Visible-Light-Mediated aza Paternò-Büchi Reaction of Acyclic Oximes and Alkenes for the Synthesis of Monocyclic Azetidines

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Abstract: The aza Paternò-Büchi reaction is a [2+2]-cycloaddition reaction between imines and alkenes that is arguably the most atom-economical method to access 4-membered nitrogen-containing heterocycles. Although the azetidine products obtained are highly desirable for pharmaceutical applications, these transformations remain limited due to challenges associated with the decreased photoreactivity of acyclic imine precursors. Currently, successful examples rely primarily on either intramolecular variants or cyclic imines. To fully realize the synthetic potential of aza Paternò-Büchi reactions, previously elusive acyclic imines must engage productively with alkenes to provide currently inaccessible azetidines. Here we report that matching of the frontier molecular orbital energies of alkenes with those of acyclic oximes can overcome these challenges and lead to the successful development of visible-light-mediated aza Paternò-Büchi reactions via triplet energy transfer catalysis. Insights obtained into this transformation are expected to inform and advance future developments in [2+2]-cycloadditions.

The development of new medicines relies on pharmaceuticals which are meticulously designed to impart the desired biological activity while minimizing associated toxicity. This balance requires precise tuning of properties for pharmaceutical candidates, and as a result, nitrogen-containing heterocycles (*N*-heterocycles), known to impart these desired properties, have become some of the most important functionalities in drug development. Today, approximately 60% of all FDA approved drugs incorporate at least one *N*-heterocycle.[1] Azetidines are 4-membered nitrogen-containing heterocycles known to impart desirable properties including increased three-dimensionality,[2,3] improved pharmacokinetics,[4–7] and decreased lipophilicity.[7] However, FDA-approved pharmaceuticals incorporating azetidines remain highly underrepresented and account for less than 1% of current medicines containing an *N*-heterocycle.[8] This is a direct consequence of limited methods available for their construction[9–11] which hinders the incorporation of azetidines into pharmaceuticals, and restrains development. A particular challenge is the synthesis of azetidines varied in the substitution of the 2- and 4-position, which is necessary for them to reach their full potential in current drug design (Fig. 1A). Thus, new methods to efficiently access azetidines are required to enable their application as improved functional handles in medicinal chemistry.

Traditionally, azetidines are accessed via nucleophilic substitution reactions of acyclic amines,[10,11] the reduction of β-lactams,[12,13] or strain release substitution of azabicyclobutanes (Fig. 1A).[14–21] However, these approaches are limited, requiring harsh conditions or pre-functionalization of the starting material. Nucleophilic substitution approaches are restricted by the higher energy conformational alignment required to achieve productive orbital overlap. Though advances have been made in the strain-release of azabicyclobutanes,[18–21] these methods primarily result in functionalization in the 3-position. Despite recent advances of hydrogen atom transfer mediated approaches to form azetidine products,[22] there is still an immense need for more efficient and general approaches to access highly functionalized azetidines. Arguably, the most direct approach to azetidines is the [2+2]-cycloaddition of imines and alkenes, known as the aza Paternò-Büchi reaction.[23] While [2+2]-cycloaddition reactions to form cyclobutanes[24,25] and oxetanes[26,27] have been well developed, the aza Paternò-Büchi reaction has remained limited due to challenges in capturing the imine excited state, which rapidly relaxes through isomerization, precluding cycloaddition (Fig. 1A).[23,28,29] Despite these limitations, visible-light-mediated aza Paternò-Büchi reactions have attracted interest in recent years as an atom-economical[30,31] transformation to access highly functionalized azetidines.[32–35] These methods are mediated by triplet energy transfer (EnT) from a photocatalyst, and generally rely on two different approaches to

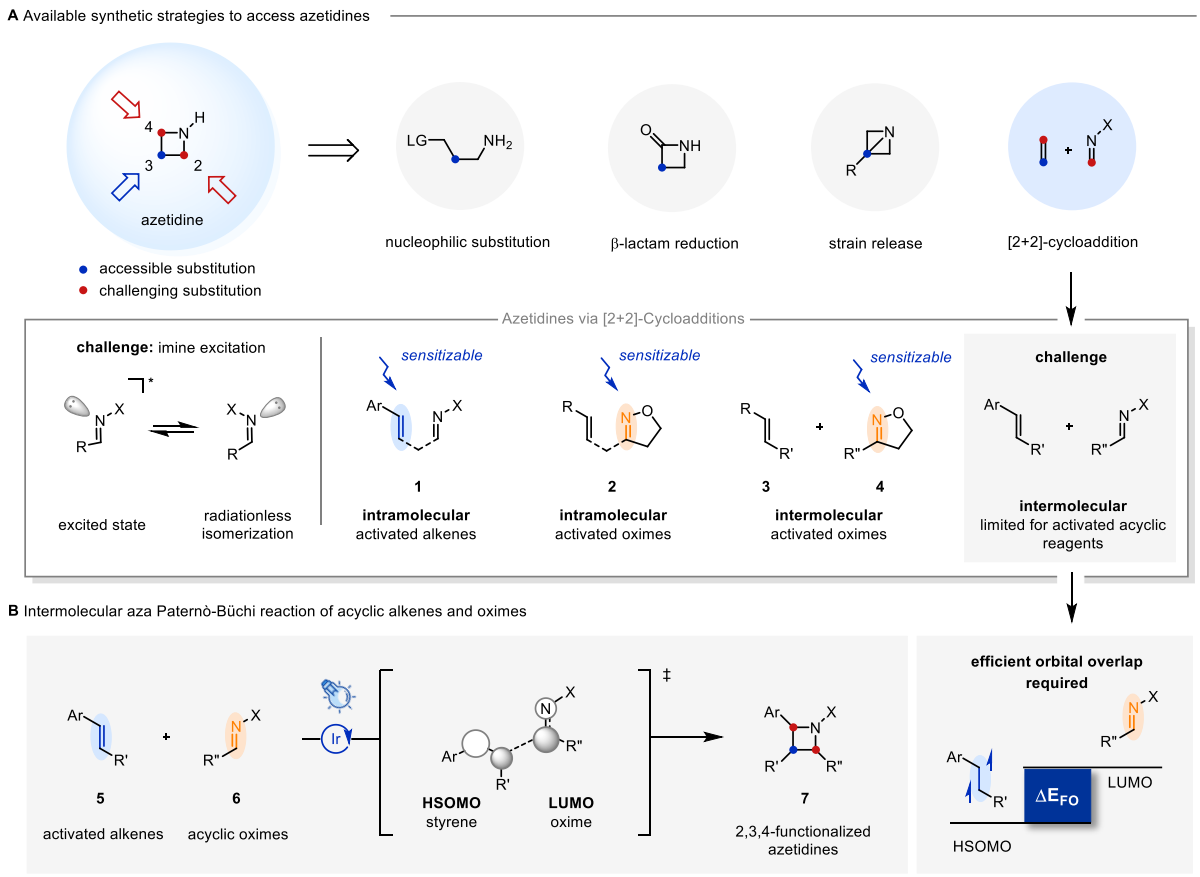


Figure 1: A. Traditional methods for azetidine synthesis include nucleophilic substitution, strain release of azabicyclobutanes, and reduction of β-lactams, which limits available substitution. The aza Paternò-Büchi reaction provides direct access to azetidines but is limited by imine isomerization. Approaches to overcome limitations to the aza Paternò-Büchi reaction are restricted to cyclic imines or intramolecular reactivity. **B.** This work describes the development of an intermolecular aza Paternò-Büchi reaction between two acyclic components which overcomes previous challenges by employing activated starting materials which favor the desired cycloaddition reaction. *Abbreviations:* LG, leaving group; HSOMO, highest singly occupied molecular orbital; LUMO: lowest unoccupied molecular orbital.

overcome the challenges associated with imine isomerization: sensitization of an activated alkene (styrene or diene, Fig. 1A) (**1**) which can react intramolecularly with an unactivated oxime or hydrazone to form the azetidine product,[32,35,36] or sensitization of an activated cyclic oxime (isoxazoline, **2**, **4**) that can undergo both inter- (**4** + **3**)[33] and intramolecular (**2**)[34] cycloaddition with an unactivated alkene. Nevertheless, none of these approaches allow direct access to monocyclic azetidines, which requires the efficient conversion of acyclic imines with alkenes and thus represents a long-standing challenge.[23] Only three examples of acyclic imines reacting in an aza Paternò-Büchi reaction have been previously reported: a single example of an exocyclic imine reacting under UV irradiation,[37] the cycloaddition of aryl sulfonyl imines and activated alkenes[38] which proceeds by a singlet state exciplex mechanism, and the recently developed Cu-mediated cycloaddition of imines relying on copper-catalyzed activation of cyclic alkenes.[39] In the case of the sulfonyl-imine cycloaddition, the reaction proceeds through singlet excitation and the formation of an exciplex which requires aryl substituents to enable π-π stacking, limiting the scope.[38] While the newly developed copper-mediated methodology allows for the use of simple acyclic imines, cyclic alkene coupling partners remain a requirement and monocyclic azetidines cannot be formed directly.[39] Additionally, both approaches rely on UV light. The development of a visible-light-mediated approach utilizing acyclic substrates could greatly expand the scope and generality of this method. To date, no visible-light-mediated aza Paternò-Büchi reaction of acyclic imines has been reported.

In an effort to overcome this challenge, attempts were made to translate our previously developed methods employing intramolecular cycloadditions of styrenes (**1**)[32] and intermolecular cycloadditions of cyclic isoxazolines (**2-4**)[33] with

no success. We hypothesized that this lack of reactivity was due to alternate relaxation pathways from the excited-state substrates including imine isomerization[28,29] and both isomerization and dimerization of styrenes[24,40,41] outcompeting the desired reaction path. We postulated that this limitation associated with the decreased photoreactivity of acyclic imines could be overcome by matching both substrates to impart a more favorable orbital overlap. By matching two activated substrates, alkene **5** and oxime **6**, a lower transition state energy for the desired cycloaddition can be achieved due to better orbital overlap, as measured by ΔE_{FO} ($\Delta E_{FO} = E_{\text{oxime LUMO}} - E_{\text{styrene HSOMO}}$), to ultimately enable the formation of the desired azetidine products (**7**) (Fig. 1B).

Our reaction design is centered on activated alkenes (e.g. styrenes (**8**) and dienes), based on their triplet energy of around 60 kcal/mol,[42] reactivity in EnT-mediated dimerization reactions,[40,41] and broad commercial availability. Simple glyoxylate oximes, which are activated by the conjugation of the oxime and ester group, were chosen as potential partners for the desired cycloaddition reaction. An initial evaluation revealed that upon sensitization with $Ir(dFppy)_3$ as the photocatalyst, styrene **8** and oxime **9** were able to undergo the desired cycloaddition reaction providing azetidine **11** in 12% yield as a mixture of diastereomers (Fig. 2). However, optimization proved challenging, leading us to employ a Design of Experiments (DOE) statistical approach (see supplementary materials for details). Employing a two factor (concentration, styrene loading) two level experimental design including center points, we found that both oxime concentration and styrene loading had a statistically significant impact on yield (Fig. 2). Based on these results, raising both the oxime concentration and the styrene loading in consecutive additions enabled the formation of the azetidine product **12** in 83% yield (67% isolated).

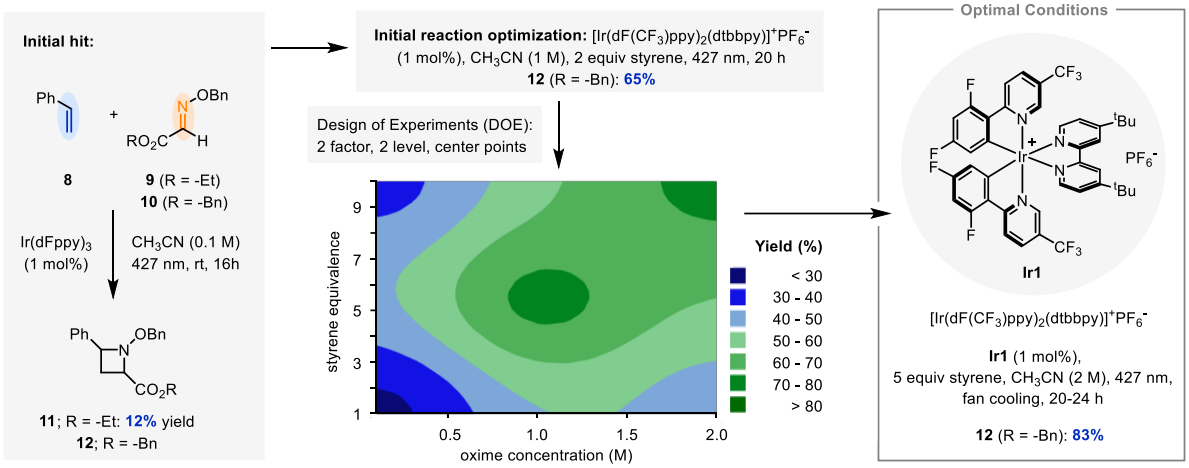
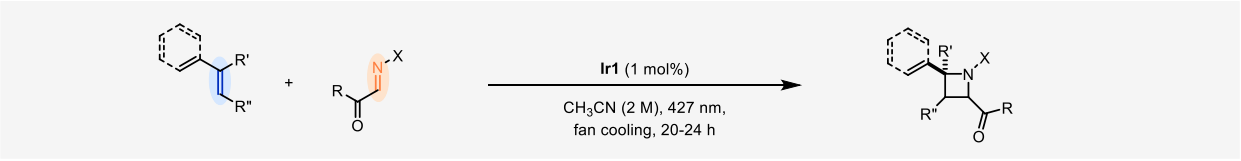


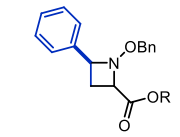
Figure 2: Initial hit for the desired reaction and subsequent optimization. A 2 factor 2 level Design of Experiments approach was employed to analyze the impact of styrene loading and oxime concentration. Both factors were found to have a significant effect on yield (see supplementary materials). Final optimization resulted in an improved yield of 83% (measured by ^{1}H NMR).

A variety of styrenes including electron neutral (**11**, **12**), electron donating (**13**-**16**) and electron withdrawing (**17**-**19**, **23**) examples are all tolerated under the optimal reaction conditions, with *para*- (**13, 14**) and *ortho*- (**16**) methoxy groups providing the highest yields of up to 80% (Table 1). Styrenes with an extended π-system are also tolerated (**22**), and heteroaryl alkenes (**30**, **31**) react to form the desired product in up to 60% yield. These heteroaryl groups such as pyridine (**30**) are highly desirable for drug discovery applications. While the mono-substituted alkenes provide azetidines with substitution in the desired 2- and 4-positions, 1,1-disubstituted (**21**) and 1,2-disubstituted (**20**) alkenes also react to form the corresponding azetidine products. Notably, the yield of **21** could be improved from 20% to 33% by a swap to hexafluoroisopropanol (HFIP) as solvent (see supplementary materials for details). HFIP has previously been shown to increase yields in triplet state cycloaddition reactions through substrate activation by H-bonding.[43,44] Trisubstituted alkenes form the products **24** and **25**, resulting in desirable spirocyclic structures. The lower yields in these cases are likely a result of steric effects also observed for tetra-substituted alkenes, for which the reaction did not proceed. Conjugated dienes are also amenable to this transformation, as they have a similar triplet energy to styrenes (ca. 60 kcal/mol), and provide **26**, **27** and **29** as azetidines with an additional terminal alkene functional handle. Azetidines **26** and **27** were isolated as a single regioisomer and diastereoisomer, demonstrating the utility of this method in accessing 2,3,4-trisubstituted azetidines from asymmetric dienes with good regioselectivity. Oximes

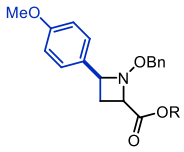
Table 1: Substrate scope of acyclic alkenes and oximes



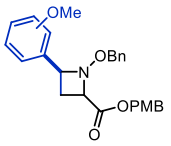
Acyclic Alkenes



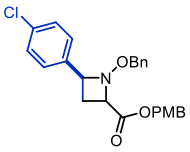
11, R = -Et 43%; 1.2:1 d.r.
12, R = -Bn 67%[a]; 1.2:1 d.r.



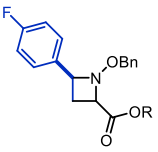
13, R = -PMB 72% (61%[b]); 1.2:1 d.r.
14, R = -Bn 73%; 1.2:1 d.r.



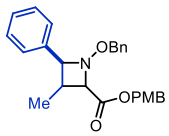
15, *meta* -OMe = 58%; 1.2:1 d.r.
16, *ortho* -OMe = 80%; 1:1 d.r.



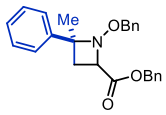
17, 50%; 1.2:1 d.r.



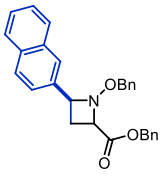
18, R = -PMB 57%; 1.2:1 d.r.
19, R = -Bn 48%; 1.2:1 d.r.



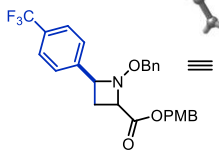
20, 49%; 1:1 d.r.



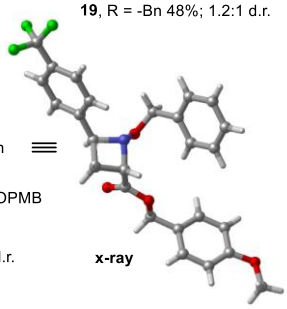
21, 20% (33%[c]); 1.4:1 d.r.



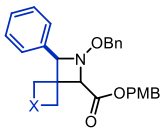
22, 35%; 4.2:1 d.r.[d]



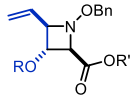
23, 33%; 1.4:1 d.r.



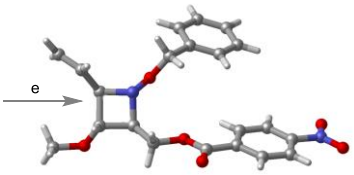
x-ray



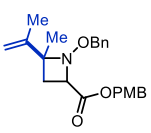
24, X = O 31%; 6.4:1 d.r.
25, X = NBoc 34%; single isomer



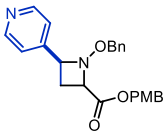
26, R = -Me, R' = -Bn 48%; single isomer[d]
27, R = -Bn, R' = -PMB 50%, single isomer[d]



28[e]
x-ray

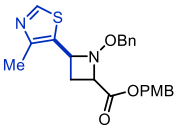


29, 49%; 1:1 d.r.[d]

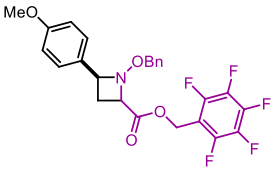


30, 55%; 1.2:1 d.r.

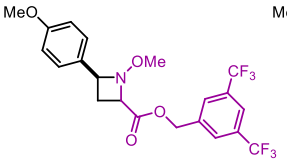
Oximes



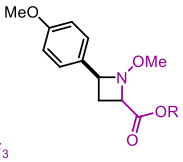
31, 60%; 1.2:1 d.r.



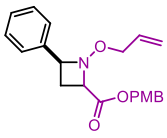
32, 61%; 1.6:1 d.r.



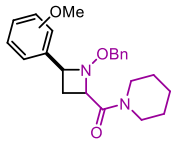
33, 70%; 1.2:1 d.r.



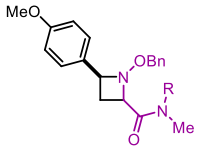
34, R = -^{n}octyl 57%; 1:1 d.r.
35, R = -PMB 70%; 1.4:1 d.r.



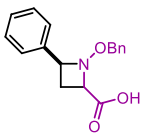
36, 61%; 1.2:1 d.r.



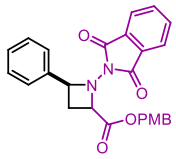
37, *ortho* -OMe = 25%; 1.8:1 d.r.[d]
38, *para* -OMe = 17%; 1.5:1 d.r.



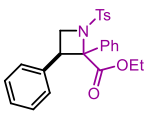
39, R = -OMe 26%; 2.2:1 d.r.[d]
40, R = H 46%; 1:1 d.r.[d]



41, 46%[f]; 1.2:1 d.r.[d]



42, 92%; 1.3:1 d.r.[g]



43, 72%; 1.2:1 d.r.[d,h]

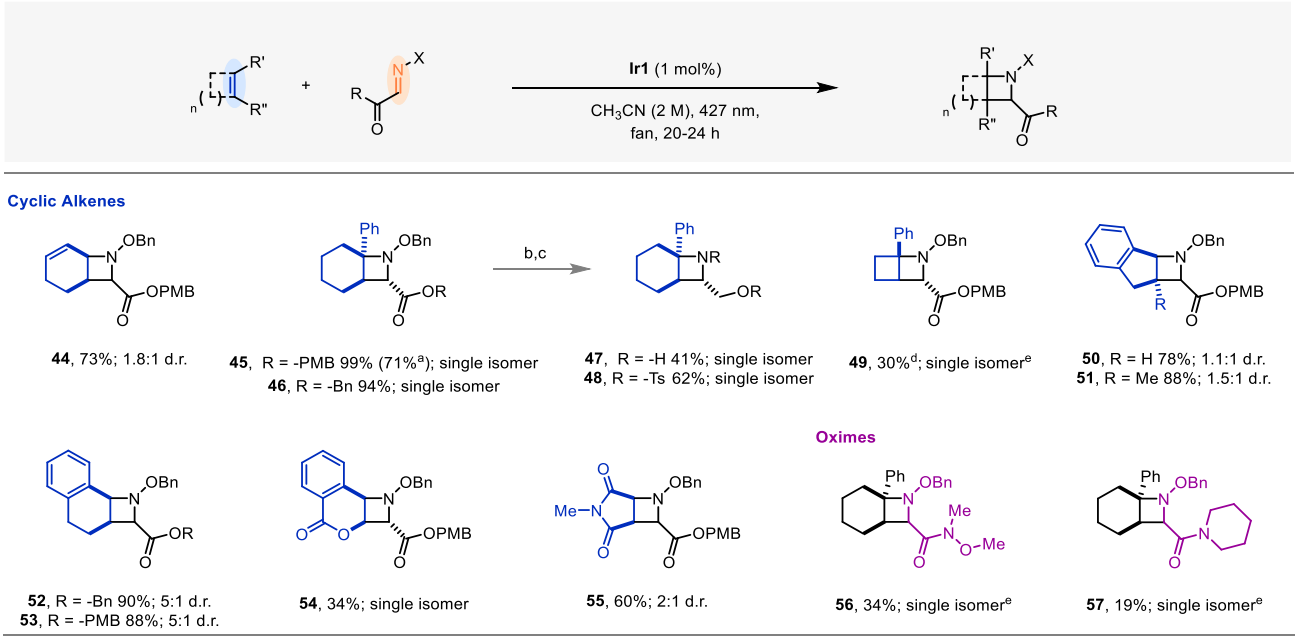
Conditions: 0.25 mmol oxime and **Ir1** (1 mol %) are added to a 1.5-dram vial with stirbar and dissolved in acetonitrile (2 M). The reaction mixture is sparged for 7-10 minutes, and alkene (0.625 mmol) is added. The reaction is irradiated with two blue LED lamps (427 nm) and fan cooled for 6 h, at which point additional alkene (0.625 mmol) is added. The reaction is irradiated for an additional 14-18 hours for a total time of 20-24 h. For solid alkenes, one addition is made prior to sparging (1.25 mmol). Yields are reported of isolated product. Diastereomeric ratios of the crude mixture are determined by ^{1}H NMR. [a] 0.15 mmol scale; [b] 2 mmol scale, 3 equiv styrene added over 6 h, 0.25 mol % **Ir1**; [c] HFIP, 2 equiv styrene, 465 nm light; [d] d.r. calculated from isolated material; [e] Treatment of **26** with Red-Al (60%), toluene, 0 °C, 30 min. Product was isolated, then treated with *para*-nitrobenzoyl chloride, DMAP, Et_3N, DCM, 2 h to form **28.** [f] run with 465 nm light. [g] run at a concentration of 0.67 M. [h] 5 equiv styrene added all at once.

with both electron withdrawing (**32**, **33**) and donating groups (**35**) on the oxime ester react comparably, with products

33 and **35** both forming with a 70% yield. Non-benzyl ester protecting groups react similarly in the transformation, providing **34** in 57% yield. Similarly, the oxime protecting group was shown to have minimal impact with methyl- (**33**-**35**) and allyl- (**36**) protected oximes providing products in yields of 61% (**36**) to 70% (**35**). While our previous visible-light-mediated aza Paternò-Büchi approaches were limited to 2-isoxazoline esters and nitriles,[33] products can be formed from oxime amides (**37**-**40**) including Weinreb amide (**39**) and an -NH containing amide (**40**) in up to 46% yield. In addition to oximes, a hydrazone was also amenable to the reaction forming **42** in an increased yield of 92%. Ketone-derived sulfonyl-imine was also shown to react to form **43**. Notably, the opposite regioisomer is formed in this case. Further research into the origin of this switch in selectivity is underway in our laboratory. Conjugated α,β-unsaturated ketones such as chalcones, which have previously been reported for [2+2]-cycloadditions to access cyclobutanes,[24] were not successful substrates for this transformation, exhibiting isomerization rather than productive [2+2]-cycloaddition with the oxime.

The optimal conditions are similarly applicable to cyclic alkenes generating bi- or tri-cyclic products in 20% to 99% yield (Table 2). Phenyl cyclohexene performs well in the reaction, resulting in the quantitative formation of **45** as a

Table 2: Substrate scope of cyclic alkenes and acyclic oximes



Conditions: 0.25 mmol oxime and **Ir1** (1 mol%) are added to a 1.5-dram vial with stirbar and dissolved in acetonitrile (2 M). The reaction mixture is sparged for 7-10 minutes, and alkene (0.625 mmol) is added. The reaction is irradiated with two blue LED lamps (427 nm) for 6 hours, at which point additional alkene (0.625 mmol) is added. The reaction is irradiated for an additional 14-18 hours for a total reaction time of 20-24 h. For solid alkenes, one addition is made prior to sparging (1.25 mmol). Yields are reported of isolated product. Diastereomeric ratios of the crude mixture are reported as determined by ^{1}H NMR. [a] Run on a 1 g, 4 mmol scale with 3 equiv alkene (added via syringe pump) and 0.25% catalyst; [b] Ester reduction using Red-Al to form azetidine alcohol (see SI for details); [c] *N–O* bond homolysis using Zn/HCl to access free azetidine **44**. Protection with TsCl prior to isolation yields azetidine **45** (see supplementary material for details); [d] Run on a 0.10 mmol scale with 2.3 equiv alkene. [e] d.r. Calculated from isolated material due to overlap in crude ^{1}H NMR**.** -PMB = *para*-methoxybenzyl

single diastereomer, presumably due to the longer triplet lifetime of the cyclic triplet alkene. Furthermore, the additional steric bulk of the alkene disfavors competing styrene dimerization, enabling increased product formation. To demonstrate the synthetic utility of this transformation in accessing free azetidines, **46** was reduced to the corresponding alcohol, which underwent *N–O* bond cleavage to form unprotected azetidine **47** or tosyl-protected azetidine **48** upon subsequent treatment with TsCl. A 6-membered diene also provides the product **44** in 76% yield, and phenyl cyclobutene undergoes the reaction to form fused bicyclic system **49**. Tricyclic systems can be generated through the reaction of fused bicyclic alkenes (**50**-**54**) with products being formed in 34% to 90% yield. Interestingly, maleimide also reacts in this transformation forming **55**, enabled by its comparable triplet energy of 55.9 kcal/mol.[45] The formation of this product shows the versatility of this method beyond styrenes and dienes. Finally, the cyclic alkene substrates also reacted with the amide-substituted oximes (**56**, **57**).

Subsequent efforts focused on a combination of experimental and theoretical investigations to understand how previous challenges associated with the photoreactivity of acyclic imines are overcome. Initial electrochemical experiments show that neither substrate would favorably undergo oxidation or reduction from the photocatalyst and are therefore consistent with a triplet energy transfer mechanism (see supplementary materials for details). Ensuing endeavors centered on determining which substrate undergoes sensitization to its triplet state. As styrene **8** and oxime **10** are both activated, either could be sensitized by the catalyst (Fig. 3A). Indeed, analysis of the crude mixture revealed that styrene dimer **58** and isomerized oxime **59** are formed, suggesting that both can access their triplet states **I1** and **I2**, respectively, under the optimal reaction conditions (Fig. 3A). Additional Stern-Volmer quenching experiments showed that styrene **8** has a much larger quenching constant (K_{SV} = 2.56 mM^{-1}) than oxime **10** (K_{SV} = 0.01 mM^{-1}), consistent with a more favorable energy transfer event with the photocatalyst. This combined with an excess of styrene **8** in the solution suggests that it is more likely for styrene to be sensitized to its triplet state **I1** and initiate the desired cycloaddition with oxime **10**. Control reactions between activated and unactivated pairings of substrates further corroborated the hypothesis that the styrene triplet state **I1** is primarily responsible for the observed reactivity (Fig. 3B, C). Specifically, styrene **8** forms trace amounts of azetidine product when paired with unactivated oxime **60**, while activated oxime **10** forms no products with unactivated alkene **61** under otherwise identical reaction conditions. Based on these results, the following mechanism for the reaction is proposed: first, styrene **8** is sensitized by the photocatalyst to its triplet state **I1** which then combines with the ground state of oxime **9** to form 1,4-biradical **I3**. This biradical then undergoes intersystem crossing (**I4**) and barrierless radical recombination to form the azetidine product **11**. The DFT-computed free energy surface for this reaction is consistent with the initial combination of the triplet styrene and ground state oxime to form the 1,4-biradical intermediate **I3** being the rate determining step (Fig. 3D, see supplementary materials for computational details).

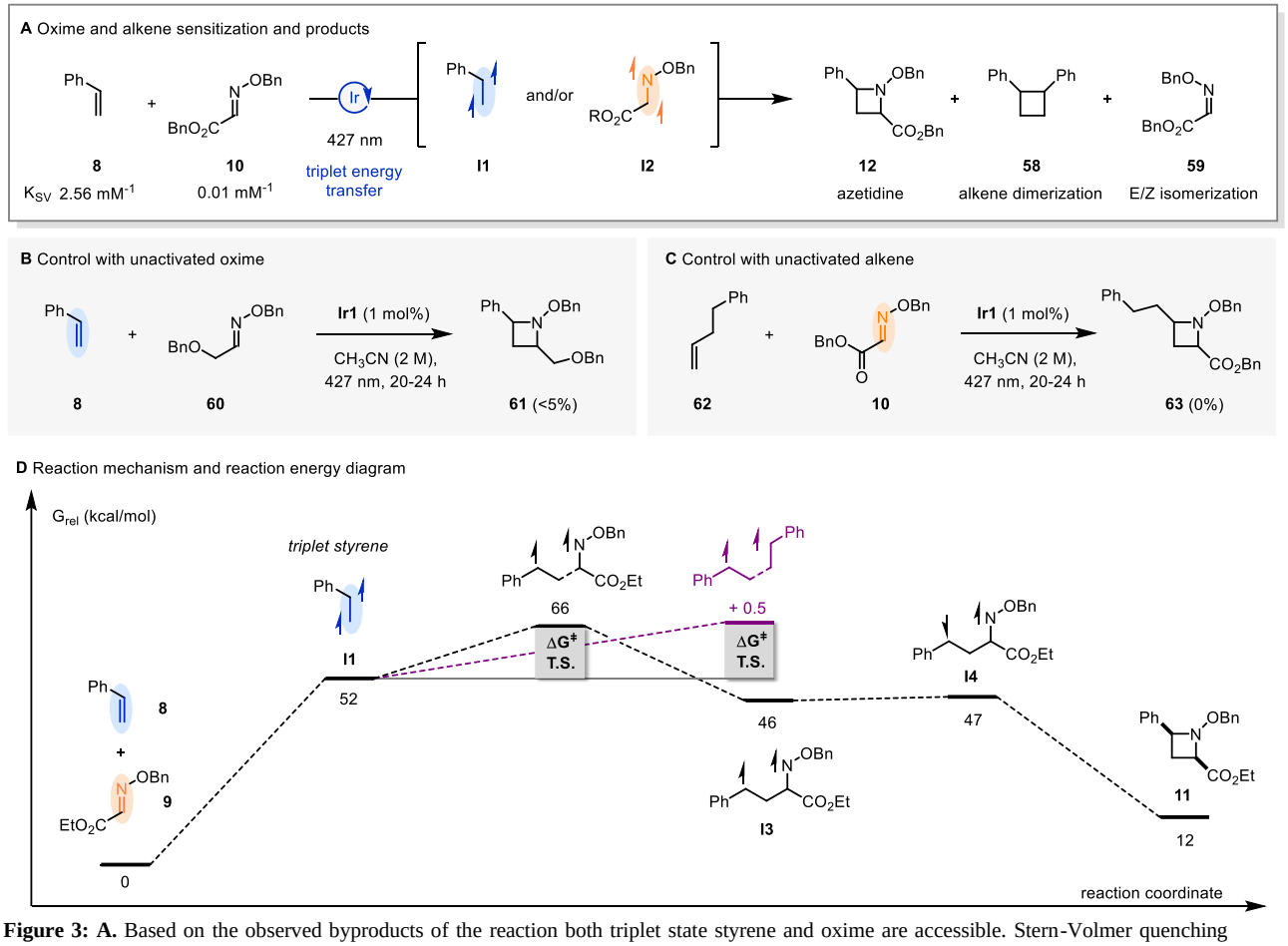


Figure 3: A. Based on the observed byproducts of the reaction both triplet state styrene and oxime are accessible. Stern-Volmer quenching studies show styrene is more readily sensitized to its triplet state by **Ir1**. **B.** Control reactions pairing an unactivated oxime with an activated alkene and **C.** an unactivated alkene with an activated oxime. **D.** The DFT-computed energy diagram for the reaction.

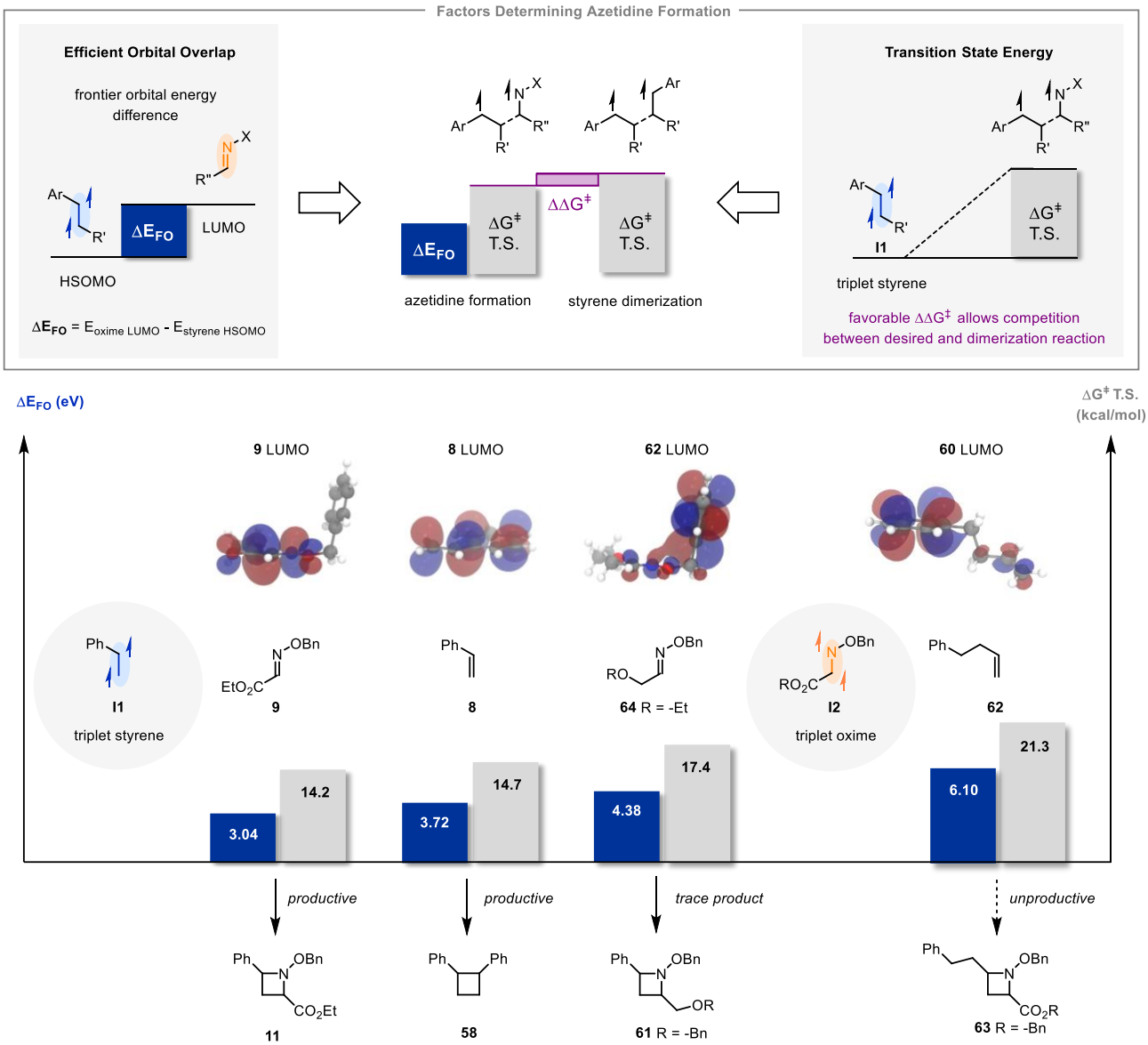


Figure 4: For productive azetidine formation, the transition state free energy ($\Delta G^{\ddagger}$ T.S.) for the desired reaction must be lower than or comparable to the transition state free energy for styrene dimerization. A lower energy transition state relies on productive orbital overlap between the styrene HSOMO and the ground state (oxime or styrene) LUMO, measured by calculating ΔE_{FO}. For the reaction of a triplet oxime **9** with an unactivated alkene **60**, the ΔE_{FO} is calculated by taking the difference in energy between the oxime HSOMO and the alkene LUMO. Comparing the transition state energy for the productive reaction to the unproductive activated/unactivated pairings explains the reactivity trends observed. Similarly, the ΔE_{FO} is higher for unproductive reactions, demonstrating the importance of the lower lying LUMO of the ground state reactant. $\Delta G^{\ddagger}$ T.S. and ΔE_{FO} are calculated by DFT. Orbital visualizations show the LUMO density of the corresponding ground state reaction partner.

Since the highest energy transition state in the transformation is the combination of the triplet styrene **8** and ground state oxime **9** (Fig. 3D), the energy of the LUMO of **9** and the HSOMO of **8** both play a role in influencing the transition state and thus the rate of the reaction. As competing styrene dimerization is observed in the reaction, the transition state energy ($\Delta G^{\ddagger}$ T.S.) for the desired aza Paternò-Büchi reaction must be low enough to compete with the styrene dimerization (Fig. 4). We hypothesized that proper matching of the frontier orbital energy levels of the alkene and oxime would result in favorable orbital interactions and consequently a lower energy transition state of the desired reaction. Specifically, additional stabilization of the oxime substrates (**9**, **10**) is enabled through conjugation with pendant electron-withdrawing substituents, which ultimately enables a matched frontier orbital interaction between these oximes and activated alkenes. To explore this hypothesis, we investigated the cycloaddition reactions of styrene

with an activated oxime (**8** and **9**), styrene with styrene (**8** and **8**), styrene with an unactivated oxime (**8** and **64**), and an activated oxime with an unactivated alkene (**9** and **62**) computationally (Fig. 4). Specifically, we incorporate thermodynamic corrections at 298K and employed the B3LYP functional[46–48] as well as the def2-TZVP[49] basis set in conjunction with the D4 dispersion correction[50] and the C-PCM solvation correction[51] for acetonitrile using the ORCA v5.0.1 software.[52] Importantly, the yield of the [2+2]-cycloadditions was found to trend with the frontier orbital energy difference (ΔE_{FO}) of the substrates, as well as with the transition state barrier ($\Delta G^{\ddagger}$ T.S.). The aza Paternò-Büchi reaction of **8** and **9** has a relatively low barrier of 14.2 kcal/mol, allowing it to compete with styrene dimerization (barrier of 14.7 kcal/mol) (Fig. 4). This result is consistent with experimental observations as both azetidine **11** and styrene dimer **58** are formed under the optimal reaction conditions. However, the reactions of unactivated/activated pairings, specifically unactivated oxime **64** and styrene **8** as well as activated oxime **9** and unactivated alkene **62** have less favorable frontier orbital energy differences and higher triplet transition state barriers, leading to lower reaction yields. This is especially evident in the reaction of the unactivated alkene with the activated oxime, where no product is observed due to poor frontier orbital energy matching (high ΔE_{FO}) and a significant transition state barrier (21.3 kcal/mol). Importantly, these results suggest that two requirements need to be fulfilled to allow for the aza Paternò-Büchi reaction of acyclic imines and alkenes to proceed: 1) the transition state energy $\Delta G^{\ddagger}$ T.S. must be low enough to compete with styrene dimerization, which is enabled by 2) well matched frontier orbital energies of the alkene and oxime substrate, as evidenced by a small frontier orbital energy difference ΔE_{FO}. We expect that the results described herein will have a direct impact on future transformations relying on the reactivity of triplet excited states.

This transformation represents the first intermolecular visible-light-mediated aza Paternò-Büchi reaction of two acyclic components. The broad scope highlights the improved generality of this method for a wide range of substrates and marks an important advancement in azetidine synthesis. Insights gained through the investigation of this transformation are expected to have implications for the further development of not only aza Paternò-Büchi reactions, but all cycloadditions employing the styrene triplet state, which have historically been limited primarily to dimerization-type reactions. The demonstration of the importance of frontier orbital energy matching to enable alkene-oxime cycloaddition to compete with alkene dimerization and form the desired product is an important advancement in our understanding to facilitate future cycloadditions beyond those of oximes and alkenes.

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The authors declare no competing financial interests.

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