Synthesis of azetidines via visible light-mediated intermolecular [2+2] photocycloaddition

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Intermolecular [2+2] photocycloadditions represent a powerful method for the synthesis of highly strained, four-membered rings. While this approach is commonly employed for the synthesis of oxetanes and cyclobutanes, the synthesis of azetidines via intermolecular aza Paternò-Büchi reactions remains highly underdeveloped. Herein we report a visible light-mediated intermolecular aza Paternò-Büchi reaction that utilizes glyoxylate oximes as reactive intermediates activated via triplet energy transfer. This approach is characterized by its operational simplicity, mild conditions and broad scope, and allows for the synthesis of highly functionalized azetidines from readily available precursors.

Four-membered azetidine heterocycles have seen increased prominence as saturated building blocks in the field of drug discovery in recent years.[1-4] The well-defined, three-dimensional structure of these sp^3-rich scaffolds not only provides access to unique chemical space, but has also been correlated to improved pharmacokinetic properties and toxicological benefits.[5-9] However, while the incorporation of azetidines into complex scaffolds is highly desirable, it is often hampered by the limited number of efficient, robust methods for their synthesis.[10-12] In this context, intermolecular [2+2] photocycloaddition reactions have recently received increased attention for the synthesis of four-membered, cyclic lead compounds.[13,14] However, this approach is currently only used to access oxetane and cyclobutane scaffolds from a corresponding excited state carbonyl or alkene, highlighting that the synthesis of azetidines via photochemical [2+2] cycloadditions, also referred to as aza Paternò-Büchi

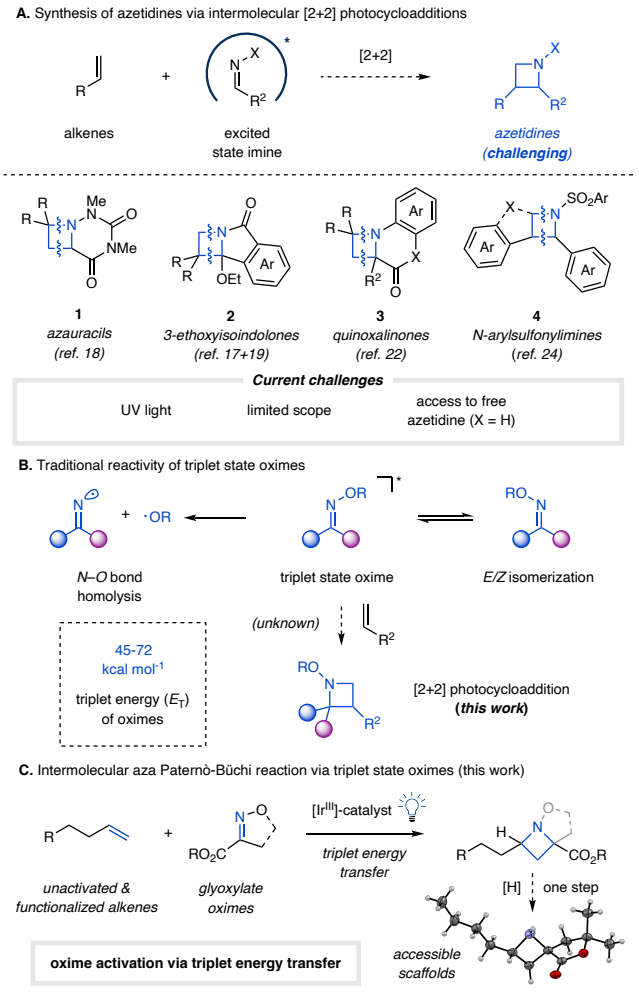
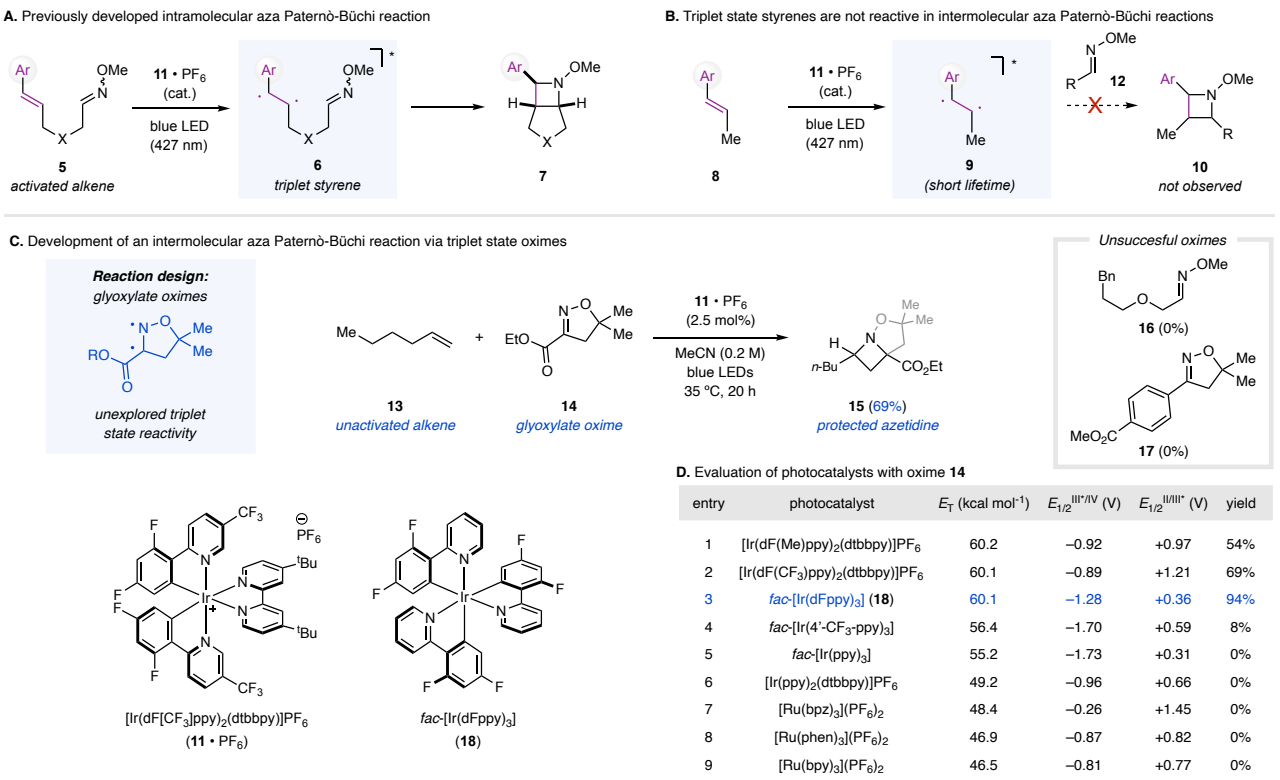


Fig. 1. Synthesis of azetidines via intermolecular [2+2] photocycloaddition. **A.** Previously accessible azetidines scaffolds via intermolecular aza Paternò-Büchi reactions **B.** Traditional reactivity of triplet state oximes **C.** This work.



entry	photocatalyst	E_T (kcal mol^{-1})	$E_{1/2}^{III*/IV}$ (V)	$E_{1/2}^{II/III*}$ (V)	yield
1	[Ir(dF(Me)ppy)$_2$(dtbbpy)]PF$_6$	60.2	–0.92	+0.97	54%
2	[Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$	60.1	–0.89	+1.21	69%
3	*fac*-[Ir(dFppy)$_3$] (**18**)	60.1	–1.28	+0.36	94%
4	*fac*-[Ir(4'-CF$_3$-ppy)$_3$]	56.4	–1.70	+0.59	8%
5	*fac*-[Ir(ppy)$_3$]	55.2	–1.73	+0.31	0%
6	[Ir(ppy)$_2$(dtbbpy)]PF$_6$	49.2	–0.96	+0.66	0%
7	[Ru(bpz)$_3$](PF$_6$)$_2$	48.4	–0.26	+1.45	0%
8	[Ru(phen)$_3$](PF$_6$)$_2$	46.9	–0.87	+0.82	0%
9	[Ru(bpy)$_3$](PF$_6$)$_2$	46.5	–0.81	+0.77	0%

Fig. 2. Development of an intermolecular aza Paternò-Büchi reaction. **A.** Previously developed intramolecular aza Paternò-Büchi reaction **B.** Triplet state styrenes are not reactive in intermolecular aza Paternò-Büchi reaction **C.** Development of an intermolecular aza Paternò-Büchi reaction relying on triplet state oximes **D.** Evaluation of visible light photocatalysts with glyoxylate oxime **14**. Conditions: Reactions performed with oxime (0.1 mmol), 1-hexene (5 equiv.) and 2.5 mol% photocatalyst in MeCN (1 mL) under blue LED irradiation (427 nm) at ambient temperature for 16-20 h. Yields were determined by ^{1}H NMR analysis from the crude reaction mixture using an internal standard. Triplet energies (E_T) and potentials ($E_{1/2}$; given versus the saturated calomel electrode) are literature values.[37]

reactions, remains a challenge.[15-16] Only a small number of imines are known to undergo intermolecular aza Paternò-Büchi reactions, mostly relying on imines such as isoindolones or azauracils, which provide photocycloadducts with limited synthetic utility (**1**-**3**) (Fig. 1A).[17-23] Maruoka demonstrated that *N*-aryl sulfonyl imines efficiently undergo the [2+2] photocycloaddition reaction to provide protected azetidines (**4**) in high yields. Unfortunately, this approach is limited to aromatic imines and styrenes as the formation of a singlet state exciplex between the imine and alkene component was essential (Fig. 1A).[24] Furthermore, the functional group tolerance is generally hampered due to the requirement of ultraviolet (UV) light irradiation to access the excited state of the imine component, which is difficult to realize on an industrial scale.

Our laboratory recently reported on the synthesis of functionalized azetidines (**7**) via an intramolecular aza Paternò-Büchi reaction[25], in which styrenes (**5**) underwent intramolecular [2+2] cycloaddition with an adjacent oxime or hydrazone (Fig. 2A).[26] The mechanistic profile of this transformation relies on a triplet state styrene (**6**) accessed via a triplet energy transfer event from a visible light photocatalyst (**11**•PF$_6$). As a result, the transformation can be carried out under very mild conditions using blue light irradiation. However, this design principle is not amenable for the development of intermolecular aza Paternò-Büchi reactions due to the short lifetime of the alkene excited state

(**9**). Triplet state styrenes simply undergo *E*/*Z* isomerization as opposed to the desired intermolecular cycloaddition (Fig. 2B).[27] To overcome this challenge, we envisioned an alternate approach for intermolecular aza Paternò-Büchi reactions that instead relies on a triplet state oxime as the reactive intermediate (Fig. 1C). Triplet state oximes have recently been utilized to generate iminyl radicals in the context of alkene or arene functionalization.[28,29] In contrast, their reactivity has not yet been explored to achieve [2+2] photocycloadditions, likely due to their preference to undergo *E*/*Z* isomerization or *N*–*O* bond cleavage reactions (Fig. 1B).[30] The successful development of an intermolecular aza Paternò-Büchi reaction relying on triplet state oximes as reactive intermediates is anticipated to significantly broaden the substrate scope of currently available protocols considering it should be applicable to a broad range of both unactivated and functionalized alkenes. Importantly, aza Paternò-Büchi reactions utilizing these types of alkenes could previously only be achieved relying on UV light irradiation. Therefore, identification of reaction conditions that are exclusively based on visible light would render this transformation significantly more general and applicable to the pharmaceutical industry.

Results

Reaction optimization. Towards the development of an intermolecular aza Paternò-Büchi reaction protocol, we focused our initial investigations on substrates featuring cyclic oximes. This modification was anticipated to increase the lifetime of the excited state intermediate by preventing rotation around the *C*–*N* bond. At the same time, we envisioned that the *N*–*O* bond in the azetidine products functions as nitrogen protecting group that could be reductively cleaved in a subsequent step. Furthermore, 1-hexene (**13**) was selected as an unactivated reaction partner that would be unable to interact with the photocatalyst. We chose [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)](PF$_6$) (**11**•PF$_6$) (E_T = 60.1 kcal mol^{-1}) as the photocatalyst for our initial studies based on its wide use as a visible light triplet sensitizer for [2+2] photocycloadditions (Fig. 2C).[31] Oxime triplet energies are not very well precedented in the literature and only exist for a small number of scaffolds.[30] Therefore, in order to investigate the ability of potential substrates to interact with the photocatalyst, we measured the photocatalyst luminescence quenching to guide our substrate evaluation. This approach allowed us to immediately eliminate unreactive substrates such as aliphatic oximes (**16**) based on their poor quenching of the iridium photocatalyst. In contrast, aromatic oxime **17** was identified as a strong quencher of **11**•PF$_6$. Interestingly, Sampedro and coworkers demonstrated that under direct UV light irradiation similar aromatic oximes can react with activated alkenes from the singlet excited state.[23] However, no reactivity was observed when we reacted **17** under our reaction conditions using **11**•PF$_6$ and visible light irradiation, suggesting that the excited triplet state of aromatic oximes may not be reactive towards [2+2] photocycloaddition reactions. Next, we tested glyoxylate oximes (**14**) as potential substrates for the intermolecular aza Paternò-Büchi

reaction. While the corresponding glyoxylate carbonyls have been extensively studied as reagents in [2+2] photocycloadditions, the reactivity of excited state glyoxylate oximes has not yet been investigated.[15] After irradiation of **14** with blue LED lights in the presence of 1-hexene and 2.5 mol% **11**•PF_6, we were able to isolate the desired azetidine product (**15**) in 69% yield. Evaluation of several commercially available photocatalysts revealed that the reaction efficiency significantly decreases with photocatalysts that have a triplet energy (E_T) below 60 kcal mol^{-1} (Fig. 2D, entries 4-9). Nevertheless, the yield of the reaction could be further improved to 94% relying on *fac*-[$Ir(dFppy)_3$] (**18**) as photocatalyst (Fig. 2D, entry 3). Importantly, photocatalysts with similar redox properties ($E_{1/2}$) to **18** did not give rise to the desired product, which is consistent with a triplet energy transfer process being operative under these conditions. We attribute the decreased yields with photocatalysts **11**•PF_6 and [$Ir(dF(Me)ppy)_2(dtbbpy)$]PF_6 of similar triplet energies to decomposition of the desired product under the reaction conditions (Fig. 2D, entries 1+2). Further optimization of reaction conditions revealed that the amount of alkene could be reduced to 1.5 equivalents, while choice of solvent, concentration and catalyst loading only had minimal effects on the yield of **15**.

Oxime scope. With optimized conditions identified, we next turned our attention to the substrate scope of the intermolecular aza Paternò-Büchi reaction. The reaction conditions were well tolerated by a wide range of functional groups, and generally provided the desired products with excellent regioselectivity, preferentially forming the *exo*-diastereomer in selectivities of up to >10:1. On preparative scale oxime **14** smoothly underwent [2+2] cycloaddition with 1-hexene in 84% yield with a diastereomeric ratio (d.r.) of 3:1 (Fig. 3A). Importantly, this result could be reproduced on 5 mmol scale to provide gram-quantities of **15**, while using lowered catalyst loadings of 0.2 mol% and an increased concentration. Substitution in the cyclic backbone of the oxime is not required as **19** could be accessed in excellent yield. Additionally, aromatic substituents (**20**, **22**), nitrogen spirocycles (**21**), ethers (**23**) or esters (**24**) were well tolerated and provided the desired azetidine products in 74-99% yield. Furthermore, the ester component of the oxime can be modified to include functional groups such as alkynes (**25**) that allow for further synthetic modifications. Substrates containing sterically encumbering substituents or electron-rich aryl groups were also found compatible, affording **26** and **27** in 98% and 88% yield, respectively. Importantly, nitrile **28** was formed in 88% yield, showcasing that functionalities other than esters can achieve successful cycloaddition. Finally, substrates containing alkene functional groups undergo intramolecular cycloaddition resulting in the formation of tricyclic azetidines such as **29**.

Alkene scope. Having established that the developed transformation tolerates various oxime substrates, we turned our attention towards evaluating the scope of the alkene component (Fig. 3B). Importantly, the developed aza

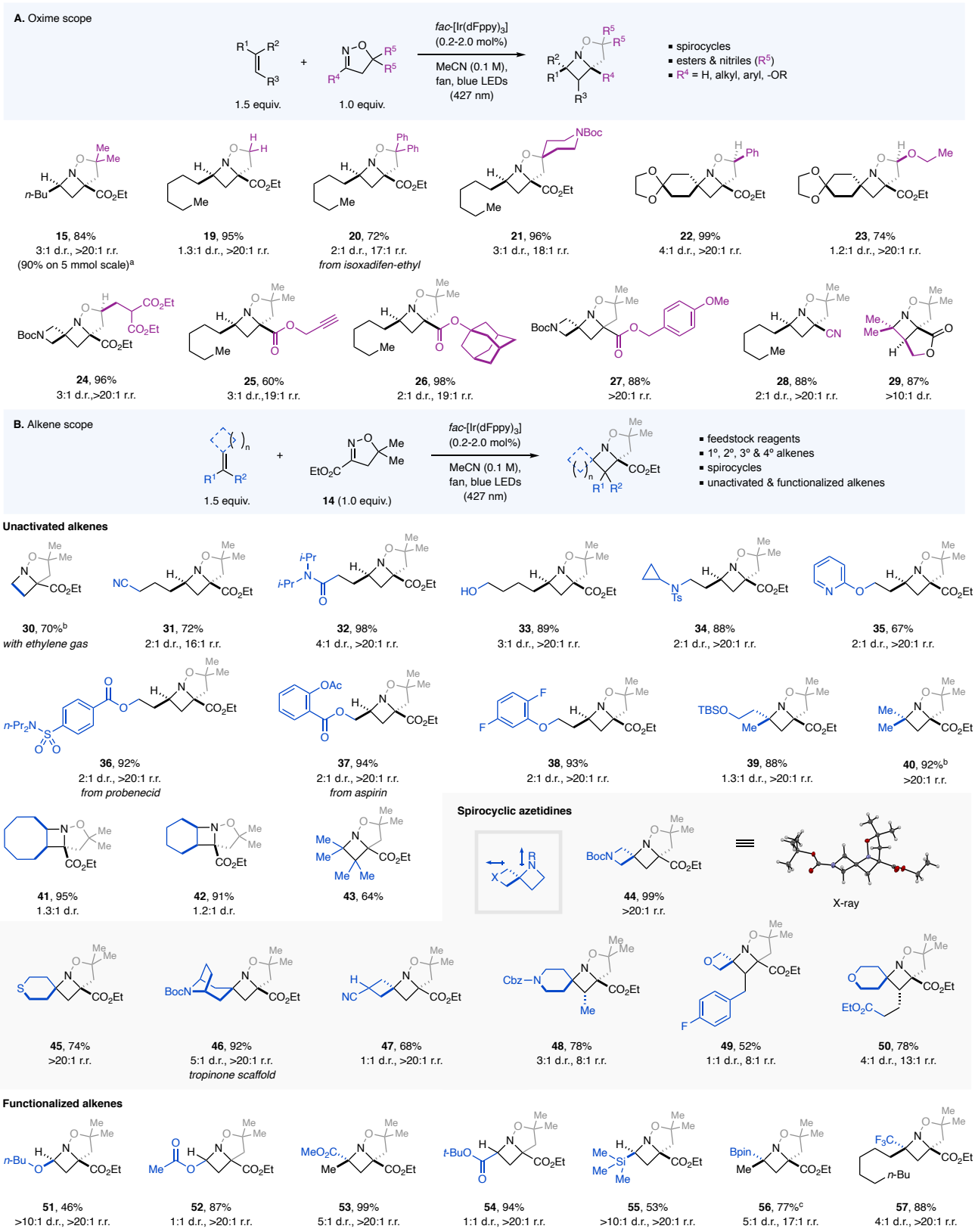


Fig 3. Substrate scope of the intermolecular aza Paternò-Büchi reaction. **A.** Oxime scope **B.** Alkene Scope. Reactions were performed with oxime substrate (0.25 mmol), alkene (1.5 equiv.) and 1.0-2.0 mol% **18** in MeCN (0.1 M) under blue LED irradiation (427 nm) at ambient temperature (fan cooling) for 16 h; isolated yields are given unless noted; diastereomer ratios (d.r.) and regioisomer ratios (r.r.) were determined by ^{1}H NMR analysis from the crude reaction mixture; [a]run on a 5 mmol scale with 0.2 mol% **18** [b]run under an atmosphere of the respective alkene (gas) in 1,2-dichloroethane; [c]yield determined by ^{1}H NMR from the crude mixture.

Paternò-Büchi reaction can be employed using chemical feedstocks as alkene sources, as shown by **30** obtained in 70% yield from the reaction of **14** with ethylene gas. Evaluation of a series of primary alkenes containing various sensitive functional groups provided azetidines **31**-**38** in high yields of 67-98%. Notably, the transformation allows for the incorporation of pharmaceutically relevant scaffolds such as probenecid or aspirin (**36**, **37**). Furthermore, 1,1-disubstituted (**39**, **40**) and internal alkenes (**41**, **42**) readily undergo cycloaddition in yields ranging from 88-95%. The developed reaction protocol was also tolerant of tetrasubstituted alkenes as demonstrated by azetidine **43**, which was isolated in 64% yield. Considering that aza-spirocycles are highly desirable building blocks in drug discovery, we evaluated a series of exocyclic alkenes that would provide access to azetidine spirocycles.[32] While these scaffolds traditionally require multistep syntheses, the developed aza Paternò-Büchi reaction protocol allows for the construction of diazaspirocycle **44** in a single step from readily available precursors in 99% yield. The structural assignment of **44** was further confirmed by X-ray crystallographic analysis. Similarly, azetidine spirocycles incorporating other nitrogen, oxygen and sulfur heterocycles (**45**-**50**) could be readily accessed in good yields. Notably, only a small erosion in regioselectivity was observed for azetidines **48**-**50**, which were obtained from the corresponding trisubstituted alkenes. Finally, functionalized alkenes were evaluated as reaction partner, and it was found that alkenes containing both electron-donating and -withdrawing substituents were compatible reaction partners with oxime **14**, giving rise to functionalized azetidines **51**-**54** in 46-99% yield. In contrast to established aza Paternò-Büchi reactions proceeding via singlet state oximes[21,23], the observed regioselectivity of the developed title reaction was found independent of the electronic properties of the alkene. This suggests unique characteristics of the triplet state reactivity of oximes and provides a complementary approach for the synthesis of functionalized azetidines. Furthermore, alkenes with synthetic handles such as silanes (**55**), boronic esters (**56**) and trifluoromethyl groups (**57**) were readily incorporated into the accessible azetidine scaffolds, highlighting their potential for incorporation of these scaffolds into more complex targets.

Synthetic applications. Currently available azetidine-containing pharmaceuticals typically feature relatively simple substitution patterns, which can be attributed to the limited availability of functionalized azetidine building blocks.[33-35] Most available azetidine scaffolds only contain substitution in the 3-position of the azetidine ring or are derived from azetidine-2-carboxylic acids (Fig. 4A). In contrast, the azetidine products obtained from the developed intermolecular aza Paternò-Büchi reaction provide previously challenging substitution patterns, and are accessed in a single step from readily available starting materials. Importantly, the *N–O* bond can be cleaved via hydrogenolysis using catalytic amounts of palladium hydroxide under a hydrogen gas atmosphere. When azetidine **15** was reacted under optimized conditions efficient *N–O* bond cleavage was achieved followed by lactone formation

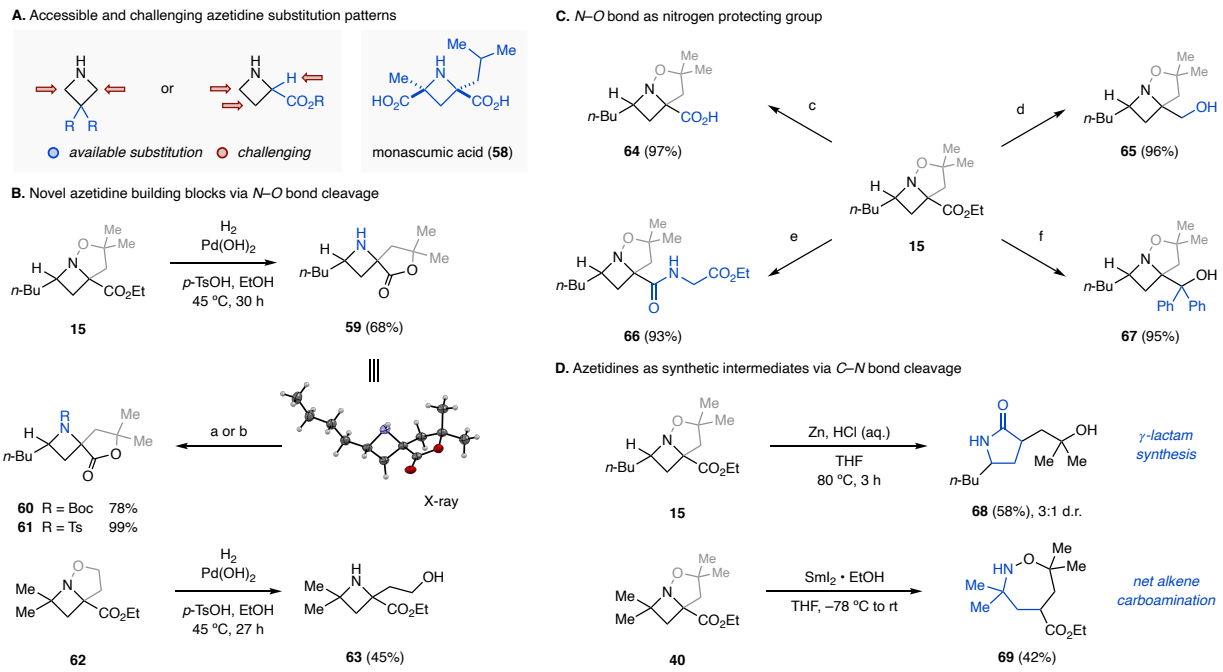


Fig 4. Synthetic modification of azetidine products. **A.** Currently available azetidine building blocks and azetidine-containing natural products **B.** Hydrogenolysis provides access to unprotected azetidines **C.** The *N–O* bond in the azetidine products is tolerant of multiple synthetic transformations **D.** Azetidines can undergo *C–N* cleavage reactions. Conditions: a) Boc_2O, DMAP, CH_2Cl_2 ,rt; (for **60**) b) *p*-TsCl, K_2CO_3, MeCN, 80 ºC (for **61**) c) LiOH, H_2O, MeOH, rt d) $LiAlH_4$, Et_2O, 0 ºC e) LiOH, H_2O, MeOH, rt; then, glycine ethyl ester•HCl, DMAP, EDC•HCl, CH_2Cl_2, rt f) PhMgBr, THF, 0 ºC.

to provide spirocyclic azetidine **59** in 68% yield, as supported by X-ray crystallographic analysis (Fig. 4B). Importantly, the unprotected azetidines can be further functionalized to access azetidines **60** and **61** in high yields of 78% and 99%, respectively. Interestingly, azetidine **62** lacking the geminal dimethyl substituents underwent hydrogenolysis to provide the acyclic amino alcohol **63** in 45% yield. The structural features of this scaffold are reminiscent of those found in azetidine amino acids such as monascumic acid (**58**).[36] Having demonstrated that the *N–O* bond in the accessible azetidine products can be readily cleaved to obtain unprotected azetidines, it can also function as a nitrogen protecting groups that is stable under various reaction conditions. For example, azetidine **15** smoothly undergoes hydrolysis (**64**), reduction (**65**), amide bond-forming (**66**) and Grignard addition reactions (**67**) in excellent yields (93-97%) (Fig. 4C). Importantly, no undesired *N–O* bond reactivity was observed in any of these transformations, highlighting the stability of the *N–O* bond as nitrogen protecting group. Finally, it is important to note that the significance of the developed intermolecular aza Paternò-Büchi reaction does not solely rely on the fact that it provides access to complex azetidine-containing compounds. The obtained azetidine products can also be utilized to afford other nitrogen heterocycles through strain-driven transformations. For example, reacting **15** under acidic conditions with zinc metal resulted in the formation of γ-lactam **68** in 58% yield. We postulate that this product is a result of two subsequent *N–O* and *C–N* bond reduction steps that are followed by lactam formation. Additionally, samarium(II) iodide–ethanol selectively reduced the *C–N* bond of **40** to provide 7-membered

hydroxylamine **69** in 42% yield. This product represents a net carboamination of the alkene used in the initial [2+2] photocycloaddition reaction.

Mechanistic investigations. Subsequent efforts were directed towards corroborating the postulated triplet energy transfer mechanism. Initial control reactions showed that the exclusion of either light or photocatalyst failed to promote [2+2] photocycloaddition. Steady-state UV-Vis absorption spectroscopy indicates that the photocatalyst **18** is the only species absorbing at 400-460 nm. To provide further insight into the reactive species initiating the cycloaddition reaction, we carried out Stern-Volmer quenching studies. No quenching was observed for the alkene (**13**), while oxime **14** was found to engage in quenching with the photocatalyst **18**. This interaction is unlikely to result from an electron-transfer process between **14** and **18** based on the insufficient redox potentials of *fac*-[Ir(dFppy)$_3$] ($Ir^{III*/II}$ = +0.36 V versus SCE; $Ir^{IV/III*}$ = –1.28 V versus SCE)[37] to oxidize or reduce **14** (E_{red} = –2.01 V; E_{ox} = +1.57 V versus SCE). In agreement with our hypothesis of a triplet energy transfer mediated mechanism, organic triplet sensitizers such as xanthone (E_T = 74 kcal mol^{-1})[38] were able to mediate the developed reaction. Irradiating oxime **14** in the presence of 20 mol% xanthone under UV light irradiation afforded the desired product **15** in 54% yield. Based on the significant decrease in reaction efficiency observed with photocatalysts that have a triplet energy below 56 kcal mol^{-1}, we postulate that the triplet energy of **14** is higher than 56 kcal mol^{-1}, and likely

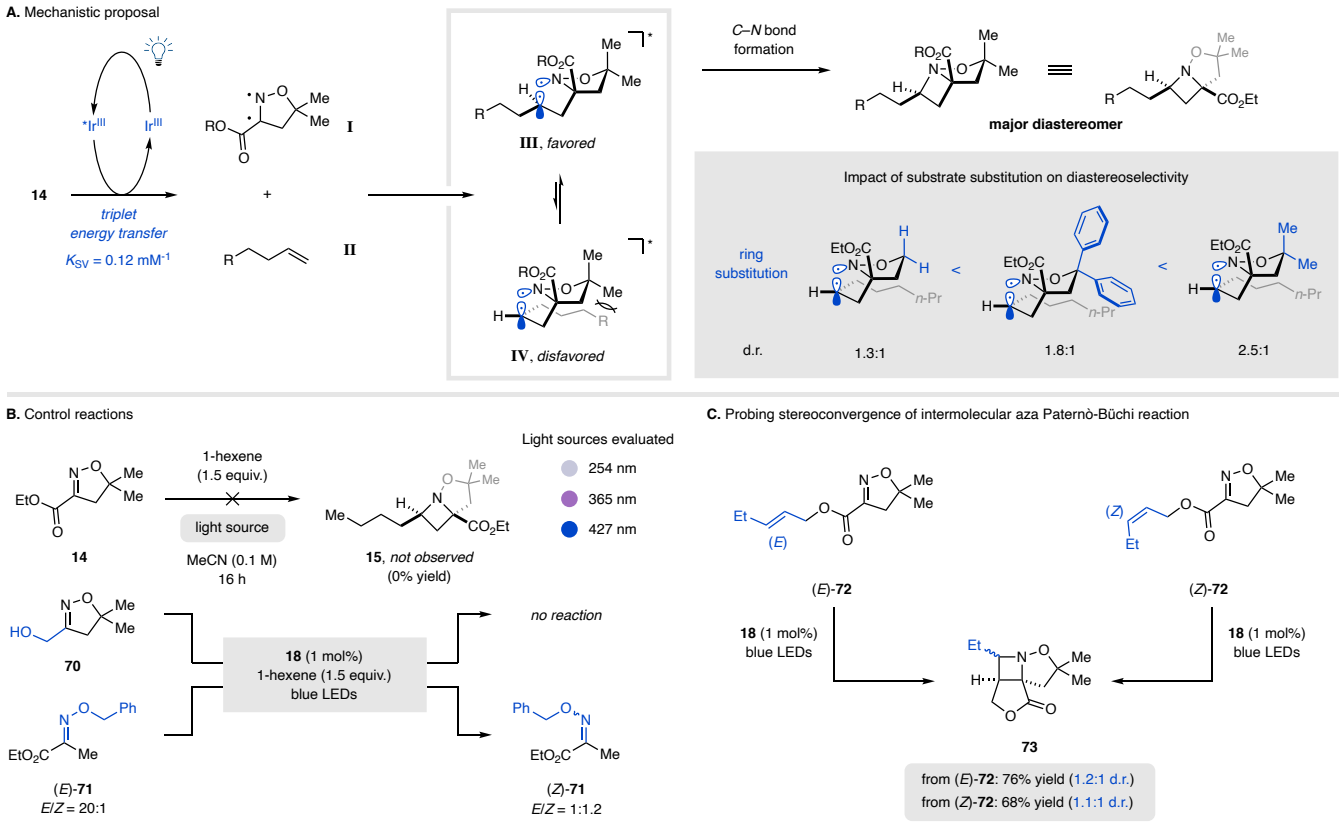


Fig 5. Mechanistic investigation of the title reaction **A.** Mechanistic proposal relying on a triplet state oxime **B.** Control reactions **C.** Probing stereoconvergence of the title reaction. K_{SV} = Stern-Volmer quenching constant

lower than 74 kcal mol^{-1}. Furthermore, oximes **70** and (*E*)-**71** lacking either an ester substituent or cyclic backbone failed to provide the corresponding azetidine products under standard reaction conditions, highlighting that these structural features are required for reactivity (Fig. 5B). Oxime isomerization of (*E*)-**71** (>20:1 *E*/*Z*) to (*Z*)-**71** (*E*/*Z* = 1:1.2) was not observed when the reaction was conducted without photocatalyst. These results suggest that energy transfer also occurs in the absence of a cyclic constraint, however, a cyclic substrate is necessary for productive reactivity by preventing isomerization around the *C*–*N* bond as a competing relaxation pathway. Considering the stepwise nature of triplet state cycloaddition reactions, we next sought to probe the existence of a corresponding biradical intermediate. We hypothesized that both (*E*)- and (*Z*)-**72** would convert to the same mixture of diastereomers upon cycloaddition as both isomers would form an identical biradical intermediate that allows for bond rotation around the *C*–*C* bond. Importantly, submitting both (*E*)- and (*Z*)-**72** to standard reaction conditions afforded **73** in nearly identical diastereoselectivity (Fig. 5C). On the basis of the performed mechanistic experiments we propose a mechanism that relies on efficient triplet energy transfer from photoexcited **18** to glyoxylate oxime **14**. Subsequently, the triplet state oxime (**I**) undergoes stepwise [2+2] cycloaddition with the alkene (**II**). Final *C*–*N* bond formation occurs upon intersystem crossing of the corresponding biradical intermediate (**III** or **IV**). We postulate that the kinetically preferred formation of the *exo*-isomer as major diastereomer results from minimized steric interactions with the oxime backbone (Fig. 5A).

Conclusion

In summary, the intermolecular aza Paternò-Büchi reaction developed herein enables the synthesis of complex azetidine scaffolds from readily available starting materials. This approach utilizes glyoxylate oximes as previously unexplored imine reagents, which are amenable to activation via triplet energy transfer from a visible light photocatalyst. In contrast to previously reported intermolecular aza Paternò- Büchi reactions, the transformation developed herein is highly functional group tolerant and amenable to a broad range of both unactivated and functionalized alkenes that could previously only be converted using UV light irradiation. Importantly, the azetidine products obtained from the developed reaction protocol can be readily converted to the corresponding unprotected azetidines, and can further function as building blocks for a diverse array of synthetic modifications. Considering the versatility of this approach, we expect that this method with provide a new reaction platform for the synthesis of previously inaccessibe azetidine scaffolds.

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