

# News & views

## Organic chemistry

# Strong chemical reducing agents produced by light

Radek Cibulka

An electrically neutral radical has been found to be a potent chemical reducing agent when excited by light. Remarkably, it is produced from a positively charged precursor that has long been used as a strong excited-state oxidizing agent. **See p.76**

When molecules absorb light, they enter an excited state and become more reactive than when in their ground state. Light energy can therefore be used to generate reactive molecules that undergo chemical transformations that would otherwise be difficult to achieve. Several powerful oxidizing agents have been generated using light excitation, but strong reductants have been more difficult to produce. On page 76, MacKenzie *et al.*<sup>1</sup> report the discovery of a light-generated molecular species that exhibits reducing properties comparable to those of alkali metals – and which is therefore one of the strongest known chemical reductants.

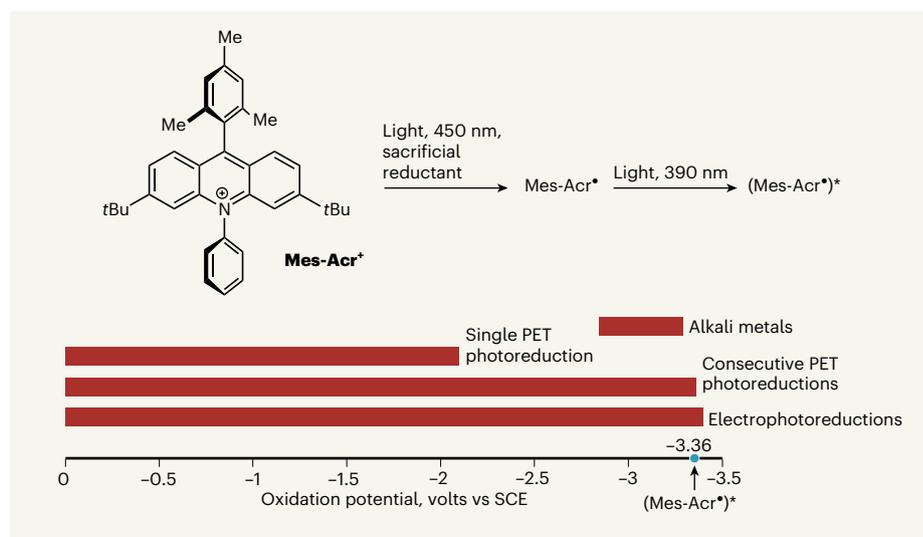
Chemical reactions mediated by visible light are important tools in organic synthesis. These reactions occur analogously to light-driven biological processes such as photosynthesis – with the help of a light-absorbing catalyst. In photoredox catalysis<sup>2</sup>, an excited catalyst molecule exchanges a single electron with a reaction partner (the substrate). During this process, which is known as photoinduced electron transfer (PET), the substrate is transformed into a reactive free radical; this undergoes a subsequent reaction to give one or more final products. Such processes usually occur at ambient temperature because their energy barrier is overcome using light energy.

Photoredox catalysis has undergone unprecedented development in the past decade, but some challenges remain. One is that no photoredox catalyst provides a reductant comparable in strength to that of alkali metals such as lithium and sodium. Alkali metals are still used in various reactions as potent reductants, despite their associated hazards and their tendency to produce undesired side products (that is, they have relatively low selectivity).

One example of a photoredox reductive process is the generation of molecular species called aryl radicals, which, when organic compounds are being synthesized, can be used as a source of aryl groups (groups derived from a benzene ring or a benzene analogue by the removal of a hydrogen atom). Aryl halide compounds, in which an aryl group is attached to a halogen atom (chlorine, bromine or iodine), are preferred starting materials for generating

aryl radicals because they are widely available and easy to handle. Aryl chlorides are the most preferred, but they are the most difficult aryl halides to reduce – as reflected by their highly negative reduction potentials. Reduction potentials quantify the tendency of a compound to acquire electrons from other compounds; for example, the reduction potential of chlorobenzene, a simple aryl chloride, is  $-2.78$  volts relative to the potential of a saturated calomel electrode (SCE), a standard reference used in reduction-potential measurements<sup>3</sup>.

It has not been possible to reduce aryl chlorides using a single PET process with visible light, because visible-light photons don't have enough energy for the task. To reduce another compound, an excited photoredox catalyst must have an oxidation potential (a measure of its ability to lose electrons to other compounds) lower than the reduction potential of the compound to be reduced. 10-Phenylphenothiazine, for example, is one of the most strongly reducing photoredox catalysts when excited by light, but the oxidation potential of excited phenothiazine is only  $-2.1$  V relative to SCE<sup>4</sup> (versus SCE) – insufficient to convert



**Figure 1 | An excited neutral radical acts as a potent reductant.** The strength of chemical reductants is quantified by their oxidation potential, which is measured in volts relative to the potential of a reference electrode (such as a saturated calomel electrode; SCE). Two of the strongest reductants are the alkali metals sodium and lithium. Relatively strong reductants can also be produced from organic molecules in light-driven processes called photoinduced electron transfers (PETs), but the oxidation potentials are insufficiently negative for many reductions<sup>3</sup>. More-negative values can be achieved using two consecutive PET steps (see ref. 5, for example), or in electrophotoreduction processes that combine an electrochemical step with a PET step<sup>8,9</sup>. The mesitylacridinium ion (Mes-Acr<sup>+</sup>) can be converted into a radical (Mes-Acr<sup>•</sup>) when irradiated by light of wavelength 450 nanometres in the presence of a sacrificial reductant. Mackenzie *et al.*<sup>1</sup> report that when this radical is irradiated by light of wavelength 390 nm, it produces an excited radical, (Mes-Acr<sup>•\*</sup>), that is a potent reductant. Me, methyl group; tBu, tertiary butyl group.

chlorobenzene into aryl radicals, for instance.

To overcome this problem, various systems have been reported that involve the use of two consecutive PET steps (see ref. 5, for example). In these approaches, a 'sacrificial' reducing agent reduces the excited catalyst molecule produced in the first step, forming a radical anion that is then excited by another photon. The resulting excited radical anion is a strong reducing agent. For instance, the excited radical anion formed from the catalyst Rhodamine 6G has an oxidation potential of  $-2.4$  V versus SCE, which is sufficiently negative to reduce aryl bromides and aryl chlorides that have a reduction-facilitating group<sup>6</sup>.

MacKenzie *et al.* now report an approach based on a salt that contains a mesitylacridinium ion (Mes-Acr<sup>+</sup>; Fig. 1). Mesitylacridinium salts have been used for almost two decades in photo-oxidation reactions<sup>7</sup> – when irradiated by visible light, the resulting excited species is a potent oxidant that takes an electron from a substrate and is thereby converted into an acridine radical (Mes-Acr<sup>•</sup>). The electrically neutral radical is converted back to Mes-Acr<sup>+</sup> by an oxidant for subsequent catalytic cycles.

The authors recognized that Mes-Acr<sup>•</sup> is a relatively stable species that absorbs light mainly from two ranges of wavelengths: 350–400 nanometres and 450–550 nm. They report that, when Mes-Acr<sup>•</sup> is irradiated with light of wavelength 390 nm, it forms an excited neutral radical that acts as an extremely strong reducing agent, with a maximum oxidation potential of  $-3.36$  V versus SCE. They propose that this large negative value is the result of charge transfer within the excited radical.

The use of an excited neutral organic radical is rare in photoredox catalysis. MacKenzie and colleagues formulated a reductive photocatalytic cycle based on Mes-Acr<sup>•</sup> using 390-nm light and a sacrificial reducing agent. This system can carry out several reduction reactions, such as the removal of tosyl groups from tosylated amine compounds (a type of reaction commonly used in organic synthesis; see Fig. 3 of the paper<sup>1</sup>). The researchers demonstrated that the new system is robust enough to work on scales that are useful for preparing compounds in the laboratory, by performing a detosylation reaction with 1.28 grams of a starting material.

The same approach can also be used to replace bromine or chlorine atoms with hydrogen atoms in aryl bromides and chlorides, respectively – such reactions are known as dehalogenations (see Fig. 2 of the paper<sup>1</sup>). This procedure is possible when various groups are present in the substrates, and it even works with 4-chloroanisole, an aryl chloride that has a reduction potential of  $-2.9$  V versus SCE.

Another approach for the catalytic production of strongly reducing species was reported simultaneously earlier this year in two papers from different groups<sup>8,9</sup>. In both

cases, a neutral organic molecule acts as the catalyst; this is reduced electrochemically on a cathode to produce a radical anion, which is then excited by visible light to form a strong reductant with an oxidation potential more negative than  $-3.0$  V versus SCE. These electrophotochemical systems were used to dehalogenate electron-rich aryl chlorides, and also in a series of arylation reactions (transformations in which an aryl group is attached to another molecule).

The use of electrochemical reduction, instead of photochemical methods, to generate radicals allows catalysts to be used that do not absorb visible light. For example, naphthalene monoimide, a catalyst used in one<sup>9</sup> of the two papers, falls into this category and cannot undergo the initial conversion to a radical anion using visible light. By contrast, once it is transformed electrochemically into a visible-light-absorbing radical, it can enter a photocatalytic cycle.

MacKenzie and colleagues' observation of the strong reductant character of excited neutral Me-Acr<sup>•</sup> will inspire investigations into whether other molecules show similar behaviour. One can also expect increased interest in other photocatalytic approaches for the production of reductive systems<sup>10–13</sup>. Taking into account the highly negative oxidation potentials observed for various light-generated agents in the current work

and by other research groups, we can look forward to new arylation reactions, and even to ambitious applications such as the Birch reduction<sup>14</sup> – a classic synthetic reaction typically performed using alkali metals.

**Radek Cibulka** is in the Department of Organic Chemistry, University of Chemistry and Technology, Prague, Prague 16628, Czech Republic.  
e-mail: cibulka@vscht.cz

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## Developmental biology

# A clock that controls human spine development

Adelaida Palla & Helen Blau

Visualization of the rhythmic oscillations of the mouse and human segmentation clocks, which are crucial to spine development, is now possible thanks to the development of sophisticated cell-culture systems. **See p.113, p.119 & p.124**

What do the flashes of a firefly and the chirpings of a cricket have in common? Both occur in a regular rhythm, which is controlled by an oscillating biological clock<sup>1</sup>. Another oscillating genetic clock controls the development of embryonic structures called somites, which give rise to the vertebrae that protect the spinal cord. Our knowledge of this segmentation clock stems almost entirely from research on animals<sup>2,3</sup>, because technical and ethical considerations limit the study of human embryos in culture. Diaz-Cuadros *et al.*<sup>4</sup> (page 113) and Matsuda *et al.*<sup>5</sup> (page 124) now report a breakthrough that enables studies

of the human segmentation clock *in vitro*. In addition, Yoshioka-Kobayashi *et al.*<sup>6</sup> (page 119) use sophisticated techniques in mice to provide insights into the mechanisms that control the mammalian segmentation clock.

Somites arise from a tissue called the presomitic mesoderm (PSM). During somite formation, temporally and spatially controlled oscillations in transcription yield gene-expression waves that propagate through the PSM along the embryo's head-to-tail axis. The result is a striped pattern of somites that forms the blueprint for the spine. Although the molecular components of the segmentation