EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

Title: CO2-Controlled Reductive Amination Reactions with NaBH4

Authors: Allan R Petersen, Jerik Mathew Valera Lauridsen, and Ji-Woong Lee

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202001408

Link to VoR: https://doi.org/10.1002/ejoc.202001408

WILEY-VCH

WILEY-VCH

FULL PAPER

CO_2-Controlled Reductive Amination Reactions with $NaBH_4$

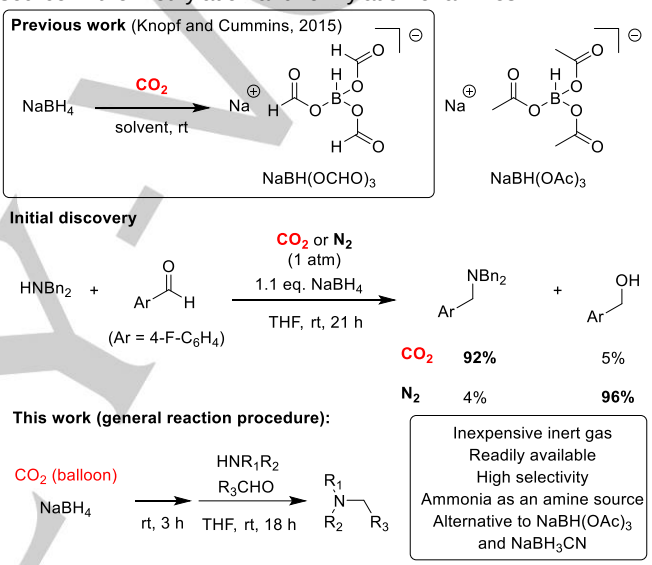
Allan R. Petersen, Jerik Mathew Valera Lauridsen, and Ji-Woong Lee*

Abstract: We report the use of CO_2 to curb the reactivity of $NaBH_4$ enabling its use in reductive amination reactions. CO_2 readily reacts with $NaBH_4$ to decrease its capacity to reduce aldehydes to alcohols while remaining able to reduce imines and iminium ions for desired alkylation reactions. The formation of $NaBH(OCHO)_3$ as a reducing reagent was critical to achieve the desired selectivity. A general protocol was established for C−N bond formation reactions and replacing $NaBH_4$ with $NaBD_4$ allowed for reductive amination with concomitant deuteration to be carried out.

Introduction

The control of chemical reactivity – nucleophilicity, electrophilicity, reduction potential and oxidation potential - is a major tool in designing organic reactions. Various types of reagents with subtle variations in chemical reactivity have been developed to provide a potentially appropriate choice of reagents for a certain class of substrate. Together with intensive reaction conditions optimization, the choice of reagents is critical to achieve the desired transformation with satisfactory yields. For example, reductive amination reactions – versatile amination reaction for pharmaceuticals,[1] agrochemicals, materials synthesis - require an appropriate reducing agent to prevent the formation of by-product by the reduction of starting material aldehyde instead of imines.[2] Therefore, chemical reactivities of hydride donors must be suppressed to achieve high selectivity toward amination products. To this end, $NaBH(OAc)_3$ or $NaCNBH_3$ are common choices[3] while, $NaBH_4$/TMSCl expands the reaction scope by enabling the reductive amination of electron-deficient anilines with ketones.[4] $NaBH_4$ has the advantage of being easy-to-handle, inexpensive, accessible, and low molecular weight.[5] The remarkable versatility of $NaBH_4$ allows for the reduction of sugars,[6] alkyl halides,[7] conjugated double bonds,[8] esters[9] and acids.[10] Yet the employment of $NaBH_4$ by itself for reductive amination would render direct reduction of ketones and aldehydes prior to desired imine reduction.[11]

The reduction of CO_2 to formic acid, by solutions of lithium borohydride, was reported in 1950.[12] The yield of formate averaged 73% of the CO_2 absorbed with methanol and B_2H_6 also identified among the reaction products. Subsequently, the reaction between CO_2 and solid $NaBH_4$ was found to yield the heteroleptic borate $NaBO(O_2CH)(OCH_3)$.[13] When the reaction was conducted in dimethyl ether, sodium triformatoborohydride ($NaBH(OCHO)_3$) was formed instead (Scheme 1). More recently, the reaction between $NaBH_4$ and CO_2 was revisited by Knopf and Cummins who found that a mixture of sodium di- and triformatoborohydride ($NaBH_2(OCHO)_2$ and $NaBH(OCHO)_3$ respectively) was formed when a solution of $NaBH_4$ in CH_3CN was sparged with CO_2.[14] In contrast, $NaBH(OCHO)_3$ was the sole product when the reaction was conducted under 300 psi of CO_2.[14] The use of $NaBH_4$ as a reducing agent for CO_2 has been investigated in the context of CO_2 capture.[15] In addition, the reduction of CO_2 by $NaBH_4$, allows for the use of CO_2 as a C1 source in the methylation and formylation of amines.[16]



Scheme 1. Top: Reaction of CO_2 with $NaBH_4$ affording $NaBH(OCHO)_3$, a congener of $NaBH(OAc)_3$. Middle: The initial discovery of CO_2 as a reactivity controller in the reductive amination of $HNBn_2$ with 4-F-benzaldehyde. Bottom: A general protocol for using CO_2 with $NaBH_4$ for reductive amination reactions.

Although $NaBH(OCHO)_3$ is a congener of $NaBH(OAc)_3$, the use of $NaBH(OCHO)_3$ as a reducing agent for reductive amination has to the best of our knowledge not yet been reported. Our on-going research program to utilize CO_2 for controlling organic reactions[17] showed promising reactivity patterns in developing new chemical reactivity of nucleophiles while improving (stereo)selectivity. Although, the reactivity and selectivity of $NaBH_4$ can conveniently be modified through the addition of reagents or Lewis acidic metals to $NaBH_4$, CO_2 has been overlooked for this purpose.[18] Herein we report the use of CO_2 as a reactivity controller for $NaBH_4$ for reductive amination reactions (Scheme 1). A chemoselective reducing agent is readily generated in situ from the reaction of $NaBH_4$ with CO_2.

Results and Discussion

CO_2 is a stable molecule, which can be involved in various chemical processes as an innocent by-product or as a solvent.[19] Recent progress in CO_2-mediated reactions showed elegant mode of actions – substrate activation,[20] in situ functional group

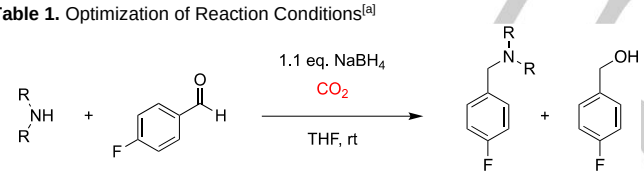
[*] Dr. A. R. Petersen, J. M. V. Lauridsen, Dr. J.-W. Lee
Department of Chemistry, Nano-Science Center
University of Copenhagen
Universitetsparken 5, Copenhagen Ø, 2100, Denmark
E-mail: jiwoong.lee@chem.ku.dk
Web: www.leegroup.dk

Supporting information for this article is given via a link at the end of the document.

protection,[21] taking advantages of CO_2: inexpensive, non-toxic, and safe.[22] Reduction and reductive amination often suffer from flammable gases and toxic reagent combinations to achieve desired chemoselectivity.[2a, 23] Therefore, we commenced our investigation in reductive amination using the combination of $NaBH_4$ and CO_2 to generate $NaBH_{4-x}(OCHO)_x$ (where x = 0-3) in situ which would exhibit lower reduction reactivity compared to the parent $NaBH_4$, thus improving chemoselectivity of the reductive amination reaction.

Our initial investigation was based upon the reductive amination of dibenzylamine **1a** with aldehyde **2a** (Scheme 1, Table 1). Prior to the addition of the amine and the aldehyde, a suspension of $NaBH_4$ in THF was vigorously stirred under a N_2 atmosphere for 2 hours. The reaction afforded the desired product in 4% yield with the remaining 96% of the aldehyde being reduced to 4-fluorobenzyl alcohol **4a** (entry 1). In comparison, when the same reaction was conducted under a CO_2 atmosphere, the desired product was obtained in 92% yield (entry 3). Further optimizations were carried out using diisopropylamine **1b** instead of dibenzylamine (entries 7-15). Sterically hindered diisopropylamine was chosen as a more challenging amine for reductive amination due to the steric hindrance, reducing the reactivity for iminium ion formation. Here the length of pre-stirring led to the differences in yield being more pronounced: 1 hour of pre-stirring afforded a yield of 33% of product **3b**, whereas 2 hours of pre-stirring yielded 56% after 18 hours (entries 7 and 9). Despite there being 19% unreacted aldehyde present, extending the reaction time from 18 to 24 hours did not increase the yield (entry 11). We tentatively propose that as the reaction progresses and the amine and aldehyde concentrations decline, CO_2 binding to the amine increasingly competes with iminium ion formation, which leads to aldehyde reduction.

Table 1. Optimization of Reaction Conditions[a]



R = Bn, **1a**
R = ^{i}Pr, 1**b**

2a

R = Bn, **3a**
R = ^{i}Pr, 3**b**

4a

Entry	R =	Duration of pre-stir (hours) [b]	Conversion (%)[c]	Yield of **3a** (%)[c]	Yield **4a** (%)[c]
1[d]	Bn	2	99	4	96
2	Bn	1	99	86	14
3	Bn	2	97	**92**	5
4[e]	Bn	2	99	**91**	9
5[f]	Bn	2	98	**97**	1
6[e]	Bn	3	97	**92**	5
7	^{i}Pr	1	99	33	67
8[g]	^{i}Pr	1	99	0	93
9	^{i}Pr	2	81	**56**	25
10[e]	^{i}Pr	2	81	54	27
12[f]	^{i}Pr	2	88	53	35
11[e]	^{i}Pr	3	72	**58**	14
13[f]	^{i}Pr	3	74	56	18
14[f],[h]	^{i}Pr	3	77	57	20
15[f]	^{i}Pr	4	67	49	18
16[i]	Bn	3	99	87	7
17[j]	Bn	3	85	72	4

[a] Unless otherwise noted, all reactions were carried out with **1a** or **1b** (1.0 mmol), **2a** (1.0 mmol), $NaBH_4$ (1.1 mmol), CO_2 balloon, and THF (17.5 mL) in a 40 mL vial at room temperature for 18 h. [b] Time that $NaBH_4$ and CO_2 react before the addition of amine and aldehyde. [c] The yields were determined by ^{1}H NMR spectroscopy of the crude product with 1,3,5-trimethoxybenzene as an internal standard. [d] Reaction conducted under a N_2 atmosphere. [e] Reaction time 24 h. [f] 1.1 mmol of **1a** or **1b** was used. [g] 1.1 mmol Bu_4NBr added. [h] After 3 hours and before the addition of **1a** and **2a**, CO_2 balloon exchanged for N_2 balloon and headspace flushed. [i] AcOH (50 mol%) was added. [j] 4Å MS 500 mg was added.

The addition of acetic acid, molecular sieves (4Å), which can promote the imine formation process, showed reasonable conversion and yields of the reductive amination product albeit with the lower product selectivity, highlighting that the imine formation reaction is not limiting the reductive amination process (entries 16 and 17).

Under optimized reaction conditions, we conducted comparison studies with conventional reducing reagents for reductive amination namely $NaBH(OAc)_3$ and $NaBH_3CN$ with the model substrates (**1a** and **2a**). As summerized in Figure 1, high yield of reductive amination product **3a** was recorded under our reaction conditions ($NaBH_4/CO_2$), while 1 equivalent of $NaBH_3CN$ or $NaBH(OAc)_3$ showed inferior conversion under otherwise identical reaction conditions. Additional experiments with a pre-formed imine (See supporting information) also confirmed the superior reactivity of the combination of $NaBH_4/CO_2$ (70% conversion) compared to $NaBH(OAc)_3$ and $NaBH_3CN$ under N_2 (2% and 50% after 18 h, respectively).

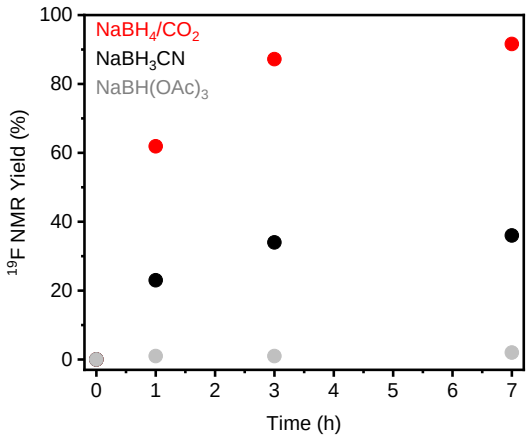


Figure 1. Time-dependent ^{19}F NMR yield of product **3a** with $NaBH_4/CO_2$ (red), $NaBH_3CN$ (black) and $NaBH(OA)_3$ (gray).

To produce the desired product involves a sequence of reactions. Firstly, $NaBH_4$ reacts with CO_2 to produce $NaBH(OCHO)_3$ (vide infra). Next, amine and aldehyde are added and react to form an imine or iminium ion. Finally, the imine is reduced by the $NaBH(OCHO)_3$ to afford the desired product. CO_2 plays a crucial role in this sequence of reactions therefore the affect of CO_2 was considered. After 3 hours of pre-stirring, swapping the CO_2 balloon for a N_2 balloon led to a higher conversion of aldehyde, yet a lower selectivity towards product (Table 1, entry 14). We postulate that keeping the CO_2 balloon attached ensures that as much $NaBH_4$ as possible is converted to $NaBH(OCHO)_3$, this can outweigh the detrimental effect of CO_2 on imine formation (Table S2, entries 2-4). Previous reports on the reaction of $NaBH_4$ with CO_2 used polar aprotic solvents dimethyl ether and CH_3CN.[13-14] THF is the primary choice as a solvent in reductive amination reactions, particularly with $NaBH(OAc)_3$.[3g, 3h] After solvent optimization (Table S1 and Table S3) our protocol showed good performance in CH_3CN, DMF and DMSO (Tables S6 and S7). At high concentrations, DMSO displayed high selectivity for reductive amination product **3a** (Table S3, entry 2 and Table S5, entry 1) albeit the low reactivity. In contrast the reductive amination reaction showed higher conversion at lower concentrations when CH_3CN or THF was used. The lower solubility of $NaBH_4$ in THF and CH_3CN compared to that in DMSO may play a role. It is worth noting that when 1.1 eq. of Bu_4NBr was added to the reductive amination reaction only the reduction product **4a** was observed (Table 1, Entry 8). As the highest yields were achieved using THF, it became the solvent of choice in our protocol. The amount of $NaBH_4$, the amount of solvent (relative to $NaBH_4$), and the time allowed for CO_2 to react with $NaBH_4$ (duration of pre-stir) are crucial for the selectivity and yield by influencing the effective concentration of "controlled" reducing reagent while reactants are in reversible iminium formation reactions (Tables S11-S14).

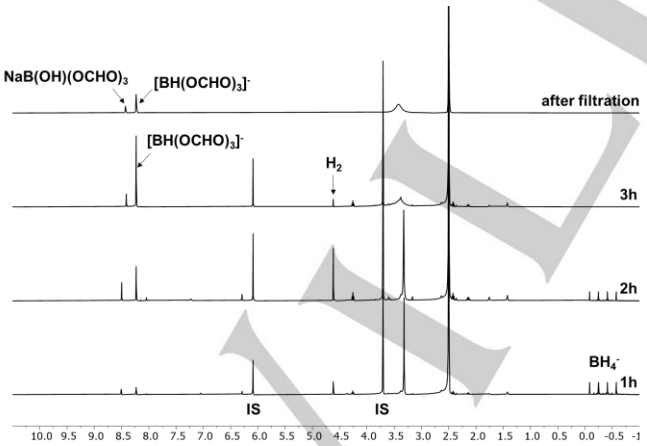
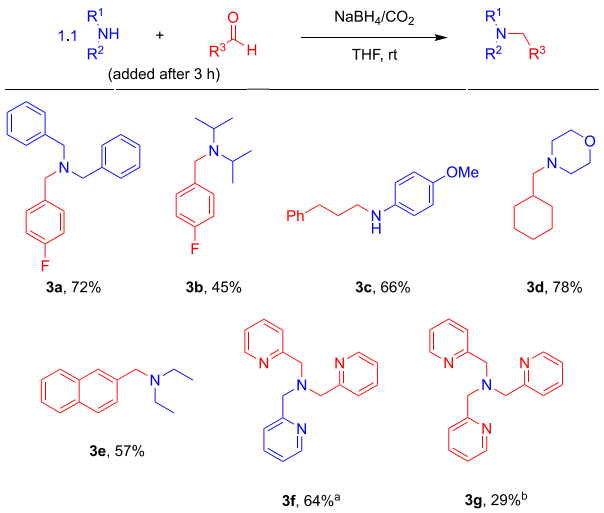


Figure 2. ^1H NMR spectra of the reaction of $NaBH_4$ with CO_2 after 1, 2 and 3 hours and after filtration (in DMSO-d_6, IS = 1,3,5-trimethoxybenzene).

To provide the insight on the "controlled" reducing reagent a reaction mixture between $NaBH_4$ and CO_2 in THF was studied using ^1H NMR spectroscopy. Spectra recorded after 1, 2 and 3 hours showed that the BH_4^- anion was consumed within 3 hours affording mainly $[BH(OCHO)_3]^-$ and a second formate-containing species (Figure 2, also see Section 3 in the supporting information). Interestingly, $[BH_3(OCHO)]^-$ and $[BH_2(OCHO)_2]^-$ were only observed in trace amounts along with H_2, a product of hydrolysis.

Further investigations were conducted to isolate potentially reactive species as a reducing reagent. Reacting $NaBH_4$ with CO_2 in THF, for 3 hours, followed by filtration and washing with diethyl ether afforded a white powder. The ^1H NMR spectrum in DMSO-d_6 of the product displayed two singlets at 8.23 ppm and 8.43 ppm (Figure 2, top). The signal at 8.23 ppm was assigned to the $[BH(OCHO)_3]^-$ anion whereas the signal at 8.43 ppm was tentatively assigned to $NaB(OH)(OCHO)_3$ or formate.[15b] The ^{13}C NMR spectrum of the product displayed two signals at 164.0 ppm and 166.5 ppm (Figure S1), which were assigned to the $[BH(OCHO)_3]^-$ anion and a formate-containing compound, respectively.[15b] The ^{11}B NMR spectrum displays a singlet at 1.4 ppm, a doublet ($^1J_{BH}$ = 129.7 Hz) at 3.2 ppm and a broad peak at 20.2 ppm, which indicates the formation of metaborate (BO_2^-), $[BH(OCHO)_3]^-$ and boric acid ($B(OH)_3$) respectively (Figure S2).[15a, 15b] By using dry diglyme as a solvent, the same material was produced on a preparative scale by reacting $NaBH_4$ under 8.5 bar of CO_2 (Figure S3-S5). The reaction between $NaBH_4$ and HCOOH in THF led to a material with similar ^1H and ^{13}C NMR spectra to those obtained from the reactions of $NaBH_4$ and CO_2 (Figures S6-S7). Taken together, the presence of metaborate and boric acid along with the hydrogen observed in the previous experiments suggests that the formate-containing species is formed by hydrolysis. Using rigorously inert conditions, analytically pure $NaBH(OCHO)_3$ has been synthesised and fully characterised by Knopf and Cummins.[14]

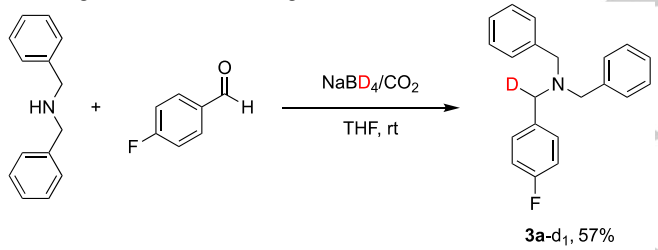
With optimized reaction conditions in our hands, we evaluated our protocol for reductive amination reactions. Primary and secondary alkyl amines were reacted with alkyl and aryl aldehydes. A variety of reductive aminations were carried out to show the versatility of the $NaBH_4/CO_2$ reagent and determine its scope and limitation (Scheme 2). Furthermore, the amines were isolated and purified to verify our protocol.



Scheme 2. Scope of reductive amination. Conditions: amine (1.1 mmol), aldehyde (1.0 mmol), $NaBH_4$ (1.1 mmol), CO_2 balloon, and THF (17.5 mL) in a 40 mL vial at room temperature for 21 h. [a] Reaction performed using amine (0.5 mmol), aldehyde (1.1 mmol). [b] Reaction performed using NH_4OAc (0.33 mmol), aldehyde (1.1 mmol).

The reductive amination of secondary alkyl amines dibenzylamine **1a** and diisoproylamine **1b** with aryl aldehyde 4-fluorobenzaldehyde afforded **3a** in 72% yield and **3b** in 45% yield respectively. Arylamine *p*-anisidine and alkyl aldehyde hydrocinnamaldehyde afforded **3c** in 66%. From the reductive amination of morpholine and alkyl aldehyde cyclohexane carboxaldehyde, **3d** was obtained in 78% yield. All products from the reductive amination of diethylamine and 2-naphaldehyde were separated and analyzed. From the reaction the desired product **3e** was obtained in 57% yield. 25% of the 2-naphaldehyde **1e** was recovered unreacted and 2-naphthalenemethanol **4e**, the result of direct reduction of the aldehyde, was obtained in 5%. The ligand tris(2-pyridylmethyl)amine (**TPA**) was obtained in 64% yield (**3f)** from the reductive amination of 2-pyridinecarboxaldehyde with 2-(aminomethyl)pyridine. If instead NH_4OAc was used as a source of NH_3, **TPA** was obtained in 29% yield (**3g**). Using this protocol the reductive amination of primary amines and even ammonia is possible. Moreover that multiple C-N bonds can be formed in one step using our protocol, demonstrating the versatility with primary, secondary and arylamines with aromatic and aliphatic aldehydes.

Preliminary mechanistic studies were performed by using sodium borodeuteride ($NaBD_4$) in conjunction with CO_2 as a method of conducting reductive amination with concomitant deuterium labelling (Scheme 3). Here **3a**-d_1 was obtained in 57% yield confirming the hydride source is in principle from $NaBH_4$ thus enabling selective D-labelling with CO_2.



Scheme 3. Reductive amination with concomitant deuterium-labelling.

Conclusions

CO_2 has a remarkable effect on reductive amination reactions using $NaBH_4$ as a pre-reducing agent. $NaBH_4$ reacts with CO_2 to afford $NaBH(OCHO)_3$ a congener of the well-known reducing agent $NaBH(OAc)_3$. Analogous to $NaBH(OAc)_3$, $NaBH(OCHO)_3$ is less active than $NaBH_4$ allowing it to preferentially reduce imines and iminium ions in the presence of aldehydes. Both $NaBH_4$ and CO_2 are cheap and readily available, even on an industrial scale. As a reagent for reductive amination reactions $NaBH_4/CO_2$ is a cheaper alternative to $NaBH(OAc)_3$ and $NaBH_3CN$ and its potential as a viable alternative will become clear with further research into this field. Whether $NaBH(OCHO)_3$ is best prepared in situ or prepared separately and added in the place of $NaBH(OAc)_3$ needs further investigation. The synthesis of $NaBH(OAc)_3$ from $NaBH_4$ and AcOH produces potentially explosive H_2 gas. The use of $NaBH_4/CO_2$ as the reducing agent ensures a safe protocol. In addition, the use of CO_2 as inert gas is another advantage: CO_2 takes the role often played by N_2 by displacing air from the reaction vessel thus preventing potential oxidation from taking place. We demonstrated selected examples of C−N bond formation reactions, which represent the utility of the protocol such that reductive amination using highly hindered diisopropylamine, arylamine *p*-anisidine and even ammonia was made possible.

Experimental Section

General Procedure for Reductive Amination Reaction

$NaBH_4$ (41.6 mg, 1.1 mmol) was added to a 40 mL vial containing a "cross-shaped" stirrer bar. The vial was briefly flame-dried under a stream of N_2 and allowed to cool. A CO_2 balloon was attached and the headspace flushed for 3 minutes. Dry THF (17.5 mL) was added via syringe. The white suspension was stirred for 3 hours at 750 rpm. Amine (1.1 mmol) and aldehyde (1.0 mmol) were added. The resultant suspension was left to stir 18 hours before being quenched with saturated $NaHCO_3$ solution (5 mL). The mixture was transferred to a round bottom flask and the vial washed with H_2O (5 mL) and THF (10 mL). THF was removed in vacuo and the pressure reduced to 200 mbar at 40 °C. The resultant aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo and subjected to further purification.

Acknowledgements

The generous support from the Department of Chemistry, University of Copenhagen, and from the Villum Fonden (00019062) is gratefully acknowledged. We also thank our analytical departments (NMR, GC/MS, LC/MS, HRMS) for their kind support.

Keywords: reductive amination • $NaBH_4$ • CO_2 • C-N bond • reduction

References

[1] a) O. I. Afanasyev, E. Kuchuk, D. L. Usanov, D. Chusov, *Chem. Rev.* **2019**, *119*, 11857-11911; b) S. A. Chambers, J. M. DeSousa, E. D. Huseman, S. D. Townsend, *ACS Chem. Neurosci.* **2018**, *9*, 2307-2330.

[2] a) E. Podyacheva, O. I. Afanasyev, A. A. Tsygankov, M. Makarova, D. Chusov, *Synthesis* **2019**, *51*, 2667-2677; b) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753-819.

[3] a) G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton, J. Johnson, *J. Am. Chem. Soc.* **1974**, *96*, 7812-7814; b) G. W. Gribble, D. C. Ferguson, *J. Chem. Soc., Chem. Commun.* **1975**, 535-536; c) G. W. Gribble, C. F. Nutaitis, *Org. Prep. Proced. Int.* **1985**, *17*, 317-384; d) G. W. Gribble, *Chem. Soc. Rev.* **1998**, *27*, 395-404; e) P. Marchini, G. Liso, A. Reho, F. Liberatore, F. Micheletti Moracci, *J. Org. Chem.* **1975**, *40*, 3453-3456; f) A. F. Abdel-Magid, C. A. Maryanoff, K. G. Carson, *Tetrahedron Lett.* **1990**, *31*, 5595-5598; g) A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849-3862; h) A. F. Abdel-Magid, S. J. Mehrman, *Org. Process Res. Dev.* **2006**, *10*, 971-1031.

[4] J. Pletz, B. Berg, R. Breinbauer, *Synthesis* **2016**, *48*, 1301-1317.

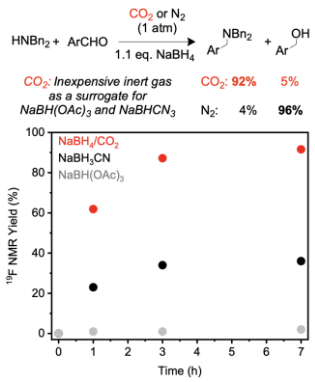
[5] D. M. F. Santos, C. A. C. Sequeira, *Renew. Sust. Energ. Rev.* **2011**, *15*, 3980-4001.
[6] a) M. Abdek-Akher, J. K. Hamilton, F. Smith, *J. Am. Chem. Soc.* **1951**, *73*, 4691-4692; b) M. L. Wolfrom, H. B. Wood, *J. Am. Chem. Soc.* **1951**, *73*, 2933-2934; c) M. L. Wolfrom, K. Anno, *J. Am. Chem. Soc.* **1952**, *74*, 5583-5584.
[7] H. M. Bell, C. W. Vanderslice, A. Spehar, *J. Org. Chem.* **1969**, *34*, 3923-3926.
[8] a) S. B. Kadin, *J. Org. Chem.* **1966**, *31*, 620-622; b) M. R. Johnson, B. Rickborn, *J. Org. Chem.* **1970**, *35*, 1041-1045.
[9] M. S. Brown, H. Rapoport, *J. Org. Chem.* **1963**, *28*, 3261-3263.
[10] A. Saeed, Z. Ashraf, *J. Chem. Sci.* **2006**, *118*, 419-423.
[11] a) T. Neilson, H. C. S. Wood, A. G. Wylie, *J. Chem. Soc.* **1962**, 371-372; b) S. K. Ghosh, M. Mandal, S. Kundu, S. Nath, T. Pal, *Appl. Catal., A* **2004**, *268*, 61-66; c) I. Pogorelić, M. Filipan-Litvić, S. Merkaš, G. Ljubić, I. Cepanec, M. Litvić, *J. Mol. Catal. A: Chem.* **2007**, *274*, 202-207; d) S. W. Chaikin, W. G. Brown, *J. Am. Chem. Soc.* **1949**, *71*, 122-125; e) H. C. Brown, E. J. Mead, B. C. Subba Rao, *J. Am. Chem. Soc.* **1955**, *77*, 6209-6213; f) H. C. Brown, K. Ichikawa, *Tetrahedron* **1957**, *1*, 221-230; g) J. H. Billman, A. C. Diesing, *J. Org. Chem.* **1957**, *22*, 1068-1070; h) D. E. Ward, C. K. Rhee, *Can. J. Chem.* **1989**, *67*, 1206-1211.
[12] J. G. Burr, W. G. Brown, H. E. Heller, *J. Am. Chem. Soc.* **1950**, *72*, 2560-2562.
[13] a) T. Wartik, R. K. Pearson, *J. Am. Chem. Soc.* **1955**, *77*, 1075-1075; b) T. Wartik, R. K. Pearson, *J. Inorg. Nucl. Chem.* **1958**, *7*, 404-411.
[14] I. Knopf, C. C. Cummins, *Organometallics* **2015**, *34*, 1601-1603.
[15] a) L. Lombardo, H. Yang, K. Zhao, P. J. Dyson, A. Züttel, *ChemSusChem* **2020**, *13*, 2025-2031; b) C. V. Picasso, D. A. Safin, I. Dovgaliuk, F. Devred, D. Debecker, H.-W. Li, J. Proost, Y. Filinchuk, *Int. J. Hydrogen Energy* **2016**, *41*, 14377-14386; c) S. Jeong, P. J. Milner, L. F. Wan, Y.-S. Liu, J. Oktawiec, E. W. Zaia, A. C. Forse, N. Leick, T. Gennett, J. Guo, D. Prendergast, J. R. Long, J. J. Urban, *Adv. Mater. (Weinheim, Ger.)* **2019**, *31*, 1904252; d) Y. Zhao, T. Wang, Y. Wang, R. Hao, W. Hui, *Chem. Eng. J.* **2020**, *380*, 122523; e) W. Zhu, J. Zhao, L. Wang, Y.-L. Teng, B.-X. Dong, *J. Solid State Chem.* **2019**, *277*, 828-832; f) Y. Zhao, Z. Zhang, *Chem. Eng. Technol.* **2015**, *38*, 110-116.
[16] a) Z. Guo, B. Zhang, X. Wei, C. Xi, *ChemSusChem* **2018**, *11*, 2296-2299; b) Q. Zou, G. Long, T. Zhao, X. Hu, *Green Chem.* **2020**, *22*, 1134-1138.
[17] a) T. Roy, M. J. Kim, Y. Yang, S. Kim, G. Kang, X. Ren, A. Kadziola, H.-Y. Lee, M.-H. Baik, J.-W. Lee, *ACS Catal.* **2019**, *9*, 6006-6011; b) J.-W. Lee, M. Juhl, A. R. Petersen, *Chem. Eur. J.* **2020**, DOI: 10.1002/chem.202003623.
[18] a) M. Periasamy, M. Thirumalaikumar, *J. Organomet. Chem.* **2000**, *609*, 137-151; b) T. Satoh, S. Suzuki, Y. Suzuki, Y. Miyaji, Z. Imai, *Tetrahedron Lett.* **1969**, *10*, 4555-4558; c) H. C. Brown, B. C. S. Rao, *J. Am. Chem. Soc.* **1956**, *78*, 2582-2588; d) N. V. Forkel, D. A. Henderson, M. J. Fuchter, *Green Chem.* **2012**, *14*, 2129-2132; e) N. V. Forkel, D. A. Henderson, M. J. Fuchter, *Tetrahedron Lett.* **2014**, *55*, 5511-5514; f) J.-L. Luche, L. Rodriguez-Hahn, P. Crabbé, *J. Chem. Soc., Chem. Commun.* **1978**, 601-602; g) A. L. Gemal, J. L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454-5459; h) A. P. Marchand, W. D. LaRoe, G. V. M. Sharma, S. C. Suri, D. S. Reddy, *J. Org. Chem.* **1986**, *51*, 1622-1625; i) S.-K. Chung, *J. Org. Chem.* **1979**, *44*, 1014-1016; j) S. W. Heinzman, B. Ganem, *J. Am. Chem. Soc.* **1982**, *104*, 6801-6802; k) J. Kollonitsch, O. Fuchs, V. Gábor, *Nature* **1954**, *173*, 125-126; l) A. Nose, T. Kudo, *Chem. Pharm. Bull.* **1981**, *29*, 1159-1161; m) I. Saxena, R. Borah, J. C. Sarma, *J. Chem. Soc., Perkin Trans. 1* **2000**, 503-504; n) S. Bhattacharyya, *Tetrahedron Lett.* **1994**, *35*, 2401-2404.
[19] J. Artz, T. E. Müller, K. Thenert, J. Kleinekorte, R. Meys, A. Sternberg, A. Bardow, W. Leitner, *Chem. Rev.* **2018**, *118*, 434-504.
[20] a) D. Riemer, B. Mandaviya, W. Schilling, A. C. Götz, T. Kühl, M. Finger, S. Das, *ACS Catal.* **2018**, *8*, 3030-3034; b) Y. Markushyna, P. Lamagni, J. Catalano, N. Lock, G. Zhang, M. Antonietti, A. Savateev, *ACS Catal.* **2020**, *10*, 7336-7342.
[21] W. Schilling, S. Das, *Tetrahedron Lett.* **2018**, *59*, 3821-3828.
[22] Y. Yang, J.-W. Lee, *Chem. Sci.* **2019**, *10*, 3905-3926.
[23] D. Chusov, B. List, *Angew. Chem. Int. Ed.* **2014**, *53*, 5199-5201.

10.1002/ejoc.202001408

WILEY-VCH

FULL PAPER

Entry for the Table of Contents



Key Topics: CO_2-Mediated Synthesis

The reactivity of $NaBH_4$ was controlled by atmospheric CO_2, thus suppressing direct reduction of aldehydes to alcohols. High selectivities towards reductive amination alkylation reactions indicate the in-situ formation of less reducing $NaBH(OCHO)_3$. This protocol provides a surrogate for conventional reducing reagents in reductive amination reactions.

Institute and/or researcher Twitter usernames: TheLeeLab_Chem