Heterogeneous Catalysis

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Acid–Base Pairs in Lewis Acidic Zeolites Promote Direct Aldol Reactions by Soft Enolization**

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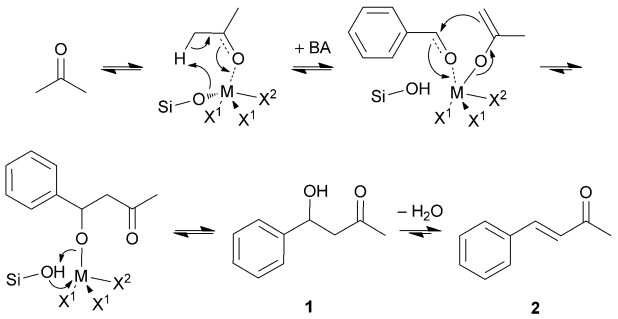
Abstract: *Hf-, Sn-, and Zr-Beta zeolites catalyze the cross-aldol condensation of aromatic aldehydes with acetone under mild reaction conditions with near quantitative yields. NMR studies with isotopically labeled molecules confirm that acid-base pairs in the Si-O-M framework ensemble promote soft enolization through α-proton abstraction. The Lewis acidic zeolites maintain activity in the presence of water and, unlike traditional base catalysts, in acidic solutions.*

Aldol condensation is a key carbon–carbon (C–C) coupling reaction in organic synthesis and has triggered considerable interest in the development of biomass conversion schemes.[1] For example, the cross-aldol reaction between furfural derivatives and acetone has been exploited to generate C_8–C_{15} hydrocarbons using metal oxides,[2] hydrotalcites,[3] and homogeneous mineral base catalysts.[4] Strong bases are typically used because they readily abstract α-protons and generate the enolate intermediate required for C–C bond formation. However, the use of base catalysts for these reactions faces major challenges. Homogeneous mineral bases are unable to activate molecules with hydroxycarbonyl groups because of the preferential formation of alkoxide ions,[1f] and they require more complex separations.[5] Solid bases are preferable, but they easily deactivate in the presence of acids,[6] such as acetic acid, which are ubiquitous in biomass processing.[7] Lewis acidic zeolites have recently emerged as exceptional catalysts for the activation of carbonyl-containing molecules,[8] thus affording the opportunity to promote aldol reactions under conditions that are generally considered unsuitable for direct C–C bond formation. Specifically, akin to hybrid organic-inorganic aminosilica materials[9] and enzymatic systems,[10] the acid-base pairs in these inorganic solids are capable of cooperatively activating carbonyl compounds, yet Lewis acidic zeolites can tolerate common poisons and regeneration by thermal treatments.

While Sn-Beta has recently been shown to promote the self-aldol addition of glycolaldehyde[1d] and the aldol condensation of 1,3-dihydroxyacetone with glyceraldehyde[1b] and formaldehyde,[1a] C–C coupling with Lewis acidic zeolites is still poorly understood. Herein we demonstrate that Hf-, Sn-, and Zr-Beta zeolites are highly active catalysts for the cross-aldol condensation of aromatic aldehydes with acetone under mild reaction conditions. Isotopic labeling studies show that framework acid-base pairs promote keto–enol tautomerization through the transfer of an α-proton to the zeolite lattice. According to the proposed mechanism shown in Scheme 1, the metal center polarizes the carbonyl group of acetone, which acidifies the α-proton. The framework oxygen atom bound to the metal atom acts as a base that abstracts the α-proton, thereby generating a silanol group and a metal enolate that readily undergoes C–C coupling with aldehydes. Copéret et al. have recently shown that similar proton-transfer steps occur during the activation of ethylene polymerization with silica-grafted chromium(III) sites.[11]



Scheme 1. Proposed reaction mechanism for the aldol condensation of benzaldehyde (BA) and acetone catalyzed by Lewis acidic Beta zeolites. M = metal atom; X^1 = the zeolite framework beginning with OSi≡; and X^2 = OSi≡ or OH.

Fully deuterated acetone ([D_6]acetone) was used for ^{13}C and ^1H NMR spectroscopic studies on the reversible keto–enol tautomerization of acetone in the presence of either Hf-Beta or Sn-Beta. As shown in Scheme S1 in the Supporting

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Information, a mechanism proceeding via a metal enolate using [D_6]acetone would result in the transfer of an α-deuterium to form a silanol group in the zeolite framework. This deuterium atom would readily scramble in the presence of unlabeled hydroxy groups. The ^{13}C NMR spectra in Figure 1 show that upon heating to 363 K for 8 hours in the

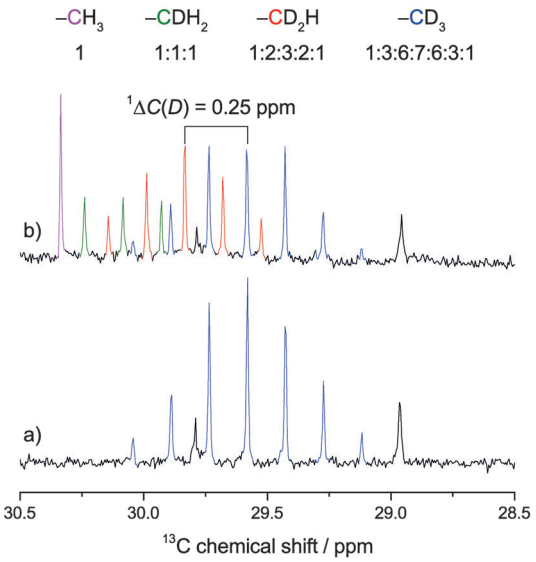
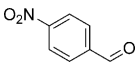
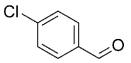
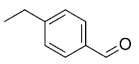
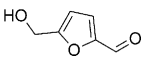


Figure 1. ^{13}C NMR spectra of [D_6]acetone before (a) and after (b) reaction in the presence of Hf-Beta and *t*BuOH at 363 K for 8 h.

presence of Hf-Beta and *tert*-butanol (*t*BuOH), [D_6]acetone progressively lost its isotopic labels. Prior to reaction, the spectrum of [D_6]acetone displayed the expected 1:3:6:7:6:3:1 septet for the methyl carbon atoms. After the reaction, a 1:2:3:2:1 quintet, a 1:1:1 triplet, and a singlet were observed, which correspond to acetone molecules with CD_2H, CDH_2, and CH_3 groups, respectively. These signals exhibit the characteristic splitting pattern resulting from ^{13}C-^{2}H *J* coupling and are shifted by −0.25 ppm, from $\delta = 29.58$ ppm, per proton added from [D_6]acetone because of the isotope effect. Deuteron–proton exchange is also supported by the observed changes in the ^{13}C NMR resonances of the carbonyl carbon atom and ^{1}H NMR signals that are consistent with methyl groups on partially deuterated acetone, as well as a decrease in the molecular weight of acetone as confirmed by mass spectrometry (see Figures S1–S3). Identical results were observed with Sn-Beta (see Figures S4 and S5). Acetone condensation products were not detected with either catalyst. Experiments conducted with reversed isotopic labeling (i.e., using acetone and [D]*tert*-butanol) showed the expected ^{13}C NMR resonance changes and larger mass fragments in the mass spectrum (see Figures S6 and S7). Importantly, control reactions with Si-Beta and without catalyst did not change the chemical environment of [D_6]acetone. We note that diffuse reflectance UV-visible (DRUV) and ^{119}Sn NMR spectra (for Sn-Beta) rule out the presence of high concentrations of extra-framework species (see Figures S12 and S13).[12] Taken together, these data clearly show that framework sites in Lewis acidic zeolites enolize acetone by activating its α-hydrogen atoms. Similarly, Bell et al. showed that oxygen atoms with increased basicity in the first coordination sphere of the active site in Sn-Beta abstract protons from hydroxy groups of glucose to facilitate ring-opening for isomerization reactions.[13] Our results are also intriguing in view of the studies by Davis et al. showing that framework sites catalyze the isomerization of glucose into fructose in water through an intramolecular CH hydride shift, whereas extra-framework SnO_2 sites catalyze the reactions by proton transfer and enolization.[14] Evidently, enolization with framework sites is dependent on the nature of the metal center, the substrate, and the solvent.

The aldol condensation of benzaldehyde (BA) with acetone in toluene was used as a model reaction to study the catalytic performance of a range of Lewis acidic zeolites (Table 1). Hf- and Zr-Beta showed the highest aldol condensation activity at 363 K, achieving conversions of more than 90% with up to 97% selectivity toward the dehydrated cross-aldol product, benzalacetone (**2**). The fact that the hydrated product, 4-hydroxy-4-phenyl-2-butanone (**1**), could not be detected indicates that the dehydration reaction is fast under these reaction conditions. The double cross-aldol condensation product dibenzalacetone (**3**) was not produced either, which is likely attributable to steric hindrance caused by the zeolite pore. Ti-Beta yielded negligible aldol condensation products. Control reactions with Al-Beta, Si-Beta, extra-framework HfO_2 nanoparticles impregnated on Si-Beta (HfO_2/Si-Beta), and reactions without the catalyst confirmed that framework Lewis acidic heteroatoms are required for catalytic activity (see Table S1).

Table 1: Cross-aldol condensation of aldehydes with acetone using Lewis acidic zeolites.[a]

Entry	Aldehyde	Catalyst	Conv. [%][b]	Selectivity [%][c]
1		Hf-Beta	91	97
		Sn-Beta	32	90
		Zr-Beta	94	98
2		Hf-Beta	38	96
		Sn-Beta	28	86
		Zr-Beta	48	97
3		Hf-Beta	69	90
		Sn-Beta	25	78
		Zr-Beta	78	90
4		Hf-Beta	27	98
		Sn-Beta	19	96
		Zr-Beta	42	>99
5		Hf-Beta	73	>99
		Sn-Beta	32	0
		Zr-Beta	72	87

[a] Reaction conditions: 0.084 M aldehyde in toluene, (mmol acetone)/(mmol aldehyde)/(mmol metal) = 150:50:1, 363 K, 5 h. [b] Conversion: [mmol(aldehyde converted)]/[mmol(aldehyde initial)] × 100. [c] Selectivity: [mmol(single cross-aldol condensation product)]/[mmol(aldehyde converted)] × 100.

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The observed difference between the various Beta zeolites is consistent with previous studies, which indicated that catalytic activity is dependent on the polarizability of the metal atom in the active site and the Brønsted basicity of the associated oxygen atom.[13] The d-block transition metals Hf and Zr possess similar electronic structures when inserted in the zeolite framework and can be expected to show similar catalytic activity, while the p-block element Sn exhibits different bonding characteristics and charge distribution through the site because of its antibonding σ* LUMO.[13,15] We next extended our study to include several BA derivatives (Table 1, entries 2–4). The observed trend in catalytic activity of the metal centers is similar to the one seen for reactions with BA: Hf ≈ Zr > Sn. Selectivity toward the desired single cross-aldol condensation product remained over 90% when using Hf- and Zr-Beta. Sn-Beta, in contrast, only reached 86 and 78% selectivity when starting from 4-nitrobenzaldehyde and 4-chlorobenzaldehyde, respectively. A comparison between BA derivatives shows a decrease in activity with the addition of both electron-withdrawing and electron-donating groups, a trend not solely characteristic of strong base or acid catalysts.[16] This mixed trend is indicative of a cooperative effect between weak acid and base sites in the zeolite. Additionally, steric limitations in the pores of zeolite Beta may impede transition-state formation for benzaldehyde analogues with larger substituents at the 4-position. The aldol reaction between 5-(hydroxymethyl)furfural (HMF) and acetone was also examined (Table 1, entry 5), as this is a potential pathway to produce liquid alkanes from biomass.[2a] Reactions with both Hf- and Zr-Beta generated the single cross-aldol product with selectivities of 99 and 87%, respectively, at similar conversions. Surprisingly, reactions catalyzed by Sn-Beta only generated undesired polymerization products.

The stability of Hf-Beta for the aldol condensation of BA and acetone was probed by reusing the catalyst with fresh solution for five consecutive batch reactions (see Figure S8). Conversion decreased by 18% between the first and second runs, and it remained constant for subsequent runs. In all cases, selectivity for **2** remained above 98%. Calcination between the fourth and fifth runs did not alter activity. Thermogravimetric analysis showed a 2% weight loss, which we ascribe to the presence of organic components within the zeolite pores after reaction (see Figure S8). These results are consistent with the observed deactivation behavior of Hf-Beta during catalytic transfer hydrogenation reactions.[17] Hot filtration tests confirmed the heterogeneous nature of the catalytic system (see Figure S9).

Organic acid impurities can deactivate strong base catalysts, while water may react undesirably with homogeneous Lewis acids. Thus, Hf-Beta was tested in the presence of these components for the aldol condensation of BA and acetone (Figure 2). Unlike traditional base catalysts, Hf-Beta was not quenched by the presence of acetic acid. Although conversion decreased by 35% upon adding 0.11 wt% acetic acid (i.e., a molar ratio of 1:5 acetic acid/BA), the zeolite generated the desired product with a selectivity of 93%. Conversely, the solid base catalyst MgO showed almost no activity in the presence of acetic acid. Furthermore, MgO only

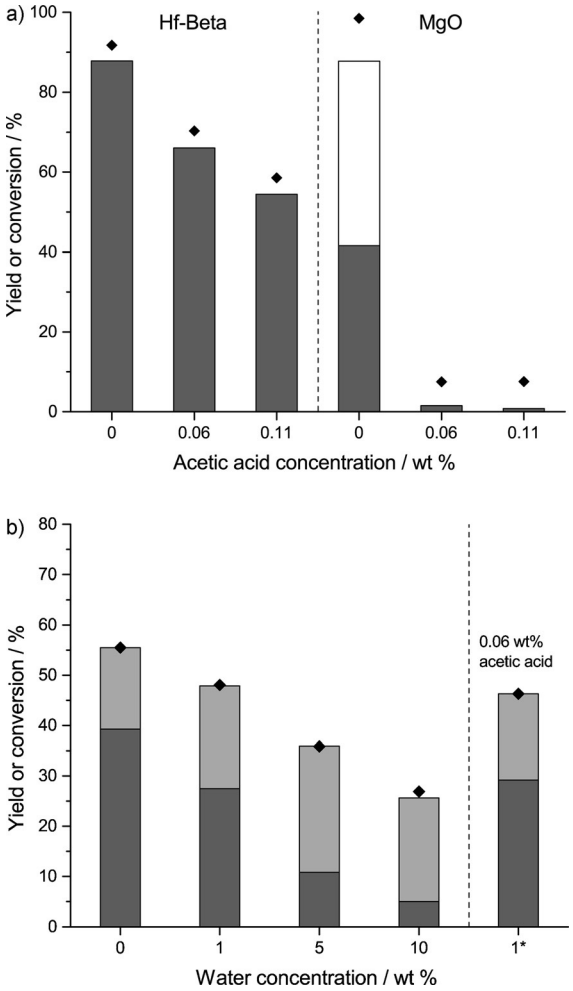

Figure 2. Effects of a) acetic acid and b) water on the aldol condensation of BA and acetone. Reaction conditions: same as those used in Table 1. MgO loaded at 2 wt% for (a), and acetone used as a solvent for (b). Acetic acid concentrations of 0.06 and 0.11 wt% correspond to molar ratios of acetic acid/BA/Hf = 5:50:1 and 10:50:1, respectively. Water concentrations of 1, 5, and 10 wt% correspond to molar ratios of water/BA/Hf = 300:50:1, 1500:50:1, and 3000:50:1, respectively. The entry marked 1* in (b) had both water and acetic acid impurities with molar ratios of water/acetic acid/BA/Hf = 300:5:50:1. Legend: Yields of **1** (■), **2** (■), and **3** (□). ◆ = conversion.

achieved 42% selectivity for **2** under acid-free conditions, primarily because of the production of **3**. Figure 2b shows that Hf-Beta is capable of catalyzing the aldol condensation with as much as 10 wt% water, although conversions decreased by 50% when compared to the dry reaction. Note that acetone was used as the solvent for the water tests because of the immiscibility of water with toluene. In pure acetone, reaction rates were lower compared to those obtained in toluene. We hypothesize that high acetone concentrations hinder BA adsorption because of competitive interaction with the Lewis acidic sites. Indeed, self-aldol reaction of acetone to form mesityl oxide and diacetone alcohol was observed in small quantities (< 2%). Reactions in acetone also displayed lower selectivity for **2** because of reduced dehydration of the aldol addition product **1**. As expected, the selectivity for **1** increased with higher water concentrations, as water is a by-product of

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aldol condensation. A reaction with both water and acetic acid impurities (Figure 2b, entry marked 1*) showed that Hf-Beta remains active even when multiple contaminants are present.

In summary, we have demonstrated that Hf-, Sn-, and Zr-Beta zeolites are active and robust catalysts for the aldol condensation of aromatic aldehydes with acetone. NMR data support a soft enolization pathway wherein the α-proton of acetone is transferred to the zeolite lattice, thereby generating a metal enolate intermediate that can readily attack a carbonyl group to form a C–C bond. These materials are especially promising because they work under conditions in which many aldol condensation catalysts are deactivated. Future work needs to focus on understanding the role of closed and open sites for aldol condensation.[18] In addition, a systematic comparison of the catalytic activity of Lewis acidic zeolites synthesized in fluoride media and those synthesized by faster post-synthetic methods should be performed.[19]

Keywords: aldol reaction · C–C coupling · heterogeneous catalysis · Lewis acids · zeolites

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