Young Career Focus: Professor Denis Chusov (Nesmeyanov Institute, Russian Federation)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Professor Denis Chusov (Nesmeyanov Institute, Russian Federation).

Biographical Sketch

Prof. D. Chusov

Denis Chusov graduated from the Moscow Chemical Lyceum (Russian Federation) and obtained his undergraduate degree from the Higher Chemical College of the Russian Academy of Sciences (Russian Federation). He defended his Ph.D. thesis under the supervision of Prof. Yuri N. Belokon at the Nesmeyanov Institute of Organoelement Compounds in Moscow (Russian Federation). He then worked as a visiting researcher at Newcastle University (UK) with Prof. Michael North and at Universite? Paris-Sud 11 (France) with Prof. Henri Kagan. His postdoctoral studies were conducted at Max-Planck-Institut fu?r Kohlenforschung (Germany) with Prof. Benjamin List. He is currently an Associate Professor at the Nesmeyanov Institute (Russian Federation).

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Prof. D. Chusov The development of highly effective catalytic systems is equally important for core academic research and industrial applications. However, nowadays the progress is typically achieved by the preparation of more structurally complex and expensive catalysts. The finding of application of simple catalysts for new reactions is one of the goals that we are focused on. Other areas of our research involve the search for new ways of activation of simple catalysts to gain higher activity in known reactions. Currently research in our group focuses on developing new selective reductive addition reactions.

SYNFORM *When did you get interested in synthesis?*

Prof. D. Chusov I believe that mathematics is the first subject which requires thinking. I have always been interested in mathematics. Once I went to a municipal mathematics olympiad and won a prize. After that, I received some invitations to various mathematics schools. My friend suggested I attend evening classes at the Moscow Chemical Lyceum; I went there and decided to enroll at the Lyceum for a full-time study. To do this, I needed to pass the entrance exams and although I got a good grade in mathematics, I failed the chemistry exam. Therefore, I needed to study chemistry over the summer to pass the exam resit in autumn.

At the Chemical Lyceum I studied many subjects including mathematics, chemistry, and human sciences. At that time, I figured out that I am very interested in organic chemistry. Fortunately, a unique situation was created in the Chemical Lyceum: students were able to carry out research in the real research institutes, so I was given an opportunity to participate in the work of a research laboratory and carry out a project in organic synthesis when I was only 16 years old.

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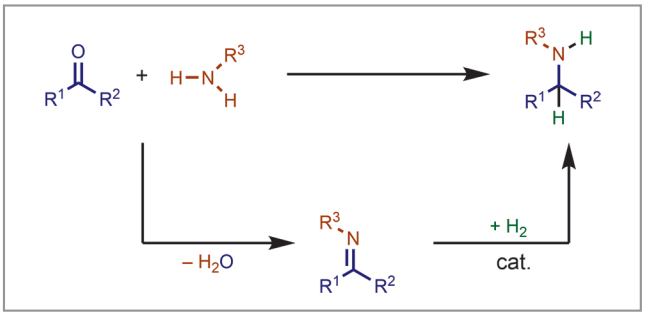
SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

Prof. D. Chusov Seems like organic chemistry still has a special place amongst the interests of students in chemical universities and schools. In this area the connection between science and art becomes more visible. It is shown in the beauty of certain syntheses, in the elegance of obtaining certain compounds, in the uniqueness of many reactions. It can be said that in organic synthesis, some kind of design at the smallest size of the objects is possible. Unfortunately, we cannot create the desired new objects with a certain consistency at the sub-molecular level. As for the prospect of organic synthesis, it is hard to imagine that in the future, medicinal chemistry or materials science can be developed without an organic or organoelement compound.

SYNFORM *Could you tell us more about your group's areas of research and your aims?*

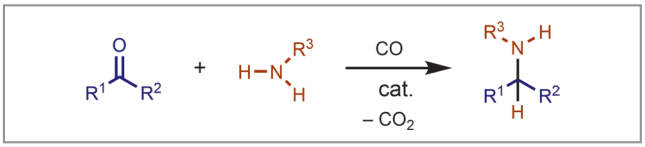
Prof. D. Chusov The main research area of our group focuses on reductive additions without an external hydrogen source. Let's look at this idea on the example of reductive amination reaction. I like this reaction very much, as the majority of medicinal chemists do, because it is a very convenient method of amine synthesis. It is a reliable method which can be applied to a wide variety of substrates. The starting materials are aldehydes or ketones and ammonia or amines. In industry, aldehydes are easily obtained from hydrocarbons, though even simple alcohols, like propanol, butanol and other terminal alcohols with higher molecular weight, are obtained from the corresponding aldehydes. On the other hand, aldehydes can be easily converted into various classes of chemical compounds.

The classical version of reductive amination involves the interaction of an aldehyde with an amine. After that we get a Schiff base and water (Scheme 1). Then molecular hydrogen with a catalyst is added to the Schiff base to obtain the target amine. Precise analysis shows that at the first step we take two hydrogen atoms from the molecules, and at the second step we add them again. That does not look like a very effecient idea, and it means that we can avoid using an external hydrogen source. Ideally, we can mix ammonia or an amine with a carbonyl compound and get a more substituted amine and oxygen (Scheme 2). However, in a reduction process it is not realistic to get an oxidizing agent such as oxygen in the end; therefore we need a reagent which is able to scavenge the oxygen atom and does not contain hydrogen atoms in it. For this purpose, we use carbon monoxide, a waste product of steel manufacturing (Scheme 3).



Scheme 1 Classical way of reductive amination

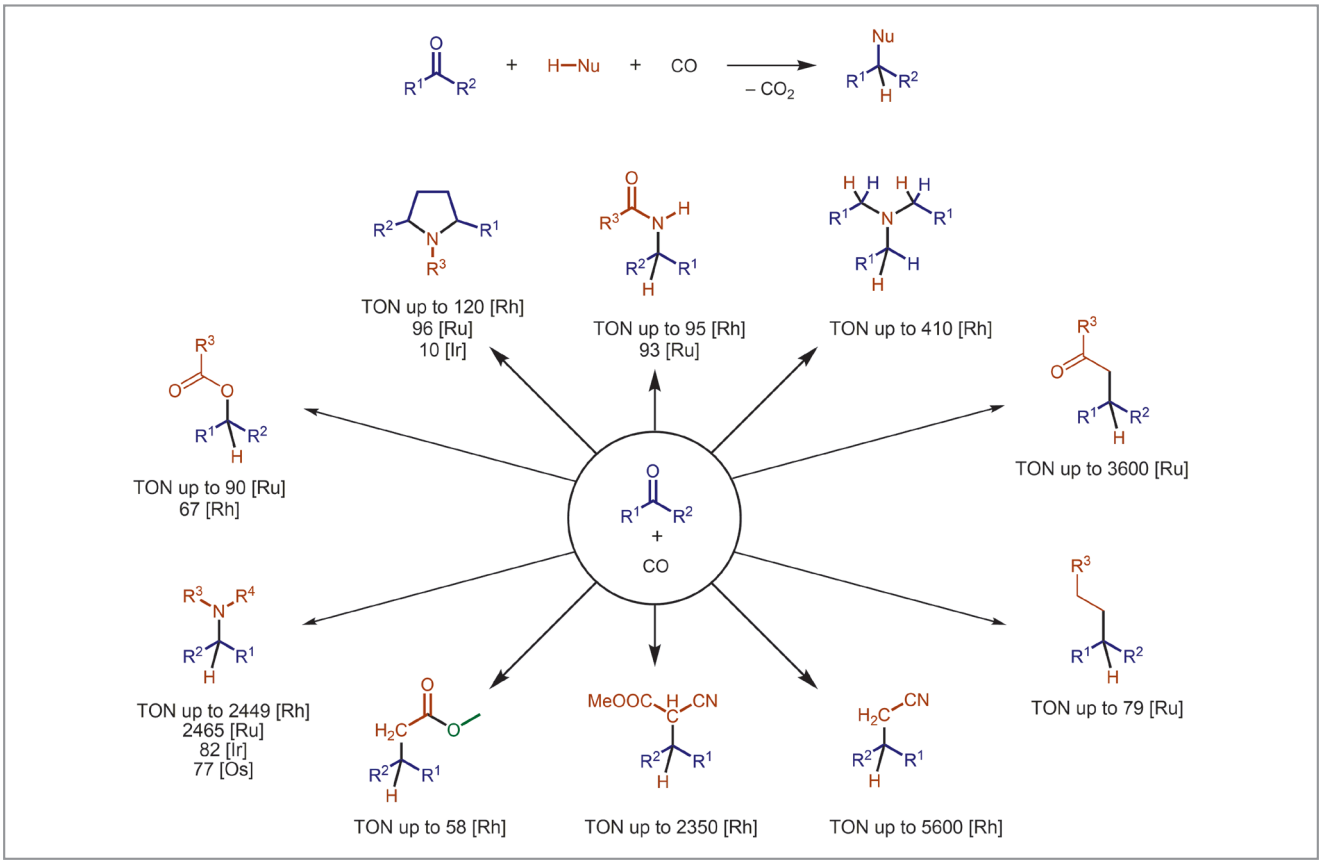
Scheme 2 Ideal way of reductive amination



Scheme 3 Reductive amination using carbon monoxide as a reducing agent

As a result, we developed even more than reductive amination protocols without an external hydrogen source (*Angew. Chem. Int. Ed.* **2014**, *53*, 5199–5201; *Org. Lett.* **2015**, *17*, 173–175; *Org. Biomol. Chem.* **2017**, *15*, 6384–6387). Interaction of any carbonyl compound with any hydrogen-containing nucleophile is in line with this concept (*Mendeleev Commun.* **2018**, *28*, 113–122). We showed that CH-acids and other CH-nucleophiles (like ketones with an α-hydrogen atom), amides, carboxylic acids can be applied in this protocol (Scheme 4). It is interesting that the method appeared to be very selective. Hydrogen and hydride agents can reduce not only various functional groups in target compounds (Table 1) (*ACS Catal.* **2016**, *6*, 2043–2046) but even the starting aldehydes and ketones, which then leads to a complete failure of the reaction (*Synthesis* **2019**, *51*, 2667–2677).

Moreover, using CO allowed us to synthesize tertiary sterically hindered amines via reductive amination (*Chem. Commun.* **2016**, *52*, 1397–1400). The classical approach with molecular hydrogen does not lead to the target amines since even reduction of an aromatic ring with hydrogen is easier than obtaining such hindered amines (Scheme 5). Even direct reductive amination of sterically hindered ketones like camphor is



Scheme 4 Reductive addition of different hydrogen-containing nucleophiles without an external hydrogen source

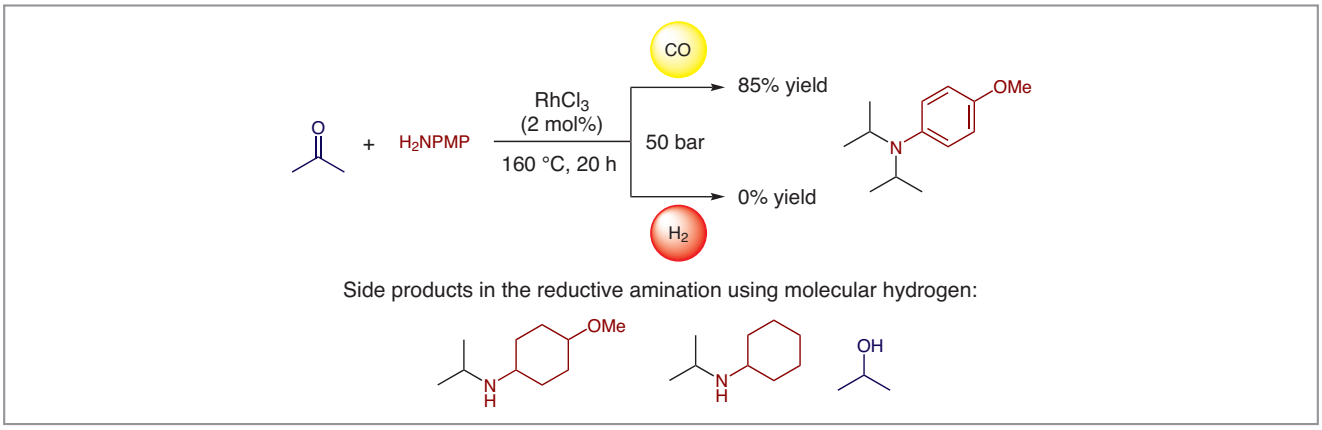
	H_2/Ni	H_2/Rh	$LiAlH_4$	$NaBH_4$	Rh/CO
R_2N-Cbz	✖	✖	✖	✔	✔
R_2N-$COCF_3$	✖	✔	✖	✖	✔
R_2N-Bn	✖	✖	✔	✔	✔
RO-Bn	✖	✔	✔	✔	✔
Ar-NO_2	✖	✖	✖	±	✔
Ar-CN	✖	✖	✖	±	✔
Ar-Br	✖	✔	±	✔	✔

Table 1 Functional group tolerance in the reductive amination reaction using different reducing agents

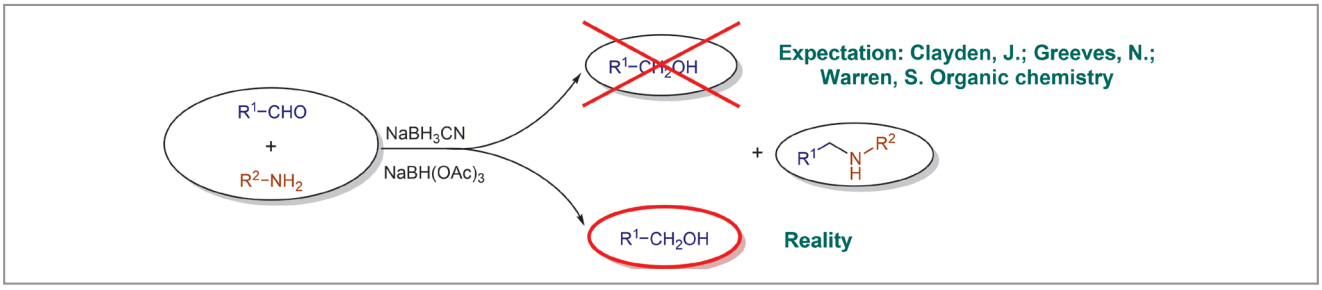
very challenging using classical reductive agents (*Org. Biomol. Chem.* **2017**, *15*, 10164–10166).

Notably, it is written in organic chemistry textbooks that for reductive amination reactions, special reducing agents exist. For example, sodium cyanoborohydride and triacetoxyborohydride selectively conduct this reaction since they do not reduce the C=O bond in an initial aldehyde (Scheme 6). However, when we read a scientific article, including the original article about sodium triacetoxyborohydride, we can see that even there the researchers show that these hydrides do reduce aldehydes.

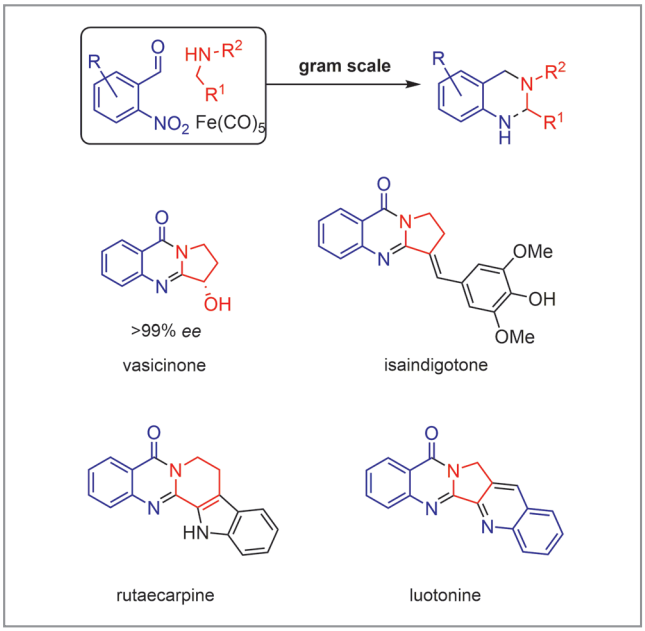
That is the reason I like our approach. It is very convenient since the reaction can be carried out without any solvent at low catalyst loadings if needed, and even at such conditions we can get nothing but the target compound in the reaction mixture at the end. Moreover, if you do not have access to carbon monoxide gas you can replace it with other non-hydrogen non-gaseous reducing agents such as metal carbonyls [e.g. iron carbonyl (*Org. Biomol. Chem.* **2017**, *15*, 10164–10166; *Eur. J. Org. Chem.* **2019**, 32–35)]. We used this approach for the total synthesis of different compounds (Scheme 7) (*J. Org. Chem.* **2020**, *85*, 9347–9360). For example, we designed the total synthesis of luotonin A from two simple compounds like nitrobenzaldehyde and hydroxyproline (Scheme 8).



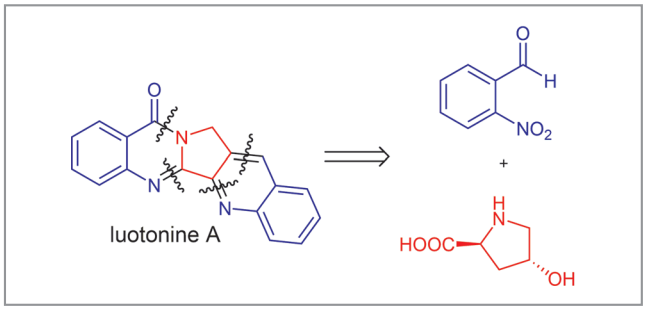
Scheme 5 Synthesis of tertiary sterically hindered amines using CO vs. H_2



Scheme 6 Advantages vs. challenge of reductive amination with sodium cyanoborohydride and sodium triacetoxyborohydride



Scheme 7 Total synthesis of vasicinone, isaindigotone, luotonin, and rutaecarpine based on reductive addition of amines to nitrobenzaldehydes without an external hydrogen source



Scheme 8 Retrosynthetic scheme of luotonin A

SYNFORM *What is your most important scientific achievement to date and why?*

Prof. D. Chusov My most significant achievement is that I chose science, and it means that now I do not have a limit in evolution at my work. And my most important scientific achievement in my opinion is the development of reduction protocols without an external hydrogen source. When we have enough hydrogen atoms in the starting compounds and all we need is to combine these compounds and reduce the

resulting molecule, we can use a reducing agent which does not contain hydrogen atoms and obtain the target compounds with tolerance to all the functional groups and even to obtain such compounds which totally could not have been obtained before.

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