Spatial Arrangement and Acid Strength Effects on Acid-Base Cooperatively-Catalyzed Aldol Condensation on Aminosilica Materials

Jeroen Lauwaert¹, Eric G. Moschetta², Pascal Van Der Voort³, Joris W. Thybaut^{1*}, Christopher W. Jones^{2**}, Guy B. Marin¹

* Corresponding author, E-mail address: Joris.Thybaut@UGent.be , Telephone number: +32 (0)9 331 17 57

** Corresponding author, E-mail address: cjones@chbe.gatech.edu , Telephone number: (1)-404-385-1683

¹ *Ghent University, Department of Chemical Technology, Laboratory for Chemical Technology, Technologiepark 914, 9052 Ghent, Belgium*

² *Georgia Institute of Technology, School of Chemical & Biomolecular Engineering, 311 Ferst Drive, Atlanta, Georgia, 30332-0100, USA*

³ *Ghent University, Department of Inorganic and Physical Chemistry, Center for Ordered Materials, Organometallics & Catalysis, Krijgslaan 281 (S3), 9000 Ghent, Belgium*

Abstract

Weak acids are known to enhance the activity of amines in aldol condensation reactions on silica-based catalysts. The effects of acid strength and arrangement of the promoting site with respect to a secondary amine have been investigated in the aldol condensation of 4-nitrobenzaldehyde with acetone. Changing the substituent of this secondary amine from a methyl to an ethyl group decreases the activity. An intramolecular OH function, provided by a primary alcohol incorporated on the β -carbon of the amine substituent exhibits a similar cooperativity as a an intermolecular OH

function provided by neighbouring surface silanols. A maximum activity was achieved when the secondary amine with the same primary alcohol containing substituent was surrounded by surface silanols, indicating the potential advantage of simultaneously activating both reactants by the formation of a hydrogen bond in contrast to the consecutive activation when there is only one promoting site in the vicinity of the amine. Changing the alcohol to stronger acids resulted in a reduced cooperativity with increasing acid strength. After removing the silanols from the surface, the activity of the catalysts which exhibit an intramolecular cooperativity retained about 68 % to 83 % of their activities while the activity of the conventional secondary amine was reduced by a factor four compared to its intermolecularly cooperative counterpart.

Keywords: Aldol reaction, acid-base catalyst, cooperative catalysis, acid strength

1 Introduction

Aminated silica materials are known to efficiently catalyze carbon-carbon coupling reactions, especially when weak acid sites are neighboring the amine function [1-13]. An adequate understanding of the cooperativity between the two types of sites is crucial for the rational design of an optimal acid-base cooperative catalyst. One can think of several catalyst properties that have an important effect on the catalytic performance of the material, such as the proximity of the promoting sites to the amines [5-8], the structure and base strength of the amine site [3-5], and the acid strength of the promoting site [8-10].

Post-synthetic grafting by means of a stirring or reflux procedure is a popular technique to functionalize silica materials with amines. During the functionalization, a fraction of the weakly acidic silanols that are intrinsically present on the silica surface is replaced with an amine-containing silane [6, 14]. It has been shown that the presence of the remaining silanols on the surface enhances the catalytic activity of the amines in the aldol condensation [1, 2, 5-9]. This cooperative effect does not only depend on the concentrations of both types of sites but also on their spatial arrangement with

respect to each other [5, 6]. Primary amine precursors have the tendency to form hydrogen bonds between each other during the grafting procedure [5, 6, 15-19]. Commonly used solvents such as toluene are typically unable to break these hydrogen bonds and, hence, primary amines remain associated to each other and are grafted in a clustered manner on the silica surface [5, 6, 15-17]. In contrast, secondary amines have a lower tendency to form such hydrogen bonds in the same solvents and are more randomly distributed over the silica surface [5]. Both the clustered and the random arrangement deviate from the ideal checkerboard pattern, meaning that at a silanol-to-amine ratio of 1, not every amine has a neighboring silanol and, hence, that the amines are not fully promoted. It has also been demonstrated that the cooperativity between amines and silanols can be tuned by controlling the alkyl chain length of the amine active site as well as the silica support pore size [7, 8]. It was found that with short alkyl chains the catalyst behaves as if the amine groups were isolated, irrespective of the presence of silanol groups. The catalytic cooperativity increases with the alkyl chain length up to a propyl chain, before leveling off for longer alkyl chains. For smaller silica pore sizes, however, the same maximum cooperativity is already established for an ethyl chain and, significantly decreases for longer chains, suggesting that the long alkyl chain in the small pores perturbs the cooperativity.

To obtain an even better control of the spacing of the cooperating sites, one can draw inspiration from homogeneous catalysis. A series of homogeneous amino acids, in which the amine and the carboxylic acid are separated by 2 to 7 methylene groups, exhibits an increase in catalytic activity with decreasing distance between the two sites [8, 20]. In addition, homogeneous amino acids such as proline and glycine are known to perform well as aldol condensation catalysts [21, 22]. In both amino acids, the amine and the carboxylic acid groups are separated by a single carbon atom. Moreover, a recent study showed that L-proline could be immobilized on mesoporous silica that contained alternating hydrophilic and hydrophobic blocks to catalyze aldol condensations and Knoevenagel-Michael cascade reactions with higher yields and enantioselectivities when compared to their homogeneous precursors [23].

Although many primary, secondary and tertiary amines have similar base strengths, these amines exhibit significant differences in catalytic activities for the aldol condensation [2-5]. This observation can be attributed to differences in ability to form enamine intermediates, which is the key intermediate for the desired reaction to proceed [5], and imine species, which deactivate the amine site [3-5]. While the crucial enamine intermediate cannot be formed on a tertiary amine, the inhibiting imine species can only be formed on primary amine active sites. As a result, a secondary amine active site that can produce the reactive enamine intermediate without forming the inhibiting imine exhibits the highest catalytic activity, provided that it is not subject to steric hindrance [5]. A recent study examined the ability of several organocatalysts to form enamine and iminium intermediates in the cross condensation of isobutraldehyde and acetone and determined that organocatalysts that could form Seebach's oxazolidinones during the reaction favored the formation of aldol-type products instead of Mannich-type products, demonstrating that the intermediates can also affect the product selectivity and not only the activity [24]. The promoting effect of the weak acid sites is often ascribed to hydrogen bond interactions between the acid and the carbonyl moiety of the reactant, which results in a higher susceptibility of the electrophilic reactant for the nucleophilic attack of the amine [1, 2, 5-9]. Replacing the weakly acidic silanols with a stronger acid site seems to have a negative impact on the activity of primary amines [8-10], which could be explained by a more favorable protonation of the amines by the strong acids than by the very weakly acidic silanols. As a result, the free electron pair of the amine, necessary for the catalytic aldol condensation cycle, is no longer available for reaction with the reactants.

Previous investigations of acid strength effects were performed on catalysts that were synthesized using an amine-containing silane and a different acid-containing silane [8-10]. Besides the protonation of the amines, differences in surface arrangements of the amine and acid sites may have interfered with the targeted effects of the base and acid strength. In this work, the effect of the acid strength of the promoting site is investigated while carefully controlling the arrangement of the sites with respect to each other. A catalyst library comprising different acid-base catalysts was synthesized

by functionalizing an SBA-15 support with (3-iodopropyl)trimethoxysilane. The iodo-group is subsequently replaced with the desired functional groups, *i.e.*, a secondary amine and an acid site separated by one carbon atom. As the iodosilane cannot form hydrogen bonds, it does not have any tendency to be grafted in a clustered manner. In addition, the grafting procedure of the iodosilane aims at a low loading, *i.e.*, 0.3 mmol Iodo/g silica, resulting in isolated sites. This procedure makes it possible to study the intramolecular interactions between the acid and the amine site independent of the intermolecular interactions between sites on different linkers. Intermolecular interactions between the amine site and surface silanols remains possible. The effect of these interactions is studied by endcapping the surface silanols using hexamethyldisilazane. The effect of the acid strength of the intramolecular promoting site on the catalyst activity is investigated in the aldol condensation of acetone with 4-nitrobenzaldehyde.

2 Procedures

2.1 Catalyst Preparation

A schematic representation of the preparation of the various catalysts is shown Scheme 1. The solid support was synthesized by condensation of tetraethylorthosilicate around pluronic P123 in an acidic solution. After severely washing the solid material and, subsequently, calcination at 550°C to remove the surfactant, about 25 g of SBA-15 was obtained. This support was functionalized with (3-iodopropyl)trimethoxysilane using a reflux procedure. Afterwards, about half of the batch of grafted SBA-15 was treated with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) to remove the remaining silanol groups. Various catalysts were prepared by replacing the iodo-group with ethylamine, ethanolamine, methyl aminoacetate or diethyl aminomethylphosphonate. Finally, the acid sites were deprotected by treating the materials with a HCl solution. These functionalizations were performed on both the SBA-15 grafted with the iodosilane as well as on the one that was subsequently treated with HMDS.

The following convention was used for labeling the various samples. The first term, *i.e.*, 'SBA', refers to the supporting material. In case where the remaining silanols groups were removed, a second term 'HMDS' was added referring to the corresponding treatment. The final term refers to the functional group. The following abbreviations were used for the different functional groups: 'I' for the iodo-group, 'A' for the secondary amine, 'AL' for the alcohol group, 'CA' for the carboxylic acid and 'PA' for the phosphoric acid. Suffix 'pr' was used for the materials in which the acid group was still protected. More details about the catalyst preparation can be found in the Supporting Information.

Scheme 1: Schematic representation of the synthesis of SBA-X. A similar scheme can be drawn for the synthesis of SBA-HMDS-X. In this case, an HMDS-treatment is included between the grafting of the iodosilane (step 1) and the replacement of the iodo-group with the desired functional group (steps 2).

2.2 Catalyst characterization

Nitrogen adsorption-desorption experiments were performed at 77 K on a Micromeritics Tristar 2030. The surface areas were determined by the Brunauer-Emmet-Teller (BET) method. The total

pore volumes and pore sizes were calculated using the Broekhoff-de Boer method with the Frenkel-Halsey-Hill modification (BdB-FHH) [25]. The X-ray diffraction (XRD) patterns were measured on a Thermo Scientific ARL X'TRA X-ray diffractometer. Fourier transform infrared (FTIR) spectroscopy was performed using a Bruker Vertex 80v with dual FTIR and FT-Raman benches and KBr and CaF₂ beamsplitters, respectively. The solid-state CP-MAS ¹³C and ³¹P NMR spectra were recorded on a Bruker 300 MHz. Elemental analysis was performed by Atlantic Microlab, Inc (Norcross, GA).

2.3 Catalyst performance testing

The activity of each catalyst was assessed via the aldol condensation of acetone (ACS Grade, 99.5%, BDH) and 4-nitrobenzaldehyde (99% Alfa Aesar), as shown in Scheme 2. It is a frequently used model reaction providing a sound basis for extrapolation towards other reactants. To compare the reference catalyst, SBA-A, with data obtained in a previous work [5], the performance of this material was tested using 4 mol% of amines with respect to the concentration of 4-nitrobenzaldehyde in the reaction mixture (0.03 M). Due to the comparatively lower activities of the other materials, their catalytic performance was assessed using 15 mol% of amines with respect to the concentration of 4-nitrobenzaldehyde. This led to higher conversions and lower experimental errors, although lower turnover frequencies (TOFs) were achieved.

The experiments were performed in a 25 mL two-neck round-bottom flask equipped with a condenser and a septum. First, the supported catalyst was added to the flask so that the desired amount of amines was present, *i.e.*, 4 or 15 mol% with respect to the 4-nitrobenzaldehyde concentration. Afterwards, 3 mL of a mixture consisting of 50 vol% acetone, 50 vol% *n*-hexane, 0.03 mmol/mL 4-nitrobenzaldehyde and 0.03 mmol/mL 1,4-dimethoxybenzene (TCI) was injected into the flask and the flask was immediately placed in an oil bath at 45 °C. The moment the flask was placed in the oil bath was taken as the start of the reaction. The reaction was monitored for 5 h by taking a sample every hour (about 100 µL) of the reaction mixture. Every sample was passed through a short silica gel bed in a cotton-plugged pipet to remove the catalyst. Approximately 2 mL of acetone was

used to wash the syringe needle and to transfer the sample to a GC vial. The samples were analyzed using a Shimadzu GCMS-QP2010S gas chromatograph equipped with an Agilent DB-1701 column (30 m x 0.25 mm internal diameter x 0.25 μ m thickness). Quantification of the conversion was performed by relating the peak surface area of 4-nitrobenzaldehyde to the amount of the internal standard, 1,4-dimethoxybenzene. All data were obtained at differential conditions, which means that the conversion depended linearly on the batch time and the TOF could be determined from the slope of the observed straight line [26]. This also means that any product, *c.q.* water, inhibition is absent. The conversion versus time plots are shown in the Supporting Information. The experimental error (*EE*) on the TOF was determined from repeat experiments and calculated using equation (1). With *N* representing the number of repeat experiments, *TOF_i* the turnover frequency observed in experiment *i* and *TOF_{av}* the average TOF. The experimental error was found to be about 4.4%.

$$EE = \frac{1.96}{TOF_{av}} \sqrt{\frac{1}{N-1} \sum_{i=1}^N (TOF_i - TOF_{av})^2} \quad (1)$$

Scheme 2: Aldol condensation of acetone and 4-nitrobenzaldehyde towards 4-hydroxy-4-(4-nitrophenyl)butane-2-one and 4-(4-nitrophenyl)-3-buten-2-one.

3 Results and discussion

3.1 Catalyst characterization

The specific BET surface areas, average pore sizes, and total pore volumes of the SBA-15 support and the different catalysts were determined from the nitrogen adsorption-desorption isotherms and are listed in Table 1. After functionalization of the SBA-15 support, a small decrease in surface area and total pore volume, resulting from the loss in free volume and the increase in catalyst mass, was observed. The average pore size of the materials that were treated with HMDS were about 1 nm

smaller than the parent SBA-15, while that of the other materials remained unaltered. Moreover, all materials retained their mesoporosity. Therefore it can be assumed that the catalysts are not subject to pore blocking. The small-angle XRD patterns of all materials, shown in the Supporting Information, exhibit three peaks that could be attributed to the (100), (110) and (200) reflections associated with the hexagonal symmetry of the SBA-15 structure [27]. These results indicate that the structure of the support remained intact after the functionalization.

The presence of the desired functional groups on the final catalytic materials was qualitatively confirmed by CP-MAS ^{13}C NMR, as shown in Figure 1. All materials exhibit three peaks around (a) 9, (b) 20 and (c) 45 ppm, which can be attributed to the propyl chains and one peak at (f) 58 ppm, corresponding to the methoxy group [6, 28]. SBA-A also exhibits two peaks at (d) 51 and (e) 17 ppm, which can be attributed to the ethyl substituent [29]. SBA-A-AL exhibits two peaks at (g) 51 and (h) 60 ppm, which can be assigned to the ethanol substituent [29]. The carboxylic acid substituent of SBA-A-CA shows two characteristic peaks at (i) 49 and (j) 171 ppm [30]. Moreover, the FTIR spectrum of SBA-A-CA, shown in the Supporting Information, also exhibits a clear carbonyl peak at 1745 cm^{-1} , indicating the presence of the carboxylic acid. In the CP-MAS ^{13}C NMR spectrum, SBA-A-PA exhibits a peak at (k) 32 ppm corresponding to the carbon between the amine and the phosphoric acid [31, 32]. In CP-MAS ^{31}P NMR, shown in the Supporting Information, the phosphoric acid exhibits a peak at 9 ppm, while no peak is observed at 28 ppm, indicating that the deprotection of the acid site was successful [33, 34].

The amine loadings were determined by means of nitrogen and iodine elemental analysis and are also listed in Table 1. No iodine was detected in the final materials, indicating that the replacement of the iodine with the desired functional groups was complete. The nitrogen content of the silanol containing materials corresponds to an amine site density ranging from 0.24 to 0.31 mmol/g. This corresponds to an average site density of 0.18 acid-base pairs per nm^2 . As the iodosilane has the tendency to be grafted randomly on the silica surface, the low average site density indicates that the

amines will most likely interact with the acid groups on the same linker and potentially also with surrounding silanols but not with the acid groups on a neighboring linker. The HMDS-treated materials have somewhat lower amine loadings than the silanol containing materials. This could be explained by the formation of ammonia during the HMDS treatment. Ammonia is able to catalyze the removal of iodine leading to lower amine loadings. These lower amine loadings and the absence of nitrogen in sample SBA-HMDS-I indicate that there are no primary amines formed during the HMDS treatment. The iodine lost by this ammonia formed during the HMDS treatment, is most likely replaced by an inert trimethylsilyl group. Hence, no effect on the obtained turnover frequency (TOF) is expected by this undesired side reaction during the HMDS treatment. The SBA-A-AL_{pr} and SBA-HMDS-A-AL_{pr} samples contain respectively, 0.65 mmol N/g and 0.46 mmol N/g, which is about twice the amount of nitrogen as expected from the iodine loading of SBA-I and SBA-HMDS-I, indicating that DIPEA was hydrogen bonded to the alcohol group of the catalyst as shown in Scheme 1, or physisorbed on the catalyst surface. After consecutively treating these samples with HCl and ammonium hydroxide solutions, the samples SBA-A-AL and SBA-HMDS-A-AL contained the expected amounts of nitrogen, meaning this excess nitrogen was effectively removed.

Table 1: Catalyst properties determined via nitrogen adsorption-desorption measurements and elemental analysis

Catalyst	BET surface area (m ² /g)	Average pore size (nm)	Total pore volume (cm ³ /g)	Amine loading (mmol/g)
SBA-15 support	912	8.0	1.10	0.00
SBA-A	704	8.1	0.96	0.27
SBA-A-AL	644	8.1	0.96	0.31
SBA-A-CA	693	7.9	0.93	0.31
SBA-A-PA	662	7.6	0.89	0.24
SBA-HMDS-A	506	7.0	0.81	0.21
SBA-HMDS-A-AL	608	7.0	0.93	0.23

SBA-HMDS-A-CA	603	7.0	0.90	0.15
SBA-HMDS-A-PA	612	7.0	0.91	0.15

Figure 1: ^{13}C CP/MAS NMR spectra and assignment to chemical groups of SBA-A, SBA-A-AL, SBA-A-CA and SBA-A-PA

3.2 Catalytic performance evaluation and interpretation

3.2.1 Reference catalysts

No conversion was observed if unmodified SBA-15 or SBA-I, were used as catalysts. This means that neither pristine, nor a iodo-group are active in the aldol condensation and the incorporation of other functional groups is necessary to catalyze the reaction. In our previous work [5], the catalytic performance of different commercially available amine-containing silanes, including (3-aminopropyl)triethoxysilane (APTES), N-methylaminopropyl-trimethoxysilane (MAPTMS), and N-cyclohexylaminopropyl-trimethoxysilane (CAPTMS), grafted upon Silicagel 60 was studied. These materials were respectively labeled Silicagel APTES, Silicagel MAPTMS and Silicagel CAPTMS. All TOFs

were obtained in the low amine loading range, ensuring that the majority of amines have a silanol in the vicinity and, hence, are fully intermolecularly promoted. The catalytic activity of the reference catalyst in this work, SBA-A, was determined at the same conditions as used in this previous work. Although all four amines have very similar base strengths [5, 35], the materials exhibit significant differences in catalytic activity for aldol condensation of acetone with 4-nitrobenzaldehyde, as shown in Figure 2. The primary amine-functionalized material Silicagel APTES exhibits a TOF of $7.80 \times 10^{-4} \pm 0.34 \times 10^{-4} \text{ s}^{-1}$. The TOFs obtained with the materials that were functionalized with secondary amines depend on the substituent of the secondary amine. A cyclohexyl substituent (Silicagel CAPTMS) leads to a much lower TOF of $3.10 \times 10^{-5} \pm 0.14 \times 10^{-5} \text{ s}^{-1}$. A secondary amine with an ethyl substituent (SBA-A) exhibits a TOF of $2.87 \times 10^{-4} \pm 0.13 \times 10^{-4} \text{ s}^{-1}$, which is in the same order of magnitude as the TOF obtained with a primary amine. The highest TOF of $3.30 \times 10^{-3} \pm 0.15 \times 10^{-3} \text{ s}^{-1}$ is obtained using a secondary amine with a methyl substituent (Silicagel MAPTMS). The high activity of a secondary amine with a methyl substituent compared to that of a primary amine can be attributed to the ability of primary amines to form inhibiting imine species [3-5]. Primary amines are able to form two imines, one by reaction with 4-nitrobenzaldehyde [3-5] and one by reaction with acetone [5]. The formation of the former can be suppressed by using an excess of acetone while the latter is in equilibrium with the reactive enamine intermediate. These species lower the concentrations of free active sites and reactive intermediates on the surface. As a result, a secondary amine active site that can yield the reactive enamine intermediate while simultaneously avoiding the formation of inhibiting imines can exhibit a higher catalytic activity. Moreover, the difference in activity between primary and secondary amines will be much more pronounced when using equimolar amounts of both reactants. Changing the substituent of the secondary amine from a methyl group to a more bulky cyclohexyl group increases the steric hindrance and lowers the activity by two orders of magnitude. The TOF obtained with a secondary amine with an ethyl substituent is about one order of magnitude lower than the TOF obtained with a methyl-substituted secondary amine. These observations suggest that the previously observed steric hindrance matters even for relatively small substituents.

Figure 2: Comparison of the turnover frequency of SBA-A (black) with the turnover frequencies of (3-aminopropyl)triethoxysilane (APTES), N-methylaminopropyl-trimethoxysilane (MAPTMS) and N-cyclohexylaminopropyl-trimethoxysilane (CAPTMS) grafted on Silicagel 60 (grey) at 45 °C using 4 mol% of amines with respect to the concentration of 4-nitrobenzaldehyde [5].

3.2.2 Intramolecular acid strength effects and spatial arrangement

To investigate the intramolecular acid strength effects on the cooperativity, the newly synthesized materials were also assessed through aldol condensation experiments with 4-nitrobenzaldehyde and acetone as reactants. The black bars in Figure 3 correspond to the TOFs obtained using the silanol-containing materials. At the investigated operating conditions the reference catalyst (SBA-A) exhibits a TOF of $1.41 \times 10^{-4} \pm 0.06 \times 10^{-4} \text{ s}^{-1}$. Incorporating an intramolecular alcohol on the amine site increases the TOF to $1.91 \times 10^{-4} \pm 0.08 \times 10^{-4} \text{ s}^{-1}$ (SBA-A-AL), indicating that in this case the active and promoting sites are in a more favorable conformation to catalyze the aldol condensation compared to a conformation in which only intermolecular surface silanols promote the activity of an amine site on a long carbon chain. However, changing the alcohol to a stronger acid site such as a carboxylic acid or a phosphoric acid decreases the TOF to $9.46 \times 10^{-5} \pm 0.42 \times 10^{-5} \text{ s}^{-1}$ (SBA-A-CA) and $7.86 \times 10^{-5} \pm 0.35 \times 10^{-5} \text{ s}^{-1}$ (SBA-A-PA), respectively, confirming that stronger acid sites have a negative impact on the activity of the amines [8-10]. These results suggest that the optimal promoting sites for the aldol condensation are H-bond donors, such as alcohols and silanols, and not strong acid sites.

The grey bars in Figure 3 correspond to the TOFs obtained using the HMDS treated materials exhibiting exclusively intramolecular cooperativity. In this case, the reference secondary amine exhibits a TOF of $3.61 \times 10^{-5} \pm 0.16 \times 10^{-5} \text{ s}^{-1}$ (SBA-HMDS-A), which corresponds to a decrease in activity of a factor four. This decrease in activity is similar to the activity decrease observed with primary amines and other secondary amines when silanols were removed [5]. Removing the silanols while the amine is still in close proximity of an alcohol, a carboxylic acid, or a phosphoric acid results in TOFs of $1.25 \times 10^{-4} \pm 0.55 \times 10^{-4} \text{ s}^{-1}$ (SBA-HMDS-A-AL), $7.88 \times 10^{-5} \pm 0.35 \times 10^{-5} \text{ s}^{-1}$ (SBA-HMDS-A-CA) and $5.57 \times 10^{-5} \pm 0.25 \times 10^{-5} \text{ s}^{-1}$ (SBA-HMDS-A-PA), respectively. This corresponds to a more limited decrease in TOFs by a factor 1.2 to 1.5. In the absence of silanols, even the amines adjacent to a ‘strong’ acid site are more active than the unpromoted amines (SBA-HMDS-A), indicating that, indeed, also stronger acids also exert a promoting effect on the activity of the amines, albeit less pronounced than that by silanols. Figure 3 also shows that in the absence of silanols, the secondary amine combined with an alcohol (SBA-HMDS-A-AL) exhibits a similar TOF as the secondary amine combined with surface silanols (SBA-A), indicating that an intramolecular primary alcohol is as efficient as an intermolecular surface silanol as promoting site for the aldol condensation. However, the highest TOF is obtained when the secondary amine is combined with both an alcohol and surface silanols (SBA-A-AL). This observation can be attributed to the joint movement of the amine and promoting alcohol site when they are located on the same linker. Due to this joint movement the amine and alcohol can bend together towards a neighbouring silanol on the silica surface, resulting in two promoting sites in the vicinity of the amine active site, *i.e.*, the intramolecular alcohol function and the intermolecular surface silanol. Subsequently, the two reactants can simultaneously be activated by the formation of a hydrogen bond instead of the consecutive activation when there is only one promoting site in the vicinity of the amine and lead to an increase in catalytic activity. Figure 4 shows that, regardless of the concentration of the reactants in the liquid phase, the probability that the necessary activated reactant is in proximity of the amine site increases with increasing number of promoting sites in vicinity of the amine. Moreover, both in the presence and absence of silanols, the

materials combining the amine with an alcohol exhibits the highest TOFs, indicating that bringing an alcohol in close proximity to the amine is beneficial for the cooperativity between the two sites. The results obtained in this work suggest that a methyl-substituted secondary amines with one or more intramolecular alcohol functions on the β -carbons would be optimal for the aldol condensation of acetone with 4-nitrobenzaldehyde, provided that the inclusion of such intramolecular alcohol functions does not significantly increase steric hindrance.

Figure 3: Turnover frequencies of the different catalysts at 45 °C using 15 mol% of amines with respect to the concentration of 4-nitrobenzaldehyde; black: catalysts without HMDS treatment combining intra- and intermolecular cooperativity (SBA-X), grey: catalysts treated with HMDS exhibiting exclusively intramolecular cooperativity (SBA-HMDS-X)

Figure 4: Comparison of the probability to activate 4-nitrobenzaldehyde in consecutive (left) and simultaneous (right) activation of the reactants

4 Conclusions

In this work, an SBA-15 support was successfully functionalized with a secondary amine and different acid groups, carefully arranged with respect to each other. Changing the substituent of a secondary amine from a methyl to an ethyl group decreased the catalytic activity in the aldol condensation. The activity of the secondary amine could be increased by incorporating an alcohol group close to the amine, showing the importance of the arrangement of the cooperative sites. However, incorporating stronger acids in the catalyst showed that intermolecular amine-silanol cooperativity or intramolecular amine-alcohol cooperativity is better than intramolecular amine-carboxylic acid or amine-phosphoric acid cooperativity. These results further support the notion that the optimal promoting sites for the aldol condensation are H-bond donors and not strong acid sites [9]. After removing the silanols from the surface, the preserved intramolecular cooperativity of the catalysts consisting of an amine and an acid site on the same linker resulted only in a minor activity loss, while the activity of the reference acid-free secondary amine decreased by a factor of 4 due to the loss of all intermolecular activity. The insights obtained in this work suggest that a silica support functionalized with a methyl-substituted secondary amines with one or more alcohol functions on the β -carbons would be optimal aldol condensation catalysts, provided that the inclusion of additional alcohol functions does not significantly increase the steric hindrance.

5 Acknowledgements

This work was supported by the Long Term Structural Methusalem Funding by the Flemish Government, the U.S. Department of Energy Office of Basic Energy Sciences through Catalysis Contract Number DEFG02-03ER15459, the Fund for Scientific Research Flanders (FWO) through Grant Number 3G006813 and a travel grant for a long stay abroad (Grant Number V428614N). The authors would like to thank Hannes Depauw of the Center for Ordered Materials, Organometallics & Catalysis for performing the XRD measurements and Dr. Johannes Leisen for recording the NMR spectra.

6 References

1. Y. Kubota, K. Goto, S. Miyata, Y. Goto, Y. Fukushima, Y. Sugi, *Chemistry Letters*, 2003, 32, 234-235
2. Y. Kubota, H. Yamaguchi, T. Yamada, S. Inagaki, Y. Sugi, T. Tatsumi, *Top. Catal.*, 2010, 53, 492-499
3. K. Kandel, S. M. Althaus, C. Peeraphatdit, T. Kobayashi, B. G. Trewyn, M. Pruski, I. I. Slowing, *J. Catal.*, 2012, 291, 63-68
4. K. Kandel, S. M. Althaus, C. Peeraphatdit, T. Kobayashi, B. G. Trewyn, M. Pruski, I. I. Slowing, *ACS Catal.*, 2013, 3, 265-271
5. J. Lauwaert, E. De Canck, D. Esquivel, P. Van der Voort, J. W. Thybaut, G. B. Marin, *Catal Today*, 2014, <http://dx.doi.org/10.1016/j.cattod.2014.08.007>
6. J. Lauwaert, E. De Canck, D. Esquivel, J. W. Thybaut, P. Van Der Voort, G. B. Marin, *ChemCatChem*, 2014, 6, 255-264
7. N. A. Brunelli, S. A. Didas, K. Venkatasubbaiah, C. W. Jones, *J. Am. Chem. Soc.*, 2012, 134, 13950-13953
8. N. A. Brunelli, C. W. Jones, *J. Catal.*, 2013, 308, 60-72
9. N. A. Brunelli, K. Venkatasubbaiah, C. W. Jones, *Chem Mater*, 2012, 24, 2433-2442
10. R. K. Zeidan, M. E. Davis, *J. Catal.*, 2007, 247, 379-382
11. R. K. Zeidan, S. J. Hwang, M. E. Davis, *Angew. Chem.-Int. Edit.*, 2006, 45, 6332-6335
12. J. A. Ma, D. Cahard, *Angew. Chem.-Int. Edit.*, 2004, 43, 4566-4583
13. J. D. Bass, A. Solovyov, A. J. Pascall, A. Katz, *J. Am. Chem. Soc.*, 2006, 128, 3737-3747
14. P. Van Der Voort, E. F. Vansant, *J. Liq. Chromatogr. Relat. Technol.*, 1996, 19, 2723-2752
15. J. C. Hicks, C. W. Jones, *Langmuir*, 2006, 22, 2676-2681
16. J. C. Hicks, R. Dabestani, A. C. Buchanan, C. W. Jones, *Chem Mater*, 2006, 18, 5022-5032
17. M. W. McKittrick, C. W. Jones, *Chem Mater*, 2003, 15, 1132-1139
18. L. D. White, C. P. Tripp, *J Colloid Interf Sci*, 2000, 227, 237-243
19. S. A. Kanan, W. T. Y. Tze, C. P. Tripp, *Langmuir*, 2002, 18, 6623-6627
20. E. L. Margelefsky, *Cooperative Catalysis by Bifunctionalized Mesoporous Silica*, 2008, California Institute of Technology.
21. B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.*, 2000, 122, 2395-2396
22. F. Tanaka, R. Thayumanavan, N. Mase, C. F. Barbas, *Tetrahedron Lett.*, 2004, 45, 325-328
23. Z. An, Y. Guo, L. W. Zhao, Z. Li, J. He, *ACS Catal.*, 2014, 4, 2566-2576
24. P. D. de Maria, P. Bracco, L. F. Castelhana, G. Bargeman, *ACS Catal.*, 2011, 1, 70-75
25. W. W. Lukens, P. Schmidt-Winkel, D. Y. Zhao, J. L. Feng, G. D. Stucky, *Langmuir*, 1999, 15, 5403-5409
26. G. F. Froment, K. B. Bischoff, *Chemical reactor analysis and design*, Wiley series in chemical engineering, Wiley, New York, 1990, xxxiv, 664 p.
27. D. Y. Zhao, J. L. Feng, Q. S. Huo, N. Melosh, G. H. Fredrickson, B. F. Chmelka, G. D. Stucky, *Science*, 1998, 279, 548-552
28. S. Radi, S. Tighadouini, Y. Toubi, M. Bacquet, *Journal of hazardous materials*, 2011, 185, 494-501
29. J. E. Sarneski, H. L. Surprenant, F. K. Molen, C. N. Reilley, *Analytical Chemistry*, 1975, 47, 2116-2124
30. C. Ye, R. Fu, J. Hu, L. Hou, S. Ding, *Magnetic Resonance in Chemistry*, 1993, 31, 699-704
31. F. K. Kalman, M. Woods, P. Caravan, P. Jurek, M. Spiller, G. Tircso, R. Kiraly, E. Brucher, A. D. Sherry, *Inorganic Chemistry*, 2007, 46, 5260-5270
32. Z. Glowacki, M. Topolski, *Magnetic Resonance in Chemistry*, 1989, 27, 897-899
33. M. L. Rueppel, J. T. Marvel, *Organic Magnetic Resonance*, 1976, 8, 19-20
34. Z. Glowacki, M. Hoffmann, M. Topolski, J. Rachon, *Phosphorus Sulfur and Silicon and the Related Elements*, 1991, 60, 67-71

35. J. J. Christensen, R. M. Izatt, D. P. Wrathall, L. D. Hansen, *Journal of the Chemical Society a - Inorganic Physical Theoretical*, 1969, 1212-1223

Graphical abstract