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Nitrogen ligand influence on the CO-assisted ruthenium-catalyzed reductive amination

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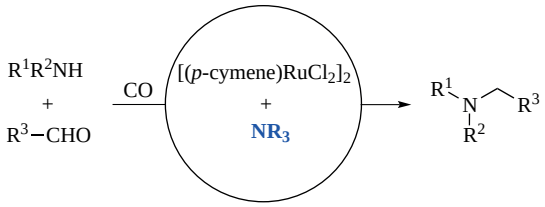
A representative set of amines and N-heterocycles was applied as additives in the CO-assisted Ru-catalyzed reductive amination of *p*-anisaldehyde with *p*-anisidine. Among the tested ligands, pyridine caused a strong activation for low active aliphatic substrates while bidentate heterocyclic ligands possess significant inhibition of catalyst for the majority of substrates.



Keywords: ruthenium, nitrogen-containing ligands, reductive amination, amines, aldehydes, carbon monoxide, catalysis.

Dedicated to the anniversary of Professor Irina P. Beletskaya in recognition of her great contribution to the development of catalysis with metal complexes.

Amines are used in preparation of dyes,[1] polymeric materials,[2] organocatalysts,[3,4] and many other fields.[5–13] A particular interest the amine functionality presents as an almost indispensable fragment of pharmaceuticals where secondary and tertiary amines are common.[14,15] Substituted amines can be synthesized by the alkylation of the parent amines with alkyl halides or sulfonates including the cross-coupling versions.[16,17] The reductive amination reaction presents an alternative method [Figure 1(*a*)].[18] It allows one to alkylate starting amine with an aldehyde employing hydrogen,[19,20] borohydrides,[21] and some other reducing agents. Both of these approaches may suffer either from a low selectivity and hazardous reagents or from an immense amount of byproducts and low functional group-tolerance. So the development of selective and 'green' synthetic methods is highly demanded.

Carbon monoxide was found to be an effective reductant for the reductive amination[22–26] and related processes.[27–29] The CO-assisted reaction leads selectively to the desired amine producing CO_2 as the only secondary product. It possesses a high tolerance to a wide range of functional groups allowing preparation of complex amines. The above mentioned virtues of CO were clearly demonstrated through the comparison with other popular reductants.[30] The reaction needs a noble metal-based catalyst (Rh, Ru, Ir or Os) to proceed.[26,31–35] Taking in mind the high activity and comparably low price of ruthenium, its compounds could be considered as most privileged catalysts for the titled process.[36] Recently, Makarova *et al.* demonstrated the acceleration of the ruthenium-catalyzed CO-assisted reductive amination by phosphine ligands [Figure 1(*b*)].[37] Various phosphines and phosphites were tested and up to 6 times activation was observed for the reaction of aromatic amines with aldehydes or ketones in the presence of $(4\text{-}ClC_6H_4)_3P$. Apart from phosphines, N-ligands present another wide-spread class of ligands.[38–42] So the investigation of amine influence on the reductive amination with CO became the aim of this work [Figure 1(*c*)].

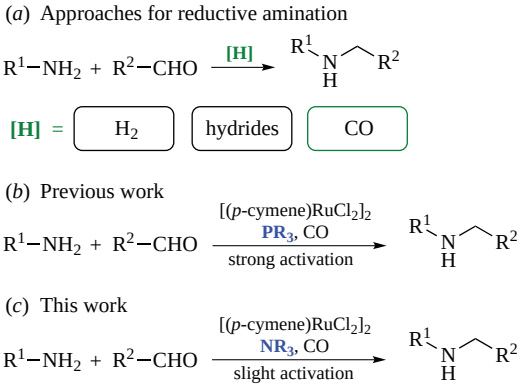
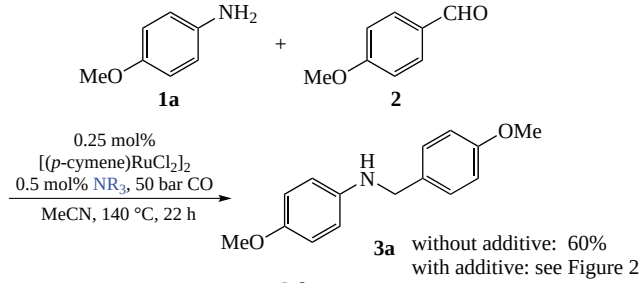


Figure 1 Approaches for the direct reductive amination.

We started our investigation from the comparison of the reaction performance in the presence of different N-containing additives. To catch their influence, the reaction conditions were chosen to provide a 60% yield of the product in the absence of additives. Various amines and heterocycles along with the non-coordinating bases were tested as ligands in the model reaction of *p*-anisidine and *p*-anisaldehyde (Scheme 1, Figure 2).



Scheme 1

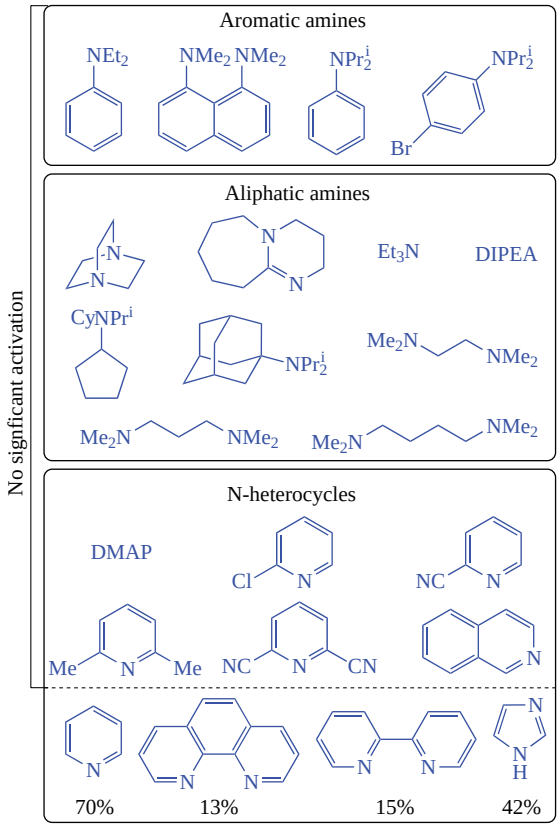


Figure 2 Influence of the 0.5 mol% additive on the yield of amine **3a** (for details, see Online Supplementary Materials).

According to Figure 2, the majority of additives did not significantly affect the reaction. While the blank reaction delivers the product in 60% yield, the addition of aromatic or aliphatic amines provides **3a** in 40–60% yield. As substrate **1a**, product **3a** and reaction intermediates (the hemiaminal or the Schiff base) being also amines compete with the additives for the ruthenium center bonding. Therefore, the 0.5 mol% loading of additives have no influence on the reaction performance. Amines like DIPEA, DBU and others have a minor negative impact on the product formation. It can be explained by a base-catalyzed shift of the imine–hemiaminal equilibrium toward a Schiff base formation.

Pyridine was found to be the only additive that accelerated the reaction (see Figure 2). The two features could be responsible for its behavior. First, pyridine possesses an optimal steric and electronic properties which provide an easier dissociation of the precatalyst dimer [(*p*-cymene)$RuCl_2$]$_2$. Pyridine stabilizes the catalyst without blocking the coordinative vacancies. Second, the basicity of pyridine is quite low (*e.g.*, pK_a value of protonated pyridine in MeCN is ~25 times lower than that of protonated imidazole[43]). So it should not alter the equilibrium between the hemiaminal and the Schiff base. Serious yield decrease was

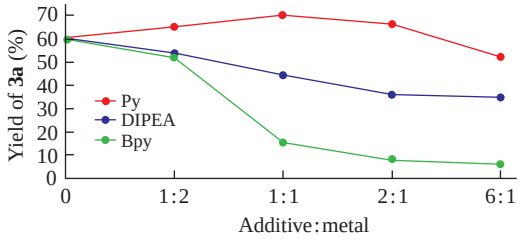


Figure 3 Effect of the additive loading on the performance of the reaction between compounds **1a** and **2** (see Scheme 1). Conditions: CO (50 bar), [(*p*-cymene)$RuCl_2$]$_2$ (0.25 mol%), amine additive (see abscissa), MeCN, 140 °C, 22 h.

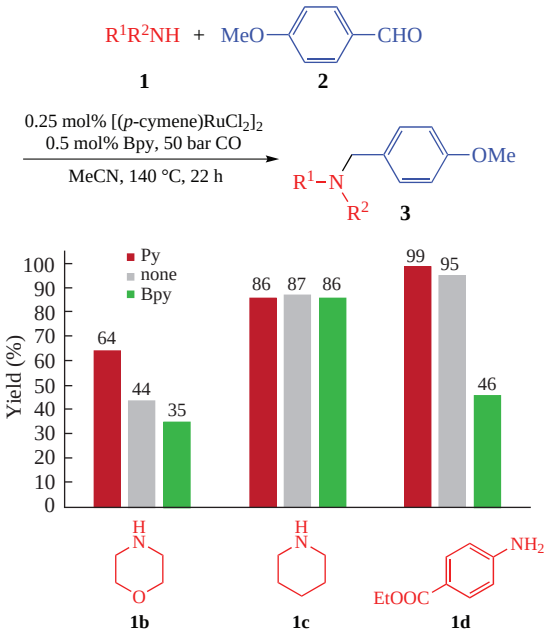


Figure 4 Influence of the additives on the amine **3** yield.

noted in the case of bidentate pyridine-like heterocycles (2,2′-bipyridine and phenanthroline). It indicates the strong coordination of these additives with ruthenium thus blocking the coordinative vacancies of metal.

Taking into account the competing of additives with the reactant for metal center, we then decided to change the metal to ligand ratio (Figure 3) for the reaction outlined in Scheme 1. The noticeable effect of additives on the reaction outcome was observed at additive/metal ratio = 1 : 1 (0.5 mol% of additive). The further raising of the pyridine amount up to additive/metal = 6 : 1 (3 mol% of additive) leads to the inhibition of the process. The maximum acceleration with pyridine as well as the strong inhibitory effect of bipyridine observed at the additive/metal ratio = 1 : 1 support the assumption that both heterocycles act as ligands. Monodentate pyridine promotes the dissociation of the ruthenium dimer [(*p*-cymene)$RuCl_2$]$_2$, while the bidentate bipyridine transforms the dimer into inert complexes. Notably, the negative effect of DIPEA on the reaction outcome increases smoothly with the increase of its loading.

Next we investigated the effect of additives in the reaction of *p*-anisaldehyde **2** with different substrates (Figure 4). Previously,[37] it was reported that phosphine ligands had no significant impact in reaction with aliphatic amines. Given that phosphines accelerate the model reaction much more efficiently than pyridine, we were surprised to observe a 1.5-fold higher yield of the reaction with morpholine **1b** when pyridine was added. Bipyridine slightly deactivates this reaction. The most nucleophilic piperidine **1c** reacted at the same rate regardless of the additives. The reaction of *p*-anisaldehyde with ethyl 4-aminobenzoate **1d** gave 95% yield without any additive and only 46% was reached in the presence of bipyridine.

To sum up, the influence of various N-containing additives acting as ligands or bases on ruthenium-catalyzed reductive amination without an external hydrogen source was investigated. Among various additives tested, the activation effect was observed only for pyridine. The plausible role of pyridine is to facilitate the dissociation of [(*p*-cymene)$RuCl_2$]$_2$ dimer. The suggested explanation is supported by the maximum activation observed at additive/metal = 1 : 1. While bidentate pyridine-like heterocycles inhibited the reaction by blocking the ruthenium center vacancies, the strong bases like DIPEA decreased the reaction yield through the shift of hemiaminal–imine equilibrium.

The influence of both activating and inhibiting additives weakens as the reactivity of the substrate increases.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.02.008.

References

1 S. Benkhaya, S. M'rabet and A. El Harfi, *Heliyon*, 2020, **6**, e03271.
2 V. Kuksa, R. Buchan and P. Kong Thoo Lin, *Synthesis*, 2000, 1189.
3 S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178.
4 P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138.
5 P. Roose, K. Eller, E. Henkes, R. Rossbacher and H. Höke, in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, 2015, https://doi.org/10.1002/14356007.a02_001.pub2.
6 Y. Shirota, *J. Mater. Chem.*, 2005, **15**, 75.
7 V. M. Korshunov, T. N. Chmovzh, G. R. Chkhetiani, I. V. Taydakov and O. A. Rakitin, *Mendeleev Commun.*, 2022, **32**, 371.
8 K. P. Trainov, R. F. Salikov, Yu. N. Luponosov, P. S. Savchenko, A. L. Mannanov, S. A. Ponomarenko, D. N. Platonov and Yu. V. Tomilov, *Mendeleev Commun.*, 2019, **29**, 304.
9 P. S. Gribov, M. V. Mikhailova, T. S. Kon'kova, Yu. N. Matyushin and A. B. Sheremetev, *Mendeleev Commun.*, 2022, **32**, 218.
10 A. N. Philippova, D. V. Vorobyeva, T. P. Vasilyeva, A. K. Mailyan, P. S. Gribanov and S. N. Osipov, *Mendeleev Commun.*, 2022, **32**, 260.
11 V. V. Levin, M. I. Struchkova and A. D. Dilman, *Mendeleev Commun.*, 2017, **27**, 139.
12 E. V. Pospelov, Y. D. Boyko, S. L. Ioffe and A. Y. Sukhorukov, *Adv. Synth. Catal.*, 2022, **364**, 2557.
13 M. Jakubczyk, S. Mkrtchyan, M. Shkoor, S. Lanka, Š. Budzák, M. Iliaš, M. Skoršepa and V. O. Iaroshenko, *J. Am. Chem. Soc.*, 2022, **144**, 10438.
14 O. I. Afanasyev, E. Kuchuk, D. L. Usanov and D. Chusov, *Chem. Rev.*, 2019, **119**, 11857.
15 A. Y. Bobrova, M. A. Novikov and Y. V. Tomilov, *Org. Biomol. Chem.*, 2021, **19**, 4678.
16 R. N. Salvatore, C. H. Yoon and K. W. Jung, *Tetrahedron*, 2001, **57**, 7785.
17 P. S. Gribanov, A. N. Philippova, M. A. Topchiy, L. I. Minaeva, A. F. Asachenko and S. N. Osipov, *Molecules*, 2022, **27**, 1999.
18 A. Yu. Sukhorukov, *Front. Chem.*, 2020, **8**, 595246.
19 T. Irrgang and R. Kempe, *Chem. Rev.*, 2020, **120**, 9583.
20 K. Murugesan, T. Senthamarai, V. G. Chandrashekhar, K. Natte, P. C. J. Kamer, M. Beller and R. V. Jagadeesh, *Chem. Soc. Rev.*, 2020, **49**, 6273.
21 A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff and R. D. Shah, *J. Org. Chem.*, 1996, **61**, 3849.
22 A. Ambrosi and S. E. Denmark, *Angew. Chem., Int. Ed.*, 2016, **55**, 12164.
23 J. W. Park and Y. K. Chung, *ACS Catal.*, 2015, **5**, 4846.
24 P. Zhou, C. Yu, L. Jiang, K. Lv and Z. Zhang, *J. Catal.*, 2017, **352**, 264.
25 M.-M. Zhu, L. Tao, Q. Zhang, J. Dong, Y.-M. Liu, H.-Y. He and Y. Cao, *Green Chem.*, 2017, **19**, 3880.
26 D. Chusov and B. List, *Angew. Chem., Int. Ed.*, 2014, **53**, 5199.
27 S. E. Denmark, M. Y. S. Ibrahim and A. Ambrosi, *ACS Catal.*, 2017, **7**, 613.
28 H.-Q. Li, X. Liu, Q. Zhang, S.-S. Li, Y.-M. Liu, H.-Y. He and Y. Cao, *Chem. Commun.*, 2015, **51**, 11217.
29 F. Ferretti, E. Barraco, C. Gatti, D. R. Ramadan and F. Ragaini, *J. Catal.*, 2019, **369**, 257.
30 E. Podyacheva, O. I. Afanasyev, A. A. Tsygankov, M. Makarova and D. Chusov, *Synthesis*, 2019, **51**, 2667.
31 K. O. Biriukov, M. M. Vinogradov, O. I. Afanasyev, D. V Vasilyev, A. A. Tsygankov, M. Godovikova, Y. V Nelyubina, D. A. Loginov and D. Chusov, *Catal. Sci. Technol.*, 2021, **11**, 4922.
32 A. R. Fatkulin, O. I. Afanasyev, A. A. Tsygankov and D. Chusov, *J. Catal.*, 2022, **405**, 404.
33 A. P. Moskovets, D. L. Usanov, O. I. Afanasyev, V. A. Fastovskiy, A. P. Molotkov, K. M. Muratov, G. L. Denisov, S. S. Zlotskii, A. F. Smol'yakov, D. A. Loginov and D. Chusov, *Org. Biomol. Chem.*, 2017, **15**, 6384.
34 S. Runikhina and D. Chusov, *Mendeleev Commun.*, 2021, **31**, 781.
35 O. I. Afanasyev, I. Cherkashchenko, A. Kuznetsov, F. Kliuev, S. Semenov, O. Chusova, G. Denisov and D. Chusov, *Mendeleev Commun.*, 2020, **30**, 112.
36 P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev.*, 2019, **119**, 2192.
37 M. Makarova, O. I. Afanasyev, F. Kliuev, Y. V. Nelyubina, M. Godovikova and D. Chusov, *J. Organomet. Chem.*, 2021, **941**, 121806.
38 A. Kumbhar, *J. Organomet. Chem.*, 2017, **848**, 22.
39 E. S. Vlasenko, I. A. Nikovskiy, Yu. V. Nelyubina, A. A. Korlyukov and V. V. Novikov, *Mendeleev Commun.*, 2022, **32**, 320.
40 L. A. Bulygina, N. S. Khrushcheva, K. A. Lyssenko and A. S. Peregudov, *Mendeleev Commun.*, 2022, **32**, 331.
41 A. A. Fateeva, I. A. Shutkov, D. M. Mazur, O. N. Kovaleva, E. R. Milaeva and A. A. Nazarov, *Mendeleev Commun.*, 2022, **32**, 186.
42 D. A. Bardonov, L. N. Puntus, I. V. Taidakov, E. A. Varaksina, K. A. Lyssenko, I. E. Nifant'ev and D. M. Roitershtein, *Mendeleev Commun.*, 2022, **32**, 198.
43 M. Lõkov, S. Tshepelevitsh, A. Heering, P. G. Plieger, R. Vianello and I. Leito, *Eur. J. Org. Chem.*, 2017, 4475.

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