

A new twist on catalytic teamwork

Catalysts working in pairs can promote more-effective reactions than can the same catalysts used sequentially. The coupling of an enzyme with a light-activated catalyst offers great potential for organic synthesis. [SEE LETTER P.355](#)

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The development of catalytic reactions is a dominant theme in chemistry, especially in industry, where major efforts are under way to develop large-scale chemical processes that are sustainable and avoid producing unnecessary waste¹. Chemical reactions can be accelerated using many types of catalyst, including metals (or their salts or complexes), small organic molecules, enzymes and light-activated catalysts. Catalysts of all types have advanced to the extent that two or more catalysts can be combined to promote cascade reactions — interconnected transformations, carried out in a single operation, to yield products with selectivities that would be difficult to achieve using the catalysts independently in sequential steps. On page 355, Litman *et al.*² report that the combination of an enzyme with a light-activated catalyst starts a cascade reaction that produces compounds that are versatile intermediates for organic synthesis.

The use of combinations of catalysts could potentially lead to step changes in the efficiency of chemical processes³. Certain combinations of enzymes with small-molecule organic catalysts or transition-metal catalysts have been of particular interest — in part because the chemistry mediated by these different catalyst types is highly complementary, and also because water is used as the main solvent, thus avoiding environmentally harmful organic alternatives. Moreover, such combinations can open up synthetic routes for constructing molecules that would not otherwise be possible⁴. The emergence of light-activated catalysts (photocatalysts) in the past few years has presented opportunities for the development of systems that combine enzymes with photocatalysts.

Enter Litman *et al.*, who have used just such a combination to promote reactions of alkenes — organic compounds that contain carbon–carbon double bonds. Many alkenes can form as isomers, known as (*E*)- and (*Z*)-isomers, which differ in the geometrical arrangement of groups attached to their double bond (Fig. 1a). Although methods exist that allow just one isomer of an alkene to be produced during synthesis, it is often cheaper and easier to prepare alkenes as

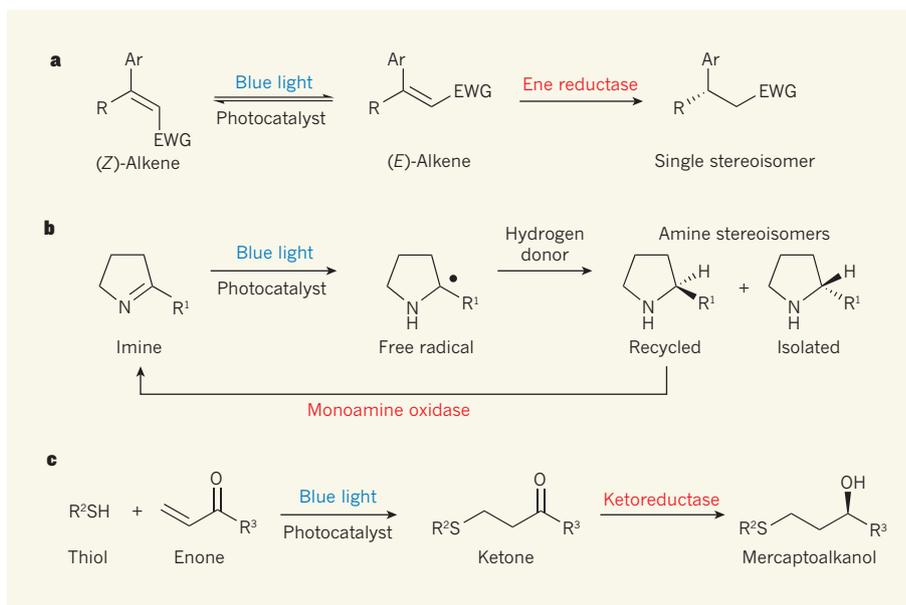


Figure 1 | Combinations of enzymes and light-activated catalysts enable organic reactions. **a**, Litman *et al.*² used a light-activated catalyst (a photocatalyst) *in situ* with an enzyme (ene reductase) to catalyse the conversion of mixtures of (*E*)- and (*Z*)-isomers of alkenes into products that form predominantly as a single stereoisomer (an isomer that contains a particular spatial arrangement of bonds). The photocatalyst promotes the interconversion of the isomers, whereas the enzyme reduces only the (*E*)-isomer. The hashed bond extends into the plane of the figure. **b**, A different photocatalyst has been used⁶ to convert imines into free radicals (dot indicates an unpaired electron), which accept a hydrogen atom from a donor to form amines as a mixture of stereoisomers. The enzyme monoamine oxidase recycles one stereoisomer back to the imine, which is therefore eventually all converted into the other stereoisomer. The solid-wedge bond extends out of the plane of the figure. **c**, Another photocatalyst promotes⁷ the addition of thiols to enones to form ketones, which can be reduced *in situ* by a ketoreductase enzyme to form mercaptoalkanols. R groups represent a variety of organic groups; Ar, aryl group; EWG, electron-withdrawing group.

mixtures of (*E*)- and (*Z*)-isomers. But using such mixtures can be problematic. Alkenes are often chemically reduced during organic syntheses — that is, the carbon–carbon double bonds are converted into single bonds. But the reduction of both types of isomer together typically yields products known as stereoisomers, which have different spatial arrangements of groups attached to a specific carbon atom and can be difficult to separate.

The ideal solution to this problem would be to combine a catalyst that converts (*E*)-alkenes into (*Z*)-alkenes (and vice versa) with a second catalyst that reduces only one of the two alkene isomers, thus yielding only one stereoisomer. For example, if the second catalyst reduces only (*E*)-alkenes, then it initially catalyses the reduction of any of that isomer

found in the original alkene mixture, and then goes on to reduce any (*E*)-isomer produced from the (*Z*)-isomer by the first catalyst. Both isomers of the alkene mixture are thus eventually consumed to make the same product. This is exactly what Litman *et al.* report in the current work.

The authors' catalytic system builds on previous work⁵ that reported the use of iridium-based photocatalysts to interconvert the (*E*)- and (*Z*)-isomers of a range of different alkenes. In the current study, Litman and colleagues combined analogues of those iridium photocatalysts with ene reductase enzymes, which reduce alkenes and are generally (*E*)-selective, although the authors also tested a (*Z*)-selective ene reductase in their system.

The researchers optimized various

parameters of their reactions, including the concentrations of the iridium catalyst, the enzyme and the enzyme's cofactor. They developed a system that reduces mixtures of (*E*)- and (*Z*)-isomers of alkenes to form a single stereoisomer, in multi-milligram quantities (Fig. 1a). The authors went on to convert the stereoisomer into a variety of biologically active molecules and key intermediates that have been used to prepare such molecules, thereby highlighting the potential application of their chemistry for preparative organic synthesis.

As Litman *et al.* point out, photocatalytic reactions typically occur at or near to room temperature, which makes them compatible with the thermal requirements of enzymatic systems. Photocatalysts also often work through mechanisms (such as outer-sphere electron transfer and energy transfer) that generate intermediates that are stable in the presence of water and tolerant of the chemical groups found in enzymes. Therefore, photocatalysts in general might be particularly suitable for being combined with enzymes for synthetic reactions.

This compatibility of photo- and enzymatic processes has been exploited in two other studies published earlier this year. In the first⁶, a water-soluble iridium catalyst was combined with the enzyme monoamine oxidase (MAO-N) to convert racemic mixtures (one-to-one mixtures of mirror-image stereoisomers known as enantiomers) of amine compounds into a single enantiomer (Fig. 1b). This process begins by generating a highly reactive free radical from a starting material (an imine). The radical is then converted *in situ* to a racemic mixture of amines. MAO-N recycles only one of the enantiomers back into the imine, and the whole process repeats until all of the imine has been converted into the enantiomer that is not the substrate for MAO-N. In the second study⁷, a photocatalytic reaction of thiols with enones was used to generate ketone intermediates that were reduced *in situ* with a ketoreductase enzyme, yielding products known as mercaptoalkanols enantioselectively (Fig. 1c).

As with all enzymatic systems, the reaction scope and scalability of Litman and colleagues' transformation will determine the extent to which it finds practical applications. For example, the alkene substrates reported in the paper are linear molecules that bear aryl groups (structural units that contain benzene rings; a substrate bearing an aryl group known as a pyridine ring is also reported). It will be interesting to see whether the chemistry can be extended to cyclic and non-aryl-bearing substrates. Moreover, the concentration of substrates used in the reactions is currently lower than would be needed for industrial processes. It remains to be seen whether the photocatalyst and enzyme will work at industrially useful substrate concentrations.

Even if the enzyme does not work under

conditions demanded by industry, or for a broad range of substrates, all is not lost. Techniques such as protein engineering and directed evolution are increasingly being used to rapidly optimize the characteristics of enzymes (such as their substrate scope, stability and selectivity) to make them compatible with industrial processes⁸. Indeed, enzymes are the ultimate tunable catalysts, and will therefore surely be combined with many other chemical catalysts in the future. ■

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VISION

Birds perceive colours in categories

Humans perceive colours in categories such as red, even though we can discern red hues including ruby and crimson. It emerges that birds also categorize colours and this affects their colour-discrimination ability. [SEE LETTER P.365](#)

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The amount of information reaching our sensory organs every second would be overwhelming if it were not for our ability to categorize it. Colour perception is a good example of this phenomenon. When we pick strawberries, we can easily discriminate between unripe fruit and fruit of the many different shades of red that indicate ripeness. Caves *et al.*¹ report on page 365 that zebra finches (*Taeniopygia guttata*) can also perceive a continuum of colours as belonging to distinct categories, a phenomenon that affects birds' ability to distinguish similar colours.

Although we can easily discriminate between the different shades of ripe strawberries, we tend to generalize and treat these shades as being equivalent. When comparing colours, if the differences between them are on the same scale of separation, our ability to perceive differences between colours from two separate categories, say 'red' and 'orange', is enhanced compared with our ability to perceive differences in colours that are both within one of these categories^{2,3}. This enhanced ability to distinguish between colours if the colours are in separate categories is called categorical colour perception.

The preconditions necessary for the ability to perceive colours in distinct categories had already been demonstrated in birds. Humans and our close relatives have evolved to have three types of colour-sensing cone cell in the eye, and birds have evolved to have four types^{4,5}. Birds have impressive

colour-discrimination abilities⁴, including the capacity to perceive the ultraviolet range of the spectrum. A remarkable earlier study⁵ provided clear evidence that birds can generalize among certain colours, and thus divide the continuum of the colours that they perceive into discrete categories. But it was not known whether this ability affects how birds perceive similar colours and whether it helps them to spot key colour differences. Caves and colleagues investigated whether birds' ability to categorize colours affects their colour-discrimination abilities, and thus whether

these animals have categorical colour perception.

“Birds are the only animals, besides primates, in which categorical colour perception has now been demonstrated.”

The authors created an ingenious experimental set-up. Female zebra finches were presented with a device in which food was hidden beneath coloured

discs. Food was present beneath bicoloured discs and absent below discs composed of a single colour. This training scheme allowed the authors to test how well the birds recognized colour differences by their ability to identify bicoloured discs when searching for food.

The authors studied a range of colours from orange to red, evenly dividing this part of the spectrum into eight shades of colour. Caves and colleagues made great efforts, using physiological models of bird colour vision, to make all of the steps between the shades equivalently