SYNTHETIC PEPTIDES IN ASYMMETRIC CATALYSIS

Reported by Erin K. Davis February 21, 2011

INTRODUCTION

Enzymes are often able to catalyze reactions with remarkable stereoselectivity and substrate specificity. The global structure of enzymes provides a cleft into which the substrate can only bind in certain orientations, while the individual structures of amino acids enable selectivity through specific contacts with the substrate. Synthetic chemists have drawn inspiration from enzymes, employing catalyst systems ranging from single amino acids to engineered proteins. Falling in the middle of these two extremes, small peptide catalysts possess several attractive attributes. Peptides containing even a small number of amino acids can provide a level of secondary structure that is adequate for the transfer of chirality.[i] Additionally, the inherent modularity of peptides allow for facile tuning of reactivity. Diverse catalyst libraries can be easily accessed through automated peptide synthesis and combinatorial split-pool techniques. This seminar will focus on recent developments in the field of synthetic peptide catalysis, including kinetic resolution, desymmetrization, and site-selective derivatization of natural products.

PEPTIDE-CATALYZED KINETIC RESOLUTION AND DESYMMETRIZATION

Compounds possessing axial chirality, such as BINAP, are valuable ligands in asymmetric synthesis. However, despite their synthetic utility and occurrence in natural products, methodology for the synthesis of axially chiral compounds has remained an underdeveloped area. Miller and co-workers recently developed a peptide-catalyzed electrophilic aromatic substitution that is atropisomer-selective, enabling the dynamic kinetic resolution of atropisomers with low barriers to interconversion. Using a tripeptide-derived catalyst and *N*-bromophthalimide as the bromine source, a variety of biaryls were produced in good yield and high e.r.[ii] Peptide-catalyzed kinetic resolution has also been investigated for other classes of substrates.

The desymmetrization of 1,3-diols is another active area of research. Hoveyda, Snapper, and co-workers demonstrated that achiral 1,3-diols could be silylated with a high degree of enantioselectivity using a dipeptide-based catalyst.[iii] The same catalyst was later applied to the enantioselective silylation of triols, enabling the synthesis of the natural products cleroindicins D, F, and C.[iv] This development was significant because silylation lacks any enzymatic precedent, unlike other methods of desymmetrization,

including acylation and sulfonylation. Miller and co-workers have shown that a π-methyl-histidine-based tetrapeptide catalyst is capable of enantioselective sulfonylations of *meso* 1,3 diols in good yield and good to excellent e.r., with lower catalyst loadings than the Hoveyda/Snapper system. [v] Similar catalysts have been employed in the phosphorylation of inositol.[vi]

PEPTIDE-CATALYZED SITE-SELECTIVE DERIVATIZATION

In nature, tailoring enzymes are capable of site-selectively modifying complex polyfunctional molecules. However, such site-selective modifications have presented a challenge for synthetic chemists. Site-selective functionalization has potential utility in the synthesis of natural product derivatives that are of biological interest. In some cases, catalysts enhance the natural reactivity of a functional group, while others are powerful enough to overcome the inherent kinetic preference for functionalization of one site over another. Screening peptide catalyst libraries can reveal catalysts that are selective for different sites on the molecule. This approach was applied in synthesizing acylated derivatives of the natural product apoptolidin A, which has been shown to selectively induce apoptosis in certain cell lines.[vii] With eight hydroxyl groups, six of them secondary, apoptolidin A presented an interesting challenge for site-selective modification. Extensive screening enabled the synthesis of three previously unknown apoptolidin A derivatives, which were then tested for biological activity.

SUMMARY

Synthetic peptide catalysts have proven to be useful for a number of transformations. Although peptide catalysts have been successful as catalysts in desymmetrization and kinetic resolutions, site-selective modification is an area in which peptide catalysts have not been as successful, due mostly to the higher demands placed on catalysts to overturn the inherent reactivity of a molecule. Gaining an advanced mechanistic understanding of these enantioselective reactions could begin to enable the rational design of catalysts for site-selective modification of natural products.

REFERENCES

[i] Colby Davie, E.A.; Mennen, S.M.; Xu, Y.; Miller, S.J., *Chem. Rev.* **2007**, *107*, 5759.
[ii] Gustafson, J.L.; Lim, D.; Miller, S.J., *Science* **2010**, *328*, 1251.
[iii] Zhao, Y.; Rodrigo, J.; Hoveyda, A.H.; Snapper, M.L., *Nature* **2006**, *443*, 67.
[iv] You, Z.; Hoveyda, A.H.; Snapper, M.L., *Angew. Chem. Int. Ed.* **2009**, *48*, 547.
[v] Fiori, K.W.; Puchlopek, A.L.A.; Miller, S.J., *Nature Chem.* **2009**, *1*, 630.
[vi] Xu, Y.; Sculimbrene, B.R.; Miller, S.J. *J. Org. Chem.* **2006**, *71*, 4919.
[vii] Lewis, C.A.; Longcore, K.E.; Miller, S.J.; Wender, P.A. *J. Nat. Prod.* **2009**, *72*, 1864.