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n-Butyllithium (1 mol %)-catalyzed Hydroboration of Aldehydes and Ketones with Pinacolborane

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A practical and efficient protocol for the hydroboration of aldehydes and ketones using a pinacolborane and alkyl lithium system is demonstrated. A systematic evaluation showed that 1 mol % *n*-butyllithium afforded catalyzed hydroboration of aldehydes and ketones in a short reaction time under ambient conditions. Excellent yield, functional group tolerance, short reaction time, low catalyst loading, and gram-scale synthesis are the salient features of the proposed protocol.

Keywords: Catalyzed hydroboration, *n*-Butyllithium, Aldehydes and ketones, Pinacolborane

Introduction

Hydroboration is an important and fundamental reaction system in organic chemistry for the reduction of unsaturated, carbonyl compounds (C═C, C═O, and C═N bonds).[1] Traditional reduction systems using active hydrides (like $LiAlH_4$) suffer from low functional group selectivity and reduce all functional groups with comparatively less yields; whereas, hydroboration using comparatively lower reductants (*i.e.*, pinacolborane [HBpin] or catecholborane) can be considered as a suitable alternative whose activity could be considerably increased catalytically.[2] In addition, the organoboranes obtained from hydroboration are remarkably valuable precursors for various chemical transformations and have tolerance for a wide range of functional groups.[3] At present, research on the catalyzed hydroboration of carbonyl compounds like aldehydes and ketones is continuously increasing, leading to its rapid application with transition metals,[4] main group-alkaline earth elements,[5] lanthanide complexes,[6] and Lewis acid/Lewis acid–base pairs.[7]

Along with the above literature, thorough investigations with readily available convenient reagents and simplification of reaction protocols have led to a new era in the field of catalyzed hydroboration. Consequently, commercially available mild reagents are being utilized as catalysts. For example, Clark *et al.*[5k] reported the sodium *tert*-butoxide-mediated (Na^tOBu) reduction of ketones using HBpin at ambient temperature. Recently, Yile Wu *et al.*[8] have reported the catalyzed hydroboration of aldehydes and ketones initiated by powdered NaOH with HBpin using a deuterated solvent and have stated the importance of nucleophilic coordination[9] with HBpin using natural bond orbital (NBO) calculations. More recently, Stachowiak *et al.*[10] have described the hydroboration of aldehydes under solvent- and catalyst-free conditions; however, this method is applicable only to aldehydes.

Despite remarkable progress over the last few years, there is still a need for eco-friendly and effective protocols. Given our interest in finding mild and selective reduction systems, we have made efforts to identify a sustainable condition for catalyzed hydroboration without the use of toxic and costly metal complexes.[11] Here, we report the hydroboration of aldehydes and ketones using HBpin catalyzed by 1 mol % commercial *n*-butyllithium in a batch system (Scheme 1). While this manuscript was in preparation, Zhangye Zhu's group reported *n*-butyllithium-catalyzed selective hydroboration of aldehydes and ketones,[12] confirming the potential of the present transformation (Scheme 1).

Results and Discussion

First, the catalyst scope and loading amounts were investigated for benzaldehyde hydroboration in THF. As shown in Table 1, when the hydroboration of benzaldehyde was performed with 0.1 mol % *n*-butyllithium in THF, 50% of the starting aldehyde remained after reaction for 3 h (entry 2 in Table 1). An increased conversion was observed with 0.5 mol % *n*-butyllithium (86% alcohol yield, entry 5 in Table 1). Next, the catalyst load was slightly increased such that the entire quantity of aldehyde was consumed. To our surprise, 1 mol % *n*-butyllithium afforded excellent conversion in 5 min of reaction time at 0 °C and room temperature (>99% conversion, entries 6 and 7 in Table 1).

Next, the other alkyl lithium catalysts were screened; accordingly, 1 mol % MeLi and *t*-BuLi were treated with benzaldehyde, and they afforded alcohol yields of 74 and 79%, respectively (entries 8 and 9 in Table 1). To determine the best solvent, hexane, toluene, diethyl ether, and dichloromethane were tested. Except toluene, the other

Scheme 1. *n*-Butyllithium-catalyzed hydroboration of aldehydes and ketones.

solvents furnished a moderate conversion (entries 10–13 in Table 1). Based on the above study, the optimal catalyst loading for benzaldehyde reduction was 1 mol % *n*-butyllithium in THF solvent.

After determining the suitable conditions, the substrate scope was investigated using various aldehydes including aromatic (hetero) and aliphatic substrates. As shown in Table 2, most aldehydes smoothly underwent hydroboration with excellent conversion in a short reaction time. Irrespective of the electronic nature, all the tested aldehydes with electron-donating/electron-withdrawing substrates underwent effective catalyzed hydroboration with 1 mol % *n*-butyllithium. Furthermore, the hetero- and polyaromatic aldehydes afforded excellent yields of corresponding alcohols (>99%). The conjugated aldehyde (cinnamaldehyde) underwent a 1,2-reduction (entry 13 in Table 2). Interestingly, the aliphatic aldehydes containing acidic hydrogen were also tolerant to *n*-butyllithium (1 mol %) under the proposed hydroboration (entries 14 and 15 in Table 2).

Then, to explore the catalytic ability, suitable ketones were screened for catalyzed hydroboration. As shown in Table 3, all the tested ketones furnished corresponding alcohols with excellent conversion under 1 mol % catalyst loading. Similar to the aldehydes, all the tested ketones with electron-donating/electron-withdrawing, heteroaromatic, and conjugated substrates smoothly underwent catalyzed hydroboration in a short reaction time. In addition, the aliphatic ketones showed excellent conversion.

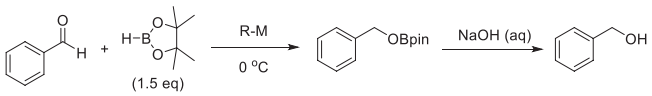
The chemoselective hydroboration of aldehydes and ketones was also investigated. As shown in Table 4, benzaldehyde selectively underwent catalyzed hydroboration in the presence of ester, amide, and nitrile functional groups. Similarly, a ketone (cyclohexanone) underwent selective hydroboration in the presence of an ester group (entries 1–4 in Table 4).

Finally, the potential of the present method was determined using a scale-up reaction. Accordingly, 10 mmol batches of 4-bromobenzaldehyde and 1-(4-bromophenyl) ethan-1-one were treated with 1 mol % *n*-butyllithium and HBpin in THF solvent; excellent conversion with good halogen tolerance was achieved (Scheme 2).

Conclusion

In summary, we have developed an efficient and environmentally benign protocol for the catalyzed hydroboration of aldehydes and ketones using 1 mol % *n*-butyllithium. This rapid method enabled all the tested aldehydes and ketones to complete catalyzed hydroboration with excellent conversion. The proposed system is economical (low catalyst loading), has a short reaction time, and allows gram-scale synthesis, making it a robust method and valuable addition to the existing literature on catalyzed hydroboration.

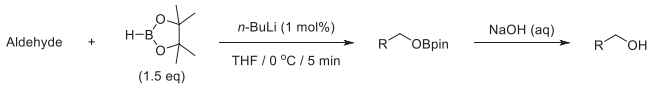
Table 1. Evaluation of reaction parameters for catalyzed hydroboration of benzaldehyde.

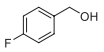
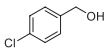
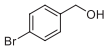
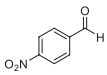
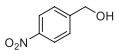
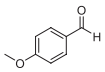
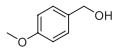
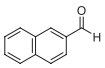
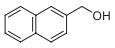
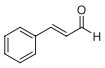
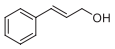
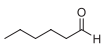
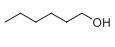
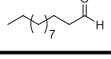
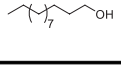


Entry	R–M	*n* (mol %)	Solvent	Time (min)	Conv.[a] (%) (SM)	Yield[b] (%) ROH/SM
1		None	THF	12 h	0 (99)	0/99
2	*n*-BuLi	0.1	THF	180	45 (54)	45/54
3	*n*-BuLi	0.5	THF	5	82 (17)	82/17
4	*n*-BuLi	0.5	THF	60	86 (13)	86/13
5	*n*-BuLi	0.5	THF	180	86 (13)	86/13
6	*n*-BuLi	1	THF	5	99 (0)	99/0
7[c]	*n*-BuLi	1	THF	5	99 (0)	99/0
8	MeLi	1	THF	5	78 (22)	74/25
9	*t*-BuLi	1	THF	5	85 (14)	79/20
10	*n*-BuLi	1	Hexane	5	57 (42)	57/42
11	*n*-BuLi	1	Toluene	5	31 (69)	30/69
12	*n*-BuLi	1	Ether	5	54 (45)	54/45
13	*n*-BuLi	1	MC	5	71 (28)	71/28

[a] Conversion was determined by an area ratio of GC.
[b] Yields were determined by GC.
[c] Reacted at room temperature.

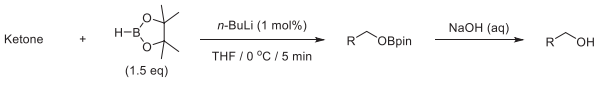
Table 2. Substrate scope for aldehyde hydroboration with 1 mol % *n*-BuLi.

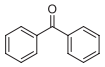
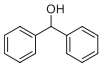
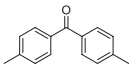
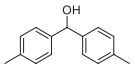
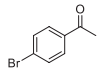
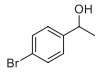


Entry	Aldehyde	Product	Yield[a] (%) (RCHO)
1			99
2			99
3			99
4[b]			99
5			99
6			99
7[c]			99
8[c]			99
9[c]			99
10[c]			99
11[d]			99
12			99
13			99
14			97 (3)
15			82 (17)

[a] Yields were determined by GC.
[b] Reactions were conducted for 30 min.
[c] Reaction carried out using *n*-BuLi of 5 mol % for 60 min.
[d] Yield was determined by NMR.

Table 3. Substrate scope for ketone hydroboration with 1 mol % *n*-BuLi.



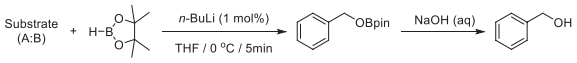
Entry	Ketone	Product	Yield[a] (%)
1			99
2			99
3			99
4			99
5			99
6			99
7			99
8			99
9			99
10[b]			99
11[b]			99
12[b]			99

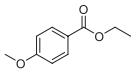
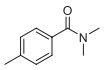
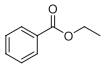
[a] Yields were determined by NMR.
[b] Yields were determined by GC.

Experimental

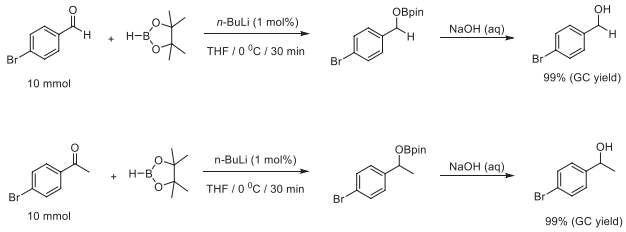
General. All glassware used was dried thoroughly in an oven, assembled hot, and cooled under a stream of dry nitrogen before use. All reactions and manipulations of air- and moisture-sensitive materials were carried out using standard techniques for the handling of such materials. All chemicals were commercial products of the highest purity, which were further purified before use by using standard methods. *n*-Butyllithium, HBpin, aldehydes, and ketones were purchased from Aldrich Chemical Company, Alfa Aesar, and Tokyo Chemical Industry Company (TCI). ^{1}H NMR spectra were recorded 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. 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. Gas chromatography (GC) analyses were performed on a Younglin Acme 6100M and 6500GC FID chromatography,

Table 4. Chemoselective-catalyzed hydroboration of aldehydes and ketones.



Entry	Substrate A	Substrate B	Yield of alcohol[a] (%) A	Yield of alcohol[a] (%) B (SM)
1			96	0 (99)
2			95	0 (99)
3			95	0 (99)
4			99	0 (99)

[a] Yields were determined by GC.



Scheme 2. Scale-up reaction of catalyzed hydroboration using *n*-butyllithium and pinacolborane.

using an 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. The following experimental procedure for the synthesis of benzyl alcohol is representative. A dry and argon-flushed flask, equipped with a magnetic stirring bar and septum, was charged with benzaldehyde (0.05 mL, 0.5 mmol), THF (5 mL), and HBpin (0.11 mL, 0.75 mmol). After cooling to 0 °C, *n*-BuLi (in hexane, 0.1 mL, 0.05 M, 0.005 mmol) was added dropwise and the mixture was stirred for 5 min at 0 °C. After completion of the reaction (GC), it was stopped by H_2O (two drops). The GC analysis showed 99% of 2-(benzyloxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Then, 1 N aqueous NaOH (5 mL) was added and stirred for 30 min. The crude mixture was extracted with diethyl ether (2 × 10 mL) and the combined organic layers were dried over $MgSO_4$. The GC analysis showed a 99% yield of benzyl alcohol. All products in Table 2 were confirmed through comparison with GC data of the authentic sample.

General Procedure for the Catalyzed Hydroboration of Ketones. The following experimental procedure for the synthesis of 1-phenylethan-1-ol is representative. A dry and argon-flushed flask, equipped with a magnetic stirring bar and septum, was charged with acetophenone (0.06 mL, 0.5 mmol), THF (5 mL), and HBpin (0.11 mL, 0.75 mmol). After cooling to 0 °C, *n*-BuLi (in hexane, 0.1 mL, 0.05 M, 0.005 mmol) was added dropwise and the mixture was stirred for 5 min at 0 °C. After completion of the reaction, it was stopped by H_2O (two drops). ^{1}H NMR analysis showed 71% of 4,4,5,5-tetramethyl-2-(1-phenylethoxy)-1,3,2-dioxaborolane and 28% yield of 1-phenylethan-1-ol. Then, 1 N aqueous NaOH (5 mL) was added and stirred for 30 min. The crude mixture was extracted with diethyl ether (2 × 10 mL) and combined organic layers were dried over $MgSO_4$. ^{1}H NMR analysis showed 99% of 1-phenylethan-1-ol (^{1}H NMR using acetonitrile as an internal standard).

Procedure for the Chemoselective Hydroboration with *n*-Butyllithium. The following experimental procedure for the reaction of benzaldehyde over ethyl 4-methoxybenzoate is representative. A dry and argon-flushed flask, equipped with a magnetic stirring bar and septum, was charged with benzaldehyde (0.05 mL, 0.5 mmol), ethyl 4-methoxybenzoate (0.08 mL, 0.5 mmol), THF (5 mL), and HBpin (0.11 mL, 0.75 mmol). After cooling to 0 °C, *n*-BuLi (in hexane, 0.1 mL, 0.05 M, 0.005 mmol) was added and the mixture was stirred for 5 min at 0 °C. After completion of the reaction (GC), it was stopped by H_2O (two drops). The GC analysis showed 99% of 2-(benzyloxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and 99% of ethyl 4-methoxybenzoate. Then, 1 N aqueous NaOH (5 mL) was added and stirred for 30 min. The crude mixture was extracted with diethyl ether (2 × 10 mL) and combined organic layers were dried over $MgSO_4$. The GC analysis showed a 99% yield of benzyl alcohol and 99% of ethyl 4-methoxybenzoate.

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