# COOPERATIVE CATALYSIS BY BIFUNCTIONALIZED MESOPOROUS SILICA

Thesis by

Eric Margelefsky

In Partial Fulfillment of the Requirements for the

degree of

Doctor of Philosophy

CALIFORNIA INSTITUTE OF TECHNOLOGY

Pasadena, California

2008

(Defended May 9, 2008)

Dedicated in loving memory to

Fay Feller

and

Dinah Margelefsky

# ACKNOWLEDGEMENTS

This dissertation would not have been possible without the help and advice of a lot of people, near and far.

Special thanks go out to my collaborators, especially Ryan Zeidan, who taught me the ins and outs of synthetic chemistry and without whose prior work on bifunctional silica catalysts none of this work would have been possible. And a heartfelt *merci beaucoup* to Véronique Dufaud and Anissa Bendjeriou. I highly enjoyed working with you both in Pasadena and I'm so glad our long-distance collaboration turned out so well. Véro's original work on bisphenol A catalysis set the groundwork for Ryan's and my later work, and her synthetic and analytical protocols made my life much easier. Anissa performed most of the organic synthesis work to create the organosilanes used in Chapter 3. I am grateful to have had the opportunity to work with both Véro and Anissa and I wish them both the best of luck in the future.

I am also grateful to my family for their loving support throughout my PhD and throughout my life. They always listened to my stories of research difficulties and experimental conundra with a sympathetic ear, even though I might as well have been speaking another language.

I am thankful to have had Dr. Sonjong Hwang running the Caltech solid-state NMR facility, who keeps the spectrometers running even when it seems that everything is conspiring to bring them down.

To all of the members of the Davis lab, who helped foster a spirit of collaboration and creativity within the group, I am grateful and lucky to have had the chance to work with so many talented, smart, and dedicated individuals. Specifically I must thank Christopher Alabi, who helped me through the numerous technical challenges and hurdles of organic synthesis, and Heather Hunt, who was always willing to listen to my problems and was there to commiserate during the tough times and celebrate the happy times (and who always let me borrow her equipment and bench-space).

Thanks as well to all of the members of my committee. Dr. Rick Flagan's insight and questions during my candidacy exam led me to think about a lot of things that I might have otherwise missed, and helped my progression immensely. Dr. Jay Labinger was very helpful in interpreting some of my results, especially the earlier ones when I was still trying to find my footing as an experimentalist. Dr. Stacey Zones is like a second advisor to all the members of the Davis lab, and we are all thankful for his selfless dedication and advice.

And finally, to Dr. Davis, thank you for your time, patience, insight, and of course, funding. I shall continue to follow the progress of research and therapeutics coming from your lab and companies, as I'm sure they will continue to make headlines.

# ABSTRACT

The objective of my work was to prepare heterogeneous catalysts that can perform cooperative catalysis. Cooperative catalysis occurs when the presence of two or more functional groups provide an acceleration of a chemical reaction beyond what is possible when either of the two species is used independently. New catalytic materials were synthesized by functionalizing mesoporous silica (SBA-15) with two different functional groups. The spatial arrangement of these two functional groups was controlled either by two-site imprinting (the two groups are covalently attached to one another by a linker, then each is tethered to the silica surface followed by spacer cleavage) or by single-site bifunctionalization (both organic functionalities are attached to the surface by a single carbon tether). The dependence of catalytic activity and selectivity on the surface arrangement (random vs. paired, distance between paired species) was investigated for several different condensation reactions.

Catalysts featuring both sulfonic acid and thiol groups were investigated for the synthesis of various bisphenols from a ketone and phenol. Alkylsulfonic acid and thiol groups were organized into pairs by ring-opening surface-bound propanesultone groups with various thiolate nucleophiles. Paired acid/thiol catalysts outperformed randomly-distributed catalysts in the synthesis of bisphenol A and bisphenol Z, whereas the synthesis of bisphenol AF was insensitive to spatial arrangement. The distance between the two groups in the acid/thiol pair was varied and the activity and selectivity were found to diminish rapidly as the acid/thiol distance grows. Catalysts containing stronger arylsulfonic acid and thiol groups were synthesized using a two-point imprinting approach

in which disulfide and sulfonate ester bonds were cleaved to generate the paired thiol and acid groups. This paired acid/thiol catalyst outperformed randomly-distributed catalysts in the synthesis of bisphenol Z, whereas the synthesis of bisphenol A was insensitive to spatial arrangement.

The second reaction investigated was the aldol reaction in order to investigate the possibility of acid/base cooperativity. A catalyst containing alkylsulfonic acid and primary amines grouped into pairs were generated by opening surface sultone rings with ammonia. This material was catalytically inactive in the aldol reaction due to acid/base neutralization, whereas randomly-distributed acid-base materials exhibit good catalytic activity. Primary amine/carboxylic acid cooperativity was also investigated, both with homogeneous amino acids and bifunctional heterogeneous silicas. While amine/acid cooperativity was conclusively demonstrated with the homogeneous catalysts, in the heterogeneous case the cooperativity due to surface silanol groups actually overshadowed the effect of the carboxylic acids.

The results obtained provide evidence that the spatial arrangement of disparate functional groups on the surface of a heterogeneous catalyst can have profound effects on the activity and selectivity of the catalyst. Spatial positioning is a catalyst parameter that should be taken into consideration in the design of inorganic/organic hybrid catalysts, and may allow (for some reactions) catalytic performance unachievable with randomly-distributed materials.

# TABLE OF CONTENTS

# LIST OF SCHEMES, FIGURES, AND TABLES

*Tables* *Page*

*Chapter 1*

# INTRODUCTION—HYBRID INORGANIC/ORGANIC MATERIALS AND COOPERATIVE CATALYSIS

The immobilization of organic catalysts is a common way to make catalysts easier to separate from a reaction mixture. There are many ways of immobilizing a homogeneous catalyst on an insoluble support; these include polymer encapsulation, covalent tethering to a polymer backbone, and covalently tethering to an inorganic framework such as silica to form an organic/inorganic hybrid material. The latter case is advantageous because of the low cost and thermal stability of silicate materials and the wide variety of low-cost organosilanes available for covalent surface modification.

There are innumerable reports in the literature of functionalizing silica materials with a single organic functionality for use in catalysis. The most common groups used for this purpose are acids and bases (for a review see Ref. 1), although more complex molecules such as cinchona alkaloids[2, 3] or enzymes[4] have also been immobilized on silica for use in heterogeneous catalysis. Immobilization on an inorganic support not only aids in the separation and recovery of the catalyst, but in some instances the heterogeneous catalyst outperforms its homogeneous analog, either due to solid/liquid partitioning which concentrates reactants near the catalytic sites, interactions with the support, or other concentration-dependent effects due to the concentration of the active catalytic sites on a 2-dimensional surface.

**Cooperative Catalysis**

While catalysts functionalized with a single functional group are sufficient for many purposes, bifunctionalized materials allow for cooperative catalysis between the two different functionalities. Cooperative catalysis is defined here as the synergistic catalytic effect of at least two different entities which act together to increase the rate of a reaction beyond the sum of the rates achievable from the individual entities alone.* By functionalizing a surface with two (or more) types of organic groups, catalytic activity and selectivity can be improved or tuned, and in some instances novel reactivity can be achieved which is impossible in solution, as in the case of acid/base cooperativity.

Cooperativity between multiple functional groups within a single catalytic site is typified by the active sites of enzymes. In these catalysts (many of which are so efficient that the reactions they catalyze are diffusion-limited due to millions of years of evolution) adjacent residues within a single active site interact with each other and with various reacting species and cofactors through covalent, electrostatic, and hydrogen-bonding interactions to increase the rate of reaction many orders of magnitude beyond the uncatalyzed rate. In these catalysts, the spatial positioning of the cooperating moieties is fixed by the enzyme's backbone, with sufficient flexibility endowed by the conformational flexibility of the backbone and the short (usually two- to four-carbon) linkers between the peptide backbone and the functional group.

The *de novo* design of bifunctional heterogeneous catalysts to take advantage of the same kind of cooperative catalytic interactions utilized by enzymes is a key challenge

* The term *cooperative catalysis* as used herein is not to be confused with the same term as used in enzyme catalysis, in which it is describes the change in the binding constant of a reactant to an allosteric enzyme by the binding of another reactant molecule, leading to sigmoidal kinetic behavior.

for the future of synthetic catalysis. There are a number of important design parameters which must be investigated. Of primary importance is the identity of the different functional groups. Once a set of two or more cooperating functional groups is chosen for a given reaction, the second design parameter is the arrangement of these groups on the surface of the catalyst. The first of these challenges has its foundation in homogeneous catalysis, in which combinatorial approaches are well suited to finding combinations of catalysts which are effective at catalyzing a given reaction. Most of the reported examples of cooperative heterogeneous catalysis utilize a set of functional groups determined by solution-phase experiments and later immobilized onto a surface.

The second of these challenges, the effect of the spatial positioning of cooperative functional groups, is unique to heterogeneous catalysis. In solution there is no well-defined spatial arrangement; the reacting molecules are constantly diffusing and rearranging, and at any given time there is a broad distribution of distances. On the surface of a solid catalyst particle, on the other hand, the catalytic species are fixed locally with respect to the surface and to one another.

In order to determine the ideal distance between cooperating groups, one must first devise a synthetic methodology by which to arrange the relevant surface species; and second, one must be able to vary this distance methodically. This dissertation is primarily focused on the former challenge, describing new methods of generating paired bifunctional surfaces and the effect of this arrangement on catalytic behavior. In the specific case of alkylsulfonic acid/thiol pairs, the latter challenge (tuning of the acid/thiol distance) is also addressed.

**Heterogeneous Cooperative Catalysis in the Literature**

Cooperativity in homogeneous catalysis has been reported using multiple monofunctional molecules (*e.g.*, two different Brønsted acids[5], a Lewis acid and amine,[6] urea and amine,[7] or a Ruthenium complex, amine base, and sodium salt[8]) or polyfunctional molecular catalysts (*e.g.*, heterobinuclear organometallic complexes,[9, 10] amine and urea/thiourea groups[11-13], or proline-type catalysts[14-16]). In each of these cases, separation and reuse of the catalyst is much more difficult than with heterogeneous catalysts. Thus heterogeneous bifunctional cooperative catalysts are highly desirable.

There have been several reports of bifunctional polymeric catalysts in which a flexible polymeric backbone is decorated with two different types of functionalities which provide cooperative catalysis.[17-20] These polymers are used as homogeneous catalysts but have the advantage of easy separation from the reaction mixture by precipitation. The flexibility of the polymer backbone makes it difficult to spatially isolate or position the different groups. Cross-linked polymers have also been used as supports for bifunctionalization;[21-23] the cross-linking eliminates catalyst solubility but still allows for the flexible catalyst particles to swell and change shape in different solvent environments.

Most heterogeneous cooperative organocatalysts reported in the literature use some form of silica as a rigid insoluble support (for a review, see Ref. 24). These include acid/thiol bifunctionalized mesoporous silica for bisphenol A synthesis[25, 26] and aldol catalysts containing amine and urea groups[27, 28] or acid and base groups.[29-31] Few reports exist in the literature of heterogeneous catalysts containing organic functional groups with a non-random spatial positioning. Homodimeric pairs of sulfonic acids[32, 33] and

amines[34, 35] have been created on silica surfaces, but while these types of materials have shown promise in molecular recognition and sensing, the reported effects of dimeric pairing on catalytic activity have been minor.

Some bifunctional materials containing a non-random spatial arrangement have been reported. Amine and sulfonic acid groups have been incorporated into mesoporous silica with some degree of spatial isolation (acidic framework and basic pores) but no catalytic properties were reported.[36] Non-covalent imprinting has been used to direct the self-assembly of multiple functional groups. In this technique, monomers are polymerized in the presence of an imprint molecule with which they interact weakly, and the imprint molecules are removed by extraction after polymerization. This method has been used to generate protease-like trifunctional catalysts but the catalytic improvement due to the imprinting process is modest.[37] In some cases the effects attributed to the imprinting process are due only to the presence of residual imprint which survives the extraction process, rather than to the organizing effect of the imprint.[38] Surface lithography has been used to pattern a monolayer with alternating stripes of imidazole and alcohol groups, which led to improved hydrolytic activity at the interface between the two groups[39] but this technique has a very limited degree of spatial resolution.

The only known report in which two different functional groups were arranged into pairs on a silica surface was published by Bass and Katz in 2006.[40] A mesoporous silica was functionalized with primary amine/thiol pairs derived from the thermolysis of a grafted xanthate/carbamate precursor, but the catalytic properties of this material were never investigated.

In this dissertation the synthesis and catalytic activity of hybrid inorganic/organic mesoporous silica catalysts functionalized with pairs of either acid and base groups or acid and thiol groups are reported. The activity of the paired catalysts is compared to that of catalysts in which the two groups are arranged randomly on the surface. In some instances, the distance between the two groups in the paired catalysts can be varied, which allows insight into the dependence of the catalytic reaction on the distance between the cooperating catalytic moieties.

**The Functionalization of SBA-15**

Mesoporous silica materials have pore diameters of 2–50 nm. These materials, such as MCM-41[41] and SBA-15,[42] are commonly used as supports for immobilizing organic catalysts. Compared to amorphous silica, mesoporous silica has a more regular structure, which leads to more uniform catalytic sites. The high surface area allows for a greater density of functional groups. Compared to microporous silicates, such as zeolites, the larger pore size of mesoporous materials allows for better reactant and product diffusion, reducing mass transfer limitations and allowing even large molecules to access the catalytic sites.

The synthesis of SBA-15 employs a triblock copolymer surfactant as structure directing agent (SDA), leading to pores 6–10 nm in diameter and with a regular hexagonal 1-D structure (see Figure 1.1). Because of its high surface area (~ 800 $m^2/g$) and high silanol density, SBA-15 is easy to functionalize with a high loading of organic functional groups, and its large pore diameter allows large molecules to enter the pores with less mass transfer limitation than materials with a smaller pore size. For these

reasons, SBA-15 was chosen as the support for all of the heterogeneous catalysts described herein.

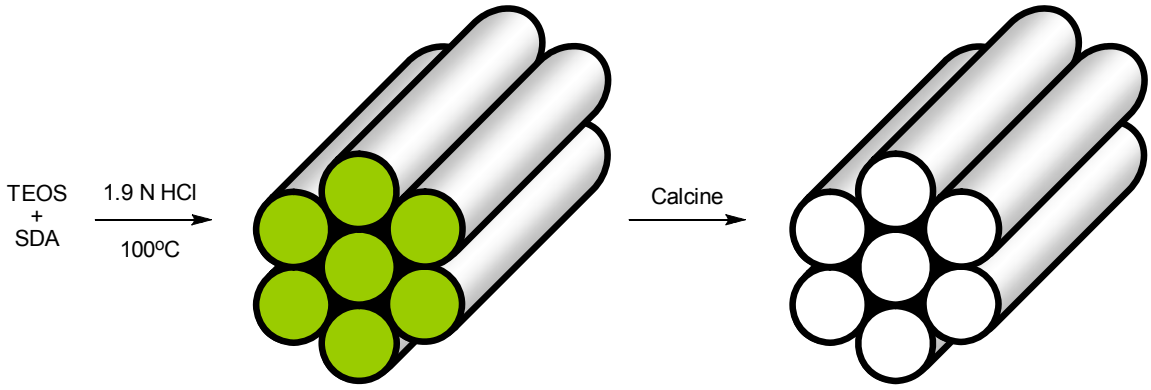



**Figure 1.1.** Synthesis of SBA-15. The structure-directing agent (SDA) is a triblock copolymer of ethylene oxide (EO) and propylene oxide (PO) with formula $(EO)_{20}(PO)_{70}(EO)_{20}$. The calcination process (at 550°C) burns out the SDA, leaving the pores empty. The silica source is tetraethyl orthosilicate (TEOS).

Silica can be functionalized with organic groups in two ways. In a direct synthesis (also known as a one-pot synthesis), a silica precursor is polymerized in the presence of functional organosilanes in a single step. Using this route to functionalized silica materials, higher loadings of functional groups can be achieved and those groups can be well distributed within the silica matrix. The disadvantages of the method include the necessity to extract the structure-directing agent (since calcination would destroy the organic functionality) and, in the case of ordered materials, the possibility of the functional silanes disrupting the long-range order. Mesoporous silicas typically become less well ordered as the organic loading increases, and microporous materials often will not crystallize in the presence of large amounts of organosilanes.

Postsynthetic modification, or grafting, involves covalently attaching organosilanes to the surface silanols of a pre-made silica material. In general, a more-reactive silane will lead to higher organic loadings but do so to give less well-distributed surfaces (*e.g.*, clustering due to silane-silane interactions and preferential grafting at pore mouths). Trichlorosilanes (highly reactive) or trialkoxysilanes (less reactive) are often used. Since the silica is synthesized before grafting, highly ordered silica geometries can be maintained even at moderately high organic loadings.

For the application of investigating the spatial organization of bifunctionalized surfaces, the grafting of trialkoxysilanes was chosen as the method of functionalization. This method leads to functional groups which are all on the pore surfaces, unlike one-pot syntheses which can lead to organic groups buried within the pore walls. Furthermore, the grafting process does not involve the harsh conditions found in one-pot syntheses (1.9N HCl, 100°C) which is important when the organosilanes feature hydrolytically sensitive functional groups, as is the case for many of the silanes described in this work. In comparing randomly-organized vs. positioned functional groups, low organic loadings are needed, so highly reactive molecules such as trichlorosilanes can be avoided. Instead, triethoxysilanes can be used, which can be equilibrated within the silica pores at room temperature before the high-temperature grafting reaction begins, minimizing pore-mouth clustering.

Additionally, a whole family of catalysts can be generated by grafting different organosilanes onto identical silicate frameworks, such that there is no difference in pore size or uniformity among the members of the family. In the case of one-pot syntheses, different batches prepared with different organosilanes (or different amounts of

organosilanes) often have slightly different pore size, surface area, or pore regularity, all of which can affect catalytic performance. Finally, calcining the SBA-15 before grafting ensures that no SDA remains in the pores; with co-condensation, the SDA must be extracted with an appropriate solvent (since post-synthetic calcination would destroy the organic functionality) and there is almost always some residual SDA in the pores after extraction.

**Summary of Bifunctional Site-Paired Catalysts Described in This Work**

As test reactions for bifunctional cooperative catalysis, two condensation reactions were chosen, each with literature precedents for bifunctional cooperativity: the reaction between a ketone and phenol to form bisphenols (such as the industrially relevant bisphenol A) catalyzed by acids and thiols; and the aldol reaction of acetone and nitrobenzaldehyde, the catalysis of which is enhanced by the presence of both acid and base groups. A summary of the four types of catalyst discussed is shown in Figure 1.2.

In the following chapters, the catalytic performance of each of these site-paired bifunctional materials is evaluated and compared with that of randomly-distributed organic groups. In some cases, the paired materials outperform the random; in others, there is no difference or (in the case of strong acid/base materials) the paired material is inactive. The key conclusion is that spatial positioning of surface organic groups is an important design criterion in heterogeneous catalysis—one that has heretofore been largely ignored. While spatial positioning is not important in every reaction, it is worthy of consideration any time cooperative catalysis is operating.

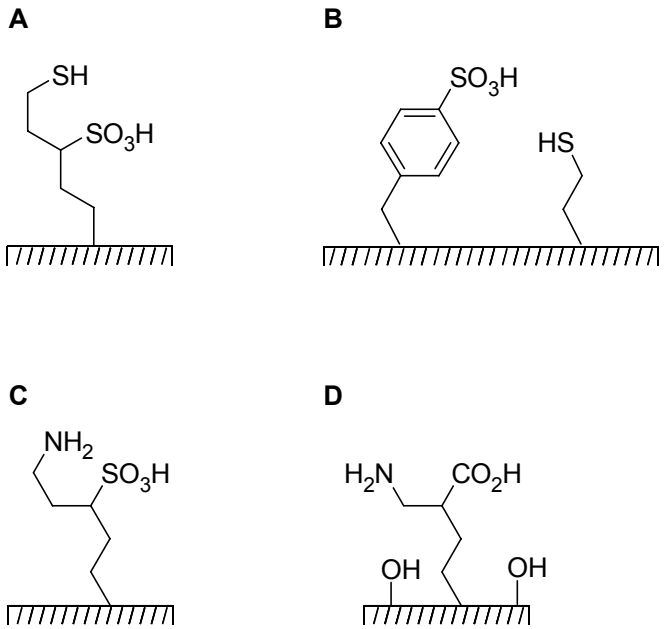



**Figure 1.2.** Summary of the four polyfunctional SBA-15 catalysts described in this work.

(**A**) Alkylsulfonic acid/thiol catalysts for the synthesis of bisphenol A

(**B**) Arylsulfonic acid/thiol catalysts for the synthesis of bisphenol A and bisphenol Z

(**C**) Alkylsulfonic acid/amine catalysts for the aldol reaction

(**D**) Carboxylic acid/amine/silanol catalysts for the aldol reaction

References


1. Molnar, A.; Rac, B. *Curr. Org. Chem.* **2006,** 10, (13), 1697.
2. Kim, H. S.; et al. *Tetrahedron* **2004,** 60, (52), 12051.
3. Motorina, I.; Crudden, C. M. *Org. Lett.* **2001,** 3, (15), 2325.
4. Sheldon, R. A. *Adv. Synth. & Cat.* **2007,** 349, (8-9), 1289.
5. Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2007**, (9), 1441.
6. Kanemasa, S.; Ito, K. *Eur. J. Org. Chem.* **2004,** 2004, (23), 4741.
7. Maher, D. J.; Connon, S. J. *Tet. Lett.* **2004,** 45, (6), 1301.
8. Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004,** 126, (42), 13632.
9. Yamagiwa, N.; et al. *J. Am. Chem. Soc.* **2005,** 127, (38), 13419.
10. Mitani, M.; et al. *Bull. Chem. Soc. Jpn.* **1996,** 69, (10), 2967.
11. Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003,** 125, (42), 12672.
12. Cao, C. L.; et al. *Org. Lett.* **2006,** 8, (14), 2901.
13. Berkessel, A.; et al. *Angew. Chem. Int. Ed. Eng.* **2005,** 44, (5), 807.
14. List, B.; et al. *J. Am. Chem. Soc.* **2002,** 124, (5), 827.
15. Brown, S. P.; et al. *J. Am. Chem. Soc.* **2003,** 125, (36), 10808.
16. Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005,** 127, (10), 3240.
17. Kwong, C. K. W.; et al. *Chem. Eur. J.* **2007,** 13, (8), 2369.
18. Miyabe, H.; et al. *Synthesis* **2006**, (19), 3295.
19. Sellergren, B.; Karmalkar, R. N.; Shea, K. J. *J. Org. Chem.* **2000,** 65, (13), 4009.
20. Wieland, S.; Panster, P. *Stud. Surf. Sci. Cat.* **1997,** 108, 67.
21. Revillon, A.; et al. *Macromolecular Symposia* **2001,** 164, 443.

22. Apel, F. N.; Conte, L. B.; Bender, H. L. U.S. Patent 3,153,001, 1964.

23. McNutt, B. W.; Gammill, B. B. U.S. Patent 3,394,089, 1968.

24. Margelefsky, E. L.; Zeidan, R. K.; Davis, M. E. *Chem. Soc. Rev.* **2008,** 37, (6).

25. Chen, C. C.; Cheng, S. F.; Jang, L. Y. *Micro. Meso. Mater.* **2008,** 109, (1-3), 258.

26. Zeidan, R. K.; Dufaud, V.; Davis, M. E. *J. Cat.* **2006,** 239, (2), 299.

27. Huh, S.; et al. *Angew. Chem., Int. Ed. Engl.* **2005,** 44, (12), 1826.

28. Huh, S.; et al. *J. Am. Chem. Soc.* **2004,** 126, (4), 1010.

29. Zeidan, R. K.; Davis, M. E. *J. Catal.* **2007,** 247, (2), 379.

30. Zeidan, R. K.; Hwang, S. J.; Davis, M. E. *Angew. Chem., Int. Ed. Engl.* **2006,** 45, (38), 6332.

31. Zhong, L.; Xiao, J. L.; Li, C. *Chin. J. Catal.* **2007,** 28, (8), 673.

32. Dufaud, V.; Davis, M. E. *J. Am. Chem. Soc.* **2003,** 125, (31), 9403.

33. Mbaraka, I. K.; Shanks, B. H. *J. Catal.* **2006,** 244, (1), 78.

34. Graham, A. L.; Carlson, C. A.; Edmiston, P. L. *Anal. Chem.* **2002,** 74, 458.

35. Katz, A.; Davis, M. E. *Nature* **2000,** 403, (6767), 286.

36. Alauzun, J.; et al. *J. Am. Chem. Soc.* **2006,** 128, (27), 8718.

37. Markowitz, M. A.; et al. *Langmuir* **2000,** 16, (4), 1759.

38. Katz, A.; Davis, M. E. *Macromolecules* **1999,** 32, (12), 4113.

39. Kisailus, D.; et al. *Proc. Natl. Acad. Sci. U. S. A.* **2006,** 103, (15), 5652.

40. Bass, J. D.; Katz, A. *Chem. Mater.* **2006,** 18, (6), 1611.

41. Kresge, C. T.; et al. *J. Am. Chem. Soc.* **1992,** 114, (27), 10834.

42. Zhao, D. Y.; et al. *Science* **1998,** 279, (5350), 548.

*C h a p t e r 2*

# THIOL/ALKYLSULFONIC ACID-PAIRED CATALYSTS FOR THE SYNTHESIS OF BISPHENOL A

**Abstract**

The synthesis and characterization of heterogeneous catalysts containing surfaces functionalized with discrete pairs of sulfonic acid and thiol groups are reported. A catalyst having acid and thiol groups separated by three carbon atoms is ca. 3 times more active than a material containing randomly-distributed acid and thiol groups in the condensation of acetone and phenol to bisphenol A and 14 times more active in the condensation of cyclohexanone and phenol to bisphenol Z. Increasing the acid/thiol distance in the paired materials decreases both the activity and selectivity. This work clearly reveals the importance of nanoscale organization of two disparate functional groups on the surface of heterogeneous catalysts.

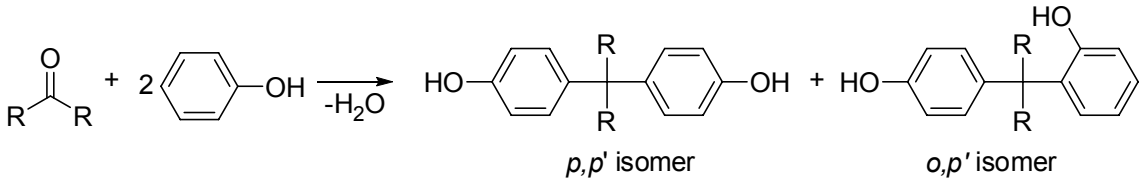
**Introduction**

There is growing interest in developing multifunctional catalyst systems where the different functional groups each play a distinctive role in the overall catalysis. Immobilization of two or more functional groups on a solid support allows for the possibility of spatial control of the different groups. They can be isolated from each other, which can be useful for sequential one-pot reactions,[1-4] or they can be intimately mixed such that direct interaction between the two groups is possible. In the latter case, the two groups can act in concert to provide activity greater than either could achieve alone (so-called cooperative catalysis).[5-10]

When seeking cooperative behavior between the functional groups, control of the distance between the reactive groups is essential in order to optimize the catalysis for a particular reaction. This is dramatically illustrated with enzymes that have multiple catalytic functional groups organized within a single active site. There have been several reports of the nanoscale arrangement of two or more *identical* functional groups on the surface of a silica catalyst,[11-15] but the arrangement of two *different* functional groups is more difficult. To our knowledge, there has been only one report of the organization of two disparate functional groups into pairs on a rigid support. Bass and Katz[16] synthesized a precursor containing carbamate and xanthate groups that was grafted onto silica and subsequently thermolyzed to generate pairs of amine and thiol groups. No catalytic results were reported from this bifunctional solid.

One reaction where cooperative, heterogeneous catalysis has been well established is the synthesis of bisphenol A from acetone and phenol. This reaction is catalyzed by strong acids, and promoted by thiols that have been shown to increase both

the yield and selectivity of *p,p'* bisphenol A over the undesired *o,p'* isomer (Scheme 2.1). Industrial processes typically employ sulfonated polystyrene resins promoted by thiols such as cysteamine, bound to the resin by acid/base pairing[17, 18]. These resins have a random arrangement of acid and thiol groups, leading to a broad distribution of acid/thiol distances.




**Bisphenol A** (R = -$CH_3$)
**Bisphenol Z** (R,R = -$C_5H_{10}$-)
**Bisphenol AF** (R = -$CF_3$)

**Scheme 2.1.** Condensation of phenol with acetone, cyclohexanone, and hexafluoroacetone to form bisphenols

The mesoporous silica SBA-15[19] is well suited as a support for immobilizing organized functional groups. Its large, uniform pore diameter (~ 6 nm) provides ample room for reactant and product diffusion, and its thick walls provide hydrothermal stability. The rigidity of the silica matrix ensures that the bound functional groups do not change their positioning (unlike polymeric supports, that have the potential to shrink and swell in different solvent environments). Furthermore, SBA-15 can be easily functionalized with a wide variety of functional groups by grafting an appropriate organosilane onto surface silanol groups in order to form covalent bonds to the surface.

We have recently shown[20] that SBA-15 functionalized with randomly-distributed arylsulfonic acid and alkyl thiol groups is an effective catalyst for the synthesis of BPA.

We also demonstrated that the acid and thiol groups must be near each other to achieve high activity and selectivity: a physical mixture of acid-functionalized and thiol-functionalized SBA-15 materials exhibited only moderate activity, whereas when the two functionalities were randomly distributed on the surface of the same SBA-15 material at high loadings (at a total organic loading ~ 0.7–1.0 mmol/g) the activity was nearly fourfold higher and the isomer ratio was sixfold higher. We also showed that in this reaction the selectivity is essentially independent of conversion, which allows for the comparison of selectivities at different levels of conversion. We hypothesized that the thiol activates the protonated acetone molecule through formation of a propylidene sulfonium species that exhibits increased electrophilicity in addition to sterically disfavoring the *o,p'* isomer (Figure 2.1). If the acid and thiol groups are located near each other, the thiol can rapidly attack the protonated acetone molecule, generating the sulfonium species faster than if the groups are spatially isolated. Therefore we hypothesized that the catalytic activity should increase as the acid/thiol distance decreases.

Here, we report the synthesis of SBA-15 with alkylsulfonic acid and thiol groups organized into discrete pairs on the silica surface with varying distances between the acid and thiol groups. The distances are fixed by changing the nature of spacing groups between the acid and thiol functions, and the different spacers also provide the ability to tune both the acid/thiol distance and the electronic properties of the thiol. The resulting bifunctional catalysts give high activity and selectivity in the synthesis of bisphenol A. Pairing of the acid and thiol groups increases catalytic activity substantially compared to a randomly-bifunctionalized catalyst.

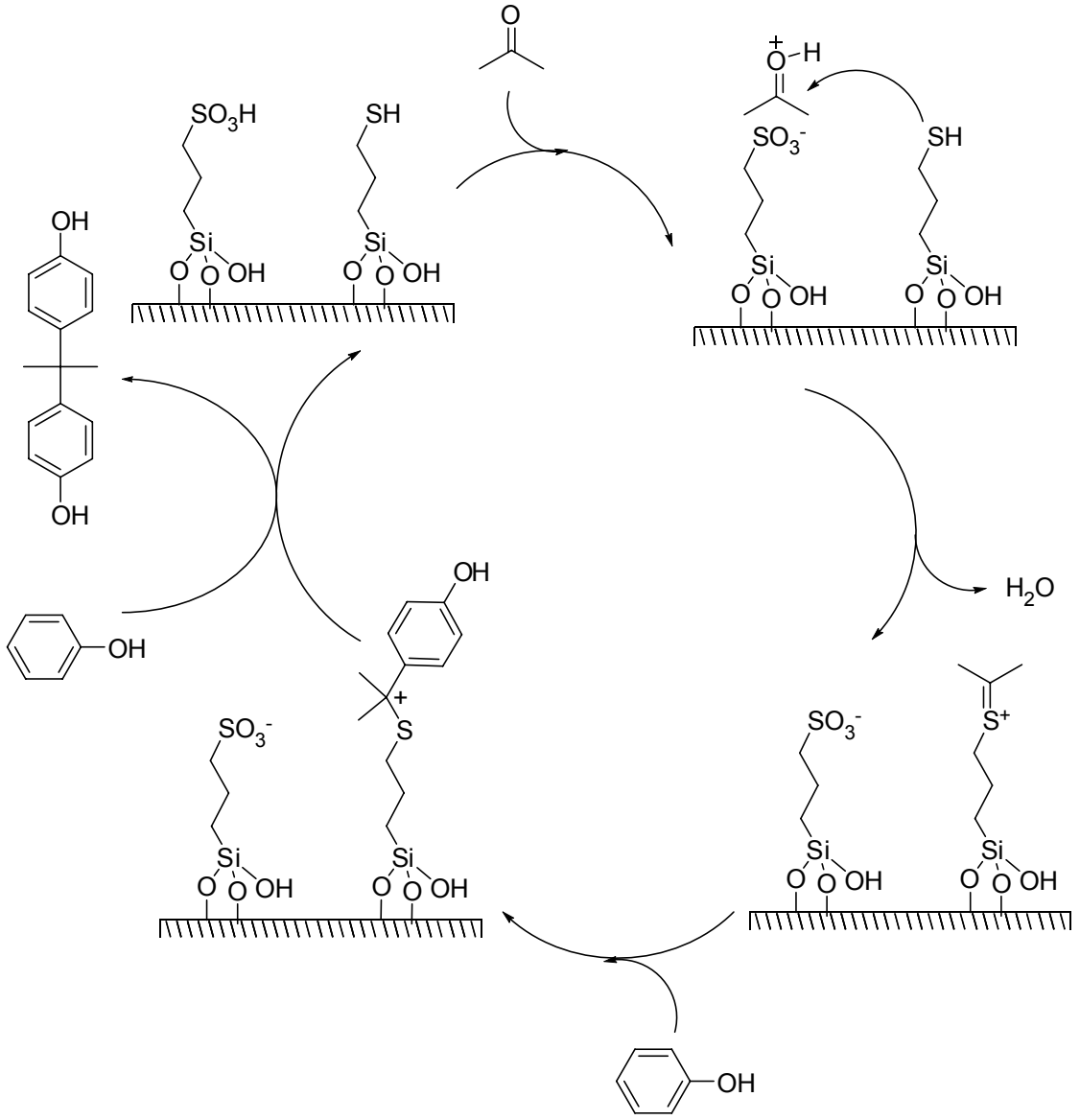


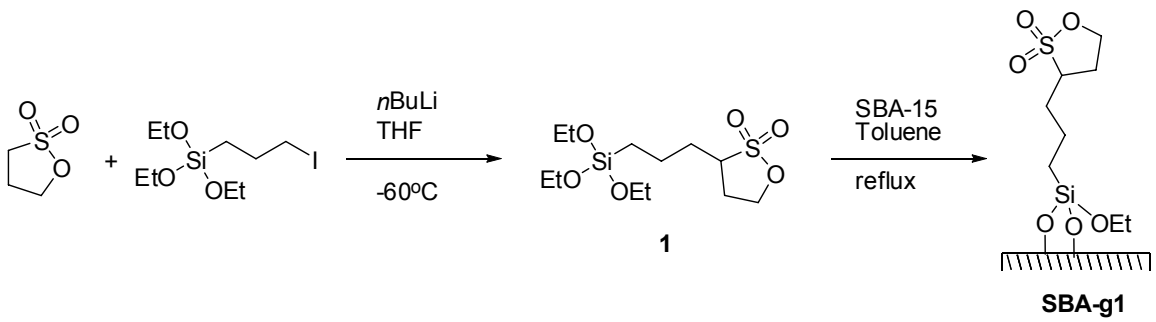

**Figure 2.1.** Proposed catalytic cycle for the synthesis of bisphenol A over a bifunctional acid/thiol catalyst. The propylidene sulfonium (bottom right) and carbocation (bottom left) intermediates are in close proximity to the pore wall, which provides the steric driving force that favors the formation of the *p*,*p*' isomer of bisphenol A.

**Results and Discussion**

Alkylsulfonic acid-functionalized mesoporous silica has been prepared through an oxidative method where surface-bound propylthiol groups are oxidized with $H_2O_2$[14, 21-25] or $HNO_3$[26] to give propylsulfonic acid groups. Such an oxidative method is unsuitable for the preparation of bifunctional catalysts when the second functionality is also oxidizable. Furthermore, the oxidation is often incomplete and leads to disulfides and other partially oxidized species.[22, 25, 26] To circumvent this difficulty we utilized a different route to alkylsulfonic acid groups based on a sultone intermediate. This intermediate serves both as a sulfonic acid precursor and as a site for anchoring a second functionality. Reaction of the sultone ring with a thiol-containing nucleophile generates the acid/thiol pair.

Sultone rings have been opened by a wide variety of nucleophiles, including halides,[27-29] phosphines,[30, 31] thiolates,[32] sulfides,[32] alkoxides,[27, 33] and amines.[33-35] In particular, if the nucleophile contains a thiol group, then the resulting material will contain pairs of acid and thiol groups.

In order to functionalize a silica surface with sultone moieties, the organosilane **1** was synthesized from 1,3-propanesultone and 3-iodopropyltriethoxysilane using a modification of the sultone alkylation method of Durst and Du Manoir.[36] Grafting of this silane onto SBA-15 in refluxing toluene resulted in the intermediate material **SBA-g1** (Scheme 2.2). **SBA-g1** is a versatile intermediate for generating bifunctional catalysts containing a sulfonic acid group and another functional group without the need for thiol oxidation.




**Scheme 2.2.** Synthesis of silane **1** and grafting onto SBA-15 to form **SBA-g1**

**SBA-g1** was characterized by cross-polarization magic angle spinning (CP/MAS) NMR, x-ray diffraction (XRD), nitrogen adsorption/desorption porosimetry, and elemental analysis. The $^{29}$Si CP/MAS NMR spectrum (Figure 2.2) shows the incorporation of organosilanes, with most bonded by two bridging oxygen atoms (the $T^2$ peak in the spectrum) as well as some singly and triply bonded silanes ($T^1$ and $T^3$ peaks, respectively).* The $^{13}$C CP/MAS NMR spectrum shows the same resonances as the molecular precursor **1** (Figure 2.3); thus, the sultone ring remains intact throughout the grafting process. The sulfur content of the materials (from elemental analysis) was used as a measure of the organic loading, and it was found that approximately 30–80% of the silane used in the grafting reaction ended up covalently bound to the surface. The XRD pattern of the functionalized material is identical to that of the parent SBA-15 and indicates that long-range ordering of the material is not affected by the grafting process (see Figure 2.4). Nitrogen adsorption/desorption porosimetry (Table 2.1, Figure 2.5)

* Q denotes quaternary silicon species (four Si-O bonds) and T denotes tertiary silicon species (three Si-O bonds). The superscript number following the Q or T denotes the number of Si-O-Si bonds attached to the center.

shows that the SBA-15 surface area drops from 810 to 613 $m^2/g$ upon grafting **1** at 0.2 mmol/g, but that the pore diameter remains constant at 6.1 nm.

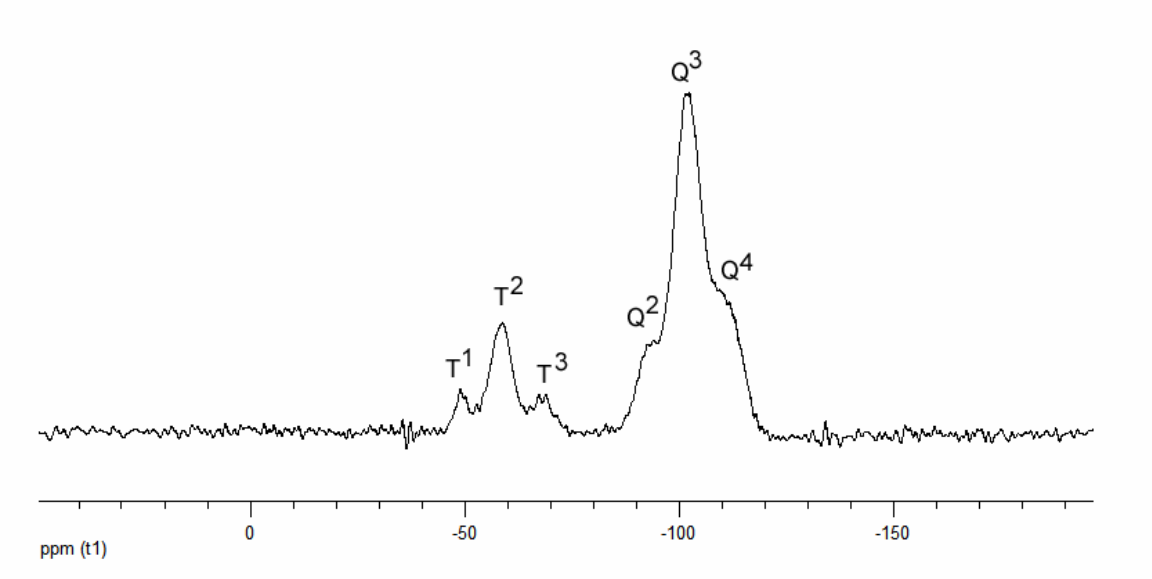



**Figure 2.2.** $^{29}Si\{^1H\}$ CP/MAS NMR spectrum of **SBA-g1** (loading = 0.7 mmol/g)

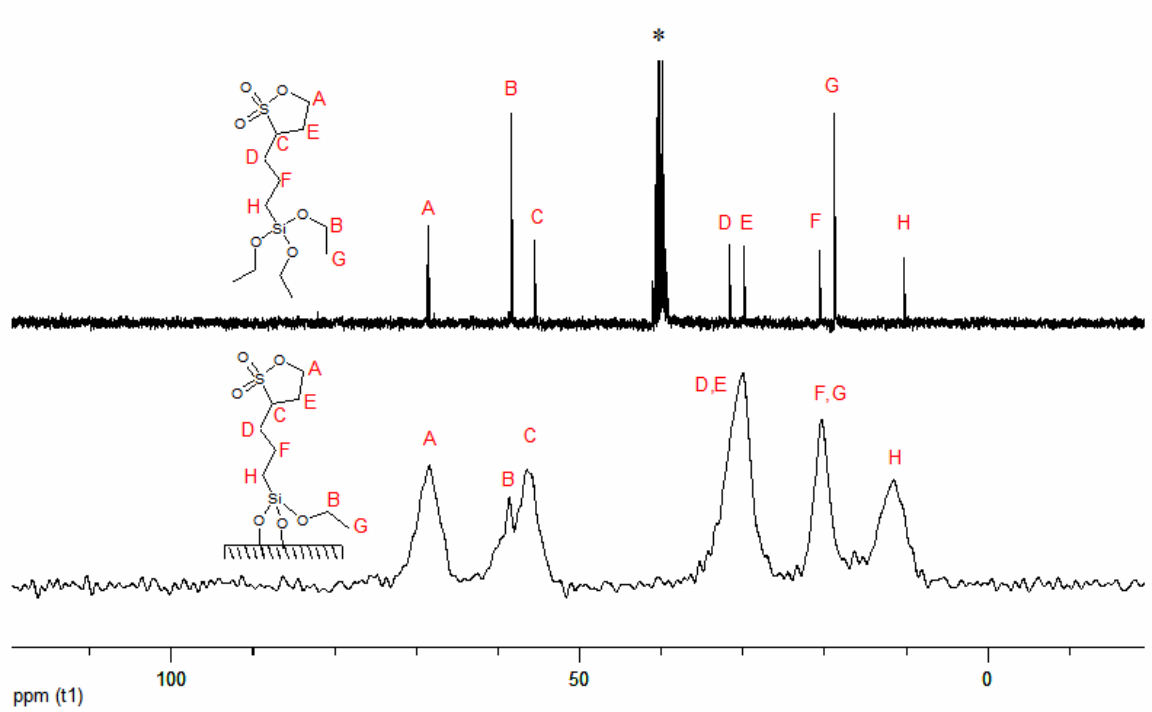



**Figure 2.3.** $^{13}C$ NMR (DMSO-$d_6$) of silane **1** (top) and $^{13}C\{^1H\}$ CP/MAS NMR of **SBA-g1** (bottom). * denotes solvent peak.

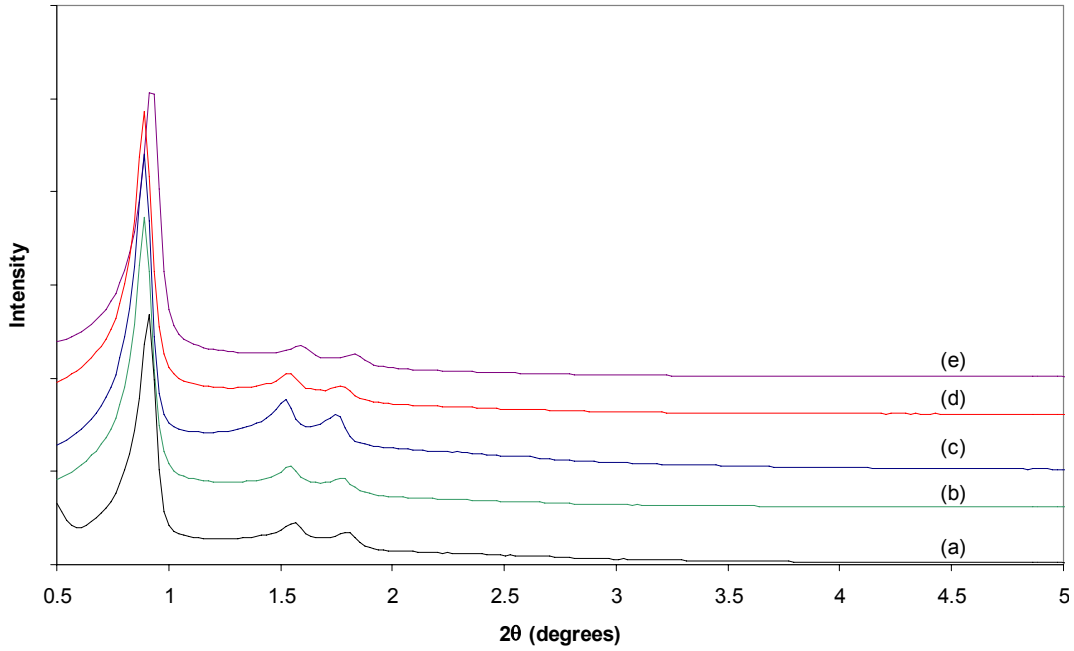



**Figure 2.4.** X-ray diffraction patterns of functionalized SBA-15 materials. (a) **SBA-15** (b) **SBA-g1** (c) **SBA-a** (d) **SBA-at-p** (e) **SBA-at-s5**

**Sultone Ring-Opening.** The sultone ring in **SBA-g1** can be hydrolyzed or thiolyzed to produce different surface groups (Scheme 2.3). Hydrolysis of the sultone in neutral water produces a solid that was used as a control catalyst because it contains acid groups but no thiols (**SBA-a**). Ring-opening with sodium hydrosulfide produces acid/thiol pairs separated by three carbon atoms (**SBA-at-p**). $^{13}$C CP/MAS NMR (Figure 2.6) shows complete ring-opening of the sultone in both cases as evidenced by the disappearance of the carbon resonance at 68 ppm. The acid loadings of these materials were measured by ion-exchange with NaCl followed by filtration and titration of the resulting HCl with NaOH.[20] The sulfur content of **SBA-at-p** was found to be twice as high as the acid content measured by titration, confirming the 1:1 ratio of acid to thiol groups. The catalyst characterization data are summarized in Table 2.1.

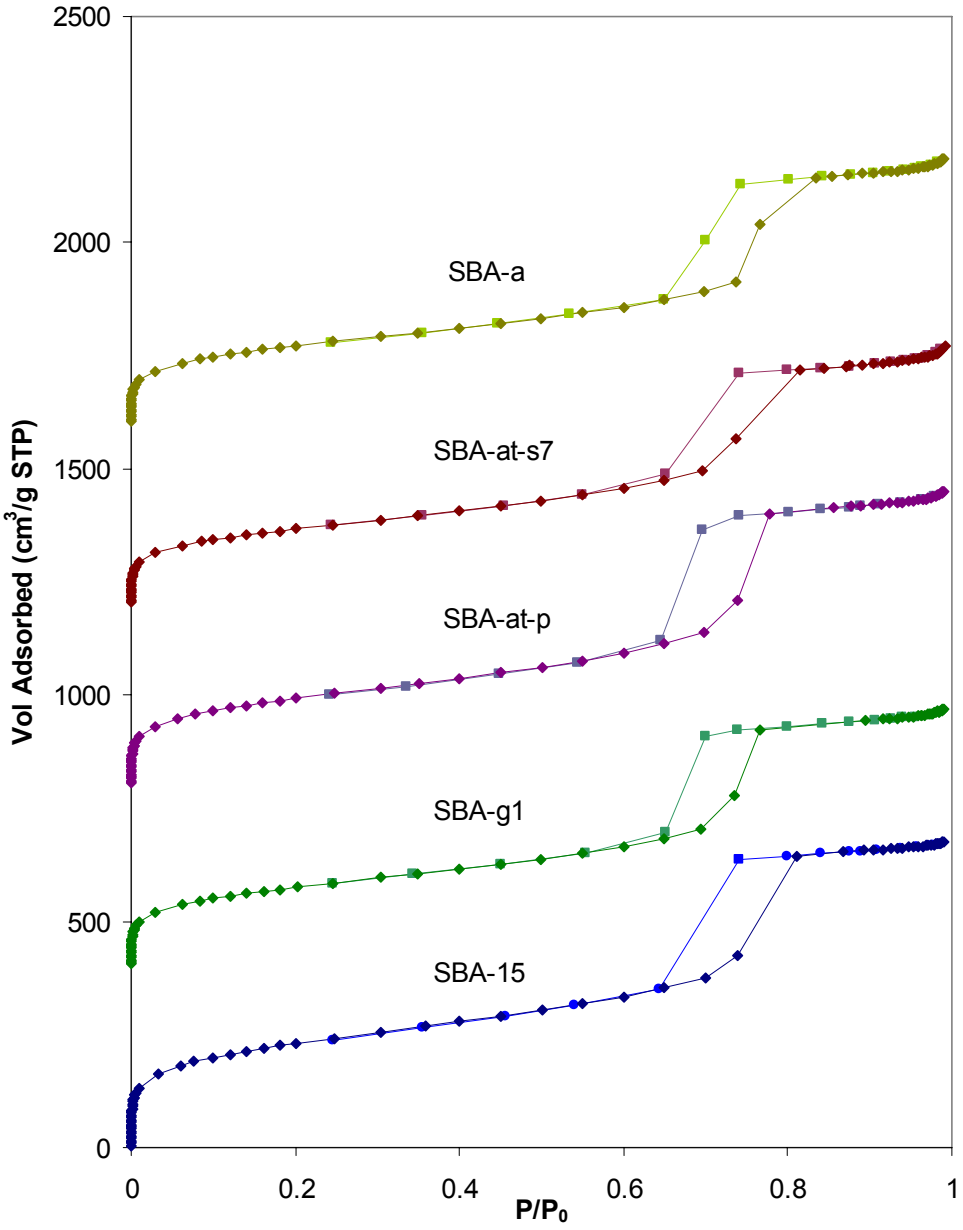



**Figure 2.5.** Nitrogen adsorption/desorption isotherms for various SBA-15 materials. Diamonds correspond to adsorption, squares to desorption. Data have been offset vertically by 400 units for clarity. The organic loading of each functionalized material is ~ 0.2 mmol/g.

| Entry | Material | d[a] (nm) | $S_{BET}$[b] ($m^2$/g) | $D_p$[c] (nm) | $H^+$[d] (mmol/g) | S[e] (mmol/g) | $S/H^+$ (expected) | $S/H^+$ (found) |
|---|---|---|---|---|---|---|---|---|
| 1 | **SBA-15** | 11.3 | 810 | 6.1 | N/A | N/A | N/A | N/A |
| 2 | **SBA-g1** | 11.5 | 613 | 6.1 | N/A | 0.26 | N/A | N/A |
| 3 | **SBA-a** | 11.6 | 603 | 6.5 | 0.17 | 0.26 | 1 | 1.5 |
| 4 | **SBA-as-p** | | | | 0.38 | 0.81 | 2 | 2.1 |
| 5 | **SBA-at-p** | 11.5 | 676 | 6.2 | 0.18 | 0.4 | 2 | 2.2 |
| 6 | **SBA-at-r** | | | | 0.18 | 1.04 | N/A | 5.8 |
| 7 | **SBA-at-s1** | | | | 0.22 | 0.54 | 3 | 2.5 |
| 8 | **SBA-at-s2** | | | | 0.18 | | | |
| 9 | **SBA-at-s3** | | | | 0.21 | | | |
| 10 | **SBA-at-s4** | | | | 0.17 | | | |
| 11 | **SBA-at-s5** | 11.1 | | | 0.2 | | | |
| 12 | **SBA-at-s6**[f] | | | | 0.16 | | | |
| 13 | **SBA-at-s7** | | 585 | 6.3 | 0.2 | 0.5 | 3 | 2.5 |
| 14 | **SBA-at-s8** | | | | 0.21 | 0.56 | 3 | 2.7 |
| 15 | **SBA-at-s9**[f] | | | | 0.18 | | | |

**Table 2.1.** Catalyst characterization data

[a] unit cell parameter, from x-ray diffraction data
[b] Surface area, calculated from adsorption branch of $N_2$ isotherm using the BET method
[c] pore diameter from BJH analysis of desorption branch of $N_2$ isotherm
[d] from titration
[e] total sulfur content, from elemental analysis (performed by QTI, Whitehouse, NJ)
[f] **SBA-at-s6** and **SBA-at-s9** turned pink upon acidification due to a trace amount of organic byproduct resulting from the decomposition of the monosodium salt of the *o*-xylyl or *o*-durenyl dithiol.

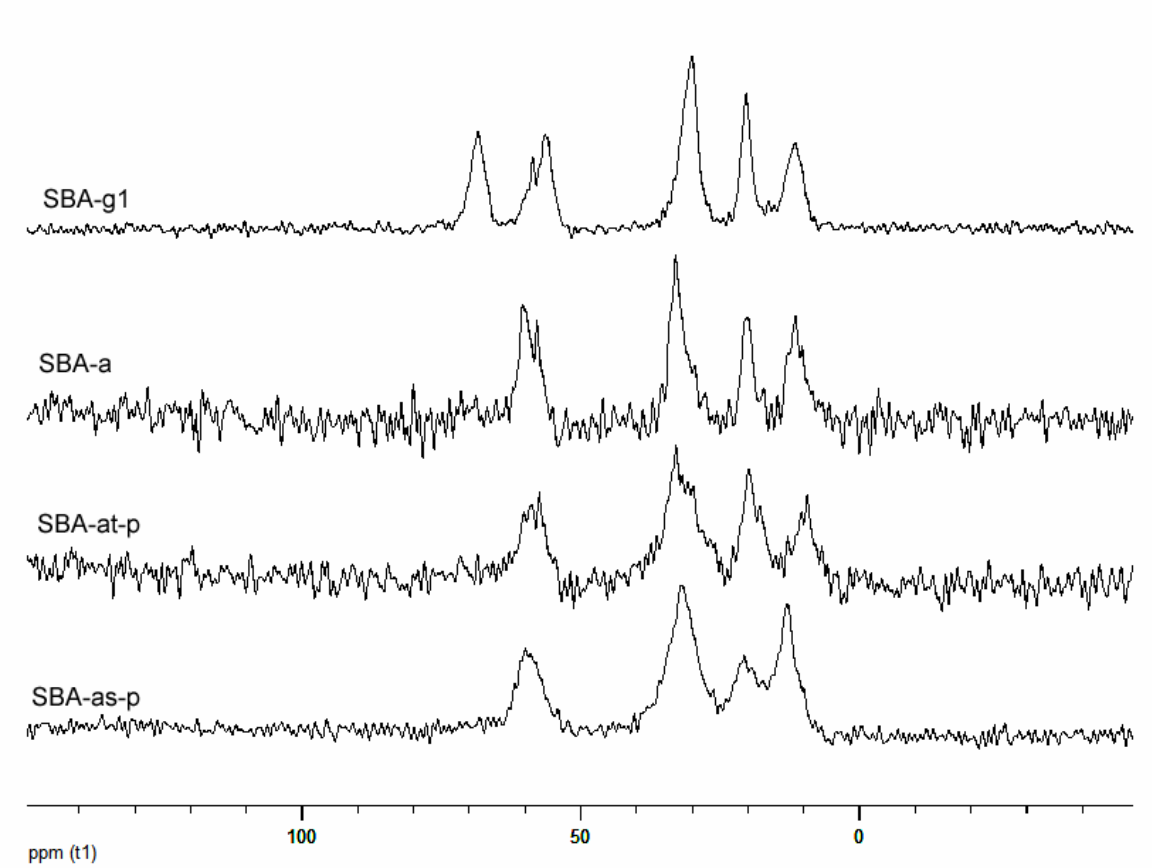
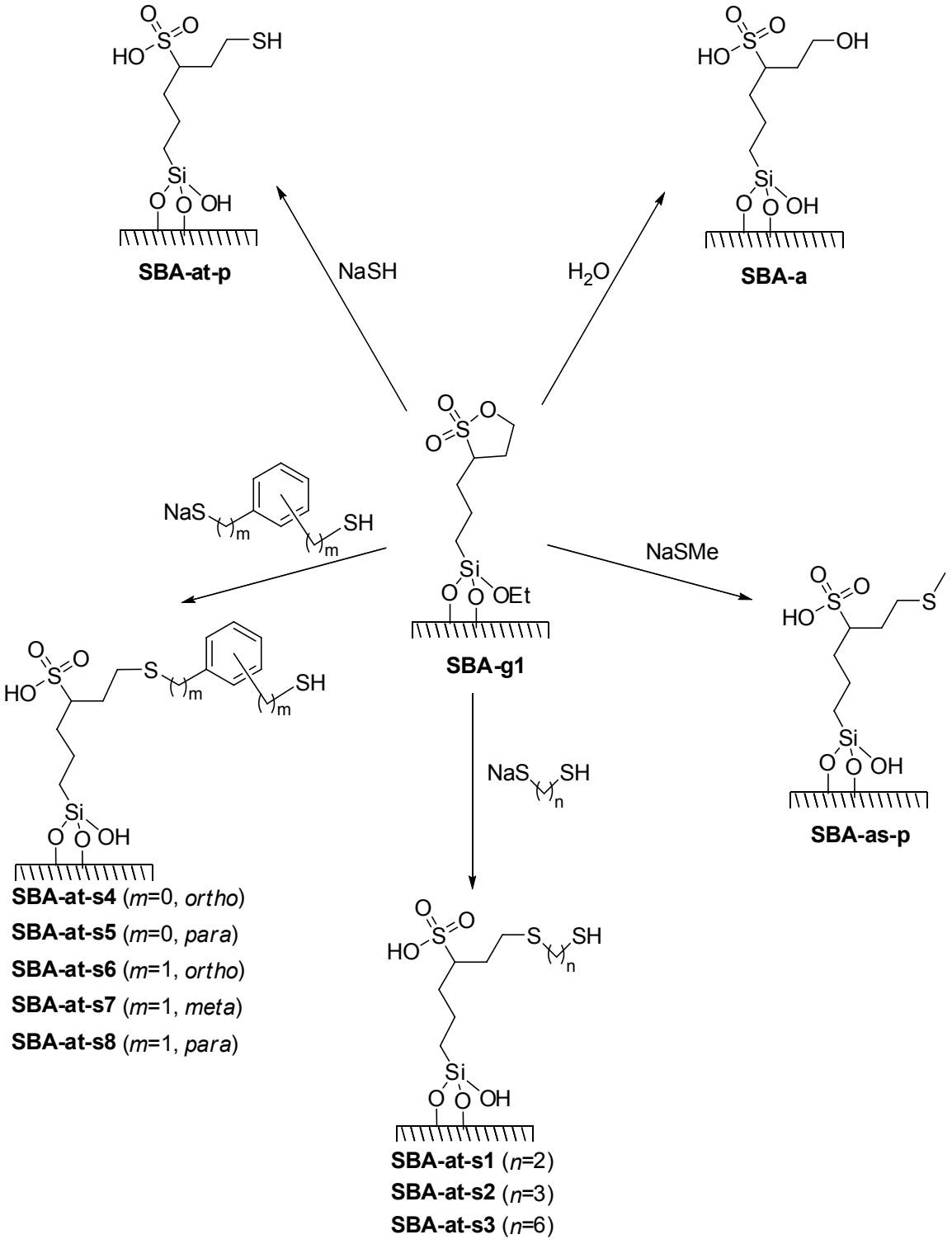



**Figure 2.6.** Comparison of $^{13}C\{^{1}H\}$ CP/MAS NMR spectra of **SBA-g1** (top) and sulfonic-acid-containing SBA-15 materials. The complete disappearance of the sultone peak at 68 ppm indicates complete ring-opening of the sultone.




**Scheme 2.3.** Ring-opening of surface-bound sultone to form sulfonic acid-containing materials

**Catalytic Reactions.** The catalysts were used in the synthesis of bisphenol A. Surface loadings were purposely maintained low (~ 0.2 mmol/g) in order to keep the resulting catalytic sites sufficiently isolated to observe the effects of discrete acid/thiol pairing. The results are given in Table 2.2. **SBA-a** gives a very low per-site yield (PSY = 3.1, defined as mmol total products / mmol $H^+$) and selectivity (1.8, defined as *p,p'*/*o,p'* product ratio) due to the lack of thiol. Addition of homogeneous thiol improves both the yield and selectivity, though both are still only modest (10 and 8.4 respectively). **SBA-at-p** is a highly active catalyst, and gives a per-site yield of 83 and a selectivity of 14. Addition of homogeneous thiol to this material decreases the per-site yield to 74, and the selectivity is slightly increased to 15. Another catalyst was prepared via sultone thiolysis with sodium methanesulfide. This material contains pairs of acid and methyl sulfide groups, and is denoted **SBA-as-p**. In the bisphenol A reaction **SBA-as-p** is only slightly better than **SBA-a** (Table 2.2, Entry 5). These results confirm that the thiol functionality is necessary for high catalytic activity, and also indicates that sulfide linkages can be used to tether other groups without substantially affecting catalysis (*vide infra*).

**SBA-at-p** materials were prepared with varying loadings of surface site pairs. It was found that as the surface density of sites increases, the activity of the catalyst decreases, but selectivity increases (Figure 2.7). These data suggest that even at the moderately low loadings used here, the paired sites are not completely isolated from each other and neighboring-site interactions affect catalysis in a significant way. At higher loadings, the paired sites are less isolated from one another, leading to greater steric interactions between pairs and between reacting acetone/phenol/bisphenol molecules and adjacent surface sites. This greater steric clash leads to lower reaction rates but enhances

the product selectivity. It is also possible that there is an effect of the greater number of surface silanols present at lower organic loadings; however, the highest loading used here was only 0.54 mmol/g, which is still low enough to leave a high silanol density (unmodified SBA-15 has a silanol density of ~ 3–5 mmol/g).[37]

| Entry | Heterogeneous Catalyst | Homogeneous Catalyst | PSY[a] | Isomer Ratio[b] |
|---|---|---|---|---|
| 1 | SBA-a | none | 3.1 | 1.8 |
| 2 | SBA-a | PrSH | 10 | 8.4 |
| 3 | SBA-at-p | none | 83 | 14 |
| 4 | SBA-at-p | PrSH | 74 | 15 |
| 5 | SBA-as-p | none | 8.1 | 2.7 |
| 6 | none | $PrSO_3H$ | 8.1 | 1.5 |
| 7 | none | $HOPrSO_3H$ | 10 | 1.7 |
| 8 | none | $HSPrSO_3H$ | 113 | 11 |

**Table 2.2.** Catalysis data in bisphenol A synthesis for heterogeneous and homogeneous catalysts. Reaction conditions: 0.02 mmol $H^+$, 0 or 0.02 mmol propanethiol, 6 mmol acetone, 24 mmol phenol, 90°C, 24 hrs

[a] Per-site yield (mmol total product / mmol $H^+$)
[b] *p,p*'/*o,p*'

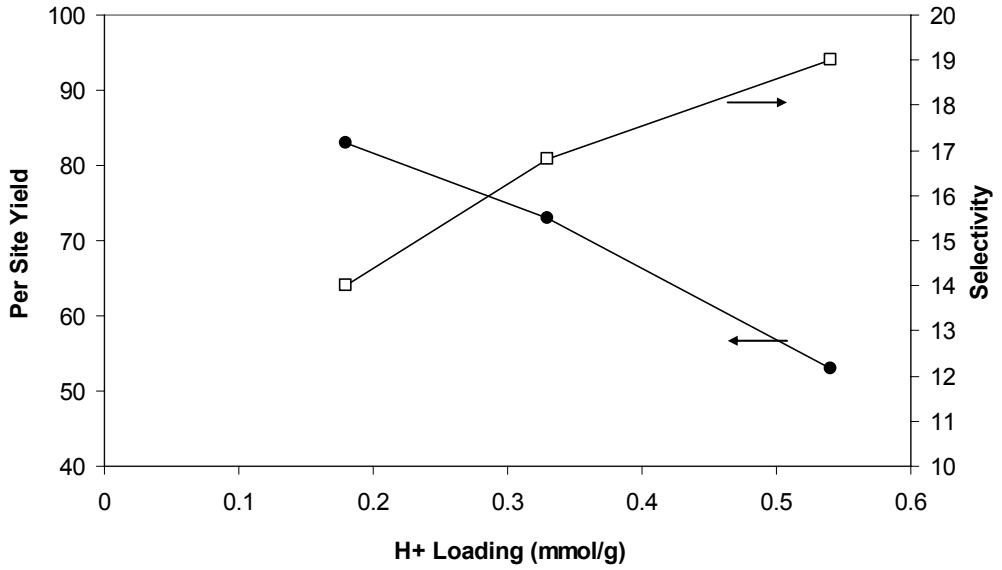



**Figure 2.7.** Effect of site density on total per-site yield (●) and selectivity (*p,p*'/*o,p*' ratio, □) of **SBA-at-p** catalysts in bisphenol A synthesis

Homogeneous analogues of **SBA-a** and **SBA-at-p** were also tested (Table 2.2, Entries 6–8). 1-Propanesulfonic acid and 3-hydroxy-1-propanesulfonic acid gave nearly identical catalytic results. This suggests that the adjacent hydroxyl group in **SBA-a** is not responsible for the poor catalytic activity of this material. The selectivity of these catalysts was similar to that of **SBA-a**, at a somewhat higher yield. 3-Mercapto-1-propanesulfonic acid also showed higher activity compared to its heterogeneous counterpart **SBA-at-p**, but somewhat lower selectivity. The reduced activity of the heterogeneous catalysts may be due to mass-transfer limitations, as the reagents must diffuse into the 1-D cylindrical pores of the SBA-15.

To investigate the possibility that the catalytic activity of **SBA-at-p** was due to surface species leaching into solution, a hot-filtration test was performed. The solid

catalyst was removed after 8 hours, and no additional conversion was detected after an additional 9 or 16 hours at 90°C (see Figure 2.8). This result, along with the observation that unfunctionalized SBA-15 exhibits no catalytic activity towards bisphenol A, suggests that the catalytic activity of **SBA-at-p** is entirely due to its surface-bound acid/thiol pairs, rather than to the silica support or leached organic species.

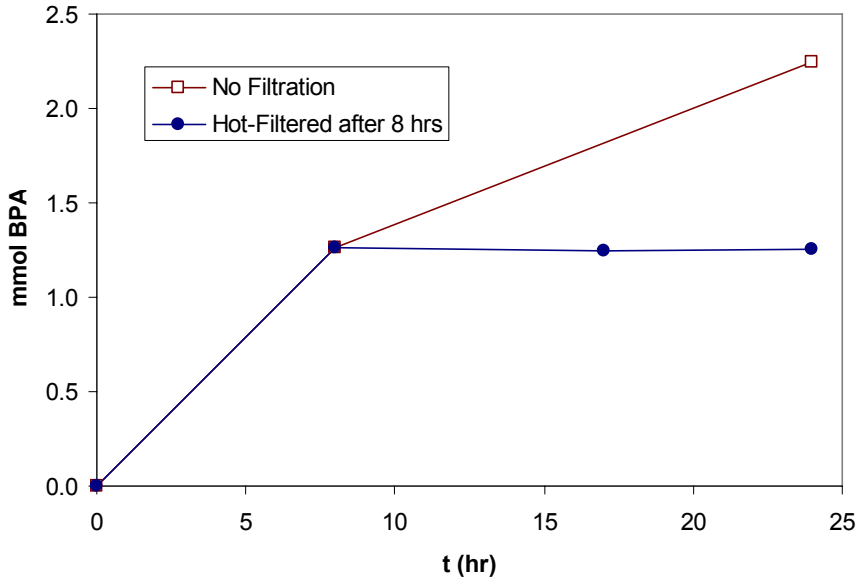



**Figure 2.8.** Hot-filtration test results with **SBA-at-p**. Reaction conditions: 0.02 mmol $H^+$, 6 mmol acetone, 24 mmol phenol, 90°C. Catalyst was removed after 8 hours and filtrate was heated at 90°C for another 16 hours.

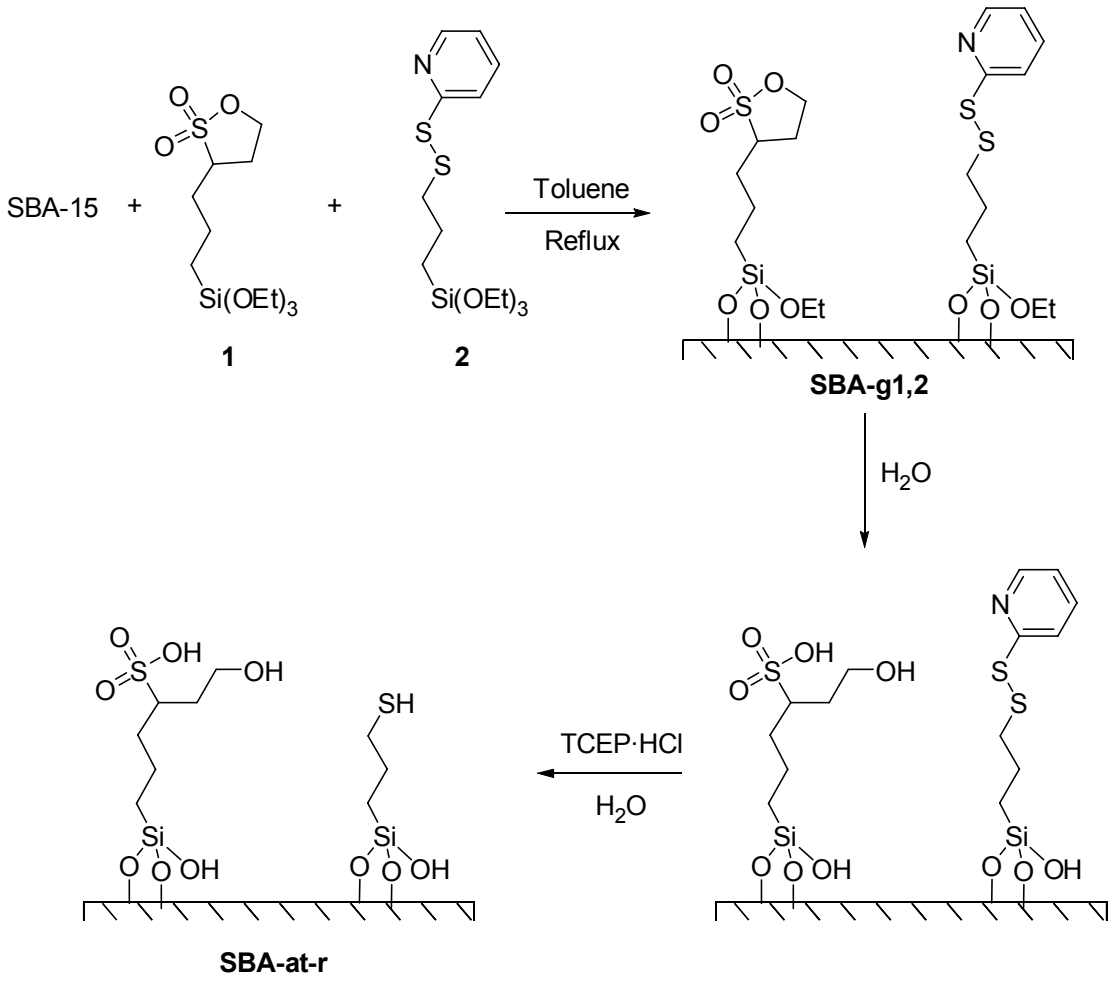
**Randomly-Distributed Acid/Thiol Catalysts.** To test the effect of site organization, a catalyst containing randomly-distributed alkylsulfonic acid and propylthiol groups was synthesized via the simultaneous grafting of two organosilanes. Silane **1** was again used as a source of alkylsulfonic acid groups since it allows for a

nonoxidative synthesis. Since sultone rings can be opened by thiols at elevated temperatures, silane **2** was used as a source of disulfide-protected thiols. **1** and **2** were grafted onto SBA-15, followed by sultone hydrolysis and disulfide reduction (Scheme 2.4). The resulting randomly-distributed acid/thiol material is denoted **SBA-at-r**. Due to the differential grafting efficiency of the two silanes, the acid/thiol ratio could not be controlled precisely at 1:1; elemental analysis showed that there were in fact nearly 5 times more thiol groups than acid groups. **SBA-at-r** exhibited good selectivity in the synthesis of BPA, but with a nearly threefold reduction in per-site yield compared to the paired material **SBA-at-p** (Table 2.3, Entries 2–3).

| Entry | Heterogeneous Catalyst | Bisphenol Product | PSY[a] | Isomer Ratio[b] |
|---|---|---|---|---|
| 1 | SBA-A | A | 3.1 | 1.8 |
| 2 | SBA-AT-p | A | 83 | 14 |
| 3 | SBA-AT-r | A | 29 | 22 |
| 4 | SBA-A | Z | 0.3 | N/A[c] |
| 5 | SBA-AT-p | Z | 14 | 14 |
| 6 | SBA-AT-r | Z | 1.0 | N/A[c] |
| 7 | SBA-A | AF | 8.4 | N/A[c] |
| 8 | SBA-AT-p | AF | 15 | N/A[c] |

**Table 2.3.** Catalysis data for heterogeneous catalysts in synthesis of various bisphenols. Reaction conditions: 0.02 mmol $H^+$, 6 mmol ketone, 24 mmol phenol, 90°C, 24 hrs. Catalyst loading ~ 0.2 mmol $H^+$/g

[a] Per-site yield (mmol total product / mmol $H^+$)
[b] *p,p*'/*o,p*'
[c] *o,p*' isomer below detection limit




**Scheme 2.4.** Simultaneous grafting of silanes **1** and **2** to form randomly-bifunctionalized sultone/disulfide material **SBA-g1,2** and subsequent deprotection to form random acid/thiol material **SBA-at-r**

To investigate the substrate scope of the heterogeneous catalysts, the ketone was varied to produce other bisphenol products. Using the more sterically hindered cyclohexanone as reactant (to produce bisphenol Z), the effect of pairing is even more pronounced (Table 2.3, Entries 4–6). Thiol-free **SBA-a** gives low activity, the randomly-bifunctionalized material gives only a small improvement, and the acid/thiol-paired catalyst has a much higher activity (14 times higher than for the randomly-distributed

catalyst). When hexafluoroacetone is used (to produce bisphenol AF), the effect of thiol promotion is greatly reduced, probably due to the greater reactivity of the fluorinated reactant (Table 2.3, Entries 7–8). The increase in activity from **SBA-a** to **SBA-at-p** is less than twofold. Thus we conclude that the improvement in catalytic activity gained by pairing acid and thiol groups varies for different condensation reactions, and is more pronounced for less-reactive ketones.

**Varying Acid/Thiol Distance.** The acid/thiol distance was varied to investigate what effects separation distance has on activity and selectivity in catalyzing the synthesis of BPA. By opening the sultone ring with the monosodium salt of a dithiol, a thiol group is tethered to the acid via a sulfide linkage. In this way it is possible to tune both the length of the acid/thiol spacer and the electronic properties of the thiol (*i.e.*, alkyl vs. phenyl vs. benzyl; see Scheme 2.3). $^{13}C$ CP/MAS NMR showed quantitative conversion of the sultone moieties to sulfonic acids for these products (Figures 2.11, 2.12). Elemental analysis revealed sulfur loadings to be approximately three times the acid loading (Table 2.1, Entries 7, 13, 14), corresponding to the expected 1:1 acid/thiol ratio, and the surface area, pore size, and long-range ordering were maintained. The resulting materials with various alkyl and aryl spacers (denoted **SBA-at-s1** through **SBA-at-s9**) were used to catalyze the BPA reaction (Table 2.4). Catalysts **SBA-at-s1**, **-s2**, and **-s3** (ring-opened by 1,2-ethanedithiol, 1,3-propanedithiol, and 1,6-hexanedithiol, respectively) showed reduced activity and selectivity compared to **SBA-at-p**, where the acid and thiol groups are in closer proximity (Table 2.4, Entries 1–4). The activity decrease with distance is quite dramatic, as increasing the length of the acid/thiol spacer by three atoms (**SBA-at-s1** vs. **SBA-at-p**) decreases the yield by a factor of two.

Additional increase in the spacer length by one atom (**SBA-at-s2**) reduces yield by another factor of two, down to a level similar to that of **SBA-at-r** (Table 2.4, Entry 3). **SBA-at-s3** exhibits similar activity to **SBA-at-s2** (Table 2.4, Entry 4).

| Entry | Heterogeneous Catalyst | Spacer Type | PSY[a] | Isomer Ratio[b] |
|---|---|---|---|---|
| 1 | SBA-at-p | none | 83 | 14 |
| 2 | SBA-at-s1 | alkyl, *n* =2 | 42 | 12 |
| 3 | SBA-at-s2 | alkyl, *n* =3 | 20 | 6.5 |
| 4 | SBA-at-s3 | alkyl, *n* =6 | 22 | 6.8 |
| 5 | SBA-at-s4 | aryl, *m* =0, *ortho* | 5.2 | 1.9 |
| 6 | SBA-at-s5 | aryl, *m* =0, *para* | 21 | 4.3 |
| 7 | SBA-at-s6 | aryl, *m* =1, *ortho* | 64 | 9.6 |
| 8 | SBA-at-s7 | aryl, *m* =1, *meta* | 37 | 7.9 |
| 9 | SBA-at-s8 | aryl, *m* =1, *para* | 47 | 7.9 |
| 10 | SBA-at-s9 | aryl, *durenyl* | 56 | 10 |

**Table 2.4.** Catalysis data in bisphenol A synthesis for heterogeneous acid/thiol spacer catalysts. Reaction conditions: 0.02 mmol $H^+$, 6 mmol acetone, 24 mmol phenol, 90°C, 24 hrs. Catalyst loading ~ 0.2 mmol $H^+$/g

[a] Per-site yield (mmol total product / mmol $H^+$)
[b] *p,p*'/*o,p*'

Catalysts **SBA-at-s4** and **-s5**, containing *ortho*- and *para*-phenylthiol groups, respectively, are both poor catalysts (Table 2.4, Entries 5–6). In particular, the *ortho* variant shows activity no better than the thiol-free material **SBA-a**. The poor activity of this material could be due to steric hindrance between the adjacent sulfide and thiol groups that could prevent the thiol from reacting with acetone. The reduced nucleophilicity of phenyl thiols vs. alkyl thiols is also likely responsible for some of the lower activity of these two catalysts.

Catalysts **SBA-at-s6**, **-s7**, and **-s8** (derived from *ortho*-, *meta*-, and *para*-xylyl dithiols, respectively) contain benzyl thiols. These materials generally show greater activity than those containing alkyl and phenyl spacers (Table 2.4, Entries 7–9). The catalyst **SBA-at-s6**, containing an *ortho*-benzyl spacer is the most active of all the spacer materials investigated here. We believe this is because the thiol is positioned such that it can point directly at the acid group and shortens the acid/thiol distance (see Figure 2.9).

A variant of the *ortho*-xylyl catalyst bearing two additional methyl groups was synthesized using the commercially available durene-$\alpha_1,\alpha_2$-dithiol. This catalyst (denoted **SBA-at-s9**; see Figure 2.10) exhibited slightly poorer activity than **SBA-AT-s6** (Table 2.4, Entry 10) with similar selectivity.

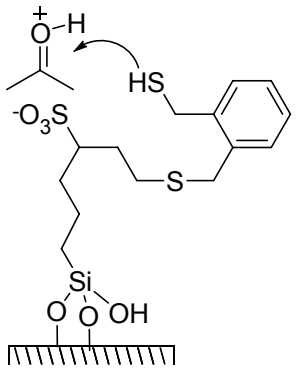
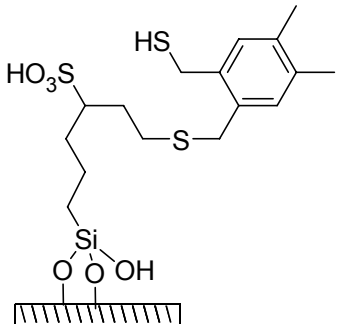



**Figure 2.9.** One possible conformation of **SBA-at-s6**, in which the thiol group is pointing directly toward the acid site, which allows for rapid attack of the thiol on the protonated acetone species.




**SBA-at-s9**

**Figure 2.10.** *Ortho*-durenyl spacer catalyst **SBA-at-s9**

## Conclusions

The distance between the acid and thiol group in a series of heterogeneous catalysts was shown to have a profound influence on the catalytic behavior in the synthesis of bisphenols. These data highlight the importance of the spatial positioning of functional groups in the development of heterogeneous catalysts, and also reveal how the nanoscale organization of catalytic surfaces can be tuned to provide a level of reactivity control unachievable through traditional random functionalization approaches.

In the case of acid and thiol groups, it was found that the catalytic activity for bisphenol synthesis is highest when the two groups are as close as possible. It may be that for other pairs of groups, such as mutually destructive ones, that the activity vs. distance behavior could be qualitatively different.

The sultone-containing silica **SBA-g1** was used here to generate acid/thiol pairs. By the reaction of this intermediate with other nucleophiles, it is possible to create a wide array of surface-paired materials.

## Experimental

**Materials.** Tetrahydrofuran (THF) and toluene were distilled over sodium immediately before use. All other solvents were analytical grade and used as received. 3-iodopropyltriethoxysilane was prepared from 3-chloropropyltriethoxysilane (Gelest) and sodium iodide according to the literature procedure.[38] Organosilane **2** was synthesized from 3-mercaptopropyltriethoxysilane and 2,2'-dipyridyldisulfide according to the literature procedure[14] followed by purification by chromatography on silica gel. Anhydrous sodium hydrosulfide was purchased from Alfa Aesar. Durene-α1,α2-dithiol was purchased from Acros Organics. All other chemicals were purchased from Aldrich and used as received. All reactions were performed under an argon atmosphere.

**3-(3-triethoxysilylpropyl)-[1,2]-oxathiolane 2,2-dioxide (Organosilane 1).** 1,3-propanesultone (2.7 g, 22 mmol) was dissolved in dry THF (50 mL). The solution was cooled to -78°C and *n*-butyllithium (1.6 M in hexanes, 14 mL, 22 mmol) was added slowly over 10 minutes. After stirring for another 10 minutes, 3-iodopropyltriethoxysilane (3.3 g, 10 mmol) was added slowly over 5 minutes. After stirring for 15 minutes, the temperature was raised to -60°C. After stirring for 9 hours, the temperature was raised to 0°C and water (50 mL) was added and the mixture was transferred to a separatory funnel. The aqueous layer was removed and the organic layer was washed with saturated NaCl solution (50 mL) and dried over anhydrous $MgSO_4$. After the solvent was removed *in vacuo*, chromatography on silica gel (3:2 hexanes/ethyl acetate, $R_f$ = 0.3) afforded **1** (0.61 g, 19%) as a colorless liquid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 4.38 (m, 2H), 3.73 (q, $J$ = 7 Hz, 6H), 3.48 (m, 1H), 2.58 (m, 1H), 2.13 (m, 1H), 1.70 (m, 2H), 1.46 (m, 2H), 1.13 (t, $J$ = 7 Hz, 9H), 0.61 (t, $J$ = 8 Hz, 2H). $^{13}$C NMR

(300 MHz, DMSO-$d_6$) δ 68.6, 58.4, 55.5, 31.6, 29.9, 20.6, 18.9, 10.3. Anal. Calcd. for $C_{12}H_{26}O_6SSi$: C, 44.15; H, 8.03; S, 9.82. Found: C, 43.05; H, 7.46; S, 9.85. HRMS (FAB+): *m/z* ($M + H^+$) ($C_{12}H_{27}SiSO_6$) Calcd, 327.1298; Found, 327.1302.

**SBA-g1 (Sultone-functionalized silica).** SBA-15 (1.0 g, synthesized according to the literature procedure[39]) was dried under flowing argon at 170°C for 4 hours. After cooling, dry toluene (50 mL) was added via syringe and the mixture was stirred vigorously to form a uniform suspension. An appropriate amount of **1** (typically ~ 0.7 mmol) 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 20 mL each). The solids were Soxhlet extracted with dichloromethane overnight, then dried under vacuum and stored under an argon atmosphere in a drybox until further use.

**SBA-a (Thiol-free sulfonic acid catalyst). SBA-g1** (0.5 g) was added to water (40 mL) and the resulting suspension was stirred at 40°C for 2 days. Then the solids were filtered, washed with water (3 x 30 mL), 0.5 N HCl (3 x 30 mL), and water (4 x 30 mL) and dried under high vacuum overnight.

**SBA-at-p (Acid/thiol-paired catalyst). SBA-g1** (0.5 g) was suspended in anhydrous DMF (15 mL). Anhydrous sodium hydrosulfide (86 mg, 1.5 mmol) was dissolved in anhydrous DMF (10 mL) and the resulting blue solution was added dropwise to the stirred silica suspension. After stirring for 24 hours at room temperature, the solids were filtered, washed with DMF (3 x 30 mL) and water (5 x 30 mL), and then suspended in 0.5 N HCl (30 mL) to acidify. After stirring for 3 hours the white solids were filtered and washed with 0.5 N HCl (3 x 30 mL) and water (5 x 30 mL) and dried under high vacuum

overnight. **SBA-as-p** was prepared with the same procedure, except that sodium methanesulfide was used in place of sodium hydrosulfide.

**SBA-at-r (Random acid/thiol catalyst).** SBA-15 (0.5 g) was grafted with **1** (0.16 g, 0.5 mmol) and **2** (0.17 g, 0.5 mmol) according to the procedure above for **SBA-g1**. The two organosilanes were added dropwise simultaneously. After Soxhlet extraction the solids were dried to afford **SBA-g1,2** as a pale beige solid. **SBA-g1,2** (0.5 g) was suspended in water (50 mL) and stirred at 40°C for 2 days. The solids were filtered, washed with water (2 x 30 mL) and 0.5 N HCl (3 x 30 mL), and suspended in an aqueous solution of tris(2-carboxyethyl)phosphine hydrochloride (0.015 M, 50 mL). This suspension was stirred at 55°C for 2 days, and then the solids were filtered, washed with water and methanol (4 x 30 mL each), and dried under high-vacuum overnight to yield **SBA-at-r** as a nearly white powder.

**SBA-at-s (Acid/thiol spacer catalysts).** Dithiol (15 mmol) was dissolved in anhydrous DMF (10 mL) and sodium hydride (60 wt% in mineral oil, 5 mmol) was added. This mixture was stirred until all solids had dissolved and then was added slowly to a suspension of **SBA-g1** (0.5g) in anhydrous DMF (10 mL). After stirring for 24 hours at room temperature, the solids were filtered, washed, and acidified as described for **SBA-at-p**.

**Acid Titration.** To the silica material to be analyzed (~ 30 mg) was added aqueous NaCl (2N, 4 mL) and the suspension was stirred for 24 hours. The solids were removed by filtration, washed with water (4 x 2 mL), and the combined filtrate was titrated with 0.01 N NaOH using phenol red as indicator.

**Catalytic Reaction—Condensation of Phenol and Ketone.** An amount of catalyst corresponding to 0.02 mmol $H^+$ (~ 100 mg) was added to a vial and dried under high vacuum at 80°C overnight. Phenol (2.2 g, 24 mmol) and ketone (6 mmol) were added and the vial was sealed under argon and stirred at 90°C for 24 hours. The catalyst was removed by filtration and washed with acetonitrile to a total filtrate volume of 25 mL, and the products were quantified by HPLC. Per-site yield was calculated on the basis of the number of acid sites present and selectivity was defined as the ratio of bisphenol isomers (*p,p*'/*o,p*').

**Acknowledgements**

This work was supported by a National Science Foundation Graduate Research Fellowship and by the Department of Energy.

# References


1. Phan, N. T. S.; et al. *Angew. Chem., Int. Ed. Engl.* **2006,** 45, 2209.
2. Motokura, K.; et al. *J. Am. Chem. Soc.* **2005,** 127, (27), 9674.
3. Helms, B.; et al. *Angew. Chem., Int. Ed. Engl.* **2005,** 44, (39), 6384.
4. Gelman, F.; Blum, J.; Avnir, D. *Angew. Chem., Int. Ed. Engl.* **2001,** 40, (19), 3647.
5. Huh, S.; et al. *Angew. Chem., Int. Ed. Engl.* **2005,** 44, (12), 1826.
6. Zeidan, R. K.; Hwang, S. J.; Davis, M. E. *Angew. Chem., Int. Ed. Engl.* **2006,** 45, (38), 6332.
7. Zeidan, R. K.; Davis, M. E. *J. Catal.* **2007,** 247, (2), 379.
8. Miyabe, H.; et al. *Synthesis* **2006**, (19), 3295.
9. Katz, A.; et al. *J. Am. Chem. Soc.* **2006,** 128, (11), 3737.
10. Kwong, C. K. W.; et al. *Chem. Eur. J.* **2007,** 13, (8), 2369.
11. Katz, A.; Davis, M. E. *Nature* **2000,** 403, (6767), 286.
12. Wulff, G.; Heide, B.; Helfmeier, G. *J. Am. Chem. Soc.* **1986,** 108, (5), 1089.
13. Tao, Y. T.; Ho, Y. H. *J. Chem. Soc., Chem. Commun.* **1988**, (6), 417.
14. Dufaud, V.; Davis, M. E. *J. Am. Chem. Soc.* **2003,** 125, (31), 9403.
15. Mbaraka, I. K.; Shanks, B. H. *J. Catal.* **2006,** 244, (1), 78.
16. Bass, J. D.; Katz, A. *Chem. Mater.* **2006,** 18, (6), 1611.
17. McNutt, B. W.; Gammill, B. B. U.S. Patent 3,394,089, 1968.
18. Wieland, S.; Panster, P. *Heterogeneous Catalysis And Fine Chemicals IV* **1997,** 108, 67.

19. Zhao, D. Y.; et al. *Science* **1998,** 279, (5350), 548.

20. Zeidan, R. K.; Dufaud, V.; Davis, M. E. *J. Catal.* **2006,** 239, (2), 299.

21. Margolese, D.; et al. *Chem. Mater.* **2000,** 12, (8), 2448.

22. Das, D.; Lee, J. F.; Cheng, S. F. *J. Catal.* **2004,** 223, (1), 152.

23. Feng, Y. F.; et al. *J. Phys. Chem. B* **2006,** 110, (29), 14142.

24. Mbaraka, I. K.; et al. *J. Catal.* **2003,** 219, (2), 329.

25. Van Rhijn, W. M.; et al. *J. Chem. Soc., Chem. Commun.* **1998**, (3), 317.

26. Lim, M. H.; Blanford, C. F.; Stein, A. *Chem. Mater.* **1998,** 10, (2), 467.

27. Helberger, J. H.; Manecke, G.; Heyden, R. *Liebigs Ann. Chem.* **1949,** 565, 22.

28. Preston, A. J.; Gallucci, J. C.; Paquette, L. A. *J. Org. Chem.* **2006,** 71, (17), 6573.

29. King, J. F.; Khemani, K. C. *Can. J. Chem.* **1989,** 67, (12), 2162.

30. Cole, A. C.; et al. *J. Am. Chem. Soc.* **2002,** 124, (21), 5962.

31. Paetzold, E.; Kinting, A.; Oehme, G. *J. Prakt. Chem.* **1987,** 329, (4), 725.

32. King, J. F.; Skonieczny, S.; Poole, G. A. *Can. J. Chem.* **1983,** 61, (2), 235.

33. Suga, K.; et al. *Aust. J. Chem.* **1968,** 21, (9), 2333.

34. Erman, W. F.; Kretschmar, H. C. *J. Org. Chem.* **1961,** 26, (12), 4841.

35. Zeid, I.; Ismail, I. *Liebigs Ann. Chem.* **1974**, 667.

36. Durst, T.; Du Manoir, J. *Can. J. Chem.* **1969,** 47, (7), 1230.

37. Shenderovich, I. G.; et al. *J. P. Chem. B* **2003,** 107, (43), 11924.

38. Matsura, V.; et al. *J. Mat. Chem.* **2004,** 14, (20), 3026.

39. Zhao, D. Y., Huo, Q.; Feng, J.; Chmelka, B.; Stucky, G. *J. Am. Chem. Soc.* **1998,** 120, (24), 6024.

**Additional Figures**—Selected NMR Spectra

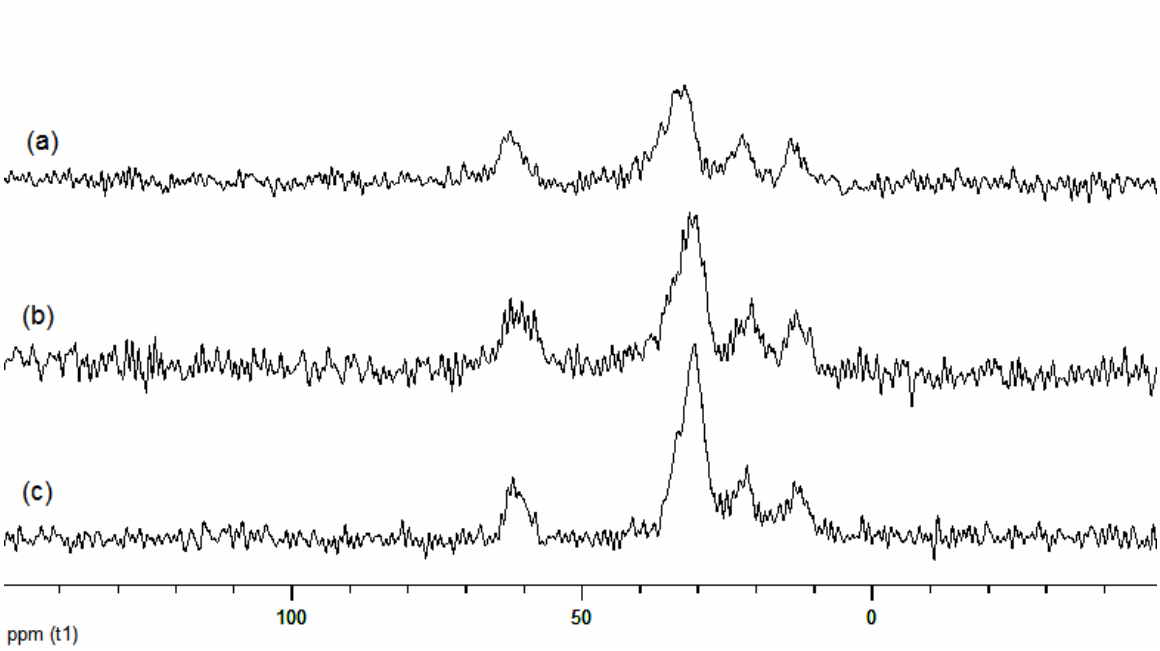



**Figure 2.11.** $^{13}C\{^{1}H\}$ CP/MAS NMR spectra of alkyl spacer materials. (a) **SBA-at-s1** (b) **SBA-at-s2** (c) **SBA-at-s3**

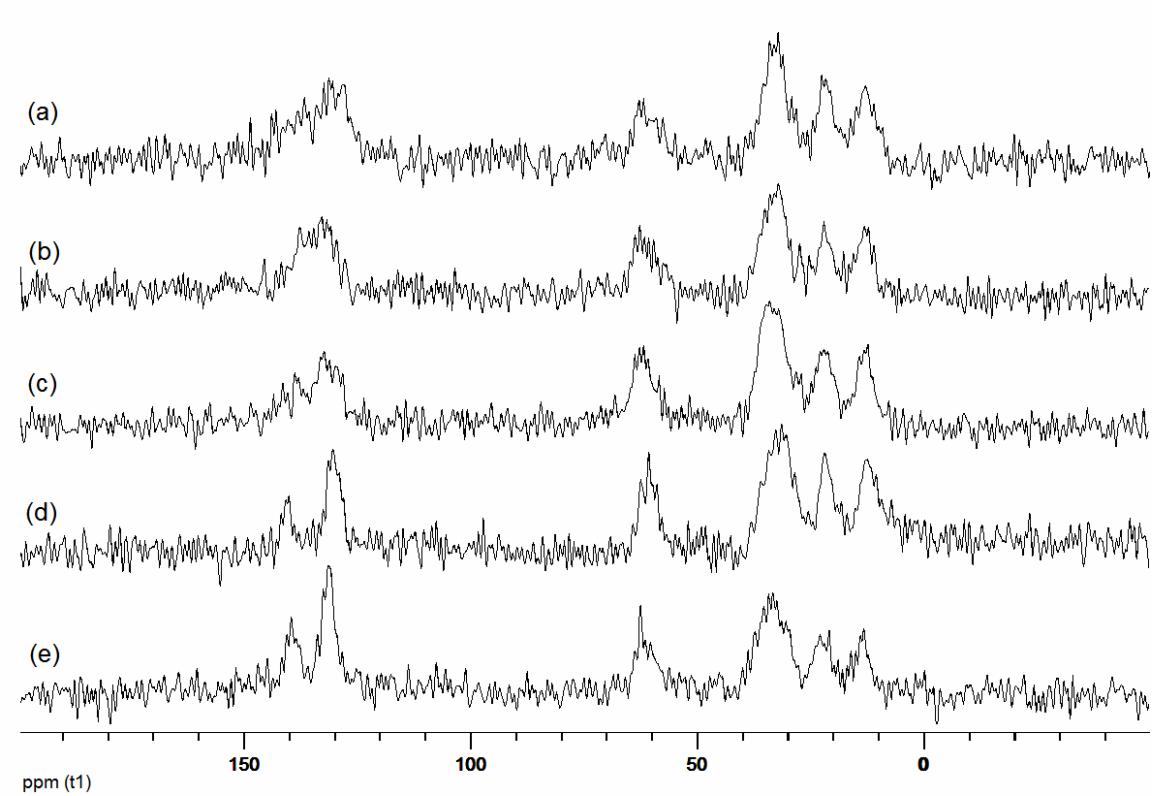



**Figure 2.12.** $^{13}C\{^{1}H\}$ CP/MAS NMR spectra of aryl spacer materials. (a) **SBA-at-s4** (b) **SBA-at-s5** (c) **SBA-at-s6** (d) **SBA-at-s7** (e) **SBA-at-s8**

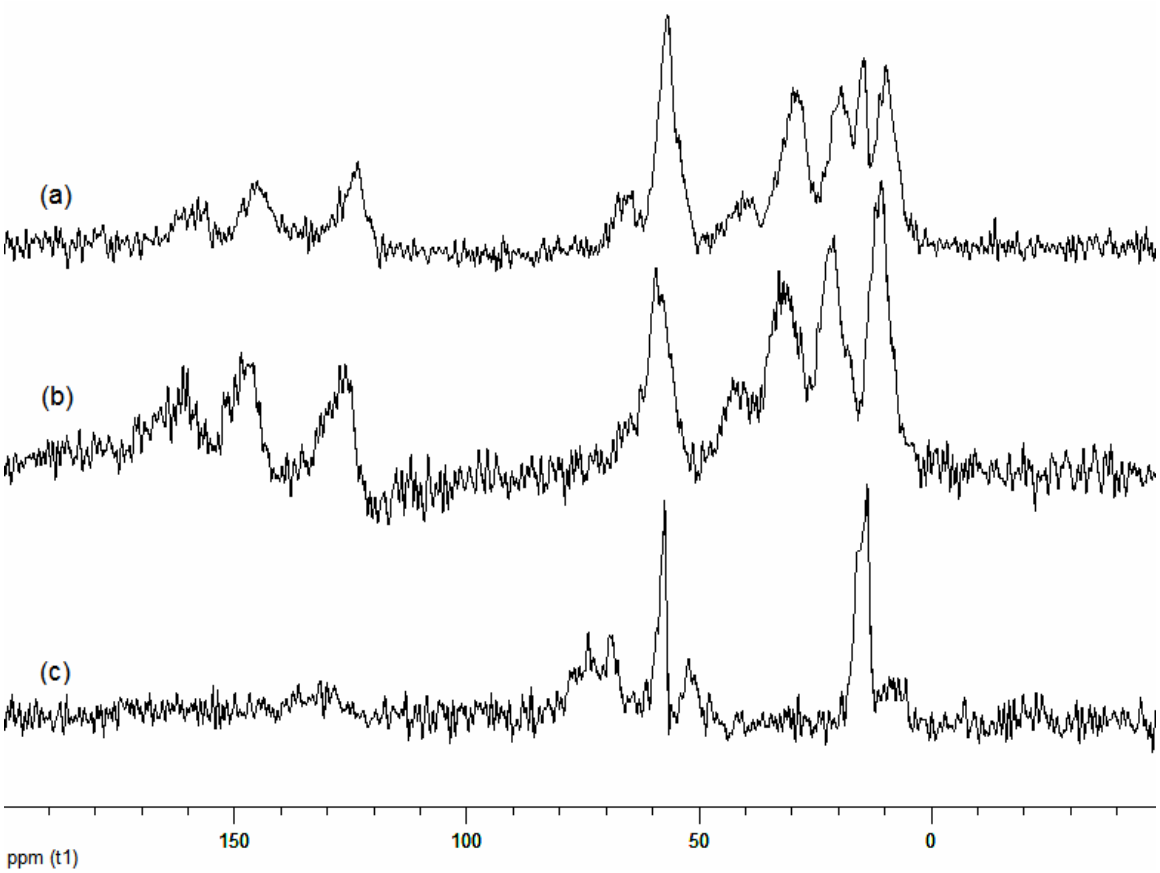



**Figure 2.13.** $^{13}C\{^{1}H\}$ CP/MAS NMR spectra of randomly-grafted materials

(a) **SBA-g1,2**

(b) after hydrolysis

(c) after disulfide reduction (**SBA-AT-r**). The disappearance of the peak at 67 ppm is due to hydrolysis of the sultone ring, and the disappearance of the aromatic peaks (125–155 ppm) indicates complete reduction of the disulfide.

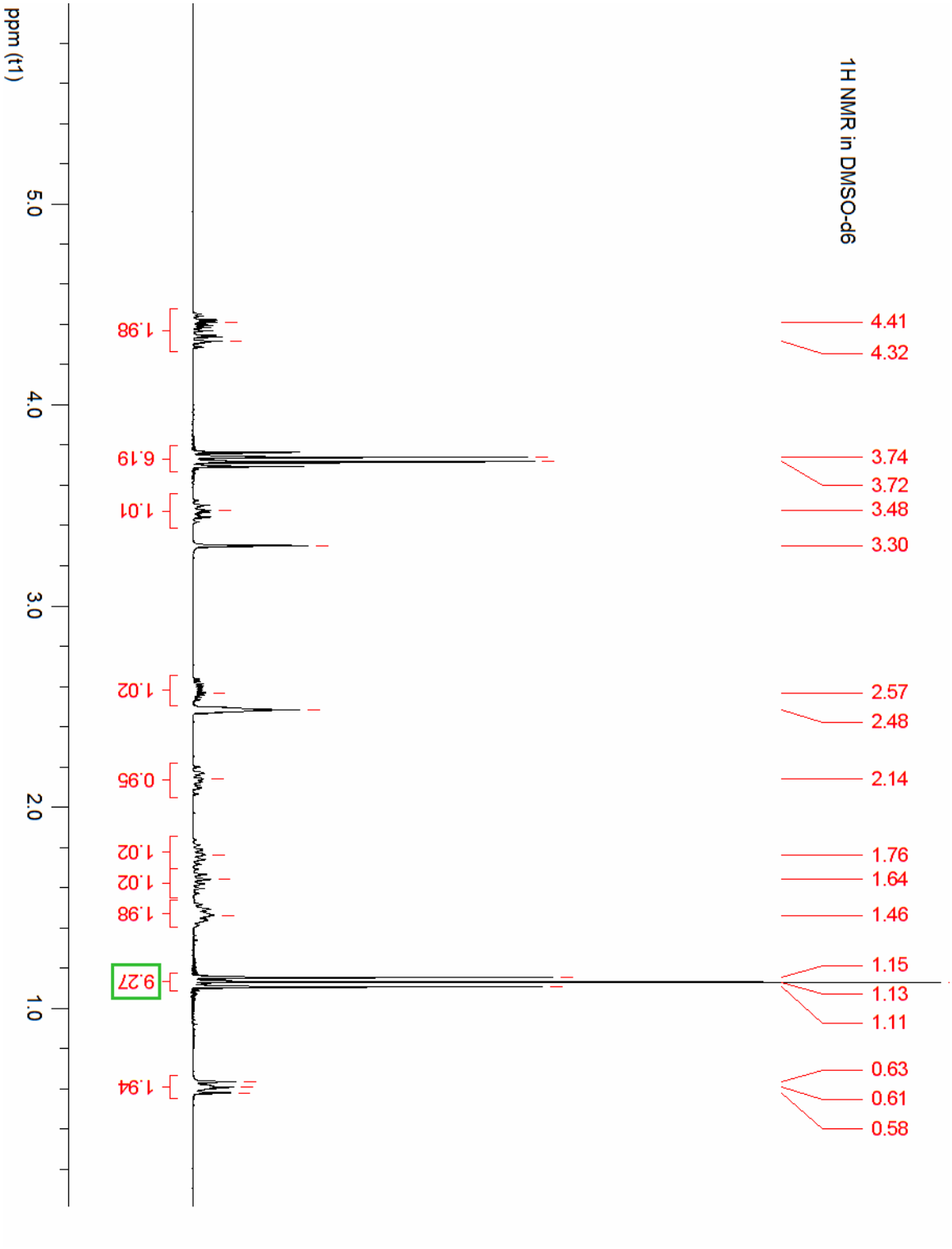



**Figure 2.14.** $^{1}$H NMR spectrum of silane **1**. Peaks at 3.30 and 2.48 ppm correspond to $H_2O$ and DMSO, respectively.

*Chapter 3*

# THIOL/ARYLSULFONIC ACID-PAIRED CATALYSTS FOR THE SYNTHESIS OF BISPHENOLS

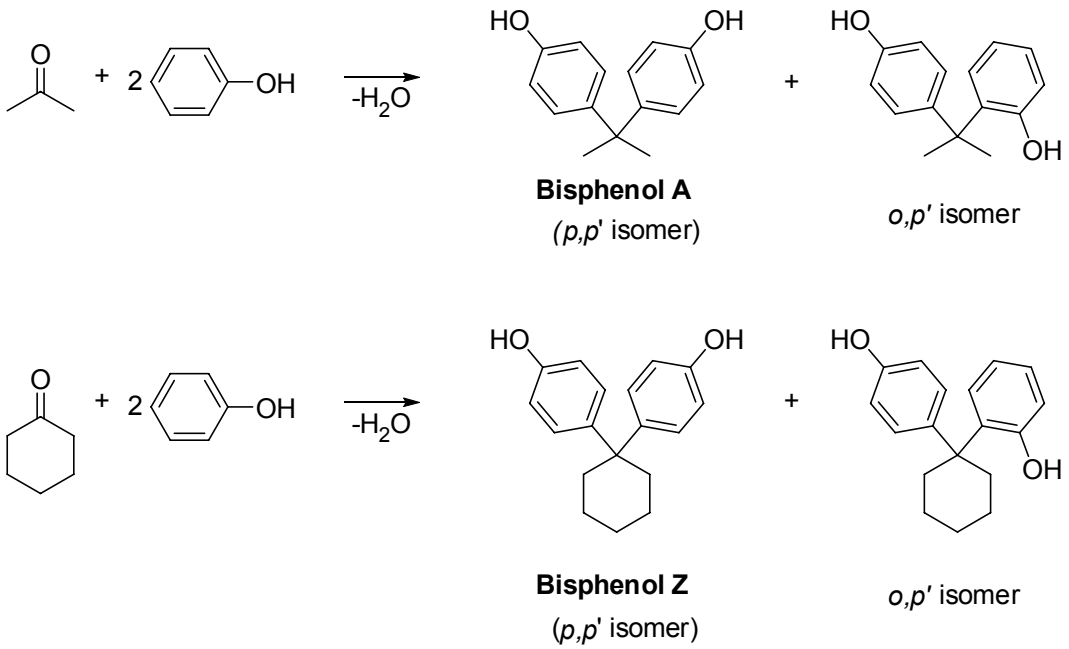
**Abstract**

We recently demonstrated that mesoporous silica materials functionalized with pairs of alkylsulfonic acid and thiol groups are excellent catalysts for the synthesis of bisphenols from the condensation of phenol and various ketones, with activity and selectivity highly dependent on the thiol/acid distance. Here, we report the synthesis and catalytic properties of a mesoporous silica bearing thiol groups paired with stronger arylsulfonic acid groups. This catalyst was generated by grafting a bissilane precursor molecule containing both a disulfide and a sulfonate ester bond onto SBA-15, followed by simultaneous disulfide reduction and sulfonate ester hydrolysis. The resulting catalyst significantly outperformed the alkylsulfonic acid/thiol paired catalyst in bisphenol A and Z synthesis, while maintaining a very high selectivity to the desired isomer *p,p*' isomer. The paired catalyst had similar activity to a randomly-bifunctionalized arylsulfonic acid/thiol catalyst in the bisphenol A reaction, but exhibited greater activity and selectivity than the randomly-bifunctionalized catalyst in the bisphenol Z reaction.

**Introduction**

Bisphenols, such as bisphenol A and bisphenol Z, are important industrial feedstocks, especially as monomers in polycarbonate polymers and resins. They are synthesized in the acid-catalyzed condensation between a ketone and phenol, yielding the desired *p,p*' isomer and a byproduct, the *o,p*' isomer (Scheme 3.1). The addition of thiols as a cocatalyst is known to improve both the rate of reaction and the selectivity to the desired isomer.

Mineral acids can be used to catalyze the bisphenol condensation reaction, but solid acid catalysts such as polymeric ion-exchange resins are typically used for commercial bisphenol production due to their non-corrosive nature and reusability. Thiols can be added either as a homogeneous feed additive or as a tethered surface species (thus avoiding product contamination with extremely malodorous thiols). Several solid catalysts bearing both acid and thiol groups attached to a solid support have been reported. Thiols have been covalently tethered to sulfonic acid-containing resins,[1, 2] and polysiloxane catalysts containing randomly alkylsulfonic acid and alkylthiol groups have also been reported to have good catalytic activity for bisphenol A.[3] Zeidan et al.[4] functionalized a mesoporous silica (SBA-15) with arylsulfonic acid and alkylthiol groups and found that the resulting catalyst exhibited good performance only when the acid and thiol groups were in close proximity on the surface (a physical mixture of acid- and thiol-containing materials gave poor results). This observation led us to design SBA-15 catalysts functionalized with discrete alkylsulfonic acid/thiol pairs, and the activity and selectivity of these catalysts was shown to increase markedly as the acid/thiol distance decreased.[5]

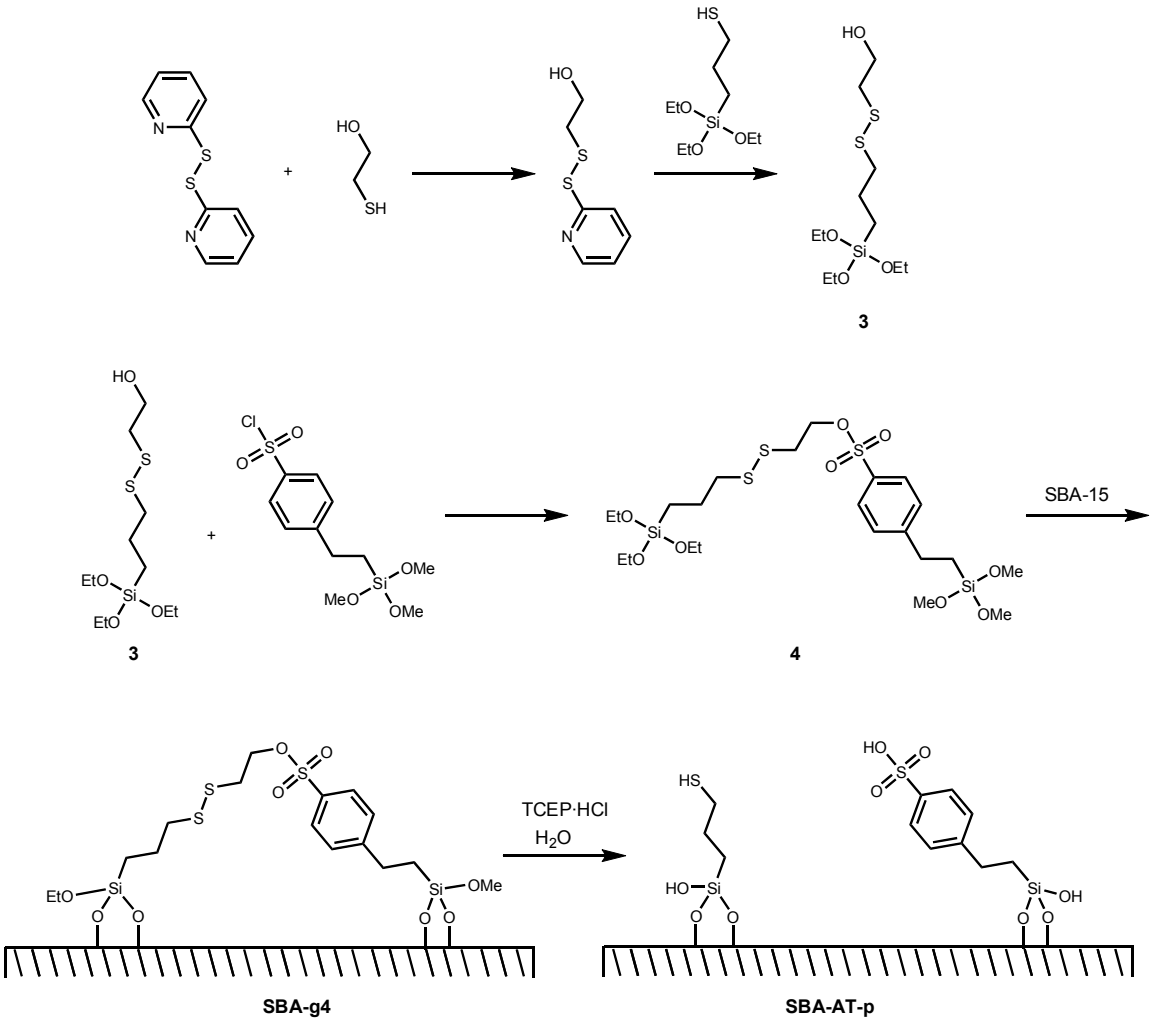



**Scheme 3.1.** Synthesis of bisphenol A (top) and bisphenol Z (bottom) from phenol and either acetone or cyclohexanone

As a further improvement upon these acid/thiol catalysts, we sought to increase the catalyst activity by increasing the strength of the acid sites. Aromatic sulfonic acids are stronger than alkylsulfonic acids, due to the delocalized pi system of the aryl ring which stabilizes the negative charge of the deprotonated acid. The difference in acidity between aryl- and alkylsulfonic acid-functionalized SBA-15 has been estimated at about 0.2 $pK_a$ units.[6]

To generate arylsulfonic acid/thiol pairs, the bissilane precursor **4** was synthesized, containing both a disulfide group and an aryl sulfonate ester separated by two carbon atoms (Scheme 3.2). After this precursor is grafted onto the silica surface, reduction of the disulfide bond and hydrolysis of the sulfonate ester affords a thiol and arylsulfonic acid group, respectively, in close proximity on the silica surface. This

material was used to catalyze the condensation between phenol and either acetone or cyclohexanone.




**Scheme 3.2.** Synthesis of disulfide silane **3** (top) and bissilane **4** (middle) and the grafting of **4** onto SBA-15 to generate disulfide/sulfonate ester-functionalized silica **SBA-g4** (bottom), the mercaptoethanol linker of which is cleaved to generate the acid/thiol-paired material **SBA-AT-p**

**Results and Discussion**

SBA-15 was functionalized with bissilane **4** (the synthesis of which is summarized in Scheme 3.2) by grafting in refluxing toluene. The resulting material is denoted **SBA-g4**. The loading was deliberately kept very low so that the effect of pairing could be seen, and the loading used was ~ 0.2 mmol/g (the same loading as our previously reported alkylsulfonic acid/thiol paired catalyst).[5] SBA-15 was chosen as a support because of its high surface area, regular pore structure, and ease of functionalization.

**SBA-g4** was characterized by $^{29}Si\{^{1}H\}$ and $^{13}C\{^{1}H\}$ cross-polarization/magic-angle spinning (CP/MAS) NMR. The tertiary silicon peaks in the $^{29}Si$ CP/MAS spectrum confirm the presence of covalently bonded organic groups (Figure 3.1, top). $T^1$, $T^2$, and $T^3$ peaks can be seen, corresponding to organosilanes grafted to the surface at one, two, and three points, respectively. Of these three peaks, the largest is $T^2$, indicating that most of the grafted silanes are covalently bonded to the surface at two points, as shown in Scheme 3.2. Because **4** contains two trialkoxysilane groups, it is possible that one end could graft to the silica surface leaving the other end free. This would be evidenced by a $T^0$ peak in the $^{29}Si$ spectrum at -41 ppm, but since no such peak is seen, it appears that nearly every precursor molecule is grafted to the surface at both ends. The $^{13}C$ CP/MAS spectrum of the grafted molecule corresponds exactly to the solution-phase spectrum of **4**, confirming that the molecule remains intact upon grafting (see Figure 3.2).

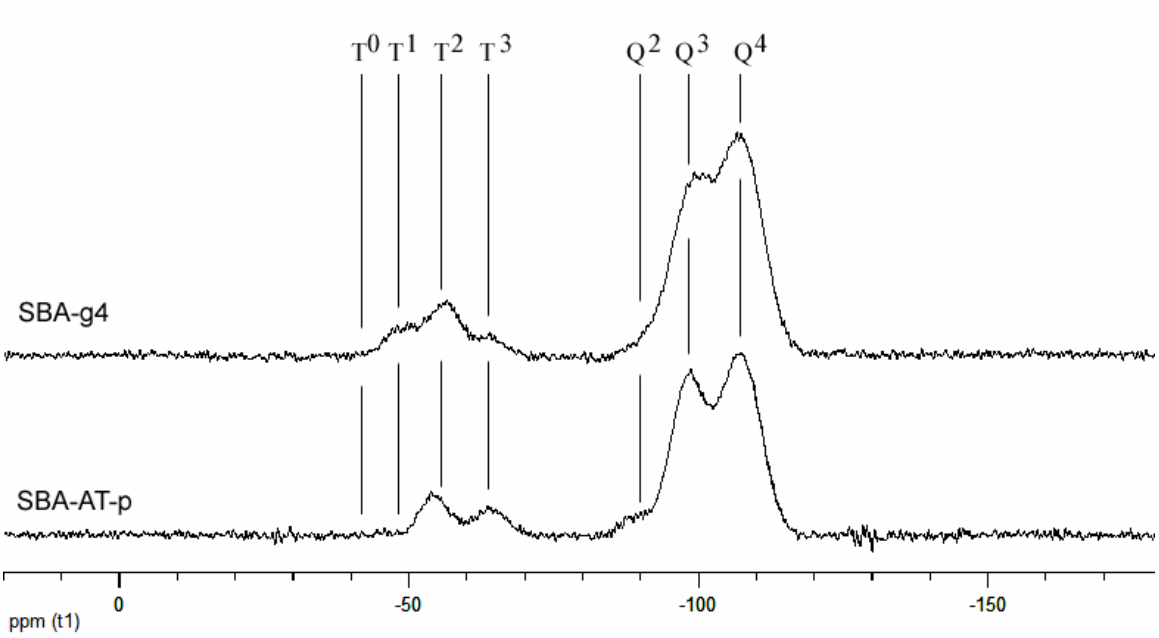



**Figure 3.1.** The $^{29}Si\{^{1}H\}$ CP/MAS spectrum of **SBA-g4** (top) shows $T^1$, $T^2$, and $T^3$ peaks corresponding to silanes covalently bonded to the surface at one, two, and three points, respectively. The absence of a $T^0$ peak at -41 ppm indicates that every grafted bissilane is attached to the surface at both ends. Following the cleavage of the mercaptoalcohol linker to form **SBA-AT-p** (bottom) the $T^3$ peak is larger, the $T^2$ peak is shifted slightly downfield, and the $T^1$ peak is nearly absent.

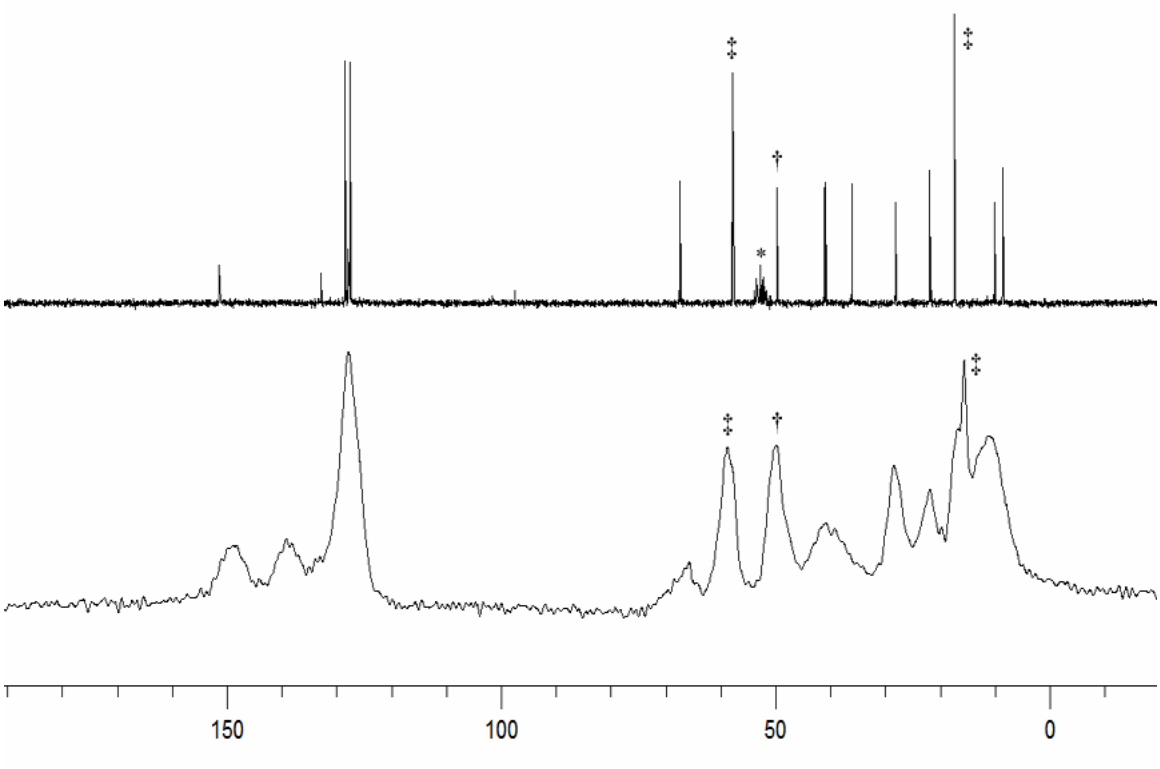



**Figure 3.2.** The $^{13}C$ NMR spectrum of bissilane **4** (top) and $^{13}C\{^{1}H\}$ CP/MAS spectrum of **SBA-g4** (bottom) confirm that the disulfide/sulfonate ester structure remains intact following the grafting reaction.

* indicates solvent peak (DMSO-$d_6$)
‡ indicates ethoxysilyl peaks
† indicates methoxysilyl peaks

The deprotection of the thiols and sulfonic acids of **SBA-g4** was accomplished in one step using aqueous tris(2-carboxyethyl)phosphine hydrochloride (TCEP·HCl). The phosphine reduces the disulfide to a thiol[7] and the weakly acidic aqueous solution hydrolyzes the sulfonate ester to a sulfonic acid. The mercaptoalcohol linker is then free to diffuse away from the acid/thiol site. The resulting deprotected material is denoted **SBA-AT-p** (for Acid/Thiol-paired; capital letters are used here to distinguish these

arylsulfonic acid/thiol materials from the alkylsulfonic acid/thiol materials discussed in the previous chapter).

The $^{13}C$ CP/MAS spectrum of **SBA-AT-p** is shown in Figure 3.3b. The peaks corresponding to the mercaptoethanol linker (37 and 68 ppm) are absent, confirming that the deprotection step is complete. The residual alkoxy peaks are also absent, as these groups are also hydrolyzed during the aqueous reaction. The $^{29}Si$ CP/MAS spectrum (Figure 3.1, bottom) shows an increase in the $T^3$ signal and a decrease in the $T^1$ signal; thus the aqueous deprotection reaction appears to further condense the alkoxysilane moieties with the surface.*

Nitrogen adsorption/desorption was used to measure the surface area and pore size distribution of these mesoporous materials (see Table 3.1). The unfunctionalized SBA-15 has a surface area of 860 $m^2/g$. After being grafted with the large bissilane **4**, the surface area drops to 230 $m^2/g$, and the pore size decreases from 6.3 to 5.8 nm. After the mercaptoethanol linker is removed, the surface area increases to 428 $m^2/g$ and the pore diameter increases to 6.0 nm. Adsorption/desorption isotherms are shown in Figure 3.7 at the end of this chapter.

Acid content was measured by ion-exchange with NaCl, followed by titration of the HCl with NaOH. Thiol content was measured by reaction with Ellman's reagent followed by spectrophotometric quantification of the liberated 2-nitro-5-mercaptobenzoate. The acid/thiol ratio was nearly unity as expected (0.21 mmol/g acid, 0.19 mmol/g thiol), but the total loading was significantly lower than might be expected based on the amount of organosilane used in the grafting reaction (0.7 mmol **4**/g SBA-

* The same phenomenon was noted by Dufaud et al.[8] for a similar aqueous TCEP treatment of organic-functionalized SBA-15.

15). The grafting efficiency of **4** is thus much lower than 100%. It is also possible that the aqueous deprotection step leads to the loss of some grafted organic groups, leaving some of the acid and thiol groups without a paired counterpart. The catalyst characterization data are summarized in Table 3.1.

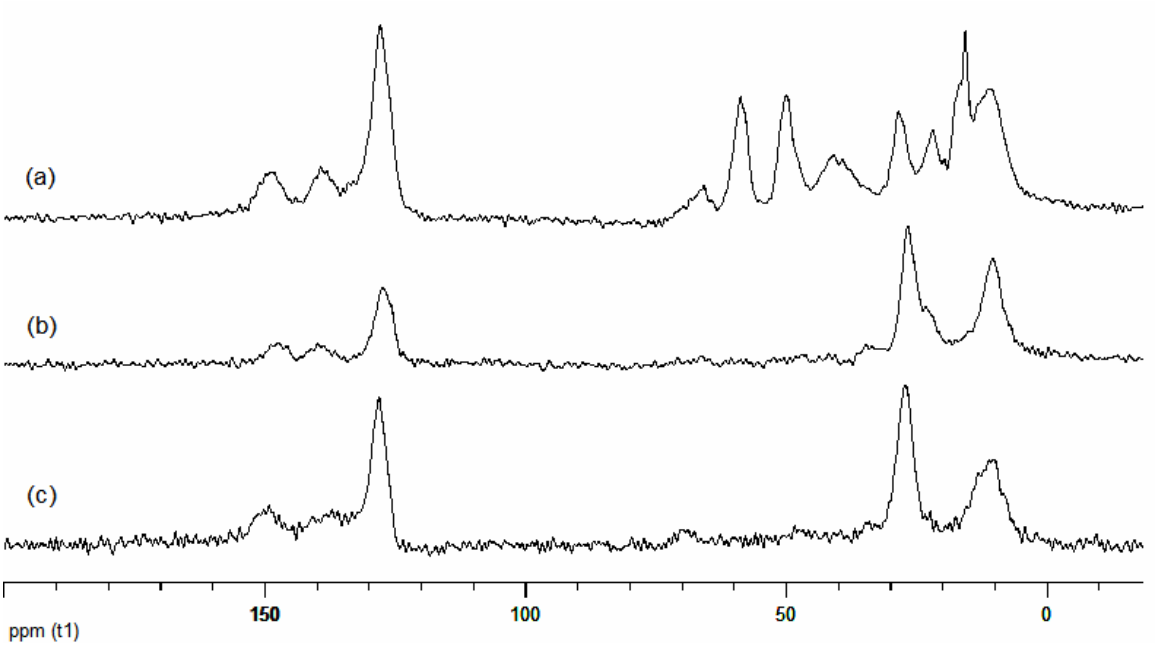
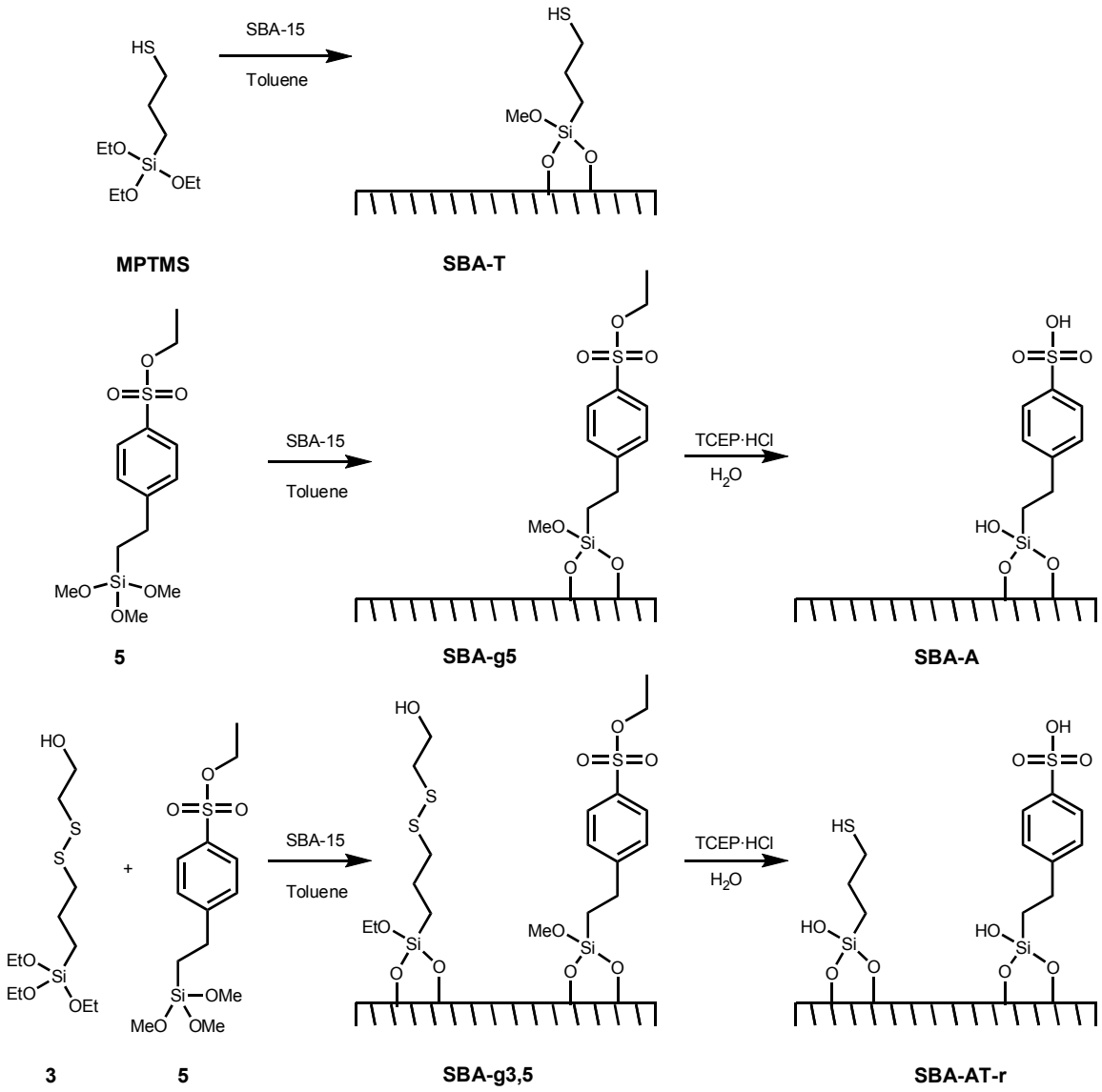



**Figure 3.3.** $^{13}C\{^{1}H\}$ CP/MAS NMR spectra of (a) **SBA-g4**; (b) **SBA-AT-p**; (c) **SBA-AT-r**

Catalysts containing only thiols, only arylsulfonic acids or randomly-distributed arylsulfonic acid and thiol groups were also synthesized (denoted **SBA-T**, **SBA-A**, and **SBA-AT-r**, respectively) according to Scheme 3.3. The acid groups were generated by sulfonate ester hydrolysis, using the same aqueous TCEP·HCl treatment employed for **SBA-AT-p**. The disulfide silane **3** was used as the source of thiol groups for **SBA-AT-r**, because a free thiol could attack the sulfonate ester during the grafting process. As expected, the $^{13}C$ NMR spectrum of **SBA-AT-r** is identical to that of **SBA-AT-p** (Figure

3.3c) because the same functional groups are present on the surface of both materials; the only difference is the spatial positioning of these groups.

With these randomly bifunctionalized materials, the thiol/acid ratio is not fixed at unity. Because previous results[4] suggest that a thiol/acid ratio greater than 1 leads to greater activity (per acid site) and selectivity, a randomly-bifunctionalized material with a thiol/acid ratio of 2 was also prepared (denoted **SBA-AT-r2**).




**Scheme 3.3.** (Top) Grafting 3-mercaptopropyltrimethoxysilane (MPTMS) onto SBA-15 generates **SBA-T**, containing only thiol sites. (Middle) Grafting sulfonate ester precursor **5** generates intermediate **SBA-g5**, which is hydrolyzed to **SBA-A**, containing only acid sites. (Bottom) Grafting both disulfide **3** and sulfonate ester **5** generates intermediate **SBA-g3,5** which is deprotected to form **SBA-AT-r**, containing randomly-distributed acid and thiol sites.

| Entry | Material | $S_{BET}$[a] ($m^2/g$) | $D_p$[b] (nm) | $H^+$[c] (mmol/g) | SH[d] (mmol/g) | $SH/H^+$ |
|---|---|---|---|---|---|---|
| 1 | **SBA-15** | 860 | 6.3 | | | |
| 2 | **SBA-g4** | 230 | 5.8 | | | |
| 3 | **SBA-A** | | | 0.20 | | |
| 4 | **SBA-AT-p** | 428 | 6.0 | 0.21 | 0.19 | 0.9 |
| 5 | **SBA-AT-r** | | | 0.13 | 0.12 | 0.9 |
| 6 | **SBA-AT-r2** | | | 0.06 | 0.13 | 2.2 |
| 7 | **SBA-T** | | | | 0.32 | |

**Table 3.1.** Catalyst characterization data

[a] Specific surface area, calculated using BET method
[b] Average pore diameter, calculated from adsorption isotherm using BJH method
[c] Acid loading, measured by ion exchange/titration
[d] Thiol loading, measured by reaction with Ellman's reagent

## Catalytic Reactions

The above materials were used to catalyze the synthesis of bisphenol A (see Table 3.2). **SBA-T** was almost completely inactive due to its lack of acid sites (Entry 1). **SBA-A** exhibited some catalytic activity, but very low selectivity due to its lack of thiol sites (Entry 2). When a physical mixture of these two catalysts was employed (Entry 3), the activity and selectivity improved only slightly beyond that for **SBA-A** alone, because the acid and thiol groups are spatially isolated and unable to interact except at the outer surfaces of the particles. When a homogeneous acid, *para*-toluenesulfonic acid (pTSA) was used, the activity was very close to that of **SBA-A**, albeit with an even lower selectivity (Entry 4). When pTSA and **SBA-T** were used together (Entry 5) the activity and selectivity were improved somewhat, as the acid was able to enter the silica pores and interact with the surface-bound thiols. The catalysts containing both acid and thiol sites in close proximity on the same silica support exhibited very high activity (total yield of 113–133 per acid site; see Entries 6–8) and good selectivity to the desired *p*,*p*' isomer.

Among the heterogeneous acid/thiol catalysts, the randomly-bifunctionalized catalyst **SBA-AT-r2** with a 2:1 thiol/acid ratio (Entry 7) gave the highest catalytic activity, with a per-site yield of 133. The 1:1 thiol/acid materials exhibited very similar activity despite the difference in the spatial positioning of the acid and thiol groups. The paired catalyst was the most selective (isomer ratio of 19.3) but was no more active than the random 1:1 catalyst. Compared to the alkylsulfonic acid-containing catalysts **SBA-a** and **SBA-at-p** discussed in the previous chapter (Entries 9–10) it is clear that the greater acid strength of the arylsulfonic acid groups leads to greater overall activity without sacrificing selectivity.

| Entry | Catalyst(s) | Thiol/Acid Ratio | PER-SITE YIELD *p*,*p*' | *o*,*p*' | Total | Isomer Ratio |
|---|---|---|---|---|---|---|
| 1 | **SBA-T**[a] | | <0.1 | <0.1 | <0.2 | |
| 2 | **SBA-A** | | 23 | 11 | 34 | 2.1 |
| 3 | **SBA-A** + **SBA-T** | 1 | 28 | 11 | 39 | 2.6 |
| 4 | pTSA | | 21 | 13 | 34 | 1.6 |
| 5 | pTSA + **SBA-T** | 1 | 35 | 12 | 47 | 2.9 |
| 6 | **SBA-AT-r** | 1 | 106 | 7 | 113 | 15.2 |
| 7 | **SBA-AT-r2** | 2 | 125 | 8 | 133 | 15.6 |
| 8 | **SBA-AT-p** | 1 | 108 | 6 | 114 | 19.3 |
| 9 | **SBA-a**[b] | | 2 | 1.1 | 3.1 | 1.8 |
| 10 | **SBA-at-p**[b] | 1 | 78 | 5.6 | 83 | 14.0 |

**Table 3.2.** Catalytic data for bisphenol A synthesis. Reaction conditions: 0.02 mmol $H^+$, 6 mmol acetone, 24 mmol phenol, 90°C, 24 hr. Per-site yield calculated as mmol product/mmol $H^+$

[a] 0.02 mmol SH was used; per-site yield calculated on basis of thiol sites instead of acid sites.
[b] Data taken from Ref 5 (see previous chapter).

The heterogeneous acid/thiol catalysts were also tested in the condensation of cyclohexanone with phenol to form bisphenol Z. This reaction is slower and has been

previously shown to be more highly sensitive to acid/thiol positioning than the bisphenol A reaction.[5] The catalytic results are shown in Table 3.3.

| Entry | Catalyst(s) | Thiol/Acid Ratio | PER-SITE YIELD *p*,*p*' | *o*,*p*' | Total | Isomer Ratio |
|---|---|---|---|---|---|---|
| 1 | **SBA-T**[a] | | 0 | 0 | 0 | |
| 2 | **SBA-A** | | 8.1 | 3.8 | 11.9 | 2.1 |
| 3 | **SBA-A** + **SBA-T** | 1 | 7.9 | 3.6 | 11.4 | 2.2 |
| 4 | **SBA-A** + PrSH | 1 | 7.3 | 4.2 | 11.5 | 1.8 |
| 5 | pTSA | | 3.2 | 2.6 | 5.8 | 1.2 |
| 6 | pTSA + **SBA-T** | 1 | 4.5 | 3.0 | 7.5 | 1.5 |
| 7 | **SBA-AT-r** | 1 | 17 | 4.0 | 21 | 4.3 |
| 8 | **SBA-AT-p** | 1 | 27 | 2.0 | 29 | 13.6 |
| 9 | **SBA-a**[b] | | 0.3 | 0[c] | 0.3 | N/A[c] |
| 10 | **SBA-at-p**[b] | 1 | 13 | 0.9 | 14 | 14.3 |

**Table 3.3.** Catalytic data for bisphenol Z synthesis. Reaction conditions: 0.02 mmol $H^+$, 6 mmol cyclohexanone, 24 mmol phenol, 90°C, 24 hr. Per-site yield calculated as mmol product/mmol $H^+$

[a] 0.02 mmol SH was used; per-site yield calculated on basis of thiol sites instead of acid sites.
[b] Data taken from Ref 5 (see previous chapter).
[c] *o*,*p*' isomer below detection limit

The yield of bisphenol Z is 3–6 times lower than that of bisphenol A at the same reaction conditions due to the lower reactivity of the cyclohexanone reactant. **SBA-A** gives a per-site yield of only 11.9 (Entry 2) and no improvement is seen when a physical mixture of **SBA-A** and **SBA-T** is used (Entry 3). Notably, no cooperativity is seen when a homogeneous thiol is used in conjunction with **SBA-A** (Entry 4) and only a minor improvement is seen with the homogeneous acid catalyst when heterogeneous thiol is added (Entries 5–6). Only when the acid and thiol groups are both immobilized on the silica surface does cooperativity become evident. **SBA-AT-r** (Entry 7) has a yield (21) and selectivity (4.3) approximately twice that of **SBA-A**. Organizing the acid and thiol sites into pairs (Entry 8) further increases the yield to 29 and imparts a very high

selectivity (13.6). Compared to the alkylsulfonic acid-containing catalyst **SBA-at-p** (Entry 10) the arylsulfonic acid/thiol-paired catalyst **SBA-AT-p** is twice as active, while retaining the same high selectivity.

These data demonstrate that catalytic cooperativity in the synthesis of bisphenol Z is much more dependent on acid/thiol distance than for bisphenol A. Combining a homogeneous acid with a heterogeneous thiol (or vice versa) does not provide the necessary proximity for good catalytic activity because the homogeneous component is dispersed throughout the liquid phase. Immobilizing both the acid and thiol onto silica fixes the groups on the two-dimensional surface, leading to greater proximity and catalytic performance. Finally, organizing the acid and thiol groups into closely spaced surface pairs leads to a further improvement in activity and a dramatic increase in selectivity that is not seen in the bisphenol A reaction.

**Conclusions**

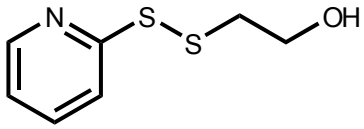
A mesoporous silica catalyst featuring arylsulfonic acid and alkylthiol groups organized in pairs was synthesized by grafting a bissilane precursor onto SBA-15, followed by linker cleavage. Compared to catalysts containing weaker alkylsulfonic acid sites, the arylsulfonic acid catalysts are more active while maintaining similar selectivities. In the bisphenol A reaction, the random and paired arylsulfonic acid/thiol catalysts exhibit similar catalytic performance, whereas in the slower bisphenol Z reaction the paired catalyst outperforms the randomly-distributed catalyst.

The acid/thiol distance in **SBA-AT-p** was set by the mercaptoethanol spacer used in the precursor. Other mercaptoalcohol linkers could be used, allowing for the acid/thiol

distance to be tuned. Replacing the alkyl spacer (which is somewhat flexible) with a more rigid one might also lead to a greater uniformity in acid/thiol distance. This fine-tuning of acid/thiol distance would be expected to be especially important for even slower bisphenol condensations, and could potentially catalyze the condensation of phenol with less-reactive ketones without requiring very high reaction temperatures, and potentially opening the door for the development of new bisphenol-based materials.

## Experimental

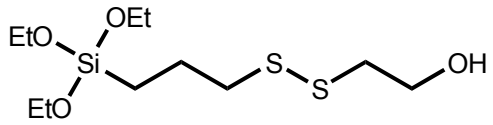
**Materials.** Dichloromethane, pentane, and toluene were dried by distillation over $CaH_2$, $CaSO_4$, and Na respectively and stored over activated 4 Å molecular sieves. All other solvents were analytical grade and used as received. Tris(2-carboxyethyl)phosphine hydrochloride was purchased from Alfa Aesar. Tetraethoxysilane (TEOS), 2-mercaptoethanol and 2-(4-chlorosulfonylphenyl)ethyltrimethoxysilane (50% in dichloromethane) were obtained from Acros Organics. 3-Mercaptopropyltriethoxysilane was purchased from Gelest. All other chemicals were purchased from Aldrich and used as received. All reactions were performed under an argon atmosphere.




**2-(Pyridin-2-yldisulfanyl)ethanol.** A solution of 2-mercaptoethanol (0.87 g, 11.1 mmol) in dry $CH_2Cl_2$ (10 mL) was added dropwise at room temperature to a solution of 2,2'-dithiopyridine (4.89 g, 22.2 mmol) in $CH_2Cl_2$ (20 mL). After complete addition of the mercaptoethanol, the solution was stirred for three hours at room temperature. The

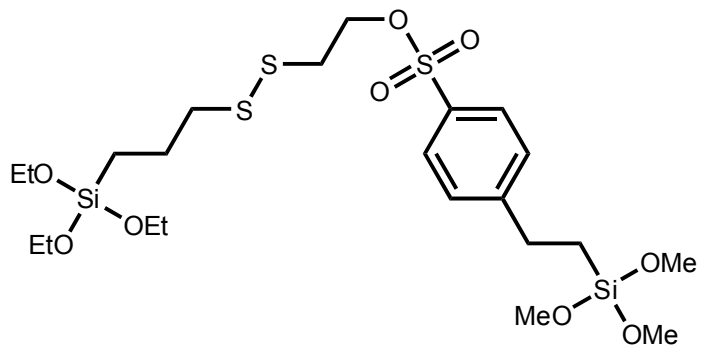
initially colorless solution turned yellow due to the production of pyridine-2-thione. After the solvent was removed *in vacuo*, chromatography on silica gel (8:2 pentane/ethyl acetate) afforded 2-(pyridin-2-yldisulfanyl)ethanol (1.4 g, 68% yield) as a yellow oil.

$^1$H NMR, $CDCl_3$, δ 2.71 ppm (t, 2H, $C_5H_4NS_2$*$CH_2$*$CH_2OH$), 3.59 ppm (q, 2H, $SSCH_2$*$CH_2$*$OH$), 5.5 ppm (t, 1H, $SSCH_2CH_2$*$OH$*), 6.89, 7.33, 8.2 ppm (m, 4H, pyridyl); $^{13}$C NMR, $CDCl_3$, δ 42.1 ppm ($SSCH_2CH_2OH$), 58.9 ppm ($SSCH_2CH_2OH$), 120.9, 121.3, 137.1, 149.2, and 159.2 ppm (pyridyl carbons).




**2-((3-(triethoxysilyl)propyl)disulfanyl)ethanol (Organosilane 3)**. A solution of 3-mercaptopropyltriethoxysilane (1.61 g, 6.74 mmol) in dry $CH_2Cl_2$ (10 mL) was added slowly via syringe to a solution of 2-(pyridin-2-yldisulfanyl)ethanol (1.40 g, 7.49 mmol) in $CH_2Cl_2$ (20 mL). The yellow solution was stirred at room temperature overnight. The crude product was purified by chromatography on silica gel (6:4 cyclohexane/ethyl acetate) to afford **3** (1.27 g, 60% yield).

$^1$H NMR, $CDCl_3$, δ 0.6 ppm (m, 2H, $SiCH_2CH_2$), 1.1 ppm (t, 9H, $SiOCH_2CH_3$), 1.6 ppm (m, 2H, $SiCH_2CH_2$), 2.6 ppm (t, 2H, $SSCH_2CH_2CH_2$), 2.7 ppm (t, 2H, $HOCH_2CH_2SS$), 3.4 ppm (br, 1H, O*H*), 3.7 ppm (q, 8H, $SiOCH_2CH_3$ and $HOCH_2CH_2SS$); $^{13}$C NMR, $CDCl_3$, δ 9.2 ppm ($SiCH_2CH_2$), 17.7 ppm ($SiOCH_2CH_3$), 22.4 ppm ($SSCH_2CH_2CH_2$), 40.9 ppm ($SSCH_2CH_2CH_2$), 41.5 ppm ($HOCH_2CH_2SS$), 58.3 ppm ($SiOCH_2CH_3$), 60.3 ppm ($HOCH_2CH_2SS$).

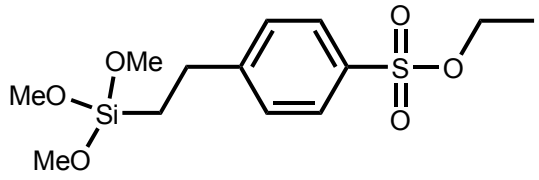



**2-((3-(triethoxysilyl)propyl)disulfanyl)ethyl 4-(2-(trimethoxysilyl)ethyl) benzenesulfonate (Bissilane 4)**. A solution of **3** (1.23 g, 3.93 mmol) and dry triethylamine (1.02 g, 10.1 mmol) in dry $CH_2Cl_2$ (20 mL) was cooled to 0°C and 2-(4-chlorosulfonylphenyl)ethyltrimethoxysilane (50% in $CH_2Cl_2$, 1.4 mL, 2.8 mmol) was added dropwise via syringe. The mixture was allowed slowly to warm to room temperature and stirred overnight. The solvent was removed *in vacuo*, and the crude product was purified by chromatography on tetramethylorthosilicate-passivated silica gel (6:4 $CH_2Cl_2$/ethyl acetate) to afford **4** (0.67 g, 40% yield).

$^1$H NMR, $CD_2Cl_2$, δ 0.7 ppm (m, 2H, Si*CH*$_2$CH$_2$CH$_2$), 1.0 ppm (m, 2H, Si*CH*$_2$CH$_2$), 1.2 ppm (t, 9H, SiOCH$_2$*CH*$_3$), 1.8 ppm (m, 2H, SiCH$_2$*CH*$_2$CH$_2$), 2.7 ppm (t, 2H, SiCH$_2$*CH*$_2$), 2.8 ppm (m, 4H, SO$_2$OCH$_2$*CH*$_2$SS and SiCH$_2$CH$_2$*CH*$_2$), 3.6 ppm (s, 9H, SiO*CH*$_3$), 3.8 ppm (q, 6H, SiO*CH*$_2$CH$_3$), 4.3 ppm (t, 2H, SO$_2$O*CH*$_2$CH$_2$SS), 7.4 ppm (d, 2H, phenyl proton β to ethyl chain), 7.8 ppm (d, 2H, phenyl proton β to sulfonate ester group).

$^{13}$C NMR, $CD_2Cl_2$, δ 9.2 ppm (Si*CH*$_2$CH$_2$CH$_2$), 10.7 ppm (Si*CH*$_2$CH$_2$), 17.7 ppm (SiOCH$_2$*CH*$_3$), 22.5 ppm (SiCH$_2$*CH*$_2$CH$_2$), 28.8 ppm (SiCH$_2$*CH*$_2$), 36.6 ppm (SO$_2$OCH$_2$*CH*$_2$SS), 41.6 ppm (SiCH$_2$CH$_2$*CH*$_2$), 50.3 ppm (SiO*CH*$_3$), 58.2 ppm (SiO*CH*$_2$CH$_3$), 68.0 ppm (SO$_2$O*CH*$_2$CH$_2$SS), 127.8 and 128.8 ppm (aromatic carbons),

133.0 ppm (aromatic carbon attached to ethyl group), 151.4 ppm (aromatic carbon attached to sulfonate ester).




**Ethyl 4-(2-(trimethoxysilyl)ethyl)benzenesulfonate (Organosilane 5).** 2-(4-chlorosulfonylphenyl)ethyltrimethoxysilane (50% in dichloromethane, 1.9 mL, 3.8 mmol) was added dropwise through a septum to a solution of dry ethanol (0.88 g, 19 mmol) and triethylamine (1.56 g, 15.4 mmol) at 0°C. After the addition, the mixture was allowed slowly to warm at room temperature. The reaction mixture was stirred at 25°C overnight. After the solvent was removed *in vacuo*, filtration on silica gel (ethyl acetate) afford **5** (0.5 g, 40% yield).

$^{1}$H NMR, $CDCl_3$, δ 0.9 ppm (m, 2H, Si*CH*$_2$CH$_2$), 1.21 ppm (t, 3H, *CH*$_3$CH$_2$O), 2.74 ppm (m, 2H, C$_6$H$_4$*CH*$_2$), 3.5 ppm (s, 9H, SiO*CH*$_3$), 4.0 ppm (q, 2H, CH$_3$*CH*$_2$O), 7.33 ppm (d, 2H, phenyl protons β to ethyl chain), 7.7 ppm (d, 2H, phenyl protons β to sulfonate ester group). $^{13}$C {$^{1}$H} NMR, $CDCl_3$, δ 10.8 (Si*C*H$_2$CH$_2$) ppm, 14.6 ppm (*C*H$_3$CH$_2$O), 28.7 ppm (C$_6$H$_4$*C*H$_2$), 50.4 ppm (SiO*C*H$_3$), 66.8 ppm (CH$_3$*C*H$_2$O), 127.8 and 128.8 ppm (aromatic carbons), 133.0 ppm (aromatic carbon attached to ethyl group), 150.8 ppm (aromatic carbon attached to sulfonate group).

**Organic-functionalized SBA-15 materials.** SBA-15 (1.0 g, synthesized according to the literature procedure[9, 10]) was suspended in dry toluene (40 mL). A solution of organosilane in toluene (10 mL) was added dropwise via syringe. The suspension was stirred for 2 hours at room temperature, then refluxed overnight. After cooling to room

temperature, the solids were filtered and washed several times with toluene and dried under high vacuum.

When two organosilanes were grafted onto the same SBA-15 material, two separate solutions of organosilane in toluene were prepared and were added dropwise simultaneously to the SBA-15 suspension.

**Surface Disulfide Reduction and Sulfonate Ester Hydrolysis.** Functionalized silica (0.5 g) containing disulfide and/or sulfonate ester surface groups was suspended in an aqueous solution of TCEP·HCl (16 mM, 50 mL) and stirred at 50°C for 48 hours. After filtration, the solids were washed with water (5 x 100 mL), then suspended in 0.5 N HCl for ~ 1 hour to acidify, followed by washing with water (5 x 100 mL). The material was then dried under high vacuum.

**Quantification of Acid Sites.** Acid-containing silica (40 mg) and 2N aqueous NaCl (4 mL) were stirred at room temperature for 24 hours. The solids were filtered off using positive air pressure filtration and were washed with water (4 x 2 mL). The combined filtrate was titrated with 0.01N NaOH using phenol red as indicator.

**Quantification of Thiol Sites.** We followed the procedure developed by Badyal et al.[11] for quantification of resin-bound thiols in organic solvents. Thiol-containing silica (5 mg) was suspended in methanol (4 mL) and 1 mL of a solution containing Ellman's reagent (4 mg/mL) and diisopropyl ethylamine (0.05mL/mL) was added. After stirring at room temperature for 4 hours, the solids were removed by syringe-filtration and the absorbance of the filtrated was measured at 412 nm, using an experimentally determined exctinction coefficient of 11 $mM^{-1}$.

**Catalytic Reaction—Condensation of Phenol and Ketone.** An amount of catalyst corresponding to 0.02 mmol $H^+$ (~ 100–200 mg) was added to a vial and dried under high vacuum at 80°C overnight. Phenol (2.2 g, 24 mmol) and ketone (6 mmol) were added and the vial was sealed under argon and stirred at 90°C for 24 hours. The catalyst was removed by filtration and washed with acetonitrile to a total filtrate volume of 25 mL, and the products were quantified by HPLC analysis. Per-site yield was calculated on the basis of the number of acid sites present and selectivity was defined as the ratio of bisphenol isomers (*p,p*'/*o,p*').

When homogeneous catalysts were used, the homogeneous catalyst was dissolved in the ketone and then added to the phenol and heterogeneous catalyst.

**Acknowledgements**

This work was done in collaboration with Dr. Veronique Dufaud and Dr. Anissa Bendjeriou of ENS-Lyon. All of the disulfide and sulfonate ester silane precursors were synthesized by Dr. Bendjeriou. This work was supported by a National Science Foundation Graduate Research Fellowship and by the Department of Energy.

# References


1. Apel, F. N.; Conte, L. B.; Bender, H. L. U.S. Patent 3,153,001, 1964.
2. McNutt, B. W.; Gammill, B. B. U.S. Patent 3,394,089, 1968.
3. Wieland, S.; Panster, P. *Stud. Surf. Sci. Cat.* **1997,** 108, 67.
4. Zeidan, R. K.; Dufaud, V.; Davis, M. E. *J. Catal.* **2006,** 239, (2), 299.
5. Margelefsky, E. L.; et al. *J. Am. Chem. Soc.* **2007,** 129, (44), 13691.
6. Mbaraka, I. K.; Shanks, B. H. *J. Cat.* **2006,** 244, (1), 78.
7. Burns, J. A.; et al. *J. Org. Chem.* **1991,** 56, (8), 2648.
8. Dufaud, V.; Davis, M. E. *J. Am. Chem. Soc.* **2003,** 125, (31), 9403.
9. Zhao, D. Y., Huo, Q.; Feng, J.; Chmelka, B.; Stucky, G. *J. Am. Chem. Soc.* **1998,** 120, (24), 6024.
10. Zhao, D. Y.; et al. *Science* **1998,** 279, (5350), 548.
11. Badyal, J. P.; et al. *Tetrahedron Lett.* **2001,** 42, (48), 8531.

**Additional Figures**

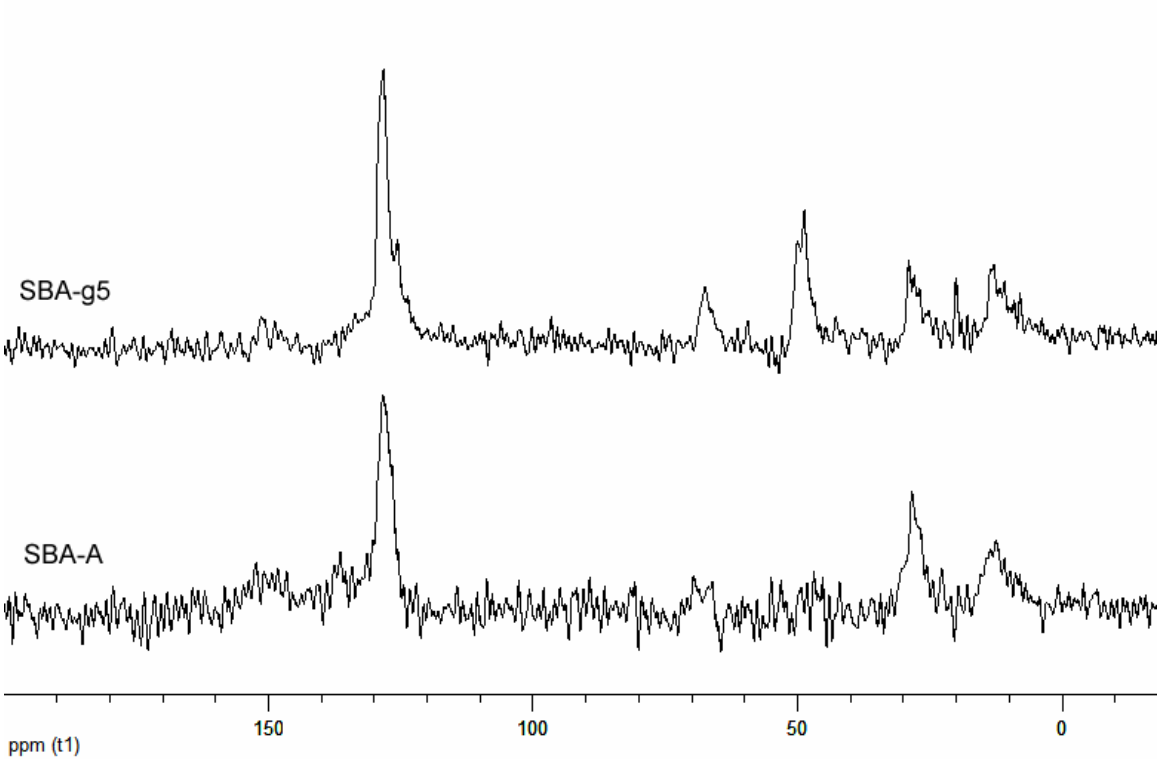



**Figure 3.4.** $^{13}C\{^{1}H\}$ CP/MAS NMR spectra of **SBA-g5** (top) and **SBA-A** (bottom). The peak at 67 ppm is due to the ethyl ester and is nearly absent in **SBA-A**. The small peak in the **SBA-g5** spectrum at 21 ppm is due to residual adsorbed toluene.

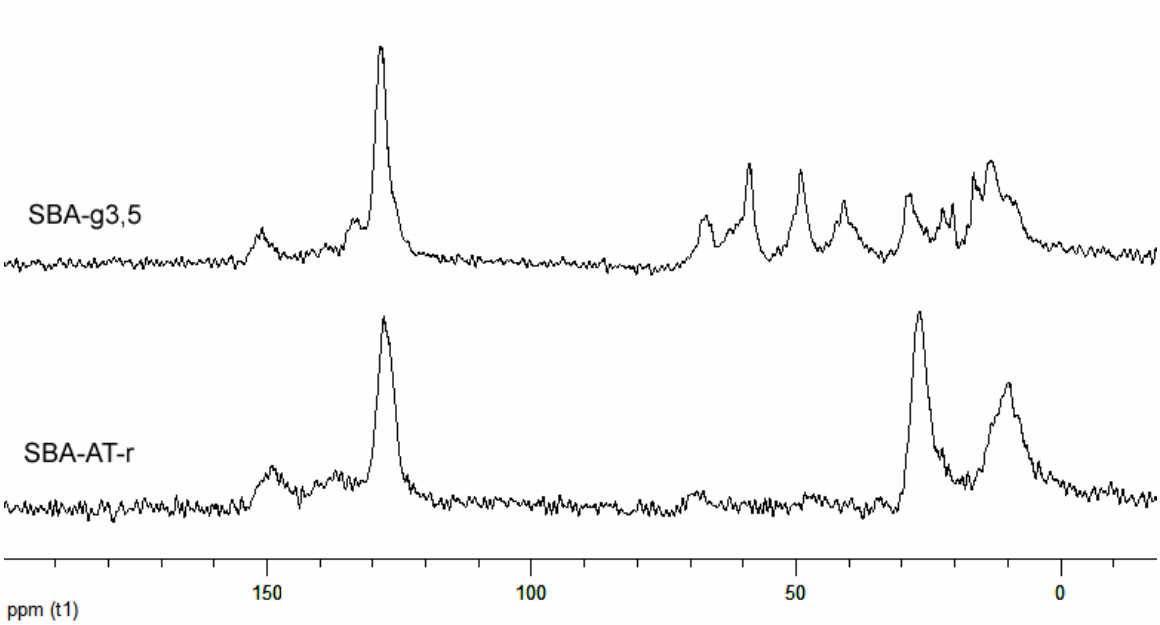



**Figure 3.5.** $^{13}C\{^{1}H\}$ CP/MAS NMR spectra of **SBA-g3,5** (top) and **SBA-AT-r** (bottom). The ethyl ester peak (67 ppm) and mercaptoethanol peaks (41 ppm, 60 ppm) are absent in **SBA-AT-r** following deprotection. The residual ethoxy (16 ppm, 58 ppm) and methoxy peaks (49 ppm) are also hydrolyzed in the deprotection process. The small peak in the **SBA-g3,5** spectrum at 21 ppm is due to residual adsorbed toluene.

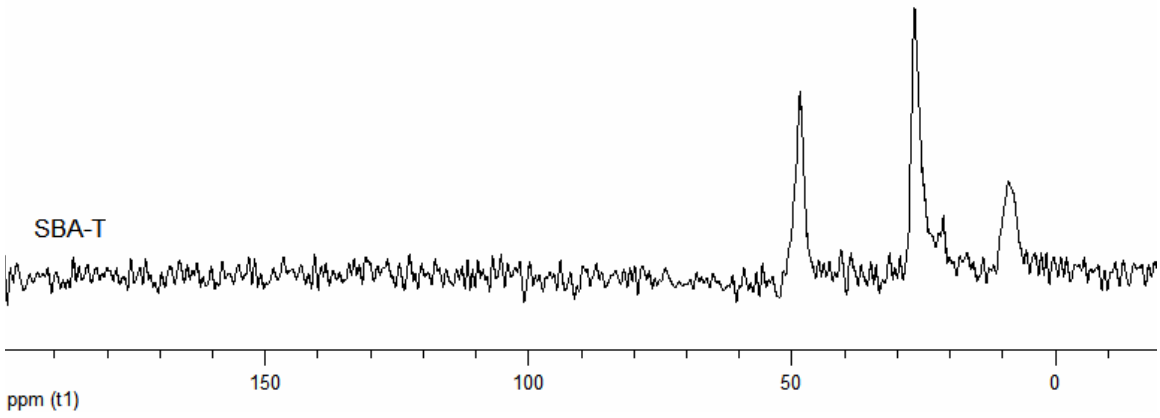
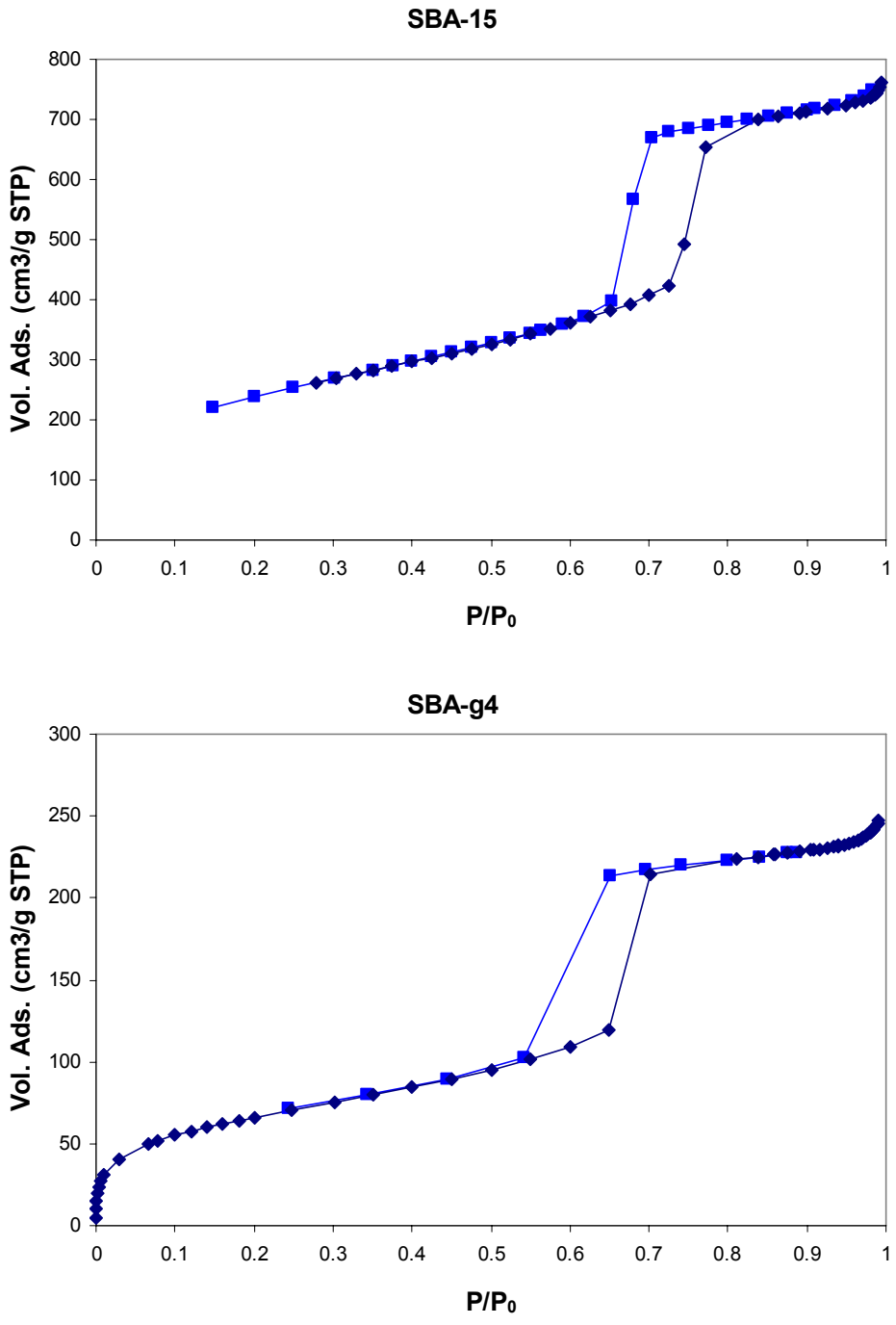
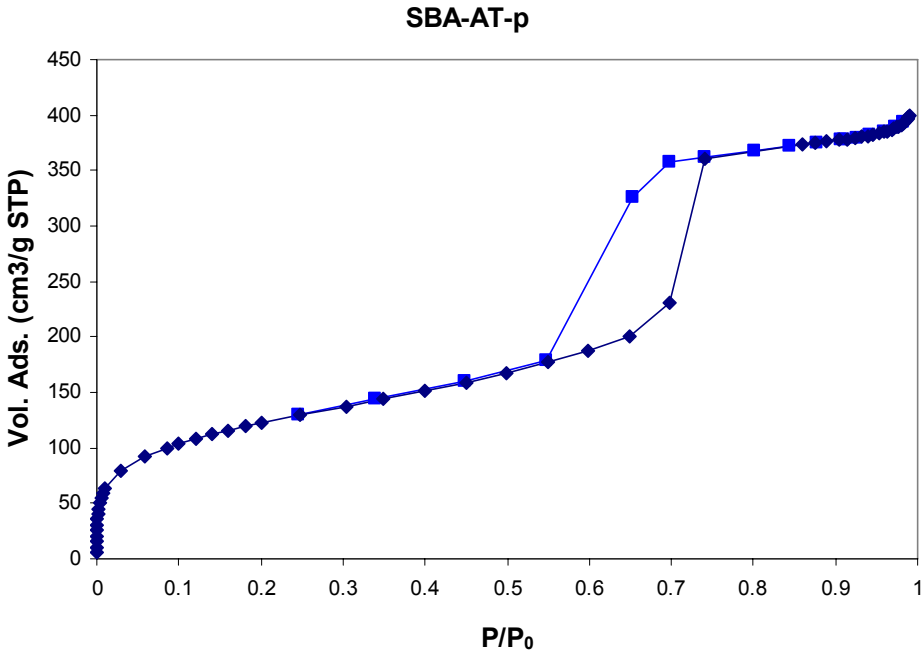



**Figure 3.6.** $^{13}C\{^{1}H\}$ CP/MAS NMR spectra of **SBA-T**. The peak at 49 ppm is due to residual methoxy groups. The small peak at 21 ppm is due to residual adsorbed toluene.

**Figure 3.7.** $N_2$ adsorption/desorption isotherms (diamonds = adsorption branch; squares = desorption branch)




SBA-AT-p
Vol. Ads. (cm3/g STP)
450
400
350
300
250
200
150
100
50
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
P/P0

*Chapter 4*

# THE SYNTHESIS OF MESOPOROUS SILICA FUNCTIONALIZED WITH SULFONIC ACID/PRIMARY AMINE PAIRS

**Abstract**

Mesoporous silica catalysts functionalized with both sulfonic acid and amine groups have been recently shown to be good catalysts for the aldol reaction of acetone and *p*-nitrobenzaldehyde. In these materials, acid and base groups were randomly-distributed in SBA-15 in a one-pot (direct) synthesis. To investigate the effect of spatial orientation of these acid and base groups, a catalyst was prepared in which sulfonic acid and amine groups are organized into pairs on the surface. This material was synthesized by first grafting onto the surface an organosilane containing a propylsultone ring, which was subsequently reacted with ammonia gas to ring-open the sultone into sulfonic acid and primary amine groups separated by a short three-carbon spacer. The resulting material is found to be completely *inactive* in catalyzing the aldol reaction, because the acid and base groups neutralize each other, while both acid-only and base-only catalysts performed significantly better. Thus the catalytic behavior of randomly-bifunctionalized acid/base catalysts is due to those acid and base groups which are tethered far enough away from each other to avoid neutralization.

## Introduction

Acids and bases can be used to catalyze a vast array of different chemical reactions. Greater catalytic activity can sometimes be achieved through a combination of acid and base catalysis, but with homogeneous catalysts, strong acids and bases neutralize each other, destroying the catalytic activity. Weak acids and weak bases can coexist in solution, and there are many reports of homogeneous cooperative catalysis between amine bases and weak acids such as carboxylic or phenolic acids. But rarely can strong acids coexist in solution with even weak bases, unless the two catalysts are designed with structural barriers to provide steric hindrance.[1, 2]

In the case of heterogeneous catalysts, on the other hand, both acid and base groups can coexist in the same solid material. Because the acids and bases are fixed spatially within the solid, they cannot neutralize each other. Acids and bases have been immobilized on two separate supports to provide two-step catalytic sequences[1, 3-6]. In these cases, the acid and base are spatially isolated from one another, and cooperative catalysis is impossible. In a recent report by Zeidan et al.,[7] arylsulfonic acids and amine bases were incorporated into mesoporous silica (SBA-15) in a one-pot synthesis and the resulting acid-base catalyst exhibited cooperative catalysis, in which the acid and base groups both contributed to the catalytic activity in the aldol reaction between acetone and *p*-nitrobenzaldehde. The acid groups could be selectively poisoned by the addition of homogeneous base, leading to reduced activity, and the base groups could be similarly poisoned by homogeneous acid, confirming the bifunctional nature of the catalyst.

We sought to investigate how the spatial positioning between the sulfonic acid and primary amine groups affect the cooperative catalytic activity. If the acid and base

groups are too far apart (*e.g.*, immobilized on two different supports) then cooperativity is impossible. Thus one would expect that acid sites in proximity to base sites are responsible for the enhanced activity of the bifunctional catalysts. But is the activity of randomly-bifunctionalized sulfonic acid/primary amine catalysts due primarily to acid and base sites tethered far enough away from one another that they cannot neutralize, or to acid and base sites in very close proximity that can directly interact with one another? To distinguish between these possibilities (see Figure 4.1), we designed a silica catalyst bearing pairs of sulfonic acid and primary amine groups. If the activity of the randomly-bifunctionalized catalyst is due to closely interacting acid/base sites, then one would expect the acid/base paired catalyst to exhibit even greater catalytic performance, because every acid site is paired to a base site. If, on the other hand, the activity of the random acid/base catalysts is due to acid and base groups that are too far apart to neutralize, then the acid/base paired catalyst should be inactive.

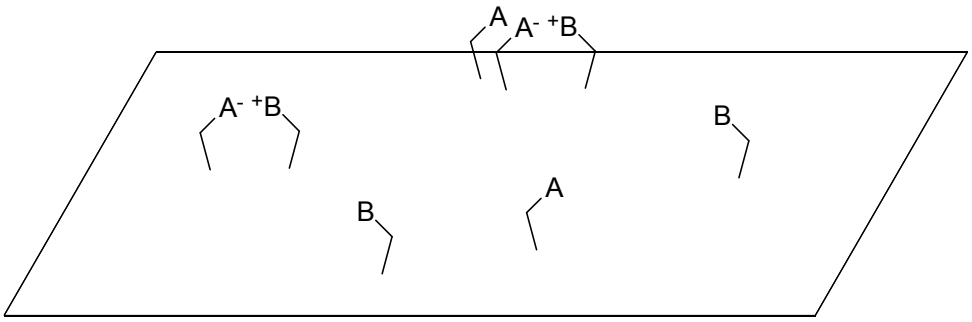



**Figure 4.1.** Schematic representation of a catalyst surface functionalized with covalently tethered, randomly-distributed acid (A) and base (B) groups. Some of these groups will be spatially isolated and unable to exchange protons, while others will be close enough to interact directly with another nearby group, allowing proton exchange and equilibration with the ion-pair form (represented by $A^-/B^+$ pairs).

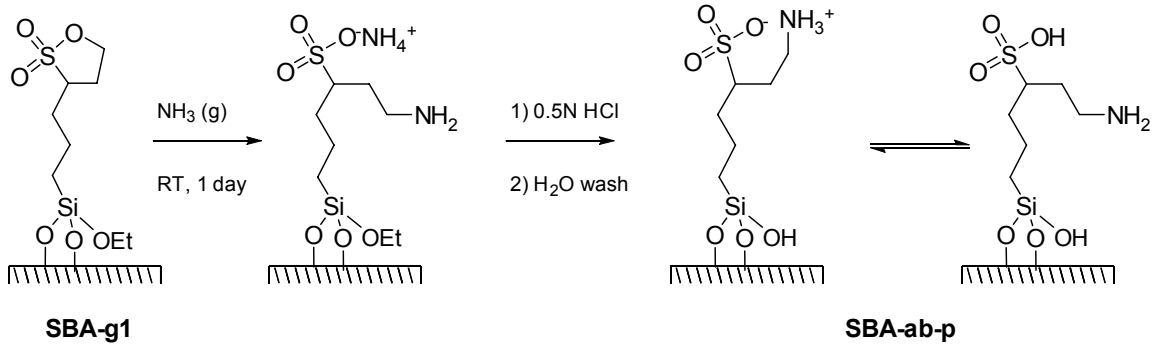
**Results and Discussion**

Silica catalysts containing sulfonic acid and primary amine pairs were prepared according to Scheme 4.1. First the sultone-containing silane **1** was grafted onto the surface of SBA-15 to form **SBA-g1** (see Chapter 2). The loading of this material was estimated by thermogravimetric analysis (TGA) to be 0.35 mmol/g.* The surface-bound sultone groups were ring-opened by reaction with gaseous ammonia, a reaction that proceeds readily at room temperature[8] to produce a sulfonic acid and a primary amine separated by a three-carbon spacer.

Initially, the basic ammonia atmosphere leads to ammonium sulfonate species that must be acidified to remove the ammonium counterions. In a procedure analogous to the synthesis procedure of Zeidan et al.[7] (in which the materials were synthesized in strongly acidic solution and then neutralized), the paired acid/base catalyst was first fully acidified with 0.5 N aqueous HCl, followed by repeated washing with water to neutralize the protonated amines. It is expected that the three-carbon linker is flexible enough that the acid and base can equilibrate between the ammonium sulfonate and free acid/base states. This material is denoted **SBA-ab-p** (acid/base pairs).

The ring-opening reaction was monitored by $^{13}C$ CP/MAS NMR. After one day of reaction with gaseous ammonia, the peak at 67 ppm has disappeared, indicating that the ring-opening reaction is complete (see Figure 4.2). The loading of the amine and amine/acid material was estimated by TGA to be ~ 0.38 mmol/g, comparable to that of the sultone starting material.

* The mass loss between 200°C and 600°C was attributed to the loss of the organic groups.




**Scheme 4.1.** Ring-opening and subsequent acidification and neutralization of sultone-grafted SBA-15, leading to **SBA-ab-p**, containing sulfonic acid/amine pairs

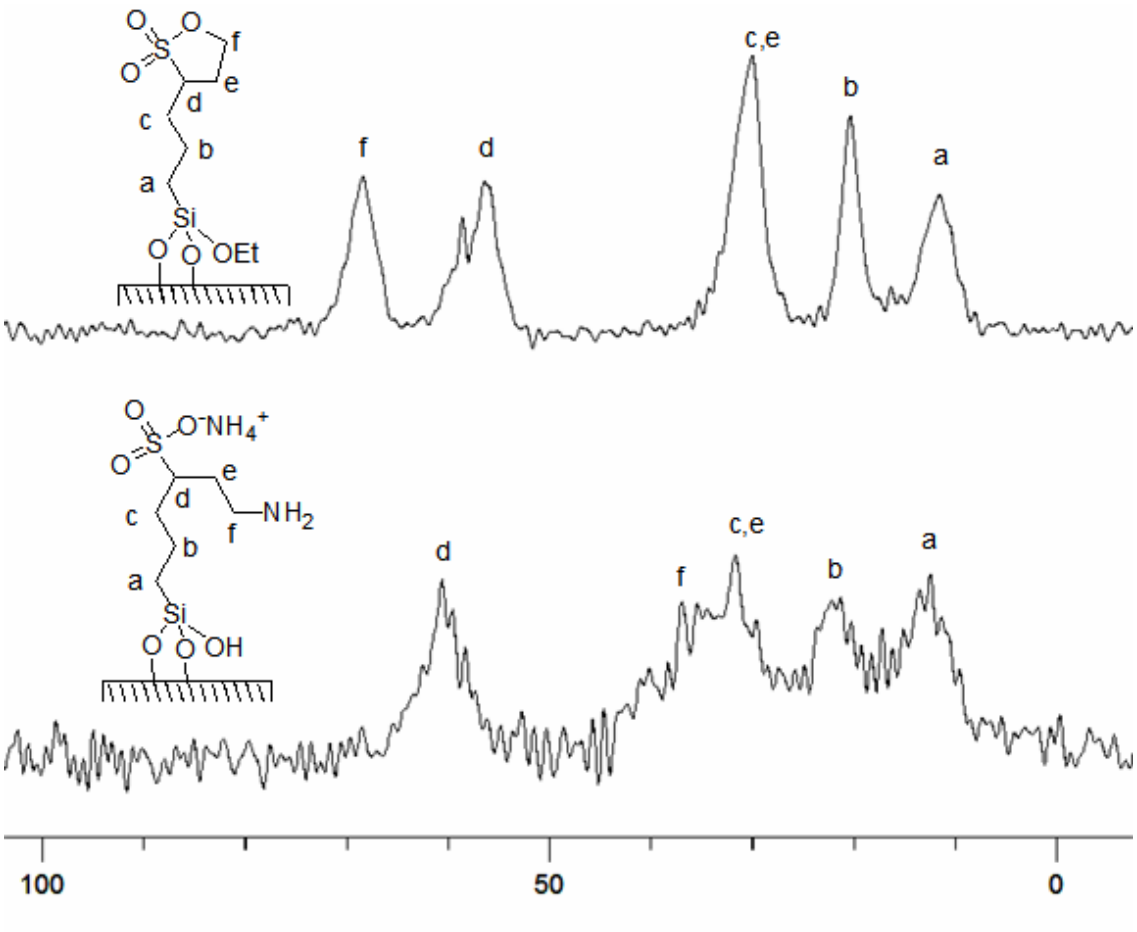
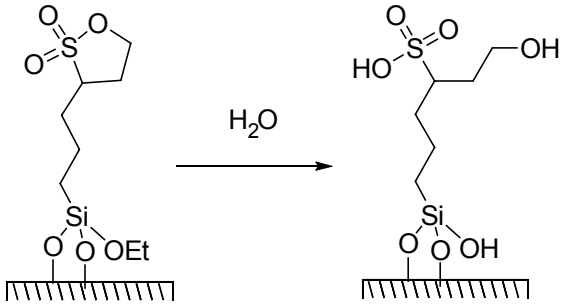



**Figure 4.2.** $^{13}C$ CP/MAS NMR spectra of sultone-functionalized **SBA-g1** before (top) and after (bottom) reaction with ammonia to form **SBA-ab-p**

A material containing only sulfonic acid groups was obtained from the same sultone-functionalized silica by hydrolyzing the sultone ring in water, as previously reported[9] (see Scheme 4.2). The resulting material, denoted **SBA-a**, contains sulfonic acid groups but no amines (a pendant hydroxyl group is tethered to the acid). The acid loading of this material was measured by ion-exchange with NaCl, followed by titration with NaOH, and was found to be 0.19 mmol $H^+$/g.[†] The lower organic loading of this material compared to the starting material (0.3 mmol/g) means that some of the organic groups are lost during the hydrolysis step.

A material containing only base groups (**SBA-b**) was prepared by grafting 3-aminopropyltriethoxysilane onto SBA-15. The amine loading of this material was estimated by TGA to be 0.6 mmol/g.




**SBA-g1** **SBA-a**

**Scheme 4.2.** Hydrolysis of the sultone groups of **SBA-g1** leads to **SBA-a**, containing sulfonic acid groups but no amines

[†] This ion-exchange/titration method cannot be used to quantify the loading of **SBA-ab-p**; with this material only a very small amount of titratable acid is generated after ion-exchange. This is due to the neutralization of any HCl formed during ion-exchange by the surface amine groups.

**Catalytic Reactions**

The acid, base, and acid/base-paired catalysts were used in the aldol reaction of acetone and *p*-nitrobenzaldehyde at 50°C. The results are shown in Table 4.1, along with the previously reported results from Zeidan et al.[7] The previously reported catalysts were generated in a one-pot synthesis with amine and/or arylsulfonyl chloride-containing organosilanes, leading to primary amine and arylsulfonic acid sites (which are substantially stronger than alkylsulfonic acids). These catalysts are here denoted **SBA-A** (acid), **SBA-B** (base), and **SBA-AB-r** (acid/base random) with capital letters used to distinguish from the grafted catalysts described above. A summary of the six catalysts is shown in Figure 4.3.

In the previously reported data (Table 4.1, Entries 1–3) the arylsulfonic acid-functionalized catalyst exhibits low catalytic activity. The amine base-functionalized catalyst **SBA-B** is substantially better, and the bifunctional material **SBA-AB-r**, containing a random distribution of acid and base sites, is nearly twice as active as **SBA-B**. Furthermore, selective acid- and base-neutralization experiments confirmed the bifunctional nature of the catalysis, in which both acid and base groups play a role.

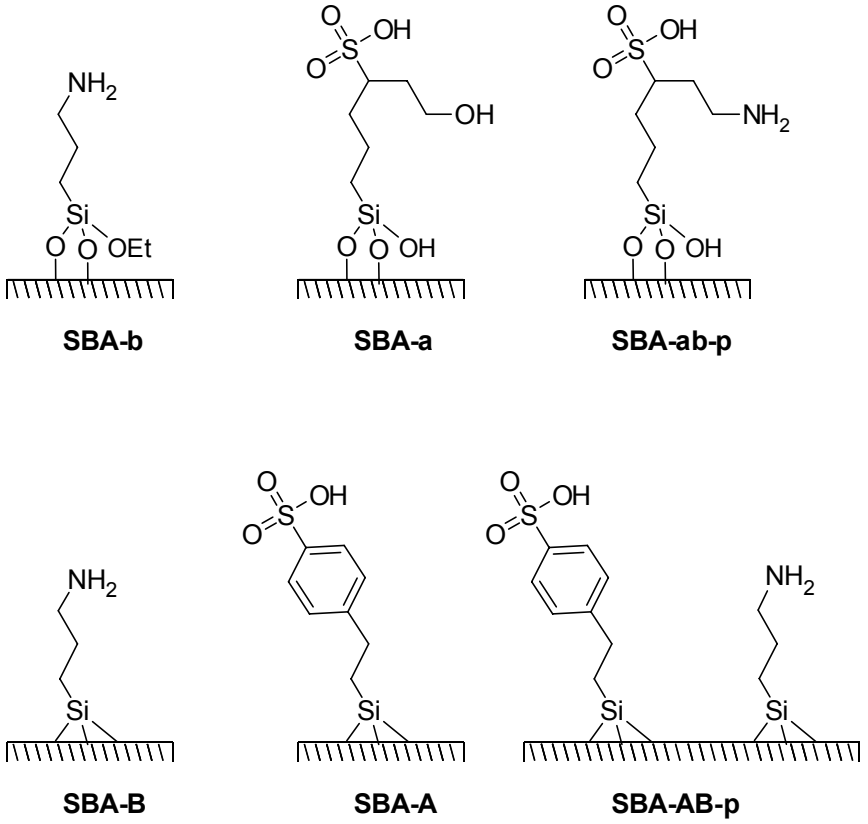
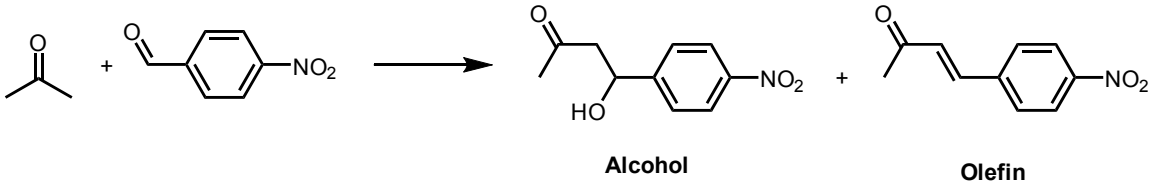



**Figure 4.3.** Summary of the grafted amine/alkylsulfonic acid SBA-15 catalysts whose synthesis is reported here (top) and the one-pot-synthesized amine/arylsulfonic acid SBA-15 catalysts of Zeidan et al.[7] (bottom)

The catalytic results of **SBA-a** and **SBA-b** are consistent with those of **SBA-A** and **SBA-B**. The acid-only material **SBA-a** exhibits lower activity than **SBA-A**, due to the weaker acid strength, but some catalytic behavior is still present (Entry 4). The amine-grafted **SBA-b** provides 94% yield, compared to only 33% for the one-pot-synthesized **SBA-B**. This difference could be due to the inaccessibility of some of the amine groups in the one-pot-synthesized material, whereas every amine group in the grafted **SBA-b** must be on the surface. It is also likely that the loading of **SBA-B** was overestimated by thermogravimetry due to residual structure-directing agent that is not

fully removed during the extraction process (a difficulty not present when silanes are grafted onto calcined silica).

**SBA-ab-p**, in which the acid and base groups are both present but are arranged into pairs, is catalytically inactive in the aldol reaction (Entry 6). Thus the pairing of the alkylsulfonic acid and amine base allows for complete neutralization of the acid and base sites, leading to a completely inactive catalyst. The high catalytic activity of **SBA-AB-r** must therefore be due to isolated acid and base groups that are too far apart to neutralize one another.




| Entry | Catalyst(s) | Sulfonic Acid Type | Loading (mmol/g)[b] | Alcohol Yield | Olefin Yield | Total Yield |
|---|---|---|---|---|---|---|
| 1[a] | **SBA-A** | aryl | 0.49 | 8% | 8% | 16% |
| 2[a] | **SBA-B** | N/A | 0.51 | 25% | 8% | 33% |
| 3[a] | **SBA-AB-r** | aryl | 0.55[c] | 45% | 17% | 62% |
| 4 | **SBA-a** | alkyl | 0.19 | 3.1% | 0.4% | 3.5% |
| 5 | **SBA-b** | N/A | 0.6 | 74% | 19% | 94% |
| 6 | **SBA-ab-p** | alkyl | 0.3[c] | 0.1% | 0.0% | 0.1% |

**Table 4.1.** Catalytic results of heterogeneous acid/base catalysts in the aldol reaction between acetone and *p*-nitrobenzaldehyde (50 mM aldehyde in acetone, 10 mol% total catalyst [acid + base], 50°C, 20 hr)

[a] Data taken from Ref. 7; catalysts prepared in one-pot synthesis.
[b] All loadings estimated by TGA except for **SBA-a**, measured by titration.
[c] In the case of bifunctional materials, loading refers to each functional group.

## Conclusions

A mesoporous silica material featuring alkylsulfonic acid and primary amine groups arranged into pairs was successfully synthesized. The aldol catalytic activity of

this acid/base-paired material was very low, compared to the sulfonic acid or amine alone. This result provides insight into the mechanism of randomly-distributed acid/base catalysts such as **SBA-AB-r**, that contain some isolated acid and base sites in addition to acid sites which are in close proximity to base sites. The proximal acid/base groups neutralize and do not contribute to the overall catalytic activity of the material, which is dominated by those acid and base groups that are isolated enough to avoid neutralization while still in close enough proximity to provide cooperative acid/base catalysis. It is unknown how many of the acid and base groups in **SBA-AB-r** are neutralized and how many are active and responsible for the catalytic behavior of this material, meaning that the true turnover number of the active sites cannot be calculated without further characterization of the acid and base sites on the catalyst.

With the knowledge that the acid and base groups must be sufficiently separated from one another, one can now begin to design materials with acid and base groups positioned into pairs at a greater distance such that they cannot neutralize. For instance, using a molecular precursor containing hydrolyzable sulfonate ester and carbamate bonds to a rigid cleavable linker, one could synthesize a material such as the one shown in Figure 4.4 that could be used to imprint a silica surface with sulfonic acid and amine pairs at a fixed distance sufficient to prevent neutralization.

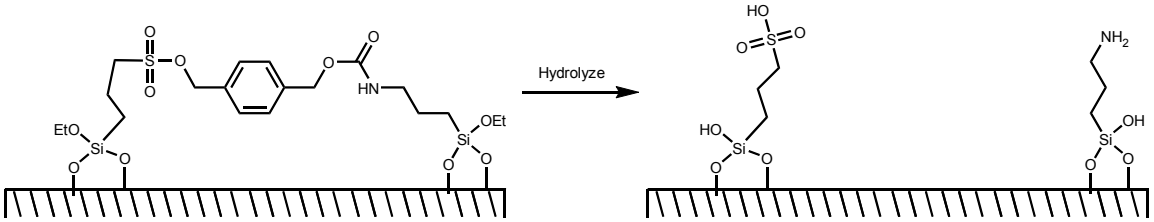



**Figure 4.4.** Proposed route to sulfonic acid/amine-paired silica in which the acid and base groups are too far apart to neutralize

## Experimental

**Materials.** Toluene was distilled over sodium immediately before use. All other solvents were analytical grade and used as received. Organosilanes were purchased from Gelest. All other chemicals were purchased from Aldrich and used as received. All reactions were performed under an argon atmosphere.

**SBA-g1.** SBA-15 (1.0 g, synthesized according to the literature procedure[10]) was dried under flowing argon at 170°C for 4 hours. After cooling, dry toluene (50 mL) was added via syringe and the mixture was stirred vigorously to form a uniform suspension. Sultone-containing organosilane **1** (0.7 mmol, synthesized according to the literature procedure[9]) 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 20 mL each). The solids were Soxhlet-extracted with dichloromethane overnight, then dried under vacuum and stored under an argon atmosphere in a drybox until further use.

**SBA-b**. The same grafting procedure was used as described above for **SBA-g1**. 3-Aminopropyltriethoxysilane (0.22 g, 1.0 mmol) was grafted onto SBA-15 (1.0 g) in refluxing toluene (50 mL).

**Ring-Opening with Ammonia.** Sultone-functionalized silica (0.36 g) was dried under high vacuum at 80°C overnight. After cooling to room-temperature, ammonia was added to the evacuated reaction flask via a balloon. After 24 hours, the ammonia was vented and the solids were acidified by slurrying in 0.5N HCl for 2 hours, followed by filtration, washing with 0.5N HCl (30 mL x 3) and water (30 mL x 5), and drying under vacuum.

**Ring-Opening by Hydrolysis.** Sultone-functionalized silica (0.5 g) was added to water (40 mL) and the resulting suspension was stirred at 40°C for 2 days. Then the solids were filtered, washed with water (3 x 30 mL), 0.5 N HCl (3 x 30 mL), and water (4 x 30 mL), and dried under high vacuum overnight. Acid loading was measured by ion-exchanged with 2N NaCl followed by titration of the resulting HCl with 0.01N NaOH.

**Catalytic Reaction—Aldol Condensation of Acetone and *p*-Nitrobenzaldehyde.** An amount of heterogeneous catalyst corresponding to 25 μmol amine and/or 25 μmol acid (0.1–0.2 g) was added to a vial and dried under high vacuum at 80°C overnight. A solution of *p*-nitrobenzaldehyde (38 mg, 0.25 mmol) in acetone (5 mL) was added and the vial was stirred under an argon atmosphere at 50°C. The reaction products (alcohol and olefin) were quantified by HPLC after filtering to remove the catalyst.

**Acknowledgements**

This work was supported by a National Science Foundation Graduate Research Fellowship and by the Department of Energy.

# References


1. Helms, B.; et al. *Angew. Chem. Int. Ed. Eng.* **2005,** 44, (39), 6384.
2. Poe, S. L.; Kobaslija, M.; McQuade, D. T. *J. Am. Chem. Soc.* **2006,** 128, (49), 15586.
3. Gelman, F.; et al. *J. Sol-Gel Sci. Tech.* **2003,** 26, (1-3), 43.
4. Gelman, F.; Blum, J.; Avnir, D. *Angew. Chem. Int. Ed. Eng.* **2001,** 40, (9), 3647.
5. Motokura, K.; et al. *J. Am. Chem. Soc.* **2005,** 127, (27), 9674.
6. Phan, N. T. S.; et al. *Angew. Chem. Int. Ed. Eng.* **2006,** 45, 2209.
7. Zeidan, R. K.; Hwang, S. J.; Davis, M. E. *Angew. Chem. Int. Ed. Eng.* **2006,** 45, (38), 6332.
8. Erman, W. F.; Kretschmar, H. C. *J. Org. Chem.* **1961,** 26, (12), 4841.
9. Margelefsky, E. L.; et al. *J. Am. Chem. Soc.* **2007,** 129, (44), 13691.
10. Zhao, D. Y., Huo, Q.; Feng, J.; Chmelka, B.; Stucky, G. *J. Am. Chem. Soc.* **1998,** 120, (24), 6024.

**Additional Figures—**Thermogravimetry data

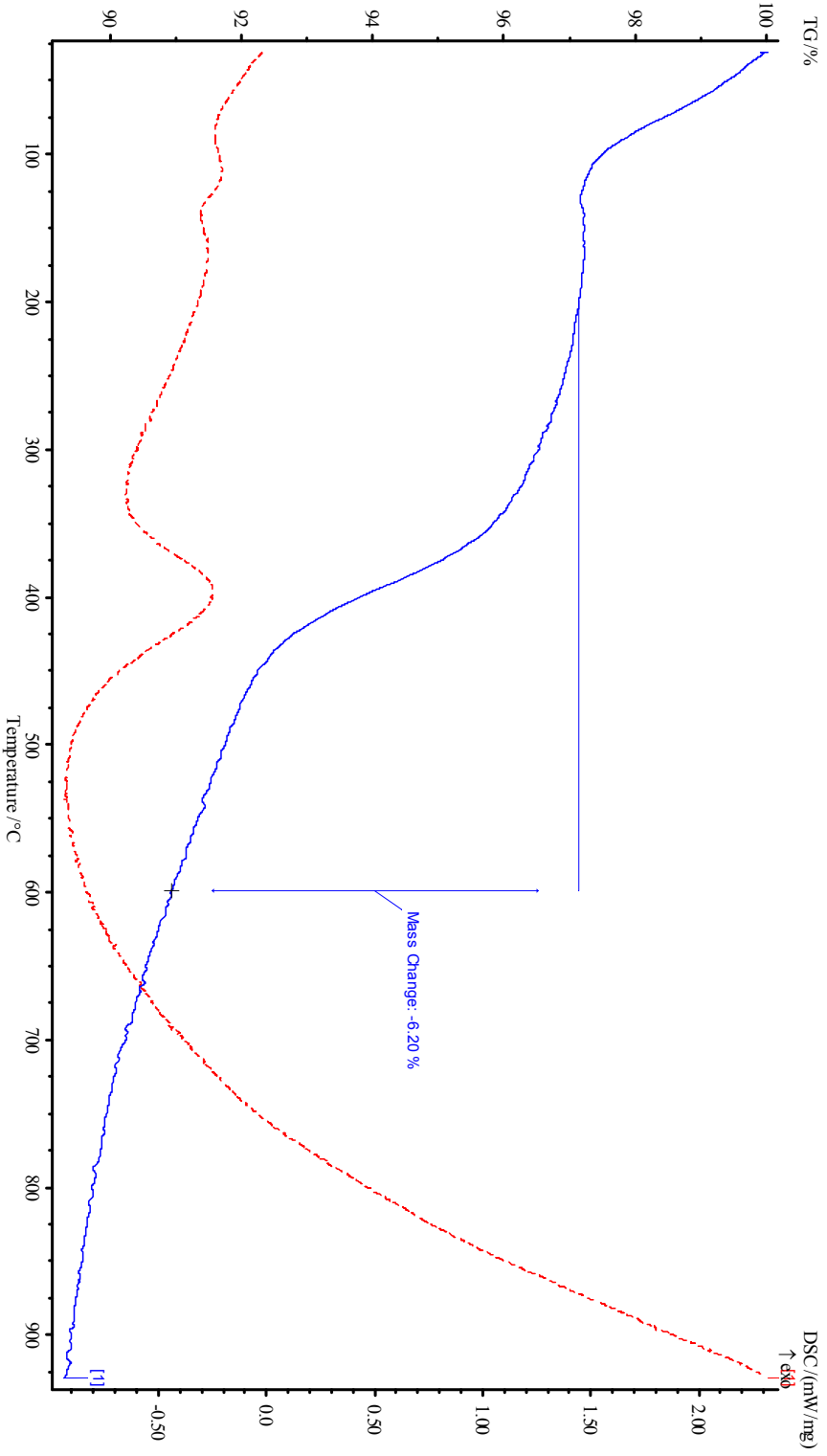



**Figure 4.5.** TGA trace for **SBA-g1**

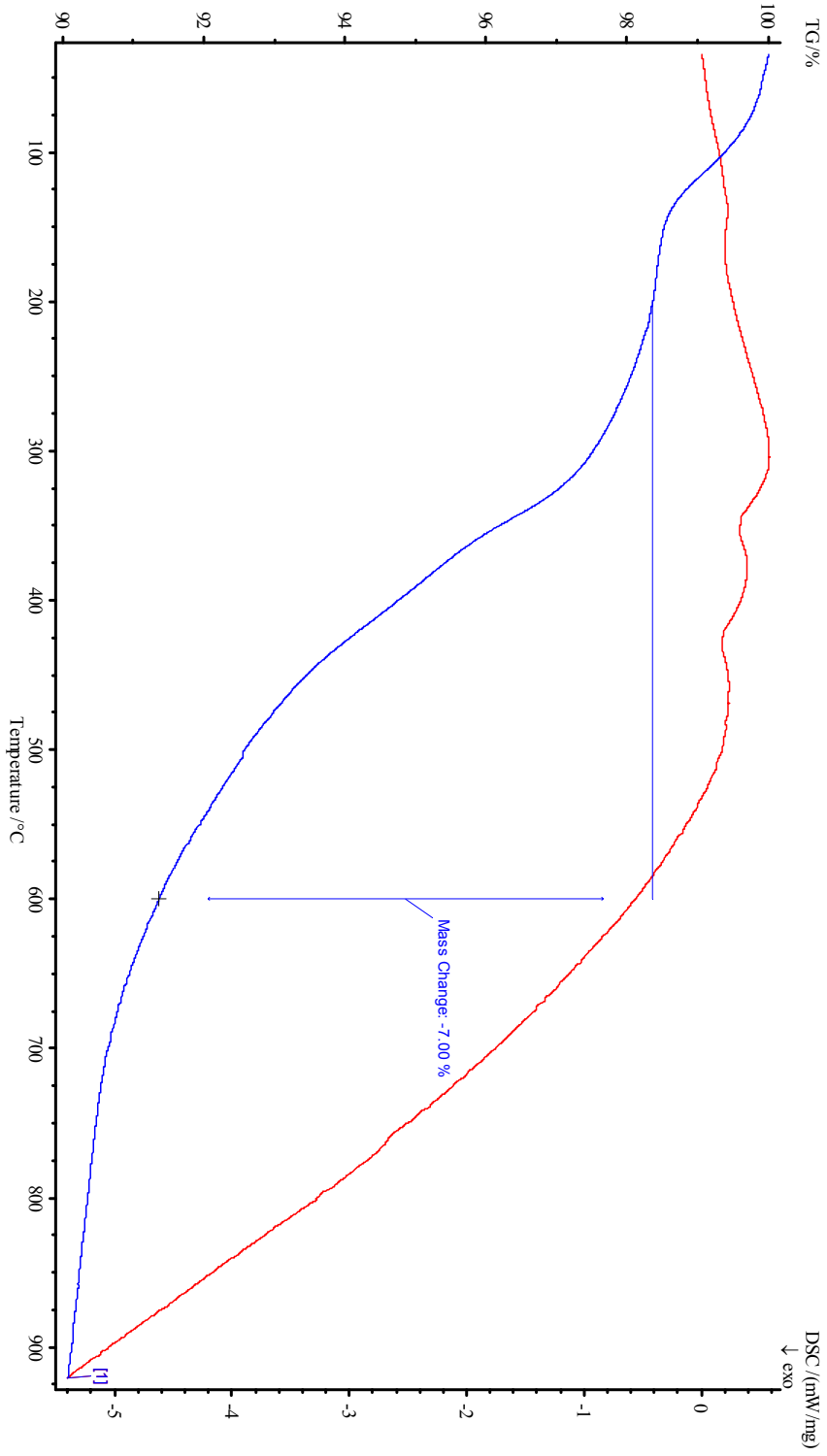



**Figure 4.6.** TGA trace for **SBA-ab-p**

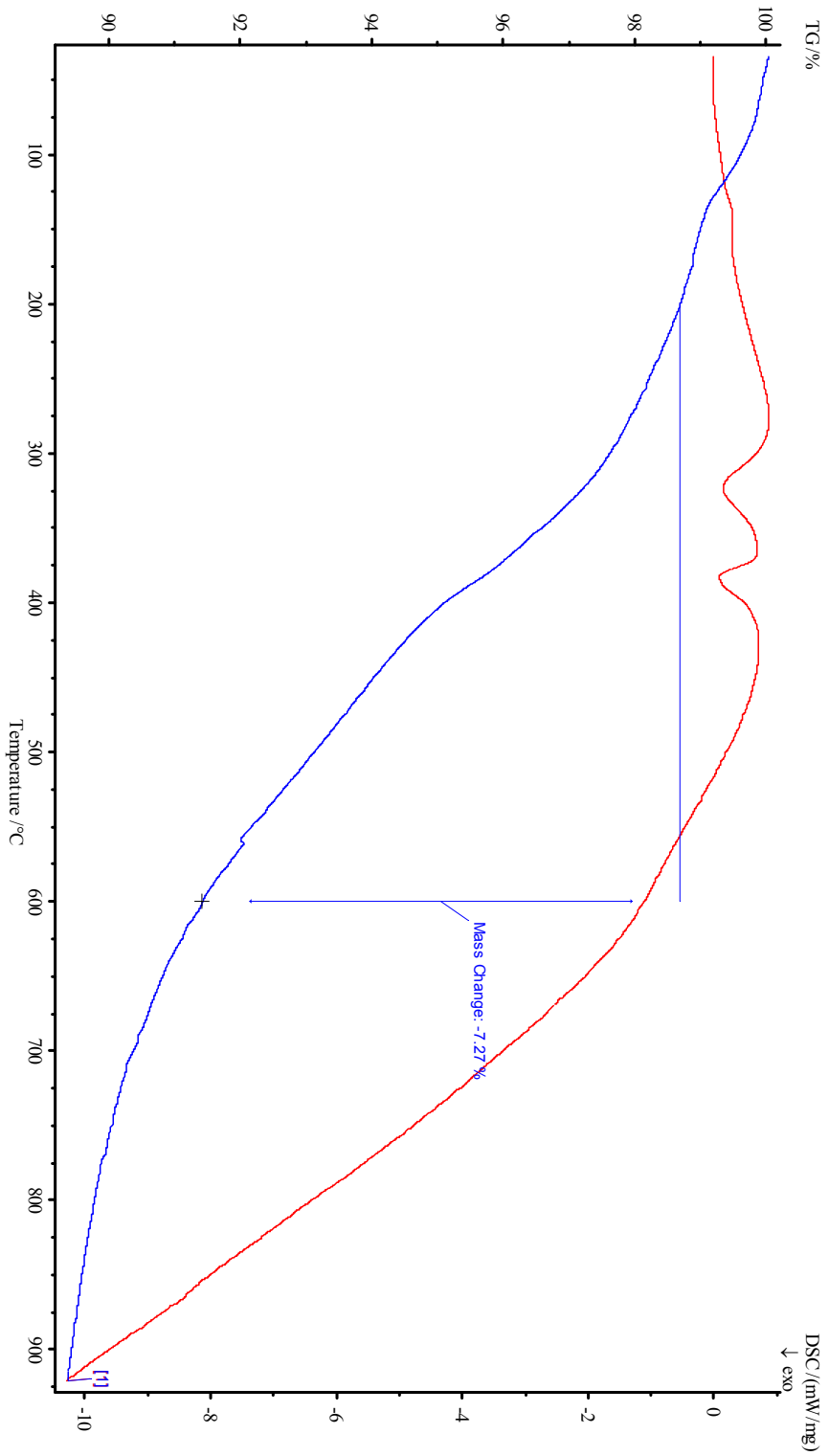



**Figure 4.7.** TGA trace for **SBA-b**

*Chapter 5*

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

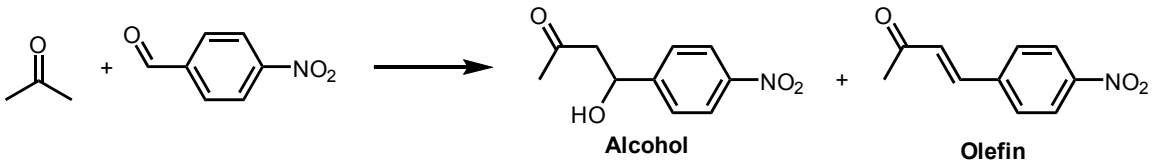
**Abstract**

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 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 acids[3]) 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.

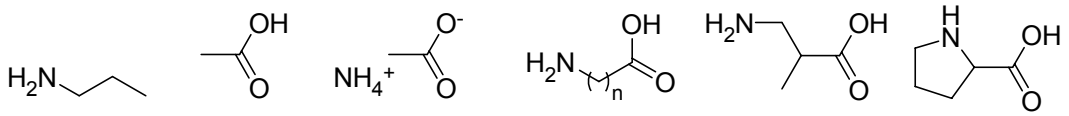



**Figure 5.1.** Amines, acids, and amino acids tested as homogeneous aldol catalysts

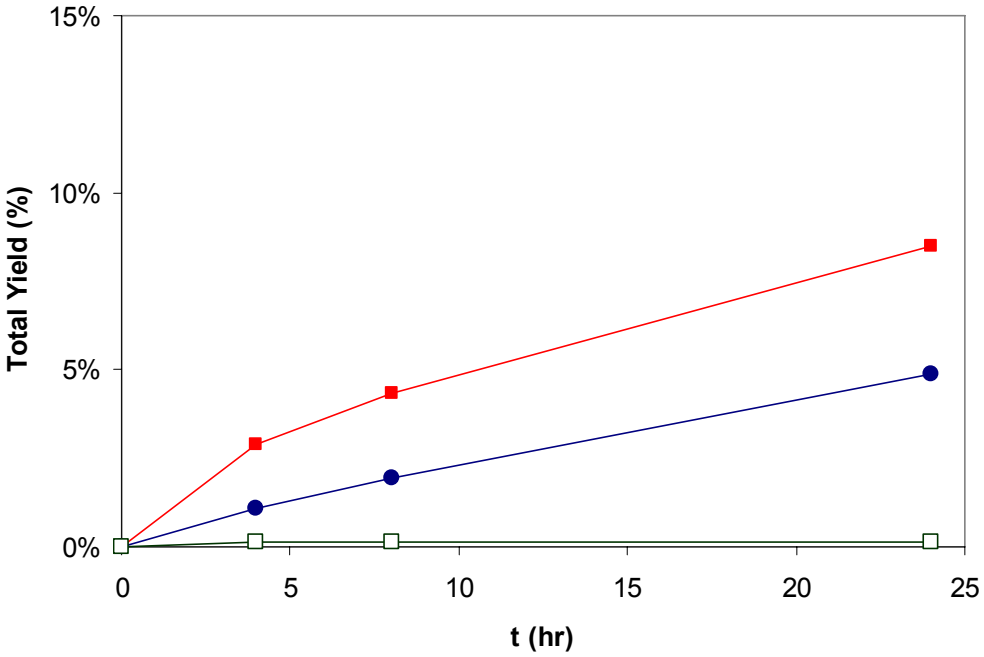



**Figure 5.2.** Aldol reaction yield (alcohol + olefin) with homogeneous catalysts: acetic acid (□), propylamine (●), and propylamine + acetic acid (■). Reaction conditions: 50 mM *p*-nitrobenzaldehyde in 1:1 acetone/methanol, 10 mol% each catalyst, 25°C

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 intermediate[6] 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.

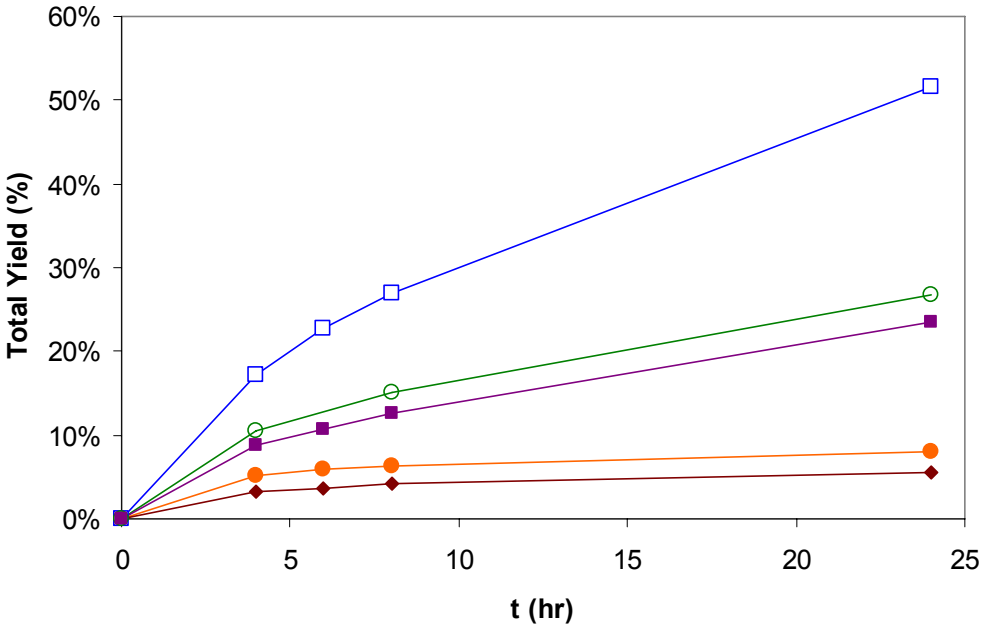



**Figure 5.3.** Kinetic profiles for aldol reaction with homogeneous amino acid catalysts. Reaction conditions: 50 mM *p*-nitrobenzaldehyde in 1:1 acetone/methanol, 10 mol% catalyst, 25°C. Catalysts: proline (□), **7** (○), **6A** (■), ammonium acetate (●), **6C** (♦)

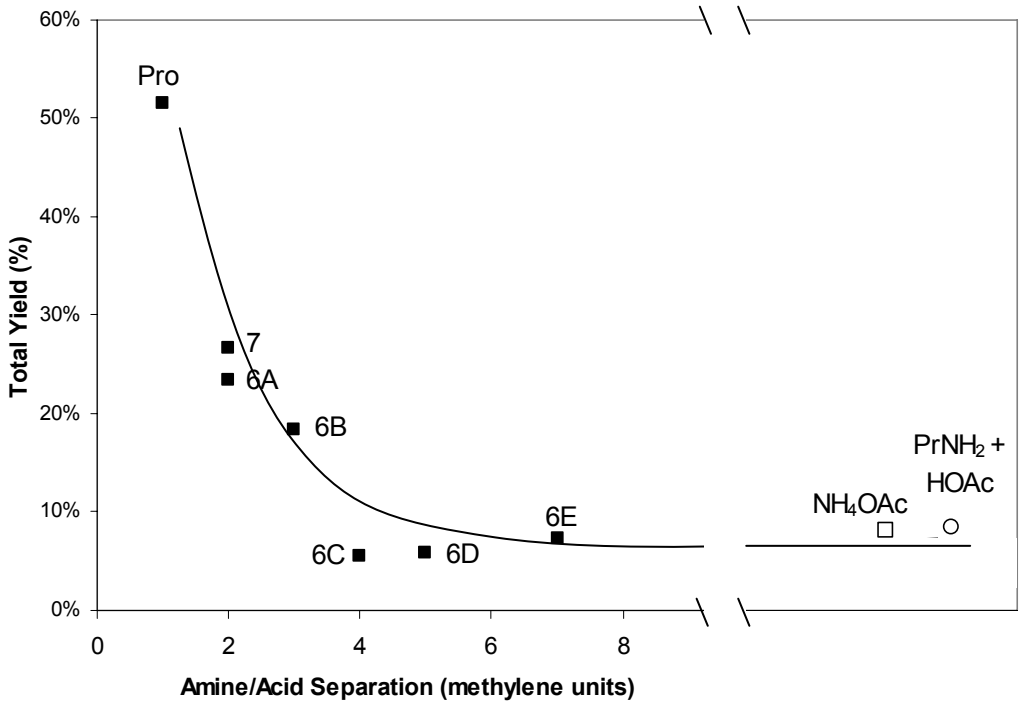



**Figure 5.4.** Total yield of aldol product formation (alcohol + olefin) for various homogeneous amino acid catalysts as a function of amine/acid separation. Reaction conditions: 50 mM *p*-nitrobenzaldehyde in 1:1 acetone/methanol, 10 mol% catalyst, 24 hrs, 25°C. The data points for ammonium acetate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

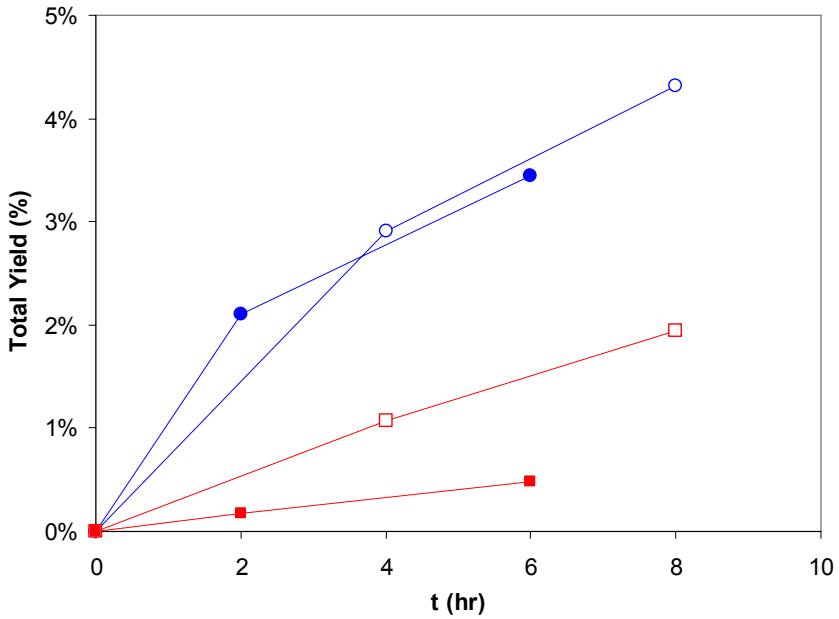



**Figure 5.5.** Comparison of kinetic profiles for aldol reaction with homogeneous catalysts propylamine (■,□) and propylamine/acetic acid (●,○). Reaction solvent: acetone (filled points) or 1:1 acetone/methanol (open points)

**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 |
| **$PrNH_2$ + HOAc** | 13 |
| **$PrNH_2$** | 42 |

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

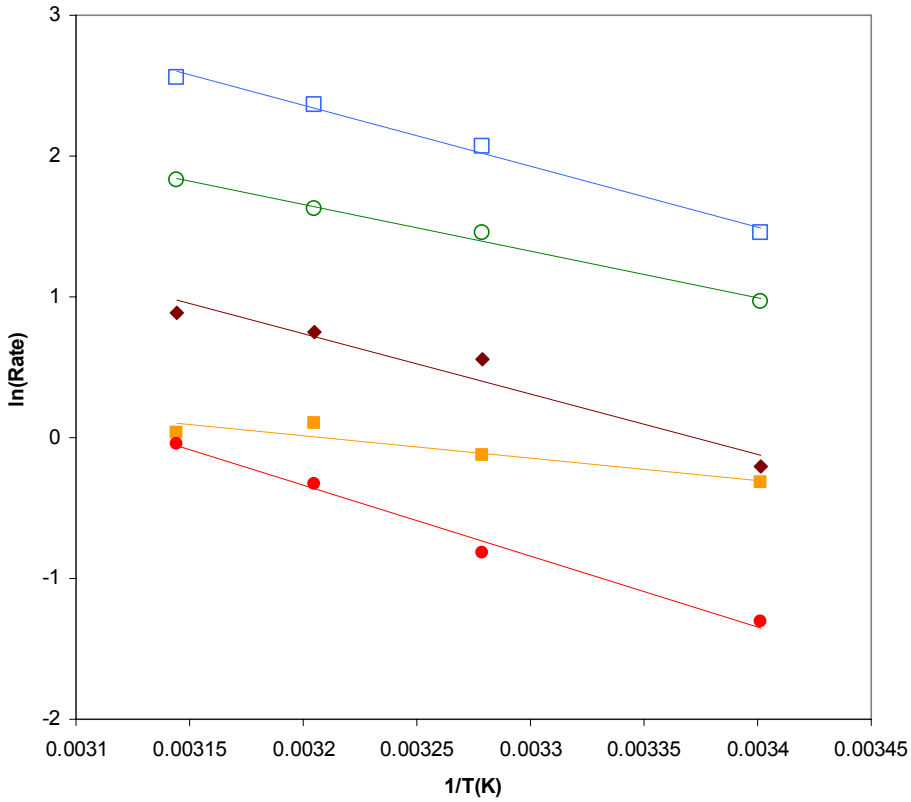



**Figure 5.6.** Arrhenius plots for homogeneous amino acid aldol catalysts. Proline (□), **7** (○), **6C** (♦), propylamine + acetic acid (■), propylamine (●). Rate data refer to the initial rate of product formation (alcohol + olefin) over the first 1–2 hours of reaction (conversion < 12%).

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.

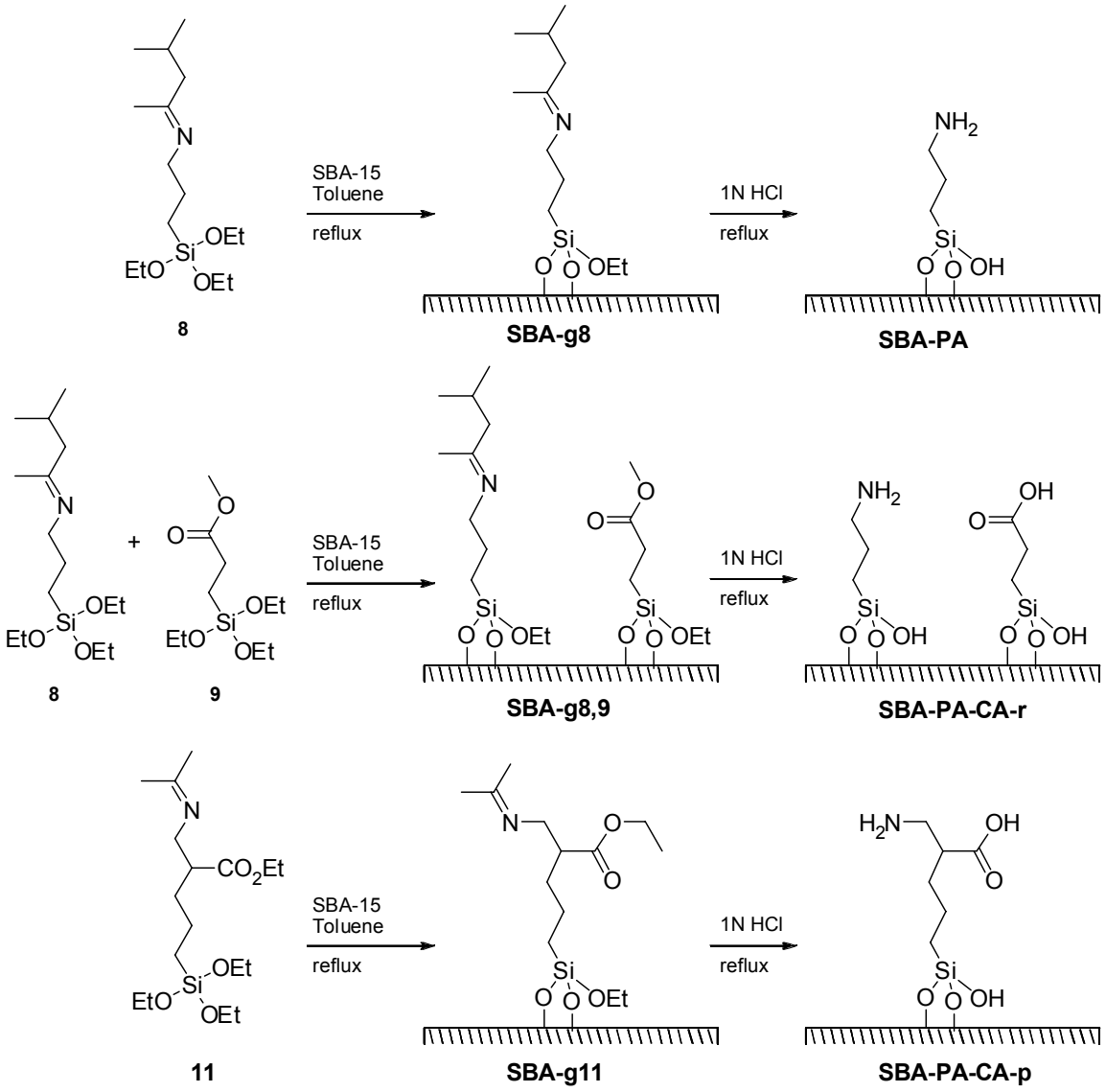
**Heterogeneous Catalysis**

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.

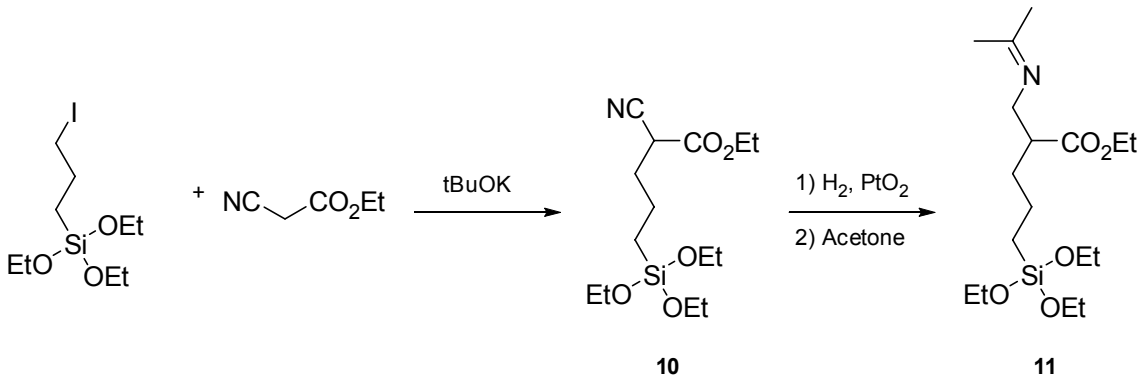
Propylamine groups were immobilized by grafting an imine-containing silane onto SBA-15, followed by hydrolysis.* The resulting material is denoted **SBA-PA**. A catalyst containing randomly-distributed propylamine and carboxylic acid groups (**SBA-PA-CA-r**) was prepared by simultaneously grafting two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

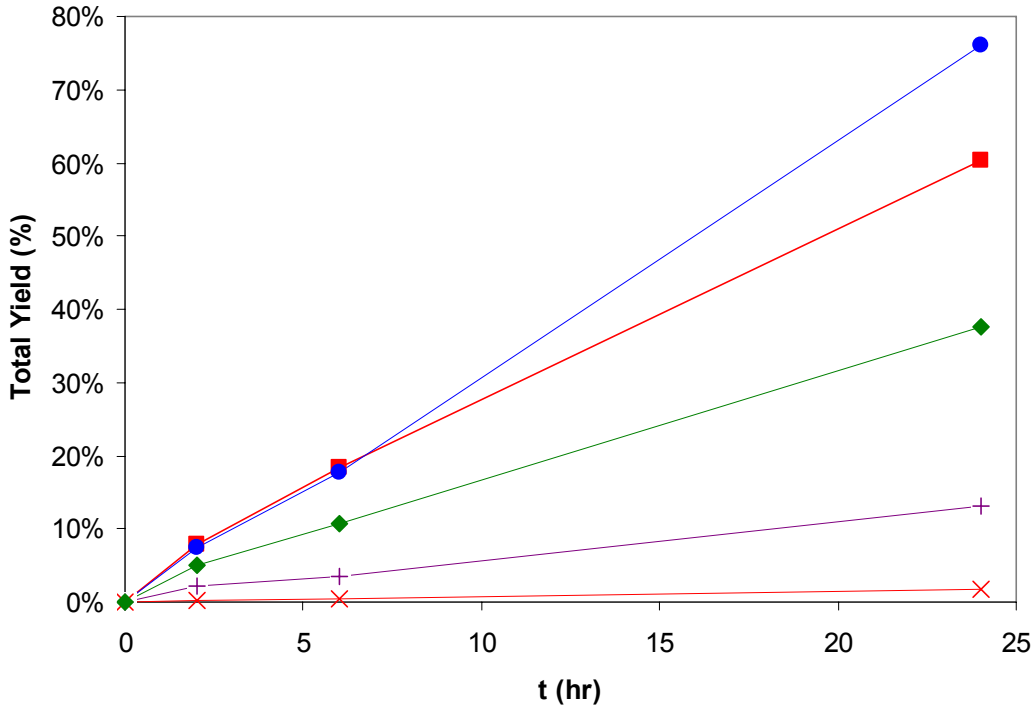



**Figure 5.7.** Kinetic profiles for aldol reaction with heterogeneous amine/acid catalysts. Reaction conditions: 50 mM *p*-nitrobenzaldehyde in acetone, 10 mol% heterogeneous amine and/or 10 mol% carboxylic acid, 25°C. Catalysts: **SBA-PA-CA-r** (●), **SBA-PA** (■), **SBA-PA-CA-p** (♦). For comparison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

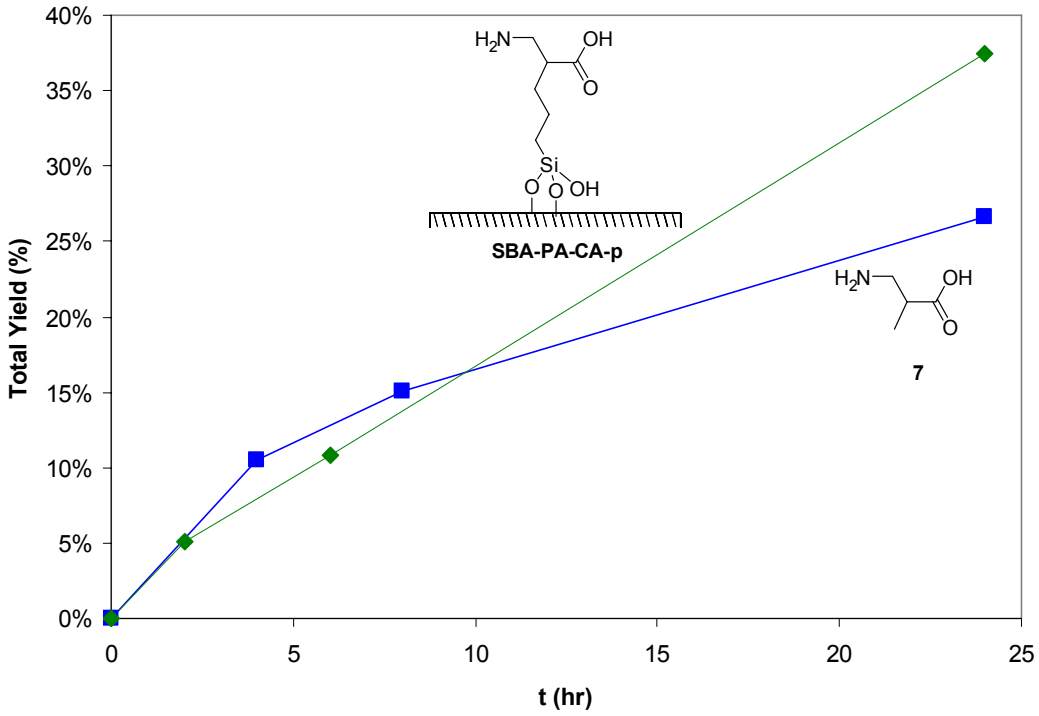



**Figure 5.8.** Comparison of kinetic profiles for aldol reaction with homogeneous and heterogeneous amino acid moieties. Catalysts: **7** (■) in 1:1 acetone/methanol, **SBA-PA-CA-p** (♦) in acetone

**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 ($pK_a$ ~ 4–5). The silanol density of SBA-15 has been estimated at ~ 4 $nm^{-2}$ which is equivalent to ~ 5 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.

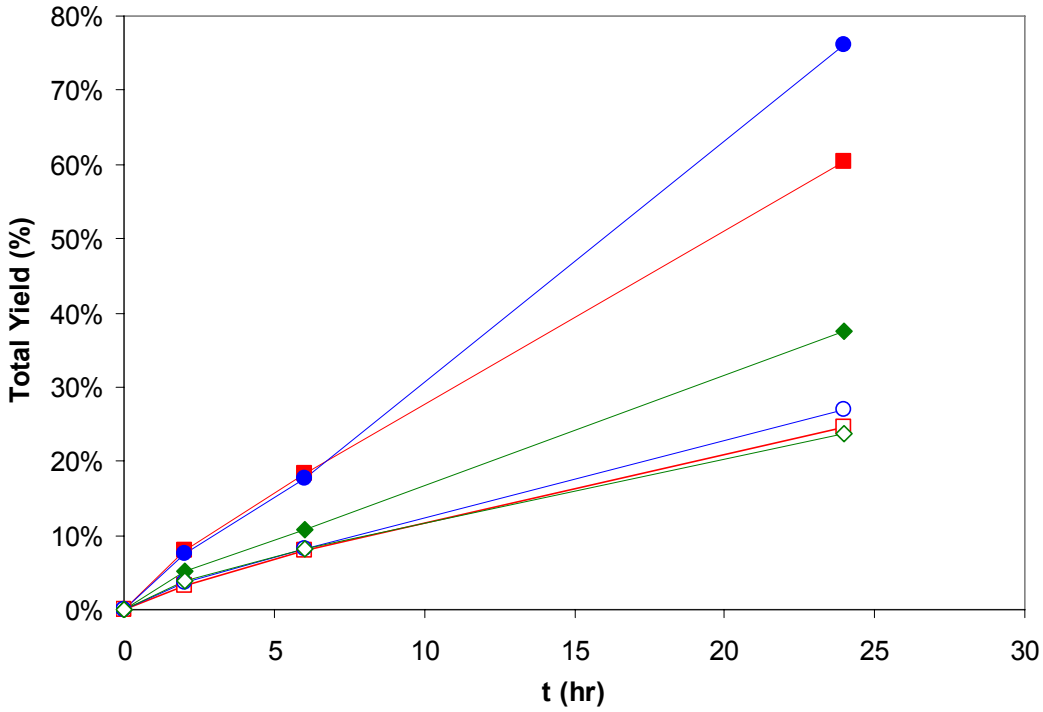



**Figure 5.9.** Comparison of kinetic profiles for aldol reaction with unsilylated (filled symbols) and silylated (open symbols) heterogeneous catalysts: **SBA-PA(-TMS)** (■,□), **SBA-PA-CA-r(-TMS)** (●,○), and **SBA-PA-CA-p(-TMS)** (♦,◊). Reaction conditions: 50 mM *p*-nitrobenzaldehyde solution in 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.

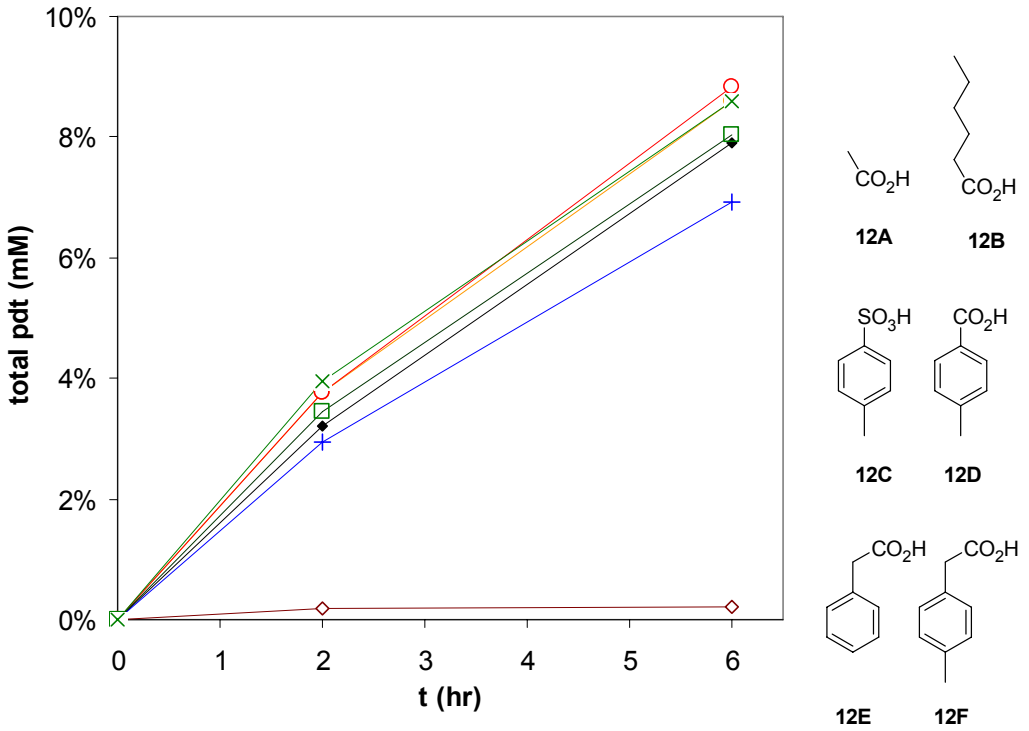



**Figure 5.10.** Total yield of aldol product formation (alcohol + olefin) catalyzed by **SBA-PA-TMS** + homogeneous acid: no acid (♦), **12A** (+), **12B** (×), **12C** (◊), **12D** (○), **12E** (●), **12F** (□). Reaction conditions: 6 mL of 50 mM *p*-nitrobenzaldehyde solution in acetone, 10 mol% heterogeneous 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-$NH_2$-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).

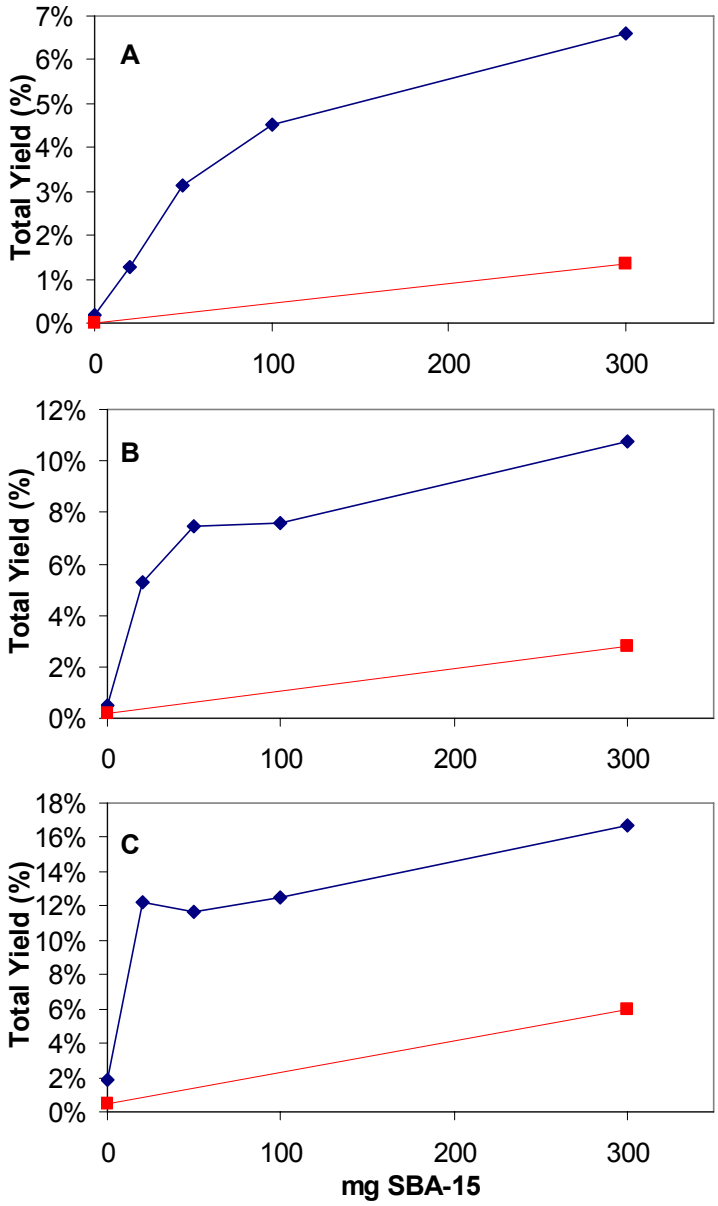



**Figure 5.11.** Total yield of aldol product formation (alcohol + olefin) catalyzed by homogeneous amine + unsilylated SBA-15 (♦) or silylated SBA-15 (■) after reaction times of: (A) 2 hrs, (B) 6 hrs, and (C) 24 hrs. Reaction conditions: 6 mL of 50 mM *p*-nitrobenzaldehyde solution in acetone, 10 mol%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

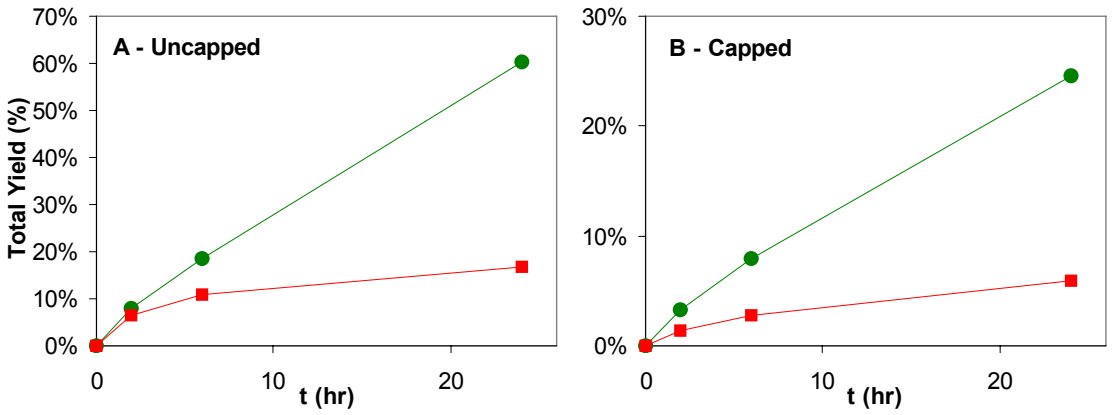



**Figure 5.12.** Kinetic profiles for aldol reaction catalyzed by SBA-15 + untethered propylamine (■) and propylamine groups tethered to silica, **SBA-PA(-TMS)** (●). In (A) the silanols of SBA-15 and **SBA-PA** are uncapped, and in (B) silanols are capped with TMS groups. Reaction conditions: 6 mL of 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.

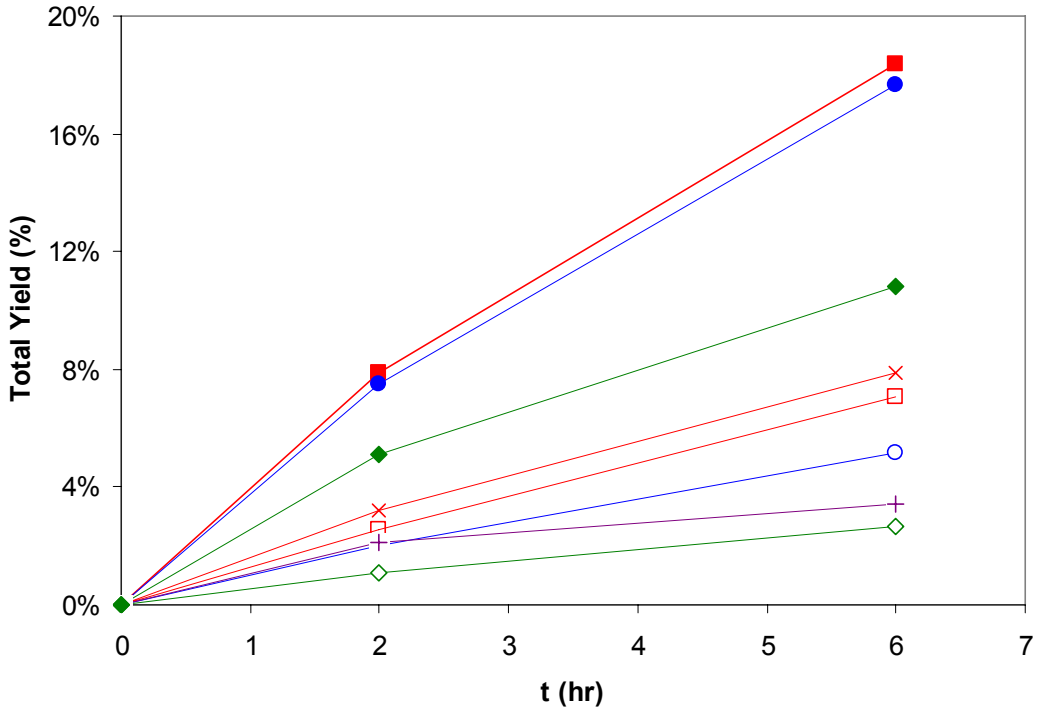



**Figure 5.13.** Comparison of kinetic profiles for aldol reaction with heterogeneous catalysts **SBA-PA** (■,□), **SBA-PA-CA-r** (●,○), and **SBA-PA-CA-p** (♦,◊). Reaction solvent: acetone (filled points) or 1:1 acetone/methanol (open points). For comparison purposes, the data for **SBA-PA-TMS** in 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).

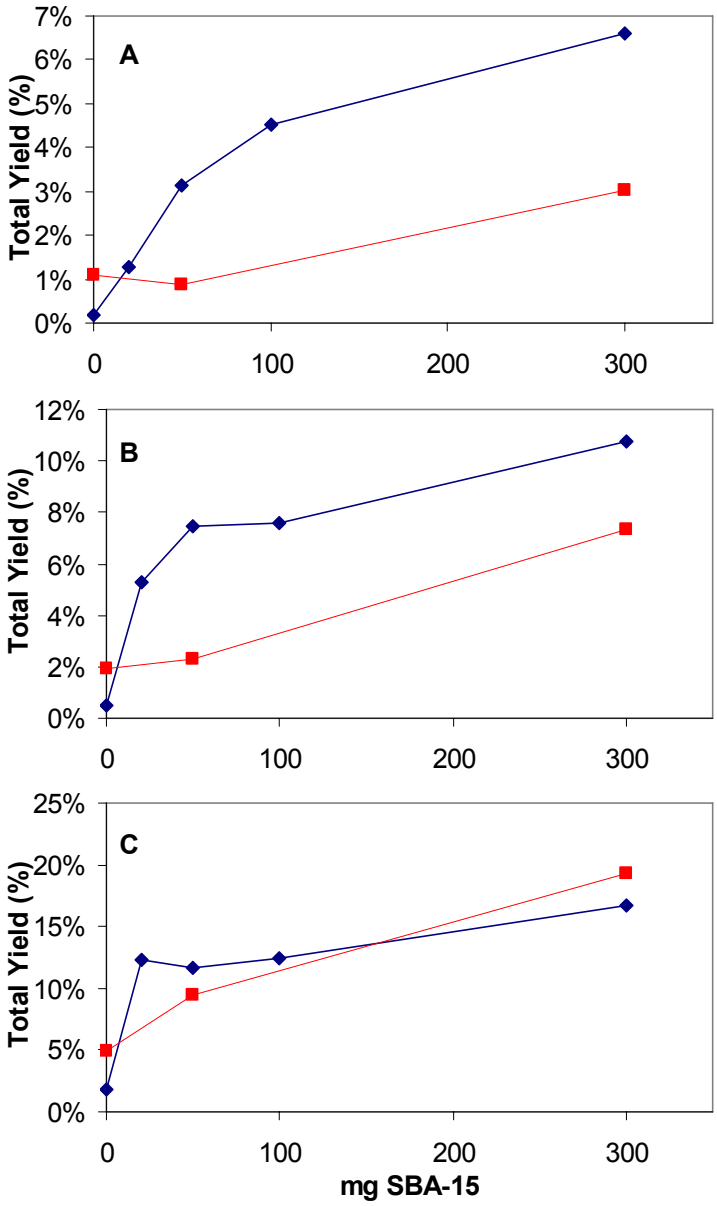



**Figure 5.14.** Total yield of aldol product formation (alcohol + olefin) catalyzed by homogeneous amine + SBA-15 after reaction times of: (A) 2 hrs, (B) 6 hrs, and (C) 24 hrs. Reaction conditions: 6 mL of 50 mM *p*-nitrobenzaldehyde solution in acetone (♦) or 1:1 acetone/methanol (■) , 10 mol% propylamine,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

$^1$H 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 μmol 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.

**Acknowledgements**

This work was supported by a National Science Foundation Graduate Research Fellowship and by the Department of Energy.

# References


1. Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002,** 58, (41), 8167.
2. Kubota, Y.; et al. *Chem. Lett.* **2003,** 32, (3), 234.
3. Funabiki, K.; et al. *Tetrahedron* **2006,** 62, (21), 5049.
4. List, B. *Acc. Chem. Res.* **2004,** 37, (8), 548.
5. Sakthivel, K.; et al. *J. Am. Chem. Soc.* **2001,** 123, (22), 5260.
6. Agami, C.; Puchot, C.; Sevestre, H. *Tet. Lett.* **1986,** 27, (13), 1501.
7. Climent, M. J.; et al. *J. Mol. Cat. A* **2002,** 182, (1), 327.
8. Climent, M. J.; et al. *Adv. Synth. & Cat.* **2002,** 344, (10), 1090.
9. Zeidan, R. K.; Hwang, S. J.; Davis, M. E. *Angew. Chem., Int. Ed. Engl.* **2006,** 45, (38), 6332.
10. Zeidan, R. K.; Davis, M. E. *J. Catal.* **2007,** 247, (2), 379.
11. List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000,** 122, (10), 2395.
12. Davis, M. E.; Davis, R. J. *Fundamentals of Chemical Reaction Engineering*. 1st ed.; McGraw-Hill: New York, 2003; Chapter 6.
13. Hicks, J. C.; et al. *Chem. Mater.* **2006,** 18, (21), 5022.
14. Mendez, A.; et al. *J. Chromatogr. A* **2003,** 986, (1), 33.
15. Nawrocki, J. *J. Chromatogr. A* **1997,** 779, (1-2), 29.
16. Shenderovich, I. G.; et al. *J. P. Chem. B* **2003,** 107, (43), 11924.
17. Inagaki, S.; Fukushima, Y.; Kuroda, K. *J. Chem. Soc., Chem. Commun.* **1993**, (8), 680.
18. Dube, D.; et al. *Micro. Meso. Mater.* **2005,** 79, (1-3), 137.

19. Zhao, X. S.; Lu, M. G. Q.; Song, C. *J. Mol. Cat. A* **2003,** 191, (1), 67.

20. Li, Y.; et al. *J. P. Chem. B* **2004,** 108, (28), 9739.

21. Matsura, V.; et al. *J. Mat. Chem.* **2004,** 14, (20), 3026.

22. Zhao, D. Y., Huo, Q.; Feng, J.; Chmelka, B.; Stucky, G. *J. Am. Chem. Soc.* **1998,** 120, (24), 6024.

23. Zhao, D. Y.; et al. *Science* **1998,** 279, (5350), 548.

## Additional Data

| | | | | Product Concentrations (mM) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 2hr | | 4hr | | 6hr | | 24hr | |
| Entry | Catalyst 1 | Catalyst 2 | Solvent | 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 | **$NH_4OAc$** | | 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

*Chapter 6*

# SUMMARY

My work has demonstrated several new ways of functionalizing mesoporous silica with discrete pairs of disparate organic functional groups. In Chapter 2, the ring-opening of surface-bound sultones was used to generate alkylsulfonic acid/thiol pairs attached to a single carbon tether. In Chapter 3, arylsulfonic acid/thiol pairs were generated using a two-point imprinting approach. In Chapter 4, the sultone approach was again used to create single-site pairs of alkylsulfonic acid and amines. And in Chapter 5, amino acid sites were pre-formed in an organosilane precursor and then grafted onto the silica surface.

The acid/thiol catalysts were shown to be very effective catalysts for the synthesis of bisphenols. Both the alkyl- and arylsulfonic acid catalysts exhibited high regioselectivity to the desired *p*,*p*' isomer of bisphenols A and Z, with isomer ratios of 14–19. It was shown that the promoting effect of thiols and the sensitivity to acid/thiol distance are both inversely related to the reactivity of the ketone. With trifluoroacetone, the effect of thiols is minimal. With acetone, acid/thiol pairing is important for catalysts with weaker acid sites (the two sites should be as close together as possible), but irrelevant when stronger acid sites are present. And finally, in the case of cyclohexanone, the least-reactive ketone studied, acid/thiol pairing leads to improved catalytic properties with both weaker and stronger acid sites.

With the acid/base catalysts discussed in Chapter 4, a different effect of pairing on aldol catalytic activity was demonstrated. When strong sulfonic acid sites coexist with weak base sites, pairing is not desirable, as the acid and base sites neutralize one another. When the two sites are randomly distributed on a catalyst surface, any observed acid/base cooperativity must be due to spatially isolated sites too far apart to neutralize.

With weaker acids, such as carboxylic acids, this isolation is unnecessary, which allows for homogeneous catalysts such as amino acids to remain active in solution. In Chapter 5, carboxylic acid and primary amine were used to catalyze the aldol reaction in solution, and the two groups exhibit cooperative catalysis, which is improved when the two groups are attached to each other with a short tether. When the acid and amine groups are untethered, binary diffusional limitations reduce the catalytic activity.

Heterogeneous silica catalysts functionalized with primary amine groups also exhibit cooperative catalysis in the aldol reaction. Amines and surface silanols are both necessary for good catalytic activity. Silanols activate reacting groups through hydrogen bonding interactions, so reaction solvents that have hydrogen-bonding ability (*e.g.*, alcohols) must be avoided.

In general, I have shown that the local arrangement of functional groups on the surface of a bifunctional heterogeneous catalyst plays a role in the catalytic activity of the material. The degree to which the catalytic activity depends on the group-to-group distance depends on the type of functional groups and the reaction being catalyzed.

*Chapter 7*

# FUTURE CONSIDERATIONS

The work I have described in the preceding chapters is only one step in the design of cooperative heterogeneous catalysts. The synthetic methodologies developed are versatile and should allow for the synthesis of other paired bifunctional catalysts. For instance, the surface-bound sultone groups described in Chapters 2 and 4 can also be ring-opened by a variety of other nucleophiles, including amines, phosphines, sulfides, and halides. There is the possibility of generating a vast library of catalysts in which sulfonic acid groups are paired with a second functionality. This ring-opening motif could also be extended to other cyclic functional groups, such as lactones or cyclic anhydrides, leading to other paired surface functional groups.

Furthermore, theoretical and computational studies might be able to provide insight into why the bisphenol Z reaction is so highly dependent on acid/thiol distance, and why the distance-dependence of the bisphenol A reaction varies with acid strength. Additionally, the details of the thiol-promotion mechanism are still not fully understood and further mechanistic studies could be of immense help in designing even better catalytic systems. As it currently stands, the fundamental origins of "distance-dependence" are not well understood.

In the aldol reaction, it is still not known why the cooperative effect of carboxylic acids was not observed when the amine groups are tethered to silica, even after the silanols were capped. It is possible that immobilizing amines and carboxylic acids on a non-siliceous support such as a polymeric resin could provide data complementary to that

described here, without the complicating effect of silanol interactions. Another possible direction would be to silylate the surface of silica first before introducing amine/acid-paired moieties, such that the carboxylic acid groups are not capped.

New and better synthetic heterogeneous catalysts will surely emerge in the future which extend the idea of polyfunctional cooperativity to other classes of reactions beyond those which are currently known to benefit from cooperative catalysis. Identifying the appropriate functional groups and organizing them with the correct spatial orientation on the surface are both key steps in designing good cooperative materials. There are still many obstacles which must be overcome before synthetic materials can approach the catalytic prowess of enzymes.

The exact distance between disparate groups in paired active sites on a catalyst surface should ideally be optimized for the reaction of interest. This optimization requires that the synthetic methodology for the creation of paired sites be amenable to fine-tuning the distance between the groups. Along these lines, new methods for characterizing the distance between disparate surface functional groups would be valuable. Bifunctional probe molecules such as *o*-phthalaldehyde, which binds to adjacent amine and thiol groups, can be used to verify the distances between two different species.[1, 2] But there are currently few such probe molecules available, and more will be needed. It would also be beneficial if the distance between the reactive groups in a two-point probe molecule could be varied, which would allow for an estimation of the distribution of group-to-group distances.

In order to rival enzymatic catalysts, two aspects of enzymes must be co-opted: the number of cooperating functional groups should be increased beyond two, and

chirality must be introduced to these polyfunctional catalysts. Though this may seem a daunting challenge, the promise of novel catalytic activity is immense.

One current technology which may be of some help in this task is combinatorial chemistry. The chemical industry uses automated combinatorial chemistry to search for catalysts well suited to a particular reaction.[3] Combinatorial approaches can be extended to search for binary catalytic systems. A similar technique is already used when both the metal center and ligand are varied in the search for an optimal organometallic catalyst,[4] but these are two components of a single catalyst. It would be valuable to consider a multi-dimensional combinatorial search as a route to finding new cooperative catalytic systems. Care must be taken in choosing the search library, since the components of a binary catalytic system can be inactive individually and lead to good activity only when both are present.[5]

The introduction of chirality into polyfunctional cooperative catalysts is already underway. The entire field of asymmetric proline catalysis relies on amine/carboxylic acid cooperativity to drive enantioselectivity. Heterogeneous acid/base catalysis using a proline-derived moiety immobilized on silica was recently demonstrated, although with modest enantioselectivity.[6] The body of literature on transcribing chirality from molecular precursors to hybrid silicas also continues to increase.[7-9] Ultimately, combining asymmetric heterogeneous catalysis with principles of cooperativity should lead to improved catalytic materials using currently available technology.

# References


1. Bass, J. D.; Katz, A. *Chem. Mater.* **2006,** 18, (6), 1611.
2. Roth, M. *Anal. Chem.* **1971,** 43, (7), 880.
3. Weinberg, W. H.; et al. *Curr. Opin. Solid State Mat. Sci.* **1998,** 3, (1), 104.
4. Stambuli, J. P.; Hartwig, J. F. *Curr. Opin. Chem. Biol.* **2003,** 7, (3), 420.
5. Kanemasa, S.; Ito, K. *Eur. J. Org. Chem.* **2004,** 2004, (23), 4741.
6. Zhong, L.; Xiao, J. L.; Li, C. *Chinese Journal of Catalysis* **2007,** 28, (8), 673.
7. Bied, C.; et al. *J. Sol-Gel Sci. Tech.* **2003,** 26, (1-3), 583.
8. McMorn, P.; Hutchings, G. J. *Chem. Soc. Rev.* **2004,** 33, (2), 108.
9. Marx, S.; Avnir, D. *Acc. Chem. Res.* **2007,** 40, (9), 768.