multiple ligand binding partners that influence a broad range of immune responses. Hence, understanding the specific gp130 ligands that orchestrate NOD2-mediated molecular events could lead to more selective, effective and safer therapeutic interventions than would globally inhibiting gp130 signalling, or targeting other clinically relevant signalling pathways, such as the Janus kinase enzymes (inhibitors for which are in late-stage clinical development for Crohn's disease).

Not everyone with Crohn's disease has *NOD2* mutations associated with disease risk. Indeed, in individuals of certain ethnic groups, such as people of Chinese, Malay or Indian heritage, disease of the ileum is a prominent clinical feature of Crohn's disease, yet *NOD2* is not associated with disease risk in this population[5,9]. Perhaps the molecular signature of activated macrophages and fibroblasts is the relevant unifying signature for individuals with Crohn's disease of the ileum. It is probable that different genetic landscapes might result in the same clinical and molecular outcomes. Hence, Nayar and colleagues' results move the field a step closer to a molecular classification of Crohn's disease that might clarify a complex condition that has approximately 200 genetic regions associated with disease risk[10], and diverse clinical manifestations.

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Synthesis

Unprecedented reactions for molecular editing

William P. Unsworth & Alyssa-Jennifer Avestro

Many scientific fields and industries rely on the synthesis of small organic molecules. A chemical reagent has been developed that allows such molecules to be made by 'deleting' nitrogen atoms from readily accessible precursors. **See p.223**

On page 223, Kennedy *et al.*[1] report a strategy for molecular editing in which nitrogen atoms are 'deleted' from organic molecules. The idea of deleting, rather than adding, atoms to molecules runs counter to the way chemists usually think about making organic molecules (with a few notable exceptions; see ref. 2, for example) . But the authors' reactions could dramatically change the way in which such synthesis is planned.

Chemists attach great pride to the idea that, given sufficient time and resources, they can synthesize almost any small organic molecule. Such efforts are the basis of many technologies that have enormous societal value, such as medicines, polymers and agrochemicals. To make the range of molecules that is needed for these applications, chemists are armed with an array of methods that promote specific chemical changes, often with exquisite selectivity.

Moreover, countless chemical-synthesis methods are discovered and published daily. Most involve relatively small, practical changes to existing methods, or modest advances in the scope of known reaction types. These advances are important – incremental improvements are crucial to scientific progress. Nonetheless, methods occasionally emerge that have more far-reaching implications. Kennedy and colleagues' chemistry is one such example. To explain why, let's consider the way in which chemical syntheses are usually conceived, using a process known as retrosynthetic analysis[3,4].

In retrosynthetic analysis, the chemist starts by considering the chemical structure of the target molecule, and then works backwards by mentally 'disconnecting' individual bonds in the target molecule – the idea being to break it down into smaller and simpler chemical fragments. A synthetic route is then devised by working out a series of reactions that leads from the fragments back to the target, in the reverse sequence. Typically, there are multiple possible ways to disconnect any given target molecule, but a key consideration is that each step in the forward chemical synthesis must be a known type of chemistry, or a reaction that can be developed. Chemists therefore typically rely on tried-and-tested disconnections for common molecular motifs, because this usually ensures that the forward synthesis is productive.

Knowledge of which bonds can (or cannot) be disconnected using established chemistry, and the ability to apply this knowledge systematically, is crucial. But there is also a large creative aspect to synthesis; indeed, many of the best syntheses are said to be on the borderline between science and art[5]. Proposing a disconnection for which no synthetic methods exist for the equivalent forward reaction requires inspiration and creativity, and subsequent development of the requisite methods is hard. But chemists will always be drawn to such challenges[6–9], because they open up strategies for synthesis that would previously have been considered impossible.

This is precisely what Kennedy *et al.* have achieved. They report a reaction that enables challenging molecular targets to be made by excising single nitrogen atoms from easily accessible starting materials (Fig. 1). The authors developed a new, easily prepared chemical reagent to promote the reaction, the mechanism of which involves an unprecedented molecular rearrangement: a molecule of nitrogen is lost from a reaction intermediate, producing two highly reactive free radicals that combine to form a new carbon–carbon (C–C) bond (see Fig. 1b of the paper[1]).

The Oxford English Dictionary defines 'synthesis' as the "combination of components or elements to form a connected whole" – so isn't deleting atoms, rather than adding them, counterproductive to this goal? The value of Kennedy and colleagues' strategy lies in the fact that the nitrogen-containing starting materials are typically much easier to make, or to source commercially, than are the analogous molecules that don't contain nitrogen. Chemists can therefore simplify their syntheses by making intermediates that contain a nitrogen atom, and then removing it later. This is similar to the way in which scaffolding aids in the construction of a skyscraper, but is removed once the main structure has been built. Notably, the removal of nitrogen fundamentally alters the molecular skeleton of the molecule, because an internal atom is lost[10–13]; this contrasts with most other molecular-editing strategies, which focus on making less drastic changes on the molecule's periphery.

A practical advantage to Kennedy and colleagues' synthetic strategy is that it mitigates the costs and safety problems associated with many established C–C bond-forming methods, which usually require expensive or toxic metal reagents. The authors also demonstrate that their chemistry can delete nitrogen from commercially available drugs and natural

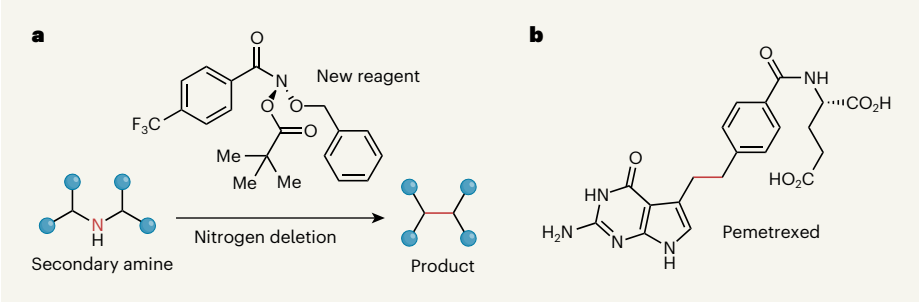

Figure 1 | Nitrogen-deletion reactions. a, Kennedy *et al.*[1] report an easily prepared reagent that removes nitrogen atoms from compounds known as secondary amines, thus providing a new way to synthesize organic molecules. The reaction produces the carbon–carbon bond shown in red in the product. Blue circles represent a variety of chemical groups. **b**, The authors demonstrate that the reactions can be used to make a range of compounds, including pemetrexed, an anticancer drug.

products, and could therefore be used to generate new biologically active compounds.

As would be expected, the reactions do not work equally well in every instance studied: the authors acknowledge that reaction yields are typically higher when the starting molecule has features that stabilize the reactive species formed when nitrogen is extruded. Nonetheless, the present scope of the reaction is easily sufficient to suggest that it will be widely adopted. Improvements that address its present limitations are likely to emerge.

Molecules made using Kennedy and colleagues' chemistry could help to stimulate advances and technologies in applied fields, beyond drug discovery, that rely heavily on the availability of efficient methods for chemical synthesis. The nitrogen-deletion strategy could also enable a long-standing dream to be fulfilled: the development of truly 'traceless' reactions, in which no evidence of the molecular features that assisted the synthesis remain in the products. Nitrogen deletion might be especially helpful for the traceless synthesis of advanced materials in which the presence of nitrogen atoms can be detrimental to function – such as molecular machines, or elastic or self-healable polymers for heat-resilient electronic devices. Although the part played by the deleted nitrogen atoms would not always be apparent in the molecules ultimately used in these applications, the atoms' impact in enabling the synthesis of the materials could be transformative.

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