Beyond acid strength in zeolites: Soft framework counteranions for stabilization of carbocations on zeolites and its implication in organic synthesis

Jose R. Cabrero–Antonino,[a] Antonio Leyva–Pérez,*[a] and Avelino Corma.*[a]

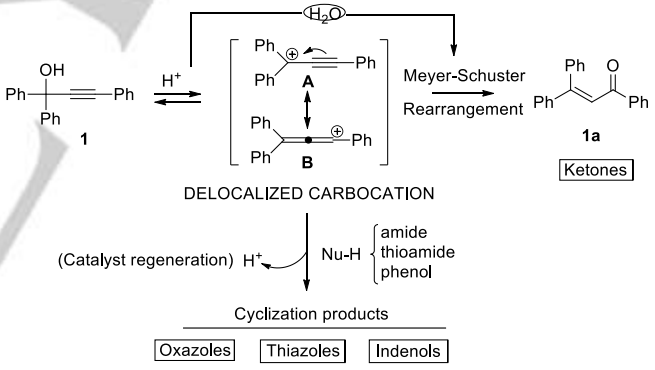
Abstract: The generation of a carbocation with an acid depends not only on the acid strength but also on the ability of the counteranion to stabilize the positive charge left behind. Here we report that despite their relatively weak acidity, zeolites are able to generate and stabilize on their surface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

Carbocations are valuable intermediates in organic synthesis with tendency to accept easily incoming nucleophiles.[1] When the positive charge is delocalized, the carbocation can act as an ambident electrophile that performs multi–functionalizations 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 counternanion. Since carbocations are soft in nature, soft counteranions with highly delocalized electron clouds such as triflate (OTf^-), triflimide (NTf_2^-), tetrafluoroborate (BF_4^-) or 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 towards 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 synthone molecules for many organic reactions catalyzed by Brønsted and Lewis acid catalysts[5] since they are dual proelectrophiles[6] that react with various nucleophiles in atom–economical processes. Since 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 any other nucleophile water often re–enters to give the Meyer–Schuster rearrangement to ketone **1a**.

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 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–labelled ^{13}C propargyl alcohol **1** (^{13}C–1,1,3–

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triphenylpropargyl alcohol **1**, see Scheme S1 in SI)[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–nuclear magnetic resonance (NMR). The results in Figure 1 show that the signal in ^{1}H–NMR at 5.52 ppm corresponding to the hydroxyl group of the alcohol decreases for the zeolite (**B** and **C**) and disappears for triflic acid (**D**), observing the increasing of the water signal at 2.15 ppm for the former and the appearance of the aromatic signals of ketone **1a** at ~8 ppm for the latter. These results indicate that, apart from **1a**, a second non–detectable product by NMR is been formed with H–USY. ^{13}C–NMR (Figure S2) confirms this point.

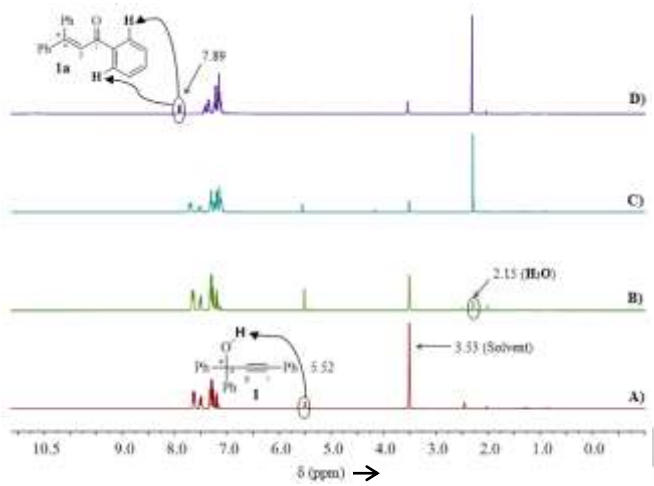

Figure 1. *In situ* ^{1}H–NMR experiments of the isotopically labelled ^{13}C–propargyl alcohol **1** in acid conditions using 1,4–dioxane–d_8 as a solvent**. A**) compound ^{13}C–**1**, **B**) compound ^{13}C–**1** in the presence of 5 wt% of H–USY zeolite at 100 ºC after 15 min, **C**) compound ^{13}C–**1** in the presence of 5 wt% of H–USY zeolite at 100 ºC after 20 h and **D**) compound ^{13}C–**1** in the presence of 20 mol% of HOTf at 100 ºC after 15 min.

To directly detect the carbocation, we performed the diffuse–reflectance UV–Vis spectroscopy measurement of the zeolite impregnated with the propargyl alcohol. We expected that the delocalized carbocation would have a high enough lifetime and extinction molar coefficient to be observed, 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 triflic acid, HCl or *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 onto H–USY with an efficiency, at least, comparable with typical strong Brønsted acids such as HCl, *p*–TSA, HOTf and $HNTf_2$.

If the formation of the carbocation would depend exclusively on the acid strength of the catalyst, the weaker acidity of H–USY zeolite should hardly give 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

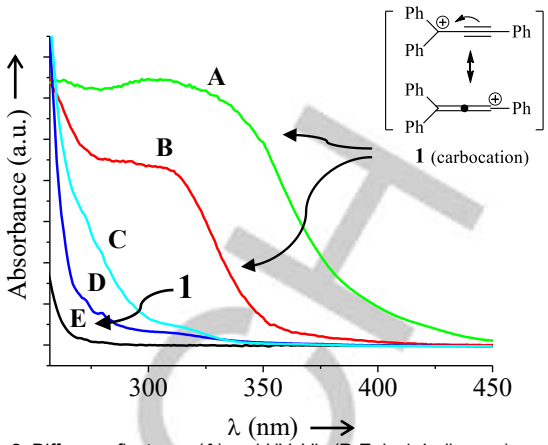

Figure 2. Diffuse–reflectance (**A**) and UV–Vis (**B-E**, in 1,4–dioxane) spectra of compound **1** in acid conditions: **A**) compound **1** impregnated in H–USY zeolite as an ethanolic solution, where the ethanol was evaporated by drying at 60 ºC, **B**) compound **1** in solution after addition of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

zeolite. A possible way to determine separately the influence of the proton and also the influence of the counteranion on the formation of the carbocation would consist in representing the activation energy (E_a) of the reaction *vs.* an acidity parameter (H_0 or pK_a) of the catalyst.[10] If the acid strength is the only responsible for the formation of the carbocation, a linear relationship between E_a and 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 found.

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 ~30–60 KJ/mol (depending on the acid parameter considered) due to the highly delocalized triflimidate anion. Remarkably, the H–USY zeolite behaves as $HNTf_2$, with a ~40 KJ/mol stabilization.

The results in Figure 3 would indicate that the efficient formation of the carbocation of **1** onto 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% isolated yield. A variety of oxazoles (compounds **3–8**), thiazoles (compounds **10–12** and **14–15**) and indenols (compounds **16–17**) can be built–up 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

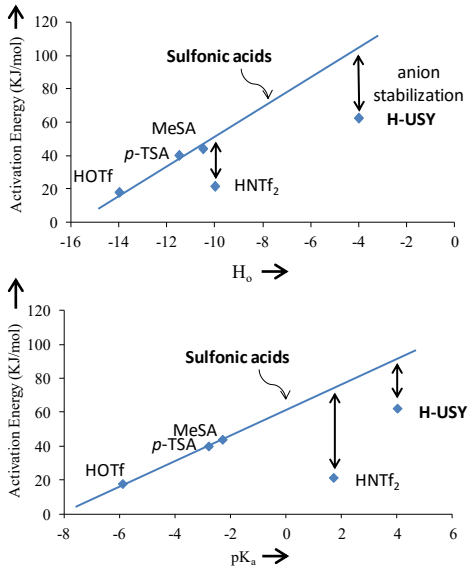

Figure 3. Activation energy–acidity values (H_0, top; pK_a, bottom) plot for different acids and H–USY zeolite. The activation energies of the reaction are calculated from the initial rate of the Meyer-Schuster rearrangement, by in–situ NMR measurements (see Figure S3 for calculations). High catalytic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

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 block 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 biological and pharmaceutical 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 to 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–S3 and Figures S5–S8 for characterization data of the solid acid catalysts). Notice that the delaminated zeolite has a higher Si/Al ratio and a lower amount of acid sites. ITQ–2 (Si/Al=25) with large accessibility gives a TOF_0 of ~600 h^{-1}, nevertheless the much lower number of acid sites in ITQ–2 gives a lower reaction rate than H–USY. The benefits of accessibility to 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 H–USY (Table S4). Besides that,

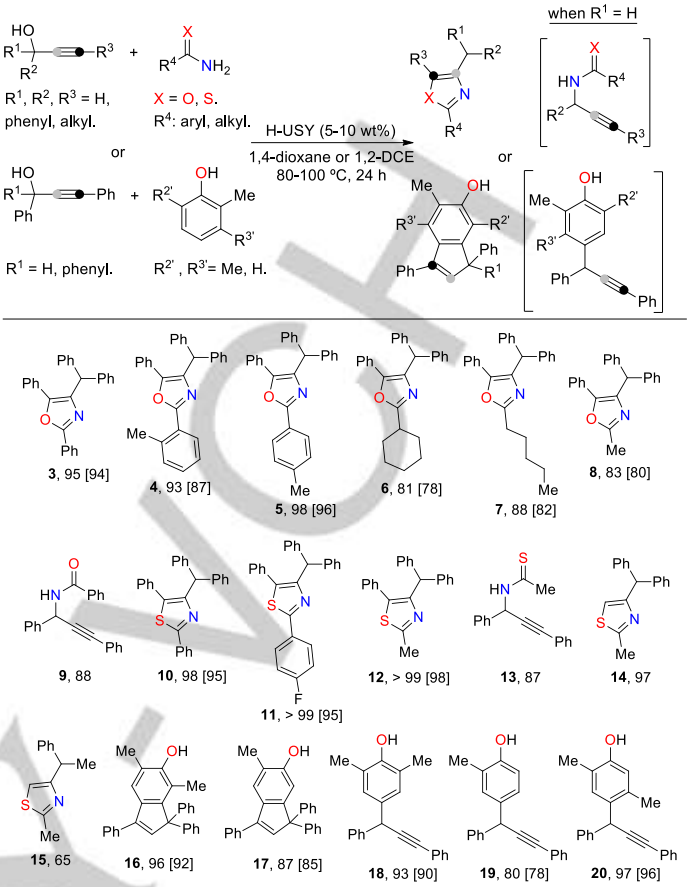

Figure 4. Scope of the cyclization reaction between substituted propargyl alcohols and various nucleophiles, catalyzed by H–USY zeolite (Si/Al = 15). GC yields, between brackets isolated yields. For the reaction of substituted propargyl alcohols with thioamides and phenols, the previous dehydration of 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 ºC for 2 h, propargyl alcohol (0.5 mmol), amide (1 mmol), and anhydrous 1,4–dioxane (4 mL) at 100 ºC for 24 h. For compounds **9–11** reaction time was 75 h. For compounds **5** and **12–16** the solvent was 1,2–DCE (4 mL). For **15** the reaction time was 48 h and for **16** 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 ºC for 72 h. For compounds **17–18** the reaction time was 24 h.

H–USY is recyclable, without losses of yield throughout six reuses (see Figure S9 in SI).

Following previously proposed mechanisms for homogeneous acid catalysts[17j–l] and the above experiments in where 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, where the first step is the formation of the carbocation on the acid sites, followed by nucleophilic attack and cyclization.

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

In summary, delocalized carbocations can be formed after dehydration of propargyl alcohols on the surface of 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 in organic synthesis in high yields and selectivity. Some of these compounds show significant biological activity as anticancer agents. The experimental procedure showed here is simple, sustainable and effective, and opens a new way to prepare complex organic molecules with zeolite catalysts.

Acknowledgements

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

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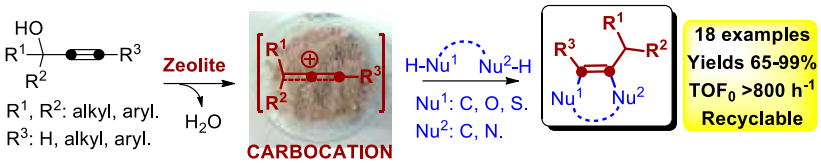

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Zeolites as active and selective catalysts by stabilizing intermediate carbocations at mild reaction conditions: Synthesis of oxazoles, thiazoles and indenols for pharma applications