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Organic synthesis set for auto-pilot

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It takes years of training, experience and chemical ingenuity to be able to make a small complex molecule. A typical natural product might contain a handful of aromatic rings, a stretch of multiple double bonds, and the odd heterocycle, all sprinkled with several chiral centres. Stitching these together in the laboratory is no easy task. In comparison, however, peptides are routinely made by machines that couple together amino acid components. Could organic synthesis ever get this simple?

That's the long-term vision of chemical suppliers Sigma-Aldrich and US researchers who have teamed up to launch a library of around 50 organic building blocks that can be stored on the shelf and clipped together to create small molecules, by repeated use of one coupling reaction.

Sigma-Aldrich's chemistry technology transfer manager Nate Wallock says the company eventually expects to market a larger library of organic components, 'sufficient to serve as a toolkit to build a wide range of molecules.' Ultimately, he hopes the approach could be automated, so that organic structures could be clipped together from modular building blocks much as peptides are today - a boon for scientists without expertise in organic chemistry, and for pharmaceutical companies who need to make large collections of molecules.

Clever coupling

The concept is based on research by Martin Burke and colleagues from the University of Illinois, who last year published a method for creating stable boronates which enclose organic components such as double bonds and aromatic rings. These molecules can be clipped together using Suzuki-Miyaura coupling, a common approach to joining carbon atoms [1,2]. In this ubiquitous palladium-catalysed reaction, a boronic acid group on one molecule reacts with a halogen on another, linking the two molecules together.

Though boronates are highly reactive and notoriously unstable, Burke's team showed that the cheap, non-toxic ligand methyliminodiacetic acid (MIDA) can act as a protecting group masking boron's activity, is stable to a wide range of synthetic reactions, and can be removed by weak aqueous base when required. MIDA-protected boronate building blocks can be stored in bottles on the shelf and can be linked reliably and repeatedly in multi-step syntheses to build up natural products, the researchers have shown [3].

Eric Gillis and Marty Burke with a stack of Sigma-Aldrich's MIDA-boronate products

So far, the new building blocks on the market haven't been used exclusively to build up molecules; rather, they are a simplifying tool for experienced chemists to use with other reactions and molecular

fragments. But the advent of commercially available MIDA boronates represents a key advance, industrial organic chemists say. 'I believe this will function as a game-changing technology and will alter the way people think about the synthesis of molecules of low, medium and high synthetic complexity. I think the potential power of this will astonish people, and the fact that it went from first disclosure to commercial product so quickly is nothing short of extraordinary,' says Peter Meinke, senior director in medicinal chemistry at Merck in New Jersey, US.

Clip chemistry

Burke points out that the idea of clipping 'modules' together to make complex molecules is particularly attractive because many natural products - just like proteins and sugars - are created in nature in this way. There are still problems, he admits - so far, the team has concentrated on linear rather than branched molecules, for example. 'Certain types of molecule are much more amenable than others - polyaryl drug-like structures, polyenes, and other natural products with sp2-hybridised carbons [all work well].' Joining sp3 carbons together with specific stereochemistry is harder.

'It is certainly very powerful because it solves a lot of prior limitations of coupling chemistry and presents a lot of opportunities for people to consider different strategies in synthesis because they do not have to worry about things like reactivity. It opens up new possibilities and has all the hallmarks of chemistry suited to robotic or parallel synthesis,' comments Lawrence Hamann, executive director in global discovery chemistry at Novartis.

Burke is confident that a synthesiser machine is possible. 'Automation is a challenge we are intensely interested in and see no reason why it cannot be solved,' he says. 'As we speak we are actively working on this. With the chemistry now in place I think it is certainly possible and we are committed to making it happen. For automation you need a stable bifunctional building block and a reaction that is pretty general that will almost always work - you can't have *ad hoc* chemistry for particular circumstances. You also need the ability to isolate the product, and reasonably high yields. I think we are half way there and I think this is a solvable problem.'

Phil Baran, an organic chemist at the Scripps Institute in La Jolla, California, says, 'This is highly significant - it is one of those rare discoveries which will carry impact both in industrial and academic settings; as for automation, I do not see why it cannot be achieved.'

Simon Hadlington

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References

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