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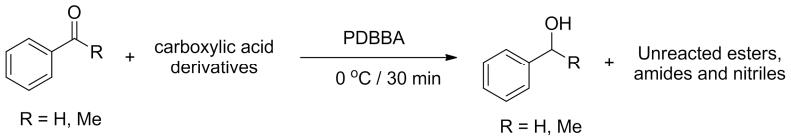

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Chemoselective reduction of aldehydes and ketones by potassium diisobutyl-*t*-butoxy aluminum hydride (PDBBA)

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ABSTRACT

t-Butoxy derivatives of DIBALH [lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA), sodium diisobutyl-*t*-butoxyaluminum hydride (SDBBA), and potassium diisobutyl-*t*-butoxyaluminum hydride (PDBBA)] were examined as chemoselective reducing agents of carbonyl compounds. Among them, PDBBA was found to be the most efficient for the reduction of aldehydes and ketones to the corresponding alcohols in the presence of ester, amide, and nitrile substituents at ambient temperature. In addition, the optimal conditions gave higher chemoselectivity for aldehydes in the presence of ketones.

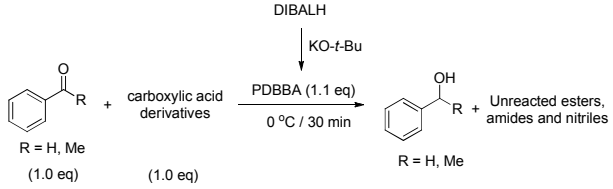
1. Introduction

Reductions are fundamental and the most frequently used chemical transformations in organic synthesis.[1] Since the invention of hydride reducing agents for functional groups like carbonyl derivatives, there has been significant progress in the development and identification of novel efficient reagents from the perspectives of chemo- and stereoselectivities.[1d-i] The ready availability of mild and efficient reducing agents that show good selectivity towards multifunctional target molecules[2] is also an important aspect of basic research and development studies. To address these issues, a wide range of reducing agents has been designed and reported by numerous research institutions and academies over many decades.[3]

The highly chemoselective reduction of aldehydes and ketones over other carbonyl compounds has been reported widely. For example, although lithium aluminum hydride ($LiAlH_4$)[4] is an extremely powerful reducing agent for most organic functional groups, it gives with no selectivity. On the other hand, sodium borohydride ($NaBH_4$)[5] is a typical cheap and selective reducing agent for aldehydes, ketones, and acyl chlorides. Sodium borohydride at low temperature (−78 °C),[6] with additive (excess Na_2CO_3),[7] resin (Dowex1-x8),[8] and in polyethylene glycol dimethyl ether (PEGDME),[9] have been reported for selective reduction of aldehydes. Generally, $NaBH_4$ reductions involve protic solvents such as methanol, ethanol, or mixed polar solvents for solubility and (or) selectivity.[5b,10]

DIBALH is an electrophilic reducing agent known for the reduction of ester and nitriles to aldehydes; it can also reduce most carbonyl derivatives efficiently.[11] Lithium pyrrolidinoborohydride ($LipyrrBH_3$) can selectively reduce only aldehydes and ketones in the presence of nitriles at higher temperatures.[12] Chemoselective reduction of aldehydes and ketones over acyl chlorides and esters using $LiAlH_4$ and silica chloride has been reported.[13] We have previously reported that potassium diisobutyl-*t*-butoxyaluminum hydride (PDBBA) can be used for the chemoselective partial reduction of esters to aldehydes in the presence of nitriles.[14]

Several other chemoselective reducing agents of aldehydes over ketones, including lithium tri-*t*-butoxyaluminum hydride (LTBA)/$NaBH_4$,[15] borohydride exchange resin (BER),[16] potassium triacetoxyborohydride ($KBH(OAc)_3$)[17] and zinc borohydride $Zn(BH_4)_2$[18] can also be used. However, some of the reported methods involve longer reaction times, high temperature, or the use of additives in large excess.



Scheme 1. Chemoselective reduction of aldehydes and ketones

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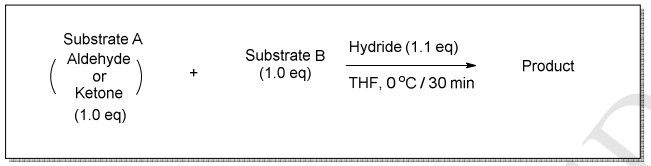
Despite the considerable progress achieved in the past few decades, there is a growing interest in identifying novel and eco-friendly chemoselective reducing agents. As part of our ongoing research, we have identified and reported[19] several efficient reducing agents *via* the simple modification of commercial reagents. Herein, we report the chemoselective reduction of aldehydes and ketones using PDBBA, easily prepared by the reaction of DIBAL-H with potassium *t*-butoxide (Scheme 1).

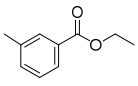
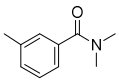
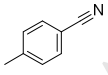
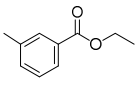
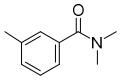
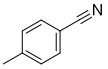
2. Results and discussion

2.1. Evaluation of chemoselective reduction with various reducing agents

First, we screened the chemoselective reducing properties of the *t*-butoxy derivatives of DIBALH, such as lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA), sodium diisobutyl-*t*-butoxyaluminum hydride (SDBBA), and PDBBA, and compared the results with those obtained with commercial DIBALH and Red-Al. Accordingly, aldehydes and ketones were reduced in the presence of ester, amide, and nitrile functionalities. The results in Table 1 suggest that aldehydes and ketones were reduced to the corresponding alcohols with all the DIBALH-based reducing agents tested (LDBBA, SDBBA and PDBBA). On the other hand, DIBALH itself and Red-Al showed poor selectivity. LDBBA and SDBBA showed relatively good selectivity for the reduction of aldehyde and ketone groups over ester groups; however, ester groups were still reduced by 12% and 8%, respectively. PDBBA showed the best chemoselectivity towards stoichiometric conversion to the desired product among the DIBALH-based reducing agents tested.

Table 1. Evaluation of reducing agents for the chemoselective



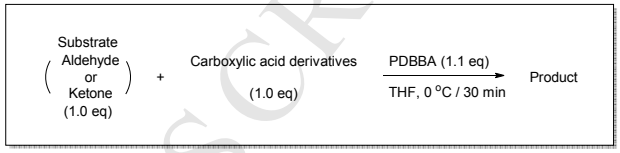
Entry	Substrate A	Substrate B	Hydride	Yield (%)[a] Substrate A S.M / ROH	Substrate B S.M / RCHO / ROH
1			DIBALH	0 / 85	95 / 0 / 4
			Red-Al	0 / 100	91 / 0 / 8
			LDBBA	0 / 98	87 / 0 / 12
			SDBBA	0 / 99	90 / 0 / 8
			PDBBA	0 / 98	99 / 0 / 0
2			DIBALH	60 / 37	61 / 31 / 5
			Red-Al	0 / 92	63 / 21 / 15
			LDBBA	0 / 100	100 / 0 / 0
			SDBBA	0 / 99	99 / 0 / 0
			PDBBA	0 / 99	99 / 0 / 0
3			DIBALH	0 / 91	98 / 0 / 0
			Red-Al	0 / 97	81 / 18 / 0
			LDBBA	0 / 99	100 / 0 / 0
			SDBBA	0 / 99	99 / 0 / 0
			PDBBA	0 / 100	99 / 0 / 0
4			DIBALH	0 / 99	92 / 2 / 0
			Red-Al	0 / 97	65 / 0 / 34
			LDBBA	0 / 100	86 / 0 / 13
			SDBBA	0 / 100	96 / 0 / 4
			PDBBA	0 / 100	99 / 0 / 0
5			DIBALH	40 / 59	69 / 0 / 28
			Red-Al	0 / 97	65 / 33 / 0
			LDBBA	0 / 97	97 / 0 / 0
			SDBBA	0 / 98	98 / 0 / 0
			PDBBA	0 / 100	100 / 0 / 0
6			DIBALH	0 / 88	93 / 0 / 0
			Red-Al	0 / 97	68 / 31 / 0
			LDBBA	0 / 99	100 / 0 / 0
			SDBBA	0 / 99	98 / 0 / 0
			PDBBA	0 / 98	100 / 0 / 0

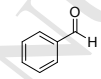
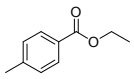
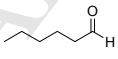
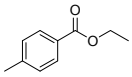
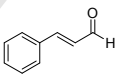
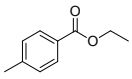
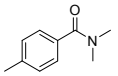
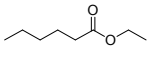
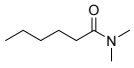
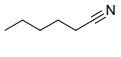
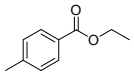
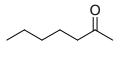
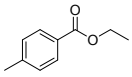
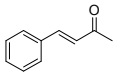
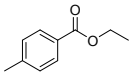
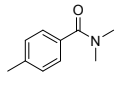
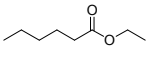
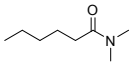
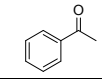
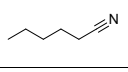
[a]Yields were determined by GC using authentic samples.

2.2. Chemoselective reduction of aldehydes and ketones over carboxylic acid derivatives.

Based on the results shown in Table 1, we chose PDBBA for functional group screening studies. Accordingly, a series of aldehydes and ketones (aromatic, aliphatic, and conjugated) was treated with PDBBA in the presence of ester, amide, and nitrile functional groups. Table 2 shows that excellent conversion was achieved for all the studied aldehydes and ketones to the corresponding alcohols at ambient temperature. A high degree of chemoselectivity was achieved with both aromatic and aliphatic functional groups. Further, conjugated aldehydes and ketones also smoothly underwent selective reduction with PDBBA (entries 1–14 in Table 2).

Table 2. Chemoselective reduction of aldehydes and ketones over several carboxylic acid derivatives

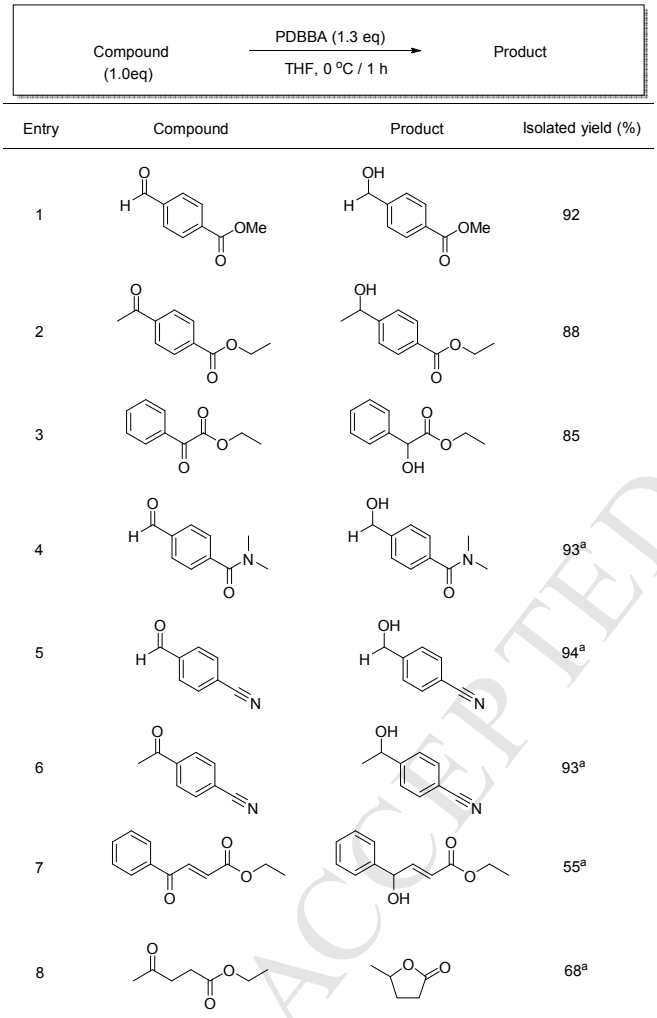


Entry	Substrate	Carboxylic acid derivatives	Yield(%)[a] Substrate S.M / ROH	Carboxylic acid derivatives S.M / RCHO / ROH
1			0 /100	99 / 0 / 0
2			0 /99	99 / 0 / 0
3			0 / 97	99 / 0 / 0
4			0 /99	99 / 0 / 0
5			0 / 98	100 / 0 / 0
6			0 / 99	98 / 0 / 0
7			9 / 91	99 / 0 / 0
8			0 / 99	99 / 0 / 0
9			0 / 99	99 / 0 / 0
10			0 / 92	99/ 0 / 0
11			0 /99	99 / 0 / 0
12			0 / 98	100 / 0 / 0
13			0 / 99	98 / 0 / 0
14			5 / 94	99 / 0 / 0

[a]Yields were determined by GC using authentic samples.

Next, the chemoselective reduction of aldehydes and ketones was performed in multifunctionalized compounds (Table 3). Accordingly, substrates containing ester, amide, and nitrile moieties along with aldehydes or ketones were reduced using PDBBA under optimized conditions (0 °C, 30 min). As expected, the aldehydes and ketones furnished the corresponding primary and secondary alcohols with good yields (88–94%) in the presence of other tested functional groups (entries 1–6 in Table 3). An α,β-unsaturated ketone having an ester moiety, ethyl (*E*)-4-oxo-4-phenylbut-2-enoate was treated with PDBBA. This reaction results in formation of a mixture of products which upon purification leads only to the isolation of the major product 4-oxo-4-phenylbut-2-enoate in 55% yield (entry 7 in Table 3). For 4-oxopentanoate, the corresponding lactone was produced after reduction followed by *in situ* cyclization in 68% yield (entry 8 in Table 3).

Table 3. Chemoselective reduction of multifunctionalized compounds with PDBBA



Entry	Compound	Product	Isolated yield (%)
1			92
2			88
3			85
4			93[a]
5			94[a]
6			93[a]
7			55[a]
8			68[a]

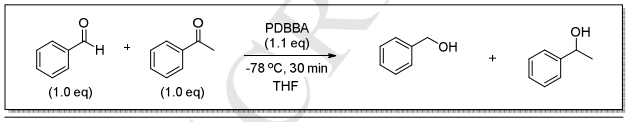
[a] PDBBA used 1.5 eq.

2.3. Chemoselective reduction of aldehydes over ketones

Under optimized conditions, aldehydes and ketones were reduced chemoselectively using PDBBA in the presence of ester, tertiary amide, and nitrile functional groups with good to excellent conversion at 0 °C for 30 min (by GC). Next, we probed the chemoselective reduction of aldehydes in the presence of ketones. Accordingly, benzaldehyde (1 mmol) and acetophenone (1 mmol) were treated with PDBBA under the optimized conditions. However, we could not obtain significant selectivity for the reduction of the aldehyde over the ketone under these conditions (a 1:1 ratio of primary and secondary alcohols was obtained). Therefore, further optimization was required to achieve better selectivity. We assumed that the reduction of the aldehyde in the presence of the ketone was mainly influenced by the temperature and solvent. To confirm this, we performed a model reaction using benzaldehyde (1 mmol) and acetophenone (1 mmol) with PDBBA for 30 min at −78 °C. From the ^{1}H NMR spectra, it was observed that, even at −78 °C with 5 mL THF, the reduction furnished primary and secondary alcohols in 84% and 11% yields, respectively.

Next, the volume of solvent was increased, and the ratio of the primary and secondary alcohols was measured. Surprisingly, upon increasing the volume of THF (10 mL), formation of the secondary alcohol was not observed, and a stoichiometric conversion to the primary alcohol was obtained (Table 4).

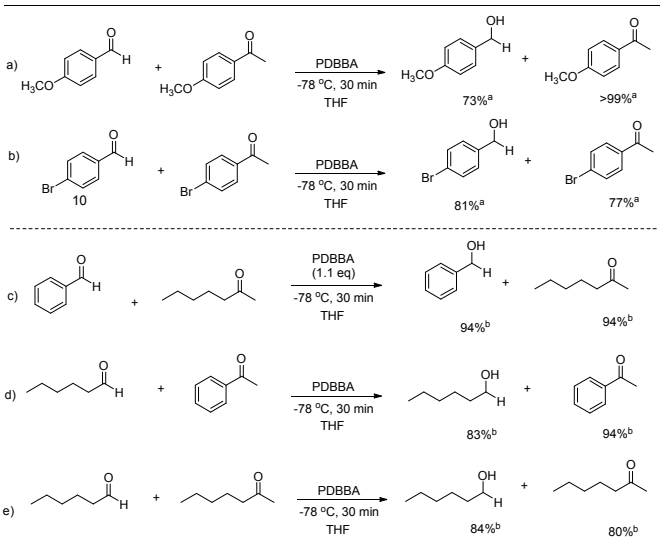
Table 4. Optimization of solvent for chemoselective reduction of aldehyde over ketone.



Entry	THF (ml)	Yield(%)[a] Primary alcohol	:	Secondary alcohol
1	5	84	:	11
2	10	>99	:	0

[a]Yields were determined by ^{1}H NMR using internal standard.

Using these modified conditions, we elaborated the scope of the chemoselective reduction of various aldehydes in the presences of ketones (Scheme 2). Electron-rich and -deficient aldehydes were treated with PDBBA, affording good to excellent selectivities with reasonable yields (73% and 81%, respectively, for entries a and b in Scheme 2). An aromatic aldehyde (benzaldehyde) was successfully reduced to the corresponding alcohol with a high degree of selectivity in the presence of the aliphatic ketone heptan-2-one (94%, entry c in Scheme 2). Next, an aliphatic aldehyde (hexanal) was smoothly and selectively reduced in the presence of either aromatic or aliphatic ketones, furnishing the primary alcohol in good yield (83% and 84%, entries d and e in Scheme 2).

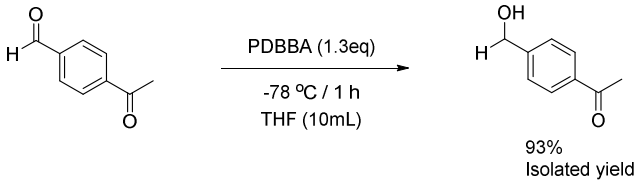


[a]Yields were determined by ^{1}H NMR using internal standerd. [b]Yields were determined by GC using authentic samples.

Scheme 2. Intermolecular chemoselective reduction of aldehydes over ketones with PDBBA.

These results encouraged us to carry out the intramolecular chemoselective reduction of 4-acetylbenzaldehyde (Scheme 3).

We easily obtained the desired product in 93% yield, suggesting that PDBBA can be an alternative chemoselective reducing agent for aldehydes over ketones.



Scheme 3. Intramolecular chemoselective reduction of 4-acetylbenzaldehyde with PDBBA

3. Conclusion

In summary, we have demonstrated that recently prepared *t*-butoxy derivatives of DIBALH, such as LDBBA, SDBBA, and PDBBA, can be used as chemoselective reducing agents for aldehydes and ketones in the presence of esters. From the experimental results, we concluded that PDBBA was the most efficient and selective reagent among the reagents studied herein. In addition, higher chemoselectivity was achieved with the modified DIBALH-based reducing agents (LDBBA, SDBBA, and PDBBA) than those obtained with commercial reducing agents. Furthermore, the value of this approach lies in the selective reduction of aldehydes in the presence of ketones using the modified reaction conditions. Therefore, the readily prepared novel reagent (PDBBA) seems to be a valuable alternative to existing hydride reagents.

4. Experimental

4.1 General methods

All glassware used was dried thoroughly in an oven, assembled hot, and cooled under a stream of dry nitrogen prior to use. All reactions and manipulations of air- and moisture sensitive materials were carried out using standard techniques for the handling of air-sensitive materials. All chemicals were commercial products of the highest purity which were further purified before use by standard methods. THF was dried over sodium-benzophenone and distilled. DIBALH, esters, aldehydes, and alcohols were purchased from Aldrich Chemical Company, Alfa Aesar and Tokyo Chemical Industry Company (TCI). ^{1}H-NMR spectra were measured at 400 MHz with $CDCl_3$ as a solvent at ambient temperature unless otherwise indicated and the chemical shifts were recorded in parts per million downfield from tetramethylsilane (δ = 0 ppm) or based on residual $CDCl_3$ (δ = 7.26 ppm) as an internal standard. ^{13}C NMR spectra were recorded at 100 MHz with $CDCl_3$ as a solvent and referenced to the central line of the solvent (δ = 77.0 ppm). The coupling constants (J) are reported in Hertz. Analytical thin-layer chromatography (TLC) was performed on glass precoated with silica gel (Merck, silica gel 60 F254). Column chromatography was carried out using 70–230 mesh silica gel (Merck) at normal pressure. GC analyses were performed on a Younglin Acme 6100GC and 6500GC FID chromatography, using an HP-5 capillary column (30m). All GC yields were determined with the use of naphthalene as internal standard and authentic samples.

4.2 Preparation of PDBBA

A dry and argon-flushed flask, equipped with a magnetic stirring bar and a septum, was charged with potassium *t*-butoxide (5.89 g, 52.5 mmol) and 50 mL THF. After cooling to 0 °C, DIBALH (50 mL, 1.0 M in hexane, 50 mmol) was added dropwise and stirred for 2 h at room temperature to give a colorless homogeneous solution. The concentration of PDBBA solution in THF-hexane was measured gasometrically by hydrolysis of an aliquot of the solution with a hydrolyzing mixture of *t*-butyl alcohol-THF (1:1) at 0 °C.

4.3 Determination of PDBBA concentration by gas burette experiment

The concentration of the prepared reducing agent (PDBBA) was measured using a gas burette apparatus as the following procedure.

A two necked round bottom flask with condenser was connected to gas burette using a laboratory Tygon tube. All the joints were double-sealed with vacuum grease and para-films. After argon gas was introduced into the measuring apparatus through round bottom flask for 5 minutes (total apparatus was filled with argon), a solution of *t*-butanol and THF in 1:1 ratio was added to the reaction vessel. To this 1 mmol of PDBBA was added with continuous stirring. The amount of hydrogen gas liberated was measured to determine the concentration of the PDBBA (experiment was repeated 3 times for consistent results).

4.4 Chemoselective reduction of aldehydes and ketones with PDBBA (Table 1 and 2)

A dry and argon-flushed flask, equipped with a magnetic stirring bar and a septum, was charged with aldehyde or ketone (0.5 mmol), carboxylic acid derivative (0.5 mmol) and 5 mL THF. After cooling to 0 °C, PDBBA (0.55 mmol) was added dropwise and stirred for 30 min at same temperature. The reaction was stopped by the addition of aqueous 1 N HCl (5 mL) and extracted with diethyl ether (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and GC analysis. All products in Table 2 were confirmed through comparison with GC data of authentic sample.

4.5 Chemoselective reduction of dicarbonyl compounds with PDBBA (Table 3)

A dry and argon-flushed flask, equipped with a magnetic stirring bar and a septum, was charged with dicarbonyl compound (1.0 mmol) and 10 mL THF. After cooling to 0 °C, PDBBA (1.3 mmol) was added dropwise and stirred for 1 h at same temperature. The reaction was stopped by the aqueous 1 N HCl (10 mL) and extracted with diethyl ether (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel afforded the desired product.

Methyl 4-(hydroxymethyl)benzoate (1): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.02 (2H, d, *J* = 8.2 Hz), 7.43 (2H, d, *J* = 8.0 Hz), 4.76 (2H, d, *J* = 5.9 Hz), 3.90 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.0, 146.0, 129.9, 129.4, 126.5, 64.81, 52.2; HRMS (EI^+): calcd for $C_9H_{10}O_3$, 166.0630; found 166.0630.

Ethyl 4-(1-hydroxyethyl)benzoate (2): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.99-7.91 (2H, m), 7.43-7.34 (2H, m), 4.94-4.83 (2H, m), 4.36-4.27 (2H, m), 1.49-1.40 (3H, m), 1.41-1.30 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.6, 151.0, 129.8, 125.3, 69.9, 61.0, 25.3, 14.3; HRMS (EI^+): calcd for $C_{11}H_{14}O_3$, 194.0943; found 194.0944.

Ethyl 2-hydroxy-2-phenylacetate (3): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.44-7.29 (5H, m), 5.15 (1H, s), 4.31-4.10 (2H, m), 1.21 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.8, 138.4, 128.6, 128.5, 126.6, 72.9, 62.3, 14.1; HRMS (EI^+): calcd for $C_{10}H_{12}O_3$, 180.0786; found 180.0788.

4-(Hydroxymethyl)-*N*,*N*-dimethylbenzamide (4): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.30-7.18 (4H, m), 4.57 (2H, s), 3.79 (1H, s), 3.04 (3H, s), 2.91 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.9, 143.3, 134.6, 127.1, 126.4, 64.2, 39.7, 35.4; HRMS (EI^+): calcd for $C_{10}H_{13}NO_2$, 179.0946; found 179.0942.

4-(Hydroxymethyl)benzonitrile (5): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.54 (2H, d, *J* = 8.0 Hz), 7.40 (2H, d, *J* = 8.0 Hz), 4.68 (2H, s), 3.24 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.7, 132.3, 127.0, 119.0, 110.6, 63.9; HRMS (EI^+): calcd for C_8H_7NO, 133.0528; found 133.0525.

4-(1-Hydroxyethyl)benzonitrile (6): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.58 (2H, d, *J* = 8.2 Hz), 7.45 (2H, d, *J* = 8.6 Hz), 4.91 (1H, q, *J* = 6.3 Hz), 2.66 (1H, s), 1.44 (3H, dd, *J* = 6.5, 0.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.4, 132.3, 126.1, 119.0, 110.8, 69.6, 25.4; HRMS (EI^+): calcd for C_9H_9NO, 147.0684; found 147.0688.

Ethyl (*E*)-4-hydroxy-4-phenylbut-2-enoate (7): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.41-7.27 (5H, m), 7.04 (1H, dd, *J* = 15.6, 4.8 Hz), 6.16 (1H, dd, *J* = 15.6, 1.7 Hz), 5.39-5.32 (1H, m), 4.18 (2H, q, *J* = 7.1 Hz), 2.14 (1H, d, *J* = 3.8 Hz), 1.27 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5, 148.4, 140.9, 128.9, 128.5, 126.6, 120.3, 73.9, 60.6, 14.3; HRMS (EI^+): calcd for $C_{12}H_{14}O_3$, 206.0943; found 206.0947.

5-Methyldihydrofuran-2(3H)-one (8): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.43-4.23 (1H, m), 2.32-2.14 (2H, m), 2.13-1.98 (1H, m), 1.62-1.45 (1H, m), 1.08 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.2, 77.1, 29.4, 28.8, 20.7; HRMS (EI^+): alcd for $C_5H_8O_2$, 100.0524; found 100.0524.

4.6 Chemoselective reduction of 4-acetylbenzaldehyde (Scheme 2)

A dry and argon-flushed flask, equipped with a magnetic stirring bar and a septum, was charged with 4-acetylbenzaldehyde (0.13 mL, 1.0 mmol) and THF (10 mL). After cooling to −78 °C, PDBBA (1.3 mmol) was added dropwise and the mixture was stirred for 1 h at the same temperature. The reaction was stopped aqueous 1 N HCl (10 mL) and extracted with diethyl ether (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel yielded 1-(4-(hydroxymethyl)phenyl)ethan-1-one (139 mg, 93%).

1-(4-(Hydroxymethyl)phenyl)ethan-1-one : ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.86 (2H, d, *J* = 8.6 Hz), 7.38 (2H, d, *J* = 8.6 Hz), 4.70 (2H, s), 2.53 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.4, 146.6, 136.1, 128.6, 126.6, 64.4, 26.7; HRMS (EI^+): calcd for $C_9H_{10}O_2$, 150.0681; found 150.0682.

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