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Reductive Transformations of Carbonyl Compounds Catalyzed by Rhodium Supported on a Carbon Matrix by using Carbon Monoxide as a Deoxygenative Agent

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An efficient method for the rhodium on carbon matrix catalyzed preparation of secondary and tertiary amines, cyanoesters, and nitriles through the reductive amination/alkylation of carbonyl compounds was developed, including a convenient procedure for the tandem formal reductive addition of acetonitrile to aldehydes. The catalyst could be reused, and at least three consecutive reaction cycles were performed with comparable efficiency. The method was shown to be compatible with functional groups prone to reduction by hydrogen and complex hydrides.

Reductive C—C and C—N bond-forming reactions are widely used as powerful and convenient tools to build up molecular complexity rapidly.[1] Whereas in the paradigm of fine laboratory synthesis classical synthetic approaches are being constantly improved and refined to meet ever-increasing stringency of requirements for reactivity, selectivity and cost, we strongly believe that the academic community should pay greater attention to optimization of synthetic tools in terms of the integral economic and environmental effects they might have if conducted on semi-industrial or industrial scale. In this context, the use of side products of the chemical industry as starting materials for novel synthetic protocols represents a very valuable concept. Our group recently discovered catalytic reductive methodology[2] that takes advantage of the deoxygenative potential of carbon monoxide and does not require an external hydrogen source, unlike conventional approaches such as reductive amination and reductive Knoevenagel condensation. As carbon monoxide is produced in multiton quantities as a side product of steelmaking,[3] it represents an abundant source for chemical synthesis and is a more atom-economical[4] alternative to many of the established synthetic agents. Moreover, despite the fact that certain precautions have to be taken while working with carbon monoxide because of its toxicity, its higher flammability limit relative to that of hydrogen represents an important advantage especially on a larger reaction scale.[5] Whereas the use of CO has been systematically investigated in the reduction of, for example, aromatic nitro groups,[6,7] its potential as a reductive agent still remains considerably underexplored.

Heterogeneous catalysis is oftentimes much more convenient with respect to homogeneous alternatives, for example, in terms of catalyst recovery and purification of the products;[8] and the intrinsic merits of heterogeneous catalytic systems are, therefore, responsible for wide applications thereof in nearly all areas of chemical industry owing to the improved economic and environmental profiles. Given that our growing toolbox of methods employing CO as a deoxygenative agent have so far involved homogeneous protocols,[2] we were particularly interested in the development of a heterogeneous system of comparable potential that would render our method more compatible with the general requirements of industrial-scale production. Thus, herein we report an atom-economical heterogeneous catalytic system equally applicable to the reductive formation of both C—N and C—C bonds that employs rhodium supported on carbon matrix as a catalyst and carbon monoxide as a deoxygenative agent.

For the initial studies on reductive amination, we decided to work on the formation of a reduced adduct of *p*-fluorobenzaldehyde with *p*-anisidine as a model reaction; the choice of a fluorinated aldehyde as a substrate was made primarily because of the convenience of NMR spectroscopy monitoring. Expectedly, no reductive amination reaction proceeded in the presence of unmodified activated carbon, whereas the use of activated carbon-supported ruthenium and rhodium (5% w/w, 0.25 mol% metal) led to the detection of a trace amount of the desired product (Table 1, entries 2 and 3).

Rhodium on the carbon support of less developed surface area demonstrated marginally greater yield, which could probably be explained by a lower degree of product absorption (Table 1, entry 4). The use of alumina-supported metals did not lead to an improvement in reaction efficiency (Table 1, entries 5 and 6). We then decided to switch to matrix supports (Table 1, entries 7 and 8); to our delight, rhodium supported on carbon matrix (Degussa Co.) demonstrated substantially improved performance: the desired product was formed in 37% yield, which increased up to 82% by changing the catalyst loading to 1 mol% (Table 1, entry 10). Solvent screening for the process catalyzed by Rh/carbon matrix showed superiority of

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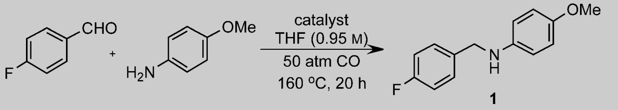
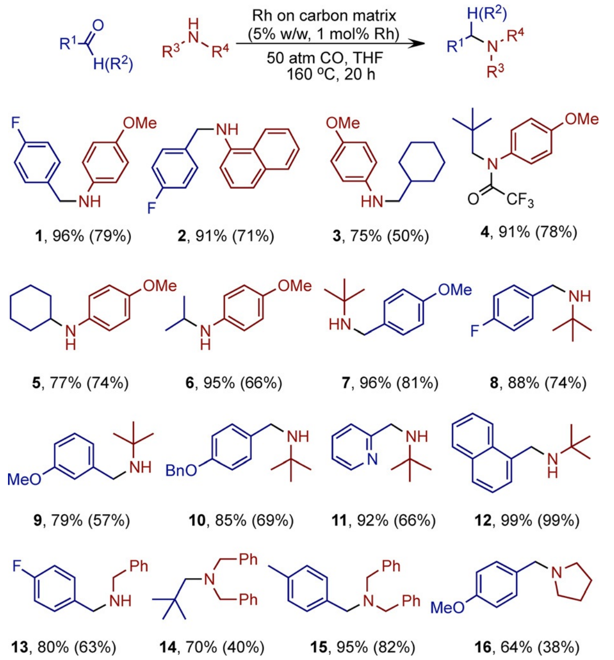
Table 1. Catalyst screening in the model reductive amination reaction.[a]



Entry	Catalyst[b]	Catalyst loading [mol %]	Yield [%][c]
1	activated carbon	0.25	0
2	Ru on activated carbon	0.25	5
3	Rh on activated carbon	0.25	3
4	Rh/C	0.25	10
5	Ru on alumina	0.25	6
6	Rh on activated alumina	0.25	4
7	Rh on alumina matrix	0.25	10
8	Rh on carbon matrix	0.25	37
9	Rh on carbon matrix	0.5	42
10	Rh on carbon matrix	1.0	82

[a] A 1:1 ratio of the amine and the aldehyde was employed. 0.2 mmol scale. [b] 5 % w/w of metal on the support. [c] The yield was determined by NMR spectroscopy with an internal standard.

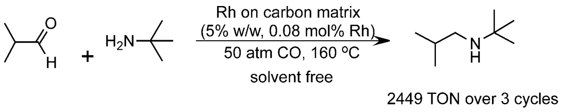


Scheme 1. Substrate scope of the reductive amination catalyzed by Rh on carbon matrix support in the presence of carbon monoxide. Yields were determined by NMR spectroscopy with an internal standard. Yields of products after chromatography are shown in parentheses. Reaction conditions: carbonyl compound (0.2 mmol), amine (0.3 mmol; for *tert*-butylamine 2.0 equiv. was used). For compound **4**, the product was isolated as the trifluoroacetamide derivative. 1 atm = 101.3 kPa.

tetrahydrofuran to all the other solvents tested (see the Supporting Information). The aldehyde/amine ratio was changed to 1:1.5, as that led to somewhat higher product yields (**1**, Scheme 1 vs. Table 1, entry 10).

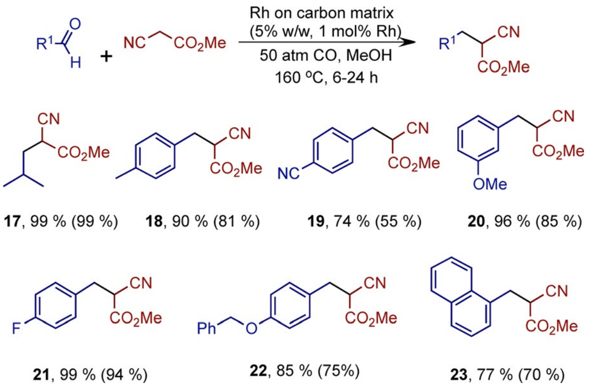
With the optimized conditions in hand, we turned to investigation to the scope of the developed methodology (Scheme 1). Model product **1** of the reaction between *p*-anisidine and *p*-fluorobenzaldehyde was isolated in 79 % yield (96 % as determined by NMR spectroscopy); a very similar outcome was obtained for 1-naphthylamine analogue **2**. Good-to-excellent yields were determined by NMR spectroscopy for *p*-anisidine-reduced adducts with aliphatic aldehydes **3** and **4**; however, those products demonstrated greater than average isolation losses (which were probably due to oxidation and absorption to silica gel and could be partially resolved by trifluoroacetylation, as in **4**, or flash chromatography of minimized duration with minimum amounts of silica gel as in **12**). Ketones such as cyclohexanone and acetone reacted well, which led to isolation of products **5** and **6** in yields of 66 and 74 %, respectively. *tert*-Butylamine furnished products **7**–**12** with a variety of aromatic aldehydes in yields of 57–99 %, which included substrates prone to be challenging under certain conditions, such as compound **10** containing a labile benzyloxy functionality and 2-pyridinecarboxaldehyde derivative **11** capable of coordination with metal complexes. Benzylamine and dibenzylamine successfully reacted with the aromatic counterparts: products **13** and **15** were isolated in yields of 63 and 82 %, respectively. Somewhat lower yields in the series were observed for more challenging pivalaldehyde adduct **14** (70 % yield observed, 40 % yield upon isolation) and pyrrolidine derivative **16** (64 % yield observed, 38 % yield upon isolation).

We tested the recyclability of the catalyst on the model reaction between *tert*-butylamine and isobutyraldehyde conducted with the metal catalyst (0.08 mol %) under solvent-free conditions (Scheme 2); after each cycle, the product was removed from the reaction vessel under reduced pressure and the process was restarted again with new portions of the reagents. The experiment demonstrated that the catalyst could be used over at least three consecutive reaction cycles [overall turnover number (TON): 2449].

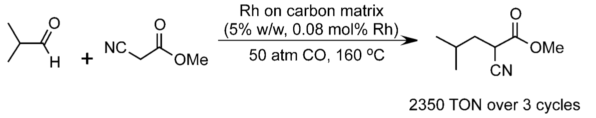


Scheme 2. Recyclability of rhodium on carbon matrix support in reductive amination.

We then considered application of the developed catalytic system to reductive Knoevenagel condensation.[2b,9] Optimization of the reaction between 1-naphthaldehyde and methyl cyanoacetate (see the Supporting Information) proved that an essentially identical set of conditions was optimum, except that methanol was a superior medium for the process. A range of substrates were successfully converted into the corresponding adducts in yields of 55–99 % (Scheme 3). Isobutyraldehyde furnished product **17** in almost quantitative yield without any self-aldol byproducts. Cyano and *O*-benzyl functionalities, labile under certain reductive conditions, were well tolerated (products **19** and **22**, isolated in yields of 55 and 75 %, respectively). Again, the catalyst was shown to be recyclable and demonstrated an overall TON of 2350 over three reaction cycles (Scheme 4).



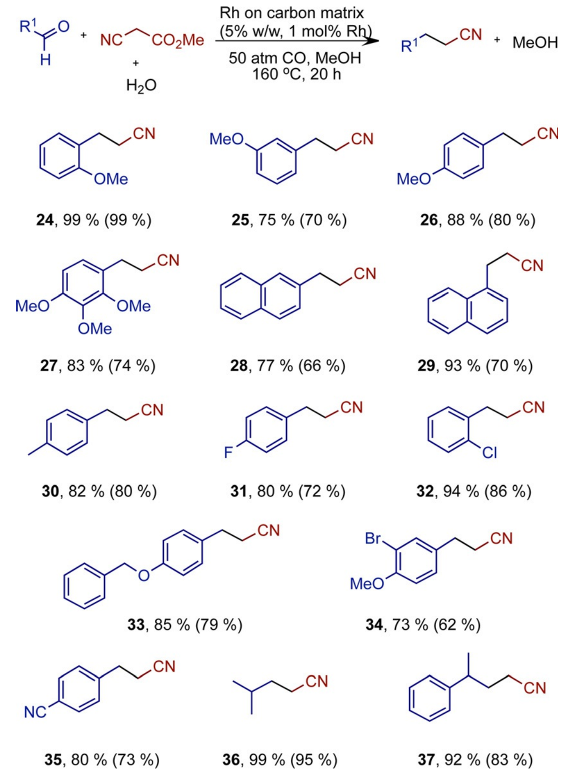
Scheme 3. Substrate scope of the reductive alkylation of aldehydes with methyl cyanoacetate catalyzed by Rh on carbon matrix in the presence of carbon monoxide. Reactions were performed with 0.2–0.6 mmol of the aldehydes. To obtain compound **22**, 2 mol% of the catalyst was used.



Scheme 4. Recyclability of rhodium on carbon matrix support in reductive alkylation.

Conducting the reaction in the presence of water (2 equiv.) enabled tandem hydrolysis and decarboxylation, which led to products of formal deoxygenative addition of acetonitrile (Scheme 5), which in the overwhelming majority of syntheses is accomplished through Horner–Wadsworth–Emmons chemistry with subsequent catalytic hydrogenation or complex hydride reduction.[10,11] The reaction proceeded equally well with electron-rich and electron-deficient aromatic substrates of various substitution patterns. Adducts of cyano-, benzyloxy-, chloro-, and bromo-substituted aromatic aldehydes (i.e., compounds **32**–**35**) as well as aliphatic substrates (i.e., compounds **36** and **37**) were successfully isolated in good-to-excellent yields. For the possible mechanism see the Supporting Information.

In summary, we developed an efficient heterogeneous catalytic system that allows the atom economical reductive amination and alkylation of aldehydes and ketones. This method takes advantage of the unique deoxygenative potential of carbon monoxide and does not require an external hydrogen source, which allows full compatibility with a range of functional groups prone to reduction by, for example, heterogeneous catalytic hydrogenation (e.g., *N*-benzyl, *O*-benzyl, cyano, halo). We also reported a convenient tandem hydrolytic decarboxylative modification of the reductive alkylation with methyl cyanoacetate, which led to products of formal deoxygenative addition of acetonitrile to aldehydes in good yields.



Scheme 5. Substrate scope of the hydrolytic decarboxylative reductive alkylation of aldehydes with methyl cyanoacetate catalyzed by Rh on carbon matrix support in the presence of carbon monoxide. Reactions were performed with 0.6 mmol of the aldehydes.

Experimental Section

General method for reductive amination

A 10 mL stainless-steel autoclave was charged with the catalyst (1.0–2.0 mol%), THF (0.2 mL), the amine (0.2–0.3 mmol), and the carbonyl compound (0.2 mmol). The autoclave was sealed, flushed with CO (3×10 atm), and then charged with the indicated pressure of CO. The reactor was placed in a preheated oil bath. After the indicated time of stirring, the reactor was cooled to room temperature and depressurized. The residue was purified by flash chromatography on silica gel.

General method for reductive alkylation by cyanoacetate

A 10 mL stainless-steel autoclave was charged with the catalyst (1.0–2.0 mol%), methanol (0.2 mL), methyl cyanoacetate (0.3 mmol), and the carbonyl compound (0.3 mmol). The autoclave was sealed, flushed with CO (3×10 atm), and then charged with the indicated pressure of CO. The reactor was placed in a preheated oil bath. After the indicated time of stirring, the reactor was cooled to room temperature and depressurized. The residue was purified by flash chromatography on silica gel.

General method for the formal reductive addition of acetonitrile

A 10 mL stainless-steel autoclave was charged with the catalyst (1.0 mol%), methanol (0.2 mL), methyl cyanoacetate (0.6 mmol), the carbonyl compound (0.6 mmol), and water (1.2 mmol). The autoclave was sealed, flushed with CO (3×10 atm), and then charged with the indicated pressure of CO. The reactor was placed in a preheated oil bath. After the indicated time of stirring, the reactor was cooled to room temperature and depressurized. The residue was purified by flash chromatography on silica gel.

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Keywords: amination · atom economy · carbon monoxide · heterogeneous catalysis · reductive alkylation

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