

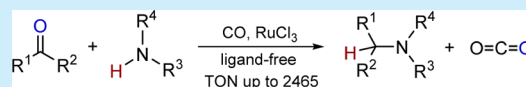
# Ruthenium-Catalyzed Reductive Amination without an External Hydrogen Source

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**S** Supporting Information

**ABSTRACT:** A ruthenium-catalyzed reductive amination without an external hydrogen source has been developed using carbon monoxide as the reductant and ruthenium(III) chloride (0.008–2 mol %) as the catalyst. The method was applied to the synthesis of antianxiety agent ladasten.



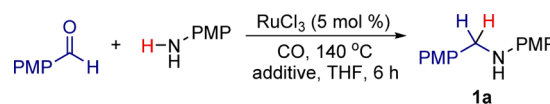
In 1991, Trost introduced the concept of atom economy,<sup>1</sup> which emphasized the importance of maximizing incorporation of all the atoms of the starting materials into the product of a given reaction thereby minimizing the amounts of chemical waste. Subsequently, valuable concepts of step and redox economies were proposed by Wender and Baran, respectively.<sup>2,3</sup> It is clear that, in the context of growing concerns associated with depletion of natural resources and pollution of the environment, atom-economical processes will receive increasing attention in both the industrial and academic world. While a substantial number of atom-economical chemical methods have been developed,<sup>3,4</sup> atom-economical redox processes remain understudied.<sup>5</sup>

Reductive amination represents one of the most convenient and versatile methods of amine synthesis.<sup>6</sup> Besides an amine and a carbonyl compound, this transformation naturally requires a source of hydrogen, usually hydrogen gas via a sequence of three high-temperature catalytic processes (conducted at 190–800 °C) followed by separation of the resulting gaseous side products (mainly carbon dioxide).<sup>7</sup> Thus, even though hydrogen gas represents an accessible and inexpensive reducing agent, it is important to keep in mind that the use of H<sub>2</sub> is not as perfectly atom-economical as it might seem if one considers the entire production scheme starting from the natural sources. We have recently reported a novel atom-economical methodology for Rh-mediated reductive amination<sup>8</sup> and reductive alkylation<sup>9</sup> of carbonyl compounds, which does not require an external hydrogen source but rather takes advantage of the deoxygenative potential of carbon monoxide. The use of CO instead of hydrogen gas or hydride agents is particularly interesting in light of the fact that carbon monoxide is produced in multiton quantities as a byproduct of the steel industry<sup>10</sup> and thus represents an abundant source for chemical synthesis. In fact, most of the worldwide production of acetic acid involves reaction of purified CO with methanol;<sup>11</sup> also, recent reports demonstrate growing interest of the academic community in the use of CO in novel synthetic methodologies.<sup>12</sup>

While we developed a highly efficient methodology of Rh-catalyzed reductive amination of carbonyl compounds using carbon monoxide as a deoxygenative agent,<sup>8</sup> the high cost of rhodium represents an important problem for the application of the protocol on preparative scale. We therefore considered development of an alternative catalytic system for this transformation which would possibly employ a less expensive metal component than a rhodium species. Ruthenium was a particularly interesting candidate being the cheapest metal of the platinum group.<sup>13</sup>

We started our studies using ruthenium trichloride in the presence of 10% of triphenylphosphine which was supposed to stabilize the catalytic species (Table 1, entry 1). The use of bidentate ligands led to inferior outcomes (entries 2–3);

**Table 1. Investigation of the Effects of Additives and Carbon Monoxide Pressure on Ru-Catalyzed Reductive Amination**



entry <sup>a</sup>	pressure, bar	additive	yield, %
1	90	PPh <sub>3</sub> (10 mol %)	22
2	90	Dppe (10 mol %)	8
3	90	Dppp (10 mol %)	6
4	90	PPh <sub>3</sub> (20 mol %)	1
5	90	PPh <sub>3</sub> (15 mol %)	2
6	90	PPh <sub>3</sub> (5 mol %)	60
7	90	none	81
8	50	none	81
9	20	none	72
10	10	none	56
11 <sup>b</sup>	10	none	89

<sup>a</sup>0.2 mmol scale. Yields were determined by NMR with internal standard. <sup>b</sup>The reaction time was increased to 24 h; the catalyst loading was decreased to 1 mol % in MeCN. PMP = *p*-methoxyphenyl.

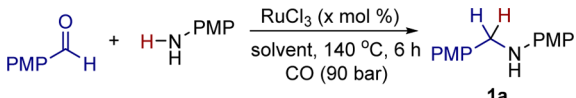
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likewise, increasing the amount of triphenylphosphine was deleterious to the product yield (entries 4–5). In fact, decreasing the content of the additive improved the performance, and the maximum yield in the series (81%) was observed when the process was conducted ligand-free (entries 6 and 7). We then investigated the effect of the carbon monoxide pressure on the reaction outcome (Table 1, entries 7–11). The reaction was found to proceed equally well when the pressure was decreased from 90 to 50 bar (entry 8). However, when the process was conducted under 20 and 10 bar of CO, the product yield dropped to 72% and 56% respectively (entries 9 and 10). Fortunately, increasing the reaction time to 24 h compensated for the loss of activity at 10 bar of CO, furnishing the product in 89% yield (entry 11). Ruthenium-mediated reductive amination could therefore be conducted at substantially lesser pressure than the one previously employed under rhodium catalysis.<sup>8</sup>

As the next step, we investigated the influence of the solvent on the efficiency of reductive amination (Table 2); the amount

**Table 2. Screening of Solvents, Temperature, and Catalyst Loadings**



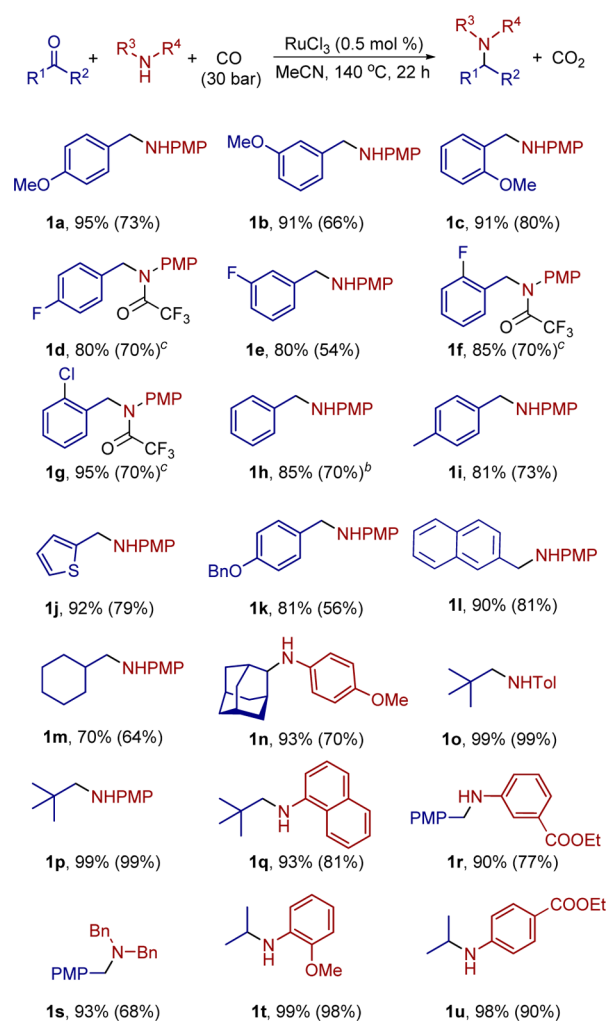
entry <sup>a</sup>	solvent	catalyst, mol %	yield, %
1	THF	2	58
2	dioxane	2	13
3	MeOH	2	26
4	EtOH	2	20
5	<i>i</i> -PrOH	2	61
6	water	2	13
7	EtOAc	2	15
8	toluene	2	20
9	benzene	2	21
10	hexane	2	11
11	solvent-free	2	25
12	MeCN	2	96
13	MeCN	1	96
14	MeCN	0.5	95
15	MeCN, 135 °C	0.5	87
16	MeCN, 130 °C	0.5	67
17	MeCN, 125 °C	0.5	63
18	MeCN, 125 °C	1	94

<sup>a</sup>0.2 mmol scale. Yields were determined by NMR with internal standard.

of the catalyst was decreased to 2 mol %. Acetonitrile appeared to be an exceptionally well suited solvent for the reaction, furnishing the product in 96% yield (entry 12). Subsequent studies showed that whereas the catalyst loading could be further decreased to as low as 0.5 mol % without any loss of efficiency of the process conducted at 140 °C, lowering the temperature resulted in inferior yields (entries 15–17). Yet, the product could be synthesized in 94% yield when the reaction was conducted at 125 °C and the catalyst loading was increased to 1 mol % (entry 18).

With these results in hand, we proceeded to investigate the substrate scope of the developed methodology under the optimized reaction conditions (Scheme 1). A wide range of aldehydes could be successfully employed, including variously substituted aromatic, heteroaromatic, and aliphatic substrates.

**Scheme 1. Studies on the Substrate Scope of Ruthenium-Catalyzed Reductive Amination<sup>a</sup>**



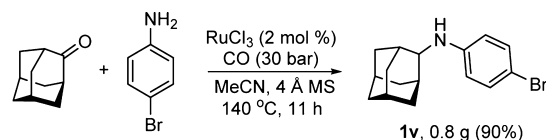
<sup>a</sup>Yields were determined by NMR with internal standard. Isolated yields are shown in parentheses. <sup>b</sup> 1 mol % of RuCl<sub>3</sub> was employed. <sup>c</sup> The product was isolated as a trifluoroacetamide derivative.

The methodology was also perfectly applicable to ketones (1n, 1t, 1u, 1v).

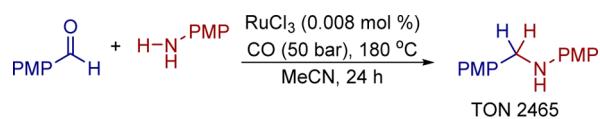
The scalability and preparative utility of the developed methodology was exemplified on the synthesis of anti-anxiety agent ladasten. Despite the lower intrinsic reactivity of 2-adamantanone with respect to less sterically challenged substrates, the gram-scale reaction with bromoaniline proceeded well and furnished product 1v in 90% yield (Scheme 2).

Importantly, as low as 0.008 mol % of the catalyst could be used; the model product between *p*-anisaldehyde and *p*-anisidine demonstrated a turnover number up to 2465 (Scheme 3).

**Scheme 2. Synthesis of Ladasten on a Preparative Scale**



### Scheme 3. Performance of the Developed Catalytic System with Lowered Catalyst Loading



In conclusion, we have reported an atom-economical reductive amination process catalyzed by ruthenium trichloride, which takes advantage of the unique deoxygenative potential of carbon monoxide and does not require an external hydrogen source. The synthetic value of the developed methodology was demonstrated by efficient preparation of a representative range of amines including gram-scale synthesis of antianxiety agent ladasten.

#### ■ ASSOCIATED CONTENT

##### Supporting Information

Detailed experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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##### Notes

The authors declare no competing financial interest.

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