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One-pot reductive amination of aldehydes and ketones with α-picoline-borane in methanol, in water, and in neat conditions☆

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Abstract—A one-pot reductive amination of aldehydes and ketones with amines using α-picoline-borane as a reducing agent is described. The reaction has been carried out in MeOH, in H_2O, and in neat conditions in the presence of small amounts of AcOH. This is a highly efficient and mild procedure that is applicable for a wide variety of substrates. In particular, this is the first successful demonstration that this type of reaction can be carried out in water and in neat conditions.

1. Introduction

In biological and chemical systems, one-pot reductive amination of aldehydes and ketones is an important transformation, which allows the direct conversion of carbonyl compounds into amines using simple operations.[1] A variety of reducing agents, such as sodium cyanoborohydride ($NaBH_3CN$),[1a,2] sodium triacetoxyborohydride [$NaBH(OAc)_3$],[3] pyridine-borane (pyr-BH_3),[4] $Ti(Oi\text{-}Pr)_4$/$NaBH_4$,[5] borohydride exchange resin,[6] $Zn(BH_4)_2/SiO_2$,[7] Bu_3SnH/SiO_2,[8] and $PhSiH_4/Bu_2SnCl_2$[9] have been developed for this conversion.

The choice of the reducing agent is very critical to the success of the reaction, since the reducing agent must reduce imines selectively over aldehydes or ketones. The reductive aminations with $NaBH_3CN$ are successfully carried out using a five-fold excess of amine at pH 6–8.[2b] However, the use of expensive and highly toxic $NaBH_3CN$ that carries the risk of having residual cyanide in the product as well as in the work-up stream, makes this procedure less attractive. Clearly the use of $NaBH_3CN$ is not acceptable in the context of green synthesis, especially in industry.

In a search for alternatives to the cyanohydroborates as reductants for reductive amination, the use of $NaBH(OAc)_3$ has been reported.[3e] Although this reagent reduces imines selectively over carbonyl compounds in 1,2-dichloroethane, solvents such as methanol or water are not suitable because of rapid reduction of the carbonyl compound or because of decomposition of the reducing agent in water. In addition, this reagent has only one available hydrogen in a molecule and 1.3–1.6 mol equiv of the reagent are necessary for the reaction. Reductive aminations with pyr-BH_3[4a] and methanolic pyr-BH_3[4b] in the presence of 4 Å molecular sieves were also reported. Very recently, it has been reported that amine-boranes possess interesting properties that could overcome the disadvantages of using $NaBH_4$ and $NaBH_3CN$.[10] It was previously reported that pyr-BH_3 was found to be superior to $NaBH_3CN$ for the reductive amination of aldehydes with piperidines.[4c] Usually pyr-BH_3 from commercial sources was utilized without further purification,[11] because this reagent is quite unstable to heat and attempted distillation of the liquid residue at reduced pressures sometimes resulted in violent decompositions.[12] Thus, extreme care must be used if this reagent is handled in large quantities. Industrial applications seem problematic, despite the availability of a patented method for purification, because of this instability that also leads to difficulty of storage for extended periods.[13] Therefore, introduction of new reagents that alleviate or eliminate the above-mentioned problems would be a useful contribution to synthetic organic chemistry. We have approached this challenge to discover a new reagent and methodology from the view point of both process chemistry and green chemistry.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.06.045

Keywords: Reductive amination; Picoline-borane; Water solvent; Neat condition.

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Table 1. Reductive amination of carbonyl compounds with pic-BH_3 in MeOH–AcOH (10:1)[a]

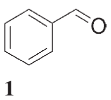
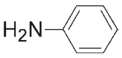
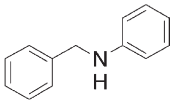
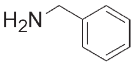
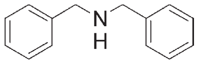
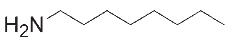
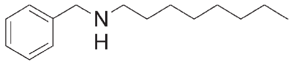
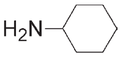
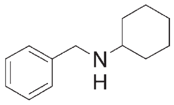
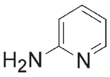
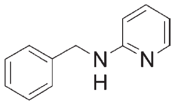
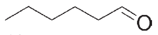
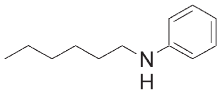
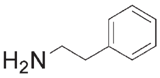
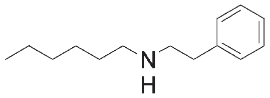
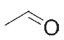
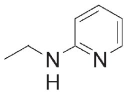
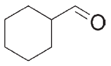
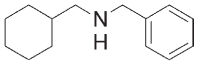
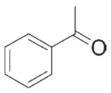
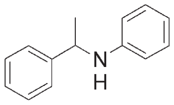
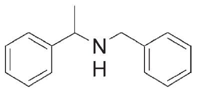
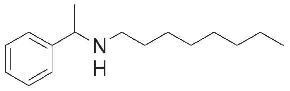
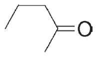
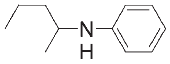
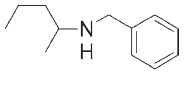
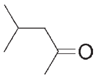
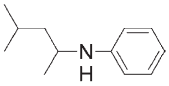
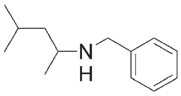
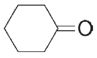
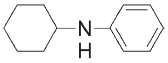
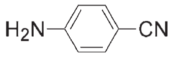
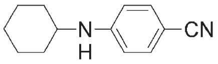
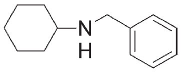
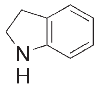
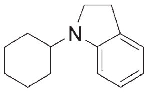
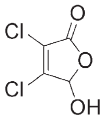
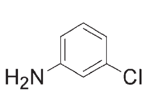
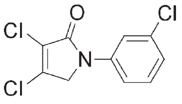
Entry	Carbonyl compound	Amine	Time (h)	Product	Yield (%)
1	 **1**	 **2**	2	 **3**	95
2	**1**	 **4**	2	 **5**	76
3	**1**	 **6**	1	 **7**	72
4	**1**	 **8**	18	 **9**	60
5	**1**	 **10**	1	 **11**	73
6	 **12**	**2**	1[b]	 **13**	82[c]
7	**12**	 **14**	1	 **15**	62[d]
8	 **16**	**10**	1	 **17**	80[e]
9	 **18**	**4**	1	 **19**	77
10	 **20**	**2**	24	 **21**	73
11	**20**	**4**	72	 **22**	72
12	**20**	**4**	24	**22**	52
13	**20**	**6**	30	 **23**	45
14	 **24**	**2**	6	 **25**	89
15	**24**	**4**	6	 **26**	79

Table 1 (*continued*)

Entry	Carbonyl compound	Amine	Time (h)	Product	Yield (%)
16	 **27**	**2**	17	 **28**	95
17	**27**	**4**	6	 **29**	80
18	 **30**	**2**	1	 **31**	95
19	**30**	 **32**	3	 **33**	73
20	**30**	**4**	1	 **9**	73
21	**30**	 **34**	1	 **35**	98
22	 **36**	 **37**	40	 **38**	76

[a] Equimolar equiv of carbonyl compounds, amines, and pic-BH_3 was used.
[b] Minute.
[c] Without addition of AcOH.
[d] Two equiv of 2-phenethylamine were used.
[e] Three equiv of acetaldehyde were used.

2. Results and discussion

2.1. Reductive amination in MeOH with α-picoline-borane

In the course of our investigations of the chemistry of amine-boranes, we have found that α-picoline-borane (pic-BH_3) is a cheap and commercially available alternative to $NaBH_3CN$ or pyr-BH_3 for the purpose of reductive amination reaction. Pic-BH_3 is superior to pyr-BH_3 in the following respects. (1) Pic-BH_3 is a commercially available crystalline solid (mp 44–45 °C) that is more stable to heat than pyr-BH_3 (melting point of pic-BH_3 was not changed after it was heated to above 150 °C). (2) Pic-BH_3 can be purified by recrystallization from hexane and be stored for long periods without noticeable decomposition. It was reported in the recently published Callery bulletin[14] that above a temperature 54 °C, pyr-BH_3 undergo a self-sustaining exothermic decomposition that may cause fire or explosions. The shelf-life of pyr-BH_3 is 6 months.

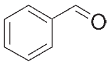
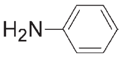
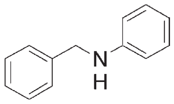
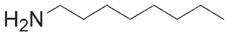
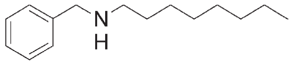
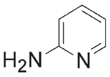
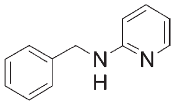
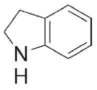
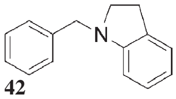
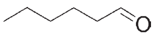
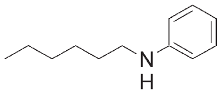
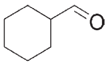
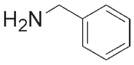
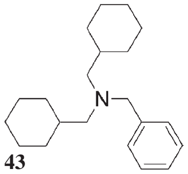
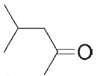
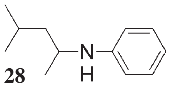
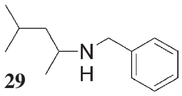
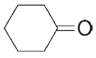
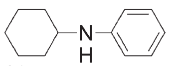
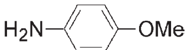
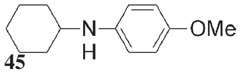
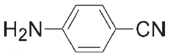
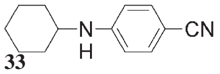
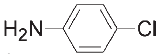
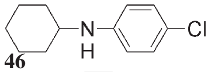
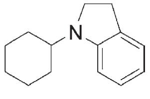
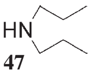
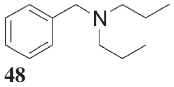
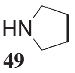
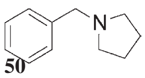
The direct reductive amination reactions were carried out in MeOH–AcOH (10:1) using pic-BH_3 as a reducing agent. The reductive amination of a wide variety of aldehydes and ketones with primary and secondary amines was successful and gave the desired products in good to excellent yields as shown in Table 1.

Equimolar amounts of amine, carbonyl compounds, and pic-BH_3 were generally used for the reaction. For most ketones, reactions were improved by the addition of AcOH. However, for hexanal (**12**), a better result was obtained without addition of AcOH (Table 1, entry 6). Recently 2-ethylaminopyridine (**17**) was synthesized from 2-aminopyridine (**10**) in three steps.[15] According to the present method **17** was obtained from **10** and acetaldehyde in a one-pot operation in 80% yield (Table 1, entry 8). More recently, the direct reductive amination of mucochloric acid has been reported and compound **38** was obtained in 65% yield using 3 equiv of $NaBH(OAc)_3$ in CH_2Cl_2–AcOH for 24 h at room temperature.[16] According to the present method **38** was obtained from the same starting compounds in 76% yield for 40 h (Table 1, entry 22).

2.2. Reductive amination in water

It is generally accepted that strict anhydrous conditions are favorable to generate imines or imminium ions, which are subsequently reduced by the reducing agents. Therefore, combinations of a reducing agent and dry molecular

Table 2. Reductive amination of carbonyl compounds with pic-BH_3 in H_2O–AcOH (10:1)

Entry	Carbonyl compound	Amine	Time (h)	Product	Yield (%)
1	 **1**	 **2**	2	 **3**	91
2	**1**	 **6**	1	 **7**	71
3	**1**	 **10**	3	 **11**	59
4	**1**	 **34**	1	 **42**	88
5	 **12**	**2**	5[a]	 **13**	73[b]
6	 **18**	 **4**	1	 **43**	91[c]
7	 **27**	**2**	17	 **28**	90
8	**27**	**4**	6	 **29**	51
9	 **30**	**2**	1	 **31**	94
10	**30**	 **44**	1	 **45**	97
11	**30**	 **32**	4.5	 **33**	74
12	**30**	 **37**	9	 **46**	91
13	**30**	**34**	1	 **35**	90
14	**1**	 **47**	3	 **48**	3[d]
15	**1**	 **49**	3	 **50**	30

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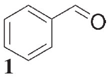
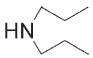
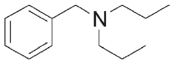
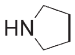
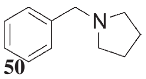
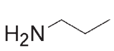
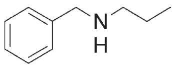
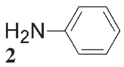
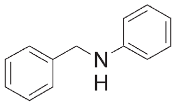
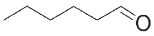
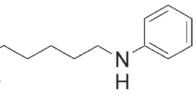
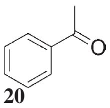
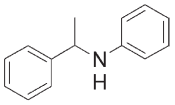
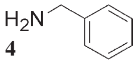
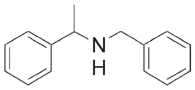
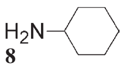
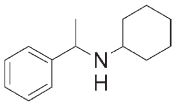
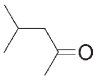
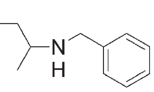
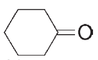
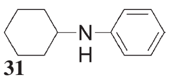
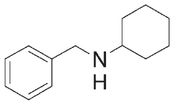
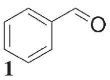
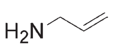
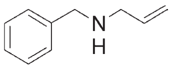
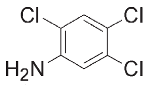
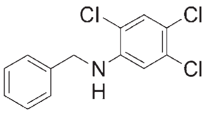
[a] Minute.

[b] Without addition of AcOH.

[c] Four equiv of cyclohexanecarboxaldehyde were used.

[d] Plus benzyl alcohol (77%).

Table 3. Solvent-free reductive amination of carbonyl compounds with pic-BH_3

Entry	Carbonyl compound	Amine	Time (h)	Product	Yield (%)
1	 **1**	 **47**	24	 **48**	48[a]
2	**1**	 **49**	10	 **50**	76[a]
3	**1**	 **51**	72	 **52**	66[a]
4	**1**	 **2**	2	 **3**	99
5	 **12**	**2**	1	 **13**	77[b]
6	 **20**	**2**	63.5	 **21**	91
7	**20**	 **4**	72	 **22**	87
8	**20**	 **8**	120	 **53**	27
9	 **27**	**4**	3.5	 **29**	63
10	 **30**	**2**	3.5	 **31**	94
11	**30**	**4**	15.5	 **9**	78
12	 **1**	 **54**	48	 **55**	65[c]
13	**1**	 **56**	24	 **57**	65[c]

[a] Three equiv of amine were used.
[b] Without addition of AcOH.
[c] Minimum amounts of MeOH were added to dissolve the solid **56**.

sieves[2,3a,d,4b,17,18] or anhydrous $MgSO_4$[19] or Na_2SO_4[20] or titanium(IV) isopropoxide[21] were employed for imine or imminium ion formation and subsequent reduction. However, it is operationally troublesome to keep anhydrous conditions during a reaction and we, therefore, have tried a solvent system containing a small amount of water (MeOH–AcOH–H_2O (10:1:1)). We have tried several examples of reductive amination reactions using the above solvent system and found that yields of products are slightly lowered, but practically the same, compared with those in the methanol solvent system.

Encouraged by the above results, we have conducted the same reductive amination reaction in water. Water is a cheap, nontoxic, nonflammable, and environmentally benign solvent. As a consequence of serious pollution problems, the use of organic transformations in water is presently undergoing a very rapid growth.[22] On the other hand, it is generally accepted that dehydration is one of the reactions that is difficult to carry out in water.[23] Reductive amination in solvents containing water has not been reported except for some aldehydes which are only available commercially as aqueous solution.[24] This is because the equilibrium formation of imines or imminium ions from carbonyl compounds and amines by elimination of water molecules is favored in anhydrous conditions and would be expected to be highly disfavored in water.

First, we carried out the reductive amination of cyclohexanone (**30**) (200 mg, 2.04 mmol) with aniline (**2**) (190 mg, 2.04 mmol) using pic-BH_3 (218 mg, 2.04 mmol) in H_2O (5 mL) and AcOH (0.5 mL) at room temperature for 2 h. Although the reaction should occur in the heterogeneous phase, the reaction mixture seemed to be homogeneous and after usual work up cyclohexylphenylamine (**31**) (334 mg, 94%) was obtained in high yield (Table 2, entry 9). The same reaction was conducted in larger scale (**30**, 3.0 g; **2**, 2.85 g; pic-BH_3, 3.27 g; H_2O, 50 mL; AcOH, 5 mL; room temperature; 3.5 h) and **31** (5.09 g, 95%) was obtained in a similar yield. This reaction is successful in water although it involves the elimination of a molecule of water. Several carbonyl compounds and amines reacted in this way and the results are presented in Table 2.

Reductive amination reactions with highly water soluble amines do not proceed satisfactorily (Table 2, entries 14 and 15). On the other hand, reactions with poorly water-soluble carbonyl compounds and amines proceed smoothly to give high yields of the products. Although, the exact role of water in these reactions is still not well understood, this might be ascribed to promotion of hydrophobic association of carbonyl compounds, amines, and pic-BH_3 in water, when respective substrates are poorly soluble in water. This could facilitate smooth formation of imines or imminium ions and subsequent reduction by pic-BH_3. In addition, a good selectivity of pic-BH_3 for reduction of imines over carbonyls is assumed.

2.3. Solvent-free reductive amination

Finally, we have undertaken the reductive amination in neat conditions. Many organic solvents are ecologically harmful, and the best solvent formulation from an ecological point of view is no solvent.[25]

Initially, we carried out the solvent-free reductive amination of cyclohexanone (3.00 g, 30.57 mmol) with aniline (2.85 g, 30.57 mmol) using pic-BH_3 (3.27 g, 30.57 mmol) at room temperature for 6 h. After the usual workup cyclohexylphenylamine (4.36 g, 81%) was obtained. The same reaction was conducted by the addition of AcOH (0.5 mL) and the product (5.05 g, 94%) was obtained in high yield. Several carbonyl compounds and amines reacted in this way and the results are presented in Table 3.

The reaction proceeded smoothly even in the case of water soluble amines to afford the corresponding products in good yields (Table 3, entries 2 and 3).

Generally, aromatic ketones are poor substrates for reductive amination protocols. In the reductive amination of acetophenone with benzylamine, the desired product was obtained with $NaBH(OAc)_3$ in 10 days in 55% yield[3e] and with a combination of pyr-BH_3 and dry molecular sieves in 10% yield.[4b] Furthermore, 1-phenylethanol, the reduction product of acetophenone, is the only isolable product from the reactions of aliphatic amines with acetophenone using pyr-BH_3 and acetic acid.[4a] On the other hand, in this neat condition using pic-BH_3 as a reducing agent, reductive amination of acetophenone proceeded smoothly to afford the corresponding amines in good yields for 72 h (Table 3, entries 6 and 7).

Solvent-free reductive amination seems to hold promise to be a highly useful technique, especially for industry. Nevertheless, workup processes, except for a few examples, invariably involve the use of solvent. Therefore, since the use of solvent should be minimized as far as possible, or even avoided altogether, devising workup conditions on a case by case basis would be necessary. However, this solvent-free process using pic-BH_3 throws a challenge to the existing reductive amination procedures, which use ecologically harmful solvents and toxic reagents.

3. Conclusion

Pic-BH_3 is a thermally stable transparent solid and can be stored on a shelf for months without appreciable loss of reducing ability. The use of pic-BH_3 eliminates the problems encountered with the use of other reducing agents such as $NaBH_3CN$, $NaBH(OAc)_3$ and pyr-BH_3. Especially, the use of water as solvent and/or solvent-free conditions can offer a great opportunity for green chemistry. In summary, we have developed an expeditious, easy-to-handle and environmentally friendly approach to the synthesis of a variety of amines through a three-component one-pot reaction of carbonyl compounds, amines, and pic-BH_3.

4. Experimental

4.1. General

All melting points were determined with a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^1H NMR spectra were measured at 270 MHz on a JEOL JNM-EX270 spectrometer with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent, unless otherwise noted. ^1H NMR spectral data are reported in parts per million (δ) relative to Me_4Si. IR spectra were recorded on a JASCO IR 810 spectrophotometer. Mass spectra were obtained with a JEOL JMS-700 spectrometer with a direct inlet system at

70 eV. Elemental analyses were performed in the Microanalytical Laboratory of this University.

All starting carbonyl compounds and amines were purchased from Tokyo Kasei Kogyo Co., Ltd and α-picoline-borane was obtained from Shiroi Yakuhin Co., Ltd and used without further purification.

4.2. Typical procedure for the preparation of 3 in MeOH–AcOH

To benzaldehyde (**1**) (200 mg, 1.88 mmol) and aniline (**2**) (176 mg, 1.88 mmol) in MeOH–AcOH (10:1, 5.5 mL) was added pic-BH_3 (201 mg, 1.88 mmol) and the reaction mixture was stirred for 2 h at room temperature. After the reaction, MeOH was evaporated in vacuo and 10% HCl (10 mL) was added to the residue. The aqueous solution was stirred for 0.5 h at room temperature, and Na_2CO_3 (ca. 2.5 g) and H_2O (10 mL) were added under cooling to make the solution alkaline. The aqueous layer was extracted with AcOEt (30 mL×2), and the combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, and concentrated. The crude product was chromatographed on a column of silica gel with AcOEt–*n*-hexane (1:6) to afford benzylphenylamine (**4**) (329 mg, 95%).

4.2.1. Hexylphenethylamine (15). Oil. IR (neat): 3300, 3030, 2930, 2860, 2820, 1610, 1500, 700 cm^{-1}; ^1H NMR (270 MHz) δ 0.87 (t, *J*=6.6 Hz, 3H), 1.15–1.60 (m, 9H), 2.60 (t, *J*=7.3 Hz, 2H), 2.76–2.92 (m, 4H), 7.15–7.35 (m, 5H); ^{13}C NMR (68 MHz) δ 14.1, 22.7, 27.1, 30.1, 31.8, 36.5, 49.9, 51.3, 125.9, 128.3, 128.5, 140.0; FAB-MS (3-nitrobenzyl alcohol) *m/z* 206 (M^++H); HR-MS (FAB) for $C_{14}H_{23}N$ Calcd 206.1909 (M^++H), found 206.1912.

4.2.2. 4-Cyclohexylaminobenzonitril (33). White crystals. Mp 114–116 °C (AcOEt–*n*-hexane); IR (KBr): 3330, 2940, 2850, 2210, 1610, 1530 cm^{-1}; ^1H NMR (270 MHz) δ 1.10–1.48 (m, 5H), 1.60–1.84 (m, 3H), 1.96–2.10 (m, 2H), 3.20–3.38 (m, 1H), 4.11 (br s, 1H), 6.52 (dt, *J*=8.7, 2.1 Hz, 2H), 7.39 (dt, *J*=8.4, 2.0 Hz, 2H); ^{13}C NMR (68 MHz) δ 24.8, 25.7, 33.0, 51.2, 97.7, 112.2, 120.5, 133.5, 150.3; EI-MS *m/z* 200 (M^+, 32.83), 157 (100). Anal. Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99, found: C, 77.71; H, 8.20; N, 13.82.

4.2.3. *N*-Cyclohexylindoline (35). Oil. IR (neat): 2930, 2850, 1610, 1490 cm^{-1}; ^1H NMR (270 MHz) δ 1.02–1.95 (m, 10H), 2.93 (t, *J*=8.4 Hz, 2H), 3.28–3.42 (m, 3H), 6.40 (d, *J*=8.1 Hz, 1H), 6.57 (td, *J*=7.3, 0.9 Hz, 1H), 6.98–7.09 (m, 2H); ^{13}C NMR (68 MHz) δ 26.1, 26.2, 28.4, 28.8, 46.7, 54.6, 106.7, 116.4, 124.2, 127.0, 129.9, 151.0; EI-MS *m/z* 201 (M^+, 46.36), 158 (100); HR-MS (EI) for $C_{14}H_{19}N$ Calcd 201.1517, found 201.1525.

4.3. Typical procedure for the preparation of 31 in H_2O–AcOH

A mixture of cyclohexanone (**30**) (200 mg, 2.04 mmol), aniline (**2**) (190 mg, 2.04 mmol), and pic-BH_3 (218 mg, 2.04 mmol) was stirred for 1 h at room temperature in H_2O–AcOH (10:1, 5.5 mL). After the reaction, 10% Na_2CO_3 (20 mL) was added and the aqueous solution was extracted with AcOEt (30 mL×2), and the combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, and concentrated. The crude product was chromatographed on a column of silica gel with AcOEt–*n*-hexane (1:3) to afford cyclohexylphenylamine (**31**) (334 mg, 94%).

4.3.1. *N*-Benzylindoline (42). Oil. IR (neat): 3030, 2920, 2830, 1610, 1490 cm^{-1}; ^1H NMR (270 MHz) δ 2.96 (t, *J*=8.3 Hz, 2H), 3.30 (t, *J*=8.3 Hz, 2H), 4.24 (s, 2H), 6.50 (d, *J*=7.8 Hz, 1H), 6.66 (t, *J*=7.2 Hz, 1H), 7.00–7.12 (m, 2H), 7.20–7.40 (m, 5H); ^{13}C NMR (68 MHz) δ 28.6, 53.6, 53.7, 106.9, 117.6, 124.4, 127.0, 127.2, 127.8, 128.3, 129.9, 138.3, 152.4; EI-MS *m/z* 209 (M^+, 100), 132 (35.54), 118 (29.45), 91 (96.68); HR-MS (EI) *m/z* for $C_{15}H_{15}N$ Calcd 209.1204, found 209.1214.

4.3.2. Benzyl-bis-cyclohexylmethylamine (43). Oil. IR (neat): 3030, 2930, 2850, 2800, 1610, 1500, 740, 700 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6) δ 0.62–0.82 (m, 4H), 0.98–1.86 (m, 18H), 2.08 (d, *J*=7.1 Hz, 4H), 3.42 (s, 2H), 7.16–7.36 (m, 5H); ^{13}C NMR (68 MHz) δ 26.3, 27.0, 31.9, 36.1, 59.9, 62.0, 126.3, 127.8, 128.7, 140.6; EI-MS *m/z* 299 (M^+, 1.89), 216 (100), 91 (39.61); HR-MS (EI) for $C_{21}H_{33}N$ Calcd 299.2613, found 299.2610.

4.3.3. *N*-Cyclohexyl-*p*-anisidine (45). Oil. IR (neat): 3380, 2930, 2850, 1620, 1510 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6) δ 1.00–1.39 (m, 5H), 1.52–1.76 (m, 3H), 1.83–1.96 (m, 2H), 2.99–3.15 (m, 1H), 3.62 (s, 3H), 4.85 (d, *J*=7.9 Hz, 1H), 6.50 (d, *J*=8.7 Hz, 2H), 6.68 (d, *J*=8.9 Hz, 2H); ^{13}C NMR (68 MHz) δ 25.1, 26.0, 33.6, 52.8, 55.8, 114.7, 114.8, 141.4, 151.6; EI-MS *m/z* 205 (M^+, 68.28), 162 (100); HR-MS (EI) for $C_{13}H_{19}NO$ Calcd 205.1467, found 205.1464.

4.3.4. (4-Chlorophenyl)cyclohexylamine (46). Oil. IR (neat): 3420, 2930, 2860, 1600, 1500 cm^{-1}; ^1H NMR (270 MHz) δ 1.05–1.46 (m, 5H), 1.50–1.83 (m, 3H), 1.95–2.10 (m, 2H), 3.14–3.26 (m, 1H), 3.52 (br s, 1H), 6.49 (dt, *J*=8.7, 2.7 Hz, 2H), 7.08 (dt, *J*=8.7, 2.6 Hz, 2H); ^{13}C NMR (68 MHz) δ 25.0, 25.9, 33.3, 51.8, 114.0, 121.1, 128.9, 145.8; EI-MS *m/z* 211 (M^++2, 16.84), 209 (M^+, 51.68), 166 (100); HR-MS (EI) for $C_{12}H_{16}ClN$ Calcd 209.0971, found 209.0990.

4.3.5. *N*,*N*-Dipropylbenzylamine (48). Oil. IR (neat): 2960, 2880, 2800, 1610, 1500, 740, 700 cm^{-1}; ^1H NMR (270 MHz) δ 0.86 (t, *J*=7.4 Hz, 6H), 1.40–1.55 (m, 4H), 2.37 (t, *J*=7.3 Hz, 4H), 3.55 (s, 2H), 7.18–7.36 (m, 5H); ^{13}C NMR (68 MHz) δ 12.0, 20.3, 55.9, 58.7, 126.4, 127.9, 128.6, 140.3; EI-MS *m/z* 191 (M^+, 2.33), 162 (38.96), 91 (100); HR-MS (EI) for $C_{13}H_{21}N$ Calcd 191.1674, found 191.1672.

4.3.6. *N*-Benzylpyrrolidine (50). Oil. IR (neat): 3040, 2970, 2800, 1610, 1500 740, 700 cm^{-1}; ^1H NMR (270 MHz) δ 1.70–1.87 (m, 4H), 2.43–2.58 (m, 4H), 3.61 (s, 2H), 7.19–7.36 (m, 5H); ^{13}C NMR (68 MHz) δ 23.4, 54.1, 60.7, 126.8, 128.1, 128.9, 139.3; EI-MS *m/z* 161 (M^+, 34.21), 91 (100), 84 (49.07), 70 (32.29); HR-MS (EI) for $C_{11}H_{15}N$ Calcd 161.1204, found 161.1205.

4.4. Typical procedure for the preparation of 22 in neat condition

To acetophenone (**20**) (1.00 g, 8.32 mmol), benzylamine (**4**)

(0.89 g, 8.32 mmol), and AcOH (0.3 mL) was added pic-BH_3 (0.89 g, 8.32 mmol) over 5 min and the reaction mixture was stirred for 72 h. After the reaction, 10% HCl (10 mL) was added and the aqueous solution was stirred for 0.5 h at room temperature. Na_2CO_3 (ca. 2.5 g) and H_2O (10 mL) were added to the solution under cooling to make the solution alkaline. The aqueous layer was extracted with AcOEt (30 mL×2), and the combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, and concentrated. The crude product was chromatographed on a column of silica gel with AcOEt–*n*-hexane (1:3) to afford *N*-benzyl-1-phenylethylamine (**22**) (1.53 g, 87%).

4.4.1. Benzylpropylamine (52). Oil. IR (neat): 3320, 3070, 3030, 2960, 2930, 2880, 2820, 1610, 1500, 740, 700 cm^{-1}; ^1H NMR (270 MHz) δ 0.92 (t, J=7.4 Hz, 3H), 1.45–1.61 (m, 3H), 2.60 (t, J=7.3 Hz, 2H), 3.79 (s, 2H), 7.19–7.36 (m, 5H); ^{13}C NMR (68 MHz) δ 11.8, 23.2, 51.3, 53.9, 126.6, 127.9, 128.1, 140.3; EI-MS *m/z* 149 (M^+, 3.56), 120 (28.15), 91 (100); HR-MS (EI) for $C_{10}H_{15}N$ Calcd 149.1204, found 149.1226.

4.4.2. Allylbenzylamine (55). Oil. IR (neat): 3300, 3060, 3020, 2910, 2800, 1640, 1600, 1495, 695 cm^{-1}; ^1H NMR (270 MHz) δ 1.44 (s, 1H), 3.28 (dt, J=5.9, 1.2 Hz, 2H), 3.79 (s, 2H), 5.11 (dd, J=10.2, 1.3 Hz, 1H), 5.20 (dq, J=17.1, 1.5 Hz, 1H), 5.85–6.04 (m, 1H), 7.20–7.38 (m, 5H); ^{13}C NMR (68 MHz) δ 51.8, 53.3, 115.9, 126.8, 128.0, 128.3, 136.6, 140.1; EI-MS *m/z* 147 (M^+, 22.95), 120 (7.78), 91 (100); HR-MS (EI) for $C_{10}H_{13}N$ Calcd 147.1048, found 147.1049.

4.4.3. *N*-Benzyl-2,4,5-trichloroaniline (57). White crystals. Mp 46–49 °C (*n*-hexane); IR (KBr): 3420, 1600, 1500, 700 cm^{-1}; ^1H NMR (270 MHz) δ 4.36 (d, J=5.4 Hz, 2H), 4.73 (bs, 1H), 6.68 (s, 1H), 7.23–7.43 (m, 6H); ^{13}C NMR (68 MHz) δ 47.9, 112.1, 117.6, 119.3, 127.2, 127.6, 128.8, 129.7, 131.5, 137.4, 143.1; EI-MS *m/z* 291 (M^++6, 0.76), 289 (M^++4, 6.57), 287 (M^++2, 20.37), 285 (M^+, 21.49), 208 (3.48), 91 (100). Anal. Calcd for $C_{13}H_{10}Cl_3N$: C, 54.48; H, 3.52; N, 4.89, found: C, 54.49; H, 3.31; N, 4.77.

5. Supplementary material

^1H NMR spectra of all products reported in Table 1–3.

References and notes

1. (a) Baxter, E. W.; Reitz, A. B. *Org. React.* **2002**, *59*, 1. (b) Hutchins, R. O.; Natale, N. R. *Org. Prep. Proced. Int.* **1979**, *11*, 201. (c) Lane, F. *Synthesis* **1975**, 135.
2. (a) Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673. (b) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
3. (a) Zhang, J.; Blazecka, P. G.; Davidson, J. G. *Org. Lett.* **2003**, *5*, 553. (b) Hammarström, L. G. J.; Smith, D. B.; Talamás, F. X.; Labadie, S. S.; Krauss, N. E. *Tetrahedron Lett.* **2002**, *43*, 8071. (c) Beshore, D. C.; Dinsmore, C. J. *Org. Lett.* **2002**, *4*, 1201. (d) Dinsmore, C. J.; Zartman, C. B. *Tetrahedron Lett.* **2000**, *41*, 6309. (e) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849. (f) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595.
4. (a) Pelter, A.; Rosser, R. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 717. (b) Bomann, M. D.; Guch, I. C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995. (c) Moormann, A. E. *Synth. Commun.* **1993**, *23*, 789.
5. (a) Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463. (b) Kumpaty, H. J.; Williamson, J. S.; Bhattacharyya, S. *Synth. Commun.* **2003**, *33*, 1411. (c) Neidigh, K. A.; Avery, M. A.; Williamson, J. S.; Bhattacharyya, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2527. (d) Bhattacharyya, S. *J. Org. Chem.* **1995**, *60*, 4928. (e) Bhattacharyya, S.; Chatterjee, A.; Williamson, J. S. *Synlett* **1995**, 1079.
6. Yoon, N. M.; Kim, E. G.; Son, H. S.; Choi, J. *Synth. Commun.* **1993**, *23*, 1595.
7. Ranu, B. C.; Majee, A.; Sarkar, A. *J. Org. Chem.* **1998**, *63*, 370.
8. Hiroi, R.; Miyoshi, N.; Wada, M. *Chem. Lett.* **2002**, 274.
9. Apodaca, R.; Xiao, W. *Org. Lett.* **2001**, *3*, 1745.
10. Alexandre, F.-R.; Pantaleone, D. P.; Taylor, P. P.; Fotheringham, I. G.; Ager, D. J.; Turner, N. J. *Tetrahedron Lett.* **2002**, *43*, 707.
11. (a) Miller, V. R.; Ryschkewitsch, G. E.; Chandra, S. *Inorg. Chem.* **1970**, *9*, 1427. (b) Brown, H. C.; Murray, K. J.; Murray, L. J.; Snover, J. A.; Zweifel, G. *J. Am. Chem. Soc.* **1960**, *82*, 4233. (c) Ashby, E. C. *J. Am. Chem. Soc.* **1959**, *81*, 4791.
12. (a) Ryschkewitsch, G. E.; Birnbaum, E. R. *Inorg. Chem.* **1965**, *4*, 575. (b) Baldwin, R. A.; Washburn, R. M. *J. Org. Chem.* **1961**, *26*, 3549. (c) Brown, H. C.; Domash, L. *J. Am. Chem. Soc.* **1956**, *78*, 5384.
13. JP Patent 112,988, **1995**..
14. *Amine Borane*; Callery Chemical Technical Bulletin, **2002**, p 9.
15. Krein, D. M.; Lowary, T. L. *J. Org. Chem.* **2002**, *67*, 4965.
16. Zhang, J.; Blazecka, P. G.; Davidson, J. G. *Org. Lett.* **2003**, *5*, 553.
17. Dinsmore, C. J.; Zartman, C. B. *Tetrahedron Lett.* **2000**, *41*, 6309.
18. Beshore, D. C.; Dinsmore, C. J. *Org. Lett.* **2002**, *4*, 1201.
19. (a) Rompaey, K. V.; Van den Eynde, I.; Kimpe, N. D.; Tourwé, D. *Tetrahedron* **2003**, *59*, 4421. (b) Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407.
20. Coe, J. W.; Vetelino, M. G.; Bradlee, M. J. *Tetrahedron Lett.* **1996**, *37*, 6045.
21. Bhattacharyya, S. *Tetrahedron Lett.* **1994**, *35*, 2401. Later it was reported that titanium(IV) isopropoxide acts as a Lewis acid to produce an aminocarbinolatotitanium(IV) complex intermediate which is reduced either directly or via transient imminium species. See Bhattacharyya, S.; Neidigh, K. A.; Avery, M. A.; Williamson, J. S. *Synlett* **1999**, 1781. Ref. 5c,d. Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552.
22. (a) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751. (b) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741.
23. Manabe, K.; Iimura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971.
24. Reductive amination of aqueous formaldehyde (10 equiv, 37% in H_2O) with amines using $NaBH_3CN$ (3 equiv.) in CH_3CN is reported (Ref. 2a). Recently, the reductive amination of aqueous formaldehyde (30% in H_2O) and glutaraldehyde (25% in H_2O) with 1-phenylpiperazine in 1,2-dichloroethane using $NaBH(OAc)_3$ (4 equiv.) is reported (Ref. 3c).
25. (a) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159. (b) Metzger, J. O. *Angew. Chem., Int. Ed.* **1998**, *37*, 2975.