

# Synthesis of Primary Amines: First Homogeneously Catalyzed Reductive Amination with Ammonia

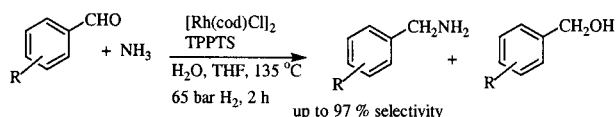
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## ABSTRACT



The synthesis of primary amines via reductive amination of the corresponding carbonyl compounds with aqueous ammonia is achieved for the first time with soluble transition metal complexes. Up to an 86% yield and a 97% selectivity for benzylamines were obtained in the case of various benzaldehydes by using a Rh-catalyst together with water-soluble phosphine and ammonium acetate. In the case of aliphatic aldehydes, a bimetallic catalyst based on Rh/Ir gave improved results.

Primary amines are of major importance in human life and chemical industry. They are particularly useful as pharmaceutically active substances, dyes, and fine chemicals. Various important methods for the synthesis of primary amines include alkylation of organic halides with ammonia, reductive amination of carbonyl compounds, hydrocyanation of alkenes followed by reduction, hydroamination of olefins, etc.<sup>1</sup> Among them, the reductive amination of carbonyl compounds constitutes one of the most convenient and practical approaches. In general, the reductive amination of carbonyl compounds is performed in the presence of heterogeneous catalysts.<sup>2</sup> The first elegant example of a homogeneously catalyzed reductive amination using primary and secondary amines was reported recently by Börner et al.<sup>3</sup> So far, no homogeneous catalytic reductive amination has been described using ammonia. Such a reaction would

be of general interest for the synthesis of the industrially most important primary amines. Unfortunately, the increased nucleophilicity of the initially produced amine may lead to the formation of a mixture of primary, secondary, and tertiary amines, thereby making the control of the chemoselectivity of the reaction difficult.

On the basis of our previous work on hydroaminomethylation reactions of olefins,<sup>4</sup> we envisioned that the use of water-soluble hydrogenation catalysts in a biphasic medium<sup>5</sup> might be a solution to this problem. This paper presents the first procedure for the selective reductive amination of aromatic and aliphatic carbonyl compounds to primary amines using ammonia in the presence of water-soluble transition metal complexes.<sup>6</sup> The reaction of benzaldehyde with ammonia served as a model reaction for studying the influence of catalysts, ligands, cocatalysts, and critical

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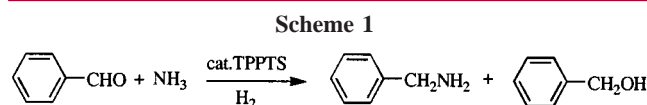
(6) We have been informed that, parallel to our work, this goal has been achieved by R. Kadyrov (Degussa AG). Kadyrov, R.; Riermeier, T. H., manuscript in preparation.

**Table 1.** Reductive Amination of Benzaldehyde<sup>a</sup>

entry	catalyst, mol %	TPPTS, mol %	NH <sub>4</sub> OAc, mol %	temperature, °C	organic solvent	yield, % <sup>b</sup>		selectivity: primary amine vs alcohol, %
						primary amine	alcohol	
1	[Ir(cod)Cl] <sub>2</sub> , 0.1 <sup>c</sup>	5.2	0	135	MTBE	6	66	8
2	[Ir(cod)Cl] <sub>2</sub> , 0.1	2.6	5	135	MTBE	42	44	49
3	[Ir(cod)Cl] <sub>2</sub> , 0.1/[Rh(cod)Cl] <sub>2</sub> , 0.025	5.2	5	135	MTBE	67	14	83
4	[Rh(cod)Cl] <sub>2</sub> , 0.025	2.6	5	135	MTBE	74	10	88
5	[Rh(cod)Cl] <sub>2</sub> , 0.1	2.6	5	135	MTBE	76	12	86
6	[Rh(cod)Cl] <sub>2</sub> , 0.025	5.2	50	115	MTBE	64	4	94
7	[Rh(cod)Cl] <sub>2</sub> , 0.025	2.6	5	95	MTBE	48	8	86
8	[Rh(cod)Cl] <sub>2</sub> , 0.05	2.6	5	135	MTBE	80	11	88
9	[Rh(cod)Cl] <sub>2</sub> , 0.05	2.6	5	135	toluene	73	9	89
11	[Rh(cod)Cl] <sub>2</sub> , 0.05	2.6	5	135	methanol	72	4	95
11	[Rh(cod)Cl] <sub>2</sub> , 0.05	2.6	5	135	THF	86	8	90
12	[Rh(cod)Cl] <sub>2</sub> , 0.05	2.6	5 <sup>d</sup>	135	THF	85	8	91
13	<b>[Rh(cod)Cl]<sub>2</sub>, 0.05</b>	<b>1.3</b>	<b>50</b>	<b>135</b>	<b>THF</b>	<b>86</b>	<b>3</b>	<b>97</b>
14	[Rh(cod)Cl] <sub>2</sub> , 0.05	2.6	0	135	THF	19	33	37

<sup>a</sup> Reaction conditions: benzaldehyde (0.034 mol), 25% aqueous ammonia (20 mL), NH<sub>3</sub>/benzaldehyde (8:1), org/aq solution (1:1), H<sub>2</sub> (65 bar), time (2 h). <sup>b</sup> Yields are determined by GC analysis with bis(methoxyethyl) ether as an internal standard. <sup>c</sup> Time = 10 h. <sup>d</sup> Octanoic acid was used instead of NH<sub>4</sub>OAc.

reaction parameters (solvent, temperature, concentration of starting materials) (Scheme 1 and Table 1).



On the basis of the successful demonstration of iridium as a hydrogenation catalyst for the reduction of isolated imines,<sup>7</sup> we initially explored the applicability of iridium complexes as precatalysts for the reductive amination of benzaldehyde with ammonia for the synthesis of primary amines. Unfortunately, low selectivity (8%) for the primary amine is observed with [Ir(cod)Cl]<sub>2</sub> as a catalyst precursor in the presence of TPPTS<sup>8</sup> (TPPTS = tris sodium salt of meta trisulfonated triphenylphosphine) as the ligand in a biphasic medium comprised of MTBE (methyl *tert*-butyl ether) and 25% aqueous ammonia at 135 °C and 65 bar of hydrogen (Table 1, entry 1). Hydrogenation of the aldehyde to the alcohol is found to be the major reaction. Although the addition of acids,<sup>9</sup> e.g., acetic acid, octanoic acid, or ammonium acetate, significantly enhances the formation of benzylamine (42% yield), formation of the alcohol is found to occur to a considerable degree (44% yield) as shown in Table 1 (entry 2). In the presence of a mixture of [Ir(cod)-

Cl]<sub>2</sub> and [Rh(cod)Cl]<sub>2</sub>, which gave superior results in domino–hydroformylation–reductive amination reactions, benzylamine is obtained in 67% yield. Interestingly, the use of [Rh(cod)Cl]<sub>2</sub> alone as a precatalyst under similar reaction conditions facilitates smooth reductive amination<sup>10</sup> with complete conversion improving significantly the selectivity for benzylamine (76%, Table 1, entries 4–5). This result is in contrast to our previous hydroaminomethylation reactions, in which the in situ reductive amination was realized only in the presence of the bimetallic catalyst system consisting of Rh and Ir complexes.

Next, the effect of cocatalysts and reaction parameters on the selective formation of benzylamine using the Rh/TPPTS catalyst system was examined (Table 1, entries 6–14). In general, chemoselectivities in the range of 85–90% are observed for benzylamine using the biphasic system consisting of aqueous ammonia and MTBE at 135 °C and 65 bar of hydrogen (Table 1, entries 3–5). In addition to benzyl alcohol, a very small amount (2–3%) of dibenzylamine is also observed as a side product. Apart from these, no other side products are detected.

(10) **General Procedure.** In a typical experiment (Table 1, entry 12), benzaldehyde (34 mmol), [Rh(cod)Cl]<sub>2</sub> (0.05 mol %), TPPTS (1.3 mol %), ammonium acetate (50 mol %), 25% aqueous NH<sub>3</sub> (20 mL), and freshly distilled THF (20 mL) were charged under an argon atmosphere into a 160 mL stainless steel autoclave equipped with a magnetic stirrer and temperature-controlled heating. The autoclave was closed, flushed once with hydrogen gas, and pressurized to 65 bar of H<sub>2</sub>, and the reaction was carried out for 2 h at a temperature of 135 °C (total pressure at 135 °C was ca. 100 bar). After the reaction, the autoclave was cooled to rt and slowly depressurized. The organic layer was collected, and the aqueous phase was treated with NaOH (0.5 g) and extracted with THF (2 × 10 mL). Bis-(methoxyethyl) ether (5 mL) was added to the combined organic phases, and the mixture was analyzed by gas chromatography. All aldehydes as well as synthesized amines and corresponding alcohols are commercially available. Therefore, benzaldehyde and products were identified by comparison with authentic samples by GC (column: cross-linked 5% PH ME Siloxane, 30 m × 0.25 mm × 0.25 μm). In addition, all products were confirmed by GC-MS.

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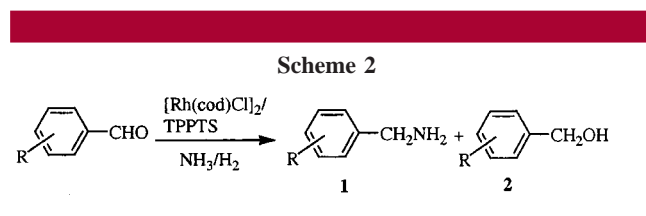
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The reaction also proceeds below 100 °C though the best results are obtained at 135 °C. At higher temperatures, ligand stability is considerably reduced, thereby making the catalyst recycle questionable. Increasing the amount of acid cocatalyst to 50 mol % almost completely suppressed the reduction of the carbonyl group, thereby achieving a selectivity of 97% for benzylamine (Table 1, entry 13). Similar to the Ir catalyst system, the Rh catalyst also leads to low yields and selectivity for benzylamine without any acid cocatalyst (Table 1, entry 14). Typically, the reactions were performed in the presence of 0.05 mol % Rh catalyst, thereby leading to catalyst turnover numbers (TON) of up to 1720. Nevertheless, further decrease in the amount of catalyst seems to be feasible as shown by Table 1, entry 4.

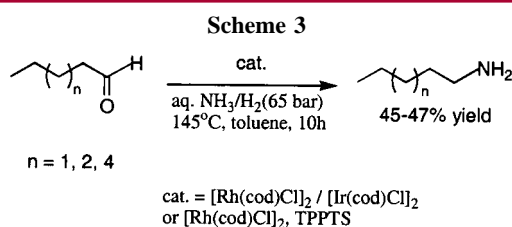
It is important in a biphasic reaction to check whether the catalyst is reusable after the reaction. For this purpose, the catalyst phase is recycled, after phase separation, in a typical experiment of benzaldehyde (Table 1, entry 13). The comparable yields of benzylamine observed in both runs suggest negligible catalyst deactivation.

Further, the reductive amination of different substituted aromatic aldehydes (Scheme 2) was studied. In all cases,



the corresponding primary amines are observed as main products with high selectivities. Only small amounts of the corresponding benzylic alcohols are produced as side products. In general, benzylic aldehydes with electron-donating groups (CH<sub>3</sub>, CH<sub>3</sub>O) give good yields of primary amines (65–85%), while those with electron-withdrawing groups (Cl, F, CF<sub>3</sub>) give lower yields (33–78%).

Apart from the reductive amination of aromatic aldehydes with ammonia, we are also interested in similar reactions of other carbonyl compounds. Some preliminary studies demonstrate the feasibility of our method for the synthesis of aliphatic primary amines from the corresponding aldehydes with ammonia as shown in Scheme 3. The reaction of hexanal with aqueous ammonia under standard conditions of benzaldehyde resulted in up to 33% yield of hexylamine. The yield of hexylamine is further improved to 45% by using a temperature of 145 °C and toluene as the solvent.<sup>11</sup> Under



**Table 2.** Reductive Amination of Substituted Benzaldehydes<sup>a</sup>

substrate	yield 1 %	yield 2 %	Selectivity 1 vs. 2 alcohol, %
	86	3	97
	75	4	95
	65	7	90
	55	8	87
	78	9	90
	77	4	95
	85	3	97
	33	5	87
	58	9	87
	62	11	85
	62	14	82

<sup>a</sup> Reaction conditions: substrate (0.034 mol), [Rh(cod)Cl]<sub>2</sub> (0.05 mol %), TPPTS (1.3 mol %), NH<sub>4</sub>OAc (50 mol %), THF (20 mL), 25% aqueous ammonia (20 mL), NH<sub>3</sub>/substrate (8:1), org/aq (1:1), H<sub>2</sub> (65 bar) temperature (135 °C), time (2 h).

similar conditions, 47% yield of pentylamine is obtained by using *n*-pentanal as the substrate. In the case of octanal, octylamine is formed in 47% yield by using the bimetallic Rh/Ir catalyst. In all cases, the formation of alcohol by the reduction of aldehyde is found to be negligible under these conditions. However, secondary amine as well as aldol condensation products are formed in considerable amounts. Nevertheless, these studies show that a homogeneously catalyzed reductive amination of aliphatic aldehydes with ammonia is possible. Further studies are in progress to improve the yield of primary amines from aliphatic aldehydes.

In summary, we have shown for the first time that reductive amination of carbonyl compounds with ammonia can be performed in the presence of soluble transition metal

(11) In a typical experiment, aldehyde (16 mmol), [Rh(cod)Cl]<sub>2</sub> (0.05 mol %), TPPTS (2.6 mol %), ammonium acetate (50 mol %), 25% aqueous NH<sub>3</sub> (20 mL), and freshly distilled toluene (10 mL) were charged under an argon atmosphere into a 100 mL stainless steel Parr autoclave equipped with an overhead stirrer and temperature-controlled heating, and the reaction was carried out at 145 °C and 65 bar of hydrogen for 10 h. After the reaction, the organic layer was collected; the aqueous layer was washed twice (5 mL) with toluene, and the combined organic layers were analyzed by GC (column: cross-linked 5% PH ME Siloxane, 30 m × 0.25 mm × 0.25 μm). The products were also confirmed by GC-MS.

complex catalysts. Up to 97% selectivity for benzylamine is achieved using water-soluble Rh catalysts. High selectivities are also obtained in the case of substituted benzaldehydes. The procedure is environmentally friendly (i.e., water is the only byproduct), and the starting materials are both inexpensive and readily available. Remarkable are the low quantities of catalyst required (0.025–0.05 mol %) for successful reactions.

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