Organic LETTERS

Letter

pubs.acs.org/OrgLett

Dichotomy of Atom-Economical Hydrogen-Free Reductive Amidation vs Exhaustive Reductive Amination

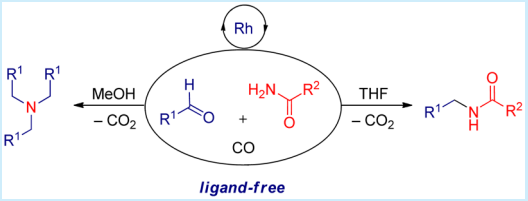
Pavel N. Kolesnikov,[†] Dmitry L. Usanov,[§] Karim M. Muratov,[†,‡] and Denis Chusov*[,†]

[†]A.N. Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences, Vavilova St. 28, Moscow 119991, Russian Federation

[‡]Dmitry Mendeleev University of Chemical Technology of Russia, Miusskaya Sq. 9, Moscow 125047, Russian Federation

Supporting Information

ABSTRACT: Rh-catalyzed one-step reductive amidation of aldehydes has been developed. The protocol does not require an external hydrogen source and employs carbon monoxide as a deoxygenative agent. The direction of the reaction can be altered simply by changing the solvent: reaction in THF leads to amides, whereas methanol favors formation of tertiary amines.

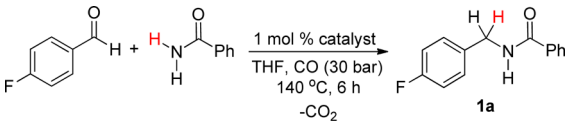


Amides are irreplaceable components of life, and therefore, the development of amide bond formation methods has received considerable attention over the past several decades. The growing interest in biocatalysis and biological properties of peptidomimetics, such as β-peptides, pseudopeptides, or peptoids, further supports the importance of new convenient, selective, and efficient ways to make amide bonds.[1] Standard protocols for amide synthesis commonly involve the use of stoichiometric amounts of agents for the activation of carboxylic acids, which is associated with additional costs, greater amounts of chemical waste, increased toxicity, and byproduct formation. It is therefore widely agreed that direct catalytic methods without the need for stoichiometric reagents comprise one of the greatest needs for the numerous research fields relying on chemical synthesis of amide bonds.[2,3]

We have recently reported novel methods for atom-economical and selective transformations of high synthetic value.[4] These include reductive alkylation, amination, and pyrrolidine synthesis, all of which do not require an external hydrogen source; instead, carbon monoxide can be efficiently employed as a deoxygenative agent.[5] We have shown that this approach can be more selective than conventional reductive protocols[6] and can provide access to compounds which are difficult to prepare otherwise.[7] Herein, we report an expansion of the concept to a fundamentally different type of chemistry on the example of one-step Rh-catalyzed reductive amidation of aldehydes without an external hydrogen source.

We began our studies with the model reaction between benzamide and *p*-fluorobenzaldehyde (Table 1). Initially, a number of rhodium metal complexes were screened, among which rhodium(II) acetate showed the most promising catalytic activity (Table 1, entries 1–5); other rhodium complexes demonstrated inferior performance. We then tested a variety of reaction media (including solvent-free conditions; Table 1, entries 6–18). Conducting the reaction in dry THF and dry ethyl acetate furnished the product in 82% and 75% yield,

Table 1. Catalyst and Solvent Optimization for the Preparation of Secondary Amides from Benzamide and *p*-Fluorobenzaldehyde



entry	catalyst	solvent	yield[a] (%)
1	$Rh_2(OAc)_4$	THF[b]	82
2	$CpRh(CO)I_2$	THF[b]	32
3	$[Rh(CO)_2Cl]_2$	THF[b]	60
4	$[(cod)RhCl]_2$	THF[b]	79
5	$RhCl_3$	THF[b]	<5
6	$Rh_2(OAc)_4$	water	13
7	$Rh_2(OAc)_4$	butanol-1	21
8	$Rh_2(OAc)_4$	ethanol	35
9	$Rh_2(OAc)_4$	methanol	40
10	$Rh_2(OAc)_4$	solvent-free	39
11	$Rh_2(OAc)_4$	MeCN	41
12	$Rh_2(OAc)_4$	MeCN[b]	45
13	$Rh_2(OAc)_4$	Et_2O	41
14	$Rh_2(OAc)_4$	toluene	45
15	$Rh_2(OAc)_4$	CH_2Cl_2	56
16	$Rh_2(OAc)_4$	EtOAc	60
17	$Rh_2(OAc)_4$	EtOAc[b]	75
18	$Rh_2(OAc)_4$	THF	50

[a]Yields were determined by NMR with internal standard. [b]Particularly dry solvents were used: 87 ppm of water in THF, 48 ppm of water in EtOAc, 15 ppm of water in MeCN.

respectively. The effect of the reaction temperature was substrate-dependent: for benzamide increasing the temperature

Received: September 8, 2017

DOI: 10.1021/acs.orglett.7b02821
Org. Lett. XXXX, XXX, XXX–XXX

led to higher yield; however, acetamide showed the opposite trend with lower yields at the temperatures above 140 °C. With the optimized conditions in hand, we proceeded to test a representative range of substrates (Figure 1).

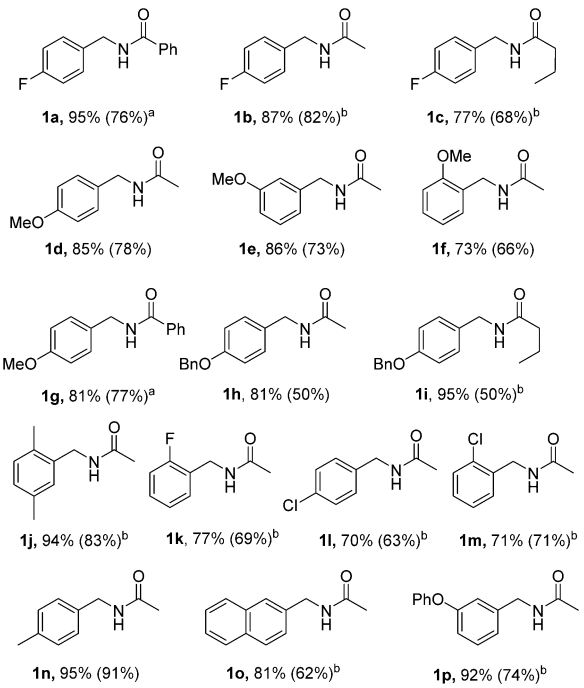


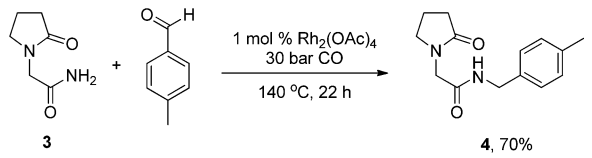
Figure 1. Investigation of the substrate scope for the Rh-catalyzed preparation of amides. 1:1 ratio of reactants, 1 mol % $Rh_2(OAc)_4$, THF, 30 bar CO, 140 °C, 22 h. Yields were determined by NMR with internal standard. Isolated yields are shown in parentheses. (a) 160 °C. (b) 1.5 equiv of the amide was used.

Good-to-excellent yields were observed for both electron-rich and electron-deficient aromatic aldehydes with various substitution patterns (**1a**–**p**). The benzyloxy moiety was shown to be stable under the reaction conditions; products **1h** and **1i** were isolated in 50% yield. Aliphatic amides worked as well as aromatic ones; generally, aromatic amides furnished higher yields at 160 °C, while aliphatic substrates reacted better at 140 °C.

We exemplified the practical significance of the developed methodology by implementation thereof into a simple one-step modification of a pharmaceutically important compound. Piracetam **3** is the parent compounds of the racetam family of drugs, which includes anticonvulsant (e.g., seletracetam, brivaracetam, levetiracetam, etc.) and nootropic agents (e.g., oxiracetam, phenylpiracetam). Substitution at the amide moiety is known to be useful for pharmaceutical activity (e.g., pramiracetam, fasoracetam, coluracetam). Our protocol allows convenient N-functionalization of piracetam to obtain compound **4** in 70% yield (Scheme 1).

We found that switching to 3:1 aldehyde/amide ratio and changing the solvent from THF to methanol leads to formation of symmetric tertiary amines. These compounds can be very useful as extractants[8] or ligands for catalytic processes;[9] however, they are rarely prepared directly from aldehydes. Previous reports[10] required the use of borohydride reductants and sometimes strictly anhydrous conditions.[11] We obtained good yields for the products with various functional groups (Figure 2). On the contrary, *o*-/*p*-alkoxy-substituted aldehydes

Scheme 1. Application of the Developed Methodology to the Modification of Piracetam



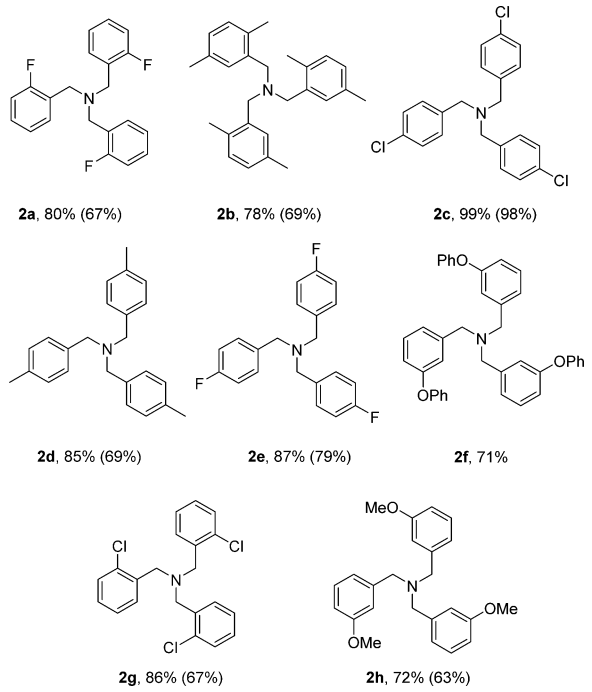


Figure 2. Investigation of the substrate scope for the Rh-catalyzed preparation of tertiary amines. 3 equiv of aldehyde and 1 equiv of acetamide were used, 0.5 mol % of $Rh_2(OAc)_4$, methanol, 30 bar CO, 130 °C, 22 h. Yields were determined by NMR with internal standard. Isolated yields are shown in parentheses.

showed poor results. Whereas the central nitrogen atom naturally comes from the starting amide, at the moment we still have somewhat limited understanding of the mechanistic details of this unusual process. Further studies in this direction are currently ongoing and will be reported in due course. A plausible mechanistic scenario is shown in Figure 3. This scheme is consistent with all our previous observations[4a] and experiments with deuterium labeling: when methanol-d_4 was employed in the reaction between *p*-tolualdehyde and benzamide, methyl-d_3 benzoate was detected as a product (see the Supporting Information).

In summary, we developed a highly efficient method for one-step preparation of secondary amides from a variety of aldehydes and primary amides. The reaction does not require an external hydrogen source and employs carbon monoxide as a deoxygenative agent, which renders our method more atom-economical in comparison to existing synthetic alternatives. The direction of the reaction can be changed to the synthesis of symmetric tertiary amines simply by changing the solvent from tetrahydrofuran to methanol. The synthetic utility of the developed method was exemplified by modification of piracetam, the parent member of a wide family of pharmaceuticals.

DOI: 10.1021/acs.orglett.7b02821
Org. Lett. XXXX, XXX, XXX−XXX

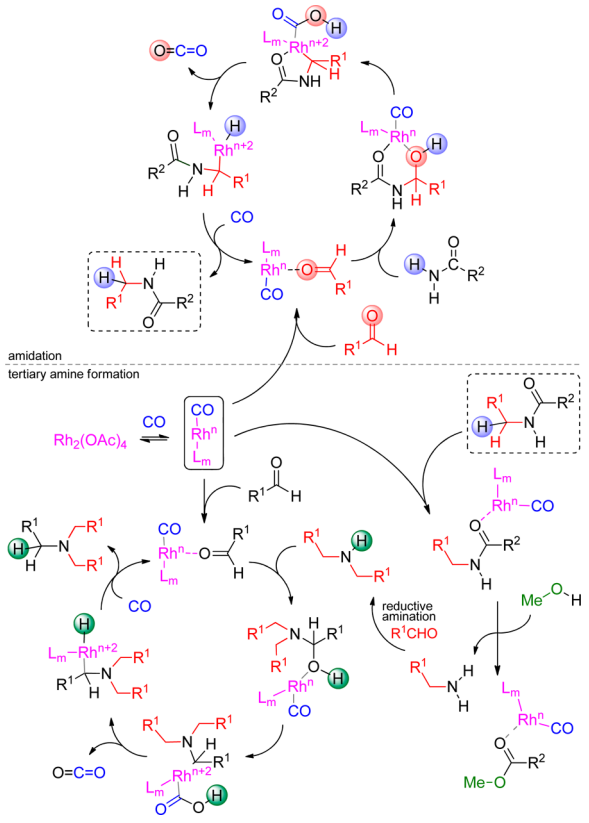


Figure 3. Possible mechanisms of reductive amidation and exhaustive reductive amination.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02821.

Detailed experimental procedures and full spectroscopic data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chusov@ineos.ac.ru, denis.chusov@gmail.com.

ORCID

Denis Chusov: 0000-0001-6770-5484

Present Address

§(D.L.U.) Harvard University, Department of Chemistry and Chemical Biology, 12 Oxford Street, Cambridge, MA 02138 (USA).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The work was financially supported by the Russian Science Foundation (grant no. 16-13-10393). The contribution of the Center for Molecule Composition Studies of INEOS RAS is gratefully acknowledged.

■ REFERENCES

(1) (a) Zultanski, S. L.; Zhao, J.; Stahl, S. S. *J. Am. Chem. Soc.* **2016**, *138* (20), 6416. (b) Xu, T.; Sha, F.; Alper, H. *J. Am. Chem. Soc.* **2016**, *138* (20), 6629. (c) Chung, S.; Sach, N.; Choi, C.; Yang, X.; Drozda, S. E.; Singer, R. A.; Wright, S. W. *Org. Lett.* **2015**, *17* (11), 2848. (d) Fang, X.; Li, H.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* **2014**, *136* (45), 16039. (e) Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2014**, *136* (20), 7253. (f) Matsumura, T.; Nakada, M. *Tetrahedron Lett.* **2014**, *55* (10), 1829. (g) Raoufmoghaddam, S.; Drent, E.; Bouwman, E. *ChemSusChem* **2013**, *6* (9), 1759. (h) Raoufmoghaddam, S.; Drent, E.; Bouwman, E. *Adv. Synth. Catal.* **2013**, *355*, 717. (i) Rubio-Perez, L.; Sharma, P.; Perez-Flores, F. J.; Velasco, L.; Arias, J. L.; Cabrera, A. *Tetrahedron* **2012**, *68*, 2342. (j) Das, B. G.; Ghorai, P. *Chem. Commun.* **2012**, *48* (66), 8276. (k) Dube, D.; Scholte, A. A. *Tetrahedron Lett.* **1999**, *40*, 2295. (l) Fache, F.; Jacquot, L.; Lemaire, M. *Tetrahedron Lett.* **1994**, *35* (20), 3313.

(2) For nontraditional strategies for amide synthesis, see: (a) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471. (b) Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405. (c) García-Álvarez, R.; Crochet, P.; Cadierno, V. *Green Chem.* **2013**, *15*, 46. (d) Park, J. H.; Kim, S. Y.; Kim, S. M.; Chung, Y. K. *Org. Lett.* **2007**, *9* (13), 2465.

(3) For other amides modification, see: (a) Zhou, Y.; Yuan, J.; Yang, Q.; Xiao, Q.; Peng, Y. *ChemCatChem* **2016**, *8* (13), 2178. (b) Wan, J.-P.; Jing, Y. *Beilstein J. Org. Chem.* **2015**, *11*, 2209. (c) Shi, Y.; Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2014**, *53* (51), 14191.

(4) (a) Chusov, D.; List, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 5199. (b) Kolesnikov, P. N.; Usanov, D. L.; Barablina, E. A.; Maleev, V. I.; Chusov, D. *Org. Lett.* **2014**, *16*, 5068. (c) Afanasyev, O. I.; Tsygankov, A. A.; Usanov, D. L.; Chusov, D. *Org. Lett.* **2016**, *18*, 5968.

(5) For the state-of-the art applications of carbon monoxide as a reducing agent, see: (a) Denmark, S. E.; Ibrahim, M. Y. S.; Ambrosi, A. *ACS Catal.* **2017**, *7* (1), 613. (b) El-Atawy, M. A.; Ferretti, F.; Ragaini, F. *Eur. J. Org. Chem.* **2017**, *2017* (14), 1902. (c) Ambrosi, A.; Denmark, S. E. *Angew. Chem., Int. Ed.* **2016**, *55* (40), 12164. (d) Cimino, A.; Moscatelli, F.; Ferretti, F.; Ragaini, F.; Germain, S.; Hannedouche, J.; Schulz, E.; Luconi, L.; Rossin, A.; Giambastiani, G. *New J. Chem.* **2016**, *40* (12), 10285. (e) Li, H.-Q.; Liu, X.; Zhang, Q.; Li, S.-S.; Liu, Y.-M.; He, H.-Y.; Cao, Y. *Chem. Commun.* **2015**, *51*, 11217. (f) Park, J. W.; Chung, Y. K. *ACS Catal.* **2015**, *5*, 4846. (g) Ferretti, F.; EL-Atawy, M. A.; Muto, S.; Hagar, M.; Gallo, E.; Ragaini, F. *Eur. J. Org. Chem.* **2015**, *2015*, 5712. (h) Denmark, S. E.; Matesich, Z. D. *J. Org. Chem.* **2014**, *79* (13), 5970. (i) Ferretti, F.; Ragaini, F.; Lariccia, R.; Gallo, E.; Cenini, S. *Organometallics* **2010**, *29* (6), 1465. (j) Denmark, S. E.; Nguyen, S. T. *Org. Lett.* **2009**, *11* (3), 781. (k) Ragaini, F.; Ventriglia, F.; Hagar, M.; Fantauzzi, S.; Cenini, S. *Eur. J. Org. Chem.* **2009**, *2009*, 2185. (l) Ragaini, F.; Gasperini, M.; Cenini, S.; Arnera, L.; Caselli, A.; Macchi, P.; Casati, N. *Chem. - Eur. J.* **2009**, *15* (32), 8064. (m) Ragaini, F. *Dalt. Trans* **2009**, *32*, 6251. (n) Ragaini, F.; Cenini, S.; Tollari, S.; Tummolillo, G.; Beltrami, R. *Organometallics* **1999**, *18* (5), 928. (o) Cenini, S.; Ragaini, F.; Tollari, S.; Paone, D. *J. Am. Chem. Soc.* **1996**, *118* (47), 11964.

(6) Afanasyev, O. I.; Tsygankov, A. A.; Usanov, D. L.; Perekalin, D. S.; Shvydkiy, N. V.; Maleev, V. I.; Kudinov, A. R.; Chusov, D. *ACS Catal.* **2016**, *6* (3), 2043.

(7) Yagafarov, N. Z.; Kolesnikov, P. N.; Usanov, D. L.; Novikov, V. V.; Nelyubina, Y. V.; Chusov, D. *Chem. Commun.* **2016**, *52*, 1397.

(8) (a) Kalidhasan, S.; Ganesh, M.; Sricharan, S.; Rajesh, N. *J. Hazard. Mater.* **2009**, *165*, 886. (b) Rajesh, N.; Subramanian, M. S. *J. Hazard. Mater.* **2006**, *B135*, 74.

(9) (a) Whiteoak, C. J.; Kielland, N.; Laserna, V.; Escudero-Adan, E. C.; Martin, E.; Kleij, A. W. *J. Am. Chem. Soc.* **2013**, *135* (4), 1228. (b) Paley, D. W.; Sedbrook, D. F.; Decatur, J.; Fischer, F. R.; Steigerwald, M. L.; Nuckolls, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 4591. (c) Chandrasekaran, A.; Day, R. O.; Holmes, R. R. *J. Am. Chem. Soc.* **2000**, *122*, 1066.

(10) For examples, see: (a) Jyothish, K.; Wang, Q.; Zhang, W. *Adv. Synth. Catal.* **2012**, *354*, 2073. (b) Glasson, C. R. K.; Meehan, G. V.;

DOI: 10.1021/acs.orglett.7b02821
Org. Lett. XXXX, XXX, XXX−XXX

Motti, C. A.; Clegg, J. K.; Davies, M. S.; Lindoy, L. F. *Aust. J. Chem.* **2012**, *65*, 1371.
(11) Lee, B. S.; Kim, J. H.; Nam, T. K.; Jang, D. O. *Bull. Korean Chem. Soc.* **2015**, *36*, 1912.

DOI: 10.1021/acs.orglett.7b02821
Org. Lett. XXXX, XXX, XXX−XXX