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Lithium *tert*-Butoxide-catalyzed Hydroboration of Carbonyl Compounds

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We report the successful hydroboration of aldehydes and ketones with pinacolborane using 1 mol % lithium *tert*-butoxide under ambient conditions. The present protocol was applicable to various aldehydes and ketones, and the corresponding boronate esters and subsequent alcohols were obtained in good to excellent yields. In addition, this high-yielding practical method could be extended to the reduction of ester groups. Under optimized conditions, LiO^tBu facilitate the hydroboration of ester groups quantitatively.

Keywords: Hydroboration, Lithium *tert*-butoxide, Aldehydes, Ketones, Esters, Pinacolborane (HBpin)

Introduction

In recent years, hydroboration reactions have gained much attention because of their simplicity and mildness as well as the practical application of resulting boron derivatives.[1] Moreover, a diverse range of catalytic systems toward hydroboration of carbonyl compounds, including transition metals,[2] main group metals,[3] lanthanide complexes,[4] and acid–base pairs have been investigated.[5] More recently, mild reagents such as commercial metal alkyls, alkoxides, and hydride reducing agents have been identified as catalysts for the efficient hydroboration of aldehydes and ketones.

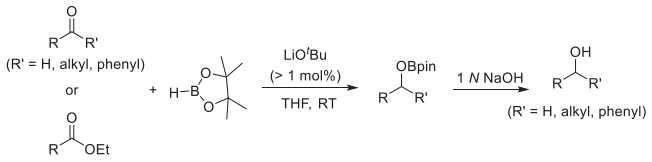
Clark *et al*. reported the alkoxide (NaO^tBu)-mediated hydroboration of ketones with pinacolborane and achieved complete reduction with 5 mol % catalyst loading.[6] More recently, Wu *et al*.[7] reported that hydroboration of aldehydes and ketones with powdered NaOH as catalyst and HBpin. Wu and coworkers reported the use of a cobalt(II) coordination polymer and KO^tBu as the activator to catalyze the hydroboration of aldehydes and ketones.[8] We previously developed an effective method for the selective hydroboration of aldehyde over ketones with sodium hydride (NaH).[9] Stachowiak *et al*.[10] reported the solvent- and catalyst-free hydroboration of aldehydes, but this method was not feasible to other carbonyl compounds. Zhu *et al*.[11] described the selective hydroboration of aldehydes and ketones using *n*-butyllithium as catalyst, thus confirming the importance of the present transformation. Each of these catalytic systems has its specific advantages in terms of yields and selectivities.

On the other hand, the preparation of alcohols from ester has been encountered during the chemical transformation of many complex natural molecule syntheses.[12] Traditional reduction systems using highly reactive metal hydrides ($LiAlH_4$, $LiBH_4$)[13] require stoichiometric amount of reagents, while metal-mediated hydrogenation requires high pressure and temperatures.[14] Therefore, metal-catalyzed hydro-functionalization (hydrosilylations/hydroboration) under ambient conditions would be most useful, and several metal-mediated hydrosilylations have been reported for ester reduction.[15] However, there are very few examples of catalyzed hydroborations for esters.[16]

Given the synthetic utility of the abovementioned transformation (hydroboration of aldehydes, ketones, and esters) and successful recent findings in this regard, we attempted to understand the effect of counter metal cation (Li^+) on catalytic hydroboration. Herein, we wish to report the lithium *tert*-butoxide (LiO^tBu) mediated hydroboration of aldehydes, ketones, and esters (Scheme 1).

Results and Discussion

First, we optimized various reaction parameters such as catalyst load, number of equivalents of the reagent (HBpin), and reaction time for aldehyde hydroboration. The results are summarized in Table 1. Accordingly, benzaldehyde was treated with 1 mol % LiO^tBu and 1.3 equiv. HBpin in THF (entry 1), and complete conversion of the aldehyde occurred in 30 min (>99%). Further, 96% conversion was achieved when the reaction was carried out with 0.5 mol % LiO^tBu (entry 2). A similar conversion (96%) was afforded with 1 mol % catalyst loading within 5 min reaction (entry 3). Up on decreasing the amount of pinacolborane (1.1 equiv), no deviation in stochiometric conversion of aldehyde was found, observed 83% of boronate ester in GC (entry 4). We mainly focused on the stochiometric conversion of benzaldehyde to the corresponding boronate ester, hence we chose the conditions corresponding to entry 1 as the optimal conditions. Further, we optimized the



Scheme 1. LiO^{t}Bu catalyzed hydroboration of aldehydes, ketones, and esters

conditions for the reaction of ketone (acetophenone), which was perfectly reduced to corresponding boronate ester with 1.3 equiv HBpin and 1 mol % LiO^{t}Bu (entry 5).

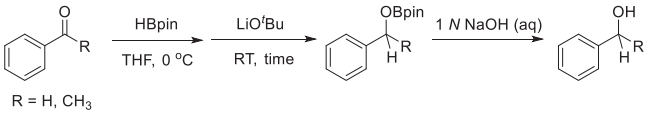
With the optimized conditions in hand, we next focused on the reduction of various aldehyde and ketones to the corresponding boronate esters, followed by conversion to the subsequent alcohols (Table 2). All the tested substrates underwent the hydroboration smoothly to allow for complete conversion of the aldehydes/ketones. Electron-withdrawing substrates were furnished stoichiometric yields, compare to electron donating ones. Heteroaryl (furan-2-carbaldehyde), conjugated (cinnamaldehyde), and aliphatic (hexanaldehyde) aldehydes also successfully underwent hydroboration with 1 mol % LiO^{t}Bu (entries 8–10). Various ketones (benzophenone, acetophenone, 4-nitro acetophenone, and cyclohexanone) were also converted smoothly, and the hydroboration proceeded stoichiometrically under similar conditions (entries 11–14).

Given the rapid hydroboration of aldehyde and ketones, we next turned our interest to the reduction of an ester group. Accordingly, the reaction conditions were optimized to achieve the maximum yield and conversion. As seen in Table 3, ethyl benzoate was treated with pinacolborane in the presence of 30 mol % LiO^{t}Bu to obtain the corresponding alcohol in 74% yield (entry 1). A similar yield was obtained when reaction time was increased (entry 2). Prior to achieving the maximum conversion, the catalyst load was slightly increased. A high yield of 99% was obtained when 0.4 equiv of the catalyst used (entry 4). Reducing the mole ratio of pinacolborane from 3.0 to 2.5 equiv reduced the yield of the alcohol to 85% (entry 5). Under reflux conditions, stoichiometric conversion was achieved with 0.3 equiv (30 mol %) of LiO^{t}Bu (entry 6). Nevertheless, a reasonable yield of the product was obtained when reaction was carried out under reflux condition with 0.2 equiv of the catalyst (89% entry 7). From the above data, we concluded that 0.4 equiv (40 mol %) of LiO^{t}Bu and 3.0 equiv of pinacolborane are required for stoichiometric hydroboration of the ester group at room temperature.

Given the successful hydroboration of ethyl benzoate, we explored the optimized conditions for expanding the substrate scope with various ester groups. The results are shown in Table 4. Most of the esters we considered were amenable to the present system and underwent quantitative conversion to the corresponding alcohols. Isopropyl benzoate reduced quantitatively under reflux condition (entry 2). While *tert*-butyl benzoate did not undergo the hydroboration due to its bulky nature (entry 3). Aromatic esters with electron-donating/electron-withdrawing substituents showed similar reactivity in this system. Polyaromatic and heteroaromatic esters reacted with pinacolborane to afford the corresponding alcohols in excellent yields (entries 11 and 12). Further, an aliphatic ester (ethyl hexanoate) smoothly underwent the catalytic hydroboration and afforded corresponding alcohol in good yield (entry 13).

Finally, chemoselective reduction was conducted for aldehyde in the presence of an ester. Accordingly, benzaldehyde was treated with pinacolborane over ethyl benzoate with excellent chemoselectivity (Scheme 2).

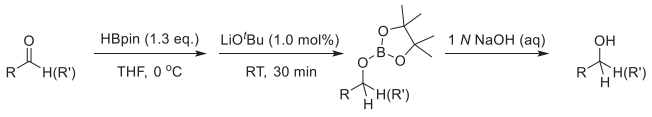
Table 1. Optimization of reaction conditions for hydroboration of aldehyde and ketones



Entry	R	Reaction condition			Conversion(%)[a] (alcohol)	Yield(%)[b]
		HBpin	LiO^{t}Bu	Time		
1	H	1.3	1.0 mol %	30 min	99 (0)	99
2	H	1.3	0.5 mol %	30 min	96 (0)	95
3	H	1.3	1.0 mol %	5 min	96 (0)	94
4	H	1.1	1.0 mol %	30 min	99 (16)	99
5[c]	CH_3	1.3	1.0 mol %	30 min	99 (0)	99

[a] Conversions were determined on the basis of the consumption of the aldehyde or ketone.
[b] Yields were determined by GC.
[c] Yields were determined by ^{1}H NMR.

Table 2. Scope of the hydroboration of aldehydes and ketones mediated by 1 mol % LiO^{t}Bu



Entry	Aldehydes	Conversion[a]	Product	Yield(%)[b]
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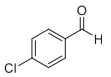
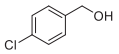
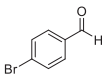
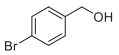
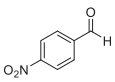
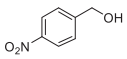
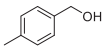
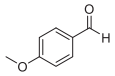
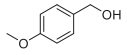
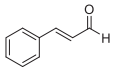
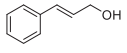
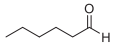
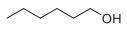
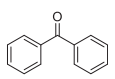
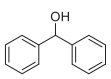
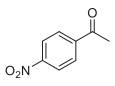
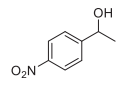
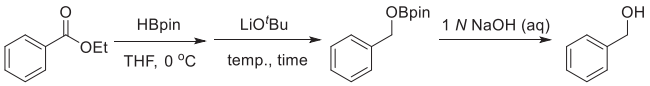
2		94		94
3		99		90
4		99		90
5		99		89
6		88(35)		88
7		79 (17)		79
8[c]		99		97
9		99		99
10		99		99
11[c]		99		99
12[c]		99		99
13[c]		99		99
14[c]		99		99

[a] Conversions were determined on the basis of the consumption of the aldehyde or ketone.
[b] Yields were determined by GC.
[c] Yields were determined by ^{1}H NMR.

Conclusion

In conclusion, we have identified an efficient catalytic system for the hydroboration of aldehydes and ketones under ambient condition. Experimental results showed that 1 mol % LiO^{t}Bu successfully enabled the hydroboration of various aldehydes and ketones with stoichiometric conversion. In addition, suitable reaction conditions for the hydroboration of esters were established. This method is a practical alternative to existing complex metal systems and is the best addition to the existing literature on catalyzed hydroboration.

Table 3. Optimization of parameters for hydroboration of ester group



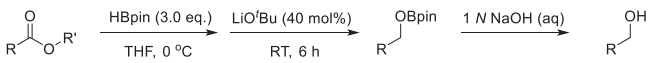
	Reaction condition				
Entry	HBpin	LiO^{t}Bu (mol %)	Time	Temp.	Yield(%)[a]
1	3.0	30	6 h	RT	74
2	3.0	30	12 h	RT	73
3	3.0	40	3 h	RT	97
4	3.0	40	6 h	RT	99
5	2.5	40	6 h	RT	85
6	3.0	30	3 h	reflux	99
7	3.0	20	24 h	reflux	89

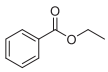
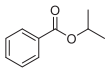
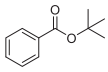
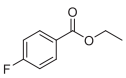
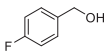
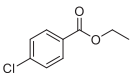
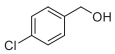
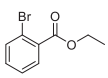
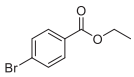
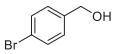
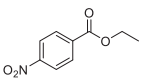
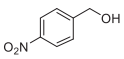
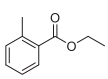
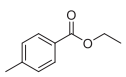
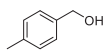
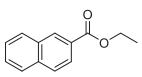
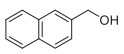
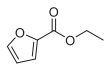
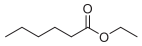
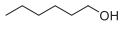
[a] Yields were determined by GC.

Experimental

General. 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 such materials. All chemicals were commercial products of the highest purity which were further purified before use by using standard methods. HBpin, aldehydes, and ketones were purchased from Aldrich Chemical Company (Seoul, Korea), Alfa Aesar (Lancashire, UK), and Tokyo Chemical Industry Company (TCI, Tokyo, Japan). ^{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 the 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 (60 F^{254}; Merck, Darmstadt, Germany). Column chromatography was carried out using 70–230 mesh silica gel (Merck) at normal pressure. GC analyses were performed on a Younglin Acme 6100 M and 6500 GC FID chromatography (Seoul, Korea), using an

Table 4. Scope of hydroboration of esters mediated by LiO^{t}Bu

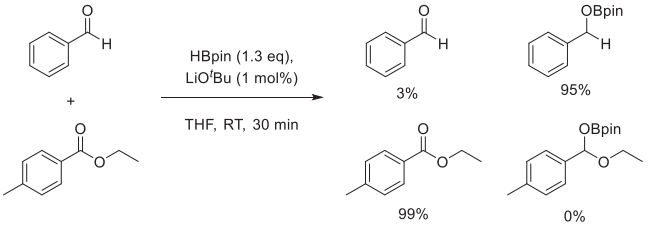


Entry	Esters	Conversion[a]	Product	Yield (%)[b]
1		99		99
2[c]		96		96
3[d]		0		0
4[e]		99		99
5[e]		99		99
6[e]		99		99
7		99		99
8[e]		99		99
9[e]		99		99
10[e]		99		99
11[f]		99		99
12[e]		99		96
13		99		90

[a] Conversions were determined on the basis of the consumption of the ester.
[b] Yields were determined by GC.
[c] Reflux 3 h.
[d] Reflux 24 h.
[e] Yields were determined by ^{1}H NMR.
[f] Reaction time was 12 h.

HP-5 capillary column (30 m). All GC yields were determined with the use of naphthalene as the internal standard and the authentic sample.

General Procedure for the Catalyzed Hydroboration of Aldehydes and Ketones. The following experimental procedure for the synthesis of benzyl alcohol is representative (Table 2). A dry and argon-flushed flask, equipped with a magnetic stirring bar was charged with benzaldehyde (0.05 mL, 0.5 mmol), pinacolborane (0.09 mL, 0.65 mmol), and 5 mL of THF at 0 °C. To this, LiO^{t}Bu (0.1 mL 0.05 M in THF, 1 mol %) was added dropwise and stirred for 30 min at room temperature. After completion of the reaction (GC), it was stopped by H_2O (two drops). GC analysis showed 99% of 2-(benzyloxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. To the reaction mixture was added 1 N NaOH (2 mL) and stirred for 1 h at room temperature. The crude mixture was extracted with diethyl ether (2 × 10 mL) and combined organic layers were dried over $MgSO_4$. GC analysis showed a 99% yield of benzyl alcohol. All products in Table 2 were confirmed through comparison with ^{1}H NMR and GC data of the authentic sample.



Scheme 2. LiO^{t}Bu catalyzed hydroboration of aldehyde over an ester

General Procedure for the Catalyzed Hydroboration of Esters. The following experimental procedure for the synthesis of benzyl alcohol from ethyl benzoate is representative (Table 4). A dry and argon-flushed flask, equipped with a magnetic stirring bar was charged with ethyl benzoate (0.07 mL, 0.5 mmol), pinacolborane (0.22 mL, 1.5 mmol), and 5 mL of THF at 0 °C. To this, LiO^{t}Bu (0.4 mL 0.5 M in THF, 1 mol %) was added dropwise and stirred for 30 min at room temperature. After completion of the reaction (GC), it was stopped by H_2O (two drops). GC analysis showed 99% of 2-(benzyloxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. To the reaction mixture was added 1 N NaOH (2 mL) and stirred for 1 h at room temperature. The crude mixture was extracted with diethyl ether (2 × 10 mL) and combined organic layers were dried over $MgSO_4$. GC analysis showed a 99% yield of benzyl alcohol. All products in Table 4 were confirmed through comparison with ^{1}H NMR and GC data of the authentic sample.

Procedure for the Chemoselective Catalytic Hydroboration of Benzaldehyde over Ethyl 4-Methylbenzoate. A dry and argon-flushed flask, equipped with a magnetic stirring bar was charged with benzaldehyde (0.05 mL, 0.5 mmol), ethyl 4-methylbenzoate (0.08 mL, 0.5 mmol), pinacolborane (0.09 mL, 0.65 mmol), and 5 mL of THF at room temperature. To this, LiO^{t}Bu (0.1 mL 0.05 M in THF, 1 mol %) was added dropwise and stirred for 30 min at the same temperature (Scheme 1). After completion of the reaction, it was stopped by H_2O (two drops). GC analysis showed 95% of 2-(benzyloxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and 99% of ethyl 4-methylbenzoate.

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