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Tetrahedron 61 (2005) 5725–5734
Tetrahedron

Direct and indirect reductive amination of aldehydes and ketones with solid acid-activated sodium borohydride under solvent-free conditions

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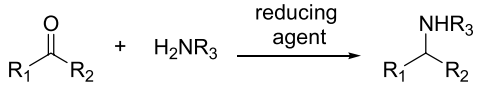
Received 24 March 2005; revised 21 April 2005; accepted 21 April 2005

Abstract—A simple and convenient procedure for reductive amination of aldehydes and ketones using sodium borohydride activated by boric acid, *p*-toluenesulfonic acid monohydrate or benzoic acid as reducing agent under solvent-free conditions is described.

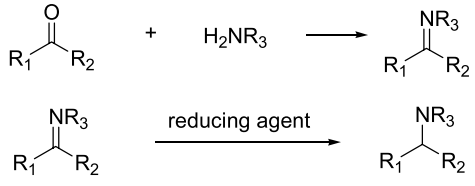
1. Introduction

The transformation of amines from aldehydes and ketones is an important method in organic synthesis because of their versatile utility as intermediates for synthesis of pharmaceuticals[1] and agrochemicals.[2] For the transformation, the two synthetic methods are commonly used. One is the reductive amination, which is termed as a direct reaction. This method allows the conversion of carbonyl functionality to an amine by directly treating a mixture of the carbonyl compound and the amine with suitable reducing agents in a single operation without preformation of an intermediate imine or iminium salt (Scheme 1). The other is a stepwise or indirect reaction, which involves the conversion of amine from the reduction of the imine derivatives isolated in a separate step (Scheme 2). As effective reducing methods for these conversions, catalytic hydrogenation,[3] metal hydride reductions using $NaBH_3CN$,[4a] $LiBH_3CN$,[4b] $(n\text{-}Bu)_4NBH_3CN$,[4c] $NaBH_3CN$–$ZnCl_2$,[4d] $NaBH_3CN$–$Ti(O^iPr)_4$,[4e] $NaBH_3CN$–$Mg(ClO_4)_2$,[4f] $NaBH(OAc)_3$,[5]



R_1, R_3 = alkyl, aryl or heterocyclic
R_2 = H, alkyl, aryl or heterocyclic

Scheme 1.



R_1, R_3 = alkyl, aryl or heterocyclic
R_2 = H, alkyl, aryl or heterocyclic

Scheme 2.

$NaBH_4$–$NiCl_2$,[6a,b] $NaBH_4$–$ZnCl_2$ (nickel boride),[6c] $NaBH_4$–$ZrCl_4$,[6d] $Ti(O^iPr)_4$–$NaBH_4$,[6d] $NaBH_4$–H_2SO_4,[6e] $NaBH_4$–wet clay-microwave,[6f] borohydride exchange resin,[7] $ZnBH_4$,[8a] $ZnBH_4$–$ZnCl_2$,[8b] $ZnBH_4$–SiO_2,[8c] pyridine–borane,[9] picoline–borane,[10] diborane–MeOH,[11] decaborane,[12] Zn–AcOH,[13] polymethylhydrosiloxane (PMHS)–$Ti(O^iPr)_4$,[14a] PMHS–$ZnCl_2$,[14b] PMHS–$BuSn(OCOR)_3$,[14c] Et_3SiH–CF_3CO_2H,[14d] $PhMe_2SiH$–$(C_6F_6)_3$,[14e] Cl_3SiH–DMF,[14f] $PhSiH_3$–Bu_2SnCl_2,[14g] $^nBu_3SnH$–DMF or HMPA,[15a] $^nBu_3SnH$–SiO_2[15b] and $^nBu_2SnIH$ or $^nBu_2$-$SnClH$[15c,d] have been reported. However, most of these reagents may have one drawback or another. For examples, catalytic hydrogenation is incompatible with compounds containing a carbon–carbon double or triple bond and other reducible functional groups such as nitro, cyano and furyl groups.[3] Cyanoborohydride and tin hydride reagents are highly toxic and generate toxic by-products such as HCN, NaCN or organotin compounds[16] upon workup and may result in the contamination of the product with the toxic compounds. Other hydrides such as zinc borohydride,[17] nickel boride[6b,16] and PHMS–$Ti(O^iPr)_4$[18] may be not

Keywords: Reductive amination; Imines; Reductions; Solvent-free reaction; Sodium borohydride.
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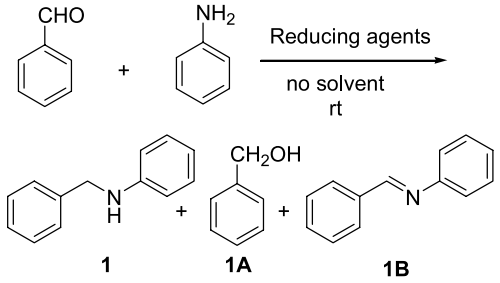
doi:10.1016/j.tet.2005.04.039

Table 1. Solvent-free reductive amination of benzaldehdye with aniline using boric acid-activated $NaBH_4$ and $NaBH_4$ alone



Method	Time (min)	Ratio of product (%)		
		1	**1A**	**1B**
A	15	35	65	0
B	15	94	6	0
C	15	64	36	0
D	20	3	97	0
E	90	5	10	85

Method A: benzaldehyde was immediately ground with a 1:1:1 mixture of aniline, $NaBH_4$ and boric acid; method B: after benzaldehyde was mixed with aniline for 10 min, the resulting mixture was ground with a 1:1 mixture of $NaBH_4$ and H_3BO_3; method C: the conditions were identical with method B except that the mixing period of benzaldehyde and aniline was 0. 5 min; method D: the conditions were identical with method A except for use of $NaBH_4$ itself; method E: the conditions were identical with method B except for use of $NaBH_4$ itself.

suitable for use of chemoselective reduction of imines having ketone, ester, amide and nitro groups, since these reagents can reduce those functional groups. Sodium borohydride is an inexpensive, safe to handle and environmental friendly reducing agent. Recently, we reported solvent-free chemoselective reduction of aldimines and ketimines including other reducible functional groups, such as ketone, carboxylic acid, ester, nitrile, amide, nitro, furyl and alkenyl groups using boric acid-activated sodium borohydride to the corresponding functionalized amine compounds.[19] This method is not only of interest from ecological point of view,[20] but also proves to be a clean, rapid and very simple procedure for the reduction of imine derivatives. We report here the details, scope, and limitations of direct and indirect process for the reductive amination of aldehydes and ketones using this methodology.

2. Results and discussion

2.1. Direct reductive amination

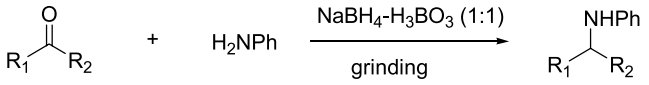
We initially examined a direct solvent-free reductive amination reaction of benzaldehyde with aniline using boric acid-activated sodium borohydride. The reaction was carried out by directly grinding a 1:1:1:1 mixture of benzaldehyde, aniline, sodium borohydride and boric acid with an agate mortar and pestle at room temperature in air until TLC showed complete disappearance of benzaldehyde. As shown in Table 1, it was interestingly found that yields of a product amine, *N*-benzylaniline (**1**) obtained were dependent on a mixing order and period of benzaldehyde and aniline. When benzaldehyde was immediately ground with a 1:1:1 mixture of aniline, boric acid and sodium borohydride (method A) for 15 min, the reaction provided **1** (35%) and benzyl alcohol (**1A**, 65%). In contrast, when benzaldehdye was mixed with aniline for 10 min under solvent-free conditions and the resulting mixture was successively ground with a 1:1 mixture of sodium borohydride and boric acid (method B), the reaction afforded **1** (94%) and **1A** (6%). This reaction gave **1** (64%) and **1A** (36%), even though the mixing period of benzaldehyde and aniline was 0.5 min (method C). On the other hand, the reaction using sodium borohydride itself in the absence of boric acid in method A (method D) gave **1** (3%) and **1A** (97%), whereas the same reaction in method B (method E) provided **1** (5%), **1A** (10%) and 85% of

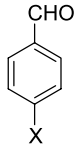
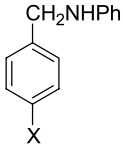
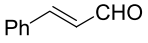
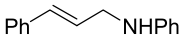
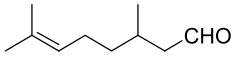
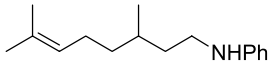
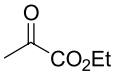
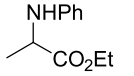
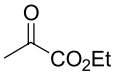
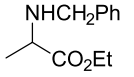
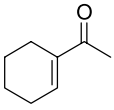
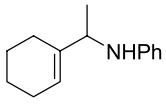
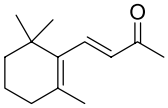
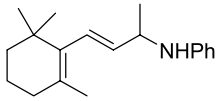
Table 2. Solvent-free reductive amination of aldehyde and ketone with $NaBH_4$ in the presence of activator[a]

Entry no.	Aldehyde/ ketone	Amine	Activator	Time (min)		Product	Yield (%)[b]
1	PhCHO	H_2NPh	H_3BO_3	15		**1**	94
2	PhCHO	H_2NPh	PTSA[c]	15		**1**	92
3	PhCHO	H_2NPh	$PhCO_2H$	15		**1**	93
4	PhCHO	$H_2NC_6H_4OMe$-*p*	H_3BO_3	10	**2**	$PhCH_2NHC_6H_4OMe$-*p*	99
5	PhCHO	H_2NCH_2Ph	PTSA	30	**3**	$PhCH_2NHCH_2Ph$	88
6	PhCHO	H_2NCH_2Ph	H_3BO_3	30		**3**	85
7	PhCHO	$H_2NC_7H_{15}$-*n*	H_3BO_3	20	**4**	*n*-$C_7H_{15}NHCH_2Ph$	93
8	PhCHO	$H_2NC_6H_{11}$-*c*	PTSA	30	**5**	*c*-$C_6H_{11}NHCH_2Ph$	62
9	PhCHO	Morpholine	H_3BO_3	30		$PhCH_2OH$	99
10	*n*-$C_7H_{15}CHO$	H_2NPh	H_3BO_3	20	**6**	*n*-$C_7H_{15}CH_2NHPh$	83
11	*n*-$C_7H_{15}CHO$	H_2NCH_2Ph	$PhCO_2H$	20	**7**	*n*-$C_7H_{15}CH_2NHCH_2Ph$	81
12	*n*-$C_7H_{15}CHO$	$H_2NC_7H_{15}$-*n*	PTSA	30	**8**	*n*-$C_7H_{15}CH_2NHC_7H_{15}$-*n*	70
13	*c*-$C_6H_{11}CHO$	H_2NPh	$PhCO_2H$	20	**9**	*c*-$C_6H_{11}CH_2NHPh$	97
14	*c*-$C_6H_{11}CHO$	$H_2NC_6H_4OMe$-*p*	H_3BO_3	20	**10**	*c*-$C_6H_{11}CH_2NHC_6H_4OMe$-*p*	94
15	*c*-$C_6H_{11}CHO$	H_2NCH_2Ph	PTSA	30	**11**	*c*-$C_6H_{11}CH_2NHCH_2Ph$	77
16	Furfural	H_2NPh	H_3BO_3	10	**12**	*N*-phenylfufrylamine	97
17	Cyclohexanone	H_2NPh	H_3BO_3	10	**13**	*c*-$C_6H_{11}NHPh$	93
18	Cyclohexanone	H_2NCH_2Ph	$PhCO_2H$	20		**5**	62
19	Cyclohexanone	Morpholine	H_3BO_3	20	**14**	*N*-Cyclohexylmorpholine	35[d]
20	Acetophenone	H_2NPh	H_3BO_3	30		PhCH(OH)Me	92

[a] After 1 equiv of aldehydes or ketones was mixed with 1 equiv of amines for 10 min at room temperature under solvent-free conditions, the resulting mixture was ground with a 1:1 mixture of $NaBH_4$ and each activator in an agate mortar and pestle.
[b] Isolated yield after column chromatography.
[c] PTSA = *p*-toluenesulfonic acid monohydrate.
[d] Cyclohexanol was obtained in a major product.

Table 3. Chemoselective reductive amination of functionalized aldehydes and ketones with H_3BO_3-activated $NaBH_4$ under solvent-free conditions[a]

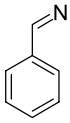
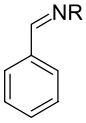
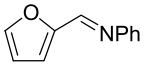
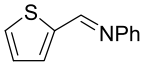
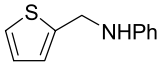
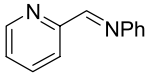
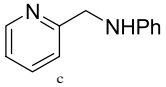
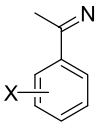
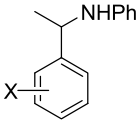
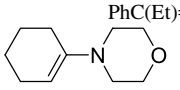
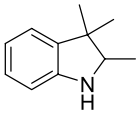
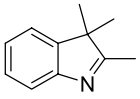


Entry no.			Time (min)				Yield (%)[a]
1		X=COMe	50		**15**	X=COMe	81
2		X=CN	40		**16**	X=CN	99
3		X=CO_2H	40		**17**	X=CO_2H	80
4		X=CO_2Me	30		**18**	X=CO_2Me	82
5		X=NHCOMe	40		**19**	X=NHCOMe	91
6		X=NO_2	50		**20**	X=NO_2	77
7			30	**21**			98
8			20	**22**			92
9			15	**23**			79
10			30	**24**			71
11			20	**25**			88
12			90	**26**			25

[a] See the corresponding footnotes in Table 2.

benzladehyde *N*-phenylimine (**1B**, 85%) even after 90 min. The results indicate that these reactions involve a competitive reduction of benzaldehyde and the imine **1B** formed from the aldehyde and aniline. Indeed, when benzaldehyde was mixed with aniline for 10 min under solvent-free condition at room temperature produced an imine product **1B** in 95% yield, which was rapidly reduced with boric acid-activated sodium borohydride to **1**, but the reduction with sodium borohydride alone was very slow (see Table 4). In these reactions, a mixing order and period of sodium borohydride and boric acid had no discernable effect on the rate of reduction and yield of product amine. To test effectiveness of other solid acids, such as *p*-toluenesulfonic acid monohydrate and benzoic acid, as activator, we compared reductive amination of benzaldehyde with aniline using those acids instead of boric acid under the identical conditions described in method B. As shown in Table 2, the reactions examined were complete within 15 min to give **1** in high yield, showing no significant difference of effectiveness on the role of activators among these acids (entries 1–3). Using the same methodolgy, the reductive aminations of structurally different aldehydes and ketones with various amines were examined. Reductive amination of benzaldehyde with other aromatic and aliphatic primary amines proceeded smoothly to give the corresponding secondary amines (entries 4–8), although the reaction with cyclohexylamine provided somewhat low yield. The reaction with a secondary amine, morpholine, produced only benzyl alcohol without formation of the desired amine (entry 9). The reactions of aliphatic and heterocyclic aldehydes, such as octanal, cyclohexanecarboxaldehyde and furfural, with various primary amines gave the desired secondary amine products in the range of 70–97% yield (entries 10–16). In the cases of ketones, cyclohexanone underwent successfully reductive amination with aniline to give *N*-phenylcyclohexylamine in 93% yield (entry 17), although the reaction with benzylamine and morpholine afforded the desired amines in lower yield (entries 18 and 19). Under the same conditions, however, reductive amination of acetopheone with aniline did not occur. The reaction afforded only reduction product of acetophenone, 1-phenylethanol (entry 20). We next examined chemoselective reductive amination of functionalized aldehydes and ketones bearing other reducible functional groups employing the same methodology using boric acid as activator. As shown in Table 3, aromatic aldehydes having ketone, cyano, carboxylic acid, ester, amide and nitro group underwent reductive amination to give the corresponding *N*-phenyl amines without reduction of any other functional groups in good yields (entries 1–6). In the case of alkenic aldehydes and ketones, such as (*E*)-cinnamaldehyde, citronellal, 1-acetylcyclohexene and β-ionone, all the reductive amination except for β-ionone were successfully achieved in excellent yield (entries 7, 8, and 11). β-Ionone reacted slowly to give the corresponding *N*-phenylamine in a very low yield, showing preferential reduction of carbonyl

Table 4. Solvent-free reduction of imine derivatives with solid acid-activated $NaBH_4$[a]

Entry no.	Imine	Activator	Time (min)	Product	Yield (%)[b]
1		None	180	**1**	26
2		H_3BO_3	10	**1**	99
3		PTSA	10	**1**	99
4		$PhCO_2H$	10	**1**	99
5	 R = *p*-$MeOC_6H_4$	H_3BO_3	10	**2**	99
6	R = *p*-$MeOC_6H_4$	PTSA	10	**2**	99
7	R = $PhCH_2$	H_3BO_3	10	**3**	99
8	R = CMe_3	H_3BO_3	10	**27** $PhCH_2NHMe_3$	99
9	R = CMe_3	$PhCO_2H$	10	**27**	99
10	R = Me	PTSA	10	**28** $PhCH_2NHMe$	99
11	*c*-$C_6H_{11}CH{=}NC_6H_4OMe$-*p*	H_3BO_3	10	**10**	99
12	*c*-$C_6H_{11}CH{=}NCH_2C_6H_5$	PTSA	10	**11**	99
13		H_3BO_3	10	**12**	99
14		$PhCO_2H$	10		99
15		H_3BO_3	10	**29** 	99
16		PTSA	10		99
17		H_3BO_3	10	**30** 	99
18		PTSA	10		99
19	 X = H	None	180	[c]	99
20	X = H	H_3BO_3	20	 **31** X = H	99
21	X = H	$PhCO_2H$	20	**31**	99
22	X = *o*-Me	H_3BO_3	20	**32** X = *o*-Me	99
23	X = *p*-Me	H_3BO_3	20	**33** X = *p*-Me	99
24	X = *p*-MeO	H_3BO_3	20	**34** X = *p*-MeO	99
25	X = *p*-Cl	H_3BO_3	60	**35** X = *p*-Cl	99
26	PhC(Me)=NC_6H_4Cl-*p*	PTSA	30	**36** $PhCH(Me)NHC_6H_4Cl$-*p*	99
27	PhC(Et)=NPh	H_3BO_3	40	**37** PhCH(Et)NHPh	99
28		H_3BO_3	20	**14**	99
29		PTSA	20	**14**	99
30		H_3BO_3	10	**38** 	99
31		PTSA	10		99
32		$PhCO_2H$	15		99

[a] Reactions were carried out by simply grinding a 1:1:1 mixture of imine, $NaBH_4$ and activator with an agate mortar and pestle at room temperature.
[b] Isolated yield.
[c] No reaction.

group (entry 12). The reaction of an α-keto ester, ethyl pyruvate, with aniline and benzylamine provided *N*-phenyl and *N*-benzyl alanine ethyl ester (**23** and **24**, respectively), in good yields (entries 9 and 10).

2.2. Indirect reductive amination (imine reduction)

All the direct solvent-free reductive aminations shown in Tables 1–3 were accompanied with reduction of the starting carbonyls to give the corresponding alcohols as side products. To eliminate such disadvantages, we developed an alternative route by a stepwise (or indirect) reductive amination via solvent-free reduction of preformed aldimine or ketimine. Initially the reduction of **1B** was examined as representative. When a 1:1 mixture of **1B** and sodium borohydride was ground in the absence of activator under solvent-free conditions, the reduction proceeded more slowly to give **1** in 26% yield even after 3 h with recovery of unreacted **1B** in 74% yield (entry 1, Table 4). In contrast, reduction of the imine in the presence of 1 equiv of each of activators using the same methodology was complete within 10 min to give the desired amine in a nearly quantitative yield.[21] Again, significant difference of effectiveness among activators was not observed (entries 2–4).[22] All the reduction of other *N*-aryl and alkyl substituted aromatic (entries 5–10), aliphatic (entries 11 and 12) and heterocyclic (entries 13–18) aldimines using the same methodology gave the corresponding secondary amines within 10 min in quantitative yields. Also, all of the aromatic ketimines (entries 20–27), an enamine (entries 28 and 29), and a cyclic imine (entries 30–32) examined were reduced to the desired amines in excellent yields. The results indicated that this procedure underwent clean reductive amination in these reaction conditions. Isolation of pure products without chromatographic separation in all most cases, high yields and the use of inexpensive reagents requiring no special handling techniques are the notable advantages of this method. However, a ketimines, aetophenone *N*-phenylimine, was not reduced by sodium borohydride alone under the identical conditions (entry 19). As shown in Table 5, this methodology also was very effective for the reduction of various aldimines and ketimines bearing other reducible functional groups, such as ketone, nitrile, carboxylic acid, ester, amide, nitro, and alkenyl groups to amines bearing those functional groups in high yields. Unlike a direct process shown in Tables 1–3, the reduction of imines had no discernable effect by a mixing order and period of reactants on the rate of reduction, yield and the formation of side

Table 5. Solvent-free chemoselective reduction of functionalized imines with solid acid-activated $NaBH_4$[a]

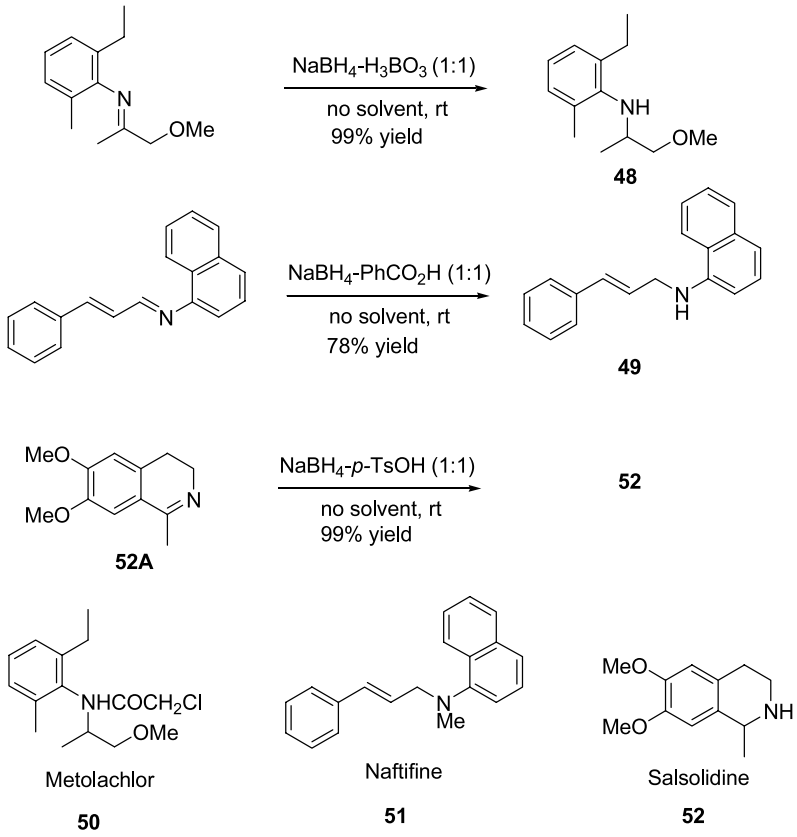
Entry no				Activator	Time (min)		Yield (%)[a]
	R_1	R_2	R_3				
1	*p*-$MeCOC_6H_4$	H	Ph	H_3BO_3	30	**15**	98
2	*p*-$MeCOC_6H_4$	H	Ph	PTSA	40	**15**	98
3	*p*-NCC_6H_4	H	Ph	H_3BO_3	30	**16**	99
4	*p*-NCC_6H_4	H	Me	$PhCO_2H$	20	**16**	97
5	*p*-NCC_6H_4	H	*n*-C_7H_{15}	H_3BO_3	40	**39**	98
6	*p*-NCC_6H_4	H	*n*-C_7H_{15}	$PhCO_2H$	40	**39**	97
7	*p*-NCC_6H_4	H	2-furyl	H_3BO_3	20	**40**	97
8	*p*-NCC_6H_4	H	2-furyl	PTSA	20	**40**	97
9	*p*-$HO_2CC_6H_4$	H	Ph	H_3BO_3	40	**17**	98
10	*p*-$MeO_2CC_6H_4$	H	Ph	H_3BO_3	30	**18**	99
11	*p*-$MeO_2CC_6H_4$	H	Ph	$PhCO_2H$	30	**18**	98
12	*p*-$MeO_2CC_6H_4$	H	Me	H_3BO_3	30	**41**	99
13	*p*-$MeO_2CC_6H_4$	H	Me	PTSA	30	**41**	99
14	*p*-$MeO_2CC_6H_4$	H	CMe_3	H_3BO_3	30	**41**	98
15	*p*-$MeO_2CC_6H_4$	H	CMe_3	PTSA	30	**42**	98
16	*p*-$MeO_2CC_6H_4$	H	CMe_3	$PhCO_2H$	30	**42**	97
17	*p*-$MeCONHC_6H_4$	H	Ph	H_3BO_3	30	**19**	98
18	*p*-$MeCONHC_6H_4$	H	Ph	PTSA	30	**19**	99
19	*p*-$O_2NC_6H_4$	H	Ph	H_3BO_3	40	**20**	99
20	*p*-$O_2NC_6H_4$	H	Ph	PTSA	40	**20**	98
21	*p*-$O_2NC_6H_5$	H	Me	H_3BO_3	30	**43**	99
22	*p*-$O_2NC_6H_5$	H	Me	$PhCO_2H$	30	**43**	97
23	(*E*)-PhCH=CH	H	Ph	H_3BO_3	20	**44**	98
24	(*E*)-PhCH=CH	H	Ph	PTSA	20	**44**	99
25	*p*-NCC_6H_4	Me	Ph	H_3BO_3	40	**45**	98
26	*p*-NCC_6H_4	Me	Ph	PTSA	40	**45**	98
27	*p*-$O_2NC_6H_5$	Me	Ph	H_3BO_3	60	**46**	97
28	*p*-$O_2NC_6H_5$	Me	Ph	$PhCO_2H$	50	**46**	98
29	1-Cyclohexenyl	Me	Ph	H_3BO_3	20	**47**	97
30	1-Cyclohexenyl	Me	Ph	PTSA	20	**47**	97

[a] See the corresponding footnotes in Table 4.

product. Finally, we went on to utilize this methodology to prepare amines **48** and **49**, which can be used as starting materials for synthesis of a herbicide, metolachlor **50** and a topical antifungal agent, naftifine **51**, respectively, and a Salsola alkaloid, salsolidine **52**. As shown in Scheme 3, both of **48** and **52** were successfully obtained from the corresponding imines in nearly quantitative yields, although **49** was obtained in 78% yield through more sluggish reduction. In such solvent-free imine reductions, solid acids used as activator may play a role to form iminium salts, which are easily and selectively reduced to the amines. However, when the reductions of **1B** and 4-acetylbenzaldehyde *N*-phenylimine derivatives with reducing systems generated from grinding a 1:1 mixture of sodium borohydride and activators were carried out, we found that the reductions showed no significant difference in comparison with those given in Tables 4 and 5, respectively. The results suggest that the reduction also occurs selectively in the condition of little chance of the formation of iminium salts by activators. With respect to reducing species of acid-activated sodium borohydride, IR and ^{11}B NMR spectroscopic data of reducing species of $NaBH_4$ activated by solid acids were summarized in Table 6. IR spectra of the reducing agents, reagent A–C, obtained from grinding 1 equiv of $NaBH_4$ with 1 equiv of boric acid, *p*-toluenesulfonic acid and benzoic acid, respectively, showed at 2381 cm^{-1} for reagent A, 2622 cm^{-1} for reagent B and 2562 cm^{-1} for reagent C as medium peaks, which are stretching vibration peaks of B–H bond. Each of ^{1}H decoupled ^{11}B NMR spectra of THF suspension of these reducing agents exhibited at -1.91 ppm for reagent A, $+25.02$ ppm for reagent B and $+23.55$ ppm for reagent C, which were different spectra from those of sodium borohydride itself.[23] Among these, ^{11}B NMR data of reagent B and C indicated the formation of acyl (or sulfonyl)oxyborohydride species [$NaBH_{4-x}(OCOR)_x$ or $NaBH_{4-x}(OSO_2R)_x$].[23] When a 1:1 mixture of $NaBH_4$ and each of activators was ground with excess triethylamine (3 equiv), ^{11}B NMR spectra of THF solution of these reagents showed at -34.40 ± 0.2 ppm indicating the formation of triethylamine–borane complex.[24] This hydride species were stable in air at least for few hours with no loss of hydride activity. Although the structure of this reducing species and the mechanism of this reduction are unclear so far, it appears that a eutectic temperature with melting point lower than the ambient temperature exists in each case. In fact, the reaction mixture became oily or sticky during grinding the mixtures even though they are powder states before grinding. Further studies on the reducing characteristics of these reducing systems for other functional groups are in progress.

3. Conclusion

We have established a direct and indirect reductive amination of aldehydes and ketones using sodium borohydride activated by inorganic and organic solid acid, such



Scheme 3.

Table 6. IR and ^{11}B NMR spectroscopic data of acid-activated $NaBH_4$

Hydride	IR (KBr, cm^{-1})	^{11}B NMR (δ)[a]
$NaBH_4$–H_3BO_3 (1:1, reagent A)	2381 (B–H), 2290	−1.91
$NaBH_4$–PTSA (1:1, reagent B)	2622 (B–H), 1417 (S=O)	+25.02
$NaBH_4$–$PhCO_2H$ (1:1, reagent C)	2562 (B–H), 1682 (C=O)	+23.55

[a] Measured in THF solution of a 1:1 grinding mixture of $NaBH_4$ and the corresponding acid.

as boric acid, *p*-toluenesulfonic acid and benzoic acid, as reducing agents under solvent-free conditions. The use of inexpensive reagents requiring no special handling techniques are the notable advantages of this method. Furthermore, due to compatibility of this reagent system with a variety of otherwise reducible functional groups, this method can provide an easy access to analogues amines bearing functionalized pendant chains.

4. Experimental

4.1. General

The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (Merck; 230–400 mesh). Melting points were uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 200 or 300 MHz. The chemical shifts are expressed as δ units with Me_4Si as the internal standard in $CDCl_3$. IR spectra were recorded on an FT-IR spectrophotometer and absorptions are reported in wave numbers (cm^{-1}).

4.2. Materials

Most of organic compounds utilized in this study were commercial products of the highest purity. They were further purified by distillation when necessary. Sodium borohydride, *p*-toluenesulfonic acid monohydrate and benzoic acid were purchased from Aldrich or Lancaster and used without further purification. Aldimines were prepared from stirring a 1:1 mixture of aldehydes and amines at ambient temperature under solvent-free conditions. Ketimines were prepared from reaction of ketones and amines according to the literature procedures.[25,26] 6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (**52A**), which is a starting material of **52** was prepared by known method.[25]

4.3. Direct solvent-free reductive amination of aldehydes and ketones

4.3.1. General procedure. An aldehyde or ketone (5 mmol) was ground with an amine (5 mmol) for 10–15 min in an agate mortar and a pestle at room temperature (ca 25 °C) under solvent-free conditions. To the resulting mixture was

added sodium borohydride (5 mmol) and each boric acid, *p*-toluenesulfonic acid monohydrate, or benzoic acid (5 mmol) and then the mixture was ground under identical conditions until TLC showed complete disappearance of the starting aldehyde. The reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (10 ml) and extracted with CH_2Cl_2 or ether (3×10 ml). The combined extract was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude products obtained were further purified by a flash column chromatography on silica-gel (230–400 mesh) using a suitable solvent as eluent. IR, ^1H and ^{13}C NMR spectra of compounds **15**–**21** and **25** obtained from this experiment are identical with those reported in literature.[19]

4.3.2. *N*-Phenylbenzylamine (1). R_f 0.66 (Et_2O/hexane 1:2); oil; 94% yield using boric acid as activator; IR (neat, cm^{-1}) 3384, 3003, 1600, 1498, 1321; ^1H NMR (200 MHz, $CDCl_3$) δ 3.94 (br s, 1H), 4.28 (s, 2H), 6.60 (d, 2H, J=7.63 Hz), 6.70 (t, 1H, J=7.33 Hz), 7.15 (t, 2H, J=7.44 Hz), 7.22–7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 48.9, 113.5, 118.2, 127.9, 128.2, 129.3, 129.9, 140.1, 148.8. Calcd for $C_{13}H_{13}N$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.24; H, 7.18; N, 7.61.

4.3.3. *N*-(*p*-Methoxyphenyl)benzylamine (2). R_f 0.59 (EtOAc/hexane 1:2); mp 48–49 °C; 98% yield using boric acid as activator; IR (KBr, cm^{-1}) 3385, 2964, 1613, 1510, 1449, 1239, 1031; ^1H NMR (200 MHz, $CDCl_3$) δ 3.59 (br s, 1H), 3.70 (s, 3H), 4.24 (s, 2H), 6.57 (d, 2H, J=8.85 Hz), 6.76 (d, 2H, J=8.85 Hz), 7.21–7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 49.8, 56.4, 114.7, 115.5, 127.8, 128.2, 129.2, 140.4, 143.1, 152.8. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.87; H, 7.15; N, 6.58.

4.3.4. Dibenzylamine (3). R_f 0.59 (EtOAc/hexane 1:2); oil; 88% yield using *p*-toluenesulfonic acid as activator; IR (neat, cm^{-1}) 3303, 3025, 2842, 2817, 1494, 1452, 734, 696; ^1H NMR (200 MHz, $CDCl_3$) δ 1.90 (br s, 1H), 3.79 (s, 4H), 7.21–7.34 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 53.6, 127.7, 129.0, 140.7. Calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66; N, 7.10. Found: C, 85.27; H, 7.65; N, 7.08.

4.3.5. *N*-Benzyl-1-heptylamine (4). R_f 0.68 (EtOAc/hexane 1:2); oil; 88% yield using boric acid as activator; IR (neat, cm^{-1}) 3202, 2955, 2926, 2856, 1455, 1166, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, 3H, J=6.74 Hz), 1.08–1.26 (m, 6H), 1.53–1.74 (m, 4H), 2.58–2.70 (m, 2H), 3.62 (dd, 1H, J=13.48, 9.08 Hz), 3.76 (br s, 1H). 4.21 (dd, 1H, J=13.48, 3.03 Hz), 7.27–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 22.9, 26.6, 27.0, 29.1, 31.9, 53.4, 60.1, 128.9, 129.3, 129.6, 134.5. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 81.91; H, 11.33; N, 6.91.

4.3.6. *N*-Benzylcyclohexylamine (5). R_f 0.68 (EtOAc/hexane 1:2); oil; 62% yield using boric acid as activator; IR (neat, cm^{-1}) 3197, 2927, 2853, 1447, 1165, 1028, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 0.72–2.05 (m, 10H), 2.71 (m, 1H), 3.40 (br s, 1H), 3.83 (dd, 1H, J=7.98, 13.75 Hz), 4.03 (dd, 1H, J=13.62, 4.26 Hz), 7.23–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 25.7, 26.9, 30.5, 56.7, 60.0, 128.6, 128.9, 129.3, 135.2. Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.39; H, 10.15; N, 7.40.

4.3.7. *N*-Phenyl-1-octylamine (6). R_f 0.80 (EtOAc/hexane 1:2); oil; 83% yield using boric acid as activator; IR (neat, cm^{-1}) 3405, 2956, 2927, 1603, 1506, 1259, 747, 691; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80–0.91 (m, 3H), 1.20–1.55 (m, 10H), 1.57–1.70 (m, 2H), 3.07 (t, 2H, J=7.15 Hz), 3.60 (br s, 1H), 6.48–6.52 (m, 3H), 7.02–7.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 23.1, 27.6, 29.6, 30.0, 32.3, 44.3, 54.2, 112.9, 117.3, 129.4, 148.7. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 81.94; H, 11.25; N, 6.79.

4.3.8. *N*-Benzyl-1-octylamine (7). R_f 0.61 (EtOAc/hexane 1:2); oil; 81% yield using benzoic acid as activator; IR (neat, cm^{-1}) 3200, 2955, 2927, 2856, 1455, 1168, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, 3H, J=7.15 Hz), 1.07–1.45 (m, 10H), 1.49–1.73 (m, 2H), 2.58–2.75 (m, 2H), 3.40 (br s, 1H), 3.62 (dd, 1H, J=13.62, 9.22 Hz), 4.20 (dd, 1H, J=13.75, 3.30 Hz), 7.20–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 22.9, 26.7, 26.9, 29.1, 31.9, 34.8, 53.6, 60.3, 129.0, 129.3, 129.5, 134.6. Calcd for $C_{15}H_{25}N$: C, 82.13; H, 11.49; N, 6.39. Found: C, 82.18; H, 11.55; N, 6.40.

4.3.9. *N*-(*n*-Heptyl)-1-octylamine (8). R_f 0.62 (EtOAc/hexane 1:2); oil; 70% yield using benzoic acid as activator; IR (neat, cm^{-1}) 3201, 2956, 2927, 2856, 1457, 1378, 1169, 1031, 724; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86–0.90 (m, 6H), 1.03–1.42 (18H), 1.60–1.69 (m, 4H), 2.26–2.42 (m, 2H), 2.64–2.85 (m, 2H), 3.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 14.6, 22.9, 23.0, 25.4, 26.9, 27.1, 29.3, 29.7, 31.8, 32.0, 32.3, 34.8, 54.4, 55.7. Calcd for $C_{15}H_{33}N$: C, 79.22; H, 14.63; N, 6.16. Found: C, 79.15; H, 14.65; N, 6.18.

4.3.10. *N*-Phenylcyclohexanemethylamine (9). R_f 0.85 (Et_2O/hexane 1:2); oil; 97% yield using benzoic acid as activator; IR (neat, cm^{-1}) 3418, 3050, 2922, 2850, 1603, 1507, 1448, 1323, 746; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88–1.01 (m, 2H), 1.13–1.29 (m, 3H), 1.54 (m, 1H), 1.64–1.81 (m, 5H), 2.90 (d, 2H, J=6.60 Hz), 3.65 (br s, 1H), 6.54 (d, 2H, J=8.53 Hz), 6.63 (t, 1H, J=7.29 Hz), 7.13 (dd, 2H, J=8.53, 7.43 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 27.1, 31.8, 38.0, 51.1, 112.9, 117.1, 129.5, 148.9. Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.45; H, 10.11; N, 7.43.

4.3.11. *N*-(*p*-Methoxyphenyl)cyclohexanemethylamine (10). R_f 0.77 (Et_2O/hexane 2:1); oil; 94% yield using boric acid as activator; IR (neat, cm^{-1}) 3318, 3025, 2971, 2878, 2789, 1515, 1493, 1045, 738, 698; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92–1.10 (m, 2H), 1.12–1.28 (m, 3H), 1.54 {m, 1H}, 1.65–1.83 (m, 5H), 2.89 (d, 2H, J=6.72 Hz), 3.36 (br s, 1H), 3.78 (s, 3H), 6.55 (d, 2H, J=8.85 Hz), 6.76 (d, 2H, J=8.85 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 27.2, 31.9, 38.2, 52.3, 56.4, 114.5, 115.6, 143.7, 152.5. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.69; H, 9.63; N, 6.40.

4.3.12. *N*-Benzylcyclohexanemethylamine (11). R_f 0.70 (EtOAc/hexane 1:2); mp 79–81 °C; 77% yield using *p*-toluenesulfonic acid as activator; IR (KBr, cm^{-1}) 3224, 2926, 2842, 1453, 1416, 1169, 902, 695; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97–1.97 (m, 11H), 2.39–2.57 (m, 2H), 3.55–3.62 (m, 2H), 4.23 (d, 1H, J=10.18 Hz), 7.24–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6, 25.9, 26.5, 30.3, 31.3, 34.2, 60.3, 60.9, 129.0, 129.3, 129.5, 134.5.

Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.65; H, 10.36; N, 6.92.

4.3.13. *N*-Phenylfurfurylamine (12). R_f 0.48 (EtOAc/hexane 1:2); oil; 97% yield using boric acid as activator; IR (neat, cm^{-1}) 3323, 3028, 2933, 2842, 2788, 1592, 1452, 1029, 737, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 3.98 (br s, 1H), 4.29 (s, 2H), 6.22 (m, 1H), 6.31 (m, 1H), 6.66 (d, 2H, $J=7.63$ Hz), 6.73 (t, 1H, $J=7.33$ Hz), 7.18 (t, 2H, $J=7.94$ Hz), 7.35 (d, 1H, $J=0.92$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.0, 107.6, 111.0, 113.8, 118.7, 129.9, 142.7, 148.3, 153.5. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.22; H, 6.44; N, 8.15.

4.3.14. *N*-Phenylcyclohexylamine (13). R_f 0.74 (EtOAc/hexane 1:2); mp 79–81 °C; 93% yield using *p*-toluenesulfonic acid as activator; IR (neat, cm^{-1}) 3401, 2939, 2853, 1602, 1502, 1196, 1058, 785; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07–1.45 (m, 5H), 1.60–1.79 (m, 4H), 2.05 (m, 1H), 3.46 (br s, 1H), 3.62 (m, 1H), 6.57 (d, 2H, $J=7.43$ Hz), 6.64 (t, 1H, $J=7.43$ Hz), 7.14 (dd, 2H, $J=8.53$, 7.43 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 25.4, 26.3, 33.8, 44.5, 52.0, 113.3, 113.4, 117.0, 117.1, 129.5, 147.5. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.27; H, 9.67; N, 7.97.

4.3.15. *N*-Cyclohexylmorpholine (14). R_f 0.23 (EtOAc/hexane 1:1); oil; 35% yield using boric acid as activator; IR (neat, cm^{-1}) 3460, 2927, 2853, 2808, 1450, 1267, 1117, 1069, 1016, 810; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08–1.30 (m, 5H), 1.63 (d, 1H, $J=10.73$ Hz), 1.78–1.91 (m, 4H), 2.18 (m, 1H), 2.56 (t, 4H, $J=4.68$ Hz), 3.72 (t, 4H, $J=4.68$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 26.6, 29.2, 50.0, 64.1, 67.7. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 70.95; H, 11.30; N, 8.29.

4.3.16. *N*-Phenylcitrolnellylamine (22). R_f 0.68 (EtOAc/hexane 1:4); oil; 92% yield using boric acid as activator; IR (neat, cm^{-1}) 3406, 2961, 2922, 2867, 1604, 1505, 1319, 747, 691; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81–1.81 (m, 5H), 0.93 (d, 3H, $J=5.50$ Hz), 1.60 (s, 3H), 1.68 (s, 3H), 1.83–2.04 (m, 2H), 3.10 (m, 2H), 3.54 (br s, 1H), 5.08 (t, 1H, $J=5.78$ Hz), 6.57 (d, 2H, $J=8.53$ Hz), 6.66 (td, 1H, $J=7.29$, 1.1 Hz), 7.14 (t, 2H, $J=7.43$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 20.1, 25.9, 26.3, 30.8, 37.0, 37.5, 42.3, 112.9, 117.3, 124.9, 129.5, 131.6, 148.7. Calcd for $C_{16}H_{25}N$: C, 83.06; H, 10.89; N, 6.05. Found: C, 83.08; H, 10.90; N, 6.04.

4.3.17. *N*-Phenylalanine ethyl ester (23). R_f 0.65 (EtOAc/hexane 1:2); oil; 79% yield using boric acid as activator; IR (neat, cm^{-1}) 3384, 3016, 2980, 2934, 1740, 1604, 1201, 1051, 784; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, 3H, $J=7.15$ Hz), 1.47 (d, 3H, $J=6.60$ Hz), 4.06–4.26 (m, 2H), 4.18 (q, 2H, $J=7.15$ Hz), 6.59 (dd, 2H, $J=8.53$, 1.1 Hz), 7.16 (dd, 2H, $J=8.53$, 7.43 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 19.4, 52.3, 61.5, 113.6, 118.5, 129.5, 146.7, 174.8. Calcd for $C_{11}H_{15}N0_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.34; H, 7.83; N, 7.24.

4.3.18. *N*-Benzylalanine ethyl ester (24). R_f 0.65 (EtOAc/hexane 1:1); oil; 71% yield using boric acid as activator; IR (neat, cm^{-1}) 3327, 3028, 3979, 2934, 1733, 1453, 1188, 1152, 1064, 737, 699; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H, $J=7.01$ Hz), 1.32 (d, 3H, $J=6.88$ Hz), 1.90 (br s, 1H), 3.77 (q, 1H, $J=6.88$ Hz), 3.66 (d, 1H, $J=12.65$ Hz), 3.80 (d, 1H, $J=12.65$ Hz), 4.18 (q, 2H, $J=7.15$ Hz), 7.23–7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 19.6, 52.3, 56.3, 61.1, 127.3, 128.5, 128.6, 139.9, 175.9. Calcd for $C_{12}H_{17}N0_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.59; H, 8.30; N, 6.69.

4.3.19. Compound 26. R_f 0.61 (EtOAc/hexane 1:4); oil; 25% yield using boric acid as activator; IR (neat, cm^{-1}) 3409, 2961, 2926, 2864, 1602, 1504, 1318, 1258, 973, 748, 691; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 3H), 0.94 (s, 3H), 1.35 (d, 3H, $J=6.60$ Hz), 1.38–1.44 (m, 2H), 1.47–1.69 (m, 2H), 1.60 (s, 3H), 1.80–1.95 (m, 2H), 3.60 (br s, 1H), 4.00 (quintet, 1H, $J=6.46$ Hz), 5.30 (dd, 1H, $J=15.82$, 6.19 Hz), 6.01 (d, 1H, $J=15.68$ Hz), 6.55–6.67 (m, 3H), 7.10–7.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 20.1, 25.9, 26.3, 30.8, 37.0, 37.5, 42.3, 112.9, 117.3, 124.9, 129.5, 131.6, 148.7. Calcd for $C_{19}H_{27}N$: C, 84.70; H, 10.10; N, 5.20. Found: C, 84.68; H, 10.09; N, 5.18.

4.4. Solvent-free reduction of imines with solid acid-activated $NaBH_4$

4.4.1. General procedure. A mixture of imine derivatives (5 mmol), sodium borohydride (5 mmol) and each boric acid, *p*-toluenesulfonic acid monohydrate or benzoic acid (5 mmol) was ground with an agate mortar and pestle at room temperature (ca 25 °C) for 0.5–1.0 h until TLC showed complete disappearance of the starting material. Work-up procedures for isolation of product amines were identical with those described in Section 4.3.1. Among those, compounds **1–3**, **10–12**, **14** and **27–38** were isolated as nearly pure form without chromatographic separation. IR, ^1H and ^{13}C NMR spectra of compounds **39–47** obtained from this experiment are identical with those reported in literature.[19]

4.4.2. *N*-(*tert*-Butyl)benzylamine (27). Oil; 99% yield using boric or benzoic acid as activator; IR (neat, cm^{-1}) 3319, 3027, 2789, 1455, 1358, 1104, 736, 700; ^1H NMR (200 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.26 (br s, 1H), 3.73 (s, 2H), 7.31–7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.8, 47.9, 51.3, 127.4, 129.1, 142.2, 155.5. Calcd for $C_{11}H_{17}N$: C, 80.93; H, 10.50; N, 8.58. Found: C, 80.95; H, 10.49; N, 8.59.

4.4.3. *N*-Methylbenzylamine (28). Oil; 99% yield using *p*-toluenesulfonic acid as activator; IR (neat, cm^{-1}) 3272, 2933, 2842, 2786, 1496, 1360, 1104, 704; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 (br s, 1H), 2.42 (s, 3H), 3.72 (s, 2H), 7.19–7.31 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 36.6, 56.6, 127.5, 128.7, 128.9, 140.8. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.30; H, 9.23; N, 11.51.

4.4.4. *N*-Phenyl-(2′-thiophenemethyl)amine (29). Oil; 99% yield using boric or *p*-toluenesulfonc acid as activator; IR (neat, cm^{-1}) 3281, 3027, 1609, 1515, 1452, 761, 734; ^1H NMR (300 MHz, $CDCl_3$) δ 3.98 (br s, 1H), 4.45 (s, 2H), 6.63 (d, 2H, $J=8.24$ Hz), 6.72 (t, 1H, $J=7.33$ Hz), 6.91–6.98 (m, 2H), 7.13–7.20 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.2, 113.8, 118.7, 125.3, 125.7, 127.5, 129.9,

143.6, 148.2. Calcd for $C_{11}H_{11}NS$: C, 69.80; H, 5.86; N, 7.40; S, 16.94. Found: C, 69.84; H, 5.95; N, 7.21; S, 16.82.

4.4.5. *N*-Phenyl-(2′-pyridinemethyl)amine (30). Oil; 99% yield using boric or *p*-toluenesulfonc acid as activator; IR (neat, cm^{-1}) 3416, 3028, 2972, 2843, 2788, 1566, 1542, 1028, 737, 700; ^1H NMR (300 MHz, $CDCl_3$) δ 4.45 (s, 3H), 6.65 (d, 2H, $J=7.63$ Hz), 6.71 (t, 1H, $J=7.33$ Hz), 7.13–7.20 (m, 3H), 7.32 (d, 1H, $J=7.63$ Hz), 7.62 (td, 1H, $J=1.53$, 7.11 Hz), 8.57 (d, 1H, $J=4.27$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.8, 1137, 118.2, 122.2, 122.7, 129.8, 137.3, 148.5, 149.7, 159.2. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.27; H, 6.67; N, 15.32.

4.4.6. *N*-Phenyl-1-phenylethylamine (31). Oil; 99% yield using boric acid as activator; IR (neat, cm^{-1}) 3411, 3055, 2926, 1602, 1503; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (d, 3H, $J=6.88$ Hz), 3.99 (br s, 1H), 4.44 (q, 1H, $J=6.69$ Hz), 6.46 (d, 2H, $J=7.43$ Hz), 6.61 (t, 1H, $J=7.29$ Hz), 7.05 (dd, 2H, $J=8.53$, 7.43 Hz), 7.17 (m, 1H), 7.2–7.34 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6, 53.8, 113.6, 117.5, 126.1, 127.2, 128.9, 129.4, 145.5, 147.5. Calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66; N, 7.10. Found: C, 85.27; H, 7.73; N, 7.08.

4.4.7. *N*-Phenyl-1-(*o*-tolyl)ethylamine (32). Oil; 99% yield using boric acid as activator; IR (neat, cm^{-1}) 3411, 3050, 3016, 2967, 2925, 2867, 1601, 1504, 1318, 749, 691; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (d, 3H, $J=6.72$ Hz), 2.42 (s, 3H), 3.97 (br s, 1H), 4.65 (q, 1H, $J=6.61$ Hz), 6.43 (d, 2H, $J=8.24$ Hz), 6.62 (t, 1H, $J=6.72$ Hz), 7.03–7.18 (m, 5H), 7.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 23.6, 50.5, 113.7, 117.8, 125.4, 127.3, 129.8, 131.3, 135.2, 143.4, 148.0. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.27; H, 8.14; N, 6.56.

4.4.8. *N*-Phenyl-1-(*p*-tolyl)ethylamine (33). Oil; 99% yield using boric acid as activator; IR (neat, cm^{-1}) 3407, 3047, 2964, 2919, 2868, 1602, 1505, 1322, 750, 693; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (d, 3H, $J=6.60$ Hz), 2.28 (s, 3H), 3.79 (br s, 1H), 4.40 (q, 1H, $J=6.69$ Hz), 6.46 (d, 2H, $J=7.70$ Hz), 6.59 (t, 1H, $J=7.29$ Hz), 7.01–7.11 (m, 4H), 7.20 (d, 2H, $J=7.98$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 25.6, 53.6, 113.6, 117.5, 126.1, 129.4, 129.7, 136.7, 142.5, 147.6. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.31; H, 8.12; N, 6.67.

4.4.9. *N*-Phenyl-1-(*p*-methoxyphenyl)ethylamine (34). Oil; 99% yield using boric acid as activator; IR (neat, cm^{-1}) 3401, 2962, 2833, 1609, 1504, 1238, 1179, 1035, 831, 751, 695; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (d, 3H, $J=6.88$ Hz), 3.74 (s, 3H), 3.82 (s, 1H), 4.41 (q, 1H, $J=6.69$ Hz), 6.48 (dd, 2H, $J=8.67$, 0.93 Hz), 6.61 (t, 1H, $J=7.29$ Hz), 6.82 (d, 2H, $J=8.80$ Hz), 7.06 (dd, 2H, $J=7.43$, 8.53 Hz), 7.24 (d, 2H, $J=8.80$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 53.2, 55.6, 113.5, 114.2, 117.4, 127.1, 129.3, 137.5, 147.5, 158.6. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.32; H, 7.62; N, 6.34.

4.4.10. *N*-Phenyl-1-(*p*-chlorophenyl)ethylamine (35). Oil; 99% yield using boric acid as activator; IR (neat, cm^{-1}) 3408, 3050, 2965, 2924, 2866, 1604, 1506, 1322, 1013, 755, 696; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, 3H, $J=6.88$ Hz), 3.83 (br s, 1H), 4.39 (q, 1H, $J=6.69$ Hz), 6.43 (d, 2H, $J=8.53$ Hz), 6.63 (t, 1H, $J=7.30$ Hz), 7.05 (t, 2H, $J=7.84$ Hz), 7.09–7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6, 53.4, 113.6, 117.8, 127.5, 129.1, 129.4, 132.6, 144.1, 147.2. Calcd for $C_{14}H_{14}NCl$: C, 72.57; H, 6.09; N, 6.04. Found: C, 72.55; H, 6.05; N, 6.12.

4.4.11. *N*-(*p*-Chlorophenyl)-1-phenylethylamine (36). Mp 59–60 °C; 99% yield using *p*-toluenesulfonic acid as activator; IR (KBr, cm^{-1}) 3432, 2997, 2866, 1596, 1496; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, 3H, $J=6.88$ Hz), 4.03 (br s, 1H), 4.40 (q, 1H, $J=6.69$ Hz), 6.38 (d, 2H, $J=8.80$ Hz), 6.99 (d, 2H, $J=9.08$ Hz), 7.17–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5, 53.9, 114.6, 122.0, 126.0, 127.3, 128.9, 129.1, 144.9, 145.9. Calcd for $C_{14}H_{14}NCl$: C, 72.57; H, 6.09; N, 6.04. Found: C, 72.52; H, 6.12; N, 6.09.

4.4.12. *N*-Phenyl-1-phenylpropylamine (37). Oil; 99% yield using boric acid as activator; IR (neat, cm^{-1}) 3411, 3025, 2963, 2930, 1604, 1509, 1318, 747, 701; ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (t, 3H, $J=7.33$ Hz), 1.81 (quintet, 2H, $J=7.10$ Hz), 4.04 (br s, 1H), 4.21 (t, 2H, $J=6.72$ Hz), 6.50 (d, 2H, $J=7.63$ Hz), 6.02 (t, 1H, $J=7.33$ Hz), 7.07 (t, 2H, $J=7.94$ Hz), 7.16–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.4, 32.3, 60.4, 113.9, 117.8, 127.2, 127.5, 129.2, 129.8, 144.6, 148.2. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.29; H, 8.17; N, 6.72.

4.4.13. 2,3,3-Trimethylindoline (38). Oil; 99% yield using benzoic or *p*-toluenesulfonic acid as activator; IR (neat, cm^{-1}) 3362, 2960, 2861, 1612, 1467, 1378, 1248, 1164, 748; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.16 (d, 3H, $J=6.33$ Hz), 1.27 (s, 3H), 3.48 (q, 1H, $J=6.51$ Hz), 3.64 (br s, 1H), 6.58 (d, 1H, $J=7.70$ Hz), 6.71 (m, 1H), 6.95–7.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.6, 22.8, 26.6, 43.7, 65.5, 109.6, 119.1, 122.5, 127.4, 139.3, 149.5. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69. Found: C, 81.82; H, 9.31; N, 8.54.

4.4.14. 1-Methoxy-2-(2′-ethyl-6′-methylanilino)propane (metolachlor base) (48). R_f 0.62 (EtOAc/hexane 1:2); oil; 99% yield using boric acid as activator; IR (neat, cm^{-1}) 3382, 2964, 2929, 2873, 1593, 1462, 1256, 1105, 756; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, 3H, $J=6.60$ Hz), 1.22 (t, 3H, $J=7.43$ Hz), 2.27 (s, 3H), 2.63 (q, 2H, $J=7.61$ Hz), 3.31 (d, 2H, $J=1.38$ Hz), 3.33 (m, 1H), 3.35 (s, 3H), 6.84 (t, 1H, $J=7.43$ Hz), 6.95–7.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0, 18.9, 19.4, 24.6, 53.2, 59.4, 76.5, 121.9, 126.7, 128.9, 130.0, 135.7, 144.5. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.26; H, 10.17; N, 6.80.

4.4.15. *N*-(*trans*-Cinnamyl)-1-naphthylmethylamine (naftifine base) (49). R_f 0.08 (EtOAc/hexane 1:2); 39–40 °C (lit.[28] 39.5–40.5 °C); 78% yield using benzoic acid as activator; IR (KBr, cm^{-1}) 3314, 3057, 3025, 2920, 2817, 1597, 1494, 1447, 967, 779, 692; ^1H NMR (300 MHz, $CDCl_3$) δ 1.88 (br s, 1H), 3.50 (dd, 2H, $J=6.33$, 1.10 Hz), 4.24 (s, 2H), 6.33 (dt, 1H, $J=15.68$, 6.26 Hz), 6.54 (d, 1H, $J=15.95$ Hz), 7.15–7.53 (m, 9H), 7.74 (d, 1H, $J=7.98$ Hz), 7.83 (d, 1H, $J=7.70$ Hz), 8.08 (d, 1H, $J=7.98$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.2, 52.1, 123.9, 125.9, 125.7, 126.0, 126.4, 126.5, 126.6, 127.7, 128.1, 128.5, 129.0, 131.9, 132.0, 135.9, 137.3. Calcd for $C_{20}H_{19}N$: C, 87.87; H, 7.01; N, 5.12. Found: C, 87.89; H, 7.02; N, 5.15.

4.4.16. 6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (salsolidine) (52). R_f 0.16 (EtOAc/MeOH 4:1); mp 47–49 °C (lit.[27] 47–49 °C); 99% yield using *p*-toluenesulfonic acid as activator; IR (KBr, cm^{-1}) 3212, 2939, 2380, 2267, 1612, 1513, 1465, 1260, 1167; ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 (d, 3H, $J=6.60$ Hz), 2.94–3.15 (m, 2H), 3.28 (m, 1H), 3.45 (m, 1H), 3.84 (s, 6H), 4.46 (q, 1H, $J=6.41$ Hz), 4.97 (br s, 1H), 6.60 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 25.6, 50.7, 56.2, 108.7, 111.3, 123.7, 125.8, 148.0, 148.3. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.57; H, 8.25; N, 6.77.

Acknowledgements

This work was supported by the Research Grant from Hallym University, Korea.

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22. For the reduction of **1B**, we also examined effect of other solid acids, such as *p*-nitro (or chloro)benzoic acids and benzene sulfonic acids, as activators. We did not observe any significant difference of effectiveness among those acids including boric acid, PTSA and benzoic acid.
23. IR and ^{11}B NMR spectra of $NaBH_4$ showed at 2610 cm^{-1} (KBr) and -36.28 ppm (in diglyme), respectively. In contrast, IR spectrum of $NaBH(OAc)_3$ purchased from Aldrich Chemical Co. exhibited at 2499 and 1682 cm^{-1} as a stretching vibration bond of B–H and C=O, respectively. ^{11}B NMR spectrum for this reagent showed at $+20.03$ ppm as major peak.
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