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Phenylboronic acid as an efficient and green catalyst for direct reductive amination of aldehydes using hantzsch dihydropyridine ester as a reducing agent

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ABSTRACT

Phenylboronic acid was found to be an efficient catalyst for direct reductive amination of aldehydes using Hantzsch dihydropyridine ester as biomimetic hydrogen source under mild conditions. The green and economical process requires only catalytic amount of phenylboronic acid and provides rapid access to the structurally diverse amines in high yields.

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KEYWORDS

Reduction;
Imine;
Lewis acid;
Hantzsch reaction.

INTRODUCTION

Reductive amination of aldehydes and ketones, in which a mixture of a carbonyl compound and an amine is treated with a reductant in a “one-pot” fashion, is one of the most useful methods for the preparation of secondary or tertiary amines and related functional compounds^[1]. The amines are structural element in a multitude of biologically active natural products and pharmaceuticals and therefore their synthesis has become an objective of high priority from the perspective of medicinal chemistry and organic synthesis^[2]. The most commonly employed procedures for reductive aminations of carbonyls utilizes boranes or metal hydrides such as NaBH₃CN, NaBH₄ as reducing agents^[3] and rely on Bronsted or Lewis acids for selective activation of imine in the presence of carbonyls. However these methods suffer from the limitations such as incompatibility with acid labile functionalities, use of

hazardous and/or expensive catalysts, inconvenience of handling and excess use of amines. To circumvent these drawbacks, one of the best alternatives is to apply organo reductants that possess excellent reproducibility. In recent years, the natural product enzyme cofactor NAD(P) and NAD(P)H have been a stimulus for the investigation of use of Hantzsch ester (**1**) and other 1,4-dihydropyridine derivatives as attractive biomimetic reducing agent for the applications in synthetic and physical organic chemistry^[4]. This conceptual blueprint of biochemical hydride reduction, wherein an enzyme and cofactor are replaced by catalysts and dihydropyridine analogues respectively, has been employed in chemical reduction of many double bond containing compounds^[5-8]. The Hantzsch esters (**1**) has been reported to be efficient biomimetic reducing agent for the reductive amination of aldehydes and ketones in the presence of Lewis acids such as Mg (II)^[9], Al₂O₃^[10] and Sc(OTf)₃^[11].

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In addition, Bronsted acids^[12-14] have also reported to be effective catalyst for this transformation. Very recently, Menche et al. reported the use of Hantzsch ester and thiourea as novel reagent–catalyst combination for a mild and selective reductive amination of aldehyde^[15] and ketones^[16]. Although these methods provide an easy access to the structurally diverse amines under mild conditions but some of these methods involve the use of expensive metal triflate or hazardous Lewis or protic acid catalysts and other require excessive use of one or more reagents and heating for longer time. Thus still there is sufficient scope to develop further milder, efficient, and environmentally benign protocol for the reductive amination of aldehydes. Our previous success on utilizing boronic acids as green and mild organo catalysts^[17] has prompted us to explore the possibility of exploiting boronic acid as catalyst in biomimetic approach for reductive amination of aldehydes. Herein, we report that phenylboronic acid catalyzed efficiently reductive amination of structurally diverse aldehydes using DHP ester as a biomimetic reducing agent in high yields and under mild conditions.

In the present paper our results concerning concomitant use of organo catalyst and organo reagent in reductive amination of aldehydes are disclosed. Our initial investigation started with the reductive amination of benzaldehyde and *p*-anisidine as a model reaction. The reaction was carried out using equimolar amount of aldehyde, amine and Hantzsch ester (**1**) in the presence of different boronic acid catalysts in THF at room temperature. The results are summarized in TABLE 1. In the absence of catalyst the reaction hardly proceeded which clearly justifies the need for the catalyst for the success of the reaction. Among the different boronic acids screened, 2-bromophenylboronic acid was found to be best catalyst followed by 3-nitrophenylboronic acid. The simple phenylboronic acid is also found to be effective catalyst and provided high yield of the prod-

TABLE 1 : Reductive amination of benzaldehyde and *p*-anisidine catalysed by boronic acids^a

Entry	Catalyst	Time (h)	Yield (%)
1	-	10	trace
2	Phenylboronic acid	10	94%
3	3-Nitrophenylboronic acid	6	98
4	2-Bromophenylboronic acid	4	> 99
5	Phenylboronic acid	7	78 ^c

^aReaction conditions: Benzaldehyde (1.0mmol), *p*-anisidine (1.0mmol) and Hantzsch ester (1.0mmol) in the presence of 5 mol % of boronic acid in THF at room temperature. ^bIsolated yields. ^c4-Phenyl-1,4-dihydropyridine ester was used as a reducing agent.

uct within 10 h. As an alternate reducing system, another dihydropyridine ester, 4-phenyl-1,4-dihydropyridine (TABLE 1, entry 6) was investigated but it was found to be less effective and provided the product in considerably lower yield than with parent ester **1**.

Though 2-bromo- and 3-nitrophenylboronic acids were found to be better catalysts than phenylboronic acid, the high cost of these boronic acids over phenylboronic acid limits their applicability. In view of our research objective to develop inexpensive and environmentally benign protocol for the organic synthesis, we considered the phenylboronic acid as a catalyst of choice for further study. Thus the present study revealed that the best reaction conditions were 1 equiv. of aldehyde, 1 equiv. of amine and 1 equiv. of Hantzsch ester in the presence of 5 mol% of phenylboronic acid in THF at room temperature for 10 h. In order to gauge the scope and generality of the present reaction conditions, structurally diverse aldehydes and amines were subjected to reductive amination using our optimized reaction conditions, Scheme 1.

The results are summarized in TABLE 2 and 3. In the entire example studied, the desired amines were obtained in high to excellent yields in short reaction times. Aromatic aldehydes bearing both electron releasing

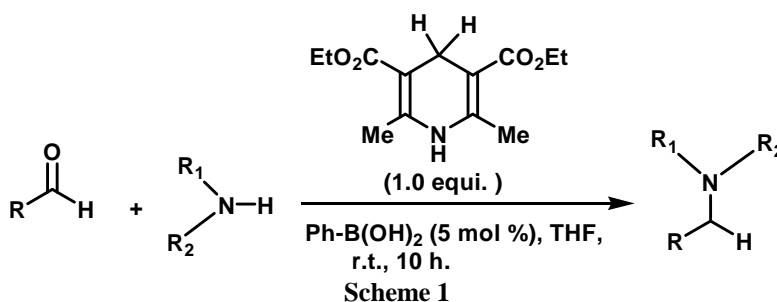
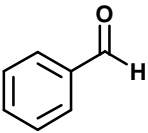
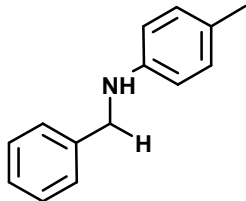
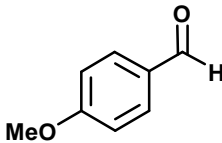
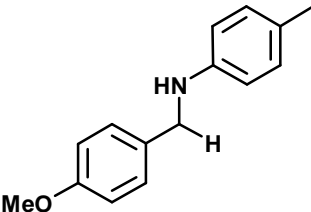
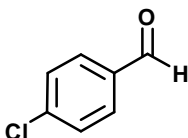
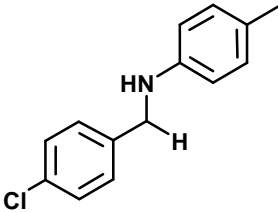
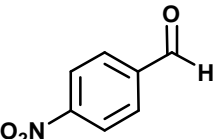
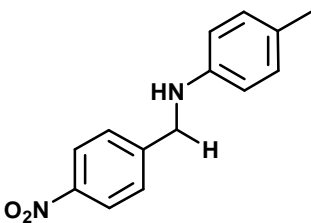
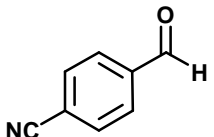
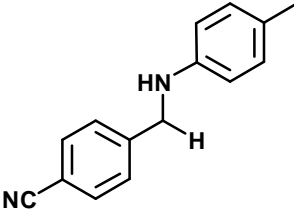
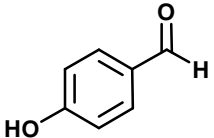
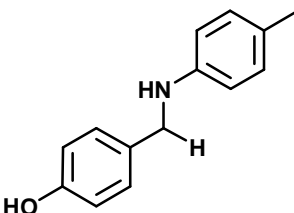


TABLE 2 : Scope of various aldehydes in reductive amination catalysed by phenyl boronic acid^a

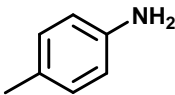
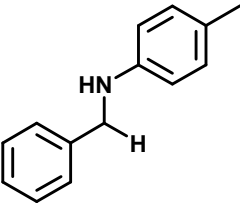
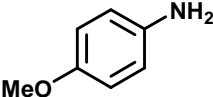
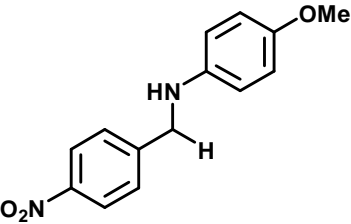
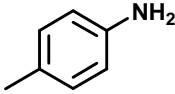
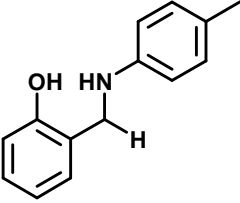
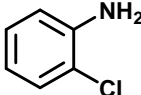
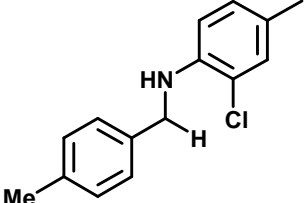
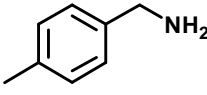
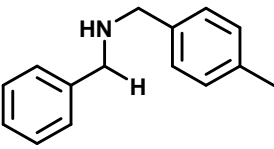
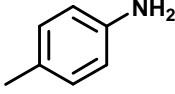
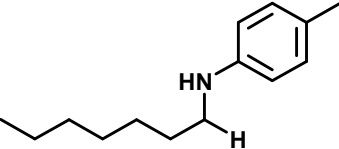
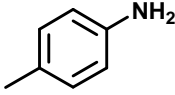
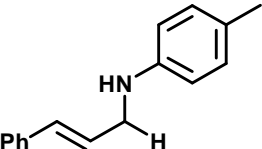
Entry	Aldehyde	Product	Yield(%) ^b
1			94
2			92
3			95
4			98
5			98
6			94

^a Reaction conditions: 1.0mmol of aldehyde, 1.0mmol of p-anisidine and 1.0mmol of DHP ester 1 in the presence of 5 mol % phenylboronic acid in THF at room temperature for 10 h. ^b Isolated yields

(TABLE 2, entry 2) as well as electron withdrawing group (TABLE 2 entry 4 and 5) participated successfully in the reductive amination. In addition to aromatic aldehydes, aliphatic aldehydes were also smoothly aminated under present reaction conditions to give high yields of the corresponding amines. Next structurally diverse aromatic amines were investigated under present

reaction conditions. The results are summarised in TABLE 3. As shown in TABLE 3, electron rich as well as electron deficient amines reacted efficiently under present reaction conditions to give well to high yields of the products. It is to be noted that sterically hindered amines such as ortho substituted amines (TABLE 3, entry 4) also provided good yield of the corresponding

TABLE 3 : Scope of various amines in reductive amination catalysed by Phenylboronic acid^a

Entry	Amine	Product	Yield (%) ^b
1			96
2			>99
3			90
4			84
5			98
6			95
7			82 ^c

^a Reaction conditions: 1.0 mmol. of aldehyde, 1.0 mmol. of amine and 1.0 mmol. of Hantzsch DHP ester in the presence of 5 mol % of phenylboronic acid in THF at room temperature for 10 h. ^b Column purified yields. ^c Concomitant reduction of conjugated double bond was observed.^[12]

aminated product under present reaction conditions. Thus the present procedure has broad scope and diversity amplification through structural variation can be achieved in one-pot fashion.

The mild reaction conditions described herein are evident by the fact that acid sensitive functionalities such

as nitro, cyano, and carbonyl, halides, hydroxyl and alkoxy group both on aldehydes as well as amines were well tolerated. It is important to note that phenylboronic acid is readily available, green and cheap catalyst and requires in very low catalytic amount^[18]. The 1,4-Dihydropyridine esters (**1**), can be synthesized at a great

ease on large scale by Hantzsch condensation reaction. Thus the present protocol represents the rare example of concomitance use of organo catalyst and organo reagent for the important reductive amination process.

In conclusion, we have developed a mild, high yielding and green protocol for the direct reductive amination of aldehydes using readily available Hantzsch ester as a biomimetic reducing agent in the presence of catalytic amount of phenylboronic acid. Though currently we have investigated the reductive amination of aldehydes only, the detail investigation as regard to applicability of the reaction conditions for ketones would be undertaken soon.

EXPERIMENTAL

The Phenylboronic acid was purchased from Sigma-Aldrich Company. The other chemicals such as aldehydes, amines and solvents such as THF, acetonitrile, ethanol etc. were purchased from S.D.Fine Chemicals, India and Colligens. The Hantzsch DHP ester was synthesized in laboratory by reported methods. The progress of the reaction was monitored by thin layer chromatography using silica gel coated plates. The petroleum ether used refers to the fraction 60-80. The products were purified by column chromatography or wherever possible by recrystallization with appropriate solvent.

General procedure for reductive amination of aldehydes

To a mixture of aldehyde (1.0 mmol), amine (1.0 mmol) and Hantzsch dihydropyridine ester (**1**) (1.0 mmol) in THF (10 ml) was added phenylboronic acid (6 mg, 5 mol %) and resulting mixture was stirred at room temperature for 10 h. After completion of reaction (TLC), the mixture was washed with NaHCO₃ and brine and finally with water. After drying over anhydrous MgSO₄, solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel (60-120 mesh) using petroleum ether ethyl acetate as eluent to give analytically pure products in 84-96% yields.

Selected spectral data

N-(*p*-Nitrobenzyl)-*p*-anisidine

¹H NMR (400 MHz, CDCl₃) δ = 3.74 (s, 3H),

4.41 (s, 2H), 6.56(d, 2H, *J* = 9.0 Hz), 6.75 (d, 2H, *J* = 9.0, Hz,) 7.54 (d, 2H, *J* = 8.8 Hz), 8.20 (d, 2H, *J* = 8.8 Hz).

MS (ESI) *m/z*: calcd for C₁₄H₁₄N₂O₃ [*M*+*H*]⁺: 226.123. Found: 226.123.

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