

go.nature.com/2kyjv51) shows sardinella being smoked, dried and hand-processed by Senegalese women and then trucked to the interior of the country, where these fish are the only affordable main source of micronutrients and animal protein. The leader of these workers emphasized in an interview in the documentary that it would be a catastrophe if the sardinella supply was interrupted, because they would have no fish to process.

Since then, this feared catastrophe has begun to happen. Despite much local consternation, more than 40 industrial fish-processing plants have been built, mainly by Chinese enterprises, along the coast of Senegal (see go.nature.com/2kva8bu) and neighbouring countries (see go.nature.com/2jtmcj). These plants process sardinella (Fig. 1) and similar small fish into an animal-feed product called fishmeal. Many of the local fisheries, which had traditionally supplied the regional markets with sardinella for human consumption, now instead supply the fishmeal plants.

These factories export their product mainly to China, which is the world's largest fishmeal importer, and it is commonly used there to feed farmed fish.

Thoughtful consumers often insist that they eat fish certified as sustainably caught. This nebulous term often implies a hope that such fish suffered as little as possible, and that their stocks are somehow being managed to ensure the continuation of an abundant supply. If such fish come from fish farms, as is the case for most salmon on offer, this, too, is considered a good thing, because it is widely thought that fish farming relieves pressure on capture fisheries. However, using sardinella to make fishmeal for farmed fish does not reduce the pressure on wild fish. Moreover, it deprives people in the developing world on low incomes of previously affordable, nutritious local fish — to aid the production of costly farmed fish that is mainly consumed in high-income countries².

When considering what fish we should eat,

given that fish is good for us, it is time to take a broader perspective about how “us” is being defined. Hicks and colleagues' work points a way forward. The information they have provided could be used to put a spotlight on fish availability when thinking of ways to prevent human disease caused by micronutrient deficiencies. ■

Daniel Pauly is at *Sea Around Us, Institute for the Oceans and Fisheries, University of British Columbia, Vancouver, British Columbia V6T 1Z, Canada.*
e-mail: d.pauly@oceans.ubc.ca

- Hicks, C. C. *et al. Nature* **574**, 95–98 (2019).
- Golden, C. D. *et al. Nature* **534**, 317–320 (2016).
- Swartz, W., Sumaila, U. R., Watson, R. A. & Pauly, D. *Mar. Policy* **34**, 1366–1373 (2010).
- Pauly, D. & Zeller, D. *Nature Commun.* **7**, 10244 (2016).
- Thiao, D., Lepout, J., Ndiaye, B. & Mbaye, A. *Aquat. Living Resour.* **31**, 25 (2018).

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SYNTHESIS

Chemical libraries from a double click

Operationally simple chemical reactions, termed click reactions, are widely used in many scientific fields. A streamlined synthesis of compounds called azides looks set to expand the role of click chemistry still further. [SEE LETTER P.86](#)

JOSEPH J. TOPCZEWSKI & EN-CHIH LIU

Generating molecules and materials that have desirable functional properties is arguably the central goal of synthetic chemistry. For example, drugs are developed to have a set of physical and pharmacological properties that can treat a specific disease safely. On page 86, Meng *et al.*¹ report a reagent that greatly simplifies the synthesis of compounds known as azides, and thereby opens up a remarkably straightforward route to making libraries of compounds that might have useful biological functions.

Altering the structures of molecules to tune their properties is much more complicated than modifying objects in the everyday world. In carpentry, for instance, the same starting materials (timber, nails and screws) and tools (saws, hammers and screwdrivers) can be used to construct objects that have diverse shapes and functions, such as chairs, doors and crates. By contrast, building structural analogues of molecules often requires very different starting materials (reagents) and tools (reactions). The need to develop a range of synthetic routes to such analogues can be a bottleneck when optimizing functional molecular properties², given

that optimization can involve the laborious, resource-intensive synthesis of hundreds, or even thousands, of structural analogues.

A way of streamlining the optimization of desired functional properties was formalized in 2001, in a concept known as click chemistry³. A reaction is defined as click chemistry if it is operationally simple, is ‘spring-loaded’ (thermodynamically driven to produce a single

product quickly), and generates new chemical bonds between two molecules. Ideally, the reactants should be used in a one-to-one ratio, rather than with an excess of one or more components (which is a common requirement for many reactions). Click reactions must be high-yielding, applicable to a broad range of compounds, and yet exceptionally selective, meaning that the chemical groups that undergo the reaction must react only with each other, and not with any other groups in the reactants. The product should also be easy to isolate or use without extensive purification. Although many synthetic reactions meet some of these criteria, surprisingly few meet all of them.

In 2002, two research groups independently reported^{4,5} that copper(I) salts are effective catalysts for reactions known as alkyne–azide cycloadditions (the copper-catalysed reaction is abbreviated as CuAAC). These reactions link an azide group (N₃) with the carbon–carbon triple bond in an alkyne compound to form a triazole ring (Fig. 1). Because the CuAAC

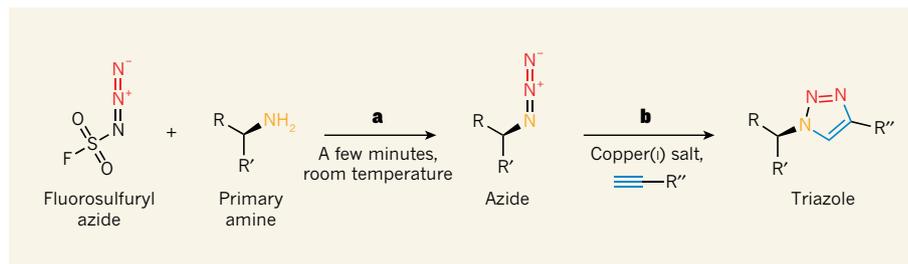


Figure 1 | A two-step click-chemistry sequence. **a**, Meng *et al.*¹ report that a reagent called fluorosulfonyl azide rapidly converts almost any primary amine into an azide at room temperature — a type of reaction known as diazotransfer. The reactions are fast and high yielding, and the reagent does not react with chemical groups other than amines; they therefore fulfil the criteria to be categorized as ‘click’ reactions. **b**, The authors show that the resulting azide solution can be used without purification in a copper(I)-catalysed click reaction with alkynes (compounds that contain carbon–carbon triple bonds) to produce products called triazoles, which are potentially useful in drug discovery. R, R' and R'' represent any chemical group or molecular fragment.

reaction fulfils all of the click criteria, it has become the poster child for click chemistry. It was the first click reaction to be widely adopted, and is now used in applications spanning many disciplines, from materials science to chemical biology^{6,7}.

Several other click reactions have emerged over the past few years. Of particular note is one known as sulfur(VI)–fluoride exchange (SuFEx), which links an oxygen or nitrogen atom to an SO₂F group. SuFEx is generally recognized as a second category of click reaction^{8,9} (unlike other click reactions, it is not a cycloaddition process), and has been used in a diverse range of chemical transformations^{9,10}.

Despite the power of CuAAC reactions, their applications would be even broader if structurally complex, azide-containing compounds were more widely available. Conventionally, organic azides are synthesized by replacing a molecular fragment called a leaving group with an azide group; the leaving group can be a variety of chemical groups or just a single atom. However, the azide anions used in these substitution reactions are highly nucleophilic (electron-rich) and therefore very reactive. Substitutions with azide anions are thus often incompatible with having other chemical groups in the molecule. Furthermore, the leaving group often needs to be made in advance from an alcohol group (OH), which can be difficult or impossible to achieve selectively on molecules that contain many chemical groups.

Alternatively, azides can be prepared from primary amines (compounds that contain NH₂ groups) by a ‘diazotransfer’ reaction. Until now, the state-of-the-art reagent used to carry out diazotransfer had been trifluoromethanesulfonyl azide¹¹ (CF₃SO₂N₃). However, the reactions often require an excess of this reagent, are slow, and do not always proceed to completion, with 60–70% as the typical yield.

Meng *et al.* have addressed these limitations by developing a more efficient diazotransfer reagent, fluorosulfonyl azide (FSO₂N₃). They report that it reacts with almost any primary amine in a one-to-one ratio, achieving a nearly 100% yield of the corresponding azide. The authors demonstrated the reagent’s substrate scope and practicality by using it to make a library of 1,224 azides in 96-well plates. It is notable that 49% of these azides had not been synthesized before, according to the authors’ literature search.

The number of azides synthesized is impressive (see Supplementary Information Section 6 of the paper¹ for a full list), but the most striking aspect of this study is the substrate scope: the reaction works for different amine subclasses, on complex molecules, and in the presence of various chemical groups. Moreover, Meng and colleagues’ diazotransfer reaction meets the speed, breadth and efficiency criteria for click chemistry.

In addition, the authors demonstrated that the prepared azide solutions can be used directly in CuAAC reactions. This opens the

door to a highly efficient and general two-step method for converting primary amines — a common chemical group in organic molecules — into triazoles. Notably, this method does not require the amines to be modified in advance to prevent unwanted side reactions at other chemical groups; nor does it require the intermediate azides to be purified.

Triazoles are functional mimics of the amide bond¹², which is found in many pharmaceutical agents and in all proteins. Triazoles can also function as surrogates for sugars in polysaccharides¹³. Meng and co-workers’ chemistry could therefore be used to synthesize well-characterized libraries of complex small molecules and biomacromolecules from readily available precursors. More broadly, the work brings us a step closer to the vision laid out by the pioneers of click chemistry^{3,5}: the development of a few operationally simple reactions that use common precursors to rapidly generate diverse libraries of (bio)molecules that have desirable functional properties. ■

NEUROSCIENCE

A daily rhythm in colour preference

Behavioural and genetic experiments have revealed that fruit flies prefer green light over other colours in the morning and evening, and always avoid blue. These colour preferences rely on different mechanisms. SEE LETTER P.108

CHARLOTTE HELFRICH-FÖRSTER

Colour vision helps animals to find nutritious food, to avoid poisonous animals and, in some cases, in social interactions¹. Colour can affect people’s mood, and their colour preferences might reflect current emotional and physiological states². Colour preferences also seem to vary through the seasons³. Lazopulo *et al.*⁴ show on page 108 that the fruit fly *Drosophila* avoids blue light, and prefers green light to red light at different times of the daily 24-hour cycle. The authors also pinpoint separate mechanisms for these behavioural responses.

Light influences various behaviours in insects, and fruit flies serve as a model in which to study the mechanisms underlying this effect. Flies avoid or are attracted to light depending on its intensity and colour and the duration and time of day of the exposure^{5,6}. However, it is unclear whether fruit flies have intrinsic colour preferences, as do primates⁷ and, if so, how these preferences are mediated.

Lazopulo *et al.* analysed video recordings of the position and movements of individual flies living in glass tubes, each of which contained three equally sized zones that were covered by

Joseph J. Topczewski and En-Chih Liu are in the Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455, USA.

e-mail: jtopczew@umn.edu

- Meng, G. *et al.* *Nature* **574**, 86–89 (2019).
- Campos, K. R. *et al.* *Science* **363**, eaat0805 (2019).
- Kolb, H. C., Finn, M. G. & Sharpless, K. B. *Angew. Chem. Int. Edn* **40**, 2004–2021 (2001).
- Rostovtsev, V. V., Green, L. G., Fokin, V. V. & Sharpless, K. B. *Angew. Chem. Int. Edn* **41**, 2596–2599 (2002).
- Tornøe, C. W., Christensen, C. & Meldal, M. *J. Org. Chem.* **67**, 3057–3064 (2002).
- Meldal, M. & Tornøe, C. W. *Chem. Rev.* **108**, 2952–3015 (2008).
- Hein, J. E. & Fokin, V. V. *Chem. Soc. Rev.* **39**, 1302–1315 (2010).
- Dong, J., Krasnova, L., Finn, M. G. & Sharpless, K. B. *Angew. Chem. Int. Edn* **53**, 9430–9448 (2014).
- Barrow, A. S. *et al.* *Chem. Soc. Rev.* **48**, 4731–4758 (2019).
- Schimmler, S. D. *et al.* *J. Am. Chem. Soc.* **139**, 1452–1455 (2017).
- Cavender, C. J. & Shiner, V. J. *J. Org. Chem.* **37**, 3567–3569 (1972).
- Pedersen, D. S. & Abell, A. *Eur. J. Org. Chem.* **2011**, 2399–2411 (2011).
- Tiwari, V. K. *et al.* *Chem. Rev.* **116**, 3086–3240 (2016).

blue, green or red filters. The authors placed food at one end of each tube, and varied the order of the coloured zones along the tubes to avoid misinterpreting flies’ preference for the zone that contained food as reflecting a colour preference. To simulate the day–night cycle, the flies were kept in light–dark conditions (12 hours of light and 12 hours of darkness), and thus the colours were visible only during the light phase. Consistent with this, the flies showed no preference for any particular coloured part of the tube during the dark phase.

During the light phase, however, the flies exhibited a complex, systematic pattern of colour preference (Fig. 1). They consistently avoided the blue-light zone; furthermore, they spent more time in the green zone than in the red zone in the early morning and late afternoon, when the flies showed bursts of activity⁸. Such timed preferences are intuitively advantageous, because some of this activity is devoted to searching for food, and flies often find food in or under green trees and bushes.

Flies lack photoreceptors (light-sensitive cells) that are specifically sensitive to red light, although their green-light photoreceptors show some sensitivity to red light⁹; thus, they