An Unprecedented Ruthenium-Catalyzed Reductive Amination of Aldehydes with Tertiary Amines

Chan Sik Cho,[*,†] Ji Hyuk Park, Tae-Jeong Kim, and Sang Chul Shim[*]

[†]*Research Institute of Industrial Technology, Kyungpook National University, Taegu 702-701, Korea*
Department of Industrial Chemistry, College of Engineering, Kyungpook National University, Taegu 702-701, Korea
Received October 12, 2001

Keywords : Aldehyde, Catalyst, Ruthenium, Reductive amination, Tertiary amine.

The reductive amination of ketones and aldehydes with amines has been used as a tool for *N*-alkylation of amines. The process generally proceeds in two tandem steps, condensation between carbonyl compounds and amines to form an imine and reduction of the imine by a reducing agent.[1,2] In sharp contrast to reductive amination of ketones and aldehydes with primary and secondary amines, little has known for that with teriary amines. During the course of our ongoing studies on homogeneous ruthenium catalysis,[3-5] we recently developed an alkyl group transfer from alkylamines to N-atom of anilines[3] as well as α-carbon atom of ketones[4] by an activation of C-N bond of alkylamines. Prompted by these findings and intrigued by diverse reactivities of ruthenium catalysis, we have directed our attention to the reductive amination of aldehydes with tertiary amines, the process requiring the activation of C-N bond of tertiary amines. Here we report an unprecedented ruthenium-catalyzed reductive amination of aldehydes with tertiary amines in an aqueous medium.[6]

Treatment of equimolar amounts of benzaldehyde (**1a**, **1**: R=Ph) and tributylamine (**2a**, **2**: R'=Bu) in an aqueous medium (dioxane-H_2O) at 180 °C in the presence of a catalytic amount of $Ru_3(CO)_{12}$ (2 mol%) under carbon monoxide pressure afforded benzyldibutylamine (**3a**) in 43% yield with concomitant formation of dibenzylbutylamine (**4a**, 7%) (Table 1). **4a** seems to be formed by an amine scrambling process under the employed ruthenium catalyst.[7] Performing the reaction in dioxane gave **3a** in only 24% yield. Carbon monoxide was necessary for the effective formation of the reductive amination product. When the reaction was carried out under argon atmosphere, the yield of reductive amination product was lower than that under carbon monoxide. This result may suggest that carbon monoxide atmosphere hinders decarbonylation *via* a hydrido acyl ruthenium intermediate formed by oxidative addition of the carbon-hydrogen bond of the aldehyde to ruthenium.[8] Lower reaction temperature resulted in lower yield of **3a** (4%, at 150 °C for 1 h; 35%, at 180 °C for 1 h). Among the activity of various ruthenium precursors examined $Ru_3(CO)_{12}$ revealed to be the catalyst of choice. Other ruthenium complexes such as $RuCl_3 \cdot nH_2O$/$3PPh_3$, $RuCl_2(PPh_3)_3$, and $RuH_2(PPh_3)_4$ were nearly ineffective (0-2% yields of **3a** were formed at 180 °C for 1 h).

Having established reaction conditions, several aldehydes and tertiary amines were screened. As shown in Table 1, the yield of **3** was not desicively affected by the position and electronic nature of the substituent on the aromatic ring of the aldehyde (runs 1-6). With polyaromatic and heteroaryl aldehydes, the corresponding reductive amination products were also formed in similar yields (runs 7 and 8). In the reaction between **1a** and several trialkylamines, the corresponding reductive amination products **3** were also produced together with **4** (runs 9-11).

Table 1. Ruthenium-catalyzed reductive amination of aldehydes (**1**) with tertiary amines (**2**)[a]

$$\underset{\mathbf{1}}{\mathrm{RCHO}} + \underset{\mathbf{2}}{\mathrm{NR'_3}} \xrightarrow[\text{dioxane-H}_2\text{O, 180 °C, 12 h}]{\mathrm{Ru_3(CO)_{12},\ CO}} \underset{\mathbf{3}}{\mathrm{RCH_2NR'_2}} + \underset{\mathbf{4}}{\mathrm{(RCH_2)_2NR'}}$$

Run	**1** (R =)	**2** (R' =)	Isolated yield (%)	
			3	**4**
1	Ph	Bu	43	7
2	4-MeC_6H_4	Bu	41	7
3	3-MeC_6H_4	Bu	40	8
4	2-MeC_6H_4	Bu	40	4
5	4-$MeOC_6H_4$	Bu	41	6
6	4-$BrOC_6H_4$	Bu	44	2
7	2-naphthyl	Bu	54	6
8	2-thiophenyl	Bu	33	4
9	Ph	isoamyl	39	6
10	Ph	hexyl	42	5
11	Ph	octyl	38	4

[a]Reaction conditions: **1** (1 mmol), **2** (1 mmol), $Ru_3(CO)_{12}$ (0.02 mmol), CO (10 atm), dioxane/H_2O (5 mL/0.2 mL), 180 °C, 12 h.

Typical experimental procedure is as follows. A mixture of **1a** (1 mmol), **2a** (1 mmol), $Ru_3(CO)_{12}$ (0.02 mmol), and dioxane/H_2O (5 mL/0.2 mL) was placed in a pressure vessel. After the system was flushed and then pressurized with carbon monoxide (10 atm), the mixture was stirred at 180 °C for 12 h. The reaction mixture was poured into brine, extracted with $CHCl_3$ and dried over Na_2SO_4. Removal of the solvent under reduced pressure left an oil, which was purified by column chromatography (ethyl acetate/hexane) to give **3a** (43%) and **4a** (7%).

In summary, we have demonstrated that aldehydes can be reductively aminated with tertiary amines in an aqueous medium in the presence of a catalytic amount of a ruthenium catalyst under carbon monoxide pressure. The present reaction is a first example for reductive amination of aldehydes with tertiary amines. On the basis of others[7c] and our recent reports,[3,4] the reaction mechanism is currently investigated.

Acknowledgment. The present work was supported by the Korea Research Foundation Grant (KRF-2001-015-DP0296). C.S.C. gratefully acknowledges a MOE-KRF Research Professor Program (2001-050-D00015).

References

1. Dayagi, S. In *The Chemistry of the Carbon-Nitrogen Double Bond*; Patai, S., Ed.; Interscience: London, 1970; Chapter 2, pp 61-147.
2. (a) In *Comprehensive Organometallic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8. (b) Hudlicky, M. *Reactions in Organic Chemistry*; American Chemical Society: Washington, D. C., 1996.
3. This transfer eventually leads to indoles and quinolines: Indoles: Cho, C. S.; Lim, H. K.; Shim, S. C.; Kim, T. J.; Choi, H.-J. *Chem. Commun.* **1998**, 995; Cho, C. S.; Kim, J. H.; Shim, S. C. *Tetrahedron Lett.* **2000**, *41*, 1811; Cho, C. S.; Kim, J. H.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2001**, *57*, 3321; Cho, C. S.; Kim, T. K.; Yoon, S. W.; Kim, T.-J.; Shim, S. C. *Bull. Korean Chem. Soc.* **2001**, *22*, 545. Quinolines: Cho, C. S.; Oh, B. H.; Shim, S. C. *Tetrahedron Lett.* **1999**, *40*, 1499; Cho, C. S.; Oh, B. H.; Shim, S. C. *J. Heterocyclic Chem.* **1999**, *36*, 1175; Cho, C. S.; Oh, B. H.; Shim, S. C.; Oh, D. H. *J. Heterocyclic Chem.* **2000**, *37*, 1315; Cho, C. S.; Kim, J. S.; Oh, B. H.; Kim, T.-J.; Shim, S. C.; Yoon, N. S. *Tetrahedron* **2000**, *56*, 7747; Cho, C. S.; Oh, B. H.; Kim, J. S.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2000**, 1885; Cho, C. S.; Kim, T. K.; Kim, T.-J.; Shim, S. C.; Yoon, N. S. *J. Heterocyclic Chem.* in press.
4. This transfer leads to regioselective α-alkyaltion of ketones: Cho, C. S.; Kim, B. T.; Lee, M. J.; Kim, T.-J.; Shim, S. C. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 958.
5. Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Org. Chem.* **2001**, *66*, 9020.
6. *Aqueous-Phase Organometallic Catalysis*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 1998.
7. For transition metal-catalyzed amine exchange reaction, see: (a) Yoshimura, N.; Moritani, I.; Shimamura, T.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1973**, *95*, 3038. (b) Murahashi, S.-I.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 348. (c) Shvo, Y.; Laine, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 753. (d) Khai, B.-T.; Concilio, C.; Porzi, G. *J. Organomet. Chem.* **1981**, *208*, 249. (e) Khai, B.-T.; Concilio, C.; Porzi, G. *J. Org. Chem.* **1981**, *46*, 1759. (f) Arcelli, A.; Khai, B.-T.; Porzi, G. *J. Organomet. Chem.* **1982**, *231*, C31. (g) Murahashi, S.-I.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* **1982**, *23*, 229. (h) Laine, R. M.; Thomas, D. W.; Cary, L. W. *J. Am. Chem. Soc.* **1982**, *104*, 1763. (i) Jung, C. W.; Fellmann, J. D.; Garrou, P. E. *Organometallics* **1983**, *2*, 1042. (j) Murahashi, S.-I. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2443.
8. (a) Kondo, T.; Akazome, M.; Tsuji, Y.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 1286. (b) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation: Direct Synthesis of Carbonyl Compounds*; Plenum: New York, 1991; pp 205-255.