EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Ruthenium-catalyzed reductive amidation without an external hydrogen source

Authors: Niyaz Z Yagafarov, Karim Muratov, Klim Biriukov, Dmitry Usanov, Olga Chusova, Dmitry S Perekalin, and Denis Chusov

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701527

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701527

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201701527

WILEY-VCH

Ruthenium-catalyzed reductive amidation without an external hydrogen source

Niyaz Z. Yagafarov,[a] Karim M. Muratov,[a] Klim Biriukov,[a] Dmitry L. Usanov,[b] Olga Chusova,[c] Dmitry S. Perekalin,[a] and Denis Chusov*[a,c]

Abstract: The catalytic reaction of aldehydes with primary amides leading to N-alkylated amides was investigated. The developed protocol employs carbon monoxide as a deoxygenative agent and therefore allows to avoid an external hydrogen source. Cyclopentadienyl ruthenium complexes demonstrated excellent catalytic efficiency and could be used at as low as 0.5-1 mol % catalyst loading. A representative number of secondary amides were successfully prepared in 70-84% yields.

Introduction

From the point of view of sustainable development, the use of industrial side products in chemical synthesis represents an interesting and promising approach. Even though the worldwide demand for carbon monoxide requires its directed synthesis, this side product of steelmaking can be produced in large excess at a given factory, and large amount of CO are ubiquitously disposed of by simple burning into carbon dioxide. In this context, we have been interested developing new atom- and step-economical reactions, which employ carbon monoxide as deoxygenative agent.[1]

The central role of amide bond in both natural biopolymers and human-made materials renders development of efficient methods for amide synthesis undoubtedly important.[2] On the grounds of our methodological paradigm we have recently developed the first protocol for reductive amidation[3] with carbon monoxide catalysed by rhodium acetate.[4] However, high cost of rhodium represents a substantial obstacle for scaled-up applications both in academic and industrial settings. Herein, we describe a detailed investigation of reductive amidation chemistry, which resulted in the development of catalytic system based on ruthenium complexes.[5]

Results and Discussion

We studied a number of potential catalysts for the model reductive amidation of p-methoxybenzaldehyde with benzamide in the presence of carbon monoxide[6] (Figure 1, Table 1).

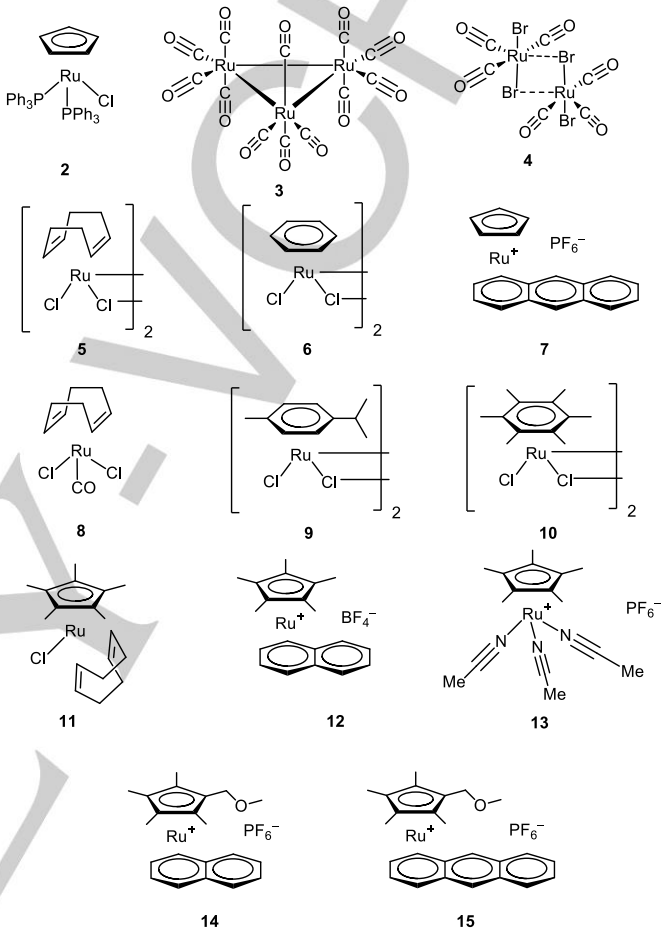


Figure 1. Ruthenium complexes tested in reductive amidation.

Unfortunately, poor results were observed for various heterogeneous catalysts (Table 1, entries 2-9); catalytic activity was detected only for rhodium-based systems. We then tested a representative list of homogeneous ruthenium precatalysts (Table 1, entries 10-27). We noticed that ruthenium complexes with bulky cyclopentadienyl ligands (**11**-**15**, entries 22-27) demonstrated superior results. Among those Cp*Ru(cod)Cl complex has lower activity, presumably because of the difficult dissociation of the Ru−Cl bond. We assume that all these complexes generate similar catalytic species with a general formula $[(C_5R_5)Ru(CO)_x]^+$.[7] The cyclopentadienyl ligand protects such species against side reactions and precipitation (note that unsubstituted Cp ligand in complexes **2** and **7** is less efficient).[8] The cationic ruthenium center plays a dual role; on one hand, it acts as a Lewis base, which facilitates condensation of an amide and an aldehyde. On the other hand, it coordinates CO ligand and activates it towards nucleophilic attack of OH group, which eventually gives CO_2 and a hydride required for reduction (vide

[a] Nesmeyanov Institute of Organoelement Compounds of Russian Academy of Sciences
119991, Vavilova St. 28, Moscow, Russian Federation
E-mail: denis.chusov@gmail.com
[b] Department of Chemistry and Chemical Biology, Harvard University
12 Oxford Street, Cambridge, MA 02138, USA
[c] Faculty of Science, RUDN University
6 Miklukho-Maklaya St., Moscow 117198, Russian Federation

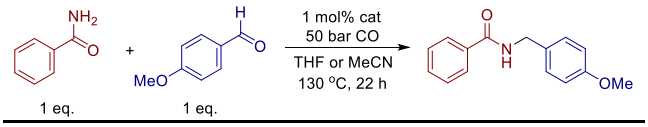
Supporting information for this article is given via a link at the end of the document.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

infra). Interestingly, the best catalysts, namely naphthalene **14** and anthracene **15** complexes displayed very similar activity in acetonitrile and diethyl ether, however only **15** remained active in toluene. After a number of tests, we chose anthracene complex **15** for further optimization, not only due to its high catalytic activity, but also because it is air-stable and can be easily obtained from $RuCl_3$.[9]

Table 1. Screening of catalysts.

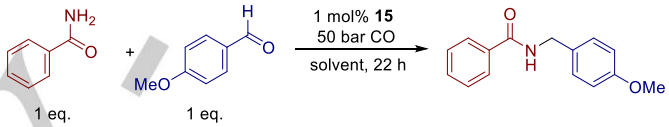


Entry	Catalyst	Yield[a], %
1[b]	$Rh_2(OAc)_4$	10
2[b]	Ni/C	0
3[b]	Pd/C	0
4[c]	Ru/C (activated charcoal)	0
5[c]	Ru/Al_2O_3 (Degussa type)	0
6[b]	Rh/Al_2O_3	3
7[b]	Rh/Al_2O_3 (Degussa type)	3
8[b]	Rh/Al_2O_3 (act)	5
9[b]	Rh/C (activated charcoal)	5
10	$CpRu(PPh_3)_2Cl$ (**2**)	0
11	$Ru(acac)_3$	1
12	$Ru_3(CO)_{12}$ (**3**)	1
13	$[(cod)RuCl_2]_2$ (**5**)	2
14	$[(benzene)RuCl_2]_2$ (**6**)	2
15	$CpRu(antracene)PF_6$ (**7**)	2
16	$[(cod)Ru(CO)Cl_2]_2$ (**8**)	4
17	$[(p\text{-cymene})RuCl_2]_2$ (**9**)	5
18	$[(C_6Me_6)RuCl_2]_2$ (**10**)	8
19	$RuCl_3$	11
20	$[Ru(CO)_3Br_2]_2$ (**4**)	1
21	$[Ru(CO)_3Br_2]_2$ (**4**) + KPF_6	9
22	Cp*Ru(cod)Cl (**11**)	7
23	Cp*Ru(cod)Cl (**11**) + KPF_6	8
24	Cp*Ru(naphthalene)BF_4 (**12**)	13
25	Cp*Ru$(MeCN)_3PF_6$ (**13**)	14
26	$(C_5Me_4OMe)Ru(naphthalene)PF_6$ (**14**)	17
27	$(C_5Me_4OMe)Ru(antracene)PF_6$ (**15**)	18

[a] 0.2 mmol scale. Yields were determined by NMR. [b] MeCN was used as a solvent; THF was used as a solvent in all other cases.

Table 2 shows the results of solvent and temperature screening. Tetrahydrofuran, ethyl acetate, acetonitrile and dichloromethane gave similar results (entries 3-6), whereas lower yields were observed for reactions in alcohols (entries 1-2). Highest yields were achieved in toluene and diethyl ether. Increasing the temperature of the reaction from 130 to 150 °C was important (36 vs. 78% yield); further heating led to slight erosion of the yield. The influence of the pressure was found to be insignificant, the reaction proceeded well even under 10 bar of CO. We found that as low as 0.5 mol% of the catalyst can be successfully employed, however, 0.1 mol% loading led to a substantial drop of the yield. We separately screened conditions for acetamide as a substrate and observed different trends compared to benzamide reactions (see Supporting Information for details). In particular, we observed a bell-shaped dependence of the reaction yields from the reaction temperature with best results achieved at 160 °C (82% yield).

Table 2. Screening of solvents and temperature.



Entry	Solvent	Temperature, °C	Yield[a], %
1	ethanol	130	4
2	methanol	130	9
3	tetrahydrofuran	130	14
4	ethyl acetate	130	17
5	acetonitrile	130	18
6	dichloromethane	130	21
7	neat	130	26
8	toluene	130	30
9	diethyl ether	130	33
10	diethyl ether	140	36
11	diethyl ether	150	78
12	diethyl ether	160	73
13	diethyl ether	170	72
14	diethyl ether	180	72

[a] 0.2 mmol scale. Yields were determined by NMR.

With the optimized conditions in hand, we tested the substrate scope of Ru-mediated amidation (Figure 2). High yields were observed for substrates with various substitution patterns (**1a**-**1o**). Only aliphatic aldehydes (**1q**) and aromatic aldehydes with electron-acceptor substituents (e.g. CF_3), (**1p**) showed lower yields, which might be due to formation of by-products cause by high electrophilicity. The opposite situation was previously observed in rhodium-catalyzed reductive

Accepted Manuscript

This article is protected by copyright. All rights reserved.

amidation with hydrogen gas, where aliphatic aldehydes gave notably better results than aromatic ones.[10] Benzyloxy group was found to be stable under the reaction conditions; product **1m** was isolated in 72% yield. No enhanced reactivity was observed for electron-rich amides (e.g. **1a** vs. **1o**).

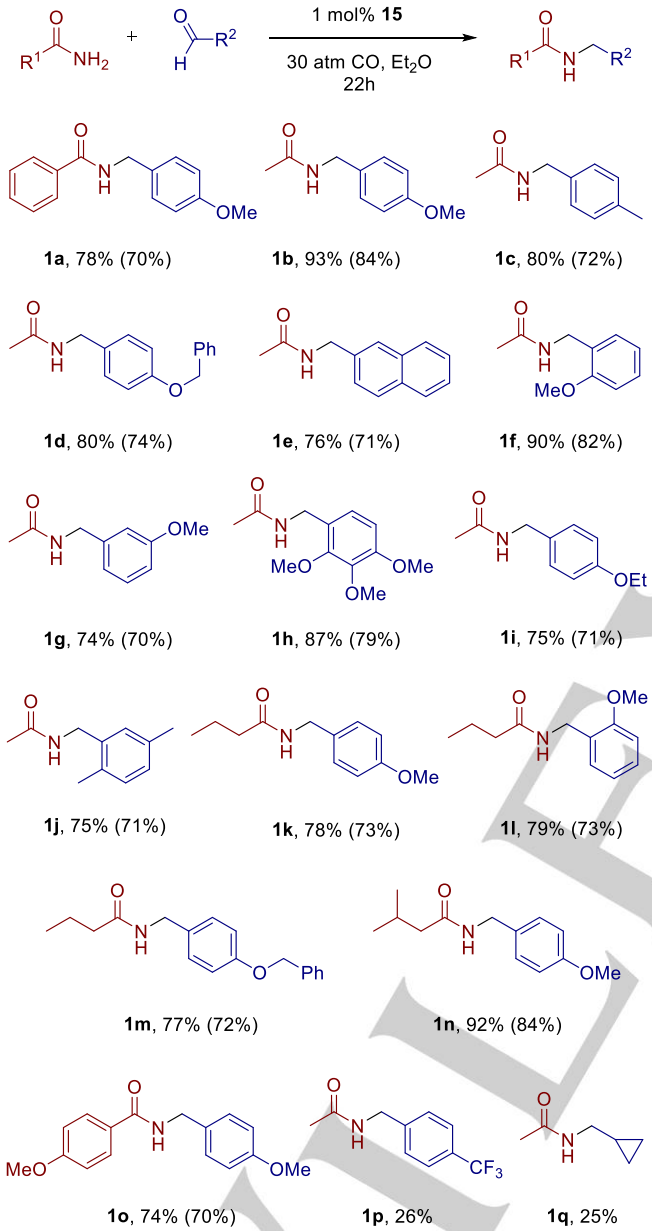


Figure 2. Substrate scope studies for the developed methodology. The reactions were conducted at 150 °C for aromatic amides and at 160 °C for aliphatic amides.

Compare to our previous results with rhodium catalyzed reaction[4] we found a few differences. Generally, rhodium is working better in different solvents but THF is the leading one. For ruthenium catalyzed version toluene and diethyl ether is the best choice. Generally, ruthenium catalysis is working better at 1 mol% of metal and rhodium at 2 mol% (1 mol% of dimer). Rhodium acetate is less efficient in case of sterically hindered substrates. Even ortho-methoxybenzaldehyde with acetamide gave only 73% yield compare to 90% in case of catalyst **15**. Aldehydes with electron-donating groups are more suitable with ruthenium catalysis, whereas substrates with electron-withdrawing groups are more suitable with rhodium catalysis.

We propose a possible mechanism based on the current observations and previous DFT calculations[1a] (Figure 3). As mentioned above, under atmosphere of carbon monoxide complex **15** is expected to generate the active species $[(C_5Me_4OMe)Ru(CO)_x]^+$ (**A**).[7] The methoxy group of C_5Me_4OMe ligand may help stabilize such species and prevent formation of inactive clusters. Coordination of amide to **A** leads to complex **B** and a protonated aldehyde, which activates it for the nucleophilic addition to give **C**. Intramolecular attack of the hydroxyl moiety on the carbonyl ligand (via **D**) can lead to species **E**. Its decarboxylation (that is similar to Hieber base reaction[11]) gives ruthenium hydride complex **F**, which intramolecularly reduces the acyl-imine to give the amine product and the regenerated catalyst. The amount of carbon dioxide in the gas phase after the reaction in agreement with the amount of the product (see SI).

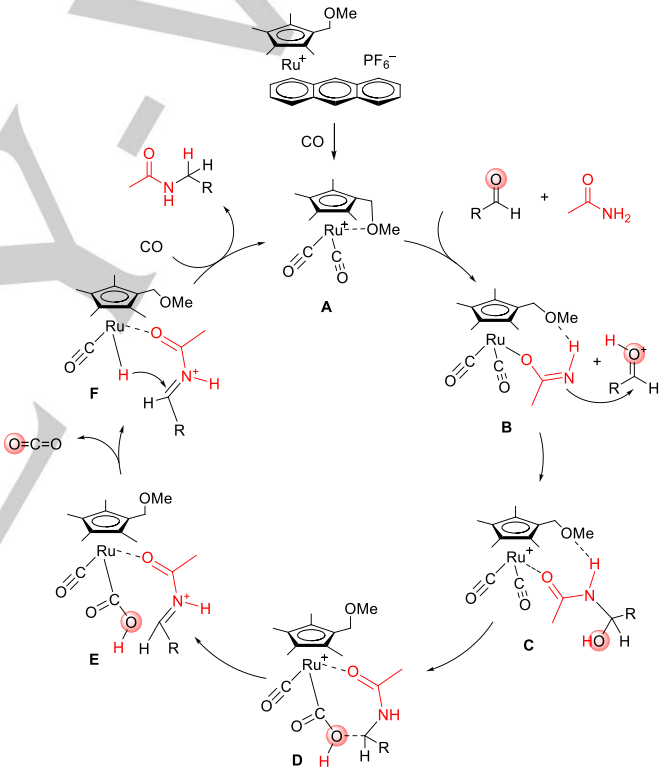


Figure 3. Plausible mechanism of the catalytic reaction.

Conclusions

In summary, we developed a catalytic system for Ru-catalyzed atom-economical reductive amidation of aldehydes. The methodology takes advantage of the unique deoxygenative potential of carbon monooxide and does not require an external hydrogen source. A representative number of secondary amides were prepared in 70-84% yields. The reaction works well for various types of amides and aromatic aldehydes. The possible mechanism for reduction via Hieber base-type reaction was proposed.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

Experimental Section

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification (THF was distilled over sodium/benzophenone, methanol was distilled over Mg). Carbon monoxide of >98% purity was obtained from NII KM (Moscow, Russia). Isolation of products on less than 200 mg scales was performed by preparative TLC (Macherey-Nagel, Silica gel 60 GF254, fluorescence quenching with UV light at 254 nm); hexane-ethyl acetate system was used as eluent. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-300, AV-400 and AV-600 spectrometers at ambient temperature. Chemical shifts δ are reported in ppm using the solvent resonance signal as an internal standard. NMR yields were calculated with HMDS (hexamethyldisiloxane) as an internal standard (unless otherwise noted). The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants are given in Hertz (Hz). HRMS (ESI-MS): spectra were recorded on Bruker micrOTOF II and Maxis instruments under electrospray ionization (ESI) conditions in a positive ion mode (interface capillary voltage: 4500 V) with a mass range m/z 50–3000 Da; external and internal calibrations were performed with Electrospray Calibrant Solution. All samples for ESI-MS were prepared in MeCN; syringe injections were used (flow rate: 3 μL/min). Nitrogen was applied as a dry gas; interface temperature was set at 180 ^{o}C. The spectra were processed with DataAnalysis software package.

Procedure: A 10 mL stainless steel autoclave was charged with 1 mol% of catalyst, the corresponding solvent, 1 eq. of the amine and 1 eq. of the amide. The autoclave was sealed, flushed three times with 10 atm 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 transferred into a flask and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. The residue was purified by flash chromatography on silica gel.

N-(4-methoxybenzyl)benzamide (1a): Cp*OMeRu(antracene)PF_6 (1.9 mg, 1 mol%, 0.0033 mmol), benzamide (40 mg, 1 eq, 0.33 mmol) and *p*-methoxybenzaldehyde (0.04 mL, 1 eq, 0.33 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 150 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 78% yield by NMR. The residue was purified by preparative thin-layer chromatography (eluent: hexane/ethyl acetate (5:1); R_f=0.20) to afford 56.0 mg (70%) of the product as a white crystals.

^{1}H NMR (CDCl3, 300 MHz, 25 °C) δ 7.76 (d, J = 7.4 Hz, 2H), 7.46 (t, J =7.4 Hz, 1H), 7.42 (t, J =7.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 6.61 (br. s, 1H), 4.53 (d, J = 5.5 Hz, 2H), 3.77 (s, 3H);

^{13}C NMR (CDCl3, 100 MHz, 25 °C) δ 167.3, 159.0, 134.4, 131.4, 130.3, 129.2, 128.5, 126.9, 114.1, 55.2, 43.5;

N-(4-methoxybenzyl)acetamide (1b): Cp*OMeRu(antracene)PF_6 (2.0 mg, 1 mol%, 0.0034 mmol), acetamide (20 mg, 1 eq, 0.34 mmol) and *p*-methoxybenzaldehyde (0.041 mL, 1 eq, 0.34 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 160 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 93% yield by NMR. The residue was purified by preparative thin-layer chromatography (eluent: hexane/ethyl acetate (1:1); R_f=0.13) to afford 51.0 mg (84%) of the product as a white crystals.

^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.18 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.04 (br. s, 1H), 4.31 (d, *J* = 5.6 Hz, 2H), 3.77 (s, 3H), 1.96 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 169.9, 158.9, 130.3, 129.1, 114.0, 55.2, 43.1, 23.1;

N-(4-methylbenzyl)acetamide (1c): Cp*OMeRu(antracene)PF_6 (2.0 mg, 1 mol%, 0.0034 mmol), acetamide (20 mg, 1 eq, 0.34 mmol) and *p*-methylbenzaldehyde (0.041 mL, 1 eq, 0.34 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 160 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 80% yield by NMR. The residue was purified by preparative thin-layer chromatography (eluent: hexane/ethyl acetate (1:1); R_f=0.23) to afford 40.0 mg (72%) of the product as a white crystals.

^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.15 (q, *J* = 8.2 Hz, 4H), 5.88 (br. s, 1H), 4.36 (d, *J* = 5.6 Hz, 2H), 2.33 (s, 3H), 1.99 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 169.8, 137.2, 135.2, 129.3, 127.8, 43.5, 23.2, 21.0;

N-(4-(benzyloxy)benzyl)acetamide (1d): Cp*OMeRu(antracene)PF_6 (2.0 mg, 1 mol%, 0.0034 mmol), acetamide (20 mg, 1 eq, 0.34 mmol) and *p*-benzyloxybenzaldehyde (72 mg, 1 eq, 0.34 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 160 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 80% yield by NMR. The residue was purified by preparative thin-layer chromatography (eluent: hexane/ethyl acetate (1:1); R_f=0.13) to afford 64.0 mg (74%) of the product as a white crystals.

^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.43-7.30 (m, 5H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 5.77 (br. s, 1H), 5.05 (s, 2H), 4.35 (d, *J* = 5.6 Hz, 2H), 1.99 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 169.8, 158.2, 136.8, 130.6, 129.2, 128.6, 128.0, 127.4, 115.0, 70.0, 43.2, 23.3;

N-(naphthalen-2-ylmethyl)acetamide (1e): Cp*OMeRu(antracene)PF_6 (2.0 mg, 1 mol%, 0.0034 mmol), acetamide (20 mg, 1 eq, 0.34 mmol) and *2*-naphtaldehyde (53 mg, 1 eq, 0.34 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 160 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 76% yield by NMR. The residue was purified by preparative thin-layer chromatography (eluent: hexane/ethyl acetate (1:1); R_f=0.18) to afford 64.0 mg (71%) of the product as a white crystals.

^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.82-7.77 (m, 3H), 7.68 (s, 1H), 7.49-7.44 (m, 2H), 7.37 (d, *J* = 8.4 Hz, 1H), 6.07 (br. s, 1H), 4.55 (d, *J* = 5.6 Hz, 2H), 2.02 (s, 3H);

Accepted Manuscript

This article is protected by copyright. All rights reserved.

^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 170.0, 135.6, 133.3, 132.7, 128.5, 127.6, 126.3, 126.3, 125.9, 125.9, 43.8, 23.2;

N-(2-methoxybenzyl)acetamide (1f): Cp*OMeRu(antracene)PF_6 (2.0 mg, 1 mol%, 0.0034 mmol), acetamide (20 mg, 1 eq, 0.34 mmol) and *o*-methoxybenzaldehyde (0.041 mL, 1 eq, 0.34 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 160 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 90% yield by NMR. The residue was purified by preparative thin-layer chromatography (eluent: hexane/ethyl acetate (1:1); R_f=0.20) to afford 51.0 mg (82%) of the product as a white crystals.

^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.27-7.24 (m, 2H), 6.92-6.86 (m, 2H), 6.07 (br. s, 1H), 4.41 (d, *J* = 5.8 Hz, 2H), 3.84 (s, 3H), 1.96 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 169.8, 157.5, 129.8, 128.8, 126.2, 120.6, 110.2, 55.3, 39.4, 23.3;

N-(3-methoxybenzyl)acetamide (1g): Cp*OMeRu(antracene)PF_6 (2.0 mg, 1 mol%, 0.0034 mmol), acetamide (20 mg, 1 eq, 0.34 mmol) and m-methoxybenzaldehyde (0.041 mL, 1 eq, 0.34 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 160 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 74% yield by NMR. The residue was purified by preparative thin-layer chromatography (eluent: hexane/ethyl acetate (1:1); Rf=0.21) to afford 43.0 mg (70%) of the product as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.26-7.21 (m, 1H), 6.85-6.79 (m, 3H), 6.04 (br. s, 1H), 4.36 (d, *J* = 5.7 Hz, 2H), 3.78 (s, 3H), 1.99 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 170.0, 159.8, 139.8, 129.7, 120.0, 113.4, 112.8, 55.2, 43.6, 23.1;

N-(2,3,4-trimethoxybenzyl)acetamide (1h): Cp*OMeRu(antracene)PF_6 (2.0 mg, 1 mol%, 0.0034 mmol), acetamide (20 mg, 1 eq, 0.34 mmol) and 2,3,4-trimethoxybenzaldehyde (67 mg, 1 eq, 0.34 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 160 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 87% yield by NMR. The residue was purified by preparative thin-layer chromatography (eluent: hexane/ethyl acetate (1:1); R_f=0.16) to afford 64.0 mg (79%) of the product as yellow crystals.

^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 6.94 (d, *J* = 8.5 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 1H), 6.04 (br. s, 1H), 4.32 (d, *J* = 5.7 Hz, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 1.95 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 169.7, 153.4, 151.8, 142.0, 124.0, 123.9, 107.1, 60.9, 60.7, 55.9, 39.0, 23.2;

N-(4-ethoxybenzyl)acetamide (1i): Cp*OMeRu(antracene)PF_6 (2.0 mg, 1 mol%, 0.0034 mmol), acetamide (20 mg, 1 eq, 0.34 mmol) and *p*-ethoxybenzaldehyde (0.047 mL, 1 eq, 0.34 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 160 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 75% yield by NMR. The residue was purified by preparative thin-layer chromatography (eluent: hexane/ethyl acetate (1:1); R_f=0.21) to afford 47.0 mg (71%) of the product as white crystals.

^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.16 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.01 (br. s, 1H), 4.31 (d, *J* = 5.6 Hz, 2H), 3.99 (q, *J* = 7.0 Hz, 2H), 1.97 (s, 3H), 1.39 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 169.9, 158.3, 130.1, 129.1, 114.5, 63.4, 43.1, 23.2, 14.7;

N-(2,5-dimethylbenzyl)acetamide (1j): Cp*OMeRu(antracene)PF_6 (2.0 mg, 1 mol%, 0.0034 mmol), acetamide (20 mg, 1 eq, 0.34 mmol) and 2,5-dimethylbenzaldehyde (0.048 mL, 1 eq, 0.34 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 160 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 75% yield by NMR. The residue was purified by preparative thin-layer chromatography (eluent: hexane/ethyl acetate (1:1); Rf=0.35) to afford 43.0 mg (71%) of the product as white crystals.

1H NMR (CDCl3, 400 MHz, 25 °C) δ7.07-6.99 (m, 3H), 5.79 (br. s, 1H), 4.36 (d, J = 5.3 Hz, 2H), 2.30 (s, 3H), 2.26 (s, 3H), 1.99 (s, 3H);

13C NMR (CDCl3, 100 MHz, 25 °C) δ 169.8, 135.7, 135.5, 133.2, 130.4, 129.4, 128.4, 41.8, 23.1, 20.8, 18.4;

N-(4-methoxybenzyl)butyramide (1k): Cp*OMeRu(antracene)PF_6 (2.0 mg, 1 mol%, 0.0034 mmol), butyramide (30 mg, 1 eq, 0.34 mmol) and *p*-methoxybenzaldehyde (0.042 mL, 1 eq, 0.34 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 160 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 78% yield by NMR. The residue was purified by preparative thin-layer chromatography (eluent: hexane/ethyl acetate (1:1); R_f=0.43) to afford 51.0 mg (73%) of the product as a white crystals.

^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.18 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.88 (br. s, 1H), 4.34 (d, *J* = 5.6 Hz, 2H), 3.77 (s, 3H), 2.15 (t, *J* = 7.5 Hz, 2H), 1.73-1.59 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 172.8, 158.9, 130.5, 129.1, 114.0, 55.2, 42.9, 38.6, 19.1, 13.7;

N-(2-methoxybenzyl)butyramide (1l): Cp*OMeRu(antracene)PF_6 (2.0 mg, 1 mol%, 0.0034 mmol), butyramide (30 mg, 1 eq, 0.34 mmol) and *o*-methoxybenzaldehyde (0.041 mL, 1 eq, 0.34 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 160 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 79% yield by NMR. The residue was purified by preparative thin-layer chromatography (eluent: hexane/ethyl acetate (1:1); R_f=0.51) to afford 51.0 mg (73%) of the product as yellow oil.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.27-7.23 (m, 2H), 7.01-6.77 (m, 2H), 6.02 (br. s, 1H), 4.42 (d, *J* = 5.8 Hz, 2H), 3.84 (s, 3H), 2.14 (t, *J* = 7.4 Hz, 2H), 1.69-1.60 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 172.6, 157.4, 129.7, 128.7, 126.3, 120.6, 110.2, 55.2, 39.2, 38.7, 19.1, 13.7;

N-(4-(benzyloxy)benzyl)butyramide (1m): Cp*OMeRu(antracene)PF_6 (2.0 mg, 1 mol%, 0.0034 mmol), butyramide (30 mg, 1 eq, 0.34 mmol) and *p*-benzyloxybenzaldehyde (72 mg, 1 eq, 0.34 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 160 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 77% yield by NMR. The residue was purified by preparative thin-layer chromatography (eluent: hexane/ethyl acetate (1:1); R_f=0.11) to afford 69.0 mg (72%) of the product as a white crystals.

^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.43-7.31 (m, 5H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 5.69 (br. s, 1H), 5.05 (s, 2H), 4.37 (d, *J* = 5.5 Hz, 2H), 2.17 (t, *J* = 7.5 Hz, 2H), 1.73-1.63 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 172.7, 158.2, 136.9, 130.8, 129.2, 128.6, 128.0, 127.4, 115.0, 70.0, 43.0, 38.7, 19.1, 13.8;

N-(4-methoxybenzyl)-3-methylbutanamide (1n): Cp*OMeRu(antracene)PF_6 (2.0 mg, 1 mol%, 0.0034 mmol), 3-methylbutanamide (34 mg, 1 eq, 0.34 mmol) and *p*-methoxybenzaldehyde (0.042 mL, 1 eq, 0.34 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 160 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 92% yield by NMR. The residue was purified by preparative thin-layer chromatography (eluent: hexane/ethyl acetate (1:1); R_f=0.58) to afford 63.0 mg (84%) of the product as a white crystals.

^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.17 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.01 (br. s, 1H), 4.33 (d, *J* = 5.6 Hz, 2H), 3.76 (s, 3H), 2.14-2.07 (m, 1H), 2.03 (d, *J* = 6.4 Hz, 2H), 0.92 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 172.4, 158.8, 130.5, 129.0, 113.9, 55.2, 45.9, 42.8, 26.1, 22.4;

4-methoxy-N-(4-methoxybenzyl)benzamide (1o): Cp*OMeRu(antracene)PF_6 (1.9 mg, 1 mol%, 0.0033 mmol), *p*-methoxybenzamide (50 mg, 1 eq, 0.33 mmol) and *p*-methoxybenzaldehyde (0.041 mL, 1 eq, 0.33 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 150 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 74% yield by NMR. The residue was purified by preparative thin-layer chromatography (eluent: hexane/ethyl acetate (1:1); R_f=0.50) to afford 63.0 mg (70%) of the product as a white crystals.

^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.74 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.86 (dd, *J* = 10.1, 8.7 Hz, 4H), 6.53 (br. s, 1H), 4.52 (d, *J* = 5.6 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C) δ 166.8, 162.1, 159.0, 130.5, 129.2, 128.7, 126.7, 114.0, 113.6, 55.3, 55.2, 43.4;

N-(4-(trifluoromethyl)benzyl)acetamide (1p): Cp*OMeRu(antracene)PF6 ((1.9 mg, 1 mol%, 0.0033 mmol), acetamide (20 mg, 1 eq, 0.34 mmol) and p-(trifluoromethyl)benzaldehyde (0.046 mL, 1 eq, 0.34 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 160 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 26% yield by NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 5.91 (s, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 2.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 142.5, 130.42 – 129.44 (m), 128.1, 125.8 (q, *J* = 3.7 Hz), 124.2 (d, *J* = 271.9 Hz), 43.3, 23.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.53 (s).

N-(cyclopropylmethyl)acetamide (1q): Cp*OMeRu(antracene)PF_6 (2 mg, 1 mol%, 0.0034 mmol), acetamide (20 mg, 1 eq, 0.34 mmol) and cyclopropanecarboxaldehyde (0.025 mL, 1 eq, 0.34 mmol) were dissolved in diethyl ether (0.2 mL). The autoclave was sealed, flushed three times with 10 atm of CO, and then charged with 30 atm CO. The reactor was placed into an oil bath preheated to 160 °C. After 22 h the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred into a flask, and the autoclave was washed with dichloromethane (2x1mL); combined solvents were removed on a rotary evaporator. 25% yield by NMR.

^{1}H NMR (400 MHz, CDCl3) δ 5.63 (s, 1H), 3.09 (dd, J = 7.0, 5.6 Hz, 2H), 1.98 (s, 3H), 1.03 – 0.88 (m, 1H), 0.55 – 0.46 (m, 2H), 0.22 – 0.15 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 44.6, 23.5, 10.8, 3.5.

Acknowledgements

We thank the Russian Foundation for Basic Research (grant No. 15-03-02548 A) and the Council of the President of the Russian Federation (Grant for Young Scientists No. МК-520.2017.3) for the financial support. O.C. and D.C. thanks the Ministry of Education and Science of the Russian Federation (Agreement number 02.a03.21.0008). The contribution of the Center for molecule composition studies of INEOS RAS is gratefully acknowledged.

[1] (a) O. I. Afanasyev, A. A. Tsygankov, D. L. Usanov, D. S. Perekalin, A. D. Samoylova, D. Chusov, *Synthesis* **2017,** *49*, 2640; (b) N. Z. Yagafarov, P. N. Kolesnikov, D. L. Usanov, V. V. Novikov, Y. V. Nelyubina, D. Chusov, *Chem. Commun.* **2016**, *52*, 1397; (c) P. N. Kolesnikov, N. Z. Yagafarov, D. L. Usanov, V. I. Maleev, D. Chusov, *Org. Lett.* **2015**, *17*, 173.

[2] (a) A. de la Torre, D. Kaiser, N. Maulide, *J. Am. Chem. Soc.* **2017**, *139*, 6578; (b) E. M. Budynina, K. L. Ivanov, I. D. Sorokin, M. Y. Melnikov, *Synthesis* **2017**, *49*, 3035; (c) S. B. Lawrenson, R. Arav, M. North, *Green Chem.* **2017**, *19*, 1685; (d) L. Gonnet, T. Tintillier, N. Venturini, L. Konnert, J.-F. Hernandez, F. Lamaty, G. Laconde, J. Martinez, E. Colacino, *ACS Sustain. Chem. Eng.* **2017**, *5*, 2936; (e) A. Yalymov, A. Bilyachenko, M. Levitsky, A. Korlyukov, V. Khrustalev, L. Shul'pina, P.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

Dorovatovskii, M. Es'kova, F. Lamaty, X. Bantreil, B. Villemejeanne, J. Martinez, E. Shubina, Y. Kozlov, G. Shul'pin, *Catalysts* **2017**, *7*, 101; (f) V. Tona, A. de la Torre, M. Padmanaban, S. Ruider, L. González, N. Maulide, *J. Am. Chem. Soc.* **2016**, *138*, 8348; (g) J. Liu, H. Li, A. Spannenberg, R. Franke, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2016**, *55*, 13544; (h) V. Porte, M. Thioloy, T. Pigoux, T.-X. Métro, J. Martinez, F. Lamaty, *Eur. J. Org. Chem.* **2016**, 3505; (i) A. N. Bilyachenko, M. M. Levitsky, A. I. Yalymov, A. A. Korlyukov, A. V Vologzhanina, Y. N. Kozlov, L. S. Shul'pina, D. S. Nesterov, A. J. L. Pombeiro, F. Lamaty, X. Bantreil, A. Fetre, D. Liu, J. Martinez, J. Long, J. Larionova, Y. Guari, A.L. Trigub, Y.V. Zubavichus, I.E. Golub, O.A. Filippov, E.S. Shubina, G.B. Shul'pin, *RSC Adv.* **2016**, *6*, 48165; (j) S. A. Ruider, N. Maulide, *Angew. Chem. Int. Ed.* **2015**, *54*, 13856; (k) M. Padmanaban, L. C. R. Carvalho, D. Petkova, J.-W. Lee, A. S. Santos, M. M. B. Marques, N. Maulide, *Tetrahedron* **2015**, *71*, 5994; (l) R. Shi, H. Zhang, L. Lu, P. Gan, Y. Sha, H. Zhang, Q. Liu, M. Beller, A. Lei, *Chem. Commun.* **2015**, *51*, 3247; (m) X. Bantreil, P. Navals, J. Martinez, F. Lamaty, *Eur. J. Org. Chem.* **2015**, 417; (n) A. N. Bilyachenko, M. S. Dronova, A. I. Yalymov, F. Lamaty, X. Bantreil, J. Martinez, C. Bizet, L. S. Shul'pina, A. A. Korlyukov, D. E. Arkhipov, M.M. Levitsky, E.S. Shubina, A.M. Kirillov, G.B. Shul'pin, *Chem. Eur. J.* **2015**, *21*, 8758; (o) B. Peng, D. Geerdink, C. Farès, N. Maulide, *Angew. Chem. Int. Ed.* **2014**, *53*, 5462; (p) X. Fang, H. Li, R. Jackstell, M. Beller, *J. Am. Chem. Soc.* **2014**, *136*, 16039; (q) D. Banerjee, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 1630; (r) X. Bantreil, N. Kanfar, N. Gehin, E. Golliard, P. Ohlmann, J. Martinez, F. Lamaty, *Tetrahedron* **2014**, *70*, 5093; (s) Y. Shi, A. V. Gulevich, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2014**, *53*, 14191; (t) J. Bonnamour, T.-X. Metro, J. Martinez, F. Lamaty, *Green Chem.* **2013**, *15*, 1116; (u) B. Peng, D. H. O'Donovan, I. D. Jurberg, N. Maulide, *Chem. A Eur. J.* **2012**, *18*, 16292; (v) T.-X. Metro, J. Bonnamour, T. Reidon, J. Sarpoulet, J. Martinez, F. Lamaty, *Chem. Commun.* **2012**, *48*, 11781; (w) X. Bantreil, C. Fleith, J. Martinez, F. Lamaty, *ChemCatChem* **2012**, *4*, 1922.

[3] For other examples of reductive amidation see: (a) S. Raoufmoghaddam, E. Drent, E. Bouwman, *Adv. Synth. Catal.* **2013**, *355*, 717; (b) B. G. Das, P. Ghorai, *Chem. Commun.* **2012**, *48*, 8276; (c) L. Rubio-Pérez, P. Sharma, F. J. Pérez-Flores, L. Velasco, J. L. Arias, A. Cabrera, *Tetrahedron* **2012**, *68*, 2342; (d) D. Dubé, A. A. Scholte, *Tetrahedron Lett.* **1999**, *40*, 2295.

[4] P.N. Kolesnikov, D.L. Usanov, K.M. Muratov, D. Chusov, *Org. Lett.* **2017**, *19*, 20, 5657.

[5] As of September 2017, the average price of rhodium is $1160 per ounce, while the average price of ruthenium is $65 per ounce. See http://www.platinum.matthey.com/prices/price-charts

[6] For the state-of-the art applications of carbon monoxide as a reducing agent see: (a) S. E. Denmark, M. Y. S. Ibrahim, A. Ambrosi, *ACS Catal.* **2017**, *7*, 613; (b) M. A. El-Atawy, F. Ferretti, F. Ragaini, *Eur. J. Org. Chem.* **2017**, 1902; (c) A. Ambrosi, S. E. Denmark, *Angew. Chem. Int. Ed.* **2016**, *55*, 12164; (d) A. Cimino, F. Moscatelli, F. Ferretti, F. Ragaini, S. Germain, J. Hannedouche, E. Schulz, L. Luconi, A. Rossin, G. Giambastiani, *New J. Chem.* **2016**, *40*, 10285; (e) H.-Q. Li, X. Liu, Q. Zhang, S.-S. Li, Y.-M. Liu, H.-Y. He, Y. Cao, *Chem. Commun.* **2015**, *51*, 11217; (f) J. W. Park, Y. K. Chung, *ACS Catal.* **2015**, *5*, 4846; (g) F. Ferretti, M. A. EL-Atawy, S. Muto, M. Hagar, E. Gallo, F. Ragaini, *Eur. J. Org. Chem.* **2015**, 5712; (h) S. E. Denmark, Z. D. Matesich, *J. Org. Chem.* **2014**, *79*, 5970; (i) F. Ferretti, F. Ragaini, R. Lariccia, E. Gallo, S. Cenini, *Organometallics* **2010**, *29*, 1465; (j) F. Ragaini, F. Ventriglia, M. Hagar, S. Fantauzzi, S. Cenini, *Eur. J. Org. Chem.* **2009**, 2185; (k) F. Ragaini, M. Gasperini, S. Cenini, L. Arnera, A. Caselli, P. Macchi, N. Casati, *Chem. Eur. J.* **2009**, *15*, 8064; (l) F. Ragaini, *Dalt. Trans.* **2009**, 6251; (m) F. Ragaini, S. Cenini, S. Tollari, G. Tummolillo, R. Beltrami, *Organometallics* **1999**, *18*, 928; (n) S. Cenini, F. Ragaini, S. Tollari, D. Paone, *J. Am. Chem. Soc.* **1996**, *118*, 11964.

[7] (a) D. S. Perekalin, A. R. Kudinov, *Coord. Chem. Rev.* **2014**, *276*, 153; (b) D. S. Perekalin, N. V. Shvydkiy, Y. V. Nelyubina, A. R. Kudinov, *Mend. Commun.* **2015**, *25*, 29; (c) D. S. Perekalin, E. E. Karslyan, E. A. Trifonova, A. I. Konovalov, N. L. Loskutova, Y. V. Nelyubina, A. R. Kudinov, *Eur. J. Inorg. Chem.* **2013**, 481; (d) L. Hintermann, L. Xiao, A. Labonne, U. Englert, *Organometallics* **2009**, *28*, 5739.

[8] P. M. Maitlis, *Chem. Soc. Rev.* **1981**, *10*, 1.

[9] A. I. Konovalov, E. E. Karslyan, D. S. Perekalin, Y. V. Nelyubina, P. V. Petrovskii, A. R. Kudinov, *Mendeleev Commun.* **2011**, *21*, 163.

[10] S. Raoufmoghaddam, E. Drent, E. Bouwman, *Adv. Synth. Catal.* **2013**, *355* , 717.

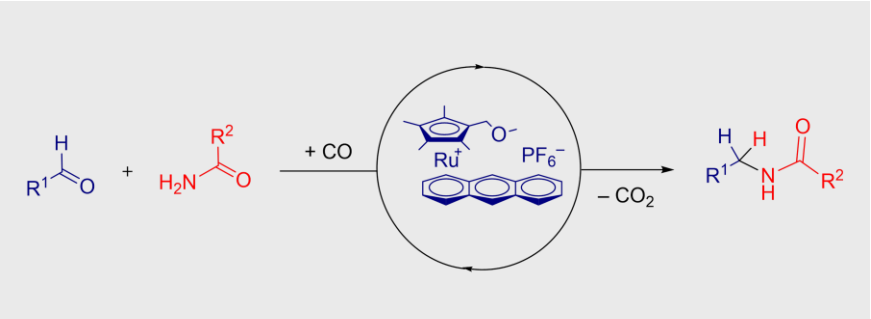
[11] A. F. Hill, *Angew. Chem. Int. Ed.* **2000**, *39*, 130.

Accepted Manuscript

WILEY-VCH

This article is protected by copyright. All rights reserved.

FULL PAPER



An amide will share hydrogen atom with an aldehyde

Key Topic*

*Niyaz Z. Yagafarov, Karim M. Muratov, Klim O. Biriukov, Dmitry L. Usanov, Olga Chusova, Dmitry S. Perekalin, Denis Chusov**

Page No. – Page No.

Ruthenium-catalyzed reductive amidation without an external hydrogen source

WILEY-VCH

Accepted Manuscript

This article is protected by copyright. All rights reserved.