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Atom Economy

Reductive Amination without an External Hydrogen Source**

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Abstract: *A method of reductive amination without an external hydrogen source is reported. Carbon monoxide is used as the reductant. The reaction proceeds efficiently for a variety of carbonyl compounds and amines at low catalyst loadings and is mechanistically interesting as it does not seem to involve molecular hydrogen.*

The reductive amination of carbonyl compounds is key for the production of amines and requires a source of hydrogen, commonly hydrogen gas (H_2) itself. However, while hydrogen is inexpensive and used on an industrial scale, mixtures with air are explosive over a wide concentration range. Other hydrogen sources may be less atom economical,[1] unstable to moisture and air, and expensive. We now report an efficient, robust, and general catalytic reductive amination that does not require an external hydrogen source but rather utilizes the existing hydrogen atoms of the amine substrate, and carbon monoxide (CO) as the reductant. This novel process potentially has economic and safety advantages.

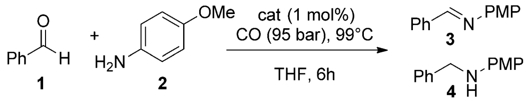
According to the U.S. Department of Energy, most hydrogen today is produced from fossil materials, such as natural gas. The main process to accomplish this is steam methane reforming (SMR),[2] which consists of two steps. The first involves reacting methane (CH_4) with steam at 750–800 °C to produce H_2 and CO. The CO byproduct is then channeled into the second step, known as the water–gas shift (WGS) reaction, in which it reacts with more steam in the presence of a catalyst to form additional H_2 and carbon dioxide (CO_2). This process itself occurs in two stages: a high-temperature shift at 350 °C and a low-temperature shift at 190–210 °C. In the final step, hydrogen gas has to be separated from carbon dioxide, unreacted methane, and carbon monoxide, and water.[3] Once purified, the resulting supply of hydrogen is utilized in a myriad of applications including reductive aminations.

Using CO directly as a reductant offers distinct advantages as three steps (with heating up to 350 °C and three different catalysts) would potentially be converted into a single step, using only one catalyst. Indeed, in addition to being a very useful C1 building block,[4–9] CO is also known to act as a reductant.[10] However, most of such reductions proceed by the water–gas shift reaction and therefore utilize hydrogen as the terminal reductant.[11,12] We now describe how carbon monoxide can also act as a reductant in catalytic reductive aminations without any external hydrogen source. To the best of our knowledge, this process is unprecedented.

Amines are a very useful and irreplaceable class of compounds that are industrially produced, for example, as pharmaceuticals and dyes, and for gas treatment, but also as reagents and catalysts.[13] One of the most important methods to synthesize amines is the reduction of imines. As a more direct and economical approach, the reductive amination of carbonyl compounds with amines avoids the separate step of imine formation. This method is more atom economical therefore requires fewer purification steps and generates less solvent waste. Alternatively, aminations of alcohols instead of carbonyl compounds, proceeding through an internal redox process have recently been developed.[14–17]

We have studied several potential catalysts for the reductive amination of benzaldehyde (**1**) with *p*-anisidine (**2**) in the presence of carbon monoxide (Table 1). We identified the rhodium acetate dimer as an efficient catalyst for this process, furnishing *N*-benzyl-4-methoxyaniline (**4**) in good yield (Table 1, entry 8). Catalysts based on ruthenium gave only traces of the product (Table 1, entries 1 and 2). Palladium- and platinum-based catalysts also did not lead to the reductive amination product under the reaction conditions (Table 1, entries 3–6). Upon solvent screening it was found that the reaction catalyzed by rhodium acetate proceeded efficiently in a variety of solvents, with the highest

Table 1: Catalyst screening.



Entry	Cat.	Products [% yield]		
		1	**3**	**4**
1	$RuCl_2(PPh_3)_3$	<1	98	1
2	$Ru_3(CO)_{12}$	<1	97	2
3	$Pd(OAc)_2$	1	99	0
4	$PdCl_2$	21	79	0
5	Pd/C	trace	>99	0
6	Pt/C	2	98	0
7[a]	Rh/C	1	49	50
8	$Rh_2(OAc)_4$	0	24	76

[a] Catalyst loading: 5 mol% of rhodium; aniline was used instead of *p*-anisidine; 100 bar CO, 140 °C, 42 h.

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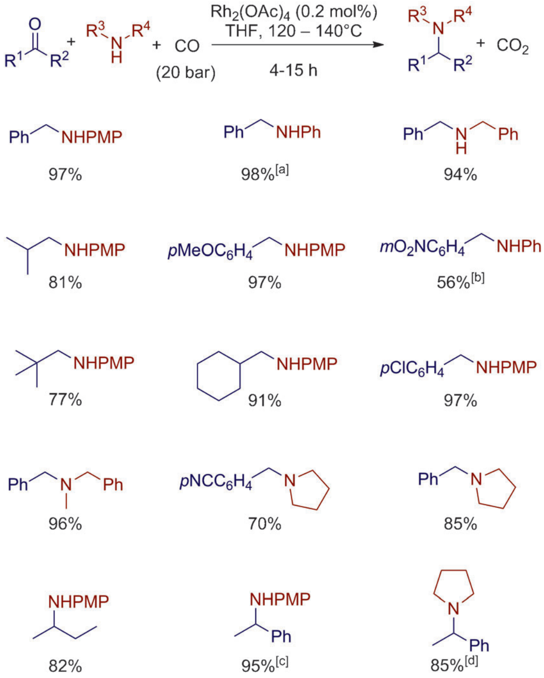
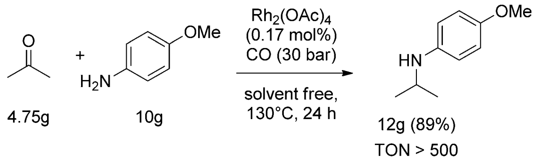
rate reached in THF (see the Supporting Information). We also tested other soluble rhodium sources such as [Rh(PPh_3)$_3$Cl], [HRh(PPh_3)$_4$], [$Rh_6(CO)_{16}$], [{$Rh(CO)_2Cl$}$_2$], [{Rh(cod)Cl}$_2$] (cod = 1,5-dyclooctadienyl), but all of them were significantly less active than rhodium(II) acetate (see the Supporting Information). As a heterogeneous catalyst, we also tested Rh/C, which proved to be active at elevated temperature (Table 1, entry 7).



Scheme 1. Substrate scope. Scale: 0.2 mmol–10 mmol carbonyl compound. Concentration of carbonyl compound from 1.0 M to solvent free. Amount of water in THF from 15 to 150 ppm. Pressure of CO was 20 bar. Autoclave was heated up to 140 °C. [a] 38 h. [b] 1.0 mol% cat., 14 h, 20 bar, 120 °C yield of trifluoroacetamide derivative. [c] 1.1 mol% cat, 15 h, 100 bar, 120 °C. [d] 0.9 mol% cat., 20 h, 85 bar, 100 °C. PMP = *p*-methoxyphenyl.

We also explored a variety of other substrate combinations in this $Rh_2(OAc)_4$-catalyzed reductive amination (Scheme 1). The reaction was found to efficiently process all relevant substrate classes including aromatic and aliphatic primary and secondary amines, and also aliphatic and aromatic aldehydes and ketones. Both electron-donating and -withdrawing groups on the aromatic substituents of the aldehydes are tolerated. The reaction is highly functional-group tolerant and even nitro- and cyano-substituted arenes can be used as substrates.

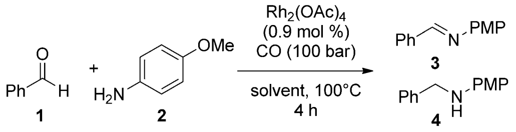
We also investigated the scalability of our reaction. Indeed, the reductive amination of acetone with *p*-anisidene can be easily conducted on a multigram scale with turnover numbers (TONs) exceeding 500 (Scheme 2).



Scheme 2. Scale up for the reductive amination with carbon monoxide.

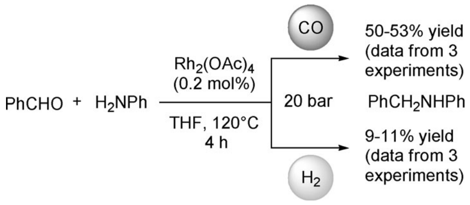
At the outset of our studies, we assumed the reaction to occur through the initial condensation of the carbonyl compound and the amine with concomitant stoichiometric liberation of water. In the next step, water would subsequently react with carbon monoxide by means of the water–gas shift reaction to produce molecular hydrogen and carbon dioxide. Hydrogenation of the imine or iminium ion with the generated hydrogen would then provide the amine. To test this mechanism, we first varied the amount of water in the reaction mixture, reasoning that increasing the water concentration should lead to an increased amount of hydrogen and thus to more product. However, in all solvents tested, we found that the addition of water resulted in a decreased rate of reductive amination (Table 2). Hydrolysis of imine **3** cannot account for these results as the amount of recovered aldehyde **1** in the presence of additional water was always lower than in its absence. Taken together, these preliminary results already suggested that the reaction might proceed by an alternative mechanism.

Table 2: The effect of water on the product distribution.



Solvent	Water	**1**	**3**	**4**
PhMe	60.0 ppm	6	75	19
$PhMe/H_2O = 3:1$		2	87	11
dioxane	162.4 ppm	5	68	27
$dioxane/H_2O = 3:1$		< 1	84	15
*i*PrOH	898.8 ppm	3	70	27
*i*PrOH/$H_2O = 3:1$		< 0.1	84	16
THF	64.9 ppm	2	39	59
$THF/H_2O = 3:1$		< 1	93	6

Interestingly, when we used hydrogen itself instead of carbon monoxide under otherwise identical conditions, we observed a significant decrease in the yield of the product (Scheme 3). Using hydrogen not only lowered the rate of the reductive amination but the reaction also became much less selective and several byproducts appeared. Consistently, $Rh_2(OAc)_4$ has not previously been used as a catalyst for



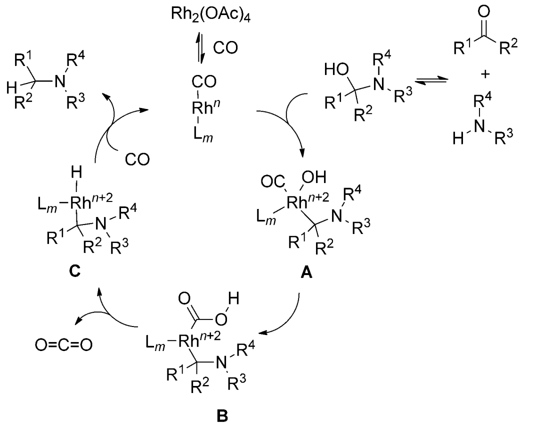
Scheme 3. Reductive amination with either carbon monoxide or hydrogen.

reductive amination with hydrogen or its various sources and rhodium-catalyzed reductive aminations in general are rare.[18]

A further indication that our process does not proceed through a water–gas shift reaction came from isotope studies. We investigated the use of deuterium gas under our reaction conditions. However, incorporation of deuterium into the final product reached only around 11 % at best (see the Supporting Information). As expected based on these results, we were unable to detect any hydrogen by in situ NMR spectroscopy and gas chromatography (GC). However, a rhodium hydride species has been detected in the ^{1}H NMR spectrum at −9.8 ppm (see the Supporting Information).

Also, the formation of carbon dioxide was established quantitatively by GC and in situ NMR spectroscopy. The formation of a rhodium carbonyl complex was furthermore detected by NMR spectroscopy in isotope incorporation studies with ^{13}CO (see the Supporting Information). This observation is consistent with the involvement of a rhodium carbonyl intermediate. No evidence for the occurrence of the water–gas shift reaction or the involvement of formate during the process was obtained, even though such possible pathways cannot be fully excluded at this point.

We propose a mechanistic pathway that is consistent with our observations and shown in Scheme 4. Accordingly, oxidative addition of a carbonylated Rh catalyst to the hemiaminal intermediate provides hydroxo complex **A**. An intramolecular hydroxylation of a Rh-bound CO ligand then leads to intermediate **B**. Its decarboxylation gives rhodium hydride species **C**, which upon reductive elimination leads to the amine product and the regenerated catalyst.



Scheme 4. Plausible mechanism of the reductive amination with carbon monoxide.

We have discovered a novel pathway for reductive amination involving carbon monoxide as the reductant. The reaction proceeds efficiently for a variety of carbonyl compounds and amines at low catalyst loadings and is mechanistically interesting as it does not seem to involve molecular hydrogen. By saving energy, additional steps, and catalysts, our process illustrates general potential for economically viable reductive condensation reactions that do not require hydrogen.

Experimental Section

General procedure: $Rh_2(OAc)_4$ (0.2 mol %) was placed in a reaction vial. Then, one equivalent of the amine was added. The reaction vial was evacuated and filled with carbon monoxide. Subsequently, solvent and one equivalent of aldehyde was added. The vial was placed into an autoclave and degassed, and carbon monoxide was added to reach the desired pressure. The autoclave was heated to the given temperature. After the indicated time, the reaction mixture was cooled to room temperature and the pressure was released. The solvent was evaporated and an NMR sample was prepared. The product was purified by chromatography.

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