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Intermolecular transposed Paternò–Büchi reactions enabled by triplet sensitization

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The canonical mechanism of the Paternò–Büchi cycloaddition involves the reaction of an excited-state carbonyl compound with a ground-state alkene to afford an oxetane. Despite a century of sustained interest in this important organic photoreaction, the mechanistically complementary reaction proceeding *via* an excited-state alkene and ground-state carbonyl compound was first reported less than a decade ago and remains relatively underdeveloped. We report herein a visible light induced photocatalytic approach towards transposed Paternò–Büchi cycloadditions. This strategy involves the use of a photosensitizer that is capable of engaging in selective triplet energy transfer to the alkene component in preference to its carbonyl reaction partner. These more general reaction conditions have enabled a thorough investigation of the synthetic opportunities afforded by the transposed Paternò–Büchi reaction.

Introduction

Oxetanes are four-membered oxygen-containing heterocycles that are valued in contemporary medicinal chemistry both as synthetic intermediates and as potential bioisosteres for carbonyl compounds.[1] Their synthesis, however, remains a challenge, particularly for highly substituted oxetane rings embedded within a structurally complex target. The most direct and atom-economical strategy for oxetane synthesis is the Paternò–Büchi cycloaddition. First described in 1909,[2] this reaction is among the oldest and most well-studied transformations in organic photochemistry. Its canonical mechanism involves reaction of an excited-state carbonyl compound with a ground-state alkene (Fig. 1A). Strategies for accessing the carbonyl (n, π*) excited state for the Paternò–Büchi have been well studied and are the subject of several excellent reviews.[3]

The "transposed" Paternò–Büchi reaction is a mechanistically distinct alternative to the classical version of this reaction that proceeds through the excited-state of the alkene rather than the carbonyl (Fig. 1B). The Sivaguru group reported the first example in 2017 in the context of an intramolecular alkene–carbonyl photocycloaddition (Fig. 1C).[4] This discovery represented a significant departure from over a century of research into photochemical oxetane synthesis; however, the reaction design required a tethering strategy to position the alkene and carbonyl groups in close proximity, limiting the scope to intramolecular cycloadditions. Subsequently, the Schmidt[5] and Pan[6] laboratories reported intermolecular transposed Paternò–Büchi reactions under UV irradiation using either a Cu(I) complex or an aromatic ketone as a sensitizer (Fig. 1D); both methods, however, are limited to strained norbornenes as the alkene partner. Thus, there remain few reports of preparatively useful transposed Paternò–Büchi reactions, and their demonstrated synthetic scope remains relatively limited.

It seems remarkable that the first example of the transposed Paternò–Büchi was reported less than a decade ago, given the long scholarly history of interest in the parent reaction. One explanation may relate to the characteristic photophysical properties of carbonyl compounds (Fig. 1E).[7] The photochemistry of aromatic ketones is dominated by low-lying n,π* excited states that are not available to simple olefinic hydrocarbons. These transitions generally enable absorptions at substantially longer wavelengths than olefins. Moreover, intersystem crossing to populate the reactive triplet state is typically more efficient for carbonyl compounds than for alkenes. Consequently, direct irradiation of a solution containing both a carbonyl compound and an alkene would most likely elicit reactions initiated by the triplet state of the carbonyl compound, not the excited-state alkene.

In contrast, the larger singlet–triplet gap associated with the π,π* state of alkenes suggests that their triplet states can be lower in energy than those of their carbonyl reaction partners, even when the alkenes exhibit absorbances significantly higher in energy (Fig. 1E). We wondered, therefore, if it might be possible to use an appropriate triplet sensitizer that would selectively populate the lower-energy alkene triplet excited state and thus enable a more general approach towards the transposed Paternò–Büchi reaction. Herein, we describe studies validating this proposal, aligning this reaction with recent reports of sensitized aza- and thia-Paternò–Büchi reactions.[8] We also describe an examination of the synthetic scope of this reaction under optimized conditions with respect to both reaction partners.

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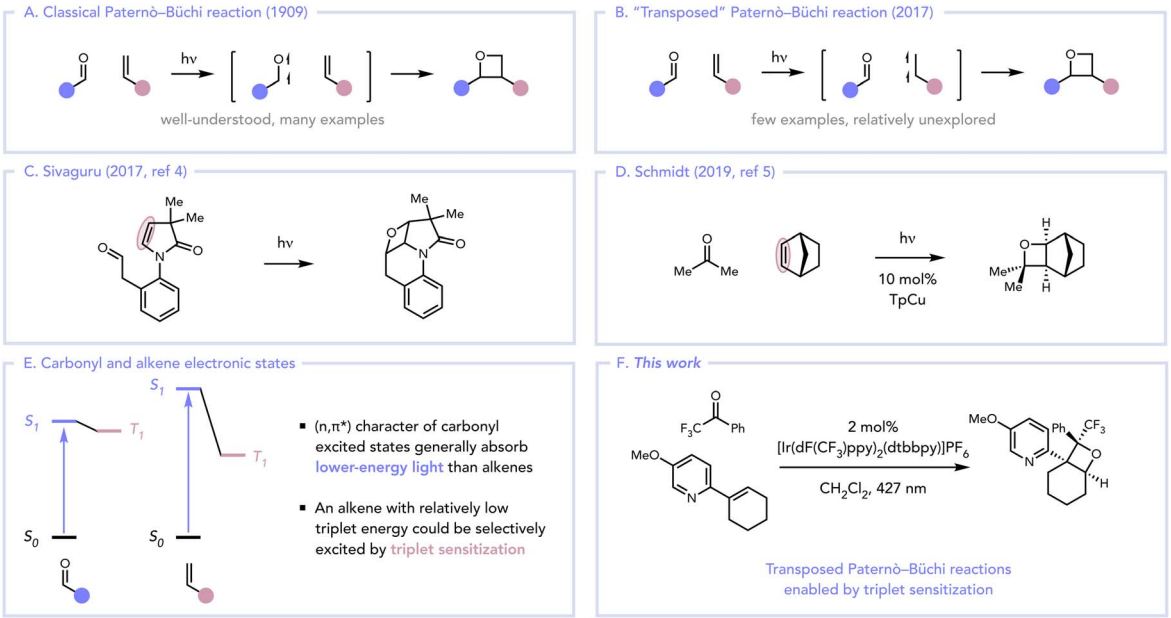

Fig. 1 Strategic design for a transposed Paternò–Büchi reaction. (A) Canonical triplet carbonyl mechanism. (B) "Transposed" mechanism through triplet alkene. (C) First report of a transposed Paternò–Büchi reaction by Sivaguru. (D) Schmidt Cu-mediated transposed Paternò–Büchi. (E) Differing electronic structures in carbonyl and alkene excited states. (F) Triplet sensitization approach to transposed Paternò–Büchi reactions.

Results and discussion

The impetus for this study arose during our recent investigation of an enantioselective Paternò–Büchi catalyzed by a chiral hydrogen-bonding Ir photocatalyst.[9] While the principal product-forming pathway was designed to proceed *via* the typical excited-state carbonyl Paternò–Büchi mechanism, our detailed study of this reaction implied the participation of a minor unselective pathway involving activation of the quinolone component by outer-sphere, collisional triplet sensitization (Fig. 2). We were intrigued by this unexpected observation. If we could generalize it to a broader range of reaction partners, we imagined it might enable a thorough investigation of the synthetic capabilities of the transposed Paternò–Büchi reaction.

Our studies began by investigating the reaction of 3-isopropoxyquinolin-2(1*H*)-one (**1**) and benzaldehyde (**4**) in the presence of $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (**6**), a common photocatalyst for energy-transfer applications. The design of this experiment was informed by the known triplet energies of **1**, **4**, and **6** (E_T = 55 kcal mol^{-1}, 72 kcal mol^{-1}, and 60 kcal mol^{-1}, respectively).[10] We surmised that exergonic triplet energy transfer from the excited state of photocatalyst **6** to alkene **1** would be feasible, while the high triplet energy of benzaldehyde **6** would make it unlikely to be similarly activated by the photocatalyst. Upon irradiation of a toluene solution of **1** and **4** with 427 nm LEDs in the presence of 2 mol% **6**, the transposed Paternò–Büchi cycloadduct **5** was obtained in 34% yield as a single diastereomer (Table 1, entry 1). The remainder of the mass consisted of alkene homodimer **7** (31%) and unreacted quinolone. Further exploration revealed improved productive reactivity in both diethyl ether and acetonitrile (entries 2 and 3), with somewhat less homodimer in acetonitrile. Decreasing the concentration of aldehyde resulted in a concomitant loss in rate (entries 4 and 5). Finally, over the course of these optimization studies, we observed that the reactions became quite warm upon irradiation. Stabilizing the temperature of the reaction flask with a water bath during irradiation resulted in an increased yield of 91%.

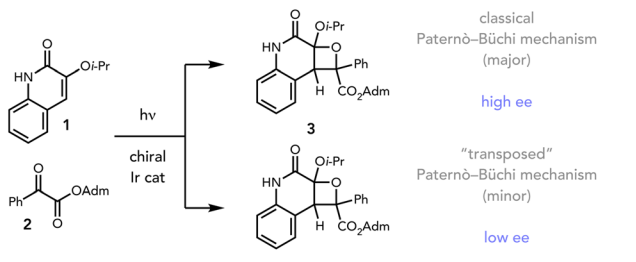

Fig. 2 Prior work: detection of a minor transposed Paternò–Büchi pathway in asymmetric oxetane synthesis (ref. 9). Adm = adamantyl.

The development of these optimized conditions enabled an initial investigation of the scope of this reaction (Fig. 3). First, a range of aromatic carbonyl reaction partners provided oxetane products in good to excellent yields. Pyridine carboxyaldehydes proved to be good substrates for the transposed Paternò–Büchi reaction (**8** and **9**). Interestingly, pyrimidine-5-carboxaldehyde gave 95% assay yield of oxetane **10**, suggesting that more electron-deficient aldehyde partners react more readily. An examination of the reactions of five-membered heteroaromatic carboxyaldehydes revealed similar trends: 2-thiazole carboxaldehyde (**11**) reacted in higher yield than its 2-thiophene analogue (**12**), and 2-furfural reacted sluggishly (**13**). Benzophenone also provided high yields of the transposed Paternò–Büchi cycloadduct (**14**). Trifluoroacetophenone required

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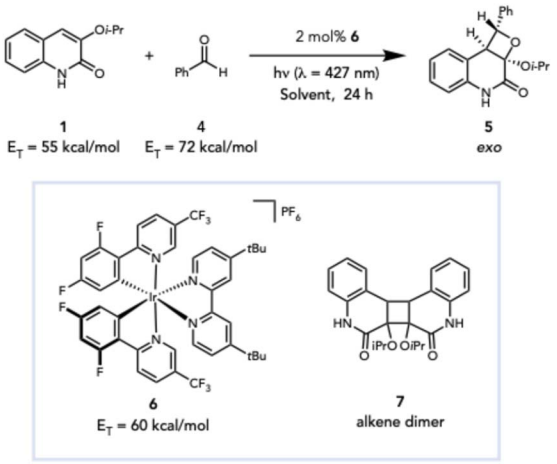
Table 1 Optimization studies for the transposed Paternò–Büchi reaction



Entry	Solvent	Equiv. 4	Yield 5[a] (%)	Dimer 7 (%)
1	Toluene	5.0	34	31
2	Et_2O	5.0	61	15
3	MeCN	5.0	63	8
4	MeCN	2.5	47	8
5	MeCN	1.0	22	5
6[b]	MeCN	5.0	91	4

[a] Assay yields determined by ^{1}H NMR analysis using CH_2Br_2 as an internal standard. [b] Reaction conducted in a water bath.

extended reaction times but furnished a mixture of diastereomeric oxetanes (**15**) in 69% yield after 48 h. The sensitivity of the reaction to the nature of the alkene component seemed more pronounced. While variation of the steric bulk of the ethereal substituent on the quinolone (**16** and **17**) and methylation of the quinolone nitrogen (**18**) were readily tolerated, structurally analogous coumarins did not produce oxetanes (**19**). The major photoproducts observed in these unsuccessful experiments were coumarin homodimers.

We next sought to explore the scope of the reaction with a less specialized class of alkene reaction partners (Fig. 4). Indene (**20**) is a convenient, commercially available alkene that can easily be sensitized by Ir photocatalyst **6** and similar triplet sensitizers. An initial experiment studying the reaction of **20** with benzaldehyde produced only trace amounts of oxetane **21**; the principal product observed was indene dimer **24**, consistent with the established propensity of **20** to undergo homodimerization under similar photocatalytic conditions.[11] However, variation of the carbonyl component recapitulated the same trends observed in their reactions with quinolones. The use of an electron-deficient *p*-CF_3-substituted benzaldehyde afforded good yields of the expected oxetane (**22**), while *p*-MeO-substituted benzaldehyde afforded no oxetane (**23**) and exclusive formation of dimer **24**. To further generalize this concept, we next examined the transposed Paternò–Büchi reaction of indene with trifluoroacetophenone and were pleased to observe high yields of oxetane **25** after a brief re-optimization that identified CH_2Cl_2 as a superior solvent for this reaction (see SI

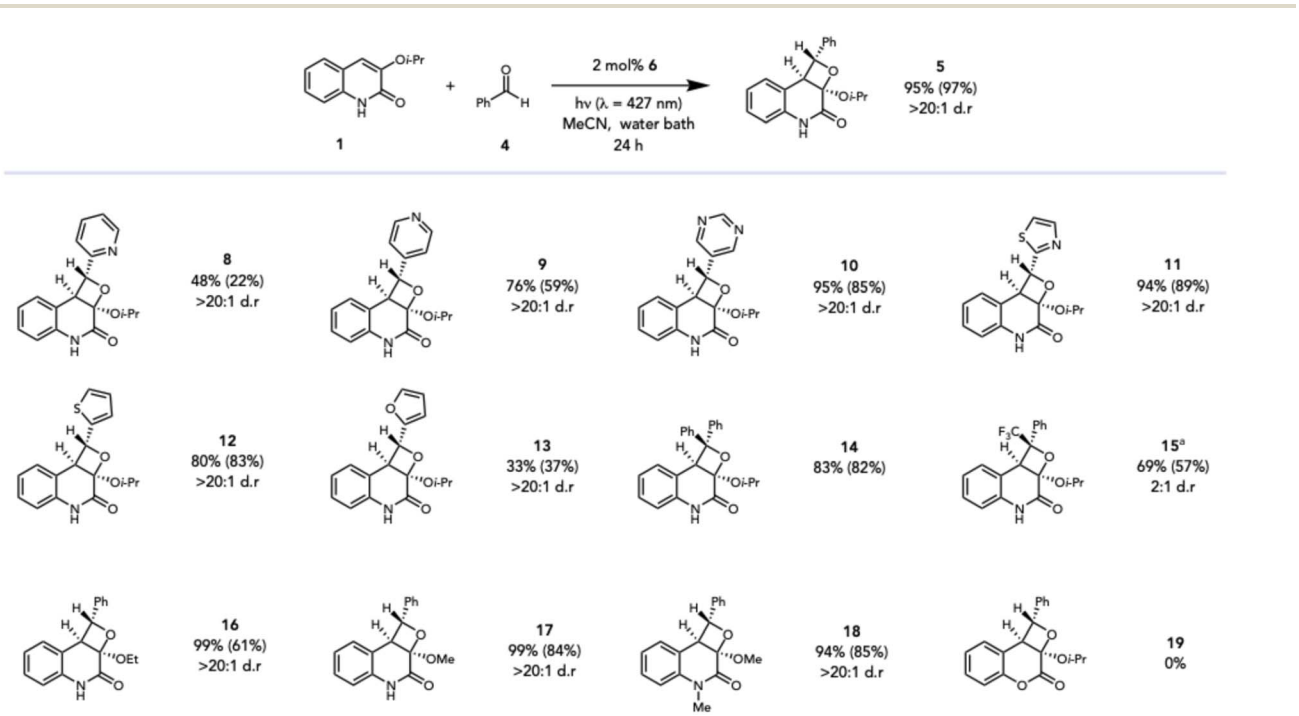


Fig. 3 Scope studies for transposed Paternò–Büchi reactions of quinolones. Assay yields and d.r. determined by crude ^{1}H NMR analysis using CH_2Br_2 as an internal standard. Isolated yields reported in parentheses. [a] Reaction conducted for 48 h.

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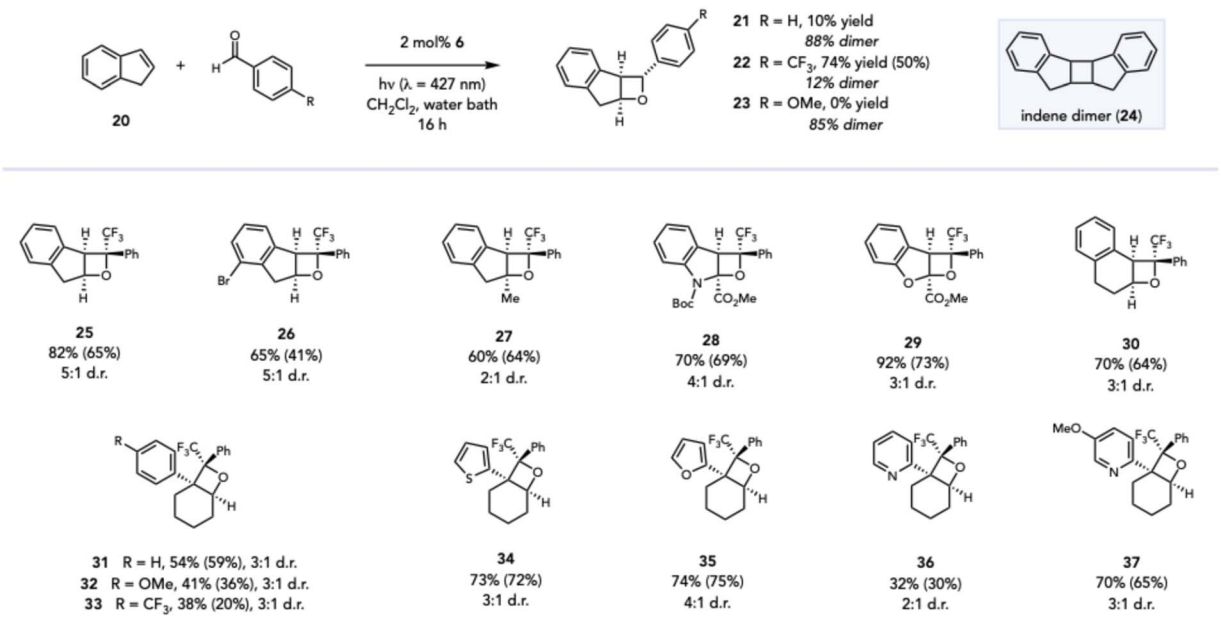

Fig. 4 Scope studies for transposed Paternò–Büchi reactions of indenes and arylcyclohexenes. Assay yields and d.r. determined by crude ^{1}H NMR analysis using CH_2Br_2 as an internal standard. Isolated yields of the combined diastereomers reported in parentheses.

for details). Previous reports have shown 2,2,2-trifluoroacetophenone to be a poor coupling partner in the classic Paternò–Büchi reaction,[12] and thus it appears clear that the transposed variation can provide complementary access to synthetically valuable oxetane products. Substitution on the aromatic ring and on the reactive alkene were each easily tolerated (**26** and **27**). Dearomative cycloadditions of *N*-Boc indole (**28**) and benzofuran (**29**) 2-carboxylate esters proceeded in good yields. The latter reaction could be conducted on 1.7 mmol scale with minimal loss of efficiency. Expansion to a six-membered dihydronapthylene also resulted in high yields of oxetane **30**. 1-Phenyl cyclohexenes proved to be good substrates, tolerating both electron-donating and withdrawing groups (**31–33**). Heterocyclic substituents were also well-tolerated. Electron-rich five-membered heterocycles such as thiophene (**34**) and furan (**35**) gave somewhat higher yields, while electron-withdrawing pyridine (**36**) gave diminished yield of oxetane. Taken together, these observations indicate that yields of the transposed Paternò–Büchi reaction are highest when a relatively electron-rich alkene is paired with a relatively electron-deficient carbonyl compound. This conclusion is aligned with Schindler's recent proposal for the mechanism of the related aza-Paternò–Büchi reaction, which attributed the ability of an oxime ether to outcompete alkene dimerization due to good matching of the frontier molecular orbital energies for each reaction component.[8b] Consistent with this expectation, introduction of an electron-releasing methoxy substituent improves the yield of the transposed Paternò–Büchi reaction of the pyridine-substituted cyclohexene, affording oxetane **37** in 70% yield.

Several lines of evidence support the hypothesis that the reactivity we observe is the result of a transposed Paternò–Büchi reaction. First, Fig. 5A summarizes the results of control experiments examining the importance of each reaction variable. Both light and photocatalyst are required for product formation, and only unreacted starting materials are observed in their absence (entries 2 and 3). Replacing Ir photocatalyst **6** with a Ru photocatalyst with a lower triplet energy also results in no reaction (entry 4), consistent with its inability to sensitize indene. If the carbonyl reactant is omitted from the reaction, clean conversion to the indene dimer is observed, as expected if **6** is serving as a triplet sensitizer for indene.

Fig. 5B summarizes the results of Stern–Volmer quenching studies that provide further corroboration of the reaction mechanism. Quenching of the luminescence of photocatalyst **6** is observed only upon addition of indene, and no quenching was observed using trifluoroacetophenone, benzaldehyde, or benzophenone. These results are in good agreement with the substantially lower triplet energy reported for indene (64 kcal mol^{-1}) compared to trifluoroacetophenone, benzaldehyde, or benzophenone (71 kcal mol^{-1}, 72 kcal mol^{-1}, and 70 kcal mol^{-1}, respectively).[10] We could rule out a radical ion mechanism by comparing the redox potentials of the substrates to those of the photocatalyst. The excited state oxidation and reduction potentials for **6** are +1.21 V and −0.89 V *vs.* SCE respectively. The oxidation potential for indene is reported as +1.66 V *vs.* SCE[13] and the reduction potential for 2,2,2-trifluoro acetophenone is −1.40 V *vs.* SCE,[14] which are both outside the window for electron transfer with the excited state photocatalyst.

We conclude, therefore, that this reaction is enabled by selective Dexter energy transfer from the excited state of photocatalyst **6*** to the alkene reaction component when its triplet energy is lower than that of its carbonyl reaction partner. When the electronic properties of the reactants are appropriately matched, the rate at which the triplet-state alkene reacts with the closed-shell carbonyl compound can outcompete the propensity of the alkene to undergo unproductive dimerization (Fig. 5C). At present,

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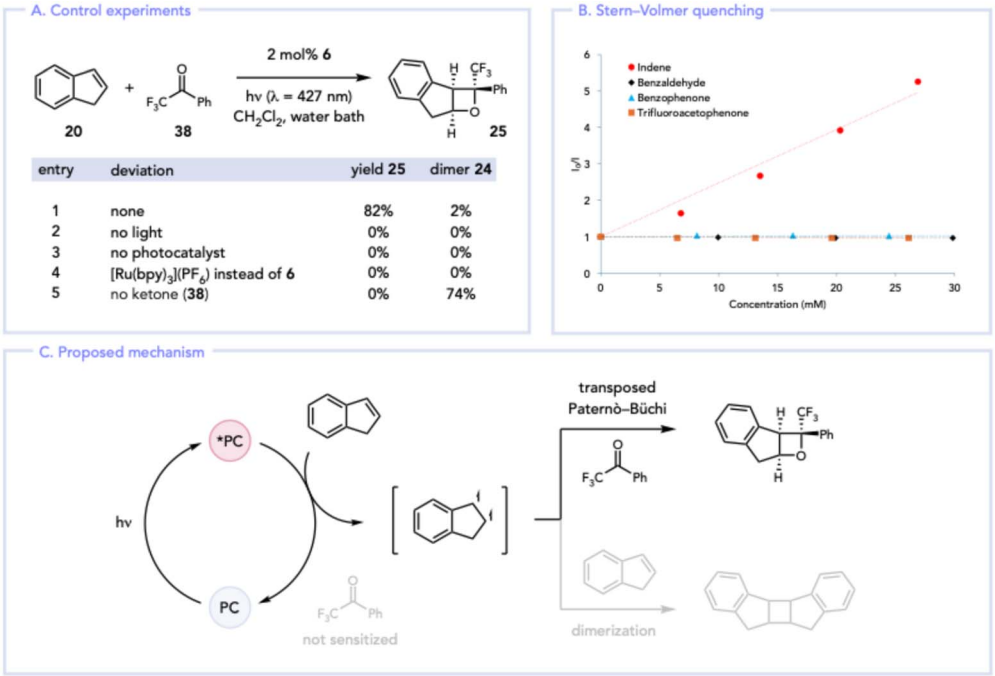

Fig. 5 Mechanistic studies for the transposed Paternò–Büchi reaction. (A) Control experiments. (B) Stern–Volmer quenching studies. (C) Proposed mechanism.

there is insufficient evidence to conclusively implicate a stepwise diradical mechanism similar to that of other triplet-state cycloaddition reactions. However, the thermodynamically favored diastereomer generally seems preferred, which could be consistent with reaction through an interconverting population of 1,4-diradical conformers. Further clarification of the cycloaddition mechanism remains of interest.

Conclusions

Triplet sensitization offers a strategy to study the relatively uninvestigated "transposed" variant of the synthetically and historically significant Paternò–Büchi reaction. This approach relies upon the ability of an appropriately chosen photocatalyst to selectively undergo Dexter energy transfer to an alkene with a low triplet energy in preference to its carbonyl partner. An initial investigation of the synthetic capabilities of this method suggests that an appropriate electronic matching between a relatively electron-rich excited-state alkene and a relatively electron-deficient carbonyl compound results in rates that outcompete facile homodimerization of the alkene. These studies further indicate potential differences in its scope compared to the direct irradiation conditions typically employed for the conventional Paternò–Büchi reaction. Together, these studies justify further investigation into the mechanism of the transposed Paternò–Büchi reaction and its ability to expand the scope of structurally complex oxetanes that are readily available by photochemical synthesis.

Author contributions

JBK and TPY conceptualized this work. TAF, OAS, and JBK designed and performed the experiments. TPY supervised the research and acquired funding. All authors contributed to the writing and editing of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: details of experimental procedures, full characterization data, and spectroscopic data. See DOI: **https://doi.org/10.1039/d5sc07826a**.

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