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Acid-modified Halloysite Nanotubes as a Stereoselective Catalyst for Synthesis of 2*H*-Chromene Derivatives by the Reaction of Isopulegol with Aldehydes

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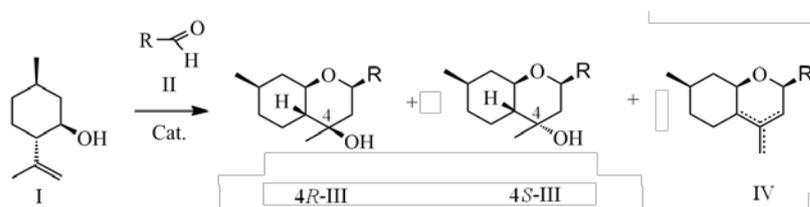
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Abstract

Acid-modified halloysite nanotubes were used for the first time as a stereoselective catalyst for synthesis of oxygen-containing heterocycles applying of allyl alcohol (-)-isopulegol condensation with aldehydes to the octahydro-2*H*-chromenol (4*R*- and 4*S*-diastereomers) as an example. The catalysts were characterized by XRF, XRD, N₂-adsorption, FTIR with pyridine and MAS NMR methods. A high ratio of 4*R*/4*S* diastereomers (7.6–14.5) under mild conditions in cyclohexane was considerably exceeding previously reported results. Unprecedented selectivity (79–83%) to 4*R* isomer of thiophenyl-substituted chromenol exhibiting high analgesic activity was achieved. An increase in stereoselectivity with a decrease in the halloysite drying temperature and catalyst acidity clearly indicates formation of 4*R* diastereomer on the weak Brønsted sites. This work is an example that control of the stereoselectivity of acid-catalyzed organic reactions can be effectively carried out by varying water content on the aluminosilicate surface. Modified halloysite nanotubes can be considered as are an extremely promising catalysts for stereoselective synthesis of heterocyclic compounds.

It is known that compounds with a chromene (benzopyran) scaffold have a broad spectrum of biological activity [1–8]. A high pharmaceutical potential and low toxicity of these substances resulted in a considerable interest in the synthesis of new chromene derivatives [3–15]. Recently, it has been shown [12, 13] that in catalytic condensation of a natural allyl alcohol (-)-isopulegol (I) with aldehydes, substituted octahydro-2*H*-chromen-4-ol (III) as 4*R*- and 4*S*-diastereomers was formed along with a dehydration products IV (Scheme 1). Different catalysts such as I₂, *p*-toluenesulfonic acid, BF₃·Et₂O, zeolites, clays were used in this reaction [5–18]. A relatively high 4*R*/4*S* ratio (9.0) with overall yields of 70–88% were observed in condensation of isopulegol (obtained by cyclization of *R*-citlonellal) with aromatic aldehydes at -78°C using scandium triflate [15]. The isomeric ratio was significantly lower (4.0) for aliphatic aldehydes as reactant [15]. In the presence of traditional Lewis acids (ZnCl₂, FeCl₃, AlCl₃) rather low yields of chromenols (12–48%) were observed [15].



Scheme 1. Condensation of isopulegol with aldehydes

Some synthesized octahydro-2*H*-chromen-4-ols on the basis of isopulegol display a pronounced physiological activity [5–8]. Thus, 4*R*-diastereomer obtained by the reaction of I with thiophene-2-carbaldehyde on K-10 clay exhibited *in vivo* prolonged analgesic effect surpassing that of Diclofenac [6]. 4*R*-isomers synthesized with 5-bromo-thiophene-2-carbaldehyde or acetone displayed a profound anti-influenza activity, whereas only poor antiviral effect was showed by 4*S*-diastereomers [7,8]. Quite recently we have demonstrated [18] that an increase in selectivity to thiophenyl-substituted chromenol with illite clay as a catalyst was observed with an increase in the initial concentrations of reactants, the catalyst to reactants ratio, and a decrease in the reaction temperature [18]. Kinetic modeling was applied to rationalize the observed regularities [18]. Considering high physiological activity of 4*R*-diastereomers of octahydro-2*H*-chromenols [6–8], development of novel stereoselective catalysts for their synthesis is a very important task. Note that the use of triflates for synthesis of physiologically active chromenols has several drawbacks including their toxicity, complexity of separation, and high costs.

Halloysite is a kaolinite group aluminosilicate mineral, the layer of which consists of Si–O tetrahedral and Al–O octahedral sheets. Morphologically it is a nanoscale multilayer tube (Fig. S1, Supplementary Information) [19,20]. This natural nanomaterial is very promising as a container for drugs delivery vehicle, additive to polymers, a component of membranes, etc [20–23]. There are very

few examples of halloysite nanotubes (HNT) application in acid catalysis [24–26], moreover HNT has not been applied as a catalyst for synthesis of heterocyclic compounds.

In the present work, reactions of (-)-isopulegol with aldehydes were investigated over commercially available halloysite from Dragon Mine (Utah, USA), which was pre-treated with HCl. Commercial montmorillonite clays K-10, K-30 and an aluminosilicate catalyst AS-36 were used for comparison. The main attention was paid on the preparation of thiophenyl-substituted octahydro-2*H*-chromenol with a high analgesic activity. The reaction was carried out without any solvent and in cyclohexane at 20–40°C. Experimental procedures are presented in Supplementary Information.

The content of Al₂O₃ in halloysite after an acid treatment decreased by 9.5%, while the specific surface area increased from 62 to 130 m²·g⁻¹ (Table S1). N₂-adsorption isotherm for the activated NHT has a typical form for mesoporous materials (Fig. S2), with the average pore diameter of 11.2 nm (Table S1). The pore size of halloysite is thus sufficiently large compared to the size of the reactants to expect that the internal surface of the material plays a significant role in catalytic properties. The crystalline structure of halloysite after modification was preserved as evidenced by the characteristic peaks in the diffractogram (Fig. S3). The SEM image of the acid-modified halloysite (Fig. 1) exhibited presence of typical nanoscale tubes, which shape did not differ from the initial solids [20, 23].

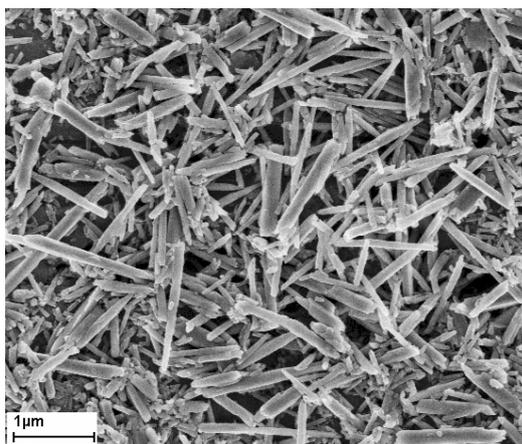


Fig. 1. SEM image of the modified halloysite

²⁹Si NMR spectrum of the initial halloysite (Fig. 2) exhibited a single peak with a chemical shift of $\delta = -91.8$ ppm, which is related to Q³ units, where one SiO₄ tetrahedron is surrounded by three analogous ones [23]. Modification by the acid resulted in additional lines at -101.4 and -110.8 ppm (Fig. 2). The signal at -101.4 ppm corresponds to (Si–O)₃Si–OH structures [23,27], which are formed because of breaking of Si–O–Al bonds between the tetrahedral and octahedral layers during pretreatment. The peak with $\delta = -110.8$ ppm (Q⁴) reflects formation of amorphous silica after the acid treatment [23]. Note that in the modified halloysite 74.8% of silicon remains in the initial state (Fig.

2). According to ^{27}Al MAS NMR spectrum, 99.0% of aluminum are in the six-coordinated state (i.e. in the octahedral layers).

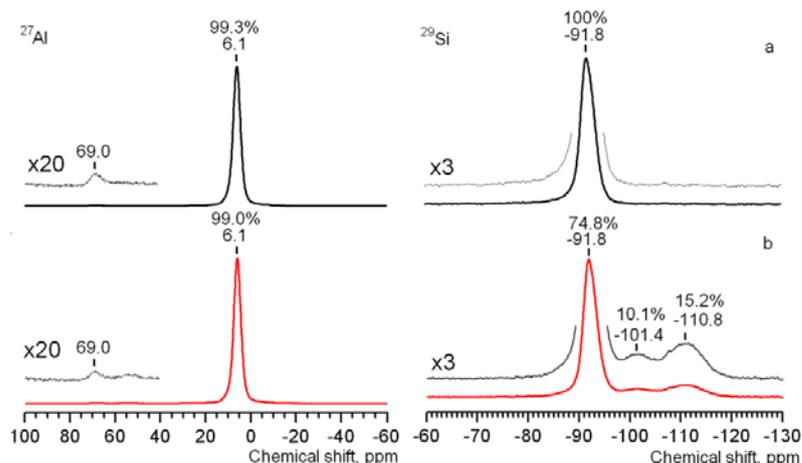


Fig. 2. ^{27}Al and ^{29}Si MAS NMR spectra of initial (a) and modified (b) HNT

After the acid treatment the concentration of acid sites (a.s.) in halloysite increased from 34 to 46 $\mu\text{mol}\cdot\text{g}^{-1}$ with both Brønsted (B) and Lewis (L) sites are present. Note that the Lewis acidity was more prominent for HNT, K-10 and K-30 with the largest L/B ratio (2.0) exhibited HNT (Table S2).

In the reaction of isopulegol with thiophene-2-carbaldehyde at 25°C a high (83.4–99.2%) substrate conversion was observed on the pretreated halloysite without any solvent (Table 1). Only 4.4% isopulegol was converted on the initial HNT. The main product was thiophenyl-substituted octahydro-2H-chromen-4-ol III present 4*R*- and 4*S*-diastereomers (Scheme 1). Selectivity to chromenol as well as to 4*R* isomer increased with a decrease of the drying temperature and the weight loss of HNT (Table 1). The highest selectivity to III (91.5%, with the 4*R*/4*S* ratio equal to 6.5) was observed in the presence of the air-dried halloysite (Table 1), which may indicate participation of water in HNT in the reaction. A detailed analysis of these results will be given below.

Table 1. Conversion of isopulegol* in the reaction with thiophene-2-carbaldehyde and products selectivity over modified halloysite without any solvent for 1 h at 25 °C

| HNT drying temperature, °C | Mass loss, % | Conversion (I), mol. % | Selectivity, mol. % | | | | 4 <i>R</i> /4 <i>S</i> |
|----------------------------|--------------|------------------------|---------------------|-----------------|-----------------|-----|------------------------|
| | | | III | 4 <i>R</i> -III | 4 <i>S</i> -III | IV | |
| 20 (air-dried) | 0 | 83.4 | 91.5 | 79.3 | 12.2 | 3.9 | 6.5 |
| 50 | 2.0 | 98.3 | 87.3 | 74.8 | 12.8 | 6.5 | 5.8 |
| 105 | 4.2 | 98.4 | 85.4 | 72.1 | 13.3 | 6.1 | 5.4 |
| 150 | 5.1 | 99.1 | 80.3 | 64.5 | 15.8 | 6.6 | 4.1 |

| | | | | | | | |
|-----|-----|------|------|------|------|-----|-----|
| 200 | 9.0 | 99.2 | 77.7 | 61.8 | 15.9 | 7.5 | 3.9 |
| 350 | 9.4 | 95.1 | 76.3 | 59.6 | 16.7 | 7.2 | 3.6 |

*Conversion of aldehyde was practically the same as for isopulegol

Considering that the highest stereoselectivity was observed with the air-dried HNT, the reaction in cyclohexane at 40°C was studied without drying of the catalysts. The overall selectivity to thiophenyl-substituted chromenol III over the modified halloysite was 90.7%, which is significantly higher than for other catalysts used (Table 2). At the same time, selectivity only to the target 4*R* diastereomer on HNT (79.0%) was comparable to that for the sum of isomers on K-10 and K-30 catalysts (Table 2). According to previously published results, the yield of the 4*R*-isomer was 69% on illite clay [18], 65% on K-10 [6] and 33.0% in the presence of H-K-10 clay [15]. Thus, the modified halloysite is an excellent catalyst for synthesis of the 4*R*-diastereomer of chromenols (79.0%) exhibiting analgesic activity. The second order rate constant *k* for the clays HNT, K-10 and K-30 increases with an increase in the a.s. concentration, whereas for AS-36 the *k* value was the lowest, which may be related to the presence of micropores [18].

Table 2. Selectivity in reaction of isopulegol* with thiophene-2-carbaldehyde in cyclohexane at 40°C

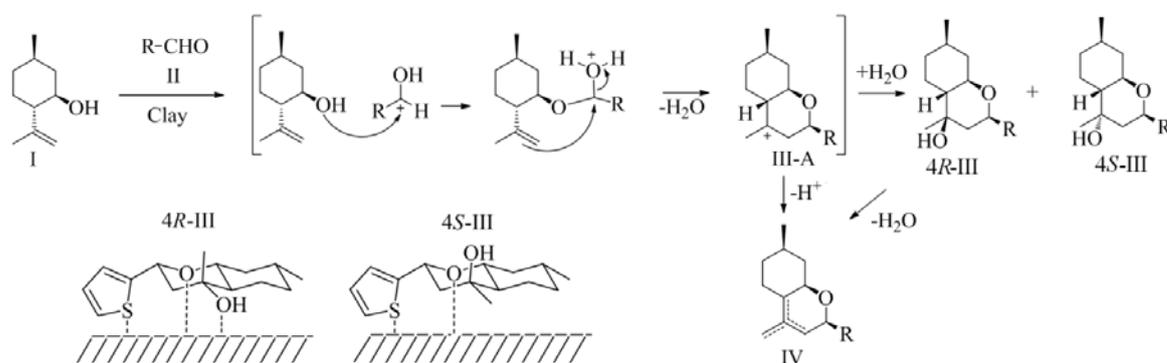
| Catalyst | Acid sites concentration, $\mu\text{mol/g}$ | <i>k</i> , $\text{L}\cdot\text{mol}^{-1}\cdot\text{min}^{-1}$ | Time, min | Selectivity, mol.% | | | | 4 <i>R</i> /4 <i>S</i> |
|---------------------|---|---|-----------|--------------------|-----------------|-----------------|------|------------------------|
| | | | | III | 4 <i>R</i> -III | 4 <i>S</i> -III | IV | |
| Modified halloysite | 46.0 | 0.03 | 360 | 90.7 | 79.0 | 11.7 | 6.3 | 6.8 |
| K-30 | 100.0 | 0.08 | 180 | 81.5 | 66.1 | 15.4 | 10.7 | 4.3 |
| K-10 | 104.0 | 0.11 | 180 | 81.6 | 66.5 | 15.1 | 10.5 | 4.4 |
| AS-36** | 153.0 | 0.01 | 420 | 83.6 | 66.3 | 17.3 | 9.9 | 3.8 |

*At 99.0% conversion **Only 50% conversion was achieved after 7 h

Selectivity to 4*R*-diastereomer increases, and to 4*S*-III decreases with decreasing a.s. concentration in the catalysts (Table 2). Simultaneously there was an increase in the 4*R*/4*S* ratio and a decrease in selectivity to dehydration by-products (IV). Thus, selective formation of the 4*R* isomer (selectivity 79.0%) on the modified halloysite can be explained by low acidity ($46.0 \mu\text{mol}\cdot\text{g}^{-1}$) of this catalyst. Note that it was recently shown that the activation energy for formation of 4*R*-isomer ($82 \text{ kJ}\cdot\text{mol}^{-1}$) was lower than for 4*S*-III ($99 \text{ kJ}\cdot\text{mol}^{-1}$) [18].

A strong dependence of stereoselectivity on the halloysite drying temperature (Table 1) requires a detailed discussion. On acid-modified clays surfaces, there are Brønsted (acidic OH– groups, H₃O⁺) and Lewis (coordinatively unsaturated and exchange Al³⁺ ions) acid sites [27]. In HNT Lewis acidity is predominant (Table S2). According to ²⁷Al NMR spectra (Figure 2) there was practically no isomorphous substitution of Al³⁺ for Si⁴⁺ in the tetrahedral halloysite layers, thus the acid sites should be located only at the ends of nanotubes. Water molecules interacting with the Lewis a.s. undergoes polarization ($[L(H_2O)_x]^{z+}=[L(OH)(H_2O)_{x-1}]^{z+1}+H^+$) and act as weak Brønsted a.s. Simultaneously acidity of these sites decreases with increasing degree of hydration [18, 27, 28].

Thus, as the halloysite drying temperature is increasing, the strength of acid sites is also increasing, concomitant with a decrease in stereoselectivity. The maximum of the 4*R*/4*S* ratio (6.8) for the air-dried HNT clearly indicates formation of 4*R* diastereomer preferably on the weak Brønsted a.s. (Scheme 2). In addition, interactions of water with HNT can be considered as poisoning of strong a.s., which is in line with the observed increase in the 4*R*/4*S* ratio with a decrease of the a.s. concentration (Table 2). Based on the results of the current work, stereoselectivity control of in acid-catalyzed reactions can be effectively realized by varying of the treatment temperature of aluminosilicate catalysts.



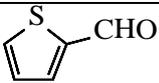
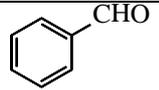
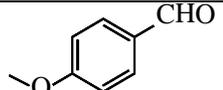
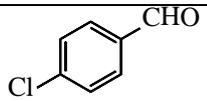
Scheme 2. The mechanism for formation of octahydro-2*H*-chromen-4-ols

An increase in selectivity to dehydration products was observed with an increase of the HNT drying temperature (Table 1) or by an increase in the concentration of a.s. (Table 2). Obviously this was accompanied by a decrease in selectivity to chromenol. Thus, dehydration occurs preferably on strong a.s. According to [18] only 4*R*-III underwent such transformation. This may be related to specific interactions of the hydroxyl in the III with the catalyst surface, which are necessary for further water removal (Scheme 2).

Considering that stereoselectivity to chromenol formation depends on the type of aldehyde [5–7,14,15], condensation of isopulegol with several aldehydes was investigated in the presence of modified HNT at 20°C to explore the reaction scope.

When conversion of isopulegol was 50%, the overall selectivity to thiophenyl-substituted octahydro-2*H*-chromen-4-ol was 94.2% with the 4*R*/4*S* equal to 7.6 (Table 3, entry 1). Selectivity to 4*R*-III isomer at 20°C was 83.3%, which is somewhat higher than at 40°C (79.0%, Table 2). Earlier it was shown that selectivity over the illite clay decreased for chromenol and increased for compounds IV with the temperature increase [18]. The activation energy for 4*R*-III formation (82 kJ·mol⁻¹) was lower than for dehydration of this isomer (91 kJ·mol⁻¹) [18].

Table 3. Products selectivity in of isopulegol condensation (at 50% conversion) with different aldehydes in cyclohexane at 20°C

| Entry | Aldehyde | Time, min | <i>k</i> , L·mol ⁻¹ ·min ⁻¹ | Selectivity, mol.% | | 4 <i>R</i> /4 <i>S</i> |
|-------|---|-----------|---|--------------------|-----|------------------------|
| | | | | III | IV | |
| 1 |  | 360 | 0.017 | 94.2 | 3.3 | 7.6 |
| 2 |  | 10 | 0.27 | 79.0 | 5.0 | 14.5 |
| 3 |  | 15 | 0.21 | 93.7 | 3.4 | 12.2 |
| 4* |  | 60 | - | 74.8 | 8.7 | 6.3 |
| 5 |  | 5 | 0.43 | 77.6 | 7.8 | 8.5 |

*Because this aldehyde is insoluble in cyclohexane, the reaction without any solvent was carried out, 99% conversion for 1 h was achieved

A very high 4*R*/4*S* ratio (12.2–14.5) with 79.0–93.7% selectivity to chromenol III was observed in the reaction of I with benzaldehyde and anisaldehyde on HNT (Table 3, entries 2,3). The diastereomers ratio over scandium triflate was lower (9.0), even the such catalyst was reported as a stereoselective one [12]. When 4-chloro-benzaldehyde was used the 4*R*/4*S* ratio on halloysite was equal to 6.4 (Table 3, entry 4). According to [6, 14], the presence of electron-acceptor substituents in the aromatic ring resulted in a sharp decrease in stereoselectivity. In condensation of I with anisaldehyde over an acid-treated K-10 clay (H-K-10) the 4*R*/4*S* value was reported as 25.0 [11]. In the current work, a much lower ratio of diastereomers (7.5) was observed on H-K-10 prepared according to procedure described in [14].

Condensation of isopulegol with aliphatic aldehydes on scandium triflate and clays typically proceeds with a relatively low stereoselectivity (4.0–5.0) [14,15]. However, in the case of

isovaleraldehyde over HNT formation of III with a high (8.5) ratio of diastereomers was observed (Table 3, entry 5), which may be related to formation of 4*R*-isomer on weak Brønsted sites. The highest rate constant was observed with isovaleraldehyde, whereas in the case of thiophene-2-carbaldehyde, it was significantly lower (Table 3).

The present work is an impressive first example of halloysite nanotubes utilization as a stereoselective catalyst for condensation of an allyl alcohol isopulegol with aldehydes. An unprecedented selectivity to 4*R*-diastereomer of thiophenyl-substituted octahydro-2*H*-chromen-4-ol possessing an analgesic effect was achieved. The 4*R*/4*S* isomers ratio increased with decreasing of catalyst acidity and the drying temperature of HNT. This clearly indicates that the key factor in formation of the 4*R*-isomer is the presence of water molecules at the ends of the nanotubes, which act as weak Brønsted acid sites. A very high stereoselectivity, significant exceeding the previously reported results, was observed in the condensation of isopulegol with aldehydes. Considering that many heterocyclic compounds have been synthesized through condensation reactions of aldehydes with alcohols or olefins, halloysite can be considered as an extremely promising catalyst for such reactants. Further research should include optimization of the acid treatment conditions, modelling reaction kinetics, and evaluation of catalyst deactivation and eventual regeneration.

Acknowledgments

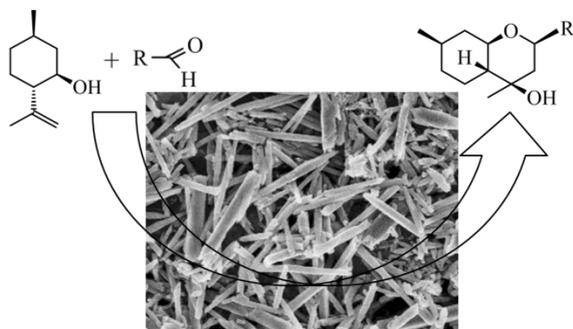
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References

1. R. Pratap, V.J. Ram, Chem. Rev. 2014, 114, 10476–10526.
2. K.U. Sadek, R.A.H. Mekheimer, M. Abd-Elmonem, A. Abdel-Hameed, M.H. Elnagdi, Tetrahedron:Asymmetry 2017, 28, 1462–1485
3. N. Majumdar, N.D. Paul, S. Mandal, B. de Bruin, W.D. Wulff, ACS Catal. 2015, 5, 2329–2366.
4. N. Thomas, S.M. Zacharian, Asian J. Pharm. Clin. Res. 2013, 6, 11–15.
5. S. Slater, P.B. Lasonkar, S. Haider, M.J. Alqahtani, A.G. Chittiboyina, I.A. Khan, Tetrahedron Lett. 2018, 59, 807–810.
6. E. Nazimova, A. Pavlova, O. Mikhalchenko, I. Il'ina, D. Korchagina, T Tolstikova, K. Volcho, N. Salakhutdinov, Med. Chem. Res. 2016, 25, 1369–1383.
7. E.V. Nazimova, A.A. Shtro, V.B. Anikin, O.S. Patrusheva, I.V. Il'ina, D.V. Korchagina, V.V. Zarubaev, K.P. Volcho, N.F. Salakhutdinov, Chem. Nat. Comp. 2017, 53, 260–264.
8. I.V. Ilyina, V.V. Zarubaev, I.N. Lavrentieva, A.A. Shtro, I.L. Esaulkova, D.V. Korchagina, S.S. Borisevich, K.P. Volcho, N.F. Salakhutdinov, Bioorg. Med. Chem. Lett. 2018, 28, 2061–2067.
9. P.N. Moquist, T. Kodama, S.E. Schaus, Angew. Chem. Int. Ed. 2010, 49, 7096–7100.

10. O. El-Sepelgy, S. Haseloff, S.K. Alamsetti, C. Schneider, *Angew. Chem. Int. Ed.* 2014, 53, 1–6.
11. N. Casanova, A. Seoane, J.L. Mascareñas, M. Gulías, *Angew. Chem. Int. Ed.* 2015, 54, 1–5.
12. L.F Silva Jr., S.A. Quintiliano, *Tetrahedron Lett.* 2009, 50, 2256–2260.
13. A. Macedo, E.P. Wendler, A.A. Dos Santos, J. Zukerman-Schpector, E.R.T Tiekink, *J. Braz. Chem. Soc.* 2010, 21, 1563–1571.
14. G. Baishya, B. Sarmah, N. Hazarika, *Synlett.* 2013, 24, 1137–1141.
15. J.S. Yadav, B.V. Subba Reddy, A.V. Ganesh, G.G.K.S. Narayana Kumar, *Tetrahedron Lett.* 2010, 51, 2963–2966.
16. M. Stekrova, P. Mäki-Arvela, N. Kumar, E. Behraves, A. Aho, Q. Balme, K.P. Volcho, N.F. Salakhutdinov, D.Yu. Murzin, *J. Mol. Cat. A: Chem.* 2015, 410, 260–270.
17. M.N. Timofeeva, V.N. Panchenko, K.P. Volcho, S.V. Zakusin, V.V. Krupskaya, A. Gil, O. S. Mikhalchenko, M. A. Vicente, *J. Mol. Cat. A: Chem.* 2016, 414, 160–166.
18. A.Yu. Sidorenko, A.V. Kravtsova, J. Wärnä, A. Aho, I. Heinmaa, I.V. Il'ina, O.V. Ardashov, K.P. Volcho, N.F. Salakhutdinov, D.Yu. Murzin, V.E. Agabekov, *Mol. Cat.* 2018, 453, 139–148.
19. D. Yuan, D Tan, F. Annabi-Bergaya, *Appl. Clay. Sci.* 2015, 112-113, 75–93.
20. P. Pasbakhsh, G.J. Churchman, J.L. Keeling, *Appl. Clay Sci.* 2013, 74, 47–57.
21. P. Pasbakhsh, R. de Silva, V. Vahedi, G.J. Churchman, *Clay Min.* 2016, 51, 479–487.
22. Y. Lvov, A. Aerov, R. Fakhrullin, *Adv. Colloid Interf. Sci.* 2014, 207, 189–198.
23. E. Abdullayev, A.Joshi, W. Wei, Y. Zhao, Y. Lvov, *ACS Nano.* 2012, 6, 7216– 7226.
24. L. Zatta, J.E.F. da Costa Gardolinski, F.Wypych, *Appl. Clay Sci.* 2011, 51, 165–169.
25. V.M. Abbasov, H.C. Ibrahimov, G.S. Mukhtarova, E. Abdullayev, *Fuel*, 2016, 184, 555–558.
26. Z. Zhao, J. Ran, Y. Jiao, W. Li, B. Miao, *Appl. Cat A:Gen.*, 2016, 513, 1–8.
27. F. Bergaya, G. Lagaly, *Handbook of Clay Science, Part A: Fundamental*, Elsevier, Amsterdam, 2013 .
28. S. Yariv, H. Cross, *Organo-Clay Complexes and Interactions*. Marcel Dekker, New York, 2002.

Nanotubes for stereoselective synthesis. Halloysite nanotubes were used for the first time as a catalyst for preparation of heterocycle compounds (octahydro-2*H*-chromenols) by condensation of allyl alcohol isopulegol with aldehydes. A very high diastereomer ratio exceeding the previously reported results with 74.8–94.2% overall selectivity was achieved. A key factor in the stereoselectivity control is the amount of water molecules on the nanotubes surface acting as Brønsted acid sites.



Keywords: Halloysite nanotubes, Stereoselective catalysis, Chromene, Acidity