Anhydrides. The reagent failed to reduce carboxylic acids such as *p*-chlorobenzoic acid and cinnamic acid at room temperature in 12 h as reported previously.[7c] The unreacted acids were quantitatively recovered after the usual workup.

Acid chlorides were rapidly and quantitatively reduced to the corresponding alcohols by using 3 equiv of the reagent at −78 °C in 30 min. Thus, acid chlorides such as benzoyl chloride and caprylyl chloride were converted into benzyl alcohol and capryl alcohol in the yields of 90% and

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Table II. Reduction of Selected Carbonyl Compounds with the Ate Complex from Dibah and *n*-BuLi in THF-Hexane

compd	molar ratio of H^-/compd	temp, °C	time, h	products	yield,[a] %
			Esters and Lactones		
methyl caprylate	3.0	−78	6.0	capryl aldehyde	(63)
				capryl alcohol	(32)
	3.0	rt	0.5	capryl alcohol	97
	1.0	−78	1.0	capryl aldehyde	(43)
				capryl alcohol	(29)
				methyl caprylate	(28)
methyl benzoate	1.0	−78	1.0	benzaldehyde	(42)
				benzyl alcohol	(28)
				methyl benzoate	(28)
	3.0	−78	4.0	benzaldehyde	(16)
				benzyl alcohol	(84)
	3.0	rt	0.5	benzyl alcohol	(96)
methyl cinnamate	3.0	rt	0.5	cinnamyl alcohol	97
methyl 10-undecenoate	3.0	rt	0.5	10-undecen-1-ol	96
methyl 1-adamantanecarboxylate	3.0	rt	0.5	1-adamantanemethanol	99
S-sec-butyl benzothioate	3.0	rt	0.5	benzyl alcohol	94
	1.0	−78	1.0	benzaldehyde	(80)
				benzyl alcohol	(8)
				S-sec-butyl benzothioate	(10)
S-sec-butyl caprylthioate	3.0	rt	0.5	capryl alcohol	97
ε-caprolactone	3.0	rt	0.5	1,6-hexanediol	80
	1.0	−78	1.0	5-hydroxyhexanal	(45)
				1,6-hexanediol	(23)
				ε-caprolactone	(30)
phthalide	3.0	rt	0.5	1,2-benzenedimethanol	87
4-*tert*-butyl-6-hexanolactone	3.0	rt	0.5	3-*tert*-butyl-1,6-hexanediol	92
			Carboxylic Acids, Acid Chlorides, and Acid Anhydrides		
p-chlorobenzoic acid	3.0	rt	12	*p*-chlorobenzoic acid	98
trans-cinnamic acid	3.0	rt	12	*trans*-cinnamic acid	98
undecylenic acid	3.0	rt	12	undecylenic acid	99
caprylyl chloride	1.0	−78	0.5	capryl alcohol	(50)
				capryl aldehyde	(4)
				methyl caprylate	(47)[b]
	3.0	−78	0.5	capryl alcohol	92
benzoyl chloride	3.0	−78	0.5	benzyl alcohol	90
p-chlorobenzoyl chloride	3.0	−78	0.5	*p*-chlorobenzyl alcohol	93
benzoic anhydride	3.0	−78	1.0	benzyl alcohol	95
				benzoic acid	97
mesitoic anhydride	3.0	−78	1.0	2,4,6-trimethylbenzyl alcohol	99
				mesitoic acid	98
phthalic anhydride	3.0	−78	1.0	phthalide	98
			Amides		
benzamide	3.0	rt	7.0	benzamide	98
caprylamide	3.0	rt	7.0	caprylamide	98
N-n-butylbenzamide	3.0	rt	7.0	*N-n*-butylbenzamide	99
N-n-butylcaprylamide	3.0	rt	7.0	*N-n*butylcaprylamide	98
N,N-diethylcaprylamide	3.0	−78	5.0	*N,N*-diethylcaprylamide	97
	3.0	rt	0.5	capryl aldehyde	(50)
				capryl alcohol	(50)
	1.0	rt	1.0	capryl aldehyde	(99), 90
				capryl alcohol	(1)
N,N-diethylbenzamide	3.0	rt	5.0	benzaldehyde	(30)
				benzyl alcohol	(67)
	1.0	0	2.0	benzaldehyde	(97)
				benzyl alcohol	(3)
N-capryloylpyrrolidine	1.0	rt	1.0	capryl aldehyde	(98), 90
				capryl alcohol	(2)
N-benzoylpiperidine	1.0	rt	0.1	benzaldehyde	(95)
				benzyl alcohol	(5)

[a] The numbers in parentheses indicate the GLC yield. Otherwise, the yields were determined by isolation. [b] The reaction mixture was treated with methanol.

92%, respectively. Partial reduction of an acid chloride to an aldehyde[19] was not observed when caprylyl chloride was reacted with 1 equiv of the reagent at −78 °C for 30 min. After the usual workup, 50% of capryl alcohol, 4% of capryl aldehyde, and 47% of methyl caprylate (resulting from methanolysis of the unreacted acid chloride) were obtained.

Acid anhydrides such as benzoic anhydride and mesitoic anhydride were cleanly reduced to an equimolar mixture of the acid and the alcohol at −78 °C in 1 h. Reduction of phthalic anhydride with the reagent followed by acid

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Table III. Reduction of Organic Halides with the Ate Complex from Dibah and *n*-BuLi in THF-Hexane at Room Temperature

compd	time	products	yield,[a] %
1-iodododecane	2 min	dodecane	98 (96)
1-bromododecane	10 min	dodecane	98 (95)
1-chlorododecane	8 h	dodecane	78
		1-chlorododecane	22
2-bromoundecane	4 h	undecane	60
		2-bromoundecane	38
cyclohexyl bromide	24 h	cyclohexane	<10[b]
		cyclohexyl bromide	90
exo-2-bromonorbornane	24 h	norbornane	5
		exo-2-bromonorbornane	95
benzyl bromide	2 min	toluene	92
benzyl chloride	20 min	toluene	95
α-methylbenzyl bromide	1 h	ethylbenzene	99
cinnamyl bromide	5 min	β-methylstyrene	100 (95)[c]
trityl bromide	24 h	triphenylmethane	(46)
		trityl bromide	(52)
β-bromostyrene	24 h	styrene	63
		β-bromostyrene	35
3-bromo-3-ethylheptane	24 h	3-bromo-3-ethylheptane	(90)[d]
p-bromotoluene	24 h	*p*-bromotoluene	(94)

[a] The yields were determined by GLC. The isolated yields are indicated in the parentheses. [b] The yield was not determined by GLC and calculated based on the unreacted halide. [c] Trace amounts of allylbenzene (<1%) were detected by GLC. [d] Trace amounts of elimination products (<3%) were detected by GLC.

hydrolysis resulted in the direct conversion of phthalic anhydride into phthalide in 98% yield. The reduction results with carboxylic acids, acid chlorides, and acid anhydrides are summarized in Table II.

Amides. Primary and secondary amides were not reduced by the reagent at room temperature and were recovered unchanged. However, tertiary amides were readily reduced to a mixture of the corresponding alcohol and the aldehyde at room temperature, whereas they were essentially inert to the reagent at −78 °C. Thus, reduction of *N,N*-diethylcaprylamide with 3 equiv of the reagent at room temperature for 30 min afforded a 50:50 mixture of capryl aldehyde and capryl alcohol. Although the tertiary amide was not completely reduced to the alcohol under the reaction conditions employed, complete reduction of the tertiary amide to the corresponding alcohol can be achieved by using a modified procedure previously described for methyl caprylate.

Partial reduction of a tertiary amide to the corresponding aldehyde is a useful reaction in organic synthesis. Such conversion has been achieved with limited amounts of hydride reducing agents such as lithium aluminum hydride,[20] lithium alkoxyaluminum hydride type reagents,[21] Dibah,[22] and disiamylborane.[23] We have found that the reagent exhibits excellent selectivity for partial reduction of tertiary amides into the corresponding aldehydes. When *N,N*-diethylbenzamide was reacted with 1 equiv of the reagent at 0 °C for 2 h, GLC analysis indicated the presence of 97% of benzaldehyde and 3% of benzyl alcohol. Reduction of tertiary amides such as *N,N*-diethylcaprylamide, *N*-capryloylpyrrolidine, and *N*-benzoylpiperidine afforded the corresponding aldehydes with greater than 95% selectivity. The results are summarized in Table II.

Organic Halides. Reduction of organic halides to the corresponding hydrocarbons is one of the fundamental reactions in organic synthesis.[24] Among many methods available for this conversion, the use of hydride reducing agents is the most effective and convenient.[25]

Reductions were usually carried out at room temperature using equimolar amounts of the reagent and the organic halide.[26] The simple primary alkyl bromide, 1-bromododecane, was completely reduced in 10 min, whereas it was inert to the reagent at −78 °C. The secondary alkyl bromide, 2-bromoundecane, was reduced much more slowly than the primary alkyl bromide. 60% conversion occurred in 4 h. The tertiary alkyl bromide, 3-bromo-3-ethylheptane, was essentially inert toward the reagent in 24 h but trace amounts (<3%) of elimination products were detected by GLC. Thus, this reagent may be valuable for the selective reduction of primary alkyl iodides and bromides without simultaneous attack on tertiary alkyl halides. 1-Chlorododecane was reduced to a 78:22 mixture of dodecane and the unreacted chloride in 8 h, whereas employment of either 2 or 3 equiv of the reagent permitted complete reduction in 8 h or 4 h, respectively. The reagent rapidly reduced simple benzyl and allyl bromides. Thus, benzyl bromide and cinnamyl bromide were instantly reduced to the corresponding hydrocarbons, whereas α-methylbenzyl bromide required 1 h for complete reduction. Trityl bromide was reduced to a 46:52 mixture of triphenylmethane and trityl bromide in 24 h. Since it was observed that a yellow color developed in the reaction mixture, presumably the reaction may

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(22) (a) Gutzwiller, J.; Uskokovic, M. *J. Am. Chem. Soc.* **1970**, *92*, 204. (b) Gutzwiller, J.; Pizzolato, G.; Uskokovic, M. *Ibid.* **1971**, *93*, 5907.

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(26) The solutions were 0.20 M in the substrate and 0.21 M in the reagent.

Table IV. Reduction of Epoxides, Nitriles, and Sulfur Compounds with the Ate Complex from Dibah and *n*-BuLi in THF-Hexane

compd	H^-/compd	temp, °C	time, h	product	yield,[a] %
1-methylcyclohexene oxide	1.5	0	0.17	1-methylcyclohexanol	(98), 93
				2-methylcyclohexanol	(2)
styrene oxide	1.5	0	0.17	1-phenylethanol	(96), 95
				2-phenylethanol	(4)
exo-2,3-epoxynorbornane	2.0	75	10	*exo*-norborneol	78[b]
				exo-2,3-epoxynorbornane	20
tridecanenitrile	3.0	−78	5	tridecanenitrile	98
	3.0	rt	24	tridecanal	(54)
				tridecanenitrile	(46)
p-bromobenzyl cyanide	1.0	rt	24	*p*-bromobenzyl cyanide	87
caprylonitrile	1.0	rt	24	capryl aldehyde	(10)
				caprylonitrile	(90)
n-butyl disulfide	2.5	0	0.17	*n*-butyl mercaptan	(98)
benzyl disulfide	2.5	0	0.17	benzyl mercaptan	95
phenyl disulfide	2.5	0	0.17	benzenethiol	91
dimethyl sulfoxide	3.0	rt	24	dimethyl sulfoxide	(99)
diphenyl sulfoxide	2.0	rt	24	diphenyl sulfoxide	98
methyl *p*-tolyl sulfone	3.0	rt	24	methyl *p*-tolyl sulfone	99
diphenyl sulfone	3.0	rt	24	diphenyl sulfone	99

[a] The numbers in parentheses indicate GLC yield. Otherwise, the yields were determined by isolation. [b] A trace amount (<1%) of *endo*-norborneol was detected by GLC.

proceed via a single-electron transfer pathway. Reaction of trityl halides by metal hydrides via a single-electron transfer pathway has been reported previously.[27] Vinyl bromide was reduced at a reasonable rate. 63% conversion occurred in 24 h. The aryl halide, *p*-bromotoluene, was inert to the reagent in 24 h and was recovered unchanged. Sterically hindered halides such as cyclohexyl bromide and *exo*-2-bromonorbornane were resistant to reduction. In the case of *exo*-2-bromonorbornane, only 5% of reduction occurred at room temperature in 24 h. The low reactivity of this reagent toward the sterically hindered halides is attributed to the bulkiness of the reagent by the steric requirement of the three butyl groups.[28]

Of special synthetic significance is the stoichiometric requirement of the reagent for the reduction of organic halides. Essentially complete utilization of the hydride of the reagent is in marked contrast to the results obtained from the reaction of hydride reducing agents with organic halides.[25j] The results presented here indicate that the reagent is a source of exceptionally powerful and selective nucleophilic hydride.

Table III summarizes the results obtained in the reduction of organic halides with the reagent.

Other Organic Compounds. Epoxides were rapidly reduced to the corresponding alcohols by 1.5 equiv of the reagent at 0 °C in 10 min.[29] Reaction of the epoxide with the reagent occurs at the less highly substituted position to give the more highly substituted alcohol in excellent isomeric purity. Thus, 1-methylcyclohexene oxide gave a mixture of 98% of 1-methylcyclohexanol and 2% of 2-methylcyclohexanol, whereas styrene oxide gave a mixture of 96% of 1-phenylethanol and 4% of 2-phenylethanol. *exo*-2,3-Epoxynorbornane, highly resistant to the usual hydride reducing agent, was reduced to a mixture of 78% of *exo*-norborneol along with a trace amount (<1%) of *endo*-norborneol and 20% of the unreacted epoxide by 2 equiv of the reagent at 75 °C in 10 h.

Nitriles were resistant to reduction and were only slowly converted to the corresponding aldehydes. Tridecanenitrile was reduced to a mixture of 54% of tridecanal and 46% of the unreacted nitrile by 3 equiv of the reagent at room temperature in 24 h, whereas it was inert to the reagent at −78 °C in 5 h. Unlike facile reduction of the nitriles with Dibah,[30] the low reactivity of the reagent is quite surprising and may provide very useful applications for the selective reduction of many other reducible functional groups in the presence of the nitrile group.

Disulfides, upon treatment with 2.5 equiv of the reagent at 0 °C for 15 min, were cleanly reduced to the corresponding thiols. Thus, diphenyl disulfide and dibenzyl disulfide were converted to benzenethiol and benzyl mercaptan in 91% and 95% yields, respectively.

Sulfoxides were essentially inert to 3 equiv of the reagent at room temperature in 24 h and the unreacted sulfoxides were recovered in essentially quantitative yields. Since it is known that lithium aluminum hydride reduces sulfoxides to sulfides,[31] the inertness of sulfoxides to the reagent is somewhat surprising. Sulfones were not reduced by the reagent unlike facile reduction of sulfones by Dibah.[32]

Experimental results for the reaction of epoxides, nitriles, and sulfur compounds with the reagent are summarized in Table IV.

(27) Ashby, E. C.; Goel, A. B.; Depriest, R. N. *Tetrahedron Lett.* **1981**, *22*, 3729.

(28) According to our unpublished results, the very low reactivity of lithium tri-*sec*-butylborohydride, the highly hindered trialkylborohydride, toward the sterically hindered halides such as cyclohexyl bromide and *exo*-2-bromonorbornane was realized. In the case of *exo*-2-bromonorbornane, reduction did not occur at room temperature in 24 h. It seems that resemblance of the ate complex from Dibah and *n*-butyllithium to lithium tri-*sec*-butylborohydride in the reduction of organic halides and many selective reductions with the ate complex due to complete utilization of the hydride indicate that the nature of the reducing agent is lithium diisobutyl-*n*-butylaluminum hydride rather than a mixture of disproportionated products.

(29) For reduction of epoxides, see: (a) Ashby, E. C.; Prather, J. *J. Am. Chem. Soc.* **1966**, *88*, 729. (b) Pasto, D. J.; Cumbo, C. C.; Hickman, J. *Ibid.* **1966**, *88*, 2201. (c) Lansbury, P. T.; Scharf, D. J.; Pattison, V. A. *J. Org. Chem.* **1967**, *32*, 1748. (d) Ashby, E. C.; Cooke, B. *J. Am. Chem. Soc.* **1968**, *90*, 1625. (e) Brown, H. C.; Yoon, N. M. *Ibid.* **1968**, *90*, 2686. (f) Murphy, D. K.; Alumbaugh, R. L.; Rickborn, B. *Ibid.* **1969**, *91*, 2649. (g) Lenox, R. S.; Katzenellenbogen, J. A. *Ibid.* **1973**, *95*, 957. (h) Krishnamurthy, S.; Schubert, R. M.; Brown, H. C. *Ibid.* **1973**, *95*, 8486. (i) Fiman, J. M.; Kish, Y. *Tetrahedron Lett.* **1982**, *23*, 2719. (j) Viti, S. M. *Ibid.* **1982**, *23*, 4541.

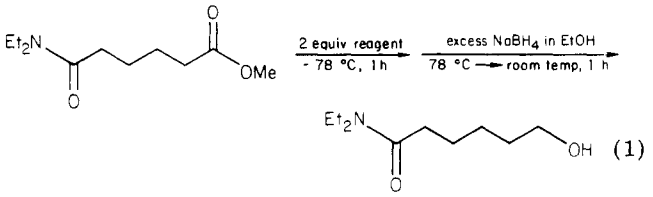
(30) (a) Miller, A. E. G.; Bliss, J. W.; Schwartzman, L. H. *J. Org. Chem.* **1959**, *24*, 627. (b) Trofimenko, S. *Ibid.* **1964**, *29*, 3046. (c) Marshall, J. A.; Andersen, N. H.; Schlicher, J. W. *Ibid.* **1970**, *35*, 858. (d) Minato, H.; Nagasaki, T. *J. Chem. Soc. C* **1966**, 1866.

(31) Brown, H. C.; Weissman, P. M.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1458.

(32) Gardner, J. N.; Kaiser, S.; Krubiner, A.; Lucas, H. *Can. J. Chem.* **1973**, *51*, 1420.

Selective Reductions. Systematic investigations of the reducing properties of the reagent toward various functional groups suggest the possibility of many selective reductions. Reduction of ketones, esters, acid chlorides, and acid anhydrides with the reagent proceeds rapidly at −78 °C. Thus, this permits the selective reductions of such groups in the presence of other reducible functional groups. Since selective reduction of an ester in the presence of other reducible functional groups such as a halide, an amide, and a nitrile is often difficult to achieve with the usual hydride reducing agents, selective reductions were carried out in tetrahydrofuran–hexane with several compounds containing an ester and other reducible groups chosen to demonstrate the synthetic utility of the reagent.

Selective reduction of an ester in the presence of a tertiary amide was examined. Reduction of methyl 5-(*N*,*N*-diethylcarbamoyl)pentanoate with 2 equiv of the reagent at −78 °C for 1 h, followed by treatment with an excess amount of ethanolic sodium borohydride (a modified procedure) resulted in only 6-hydroxy-*N*,*N*-diethylhexanamide in 83% yield (eq 1). The tertiary amide group

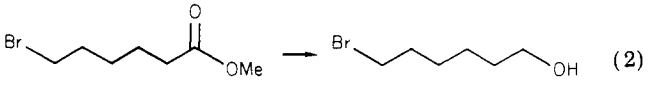


(1)

(83% isolated)

was completely inert under the reaction conditions employed.

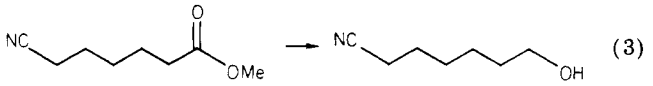
Similarly, the inertness of organic halides and nitriles toward the reagent at −78 °C allows the selective reduction of an ester in the presence of such groups. Thus, methyl 6-bromohexanoate was selectively reduced to 6-bromohexanol in 95% yield using a modified procedure described above (eq 2), whereas methyl 6-cyanohexanoate was re-



(2)

(95% isolated)

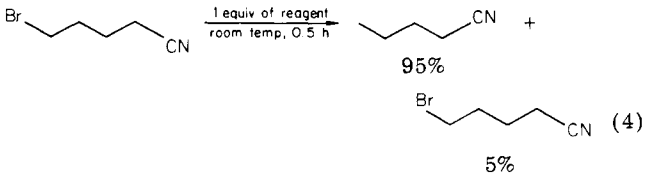
duced to 6-cyanohexanol in 80% yield under the same reaction condition (eq 3). Furthermore, selective reduction



(3)

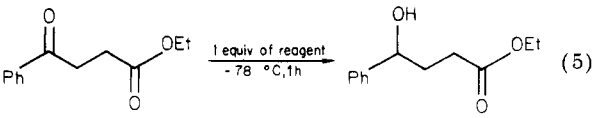
(80% isolated)

of primary alkyl bromides in the presence of nitriles can be achieved by this reagent. Reaction of 5-bromovaleronitrile with 1 equiv of the reagent at room temperature for 30 min gave a 95:5 mixture of valeronitrile and the unreacted starting material without simultaneous reduction of the nitrile group (eq 4).



(4)

Even more important is the observation that the reagent is capable of reducing selectively a ketone in the presence of an ester. Reduction of ethyl 3-benzoylpropionate with 1 equiv of the reagent at −78 °C for 1 h afforded ethyl 4-hydroxy-4-phenylbutanoate in 98% yield[33,34] (eq 5). In

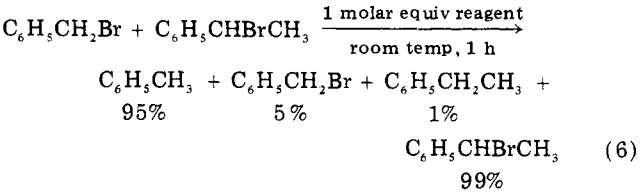


(5)

(98% isolated)

view of the fact that this reagent is a powerful reducing agent, the exceptional selectivity is quite remarkable. Such selectivity can be obtained with mild reducing agents such as sodium borohydride and lithium tri-*tert*-butoxyaluminum hydride.

The reactivity of organic halides toward the reagent makes possible the selective reduction of simple primary bromides in the presence of secondary bromides. Thus, reduction of an equimolar mixture of benzyl bromide and α-methylbenzyl bromide with a stoichiometric amount of (1 molar equiv) of the reagent at room temperature for 1 h gave toluene in 95% yield without significant reduction of α-methylbenzyl bromide as shown in eq 6.



(6)

Conclusion

The present study confirms the versatility of the ate complex generated from Dibah and *n*-butyllithium as a reducing agent. The reagent has unique and unusual reducing properties different from those obtained with lithium aluminum hydride, Dibah, and other hydride reducing agents. In its reducing abilities toward various functional groups, the reagent is shown to be an exceptionally powerful reducing agent, comparable to trialkylborohydrides, but a highly selective reducing agent, capable of achieving many selective reductions. Thus, the ate complex generated from Dibah and *n*-butyllithium should find many useful applications in organic synthesis.

Experimental Section

Proton nuclear magnetic resonance spectra were obtained on a Varian A-60 Spectrometer. Infrared spectra were measured on a Perkin-Elmer 267 Spectrometer. Gas chromatographic (GLC) analyses of product mixtures and purified samples were performed on a Varian 2800 Gas Chromatograph. All analyses were carried out on 7 ft × 0.125 in. or 12 ft × 0.125 in. 10% Carbowax 20M on 60/80 mesh Chromosorb W, 6 ft × 0.125 in. 5% KOH-5% Carbowax 20M on 60/80 mesh Chromosorb W, and 10 ft × 0.125 in. 10% THEED on 60/80 mesh Chromosorb W, 6 ft × 0.125 in. 10% SE-30 on 60/80 mesh Chromosorb W, and 6 ft × 0.125 in. 5% FFAP on 60/80 mesh Chromosorb W. Analytical thin-layer chromatography was performed on precoated silica gel glass plates (0.25 mm, 60F-254, E. Merck) and silica gel (Activity III, 04526, ICN) was used for column chromatography.

Toluene was distilled over sodium under nitrogen and tetrahydrofuran was distilled from sodium benzophenone under nitrogen. Most of the organic compounds utilized in this study were commercial products of the highest purity. Some compounds including 3-methyl-3-penten-2-one and 2,2,6,6-tetramethyl-4-

(33) 1% of the unreacted starting material was isolated.

(34) When an equimolar mixture of 3-pentanone and methyl caprylate was reacted with 1 molar equiv of the reagent at −78 °C for 1 h, 93% of 3-pentanol was obtained along with 7% of 3-pentanone without reduction of methyl caprylate.

hepten-3-one were prepared by known procedures.[35,36] The products obtained were readily available materials in many cases. If not, identification was effected through alternate preparation by known procedures. All glasswares were dried in a drying oven and cooled under nitrogen. All reduction experiments were carried out under nitrogen, and hypodermic syringes were used to transfer the solutions.

Since the reactions performed are all similar in many respects, typical reactions will be described as specific examples.

Preparation of the Ate Complex from Dibah and *n*-BuLi in THF–Hexane. In a 250-mL flask with a magnetic stirring bar and a rubber septum under nitrogen was placed diisobutylaluminum hydride (2.80 M in hexane, 15.0 mL, 42 mmol). THF (42.8 mL) was added and the flask was immersed in an ice bath. *n*-Butyllithium in hexane (1.60 M, 26.2 mL, 42 mmol) was slowly added to the flask with stirring, and the resulting solution was stirred for an additional 30 min to give a solution of the ate complex generated from Dibah and *n*-butyllithium (0.50 M) in THF–hexane. A suspension of the ate complex from Dibah and *n*-butyllithium in toluene–hexane was prepared in the same manner by substituting toluene for THF. The hydride concentration of the reagent was determined by GLC analysis of reduction products in the reduction of 4-*tert*-butylcyclohexanone. To a stirred solution of 4-*tert*-butylcyclohexanone (310 mg, 2.0 mmol) in THF (4 mL) was added the solution of the ate complex from Dibah and *n*-butyllithium (0.5 M, an expected value, 2.0 mL) in THF–hexane or toluene–hexane at 0 °C under nitrogen. The reaction mixture was stirred for 30 min at 0 °C and treated with saturated NaCl solution. The organic layer was separated, dried over anhydrous $MgSO_4$, and subjected to GLC. The hydride concentration determined by GLC analysis was corresponded to the expected value within 3% error range in all cases.

Reduction of 2,2,6,6-Tetramethyl-4-hepten-3-one in Toluene–Hexane. 2,2,6,6-Tetramethyl-4-hepten-3-one (170 mg, 1.0 mmol) was placed in a 25-mL flask with a magnetic stirring bar and a rubber septum under nitrogen. After toluene (4 mL) was added, a suspension of the ate complex from Dibah and *n*-butyllithium (3 mL of 0.50 M solution, 1.5 mmol) in toluene–hexane was added dropwise over 5 min with vigorous stirring in a dry ice–acetone bath. After 3 h of being stirred at −78 °C, the reaction mixture was quenched with methanol (0.5 mL). After a dry ice bath was removed, 10% aqueous HCl solution (4 mL) was added and the reaction mixture was stirred for 30 min at room temperature. The aqueous layer was separated and extracted twice with diethyl ether. The combined organic layers were washed with 10% aqueous HCl solution, water, and saturated NaCl solution, dried over anhydrous $MgSO_4$, and then evaporated to dryness under reduced pressure. The residue was purified by filtration through a pad of silica gel with methylene chloride to give the allylic alcohol (168 mg, 99%). The product was analyzed by GLC on 7 ft × 0.125 in. 10% Carbowax 20M column at 130 °C and further identified by NMR, IR, and TLC.

Reduction of Methyl Caprylate in THF–Hexane Using a Modified Procedure. In a 50-mL flask methyl caprylate (158 mg, 1.0 mmol) was placed, and THF (5 mL) was added. A dry ice–acetone bath was placed under the flask, and the ate complex from Dibah and *n*-butyllithium (4.0 mL of 0.50 M solution, 2.0 mmol) in THF–hexane was added. After 1 h of being stirred at −78 °C, the reaction mixture was further treated with sodium borohydride in ethanol (10 mL of 0.3 M solution, 3.0 mmol), allowed to warm to room temperature over 1 h, and hydrolyzed with 10% aqueous HCl solution. After diethyl ether (20 mL) was added, the aqueous layer was separated and extracted three times with diethyl ether. The combined organic layers were washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and evaporated to dryness under reduced pressure to give capryl alcohol (174 mg, 95%). The purity of the product was analyzed by GLC on 7 ft × 0.125 in. 10% Carbowax 20M column at 120 °C and the product was further identified by boiling point, NMR, and IR.

Partial Reduction of *N,N*-Diethylcaprylamide to Capryl Aldehyde with 1 Equiv of the Reagent in THF–Hexane. In a 50-mL flask were placed *N,N*-diethylcaprylamide (298 mg, 1.5 mmol) and dodecane (255 mg, 1.5 mmol) as an internal standard, and THF was (4.5 mL) added. After the ate complex from Dibah and *n*-butyllithium (3 mL of 0.5 M solution, 1.5 mmol) in THF–hexane was added to the stirred solution at room temperature, the reaction mixture was stirred for 1 h and hydrolyzed with 10% aqueous HCl solution (4 mL). After diethyl ether (10 mL) was added, the aqueous layer was separated and extracted twice with diethyl ether. The combined organic layers were washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and evaporated to dryness under reduced pressure. The residue was dissolved in methylene chloride (3 mL) and the resulting solution was subjected to GLC analysis (6 ft × 0.125 in. 5% KOH-5% Carbowax 20M), which showed the presence of 99% capryl aldehyde and 1% capryl alcohol.

Reduction of Methyl 6-Bromohexanoate in THF–Hexane. In a 50-mL flask was placed methyl 6-bromohexanoate (209 mg, 1 mmol). THF (5.5 mL) was added and the flask was immersed in a dry ice–acetone bath. The ate complex from Dibah and *n*-butyllithium (4 mL of 0.50 M solution, 2.0 mmol) was slowly added to the flask at −78 °C. After 1 h of being stirred at −78 °C, the reaction mixture was treated with sodium borohydride in ethanol (10 mL of 0.3 M solution), allowed to warm to room temperature over 1 h, and hydrolyzed with 10% aqueous HCl solution (4 mL). After diethyl ether (20 mL) was added, the aqueous layer was separated and extracted with diethyl ether. The combined organic layers were washed with 10% aqueous HCl solution, water, and saturated NaCl solution, dried over anhydrous $MgSO_4$, and evaporated to dryness under reduced pressure to give 6-bromohexanol (191 mg, 95%). The purity of the product was >99% according to GLC analysis on 7 ft × 0.125 in. 10% Carbowax 20M. The identity of the product was further confirmed by NMR and IR.

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Registry No. 1, 565-62-8; 2, 1653-94-7; 3, 122-57-6; 4, 94-41-7; 5, 930-68-7; 6, 99-49-0; 7, 78-59-1; 8, 930-30-3; $(i\text{-Bu})_2AlH$, 1191-15-7; methyl caprylate, 111-11-5; methyl benzoate, 93-58-3; methyl cinnamate, 103-26-4; methyl 10-undecenoate, 111-81-9; methyl 1-admantanecarboxylate, 711-01-3; *S-sec*-butyl benzothioate, 13291-43-5; *S-sec*-butyl caprylthioate, 89363-63-3; ε-carpolactone, 502-44-3; phthalide, 87-41-2; 4-*tert*-butyl-6-hexanolactone, 34680-83-6; *p*-chlorobenzoic acid, 74-11-3; *trans*-cinnamic acid, 140-10-3; undecylenic acid, 112-38-9; caprylyl chloride, 111-64-8; benzoyl chloride, 98-88-4; *p*-chlorobenzoyl chloride, 122-01-0; benzoic anhydride, 93-97-0; mesitoic anhydride, 5745-51-7; phthalic anhydride, 85-44-9; benzamide, 55-21-0; caprylamide, 629-01-6; *N*-*n*-butylbenzamide, 2782-40-3; *N*-*n*-butylcaprylamide, 24928-30-1; *N,N*-diethylcaprylamide, 996-97-4; *N,N*-diethylbenzamide, 1696-17-9; *N*-capryloylpyrrolidine, 20299-80-3; *N*-benzoylpiperidine, 776-75-0; 1-iodododecane, 4292-19-7; 1-bromododecane, 143-15-7; 1-chlorododecane, 112-52-7; 2-bromoundecane, 39563-54-7; cyclohexyl bromide, 108-85-0; *exo*-2-bromonorbornane, 2534-77-2; benzyl bromide, 100-39-0; benzyl chloride, 100-44-7; α-methylbenzyl bromide, 585-71-7; cinnamyl bromide, 4392-24-9; trityl bromide, 596-43-0; β-bromostyrene, 103-64-0; 3-bromo-3-ethylheptane, 86119-63-3; *p*-bromotoluene, 106-38-7; 1-methylcyclohexene oxide, 1713-33-3; styrene oxide, 96-09-3; *exo*-2,3-epoxynorbornane, 3146-39-2; tridecanenitrile, 629-60-7; *n*-butyl disulfide, 629-45-8; benzyl disulfide, 150-60-7; phenyl disulfide, 882-33-7; dimethyl sulfoxide, 67-68-5; diphenyl sulfoxide, 945-51-7; methyl *p*-tolyl sulfone, 3185-99-7; diphenyl sulfone, 127-63-9; *p*-bromobenzyl cyanide, 16532-79-9; caprylonitrile, 124-12-9; methyl 6-bromohexanoate, 14273-90-6.

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