The relationship between enzyme design and synthetic methodology is evaluated with regard to Arnold and co-workers’ report of a novel aziridination enzyme.

Figure 1. Cytochrome P450s are powerful oxidation enzymes.

Arguably, there has never been any evolutionary pressure to produce the high-energy nitrogen analogue of dioxygen.

Synthetic chemists have created several imaginative approaches to transition metal-based aziridination of alkenes by using metal catalysts including those with salen ligand-based systems. Interestingly, some methods rely on heme-inspired metal porphyrins, much like the center of the P450. The rarity of aziridines in nature provides an impetus to investigate these rings, particularly their nucleophilic ring-opening transformations. Because of the poor leaving group ability of the “RNH−” functionality, the parent NH aziridines are of limited utility compared to their epoxide congeners.

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that enjoy a healthier relationship with the more stable “RO−” leaving group. Thankfully, in the lab, aziridines’ electrophilic properties can be modulated by the attachment of an electron-withdrawing group to nitrogen. Arnold and co-workers were able to teach P450 a new trick, coaxing this powerful enzyme to accept nitrenes as opposed to the more familiar oxene ligands (Figure 2).1

Toluenesulfonyl azide acts as the nitrogen-based oxidant in this chemistry. The dinitrogen evolution that accompanies aziridination is the driving force of this new synthesis. From a chemist’s standpoint, high enantioselectivity of the reaction is a particularly useful feature, although the reliance on toluenesulfonyl chemistry is somewhat limiting, given the relatively harsh conditions needed to remove this protecting group at a later stage. Screening of additional generations of these enzymes could select for those able to use the nosyl group and would result in a more user-friendly version of the reaction. In addition, the substrate scope is heavily skewed toward aromatic group-containing alkenes. It will be interesting to see how aliphatic molecules, which are often more synthetically useful than their aromatic counterparts, fare in this transformation.

Arnold’s report is an important milestone in this storied field of inquiry as it shows that biological systems can be quite proficient in transferring nitrene ligands to alkenes, provided that P450s are tricked into this new role by unnatural oxidants such as azides. Arnold astutely points out that this aziridination represents only one of myriad reactions that might be possible by manipulating the natural promiscuity of enzymes through evolution; this opportunity should continue to inspire scientists’ creativity.

Professor Yudin blogs about chemistry at the amphoteros blog.

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