Organic chemistry

Game-changing recipe for chemical building blocks

Valerie A. Schmidt

Chemists generally regard benzene rings as preformed units that are elaborated to build larger molecules. This idea has now been challenged in reactions for making anilines – precursors of many high-value chemical products. **See p.75**

Decades of research have provided chemists with the tools to synthesize a diverse array of organic molecules in short sequences of high-yielding reactions, making use of inexpensive and widely available chemical building blocks. When a new reaction is reported that fundamentally alters the idea of what can be used as a building block, it can be a game changer. On page 75, Dighe *et al.*[1] report one such potentially transformative reaction that uses light and two transition-metal catalysts to make products known as anilines – key ingredients for making pharmaceuticals, agrochemicals, dyes, electronic materials and polymers[2,3].

When chemists describe certain organic molecules as being aromatic, they aren't referring to their smell. They're actually describing molecules – such as those that contain benzene rings – that have a certain number of electrons interlocked into circular systems, thereby lowering the energy of the molecule concerned. Anilines are benzene rings with a nitrogen atom attached, and do often have a fishy smell. But their odour is one of the least noteworthy things about them.

Aniline groups were present in three of the top ten highest-grossing global pharmaceuticals in 2019 – Eliquis (apixaban), Revlimid (lenalidomide) and Xarelto (rivaroxaban), combined retail sales of which surpassed US$28 billion (see go.nature.com/2dirpwf; ref. 4). Aniline compounds are also precursors for one of the two monomers needed to produce polyurethane materials, which in turn are used to make everything from stretchy fabrics and compressible foams to the wheels of skateboards and rollercoasters[5]. These are all high-value commercial products, so finding versatile ways to make anilines from abundant chemicals is of great interest.

Simple anilines are generally derived from benzene, toluene and xylenes (BTX) – petrochemicals available at low cost in bulk quantities. These building blocks contain a benzene ring in which a carbon–hydrogen (C–H) bond can be replaced with a carbon–nitrogen (C–N) bond without disrupting the aromatic system, thus producing the nitrogenated aromatic framework of an aniline. This method for making anilines is known as the nitration–reduction pathway[2] (Fig. 1a).

Alternatively, carbon–halogen bonds in BTX derivatives can be replaced by C–N bonds[6], either using a strong base if the benzene ring is highly activated, or using sophisticated metal catalysts. Such reactions are broadly known as aromatic substitutions (Fig. 1b). Fundamentally, nitration–reduction pathways and aromatic substitutions both revolve around the entrenched idea that complex aromatic molecules are made only from building blocks that already contain aromatic rings. Aromatic frameworks are therefore generally not made from scratch during organic synthesis, but instead are used as raw materials that are 'decorated' with other chemical groups.

This is similar to how bakers think about making an apple pie. Apple pies are made using pastry dough for the crust and apples for the filling. Apples are the only ingredient that can be used, because there is no way to make an apple filling from other ingredients. Fortunately for bakers, apples are relatively inexpensive and widely available in most areas, but the resources needed to plant, grow, harvest and distribute the ripened fruit are taken for granted. This parallels the historical use of BTX as cheap, widely available 'ingredients' for making more-complex molecular targets. The time-intensive geological process by which crude oil is produced from organic material, and the many resources needed to extract the oil, to isolate BTX from it and to distribute the chemicals for use in manufacturing processes, are also taken for granted.

But what if apples weren't the only ingredient that could be used for the filling? What if apple seeds – which contain all the basic genetic information needed to produce an apple – and a few speciality spices could somehow be used instead, and still produce a perfect apple pie? In this (admittedly far-fetched) scenario, the idea that apples are the only basic ingredient of an apple pie would have to be altered. Dighe *et al.* have essentially performed the chemical equivalent of making apple pie from apple seeds.

The authors have leveraged the inherent propensity of nitrogen-containing compounds called amines to react with carbonyl (C=O) groups to form a C–N bond. These

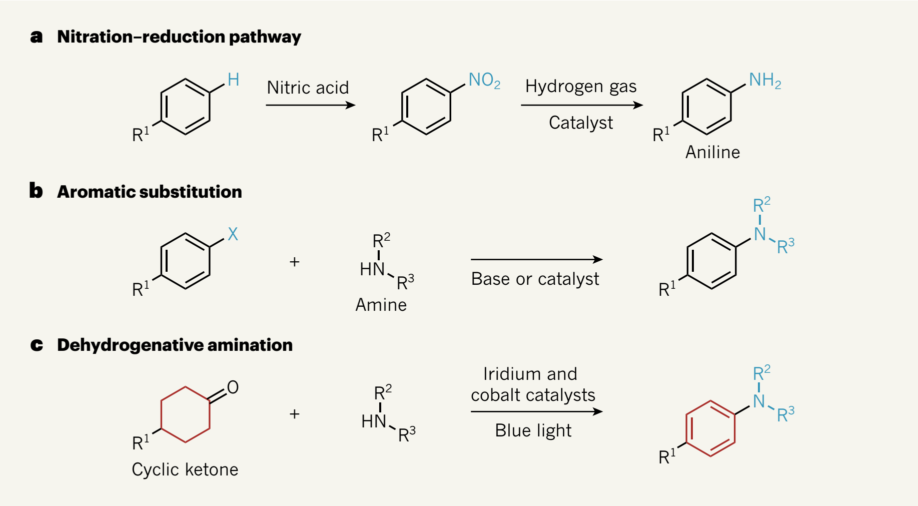

Figure 1 | Methods for synthesizing anilines. a, In the two-step nitration–reduction pathway, a hydrogen atom on a benzene ring is replaced by a primary amine group (NH_2); hydrogens on other carbon atoms are not shown. **b**, In aromatic substitutions, a halogen atom (X) is displaced by an amine, in the presence of either a base or a catalyst. In **a** and **b**, the benzene ring of the aniline comes from the starting material, and only groups (blue) attached to the ring are altered. **c**, Dighe *et al.*[1] report dehydrogenative amination reactions in which the benzene ring of the aniline is made from the ring of a cyclic ketone (rings shown in red), and a carbonyl (C=O) group is converted into an amine group (blue). The reactions require a light-activated iridium catalyst and a cobalt catalyst. R^1 can be any chemical group; R^2 and R^3 represent a hydrogen atom or any hydrocarbon group.

reactions produce compounds known as enamines that contain a non-aromatic ring, which can readily lose an electron to a light-activated iridium catalyst (see Fig. 1b of the paper[1]). Loss of an electron produces a reactive intermediate called an enaminium radical, which contains an unpaired electron. This radical then engages a cobalt catalyst, which removes hydrogen atoms sequentially from the non-aromatic ring, thereby forming the aromatic ring of an aniline. This overall process is termed dehydrogenative amination (Fig. 1c), and it allows anilines to be produced from non-aromatic precursors.

Light-activated iridium catalysts have previously been used for single-electron oxidations[7] (processes in which an electron is lost from a molecule), and cobalt catalysts have also been used to remove hydrogen atoms from molecules[8]. But by melding these two processes together, Dighe *et al.* have produced a reaction that is greater than the sum of its parts. Other methods for preparing aromatic rings from scratch have previously been reported[9,10], but have been challenging to use for organic synthesis.

The authors demonstrate that their reaction can make a wide array of anilines, nearly two-thirds of which contain structural motifs commonly found in biologically active compounds or pharmaceuticals. Indeed, the authors show that their reactions can be used to make seven medicines, including the local anaesthetic lidocaine and the cardiovascular drug vesnarinone. The use of dehydrogenative amination to synthesize those two compounds avoids the problems of the current industrial production routes, which start from aromatic building blocks.

Dighe and colleagues' reactions might be beneficial when nitration–reduction approaches do not occur selectively at a single C–H bond on an aromatic ring, or when aromatic substitutions are low-yielding or prohibitively expensive. However, nitration–reduction pathways are generally reliable and scalable, and use inexpensive starting materials, and have therefore enabled the industrial-scale synthesis of anilines — this is, in part, why aniline-containing compounds are so widely used. By contrast, the chemical-engineering processes needed to scale up Dighe and co-workers' light-activated, iridium-catalysed chemistry is unknown, and will be a factor that affects how extensively the reactions are adopted for the production of commercial chemicals. Moreover, iridium is one of the rarest elements in Earth's crust, limiting supplies of the catalyst and increasing its cost.

Nevertheless, Dighe *et al.* have shown that aniline synthesis need not be bound by conventions that dictate the use of preformed aromatic rings. Time will tell whether the authors' reactions will completely replace the status quo, but having the freedom to choose from an increased range of options for making anilines is a wonderful thing.

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Archaeology

Evidence grows for early peopling of the Americas

Ruth Gruhn

The long-debated timing of the peopling of the Americas comes into focus, thanks to some archaeological findings. What are the implications of a revised timeline for our understanding of these earliest inhabitants? **See p.87 & p.93**

Ardelean *et al.*[1] (page 87) and Becerra-Valdivia and Higham[2] (page 93) report evidence that the initial human settlement of the American continent happened earlier than is widely accepted, and some of this evidence suggests that expansion into the continent began at least 10,000 years earlier than was generally suspected. A study of radiocarbon dating of early archaeological sites by Becerra-Valdivia and Higham reveals that interior regions of Alaska, Yukon in Canada and the continental United States were already widely populated before 13,000 years ago. For decades, that time frame was widely considered to mark the earliest possible date of initial entry, until data from sites more than 13,000 years old in North and South America, first reported in the 1970s, raised the possibility of earlier arrivals[3–5]. Archaeological excavations in Chiquihuite Cave in northern Mexico by Ardelean and colleagues provide evidence of human occupation about 26,500 years ago. This Mexican site now joins half a dozen other documented archaeological sites in northeast and central Brazil that have yielded evidence suggesting dates for human occupation between 20,000 and 30,000 years ago[6–12].

Following discoveries in the 1930s on the American Great Plains of distinctive, well-crafted stone spear points — of a type connected with the Clovis culture — alongside bones of mammoths, mastodons and a now-extinct bison species, archaeologists maintained, for many of the following decades, that the earliest people in the Americas were specialized big-game hunters who very rapidly expanded into North and South America, within 1,000 years of initial entry[13]. This model became known as the Clovis-first theory. It was later established that Clovis technology did not reach the southern continent. The time of their entry from Alaska into what is now the continental United States was thought to coincide with the opening of an ice-free corridor (Fig. 1) by around 13,000 years ago between the great northern continental ice sheet (called the Laurentide Ice Sheet) and the ice-covered northern Rocky Mountains (the Cordilleran Ice Sheet) in western Canada.

However, beginning in the mid-1970s, researchers identified archaeological sites in the Americas dated to earlier than 13,000 years ago, especially in South America. For example, the site of Monte Verde II in south-central Chile, initially dated to 14,500 years ago[3], is a well-preserved open settlement with wooden structures and artefacts indicating a lifestyle based mainly around a diet of plants (subsequent discoveries revealed earlier occupations of this site[14]). Other early archaeological sites in South America on the Pacific coast, in the northern and central Andes, on the Caribbean coast, in the Brazilian uplands, in the Amazon basin, and on the Patagonian steppe in Argentina indicate that all major