



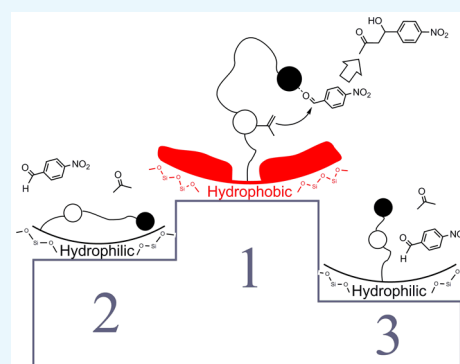
Inter- and Intramolecular Cooperativity Effects in Alkanolamine-Based Acid–Base Heterogeneous Organocatalysts

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Supporting Information

ABSTRACT: Intramolecular cooperativity in heterogeneous organocatalysts is investigated using alkanolamine-functionalized silica acid–base catalysts for the aldol condensation reaction of 4-nitrobenzaldehyde and acetone. Two series of catalysts, one with and one without silanol-capping, are synthesized with varied alkyl linker lengths (two to five) connecting secondary amine and terminal hydroxyl functionalities. The reactivity of these catalysts is assessed to determine the relative potential for intermolecular (silane amine–surface silanol) vs intramolecular (amine–hydroxyl within a single silane) cooperativity, the impact of inhibitory surface–silane interactions, and the role of alkyl linker length and flexibility. For the array of catalysts tested, those with longer linker lengths generally give increased catalytic activity, although the turnover frequency trends differ between catalysts with and without surface silanol capping. Catalysts with alkyl-substituted amines lacking a terminal hydroxyl demonstrate an adverse effect of chain length, where the larger alkyl substituent on the amine provides steric hindrance depressing catalytic activity, while giving additional evidence for improved rates afforded by intramolecular cooperativity in the alkanolamine materials. The silanol-capped alkanolamine catalyst with the longest alkyl linker is found to be the most active alkanolamine catalyst due to its hydrophobized surface, which removes hypothesized silanol–alkanolamine inhibitory interactions, with the sufficient length and flexibility of its amine–hydroxyl linker allowing for favorable conformations for cooperativity. This study demonstrates the feasibility of and important factors affecting intramolecular cooperative activity in acid–base heterogeneous organocatalysis.



■ INTRODUCTION

Carbon–carbon coupling reactions are essential steps in many chemical syntheses including pharmaceutical production and fuel synthesis from biomass.^{1,2} Many highly selective carbon–carbon bond formation steps are commonly performed with expensive homogeneous transition metal–complex catalysts that may suffer from process and scaling limitations. Inspired by enzymatic catalysis, in which a precisely shaped substrate binding “pocket” with specific proximal amino acid functional groups stabilizes a reaction transition-state, heterogeneous cooperative organocatalysts can be designed for controlled selectivity and can incorporate multiple proximal functionalities that would quench homogeneously, like acids and bases.³ This acid–base functionality may catalyze various reactions, including the C–C bond-forming aldol condensation reaction that is commonly performed industrially with homogeneous NaOH as well as others like the Michael addition, Henry reaction, and Knoevenagel condensation.^{4–6} Supported on stable porous solids, these catalysts can be used in flow systems and at moderately high temperatures, overcoming many disadvantages of homogeneous metal complexes.^{7,8} Typical supports for these materials are mesoporous silicas, which provide a weakly acidic solid phase with high surface area that may be readily augmented

with catalytic functional groups such as amines to form acid–base catalysts.^{3,8} Silica SBA-15 is commonly used as a support due to its straight mesoscale pores (~5–10 nm), which are large enough to minimize confinement effects and help ensure site isolation for even relatively large (~1 nm) functional groups.^{9,10}

Such multifunctional acid–base catalysts have been used for cooperative and cascade reactions, often with two or three functional aspects contributing to these capabilities.^{11–14} In many cases, the support effect of a weakly acidic silica or alumina is key to the functionality of the catalyst.^{15,16} Removal of the Brønsted acidic silanols of support surfaces by hydrophobic capping with hexamethyldisilazane (HMDS) greatly reduces the activity of base-functionalized silicas by preventing acid–base cooperativity.^{17–19} Rational mechanisms with and without silanol capping have been established for the aldol condensation of benzaldehydes with acetone catalyzed by nucleophilic amine and a cooperative weak acid.^{17,20,21} The polarity of the support also affects the conformations of functional groups and the degree to which they associate with

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the exposed surface.^{22,23} To achieve bifunctional activity with an inert support, for one cooperative transformation of a multifunctional material for cascade catalysis or to ensure proximal positioning of cooperative species, bifunctional moieties capable of intramolecular cooperativity are an attractive type of catalytic functionality.

Effective intramolecular acid–base catalysis for the aldol condensation was demonstrated with homogeneous proline catalysts, a chiral amino acid containing a secondary amine and a carboxylic acid.²⁴ Proline-like moieties immobilized on silica supports achieved similar intramolecular catalytic activity for this reaction.²⁵ The rigid structure of proline catalysts prevented protonation of the base by the nearby carboxylic acid. Co-grafting-separated primary amine and carboxylic acid silanes suffer from spacing and pairing shortcomings as well as the potential for acid–base quenching.¹⁸ The positioning of a carboxylic acid or other stronger acid relative to cooperative amines is therefore crucial, but weakly acidic silanols do not exhibit the same protonation problem regardless of amine proximity or flexibility.⁹ Similar silica materials functionalized by grafted alkyl amine moieties containing multiple amines with linear or branched connectivity capture CO₂ through intramolecular mechanisms within isolated sites.²⁶ Supported organocatalytic sites consisting of secondary amines with various pendant acids contained within the same silyl moiety with short alkyl spacing provided evidence of enhanced base-specific activity with the incorporation of a terminal alcohol, suggesting an additive benefit provided by an additional proximal hydroxyl group.²⁷

Fundamental investigation of supported organocatalytic active sites requires site isolation on the support surface, which may be achieved through various synthetic methods and with low functional loadings depending on the total surface area and the grafted moiety size. Functionalization by co-condensation of aminosilanes fails to achieve site isolation even at very low loadings.²⁸ Solvent polarity and dielectric constant strongly impact the density and site isolation of grafted silanes.^{29,30} Nonreactive equilibration of silanes with the support surface prior to grafting at elevated temperatures may help reduce silane clustering.⁹ Syntheses involving substitutions of silanes with terminal halides or clicks to azide functionalities reduce silane–silane interactions, which decrease dispersion during grafting.^{27,31,32} Site isolation does not always yield the most effective catalyst, as some intersilane cooperativities at moderate loadings were most effective for the Henry reaction.³³ Still, sufficient availability of cooperative silanols and minimizing clustering of base sites are important for effective catalysts.^{17,19} Although intersilane cooperativity may increase catalytic activity in some cases, fundamental studies of isolated bifunctional moieties for catalysis depend on effective isolation of sites with maximum dispersion and low loading.

This work further investigates the capabilities and contributions of intramolecular cooperativity with silica-supported alkanolamine (AA) based catalysts by controlling the amine–hydroxyl linker length and by isolating the intramolecular catalysis through capping of surface silanols. Specifically, a series of four catalysts and a parallel series of HMDS-capped counterparts (Figure 1) with varied linker lengths of 2–5 methylene units were synthesized from the previously described multistep functionalization method.²⁷ The catalysts were characterized to describe their structure and define their amine loadings, followed by catalytic testing in

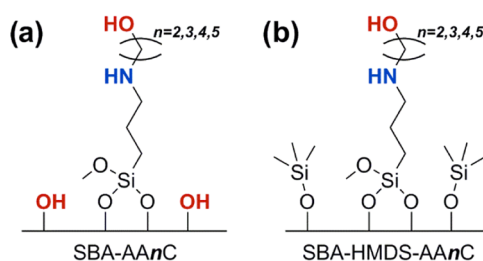
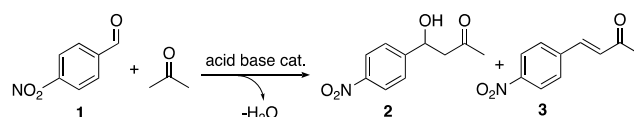


Figure 1. Chemical structure and naming convention of synthesized alkanolamine (AA) bifunctional catalysts grafted on SBA-15 with (b) and without (a) HMDS-capping of surface silanols. Catalytically active basic species (secondary amines) are shown in blue and weakly acidic species (surface silanols, terminal hydroxyls) in red.

batch aldol condensation reactions (Scheme 1). The kinetic experiments allow for quantitative comparison of the materials via initial reaction rates as turnover frequencies (TOFs).

Scheme 1. Aldol Condensation of 4-Nitrobenzaldehyde (4-NB) (1) and Acetone and Its Major Products, 2 and 3



The uncapped alkanolamine catalyst series (Figure 1a) with available surface silanols probes the potential additive benefit of incorporating both intra- and intermolecular cooperativities in these organocatalysts, whereas the HMDS-capped catalysts (Figure 1b) have hydrophobic support surface chemistry and comparatively highlight intramolecular cooperativity and its relative catalytic activity. The Si–amine linker length has previously been studied experimentally^{18,34} and with molecular dynamics simulations,²³ whereby it was found that three and four-carbon spacings were optimal for flexibility and preferential conformations to maximize cooperative activity with the surface silanols. To isolate only one steric factor, the silicon–amine linker length was fixed at three carbons for all catalysts. Transition-state conformation and energetics may impact the specific optimal linker length in promoting intramolecular interactions. Additionally, catalysts with alkyl instead of alkanol substituents were tested to study the steric effects of alkyl substituents separately from the potential for intramolecular cooperativity with pendant hydroxyl groups. Compared with simpler aminosilane–silanol cooperative catalysis systems, this report is constructive in suggesting whether the design of an intramolecular bifunctionality leads to improved catalytic function. This study attempts to establish intramolecularity as a feasible mode of cooperativity in bifunctional catalysis and discusses its potential limitations.

RESULTS AND DISCUSSION

Catalyst Synthesis and Characterization. The textural properties of the bare SBA-15 support (average pore size = 6.2 nm) and functionalized silica samples, as determined by nitrogen physisorption, are listed in Table 1. The functionalized materials demonstrated an expected decrease in Brunauer–Emmett–Teller (BET) surface area, pore volume and average pore size with iodosilane grafting, HMDS-capping, and alkanolamine substitution, which resulted in relatively bulky (~1 nm) surface-grafted functional groups. The success

Table 1. Textural Properties and Silane Loadings of all Materials as Determined by Nitrogen Physisorption and Combustion Elemental Analysis

material	BET surface area (m ² /g)	total pore volume (cm ³ /g)	silane loading ^a (mmol/g)
SBA-15 support	820	0.78	
SBA-I	804	0.82	0.19 ± 0.01
SBA-I-HMDS	461	0.64	0.15 ± 0.01
SBA-AA2C	539	0.67	0.28 ± 0.03
SBA-AA3C	377	0.65	0.37 ± 0.10
SBA-AA4C	431	0.61	0.32 ± 0.07
SBA-AA5C	407	0.61	0.27 ± 0.05
SBA-HMDS-AA2C	569	0.61	0.30 ± 0.04
SBA-HMDS-AA3C	431	0.71	0.26 ± 0.01
SBA-HMDS-AA4C	430	0.68	0.28 ± 0.07
SBA-HMDS-AA5C	447	0.61	0.25 ± 0.03

^aSilane loadings for SBA-I and SBA-I-HMDS are calculated from iodine mass fraction from combustion elemental analysis; silane loadings for all other materials are calculated from nitrogen elemental analysis.

of the known HMDS-capping method from SBA-I to SBA-I-HMDS was confirmed by a decrease in surface area, thermogravimetric analysis, and C and H wt % increases from elemental analysis (Supporting Information). Capping by HMDS removes all accessible silanols on the silica support area while leaving the grafted iodosilane moieties intact for subsequent substitution. To measure the stability of the HMDS capping during the post-substitution acid washing step, a batch of HMDS-capped SBA-15 HMDS was treated with the acid washing treatment used during the substitution workup. A minor reduction in mass lost during thermogravimetric analysis was noted in the capped silica after washing with acid, indicating that some limited removal of HMDS-capping groups may occur during the substitution step (Figure S3).

The loading of functional groups was determined by CHNI combustion elemental analysis performed in triplicate to sufficiently capture the error and resulting standard deviations inherent to the technique for low elemental contents (Table 1). A low grafting density of iodosilanes based on literature metrics for site isolation²⁶ was confirmed by the iodine content of SBA-I. The functionalization approach using a bulky halide silane combined with anhydrous dispersion for 24 h prior to

condensation at elevated temperatures has been shown to result in good dispersion and site isolation (here: ~0.45 site/nm²) of grafted silanes. Full substitution of iodosilane moieties was confirmed by the lack of iodine detected by elemental analysis after amine substitution. The nitrogen content of each catalyst was used to determine the molar quantity of functional groups present and was similar to the initial iodosilane loadings. A slight change in mass-specific loading was observed due to the decrease in total functionalized sample mass from the substitution of the heavy iodine with the lighter alkanolamine molecules, partial removal of HMDS caps, and from error inherent to the elemental analysis measurements.

Kinetic Experiments and Analysis of Catalyst Activity.

Secondary amines with short alkyl substituents (e.g., methyl) are effective basic sites that may cooperate effectively with surface silanols for acid–base catalysis of the aldol condensation. Weakly acidic silanol groups on the silica surface are understood to act as intermolecular cooperative partners with amines in catalyzing aldol condensation reactions (Figures 3a and S4a). An increase in silanol availability has been shown to increase the activity of amine sites in similar aminosilica catalysts for aldol condensations.¹⁹ As such, the addition of a terminal alkyl-linked hydroxyl group proximal to the amine could potentially be expected to improve cooperative availability and increase activity. Uncapped alkanolamine catalysts have the potential for intermolecular (silane amine–surface silanol) as well as intramolecular (silane amine–silane hydroxyl) cooperativity, whereas HMDS-capped variants may exhibit primarily only intramolecular (silane amine–silane hydroxyl) cooperativity. Although the synthesis method employed here minimizes silane clustering during surface grafting, some variations around the resulting average spacing (0.45 site/nm²) of sites could yield sites in sufficient proximity for intermolecular (silane–silane) cooperativity. The full length of the silyl alkanolamine moieties varies from ~8 to 12 Å, and there may exist conformations where some intersilane cooperativities occur between partially clustered silanes (silane amine, to adjacent silane hydroxyl, Figure S5). This possibility may contribute some intermolecular cooperativities to HMDS-capped catalysts, which otherwise could exhibit acid–base cooperativity only intramolecularly within a silyl alkanolamine. The distance between average spaced sites should be too great for this intersilane cooperativity, however, some minor contributions to overall activity may be attributed

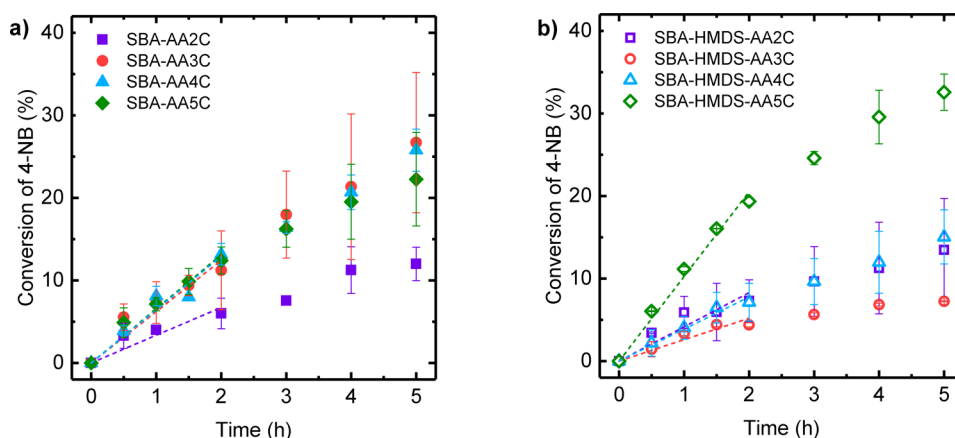


Figure 2. Conversion of 4-nitrobenzaldehyde over time catalyzed by (a) uncapped and (b) HMDS-capped alkanolamine catalysts. Linear fits for initial rates used to calculate TOFs are shown.

to closer than average sites within reasonable variation of the average site spacing. Additionally, partial HMDS removal during substitution would result in a small number of surface silanols in capped materials. This effect is minor but may lead to some surface–silane cooperativity in primarily hydrophobized catalysts.

Reaction kinetics for the batch aldol condensation reactions of 4-nitrobenzaldehyde with acetone performed with the capped and uncapped alkanolamine catalyst series are shown in Figure 2. Catalysts with alkyl linker lengths of three to five showed nearly identical catalytic activity, whereas the two-carbon linker catalyst, SBA-AA2C, had significantly lower activity. The relatively short spacing between the amine and the hydroxyl group on the AA2C material may reduce flexibility and conformational freedom, similar to how alkyl primary amine catalysts previously studied have showed a requisite minimum three-carbon linker to achieve a maximum in catalytic activity in intermolecular cooperativity with silanols on the surface.³⁴ This structural restriction could lead to low intramolecular cooperativity, whereas surface silanol cooperativity as well as minor contributions from adjacent silane–silane cooperativity and base-only mechanisms maintained some levels of activity. Compared to the catalysts with longer alkanol substituents, the short ethyl alcohol substituent could reduce cooperativity with neighboring silanes. The 3–5C catalysts, however, may have adequate spacing and flexibility for some intramolecular cooperative functions, leading to increased rates relative to the small spacer catalyst (Figure 2). However, no significant improvement of catalytic activity was observed when increasing the alkyl spacer length beyond three carbons, as the additional alkyl spacing may not further improve the cooperative benefit of the pendant hydroxyl group for uncapped catalysts.

Key differences were observed between catalysts with and without HMDS capping, indicative of the important effects of surface silanols on reactivity. Reaction data for the HMDS-capped alkanolamine catalyst series (Figure 2b) showed a clear dependence on spacer length, noting that this was a different trend than observed in the uncapped series. Without surface silanols necessary for intermolecular surface–silane amine acid–base cooperativity, this series of materials reflects primarily the effects of the intramolecular interactions between the terminal hydroxyl group and the amine in the alkanolamine moieties (Figure 3b). Catalysts with less than five-carbon alkyl linkers had relatively low rates that were approximately indistinguishable, in part due to the error inherent to both catalyst loading and performance measurements. A dramatic jump in catalytic activity was noted for the capped five-carbon

catalyst, SBA-HMDS-AA5C. This longest linker length catalyst was evidently quite effective for intramolecular cooperative catalysis and was the most active alkanolamine catalyst studied here. The hydrophobized surface resulting from HMDS-capping may decrease the propensity for the relatively long alkanolamine moiety to lay flat or associate with the pore surface, leaving it readily accessible to reactive species near the catalyst surface.^{23,36} In uncapped materials, strong hydrogen bonding interactions between secondary amines or terminal hydroxyl groups with the polar surface may poison potential active sites. Hydrophobic interactions of alkyl linkers with HMDS-capped surfaces may occur but would not occupy catalytic species as in uncapped materials. The long linker length may afford the flexibility requisite for the specific conformation(s) of intramolecular acid–base cooperativity involving the enamine intermediate and local activation of the aldehyde group of 4-NB (Figure 3b).^{20,27}

Comparison of the TOFs for the uncapped and capped alkanolamine catalyst series is shown in Figure 4. The HMDS-

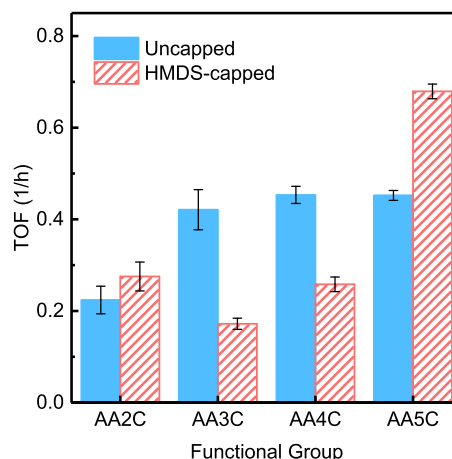


Figure 4. Turnover frequencies of uncapped and HMDS-capped alkanolamine catalyst series for the aldol condensation reaction.

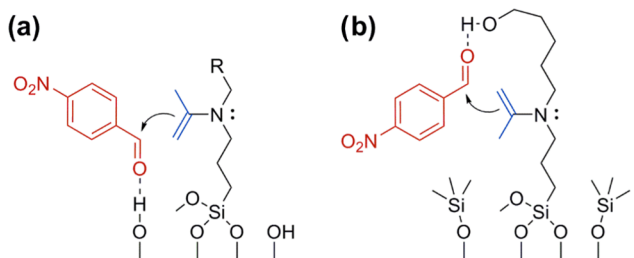


Figure 3. Proposed conformation for the C–C bond-forming steps of intermolecular- (a, surface–silane) and intramolecular (b, silane–silane)-catalyzed aldol condensation reactions of acetone and 4-nitrobenzaldehyde. Full proposed pathways are shown in Figure S3.

capped 2C catalyst had a nearly identical TOF as its uncapped counterpart, indicating that the surface capping did not significantly decrease activity, and that the measured catalytic function may be attributed to some minor extents of silane–adjacent silane cooperativity as well as the known but slower base-only mechanism observed in HMDS-capped aminosilica materials.¹⁹ Details of how the electronics of such substituent may affect the catalysis was not explored in this study. The 3–4C HMDS-capped catalysts showed reduced TOFs compared to their uncapped counterparts, indicative of the benefit of intermolecular cooperativity with surface silanols when intramolecular cooperativity may not be significant due to the intermediate linker length and flexibility. The 5C-capped catalyst demonstrated the greatest alkanolamine catalyst TOF, a surprising result as HMDS-capping of surface silanols has generally reduced aminosilane catalytic activity in relevant literature examples.^{19–21,27,34,37} An alkyl linker length of five carbons is apparently sufficient for effective intramolecular activity, and the catalytic function of SBA-AA5C may be relatively inhibited by stronger noncovalent polar interactions with hydrophilic surface silanols (Figure S4).^{22,23,38} This longest chain length may additionally increase the possibility of silane amine–adjacent silane hydroxyl cooperativity. Although the benefit of intermolecular (surface–silane) cooperativity is

lost by HMDS-capping, the surface hydrophobization appears to highlight the primarily intramolecular function of an appropriately spaced alkanolamine moiety.

For all alkanolamine catalysts studied, TOFs under 1 h^{-1} were measured (Figure 4), markedly lower than that of catalyst using a simpler secondary (methyl) amine moiety (SBA-A1C, Figure 6). Hydrogen bonding or other noncovalent interactions between the amine and/or terminal hydroxyl and the surface silanols could reduce the availability of amines able to initiate the proposed catalytic mechanism (Figure S4). The alkyl tail of the alkanolamine functional groups may also lead to reduced conformational freedom and increased steric hindrance, further decreasing organocatalytic activity.³⁹ Despite the relatively lower activity of the alkanolamine materials in comparison to SBA-A1C, insight into the nature of intramolecular cooperativity may be afforded by analysis of their catalytic function.

The negative effects of steric hindrance and bulk due to the pendant alkyl group were investigated with a set of secondary amine catalysts (SBA-A5C and SBA-HMDS-A5C) with a pentyl substituent lacking a terminal hydroxyl and as such no potential for intramolecular or intersilane cooperativity (Figure 5). The inhibiting effect of a large substituent group is

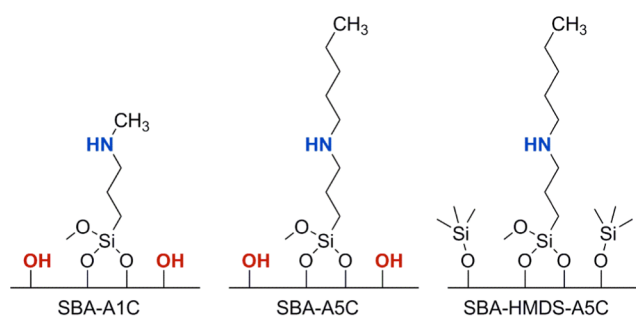


Figure 5. Chemical structure and naming convention for alkyl-only-substituted secondary amine-functionalized catalysts (methyl: SBA-A1C, pentyl: SBA-A5C, and SBA-HMDS-A5C).

demonstrated by comparing the activity of SBA-A1C with SBA-A5C, which differ only in the size of the pendant alkyl group. SBA-A1C has a significantly greater TOF than SBA-A5C (Figure 6), evidence that the potential benefit of a terminal hydroxyl group is counteracted significantly by the negative effect of a bulky substituent to the amine.

Finally, the similar rates observed with SBA-AA5C and SBA-A5C demonstrate that both have key limitations in comparison to the best intramolecular (SBA-HMDS-AA5C) and intermolecular (SBA-A1C) analogs. SBA-AA5C lacks the hydrophobized HMDS-terminated surface that apparently helps drive the intramolecular catalytic function of SBA-HMDS-AA5C (Figure 3), and SBA-A5C suffers from the effects of steric hindrance related to its large pentyl substituent (Figure 5) compared to A1C. SBA-A5C also lacks the intramolecular and intersilane cooperative potentials of SBA-AA5C. The cooperative effect of surface silanols in acid–base catalysis with aminosilanes has been shown to reach a maximum when sufficient silanol–amine spacing is achieved.¹⁹ A similar effect with the terminal hydroxyl of an alkanolamine moiety is observed here, wherein SBA-HMDS-AA5C is the best performing intramolecularly cooperative catalyst studied here. However, these two types of cooperativity may not be additive, as seen by the activity of the SBA-AA5C material. Since the

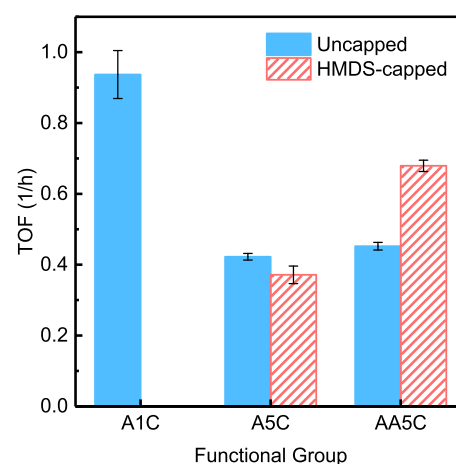


Figure 6. Comparison of TOFs for the best performing alkanolamine catalysts (AA5C) with alkyl-only-substituted secondary amine catalysts (SBA-A1C, SBA-A5C, SBA-HMDS-A5C).

number of basic sites on the catalyst is the limiting factor predetermined by the silane loading, the surface silanols in a simple aminosilane catalyst, e.g., SBA-A1C, may already provide adequate availability of cooperative acid sites. In addition, the long-chain substituents may lead to inhibitive steric effects (SBA-A5C), and alkanolamine–surface polar interactions (multipoint H-bonding) may reduce the availability of active sites (SBA-AA5C).

Comparison to Previous Works. The catalytic rates observed in this study were internally consistent and reproducible but contrast higher rates shown with similar SBA-AA2C materials in a previous work (Figure 7).²⁷ In initial

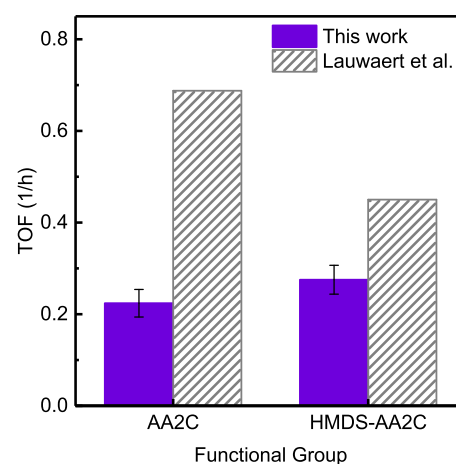


Figure 7. Comparison of capped and uncapped SBA-AA2C catalyst TOFs reported in this work and by Lauwaert et al.²⁷

studies, directly following the procedure from the referenced work for iodosilane grafting, using a large excess of silane and noninert headspace gas environments, we consistently found much higher functional group loadings (0.6–0.7 mmol/g) in contrast to the low loadings (0.15–0.3 mmol/g) reported in the cited work. To ensure sufficient catalyst site isolation and avoid the formation of inactive tertiary amines resulting from a single amine replacing two terminal iodines, a low functional group loading was instead achieved by adopting the silane grafting procedure described by Brunelli et al.¹⁸ This method begins with equilibration under inert conditions, allowing the

silane to spread evenly on the mesopore surface before condensation forming covalent grafting bonds during the heated grafting step. This results in an increased grafting yield and was repeated, resulting in consistent iodophilic loadings.

CONCLUSIONS

Intramolecular cooperativity in heterogeneous organocatalysis was investigated with alkanolamine bifunctional acid–base catalysts supported on mesoporous silica. Parallel series of catalysts with and without HMDS-capping of surface silanols were synthesized with varied secondary amine–terminal hydroxyl alkyl linker lengths from two to five in the alkanolamine functionality, tested in batch aldol condensation reactions of 4-nitrobenzaldehyde and acetone, and compared via their initial reaction rates as TOFs. In uncapped alkanolamine catalysts, in which inter and intramolecular cooperativities are possible, alkyl linkers of at least three carbons were shown to be more active than a short two-carbon spacer. With HMDS-capped materials, in which silanol–silane cooperativity is removed, a strong dependence on linker length was found, and the five-carbon alkyl linker catalyst demonstrated a significantly greater TOF than those of two to four-carbon linker catalysts.

Contrary to most prior aminosilica catalyst literature, HMDS-capping yielded the catalyst with the greatest activity for the aldol condensation reaction in this work. Uncapped catalysts were hindered by hypothesized polar interactions between the catalyst moiety and the support surface as well as sterically by the bulky alkyl chain substituent. The hydrophobized surface of the capped five-carbon linker catalyst drove active site availability, and its relatively long and flexible alkyl linker allowed for favorable conformations for intramolecular cooperativity. Several alkyl-substituted secondary amine catalysts lacking a terminal hydroxyl were studied as key control materials. A simple methyl-substituted aminosilica catalyst had the greatest catalytic activity, but a pentyl-substituted material showed significantly reduced activity, highlighting the effect of steric hindrance. The pentyl-substituted materials performed more poorly than their alkanolamine analogs, indicative of the benefit of intramolecular cooperativity with a terminal alcohol group.

Although the coexistence of the intramolecular and intermolecular cooperativities through the addition of terminal hydroxyl groups has been previously reported to enhance catalytic activity, the present work explores several complicating factors including polar surface–silane interactions and steric effects. Sufficient amine–hydroxyl carbon spacer length is required for effective intramolecular cooperativity, and surface hydrophobization by HMDS-capping may enhance the reaction rates of intramolecularly cooperative moieties. An intramolecular catalytic mechanism is not as effective as the well-studied intermolecular surface silanol–aminosilane acid–base cooperativity, but reasonable activity may be achieved in a single silyl alkanolamine with adequate spacing and a hydrophobic support surface. These results support the feasibility of intramolecularly cooperative bifunctional catalytic moieties but underscore important considerations and limitations to their function.

MATERIALS AND METHODS

Materials. Dimethyl sulfoxide (DMSO, 99.9%), toluene (99.5%), and hexane (98.5%) were purchased from BDH.

Anhydrous toluene (99.8%), Reagent Plus acetone ($\geq 99\%$), Poly(ethylene glycol)-*block*-poly(propylene glycol)-*block*-poly(ethylene glycol) (Pluronic P123, average $M_n \sim 5800$), tetraethyl orthosilicate (TEOS, 99.0%), *N,N*-diisopropylethylamine (DIPEA, 99.9%), hydrochloric acid (37 wt %), ethanolamine ($>98\%$), 5-amino-1-pentanol (95%), and 4-nitrobenzaldehyde (4-NB, 98%) were obtained from Sigma Aldrich. (3-Aminopropyl)trimethoxysilane (IPTMS, 97%), ammonium hydroxide (28 wt % in H_2O), 3-amino-1-propanol (99%), and 4-amino-1-butanol (98%) were acquired from Alfa Aesar. 1,4-Dimethoxybenzene (DMB, $>99\%$) was produced by Tokyo Chemical Industry (TCI), and ethanol (99.5%) was produced by VMR Koptec.

Synthesis of Mesoporous Silica Support SBA-15. The mesoporous silica support, SBA-15, was synthesized according to prior methods by polymer-directed assembly of silica precursors followed by calcination.²⁷ Two batches were synthesized by the following method and subsequently combined after initial characterization. First, 24.0 g of Pluronic P123 was dissolved in 636 mL of distilled water and 120 mL of 12 M hydrochloric acid in a 2 L Erlenmeyer flask. After the P123 was fully dissolved, 46.26 g of tetraethyl orthosilicate (TEOS) was added, and the solution was magnetically stirred for 20 h at 40 °C in an oil bath. The magnetic stir bar was then removed, and the mixture was heated to 100 °C for 24 h without stirring and loosely covered. The product was then filtered with several liters of distilled water and dried overnight at 75 °C. The dried product was calcined with the following procedure: (1) ramp to 200 °C at 1.2 °C/min, (2) hold at 200 °C for 1 h, (3) ramp to 550 °C at 1.2 °C/min, (4) hold at 550 °C for 12 h, (5) cool to room temperature. The calcined product was gently ground and then dried under vacuum at 120 °C overnight.

Grafting of Iodopropyltrimethoxysilane on SBA-15. Silane grafting methods were adapted from previous works.^{18,27} Batches (8, 1 g) of SBA-15 were treated identically with the following procedure and combined after grafting and recollection. Each batch was dried under vacuum at ~ 10 mTorr at 120 °C overnight prior to grafting. Under a nitrogen atmosphere, 25 mL of anhydrous toluene was added to the dried silica, which was dispersed with stirring to visual homogeneity. Then, 0.5 mmol of iodopropyltrimethoxysilane (IPTMS, stored under N_2) was added to the mixture, which was stirred at room temperature for 24 h to allow for even distribution of IPTMS across the SBA-15 surface area. Next, 20 μ L of deionized water was added to the mixture, which was then stirred at 80 °C another 24 h, yielding a light pink mixture after reaction. The product was washed with 100 mL of each of toluene, hexane, and ethanol and then dried under vacuum at 120 °C overnight. The 8 batches were combined after drying; the combined IPTMS-grafted SBA-15 is referred to as SBA-I.

HMDS Capping of Surface Silanols. Roughly, half of the SBA-I was separated to be capped with hexamethyldisilazane (HMDS) to remove the remaining surface silanols.³⁵ First, 4.5 g of SBA-I was stirred in 90 mL of anhydrous toluene and purged with argon for 1 h. Then, 55.8 mmol of HMDS was added by syringe to the mixture and stirred for 24 h. The product was washed with 300 mL of toluene, hexane, and ethanol and dried under vacuum at 120 °C overnight. The nomenclature for HMDS-capped materials in this study is SBA- x -HMDS, where x refers to the grafted functionality (e.g., I).

Alkanolamine Substitution. A series of catalysts were synthesized by substituting the iodine of the grafted IPTMS with alkanolamines of varying carbon linker lengths (2–5C) between the amine and alcohol groups.²⁷ Substitution reactions were performed identically with both SBA-I and SBA-I-HMDS materials. For each substitution, 500 mg of IPTMS-grafted silica (containing 0.08–0.1 mmol iodosilane) was dispersed in 8.33 mL of DMSO with 6.67 mmol of the desired alkanolamine. Subsequently, 2 mL of *N,N*-diisopropylethylamine (DIPEA) was added, and the mixture was stirred at 110 °C for 48 h, developing a brown color as iodine species was liberated. The product was filtered with 100 mL of each of DMSO, hexane, and ethanol. The recovered pale beige solid was stirred with 33.3 mL of 2 M HCl (aq) at room temperature for 6 h to remove bound DIPEA. The product was then washed with 100 mL of distilled water and 33.3 mL of 2 M ammonium hydroxide (28%) and dried under vacuum at 120 °C overnight. The nomenclature for each catalyst is SBA(-HMDS)-AA_{*n*}C, where *n* refers to the alkanolamine carbon linker length (e.g., 2 for ethanolamine), as seen in Figure 1.

Catalyst Characterization. Nitrogen physisorption experiments were performed at 77 K on Micromeritics Tristar 2030, and surface areas were determined by the Brunauer–Emmett–Teller (BET) method. CHNI combustion elemental analysis was performed by Atlantic Microlab, Inc. (Norcross, GA) to identify the iodine and nitrogen contents, which were used to determine the functional group loadings and therefore catalyst site density. Duplicates of elemental analyses were conducted to estimate uncertainty in loadings from error in EA data due to the low grafting densities.

Catalyst Testing. Catalyst testing was performed with aldol condensation reactions (Scheme 1) of 4-nitrobenzaldehyde (4-NB) and acetone (excess, used as a reactant and solvent) with 1,4-dimethoxybenzene (DMB) as an internal standard. Generally, 3 mL of reactions containing 30 mM 4-NB and DMB and 15 mol % catalyst (based on amine content) was run at 45 °C for 5 h. The catalyst was dried overnight under vacuum at 120 °C and then weighed and added to a 25 mL of two-neck round-bottom flask and magnetically stirred in 1.5 mL of acetone. Two-neck reaction flasks were fit with a condenser and a rubber septum. Once dispersed, 1.5 mL of a solution containing 60 mM 4-NB and DMB was added to the mixture via syringe and stirred briefly. Reaction aliquots of 50–100 μL were taken via needle and syringe and filtered through a wetted 1–2 cm plug of silica before dilution into acetone for analysis by gas chromatography. The reaction was monitored for 5 h, with time points taken at every 30 min during the first 2 h and every hour thereafter, during the latter 3 h. The reaction aliquots were analyzed by flame ionization detector (FID) using a Shimadzu GC-2010 gas chromatograph. The reactant conversions were evaluated by GC FID integrations relative to the internal standard, DMB. Experiments with each catalyst were repeated at least three times. Turnover frequencies (TOFs) were calculated from regression of approximately linear initial rates at short times.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b02690.

Validation of halide substitution synthesis approach; thermogravimetric analyses of HMDS capping; reactions with analogous homogeneous catalysts; elemental analysis data; aldol condensation reaction mechanisms; depictions of surface–silane interaction and intersilane cooperativity (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Li, C. J. Organic Reactions in Aqueous Media with a Focus on Carbon–Carbon Bond Formations: A Decade Update. *Chem. Rev.* **2005**, *105*, 3095–3165.
- (2) Huber, G. W.; Iborra, S.; Corma, A. Synthesis of Transportation Fuels from Biomass: Chemistry, Catalysts, and Engineering. *Chem. Rev.* **2006**, *106*, 4044–4098.
- (3) Shylesh, S.; Thiel, W. R. Bifunctional Acid–Base Cooperativity in Heterogeneous Catalytic Reactions: Advances in Silica Supported Organic Functional Groups. *ChemCatChem* **2011**, *3*, 278–287.
- (4) Notz, W.; Tanaka, F.; Barbas, C. F. Enamine-Based Organocatalysis with Proline and Diamines: The Development of Direct Catalytic Asymmetric Aldol, Mannich, Michael, and Diels–Alder Reactions. *Acc. Chem. Res.* **2004**, *37*, 580–591.
- (5) Huh, S.; Chen, H. T.; Wiench, J. W.; Pruski, M.; Lin, V. S. Y. Cooperative Catalysis by General Acid and Base Bifunctionalized Mesoporous Silica Nanospheres. *Angew. Chem., Int. Ed.* **2005**, *44*, 1826–1830.
- (6) Motokura, K.; Tanaka, S.; Tada, M.; Iwasawa, Y. Bifunctional Heterogeneous Catalysis of Silica–Alumina-Supported Tertiary Amines with Controlled Acid–Base Interactions for Efficient 1,4-Addition Reactions. *Chem. - Eur. J.* **2009**, *15*, 10871–10879.
- (7) Margelefsky, E. L.; Zeidan, R. K.; Davis, M. E. Cooperative Catalysis by Silica-Supported Organic Functional Groups. *Chem. Soc. Rev.* **2008**, *37*, 1118–1126.
- (8) Ferré, M.; Pleixats, R.; Wong Chi Man, M.; Cattoën, X.; Seifert, A.; Ernst, S.; Thiel, W. R.; Martinez, J.; Martra, G.; Toulemon, D.; et al. Recyclable Organocatalysts Based on Hybrid Silicas. *Green Chem.* **2016**, *18*, 881–922.
- (9) Brunelli, N. A.; Jones, C. W. Tuning Acid–Base Cooperativity to Create next Generation Silica-Supported Organocatalysts. *J. Catal.* **2013**, *308*, 60–72.
- (10) García, A.; Slowing, I. I.; Evans, J. W. Pore Diameter Dependence of Catalytic Activity: P-Nitrobenzaldehyde Conversion to an Aldol Product in Amine-Functionalized Mesoporous Silica. *J. Chem. Phys.* **2018**, *149*, No. 024101.
- (11) Zeidan, R. K.; Davis, M. E. The Effect of Acid–Base Pairing on Catalysis: An Efficient Acid–Base Functionalized Catalyst for Aldol Condensation. *J. Catal.* **2007**, *247*, 379–382.
- (12) Huang, Y.; Xu, S.; Lin, V. S. Y. Bifunctionalized Mesoporous Materials with Site-Separated Brønsted Acids and Bases: Catalyst for a Two-Step Reaction Sequence. *Angew. Chem., Int. Ed.* **2011**, *50*, 661–664.
- (13) Biradar, A. V.; Patil, V. S.; Chandra, P.; Doke, D. S.; Asefa, T. A Trifunctional Mesoporous Silica-Based, Highly Active Catalyst for

One-Pot, Three-Step Cascade Reactions. *Chem. Commun.* **2015**, *51*, 8496–8499.

(14) Motokura, K.; Tada, M.; Iwasawa, Y. Layered Materials with Coexisting Acidic and Basic Sites for Catalytic One-Pot Reaction Sequences. *J. Am. Chem. Soc.* **2009**, *131*, 7944–7945.

(15) Motokura, K.; Tada, M.; Iwasawa, Y. Heterogeneous Organic Base-Catalyzed Reactions Enhanced by Acid Supports. *J. Am. Chem. Soc.* **2007**, *129*, 9540–9541.

(16) Shylesh, S.; Wagener, A.; Seifert, A.; Ernst, S.; Thiel, W. R. Mesoporous Organosilicas with Acidic Frameworks and Basic Sites in the Pores: An Approach to Cooperative Catalytic Reactions. *Angew. Chem., Int. Ed.* **2010**, *49*, 184–187.

(17) Xie, Y.; Sharma, K. K.; Anan, A.; Wang, G.; Biradar, A. V.; Asefa, T. Efficient Solid-Base Catalysts for Aldol Reaction by Optimizing the Density and Type of Organoamine Groups on Nanoporous Silica. *J. Catal.* **2009**, *265*, 131–140.

(18) Brunelli, N. A.; Venkatasubbaiah, K.; Jones, C. W. Cooperative Catalysis with Acid-Base Bifunctional Mesoporous Silica: Impact of Grafting and Co-Condensation Synthesis Methods on Material Structure and Catalytic Properties. *Chem. Mater.* **2012**, *24*, 2433–2442.

(19) Lauwaert, J.; De Canck, E.; Esquivel, D.; Thybaut, J. W.; Van Der Voort, P.; Marin, G. B. Silanol-Assisted Aldol Condensation on Aminated Silica: Understanding the Arrangement of Functional Groups. *ChemCatChem* **2014**, *6*, 255–264.

(20) Kandel, K.; Althaus, S. M.; Peeraphatdit, C.; Kobayashi, T.; Trewyn, B. G.; Pruski, M.; Slowing, I. I. Substrate Inhibition in the Heterogeneous Catalyzed Aldol Condensation: A Mechanistic Study of Supported Organocatalysts. *J. Catal.* **2012**, *291*, 63–68.

(21) Collier, V. E.; Ellebracht, N. C.; Lindy, G. I.; Moschetta, E. G.; Jones, C. W. Kinetic and Mechanistic Examination of Acid-Base Bifunctional Aminosilica Catalysts in Aldol and Nitroaldol Condensations. *ACS Catal.* **2016**, *6*, 460–468.

(22) Mao, K.; Kobayashi, T.; Wiench, J. W.; Chen, H.-T.; Tsai, C.-H.; Lin, V. S.-Y.; Pruski, M. Conformations of Silica-Bound (Pentafluorophenyl) Propyl Groups Determined by Solid-State NMR Spectroscopy and Theoretical Calculations. *J. Am. Chem. Soc.* **2010**, *132*, 12452–12457.

(23) Kim, K. C.; Moschetta, E. G.; Jones, C. W.; Jang, S. S. Molecular Dynamics Simulations of Aldol Condensation Catalyzed by Alkylamine-Functionalized Crystalline Silica Surfaces. *J. Am. Chem. Soc.* **2016**, *138*, 7664–7672.

(24) List, B.; Lerner, R. A.; Barbas, C. F. Proline-Catalyzed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

(25) Elmekawy, A. A.; Sweeney, J. B.; Brown, D. R. Efficient Synthesis of Supported Proline Catalysts for Asymmetric Aldol Reactions. *Catal. Sci. Technol.* **2015**, *5*, 690–696.

(26) Yoo, C. J.; Lee, L. C.; Jones, C. W. Probing Intramolecular versus Intermolecular CO₂ Adsorption on Amine-Grafted SBA-15. *Langmuir* **2015**, *31*, 13350–13360.

(27) Lauwaert, J.; Moschetta, E. G.; Van Der Voort, P.; Thybaut, J. W.; Jones, C. W.; Marin, G. B. Spatial Arrangement and Acid Strength Effects on Acid-Base Cooperatively Catalyzed Aldol Condensation on Aminosilica Materials. *J. Catal.* **2015**, *325*, 19–25.

(28) Kobayashi, T.; Singappuli-Arachchige, D.; Wang, Z.; Slowing, I. I.; Pruski, M. Spatial Distribution of Organic Functional Groups Supported on Mesoporous Silica Nanoparticles: A Study by Conventional and DNP-Enhanced ²⁹Si Solid-State NMR. *Phys. Chem. Chem. Phys.* **2017**, *19*, 1781–1789.

(29) Sharma, K. K.; Anan, A.; Buckley, R. P.; Ouellette, W.; Asefa, T. Toward Efficient Nanoporous Catalysts: Controlling Site-Isolation and Concentration of Grafted Catalytic Sites on Nanoporous Materials with Solvents and Colorimetric Elucidation of Their Site-Isolation. *J. Am. Chem. Soc.* **2008**, *130*, 218–228.

(30) Anan, A.; Sharma, K. K.; Asefa, T. Selective, Efficient Nanoporous Catalysts for Nitroaldol Condensation: Co-Placement of Multiple Site-Isolated Functional Groups on Mesoporous Materials. *J. Mol. Catal. A: Chem.* **2008**, *288*, 1–13.

(31) Moschetta, E. G.; Sakwa-Novak, M. A.; Greenfield, J. L.; Jones, C. W. Post-Grafting Amination of Alkyl Halide-Functionalized Silica for Applications in Catalysis, Adsorption, and ¹⁵N NMR Spectroscopy. *Langmuir* **2015**, *31*, 2218–2227.

(32) Nakazawa, J.; Smith, B. J.; Stack, T. D. P. Discrete Complexes Immobilized onto Click-SBA-15 Silica: Controllable Loadings and the Impact of Surface Coverage on Catalysis. *J. Am. Chem. Soc.* **2012**, *134*, 2750–2759.

(33) Sharma, K. K.; Buckley, R. P.; Asefa, T. Optimizing Acid-Base Bifunctional Mesoporous Catalysts for the Henry Reaction: Effects of the Surface Density and Site Isolation of Functional Groups. *Langmuir* **2008**, *24*, 14306–14320.

(34) Brunelli, N. A.; Didas, S. A.; Venkatasubbaiah, K.; Jones, C. W. Tuning Cooperativity by Controlling the Linker Length of Silica-Supported Amines in Catalysis and CO₂ Capture. *J. Am. Chem. Soc.* **2012**, *134*, 13950–13953.

(35) Hicks, J. C.; Dabestani, R.; Buchanan, A. C.; Jones, C. W. Spacing and Site Isolation of Amine Groups in 3-Aminopropyl-Grafted Silica Materials: The Role of Protecting Groups. *Chem. Mater.* **2006**, *18*, 5022–5032.

(36) Huh, S.; Wiench, J. W.; Yoo, J. C.; Pruski, M.; Lin, V. S. Y. Organic Functionalization and Morphology Control of Mesoporous Silicas via a Co-Condensation Synthesis Method. *Chem. Mater.* **2003**, *15*, 4247–4256.

(37) Shylesh, S.; Wagener, A.; Seifert, A.; Ernst, S.; Thiel, W. R. Bifunctional Mesoporous Materials with Coexisting Acidic and Basic Sites for C-C Bond Formation in Co-Operative Catalytic Reactions. *ChemCatChem* **2010**, *2*, 1231–1234.

(38) Tsai, C. H.; Chen, H. T.; Althaus, S. M.; Mao, K.; Kobayashi, T.; Pruski, M.; Lin, V. S. Y. Rational Catalyst Design: A Multifunctional Mesoporous Silica Catalyst for Shifting the Reaction Equilibrium by Removal of Byproduct. *ACS Catal.* **2011**, *1*, 729–732.

(39) Lauwaert, J.; De Canck, E.; Esquivel, D.; Van Der Voort, P.; Thybaut, J. W.; Marin, G. B. Effects of Amine Structure and Base Strength on Acid-Base Cooperative Aldol Condensation. *Catal. Today* **2015**, *246*, 35–45.