<Broader subject> Photochemistry

<Title> A light touch for complex products

<Standfirst> The [2+2] photocycloaddition of two double bond moieties is arguably the most efficient way to form a four-membered ring, but this route is rarely used to construct azetidine rings. Now, the development of an isoxazoline carboxylate cycloaddition partner offers a general approach to synthesize diverse azetidine products.

<Author> Susannah C. Coote

The photocycloaddition of an alkene with an aldehyde or a ketone – the Paternò-Büchi reaction[1] – allows direct access to oxetane rings (Fig. 1a). Similarly, the aza-Paternò-Büchi reaction involves the photocycloaddition of an alkene with an imine to yield an azetidine ring (Fig. 1b). It is, however, much less well-developed than the Paternò-Büchi reaction. One reason is that the aza-Paternò-Büchi reaction is more complex than its traditional counterpart as imines are capable of photochemical *E*-*Z* isomerisation, which competes with (and typically precludes) the desired cycloaddition. Azetidines are usually prepared using cyclisation reactions, ring-contraction/expansion processes or through reduction of azetidinones[2], all of which generally require several steps. The aza-Paternò-Büchi reaction does offer an alternative method to construct azetidine rings in a single step, but few examples of this reaction have been reported.

As azetidines are of considerable interest in agrochemistry and medicinal chemistry[2], methods for simple and direct access to these compounds are highly sought after. To promote azetidine formation, cyclic imine derivatives (which cannot undergo *E*-*Z* isomerisation) have been employed, but the imine partners chosen yielded azetidine products that are not amenable to further derivatisation, thus only a narrow range of azetidine products was accessible. Now, writing in *Nature Chemistry*, Corinna Schindler and

colleagues have developed a broadly applicable, visible light-promoted aza-Paternò-Büchi process that enables the preparation of diverse azetidine products by employing an isoxazoline carboxylate cycloaddition partner[3] (Fig. 1c).

Schindler and co-workers recently published a protocol for intramolecular aza-Paternò-Büchi reactions[4], but this method cannot be applied to the corresponding intermolecular reactions since the lifetimes of the relevant excited states are not sufficiently long enough to allow bond formation between two separate molecules. Whilst Maruoka and co-workers succeeded in developing the intermolecular aza-Paternò-Büchi reactions of *N*-arylsulfonylimines with alkenes[5], the reaction was limited to activated alkenes, and the aryl group in the imine was essential. Thus, Schindler and colleagues chose to focus on a different imine component: a 2-isoxazoline-3-carboxylate. Very few aza-Paternò-Büchi reactions of 2-isoxazolines have previously been reported, all of which are based on 3-aryl-2-isoxazoline **1** (Fig. 1b), and they all require irradiation with relatively high-energy ultraviolet light (300 nm), which may induce unwanted side reactions through activation of additional reaction pathways. The reaction partners in these previous examples were (hetero)arenes and the scope was very limited: benzene[6], furan[7], thiophene[7] and indene[8] gave the expected azetidine products, albeit in low-to-moderate yields, with the (hetero)arene being employed as both reagent and solvent. Other electron-rich alkenes did not undergo cycloaddition, although the reaction scope was more recently extended to ethyl acrylate[9]. Nevertheless, a ten-fold excess of the alkene was required to generate azetidine products in only moderate yields, again using relatively high-energy ultraviolet irradiation. Interestingly, the aza-Paternò-Büchi reactions of **1** were reported to proceed via the singlet excited state (typically very short-lived), and it was suggested that the rate of intersystem crossing from the singlet to the corresponding triplet excited state (typically much longer-lived) was greatly decreased by the presence of the oxygen atom within the cycle, thus precluding any reactivity mediated by the triplet state[6].

The latest research from Schindler and co-workers combines several innovations to circumvent the limitations inherent to the previously reported aza-Paternò-Büchi reactions[3]. Firstly, a new 2-isoxazoline carboxylate reaction partner (**2**) was chosen, swapping the aryl ring in **1** for an ester moiety, which exhibits complementary photochemical reactivity to **1**. As a result of this change, the mechanism of the newly developed aza-Paternò-Büchi is rather different to the previous examples, as it is proposed that the triplet excited state of the isoxazoline reacts with an alkene rather than the singlet excited state. The triplet excited state of **2** is accessed indirectly through triplet energy transfer from a suitable triplet sensitiser rather than through intersystem crossing from the singlet excited state, thereby avoiding the singlet excited state entirely. The choice of an iridium complex (**3**) as the triplet sensitiser also allows the use of lower-energy visible light, rather than ultraviolet light, making the protocol more attractive from a safety standpoint, as well as tolerant of a wider range of functional groups.

The broad scope of alkene partners is particularly impressive, including both activated and non-activated alkenes, and the azetidine products are delivered in moderate to excellent yields with very high regioselectivities but lower diastereoselectivities. Various mono-, di- and trisubstituted non-functionalised alkenes were successfully employed, as well as ethylene itself and one example of a tetrasubstituted alkene. Similarly, exocyclic alkenes allow access to diverse spirocyclic azetidine products, and both electron-rich and electron-poor functionalised alkenes are suitable reaction partners; examples include a vinyl ether, vinyl acetate, acrylates, a vinyltrimethylsilane and a vinylboronate. The latter examples are particularly valuable as the synthetic handles incorporated into the azetidine product give the potential for further manipulation to varied products. Finally, the azetidine products obtained can be transformed into an even wider range of derivatives by standard functional group transformations. For example, the ester group originating from the isoxazoline reagent can be easily converted into the corresponding carboxylic acid, amide or alcohol products, or the N–O bond can be cleaved through hydrogenolysis to give further azetidine products.

This versatile and convenient aza-Paternò-Büchi protocol greatly simplifies access to diverse azetidine products that will undoubtedly find wide application within the pharmaceutical industry. Until now, the variety of available functionalised azetidine building blocks has been limited, and most available azetidines incorporate substitution only in the 3-position, or are derived from azetidine-2-carboxylic acids. The winning combination of wide alkene scope, readily available starting materials and straightforward synthetic manipulation of the azetidine products enables access to previously inaccessible substitution patterns, including complex spirocyclic examples. Successful scale-up to gram-scale reaction, using lowered catalyst loading, is particularly encouraging for the future application of this process. If further scale-up can be easily achieved, this work has the potential to become a 'go-to' protocol for the synthesis of complex azetidines.

Despite the versatility of this newly developed aza-Paternò-Büchi protocol, challenges remain that are well worth addressing, such as the low diastereoselectivity of the reaction. Future studies should focus on developing strategies for effective diastereocontrol. Furthermore, the protocol relies on an expensive iridium-based triplet sensitiser, which could discourage use of the strategy on larger scales. Employing alternative, cheaper triplet sensitisers would render the protocol even more accessible and attractive to researchers in assorted fields.

<Affiliation> Susannah Coote is at the Department of Chemistry, Lancaster University, Lancaster, LA1 4YB, United Kingdom
<email address> s.coote@lancaster.ac.uk
<@Twitter handle> @suscoote

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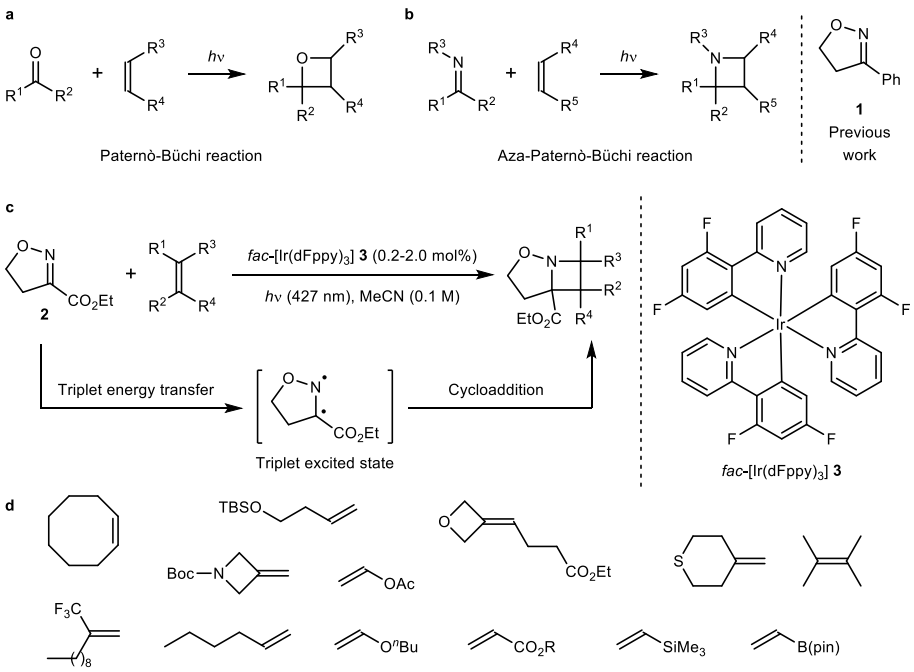

Fig. 1 | The development of a broadly applicable protocol for intermolecular aza-Paternò-Büchi reactions to generate diverse azetidine products. **a**, Typical Paternò-Büchi reaction between a carbonyl compound and an alkene. **b**, Typical aza-Paternò-Büchi reaction between an imine derivative and an alkene; previous work has focused on 3-aryl-2-isoxazoline **1**. **c**, Visible light-promoted triplet energy transfer from iridium catalyst **3**

generates the triplet excited state of isooxazoline **2**, which subsequently undergoes cycloaddition with a wide range of alkenes (**d**) to give assorted azetidine products.

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