further research is needed to confirm whether they can be generalized to other species.

Grant and Grant frame their study as a test of sexual imprinting, but acknowledge that the correlations they observed could also arise if mating preferences were inherited genetically. There has been increasing support for the idea that sexual imprinting can reinforce reproductive isolation in birds and other species[5]. However, evidence for the existence of genetically inherited mating preferences in birds is limited. It is not yet clear whether learnt behaviour has a greater effect on mate choice than does genetic inheritance, or whether these inherited effects have been under-studied. Disentangling the roles of inherited and learnt mate preferences, and their consequences for speciation, is a key challenge for the future[7].

The most powerful tests for identifying sexual imprinting use an experimental 'cross-fostering' approach, in which offspring are swapped early in life and reared by unrelated individuals of the same or a different species[8]. There is also increasing interest in directly quantifying the genetic basis of mate choice using DNA sequencing[9]. We anticipate that future studies will combine experimental and genetic approaches to understand when and why learnt and inherited mating preferences evolve.

Grant and Grant's findings hint that sexual imprinting might have different effects in males and females and across different species. In a cross-fostering experiment in wild mice published last year, the strength of sexual imprinting differed substantially between two species[8]. Furthermore, in the mouse species in which imprinting was weaker, only males showed signs of imprinting. Why imprinting might be weaker and inherited preferences stronger in females of some species is not clear. This could occur if matings between species require more investment in time or effort from females than males, or if mate-choice patterns are influenced by differences in the extent of parental care or the social environment. The effects of inherited and learnt mate preferences are likely to be complex, and studies of a broad range of biological systems might be required to uncover their relative roles in nature.

The work by Grant and Grant links individual variation in mating preferences in Darwin's finches to the evolution of reproductive isolation, which is central to speciation. Sexual imprinting could have a role both in the 'classic' model of speciation, in which one species separates into two, and in the rarer process of speciation through hybridization, in which two different species mix to create a new one (Fig. 1). The possibility that Darwin's finches show sexual imprinting should encourage further experimental tests in other species to determine the role of imprinting in natural populations. Understanding how mating preferences evolve will shed light on the processes shaping past, present and future biodiversity. ■

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ORGANIC CHEMISTRY

An exciting tool for asymmetric synthesis

A catalytic process driven by visible light converts a mixture of mirror-image isomers of compounds called allenes to a single mirror-image isomer — opening up avenues of research for synthetic chemistry. SEE LETTER P.240

CHENG YANG & YOSHIHISA INOUE

Molecules can exhibit a handedness, known as chirality. This is crucial to many aspects of chemistry and biology because the mirror-image isomers (enantiomers) of a chiral molecule can have distinctly different properties, reactivities and chemical or biological functions. For example, nature often uses just one enantiomer of a family of molecules as building blocks to construct sophisticated structures such as DNA, and in other biological processes. The development of methods for synthesizing chiral molecules asymmetrically — predominantly as a single enantiomer — is therefore one of the most important goals in organic and medicinal chemistry. On page 240, Hölzl-Hobmeier *et al.*[1] report an approach that can also be used to achieve a seemingly impossible task in asymmetric synthesis: the light-induced, catalytic and apparently irreversible formation of single enantiomers of molecules called allenes from a one-to-one mixture of enantiomers (a racemic mixture).

One modern approach to asymmetric synthesis is to use light to induce the formation of a particular enantiomer of a molecule, a strategy called photochirogenesis. Often complementary to conventional methods of asymmetric synthesis, photochirogenesis is useful for making single enantiomers of molecules

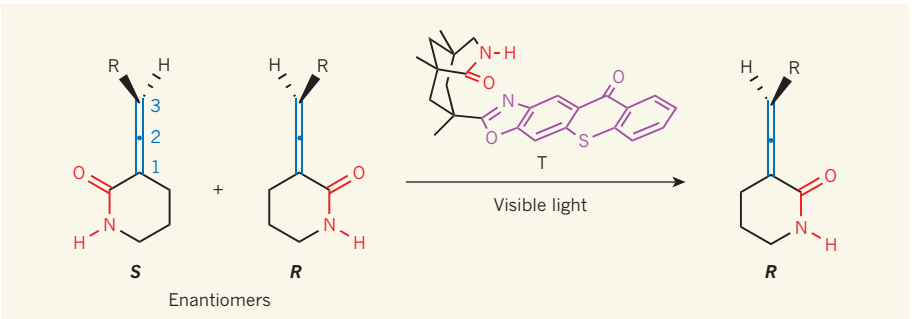

Figure 1 | A light-activated deracemization process. In allene molecules, one carbon atom (designated C2) forms double bonds to its neighbouring carbon atoms (C1 and C3; allene structure shown in blue). If two different groups are attached to each of C1 and C3, two mirror-image isomers (enantiomers) of the allene can form. Hölzl-Hobmeier *et al.*[1] report a light-driven process known as a deracemization, in which a one-to-one mixture of allene enantiomers (*S* and *R*) is converted into just the *R*-enantiomer. The reaction requires a catalyst called an enantiomeric photosensitizing template (T), which contains a photosensitizer group (purple) that allows it to absorb visible light and transfer the energy to the allene. The motifs in red allow T to form a complex with *S* and *R*, as needed for the deracemization. R within the enantiomers represents various chemical groups; the solid wedge and the broken wedge represent bonds that project above and below the plane of the page, respectively.

50 Years Ago

The Acting Administrator of the National Aeronautics and Space Administration … shows every sign of confidence that two Americans will tramp about on the surface of the Moon some time next year. The last flight of a team of three astronauts in October seems enormously to have cheered up those responsible for the Apollo programme. Even the accident this weekend which destroyed one of the machines being used to test the rocket system for descending the last few hundred feet to the surface of the Moon seems to have left them unmoved … Plans are now well advanced for the journey around the Moon of the Apollo 8 spacecraft, now assembled at Cape Kennedy, due to begin some time during the week of December 21.
From *Nature* 14 December 1968

100 Years Ago

A writer in the *Times*, directing attention to the fact that a large number of Royal Air Force officers will shortly be demobilised, suggests that they might profitably be employed in making an aerial photographic survey of the British Isles. He believes that this would prove useful to surveyors, architects, engineers, and others. While fully endorsing this writer's opinion that it would be unfortunate to lose the expert services of these flying officers … we cannot agree that a series of aerial photographs could be of great service to surveyors and engineers. Such photographs show the landscape from a new point of view, but they naturally lack the accuracy of carefully drawn topographical maps. On the other hand, such a survey might be of considerable value in the progress of flying for commercial and other purposes. Many attempts have been made to devise suitable maps for airmen, but even the best available leave much room for improvement.
From *Nature* 12 December 1918

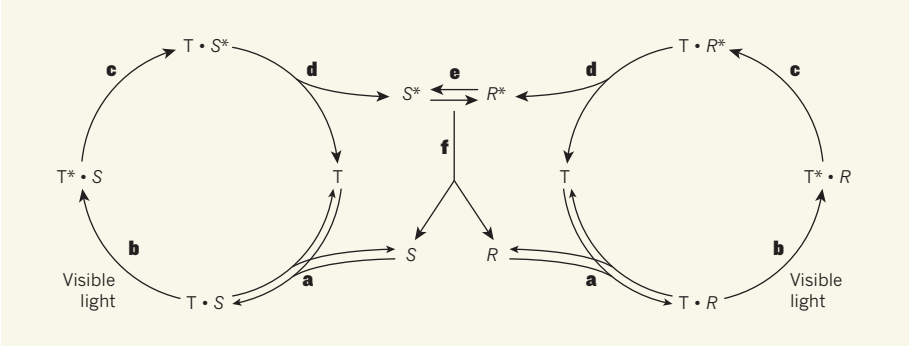

Figure 2 | A plausible mechanism for light-activated deracemization. **a**, T reversibly forms a complex with either *S* or *R*. **b**, Visible light excites T to generate an excited 'triplet' state (T*). **c**, Energy from T* is transferred to *S* or *R*, which enter triplet states (*S** or *R**, respectively), and T returns to its ground state. **d**, The T·*S** (or T·*R**) complex comes apart, releasing T and *S** (or *R**). **e**, **f**, The excited molecules can interconvert (**e**), and eventually relax to their ground states (**f**). However, thermodynamic factors in step **a** and kinetic factors in step **c** ensure that most of the molecules end up as *R*, rather than *S*.

that are difficult or tedious to prepare when in their ground states, but more easily made using light-induced (photochemical) reactions that proceed through electronically excited states.

Nevertheless, achieving highly enantioselective photochirogenesis is not a trivial matter, because excited molecules are short-lived and highly reactive, and because it is difficult to precisely control the stereochemistry — the geometrical arrangement of groups in a molecule — of products formed from reactions of excited molecules. The control problem has been overcome using a supramolecular approach[2], in which a 'guest' molecule is fixed into a particular position and orientation within a chiral 'host' environment to enable better stereochemical control of the guest's reactions. Hölzl-Hobmeier and co-workers have developed a new take on supramolecular photochirogenesis that they apply to allenes.

Allenes are organic molecules in which one carbon atom (designated C2) forms a double bond to both of its neighbouring carbon atoms (C1 and C3; Fig. 1). These molecules can assume a type of chirality known as axial chirality if two different groups are attached at each of C1 and C3. In their study, Hölzl-Hobmeier and colleagues used axially chiral allenes that have a lactam group attached at C1. The enantiomeric form of these allenes is fixed when they are in their ground states, but they spontaneously interconvert between the two enantiomers when excited to a state known as a triplet[3].

The lactam group is designed to form pairs of hydrogen bonds with a molecule known as an enantiomeric photosensitizing template (T), which was developed previously by workers from the same research group[4]. T forms complexes with the allene, within which it can absorb visible light and transfer the energy to the allene, exciting the latter to a triplet state[5].

So how does T induce the conversion of a racemic mixture of allenes into a single enantiomer, a process known as deracemization? The process begins with the formation of a complex of T with either of the two enantiomers (which are known as the *S*- and *R*-enantiomers, hereafter referred to simply as *S* and *R*; Fig. 2). Irradiation of the resulting complex T·*S* (or T·*R*) by visible light excites T into a triplet state (T*), which then transfers energy to *S* (or *R*). The excited molecule *S** (or *R**) is then released from the complex, regenerating free T for another catalytic cycle. The liberated excited molecules then undergo racemization, and — in the absence of any factors that discriminate between the two enantiomers — eventually relax to form both *S* and *R* products in the ground state in equal quantities.

However, the overall deracemization process can be enantioselective depending on two things: one is how strongly T binds to *S* to form a complex compared with how strongly it binds to *R*; the other is the relative rate at which energy is transferred from T* to *S* and from T* to *R*. For an allene that carries an extremely bulky group known as a *tert*-butyl, Hölzl-Hobmeier and colleagues' experiments show that T binds to *S* about five times more strongly than it does to *R*. This makes sense in the context of the authors' computational simulations, which show that *S* and *R* stack above T in their respective complexes, but that *S* stacks more closely to T than *R* does (see Fig. 4a of the paper[1]) — which suggests that T·*S* is thermodynamically more stable than T·*R*.

Moreover, the enantiomeric excess (e.e.) — a measure of the ratio of enantiomers in a sample of a chiral compound, where 100% indicates the presence of just one enantiomer — reported by Hölzl-Hobmeier *et al.* for the deracemized allene is 96% in favour of *R*. The rate of energy transfer for T* to each of the two enantiomers can therefore be calculated, and it emerges that the rate of energy transfer to *S* is about ten times the rate of transfer from T* to *R*.

The chiral environment generated by T for the allene in the complex therefore has dual, synergistic roles that lead to the extraordinarily high e.e.: when T is in its ground state,

there is a thermodynamic preference for it to bind to *S* rather than to *R*; and when T is in its excited state, kinetic factors greatly favour energy transfer to *S* compared with transfer to *R*. Impressively, the authors demonstrated that they could even use their method to convert a sample of the *S*-isomer of the *tert*-butyl-bearing allene (which had an e.e. of 95%) to the *R*-isomer (which had an e.e. of 96%).

Hölzl-Hobmeier and colleagues did not make a wide survey of which chemical groups could be attached to the allenes without disrupting the enantioselectivity of the deracemization, so this remains to be explored. However, groups that could disturb the hydrogen bonding between T and the allene would need to be avoided or protected (temporarily converted into another group that does not interfere with the hydrogen bonding). Nevertheless, the authors show that 17 racemic allenes bearing a variety of groups (see Fig. 3 of the paper[1]) can be deracemized to produce single enantiomers of 89–97% e.e. in good to excellent chemical yields (52–100%). These e.e. values far exceed the value (3.4%) obtained for the first reported deracemization of an allene[6] in the early days of photochirogenesis research. Another attractive feature of the new method is that it uses a small amount of catalyst (only 2.5 mol% compared with the amount of allene used).

The authors' findings unequivocally demonstrate that supramolecular photochirogenesis, when appropriately designed, can be a powerful tool for asymmetric synthesis that cannot be achieved using conventional, heat-activated reactions. The new reactions might be limited by the need to append hydrogen-bonding groups to both the substrate and the photosensitizing template, and by the narrow range of compounds to which they are immediately applicable (which include sulfoxides and binaphthyl compounds). Nevertheless, the general concept and methodology, as well as the mechanistic details revealed by this study, will generate much discussion and open up fresh avenues of research. ■

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MICROBIOLOGY

Bacterial molecules target viral DNA

Bacteria can use specific protein–based strategies to defend individual cells against viruses. Evidence that bacterial small molecules also target viruses provides fresh insights into how bacteria thwart viral infection. SEE LETTER P.283

MARTHA R. J. CLOKIE

To enjoy beautiful environments, we might need to defend ourselves against the resident pests, from midge flies on Scottish hillsides to mosquitoes in tropical jungles. If pests are numerous and diverse, a broad-spectrum defence strategy, such as spraying an insect repellent, can be best. Bacteria can also use general defences to combat their viral predators, in addition to having a plethora of more-specific defences that target particular viruses. On page 283, Kronheim *et al.*[1] report their analysis of an antiviral defence system that can protect more than one bacterial species. These findings could have major implications for our understanding of how bacteria and viruses interact.

Viruses that infect bacteria are known as bacteriophages, or just phages, and they have key roles in shaping bacterial evolution, population dynamics and physiology. Phages are considered to be the most abundant and diverse biological entities on Earth[2], and it is essential to consider them when trying to gain a full understanding of the bacterial world. Yet despite their importance, there are huge gaps in our knowledge. In many cases, information about phage host ranges (the types of bacterium that a particular phage can infect) is limited. Certain aspects of how bacteria defend themselves against phage attack are also mysterious.

Most bacterial species make numerous and diverse metabolites (small-molecule products of metabolism) that can provide widespread protection against attack from fungi and other types of bacterium. By contrast, most of the well-understood anti-phage defences in bacteria involve proteins, which often offer protection only at the level of the individual cell that makes the protein, rather than providing protection for a bacterial population. One such common bacterial defence is modification of the microbial cell surface to prevent phage attachment. Another strategy, called the CRISPR–Cas defence system[3], depends on an infected bacterium recognizing and capturing sequences from the viral genome and using these to prime a response that kills viruses containing a copy of the captured sequences. Some bacteria take the approach of adding methyl groups to their DNA and degrading all unmethylated, and therefore foreign, DNA[4]. Many other fascinating examples of these 'single-cell' defence strategies exist[5].

Broad-spectrum antiviral defence mechanisms in bacteria do occur but are less well known. For example, bacteria can shed vesicles from their outer membranes to 'mop up' phages[6]. The shortfall of examples in this category probably reflects the limited scope of previous research rather than a lack of such systems per se. Bacteria and phages have coevolved over approximately 3.9 billion years[7], so it seems reasonable to speculate that nonspecific mechanisms might have a key role in bacterial defences. Arguably, such broad-based systems might have a longer evolutionary history than do the more-specific types of defence, and might have shaped the development of the subsequent targeted strategies.

Kronheim and colleagues began to investigate how bacteria might target phages by testing the ability of a total of 4,960 molecules from a drug-discovery library to prevent a phage called lambda from infecting the model bacterium *Escherichia coli*. This revealed 11 molecules that can limit the success of phage infection. Nine of these can embed within DNA and are called DNA-intercalating agents. Out of the 11 molecules, 4 belong to a group known as the anthracyclines. These include the naturally occurring compounds daunorubicin and doxorubicin, which are used as anticancer drugs. The dual ability of these molecules to target cancer cells and phages raises the question of whether they act by recognizing modified DNA.

"One type of molecule can defend diverse species of bacterium against many different types of phage."

The anti-phage effects of daunorubicin and doxorubicin were first discovered more than 50 years ago[8–10]. Yet, strangely, insights[8–10] that bacteria can produce DNA-intercalating agents that target phages did not come to prominence. Research[11–14] from the 1940s and 1950s also demonstrated that several other antibiotics could prevent phage infection. However, these observations were not interpreted as an indication that the molecules were