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Reductive Amidation without an External Hydrogen Source Using Rhodium on Carbon Matrix as a Catalyst

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Abstract: An efficient method for preparation of secondary amides from primary amides and aldehydes using rhodium on carbon matrix as catalyst was developed. The method does not require any external hydrogen source and carbon monoxide is used as a reducing agent. The most active rhodium catalysts were characterized by BET, TEM and XPS techniques. Unexpectedly, it was found that heterogeneous rhodium on carbon matrix works as precatalyst for homogenous active species due to leaching of rhodium to the solution. Various secondary amides were synthesized and checked for antifungal activity. 4-Methoxy-N-(4-methoxybenzyl)benzamide demonstrated promising activity against *Rhizoctonia Solani.*

Amides are an important class of organic compounds because of their wide applications in various fields. Nearly 25% of all pharmaceutical drugs currently on the market contain an amide bond.[1] Peptidomimetics, pseudopeptides, β-peptidoids comprise an important class of drug molecules.[2] Moreover, amide bond coupling is one of the most frequent transformations in medicinal chemistry.[3] Conventional methods for synthesis of amides require the usage of stoichiometric amounts of additives which causes low atom efficiency and formation of stoichiometric amounts of wastes. Therefore, development of new and efficient methods of amide synthesis is important for pharmaceutical chemistry.[4]

For the last decade there was a growing interest in nonclassical routes for amide synthesis.[5,6] These methods include direct catalytic condensation of carboxylic acids with amines using boron-based catalysts, catalytic amidation of esters, oxidative amidation of primary alcohols or aldehydes, and carbonylative amidation of aryl halides. Among them reductive amidation of aldehydes is a potentially powerful method for modification of amides because of its high atom efficiency.[7] Hydrogen or silanes are usually used as reducing agents for this transformation. Since both reducing systems have a hydride source, they can have low tolerance to potentially reducible functional groups. Moreover, there are other disadvantages of these systems like low step economy (e.g. production of silanes) and disposal of stoichiometric wastes. In case of potential industrial applications, it is highly desirable to use inexpensive and accessible components.

Carbon monoxide is a multimillion ton byproduct of steel making industry. Moreover, the use of CO is attractive from environmental point of view. It can be obtained by gasification of biomass.[8] Previously in our group we demonstrated the unique deoxygenative potential of carbon monoxide.[9a] The use of carbon monoxide proved to be effective in reductive alkylation[9b], amination[9c], and esterification[9d] reactions of carbonyl compounds. The key advantage of this reducing agent is the lack of external hydrogen source, which leads to unique selectivity often surpassing more traditional, hydride-based reducing agents.[9e] Previously, we developed a method for reductive amidation with carbon monoxide as the reducing agent using homogeneous rhodium and ruthenium catalysts.[7f,7g] We decided to develop a method of reductive amidation using heterogeneous catalysis which might be more suitable for potential industrial application of this method. Herein we report reductive amidation on rhodium on carbon matrix.

We started with investigation of catalytic activity of various commercially available rhodium and ruthenium catalysts on different supports. We have chosen the reaction between *p*-anisaldehyde and acetamide as a model reaction due to clear and precise analysis of its reaction mixture using ^{1}H NMR spectroscopy (Table 1). In general, rhodium catalysts demonstrated higher activity than ruthenium catalysts (Entries 1-5 *vs*. entries 6-9). Alumina supports are less effective than carbon supports (Entries 1-3 *vs*. entries 4-5). Among the rhodium on carbon supports rhodium on carbon matrix demonstrated superior activity and afforded desired product **1a** with highest yield (Entry 1). Therefore, we have chosen rhodium on carbon matrix as catalyst for further optimization of reaction conditions.

Solvent screening demonstrated that Et_2O is the optimal solvent for this transformation (Table 2, Entry 2), although toluene, ^{t}BuOH, and ^{i}PrOH were also efficient (Entries 1, 6, and 7). Presence of water significantly decreased selectivity of the formation of the target amide **1a** and lead to the formation of symmetrical tertiary amine **2a**. The amine **2a** could be formed through hydrolysis of acetamide or target amide **1a** and consequential reductive amination. Removal of water from the catalyst under vacuum allowed to increase selectivity towards formation of alkylated amide **1a**. It also improved reproducibility of the reaction results. Primary alcohols such as MeOH, EtOH and ^{n}BuOH favoured formation of the tertiary amine **2a** (Entries 8-10). Higher pressure did not influence the reaction outcome, while decrease of pressure to 20 bar significantly reduced conversion of the aldehyde and the product yield. Dilution of reaction mixture led to further increase of product yield (Entry 12). Overall, amide **1a** can be obtained in 93% yield under optimized conditions.

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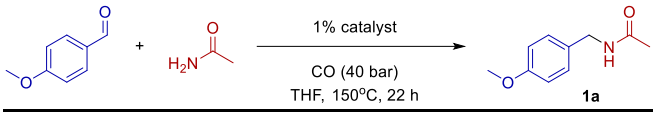
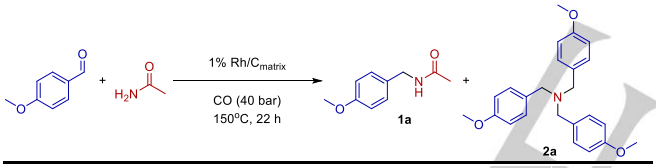
Table 1. Catalysts screening.



Entry[a]	Catalyst	Aldehyde conversion [%]	Yield [%]
1	Rh on carbon matrix	97	58
2	Rh on activated charcoal	48	18
3	Rh on carbon	43	21
4	Rh on activated alumina	24	7
5	Rh on alumina (Degussa-type)	45	7
6	Ru on activated charcoal	10	0
7	Ru on activated carbon (reduced, 50% water)	14	2
8	Ru on alumina	47	5
9	Ru on activated alumina	45	7

[a] In all cases 5% wt of the metal on support were used. 0.2 mmol of acetamide, 1:1 ratio of acetamide and *p*-anisaldehyde, yield was determined by NMR with mesitylene as internal standard.

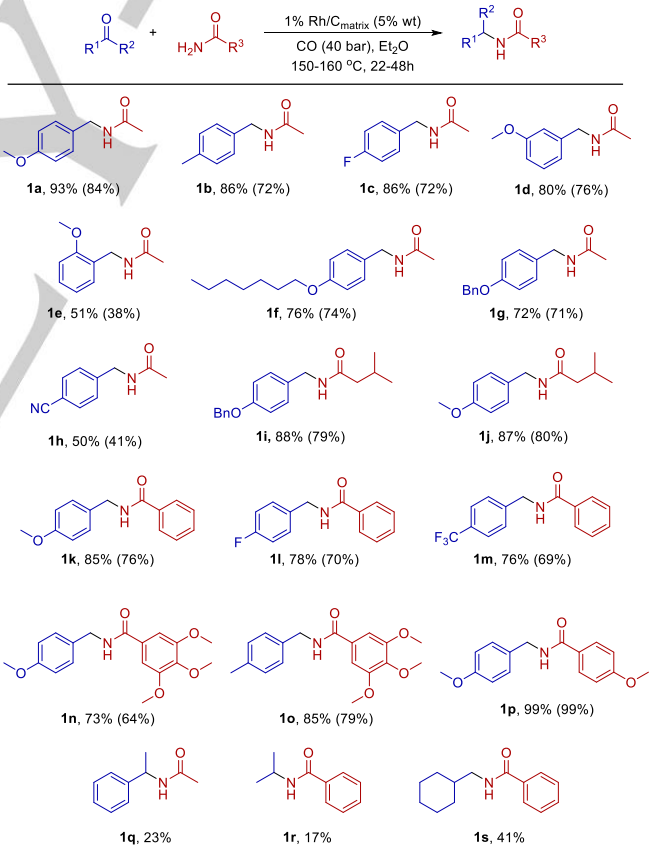
Table 2. Solvent screening



Entry[a]	Solvent	Aldehyde conversion [%]	Yield of **1a** [%]	Yield of **2a** [%]
1	toluene	>99	70	5
2	Et_2O	>99	79	6
3	THF	97	58	17
4	CH_2Cl_2	43	24	traces
5	CH_3CN	53	24	8
6	^{t}BuOH	>99	77	7
7	^{i}PrOH	>99	73	9
8	^{n}BuOH	>99	22	42
9	EtOH	>99	35	35
10	MeOH	>99	5	28
11	H_2O	>99	17	47
12[b]	**Et_2O**	**>99**	**93**	**3**

[a] 5% wt of the rhodium on carbon matrix were used. 0.2 mmol of acetamide, 1:1 ratio of acetamide and *p*-anisaldehyde, 1M, yield was determined by NMR with mesitylene as internal standard. [b] 0.5M.

We then examined scope and limitations of the reaction (Scheme 2). Different aromatic aldehydes can be used in this transformation. Aldehydes bearing electron-donating functional groups show higher activity than aldehydes with electron-withdrawing groups (**1a**, **1b**, **1f**, **1g** *vs*. **1h**, and **1k** *vs*. **1m**). The system is also sensitive to sterical hindrance. The use of aldehydes with *ortho* substituents led to lower yields than those with *meta* and *para* substituents (**1a**, **1d** *vs*. **1e**). Ketones react poorly under these conditions due to their lower electrophilicity and higher sterical hindrance (**1q, 1r**). Another limitation of the method is inability of using aliphatic aldehydes. In the reaction conditions they form complex mixtures of self-aldol condensation products due to high reaction temperature which results in low yield of target amide (**1s**). Different types of amides can be used. Aliphatic and aromatic amides afford products in similar yields (**1a**, **1j**, **1k**, **1n**, and **1p**). Electron-donating groups in benzamide derivatives increase product yield (**1p** *vs*. **1n** *vs*. **1k)**. Catalytic system demonstrated tolerance to different functional groups such as -OBn and -CN, which can be reduced in amidation reactions involving external hydrogen source such as H_2 or hydrides.



Scheme 1. Investigation of substrate scope. 1 mmol of amide, 1:1 ratio of amide and aldehyde, yield was determined by ^{1}H NMR with mesitylene as internal standard. Isolated yield is placed in parenthesis.

Study of biological activities of new compounds is important for drug development and agricultural chemistry. Herein, we

investigated the activity of synthesized amides *in vitro* against three phytopathogenic fungi *Fusarium sambucinum (F.s.*), *Fusarium oxysporum* (*F.o.*) and *Rhizoctonia Solani* (*R.s.*) (Table 3). The effect of the tested compounds on the mycelium radial growth in the potato-saccharose agar media was measured in a concentration 30 mg/L. The tested amides showed low to moderate activity against *F. sambucinum* and *F. oxysporum*. However, they showed moderate to high activity in case of *R. solani.* The results showed that the synthesized amides possess a selective antifungal activity against one of the three tested fungi, which can be very valuable since it allows target plants treatment against particular fungi. In general, benzamide (**1k**-**1p**) derivatives demonstrated higher antifungal activity in comparison to acetamide (**1a**-**1h**) and isovaleramide (**1i**-**1j**) derivatives. Although amide **1f**, containing *p*-heptoxybenzyl substituent, also demonstrated high antifungal activity against *R. solani*. Furthermore, activities of **1f**, **1l**, **1n**, **1o** and **1p** against *R. solani* exceeded those of triadimefon, which was used as a reference fungicide and showed only 36% inhibition under these conditions. Amide **1p** appeared to be the most active among all tested compounds and showed 79% inhibition of mycelium growth. Interestingly, amide **1n**, which contains two more methoxy groups was less active (51%). Therefore, these compounds showed promising antifungal activity and require further studies.

Table 3. Study of antifungal activity of synthesized amides by calclulation of growth inhibition rates for three different fungi *Fusarium sambucinum (F.s.*), *Fusarium oxysporum* (*F.o.*) and *Rhizoctonia Solani* (*R.s.*).[a]

Entry	Amide	*F.s.*	*F.o.*	*R.s.*
1	**1a**	13%	5%	28%
2	**1b**	5%	4%	19%
3	**1c**	10%	3%	6%
4	**1d**	11%	6%	24%
5	**1f**	10%	11%	60%
6	**1g**	5%	16%	19%
7	**1i**	9%	16%	40%
8	**1j**	3%	12%	14%
9	**1k**	11%	4%	29%
10	**1l**	3%	9%	55%
11	**1m**	8%	0%	28%
12	**1n**	14%	17%	51%
13	**1o**	14%	0%	42%
14	**1p**	13%	27%	79%

[a] Plates were incubated at 24 ℃ and the growth inhibition rates (I) were calculated after 72h. The effect of the tested compounds was measured in a concentration 30 mg/L

Afterwards we conducted a comparative study of the tested catalysts in order to explain the differences in their activity shown in Table 1. Firstly, the results showed great difference in activities depending on the type of support, even between different carbon supports. It can be related to pore size which can have significant impact on catalytic activity. In order to check the influence of porosity on catalytic activity, we measured specific surface area by adsorption using BET isotherm. We measured the surface area for rhodium on carbon matrix, rhodium on activated charcoal and rhodium on carbon. However, differences in surface area between the catalysts appeared to be insignificant (see supporting information) pointing on another origin of difference in catalytic activity. We then studied morphology of these three catalysts using TEM (Figure 1). For rhodium on carbon matrix (Figures 1a and 1b), regardless of the presence of catalyst drying step, the mean particles size was about 2.0 nm (approximate size range – 1.5-3.0 nm). Morphology of the support did not depend on the catalyst pretreatment. In the case of rhodium on carbon and rhodium on activated charcoal the size of the metal particles was somewhat higher and the particles agglomeration was more pronounced (Figures 1c and 1d). The mean size of metal particles was about 3.0 nm (approximate size range – 2.0-4.0 nm) in the case of carbon support and about 2.5 nm (approximate size range – 1.5-3.5 nm) in the case of activated charcoal support. The morphology of carbon materials had no notable features in both cases. It is important to mention that for all samples under study the spatial distribution of the metal on carbon-based material was non-uniform and particles sizes varied from site to site. Nevertheless, on the basis of electron microscopy data one can conclude that there is no significant difference in the catalyst nano-structure, which could have such a notable impact on the catalytic reaction outcome.

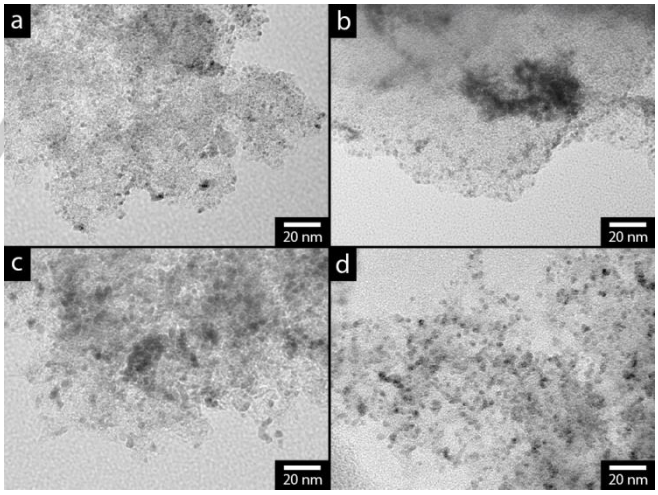


Figure 1. TEM images of rhodium on carbon matrix (**a**), rhodium on carbon matrix after drying in vacuo (**b**), rhodium on carbon (**c**) and rhodium on activated charcoal (**d**).

We then decided to investigate catalyst stability and turnover (see supporting information). We found that on the second cycle the activity of the catalyst significantly decreased, and product yield dropped below 30%. On the third cycle yield of the product was almost the same. These results can be explained by

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passivation of active centers or by leaching of rhodium to solution and deactivation of these rhodium particles during recycling.

We tested these possibilities by analysis of the catalyst after reaction by TEM (Figure 2). No metal particles or agglomerates can be seen on the sample, which supports theory of rhodium leaching during the reaction.

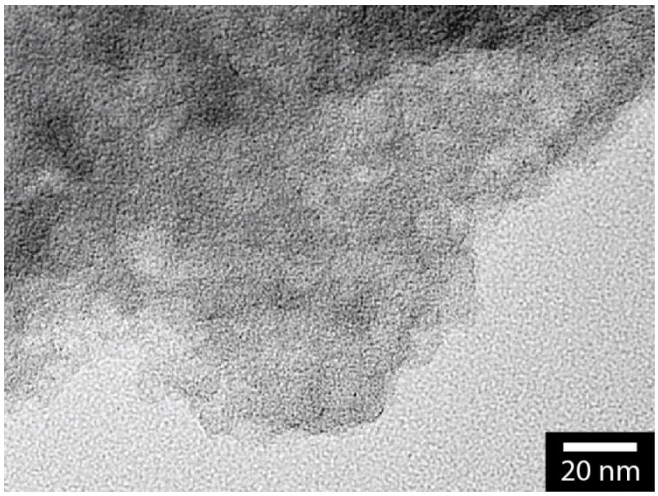
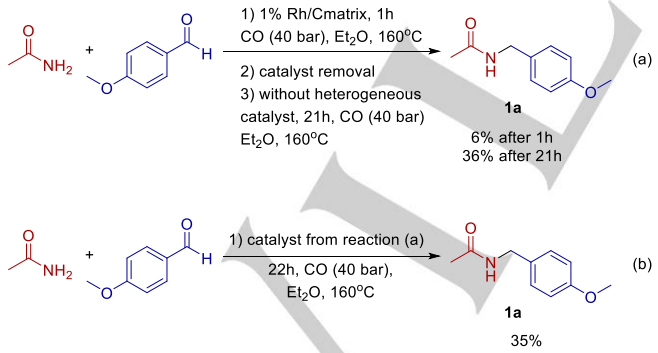


Figure 2. TEM image of rhodium on carbon matrix after reaction.

To confirm the leaching of the catalyst into solution we conducted an experiment similar to hot-filtration experiment. First, we packed the catalyst in a piece of filter paper and placed it into an autoclave with starting materials. After one hour of heating the catalyst was removed and reaction mixture was heated further for 21 hours. Analysis of reaction mixture after one hour with catalyst and after 21h without heterogeneous particles proved that leaching occurs since formation of the product continued after removal of the catalyst (Scheme 2, a).



Scheme 2. Analysis of catalyst leaching.

Moreover, colour of the reaction mixture after one hour was deep red which indicates the presence of rhodium complexes. After 21 hours colour of the reaction mixture changed to pale-yellow. To the catalyst that was removed from reaction (a) on Scheme 2 another portion of starting material was added. Target amid was formed in 35% yield (Scheme 2, (b) which is considerably lower than in standard conditions. ICP-AES also confirmed leaching of rhodium (see Supporting information).

In order to determine oxidation states of rhodium, the catalysts were analysed with XPS (Figure 3). The spectra of rhodium on carbon matrix **1** and **2** practically coincide in shape and position. The Rh $3d_{5/2}$ and Rh $3d_{3/2}$ peaks at 309.8 and 314.7 eV respectively can be assigned to Rh_2O_3•$5H_2O$ (309.6 eV) [10]. In contrast to the spectrum of rhodium on carbon matrix, three states giving Rh $3d_{5/2}$ peaks at 307.5/308.7/309.8 and 307.3/308.7/309.8 eV, which can be assigned to Rh, Rh_2O_3 and Rh_2O_3·$5H_2O$, were deconvoluted in those of rhodium on carbon **3** and rhodium on activated charcoal **4**, respectively. Their corresponding intensity ratios are 0.44/0.37/0.19 and 0.43/0.45/0.12.

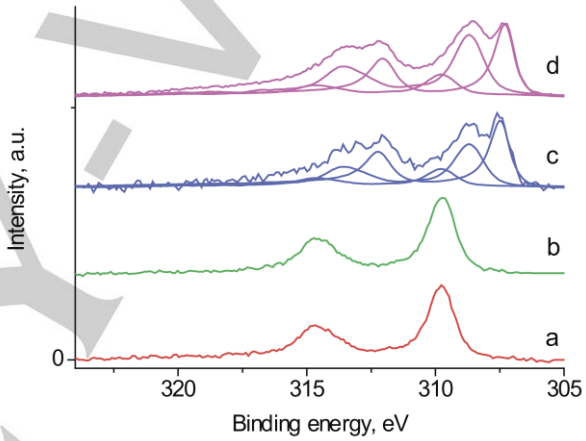


Figure 3. Rh 3d photoelectron spectra of rhodium on carbon matrix (**a**), rhodium on carbon matrix after drying in vacuo (**b**), rhodium on carbon (**c**) and rhodium on activated charcoal (**d**).

From this data it seems that only rhodium (III) is active in reductive amidation since both rhodium on carbon and activated charcoal showed at least twice less activity than rhodium on carbon matrix. Therefore, rhodium on carbon matrix works more like homogeneous catalyst than heterogeneous, which was confirmed by leaching of catalyst from the support. To confirm that rhodium (III) can catalyse the reaction, we tested the activity of $RhCl_3$ in the model reaction (Scheme 3, a). Under these conditions $RhCl_3$ demonstrated some catalytic activity although it was less active than rhodium on carbon matrix. We also tested activity of $Rh_6(CO)_{16}$ as a homogeneous source of rhodium (0). Interestingly it demonstrated catalytic activity comparable with rhodium on carbon matrix (Scheme 3, b). So rhodium on carbon matrix is giving the "cocktail" of catalysts[11] in which homogeneous species seem to be much more active.

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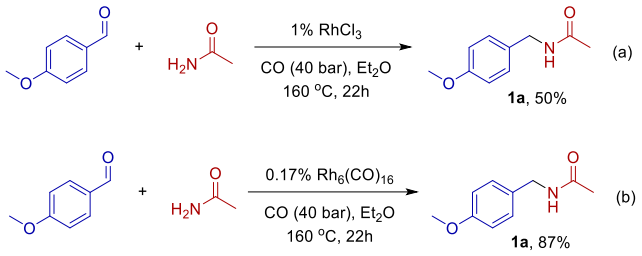
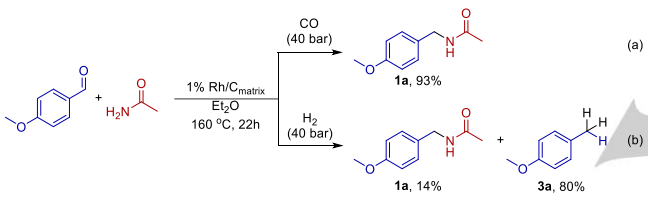


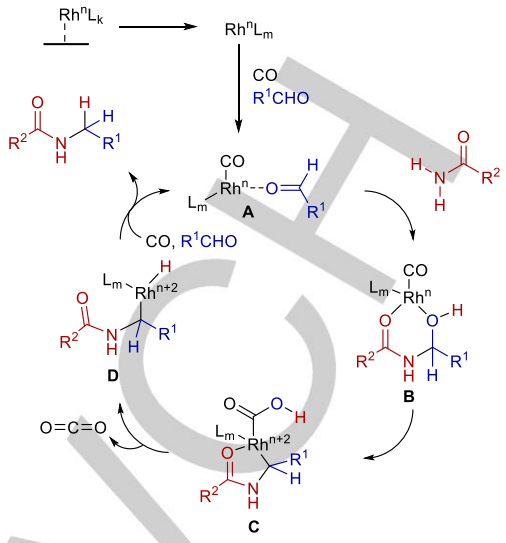
Scheme 3. Activity of rhodium (III) and rhodium (0) in reductive amidation.

As it was shown previously in our group, carbon monoxide possesses unique selectivity because of the lack of external hydrogen source. Here we decided to compare the selectivity of carbon monoxide with hydrogen (Scheme 4). While the usage of carbon monoxide allowed to synthesise the product in nearly quantitative yield, the use of hydrogen mainly resulted in reduction of aldehyde to the corresponding alcohol and further hydrogenolysis to the substituted toluene **3a** with some formation of the desired product.



Scheme 4. Activity of rhodium (III) and rhodium (0) in reductive amidation.

Plausible mechanism is shown on Scheme 5, based on our results herein and our previous studies. At first rhodium species are leached from carbon matrix into the solution either by coordination with carbon monoxide and aldehyde or by itself with the following coordination of carbon monoxide and aldehyde. Addition of the amide to the carbonyl group results in the formation of intermediate **B**. Intramolecular hydroxylation of Rh-bound CO ligand leads to intermediate **C**, with following decarboxylation and formation of intermediate **D**. Finally, reductive elimination leads to formation of the target amide and the regenerated catalyst.



Scheme 5. A plausible mechanism of reductive amidation with rhodium on carbon matrix.

To conclude, we developed a new catalytic system for reductive amidation of aldehydes without external hydrogen source using rhodium on carbon matrix as a catalyst. Substrate scope of the reaction was evaluated, and it was shown that various amides and substituted aromatic aldehydes can be utilized in this reaction. Less active carbonyl compounds such as ketones poorly undergo this transformation. Aliphatic aldehydes also can not be used because of various side reactions. Moreover, antifungal activity of the synthesized amides was evaluated. Particularly, 4-methoxy-N-(4-methoxybenzyl)benzamide demonstrated high activity against *Rhizoctonia Solani* which surpasses the activity of commercially used Triadimefon. Catalysts were studied using BET, TEM and XPS techniques. According to XPS data the most active catalyst (rhodium on carbon matrix) does not contain Rh(0) species and contains only Rh(III) species, which provides its higher catalytic activity.

Experimental Section

General procedure for reductive amidation

A 10 mL stainless steel autoclave was charged with 1 mol% of catalyst, the corresponding solvent, 1 eq. of the aldehyde and 1 eq. of the amide, and magnetic stirring bar. The autoclave was sealed, flushed with 5 bar of CO, and then charged with the indicated pressure of CO. The reactor was placed into a preheated oil bath. After the indicated time, the reactor was cooled to room temperature and depressurized. The reaction mixture was filtrated from catalyst and solvents were removed on a rotary evaporator.

TEM

Before measurements the samples were deposited on the 3 mm carbon-coated copper grids from isopropanol suspension. Samples morphology was studied using Hitachi HT7700 transmission electron microscope. Images were acquired in bright-field TEM mode at 100 kV accelerating voltage.

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Keywords: Amidation • Homogeneous catalysis • Heterogeneous catalysis • Reduction • Carbon monoxide

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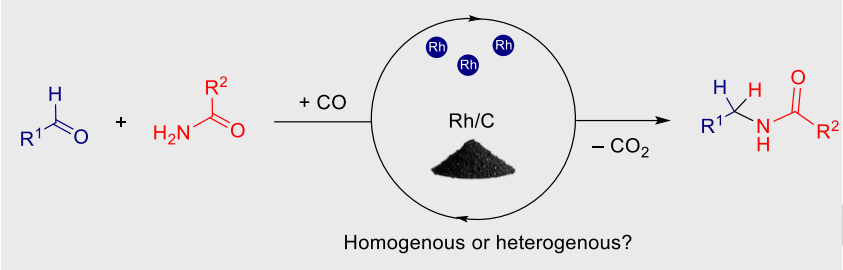

Leaching forever. Rhodium on carbon matrix was successfully applied as a catalyst for reductive amidation without an external hydrogen source. It was found that the reaction proceeds in homogeneous mode. The products were tested for antifungal activity.

*Alexey A. Tsygankov, Maria Makarova, Oleg I. Afanasyev, Alexey S. Kashin, Alexander V. Naumkin, Dmitry A. Loginov, Denis Chusov**

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Reductive Amidation without an External Hydrogen Source Using Rhodium on Carbon Matrix as a Catalyst