because it deliberately positions itself as an exploratory data analysis across different environments and sample types. This produces certain constraints on the inferences that can be made, because environmental data collected for the samples were not always measured in the same way in different environments.

The debate about the relative merits of data-driven and hypothesis-driven experimental approaches is not new, and there are examples of each of these approaches providing scientific insights. This study is an excellent example of the former, even if concessions had to be made regarding the selection of variables that could be used for analyses across all the environments.

Thompson and colleagues made several findings. For example, they investigated whether existing theories about the relationship between species richness (as monitored by the diversity of 16S rRNA sequences) and temperature and pH across environments were consistent with their data. For example, there is a model that proposes a steady logarithmic rise of microbial richness with increasing temperature[7,8]. Surprisingly, in contrast to this theory, the authors found that microbial biodiversity peaks at a relatively narrow pH and temperature range and then drops again.

The authors also observed an unexpectedly high amount of 'nestedness' among samples from different environments: samples showing low biodiversity were always present as microbial subsets of other, high-biodiversity samples, irrespective of the sample origin. Notably, this pattern of nestedness was mostly observed for microbial analyses above the level of genus — when analysed at the level of species, or when different strains of the same species were analysed, a strong decrease in nestedness was observed.

The value of the Earth Microbiome Project will extend far beyond what is reported in the present paper. The project provides a resource that will keep microbial ecologists and evolutionary biologists busy for years. More than 60 publications have already been published using subsets of the data that had been released previously [6]. By implementing and fiercely pursuing this open-access model, Thompson and colleagues emphasize the value of collaboration and sharing over competition, which is unfortunately still too frequent in the scientific community. ■

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ORGANIC CHEMISTRY

Super-reactive catalyst for bond cleavage

Carbon–hydrogen bonds in organic molecules can be cut to install other chemical groups on the carbon atom, but these reactions have been limited. A catalytic palladium complex opens up fresh opportunities. SEE LETTER P.489

JOANNA WENCEL-DELORD & FRANÇOISE COLOBERT

Compounds such as drugs, agrochemicals and plastics are prepared from simple chemical precursors through multistep synthetic routes. Accordingly, strategies that permit straightforward conversion of simple starting materials into the desired molecular structures, avoiding the additional steps and fancy tricks often needed for chemical transformations, are urgently needed. On page 489, Wang *et al.*[1] report a remarkable advance that addresses this issue using a strategy known as non-directed C–H functionalization.

The basic components of all organic molecules are carbon and hydrogen atoms. The strong C–H bonds that form between these atoms account for the stability of organic molecules, but they also make it difficult to modify such molecules by selectively replacing hydrogen atoms with other chemical groups. Moreover, replacing a single hydrogen can be difficult without destroying the whole molecular system, because of the 'harsh' reaction conditions that are generally required. Solving these problems has been a real challenge for organic chemists, and has led to the establishment of a field known as C–H bond functionalization[2,3]. The most extensively explored solution involves using transition metals — particularly the noble metals, which under certain conditions are sufficiently active to cleave C–H bonds.

Another fundamental issue is how to target one hydrogen selectively in the presence of many others that have very similar chemical

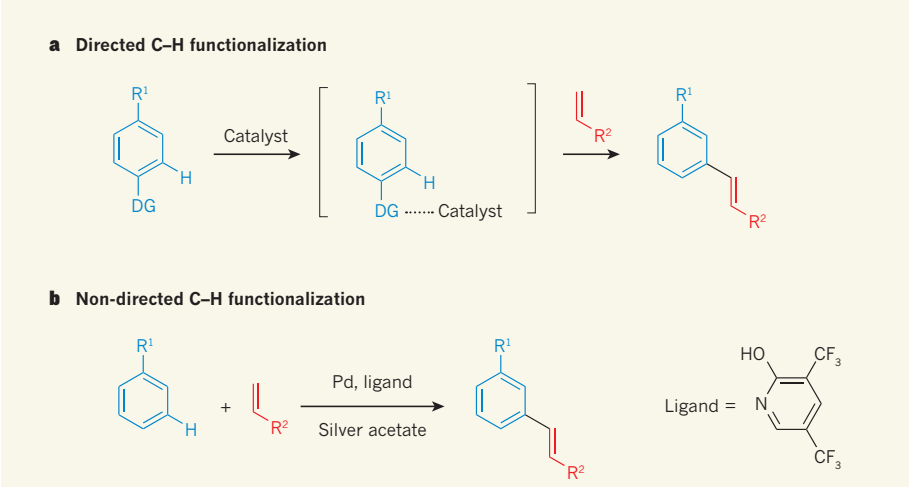

Figure 1 | A non-directed, palladium-catalysed C–H functionalization. a, In directed C–H functionalization reactions, such as the one depicted here, a directing group (DG) on the starting material guides (dotted line) the catalyst to a single hydrogen atom; only the reactive hydrogen atom on the benzene ring is shown. R^1 and R^2 represent any chemical group. Square brackets indicate a transiently formed state. The catalyst is typically a palladium, rhodium or ruthenium complex. **b**, Wang *et al.*[1] report a catalyst for non-directed C–H functionalizations. The highly active and robust catalyst is formed *in situ* from a palladium (Pd) source and a finely tuned ligand (a 2-pyridone molecule), and cleaves C–H bonds on both electron-rich and electron-poor substrates in the presence of silver acetate. The selectivity of the reactions for the hydrogen atom shown is moderate to good.

properties. Currently, two main strategies are used to solve the selectivity issue. The first is known as non-directed C–H functionalization, and relies on the fact that the structure of a molecule confers slightly different properties on different C–H bonds, thus enabling the preferential reaction of one hydrogen out of several others[4,5].

The second strategy is called the directing-group approach: a chemical group attached to a molecule acts as a hook that catches a catalyst and directs it to a specific C–H bond[6] (Fig. 1a). This strategy is widely used because it enables reactions that are often otherwise unachievable to be performed highly selectively. But it has a considerable drawback — the directing group generally needs to be attached to the molecule in a separate, preliminary step, and then later removed. These additional steps lower the overall efficiency of the process and generate more waste than is formed in non-directed C–H functionalizations. The non-directed approach is therefore more attractive, but also much more difficult to achieve, as shown by the scarcity of literature on this topic.

C–H functionalization reactions of aromatic compounds (which contain benzene rings or their analogues) are potentially of great use for organic synthesis. Heteroaromatic compounds typically contain rings that incorporate nitrogen, sulfur or oxygen atoms, and are good substrates for non-directed C–H functionalization. This is because the presence of those atoms within an aromatic structure allows the different hydrogen atoms on the ring to be easily discriminated.

By contrast, non-directed C–H functionalization is much less established for simple aromatics (those that contain rings made up only of carbon atoms)[7]. Such substrates generally have poor reactivity, and the reactions, if they occur, are typically not selective for specific C–H bonds — mixtures of several products are obtained. To overcome the first limitation, simple aromatics are usually used in much greater quantities than is suggested by the stoichiometry of the reaction. Indeed, they are commonly used as the solvent for the reaction. This greatly reduces the environmental and economic sustainability of the overall process.

Wang *et al.* propose a new solution to address the non-directed C–H functionalization of simple aromatics. The authors discovered that the combination of a catalytic metal (palladium) with a particular ligand (a 2-pyridone; Fig. 1b) greatly alters the outcome of the transformation, compared to the outcome when no ligand is used. The ligand binds closely to the metal atom, which not only makes the resulting catalyst unusually reactive, but also protects it from degradation.

Remarkably, this 'super-reactive' palladium complex cleaves the C–H bonds of various aromatic substrates, including electron-poor ones, which generally perform badly or fail in such reactions. Another fundamental advantage arising from the increased reactivity of this complex is that the aromatic substrates can be used as the limiting reagent[8] (in lower molar quantities than the other reagents), rather than in much larger quantities. Moreover, the reactions produce rather high yields (60–80%), limiting waste from the unconsumed substrate.

Notably, the binding of the ligand to the metal allows better recognition of the substrate by the resulting catalyst than that achieved by the 'naked' metal, resulting in improved (albeit still rather moderate) selectivity for one particular C–H bond out of several others. Wang *et al.* demonstrate the practical utility of their reactions by using them to convert a few drug molecules and natural products into more-complex structures. Such transformations are of interest to researchers in the pharmaceutical industry.

Some limitations still need to be overcome to realize the full potential of these reactions. In particular, achieving total selectivity for a particular C–H bond is crucial. Ideally, the selectivity should be controlled completely by the catalyst so that substrates can be modified predictably, preferably at positions that are usually difficult to target. The reactions currently require a relatively large amount of catalyst, and the addition of a silver salt; if the amounts of these two compounds could be reduced, then the transformations would become even more attractive, particularly for industrial processes. Last, but not least, Wang *et al.* use their catalyst to install two types of chemical group onto substrates. If other groups could also be introduced, then the potential of the reactions would expand greatly.

This work represents an important step forward in catalytically modifying simple molecules without resorting to directing groups. By expanding the range of molecules that can undergo C–H functionalization reactions, Wang and colleagues' strategy opens up fresh avenues for synthetic chemistry, and will no doubt rapidly become a useful tool for organic chemists. ■

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EPITRANSCRIPTOMICS

Layered-up regulation in the developing brain

Modification of messenger RNAs through a process called m^{6}A methylation facilitates dynamic temporal regulation of RNA levels in neural precursor cells, enabling fine-tuning of developing neuronal circuits in the brain.

J. DAVID SWEATT

One of the most highly evolved structures in the human brain is the cerebral cortex[1], which contains precisely structured layers of neurons that are involved in many aspects of cognition, including information processing and memory storage. During brain development, both the birth of neurons and their time-dependent wiring into complex functional circuits that span multiple neuronal layers must be carefully regulated to ensure normal cortical function. However, the molecular mechanisms that underlie these developmental processes remain mysterious. Writing in *Cell*, Yoon *et al.*[2] report an analysis of gene regulation in the developing mouse cortex. Their work reveals a mechanism that mediates precise temporal control over gene expression to ensure proper function of neuronal precursors called radial glia.

The authors investigated a major player in gene regulation[3–9] — the chemical attachment of a methyl group to a particular nitrogen atom of the nucleoside adenosine in messenger RNA. Such adenosine N^6-methylation (dubbed m^{6}A methylation) is catalysed in cells by Mettl3 and Mettl14 enzymes, among others[7–9].