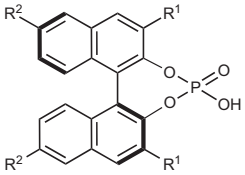
ASYMMETRIC SYNTHESIS

Catalysis exposed

Science **340**, 737–743 (2015)



Every chemist is well aware of the benefits of efficient catalysts. They can give significant advantages when formulating a synthetic strategy — particularly when trying to control reaction enantioselectivity — and form the basis of countless industrial processes, many of which would not be economical otherwise. However, despite their prevalence, there is still much that we do not know about complex catalytic processes. The ideal situation of rationally designing catalysts with predictable chemical reactivity is therefore an unachieved goal, and is hampered by our inability to decipher and control the way in which they work.

Led by Matthew Sigman at the University of Utah and F. Dean Toste at the University of California, Berkeley, a team of researchers have now developed a combined experimental and computational strategy to determine how the structural properties of a catalyst that interacts non-covalently with its substrate can dictate the reaction outcome. They concentrate their study on a particularly puzzling set of asymmetric C–N coupling reactions catalysed by 1,1′-bi-2-naphthol (BINOL)-derived chiral phosphoric acids, chosen specifically because the rationale for their enantioselectivity is not immediately clear. They initially generate a library of catalysts based on this BINOL–phosphoric acid scaffold with the structure of each molecule differing in a systematic way; the procedure is also repeated to create a library of systematically modified substrates. Sigman, Toste and colleagues classify each of these individual changes based on their geometric and electronic properties. Then, through experimental examination, they determine how each of these small modifications influences the course of the catalytic reaction, and in particular, the observed enantioselectivity.

A diverse network of data is generated linking specific changes in structure to reaction outcomes, and when processed using linear regression algorithms, the factors controlling the catalytic reaction and its observed enantioselectivity are revealed. The resulting computational model is then used to accurately predict the enantioselectivity of further catalyst–substrate combinations. This method may now present a general approach for the analysis of other complicated catalytic systems. *JH*

NANOMEDICINE

MOFs deliver

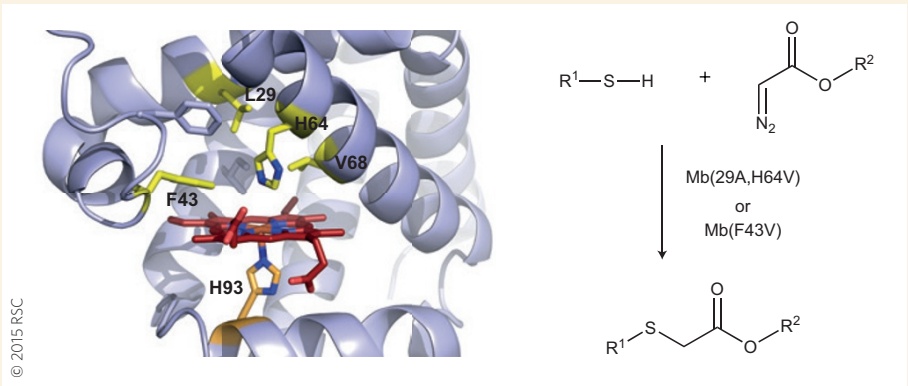
Chem. Sci. **6**, 1640–1644 (2015)

Deploying drugs throughout the body via a patient's bloodstream is not only wasteful, but can also have adverse effects on healthy tissues. Minimizing such side effects not

BIOCATALYSIS

Harnessing haemoproteins

Chem. Sci. http://dx.doi.org/10.1039/c5sc00080g (2015)



Carbon–sulfur bonds occur in a wide variety of bioactive molecules including pharmaceuticals, however, the most direct synthetic route to their formation — by means of metal-catalysed insertion of diazo-compounds into thiol groups — often suffers from side-reactions and a lack of enantioselectivity. This can hinder the synthesis of complex frameworks. Now, Rudi Fasan and co-workers at the University of Rochester, USA, have shown that the protein myoglobin (Mb) can be engineered to catalyse this reaction, with almost complete conversion in some cases. This, they say, is the first example of a biocatalytic synthesis of thioethers based on an intermolecular carbene insertion.

Initially the team investigated whether wild-type sperm whale myoglobin showed any catalytic activity for this reaction. The insertion of α-ethyl diazoacetate into the S–H group of thiophenol showed that the haem centre was capable of catalysing almost quantitative conversion, although the turnover properties were modest. In an effort to improve the catalytic properties, Fasan and co-workers developed variant proteins with mutations around the active site (pictured; targeted residues are yellow, the haem cofactor is red). Several mutations that significantly improved the turnover number were identified, with one double mutant — Mb(L29A, H64V) — showing the highest activity.

Synthetically useful catalysts should ideally tolerate a wide range of reactants, so next the team tested the double mutant against a range of different α-diazoesters and alkyl mercaptans or substituted thiophenols. Although the yield and turnover numbers varied, the double mutant was capable of catalysing the insertion reaction using a wide range of starting materials. The catalytic efficiencies observed are one to two orders of magnitude higher than have been observed for similar insertion reactions with transition metal catalysts. Although this double mutant did not show any enantioselectivity, another variant, Mb(F43V), did. Optimizing the conditions enabled Fasan and co-workers to get an enantiomeric excess of 49%. Furthermore, it was shown that the variant myoglobins could be suitable for preparative synthetic chemistry by carrying out larger-scale syntheses and proving their scalability. *RJ*