ORGANIC CHEMISTRY

Facial recognition for molecules

A catalyst has been developed that recognizes the topology of just one face of a planar reaction intermediate. Remarkably, this enables one mirror-image isomer of the reaction product to be made selectively. SEE ARTICLE P.447

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Complex 3D molecules are ubiquitous in daily life, with functions in everything from high-performance materials to smart medicines. Just as 3D shape often reflects function on the macroscopic scale, so, too, does it determine microscopic behaviour. When building 3D molecules for applications, chemists must therefore develop synthetic routes that ensure that each atom is correctly positioned in the final product. However, even if such precision is achieved, some molecules can be produced as mirror-image isomers (enantiomers), and their properties might vary widely, affecting their use in applications. On page 447, Wendlandt *et al.*[1] report a reaction that not only enables the synthesis of single enantiomers of molecules, but does so using a reaction mechanism that was thought to be intrinsically lacking in enantioselectivity.

A rich arsenal of synthetic methods is available to connect molecular fragments in a highly predictable manner, and substitution processes are among the most powerful of these. Known as S_N1 or S_N2 reactions, these processes share a common requirement for an electron-rich species (a nucleophile) and an electron-deficient species (an electrophile). However, the two reaction types proceed by distinct mechanisms.

In S_N2 reactions, the approach of the nucleophile towards the reactive centre of the electrophile leads to the extrusion of a chemical group, known as the leaving group (Fig. 1a). The leaving group on the electrophile is then replaced — substituted — by the nucleophile. The bonds around the reaction centre behave much like the spokes of an umbrella turning inside out on a stormy day. This highly orchestrated mechanism ensures that the 3D geometry in the tetrahedral framework of bonds around the reaction centre is inverted, and the 'information' about that geometry, encoded by the framework (the stereochemical information), is not lost. In other words, only one enantiomer of the product is formed.

By contrast, the S_N1 reaction involves the initial extrusion of the leaving group — independently of the nucleophile — to generate a charged species called a carbocation (Fig. 1b).

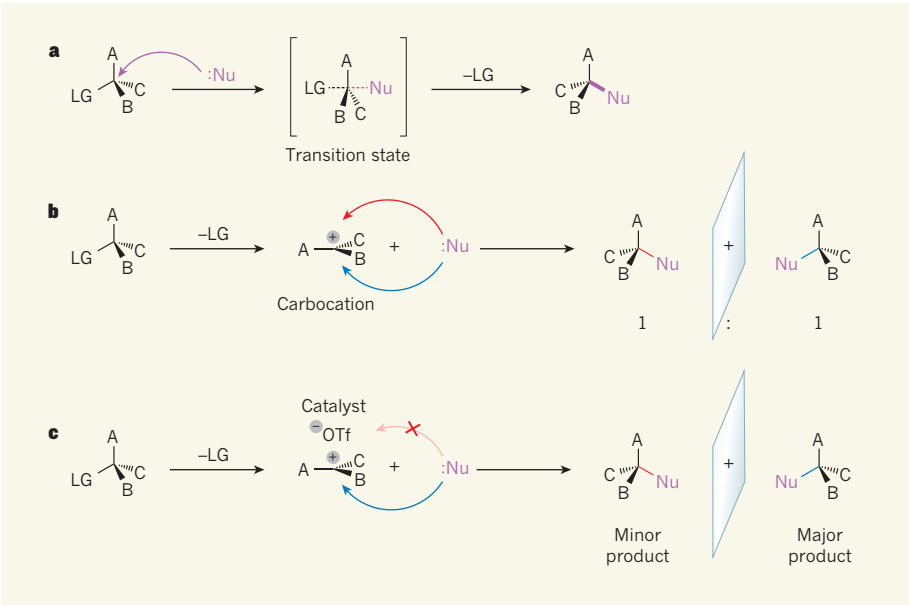

Figure 1 | Mirror-image selectivity in substitution reactions. **a**, In an S_N2 reaction, a reactant called a nucleophile (Nu; dots indicate a lone pair of electrons) attacks a carbon atom in an organic molecule from the side opposite to a 'leaving' group (LG). A, B and C can be any atom or group. In the transition state, the bond between the carbon atom and the LG is partly broken, and a bond between Nu and the carbon atom is partly formed (partly broken and partly formed bonds are shown as dashed lines). The bond to the LG then breaks, and a single product is formed. **b**, In the S_N1 reaction, the LG is released first, and a planar, charged intermediate called a carbocation forms. Because the Nu can attack the carbocation equally easily from either side, the product forms as a 1:1 ratio of mirror-image isomers (enantiomers). **c**, Wendlandt *et al.*[1] report an S_N1 reaction in which a small-molecule catalyst and a triflate ion ($^-$OTf) bind to one side of the carbocation, directing the nucleophile to the other side. One enantiomer is therefore produced preferentially.

Because this intermediate is planar, it can be intercepted by the nucleophile from either face, to generate the reaction product as a one-to-one mixture of enantiomers, thus losing the stereochemical information in the electrophile. Wendlandt *et al.* overcome this long-standing stereochemical limitation by reporting an enantioselective S_N1 reaction.

The authors' method can be thought of as emulating biometric facial recognition: they use a small-molecule catalyst to discriminate between the two faces of the transient carbocation. Much as algorithms efficiently analyse structural features of faces, the catalyst identifies one face of the cation and thus directs the nucleophile to the other (Fig. 1c). This facial discrimination manifests in the high enantioselectivity of the reaction. The formation of one-to-one mixtures of enantiomers is prevented, but, in contrast to the S_N2 reaction, the stereochemical information in the starting material is irrelevant. The reaction is therefore said to be enantioconvergent.

The small-molecule catalyst used by Wendlandt and colleagues is combined with a Lewis acid (a molecule that accepts electron pairs from other molecules), to generate a negatively charged complex that can be thought of as the active form of the catalyst. This type of combination is common in nature, and often facilitates reactions that would be impossible using the catalyst alone. In the present study, the active catalyst activates electrophiles known as propargyl acetates by removing the leaving group (the acetate), forming a carbocation intermediate. This positively charged intermediate interacts with the negatively charged active catalyst to form an ion pair; such ion pairing has previously been used

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in other types of enantioselective catalytic reaction[2]. The active catalyst recognizes one face of the planar cation, shielding it so that only the opposite face can interact with an approaching nucleophile. The products of this S_N1 reaction are thus obtained predominantly as one enantiomer.

Not only does Wendlandt and co-workers' study transform an S_N1 reaction into a catalytic, enantioconvergent process, but it also constitutes a powerful synthetic route for preparing molecular motifs called quaternary carbon centres[3,4], which are notoriously challenging to make enantioselectively. Quaternary carbon centres have four different carbon-based substituents attached to a central carbon atom, and are commonly found in biologically active, naturally occurring compounds, such as morphine or various steroids. A great deal of structural diversity could be generated by varying each of the four substituents, making quaternary carbon centres valuable starting points for drug discovery. The authors' study is a breakthrough in that it allows readily accessible racemic mixtures (one-to-one mixtures of enantiomers) of starting materials to be quickly processed to make structurally complex molecular scaffolds containing these motifs.

Wendlandt *et al.* exemplify their reaction using substrates that contain structural groups specifically chosen to stabilize the intermediate cation. However, the underlying concept is general, and will certainly be translated to related classes of reaction. The reported products are striking because the carbon atoms attached to the central atom in the quaternary centre represent a diverse range of electron orbitals (*sp*, sp^2 and sp^3). This means that the groups attached to the central atom have markedly different geometries and reactivities. Future work in which the four groups are varied will therefore produce highly versatile libraries of molecules that could be used in a wide range of reactions for synthesis, and allow the exploration of a large amount of 'chemical space' — the vast array of all possible molecules. ■

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EPIDEMIOLOGY

A broader look at paediatric HIV infection

An epidemiological study of adolescents who had acquired HIV around the time of birth highlights how high-income countries benefit from the ability to begin treating all infected children in the first years of life.

PATRICIA M. FLYNN

It is estimated that more than 2.1 million children under 15 years of age are living with HIV infection worldwide (see Statistical Tables at go.nature.com/2qqvksh). Almost all of these children received the retrovirus from their mother, either around the time of birth (the perinatal period) or through breastfeeding. Writing in *PLoS Medicine*, the CIPHER (Collaborative Initiative for Paediatric HIV Education and Research) Global Cohort Collaboration[1] has shed light on the population of children who survive perinatal HIV infection, living into adolescence and beyond. The collaboration's far-reaching epidemiological study emphasizes the importance of early antiretroviral therapy (ART) for improving survival rates and clinical outcomes.

Before the availability of ART, the mortality rate of babies perinatally infected with HIV was 25% by 2 years of age[2]. Today, a much higher percentage of perinatally infected children survive into adolescence, but this population is little studied compared with other cohorts of people with HIV. Furthermore, it has been unclear whether or how perinatally acquired HIV might differentially affect adolescents living in different parts of the world.

The CIPHER investigators combined data from researchers in 12 regions of the world who followed adolescents with perinatal HIV infection. For a total of 38,187 adolescents, the authors report factors such as the age at which ART began, the person's growth record, whether or not they dropped out of their treatment programme, and survival. Individuals were tracked from their first clinic visit and first ART treatment until 15 years of age, and data were collected from the 1980s or 1990s (depending on region) until 2014.

These data allowed the CIPHER researchers to compare adolescents in different countries, regions and country income levels. Their analysis demonstrates that country income level is associated with the stage of life at which ART typically begins. Not surprisingly, the initiation of both care and ART occurred much earlier in the high-income countries included in the study (14 European countries and the United States) than in other areas of the world. Specifically, children first visited a clinic at a median of 1.1 years of age and began ART at a median of 2.5 years in high-income countries, compared with 7.1 years and 8.0 years, respectively, in the low-income countries studied (26 countries in sub-Saharan Africa).

Growth is delayed in children with HIV infection[3], and was markedly different between high- and low-income countries. The authors found that height-for-age scores were higher in high-income countries than in countries at other income levels at the times when the person first visited the clinic and began ART. In all regions, growth levels began to catch up after ART began. But the height-for-age scores achieved by children in high-income countries at the age of 10 and at the time of the last recorded clinic visit were similar to those of children and adolescents who did not have HIV. By contrast, height-for-age scores for

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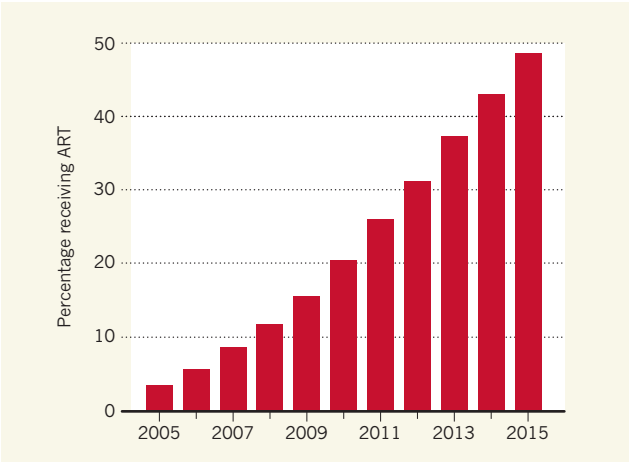

Figure 1 | Prevalence of antiretroviral therapy (ART) for children living with HIV in low- and middle-income countries. Between 2005 and 2015, the percentage of children under 14 years of age who were living with HIV in low- and middle-income countries and who were receiving ART rose from less than 5% to 49%. But the CIPHER Global Cohort Collaboration[1] reports that these children typically began ART later in life than their counterparts in high-income countries.

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