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Beyond Acid Strength in Zeolites: Soft Framework Counteranions for Stabilization of Carbocations on Zeolites and Its Implication in Organic Synthesis**

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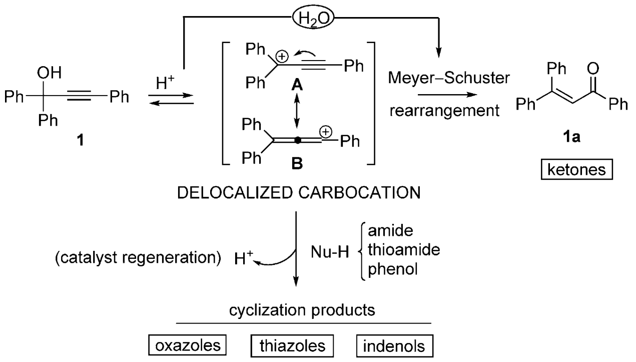
Abstract: *The generation of a carbocation with an acid depends not only on the acid strength but also on the ability of the counteranion to stabilize the positive charge left behind. Here we report that despite their relatively weak acidity, zeolites are able to generate and stabilize medium-size (molecular weight ≈300 Da) delocalized carbocations on their surface under mild reaction conditions, as it can be done by strong Brønsted or Lewis acids in solution. The zeolite thus acts as a soft macroanion, prolonging the lifetime of the carbocation sufficiently to perform multifunctionalization reactions with amides, thioamides, and phenols, with high yield and selectivity. Biological studies show that some of the products obtained here present significant inhibition activity against colon cancer cells, illustrating the new possibilities of zeolites to prepare complex organic molecules.*

Carbocations are valuable intermediates in organic synthesis with a tendency to easily accept incoming nucleophiles.[1] When the positive charge is delocalized, the carbocation can act as an ambident electrophile that performs multifunctionalizations in one-pot. Among the myriad of methods to generate carbocations, the most common is the removal of a leaving group on the carbon atom by acidification and stabilization of the positive charge left behind by a suitable counteranion. Because carbocations are soft in nature, soft counteranions with highly delocalized electron clouds such as triflate (OTf^-), triflimide (NTf_2^-), tetrafluoroborate (BF_4^-), and hexafluoroantimonate (SbF_6^-) are commonly employed, despite the inherent difficulties to handle such strong acids in solution ($H_0 < 12$).

Aluminosilicates are solid acids with industrial applications for ion-exchange, gas separation, and catalysis.[2] Between them, zeolites are by volume the most used catalysts worldwide, with an important impact in both petrochemical and fine chemical industries, but its use in advanced organic processes for medium-size molecules with molecular weights >300 Da is still limited due to pore size restrictions and relatively low acid strength.[3] However, zeolites can stabilize carbocations by the high degree of delocalization of the negative charge across the zeolite framework, so if a zeolite with larger external surface area could efficiently form and stabilize carbocations of synthetic interest on the surface, the number of catalytic transformations for advanced organic synthesis with zeolites would increase significantly. Such well-stabilized carbocation intermediates are also found in some "transition-metal-catalyzed" reactions where in situ-generated acids are the catalytically active species.[4]

Here we show that different zeolites can generate and stabilize delocalized carbocations after dehydration of propargyl alcohols, under mild reaction conditions, and then catalyze the synthesis of a variety of bioactive oxazoles, thiazoles, and indenols with high yield, selectivity, and turnovers, giving water as the only by-product. Most importantly, the catalysts are very stable toward deactivation.

Scheme 1 shows the equilibrium reaction of propargyl alcohol **1** with a proton to generate a delocalized carbocation. Propargyl alcohols have been presented in the last years as synthons for many organic reactions catalyzed by Brønsted and Lewis acid catalysts,[5] because they are dual proelectrophiles[6] that react with various nucleophiles in atom-economical processes. Because water can re-enter in the absence of any other nucleophile, the formation of the carbocation can be indirectly observed by the presence of the Meyer–Schuster product **1a**.



Scheme 1. Formation of a delocalized carbocation from propargyl alcohol **1** with an acid, and catalytic addition of amides, thioamides, and phenols to give oxazoles, thiazoles, and indenols, respectively. In the absence of another nucleophile water often re-enters to give the Meyer–Schuster rearrangement to ketone **1a**.

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Though reactant **1** is too large to diffuse through the pores of a large-pore zeolite like faujasite, it may react on the acid sites accessible through the external surface of the zeolite and may generate the corresponding carbocation. To test that possibility, we selected an USY acidic zeolite (Si/Al ratio = 15) that presents mesopores, giving larger external surface area than the starting NaY zeolite. Then, an ethanolic solution of compound **1** was added on H-USY and a rapid change of color was observed. In situ infrared experiments (IR, Figure S1 in the Supporting Information, SI) showed the formation of minor amounts of ketone **1a**,[7] which may indicate that the delocalized carbocation given in Scheme 1 is being formed and, at some extent, reacting with H_2O. To further confirm this, we synthesized the isotopically-labeled ^{13}C-propargyl alcohol **1** (^{13}C-1,1,3-triphenylpropargyl alcohol **1**; Scheme S1)[8] and the evolution of the marked substrate in solution in the presence of catalytic amounts of H-USY (5 wt%) or triflic acid (HOTf, 20 mol%) was followed by in situ ^{1}H and ^{13}C NMR spectroscopy. The results in Figure 1 show that the signal in the ^{1}H NMR spectrum at 5.52 ppm corresponding to the hydroxy group of the alcohol slighty decreases for the zeolite (**B** and **C**) and disappears for triflic acid (**D**). Additionally, an increase of the water signal at 2.15 ppm was observed for the zeolite (**B** and **C**) and aromatic signals of ketone **1a** appeared at ca. 8 ppm for triflic acid (**D**). These results indicate that a minor product is formed with H-USY that cannot be detected by NMR spectroscopy. A ^{13}C NMR measurement (Figure S2) confirms this point.

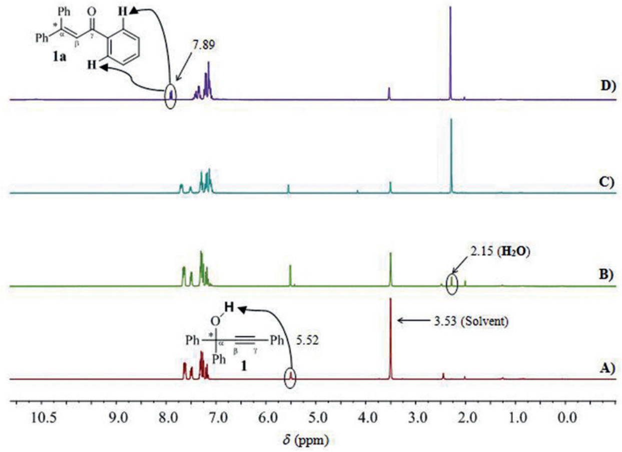

Figure 1. In situ ^{1}H NMR experiments of the isotopically labeled ^{13}C-propargyl alcohol **1** in acid conditions using 1,4-dioxane-d$_8$ as a solvent. A) compound ^{13}C-**1**; B) compound ^{13}C-**1** in the presence of 5 wt% of H-USY zeolite at 100 °C after 15 min; C) compound ^{13}C-**1** in the presence of 5 wt% of H-USY zeolite at 100 °C after 20 h; and D) compound ^{13}C-**1** in the presence of 20 mol% of HOTf at 100 °C after 15 min.

To directly detect the carbocation, we performed diffuse-reflectance UV/Vis spectroscopy measurements of the zeolite impregnated with the propargyl alcohol. We expected that the delocalized carbocation would have a long enough lifetime to observe the extinction molar coefficient, even at very low concentration. Figure 2 shows a new band in the UV/Vis spectrum of the H-USY zeolite after impregnation with **1** (line A), and this band nicely fits with that of the carbocation generated in solution with a catalytic amount of a very soft acid such as triflimidic acid (line B). Notice that the intensity of the band decreases for harder acids than triflimidic acid such as HCl and *para*-toluenesulfonic acid (*p*-TSA; lines C and D). These results are in line with the lower amount of ketone **1a** detected by NMR with the H-USY zeolite and triflimidic acid, suggesting that the carbocation forms and stays longer with the softer acids. Thus, we can say that the carbocation of **1** can be formed on H-USY with an efficiency that is, at least, comparable with typical strong Brønsted acids such as HCl, *p*-TSA, HOTf, and $HNTf_2$.

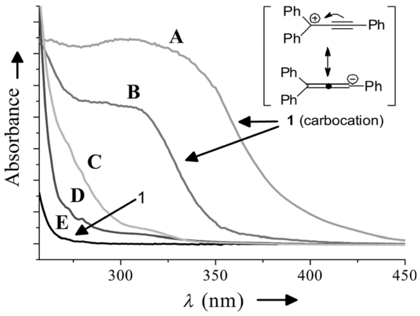

Figure 2. Diffuse-reflectance (A) and UV/Vis (B–E) (in 1,4-dioxane) spectra of compound **1** under acidic conditions: A) compound **1** impregnated in H-USY zeolite as an ethanolic solution, of which the ethanol was evaporated by drying at 60 °C; B) compound **1** in solution after addition of 5 mol% of triflimidic acid $HNTf_2$ at 100 °C; C) compound **1** after addition of 5 mol% of HCl at 100 °C; D) compound **1** after addition of 5 mol% of *p*-TSA at 100 °C; and E) compound **1**.

If the formation of the carbocation would exclusively depend on the acid strength of the catalyst, the weaker acidity of the H-USY zeolite should hardly promote the reaction according to its much lower pK_a (or H_0) value.[9] Thus another factor such as the properties of the counteranion is playing a key role on the formation and stabilization of the carbocation on the zeolite. A possible way to determine the influence of the proton and of the counteranion on the formation of the carbocation separately would consist in correlating the activation energy (E_a) of the reaction with an acidity parameter (H_0 or pK_a) of the catalyst.[10] If the acid strength is the only responsible factor for the formation of the carbocation, a linear relationship between E_a and the acid strength should be found. On the other hand, if the counteranion is further stabilizing the carbocation, a lower E_a of that expected from the corresponding pK_a of the acid will be observed.

Figure 3 shows that a straight line is found for different sulfonic acids (methylsulfonic MeSA, *p*-TSA, and TfOH) indicating that mainly the acid strength controls the carbocation formation when sulfonate is the counteranion. However, triflimidic acid $HNTf_2$ shows a similar activation energy than TfOH despite having a much lower acidity,[11] with an additional stabilization of ca. 30–60 kJ mol^{-1} (depending on the acid parameter considered) due to the highly delocalized triflimidate anion. Remarkably, the H-USY zeolite behaves like $HNTf_2$, with a stabilization of about 40 kJ mol^{-1}.

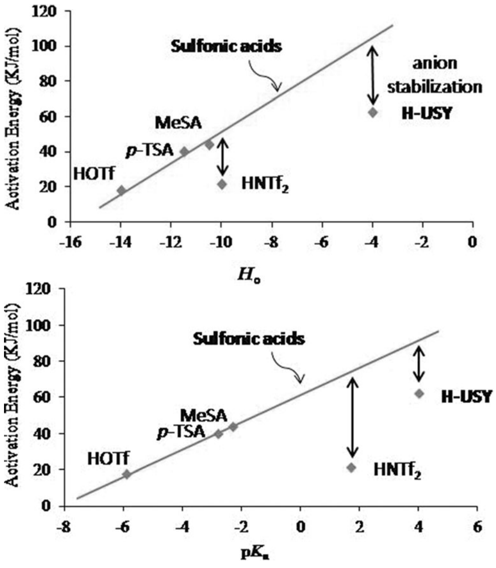

Figure 3. Activation energy–acidity values (H_0, top; pK_a, bottom) plot for different acids and H-USY zeolite. The activation energies of the reaction are calculated from the initial rate of the Meyer–Schuster rearrangement, by in situ NMR measurements (see Figure S3 for calculations). High catalytic loadings of H-USY (120 wt %) and $HNTf_2$ assure rapid formation of the ketone.

The results in Figure 3 would indicate that the efficient formation of the carbocation of **1** on H-USY occurs after stabilization by the delocalized framework of the solid, thus overriding the necessity of having a strong acidity in the reaction medium. In other words, the softness of acid zeolites helps to stabilize soft carbocation intermediates, giving a chance to the zeolites for catalyzing reactions occurring through such a type of carbocations.

Figure 4 shows the results for the reaction between different propargyl alcohols and nucleophiles such as aryl and alkyl amides, aryl and alkyl thioamides, and mono- or dimethyl-substituted phenols when catalyzed by 5–10 wt % of H-USY (Si/Al = 15). For instance, when **1** was reacted with benzamide **2** the corresponding oxazole **3** was cleanly formed in 94 % yield. A variety of oxazoles (compounds **3**–**8**), thiazoles (compounds **10**–**12** and **14**–**15**), and indenols (compounds **16**–**17**) can be constructed from trisubstituted propargyl alcohols with high conversions and selectivities. Meanwhile, the products obtained for disubstituted propargyl alcohols (compounds **9**, **13**, and **18**–**20**) are those corresponding to simple nucleophilic substitutions.[12] Notice that this modular approach is suitable for the synthesis of compound libraries.

The products in Figure 4 have further synthetic use and a potential biological activity. For instance, oxazoles constitute an important member of the aromatic heterocycle family[13] with wide use as building blocks in organic synthesis[14] and as biologically active molecules.[15] Thiazoles and indenols are also important heterocycles in organic synthesis, present in many natural products and in biologically and pharmaceutically active compounds.[16] A list with some reported synthetic methods for these molecules is included in the SI (Table S1) and, despite the plethora of Brønsted and Lewis acid catalysts previously used for these reactions,[17] the turnover numbers (TON) and turnover frequencies (TOF, h^{-1}) achieved to date are always < 100, selectivity and catalyst amount varies widely, and no solid catalysts have been reported.[18,19]

H-USY gives a $TOF_0 = 845\ h^{-1}$ (Figure S4) for the synthesis of oxazole **3**, which is significantly higher than that for any other acid catalyst reported to date and for any other nucleophilic addition to a propargyl alcohol, as far as we know. Since even in the mesoporous H-USY zeolite there is an important part of the microporous surface that is not accessible to the bulky reactant, a 2D-layered ITQ-2[20] delaminated zeolite with a higher external surface area was also used as a catalyst (see Tables S2 and S3 and Figures S5–S8 for characterization data of the solid acid catalysts). Note that the delaminated zeolite has a higher Si/Al ratio and a lower amount of acid sites. ITQ-2 (Si/Al = 25) with large

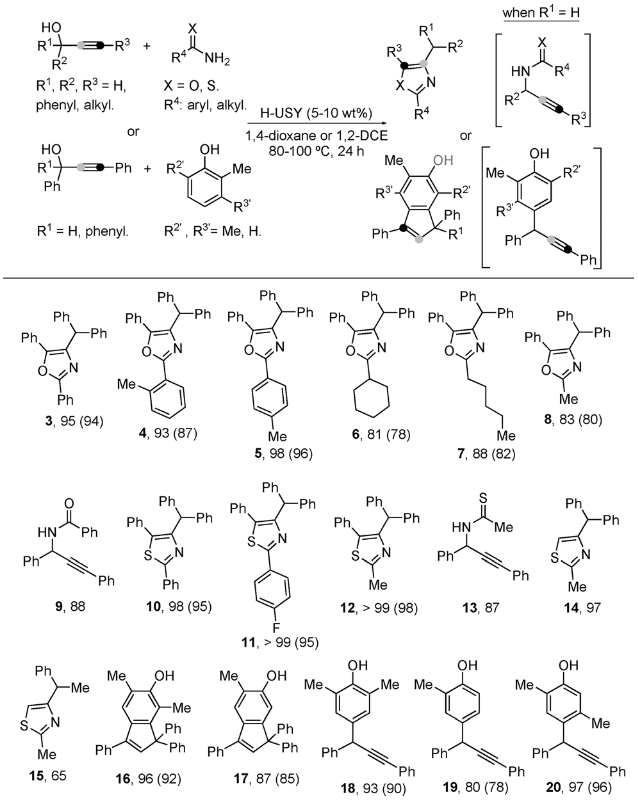

Figure 4. Scope of the cyclization reaction between substituted propargyl alcohols and various nucleophiles, catalyzed by H-USY zeolite (Si/Al = 15). GC yields [%], yields [%] of isolated products in parentheses. For the reaction of substituted propargyl alcohols with thioamides and phenols, the previous dehydration of the H-USY zeolite was not necessary. Reaction conditions for compounds **3** and **6**–**11**: H-USY zeolite (5 wt %) previously dehydrated under vacuum at 300 °C for 2 h, propargyl alcohol (0.5 mmol), amide (1 mmol), and anhydrous 1,4-dioxane (4 mL) at 100 °C for 24 h. For compounds **9**–**11** reaction time was 75 h. For compounds **5** and **12**–**16** the solvent was 1,2-DCE (1,2-dichloroethane, 4 mL). For **15** the reaction time was 48 h and for **16** it was 100 h. For compounds **17**–**21**: H-USY zeolite (10 wt %), propargyl alcohol **1** (0.5 mmol), phenol (1 mmol), and anhydrous 1,2-DCE (4 mL) at 80 °C for 72 h. For compounds **17**–**18** the reaction time was 24 h.

accessibility gives a TOF_0 of ca. $600\,h^{-1}$; nevertheless, the much lower number of acid sites in ITQ-2 gives a lower reaction rate compared to that of H-USY. The benefits of accessibility of the acid sites are also illustrated by the increase in TOF_0 found for the H-Beta zeolite in nanocrystalline form[21] when compared with the regular H-Beta zeolite. Amorphous aluminosilicates such as silica-alumina and standard MCM-41 were tested and their activity was lower than that of H-USY (Table S4). Besides that, H-USY is recyclable without loss of yield throughout six reuses (Figure S9).

Following previously proposed mechanisms for homogeneous acid catalysts[17j–l] and the above experiments in which the intermediate carbocation was detected, Scheme 1 shows what could be a general mechanism for the nucleophilic addition to propargyl alcohols with a zeolite catalyst. The first step is the formation of the carbocation on the acid sites, followed by nucleophilic attack and cyclization.

Complementary to the catalytic work, the biological activity against colon cancer cells for a series of molecules synthesized by the above zeolite-catalyzed procedure is presented (Figure S10 and Tables S5 and S6).[22] The inhibition percentages in Colo 320 KrasSL cells at a concentration of 0.2 μM were significant for most of the compounds, and **16** and **20** showed IC_{50} values for hNCI-H716 and mSTC-1 cell lines similar to those of the currently used drugs Irinotecan and 5-fluorouracil.[23] These results show the possibilities of using zeolites for the preparation of bulky bioactive anticancer molecules.

In summary, delocalized carbocations can be formed after dehydration of propargyl alcohols on the surface of the H-USY zeolite due to the stabilization of the carbocation by the highly delocalized negative charge of the solid framework. The in situ addition of different amides, thioamides, and phenols to the carbocations proceeds with a catalytic efficiency comparable to much stronger homogeneous acids to give a variety of heterocycles, fused cycles, and other products of interest for organic synthesis in high yields and selectivity. Some of these compounds show significant biological activity as anticancer agents. The experimental procedure shown here is simple, sustainable, and effective, and opens a new way to prepare complex organic molecules with zeolite catalysts.

Keywords: carbocations · cycloaddition reactions · heterogeneous catalysis · propargyl alcohols · zeolites

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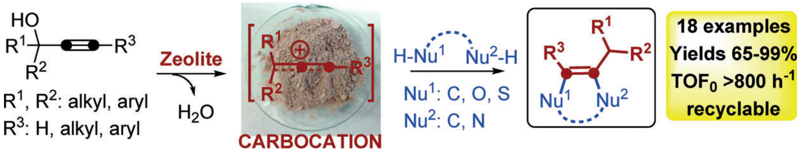

Stabilized carbocations: Zeolites are able to generate and stabilize medium-size (molecular weight ≈300 Da) delocalized carbocations on their surface under mild conditions to perform multifunctionalization reactions with catalytic activities comparable to that of strong homogenous Brønsted acids. Some of the products obtained here exhibit significant inhibition percentages against colon cancer cells.