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# Catalytic utilization of converter gas – an industrial waste for the synthesis of pharmaceuticals†

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Converter gas is a large scale waste product that is usually burned to carbon dioxide and contributes to the world emission of greenhouse gases. Herein we demonstrate that instead of burning the converter gas can be used as a reducing agent in organic reactions to produce valuable pharmaceuticals and agrochemicals. In particular, amide-based selected drug molecules have been synthesized by a reaction of aromatic nitro compounds and carboxylic acids in the presence of converter gas. In addition, we showed that this gas can also be conveniently utilized to carryout classical reductive amination reaction.

## Introduction

Converter gas is one of the largest waste products of the steel industry.<sup>1</sup> Each year millions of tons of converter gas is formed.<sup>2</sup> Typically this gas is burned to carbon dioxide which is then released to the atmosphere and makes a significant contribution to the world emission of greenhouse gases (Fig. 1).<sup>3,4</sup> While the emission of greenhouse gases from burning fossil fuels can be reduced by using other energy sources (such as electricity from solar, hydro, or nuclear plants), emissions from steel production are currently unavoidable. Therefore, it is highly desirable not to burn converter gas but rather to apply it in the chemical industry for the synthesis of valuable products. Herein, we address this challenge and demonstrate that converter gas can be used as a reducing agent for the production of a variety of organic chemicals including pharmaceuticals.

The composition of converter gas depends on the temperature of the steel-making process, but typically it contains 60–95% of CO, as well as N<sub>2</sub> and CO<sub>2</sub> as the main components.<sup>5</sup> During the traditional burning process, the converter gas acts essentially as a reducing agent for atmospheric oxygen.

Therefore, it may be also possible to use it in a similar manner for reduction of organic compounds. Recently we and others have used CO as a reducing agent in various transformations.<sup>6–9</sup> In the course of these studies, we found that converter gas can be used for the direct amidation of nitroarenes and carboxylic acids without any additives or coupling agents (Scheme 1). This atom- and step-economic process converts the industrial starting materials into valuable amide derivatives. The amide bond is one of the most important bonding motifs in organic chemistry and provides the basis for the unique physical and biological properties of many high-performance materials, natural products and biology related molecules.<sup>10–12</sup> Consequently, amides<sup>13–15</sup> and

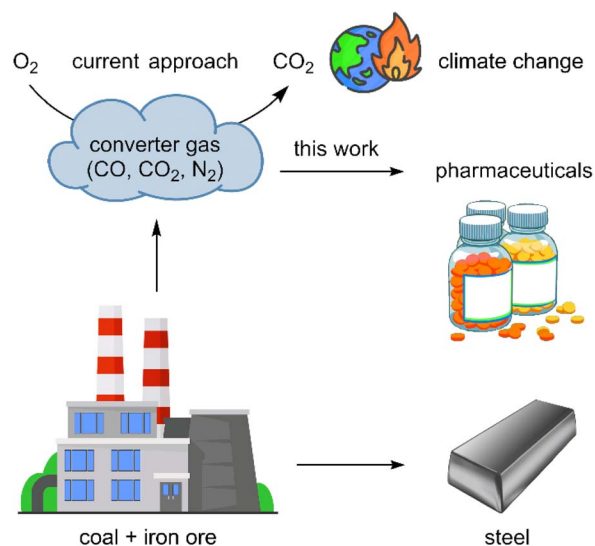


Fig. 1 The formation and possible applications of converter gas for production of pharmaceuticals, polymers, and other chemicals.

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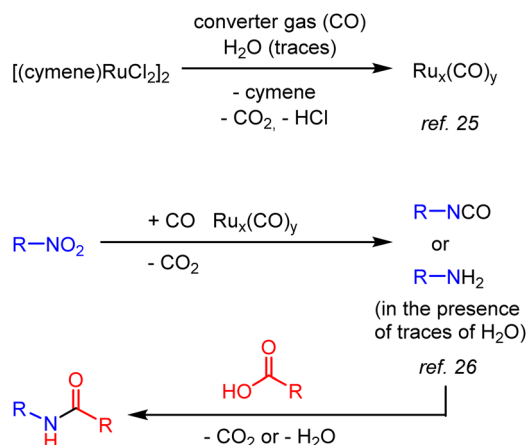
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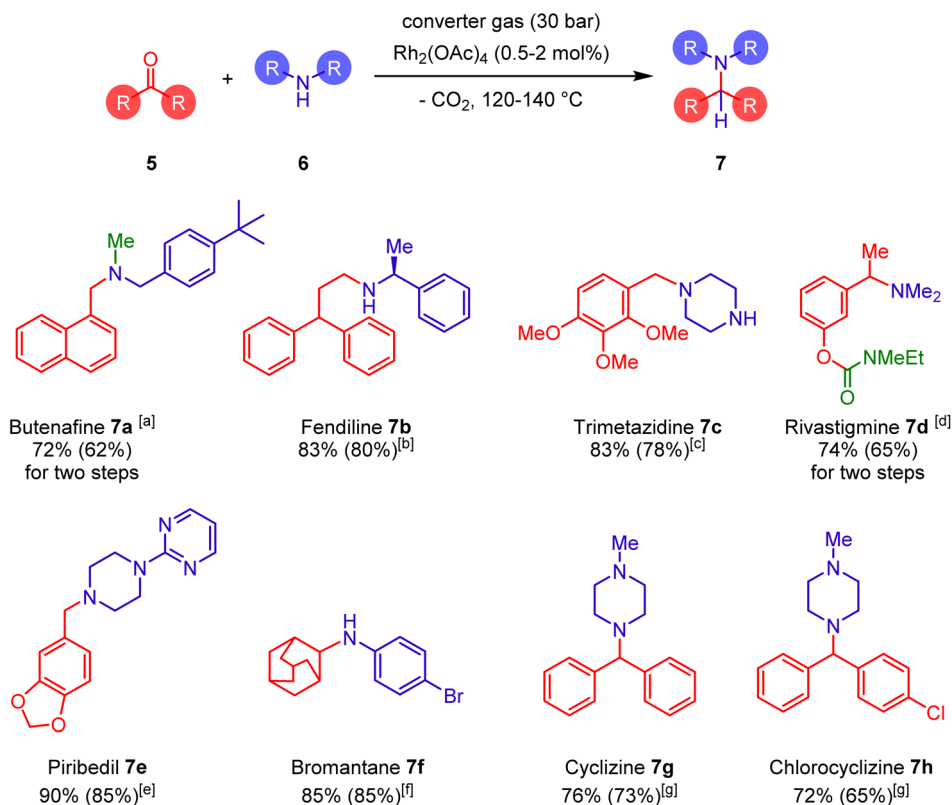
Scheme 2 Possible mechanism of the catalytic amidation reaction.

The exact mechanism of the catalytic amidation is not clear, but we can propose a possible sequence based on experimental observations and previous literature reports<sup>7,22–24</sup> (Scheme 2). First the nitro compounds are reduced by CO in the presence of

ruthenium carbonyl species<sup>25</sup>  $\text{Ru}_x(\text{CO})_y$  to give isocyanates or amines.<sup>26</sup> Then isocyanates or amines can react with carboxylic acid to give the desired amide similar to the known organic transformation. The detailed discussion of the possible mechanism is provided in the ESI†

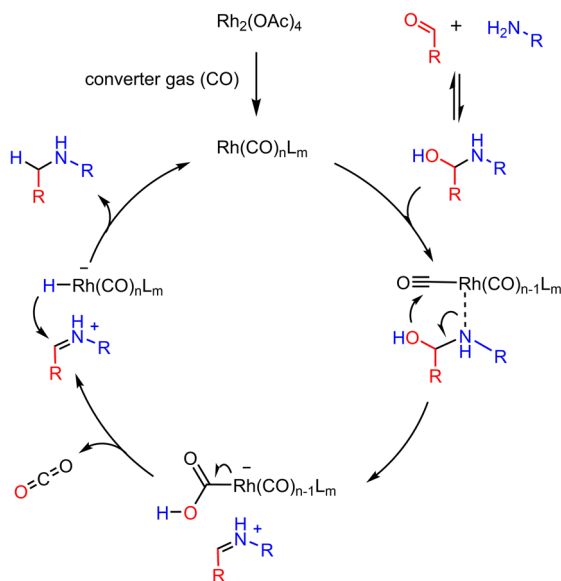
In order to prove that converter gas can be used in a general manner for other reductive transformations, we explored another important reaction involving the formation of C–N bonds, namely, the reductive amination (Scheme 3).<sup>27–32</sup>

Indeed, it was found that this reaction between readily available carbonyl compounds and amines proceeded in the presence of converter gas and was catalysed by a simple rhodium acetate without any additional expensive ligands. This way we synthesized antifungal agent butenafine (**7a**) directly from formaline, naphthaldehyde, and 4-*tert*-butylbenzylamine. Further expansion of this method provided other drugs such as fendiline (**7b**), trimetazidine (**7c**), rivastigmine (**7d**), piribedil (**7e**), bromantane (**7f**), cyclizine (**7g**), and chlorocyclizine (**7h**) (detailed reaction conditions are provided in the ESI†). Once again, the reaction displayed excellent selectivity and was not inhibited by various functional groups.



Scheme 3 Catalytic reductive aminations using converter gas: synthesis of selected pharmaceuticals. Reaction conditions (detailed reaction conditions are provided in the ESI†): <sup>a</sup> 0.5 mol% of  $\text{Rh}_2(\text{OAc})_4$ , 1.5 equiv. **6**, 1 equiv. of **5**, 30 bar of converter gas, 120 °C, 22 h. After 22 h 2.20 equiv. of formaline were added for an additional 22 h to achieve methylation (highlighted by green color); <sup>b</sup> 0.5 mol% of  $\text{Rh}_2(\text{OAc})_4$ , 1.1 equiv. of **6**, 1 equiv. of **5**, 30 bar of converter gas, 140 °C, 22 h; <sup>c</sup> 1 mol% of  $[(\eta^4\text{-cyclooctadiene})\text{Rh}(\eta^6\text{-2,3,6,7-tetramethoxy-9,10-dimethylantracene})\text{BF}_4]$ , 10 equiv. of **6**, 1 equiv. of **5**, 30 bar of converter gas, 120 °C, 22 h; <sup>d</sup> reductive amination step: 0.5 mol% of  $\text{Rh}_2(\text{OAc})_4$ , 5 equiv. of **6**, 1 equiv. of **5**, 30 bar of converter gas, 120 °C, 48 h. C(O)NMeEt group highlighted by green color was introduced in the next step; <sup>e</sup> 0.5 mol% of  $\text{Rh}_2(\text{OAc})_4$ , 1 equiv. of **6**, 1 equiv. of **5**, 30 bar of converter gas, 120 °C, 22 h; <sup>f</sup> 0.5 mol% of  $\text{Rh}_2(\text{OAc})_4$ , 1 equiv. of **6**, 2 equiv. of **5**, 42 bar of converter gas, 120 °C, 22 h; <sup>g</sup> 2 mol% of  $\text{Rh}_2(\text{OAc})_4$ , 5 equiv. of **6**, 1 equiv. of **5**, 45 bar of converter gas, 130 °C, 48 h.





Scheme 4 Possible mechanism for reductive amination by CO in the presence of a rhodium catalyst.

As in the previous case, the main role of converter gas is to remove the oxygen atoms from the carbonyl molecules. We assume that rhodium species first coordinate with CO, which is then attacked by the OH group of the hemiaminal intermediate to give the Rh-COOH group. Its further decarboxylation gives rhodium hydride species, which immediately reduce the iminium cation similar to previous reports<sup>33,34</sup> (Scheme 4).

## Experimental

### Preparation of converter gas

The model converter gas was prepared in a 40 liter gas cylinder at room temperature. The gas cylinder was filled with 29 bar of carbon monoxide, followed by 10 bar of carbon dioxide and 11 bar of nitrogen.<sup>35</sup>

### General procedure for the reductive amidation

The ruthenium catalyst  $[(p\text{-cymene})\text{RuCl}_2]_2$  (0.5–1 mol%), nitroarene, acetic acid, THF, and a magnetic stirring bar were placed into an autoclave. The autoclave was sealed, flushed three times with 10 bar of converter gas, and then charged with 30 bar of converter gas. The autoclave was placed into an oil bath preheated to the required temperature (140–180 °C). After the indicated time (typically 20 h), the autoclave was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was additionally washed with dichloromethane ( $2 \times 1$  mL). The solvents were removed using a rotary evaporator, and the residue was analyzed by NMR.

### General procedure for the reductive amination

Rhodium(II) acetate (0.5–2 mol%), amine, and the carbonyl compound were placed into an autoclave. The autoclave was sealed, flushed three times with 10 bar of converter gas, and

then charged with 45 bar of converter gas. The reactor was placed into an oil bath preheated to the required temperature (120–140 °C). After the indicated time (20–48 h), the autoclave was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask and the autoclave was additionally washed with dichloromethane ( $2 \times 1$  mL). The solvents were removed using a rotary evaporator, and the residue was analyzed by NMR.

## Conclusions

To conclude, we have demonstrated that, instead of burning converter gas, it can be conveniently used to synthesize valuable organic life science products. The generality of this approach is showcased in the preparation of several current pharmaceuticals *via* the reductive amidation protocol as well as *via* more classical reductive amination. We believe that converter gas can be used for many other atom- and step-economical reduction transformations in the near future. In particular, converter gas from steel plants might replace natural gas sources in well-known large-scale industrial processes involving CO such as synthesis of acetic acid,<sup>36–38</sup> hydroformylation,<sup>39–41</sup> urea synthesis,<sup>8,42–44</sup> *etc.* Hopefully, this discovery will attract other researchers to develop chemical processes involving converter gas.

## Data availability

All data associated with this report may be found in the ESI.†

## Author contributions

S. A. R., O. I. A., E. A. K. carried out all experiments, D. S. P. carried out quantum chemical modelling. D. C. generated an idea of the paper and coordinated all project. R. V. J. and M. B. involved in the development of this project. O. I. A., D. S. P., R. V. J., M. B., D. C. wrote the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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