Synthesis of pharmaceutically relevant terpene amines via one-pot alcohol amination over gold catalysts

Yuliya S. Demidova,[a,b,*] Irina L. Simakova,[a,b] Evgeny V. Suslov,[c] Evgeny S. Mozhajcev,[c] Konstantin P. Volcho,[b,c] Nariman F. Salakhutdinov,[b,c] Andrey V. Simakov,[d] Dmitry Yu. Murzin[e]

[a]*Boreskov Institute of Catalysis, Novosibirsk, 630090, Russia*
[b]*Novosibirsk State University, Novosibirsk, 630090, Russia*
[c]*Novosibirsk Institute of Organic Chemistry, Novosibirsk, 630090, Russia*
[d]*Universidad Nacional Autónoma de México, Centro de Nanociencias y Nanotecnología, Ensenada, 22860, México*
[e]*Process Chemistry Centre, Åbo Akademi University, Turku/Åbo, FI-20500, Finland*
**Corresponding author: demidova@catalysis.ru*

Abstract: *One-pot terpene alcohols amination was studied over nanosized gold catalysts supported on metal oxides with equimolar amounts of the substrates under nitrogen pressure. The products distribution and conversion were found to depend on support nature, catalyst redox activation and active metal component composition. The reaction kinetics was modeled based on the mechanistic considerations with the catalyst deactivation step introduced into the mechanism. The effect of the substrate structure was explored. Introduction of hydrogen donors was efficient for controlled hydrogenation of C=N bond preserving C=C bond without addition of external molecular hydrogen resulting in the enhanced yield of the desired amine.*
Keywords: amination, gold catalyst, biomass.

1. Introduction

Amines are important chemicals *per se* and as building blocks in production of valuable compounds for several applications. Bio-derived natural extractives such as terpenes due to their molecular structure represent very attractive starting materials for fine and specialty chemicals. Utilization of natural terpenoids, which often possess biological activities, as platform molecules can provide new opportunities for the synthesis of efficacious chemicals for human disease prevention and therapy [1].

One-pot alcohol amination is considered as an effective approach for C-N bond formation and for the synthesis of complicated amines. The results of our previous work have shown that gold catalysts are rather active in one-pot amination of a natural terpene alcohol myrtenol leading to predominant hydrogenation of C=N bond in the final step instead of a more reactive C=C group of myrtenol (Fig. 1) [2, 3]. The main objective of the present work was to study general regularities of this reaction over gold catalysts in order to develop an approach for direct production of terpene amines minimizing influence of the side reactions.

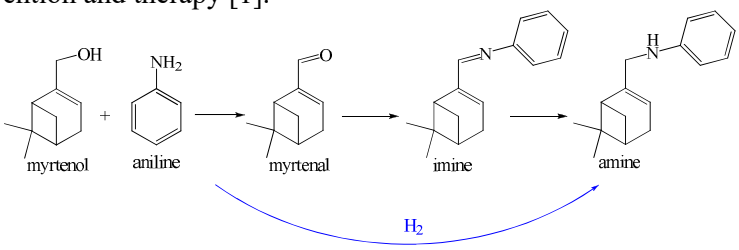

Figure 1. One-pot myrtenol amination with aniline over Au catalysts [2].

2. Experimental

Liquid-phase monoterpene alcohol amination was carried out in a stainless-steel reactor, equipped with an electromagnetic stirrer (1100 ppm) and a sampling system. In a typical experiment, a mixture of the monoterpene alcohol (1 mmol), primary amine (1 mmol) and gold catalyst (92 mg) in toluene (10 ml) was intensively stirred at 413-453 K under N_2 atmosphere. The reaction mixture was analyzed by GC, GC-MS and ^{1}H- and ^{13}C-NMR. A series of gold catalysts including Au and AuPd samples over metal oxides (ZrO_2, MgO, Al_2O_3, CeO_2, La_2O_3) were prepared by deposition-precipitation method using urea as a precipitating agent, pre-treated under oxidizing or reducing atmosphere and characterized by TEM, XPS, TPR/TPO-MS.

3. Results and discussion

To study the effect of the catalyst support and redox thermal pre-treatment and finally to determine an optimal catalytic system a series of nanosized gold catalysts over ZrO_2, Al_2O_3, CeO_2 and La_2O_3 pre-treated under oxidizing or reducing atmosphere were tested in one-pot myrtenol amination. The catalytic performance in each step was found to be strongly dependent on acid-base properties of the support requiring a certain balance between different sites for efficient alcohol amination [2]. Among the tested catalysts gold supported on ZrO_2 with both acidic and basic surface sites afforded the most efficient myrtenol transformations resulting in total conversion of myrtenol and selectivity to the target amine ca. 53% [2]. The basic sites on metal oxide surface were suggested to be required for the initial alcohol activation, while availability of protonic groups was important for the target amine formation. Differences in activity and selectivity for pre-reduced and pre-oxidized catalysts were proposed to be mainly related to an extent of support basicity modification by residual ammonia [3].

The reaction kinetics was modeled based on the mechanistic considerations with the catalyst deactivation step introduced into the mechanism [4]. The developed model is a very generic one and can be used for a number of other hydrogen borrowing reactions. To improve selectivity to the desired product an effect on the reaction of external hydrogen sources, including molecular hydrogen, alcohols, formic acid, was studied [5, 6]. Predominant hydrogenation of either C=N bond or both C=N and C=C bonds in the presence of Au/ZrO_2 catalyst was observed depending on the type of hydrogen source, addition time or reaction temperature. The hydrogen donors introduction was efficient for controlled hydrogenation of the C=N bond preserving the C=C bond without addition of external molecular hydrogen [6]. Application of 2-propanol allowed an increase of selectivity to the target amine with maximum yield of 68% being reached at the molar ratio of 2-propanol/myrtenol = 0.5 compared to 52% in the absence of any additive. The substrates structures were also varied to obtain potential biological active compounds and to study their physiological properties. The noticeable effect of both alcohol and amine was demonstrated and explored. A good correlation was found between the substrate structure and reactivity using the Hammett equation. The biological activity of the selected molecules was studied.

4. Conclusions

One-pot biomass-based alcohols amination was studied in detail including optimization of the catalyst and reaction conditions aiming at synthesis of biologically active compounds. Catalytic activity and product distribution in one-pot alcohol amination can be tuned by the metal oxide support properties, namely acidity and basicity, interactions of Au with other metals and conditions of the catalyst pre-treatment. A mechanistic model for hydrogen borrowing reaction taking into account catalyst deactivation was developed from the proposed reaction mechanism resulting in a kinetic model, which was able to describe experimental data with sufficient accuracy. An efficient approach to enhance the amine yield by introduction or generating additional hydrogen required for C=N bond hydrogenation with preserving the C=C bond was proposed. The amines with the different structures were obtained and the biological activity of the selected molecules was studied. This work is supported by RFBR grant № 16-33-60028.

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