

Quantitative Synthesis of Aldehydes from Weinreb Amides Using Lithium Diisobutyl-*t*-Butoxyaluminum Hydride (LDBBA)

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Over the past several years, we have developed novel reducing agents for the partial reduction of carboxylic acid derivatives to aldehydes, which are valuable intermediates in the synthesis of complex natural products with significant biological activity as well as other useful materials. Among these reducing agents, lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA), sodium diisobutyl-*t*-butoxyaluminum hydride (SDBBA), and potassium diisobutyl-*t*-butoxyaluminum hydride (PDBBA), the *t*-butoxy derivatives of diisobutylaluminum hydride (DIBALH), are particularly effective to produce aldehydes in synthetically useful yields.^{1–4} LDBBA is now commercially available from Sigma-Aldrich Company.

As part of our research program we decided to attempt the partial reduction of carboxylic acid derivatives of the valuable Weinreb amides,⁵ which are versatile building blocks that could act as useful intermediates for the preparation of aldehydes and ketones, using LDBBA, SDBBA, and PDBBA (Scheme 1).

Weinreb has described two types of general reducing agents DIBALH and lithium aluminum hydride (LAH), for the partial reduction of Weinreb amides to aldehydes.^{5a} However, the yields of the desired aldehydes are relatively low (67–76%) even at –78 °C, in contrast to those of ketones that

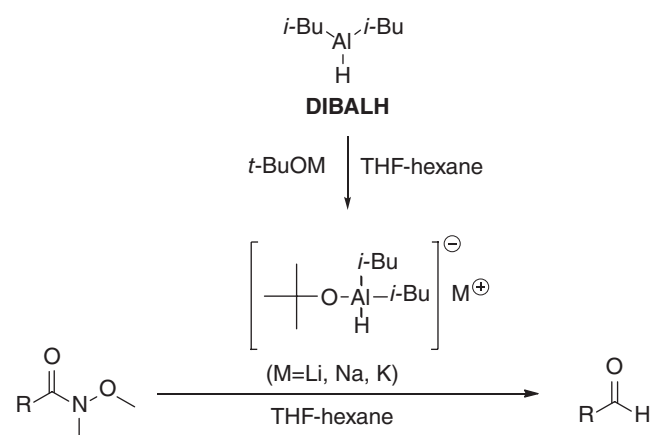
can achieve 90% yields, although some derivatives are converted to the corresponding aldehydes in excellent yields.⁶ In addition, Georg and coworkers demonstrated that Weinreb amides can be readily reduced with Cp₂Zr(H)Cl at room temperature to give aldehydes in 85–94% yield.⁷ And very recently, Singaram *et al.* have reported that chloromagnesium dimethylaminoborohydride (MgAB) is a very useful partial reducing agent for the synthesis of aldehydes from Weinreb amides.⁸ Herein, we report a general and efficient method for the synthesis of aldehydes from Weinreb amides, through partial reduction using metal diisobutyl-*t*-butoxyaluminum hydrides.

We initially carried out an evaluation of the reducing properties of LDBBA, SDBBA, and PDBBA for the partial reduction of representative aromatic and aliphatic Weinreb amides to aldehydes. Fortunately, we found that LDBBA, SDBBA, and PDBBA had excellent partial reducing ability for the desired reaction at a mild reaction temperature (0 °C). Of these hydrides, we selected LDBBA as the most useful because SDBBA and PDBBA require longer reaction times (Table 1).

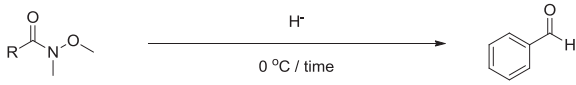
Thus, we used LDBBA for the synthesis of aldehydes from representative Weinreb amides, under the optimized reaction conditions, with 1.1 equiv of LDBBA at 0 °C for 30 min. The results are summarized in Table 2.

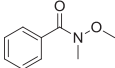
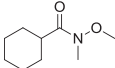
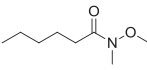
As shown in Table 2, *N*-methoxy-*N*-methylbenzamide and its derivatives, containing electron-withdrawing and electron-donating substituents were smoothly converted to the corresponding aldehydes in quantitative yields (entries 1–8, Table 2). Similarly, all other reactions readily proceeded with quantitative yields for a range of substrates, including heteroaromatics, *N*-methoxy-*N*-methylnicotinamide, and *N*-methoxy-*N*-methyl-2-furoamide (entries 9 and 10, Table 2); a polyaromatic, *N*-methoxy-*N*-methyl-2-naphthylamide (entry 11, Table 2); aliphatic substrates (entries 12 and 13, Table 2); and an α,β -unsaturated Weinreb amide (entry 14, Table 2). This demonstrates the broad scope of the reaction in terms of the substituent on the Weinreb amide. The isolated yields correlated well with those determined by GC (entries 1 and 12, Table 2).

Subsequently we studied the reducing characteristics of LDBBA for the partial reduction of other carboxylic acid



Scheme 1. Synthesis of aldehydes from Weinreb amides using the novel reducing agent.

Table 1. Evaluation of metal diisobutyl-*t*-butoxyaluminum hydrides for the synthesis of aldehydes from Weinreb amides.


Weinreb amide	H ⁻	H ⁻ (equiv)	Time (h)	Yield (%) ^a
	LDBBA	1.1	0.5	>99
	SDBBA	1.1	3.0	>99
	PDBBA	1.1	9.0	99
	LDBBA	1.1	0.5	>99
	SDBBA	1.1	0.5	87
			3.0	>99
	PDBBA	1.1	0.5	5
		1.1	9.0	41
	LDBBA	1.1	0.5	>99
	SDBBA	1.1	3.0	>99
	PDBBA	1.1	9.0	94

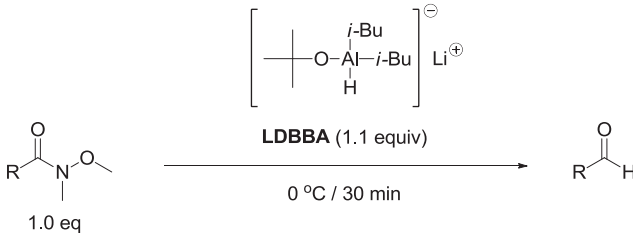
^a Yields were determined by GC.

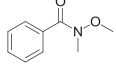

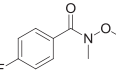

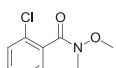

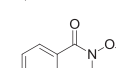

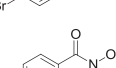

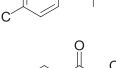

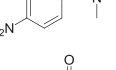

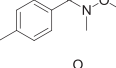

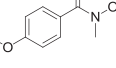

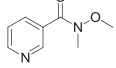

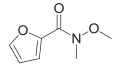

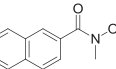

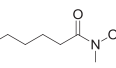

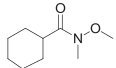

derivatives. We attempted the chemoselective reduction of Weinreb amides in the presence of a similar ester and standard *N,N*-dialkyl tertiary amide, which could be predicted to be either more reactive or similarly reactive to Weinreb amides. However, when 1:1 mixtures of the Weinreb amide and the ester or tertiary amide were subjected to LDBBA, the reactions successfully afforded the corresponding aldehyde from the Weinreb amide with almost no reduction of the other carboxylic acid derivatives (Table 3). Thus, gratifyingly, we found LDBBA to be a promising, and useful chemoselective reducing agent.

In conclusion, we have developed a general and useful method for the selective synthesis of aldehydes from Weinreb amides, with no over-reduction to the alcohol, using LDBBA, which can be readily prepared from DIBALH and is also commercially available. The advantages of the present method include quantitative product yields, a short reaction time, and mild reaction conditions (0 °C). Therefore, we believe that LDBBA has great potential as a broadly applicable, alternative partial reducing agent for the synthesis of aldehydes from Weinreb amides in organic synthesis. Furthermore, LDBBA could selectively reduce Weinreb amides to the corresponding aldehydes in the presence of esters and tertiary amides.

Experimental

General. All glassware was dried thoroughly in an oven, assembled hot, and cooled under a stream of dry nitrogen prior to use. All reactions and manipulation of air- and moisture-sensitive materials were carried out using the standard techniques for handling air-sensitive materials. All chemicals were commercial reagents of the highest purity, which were further purified by standard methods before use. Tetrahydrofuran

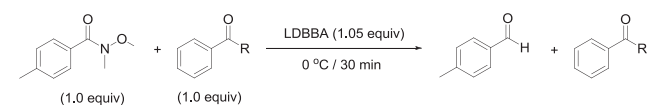
Table 2. Synthesis of aldehydes from representative Weinreb amides using LDBBA.


Entry	Weinreb amide	Product	Yield (%) ^a
1			>99 (98)
2			>99
3			>99
4			>99
5			>99
6			>99
7			>99 (97)
8			>99
9			>99
10			>99
11			>99
12			>99 (97)
13			>99 (96)
14			>99

^a Yields were determined by GC. Isolated yields are shown in parentheses.

(THF) was dried over sodium-benzophenone and distilled. Weinreb amides were prepared according to the literature procedure.^{2a} Gas chromatography (GC) analyses were performed

Table 3. Chemoselective partial reduction of Weinreb amide to aldehyde with LDBBA at 0 °C in the presence of an ester or a standard tertiary amide.



Entry	R	Product ^a
1		
2		

^a Yields were determined by GC.

on a Yonglin (Anyang-si, South Korea), Acme 6000M FID chromatograph using an HP-5 (5%-diphenyl-95%-dimethylsiloxane copolymer, 30 m) capillary column. All GC yields were determined with the use of a mixture of naphthalene as an internal standard and an authentic sample of the product.

Preparation of LDBBA. To a solution of *t*-butyl alcohol (5.26 mL, 55 mmol) in THF (25 mL) was added *n*-butyllithium (22 mL, 2.5 M in hexane, 55 mmol) at 0 °C. After stirring for 1 h at room temperature, DIBALH (50 mL, 1.0 M in hexane, 50 mmol) was added dropwise to the reaction mixture at 0 °C and the mixture was stirred for a further 2 h at room temperature to obtain a colorless homogeneous solution. The concentration of LDBBA solution in THF-hexane was measured gasometrically by the hydrolysis of an aliquot of the solution with a hydrolyzing mixture of *t*-butyl alcohol-THF (1:1) at 0 °C. The LDBBA solution was stable in the refrigerator for 6 months without any appreciable reduction of the hydride content.

Partial Reduction of Weinreb Amides to the Corresponding Aldehydes. The following experimental procedure for the partial reduction of *N*-methoxy-*N*-methylbenzamide to benzaldehyde is representative. A dry, argon-flushed flask, equipped with a magnetic stirring bar and a septum, was charged with *N*-methoxy-*N*-methylbenzamide (0.08 mL, 0.5 mmol) and THF (5 mL). After cooling to 0 °C, LDBBA (1.38 mL, 0.4 M 0.55 mmol) was added dropwise and the mixture was stirred for 30 min at the same temperature. The reaction was quenched with 1N aqueous HCl (5 mL) and the product was extracted with diethyl ether (10 mL). The organic layer was dried over anhydrous magnesium sulfate. GC analysis showed quantitative conversion to benzaldehyde. All products in Table 2 were confirmed through a comparison with the GC data of an authentic sample.

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