Visible Light-Mediated [2+2] Cycloaddition for the Synthesis of Azetidines via Energy Transfer

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Abstract

Due to the lack of synthetic methods for their synthesis, azetidines are an underrepresented class of nitrogen-containing heterocycles. Herein, we describe the development of a mild, general protocol for the synthesis of azetidines relying on a visible light-mediated [2+2] cycloaddition between oximes and olefins catalyzed by an iridium photocatalyst. This approach is characterized by its operational simplicity, low catalyst loadings and functional group tolerance. Mechanistic investigations suggest that a triplet energy transfer mechanism is operative.
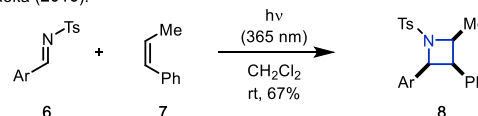
Azetidines[1,2] are four-membered, nitrogen-containing heterocycles that have seen increased interest in discovery chemistry in recent years.[3] Cobimetinib (**1**)[4], delafloxacin (**2**)[5], and baricitinib (**3**)[6] are promising lead compounds currently undergoing clinical trials that contain azetidines as core structural motifs (Fig. 1A). Biologically active azetidines, such as penaresidin (**4**) and mugineic acid (**5**), have been isolated from natural sources[2] (Fig. 1A). Compared to their 5- and 6-membered ring analogs, azetidines are characterized by their rigid conformations and are known to exhibit superior physicochemical properties as well as metabolic stability.[7] Despite these desirable characteristics, azetidines are far less prevalent as scaffolds in medicinal chemistry, which is often attributed to a lack of efficient synthetic methods for the construction of these strained, four-membered heterocycles.[1] Current strategies for the synthesis of functionalized azetidines are most often based on intramolecular substitution reactions with nitrogen nucleophiles, intramolecular alkylations or the reduction of β-lactams.[1,8,9] Analogous to the Paternò-Büchi[10] reaction, in which an excited state carbonyl undergoes a [2+2] cycloaddition with an olefin, an aza Paternò-Büchi reaction between an imine and olefin would provide an efficient way for the synthesis of azetidines. However, in comparison to carbonyls, imines show decreased photoreactivity as a consequence of additional relaxation pathways accessible upon excitation, such as E/Z isomerization.[11] As a result, successful reports remain scarce and often require rigid imine and olefin-containing systems predisposed for cycloaddition[12] or cyclic imines bearing electron-withdrawing substituents, such as isoindolones[13] and azauracils.[14,15] More recently, the Maruoka group developed an intermolecular [2+2] photocycloaddition between N-aryl-sulfonylimines (**6**) and styrenes (**7**) proceeding in up to 67% yield. (Fig. 1B).[16] Notably, the reaction was found to be stereospecific, which was attributed to an operative singlet state
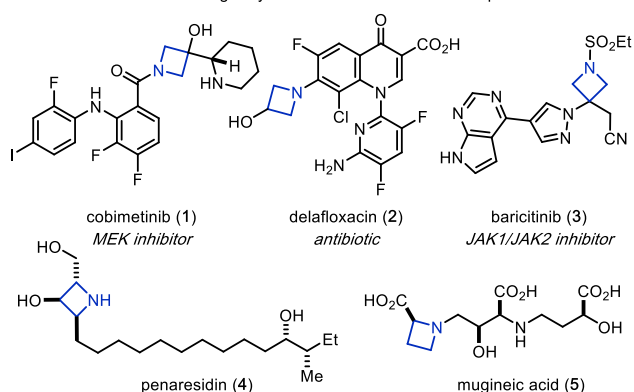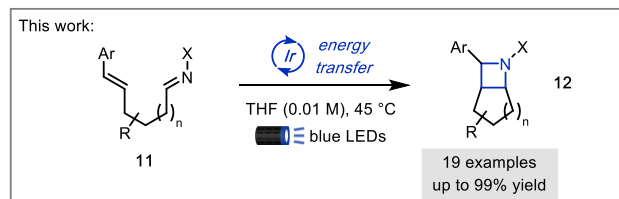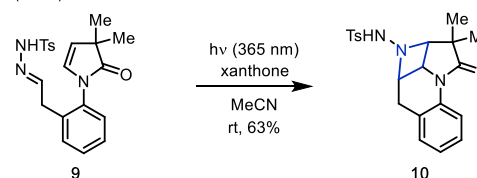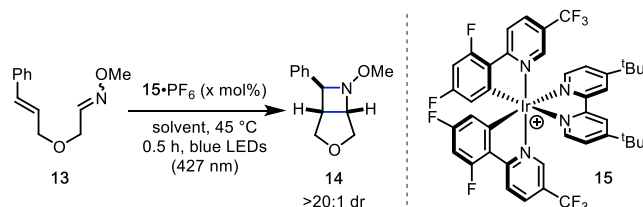

Figure 1. Previous [2+2] cycloaddition strategies towards azetidines and this approach.

Table 1. Reaction optimization.

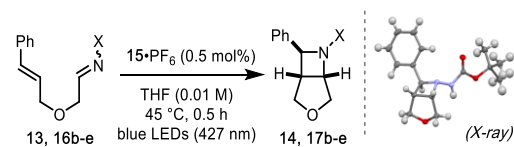| entry	photocatalyst (mol%)	solvent	conc. [M]	yield[a]
1	**15·PF$_6$** (2.5)	CH$_2$Cl$_2$	0.025	72%
2	**15·PF$_6$** (2.5)	MeOH	0.025	87%
3	**15·PF$_6$** (2.5)	EtOAc	0.025	87%
4	**15·PF$_6$** (2.5)	Acetone	0.025	86%
5	**15·PF$_6$** (2.5)	MeCN	0.025	88%
6	**15·PF$_6$** (2.5)	THF	0.025	93%
7	**15·PF$_6$** (2.5)	THF	0.01	97%
8	**15·PF$_6$** (2.5)	THF	0.05	88%
9	**15·PF$_6$** (2.5)	THF	0.10	90%
10	**15·PF$_6$** (1.0)	THF	0.01	96%
11	**15·PF$_6$** (0.5)	THF	0.01	98%
12	-	THF	0.01	-
13[b]	**15·PF$_6$** (0.5)	THF	0.01	-

Conditions: Performed on 0.1 mmol scale under irradiation with a blue LED light (427 nm) for 0.5 h at ambient temperature; [a]yield determined by quantitative ^{1}H NMR analysis from the crude mixture using an internal standard; [b]run in the dark.

imine undergoing the photocycloaddition reaction. The Siva-guru group developed an intramolecular aza Paternò-Büchi reaction protocol between oximes or hydrazones and cyclic enamides (**9**) to form azetidines (**10**) as cycloaddition products in up to 79% yield (Fig. 1b).[17] In contrast to previous photocycloaddition reactions involving imines, the authors propose a triplet sensitization mechanism, in which a triplet state enamide initiates the photocycloaddition after energy transfer from a sensitizer. However, the relatively high triplet energy of enamides limits the reaction to triplet sensitizers such as xanthone (E_T = 74 kcal mol^{-1}), which do not absorb in the visible light region and require the use of high-energy UV light. In addition, competing electron-transfer processes can occur that result in catalyst decomposition, reduced yields and limited functional group tolerance.[18] With the goal to develop a mild and robust [2+2] cycloaddition protocol for the synthesis of azetidines relying on visible light activation, we took inspiration from pioneering work by the Yoon group, who reported the [2+2] cycloaddition of styrenes and dienes to form cyclobutanes via an energy-transfer mechanism.[19,20] Both styrenes and dienes possess lowest-lying triplet states that are accessible with visible light photocatalysts such as Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (**15·PF$_6$**).[21] We hypothesized that a triplet state styrene, accessed through an energy transfer process from a suitable visible light photocatalyst, might be capable of engaging in a [2+2] cycloaddition with a C=N double bond to form the azetidine product. Furthermore, the reduced redox potentials of common visible light photocatalysts compared to sensitizers such as xanthone render undesired electron-transfer processes less likely, which would potentially allow for lower catalyst loadings and increased functional group tolerance. With this design principle in mind, we chose oxime **13** (mixture of *E/Z* oxime isomers) bearing an (*E*)-styrene as a starting point for our investigations. Oximes provide significant advantages over imines as substrates considering their increased stability towards hydrolysis. Irradiation of **13** with a 40 W blue LED light (427 nm) in the presence of 2.5 mol% **15·PF$_6$** resulted in the rapid formation of azetidine **14** as sole product of the reaction in very good yield and excellent diastereoselectivity (>20:1 d.r.) for a wide range of solvents (Table 1, entry 1–5). By switching to THF as solvent and lowering the concentration, the yield could be further improved (Table 1, entry 7). Remarkably, the catalyst loading could be reduced to loadings as low as 0.5 mol% **15·PF$_6$** without the need for increased reaction time. Finally, control reactions revealed that both light and photocatalyst were necessary for the [2+2] photocycloaddition to proceed (Table 1, entry 12–13).

With optimized conditions in hand, we next evaluated different oximes and hydrazones for their ability to undergo the [2+2] cycloaddition (Table 2). It should be noted that all substrates were prepared and used as mixtures of *E/Z* oxime or hydrazone isomers, however, the ratio was found to have no impact on the reaction outcome. *O*-Benzyl oxime **16b** converted smoothly to **17b** in 96% yield and very good diastereoselectivity, providing similar results as the *O*-methyl oxime **13**. Notably, the reaction can be performed on gram scale at slightly higher concentration with no significant decrease in yield. Free oxime **16c** and *N*-Boc hydrazone **16d** were reacted under the optimized condition, and the corresponding azetidines **17c** and **17d** were isolated in 54% and 62% yield, respectively. Interestingly, no reaction was observed with *N,N*-dimethyl hydrazone **17e** and only unreacted starting material was recovered from the reaction mixture. Next, we sought to expand the substrate scope of the [2+2] cycloaddition

Table 2. Evaluation of oxime and hydrazone substrates.

entry	substrate (*Z/E*)		yield	d.r.
1	13	N–OMe (1:1.3)	96% / 91%[b]	>20:1 / >20:1
2	16b	N–OBn (1:1.3)	96% / 90%[b]	16:1 / 20:1
3	16c	N–OH (1:1.1)	54%	>20:1
4	16d	N–NHBoc (1:2.6)	62%	13:1
5[a]	16e	N–NMe$_2$ (*E* only)	0%	-

Conditions: Reactions were performed with 0.25 mmol substrate and 0.5 mol% **15·PF$_6$** in THF (0.01 M) at ambient temperature under blue LED irradiation (427 nm) for 0.5 h; d.r. was determined by ^{1}H NMR from the crude reaction mixture; [a]run for 16 h; [b]reaction performed on gram scale.

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Figure 2. Scope of the [2+2] cycloaddition reaction.
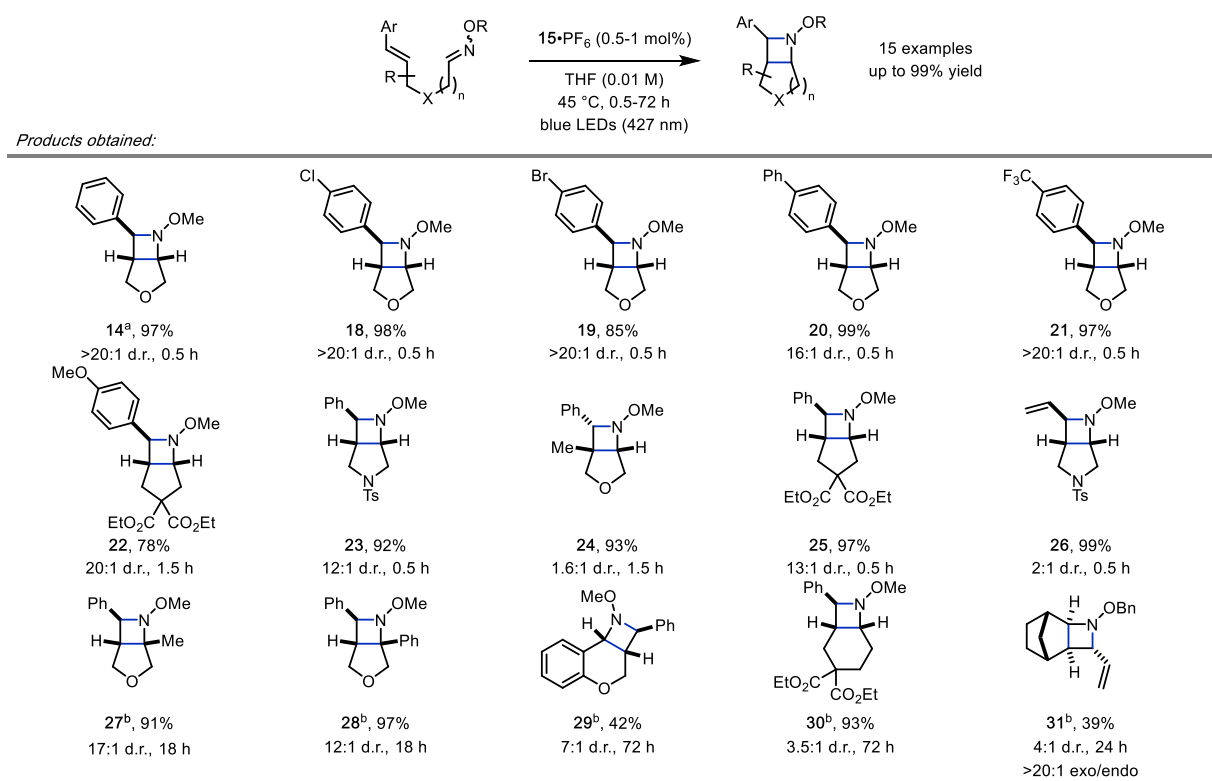
Conditions: Reactions were performed with 0.25 mmol (*E*)-styrene substrate (mixture of *E*/*Z* oxime isomers) and 0.5 mol% **15**•PF$_6$ in THF (0.01 M) at ambient temperature under blue LED irradiation (427 nm) unless noted; diastereomeric ratios were determined by ^{1}H NMR from the crude reaction mixture; [a]starting with (*Z*)-styrene; [b]with 1 mol% **15**•PF$_6$ in degassed THF (0.01 M) under N$_2$ atmosphere.

(Fig. 2). In agreement with a mechanism proceeding through a triplet manifold, we observed that (*Z*)-**13** gave identical results in the [2+2] cycloaddition as (*E*)-**13**. This stereoconvergence is characteristic for triplet state styrenes as the same triplet state intermediate is accessed from both the (*E*)- and (*Z*)-isomer. The optimized conditions proved efficient for a variety of electronically diverse styrenes including both electron-rich and electron-deficient styrenes, affording the corresponding azetidines in excellent yield and diastereoselectivity (**18**–**22**). Furthermore, different substitution patterns on the styrene moiety as well as the substrate backbone including esters and sulfonamides were well tolerated (**23**–**25**). We also evaluated dienes upon their ability to undergo the developed cycloaddition reaction. Dienes were previously reported by the Yoon group to engage in [2+2] cycloadditions to form cyclobutanes bearing an exocyclic olefin that allows for further functionalization.[20] After reacting the corresponding diene under the optimized conditions, azetidine **26** was isolated as the sole product of the reaction in 99% yield. Notably, we were unable to detect any products arising from a [4+2] cycloaddition, a potential competing side reaction. While the cycloaddition could be readily conducted under ambient atmosphere, we observed significant amounts of solvent decomposition for substrates that required extended reaction times arising from reaction with atmospheric oxygen. However, by simply degassing the reaction mixture prior irradiation and slightly increasing the catalyst loading to 1 mol%, substrates could be successfully converted to the corresponding products with minimal amounts of solvent decomposition. Under these conditions, oximes derived from methyl and phenyl ketones were converted to the corresponding azetidines **27** and **28** in excellent yield. We also evaluated the feasibility of substrates forming azetidines fused to six-membered rings upon [2+2] cycloaddition. These corresponding substrates were found to be significantly less reactive, nevertheless, chromane **29** and cyclohexane **30** were obtained after irradiation for 72 hours in 42% and 93% yield, respectively. Finally, the developed protocol allows for access of strained bridged bicycles such as **31** in 39% yield.

Subsequent efforts focused on investigating the mechanism of the [2+2] cycloaddition reaction. The excited state redox potentials of **15**•PF$_6$ ($E_{1/2}^{III*/II}$ = +1.21 V vs. SCE; $E_{1/2}^{IV/III*}$ = –0.89 V vs. SCE)[22] are not sufficient for an effective oxidation or reduction of substrate **13**, thus, rendering a photoredox process unlikely. Instead, a series of control experiments indicated that a triplet energy transfer mechanism from the photocatalyst to the styrene moiety of the substrate is likely to be operative. Consistent with this hypothesis, when substrate **32** bearing a terminal olefin with a significantly higher

triplet state energy than a styrene (approx. 76–84 kcal mol^{-1}) was submitted to the standard conditions, no azetidine formation (**33**) was observed, and unreacted starting material was recovered from the reaction mixture (Fig. 3).[23] Styrenes possess a triplet energy of approximately 60 kcal mol^{-1}, which suggests that **15**·PF$_6$ (E_T = 62 kcal mol^{-1}) is capable of sensitizing substrate **13**. On the other hand, the reaction efficiency significantly decreases with photocatalysts that have a triplet energy below 60 kcal mol^{-1}. While *fac*-Ir(ppy)$_3$ (E_T = 58 kcal mol^{-1}) is still able to mediate product formation, albeit less efficiently, Ru(bpy)$_3^{2+}$ (E_T = 49 kcal mol^{-1}) does not catalyze the [2+2] cycloaddition at all (Fig. 3).[24] Next, we conducted a time study to probe for styrene *E/Z* isomerization under the reaction conditions, a relaxation pathway typically observed for triplet state styrenes.[25,26,27] Indeed, the time study revealed that *E/Z* isomerization of pure (*E*)-**13** occurs at a similar rate as the productive [2+2] cycloaddition, leading to an initial build-up of (*Z*)-isomer that is eventually converted to the product. This data provides further evidence for the hypothesized triplet sensitization mechanism. Finally, a Stern-Volmer quenching study shows that the styrene moiety of substrate (*E*)-**13** is necessary for productive quenching of photocatalyst **15**·PF$_6$. In contrast, oxime **34** lacking the styrene functionality but otherwise identical with **13** does not quench **15**·PF$_6$ (Fig. 3). Therefore, a mechanism proceeding through a photosensitized oxime can be ruled out, which confirms our initial reaction design as the discrete photophysical properties of **15**·PF$_6$ only allow for selective triplet energy transfer to the styrene, while unproductive processes such as electron transfer to the oxime do not occur.

The developed [2+2] cycloaddition protocol allows for rapid access to highly functionalized azetidines under mild conditions, which can undergo further transformations to result in valuable building blocks (Fig. 4). The oxime *N–O* bond can be readily cleaved with zinc metal under acidic conditions providing **35** in 87% yield. Furthermore, hydrogenolysis conditions facilitate reductive cleavage of the azetidine ring to generate 3-aminotetrahydrofuran **36** in 98% yield after tosylation of the primary amine.

In summary, we have developed a general and catalytic method for the synthesis of highly functionalized azetidines through a [2+2] cycloaddition between oximes or hydrazones and olefins. The design principle of this transformation relies on an energy transfer mechanism utilizing a visible light photocatalyst, which allows to perform the [2+2] cycloaddition under very mild conditions. We expect that this strategy will provide a new platform for the synthesis of azetidines and will facilitate the development of new enabling [2+2] cycloadditions involving carbon–nitrogen double bonds.

Figure 3. Mechanistic investigations of the title reaction.
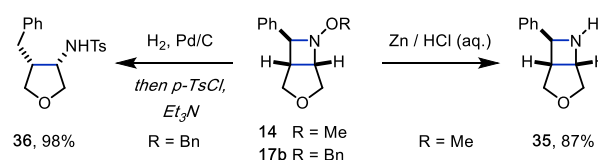
Figure 4. Selected modifications of azetidine products.

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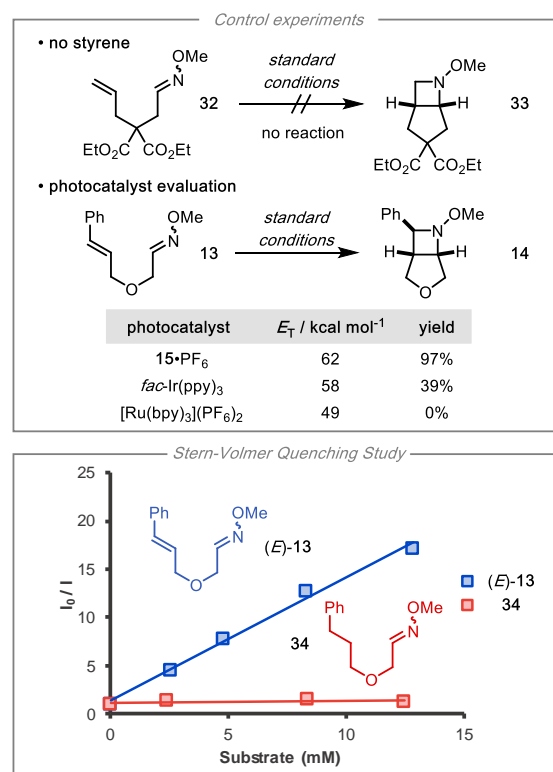
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