

*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.<sup>1, 2</sup> 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.<sup>3</sup> 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,<sup>4</sup> 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.<sup>5</sup>

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.<sup>6</sup> The body of literature on transcribing chirality from molecular precursors to hybrid silicas also continues to increase.<sup>7-9</sup> 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.