was reduced in AD mice lacking astrocytic IL-3.

The authors next identified the targets of IL-3 in the brain. They found that microglia express the IL-3 receptor IL-3Rα, and that levels of this receptor are substantially increased with age and in the AD model compared with young, wild-type mice. Deleting IL-3Rα specifically from microglia in the AD mice resulted in effects on Aβ plaque burden and memory similar to those observed in AD mice lacking IL-3 in astrocytes.

Strikingly, McAlpine and colleagues found that injecting IL-3 into the brains of AD mice could reduce Aβ build-up and stimulate the clustering of microglia around Aβ plaques (Fig. 1). Continuous delivery of IL-3 into the brains of IL-3-deficient AD mice over four weeks resulted in a remarkable reduction in the size and amount of plaques and the levels of soluble Aβ, as well as improvements in short-term memory relative to results seen in AD mice injected with an inactive control substance. This is a key finding with potential therapeutic implications.

Interest in the role of microglia in AD has increased dramatically since the discovery that a variant of the gene encoding the receptor protein TREM2, which is expressed by microglia, is associated with risk for AD[9]. McAlpine *et al.* show that *Il3ra* is enriched in a previously described subset of 'disease-associated microglia' that are activated through the TREM2 receptor[10]. Moreover, the authors found that deletion of *Trem2* prevented the increase in microglial expression of IL-3Rα in their AD model, raising the question of whether *TREM2* mutations associated with AD risk in humans might prevent this protective IL-3-dependent response.

Indeed, the authors also found evidence that this pathway is at work in the human brain. In brain tissue from individuals who had died with AD, the authors observed astrocyte expression of IL-3 and higher microglial expression of IL-3Rα than in the brains of age-matched individuals without AD. Moreover, the amount of microglial IL-3Rα expression correlated with the length of time for which these individuals had been diagnosed with AD, as well as with the accumulation of Aβ plaques.

How does IL-3 promote the protective functions of microglia? The authors found that in AD mice lacking IL-3, microglia did not cluster around plaques, and plaque deposition was greater than in AD mice. In experiments with human microglia in culture, treating these cells with IL-3 promoted migration towards AD-associated protein aggregates.

It is important to keep in mind that IL-3 might offer protection through more than one mechanism. For example, IL-3 was particularly abundant in astrocytes at the blood–brain barrier, which controls the passage of proteins and cells from the circulatory system to the brain. Populations of immune cells called macrophages, which reside at the brain's borders, might have been targeted by some of the genetic tools used to manipulate IL-3Rα expression. Such cells could also be affected by IL-3 to alter the entry of molecules or cells into the brain. Although McAlpine *et al.* examined some aspects of the integrity of the blood–brain barrier and found it to be intact, other unmeasured variables such as active transport of blood-borne molecules to the brain could be affected[11].

In addition, it is possible that other brain cell types could express the IL-3 receptor in some contexts and respond to IL-3. Further dissecting the impact of IL-3 signalling on other cellular players will be a crucial next step.

Nonetheless, these findings are an exciting advance in understanding the role of astrocytes and microglia in AD, a disease that is notoriously difficult to treat and that currently lacks any curative or restorative therapies. Although caution should be exercised in translating these findings to the clinic, particularly given the role of IL-3 and IL-3Rα in certain autoimmune disorders[12], this study raises the intriguing idea that IL-3 or related molecules could have therapeutic potential in AD. Could this be one step towards personalized therapy for individuals with AD who carry a risk-associated *TREM2* variant? Further defining the roles of IL-3 in health and disease will be essential to fulfil the promise of McAlpine and colleagues' findings.

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Organic chemistry

Boron groups installed directly into molecules

Christine M. Le

Compounds called borylated azines have untapped potential for organic synthesis, but have faced problems associated with their preparation, stability and reactivity. A new class of these compounds provides a solution. **See p.677**

The search for new pharmaceutical drugs by medicinal chemists relies on the synthesis of diverse compound libraries for biological testing. Of the reactions used for this purpose, those involving boron-containing organic molecules (known as organoboron compounds) are among the most popular because of the commercial availability and wide reactivity of these reagents[1]. On page 677, Kim *et al.*[2] report a method for the synthesis of organoboron compounds called borylated azines. The authors demonstrate that these compounds can participate in reactions common to other organoboron compounds, but offer distinct advantages, such as ease of preparation and impressive stability. Importantly, these reagents will allow a full exploration of the therapeutic potential of molecules that have previously been difficult to prepare.

Azines are nitrogen-containing analogues of benzene rings and are present in many of the top-selling pharmaceuticals approved by the US Food and Drug Administration (see go.nature.com/2dirpwf). These medicines target several disease areas, including arthritis, diabetes and several types of cancer. If a boron-containing group is attached to an azine, the resulting borylated azine can be used as a reagent for the synthesis of many different azine-containing molecules — a crucial process for diversifying compound libraries. Kim *et al.* explored the use of transformations called C–H functionalization reactions to prepare borylated azines.

Although once regarded as an academic curiosity, C–H functionalization reactions are now a powerful methodology in organic synthesis. In these processes, a carbon–hydrogen

(C–H) bond is converted into a carbon–X bond, where X can be any atom other than hydrogen. C–H functionalization can greatly streamline a synthetic procedure by reducing the number of steps it takes to get to a specific target molecule.

Borylated azines are typically synthesized from their bromine-containing analogues (Fig. 1a). But although these brominated starting materials are commercially available, they are more costly than the equivalent azines that lack a bromine atom. For example, 2-bromopyridine can be about 25 times more expensive per mole than pyridine, which reflects the cost of the synthetic steps needed to attach a bromine atom to pyridine[3].

A C–H functionalization reaction that directly introduces a boron-containing group to an azine can bypass these steps, saving valuable time and resources. If the conventional synthetic approach is like a bus route that has multiple transfers, C–H functionalization is like a non-stop express train. But before boarding this train, it is crucial to make sure that it stops at your desired destination: azines often have several C–H bonds, which means that synthetic chemists must devise clever strategies to ensure that only the desired C–H bond reacts, rather than another.

The development of iridium-catalysed borylation methods was a notable advance in the field of C–H functionalization[4]. With azines, however, iridium-catalysed borylation occurs at a C–H bond distal to the nitrogen atom in the azine ring, mainly at the β-position (the second-nearest position to the nitrogen). These methods cannot provide products with a boron group adjacent to the nitrogen (the α-position), which, in turn, means that the borylated products cannot be used to make molecules in which the azine ring is connected at the α-position. This is a notable limitation, because many drug molecules contain azines attached at that site.

Kim and colleagues have now solved this problem by taking advantage of the inherent reactivity of azines towards radicals — atoms or molecules that contain an unpaired electron. This reactivity was heavily explored by the chemist Francesco Minisci in the 1960s with 'alkyl' radicals, which have the unpaired electron centred on a carbon atom. In the presence of acid, carbon-centred radicals react with azines predominantly at the α-position, leading to attachment of a carbon atom to that site and loss of a hydrogen atom[5].

In their work, Kim *et al.* show that boron-centred radicals can react similarly, allowing boron-containing groups to be installed at the α-position and providing products that currently cannot be made using iridium-catalysed reactions (Fig. 1b). If the reactive α-sites are blocked by attached chemical groups, borylation can occur at other positions around the azine ring. The authors' key discovery was that an amine-borane reagent ($Me_3N{\cdot}BH_3$, where Me is a methyl group, CH_3), in the presence of an organic catalyst, acid and light, can form boron-centred radicals with the necessary reactivity for Minisci-type chemistry.

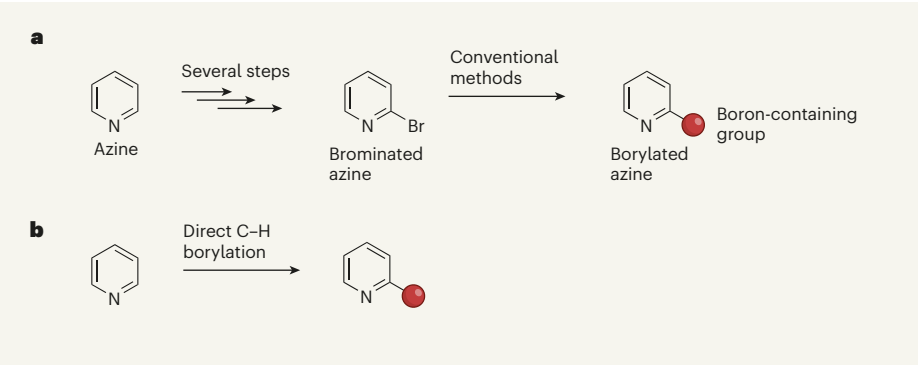

Figure 1 | The synthesis of borylated azines. a, Azines are analogues of benzene rings that contain one or more nitrogen atoms — the example shown is called a pyridine. Azines that bear a boron-containing group are called borylated azines, and are useful intermediates for organic synthesis. Conventional methods for making borylated azines involve adding a bromine atom to the starting azine (which might take several steps), and then replacing the bromine atom with the boron-containing group. **b**, Kim *et al.*[2] now report that a method known as C–H functionalization can be used to attach a boron-containing group directly at the α-position of an azine. The resulting products are useful for making compounds with various other groups at the α-position — a common molecular motif in pharmaceutical compounds.

An added benefit of Kim and co-workers' chemistry is that it installs an amine-borane group (BH_2-NMe_3) in the azine. The amine portion of the group (NMe_3) confers stability on the borylated azine — without it, the boron atom has an incomplete shell of valence electrons and could undergo reactions that lead to the compound's decomposition. Indeed, the authors' borylated azines are stable enough to be stored in ambient conditions for several months, without the need for specialized storage.

"The authors' work provides products that currently cannot be made using iridium-catalysed reactions."

Stable compounds can be unreactive, especially if the site of reactivity is blocked off — and in this case, the boron centre is blocked off by the attached amine group. Chemists might therefore be wondering whether further reactions of the borylated azines are possible. The answer is yes: these compounds can participate in oxidations, and in various 'cross-coupling' reactions to form other types of bond (such as carbon–carbon, carbon–nitrogen and carbon–oxygen bonds), providing entry to medicinally relevant molecular scaffolds. The yields of some of the cross-coupling reactions are modest, but α-borylated azines are generally challenging substrates for cross-coupling, owing to their tendency to decompose through protodeboronation (replacement of the boron group with a hydrogen).

It would now be useful to know whether these borylated azines can participate in reactions in which the amine-borane group is replaced with a fluorine atom[6]. Fluorine-containing groups are valuable motifs in medicinal chemistry, and therefore having access to fluorinated azines could be transformative in drug discovery. Moreover, if the authors' chemistry can be used to incorporate fluorine into molecules as the final step of a synthesis, it might be possible to use it to label pharmaceutical compounds with a radioactive fluorine-18 atom — thereby allowing the compounds to be visualized in the body using positron emission tomography imaging[7]. Finally, given the balanced stability and reactivity profile of Kim and colleagues' borylated azines, it will be interesting to see whether unique synthetic applications emerge for these reagents, particularly in situations for which conventional organoboron compounds fall short.

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