Accepted Manuscript

Title: Selectivity control in one-pot myrtenol amination over Au/ZrO_2 by molecular hydrogen addition

Author: Yu.S. Demidova E.V. Suslov I.L. Simakova E.S. Mozhajcev D.V. Korchagina K.P. Volcho N.F. Salakhutdinov A. Simakov D.Yu. Murzin

PII: S1381-1169(16)30435-6
DOI: http://dx.doi.org/doi:10.1016/j.molcata.2016.10.034
Reference: MOLCAA 10097

To appear in: *Journal of Molecular Catalysis A: Chemical*

Received date: 20-8-2016
Revised date: 10-10-2016
Accepted date: 12-10-2016

Please cite this article as: Yu.S.Demidova, E.V.Suslov, I.L.Simakova, E.S.Mozhajcev, D.V.Korchagina, K.P.Volcho, N.F.Salakhutdinov, A.Simakov, D.Yu.Murzin, Selectivity control in one-pot myrtenol amination over Au/ZrO2 by molecular hydrogen addition, Journal of Molecular Catalysis A: Chemical http://dx.doi.org/10.1016/j.molcata.2016.10.034

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Selectivity control in one-pot myrtenol amination over Au/ZrO_2 by molecular hydrogen addition

Yu.S. Demidova[1,2], E.V. Suslov[3], I.L. Simakova[1,2,*], E.S. Mozhajcev[3], D.V. Korchagina[3], K.P. Volcho[2,3], N.F. Salakhutdinov[2,3], A. Simakov[4], D.Yu. Murzin[5]

[1]*Boreskov Institute of Catalysis, pr. Lavrentieva, 5, 630090, Novosibirsk, Russia*

[2]*Novosibirsk State University, Pirogova 2, 630090, Novosibirsk, Russia*

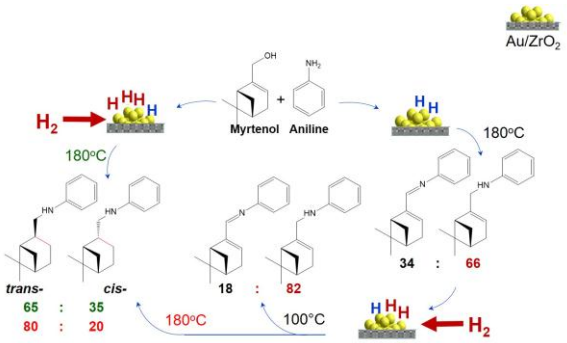
[3]*Novosibirsk Institute of Organic Chemistry, pr. Lavrentieva, 9, 630090, Novosibirsk, Russia*

[4]*Universidad Nacional Autónoma de México, Centro de Nanociencias y Nanotecnología, km. 107 carretera Tijuana a Ensenada, C.P. 22860, Ensenada, Baja California, México*

[5]*Process Chemistry Centre, Åbo Akademi University, FI-20500, Turku/Åbo, Finland*

[*]E-mail: simakova@catalysis.ru

Graphical abstract



ACCEPTED MANUSCRIPT

Highlights

- H_2 addition enhances selectivity to target amines in one-pot amination over Au/ZrO_2
- H_2 insertion at 100°C provides selective C=N saturation without hydrogenating C=C bond
- H_2 addition at 180°C provokes saturation of both C=C and C=N bonds
- Higher *trans*-amine selectivity after H_2 addition at 180°C at full myrtenol conversion

ABSTRACT

The one-pot myrtenol amination was studied over Au (3 wt.%) /ZrO_2 catalyst under mixed N_2/H_2 atmosphere (9 bar). The effect of hydrogen addition was explored with the aim to increase selectivity to the target amines. Hydrogen addition timing depending on myrtenol conversion and hydrogenation temperature affected selectivity to the reaction products. Hydrogen addition (1 bar) after almost complete myrtenol conversion at 100°C increased the yield to amine up to 68% preserving C=C bond in the initial myrtenol structure. Hydrogen addition at 180°C irrespective of the myrtenol conversion level provoked reduction of both C=C and C=N bonds with formation of two diastereomers (yield up to 93%), with trans-isomer formation being preferred when hydrogen was added at almost complete myrtenol conversion. It was shown, that in the presence of a gold catalyst controlled hydrogenation of competitive C=C and C=N groups can be performed during one-pot alcohol amination by regulation of the reaction conditions.

Keywords: one-pot alcohol amination, hydrogen borrowing, gold, biomass, selectivity control, competitive hydrogenation, monoterpenoid.

Introduction

Amines are important chemicals *per se* and as building blocks for the production of valuable compounds in a number of industries. Bio-derived natural extractives such as terpenes

ACCEPTED MANUSCRIPT

due to their molecular structure represent very attractive starting materials for producing fine and specialty chemicals [1,2] Utilization as platform molecules of natural terpenoids, which often possess biological activities, can provide new opportunities for the synthesis of efficacious chemicals for human disease prevention and therapy. In particular, terpene amines, synthesized from renewable raw materials, were shown to exhibit specific physiological properties and can be used as intermediates of potential drugs for neurological diseases [3,4,5 -6].On the other hand, terpenoids are highly reactive. There is a variety of different transformations such as, for example, isomerization that can occur along with the target reaction resulting in selectivity decrease [7,8,9,10,11,12,13,14] Thus, selective synthesis of terpenoid amines is a challenging task.

One-pot alcohol amination is considered as an effective approach for C-N bond formation and for the synthesis of complicated amines .[15] The overall reaction generally proceeds through three consecutive steps: alcohol activation (dehydrogenation) to a more reactive carbonyl compound, which then reacts with an amine to form condensation products, and finally transfer of hydrogen subtracted from the alcohol during first step to the imine with the target amine formation. This approach in theory allows selective production of secondary amines without formation of a tertiary amine.

In our previous work interactions of widespread monoterpenoid myrtenol with aniline leading to formation of a corresponding amine were studied (Figure 1). It was shown that gold catalysts exhibited promising catalytic activity along with a low impact of such side reactions as reduction of the reactive C=C group of myrtenol by hydrogen formed in the first step (Figure 1) [16,17,18] Basicity of catalyst support strongly affects effectivity of gold catalysts in alcohols activation [19] Indeed, the catalytic performance in myrtenol amination was shown to depend on acid–base properties of the selected catalyst supports [**Error! Bookmark not defined.**] as well as on the catalyst redox pretreatment [**Error! Bookmark not defined.**]. Based on these experimental data a detailed analysis of the reaction in terms of catalytic sites required for direct

ACCEPTED MANUSCRIPT

one-pot alcohol amination was performed. Among the catalysts tested in our studies Au/ZrO_2 pre-treated under oxidizing atmosphere was found to be optimal in terms of the target amine yield [**Error! Bookmark not defined.**].

*Based on kinetic data of myrtenol amination with aniline earlier published in [**Error! Bookmark not defined.**] it can be tentatively proposed that hydrogenation of imine is somewhat slower than other steps, therefore debottlenecking of this step by introducing addition hydrogen is beneficial for the overall process.* Such approach is of general interest for so-called hydrogen borrowing reactions, when hydrogen generated in a dehydrogenation step is transferred to an intermediate imine.

In the current study, therefore the effect of molecular hydrogen addition into the reaction system on the products selectivity was studied with the main aim to develop approaches for the direct terpene amines production minimizing influence of the side reactions.

2. Experimental/methodology

2.1. Catalysts preparation and characterization

The same sample of Au/ZrO_2 catalyst described well in our previous work was used [**Error! Bookmark not defined.**]. Commercial monoclinic ZrO_2 (Alfa Aesar) with surface area 110 m^2/g, pore volume 1.21 cm^3/g and pore diameter 6.6 nm was selected as a support, which in the powder form with the particles size below 40 μm was used for catalyst preparation. Au/ZrO_2 catalyst (3 wt.% according to ICP) was synthesized by deposition-precipitation technique using $HAuCl_4$ (Alfa-Aesar) as a gold precursor and urea as a precipitating agent similar to the procedure described elsewhere [20] In order to remove the excess of chloride after gold deposition, the sample was washed with a solution of NH_4OH (pH ca. 10), as in [21,22] Thereafter the catalyst was washed with deionized water, filtered and dried at room temperature for 24 h. Before the catalytic tests, the sample was oxidized in air flow under a temperature increase to 350^{o}C with a ramp rate of 20^{o}C/min.

ACCEPTED MANUSCRIPT

The prepared Au/ZrO_2 catalyst was analyzed with an inductively coupled plasma atomic emission spectroscopy (ICP-AES) using a Varian Liberty 110 ICP Emission Spectrometer.

Specific surface area and pores of the samples were determined with the BET method by physisorption of nitrogen in a Tristar II 3020 Micromeritics equipment. Prior to measurements, the samples were treated in vacuum (0.05 mbar) at 350°C for 12 hours.

Transmission electron microscopy (TEM) was performed with a JEOL 2010 microscope. Before TEM measurements the samples were dispersed in isopropanol and dropped on a copper grid coated with a carbon film. To estimate the value of a mean diameter of Au nanoparticles more than 250 particles were counted. The mean diameter (d_m) of particles was calculated using the following equation: $d_m = \frac{\sum_i (x_i d_i)}{\sum_i x_i}$, where x_i is the number of particles with diameter d_i.

The electronic state of gold species was studied by X-ray photoelectron spectroscopy (XPS) with Kratos AXIS 165 photoelectron spectrometer using monochromatic AlK_{α} radiation (hv = 1486.58 eV) and fixed analyzer pass energy of 20 eV. All measured binding energies (BE) were referred to the C1s line of adventitious carbon at 284.8 eV. The spectra fitting was done using Shirley background estimation over the energy range of the fit.

2.2. Catalytic experiments

Liquid-phase (-)-myrtenol amination was performed in a stainless steel reactor, equipped with an electromagnetic stirrer (1100 rpm) and the sampling system. A mixture of (-)-myrtenol (1 mmol), aniline (1 mmol) and the catalyst (92 mg) in toluene (10 ml) was typically used. Generally two types of experiments were carried out depending on when addition of molecular hydrogen in the reaction system was performed, before or after initial (-)-myrtenol conversion. For the former case of hydrogen being initially added to the system, the reaction was performed at 180°C under N_2/H_2 atmosphere with H_2 partial pressure 1-2 bar and total pressure 9 bar. In the later case when hydrogen was introduced at almost complete (-)-myrtenol conversion hydrogen

ACCEPTED MANUSCRIPT

partial pressure was 1 bar (total N_2/H_2 9 bar) and the temperature was 100 or 180°C, while prior to hydrogen addition the reaction was carried out at 180°C under N_2 atmosphere.

(-)-Myrtenol conversion was studied separately both in the presence or absence of molecular hydrogen. In a typical experiment, a mixture of (-)-myrtenol (1 mmol), Au/ZrO_2 catalyst (92 mg) in toluene (10 ml) was intensively stirred at 180°C under N_2 or N_2/H_2 (8/1) atmosphere with the total pressure 9 bar. N-(((1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)aniline (imine (1)) was hydrogenated using 1 mmol of the substrate and 92 mg of Au/ZrO_2 catalyst in 10 ml of toluene at 180°C under N_2/H_2 (8/1) pressure 9 bar.

The measurements of catalytic activity were performed in the kinetic regime. The impact of internal diffusion was determined through estimation of the Weisz-Prater criterion [**Error! Bookmark not defined.**]. The impact of external diffusion and namely mass transfer limitation through the liquid-solid interface was evaluated by the corresponding criterion calculation [23,24]

N-(((1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)aniline (imine (1)) was synthesized from (-)-myrtenal and aniline. (-)-Myrtenal (0.15 g, 0.1 mmol) was added to a solution of aniline (0.093 g, 0.1 mmol) in methanol (3 mL). The mixture was stirred for 2 h, and then the solvent was distilled off, giving imine (1) (0.216 g (95%)). ^{1}H NMR and ^{13}C NMR spectra of imine (1) were in good agreement with the ones described earlier [**Error! Bookmark not defined.**].

4-bromo-N-(((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)aniline was synthesized from (-)-myrtenal and 4-bromoaniline. (-)-Myrtenal (0.155 g, 1.03 mmol) was added to a solution of p-bromoaniline (0.175 g, 1.02 mmol) in methanol (3 mL). The mixture was stirred for 3 h, then sodium borohydride powder (0.236 g, 6.24 mmol) was added to the solution. The resulting suspension was stirred at room temperature for 12 h, then methanol was distilled off and the residue was suspended in brine (15 mL). The solution was treated with ethyl acetate (3×15 mL), combined organic solutions were dried over Na_2SO_4, then drying agent was filtered

ACCEPTED MANUSCRIPT

off and the solvent was distilled off, giving 4-bromo-N-(((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)aniline (0.310 g (98%)).

2.3. Product analysis

Aliquots were withdrawn from the reactor at appropriate time intervals and analyzed by gas chromatography using a SLB-5ms column (length 30 m, inner diameter 0.25 mm and film thickness 0.25 μm, gas carrier He, 40 ml/min) and a flame ionization detector operating at 300°C. Additionally the products structure was confirmed by analysis with gas chromatograph-mass spectrometer (Agilent 7000 GC/MS Triple Quad, HP-5MS column) as well as ^{1}H- and ^{13}C-NMR.

^{1}H- and ^{13}C-NMR spectra: *Bruker DRX-500* spectrometer (500.13 MHz (^{1}H) and 125.76 MHz (^{13}C)) in the $CDCl_3$ solutions of the substances; chemical shifts δ in ppm rel. to residual chloroform [δ(H) 7.24, δ(C) 76.90 ppm], *J* in Hz. The structure of the compounds was elucidated by analyzing the NMR spectra of ^{1}H and ^{13}C with the attraction of the spectra of the dual resonance of ^{1}H – ^{1}H, two-dimensional spectra of the heteronuclear of ^{13}C – ^{1}H of correlation on the straight constants of spin-spin interaction (C – H COSY, $^{1}J_{C,H}$ 160 Hz). The signal multiplicity in the ^{13}C NMR spectra was determined from the *J* modulation (JMOD). Elemental composition was determined by data of mass spectra recorded on a Agilent 7200 Accurate Mass Q-TOF GC/MS with ionization by electron impact 70 eV (HP-5MS column).

The structure of compounds 1 and 4 (Figure 1) was established in our previous work by ^{1}H- and ^{13}C-NMR [**Error! Bookmark not defined.**]. Amine (2) was earlier described in [25] In the current work *trans*- and *cis*-isomers of amine (4) were characterized by ^{1}H- and ^{13}C-NMR. NMR and HR-MS data of compounds (*trans*-(4) and *cis*-(4)) are presented in the supplementary materials. *^{1}H NMR and ^{13}C NMR spectra of 4-bromo-N-(((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)aniline are also presented in the supplementary materials.*

ACCEPTED MANUSCRIPT

The selectivity to the product was calculated based on the following equation: selectivity = yield of the product/total yield of all products. Diastereomeric excess (d_e) was defined as the absolute difference between the mole fractions (%) of each diastereomer.

3. Results and discussion

3.1. Catalytic results

Au/ZrO_2 catalyst used in this study was selected as an optimal one based on our previous research, where the catalyst characterization was presented in detail [**Error! Bookmark not defined.**, **Error! Bookmark not defined.**]. Au (3 wt. %)/ZrO_2 catalyst with the gold particle size 2.5 nm estimated from TEM images was obtained by deposition-precipitation method using urea followed by the catalyst pre-treatment under oxidizing atmosphere [**Error! Bookmark not defined.**]. The gold nanoparticles found by TEM in the studied sample were characterized with a semispherical shape practically without any well detectable crystallographic planes. According to XPS data the catalyst was characterized by the presence of mainly metallic gold species (76%) and some fraction of gold cations (24%) seem to be located in the gold-support surface interface [**Error! Bookmark not defined.**, **Error! Bookmark not defined.**]. *It is worth to note that along with effect of gold oxidation state studied by XPS other aspects, such as gold nanoparticles size and effect of the support have been addressed in detail in [**Error! Bookmark not defined.**]*.

First myrtenol amination with aniline was studied over Au/ZrO_2 catalyst under N_2 atmosphere at 180°C [**Error! Bookmark not defined.**]. During the reaction besides generation of expected products, myrtenal and its imine (1) and amine (2), additionally formation of myrtanol as well as myrtanal with the saturated C-C bond and the corresponding imine (3) and amine (4) occurred (Figure 1). Nevertheless, Au/ZrO_2 catalyst favored rather C=N that C=C bond hydrogenation under inert atmosphere when only a stoichiometric amount of hydrogen

ACCEPTED MANUSCRIPT

could be formed during the reaction resulting in a small amount of products with the saturated C-C bond (<10%) (Figure 2a). The only limitation for selective secondary amine production without changes in the initial myrtenol structure was slow C=N bond hydrogenation after complete initial myrtenol conversion which was providing hydrogen. Amine (2) was formed with about 54% selectivity at nearly complete myrtenol conversion reaching 98% (Figure 2a).

In order to enhance selectivity towards the desired product, the influence of hydrogen addition was explored. First, the reaction was studied under mixed N_2/H_2 atmosphere at initial H_2 partial pressure 1-2 bar and total pressure 9 bar at 180°C. In this case temperature decrease was considered not to be appropriate since the initial step of alcohol dehydrogenation to aldehyde requires elevated temperature [**Error! Bookmark not defined.**]. It was found that the excess of hydrogen at 180°C provoked fast hydrogenation of both unsaturated C=C and C=N bonds leading to selective formation of amine (4) (Figure 2 b). Selectivity to amine (4) reached 93% in 7 h under 1 bar H_2 partial pressure. *Note that the reaction rate at H_2 partial pressure 1 bar was about 1.5 fold higher compared to the reaction performed only under inert atmosphere. Hydrogen addition can lead to less prominent deactivation caused by imine oligomerization or polymerization [26]*. At the same time, the reaction rate was also shown to be affected by hydrogen pressure. Thus, an increase in hydrogen pressure from 1 to 2 bar supressed the initial step of myrtenol dehydrogenation, while favoring C=C bond hydrogenation in myrtenol and myrtenal (Figure 2c). Since hydrogenation of C=C bond in myrtenol results in creation of a new asymmetric center, the different diastereomers can be formed. In the present case, based on ^{1}H and ^{13}C NMR data (Supplementary materials), *trans*- and *cis*-isomers were detected, with predominant formation of amine (4) with *trans*-orientation of phenyl group to gem-dimethyl fragment. Diastereomeric excess was shown to depend on the reaction condition (Table 1). The increase of hydrogen pressure from 1 to 2 bar (line 1 and 2) led to a decrease in diastereomeric excess from 30% to 24% at complete myrtenol conversion, respectively. In both cases diastereomeric excess decreased along the reaction starting from 75% and 40% at myrtenol

ACCEPTED MANUSCRIPT

conversion 25% for 1 to 2 bar of H_2, respectively. According to the thermodynamic calculations performed by using molecular modeling program HyperChem 8.0 (semi-empirical PM3 method) for both imine (3) and amine (4) *trans*-isomer was detected to be slightly more stable, with the energy difference between diastereomers being 11 and 6 kJ/mol, respectively. Thus, in this case predominant *trans*-isomer formation seems to occur because of thermodynamic but not kinetic control. Note that selective formation of diastereomers is considered to be of interest, particularly, for synthesis of biologically active compounds.

An alternative approach to improve selectivity to amine was to introduce molecular hydrogen in the system after complete conversion of initial myrtenol with the aim to diminish an impact of C=C bond hydrogenation at least on the first stage. The second part of the reaction in the presence of hydrogen was carried out at 100 and 180°C to explore the effect of temperature on selectivity to the reaction products. As can be seen from Figure 3a hydrogen addition at 100°C resulted in controlled hydrogenation of the C=N bond and amine (2) yield increase up to 68% compared to 54% for the reaction performed only under nitrogen atmosphere. The temperature increase to 180°C favored hydrogenation of both C=N and C=C bonds (Figure 3b) as it was observed prior to reaction initiation. A profound difference between the experiments was associated with diastereomeric excess of amine (4). Formation of the *trans*-isomer was more selective with the d_e value being about two fold higher when hydrogen was added after myrtenol consumption (Table 1, line 3). *Interestingly, when aniline was replaced by 4-bromaniline the impact of C=C bond hydrogenation was noticeable even under nitrogen atmosphere and only formation of products with the saturated C-C bond was detected. At the same time the initial reaction rate increased 1.7 fold compared to aniline.*

Selectivity to the corresponding imine and amine with the saturated C-C bond was 49 and 22% under nitrogen atmosphere, respectively, while the corresponding values of 29% and 43% were observed after hydrogen addition at 100°C in 3 h. Worth to note that in the presence of Au/ZrO_2 catalyst even under hydrogen atmosphere hydrodehalogenation of 4-bromaniline previously

ACCEPTED MANUSCRIPT

reported in the literature [27] was suppressed. Unexpected activity in C=C bond hydrogenation seems to be related to the catalyst modification by the reaction substrates or with the electronic effect of the substituent. These results clearly demonstrate that although Au/ZrO_2 can be used with other amines not only aniline, optimal conditions should be carefully defined depending on the substrate structure.

At the same time, generally hydrogenation of compounds containing pinane fragment in the presence of metal catalysts mainly resulted in corresponding *cis*-isomer formation because of steric hindrance [**Error! Bookmark not defined.**, **Error! Bookmark not defined.**]. Thus, in our case predominant formation of t*rans*-isomer demonstrated that the C=C hydrogenation can occur via more complicated mechanism such as intermolecular hydrogen transfer from C-N to C=C bond. Apparently a separate study is required to the clarify hydrogenation mechanism.

Previously amine (2) was only obtained with the yield of 60% via allylic amination catalyzed by $[Cp^*Fe(CO)_2]_2$ [28]. The synthesis of amine (4) was not published before, whereas the *cis*-isomers of compounds with the similar structure containing methyl and methoxy functional groups in phenyl fragment were obtained with yield about 91% and 67%, respectively [29,30].

The obtained results suggest that diastereoselectivity for amine (4) can be regulated at the steps of myrtenol/myrtenal hydrogenation and corresponding imine (3) formation. To elucidate regularities of the products formation hydrogenation of myrtenol and imine (1) was studied at 180°C under N_2/H_2 atmosphere (9 bar) at H_2 partial pressure of 1 bar. In the case of myrtenol formation of the corresponding alcohol and aldehyde with the saturated C-C bond in the presence of hydrogen occurred, with the diastereomeric excess for myrtanol and myrtanal being about 84% and 76%, respectively (Figure 4a). Relatively selective formation of *trans*-myrtanol and *trans*-myrtanal during myrtenol transformation under hydrogen was observed. Worth to note, that hydrogen addition in small amounts (1 bar) did not prevent initial alcohol dehydrogenation in the presence of Au/ZrO_2 catalyst. Under nitrogen pressure myrtenol was

ACCEPTED MANUSCRIPT

mainly converted to myrtenal with a low yield of products with the saturated C-C bond, *with the reaction rate being 1.5 fold lower compared to myrtenol conversion in the presence of aniline*.

The results for imine (1) hydrogenation demonstrated that in the presence of Au/ZrO_2 catalyst the consecutive hydrogenation of C=N bond followed by C=C bond hydrogenation occurred (Figure 4b). The obtained data additionally demonstrate that the gold catalyst is active rather in C=N than C=C bond hydrogenation. At the same time, the diastereomeric excess was close to 60% at total imine consumption, with this value being decreased up to 50% in 10 hours (Figure 4b). Thus, since trans-isomer formation is thermodynamically controlled, in this case direct trans-cis isomerization is not favorable as, for example, was shown in [31,32,33] for several cases of C=C double bond hydrogenation in olefins or cycloalkenes. Therefore, other explanations should be invoked to account for rather moderate, but not negligible changes in stereoselectivity. Such explanations can include for example involvement of hydrogen transfer, faster side reactions of the trans-isomer, or changes in the geometry of adsorbed imine (3) favoring cis-formation. In the latter case such changes depend on coverage of other species which certainly is influenced by the liquid-phase composition. It is apparently clear that a separate theoretical study is needed to reveal the origin of this intriguing and unusual stereoselectivity.

In summary, in the current work approaches for controlled selective synthesis of complicated terpene amines via one-pot alcohol amination were presented. Addition of hydrogen into the reaction system allowed an increase of selectivity to the final product amine. Hydrogen addition at 100°C resulted in controlled hydrogenation of the C=N bond and amine (2) yield increase up to 68% compared to 54% for the reaction performed only under nitrogen atmosphere. The temperature increase up to 180°C led to both C=C and C=N bonds hydrogenation with formation of two diastereomers. *Trans*-isomer of amine (4) was formed more selectively when hydrogen was added after myrtenol consumption. *It should be emphasized that the values of diastereoselectivity are rather modest keeping in mind that higher diastereoselectivity is*

ACCEPTED MANUSCRIPT

desirable for potential industrial applications. At the same time it should be mentioned that in organic synthesis there are plenty of different approaches to enrich diastereoselectivity including separation based on differences in physicochemical properties of diastereomers. Typically, separation is performed using crystallization relying on the fact that diastereomeric excess in the crystallized phase is different from the initial composition [34]. Such approaches will be apparently required also in the current case to obtain the desired diastereoselectivity.

Furthermore, for the initial substrates, containing a reactive C=C bond, such as myrtenol, controlled synthesis of both amines with saturated and unsaturated C=C bonds can be performed by regulation of the reaction condition namely temperature and timing of hydrogen addition. Regarding these results the next step to increase the process efficiency is considered to be using of more safe and often more readily available in fine chemicals industry hydrogen sources such as alcohols, formic acid *etc.*

*At the same time it is worth to note that external hydrogen addition was proposed to compensate insufficient hydrogen formation on the surface of gold particles due to non-specific myrtenol dehydrogenation involving both support active sites and gold nanoparticles. Earlier it was clearly demonstrated that alcohol dyhydrogenation can occur both in the presence and absence of gold nanoparticles, while hydrogen formation was observed only in the presence of gold [**Error! Bookmark not defined.**, [35,36]]. Despite the initial alcohol activation on the basic sites of the support, alcohol dehydrogenation proceeding only on the support active sites did not produce hydrogen species needed for further hydrogenation.*

4. Conclusions

In this work the effect of hydrogen addition on one-pot myrtenol amination in the presence of Au/ZrO_2 catalyst was studied with the aim to remove limitations on the last step of imine hydrogenation to amine and to control selectivity to the target product. Bio-based alcohol myrtenol with a competiting C=C functional group was used to develop approaches for the

ACCEPTED MANUSCRIPT

synthesis of amines with different structure on gold catalyst. Depending on the time of hydrogen addition or hydrogenation temperature 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. Thus, hydrogen addition (1 bar) after almost complete myrtenol conversion at 100°C led to an increase in the amine yield up to 68% with preservation of C=C bond in the initial myrtenol structure compared to 54% for the reaction performed only under nitrogen atmosphere. Addition of hydrogen at 180°C irrespective of the myrtenol conversion level provoked reduction of both C=C and C=N bonds with formation of two diastereomers. According to ^{1}H and ^{13}C NMR data mainly *trans*-isomer was produced. Hydrogen addition at the start of reaction at 180°C led to a faster formation of the target amine accompanied by two fold decrease in diastereomeric excess from 60% to 30% compared to hydrogen introduction after myrtenol consumption. The results demonstrate that in the presence of the gold catalyst controlled competitive hydrogenation of C=C and C=N groups can be performed during one-pot alcohol amination by regulation of the reaction conditions. In particular, amines with different structures can be synthesized starting from one initial biomass-derived myrtenol.

Acknowledgements

The authors acknowledge the financial support of RFBR (Russia) through grant No 16-33-60028. Prof. Andrey Simakov expresses his gratitude to CONACyT (México) for the financial support through Grant 179619. The authors are grateful to S. Beloshapkin, M. Estrada for their help in carrying out this work.

ACCEPTED MANUSCRIPT

References

[1] M. Golets, S. Ajaikumar, J.-P. Mikkola, Chem. Rev. 115 (9) (2015) 3141–3169.

[2]D.Yu. Murzin, I.L. Simakova, Catal. Ind. 3 (3) (2011) 218-249.

[3]I.G. Kapitsa, E.V. Suslov, G.V. Teplov, D.V. Korchagina, N.I. Komarova, K.P. Volcho, T.A. Voronina, A.I. Shevela,. N.F. Salakhutdinov, Pharm. Chem. J. 46(5) (2012) 263-265.

[4]T.G. Tolstikova, E.A. Morozova, A.V. Pavlova, A.V. Bolkunov, M.P. Dolgikh, E.A. Koneva, K.P. Volcho, N.F. Salakhutdinov, G.A. Tolstikov, Dokl. Chem. 422(2) (2008) 248–250.

[5]D.I. Park, H.G. Kim, W.R. Jung, M.K. Shin, K.L. Kim, Neuropharmacology, 61 (2011) 276-282.

[6]A.A. Silver, R.D. Shytle, K.H. Sheehan, D.V. Sheehan, A. Ramos, P.R. Sanberg, J. Am. Acad. Child Adolesc. Psychiatry 40 (2001) 1103–1110.

[7]A. Torozova, P. Mäki-Arvela, A. Aho, N. Kumar, A. Smeds, M. Peurla, R. Sjöholm, I. Heinmaa, D.V. Korchagina, K.P. Volcho, N.F. Salakhutdinov, D.Yu. Murzin. J. Mol. Catal. A 397 (2015) 48–55.

[8] M. Stekrova, N. Kumar, P. Maki-Arvela, A. Aho, J. Linden, K.P. Volcho, N.F. Salakhutdinov, D.Yu. Murzin, Reac. Kinet. Mech. Cat. 110 (2013) 449-458.

[9] [1] S. Kurbakova, I. Il'ina, A. Pavlova, D. Korchagina, O. Yarovaya, T. Tolstikova, K. Volcho, N. Salakhutdinov, Med. Chem. Res. 23 (2014) 1709–1717.

[10] Yu.S. Demidova, E.V. Suslov, O.A. Simakova, I.L. Simakova, K.P. Volcho, N.F. Salakhutdinov, D.Yu. Murzin, Catal. Today 241 (2015) 189–194.

[11] Yu.S. Demidova, E.V. Suslov, O.A. Simakova, K.P. Volcho, N.F. Salakhutdinov, I.L. Simakova, D.Yu. Murzin, J. Mol. Catal. A 420 (2016) 142–148.

[12] Yu.S. Demidova, O.V. Ardashov, O.A. Simakova, I.L. Simakova, K.P. Volcho, N.F. Salakhutdinov, D.Yu. Murzin, J. Mol. Catal. A 388-389 (2014) 162–166.

[13 I.L. Simakova, Yu. S. Solkina, B. L. Moroz, O.A. Simakova, S.I. Reshetnikov, I.P. Prosvirin, V.I. Bukhtiarov, V.N. Parmon, D.Yu. Murzin, Appl. Catal. A: Gen. 385 (2010) 136–143.

ACCEPTED MANUSCRIPT

[14] I.L. Simakova, Yu. S. Solkina, I.V. Deliy, J. Wärnå, D.Yu. Murzin, Appl. Catal. A: Gen. 356 (2) (2009) 216-224.

[15] K. Shimizu, Catal. Sci. Technol. 5 (2015) 1412-1427.

[16] Yu.S. Demidova, I.L. Simakova, M. Estrada, S. Beloshapkin, E.V. Suslov, D.V. Korchagina, K.P. Volcho, N.F. Salakhutdinov, A.V. Simakov, D.Yu. Murzin, Appl. Catal. A: Gen. 464-465 (2013) 348-356.

[17] Yu.S. Demidova, I.L. Simakova, J. Wärnå, A.V. Simakov, D.Yu. Murzin, Chem. Eng. J. 238 (2014) 164-171.

[18] I.L. Simakova, Yu.S. Demidova, M. Estrada, S. Beloshapkin, E.V. Suslov, K.P. Volcho, N.F. Salakhutdinov, D.Yu. Murzin, A.V. Simakov, Catal. Tod., 2016, *http://dx.doi.org/10.1016/j.cattod.2016.01.044*.

[19] V.V. Costa, M. Estrada, Yu. Demidova, I. Prosvirin, V. Kriventsov, R.F. Cotta, S. Fuentes, A. Simakov, E.V. Gusevskaya, J. Catal. 292 (2012) 148–156.

[20] R. Zanella, S. Giorgio, C.R. Henry, C. Louis, J. Phys. Chem. B (2002), 106, 7634-7642.

[21] S. Ivanova, V. Pitchon, Y. Zimmermann, C. Petit, Appl. Catal. A: Gen. 298 (2006) 57-64.

[22] E. Smolentseva, B.T. Kusema, S. Beloshapkin, M. Estrada, E. Vargas, D.Y. Murzin, F. Castillon, S. Fuentes, A. Simakov, Appl. Catal. A: Gen. 392 (2011) 69-79.

[23] S. Demirel, M. Lucas, J. Wärnå, T. Salmi, D.Yu. Murzin, P. Claus, Top. Catal. 44 (2007) 299-305.

[24] P.L. Mills, R.V. Chaudhari, Catal. Tod. 37 (1997) 367-404.

[25] Y.-J. Cherng, J.-M. Fang, T.-J. Lu, Tetrahedron: Asymmetry 6 (1995) 89–92.

[26] *D. Ruiz, A. Aho, K. Eränen, J. Wärnå, R. Leino, D.Yu. Murzin, Chem. Eng. J., 2016, doi: http://dx.doi.org/10.1016/j.cej.2016.08.083*

[27] V.P. Sivcev, D.V. Korchagina, E.V. Suslov, K.P. Volcho, N.F. Salakhutdinov, V.I. Anikeev, J. of Supercritical Fluids 86 (2014) 137–144.

[28] M.K. Kolel-Veetil, M.A. Khan, K.M. Nicholas, Organometallics 19 (2000) 3754-3756.

ACCEPTED MANUSCRIPT

[29] W. Zhou, M. Fan, J. Yin, Y. Jiang, D. Ma, J. Am. Chem. Soc. 137 (2015) 11942-11945.

[30].P. Sinha, C.C. Kofink, P. Knochel, Org. Lett. 8 (17) (2006) 3741-3744.

[31].D.Yu. Murzin, I.L. Simakova, J. Mol. Catal. A 286 (1-2) (2008) 156-161.

[32] A.K. Neyestanaki, P. Mäki-Arvela, H. Backman, H. Karhu, T. Salmi, J. Väyrynen, D.Yu. Murzin, J. Catal. 218 (2003) 267-279.

[33] I.V. Deliy, I.L. Simakova, N. Ravasio, R. Psaro, Appl. Catal. A: Gen. 357 (2) (2009) 170-177.

[34] N. M. Maier, P. Franco, W. Lindner, J. Chromatogr. A 906 (2001) 3–33.

[35] Z. Martinez-Ramirez, J.A. Gonzalez-Calderon, A. Almendarez-Camarillo, J.C. Fierro-Gonzalez, Surface Science 606 (15-16) (2012) 1167-1172.

[36] E.O. Conzales-Yañez, G.A. Fuentes, M.E. Hernández-Terán, J.C. Fierro-Gonzalez, Appl. Catal. A: Gen. 464-465 (2013) 374-383.

ACCEPTED MANUSCRIPT

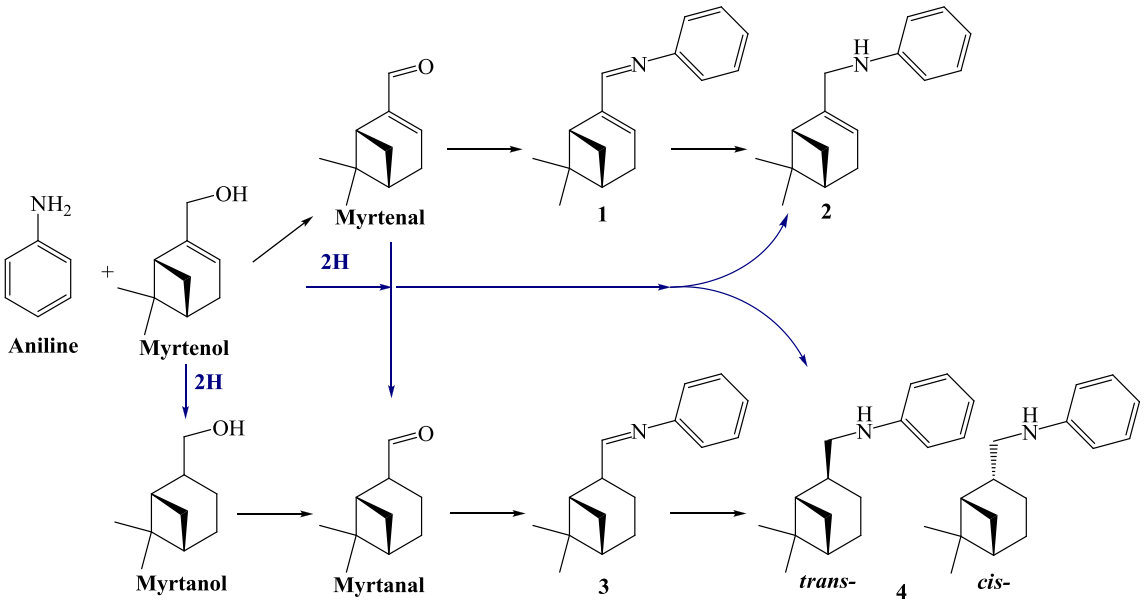


Fig. 1. Myrtenol amination with aniline over Au catalysts [**Error! Bookmark not defined.**].

ACCEPTED MANUSCRIPT

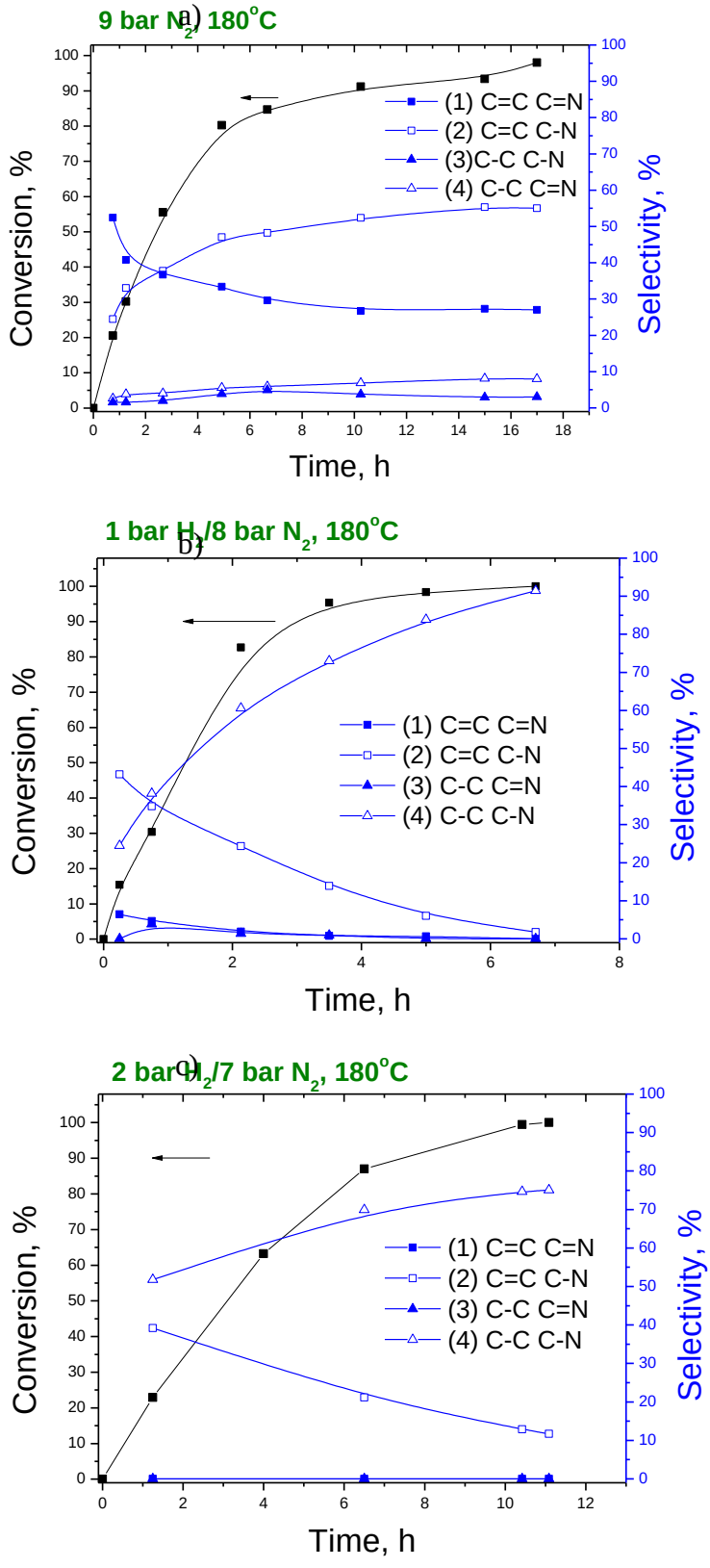


Fig. 2. The effect of hydrogen presence and it partial pressure (without hydrogen (a), 1 bar (b) and 2 bar (c)) on myrtenol conversion and selectivity to the reaction products. The reaction conditions: T = 180°C, myrtenol 1 mmol, aniline 1 mmol, toluene 10 ml, catalyst 1.4 mol. % Au, 9 bar N_2/H_2.

ACCEPTED MANUSCRIPT

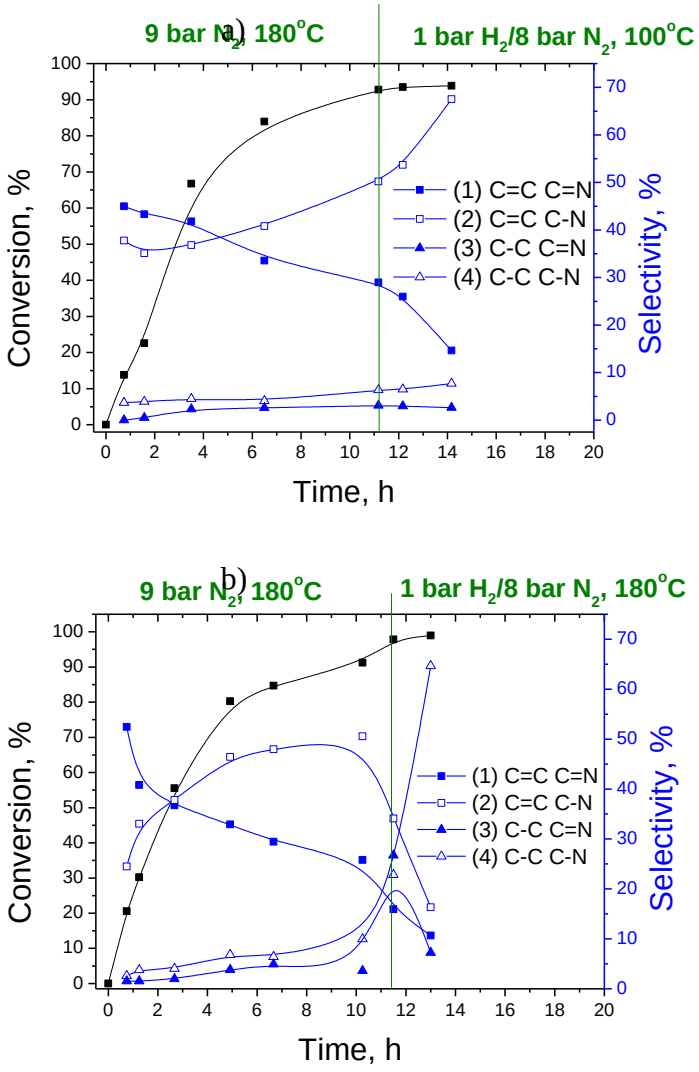


Fig. 3. The effect of hydrogen addition on selectivity to the reaction products at 100 (a) and 180°C (b) after almost complete myrtenol conversion. The reaction conditions: 1) T = 180°C, myrtenol 1 mmol, aniline 1 mmol, toluene 10 ml, catalyst 1.4 mol. % Au, 9 bar N_2; 2) T = 100 and 180°C, 9 bar N_2/H_2.

ACCEPTED MANUSCRIPT

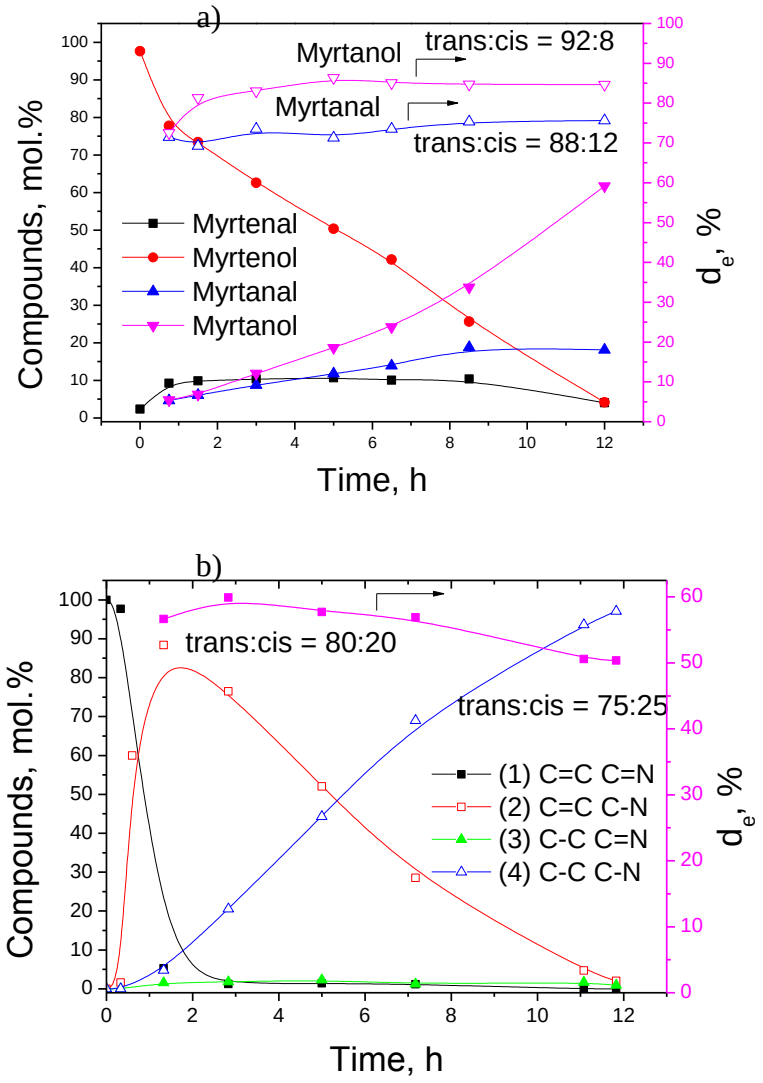


Fig. 4. The products distribution and diastereomeric excess (d_e) as a function of the reaction time during myrtenol and N-((6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)aniline (imine (1)) hydrogenation. The reaction conditions: T = 180°C, initial substrate 1 mmol, toluene 10 ml, catalyst 1.4 mol. % Au, 9 bar total, N_2/H_2 = 8/1.

ACCEPTED MANUSCRIPT

Table 1. Effect of the reaction conditions on the content of amine (4) diastereomers and diastereomeric excess value at complete myrtenol conversion.

Conditions	*trans*-, %	*cis*-, %	*de*, %	Figure
1 bar H_2, 8 bar N_2, 180°C	65	35	30	2b
2 bar H_2, 7 bar N_2, 180°C	62	38	24	2c
9 bar N_2, 180°C/ 1 bar H_2, 8 bar N_2, 180°C	80	20	60	3b