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Dichlorobis(1,4-diazabicyclo[2.2.2]octane)(tetrahydroborato)zirconium(IV), $[Zr(BH_4)_2Cl_2(dabco)_2]$(ZrBDC), as a New, Stable, and Versatile Bench Top Reducing Agent:[1] Reduction of Imines and Enamines, Reductive Amination of Aldehydes and Ketones and Reductive Methylation of Amines

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The reducing agent is easily prepared in an almost quantitative yield from commercially available starting materials. This compound is stable under mild aqueous acidic conditions (pH 4–6) and survives in H_2O for several days without losing its reducing abilities. ZrBDC has been successfully used for the reduction of imines and enamines, reductive amination of aldehydes and ketones, and reductive methylation of amines.

Transition metal tetrahydroborates such as copper(II) tetrahydroborate, $Zn[BH_4]_2$, $Zr[BH_4]_4$, and $Ti[BH_4]_3$ are very reactive, volatile, unstable, and difficult to handle and can not be easily used in organic synthesis as reducing agents without modification.[2] The use of the ligand can induce considerable stabilities in these transition metal tetrahydroborates. One of the examples is $Zn[BH_4]_2$, which is not stable at room temperature and inflames with explosion when it is exposed to moisture; yet its metal-ligand complexes; $[Zn(BH_4)_2(dabco)]$ and $[Zn(BH_4)_2(Ph_3P)]$, are highly stable, white powders that can be used as bench top reagents for the reduction of varieties of functional groups.[3] Therefore, such modified tetrahydroborate complexes constitute a class of hydride transfer agents, but their reducing abilities in organic syntheses are not properly explored. There are moreover, very few examples in the literature of the use of such compounds in organic synthesis. $[Cu(BH_4)(Ph_3P)_2]$[4] is an example in which the BH_4^- moiety is deactivated to the extent that it only reduces acyl chlorides to the aldehydes, whereas $NaBH_4$ reduces acyl chlorides to their corresponding alcohols. The other reported compounds are $[Cu_2(BH_3CN)(Ph_3P)_4]$[5] and $[Zr(BH_4)(Cp)_2(Cl)]$,[6] these have been used for the reduction of a limited number of carbonyl compounds. The use of poly(vinylpyridine) supported zinc tetrahydroborate as a stable polymeric metal tetrahydroborate has been reported.[7] The other reported modified zinc tetrahydroborate is $[Zn(BH_4)_2(pyz)]_n$ which is stable to heat but explodes violently into flames when put in contact with water.[8] Very recently, the preparation of zinc tetrahydroborate-crown ethers has been appeared in the literature[9] but to the best of our knowledge, their applications have not been reported yet. According to the literature, $Zr[BH_4]_4$ is a highly volatile colorless solid, melting around room temperature, inflaming in air, and hydrolyzing with explosive rapidity. When allowed to stand at 25 °C it slowly decomposes liberating hydrogen gas.[2] Therefore, it cannot be considered as an easily applied bench top reducing agent. Recently, it is reported that a mixture of $ZrCl_4$ and $NaBH_4$ in THF can be used as a versatile system for the reduction of variety of organic substrates. In this report, the authors have claimed that in situ generation of $Zr[BH_4]_4$ is responsible for the reductions they have studied.[10]

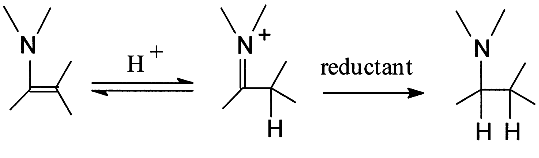
Preparation of amines from easy available precursors is important in organic synthesis. Amines and their derivatives are known to show biological activities and are important precursors that are used in pharmaceutical and agricultural industries.[11] Preparation of amines via transformation of carbonyl compounds to their imines or enamines, and their subsequent reduction to the corresponding amines by tetrahydroborate agents has been studied. Sodium cyanotrihydroborate ($Na[BH_3CN]$) is a well-known reagent for the reduction of enamines and for reductive amination of aldehydes and ketones. Even though this reagent has been popular for carrying out these transformations, it suffers seriously from high toxicity and usually low yields of the products.[12] Zinc-modified cyanotrihydroborate has also been employed for the reductive preparation of amines from enamines and for amination of carbonyl compounds.[13] $Na[BH_3CN]$ in the presence of $TiCl_4$ has been also applied for the reductive preparation of amines from carbonyl compounds.[11] Triacetoxyhydroborate $Na[BH(OAc)_3]$[14] is a reagent of choice for this purpose. This reagent should be used in acetic acid, a corrosive compound, and encounters drawbacks for the preparative protocols.[15] Some other methods used for this purpose include borane–pyridine,[16] $BH_3S(Me)_2$[17] and $Ti(O^iPr)_4/NaBH_4$.[18] Recently, $NaBH_4$ on wet clay under solvent-free conditions has been used for the reductive amination of carbonyl compounds under microwave irradiation.[15] Tetrahydroborate exchange resin has also been used for the reductive amination reaction.[19]

It is reported that zirconium and its salts generally have low systemic toxicity.[20] In continuation of our studies on the preparation of stabilized transition metal tetrahydroborates, we have recently prepared a stable modified zirconium(IV) tetrahydroborate: dichlorobis(1,4-diazabicyclo[2.2.2]octane)(tetrahydroborato)zirconium(IV), $[Zr(BH_4)_2Cl_2(dabco)_2]$ (ZrBDC). This compound has been employed for the efficient and selective reduction of carbonyl functionality to their alcohols in organic solvents and also in aqueous media.[1] Now we report that ZrBDC can be easily applied for the efficient preparation of amines by the reduction of imines and enamines, reductive amination of aldehydes and ketones, and reductive methylation of amines.

Results and Discussion

Dichlorobis(1,4-diazabicyclo[2.2.2]octane)(tetrahydroborato)zirconium(IV), $[Zr(BH_4)_2Cl_2(dabco)_2]$ (ZrBDC) was prepared by the addition of an ethereal solution of $LiBH_4$ to anhydrous $ZrCl_4$ under inert atmosphere with stirring. After 12 h, an ethereal solution of dabco was added dropwise to the resulting slurry[21] and the stirring was continued for another 10 h to produce a dark brown solid. The resulting precipitates were filtered, washed with ether, and dried under vacuum to afford a white powder. For further purification, the resulting powder was washed with dry THF and Et_2O respectively and was left under vacuum overnight. ZrBDC was isolated as a white, stable, non-hygroscopic powder in 97% yield. ZrBDC could be stored at room temperature for months without significant change in its reducing power as determined by iodometric titration.[22] This modified tetrahydroboratozirconium is much more stable than $NaBH_4$ in H_2O, CH_3OH, and C_2H_5OH, and in mild aqueous acidic media (pH 4–6). The proposed chemical formula of the compound was established by IR, NMR, iodometric, potentiometric, and UV/vis spectroscopic studies.[22–26] IR (KBr, dabco species) ν (cm^{-1}) 2974s, 2963s, 2897s, 1623m, 1458s, 1324s, 1056s, 993s, 846s, 702b, and for BH_4^- species, ν (cm^{-1}) 2383s, 2373s, 2306s, 2268s, 1155s. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.42 (broad band, 8H, two BH_4^-), that its coupling constant and the pattern are similar to the reported data for $Zr(BH_4)_4$,[23b] 2.9 (AA′BB′ pattern,[24] 24H of CH_2 groups). ^{13}C NMR ($CDCl_3$, 63 MHz) δ 51.7, 52.1 (two different CH_2 groups). Determination of BH_4^- content was conducted by iodometric titration method,[22] quantitative measurement of chloride content was proceeded by potentiometric titration technique,[25] and quantitative measurement of Zr was conducted by UV/vis spectrophotometric method.[26] Salts of zirconium show low human toxicity,[20] therefore, the presented reagent is a good competitor with the highly toxic $Na[BH_3CN]$ for the reduction of C=N.

Reduction of Imines and Enamines. Efficient reduction of imines and enamines to their corresponding amines is of practical importance. It is generally accepted that the enamine reduction occurs through the iminium-type intermediate, which can be generated via protonation of the enamine by protic acids (Scheme 1).[12a]



Scheme 1.

Here we report a facile preparation of amines from imines and enamines using ZrBDC as a reductant. In order to optimize the reaction conditions, the reduction of morpholine enamine of cyclohexanone as a model compound in CH_3OH was studied. The reaction proceeded under neutral conditions and the pH of the media was adjusted by the addition of a 10% aqueous solution of HCl in methanol. We have observed that lowering the pH of the reaction media (pH 5–6) increases the rate of the reaction. The reaction was very slow at room temperature but was performed well under reflux conditions to produce the desired amine in 91% isolated yield. We have found that hydrolytic cleavage of the iminium cation to its carbonyl compound did not occur under such reaction conditions.

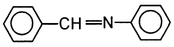
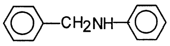
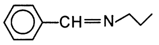
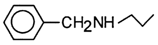
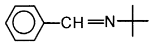
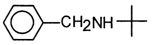
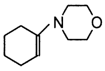
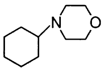
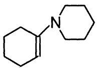
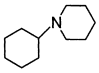
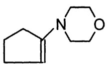
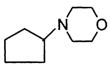
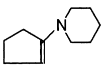
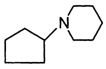
In order to show the general application of the method, we have converted structurally different enamines and imines to their amines under similar reaction conditions. The results are shown in Table 1. We have also compared some of our results with those reported for $Na[BH_3CN]/ZnCl_2$[13] and $Na[BH_3CN]$[12] in Table 2.

Reductive Amination of Aldehydes and Ketones. In biological and chemical systems, the reductive amination of aldehydes and ketones is an important transformation which allows the direct conversion of carbonyl compounds into amines.[29] Reports describing the synthesis of amines using reductive amination procedures include tetrahydroborate exchange resin,[19] borane-pyridine in AcOH,[16] $Ti(O^iPr)_4/NaBH_4$,[18] $Na[BH(OAc)_3]$,[14] $Li[BH_3CN]$,[30] $Na[BH_3CN]$,[12] $Na[BH_3CN]$ in combination with $TiCl_4$[11] and $ZnCl_2$,[13] and $NaBH_4$/wet clay/microwave irradiation.[15] $NaBH_4$ has been also used for N-alkylation of primary aromatic amines in a highly acidic (H_2SO_4) medium.[31] The most widely used reagents for this aim are: a) the highly toxic $Na[BH_3CN]$ such reactions should be conducted in highly acidic conditions (5 M HCl/CH_3OH) and suffer from low to moderate yields and sometimes from long reaction times.[12a] This reagent is also sluggish for the reductive amination of aldehydes with anilines bearing electron-withdrawing groups.[14a,32] b) $Na[BH(OAc)_3]$ in the presence of acetic acid which is corrosive; such reactions also suffer from moderate yields of the amine products and long reaction times.[14b] Therefore, introduction of new reagents in order to improve or eliminate some of the above-mentioned problems is a useful contribution to synthetic organic chemistry.

The generally accepted reaction steps for a reductive amination are shown by the following reactions (1–3, Scheme 2). Reactions 3 and 4 show that two competitive reductive reactions (C=N vs C=O) are inevitable and will occur in the reductive amination of carbonyl compounds.[16]

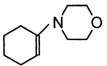
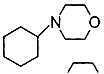
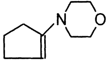
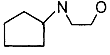
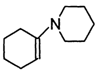
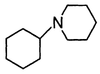
Now, we report that in the presence of ZrBDC, efficient and smooth reductive amination of a variety of carbonyl compounds proceeded well in the presence of amines under neutral conditions. The pH of the media was adjusted to neutrality by the addition of 10% aqueous solution of HCl in methanol. Under such a condition, ZrBDC did not reduce the carbonyl compounds in the reaction mixture, whereas the imine intermediate was converted easily to the corresponding amines. However, the absence of formation of any hydroxy compound in these reductions suggests that the overall process would proceed successfully if a reasonable concentration of imines is available and the reaction conditions could discriminate between

Table 1. Reduction of Imines and Enamines with ZrBDC in Methanol[a)]

Entry	Substrate	Product[b)]	Time/h	Isolated yield[Ref.]/%
1			0.5	94[13]
2			4	87[27]
3			5	90[14c]
4			7	91[13]
5			10	88[13]
6			6	86[13]
7			7.5	82[28]

a) All reactions were carried out under reflux and neutral conditions; the molar ratio of reagent/substrate was 1 : 1. b) All compounds gave satisfactory spectral analyses.

Table 2. Comparison of the Results Obtained by Using ZrBDC with $Na[BH_3CN]/ZnCl_2$ and $Na[BH_3CN]$ for the Reduction of Enamines

Entry	Enamine	Product	ZrBDC		$Na[BH_3CN]/ZnCl_2$[13]		$Na[BH_3CN]$[12]	
			Time h	Yield[a)] %	Time h	Yield[a)] %	Time h	Yield[a)] %
1			7	91	0.5	73	0.2	80
2			6	86	0.5	90	0.5	81
3			10	88	1	85	—	—

a) Isolated yield.

$$R^1R^2CO + R^3NH_2 \rightleftharpoons R^1R^2C(OH)NHR^3 \qquad (1)$$

$$R^1R^2C(OH)NHR^3 \rightleftharpoons R^1R^2C{=}NR^3 + H_2O \qquad (2)$$

$$R^1R^2C{=}NR^3 \xrightarrow{\text{reductant}} R^1R^2CHNHR^3 \qquad (3)$$

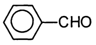
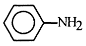
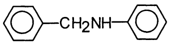
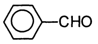
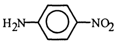
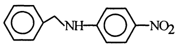
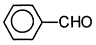
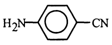
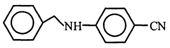
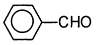
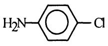
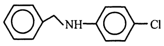
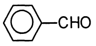
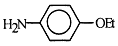
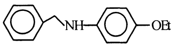
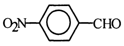
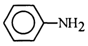
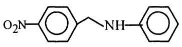
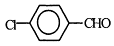
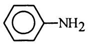
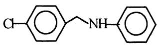
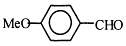
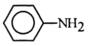
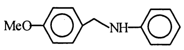
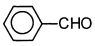
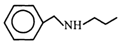
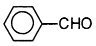
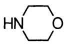
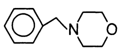
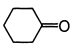
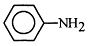
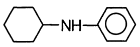
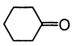
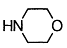
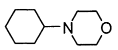
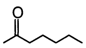
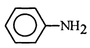
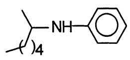
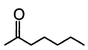
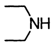
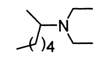
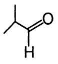
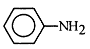
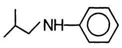
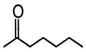
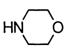
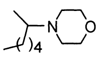
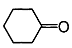
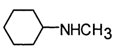
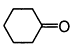
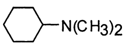
$$R^1R^2C{=}O \xrightarrow{\text{reductant}} R^1R^2CHOH \qquad (4)$$

Scheme 2.

the reduction of the imine intermediate (reaction 3) and the carbonyl compound present in the reaction mixture (reaction 4). In general, the reactions were carried out with 4 equiv of the primary amine or 2 equiv of the secondary amine by use of 1 equiv of ZrBDC in refluxing methanol. The results of this study are summarized in Table 3. We have observed that reductions under acidic conditions (pH 5) proceeded with faster reaction rates.

We have also studied the catalytic roles of different Lewis acids such as $ZrCl_4$, $AlCl_3$, $FeCl_3$, $CeCl_3{\cdot}7H_2O$, and $ZrOCl_2{\cdot}8H_2O$ for the reductive anilation of benzaldehyde as a reaction model. It was found that $ZrCl_4$ was the most effective catalyst among the Lewis acids we have used for this purpose. The reaction proceeded easily in CH_3OH under reflux conditions in the presence of 0.5 molar equivalents of $ZrCl_4$. In order to show the general applicability of this method, we have

Table 3. Reductive Amination of Aldehydes and Ketones Using ZrBDC in Methanol[a)]

Entry	Compound	Amine	Product[b)]	Method I		Method II	
				Time/h	Yield[c)] Ref./%	Time/h	Yield[c)]/%
1				4	87[13]	0.4	90
2				24	85[14a]	0.1	97
3				24	88[33a]	0.1	94
4				13	96[33]	0.2	92
5				10	98[34]	1	96
6				16	90[15]	0.2	94
7				10	91[15]	0.4	95
8				7	97[15]	0.6	96
9				24	84[35]	2	85
10				36	88[12a]	24	86
11				2	84[13]	0.5	87
12				2.5	80[12b]	0.3	80
13				8	89[14b]	1.8	92
14				48	83[14b]	36	87
15				1	84[12a]	—	—
16				12	86[14b]	—	—
17		CH_3NH_2		1	78[12]	—	—
18		$HN(CH_3)_2$		8	82[12]	—	—

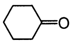
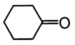
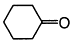
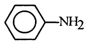
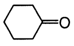
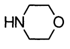
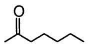
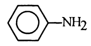
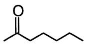
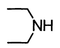
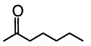
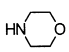
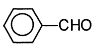
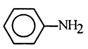
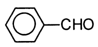
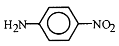
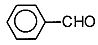
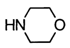
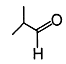
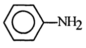
a) All reactions were carried out under reflux conditions and molar ratio of reagent/carbonyl compound/amine was 1/1/4 (primary amine) and 1/1/2 (secondary amine). b) All compounds gave satisfactory spectral analyses. c) All yields are isolated yields. Method I: Reactions were carried out under neutral conditions using 10% HCl/CH_3OH for the pH adjustment. Method II: Reactions were carried out in the presence of 0.5 molar equivalents of $ZrCl_4$.

applied this procedure for the reductive amination of structurally different carbonyl compounds with different amines (Method II). Reactions conducted in the presence of this catalyst produced amines in higher yields with shorter reaction times in comparison with the similar reactions conducted by method I, as shown in Table 3. By this method, varieties of carbonyl compounds in the presence of different amines were converted easily and smoothly to the secondary and tertiary amines in high yields. Weakly acidic anilines like nitro- and cyanoanilines do not usually undergo clean reductive amination reactions. Na[BH_3CN], the most widely used reagent for the reductive amination of aldehydes and ketones, is a sluggish and inefficient reagent for this purpose.[14a] We have found that 4-nitroaniline and 4-cyanoaniline react efficiently with aromatic aldehydes within 0.1 h in the presence of ZrBDC and 0.5 molar equivalents of $ZrCl_4$ in refluxing CH_3OH to produce their corresponding amines in 97 and 94% yields, respectively. Similar reactions proceeded in lower yields (85 and 88%) and in much longer reaction times (24 h) when the pH of the reaction media was adjusted by HCl in methanol. The mildness of the reaction media, low toxicity of the reagent, and high reaction rates accompanied with high yields of the products make this protocol a useful addition to the tetrahydroborate category of reagents used for this purpose.

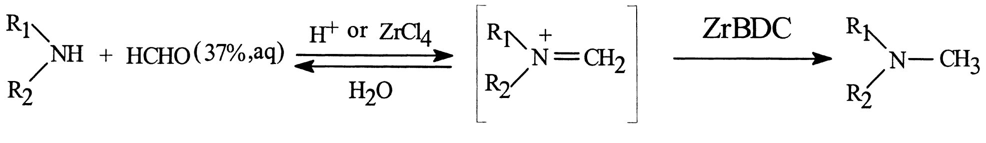
In order to show the merit of the presented method, we have compared the results with some other methods used for this purpose in Table 4.

Reductive Methylation of Amines. Introduction of methyl groups into primary or secondary amines by reductive alkylation (Scheme 3) is a useful method for the preparation of tertiary methylated amines.[13,16,36] Na[BH_3CN] has been used for this transformation in methanol but a mixture of starting mate-

Table 4. Comparison of ZrBDC and the Other Reducing Agents in Reductive Amination of Carbonyl Compounds

Entry	Carbonyl compound	Amine	ZrBDC Method I Time h	ZrBDC Method I Yield %	ZrBDC Method II Time h	ZrBDC Method II Yield %	Other Reducing Agents[a)–f)] Time h	Yield %	Time h	Yield %	Time h	Yield %
1		CH_3NH_2	1	78	—	—	—	41[a)]	18	73[b)]	3	98[c)]
2		$HN(CH_3)_2$	8	82	—	—	—	43[a)]	20	75[d)]	—	—
3			2	84	0.5	87	1	42[e)]	2	93[c)]	—	—
4			2.5	80	0.3	80	—	79[a)]	—	—	—	—
5			8	97	1.8	92	96	74[f)]	—	—	—	—
6			48	83	36	87	192	44[f)]	—	—	—	—
7			12	86	—	—	27	73[f)]	—	—	—	—
8			4	87	0.4	90	1	88[e)]	2	93[c)]	—	—
9			24	85	0.1	97	1.5	85[f)]	—	—	—	—
10			36	88	24	86	1	83[c)]	—	—	—	—
11			1	84	—	—	—	78[a)]	—	—	—	—

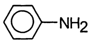
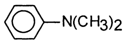
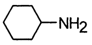
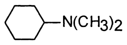
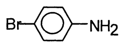
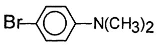
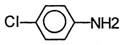
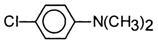
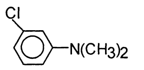
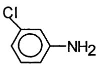
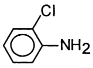
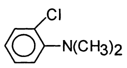
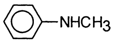
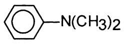
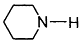
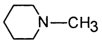
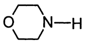
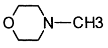
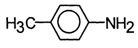
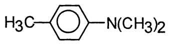
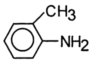
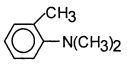
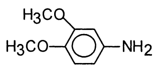
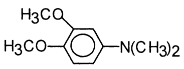
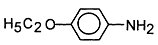
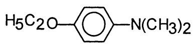
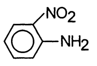
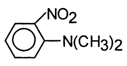
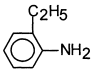
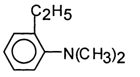
a) Na[BH_3CN][12]. b) Ti(^{i}OPr)$_4$, CH_3NH_2·HCl, Et_3N, and $NaBH_4$.[18a] c) Zinc-modified cyanotrihydroborate.[13] d) Ti(O^{i}Pr)$_4$ and $NaBH_4$.[18b] e) Tetrahydroborate exchange resin.[19] f) Na[BH(OAc)$_3$].[14]



Scheme 3.

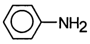
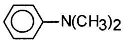
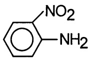
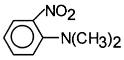
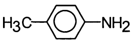
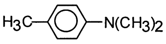
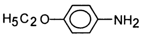
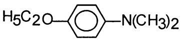
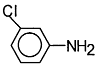
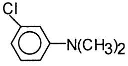
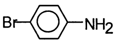
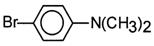
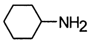
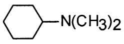
rial and partially methylated products has been produced. This drawback has been eliminated by using this reagent in aprotic solvents.[37] We here report the preparation of methylated amines by the reaction of amines with 37% aqueous solution of formaldehyde in the presence of ZrBDC by two methods: a) in refluxing methanol under neutral conditions, and b) by using ZrCl$_4$ (0.5 molar equiv) in methanol at room temperature. The results of this study are tabulated in Table 5.

Table 5. Reductive Methylation of Amines with ZrBDC in Methanol[a)]

Entry	Compound	Product[b)]	Method I		Method II	
			Time/h	Yield[c)] [Ref.]/%	Time/h	Yield[c)]/%
1			0.1	80[12b]	0.1	83
2			0.1	81[12b]	0.1	85
3			0.75	95[12b]	0.1	95
4		 	1	92[38]	0.1	90
5			1.7	89[12b]	0.7	97
6			3.5	91[38]	1	94
7			1	82[36c]	0.3	85
8			0.1	88[39]	0.1	88
9			0.1	85[39]	0.1	87
10			0.3	87[13]	0.1	91
11			0.3	90[36c]	0.1	95
12			1.5	97[40]	—	—
13			0.5	95[12b]	—	—
14			1.5	94[13]	—	—
15			2	89[41]	—	—

a) The molar ratio of the reagent/amine/37% aqueous formaldehyde in all reactions were 1/1/5.
b) All compounds gave satisfactory spectral analysis. c) All yields are isolated yields. Method I: Reactions were carried out in refluxing methanol under neutral conditions using 10% HCl/CH$_3$OH for the pH adjustment. Method II: Reactions were carried out in the presence of 0.5 molar ratio of ZrCl$_4$ in CH$_3$OH at room temperature.

Table 6. Comparison of the Results Obtained by ZrBDC, Na[BH_3CN]/$ZnCl_2$, and Na[BH_3CN] for the Reductive Methylation of Amines

Entry	Amine	Product	ZrBDC				Na[BH_3CN]/$ZnCl_2$[13]		Na[BH_3CN][12]	
			Time	Yield	Time	Yield	Time	Yield	Time	Yield
			h	%	h	%	h	%	h	%
1			0.1	80	0.1	83	2	86	2	92
2			1.5	94	—	—	2	90	—	—
3			0.3	87	0.1	91	2	83	—	—
4			0.5	95	—	—	—	—	1	85
5			1.7	89	0.7	97	—	—	3	86
6			0.75	95	0.1	95	—	—	1	87
7			0.1	81	0.1	85	—	—	2	84

We have also compared some of the results obtained by ZrBDC with other methods used for this purpose in Table 6.

Conclusion. Dichlorobis[1,4-diazabicyclo[2.2.2]octane](tetrahydroborato)zirconium(IV), [$Zr(BH_4)_2Cl_2(dabco)_2$] (ZrBDC), a stable and a versatile bench top reducing agent is easily prepared in an almost quantitative yield from commercially available starting materials. ZrBDC is a white powder and unlike its mother compound Zr[BH_4]$_4$, is thermally stable and so safe that it could be stored for months without appreciable loss of its reducing ability. This reagent tolerates acid conditions and is stable in protic organic solvents and water. The preparation of the reagent is easy (in 97% yield) and unlike its polymer supported analogue [cross-linked PVP4-Zr (BH_4)$_4$] is quite reproducible by different hands.[42] ZrBDC is a good substitute for Na[BH_3CN] for the preparation of amines from imines, enamines, reductive amination of carbonyl compounds, and reductive methylation of amines. The use of ZrBDC eliminates the problem encountered by using Na[BH_3CN] such as residual cyanide in the product and in the waste stream. Moreover, the mildness, easy reaction work up, efficiency, selectivity, high reaction rates and yields, and lack of requirement of an inert atmosphere, make this new stabilized transition-metal tetrahydroborate a useful addition to the category of reagents used for the reductive preparation of amines.

Experimental

General: All products are known compounds. All yields refer to isolated products. The products were purified by column chromatography and the purity determinations of the products were accomplished by GLC on a Shimadzu model GC-8A instrument or by TLC on Silica-gel polygram SIL G/UV254 plates, and mass spectra were run on a Shimadzu GC MS-QP 1000EX at 20 eV. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. The NMR spectra were recorded on a Bruker Avance DPX 250 MHz instrument.

Preparation of Dichlorobis(1,4-diazabicyclo[2.2.2]octane)(tetrahydroborato)zirconium(IV), [$Zr(BH_4)_2Cl_2(dabco)_2$], (ZrBDC): A slurry was produced by the addition of an ethereal solution of $LiBH_4$ (0.344 mol) to anhydrous $ZrCl_4$ (0.069 mol) under inert atmosphere and the resulting slurry[21] was stirred for 12 h. Then an ethereal solution of DABCO (0.138 mol) was added dropwise to the slurry and stirring was continued for 10 h to produce a dark brown solid. The resulting solid was filtered, washed with Et_2O, and dried under vacuum to afford a white powder. For further purification, the resulting powder was washed with dry THF and dry Et_2O, respectively, and was left under vacuum overnight. ZrBDC was isolated as a white, stable, non-hygroscopic powder in 97% yield.

A Typical Procedure for the Reduction of Imines and Enamines with ZrBDC: In a round-bottomed flask (25 mL) equipped with a magnetic stirrer and a condenser, a solution of *N*-benzylideneaniline (0.18 g, 1 mmol) in methanol (5 mL) was prepared and acidified to neutral conditions with 10% aqueous solution of HCl in methanol. The reducing agent (0.416 g, 1 mmol) was added to the solution. The mixture was refluxed with stirring (0.5 h), and then silica-gel (2 g) was added to the resulting mixture. Methanol was evaporated and the resulting mass was applied on a silica-gel column and eluted with petroleum ether (bp 60–80 °C)/EtOAC: 10/1 (150 mL). Evaporation of the solvent afforded almost pure *N*-benzylaniline (0.172 g, 94% yield, Table 1, entry 1).

A Typical Procedure for Reductive Amination of Aldehydes and Ketones, Method I: The preparation of *N*-cyclohexylaniline is representative. To a stirred solution of cyclohexanone (0.196 g, 2 mmol) and aniline (0.745 g, 8 mmol) in methanol (5 mL), the reducing agent (0.832 g, 2 mmol) was added and the pH was adjusted to neutral conditions by the 10% aqueous solution of HCl in MeOH. The mixture was refluxed (2 h) and then silica-gel (2 g) was added. Methanol was evaporated and the resulting material was applied on a silica-gel column and eluted with hexane/EtOAc: 10/1 (100 mL). After evaporation of the solvent, almost pure *N*-cyclohexylaniline was obtained (0.27 g, 84% yield; Table 3, entry 11).

Method II: The preparation of *N*-benzylaniline is representative. To a stirred solution of benzaldehyde (0.212 g, 2 mmol) and aniline (0.745 g, 8 mmol) in methanol (5 mL), the reducing agent (0.832 g, 2 mmol) and $ZrCl_4$ (0.233 g, 1 mmol) were added. The mixture was refluxed (0.4 h) and then silica gel (2 g) was added.

Methanol was evaporated and the resulting material was applied on a silica-gel column and eluted with hexane/EtOAc: 10/1 (75 mL). After evaporation of the solvent almost pure *N*-benzylaniline was obtained (0.33 g, 90% yield; Table 3, entry 1).

A Typical Procedure for Reductive Methylation of Amines, Method I: The preparation of 4-bromo-*N*,*N*-dimethylaniline is representative. In a round-bottomed flask (25 mL) equipped with a magnetic stirrer and a condenser, a solution of 4-bromoaniline (0.172 g, 1 mmol) and 37% aqueous formaldehyde (0.4 mL, 5 mmol) in methanol (5 mL) was prepared and neutralized with a 10% aqueous solution of HCl in methanol. The reducing agent (0.416 g, 1 mmol) was added and refluxed with stirring (0.75 h) and then silica-gel (2 g) was added. Methanol was evaporated and the resulting solid was applied on a silica-gel column and eluted with petroleum ether (bp 60–80 °C)/EtOAC: 10/1 (130 mL). Evaporation of the solvent afforded almost pure 4-bromo-*N*,*N*-dimethylaniline (0.19 g, 95% yield; Table 5, entry 3).

Method II: The preparation of 3-chloro-*N*,*N*-dimethylaniline is representative. A solution of 3-chloroaniline (0.127 g, 1 mmol) and 37% aqueous formaldehyde (0.4 mL, 5 mmol) in methanol (5 mL) was prepared. The reducing agent (0.416 g, 1 mmol) and ZrCl$_4$ (0.116 g, 0.5 mmol) were added and after stirring (0.7 h), silica-gel (2 g) was added to the mixture. Methanol was evaporated and the resulting mass was applied on a silica-gel column and eluted with petroleum ether (bp 60–80 °C)/EtOAC: 10/1 (130 mL). Evaporation of the solvent afforded almost pure 3-chloro-*N*,*N*-dimethylaniline (0.15 g, 97% yield, Table 5, entry 5).

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