

of the ORR, and that theoretical work can effectively support the search for improved catalytic materials.

Despite this advancement, fuel-cell electrocatalysts still face many challenges. If we consider both theoretical and experimental work, further developments can be achieved by bridging the gap between our understanding of model systems and our observations of state-of-the-art applied-fuel-cell catalysts. Whereas model studies suggest that the activity targets for automotive fuel-cell applications can be met, no such high-surface-area catalyst of comparable activity has yet been found. The key challenge, however, lies in the development of strategies to stabilize desired catalyst structures.

At present, core-shell particles that possess an inexpensive, non-noble core surrounded by a Pt shell are extensively discussed as promising fuel-cell catalyst materials. Nonetheless, to make them viable for fuel-cell applications, these core-shell structures must be stabilized under the harsh fuel-cell operating conditions. As Nørskov and co-workers point out, although the proposed Pt<sub>3</sub>Sc and Pt<sub>3</sub>Y catalysts will not be thermodynamically stable in fuel cells, their stability is enhanced by the kinetically hindered diffusion of Y or Sc from the alloy interior to the surface. This is indeed a first step towards a stabilization of such alloy catalysts; and together with other recent

progress in this field, nourishes the hope that the large-scale application of fuel cells can become a future reality. □

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## TOTAL SYNTHESIS

# Expanding the art of synthesis

The highly selective oxidation of just one carbon-hydrogen bond out of almost 50 in a late-stage precursor can be used to construct the macrocyclic core on which the erythromycin antibiotics are based, and demonstrates the potential of such C-H activation approaches for natural product synthesis.

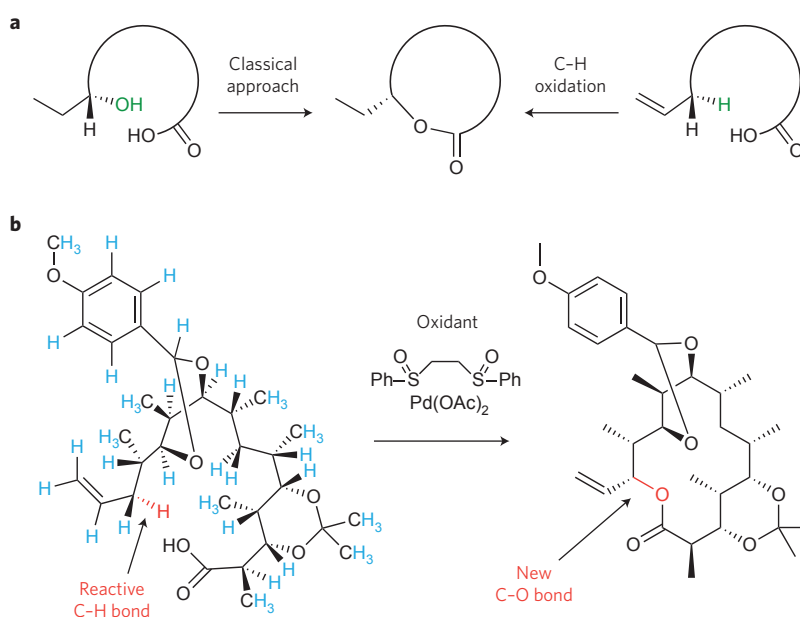
Huw M. L. Davies

Organic compounds consist of relatively unreactive C–C and C–H bonds, which make up the basic framework of the structure, interspersed with a variety of reactive components — so-called functional groups. The typical challenge of organic synthesis is to modify these multiple functional groups in a selective and efficient manner, allowing for the conversion of readily available starting materials into complex target compounds. The number of possible permutations on how a particular target could, in principle, be formed is enormous and even computational algorithms for determining the optimum approach are of limited help.

Choosing a synthetic route to a specific target compound is therefore not straightforward and researchers often take different paths to get to the same molecule. The ‘art in organic synthesis’ is a term that was introduced over 50 years ago by the legendary organic chemist R. B. Woodward to describe the beauty associated with the elegant approaches that can be used for the construction of complex, naturally occurring compounds<sup>1</sup>. Such ‘art’ is achieved through the implementation of unusual and elegant strategies that enable a complicated target molecule to be assembled in a minimum number of steps with the greatest synthetic efficiency<sup>2</sup>.

The reactivity of an organic compound is typically characterized by the types of functional groups that it contains. For

example, ethanol, a two-carbon alcohol, will have similar chemical behaviour to other alcohols containing much longer carbon



**Figure 1** | C-H oxidative cyclization for natural product synthesis. **a**, Comparison of the classical and the C-H oxidative approaches to generate macrolide rings. **b**, Stang and White<sup>8</sup> used the C-H oxidative cyclization approach at a late stage in the synthesis of the macrolide 6-deoxyerythronolide B. The starting substrate has 29 different C-H bonds, but only the C-H bond marked in red is reactive, whereas the C-H bonds marked in blue are left unchanged.

chains. This type of analysis has been the mainstay of organic chemistry for many years, but is starting to be challenged with the discovery of reagents and catalysts that are capable of selectively functionalizing C–H bonds<sup>3–6</sup>. Thus, C–H bonds that would have previously been assumed to be unreactive can now be considered as reactive sites for further manipulation.

For C–H functionalization to become broadly applicable, however, it is necessary to develop procedures that will recognize the different types of C–H bonds present in an organic compound. Furthermore, this needs to be achieved even in the presence of other functional groups. In particular, the White group at the University of Illinois, Urbana-Champaign has been developing selective methods for C–H oxidation by conversion of C–H bonds into C–O bonds<sup>7</sup>. Now, on page 547 of this issue, Stang and White describe an impressive example of selective C–H oxidation at a late stage in a natural product synthesis, on a substrate that contains multiple functional groups and C–H bonds<sup>8</sup>. This is a beautiful example of the potential of a C–H functionalization strategy for streamlining the synthesis of complex natural products.

The target compound in this work is a 14-membered-ring polyketide macrolide called 6-deoxyerythronolide B. The classic approach for the synthesis of this type of natural product is to conduct the ring-

closure late in the synthesis, condensing an alcohol with a carboxylic acid functional group (Fig. 1a). Because the stereochemistry of the alcohol is set, the cyclization can produce only a single three-dimensional form of the cyclized product. In contrast, the new route developed by Stang and White relies on an oxidative cyclization strategy in which one of the numerous C–H bonds is selectively oxidized and then reacts with the carboxylate group to form the lactone. This allows the use of a simpler substrate and opens up the possibility for the formation of two distinct stereoisomers of the final product.

The substrate used for the critical C–H oxidative cyclization is shown in Fig. 1b. This compound contains a total of 47 C–H bonds, of which 29 are chemically different. Stang and White have developed a special palladium catalyst that is capable of distinguishing between the different C–H bonds, such that only a single isomer of the cyclized product is formed. The exquisite control of the three-dimensional structure is achieved by using conditions whereby the palladium is able to bind to the two reactive components of the substrate, creating a well-defined template for macrocycle formation. However, significant quantities of another stereoisomer can also be produced by appropriate modifications of the reaction conditions. Addition of fluoride disrupts the templating affect and reduces the

diastereomeric ratio of the reaction from greater than 40:1 to approximately 1.3:1.

The examples presented by Stang and White highlight the potential of C–H functionalization in organic synthesis, while also demonstrating the major challenges that still need to be overcome in this field of chemistry. The palladium catalyst is remarkably selective, but the substrate needs to be recovered and recycled through the reaction conditions two further times to achieve a reasonable conversion to the product. Nevertheless, this work will stimulate interest in applying C–H functionalization to the synthesis of complex targets and will encourage research towards developing new types of catalysts that display similarly high selectivity, while achieving even greater reactivity. □

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## NITROGEN FIXATION

# One electron at a time

Dinitrogen ligands — key for understanding how atmospheric nitrogen can be reduced — almost exclusively have even-numbered oxidation states. Now, however, lanthanide complexes with  $[\text{N}_2]^{3-}$  ligands have been synthesized and investigated.

Paul J. Chirik

The conversion of atmospheric nitrogen,  $\text{N}_2$ , to more valuable compounds is a challenge that has confronted chemists for over a century. Molecules containing nitrogen atoms are the cornerstone of modern society, from blockbuster pharmaceuticals to fertilizers. Although  $\text{N}_2$  surrounds us, comprising 78% of our atmosphere, it presents both kinetic and thermodynamic obstacles for developing reaction chemistry.

The strength of the nitrogen–nitrogen triple bond is 225 kcal mol<sup>-1</sup>, second only to carbon monoxide (257 kcal mol<sup>-1</sup>). Dinitrogen is by definition nonpolar, making

it a poor ligand for many transition metals, especially when compared with CO. When acting as a ligand, the commonly observed oxidation states are 0, 2– and 4–, but now William Evans and colleagues report in the *Journal of the American Chemical Society* the existence of lanthanide complexes with unprecedented  $[\text{N}_2]^{3-}$  ligands<sup>1</sup>.

In nature, nitrogen is reduced by nitrogenase enzymes, which contain large metalloproteins and promote a sequence of proton-coupled electron-transfer reactions to accomplish the reduction. Industrially, the Haber–Bosch ammonia synthesis hydrogenates  $\text{N}_2$  at high temperature and

pressure over an iron–ruthenium surface. The fossil-fuel inputs for this process are high, inspiring the search for alternatives, and for the past four decades, soluble transition metal complexes with  $\text{N}_2$  as one of the ligands have allowed chemists to conduct fundamental studies into dinitrogen reduction.

Bimetallic compounds where the  $\text{N}_2$  ligand is bound ‘side-on’ between the two metal centres have attracted considerable attention because effective  $\pi$ -backbonding reduces the  $\text{N}\equiv\text{N}$  bond and opens pathways for subsequent functionalization reactions<sup>2</sup>. In this arrangement, the oxidation state