



# Copper diisobutyl-*t*-butoxyaluminum hydride: A novel reagent for chemoselective reduction of tertiary amides over esters

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## ABSTRACT

We demonstrate that copper diisobutyl-*t*-butoxyaluminum hydride, readily prepared from lithium diisobutyl-*t*-butoxyaluminum hydride and CuI, effectively and chemoselectively reduces tertiary amides over esters at ambient temperature, affording the corresponding aldehydes in excellent yields.

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Chemoselective hydride reducing agents allowing quantitative conversion into the desired product are highly sought after,<sup>1</sup> ideally being affordable and thus suitable for general-purpose use. In view of this demand, the past decades have witnessed the development of a large number of such reagents (prepared by modifying highly reactive metal hydrides), with their selectivities mainly determined by the steric/electronic properties of substituents and reagent mildness.<sup>2,3</sup> For instance, lithium aluminum hydride<sup>4</sup> is an extremely powerful agent reducing most organic functional groups and thus leaving almost no room for selectivity. However, derivatives such as lithium tri-*t*-butoxyaluminum hydride,<sup>5</sup> bis (4-methyl-1-piperazinyl)aluminum hydride,<sup>6</sup> and lithium tris (diethylamino)aluminum hydride<sup>7</sup> have been reported as mild and efficient reducing agents with reactivities similar to that of NaBH<sub>4</sub>.<sup>8</sup> Likewise, other reducing agents have also been successfully modified to achieve stereo- and chemoselective reduction.<sup>9</sup>

The reduction of amides to aldehydes is an important and well-studied chemical transformation.<sup>10</sup> However, this transformation is difficult to accomplish in the presence of the more reactive ester moieties, with only few reagents reported to be suitable for this purpose, e.g., the Schwartz reagent (Cp<sub>2</sub>Zr(H)Cl),<sup>11</sup> LiBH (CHMeEt)<sub>3</sub>,<sup>12</sup> CIMg<sup>+</sup>(H<sub>3</sub>BNMe<sub>2</sub>)<sup>-</sup>,<sup>13</sup> and [Mo(CO)<sub>6</sub>]/TMDS.<sup>14</sup> Despite the significant progress achieved using these systems, such reagents are very expensive and highly sensitive. Furthermore, some of the above systems require additional synthetic steps or

suitable for either aromatic or aliphatic substrates. Consequently, efficient and readily available amide to aldehyde reducing agents applicable to both aromatic and aliphatic substrates are still in high demand.

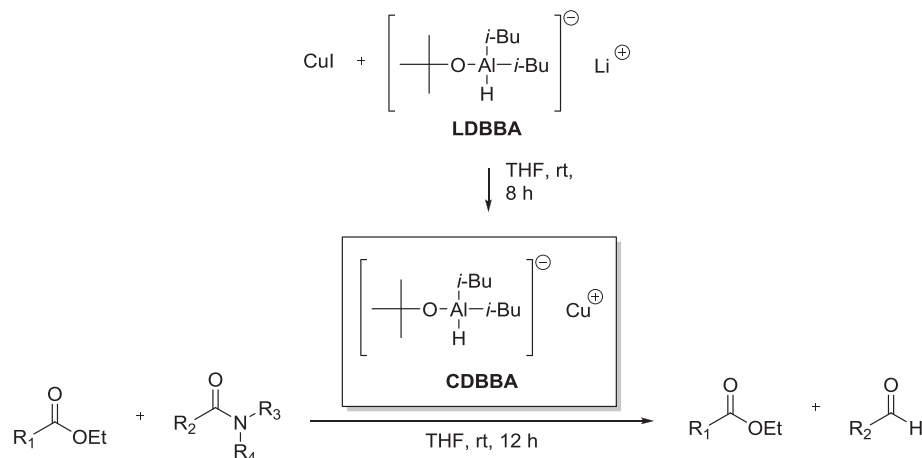
As part of our ongoing search for highly efficient reducing agents, we have identified several promising species such as lithium diisobutylmorpholinoaluminum hydride (LDBMOA),<sup>15</sup> lithium diisobutylpiperidinoaluminum hydride (LDBPA),<sup>16</sup> lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA),<sup>17</sup> sodium diisobutyl-*t*-butoxyaluminum hydride (SDBBA),<sup>18</sup> and potassium diisobutyl-*t*-butoxyaluminum hydride (PDBBA).<sup>19,20</sup> Herein, we report the chemoselective reduction of tertiary amides to aldehydes in the presence of esters using copper diisobutyl-*t*-butoxyaluminum hydride (CDBBA) (Scheme 1).

The CDBBA was readily prepared by the reaction of LDBBA with CuI at room temperature,<sup>21,22</sup> and its reactivity was determined by reducing various carboxylic acid derivatives. Surprisingly, treatment of tertiary amides and esters with CDBBA at room temperature resulted in the reduction of the relatively less reactive tertiary amides to aldehydes in reasonable yield, leaving esters unreacted. In view of this interesting observation, we systematically studied the chemoselective reduction of tertiary amides in the presence of esters using variable conditions like temperature, reagent:substrate mole ratios, and solvents to optimize the yields of the desired aldehydes (Table 1).

Table 1 shows that moderate tertiary amide conversion and high selectivity over ester reduction were observed at 0 °C with a 10:1.0 (mol/mol) reagent:substrate ratio in THF (entry 1). Better

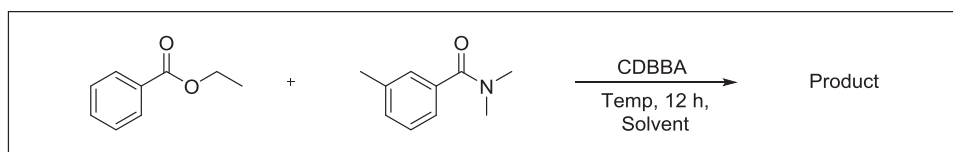
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**Scheme 1.** Chemoselective reduction of tertiary amides over esters with CDBBA.

**Table 1**  
Optimization of the chemoselective tertiary amide reduction.



Entry	CuI:LDBBA	CDBBA (eq)	Temp	Solvent	Yield (%) <sup>a</sup> Ester/ROH/RCHO Amide/ROH/RCHO
1	1.1:1.0	10.0	0 °C	THF	94/1/4 18/1/71
2	1.1:1.0	10.0	rt	THF	81/3/6 0/6/94
3	1.1:1.0	8.0	rt	THF	94/0/1 0/0/97
4				Hexane	93/0/5 13/6/76
5				Ether	97/0/3 24/4/72
6				MC	92/0/2 26/2/69
7				Toluene	93/3/4 19/5/76
8	1.1:1.0	4.0	rt	THF	99/0/0 32/0/63
9	1.0:2.0	8.0	rt	THF	0/7/75 12/5/63
10	2.0:1.0	8.0	rt	THF	97/0/0 55/0/34

<sup>a</sup> Yields were determined by GC.

aldehyde yields were achieved at room temperature; however, decreased selectivity and over-reduction (i.e., alcohol formation) were observed (entry 2). To overcome this issue, the reagent:substrate mole ratio was changed to 8.0:1.0, affording an increased aldehyde yield and higher selectivity (entry 3). The use of other solvents such as hexane, ether, dichloromethane, and toluene resulted in moderate reduction yields and greater selectivity (entries 4–7). A further decrease of the reagent:substrate molar ratio from 8.0:1.0 to 4.0:1.0 (THF) decreased the amide to aldehyde conversion, whereas the ester remained unreacted (entry 8). Finally, we investigated the effect of the CuI:LDBBA ratio, revealing that deviations from the 1.1:1.0 value resulted in either simultane-

ous ester and tertiary amide reduction or decreased yield of aldehyde from tertiary amide (entries 9 and 10).

Based on the above data, it was concluded that the 8.0:1.0 reagent:substrate ratio was optimal, resulting in excellent tertiary amide to aldehyde conversions in the presence of an ester group. In the next step, the efficiency of CDBBA was tested by screening a series of aromatic and aliphatic tertiary amides and Weinreb amides under optimal conditions.

As shown in Table 2, most of the tested tertiary amides could be converted into the corresponding aldehydes in good to excellent yields, with the electron donating/withdrawing nature of tertiary amide substituents have shown similar effect on selectivity and

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