

First example of direct reductive amination of aldehydes with primary and secondary amines catalyzed by water-soluble transition metal catalysts

André Robichaud and Abdelaziz Nait Ajjou*

Department of Chemistry and Biochemistry, University of Moncton, Moncton, New-Brunswick, Canada E1A 3E9

Received 22 February 2006; revised 22 March 2006; accepted 23 March 2006

Available online 12 April 2006

Abstract—An unprecedented efficient and highly selective direct reductive amination of aldehydes with primary and secondary amines in water using gaseous hydrogen and water-soluble catalysts is developed. The catalytic system formed in situ from Pd(PhCN)₂Cl₂ and 2,2'-biquinoline-4,4'-dicarboxylic acid dipotassium salt (BQC), allows full conversion of aldehydes and the formation of desired alkylated amines with excellent yields and selectivities. The catalytic system is stable and can be recycled and reused three times without loss of activity.

© 2006 Elsevier Ltd. All rights reserved.

Amines and their derivatives are highly versatile building blocks for various organic substrates and are essential precursors to a variety of biologically active compounds, such as pharmaceuticals¹ and agrochemicals.² Amines and their derivatives are widespread among natural products and pharmaceutical industries abound with drugs based on amine moieties.³ Consequently, synthesis of amines is a very active field in medicinal chemistry and modern organic synthesis. The direct reductive amination (DRA) of aldehydes and ketones with amines to target higher alkylated amines is an elegant and a powerful methodology.⁴ It can be carried out under mild conditions, and is compatible, in some cases, with many functional groups. In addition, it is based on commercial substrates that are widely available and the experimental operations are simple. The two commonly used direct reductive amination processes are based on either hydride reducing agents or catalytic hydrogenation. Among the hydride reducing agents,^{5–9} different borohydrides are frequently used to carry out this transformation, mainly sodium cyanoborohydride (NaBH₃CN)⁵ and sodium triacetoxyborohydride (NaBH(OAc)₃).⁶ However, the processes based on such reducing agents have many limitations.

Furthermore, they are not environmentally friendly and are not accepted in the concept of *green chemistry*. In general, it is necessary to use excess amount of amines in order to limit or prevent the competitive reduction of carbonyl groups. In addition, they frequently generate undesirable wasteful salts. NaBH₃CN is expensive and highly toxic. Moreover, it may contaminate the product with cyanide¹⁰ and generates toxic byproducts HCN and NaCN upon work-up. NaBH(OAc)₃ is flammable, water-reactive, and poorly soluble in most of the commonly used organic solvents. Pyridine–BH₃⁷ and tin hydride⁸ are also used for the reductive amination of aldehydes and ketones. Pyridine–BH₃ is unstable to heat and must be handled with extreme care,¹¹ while tin hydride and its organotin byproducts are highly toxic.¹² Consequently, there is still tremendous demand for new processes that satisfy increasing environmental concerns and constraints. Direct reductive amination of carbonyl compounds were also performed by hydrogenation methods. In contrast to hydride reducing agents, the use of molecular hydrogen is attractive from economical and ecological viewpoints, despite its incompatibility with some functional groups such as carbon–carbon double and triple bonds. While the literature abounds with heterogeneous hydrogenation processes,^{4c,13} little attention has been paid to the direct reductive amination which are catalyzed by homogeneous catalysts.¹⁴ Most recently, Sajiki and co-workers described a selective monoalkylation of both aromatic

Keywords: Water-soluble catalyst; Reductive amination; Aldehydes; Molecular hydrogen; Secondary amines; Tertiary amines.

* Corresponding author. Tel.: +1 506 858 4936; fax: +1 506 858 4541; e-mail: naitaja@umoncton.ca

and aliphatic amines using nitriles as an alkylating agent and Pd/C or Rh/C as the catalysts.¹⁵ DRA is mostly performed in costly and toxic organic solvents. Furthermore, anhydrous conditions were applied in order to avoid the decomposition of the reducing agents or catalysts, and to enhance the generation of the intermediate imines or iminium ions. If direct reductive amination of carbonyl compounds could be performed in water, the processes would attract considerable interest. Thus, the challenging development of effective catalysts or reagents that tolerate water is highly desirable.

Recently, Kikugawa and co-workers demonstrated that DRA can be carried out in water using α -picolineborane as the reducing agent.^{9a} Beller and co-workers reported the first DRA of aldehydes with ammonia using molecular hydrogen and water-soluble catalysts.^{14a} Excellent results were obtained, however, organic solvents such as THF or methyl *tert*-butyl ether were used. Moreover, the reactions were performed at high temperature (135 °C) and high hydrogen pressure (65 bars). We, recently, reported different organic transformations in water.¹⁶ To the best of our knowledge there are no reports concerning selective synthesis of secondary or tertiary amines using DRA based on molecular hydrogen and water-soluble transition metal catalysts. In this letter we are pleased to report an unprecedented highly efficient direct reductive amination of aldehydes with primary and secondary amines catalyzed by water-soluble transition metal complexes under hydrogen pressure. The catalysts are generated in situ using TPPTS (P(*m*-C₆H₄SO₃Na)₃) or BQC (2,2'-biquinoline-4,4'-dicarboxylic acid dipotassium salt).

In order to test the catalytic activity of various systems, direct solvent-free reductive amination of benzaldehyde with equimolar amount of benzylamine was chosen as a model reaction. Interestingly, the results summarized in Table 1 indicate that the systems studied afforded the anticipated dibenzylamine without detectable tertiary amine (tribenzylamine). Generally, excess amount of amines is necessary in order to avoid over alkylation. The water-soluble ligands, TPPTS and BQC, allowed full conversion of benzaldehyde in all the cases and gave

dibenzylamine in good to excellent yields in most cases, in spite of the presence of benzyl alcohol and *N*-benzylidenebenzylamine (imine) as byproducts. BQC showed better selectivity than TPPTS for the formation of dibenzylamine, except in the case of [Rh(COD)Cl]₂/BQC where secondary amine and the corresponding imine were formed in 45% and 31% yields, respectively (Table 1, entry 6). The best result was reached by the catalytic system Pd(PhCN)₂Cl₂/BQC (Table 1, entry 8).

One important aspect of aqueous-phase catalysis is the ability to recover and recycle the catalyst after its separation from the reaction products by simple decantation. The stability of Pd(PhCN)₂Cl₂/BQC is evidently very good as the catalyst aqueous solutions can be reused without loss of activity and selectivity for dibenzylamine (Table 1, entries 8–10).¹⁷

In the light of these excellent results, various aldehydes were subjected to DRA with different amines, using the above reaction process, in order to explore the scope and limitations of Pd(PhCN)₂Cl₂/BQC (Table 2).¹⁸ Under our standard conditions, reductive amination of aldehydes with primary amines proceeded smoothly with full conversion of aldehydes and excellent yields (82–99%) of the desired alkylated amines (Table 2, entries 1–7). DRA of acetophenone was sluggish and only a conversion of 88% was reached and the alkylated amine was obtained with 44% yield and 50% selectivity (Table 2, entry 8). The result is however interesting since acetophenone has been shown to be an inert^{9b} or a difficult substrate^{6,9d} in some reported reductive aminations. Tertiary amines were also prepared easily with excellent yields and selectivities. Indeed, benzaldehyde and dodecylaldehyde underwent successful reductive amination with dihexylamine yielding the corresponding tertiary amines with full conversion and excellent yields (Table 2, entries 9 and 10). Under the same condition, DRA of benzaldehyde with sterically hindered dibenzylamine or diisopropylamine did not occur. The reactions afforded only 1-phenylethanol in 100% yield (Table 2, entries 11 and 12).

In conclusion, we described an unprecedented synthesis of secondary and tertiary amines in water by direct

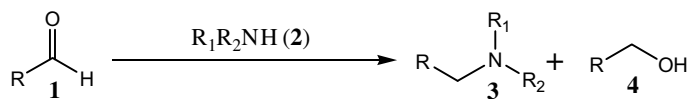
Table 1. DRA of benzaldehyde with benzylamine catalyzed by different water-soluble systems^a

Entry	Catalytic system	Conversion %	Dibenzylamine yield (%)	<i>N</i> -Benzylidenebenzylamine yield (%)	PhCH ₂ OH yield (%)
1	[Ir(COD)Cl] ₂ /TPPTS	100	71	0	29
2	[Ir(COD)Cl] ₂ /BQC	100	93	0	7
3	Pt(COD)Cl ₂ /TPPTS	100	69	6	23
4	Pt(COD)Cl ₂ /BQC	100	91	0	7
5	[Rh(COD)Cl] ₂ /TPPTS	100	86	0	8
6	[Rh(COD)Cl] ₂ /BQC	100	45	31	9
7	Pd(PhCN) ₂ Cl ₂ /TPPTS	100	90	0	9
8	Pd(PhCN) ₂ Cl ₂ /BQC	100	95	0	5
9 ^b	Pd(PhCN) ₂ Cl ₂ /BQC	100	95	0	5
10 ^c	Pd(PhCN) ₂ Cl ₂ /BQC	100	93	0	7

^a Reaction conditions: benzaldehyde (2.5 mmol), benzylamine (2.5 mmol), catalyst (0.025 mmol), ligand (0.15 mmol), water (10 mL), H₂ (200 psi), 100 °C.

^b Second cycle of entry 8.

^c Third cycle of entry 8.

Table 2. DRA of various aldehydes with different amines catalyzed by Pd(PhCN)₂Cl₂/BQC^a

Entry	Aldehyde (1)	Amine (2)	Conversion (%)	Alkylated amine (3) yield (%)	Alcohol (4) yield (%)
1	PhCHO	PhCH ₂ NH ₂	100	95	5
2	PhCHO	CH ₃ (CH ₂) ₅ NH ₂	100	97	3
3	PhCHO	PhCH ₂ CH ₂ NH ₂	100	99	0
4	PhCHO	(CH ₃) ₂ CHNH ₂	100	90	10
5	<i>p</i> -CH ₃ O-C ₆ H ₄ CHO	PhCH ₂ NH ₂	100	93	7
6	<i>p</i> -CH ₃ O-C ₆ H ₄ CHO	CH ₃ (CH ₂) ₅ NH ₂	100	99	0
7 ^b	CH ₃ (CH ₂) ₁₀ CHO	CH ₃ (CH ₂) ₅ NH ₂	100	90	0
8	PhCOCH ₃	CH ₃ (CH ₂) ₅ NH ₂	88	44	44
9	CH ₃ (CH ₂) ₁₀ CHO	(CH ₃ (CH ₂) ₅) ₂ NH	100	93	0
10	PhCHO	(CH ₃ (CH ₂) ₅) ₂ NH	100	99	0
11	PhCHO	<i>i</i> Pr ₂ NH	100	0	100
12	PhCHO	(PhCH ₂) ₂ NH	100	0	100

^a Reaction conditions: aldehyde (2.5 mmol), amine (2.5 mmol), Pd(PhCN)₂Cl₂ (0.025 mmol), BQC (0.15 mmol), water (10 mL), H₂ (200 psi), 100 °C.

^b Tertiary amine was obtained with 8% yield.

reductive amination of aldehydes with primary and secondary amines. The reaction is performed under molecular hydrogen pressure using Pd(PhCN)₂Cl₂/BQC. The catalytic system is stable and can be recycled and reused three times without loss of activity and selectivity.

Acknowledgements

We are grateful to NSERC of Canada and to FESR of University of Moncton for financial support of this research.

References and notes

- (a) Merla, B.; Risch, N. *Synthesis* **2002**, 1365; (b) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385.
- Sharp, D. B. In *Herbicides: Chemistry, Degradation, and Mode of Action*; Kearney, P. C., Kaufman, D. D., Eds.; Marcel Dekker: New York, 1988; Chapter 7.
- Henkel, T.; Brunne, R. M.; Mueller, H.; Reichel, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 643.
- (a) Hutchins, R. O.; Hutchins, M. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, p 25; (b) Hudlicky, M. *Reductions in Organic Chemistry*, 2nd ed.; ACS Monograph 188, 1996; p 187; (c) Tarasevich, V. A.; Kozlov, N. G. *Russ. Chem. Rev.* **1999**, *68*, 55.
- (a) Lane, C. F. *Synthesis* **1975**, 135; (b) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897; (c) Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552.
- Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.
- (a) Pelter, A.; Rosser, R. M.; Mills, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 717; (b) Bomann, M. D.; Guch, I. C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995.
- Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synthesis* **2000**, 558, and 789.
- (a) Sato, S.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. *Tetrahedron* **2004**, *60*, 7899; (b) Cho, B. T.; Kang, S. K. *Tetrahedron* **2005**, *61*, 5725; (c) Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463; (d) Apodaca, R.; Xiao, W. *Org. Lett.* **2001**, *3*, 1745.
- Moormann, A. E. *Synth. Commun.* **1993**, *23*, 789.
- (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.
- Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, 1987; p 6.
- (a) Ikenaga, T.; Matsushita, K.; Shinozawa, J.; Yada, S.; Takagi, Y. *Tetrahedron* **2005**, *61*, 2105; (b) Heinen, A. W.; Peters, J. A.; van Bekkum, H. *Eur. J. Org. Chem.* **2000**, 2501; (c) Birtill, J. J.; Chamberlain, M.; Hall, J.; Wilson, R.; Costello, I. In *Catalysis of Organic Reactions*; Herkes, F. E., Ed.; Dekker: New York, 1998; p 255.
- (a) Gross, T.; Seayad, A. M.; Ahmad, M.; Beller, M. *Org. Lett.* **2002**, *4*, 2055; (b) Kadyrov, R.; Riermeier, T. H.; Dingerdissen, U.; Tararov, V.; Börner, A. *J. Org. Chem.* **2003**, *68*, 4067; (c) Imao, D.; Fujihara, S.; Yamamoto, T.; Ohta, T.; Ito, Y. *Tetrahedron* **2005**, *61*, 6988; (d) Chi, Y.; Zhou, Y.-G.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 4120; (e) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Börner, A. *Chem. Commun.* **2000**, 1867.
- Sajiki, H.; Ikawa, T.; Hirota, K. *Org. Lett.* **2004**, *6*, 4977.
- (a) Boudreau, J.; Doucette, M.; Nait Ajjou, A. *Tetrahedron Lett.* **2006**, *47*, 1695; (b) Nait Ajjou, A.; Pinet, J.-L. *Can. J. Chem.* **2005**, *83*, 702; (c) Nait Ajjou, A.; Pinet, J.-L. *J. Mol. Catal. A: Chem.* **2004**, *214*, 203; (d) Ferguson, G.; Nait Ajjou, A. *Tetrahedron Lett.* **2003**, *44*, 9139; (e) Nait Ajjou, A. *Tetrahedron Lett.* **2001**, *42*, 13; (f) Djoman, M. C. K.-B.; Nait Ajjou, A. *Tetrahedron Lett.* **2000**, *41*, 4845.
- The aqueous phase obtained after the removal of solvents was re-used with a fresh charge of the benzaldehyde (2.5 mmol) and benzylamine (2.5 mmol).
- Typical procedure for the reductive amination of aldehydes with amines: In a glass liner of a 45 mL autoclave and under an atmosphere of nitrogen, Pd(PhCN)₂Cl₂ (0.025 mmol) and BQC (0.15 mmol) were dissolved in degassed water (10 mL) at room temperature. Then the aldehyde (2.5 mmol) was introduced, followed by the amine (2.5 mmol), and the resulting solution was white-opaque. The autoclave was flushed several times with 40 psi of N₂ and then purged with hydrogen. After the autoclave was pressurized to 200 psi of hydrogen, it was placed in an oil bath at 100 °C for 24 h. The autoclave was

cooled to room temperature, the remaining hydrogen was vented and the mixture was extracted three times with dichloromethane (3 mL). The combined organic layers were dried (MgSO_4), evaporated to dryness and the resulting products were analyzed. *N*-Benzylidenebenzyl-

amine, dibenzylamine, *N*-isopropylbenzylamine, *N*-benzyl-2-phenylethylamine, and the alcohols were identified by ^1H NMR and ^{13}C NMR and compared to authentic commercial samples. The other amines were all characterized by ^1H NMR, ^{13}C NMR, and mass spectrometry.