& Stewart, F. J. in *The Prokaryotes* Vol. 1 (eds Dworkin, M., Falkow, S., Rosenberg, E., Schleifer, K.-H. & Stackebrandt, E.) 475–507 (Springer, 2006).
4. Spiess, F. N. *et al. Science* **207**, 1421–1433 (1980).
5. Van Dover, C. L. *et al. Mar. Policy* **90**, 20–28 (2018).
6. Karson, J. A., Kelley, D. S., Fornari, D. J., Perfit, M. R. & Shank, T. M. *Discovering the Deep: A Photographic Atlas of the Seafloor and Ocean Crust* (Cambridge Univ. Press, 2015).
7. Rogers, A. D. *et al. PLoS Biol.* **10**, e1001234 (2012).
8. Ravaux, J. *et al. PLoS ONE* **8**, e64074 (2013).
9. Kashefi, K. & Lovley, D. R. *Science* **301**, 934 (2003).
10. Van Dover, C. L., Szuts, E. Z., Chamberlain, S. C. & Cann, J. R. *Nature* **337**, 458–460 (1989).
11. Thatje, S., Marsh, L., Roterman, C. N., Mavrogordato, M. N. & Linse, K. *PLoS ONE* **10**, e0127621 (2015).
12. Yao, H. *et al. Proc. Natl Acad. Sci. USA* **107**, 987–992 (2010).
13. Martin, W., Baross, J., Kelley, D. & Russell, M. J. *Nature Rev. Microbiol.* **6**, 805–814 (2008).
14. Barge, L. M. & White, L. M. *Astrobiology* **17**, 820–833 (2017).
15. Bellingham, J. G. & Rajan, K. *Science* **318**, 1098–1102 (2007).
16. Liu, S., Hu, J., Zhang, R., Dai, Y. & Yang, H. *Chin. J. Mech. Eng.* **29**, 863–870 (2016).

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ORGANIC CHEMISTRY

Decoration of molecules made easy

The ability to attach a variety of chemical groups to one position in a molecule facilitates the search for compounds that have useful properties. Reactions have been reported that could transform how chemists do this. SEE LETTER P.223

ERIC M. FERREIRA

Chemists have spent decades developing and refining the tools for constructing bonds in complex organic molecules — especially carbon–carbon (C–C) bonds, which form the framework of such molecules. Metal-catalysed cross-coupling reactions generate C–C bonds from carbon–halogen bonds, and have long been go-to reactions for synthesis. In an exciting report on page 223, Berger *et al.*[1] describe an alternative cross-coupling strategy that uses a special type of carbon–sulfur (C–S) bond as a proxy for carbon–halogen bonds. Notably, this C–S bond is activated so that it becomes the most reactive site in a molecule for cross-coupling, and it can be installed directly at individual molecular positions with unprecedented levels of selectivity. The authors' work could therefore reshape the strategic use of cross-coupling reactions for organic synthesis.

The aim of synthetic chemistry is generally to make molecules that have a desired function — such as binding to an enzyme or emitting light of a specific colour. This, in turn, requires the chemical groups in the molecules to be connected in a particular way, or to have a specific spatial arrangement. Chemists would ideally like to have the tools to set up desired connectivities and spatial arrangements in any molecule. Great strides have been made towards this goal, but difficulties remain.

The problems are analogous to the challenge of hanging pictures on plaster walls. The optimum situation is to be able to place a picture at any desired position. But in the days when nails were the only option for hanging artwork, one was restricted to positions at which the wall plaster was backed by wooden studs — which raised the problem of finding the studs. Mistakes could be made that would damage the walls. New technology has simplified the problem: electronic stud finders make detection simple, and hooks that stick to walls using damage-free adhesives offer more-flexible alternatives to nails. With these better tools, we can now hang pictures in nearly any arrangement we desire, with minimum fuss.

Molecules can be thought of as blank walls: we need to be able to decorate them with chemical groups in specific arrangements, but the reactions available have restricted the positions that can be accessed, and/or have been difficult to target to specific positions. Metal-catalysed cross-couplings[2] have been tremendously valuable for molecular decoration. This family of reactions allows a remarkably wide range of groups to be attached to molecules through the formation of a C–C bond, but the carbon atoms to be decorated must already have a halogen atom attached. Methods for installing halogens predominantly at specific carbons in a molecule exist, but have varying degrees of site selectivity. More-selective means of making carbon–halogen bonds (or equivalent motifs that can also take part in cross-couplings) would be greatly enabling.

Reactions known as metal-catalysed C–H bond functionalizations[3], which can convert carbon–hydrogen (C–H) bonds to C–C bonds, were developed in part to circumvent the limitations of cross-couplings — why bother installing a halogen if you can instead convert one of the many C–H bonds found in all organic molecules selectively and directly to the C–C bond of your desired product?

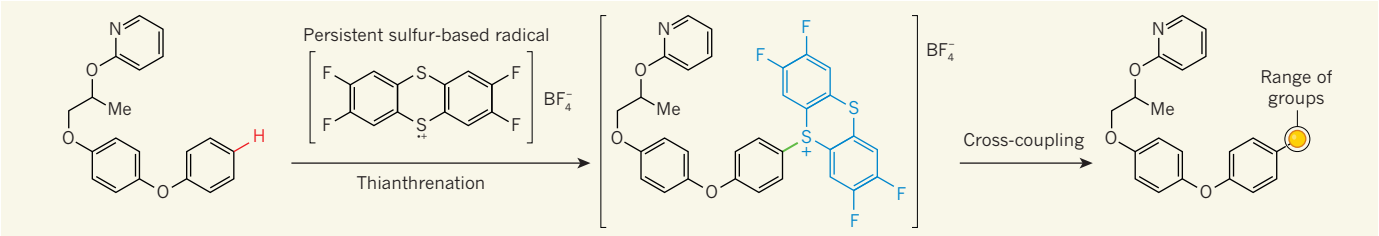

Figure 1 | A method for the site-selective modification of complex molecules. Berger *et al.*[1] report that a chemical species known as a persistent sulfur-based radical, generated *in situ*, reacts with structurally complex molecules at just one carbon–hydrogen (C–H) bond (shown in red in this example; other C–H bonds in the molecule are not shown). Which C–H bond reacts depends on the electronic and structural properties of the reactant. The products are compounds that bear a thianthrenium group (blue; the dot on the lower sulfur atom represents an unpaired electron). A carbon–sulfur bond (green) in these products can take part in a variety of metal-based cross-coupling reactions, thus allowing a wide range of chemical groups to be attached at the carbon atom in the original C–H bond. Me, methyl group.

But despite impressive advances, metal-catalysed C–H functionalizations are not yet applicable to as broad a range of compounds as are cross-couplings, and they generally have site-selectivity issues similar to those of halogen-installing reactions.

Berger *et al.* now describe a development that could help to address the issues of molecular decoration. Inspired by research from almost 50 years ago[4], the authors report a highly selective method for replacing the hydrogen of a C–H bond with a group called a thianthrenium, thereby generating a new C–S bond (Fig. 1). The thianthrenium group then serves as a halogen proxy for a broad array of cross-coupling reactions.

The first step of the process — the thianthrenation step — is strikingly site-selective. This is because the thianthrenium group derives from a species known as a persistent sulfur-based radical[5,6]; the use of this radical promotes a reaction that discriminates clearly between the many C–H bonds in a given molecule. Berger *et al.* demonstrate that this selectivity holds across a wide range of molecules, and thereby provide data that will help chemists to work out which site is likely to react in complex molecules that have several potentially reactive C–H bonds. Essentially, in almost all of the cases evaluated, only one C–H bond reacts, with the selectivity dictated by the electronic and structural characteristics of each molecule.

Equally impressive is the breadth of the cross-coupling reactions that can be carried out using the thianthrenated compounds, in which the C–S bond acts as an 'activated' carbon–halogen bond[7]. A variety of palladium-catalysed cross-couplings are effective and, in the most notable examples, the thianthrenium group reacts in preference to carbon–halogen bonds or other similarly reactive groups. The authors also find that their thianthrenium compounds work in other types of cross-coupling reaction, such as copper-mediated processes and 'photoredox' couplings.

About half of the molecules tested by Berger and colleagues in their reactions are pharmaceutical compounds, which demonstrates the potential value of this chemistry to medicinal chemists. Having the ability to decorate structurally complex molecules with different chemical groups is particularly useful for synthesizing analogues of biologically active compounds in drug-discovery programmes[8]. It is difficult to think of a comparable reaction that works for this purpose as selectively and with as broad a range of substrates as the newly reported chemistry.

Nevertheless, these reactions might not be applicable to all molecules. Some chemical groups are sensitive to the thianthrenation conditions (which are oxidizing), and might therefore take part in oxidative side reactions. Moreover, the thianthrenated compounds have not yet been shown to take part in certain widely used cross-coupling reactions (notably, amination reactions, which generate carbon–nitrogen bonds). More work is needed to develop such reactions.

Finally, the site selectivity of the thianthrenation step is governed entirely by the electronic and structural properties of the reactant molecule. It will be interesting to see whether alternative C–H sites on molecules can be selectively thianthrenated using different protocols.

In the meantime, Berger *et al.* have established the foundations of a compelling new approach for cross-coupling that takes advantage of C–H functionalization. In effect, the authors have developed an adhesive for decorating molecules that makes it much easier to generate any structure that we might need. ■

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1. Berger, F. *et al. Nature* **567**, 223–228 (2019).
2. Wu, X.-F., Anbarasan, P., Neumann, H. & Beller, M. *Angew. Chem. Int. Edn* **49**, 9047–9050 (2010).
3. Chen, X., Engle, K. M., Wang, D.-H. & Yu, J.-Q. *Angew. Chem. Int. Edn* **48**, 5094–5115 (2009).
4. Shine, H. J. & Silber, J. J. *J. Org. Chem.* **36**, 2923–2926 (1971).
5. Griller, D. & Ingold, K. U. *Acc. Chem. Res.* **9**, 13–19 (1976).
6. Romero, K. J., Galliher, M. S., Pratt, D. A. & Stephenson, C. R. J. *Chem. Soc. Rev.* **47**, 7851–7866 (2018).
7. Srogl, J., Allred, G. D. & Liebeskind, L. S. *J. Am. Chem. Soc.* **119**, 12376–12377 (1997).
8. Cernak, T., Dykstra, K. D., Tyagarajan, S., Vachal, P. & Krska, S. W. *Chem. Soc. Rev.* **45**, 546–576 (2016).

MEDICAL RESEARCH

Malaria parasite tackled in mosquitoes

Insecticides that kill mosquitoes have helped to fight malaria, but insecticide resistance is rising. Treating mosquitoes with drugs that target the disease-causing parasite offers another way of tackling malaria. SEE LETTER P.239

JANET HEMINGWAY

Any long-term programme for disease control that relies on one type of intervention has a high probability of failure owing to the development of treatment resistance. Efforts to limit malaria by using insecticides to kill female mosquitoes, which transmit the disease-causing *Plasmodium* parasite, are no exception: mosquito resistance to insecticides is on the increase. On page 239, Paton *et al.*[1] report a non-insecticidal intervention that stops mosquitoes from transmitting malaria and that might offer a way to reduce the reliance on insecticides alone as a means of malaria prevention.

It is estimated[2] that mosquito control using bed nets impregnated with long-lasting insecticides called pyrethroids, and indoor insecticide spraying, resulted in 1.3 billion fewer