

Hydrogen-Free Cobalt–Rhodium Heterobimetallic Nanoparticle-Catalyzed Reductive Amination of Aldehydes and Ketones with Amines and Nitroarenes in the Presence of Carbon Monoxide and Water

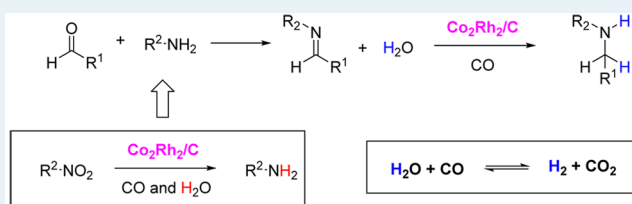
Jang Won Park and Young Keun Chung*

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-747, Korea

S Supporting Information

ABSTRACT: Cobalt–rhodium heterobimetallic nanoparticle-catalyzed reductive amination of aldehydes and ketones with amines in the presence of 5 atm carbon monoxide without an external hydrogen source has been developed. Water added and generated in situ produces hydrogen via a water–gas-shift reaction. The reaction can be extended to the tandem reduction of aldehydes and ketones with nitroarenes. The catalytic system is stable under the reaction conditions and could be reused eight times without losing any catalytic activity.

KEYWORDS: heterogeneous catalysis, amination, reduction, carbon monoxide, water



Homogeneous transition-metal-complex-catalyzed direct reductive amination procedures are well developed.¹ Two types of reducing agents are employed for direct reductive amination of aldehyde with amines:² based on metal-catalyzed hydrogenation and hydride reducing agents (Scheme 1a).³ Recently, alternatives to the use of hydrogen or hydride have been reported.⁴ Chusov and List⁵ recently described a Rh-catalyzed reductive amination of aldehydes with aryl amines (Scheme 1b). Their amination utilizes the existing hydrogen atoms of the amine substrates and high pressures of carbon monoxide (20–100 bar) as the reductant in THF at 120–140 °C. A method of reduction without an external hydrogen source is a highly desirable process. Inspired by the work, we envisioned in situ generated water as a hydrogen source. If a reductive amination of aldehydes with amines was carried out in the presence of carbon monoxide, the liberated water in the condensation reaction might react with carbon monoxide to give hydrogen and carbon dioxide in the presence of a water–gas-shift reaction catalyst. Then the generated hydrogen molecule can act as a reducing agent, resulting in producing amines. Several decades ago, Iqbal reported the use of carbon monoxide and water in the reduction of a nitro group in nitroarene compounds.⁶

The emergence of transition-metal nanoparticles has led to an explosive growth in catalysis.⁷ Transition-metal nanoparticles are potentially attractive catalysts due to their high catalytic activities and synergistic effects. Recently, the use of heterobimetallic nanoparticles as catalysts has attracted much attention because their catalytic performance is generally superior to that of a single nanoparticle by itself, and there is potential to create new types of catalysts for reactions which may not be achieved by monometallic catalyst.⁸ We reported

that cobalt/rhodium heterobimetallic nanoparticles (Co₂Rh₂, derived from Co₂Rh₂(CO)₁₂) immobilized on charcoal (Co₂Rh₂/C) were quite useful catalysts in carbonylation⁹ and/or hydrogenation reactions (Scheme 1c).¹⁰ In the hope of finding new catalytic amination system, we decided to use Co₂Rh₂/C as catalyst in the reductive amination between aldehydes (or ketones) and amines in the presence of carbon monoxide without any external hydrogen source. We found that the catalytic system was quite effective in the reductive amination of aldehydes or ketones with amines in the presence of 5 atm CO in wet THF at 100 °C for 12 h (Scheme 1d). We herein communicate our preliminary results. Recently, Franke and Beller reported¹¹ Ru-catalyzed hydroaminomethylation of olefins with an amine using a water–gas-shift reaction (40 bar CO used). The Co₂Rh₂/C-catalyzed reductive amination could be conducted at substantially lesser pressure than the one previously employed under rhodium and ruthenium catalysis.^{5,12}

Initially, the reaction of benzaldehyde (1a) with 4-methoxyaniline (2a) to afford the amination product, *N*-benzyl-4-methoxyaniline (3aa), was chosen as the model reaction in the presence of Co₂Rh₂/C (5 mol %) in THF at 100 °C (Scheme 2). After workup, 3aa was isolated in 65% yield with a concomitant formation of an imine, *N*-(4-methoxyphenyl)-1-phenylmethanimine, 4aa, in 20% yield.

Encouraged by the above observation, we decided to optimize the reaction conditions for the amination of 1a with 2a under 5 atm CO (Table 1). Decreasing the reaction time

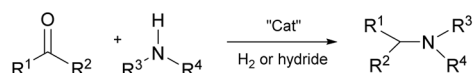
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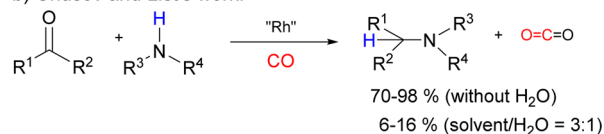
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Scheme 1. Reductive Amination Reactions^{3,5}/ Hydrogenation¹⁰

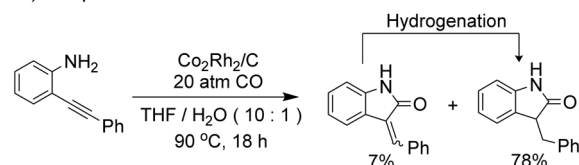
a) Previous work:



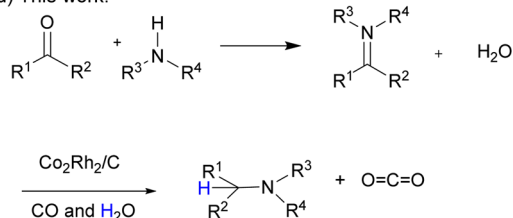
b) Chusov and List's work:



c) Our previous work:



d) This work:



Scheme 2. Initial Observation

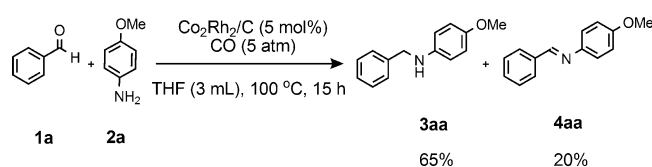
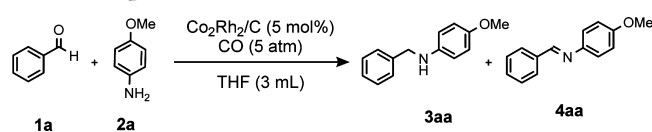


Table 1. Optimization of the Reaction Conditions

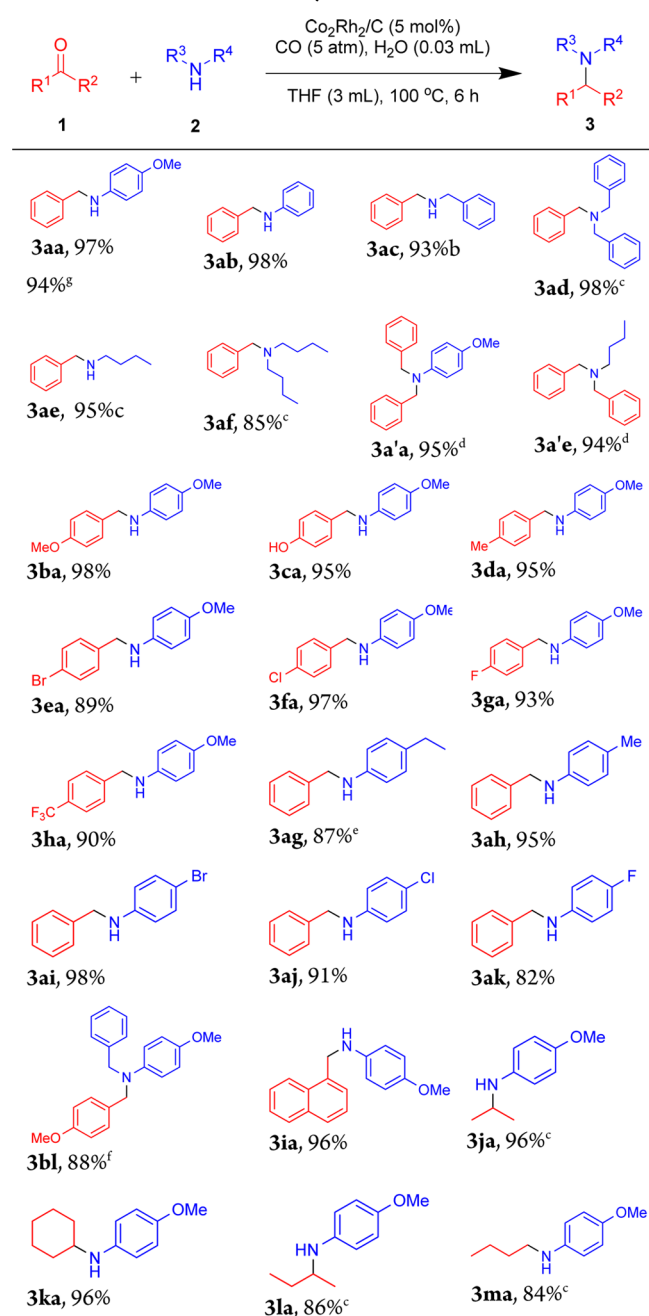


entry	H ₂ O (mL)	temp (°C)	time (h)	yield (%) ^a	
				3aa	4aa
1	0	100	15	65	20
2	0	100	6	52	20
3 ^b	0	100	6	0	98
4	0.3	100	6	94	0
5	0.3	85	6	0	98
6	0.3	90	6	36	62
7	0.3	95	6	80	17
8 ^c	0.3	100	6	54	44
9	0.03	100	6	98	0
10	0.03	120	3	97	0
11 ^d	0.03	100	6	17	80
12	0.03	100	6	23	75
13 ^e	0.03	100	6	0	97

^aIsolated yield. ^bIn the presence of molecular sieves (3 Å). ^c3 mol % Co₂Rh₂/C used. ^dUnder 3 atm CO. ^eIn toluene.

from 15 to 6 h led to formation of a mixture of **3aa** and **4aa** in 52% and 20%, respectively (entry 2). In the presence of molecular sieves (3 Å), no amine product was isolated. Instead, **4aa** was isolated in 98% yield (entry 3). This observation suggested that water was needed for hydrogenation of **4aa**. Water generated in the formation of **4aa** would react with carbon monoxide by means of the water–gas-shift reaction to produce molecular hydrogen and carbon dioxide. Thus, we varied the amount of water in the reaction mixture (water/THF, from 0.3 mL/3.0 to 0.03 mL/3.0 mL) to know how the water concentration influences the hydrogenation of **4aa** (entry 4 vs 9). The reaction was highly sensitive to the reaction temperature and the amount of catalyst used (entry 4–8). Lowering the reaction temperature from 100 to 85 °C completely blocked the formation of an amine. Moreover, the reaction was highly sensitive to the amount of Co₂Rh₂/C used (entry 4 vs 8). Decreasing the amount of catalyst from 5 mol % to 3 mol % led to the formation of a mixture of **3aa** and **4aa** in 54% and 44% yield, respectively. The best yield (98%) of **3aa** was observed when the reaction carried out in the presence of 5 mol % of Co₂Rh₂/C in a mixture solvent of water and THF (0.03 mL/3.0 mL) at 100 °C for 6 h. When the reaction was carried out at 120 °C (entry 10), the reaction time could be shortened with a high yield (97%). The reaction was highly sensitive to the CO pressure and reaction time. Under 3 atm of CO, a mixture of **3aa** and **4aa** was formed in 17% and 80% yields, respectively (entry 11). For 3 h of reaction time, a mixture of **3aa** and **4aa** was obtained in 23% and 75% yields, respectively (entry 12). When the same reaction was carried out in toluene, **4aa** was obtained as the sole product (entry 13). Therefore, the optimum reaction conditions were as follows: 5 mol % Co₂Rh₂/C in 0.03 mL of H₂O and 3.0 mL of THF at 100 °C for 6 h of reaction time. In general, strict anhydrous conditions are favorable in the transition metal-catalyzed reductive amination, and it is operationally troublesome to keep anhydrous conditions during a reaction. However, the present operationally simple catalytic system was quite effective for the amination in the presence of water, using the solvent (THF) without purification.

With the optimized reaction conditions in hands, the substrate scope of the reaction was examined (Table 2). The amination reaction was found to be effective for all relevant substrates, including aromatic and aliphatic primary and secondary amines as well as aliphatic and aromatic aldehydes and ketones. Both electron-donating (OMe, OH, and Me) and -withdrawing (F, Cl, Br, CF₃) groups on the aromatic substituents of the aldehydes and amines are tolerated. Functional groups such as hydroxyl and halo groups are tolerant in the reaction. However, a vinyl group is completely hydrogenated (**3ag**). The reductive amination reaction shows excellent generality for a variety of aldehydes and primary and secondary amines with very good to excellent yields. The lowest yield (**3ak**, 82%) was observed with 4-fluoroaniline. Generally, the use of an aryl aldehyde or aryl amine gave a relatively higher yield than that of an aliphatic aldehyde (**3ma**, 84%), ketone (**3la**, 86%), or amine (**3af**, 85%). When 2 equiv of an aldehyde was used, a tertiary-amine with two substituents from the aldehyde was isolated in excellent yields (**3a'a**; 95%: **3a'e**; 94%). When a secondary amine with two different substituents was reacted with another aldehyde, an unsymmetrical tertiary amine having three different substituents was isolated in high yields. Reaction of *N*-benzyl-4-methoxyaniline (**3aa**) with 4-methoxybenzaldehyde (**1b**) afforded *N*-benzyl-4-

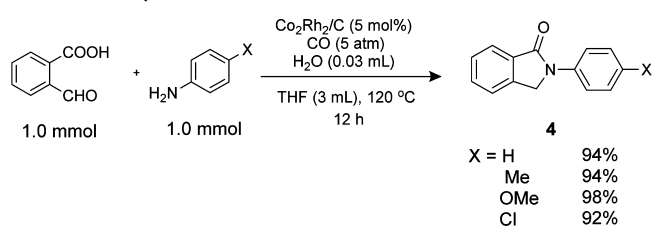
Table 2. Amination of Aldehydes and Ketones with Amines^a

^aReaction conditions: aldehyde (1.0 mmol), amine (1.0 mmol), H₂O (0.03 mL), CO (5 atm), and Co₂Rh₂ catalyst (5 mol %, 90 mg) in 3 mL of THF at 100 °C for 6 h. Isolated yield. ^b6 h and 130 °C. ^c12 h and 130 °C. ^dAldehyde (2.0 mmol) used, 14 h, 130 °C. ^e4-Vinylaniline used. ^f14 h and 100 °C. ^gGram scale (2.0 g of 3aa)

methoxy-*N*-phenylaniline (3bl) in 88% yield. Thus, the catalytic reaction process developed in this study provided an easy way to make secondary and tertiary amines from various aldehydes and amines. In addition, the reaction can be conducted on a gram-scale (2.0 g of 3aa, 94% yield).

The amination of aldehydes can be extended to the reactions of 2-formylbenzoic acid. Reaction of 2-formylbenzoic acid with anilines afforded excellent yields of isoindolin-1-ones (4) (Scheme 3). The highest yield (98%) was observed with 4-methoxyaniline.

Scheme 3. Synthesis of Isoindolin-1-ones



Generally, aromatic amines are produced by a catalytic reduction of nitroarenes.¹³ Therefore, the use of nitroarenes instead of aromatic amines in the reductive amination of aldehydes is highly desirable because it does not need prior reduction of the respective nitroarenes. Hydrogenation of nitroarenes over catalyst in the presence of CO and water has a long history.¹⁴ However, the tandem reductive amination is relatively rare.¹⁵ It is still highly desirable to develop an effective catalyst for this transformation. Thus, we decided to study the use of nitroarenes as an amine source in the amination of aldehydes and ketones. The optimum reaction conditions were as follows: 5 mol % Co₂Rh₂/C in 0.15 mL of H₂O and 3.0 mL of THF at 120 °C for 24 h (for screening the reaction conditions, see SI). The results were summarized in Table 3.

All the yields observed with nitroarenes (entries 1–16) were slightly lower than those observed with amines. However, as shown in Table 2, the reactions of benzaldehyde with various nitroarenes except with 4-fluoro- and 4-chloroaniline still afforded *N*-benzyl-anilines in excellent yields. With 4-fluoro and 4-chloroanilines (entries 4 and 5), the corresponding secondary amines were isolated in 75% and 76% yield, respectively. Interestingly, the reaction was tolerant of an ester group (entry 7). 1-Nitronaphthalene also afforded an excellent yield (90%) of the corresponding amine (entry 8). Benzaldehydes having an electron-withdrawing group afforded slightly lower yields than those with an electron-donating group (entries 9–11 vs 12–14). Aliphatic ketones such as acetone and cyclohexanone also afforded the corresponding amines in high yields (entries 15 and 16). However, acetone (74%) was not a good substrate as cyclohexanone (88%). Reaction of 1-methoxy-4-nitrobenzene with 2,5-hexandione afforded 1-(4-methoxyphenyl)-2,5-dimethyl-1*H*-pyrrole (5), in 93% yield (entry 17). An intramolecular reaction of 3-(2-nitrophenyl)-acrylaldehyde afforded quinolone (6) in 90% yield (entry 18). For entries 17 and 18, the reduction of nitro group was observed, but the reductive amination product was not formed. The amination of aldehydes and ketones with nitroarenes were quite effective under our reaction conditions. However, when 1-nitrohexane was used as a nitrogen source, no amination was observed.

When a reaction of benzaldehyde with 1-methoxy-4-nitro-methoxybenzene was conducted in the presence of D₂O, deuterated amine was observed (Scheme 4). Thus, sequential reactions of hydrogenation and amination occurred under our reaction conditions.

When we used hydrogen itself instead of carbon monoxide under identical conditions, the expecting product was obtained with a comparable yield (Scheme 5).

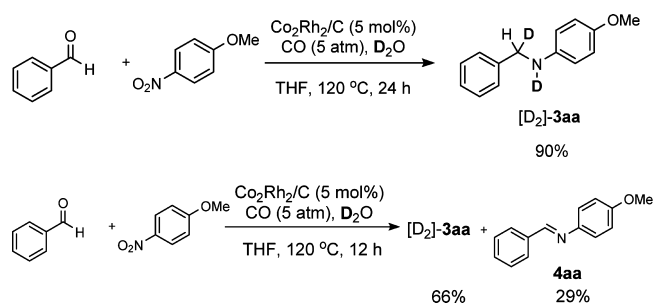
The reusability of Co₂Rh₂/C was also examined for the amination of 1a with 2a (Table 4). After reaction, the catalyst was filtered from the reaction mixture, dried in vacuum, and reused for the further catalytic reaction. The catalytic system is stable under the reaction conditions. The catalyst maintained

Table 3. Amination of Aldehydes and Ketones with Nitroarenes^a

Entry	Aldehyde or Ketone	Nitroarene	Product	Yield (%) ^b	Entry	Aldehyde or Ketone	Nitroarene	Product	Yield (%) ^b
1				92	10				90
2				90	11				92
3				90	12				87
4				76	13				80
5				75	14				84
6				93	15				74
7				91	16				88
8				90	17				93
9				89	18				90

^aReaction conditions: aldehyde (0.5 mmol), nitroarene (0.5 mmol), H₂O (0.15 mL), CO (5 atm) and Co₂Rh₂ catalyst (5 mol %, 45 mg) in 3 mL of THF at 120 °C for 24 h. ^bIsolated yield.

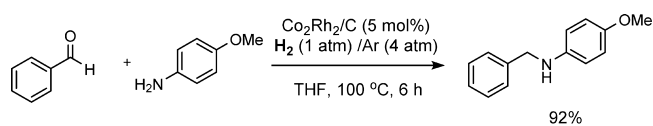
Scheme 4. Deuterium-Labeling Experiment



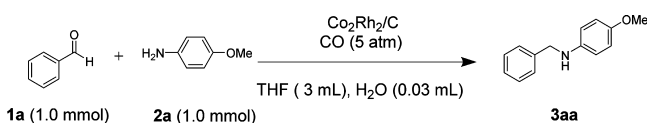
its high level of activity even after being reused eight times (97%, 95%, 94%, 92%, 92%, 93%, 90%, and 92%, respectively); the maximum reusability has not been tested.

In conclusion, we have developed the first Co₂Rh₂ nanoparticles/charcoal-catalyzed reductive amination of alde-

Scheme 5. Reductive Amination with Hydrogen Gas



dehydes and ketones with amines using a water–gas-shift reaction instead of hydrogen. Advantageously, no complicated ligands or additional acid or base is needed. The reaction can be extended to the tandem reduction of aldehydes and ketones with nitroarenes. The experimental simplicity and the reusability are especially attractive and should encourage the use of this catalytic system among synthetic chemists and in industrial application. Further investigations of the present catalytic system to other reactions are ongoing in our laboratory.

Table 4. Reuse of Co₂Rh₂/C Catalyst for Reductive Amination of 1a with 2a^a

entry	catalyst	yield (%) ^b
1	Co ₂ Rh ₂ 5 mol %	97
2	recovered from no. 1	95
3	recovered from no. 2	94
4	recovered from no. 3	92
5	recovered from no. 4	92
6	recovered from no. 5	93
7	recovered from no. 6	90
8	recovered from no. 7	92

^a1a (1.0 mmol), 2a (1.0 mmol), H₂O (0.03 mL), CO (5 atm), and Co₂Rh₂ catalyst (5 mol %, 90 mg) in 3 mL of THF at 100 °C for 6 h.

^bIsolated yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01198.

General experimental procedure and characterization of all compounds are provided (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ykchung@snu.ac.kr.

Notes

The authors declare no competing financial interest.

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