

Chapter 5

COOPERATIVE CATALYSIS BY PRIMARY AMINES AND CARBOXYLIC ACIDS IN THE DIRECT ALDOL REACTION

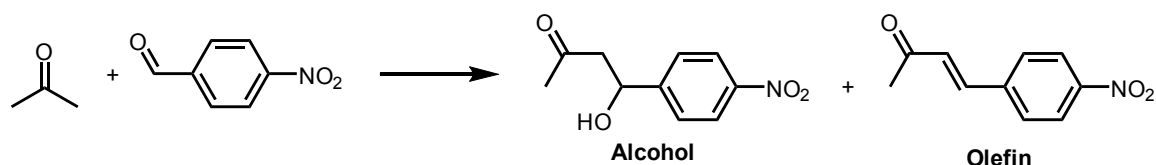
Abstract

Amines and weak acids have been shown to exhibit cooperative catalysis for the direct aldol reaction. The nature of this cooperative catalysis was investigated using homogeneous amines, acids, and amino acids in the aldol reaction between acetone and *p*-nitrobenzaldehyde, and the presence of both functionalities is required to achieve good catalytic activity. The amine/acid cooperativity of amino acids is shown to be distance-dependent; as the amine/acid distance increases, the catalytic activity decreases until the two groups are separated by four methylene units, after which the activity is unaffected by further increases in distance. Heterogeneous catalysts were also investigated by functionalizing mesoporous silica (SBA-15) with primary amine and carboxylic acid groups randomly or grouped into pairs. The silica-supported catalysts outperformed the homogeneous amino acids due to cooperativity between the amines and surface silanol groups, whereas carboxylic acid groups had no effect. The effect of the silanol groups could be attenuated by capping with trimethylsilyl groups or by adding methanol as a cosolvent.

Introduction

The aldol reaction between a ketone and aldehyde can be catalyzed by either strong bases or acids. Recently, however, it has been shown in many instances that the presence of acids of varying strength in addition to amine bases can drastically accelerate the rate of reaction. Both strong acids (pTSA, TfOH)¹ and weak acids (such as silica^{2, 3} and carboxylic acids³) have been used as aldol cocatalysts with amines. Of particular interest is the high activity of proline as an asymmetric aldol catalyst,⁴ in which the secondary amine and carboxylic acid moieties of the molecule are both necessary for good activity and enantioselectivity. The reaction is thought to proceed via an enamine intermediate which is formed from the secondary amine and ketone.⁴⁻⁶ Heterogeneous catalysts containing acid and base sites have also been demonstrated to exhibit cooperativity in the aldol reaction.^{7, 8}

Kubota et al.² studied the catalysis of the direct aldol reaction between acetone and *p*-nitrobenzaldehyde (see Scheme 5.1) using various secondary amine catalysts at 30°C. The amines alone showed very low activity (6–11% conversion) but when mesoporous silica (FSM-16 or MCM-41) was added as a cocatalyst, the conversion increased to 97–99%. When amorphous silica was used instead of mesoporous, the conversion was only 59%, suggesting that the higher quantity of weakly acidic silanol groups in the mesoporous materials is responsible for the greater catalytic activity of these silicates.



Scheme 5.1. Aldol condensation between acetone and *p*-nitrobenzaldehyde. The initial product formed is the alcohol, which can then be dehydrated to form the olefin product.

Zeidan et al.^{9, 10} synthesized bifunctional catalysts in which acidic and basic organic groups were immobilized on the surface of mesoporous silica SBA-15 in a one-pot synthesis. These materials were investigated in the catalysis of the same aldol reaction between acetone and *p*-nitrobenzaldehyde. The bifunctional catalyst exhibited higher activity than monofunctional materials containing only the acid or base groups alone. In bifunctional catalysts containing both amine groups and an acidic group, a decreased acidity of the acidic group led to increased catalytic activity (carboxylic > phosphonic > arylsulfonic). The most active catalyst was the one containing primary amines and carboxylic acids, which had an activity much greater than amine-only catalysts and carboxylic acid-only catalysts (the latter of which was completely inactive).

To provide further insight into the nature of amine/carboxylic acid cooperativity, I investigated the activity of homogeneous catalysts bearing primary amines and carboxylic acids in the aldol reaction. Separate amine- and acid- containing molecules were tested, as were amino acids containing both functionalities with varying spacer lengths. Heterogeneous catalysts on SBA-15 supports were synthesized with primary amine and carboxylic acid groups (either randomly-distributed or arranged into pairs) and their activity in the aldol reaction was also studied.

Results and Discussion

Homogeneous Catalysts

As model homogeneous catalysts, propylamine, acetic acid, and various amino acids (see Figure 5.1) were used to catalyze the aldol reaction between *p*-nitrobenzaldehyde and acetone at room temperature. Reaction progress was defined by the total amount of aldol products (alcohol + olefin) present. 1:1 Acetone/methanol was used as the reaction solvent because amino acids have a low solubility in acetone alone. All raw catalytic data can be found in Table 5.2 at the end of this chapter.

Acetic acid alone is catalytically inactive, with only trace amount of aldol products produced (see Figure 5.2). Propylamine alone has a higher activity but is still a very poor catalyst. When both propylamine and acetic acid are present, however, the catalytic activity is approximately twice as high as for propylamine alone, indicating a strong cooperative effect between these two catalysts. The overall yield is still low (only 8.5% total yield after 24 hours) so there is much room for improvement.

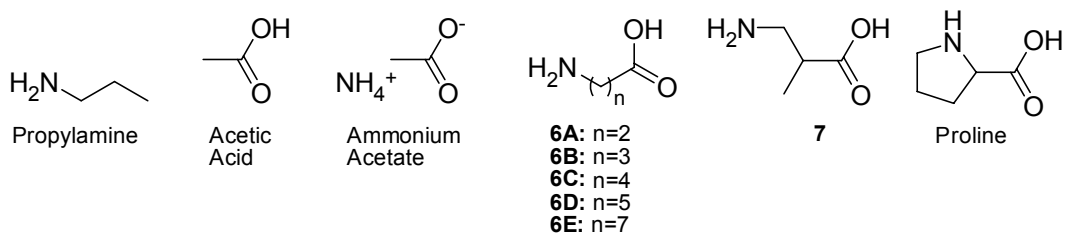


Figure 5.1. Amines, acids, and amino acids tested as homogeneous aldol catalysts

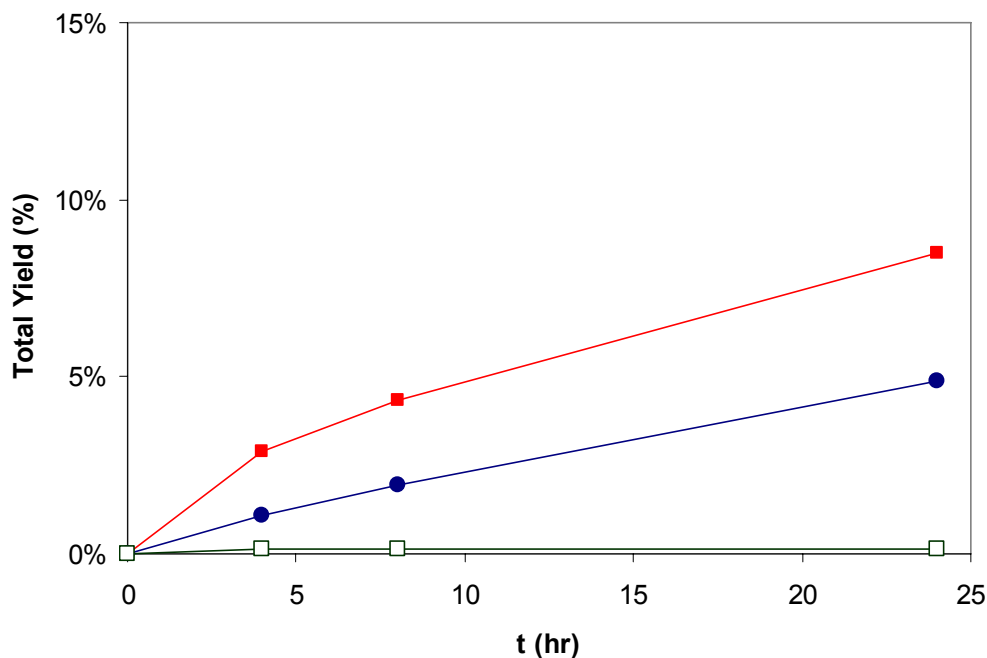


Figure 5.2. Aldol reaction yield (alcohol + olefin) with homogeneous catalysts: acetic acid (□), propylamine (●), and propylamine + acetic acid (■). Reaction conditions: 50 mM *p*-nitrobenzaldehyde in 1:1 acetone/methanol, 10 mol% each catalyst, 25°C

When propylamine and acetic acid coexist in solution, an equilibrium is established with a mixture of both free and protonated amine, and free and deprotonated acid. One would expect that the salt of an amine and a carboxylic acid would generate the same equilibrium composition of protonated and deprotonated species and give similar catalytic activity, and in fact when ammonium acetate is used as catalyst, the result is similar to when the separate amine and acid are used (see Figure 5.3) giving 8% yield after 24 hours.

The spatial positioning of the homogeneous primary amine and carboxylic acid groups was investigated using linear amino acids consisting of a linear alkyl chain (of

length n) with a primary amine at one end and a carboxylic acid at the other (**6A–6E**). The catalytic results are shown in Figure 5.4 with some representative kinetic profiles shown in Figure 5.3. Catalysts with longer spacers (**6C**, **6D**, **6E**) all exhibited similar activity to each other and to the propylamine/acetic acid and ammonium acetate catalysts. All of the catalysts show similar kinetic profiles in which the reaction rate decreases with time, even at low yields.

For shorter spacer lengths (**6A** and **6B**; $n = 3$ and 2 respectively) the activity increases as the two functional groups are brought closer to each other (see Figure 5.4). Glycine ($n = 1$) could not be tested due to its low solubility in organic solvents, but proline (often employed as an asymmetric aldol catalyst)^{5, 11} is more soluble in methanol/acetone and was tested. Proline had the best performance of any homogeneous catalyst tested here, which could be due in part to the short amine/acid distance, but is also due to its secondary amine group, which forms an enamine intermediate⁶ more rapidly than a primary amine. We conclude that the amine/carboxylic acid distance is a key design parameter for small-molecule aldol catalysts up to a certain distance (approximately four methylene units) after which the catalytic activity is insensitive to distance.

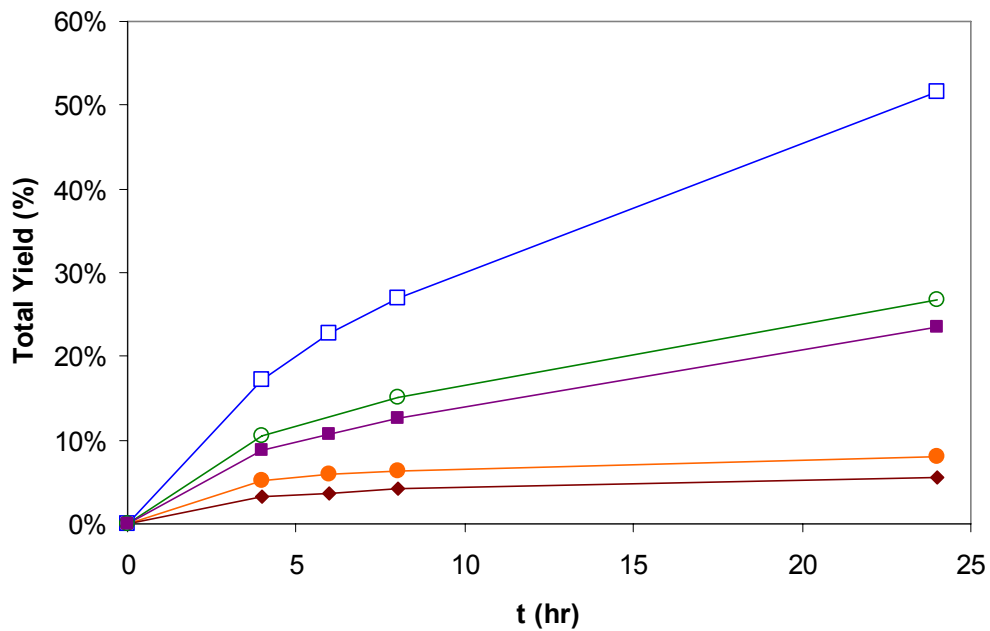


Figure 5.3. Kinetic profiles for aldol reaction with homogeneous amino acid catalysts.

Reaction conditions: 50 mM *p*-nitrobenzaldehyde in 1:1 acetone/methanol, 10 mol% catalyst, 25°C. Catalysts: proline (□), 7 (○), 6A (■), ammonium acetate (●), 6C (◆)

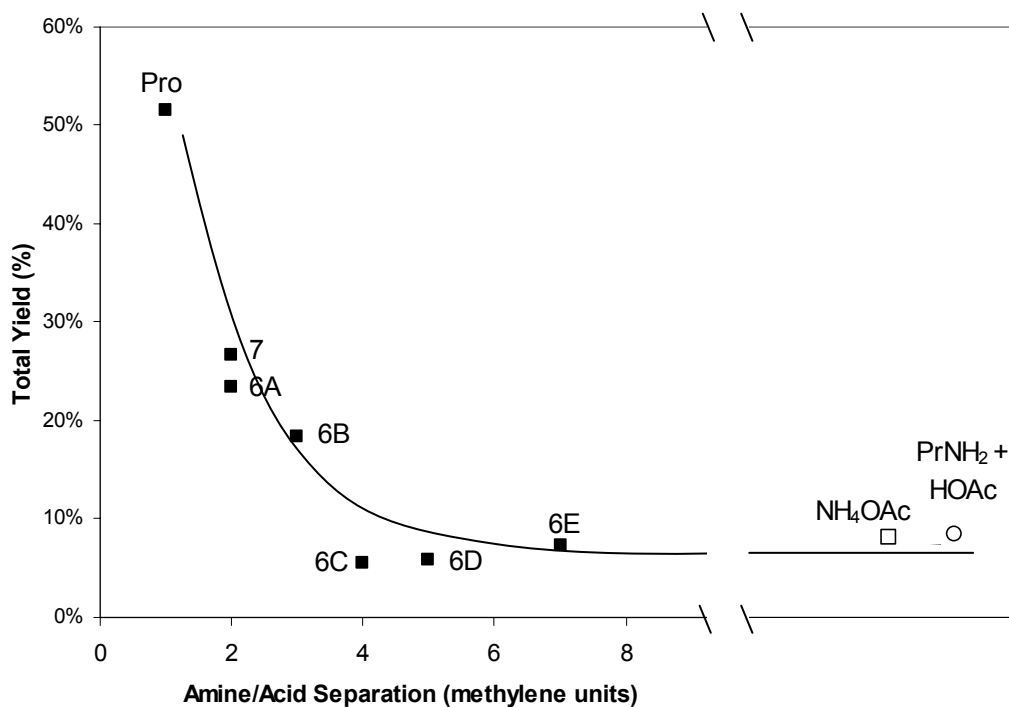


Figure 5.4. Total yield of aldol product formation (alcohol + olefin) for various homogeneous amino acid catalysts as a function of amine/acid separation. Reaction conditions: 50 mM *p*-nitrobenzaldehyde in 1:1 acetone/methanol, 10 mol% catalyst, 24 hrs, 25°C. The data points for ammonium acetate (□) and propylamine + acetic acid (○) are also shown, arbitrarily placed at a large amine/acid separation.

The effect of chain branching on homogeneous catalytic activity was investigated by comparing the activity of the unbranched $n=2$ catalyst (β -alanine, **6A**) to a branched analog (3-aminoisobutyric acid, **7**). Both have primary amine and carboxylic acid groups separated by two carbon atoms, but the extra methyl group of **7** confers a somewhat greater catalytic activity (the highest activity, in fact, of any of the primary amine/carboxylic acid molecules tested here).

To determine whether the addition of methanol as a cosolvent had an effect on the rate of reaction, reactions were run with propylamine or propylamine and acetic acid in either acetone or 1:1 acetone/methanol (Figure 5.5). For the propylamine catalyst, the reaction rate increased about threefold with the presence of methanol (although the rate is still quite slow). With both propylamine and acetic acid as cocatalysts, the presence of methanol had no effect. It is likely that the weak hydrogen-bond donating character of methanol provides some electrophile-activation analogous to that of the carboxylic acid catalysts, and hence provides a small rate improvement when only the amine is present. When a stronger carboxylic acid is present as cocatalyst, its effect overpowers the effect of the methanol.

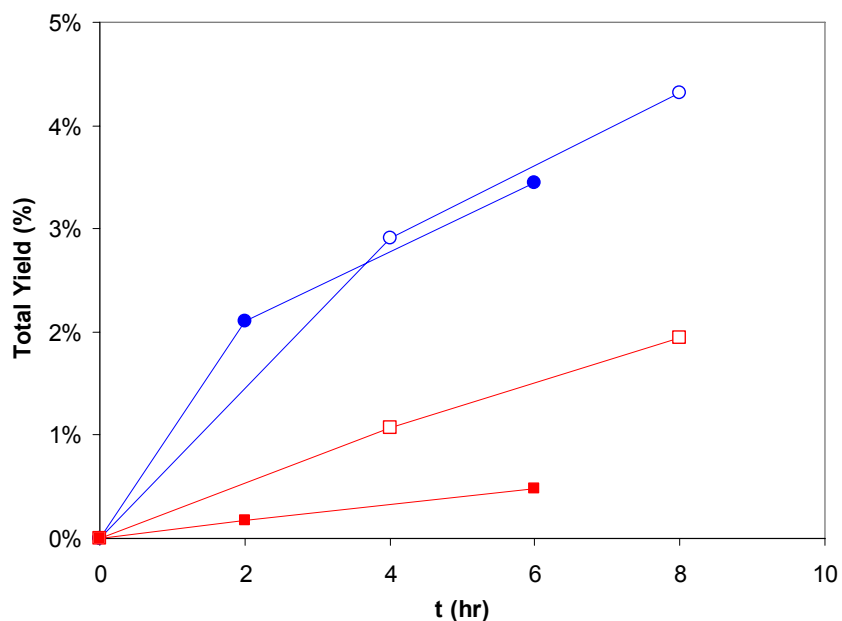


Figure 5.5. Comparison of kinetic profiles for aldol reaction with homogeneous catalysts propylamine (■, □) and propylamine/acetic acid (●, ○). Reaction solvent: acetone (filled points) or 1:1 acetone/methanol (open points)

Effect of Temperature

To assess how the amine and carboxylic acid groups stabilize the transition state of the aldol reaction, we sought to measure the activation energy of the reaction for a number of different catalysts. The reaction temperature was varied from 21°C to 45°C and an Arrhenius plot of the data was used to calculate activation energies (E_a) for each catalyst (Figure 5.6).

Though the rate data for the different catalysts span three orders of magnitude, the activation energies do not vary widely (Table 5.1). The highest E_a observed is for propylamine, which has no carboxylic acid group. The best catalyst, proline, has the same apparent E_a as **6C**, which is a far worse catalyst. The lowest E_a is actually observed for the propylamine/acetic acid combination. This lower apparent activation energy for the amine/acid combination is further evidence for the cooperative nature of the catalysis, in which both the amine and acid must come together to catalyze the reaction; when the amine and acid are not attached to each other, the reaction depends on them meeting by diffusion. This binary diffusional limitation results in a lower apparent E_a , since diffusion is a nearly unactivated process.¹²

Catalyst	E_a (kJ/mol)
Proline	36
7	27
6C	36
PrNH₂ + HOAc	13
PrNH₂	42

Table 5.1. Apparent activation energies (E_a) for homogeneous catalysts in 1:1 acetone/methanol

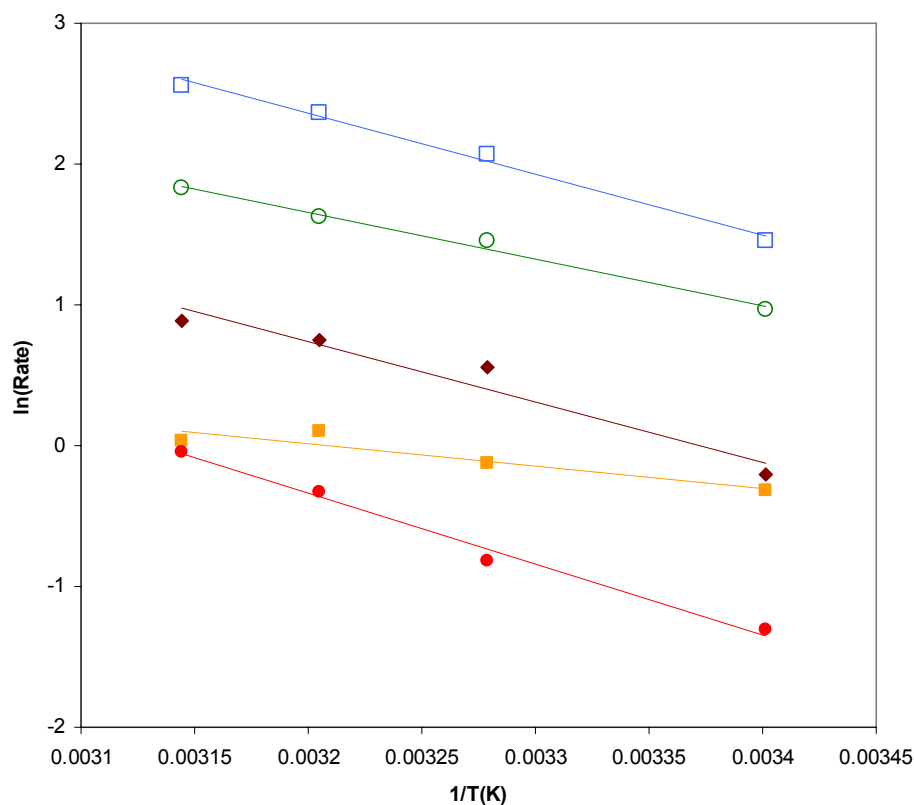


Figure 5.6. Arrhenius plots for homogeneous amino acid aldol catalysts. Proline (□), **7** (○), **6C** (◆), propylamine + acetic acid (■), propylamine (●). Rate data refer to the initial rate of product formation (alcohol + olefin) over the first 1–2 hours of reaction (conversion < 12%).

The lack of correlation between E_a and catalytic activity with these homogeneous catalysts suggests that the cooperative effect of amine/acid proximity is due primarily to an increase in the collision rate rather than transition state stabilization; *i.e.*, that the amine and acid have the same transition state-stabilizing effect whether random or paired, but that when the groups are adjacent to each other, there is a greater chance of collision between the amine- and acid-activated reactants.

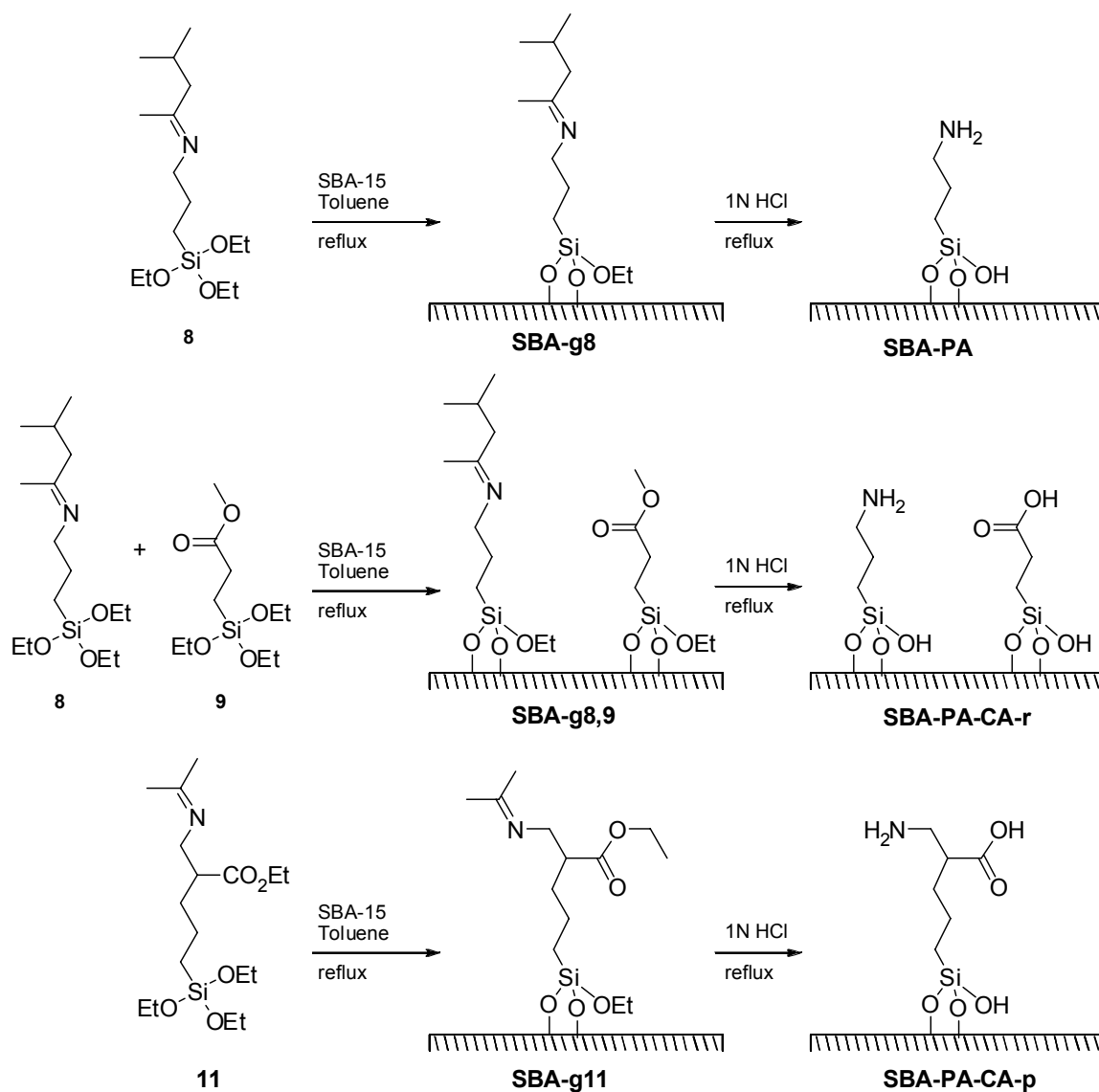
Heterogeneous Catalysis

Next, heterogeneous catalysts were investigated for aldol activity. The mesoporous silica SBA-15 was used as the solid support, and organosilanes were grafted onto the silica surface by refluxing in toluene.

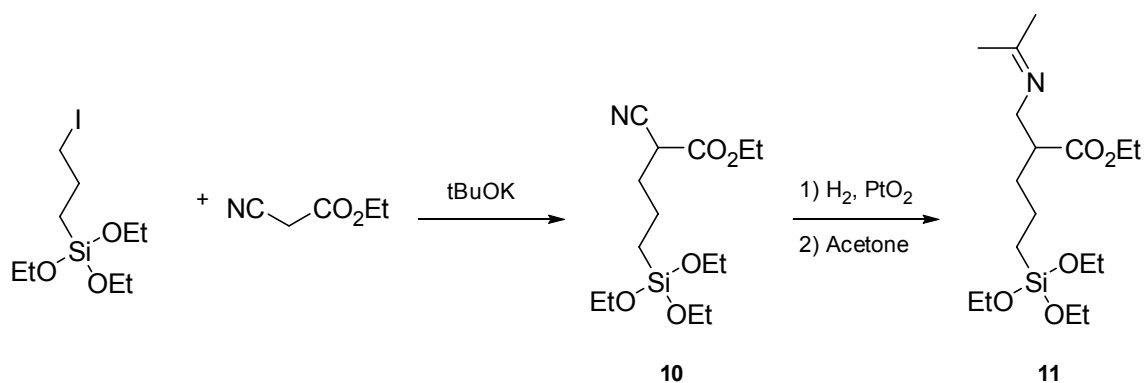
Propylamine groups were immobilized by grafting an imine-containing silane onto SBA-15, followed by hydrolysis.* The resulting material is denoted **SBA-PA**. A catalyst containing randomly-distributed propylamine and carboxylic acid groups (**SBA-PA-CA-r**) was prepared by simultaneously grafting two organosilanes, one containing an imine and the other an ester, followed by hydrolysis (see Scheme 5.2).

Based on the observations of proximity-dependence in amine/carboxylic acid cooperativity in homogeneous catalysis, organosilane **11** was designed (see Scheme 5.3) in order to functionalize SBA-15 with amine/acid paired sites with a structure similar to the active homogeneous catalyst **7**. The amine and acid groups were protected as an imine and ester, respectively. After grafting onto silica, the imine and ester groups are hydrolyzed to amine and carboxylic acid groups respectively, and the solid is washed with copious water to neutralize the protonated amines. The resulting material containing pairs of propylamine and carboxylic acid groups is denoted **SBA-PA-CA-p**.

* The use of an imine as a protecting group for the primary amines is intended to prevent agglomeration of the silanes during grafting, which happens when unprotected amine-containing silanes are grafted, due to amine/amine and amine/silanol hydrogen-bonding interactions.¹³



Scheme 5.2. Synthesis of heterogeneous catalysts **SBA-PA** (top), **SBA-PA-CA-r** (middle), and **SBA-PA-CA-p** (bottom) by grafting imine and/or ester-containing silanes, followed by hydrolysis



Scheme 5.3. Synthesis of imine/ester silane precursor **11**

The organic loading of all heterogeneous catalysts was kept very low (0.1 mmol/g) in order to keep the groups spatially isolated, allowing the paired and randomly-bifunctionalized materials to be compared. The low organic loading of these grafted catalysts also maintains a high density of silanol groups, which it was found played a significant role in the catalytic activity (*vide infra*).

The aldol catalytic activity of these heterogeneous catalysts is shown in Figure 5.7. The heterogeneous catalysts were far more active than homogeneous propylamine or propylamine/acetic acid. In contrast to what was seen with the homogeneous amino acids, the addition of carboxylic acid groups did not improve the catalyst activity. **SBA-PA-CA-r** had activity very similar to **SBA-PA**, and **SBA-PA-CA-p** actually showed the lowest activity of the three (although still higher than any of the homogeneous primary amine/acid catalysts).

In general, the kinetic profiles for the heterogeneous catalysts are much more linear than for the homogeneous amino acids (compare to Figure 5.3) indicating that they do not suffer the same gradual decrease in activity exhibited by the homogeneous catalysts. This difference is highlighted in Figure 5.8, which compares the catalytic data

for paired amine/acid catalyst **SBA-PA-CA-p** to its homogeneous analog **7**. Initially, the homogeneous and heterogeneous catalysts give similar reaction rates. But after 24 hours, the homogeneously-catalyzed reaction has slowed down, while the heterogeneously-catalyzed reaction has not, leading to a better yield with the heterogeneous catalyst.

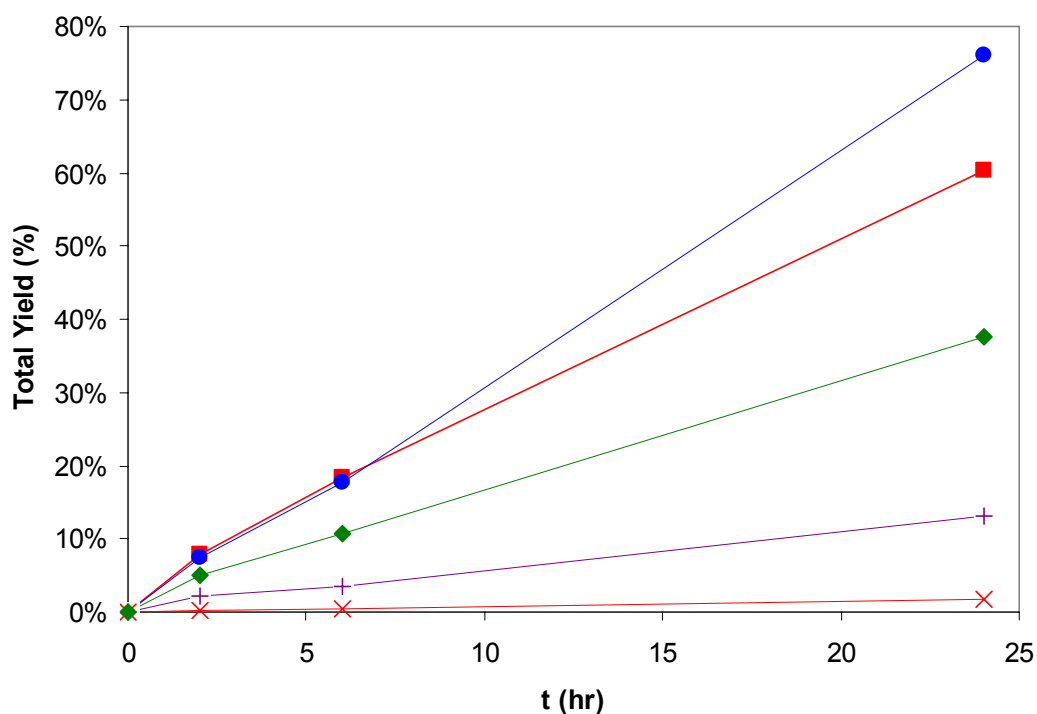


Figure 5.7. Kinetic profiles for aldol reaction with heterogeneous amine/acid catalysts. Reaction conditions: 50 mM *p*-nitrobenzaldehyde in acetone, 10 mol% heterogeneous amine and/or 10 mol% carboxylic acid, 25°C. Catalysts: **SBA-PA-CA-r** (●), **SBA-PA** (■), **SBA-PA-CA-p** (◆). For comparison purposes, data for homogeneous catalysts is also shown: propylamine + acetic acid (+), propylamine (×).

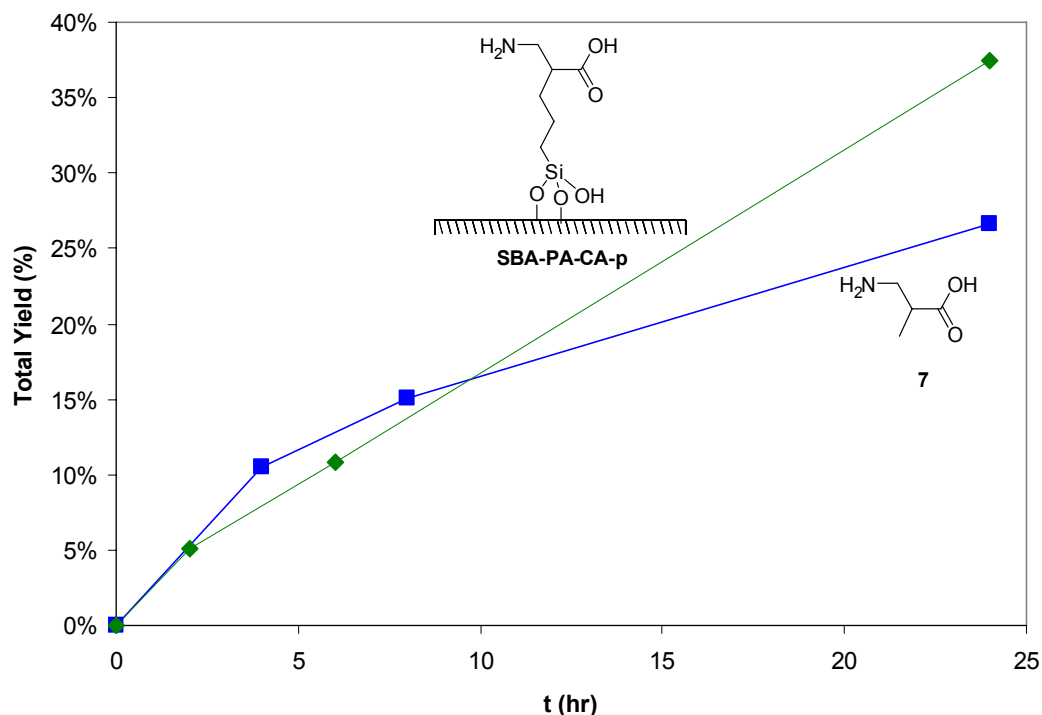


Figure 5.8. Comparison of kinetic profiles for aldol reaction with homogeneous and heterogeneous amino acid moieties. Catalysts: **7** (■) in 1:1 acetone/methanol, **SBA-PA-CA-p** (◆) in acetone

Role of Silanol Groups

The high activity of the heterogeneous amine catalysts compared to homogeneous amines suggests that the silica surface is playing an important catalytic role. The pK_a of silanols on functionalized silica has been reported to be between 3 and 7, depending on the type of bulk silica and the exact nature of the silanol group (isolated, geminal, vicinal, etc.).¹⁴⁻¹⁶ Thus the acid strength of the silanol groups in SBA-15 is likely to be similar to that of a carboxylic acid ($pK_a \sim 4-5$). The silanol density of SBA-15 has been estimated at $\sim 4 \text{ nm}^{-2}$ which is equivalent to $\sim 5 \text{ mmol/g}$.¹⁶

To investigate the role of the silanol groups in aldol catalysis, various catalytic experiments were carried out with heterogeneous catalysts whose surface silanols had been capped with trimethylsilyl (TMS) groups by reaction with hexamethyldisilazane (HMDS). The HMDS caps both silanol and carboxylic acid groups with TMS groups and renders the surface highly hydrophobic. These silylated materials are denoted **X-TMS**.

When catalyst **SBA-PA** is silylated (**SBA-PA-TMS**), its activity decreases by ~50% (see Figure 5.9). The activity is still higher than homogeneous propylamine, however, which can be attributed to the increased local reactant concentration caused by adsorption onto the surface or to residual uncapped silanols. The catalytic results of **SBA-PA-CA-p-TMS** and **SBA-PA-CA-r-TMS** are identical to that of **SBA-PA-TMS**, because the carboxylic acid groups of the former two catalysts are capped with TMS groups. The reduction in activity following silylation confirms the catalytic role played by the silanol groups.

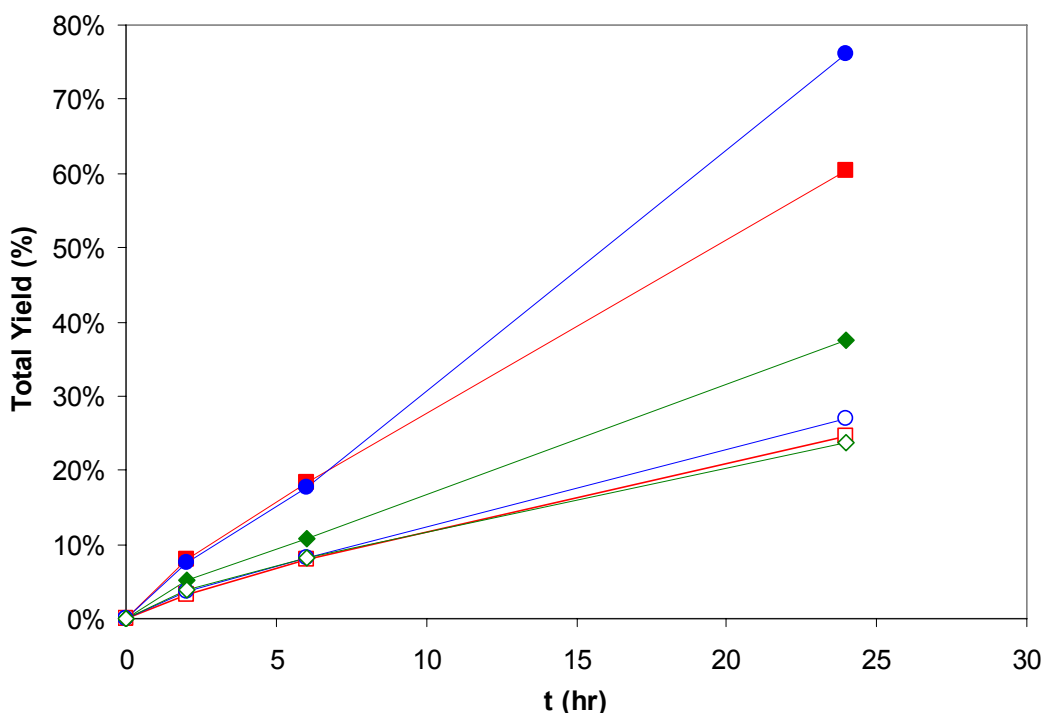


Figure 5.9. Comparison of kinetic profiles for aldol reaction with unsilylated (filled symbols) and silylated (open symbols) heterogeneous catalysts: **SBA-PA(-TMS)** (■, □), **SBA-PA-CA-r(-TMS)** (●, ○), and **SBA-PA-CA-p(-TMS)** (◆, ◇). Reaction conditions: 50 mM *p*-nitrobenzaldehyde solution in acetone, 10 mol% amine, 25°C

Next, homogeneous acids were added as cocatalysts along with **SBA-PA-TMS** (Figure 5.10). Quite surprisingly, the homogeneous carboxylic acids had a negligible effect on the rate of reaction. When pTSA was used, on the other hand, the strong sulfonic acid groups neutralized the heterogeneous amines, completely shutting down the catalytic activity. This result confirms that at least some of the carboxylic acids (**12D**, **12E**, **12F**, which are structural analogs of pTSA) are able to diffuse into the silica pores and interact with the amines, and yet no cooperative catalytic activity is seen.

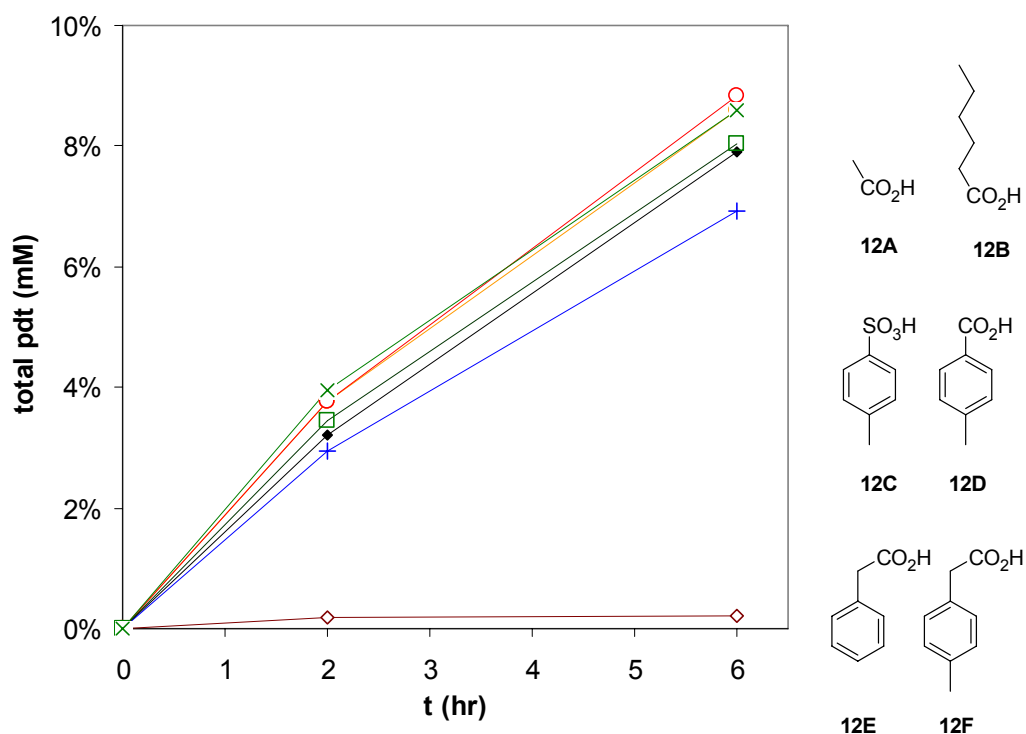


Figure 5.10. Total yield of aldol product formation (alcohol + olefin) catalyzed by **SBA-PA-TMS** + homogeneous acid: no acid (◆), **12A** (+), **12B** (×), **12C** (◇), **12D** (○), **12E** (●), **12F** (□). Reaction conditions: 6 mL of 50 mM *p*-nitrobenzaldehyde solution in acetone, 10 mol% heterogeneous amine, 10 mol% acid, 25°C

Catalytic reactions were performed with a constant loading of homogeneous propylamine and varying amounts of (unsilylated) SBA-15 added. The results are shown in Figure 5.11. Adding SBA-15 to the propylamine-catalyzed reaction increases the yield considerably. This is consistent with the results reported by Kubota et al.² for secondary amine and mesoporous FSM-16 cocatalysts for this same aldol reaction under similar reaction conditions.[†] However, when Kubota et al. used *primary* amines (including

[†] 5 mL of 200 mM aldehyde in acetone, 10 mol% amine, 120 mg FSM-16, 30°C, 6 hr

propylamine), they did not see any promoting effect of FSM-16. This discrepancy is surprising given the similarities between SBA-15 and the hexagonal FSM-16, although FSM-16 does have a smaller pore diameter (2–3 nm vs. 6 nm for the SBA-15 used here).¹⁷

Although SBA-15 accelerates the propylamine-catalyzed reaction considerably, no acceleration is seen when SBA-15 is added to the homogeneous amino acid catalyst **7** (Table 5.2, Entry 7). This is presumably because the carboxylic acids of **7** already activate the reacting molecules and adding silanols provides no additional activation.

With propylamine/SBA-15, the reaction rate increases as the amount of SBA-15 increases, even when a large excess of SBA-15 is used relative to amine. This result provides insight into the mechanism of amine/silanol cooperativity in this catalytic system. Among the possible explanations for how the presence of silica enhances the rate of aldol reaction are: amine activation by adsorption onto or hydrogen-bonding to silanol groups, activation of the ketone, aldehyde or enamine intermediate by silanol groups, or reactant concentration by surface adsorption. If the silanol groups served to activate the amine or the enamine intermediate, then once the silanol groups greatly outnumber the amines, then further increasing the amount of silica should have no additional effect. In fact, the reaction rate increases even to a silanol/amine ratio of ~400. Therefore amine and enamine activation are ruled out, while ketone/aldehyde activation and local concentration effects are plausible.

To investigate the role played by increased local reactant concentrations by adsorption onto the silica surface, silylated SBA-15 (**SBA-TMS**) was used in place of unmodified SBA-15 (Figure 5.11). When **SBA-TMS** was used as a cocatalyst with

propylamine, there was still a rate enhancement, though the effect was much weaker than with uncapped SBA-15. This could be due to the presence of some remaining uncapped silanol groups, but is more likely due to adsorption of propylamine and aldehyde on the silylated silica surface, leading to greater local concentrations of amine and aldehyde. Furthermore, the rate enhancement is far less than when the aminopropyl groups are actually tethered to the silylated silica surface. Thus the rate-enhancing effect of silylated silica cannot be due to residual uncapped silanol groups alone, since both **SBA-NH₂-TMS** and **SBA-TMS** should have a similar number of uncapped silanols.

Effect of methanol on silanol interactions

As described above, methanol was shown to provide a modest rate acceleration for a homogeneous amine catalyst, while having no effect on homogeneous amine/carboxylic acid cocatalysis. Methanol can form hydrogen bonds to the reacting molecules (for instance, to the ketone or aldehyde carbonyls). If the catalytic role of the silanol groups in the heterogeneous catalysts is attributed to hydrogen-bonding to the reacting aldehyde, then the presence of a large excess of methanol (a weaker hydrogen-bond donor) would be expected to interrupt the aldehyde-silanol interactions and consequently *reduce* the rate of reaction (in marked contrast to the homogeneous case). This is in fact seen: when 50% methanol was used as a cosolvent, the reaction rate decreased for all of the heterogeneous catalysts tested (Figure 5.13).

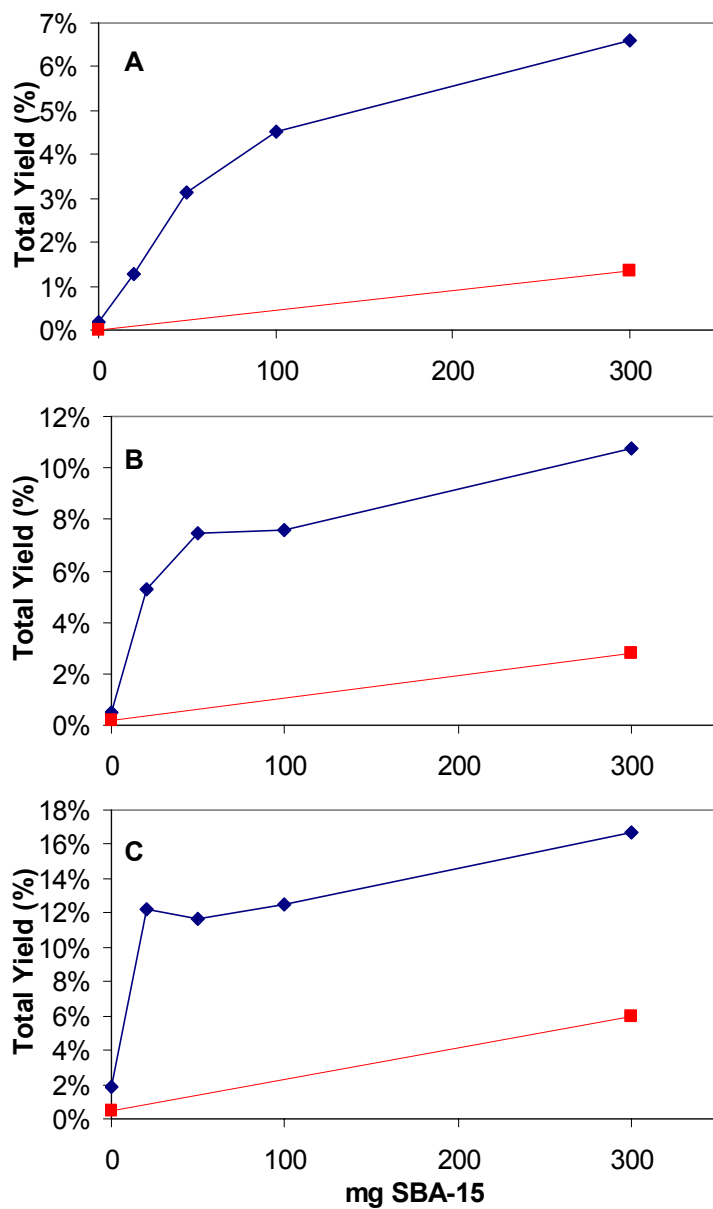


Figure 5.11. Total yield of aldol product formation (alcohol + olefin) catalyzed by homogeneous amine + unsilylated SBA-15 (◆) or silylated SBA-15 (■) after reaction times of: (A) 2 hrs, (B) 6 hrs, and (C) 24 hrs. Reaction conditions: 6 mL of 50 mM *p*-nitrobenzaldehyde solution in acetone, 10 mol% propylamine, 25°C

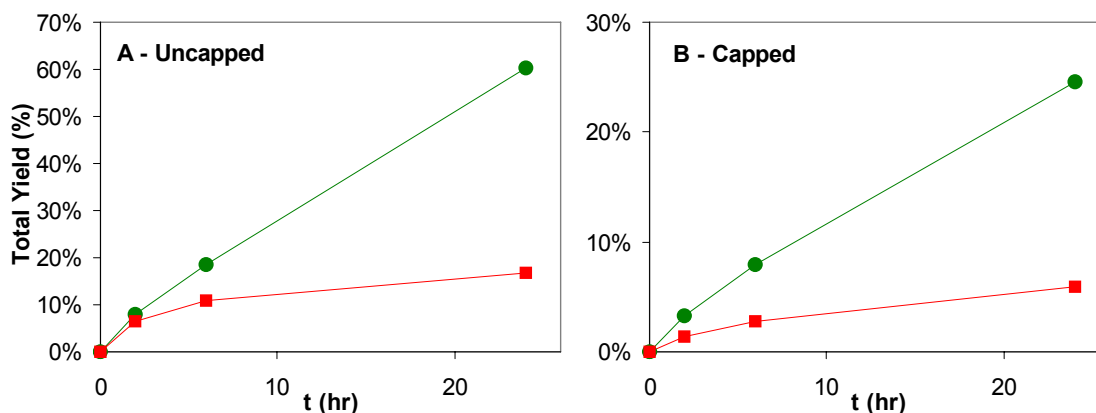


Figure 5.12. Kinetic profiles for aldol reaction catalyzed by SBA-15 + untethered propylamine (■) and propylamine groups tethered to silica, **SBA-PA(-TMS)** (●). In (A) the silanols of SBA-15 and **SBA-PA** are uncapped, and in (B) silanols are capped with TMS groups. Reaction conditions: 6 mL of 50 mM *p*-nitrobenzaldehyde solution in acetone, 10 mol% amine, 300 mg silica, 25°C

This result underscores the qualitative distinction between the role of silanol groups and carboxylic acid groups in accelerating the aldol reaction. The carboxylic acids protonate the ketone and/or aldehyde, whereas the silanols only form hydrogen bonds to them. This is consistent with literature reports that, despite the acidity of silanols being similar to that of carboxylic acids, mesoporous silicas adsorb basic molecules primarily through hydrogen-bonding, rather than protonation.¹⁸⁻²⁰

Furthermore, in the case of the heterogeneous amine catalyst, the reaction profile when methanol is added is nearly identical to that obtained from catalyst silylation (Figure 5.13). This confirms that the methanol is effectively eliminating silanol/reactant interactions.

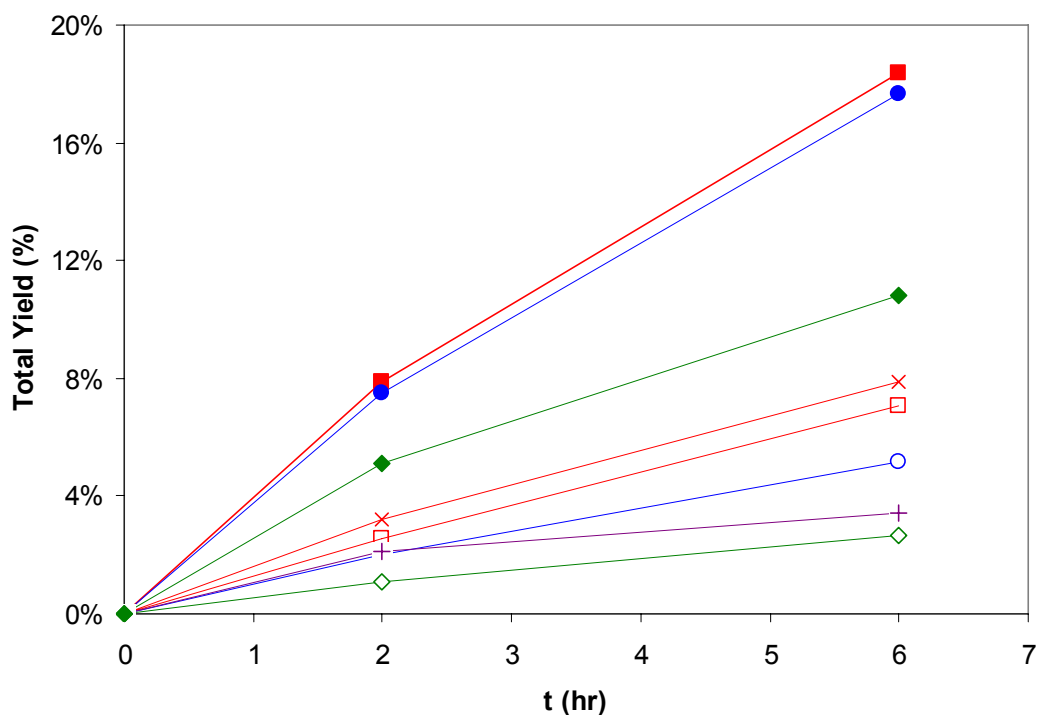


Figure 5.13. Comparison of kinetic profiles for aldol reaction with heterogeneous catalysts **SBA-PA** (■, □), **SBA-PA-CA-r** (●, ○), and **SBA-PA-CA-p** (◆, ◇). Reaction solvent: acetone (filled points) or 1:1 acetone/methanol (open points). For comparison purposes, the data for **SBA-PA-TMS** in acetone (×) and propylamine/acetic acid in 1:1 acetone/methanol (+) are also shown.

Similarly, when SBA-15 and homogeneous propylamine were used as cocatalysts, the addition of methanol reduced the effect of the SBA-15, leading to lower yields after 2 hours and 6 hours of reaction time (see Figure 5.14 A,B). However, the presence of methanol does speed up the propylamine-catalyzed reaction in the absence of SBA-15, so after 24 hours the methanol-containing reactions give similar yields to the methanol-free ones even though the accelerating effect of the SBA-15 is diminished (Figure 5.14C).

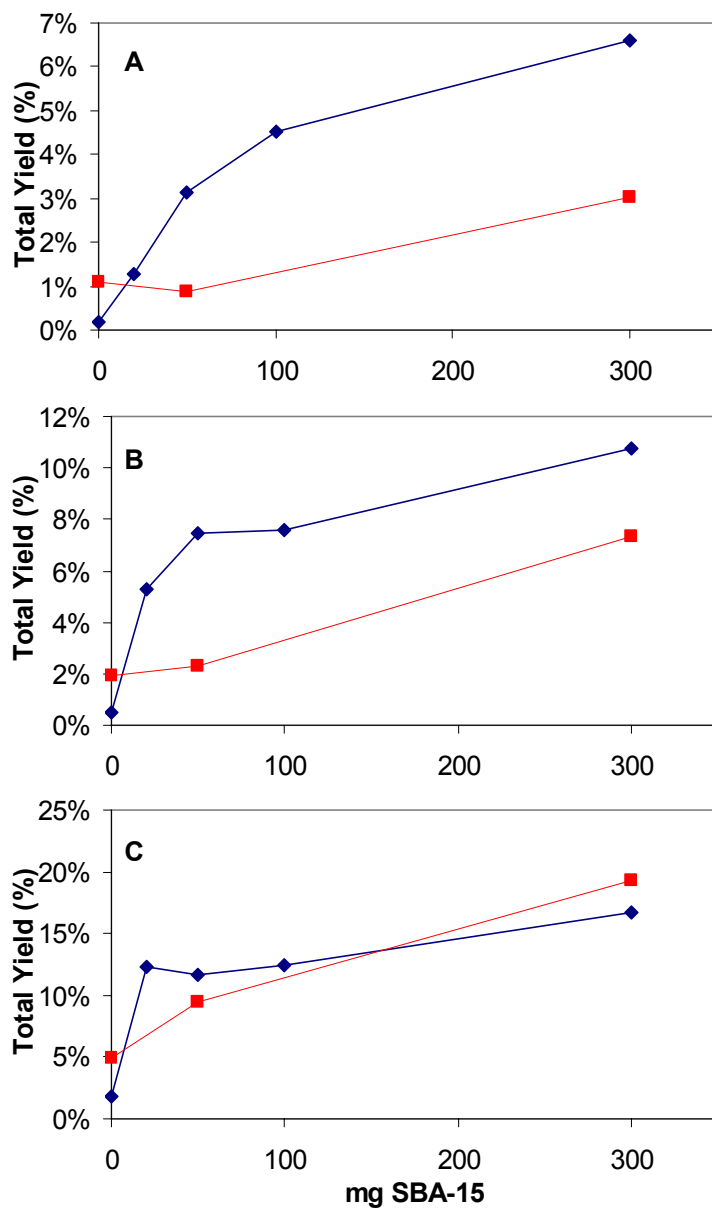


Figure 5.14. Total yield of aldol product formation (alcohol + olefin) catalyzed by homogeneous amine + SBA-15 after reaction times of: (A) 2 hrs, (B) 6 hrs, and (C) 24 hrs. Reaction conditions: 6 mL of 50 mM *p*-nitrobenzaldehyde solution in acetone (◆) or 1:1 acetone/methanol (■), 10 mol% propylamine, 25°C

Conclusions

In the direct aldol reaction between acetone and *p*-nitrobenzaldehyde at room temperature, cooperativity between primary amine and carboxylic acid groups in homogeneous catalysts was shown to increase activity greatly beyond that of monofunctional catalysts. This cooperativity is dependent on distance, with the best activity found for 3-aminoisobutyric acid, in which two carbon atoms separate the amine and acid groups. As the amine/acid distance increases beyond four carbon atoms, the catalytic activity becomes insensitive to further changes in distance. The rate of reaction decreases as the reaction proceeds.

With SBA-15-tethered amine groups, the catalytic activity is much greater than for the homogeneous catalysts. The silanol groups on the silica surface activate the reactants by hydrogen bonding, an effect which can be eliminated by capping the silanols or adding methanol as a cosolvent. The tethering of the amines onto the surface also increases the catalytic activity compared to untethered amines. When carboxylic acids are present (either in solution or tethered to the surface), they do not improve the catalytic performance. Unlike with the homogeneous catalysts, the rate of reaction is essentially constant as the reaction proceeds.

Experimental

Materials. Toluene was distilled over sodium immediately before use. All other solvents were analytical grade and used as received. 3-iodopropyltriethoxysilane was prepared from 3-chloropropyltriethoxysilane and sodium iodide according to the literature procedure.²¹ Commercial organosilanes were purchased from Gelest. All other

chemicals were purchased from Aldrich and used as received. All reactions were performed under an argon atmosphere.

Ethyl 2-cyano-5-(triethoxysilyl)pentanoate (Organosilane 10). Ethyl cyanoacetate (1.6 g, 14 mmol) was added to a solution of *t*BuOK in *t*BuOH (1 M, 9 mL), followed by addition of 3-iodopropyltriethoxysilane (3.1 g, 9.4 mmol). After refluxing for 24 hours, the solvent was removed *in vacuo* and pentane was added (30 mL). After filtering to remove the salts, the pentane was evaporated, and the yellow liquid crude was purified using chromatography on silica gel (4:1 hexanes/ethyl acetate, $R_f = 0.3$) afforded **1** (1.5 g, 50%) as a colorless liquid. ^1H NMR (300 MHz, CDCl_3) δ 4.26 (q, $J = 7$ Hz, 2H), 3.81 (q, $J = 7$ Hz, 6H), 3.51 (t, $J = 7$ Hz, 1H), 1.99 (q, $J = 7$ Hz, 2H), 1.62 (m, 2H), 1.31 (t, $J = 7$ Hz, 3H), 1.22 (t, $J = 7$ Hz, 9H), 0.66 (m, 2H). ^{13}C NMR (300 MHz, CDCl_3) δ 166.4, 116.7, 62.8, 58.6, 37.4, 32.8, 20.6, 18.4, 14.1, 9.9.

Ethyl 2-((propan-2-ylideneamino)methyl)-5-(triethoxysilyl)pentanoate (Organosilane 11). To a solution of organosilane **10** (0.45 g, 1.4 mmol) in absolute ethanol (25 mL) was added PtO_2 (65 mg), and hydrogen gas was purged through the headspace. After stirring vigorously under a hydrogen atmosphere for 24 hours, the reaction mixture was filtered over Celite to remove the PtO_2 , and acetone was added (10 mL). After stirring for 15 minutes, the solvent was removed *in vacuo*, and the crude product was purified using chromatography on silica gel (1:2 acetone/ethyl acetate, $R_f = 0.25$) afforded **2** (0.22 g, 44%) as a slightly straw-colored liquid. ^1H NMR (300 MHz, CDCl_3) δ 4.13 (q, $J = 7$ Hz, 2H), 3.80 (q, $J = 7$ Hz, 6H), 3.31 (m, 2H), 2.78 (m, 1H), 1.97 (s, 3H), 1.82 (s, 3H), 1.58 (m, 2H), 1.45 (m, 2H), 1.24 (t, $J = 7$ Hz, 3H), 1.21 (t, $J = 7$ Hz, 9H), 0.62 (m, 2H). ^{13}C NMR (300 MHz, CDCl_3) δ 175.9, 156.6, 60.3, 58.5, 53.8, 47.0,

34.3, 29.5, 20.9, 18.9, 18.5, 14.5, 10.6. HRMS (EI+): m/z ($M + H^+$) ($C_{17}H_{35}NO_5Si$)
Calcd, 362.2363; Found, 362.2367.

2-(Carbomethoxy)ethyltriethoxysilane (Organosilane 9). 2-(Carbomethoxy)ethyltrichlorosilane (5.06 g, 22.8 mmol, containing ~ 40% 1- isomer) was added dropwise to a solution of ethanol (15 mL) and triethylamine (10 mL) in THF (250 mL). A white precipitate forms immediately. After stirring for 3 hours, the solvent was removed *in vacuo*, pentane was added, and the solids were removed by filtration. Evaporation of pentane led to crude product as a yellow oil. Vacuum distillation (0.5 Torr, 60°C) afforded **9** as a colorless oil (2.1 g, 37% yield) containing ~ 40% 1-(carbomethoxy)ethyltriethoxysilane.

1H NMR (300 MHz, $CDCl_3$) δ 3.80 (q, $J = 7$ Hz, 6H), 3.60 (s, 3H), 2.33 (m, 1-isomer), 2.16 (q, $J = 7$ Hz, 2H), 1.21 (d, $J = 7$ Hz, 1-isomer), 1.16 (t, $J = 7$ Hz, 9H), 0.88 (m, 2H).
 ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.4, 59.2, 51.7, 27.8, 27.0 (1-isomer), 18.3, 11.0 (1-isomer), 5.7.

Organic-functionalized SBA-15 materials. SBA-15 (1.0 g, synthesized according to the literature procedure^{22, 23}) was dried under vacuum at 125°C for 3 hours. After cooling, dry toluene (40 mL) was added via syringe and the mixture was stirred vigorously to form a uniform suspension. A solution containing organosilane (0.1 mmol) in toluene (10 mL) was added dropwise via syringe. The suspension was stirred for 45 minutes at room temperature, then refluxed for 16 hours. After cooling to room temperature, the solids were filtered and washed with toluene and dichloromethane (3 x 30 mL each), then dried under high vacuum.

When two organosilanes were grafted onto the same SBA-15 material, two separate solutions of organosilane (each containing 0.1 mmol) in toluene were prepared and were added dropwise simultaneously to the SBA-15.

Deprotection of Surface Amine and Carboxylic Acid groups. To hydrolyze the imine and ester groups, the functionalized SBA-15 (1 g) was refluxed in 1 N HCl (100 mL) for 24 hours. After filtration, the solids were washed with 1 N HCl (3 x 50 mL) and water (5 x 100 mL) and dried under vacuum.

Silanol Capping. Silica (1.0 g) was dried under high vacuum at 80°C overnight, then suspended in anhydrous cyclohexane (50 mL) and hexamethyldisilazane (2 g, 12 mmol) was added. The suspension was stirred at room temperature for 1 day, followed by filtration and washing with cyclohexane (50 mL x 3) and methanol (50 mL x 5) and drying under vacuum.

Catalytic Reaction—Aldol Condensation of Acetone and *p*-Nitrobenzaldehyde. An amount of heterogeneous catalyst corresponding to 30 μ mol amine and/or carboxylic acid (~ 300 mg) was added to a vial and dried under high vacuum at 80°C overnight. A solution of *p*-nitrobenzaldehyde (45 mg, 0.3 mmol) in acetone (6 mL) was added and the vial was stirred under an argon atmosphere at the reaction temperature. Aliquots were sampled by syringe, filtered to remove the catalyst, and the reaction products (alcohol and olefin) were quantified by HPLC.

When 1:1 MeOH/acetone was used as solvent, the *p*-nitrobenzaldehyde was dissolved in 3 mL acetone, and this solution was added to the catalyst, followed by 3 mL of methanol.

In the case of homogeneous amino acid catalysts, most of which had low acetone solubility, the catalyst (30 μmol) was first dissolved in methanol (3 mL) and a solution of *p*-nitrobenzaldehyde (45 mg, 0.3 mmol) in acetone (3 mL) was added.

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Additional Data

Entry	Catalyst 1	Catalyst 2	Solvent	Product Concentrations (mM)							
				2hr		4hr		6hr		24hr	
				Alcohol	Olefin	Alcohol	Olefin	Alcohol	Olefin	Alcohol	Olefin
1	6A		A/M			3.9	0.5	4.7	0.6	9.9	1.9
2	6B		A/M			3.1	0.2			8.4	0.8
3	6C		A/M			1.6	0.0	1.8	0.0	2.6	0.1
4	6D		A/M			1.4	0.2			2.7	0.3
5	6E		A/M			1.6	0.1			3.3	0.3
6	7		A/M			4.8	0.5			11.0	2.3
7	7	SBA-15 (300 mg)	A/M			3.6	0.3			10.7	2.3
8	Proline		A/M			8.1	0.4	10.8	0.5	24.6	1.2
9	NH ₄ OAc		A/M			2.6	0.0	2.9	0.0	3.9	0.1
10	PrNH ₂		A/M			0.5	0.0			2.4	0.0
11	HOAc		A/M			0.1	0.0			0.1	0.0
12	PrNH ₂	HOAc	A/M			1.4	0.0			4.0	0.2
13	PrNH ₂	HOAc	A	1.1	0.0			1.7	0.0	6.5	0.03
14	SBA-PA		A	3.7	0.3			8.2	1.0	26.2	3.9
15	SBA-PA-CA-r		A	3.4	0.3			7.7	1.1	33.1	5.0
16	SBA-PA-CA-p		A	2.5	0.1			5.0	0.4	17.1	1.6
17	SBA-PA		A/M	1.2	0.1			3.1	0.4	11.7	1.7
18	SBA-PA-CA-r		A/M	0.9	0.1			2.3	0.3		
19	SBA-PA-CA-p		A/M	0.5	0.0			1.2	0.2	4.1	0.8
20	SBA-PA-TMS		A	1.5	0.1			3.8	0.2	11.6	0.7
21	SBA-PA-CA-r-TMS		A	1.7	0.1			3.9	0.2	12.5	1.0
22	SBA-PA-CA-p-TMS		A	1.9	0.0			3.9	0.1	11.4	0.4
23	SBA-PA-TMS	HOAc	A	1.4	0.1			3.3	0.2		
24	SBA-PA-TMS	12B	A	1.9	0.04			4.2	0.1	12.1	0.6
25	SBA-PA-TMS	12C (pTSA)	A	0.1	0.0			0.1	0.0	0.1	0.0
26	SBA-PA-TMS	12D	A	1.8	0.1			4.2	0.2	13.9	0.8
27	SBA-PA-TMS	12E	A	1.8	0.1			4.1	0.2		
28	SBA-PA-TMS	12F	A	1.7	0.1			3.8	0.2	12.3	0.8
29	SBA-15		A	0.1	0.0			0.1	0.0	0.1	0.0
30	PrNH ₂		A	0.1	0.0			0.2	0.0	0.9	0.0
31	PrNH ₂	SBA-15 (20 mg)	A	0.6	0.0			2.6	0.04	5.8	0.3
32	PrNH ₂	SBA-15 (50 mg)	A	1.5	0.02			3.6	0.1	5.2	0.6
33	PrNH ₂	SBA-15 (100 mg)	A	2.2	0.1			3.5	0.3	5.3	0.9
34	PrNH ₂	SBA-15 (300 mg)	A	3.1	0.2			4.6	0.8	6.8	1.5
35	PrNH ₂	SBA-TMS (300 mg)	A	0.7	0.01			1.3	0.1	2.6	0.4
36	PrNH ₂	SBA-15 (50 mg)	A/M	0.4	0.0			1.1	0	4.6	0.1
37	PrNH ₂	SBA-15 (300 mg)	A/M	1.5	0.03			3.5	0.2	8.9	0.7

Table 5.2. Raw data for aldol catalysis. Solvent: A = acetone; A/M = 1:1

acetone/MeOH. Reaction conditions: 6 mL of 50 mM *p*-nitrobenzaldehyde solution, 10

mol% amine and/or acid, 25°C