

Hydrogen on the move



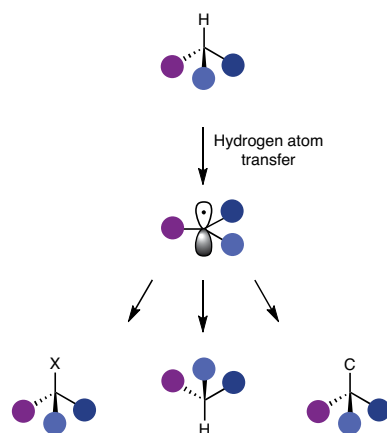
In this issue, we focus on the use of hydrogen atom transfer for the functionalization of C(sp³)-H bonds.

Developing sustainable synthetic routes from simple chemical feedstocks to complex molecules is a major driver for research in both industrial and academic settings. To achieve this goal, synthetic methods must be capable of selectively functionalizing unreactive bonds within cheap chemical feedstocks. One synthetic approach which addresses this challenge is the functionalization of C(sp³)-H bonds enabled by hydrogen atom transfer (HAT). HAT is the oxidation of a substrate, moving a proton and an electron to a reagent or catalytic species¹.

In the case of the functionalization of C(sp³)-H bonds, the C-H bond is broken to generate a reactive carbon-centred radical. These radical intermediates can engage with radical acceptors² and transition-metal catalysts³ or form alternative reactive intermediates⁴ such as cations or anions. Classical generation of carbon-centred radicals typically involves the formation of an activated substrate, such as an alkyl halide, followed by cleavage of the weak C-halogen bond⁵. In comparison, HAT of C(sp³)-H bonds provides a more efficient synthetic route to carbon-centred radicals, negating the requirement of generating an activated substrate. However, methods to perform HAT on C(sp³)-H bonds traditionally use harsh reagents and conditions, such as reactions with alkyl, alkoxy, peroxide or chlorine atom radicals⁶. Recent advances in the areas of photo-^{7,8} and electrochemical catalysis⁹ have allowed the development of mild reaction conditions for the functionalization of C(sp³)-H bonds, using HAT.

In this Issue of *Nature Synthesis*, we collate a range of research articles overviewing how HAT synthetic approaches are used for the functionalization of C(sp³)-H bonds. Specifically, how catalytically-, electrochemically- and photomediated HAT of C(sp³)-H bonds have been applied in organic synthesis, and how technology has been used to further enable these transformations.

In complementary [Review](#) and [Perspective](#) articles, Lei, Yi and co-workers and Ohmatsu



and Ooi highlight electrochemical and photocatalytic approaches, respectively, to the dehydrogenative cross-coupling of C(sp³)-H bonds using HAT. Lei, Yi and co-workers overview anodic C(sp³)-H bond oxidative functionalization and compare a range of dehydrogenative cross-coupling methods to generate C(sp³)-C and C(sp³)-heteroatom bonds. Ohmatsu and Ooi outline how photocatalytic HAT has been applied to dehydrogenative coupling between C(sp³)-H and C-H bonds, enabling C-C bond formation without the need for organometallic or organic halide reagents. Some of the challenges discussed in these articles are the site selectivity of the HAT process and the ability to achieve stereocontrol in the cross-coupling approaches. For substrates with multiple C(sp³)-H bonds, the HAT process can be unselective. Whilst catalyst design may be used to control site selectivity, it remains an area for future development. Imparting stereocontrol in the cross-coupling reactions may involve intercepting the carbon-centred radical intermediate with a chiral catalyst. Chiral catalysts for this purpose could be identified through screening combinations of metal salts and chiral ligands under photo- and electrochemical conditions.

In a [Q&A](#), we learn from Alison Wendlandt how photocatalysis can be used in combination with HAT reagents to selectively epimerize sugar and polyol chemical feedstocks to produce rare sugar isomers. It is discussed how predicting the site selectivity for the HAT process with complex substrates is still difficult, and how observed site selectivity is not simply

a product of C-H bond enthalpy, but a result of product-catalyst interactions.

A [Q&A](#) with Timothy Noël, reveals how technological advances have expanded the scope and improved the efficiency of photocatalytic methods for C(sp³)-H functionalization using HAT. Flow chemistry methods are described that allow gaseous alkane chemical feedstocks to be used in these reactions, including reactions in which the corresponding batch reactions were unsuccessful. The application of membrane technology has allowed efficient recycling of one of the most used photocatalysts for these reactions. The challenges faced when photocatalytic processes are scaled up are described, and it is discussed how innovations in flow chemistry and catalyst recycling can address these challenges.

Finally, through a quartet of Research Highlights, we learn how state-of-the-art [electrochemical](#), [metallaphotoredox](#), [photomediated](#) and [HAT-initiated catalytic](#) methods are addressing the challenges which face the practitioners of HAT for C(sp³)-H functionalization.

The development of methods for C(sp³)-H functionalization using HAT, which form products with excellent and predictable site selectivity and that are stereoselective will likely be the focus of further research in the area. Efforts to facilitate reaction scale-up and develop enabling technologies to allow straightforward application of these synthetic strategies in industrial settings are also expected to be made. Undoubtedly, the coming years will see the community developing more efficient and sustainable HAT processes.

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