reactions, usually with chiral catalytic systems, but stereocontrol of cycloadditions promoted by light has proved to be more challenging. This is primarily due to the difficulty of eliminating background reactivity in which reagents that are free from the chiral influence of the catalyst are also photochemically activated and react non-stereoselectively.

Now, a group of researchers from University of Wisconsin–Madison led by Tehshik Yoon have developed a catalytic system that promotes [2 + 2] photochemical cycloaddition of α,β-unsaturated ketones with a high degree of stereocontrol. Photochemically promoted [2 + 2] cycloadditions are the simplest class of this type of reaction and are particularly useful for preparing strained cyclobutane systems. The development hinges on a simple principle that eliminates the problem of background reaction: the catalyst is photoexcited but the reaction substrate is not. The researchers have developed a dual catalyst system to achieve selectivity. The first catalyst is a gadolinium- or europium-based Lewis acid with a chiral dipeptide ligand that coordinates an aryl α,β-unsaturated ketone and provides the chiral environment for asymmetric induction.

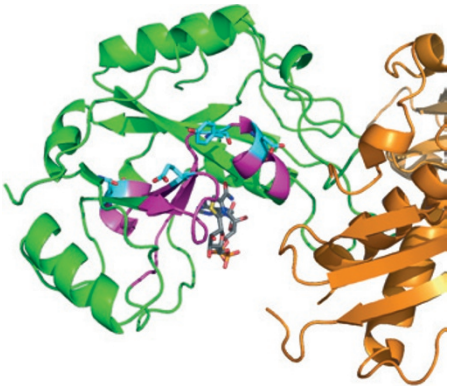
The crucial step involves the single-electron reduction of this activated substrate by a second catalyst, a ruthenium(I) complex, which is generated by visible light irradiation of a ruthenium(II) precursor. After activation and reduction, the substrate then undergoes asymmetric [2 + 2] cycloaddition with an alkyl vinyl ketone giving enantio-enriched substituted cyclobutane products. The key feature of this reaction — that no unwanted background reaction occurs — is illustrated neatly by a lack of reaction if any of the reaction components are removed. The system also incorporates a great deal of flexibility due to the independent roles of the two catalysts and may give a basis for extension to other asymmetric photochemically induced cycloadditions. *PM*

PROTEIN DESIGN

Eliminating epitopes

Proc. Natl Acad. Sci. USA http://dx.doi.org/10.1073/pnas.1321126111 (2014)

Preventing a response from the immune system is one of the main problems hindering the development of protein pharmaceuticals. Such a response is caused by cells in the immune system binding to parts of the protein (known as epitopes) and thereby recognizing that the protein is not naturally produced by the body. This can lead to the production of antibodies that bind to



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the protein, reducing or eliminating its therapeutic effect. Introducing mutations into epitopes is one method of preventing the immune system from recognizing the foreign nature of the protein and thus reducing the immune response. However, introducing enough mutations into the protein's amino acid sequence whilst retaining its overall structure, stability, biological function — and clinical effectiveness — is extremely difficult.

A team led by Chris King at the University of Washington, has now integrated a machine-learning approach with computational protein re-design techniques to enable the removal of epitopes from two proteins. The process involves identifying the epitopes contained within a protein's sequence using computational predictions that include data from binding experiments. The protein's sequence is then improved using a function that introduces mutations whilst retaining the overall structure and penalising the inclusion of sequences known, or calculated to be, epitopes. Mutations in the most stable structures are then combined in a stepwise manner to generate optimized variants. This approach was found to introduce mutations that were similar to previous attempts to de-immunize proteins that used alternative experimental techniques.

To demonstrate the potential of their approach the team attempted to remove three previously identified epitope regions from the toxin domain of a cancer therapeutic called HA22. This therapeutic has been shown to be effective for treating leukemia; however, it can generate an immune response that neutralizes its effectiveness. King and colleagues succeeded in developing several variants that retained similar activity to the original protein. The two most active variants were then tested in patients and produced a significantly reduced immune response. *RJ*

Written by Enda Bergin, Claire Hansell, Paul MacLellan and Russell Johnson.

blogroll

The process

Bloggers shed light on the highs and lows of synthetic chemistry.

Resisting the temptation to tackle this retrosynthetically, let's start at the start. Every project begins with an idea and, blogging at amphoteros, Andrei Yudin outlines (http://go.nature.com/erawn2) the supervisor's joy in bequeathing a crazy idea to a grad student: "as long as none of them violate any laws of thermodynamics, they will be eventually reduced to practice (and improved!) by our capable graduate students and postdocs."

Tasked with turning that idea into reality, the student dives into the literature in search of precedent. Dr Freddy of Synthetic Remarks picks up the tale with a rundown (http://go.nature.com/RVHORa) of the quirks and deficiencies of certain experimental protocols that provoke widespread angst amongst synthetic chemists. Both his post and the follow-up at Derek Lowe's In The Pipeline (http://go.nature.com/JHphjQ) prompted numerous further examples from readers. We've all been there.

With that minefield traversed, it's into the fumehood. There, sooner or later, we all must face what Brandon Findlay of Chemtips calls "the black tar phase" — that one stubborn reaction that simply refuses to be tamed (http://go.nature.com/ttjb2K). He draws out the lessons learned in his struggle with an uncooperative transformation, ultimately advising: "pick what works and discard the rest."

At long last, the final stage arrives. You've navigated the literature. You've beaten the black-tar phase. You've done your experiments, controlling for the possibility that the light at the end of the experimental tunnel is a train. The spoils of publication are yours. The Baran lab's communal blog, Open Flask, regularly fills in the backstories to their published chemistry, with Young Brando's light-hearted look (http://go.nature.com/IZHZin) at a recent paper neatly encapsulating the whole process, from idea to reality.

Written by fluorogrol, who blogs at http://betterlivingthroughchemistry.ghost.io/