Zeolites

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Metalloenzyme-Like Zeolites as Lewis Acid Catalysts for C–C Bond Formation

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The use of metalloenzyme-like zeolites as Lewis acid catalysts for C–C bond formation reactions has received increasing attention over the past few years. In particular, the observation of direct aldol condensation reactions enabled by hydrophobic zeolites with isolated framework metal sites has encouraged the development of catalytic approaches for producing chemicals from biomass-derived compounds. The discovery of new Diels–Alder cycloaddition/dehydration routes and experimental and computational studies of Lewis acid catalyzed carbonyl–ene reactions have given a further boost to this rapidly evolving field.

1. Introduction

Zeolites are crystalline microporous aluminosilicates that can have both Brønsted and Lewis acid sites, making them attractive heterogeneous catalysts for the synthesis of chemical intermediates and fine chemicals.[1] Owing to their tunable active sites and (hydro)thermal stability, synthetic zeolites are not only the most widely used catalysts in petroleum cracking and reforming processes, but also have the potential to be used for the conversion of biomass into fuels and chemicals.[2] Recently, research on the catalytic applications of zeolites has entered an exciting new phase wherein metal centers with open coordination sites incorporated into the framework of hydrophobic zeolites are used as Lewis acids to activate oxygenated molecules containing carbonyl and hydroxy groups.[3] The unique catalytic properties of these materials arise from the ability of tetrahedrally coordinated heteroatoms, such as Hf, Zr, and Sn, to accept electron pairs from reactants without inducing a charge imbalance in the framework.[4] Importantly, unlike most Lewis acid catalysts, these materials maintain their catalytic activity in the presence of protic polar solvents such as water.[3f,5] Several Reviews describe the design and application of such hydrophobic zeolites for catalyzing the conversion of biomass-derived compounds, including carbohydrate isomerization and epimerization, Baeyer–Villiger oxidation and Meerwein–Ponndorf–Verley (MPV) reduction reactions.[2c,3f,5,6] However, the use of Lewis acid zeolites has not been reviewed in the context of C–C bond formation chemistry, nor has it been well discussed from a mechanistic point of view that takes into account the cooperative interactions of Lewis acidic centers with Brønsted acid and base sites.

Facilitating cooperative interactions among sites in heterogeneous catalysts has proven to be a powerful approach for promoting C–C coupling reactions.[7] Analogies can be drawn to enzymatic systems. For example, class II aldolases catalyze the direct aldol reaction of dihydroxyacetone phosphate (DHAP) and aldehydes through cooperative activation of DHAP. The proposed transition-state model for the active sites of this lyase shows that the Lewis acidic site Zn^{II} coordinates to the carbonyl oxygen atom of the ketone donor, while a glutamate residue functions as a Brønsted base for abstraction of the α-proton.[8] For hydrophobic pure silica zeolites, acid–base interactions are critically dependent on physical properties such as the polarizability of the metal atom in the active site and the Brønsted basicity of the oxygen atoms bound to the metal atom.[9] Herein, we review the use of metalloenzyme-like zeolites for C–C coupling reactions, with a special emphasis on direct aldol/retro-aldol, Diels–Alder cycloaddition/dehydration and carbonyl–ene reactions. Advances in the mechanistic understanding of soft enolization are discussed with the overarching goal of providing insights for the design of improved zeolite catalysts. Although C–C bond formation through nucleophilic addition reactions has also been demonstrated by stabilization of carbocations on aluminosilicate zeolites,[10] a discussion of these catalysts is beyond the scope of this Minireview.

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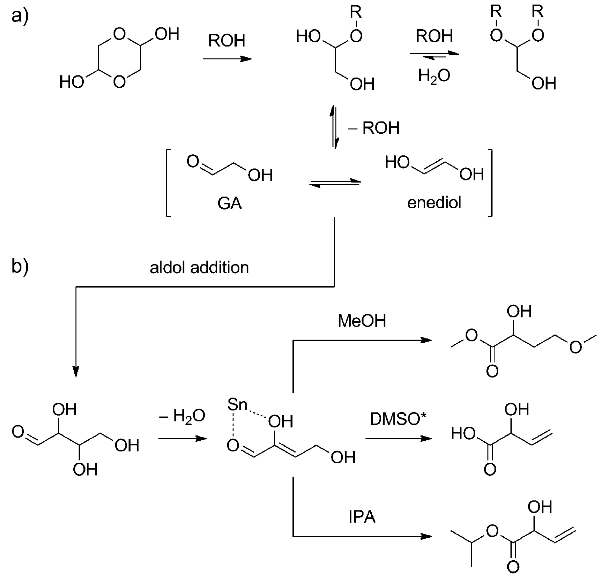
2. Direct Aldol/Retro-Aldol Reactions

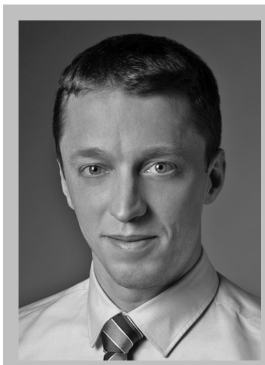
Recent reports have shown that Sn sites incorporated into a zeolite framework with the *BEA topology (Sn-Beta) catalyze the aldol condensation of glycolaldehyde (GA), which is a main component of biomass-derived pyrolysis oil.[11] Holm et al. first observed the formation of methyl vinylglycolate in a reaction of GA with Sn-Beta in methanol, implying the occurrence of C–C coupling of GA through aldol condensation.[11b] They attributed a concomitant formation of methyl lactate to a reaction sequence involving the simultaneous occurrence of both aldol and retro-aldol reactions. Similar interpretations have been made concerning the retro-aldol activity of Lewis acidic zeolites for the direct formation of lactic acid and methyl lactate from hexoses,[12] and the conversion of glucose into furfural and formaldehyde.[13]

Inspired by these results, Dusselier et al. exploited the one-pot catalytic conversion of GA into C4 α-hydroxy acids and their esters.[11a] Through the use of Sn halides as homogeneous catalysts and the appropriate choice of solvent, they were able to combine the aldol-based C–C coupling of GA with the transformation of tetroses into α-hydroxy acids. An important finding was that crystalline dimeric GA readily converted into its acetal when mixed with alcoholic solvents (Scheme 1 a). A ^{13}C NMR spectroscopy study further showed that $SnCl_4{\cdot}5H_2O$ catalyzes this acetalization through the Brønsted acidity originating from the dissociation of the chloride ligands. Formation of the aldol substrates, GA and its enediol, is said to occur by water-promoted hydrolysis of the acetal. Subsequently, a series of cascade reactions in different solvents enabled the synthesis of polyester building blocks methyl-4-methoxy-2-hydroxybutanoate, vinyl glycolic acid, and isopropyl vinyl glycolate (Scheme 1 b). Dijkmans et al. later noticed a similar aldol activity for a heterogeneous catalyst prepared by grafting $SnCl_4$ onto a partially dealuminated Beta zeolite.[7b] Characterization by ^{119}Sn Mössbauer, X-ray photoelectron spectroscopy (XPS), UV/Vis, X-ray diffraction (XRD), and ^{119}Sn MAS NMR spectroscopy confirmed the presence of both Brønsted acidic tetrahedral Al and Lewis acidic Sn^{IV} in the zeolite framework. The reaction with 1,3-dihydroxyacetone (DHA) in ethanol at 90 °C predominantly yielded ethyl lactate along with trace amounts of hexoses resulting from the aldol reaction between DHA and its isomerization product, that is, glyceraldehyde. Although further mechanistic studies remain to be conducted, the preliminary data suggest that close proximity of the Brønsted and Lewis acid sites in the zeolite framework is needed to attain a synergetic catalytic effect.



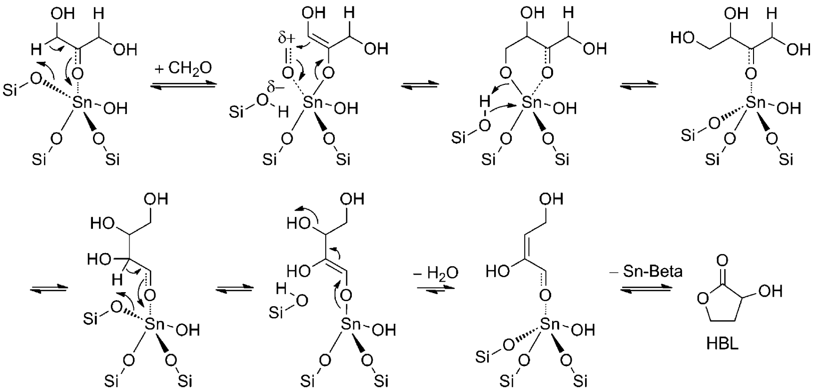
Scheme 1. a) Proposed catalytic transformation of GA in alcoholic solvents (R = methyl, ethyl, or isopropyl). b) Subsequent conversion of GA and its enediol into methyl-4-methoxy-2-hydroxybutanoate, vinyl glycolic acid, and isopropyl vinyl glycolate. MeOH = methanol, DMSO = dimethylsulfoxide, IPA = isopropyl alcohol. The asterisk indicates that acetal formation could not be observed in non-alcoholic solvents.

Our group demonstrated the application of Sn-Beta for the catalytic C–C coupling between DHA and formaldehyde to form the synthetically useful compound α-hydroxy-γ-butyrolactone (HBL).[14] Based on spectroscopic and computational analyses, we presented a mechanistic hypothesis that involves the polarization of the carbonyl group of DHA and a transfer of its α-proton to the framework oxygen atom connected to Sn (Scheme 2). This sequence, commonly referred to as soft enolization,[15] results in the formation of a Sn-enolate intermediate and the cleavage of one Si–O–Sn ensemble. Subsequent aldol addition of formaldehyde leads



Dr. Stijn Van de Vyver received his Ph.D. in Bioscience Engineering under supervision of Prof. Bert Sels and Prof. Pierre Jacobs at the KU Leuven. In 2012, he was awarded fellowships from the Research Foundation - Flanders, the Belgian American Educational Foundation, the "Plateforme pour l'Éducation et le Talent" and the Fulbright Program to do postdoctoral research at the Massachusetts Institute of Technology (MIT) with Prof. Yuriy Román. He has recently accepted a position as R&D Project Leader at Eastman Chemical Company in Ghent (Belgium).

Prof. Yuriy Román obtained his B.S.E. in Chemical Engineering at the University of Pennsylvania and completed his Ph.D. at the University of Wisconsin-Madison under the guidance of Prof. James Dumesic. Before joining the Department of Chemical Engineering at MIT, he completed a postdoc at Caltech, working with Prof. Mark E. Davis on zeolite synthesis. His research lies at the interface of heterogeneous catalysis and materials design, where a wide range of synthetic, spectroscopic, and reaction engineering tools are applied to study the chemical transformation of molecules on catalytic surfaces.



Scheme 2. Proposed mechanistic pathway for the C–C coupling reaction between DHA and formaldehyde catalyzed by the framework Lewis acidic Sn sites in Sn-Beta.

to formation of erythrulose, which readily isomerizes into erythrose through a 1,2-hydride shift and further lactonizes into HBL by retro-Michael dehydration and an intramolecular hemiacetal reaction. Significant amounts of C_5 sugars were obtained, indicating the occurrence of two consecutive aldol additions. This tentative reaction pathway is different from the one postulated by Yamaguchi et al. for Sn halides, which involves the tautomerization and dehydration of DHA to pyruvic aldehyde (PA).[16] In both cases, however, Sn enolates are inferred to be formed through deprotonation of a C–H bond in the α-position to the carbonyl group of DHA or PA. It is important to mention that when testing the Sn-Beta catalyst in a fixed-bed flow reactor at 160 °C, its activity remained relatively stable over the course of at least 48 h.[14] A decrease in DHA conversion from 95 to 87 % was shown to be at least partially due to micropore collapse. As for reactions performed in batch mode, Sn-Beta and $SnCl_4$ afforded yields of 68 and 70 %, respectively, at almost complete conversion ($\geq$ 98 %).[14,16b] Finally, by coupling the C–C bond formation reaction with transfer hydrogenation of formaldehyde, we have demonstrated the cascade synthesis of HBL from other biomass-derived compounds, such as glycerol and ethylene glycol.[14,17]

A follow-up study focusing on the keto–enol tautomerization mechanism confirmed that these Lewis acidic zeolites promote soft enolization through α-proton abstraction.[18] Specifically, fully deuterated acetone ([D$_6$]acetone) was heated to 90 °C in the presence of metal-substituted Beta zeolites and *tert*-butanol, and subsequently analyzed by ^{13}C and ^{1}H NMR spectroscopy. Within 8 h, a significant degree of deuterium–proton exchange had occurred, demonstrating C–D bond activation and subsequent transfer of an α-deuterium atom to the zeolite lattice. UV/Vis and ^{119}Sn NMR spectroscopy analyses ruled out the presence of high concentrations of extra-framework tin oxide species, corroborating that keto–enol tautomerization is mainly catalyzed by the framework metal active centers. Control reactions with Si-Beta and without catalyst did not lead to any change in the chemical environment of [D$_6$]acetone. When carrying out a series of cross-aldol condensation reactions of aromatic aldehydes with acetone, Sn-, Hf-, and Zr-Beta exhibited excellent catalytic performance, featuring near quantitative yields and high stability even in the presence of water and acetic acid.

The cooperative mechanism described above can be reconciled with our understanding of the vapor-phase cross-aldol condensation of acetaldehyde and formaldehyde to form acrolein.[19] Deliberations regarding catalyst design, alongside consideration of the similar electron densities on the oxygen atoms of both aldehydes,[20] have led to new approaches towards balancing acidic and basic properties of heterogeneous catalysts. Following upon reports on the use of MgO-ZSM-5, Y faujasite, mordenite, and SAPO-34,[21] Dumitriu et al. investigated the correlation between surface properties of MFI type zeolites and their catalytic activity.[19] They tuned the Brønsted and Lewis acidic properties of ZSM-5 zeolites by varying the Si/M^{3+} ratio as well as by isomorphously substituting Si by Al, Ga, Fe, and B in the framework. While the aldol condensation activity was shown to strongly depend on the concentration of accessible Brønsted acid sites, the selectivity to acrolein seemed to be mostly influenced by the presence of Lewis acid sites. Notably, the reactions were carried out at temperatures of 300 °C and higher to prevent the self-condensation of acetaldehyde into crotonaldehyde.

Very recently, Sushkevich et al. demonstrated the catalytic conversion of ethanol into 1,3-butadiene over Ag-promoted Zr-Beta.[22] Owing to its availability from carbohydrate biomass, ethanol is considered as an attractive source for sustainable production of 1,3-butadiene.[23] The reaction catalyzed by Zr-Beta is thought to proceed through five steps: dehydrogenation of ethanol into acetaldehyde, aldol addition of acetaldehyde, dehydration of 3-hydroxybutanal into crotonaldehyde, MPV reduction of crotonaldehyde into crotyl alcohol, and dehydration of crotyl alcohol into 1,3-butadiene [Eqs. (1)–(5)].[24]

Ag-containing catalysts accelerate ethanol dehydrogenation,[25] whereas Zr-based Lewis acids can catalyze both aldol condensation of acetaldehyde[26] and MPV reduction of crotonaldehyde with ethanol.[27] The best results were ob-

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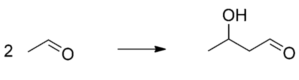

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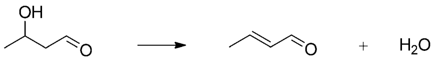

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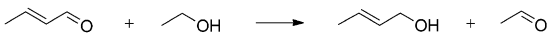

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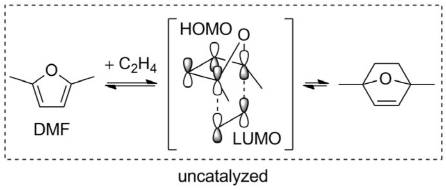


Scheme 3. Diels–Alder cycloaddition/dehydration reaction for the conversion of DMF and ethylene into *p*-xylene.

tained for a Zr-Beta catalyst with a Si/Zr ratio of 100 promoted with 1 wt% Ag, achieving a selectivity of 56% for 1,3-butadiene at 48% conversion.[22] Side reactions included the dehydration of ethanol into diethyl ether and ethylene, the Tishchenko reaction of acetaldehyde, and the cross-condensation of acetaldehyde with crotonaldehyde. In situ IR spectroscopic studies on the related aldol condensation of acetaldehyde catalyzed by ZrO_2-SiO_2 indicated a concerted mechanism involving Lewis and Brønsted acid sites.[26] According to the proposed mechanism, Zr sites incorporated into a silica framework induce Brønsted acidity on the silanol groups. Interaction of the carbonyl group of acetaldehyde with the Zr atom favors the abstraction of a proton from the methyl group. Aldol addition to a second acetaldehyde molecule, followed by dehydration of 3-hydroxybutanal, results in formation of crotonaldehyde. As for the coordination state of the active site, a correlation was noted between the amount of tetrahedrally coordinated open Zr sites ((HO)-Zr-$(OSi)_3$) and the catalytic activity of Zr-Beta for the conversion of ethanol into butadiene.[48] Sushkevich et al. speculate that non-hydrolyzed or closed Zr sites (Zr-$(OSi)_4$) are catalytically less active due to their lower acid strength and more restricted steric accessibility.

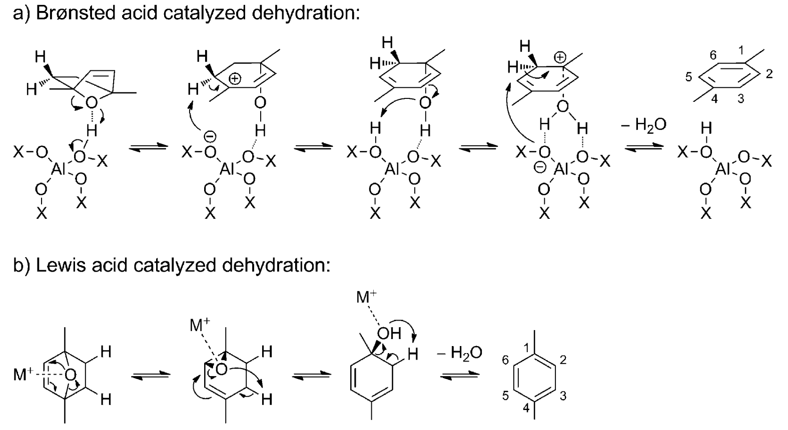
Continued research into aldol-type reactions is needed and can be anticipated to accelerate breakthroughs in the synthesis of many industrially relevant compounds, such as 2,6-dimethyl-5-hepten-1-al.[28] Considering the progress made in the integration of chemical and biological catalysis,[29] we are attempting to use biosynthetically derived compounds as reactants for some of the aldol reactions discussed above.

3. Diels–Alder Cycloaddition/Dehydration Reactions

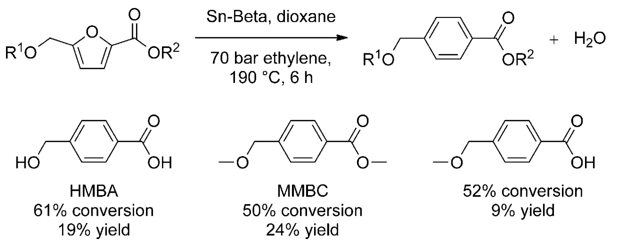
One Lewis acid catalyzed process that has recently attracted significant attention is the Diels–Alder cycloaddition between 2,5-dimethylfuran (DMF) and ethylene with subsequent dehydrative aromatization of 1,4-dimethyl-7-oxabicyclo[2.2.1]hept-2-ene into *p*-xylene (Scheme 3).[30] Density functional theory (DFT) studies suggest that although the [4+2] cycloaddition step is thermally feasible, Lewis acid sites can further lower the activation requirements by decreasing the HOMO–LUMO gap of the interacting molecules.[31] The significance of this catalytic effect is shown to depend on the arrangement between the addends and the catalytic center: if ethylene binds to the Lewis acid, the ethylene becomes even more electron poor; however, if DMF binds to the Lewis acid, the DMF becomes less electron rich, which makes cycloaddition to an already electron-deficient ethylene molecule more difficult.

While others considered H-Beta zeolites for this reaction,[32] Nikbin et al. performed electronic-structure calculations to study the catalytic activity of protonated (H-Y) and alkali-exchanged Y zeolites (Li-, Na-, K-, Rb-, and Cs-Y).[33] Previously, Williams et al. had shown that the reaction rate of *p*-xylene production is independent of the number of available Brønsted acid sites on H-Y zeolites.[30c] This proved to be consistent with computed free-energy profiles showing that the uncatalyzed Diels–Alder reaction is the rate-limiting step under the reported reaction conditions.[33] Regarding the catalytic activity of alkali-exchanged Y zeolites, it is found that especially small cations, such as Li^+ and Na^+, are strongly embedded in the zeolite framework, carrying charges of $+0.79$ and $+0.89$, respectively. Inductive effects of the framework appear to diminish the ability of the cations to withdraw electron density from DMF, which therefore remains nucleophilic. It is further concluded that the conversion of DMF into *p*-xylene starts by preferential adsorption of DMF at the active site of the zeolite and that the reaction is $\text{HOMO}_{\text{donor}}$- and $\text{LUMO}_{\text{donor}}$-controlled, following a bidirectional electron-flow mechanism.

The activation energy barrier for the second step in Scheme 3, that is, the dehydration of the oxanorbornene derivative to *p*-xylene, has been well characterized, with values as high as 60 kcal mol^{-1}.[31,33] In agreement with experimental findings,[31] the requisite oxygen-bridge opening only occurs in the presence of Brønsted or Lewis acid catalysts at reaction temperatures ranging from 200 to 300 °C. As shown in Scheme 4a, the Brønsted acid catalyzed mechanism is initiated through a fast proton transfer from the active site of the zeolite to the bridge oxygen atom, resulting in the opening of the oxanorbornene oxygen bridge and the formation of water through proton transfer from the C5 carbon to the oxygen atom.[33] The second proton transfer from the C6 carbon to a framework oxygen atom releases *p*-xylene and regenerates the Brønsted acid site to initiate a new catalytic cycle. Mechanistically, Lewis acid catalyzed dehydrative aromatization proceeds less readily because the oxanorbornene derivative needs to be properly coordinated to the cation through its heteroatom. The conversion into *p*-xylene takes place through a series of steps involving the breaking of the C4−O bond, formation of the C6−O bond and the C3−C4 double bond, and two intramolecular proton transfers (Scheme 4b). Taken together, the mechanistic scenario that evolves from DFT calculations provides a rationale for carefully tuning the ratio of Brønsted to Lewis acid



Scheme 4. Proposed mechanistic pathways for the a) Brønsted and b) Lewis acid catalyzed dehydration of 1,4-dimethyl-7-oxabicyclo[2.2.1]hept-2-ene to *p*-xylene. M = Li, Na, K, Rb, or Cs.



Scheme 5. Selected examples of Sn-Beta catalyzed Diels–Alder cycloaddition/dehydration reactions of oxygenated furans with ethylene.

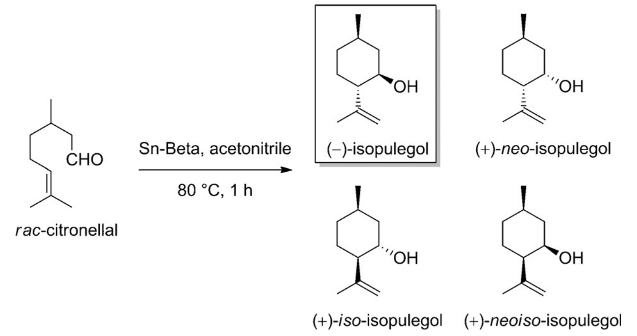
sites to accelerate both the cycloaddition and the dehydrative aromatization steps.

As an interesting variation, Pacheco and Davis investigated the application of Sn- and Zr-Beta for the Diels–Alder reaction between ethylene and various oxidized derivatives of 5-hydroxymethylfurfural (HMF) (Scheme 5).[12b,34] Given that *p*-xylene is commonly oxidized to terephthalic acid, the synthetic value of this reaction lies in C–C bond formation between HMF and ethylene without having to reduce HMF into DMF. The electron-donating methyl groups in DMF make the diene more reactive towards ethylene in the presence of homogeneous Lewis acids or heterogeneous Brønsted acids. On the other hand, oxidized derivatives of HMF contain electron-withdrawing groups, making them considerably less reactive towards [4+2] cycloaddition reactions with ethylene.

Experiments combining 5-(hydroxymethyl)furoic acid (HMFA) with ethylene under high pressure and Sn-Beta as the catalyst afforded 19 % yield of 4-(hydroxymethyl)benzoic acid (HMBA) at 61 % conversion. The substrate choice was motivated by reports of the quantitative oxidation of HMF to HMFA using Au nanoparticle catalysts under mild conditions (65–130 °C, 10 bar air).[35] Sn-containing mesoporous silica (Sn-MCM-41) and amorphous silica were found to be less effective to promote the Diels–Alder cycloaddition/dehydration reactions, indicating an important role of confinement effects within the microporous Beta framework. Although more work is required to fully understand the reaction mechanism, it is interesting to note that control reactions with Al-Beta led to coke formation owing to the high concentration of Brønsted acid sites. The results further demonstrate that higher yields can be achieved by protecting the hydroxymethyl and acid groups of HMFA with methanol, enabling, for example, the synthesis of methyl 4-(methoxymethyl)benzenecarboxylate (MMBC). HMBA and MMBC can be oxidized to form bio-based terephthalic acid and dimethyl terephthalate, respectively. Although the examples provided refer only to Diels–Alder cycloaddition/dehydration reactions with oxidized products of HMF, similar catalytic behavior is conceivable starting from mono- and diethers of HMF (e.g., 2,5-bis(ethoxymethyl)furan).[36] Oxidation of the alkoxymethyl substituents from such furans is easier than oxidation of methyl groups since the substituents are already partially oxidized.[37]

4. Carbonyl–Ene Reactions

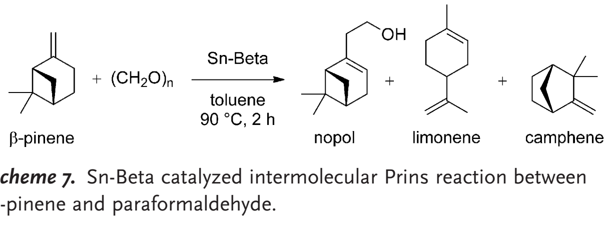
The ene reaction involving carbonyl enophiles usually has a higher activation energy than the analogous Diels–Alder reaction because it requires the breaking of a C–H σ bond.[38] One valuable example of the use of Lewis acidic zeolites for carbonyl–ene reactions is the ring closure of citronellal to (±)-isopulegol, an intermediate in the industrial synthesis of (±)-menthol (Scheme 6). The key feature of this cyclization



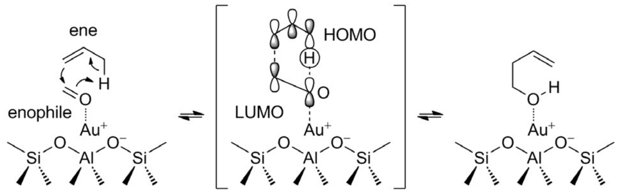
Scheme 6. Sn-Beta catalyzed intramolecular cyclization of citronellal to (−)-isopulegol and its isomers.

lies in the diastereoselective formation of (−)-isopulegol as other isomers are less interesting from a commercial point of view.[39] Sporadic reports have identified metal-substituted zeolites with *BEA and MFI framework topologies as suitable catalysts for this process.[39,40] For instance, Corma and Renz reported a superior catalytic performance of Sn-Beta compared with conventional heterogeneous catalysts.[40d] Using acetonitrile as solvent, citronellal was almost fully converted after 1 h reaction at 80 °C with a selectivity to isopulegol higher than 85 % and a diastereoselectivity of 85 %. Additional reactions performed in a packed-bed reactor demonstrated that both conversion and diastereoselectivity remain constant for at least 48 h at 99 % and 83 %, respectively. Congruent with studies on the cyclization of citronellal over Zr-Beta and Ni/Zr-Beta[40a–c] and supported by ammonia temperature-programmed desorption (NH_3-TPD) and pyridine IR spectroscopy, the experimental data point towards a mechanism requiring strong Lewis acidic and weak Brønsted basic sites. The proton abstraction required for the ring closure of citronellal is thought to occur through a similar mechanism as depicted for the enolate formation from DHA (Scheme 2), both involving the cooperative action of the Lewis acidic metal center[39] and the basic oxygen atom in its first coordination sphere.[40c] Moreover, a comparison of initial cyclization rates for Sn-Beta samples prepared by various post-synthetic methods indicates that the catalytic activity increases with the number of open Sn sites, as was also observed for Baeyer–Villiger oxidation reactions.[41] The main factor governing the diastereoselectivity is shown to be the limited space around the framework metal center. An effective method to further exploit this pore confinement effect consists of using branched nitriles as solvents.

The intermolecular Prins reaction between β-pinene and paraformaldehyde has been investigated as a means for producing nopol (Scheme 7). The reaction has been studied using heterogeneous catalysts, such as $FePO_4$, Zn-MCM-41, Zn-Al-MCM-41, and Zr-SBA-15.[42] In 2007, Corma and Renz reported the application of Sn-Beta and Sn-MCM-41 as active and selective Lewis acid catalysts.[43] It was found that the catalysts are water resistant and that they can be easily recycled and regenerated in multiple runs. Recently, Marakatti et al. reported an improved set of conditions for this reaction, using ion-exchange as an alternative method to prepare the catalysts.[44] A screening of several metal ions led to the selection of Zn-Beta as the most effective catalyst for the synthesis of nopol. The best results were obtained for a low Brønsted to Lewis acid ratio of 0.06, achieving 93 % nopol selectivity at 92 % conversion with α-pinene, limonene, and camphene being the main byproducts.



Scheme 7. Sn-Beta catalyzed intermolecular Prins reaction between β-pinene and paraformaldehyde.



Scheme 8. Carbonyl–ene reaction of propene with formaldehyde over Au^I exchanged FAU zeolites.

In contrast to the transformations discussed above, the Prins reaction of propene with formaldehyde has been scarcely explored (Scheme 8).[38,45] The reaction product, 3-buten-1-ol, is used as a monomer in copolymerization reactions with polypropylene and as intermediate for tetrahydrofuran synthesis. Alternatively, the dehydration of this Prins reaction product could provide a new route for the production of 1,3-butadiene. Wannakao et al. performed DFT calculations to investigate the reaction over metal-exchanged faujasite (FAU) zeolites.[45a] It was shown that the nanocages of Na-FAU zeolites suppress self-polymerization and decomposition of formaldehyde without the formaldehyde losing its reactivity toward nucleophiles.[46] For the carbonyl–ene reaction, formaldehyde encapsulation is followed by coadsorption of propene to the encapsulated complex and a concerted transformation to 3-buten-1-ol. A comparison of Group 11 metal cations shows the highest activity for Au^+ exchanged FAU zeolites, primarily because of the high charge transfer between the Au^+ ion and the reactant molecules. A natural bond orbital (NBO) analysis revealed that the 6s orbital of the Au atom plays a crucial role by inducing a charge on the probe molecules, and that this inductive effect is further enhanced by the framework of the zeolite. Despite the demonstrated potential of Au-exchanged FAU zeolites, it should be noted that the high desorption energy could be problematic for industrial applications.

5. Summary and Outlook

The research highlighted in this Minireview shows the potential of metalloenzyme-like zeolites for catalyzing direct C−C bond formation reactions. The Sn-Beta catalyzed aldol condensation reactions with glycolaldehyde, 1,3-dihydroxyacetone, and formaldehyde are powerful examples of C−C coupling reactions in carbohydrate chemistry, a field which has been traditionally associated with base catalysis. It is instructive to note that the reactions exemplified in the context of soft enolization are controlled by proton-transfers from C−H bonds.[18] With increasing attention being paid to Lewis acid–base interactions in metal-substituted Beta zeolites, we anticipate that such C−H bond activations will be an important focus of future studies. For example, using NMR spectroscopy on absorbed probe molecules may provide insights into the exact configuration of the framework metal centers and the mechanistic role of open and closed sites for direct aldol/retro-aldol reactions.[47] It would be equally beneficial to gain a better understanding of the role of Lewis acidic centers in catalyzing the Diels–Alder cycloaddition/dehydration reactions. Finally, whereas the cyclization of citronellal and the Prins reaction between β-pinene and paraformaldehyde have been achieved with high product selectivities, the reaction of propene with formaldehyde has been limited to a few computational studies. Accordingly, our current research efforts are directed towards experimentally validating this approach, and further broadening the synthetic utility of metalloenzyme-like zeolites in other C−C bond formation reactions.

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