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**Citation for published version:**

Zuo, W-F, Liu, Q, Xie, X, Pang, Q, Li, W, Peng, C, Li, X & Han, B 2023, 'Lighting the way to diverse cyclic architectures: expanding the horizons with photogenerated ketenes in sustainable chemistry', *Organic Chemistry Frontiers*. <https://doi.org/10.1039/D3QO00831B>

**Digital Object Identifier (DOI):**

[10.1039/D3QO00831B](https://doi.org/10.1039/D3QO00831B)

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Peer reviewed version

**Published In:**

Organic Chemistry Frontiers

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# Lighting the Way to Diverse Cyclic Architectures: Expanding the Horizons with Photogenerated Ketenes in Sustainable Chemistry

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Received 00th January 20xx,  
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Light is a fundamental energy source that has considerably driven scientific progress, especially in the fields of synthetic chemistry and pharmaceuticals. Visible-light-mediated synthetic chemistry has revolutionized conventional bond formation and enabled previously inaccessible chemical processes under mild conditions. However, the continuous consumption of photocatalysts and corresponding additives has led to system complexity and cost escalation, making the development of photoactivated substrates a promising yet challenging research frontier. Recently, the emerging photogenerated ketenes as a potent class of organic compounds has provided a promising solution to the challenges associated with classic ketene preparation and application, with reduced preparative costs and simplified processes. This review highlights how photogenerated ketenes have simplified and accelerated the synthesis of diverse cyclic architectures through [2 + n] cyclization reactions and complex natural products through Danheiser benzannulation. Significantly, their successful application in flow chemistry has demonstrated remarkable potential for industrialization. Despite challenges in terms of limited cyclic architectures, elusive mechanisms, and challenging chiral control, ongoing efforts investigating the chemical behaviors of photogenerated ketenes and exploring their potential applications hold promise for breakthrough discoveries possible, propelling the field forward sustainably.

## 1. Introduction

Ranging from cyanobacteria releasing oxygen through photosynthesis to higher organisms synthesizing vitamin D upon sunlight exposure, light, a fundamental and essential energy source, has profoundly shaped life's formation and evolution.<sup>1-3</sup> Harnessing this powerful energy source significantly drive scientific advancements, particularly in synthetic chemistry and pharmaceutical industry.<sup>4-6</sup> In recent years, visible-light-mediated synthetic chemistry has unlocked unconventional bond formation and elusive chemical processes under mild conditions.<sup>7-9</sup> However, this method often demands photocatalysts, increasing system complexity and costs due to the continuous consumption of precious metals and corresponding additives.<sup>10</sup> While organic photosensitizers present a cost-effective alternative, their lower redox properties and instability compromise prevalence.<sup>11</sup> Thus, the development of substrates capable of directly harnessing and converting light energy has become a promising yet challenging frontier.

Ketenes, a class of compounds with functional groups featuring cumulated dienes, display remarkable chemical reactivity owing to their electron-deficient *sp* hybrid carbons. This reactivity leads to the assembly of a variety of fascinating architectures.<sup>12</sup> Nevertheless, ketenes' instability, sensitivity to

water and oxygen, and dimerization propensity pose significant challenges. To propel ketenes' advancements and applications, innovative and robust strategies are urgently needed. One promising strategy is the Wolff rearrangement, discovered by Prof. Johann Ludwig Wolff in 1902, which converts  $\alpha$ -diazo ketones into ketenes.<sup>13</sup> Although  $\alpha$ -diazo ketones are unstable, they generate highly reactive ketene intermediates through rearrangement reactions under thermal or transition metal catalytic conditions.<sup>14-18</sup> Embracing sustainable chemistry principles, researchers have initiated exploring visible-light-mediated approaches to generate ketenes through sequential  $\alpha$ -diazo ketone photogeneration and Wolff rearrangement, which then directly take part in various chemical transformation.<sup>19-22</sup> Additionally, ketenes have been recognized as efficient synthons in [2 + n] cycloaddition sequence.<sup>23,24</sup> Since the comprehensive review of the past century of ketene chemistry by Thomas T. Tidwell, cycloaddition reactions involving photogenerated ketenes have garnered interest over the last two decades, offering novel, eco-friendly synthesis methods for constructing diverse heterocyclic architectures.<sup>12, 25, 26</sup> Regrettably, this significant research achievement remains inadequately documented and insufficiently scrutinized.

In this context, this review will emphasize on the versatile photogenerated ketenes, generated from Wolff rearrangement of  $\alpha$ -diazo ketones, which participate in various cyclization reactions, encompassing our contributions to this booming area. By appropriately organizing the existing literature according to photogenerated ketenes' reaction patterns and their applications in the synthesis of diverse heterocyclic molecules and intricate natural products as well as in the burgeoning field of flow chemistry, we aspire to highlight the significant research advancements within this field. A profound understanding of photoactivation in ketene-mediated

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cycloaddition reactions paves the way for the construction of a diverse array of valuable cyclic architectures, thereby expanding the boundaries of possibility in this fascinating realm of chemistry.

## 2. Photogenerated Ketenes and Their Role in Organic Synthesis

### 2.1 Characteristics and reaction patterns of photogenerated ketenes

In 1951, nearly fifty years after Hermann Staudinger's discovery of diphenylenones and Wolff's proposed rearrangement of diazo ketones, Horner reported the first photochemical production of ketenes, a discovery that greatly enhanced the enduring vitality of ketenes chemistry.<sup>27</sup> Since then, ketenes have been a key reaction intermediate in organic synthesis, with consistent high research interest from 2003 to the present, and an increasing trend in research on photogenerated ketenes, extending to various fields including chemistry, polymer science, and physics (Scheme 1a and 1b). Ketenes are characterized by an unusual 'heteroallenic' bond structure, which gives rise to their unique reactivity.<sup>28</sup> The ketene's highest occupied molecular orbital (HOMO) is located perpendicular to the plane of the ketene, while the lowest unoccupied molecular orbital (LUMO) is located within that plane (Scheme 1c). This orientation allows for a large negative charge on the oxygen and  $\beta$ -carbon, while a similarly large positive charge is placed on the  $\alpha$ -carbon. Photogenerated ketenes provide a simplified approach to the preparation of ketene intermediates while retaining the same reaction pattern diversity of ketenes, such as cycloaddition, nucleophilic  $S_N$  substitution and electrophilic addition. Of particularly, the use of photogenerated ketenes in the construction of various cyclic molecules is the most representative branch of research.

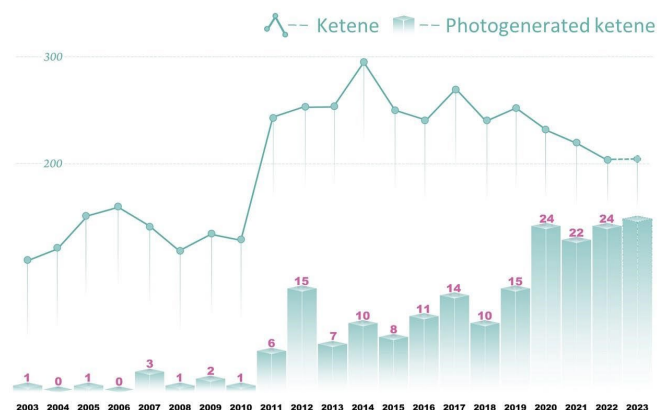
### 2.2 Photoactivation in Wolff rearrangement of $\alpha$ -diazo ketones

$\alpha$ -diazo ketones have emerged as one of indispensable reagents, owing to their facile synthesis and convenient preservation properties. Their structures, which encompass multiple resonance forms, display enhanced stability compared to conventional diazo compounds. This feature is attributable to the presence of an electron-withdrawing group at the  $\alpha$ -position, facilitating the delocalization of the negative charge from the carbene to the carbonyl group. While Wolff rearrangements have been extensively employed in Arndt-Eistert reactions and ring contraction methods, contemporary investigations persist in unveiling novel synthetic methodologies involving reactive ketenes.

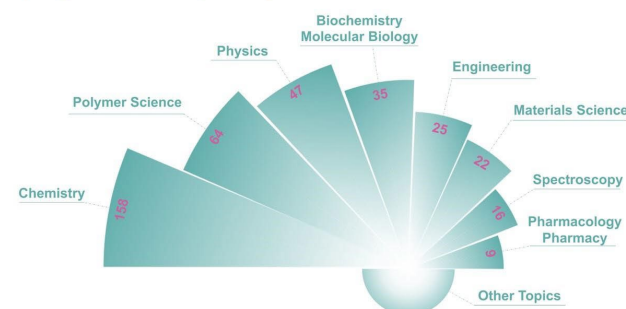
In contrast to conventional Wolff rearrangement reactions, which often necessitate heating or transition metal catalysis, visible-light-induced  $\alpha$ -diazo ketone rearrangement reactions provide a multitude of advantages, such as mild reaction conditions, environmentally benign and non-toxic characteristics, and the release of nitrogen gas as the sole by-product. These reactions yield highly reactive ketene species **I** through alkyl 1,2-migration of carbene intermediates, which

can be harnessed for various synthetic applications, without addition of extra photocatalysts or photosensitizers (Scheme 1c). Although the mechanistic underpinnings of the Wolff rearrangement remain a topic of considerable debate due to the interplay between synergistic and stepwise pathways, a preponderance of evidence suggests that light-induced ketene formation favours a stepwise process, during which the presence of an acyl carbene can be detected.<sup>29–32</sup>

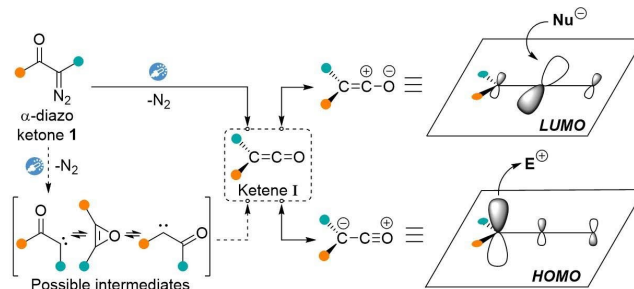
#### a) Research on ketene chemistry



#### b) Application of photogenerated ketene



#### c) Mechanism and structure of ketene



Scheme 1. a) Number of papers published on Web of Science per year from 2003 to present for response queries (ketenes) vs. (ketenes and (light or photo)). b) Analysis of the number of articles per year on Web of Science for response queries (ketenes and (light or photo)) in various research areas from 2003 to present. c) The frontier molecular orbitals of ketene and the conversion of  $\alpha$ -diazo ketones to ketenes under photochemical conditions.

## 3. Photogenerated Ketenes Facilitating Diverse Cyclic Architectures Assembly

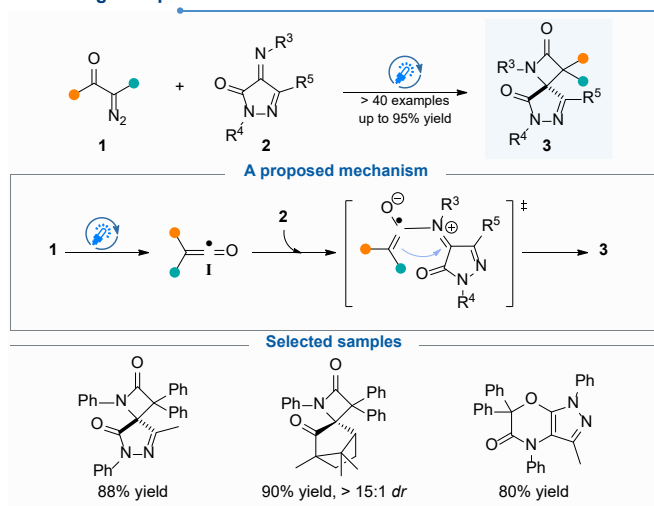
Photogenerated ketenes have emerged as a promising alternative to classical ketenes, due to the limitations associated with the latter's

preparation and preservation. Cycloaddition, a critical aspect of ketene chemistry, has been hindered by harsh preparation conditions and instability. To address this challenge, the use of photogenerated ketenes from  $\alpha$ -diazo ketone rearrangements as highly reactive intermediates has gained traction as a more direct and modest strategy for constructing valuable modules. The following sections will present significant and relevant cases demonstrating the potential of photogenerated ketenes in advancing the field of cycloaddition.

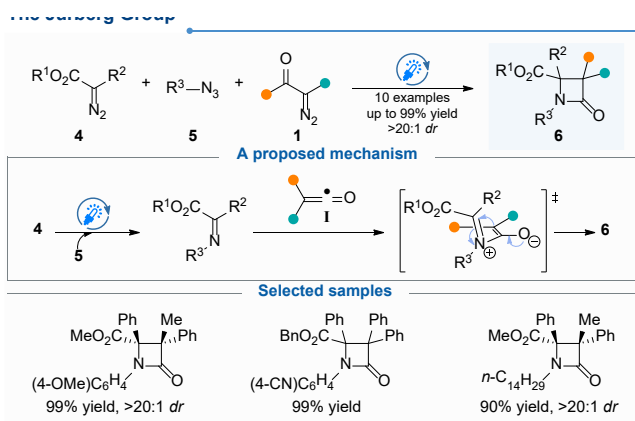
### 3.1 Elegant strategies towards valuable $\beta$ -lactams

The synthesis of valuable  $\beta$ -lactams via ketene-mediated [2 + 2] cyclization reactions is a crucial pathway in organic synthesis. In 2022, our group established a visible-light-mediated sequential reaction strategy that combines Wolff rearrangement with Staudinger cyclization, using *in situ* generated ketenes **I** and pyrazolone ketimines **2** to create valuable spiro-pyrazolone- $\beta$ -lactams **3** (Scheme 2).<sup>33</sup> This approach offers a reliable solution for synthesizing spiro-pyrazolone- $\beta$ -lactams with high yields, excellent substrate tolerance, and gram-scale production while providing direct access to multisubstituted pyrazole-morpholine skeletons. Optimization of the reaction conditions revealed that the wavelength of visible-light plays a critical role in enhancing reaction rates, and controlled experiments demonstrated the importance of visible-light-mediated irradiation in cyclization. Furthermore, a plausible mechanism was suggested to explain the observed efficiency.

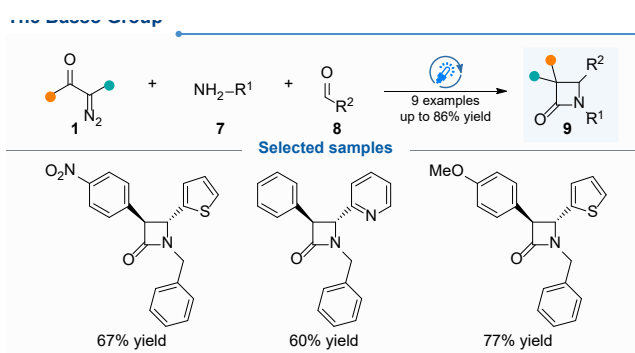
Prior to our work above, Igor D. Jurberg and colleagues proposed an innovative strategy for the visible-light-mediated synthesis of  $\beta$ -lactams from aryl diazoacetate **4** (Scheme 3).<sup>34</sup> This process begins with the photolysis-generated free carbene intermediate, which reacts with azide **5** to form an imine.



Scheme 2. Photogenerated ketenes undergo Wolff rearrangement and Staudinger cycloaddition with pyrazolone ketimines to construct spiro-pyrazolone- $\beta$ -lactams.



Scheme 3. Visible-light-mediated strategies employing photogenerated ketenes and aryl diazoacetates for the synthesis of multi-substituted  $\beta$ -lactams.



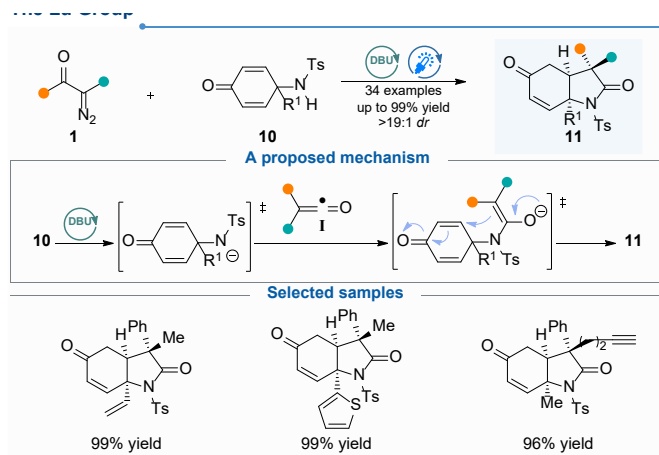
Scheme 4. Three-component reaction of photogenerated ketenes, aldehydes, and amines leading to the synthesis of  $\beta$ -lactams.

Subsequently, the imine undergoes a sequential reaction with a photochemically promoted ketene intermediates **I** to yield  $\beta$ -lactams **6**. Remarkably, this novel approach obviates the need for rigorous water removal and air isolation, rendering it more cost-effective than metal-catalyzed or thermally promoted alternatives.

Historically, the Staudinger reaction has faced challenges in developing three-component reactions between ketenes, amines, and carbonyl derivatives, primarily due to the intrinsic reactivity between ketenes and amines, as well as the typical ketene precursor chlorides. To address this issue, Basso's group introduced the first three-component Staudinger reaction involving amines **7**, aldehydes **8**, and  $\alpha$ -diazo ketones **1** (Scheme 4).<sup>35</sup> The key to the success of this reaction is the excess aldehyde, which expedites amine consumption and drives the imine formation equilibrium, while the diazonium remains inert to the aldehyde. Although the isolated yield of this innovative one-pot reaction is lower than that of the reaction with a preformed imine likely due to incomplete imine formation, its synthetic simplicity and amenability to automated production compensate for this drawback.

### 3.2 Advancements in accessing five-membered architectures

Blue light-mediated protocols that utilize ketenes with various substrates and catalytic modes have proven to be useful in constructing biological structures. Hydroindoles, a distinct class of scaffolds, are ubiquitously found in various natural products and synthetic pharmaceuticals. In 2021, the Lu group reported

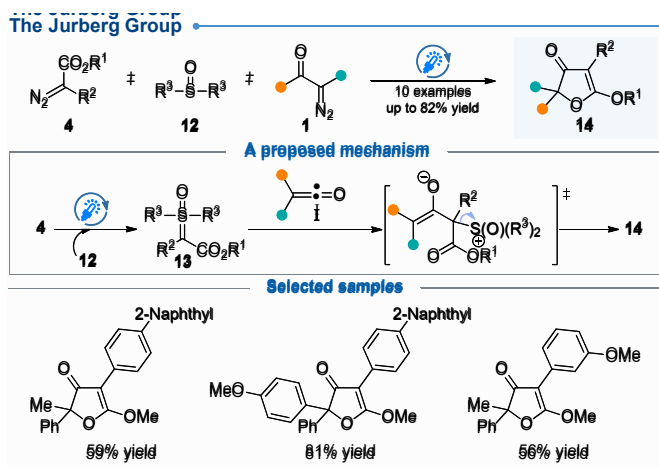


Scheme 5. Desymmetric [3 + 2] cycloaddition reaction of para-quinamines with photogenerated ketenes for synthesizing hydroindoles.

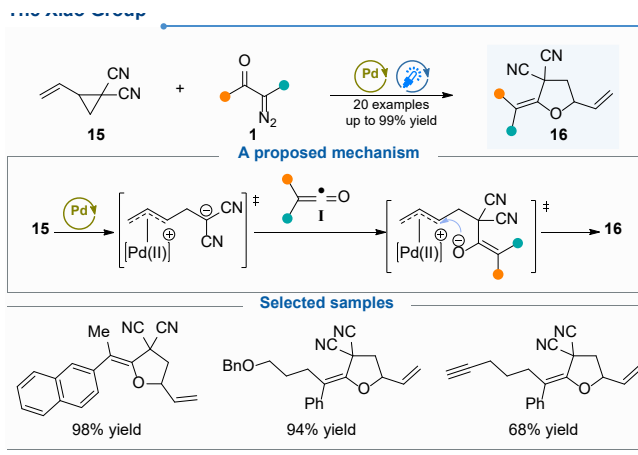
an unprecedented method for synthesizing hydroindoles **11** via DBU-catalyzed desymmetric [2 + 3] cycloaddition reactions between photogenerated ketenes **I** from  $\alpha$ -diazo ketones **1** and para-quinolines **10** (Scheme 5).<sup>36</sup> The synthetic strategy initiated with a nucleophilic attack of para-quinolines on photogenerated ketenes following deprotonation, ultimately yielding a range of hydroindoles with all-quaternary carbon centers and near-complete diastereo-selectivity.

In the same year, Igor D. Jurberg's group described a blue light-mediated reaction of aryl diazoacetate **4** with sulfoxide **12**, producing corresponding sulfoxonium ylides **13**. Subsequent reactions with photogenerated ketenes **I** generated 5-alkoxy-2,2,4-trisubstituted furan-3(2H)-ones **14** (Scheme 6).<sup>34</sup> This innovative synthetic strategy originates from an aryl diazoacetate precursor and allows for the direct preparation of valuable intermediates such as sulfoxonium ylides and hydrogenated furanones, potentially broadening its applicability in fields like organic synthesis.

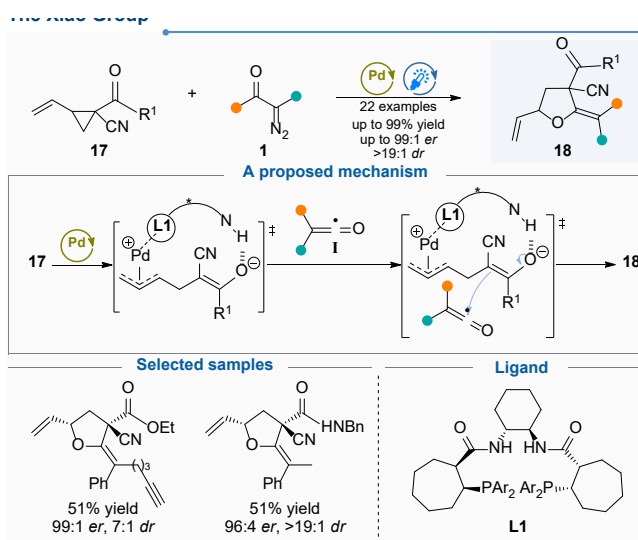
Although recent advancements have identified ketenes as promising C2 synthons for [2 + n] cyclization reactions, in a rare number of cases, [2 + 3] cyclization reactions have unexpectedly involved C=O rather than C=C. In 2019, the Xiao group introduced a novel sequential [2 + 3] cycloaddition reaction of



Scheme 6. Visible-light-mediated strategies for assembling multi-substituted furan-3(2H)-ones using aryl diazoacetates and arylsulfoxides.



Scheme 7. Synthesis of tetrahydrofurans through a light-induced Wolff rearrangement/Pd-catalyzed [3 + 2] cycloaddition sequence.



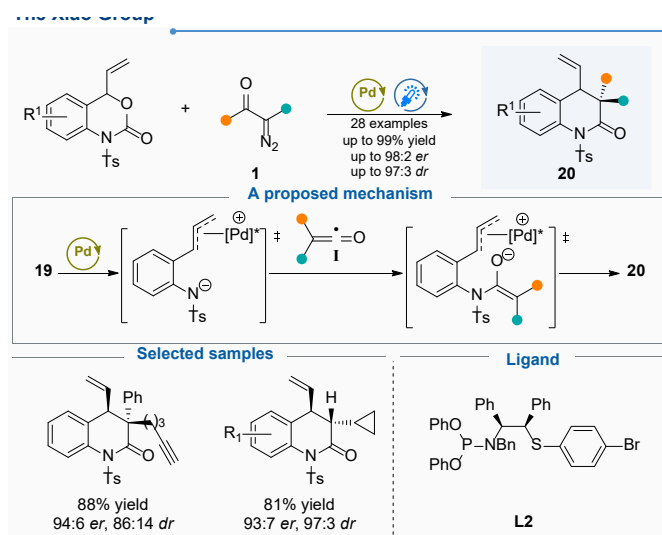
Scheme 8. Pd-catalyzed asymmetric [2 + 3] cycloaddition of photogenerated ketenes with D-A cyclopropanes.

ketenes **I** and vinyl cyclopropanes (VCPs) **15** utilizing a photogenerated/palladium-catalyzed synergistic mode (Scheme 7).<sup>37</sup> During ring closure, the anticipated C-allyl alkylation was unexpectedly superseded by selective O-allyl alkylation, culminating in the formation of highly functionalized tetrahydrofuran structures **16** via [2 + 3] cycloaddition pathway involving C=O. However, attempts to asymmetric variants yielded only moderate enantiomeric induction (75:25 er).

This limitation was removed in a further protocol. Alternative VCPs **17** bearing two disparate electron-withdrawing groups achieved this highly diastereoselective and asymmetric [2 + 3] cycloaddition reaction, delivering a promising chiral tetrahydrofuran backbone **18** (Scheme 8).<sup>38</sup> Mechanistic studies have shown that remote stereospecific substrate induction via hydrogen bonding of the chiral ligand is crucial for success.

### 3.3 Advancements in accessing diverse six-membered heterocycles

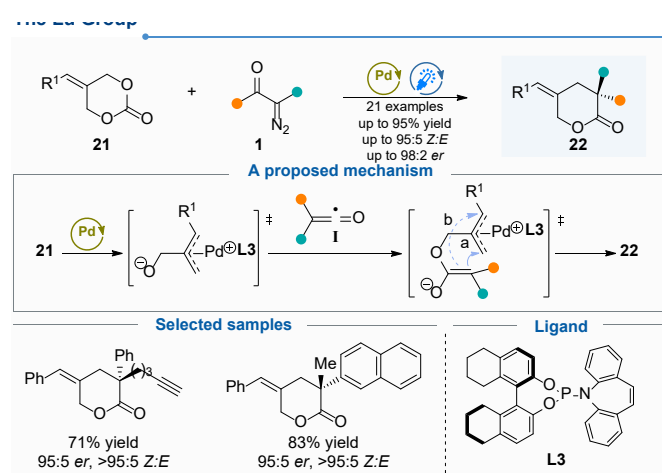
Similarly, the catalytic asymmetric cycloaddition of photogenerated ketene intermediates **I** presents a novel approach for synthesizing six-membered chiral heterocyclic molecules. As early as 2017, the Xiao group successfully



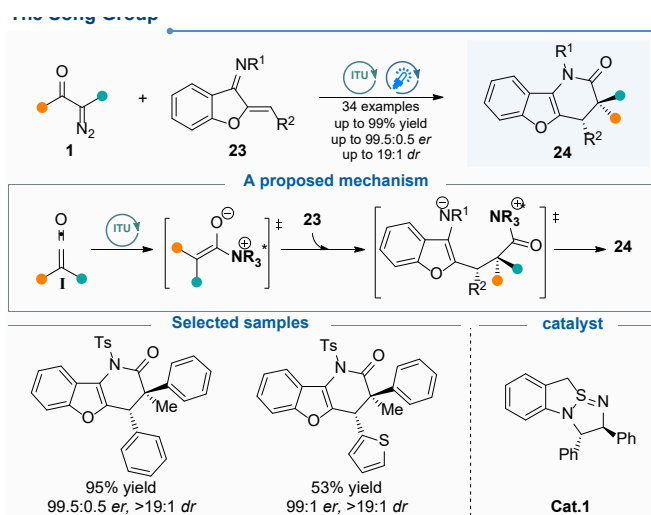
Scheme 9. Enantioselective [2 + 4] cycloadditions of photogenerated ketenes and vinyl benzoxazinones via sequential photoactivation and palladium catalysis.

developed a light-induced Wolff rearrangement/palladium-catalyzed asymmetric [2 + 4] cycloaddition sequential strategy for producing diverse chiral quinolones **20** (Scheme 9).<sup>39</sup> The reaction employed only visible light as a clean reagent and energy source, releasing non-toxic nitrogen. Notably, the photolytic Wolff rearrangement of  $\alpha$ -diazo ketones which can generate ketenes without traces under mild conditions, has addressed compatibility issues between ketenes and their preparation processes with transition metals. On one hand, ketenes, being highly electron-deficient species, may be sensitive to low-valent transition metals, leading to decarbonylation and aggregation.<sup>40-42</sup> On the other hand, the reactive acyl chloride in the process of synthesizing ketenes using acyl chloride and amine may impede the transition metal-catalyzed organic transformations.<sup>43</sup>

In another protocol, photogenerated ketenes **I** facilitated the construction of structurally unique oxygen-containing heterocycles through a compatible mode (Scheme 10).<sup>44</sup> The rapid capture of the oxygen-1,4-dipole, generated *in situ* from 2-alkylidenemethylenecarbonate **21** under Pd catalysis, by the ketenes **I** produces highly functionalized chiral lactone



Scheme 10. Enantioselective [2 + 4] cycloaddition of photogenerated ketenes and oxo-1,4-dipoles.

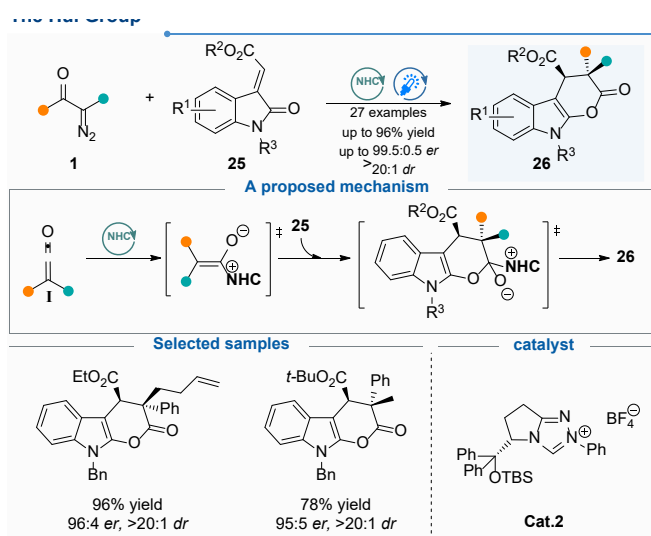


Scheme 11. Enantioselective [2 + 4] cyclization of photogenerated ketenes with azadienes by sequential photoactivation/isothioureacatalysis.

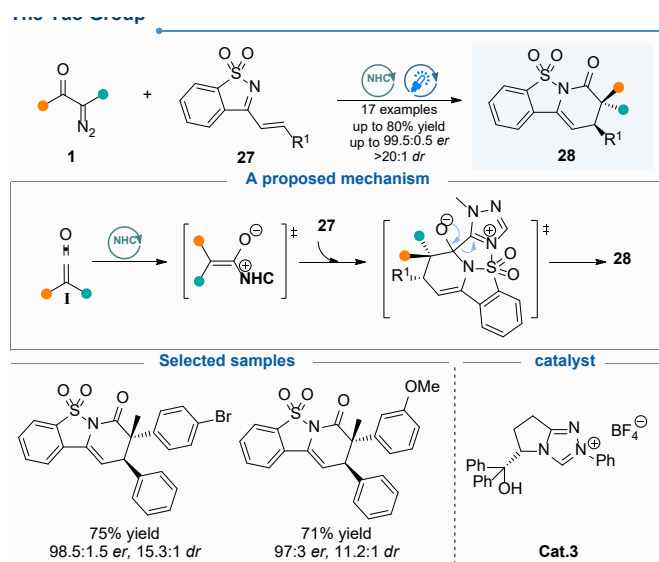
skeletons **22** containing quaternary carbon stereocenters with high reaction efficiency and selectivity. This constitutes another vital example of the combined strategy of visible-light induction and transition metal catalysis in chiral heterocycle construction.

Synergistic catalysis of photoactivation and organocatalytic strategies using ketenes remains a significant challenge, as few examples combine photoactivation with organocatalysis for establishing ketene chiral environments.<sup>45, 46</sup> In 2019, Song's group integrated Wolff rearrangement and isothioureacatalyzed sequential reactions, developing an effective strategy for allowing stereocontrol of all-carbon quaternary centers (Scheme 11).<sup>47</sup> The C1-ammonium enolates produced by photogenerated ketenes **I** in the presence of isothioureacatalyst **Cat.1** were delivered with auronederived  $\alpha,\beta$ -unsaturated imine **23** to benzofurane-fused dihydropyridinone derivatives **24** with high enantio- and diastereo-selectivity.

Similarly, N-heterocyclic carbene (NHC)-catalyzed synthesis is also an efficient method for forming enolate intermediates. In 2020, Hui's group first disclosed an elegant strategy for synthesizing tetrahydropyrano[2,3-b]indoles **26** through



Scheme 12. Stereoselective [2 + 4] cycloaddition of photogenerated ketenes and 3-alkylloxindoles.

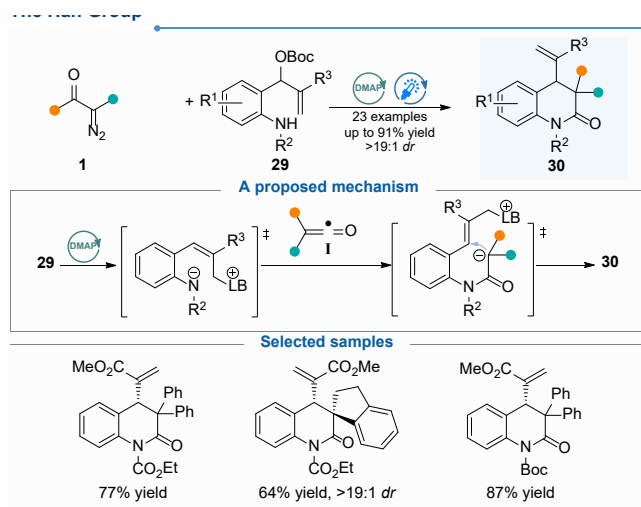


Scheme 13. Asymmetric [2 + 4] annulation of photogenerated ketenes and saccharine-derived azadienes.

sequential Wolff rearrangement and NHC catalysis between  $\alpha$ -diazo ketones **1** and 3-alkylidene-indole substrates **25** (Scheme 12).<sup>48</sup> Photogenerated ketenes from  $\alpha$ -diazo ketones bind to NHC, forming enolate intermediates with a chiral environment and participate in subsequent cyclization reactions, ultimately preparing functionalized indole derivatives. Products featuring all-carbon-quaternary stereocenters were obtained in good yields, enantioselective and diastereoselective manners.

In a subsequent study by Yao's group, chiral dihydropyridones containing sulfonamide structures **28** were prepared via photogenerated ketenes **I** and saccharine-derived azadienes **27**, employing the same reaction pattern as Hui's group (Scheme 13).<sup>49</sup> This protocol exhibited mild reaction conditions, satisfactory enantio- and diastereo-selectivity. Furthermore, a catalyst-free version was also disclosed in their work, providing products with high yield and excellent diastereoselectivity.<sup>50</sup>

Building on previous research in organocatalysis<sup>51</sup> and

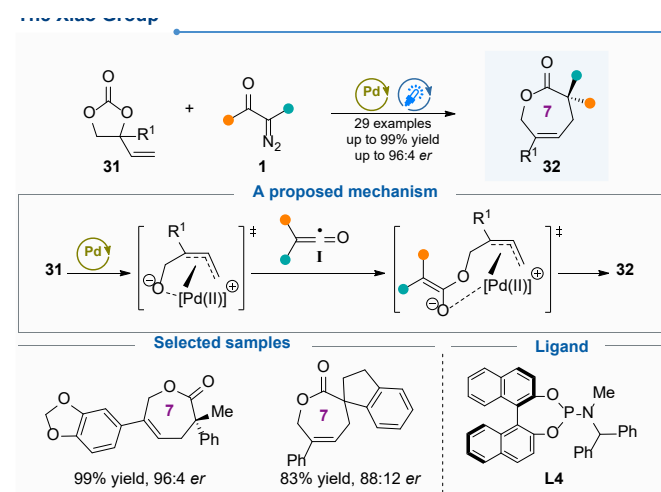


Scheme 14. A synergistic [2 + 4] cyclization strategy between photogenerated ketenes and *ortho*-amino MBH carbonates.

continued interest in medicinal chemistry<sup>52</sup>, our group recently reported a synergistic catalytic mode that combines photolysis and Lewis base catalysis using photogenerated ketenes **I** and *ortho*-amino MBH carbonates **29** to access multifunctional dihydroquinolinone frameworks **30** (Scheme 14).<sup>53</sup> Although an attempt at an asymmetric version did not yield satisfactory results, this powerful [2 + 4] cyclization approach further extends the application of photogenerated ketenes in photo/organocatalytic modes.

### 3.4 Ambitious Attempts to Achieve Medium-Sized Architectures

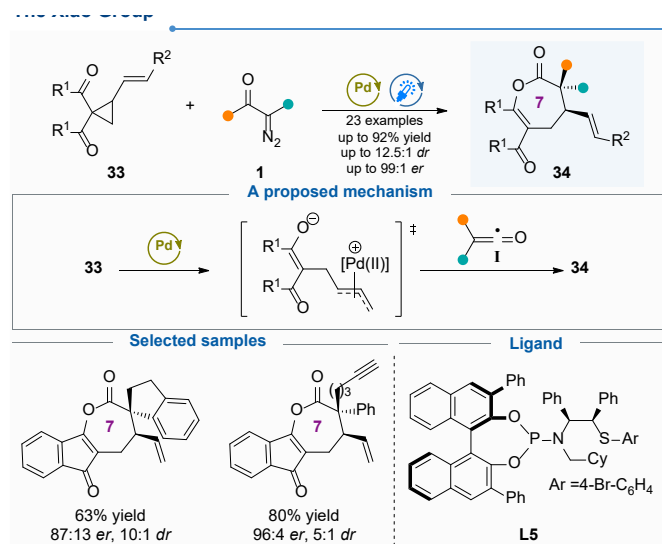
Medium-sized heterocycles are present in numerous biologically active natural products and synthetic molecules with essential medicinal properties. Developing elegant synthetic strategies for constructing these valuable molecules has been a challenging task in organic chemistry. The Xiao group disclosed a protocol for the enantioselective [2 + 5] cycloaddition of vinylidene carbonate **31** and  $\alpha$ -diazo ketones **1**, enabling the synthesis of various seven-membered lactones **32** with challenging chiral quaternary stereocenters through enantioselective capture of palladium-containing 1,5-dipole intermediates by photogenerated ketenes **I** (Scheme 15).<sup>54</sup>



Scheme 15. Enantioselective capture of 1,5-dipoles by photogenerated ketenes for the construction of seven-membered lactones.

Distinct from all-carbon 1,3-dipoles, the reactivity of palladium-catalyzed VCP can be converted to oxygen-1,5-dipoles to achieve the construction of many oxygen-containing heterocycles. The Xiao group described the asymmetric [2 + 5] cycloaddition reaction of VCPs **33** with photogenerated ketenes **I** to highly functionalized seven-membered lactones **34** under palladium-catalyzed/light-driven conditions (Scheme 16).<sup>55</sup> This protocol overcame the extremely challenging chemo- and periselectivities. This reactive transformation illustrated in this work also highlights the potential of photogenerated ketenes **I** for synthesizing these challenging intermediate-sized rings.

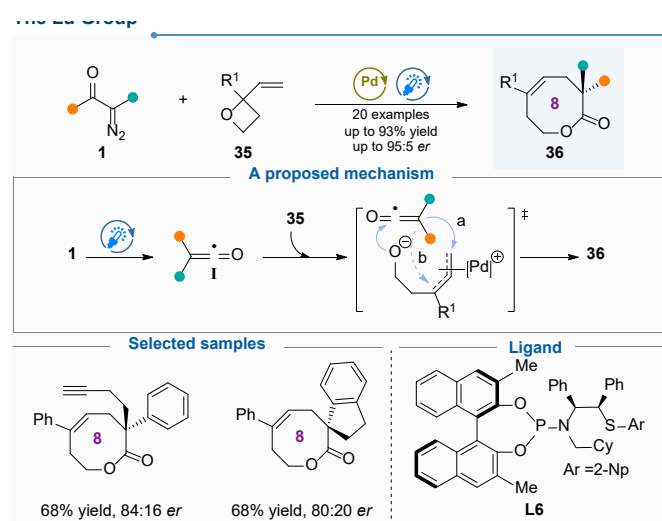
Turning our attention to more formidable scaffolds is essential due to their unique biological effects and practical value as multifunctional intermediates. Despite unfavourable entropic factors and transannular interactions that have limited synthetic strategies for these scaffolds, some breakthroughs



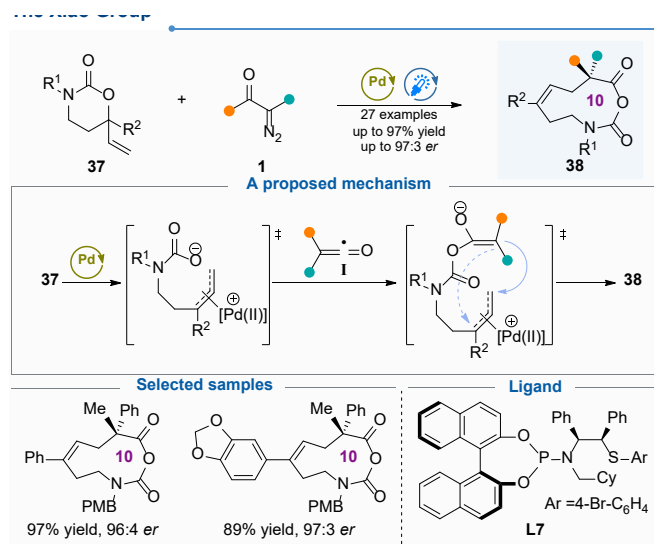
Scheme 16. Asymmetric [2 + 5] dipole cycloaddition of photogenerated ketenes with vinylcyclopropanes.

have been achieved. For instance, the Lu group ingeniously reported the asymmetric [2 + 6] dipole cyclization of photogenerated ketenes **I** and vinyl oxetanes **35** to directly access these valuable chiral eight-membered lactone-containing scaffolds **36** (Scheme 17).<sup>56</sup> The palladium-containing 1,6-dipole undergoes nucleophilic addition to the photogenerated ketenes **I**, forming important zwitterionic intermediates. Subsequent intramolecular asymmetric allylic alkylation smoothly yields a series of eight-membered compounds containing all-carbon quaternary stereocenters.

In another study, the Xiao group disclosed a [2 + 8] higher order cycloaddition reaction between vinyl carbamates **37** and  $\alpha$ -diazo ketones **1**, which goes beyond the traditional photoinduced/palladium-catalyzed synergistic process (Scheme 18).<sup>57</sup> The multifunctional precursor **37** retains its CO<sub>2</sub> under palladium catalysis, generating unusual 1,8-dipoles. The enantioselective capture of the carbonate anion by the photogenerated ketenes **I** and subsequent intramolecular allylation provided the desired ten-membered monocyclic



Scheme 17. Asymmetric [2 + 6] dipolar annulation to construct enantioenriched eight-membered lactones.



Scheme 18. Asymmetric [2 + 8] dipolar cycloadditions of photogenerated ketenes and vinyl carbamates constructing ten-membered monocyclic architectures.

product **38**. This protocol successfully overcame the challenging high stereo-, chemo-, and peri-selectivities.

Represented an important branch of ketene chemistry, photogenerated ketenes have captured the attention of organic chemists due to their fascinating properties. Through sustained efforts, significant advances have been achieved, resulting in valuable strategies that not only expand the establishment of ketene methodology but also extend its application to the transformation of complex natural products and bioactive molecules, as described in the following section.

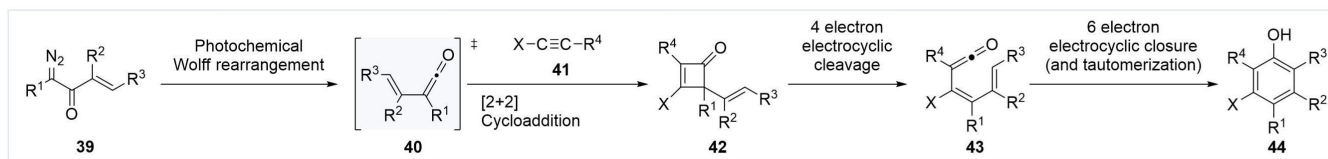
#### 4. Unleashing Photogenerated Ketenes' Potential in Complex Natural Product Synthesis

The Danheiser benzannulation is a crucial method in which photogenerated ketenes from  $\alpha$ -diazo ketones are utilized in the construction of highly functionalized complex molecules (Scheme 19a).<sup>58</sup> Typically, unsaturated  $\alpha$ -diazo ketones **39** undergo Wolff rearrangement under photochemical conditions to generate the corresponding ketene intermediate **40**, which is then captured by ketenophilic acetylene **41** to form a cyclobutenone derivative **42**. This intermediate then undergoes sequential 4 $\pi$  electrocyclic cleavage, 6 $\pi$  electrocyclic closure, and tautomerization to yield the multisubstituted phenol conformation **44**.

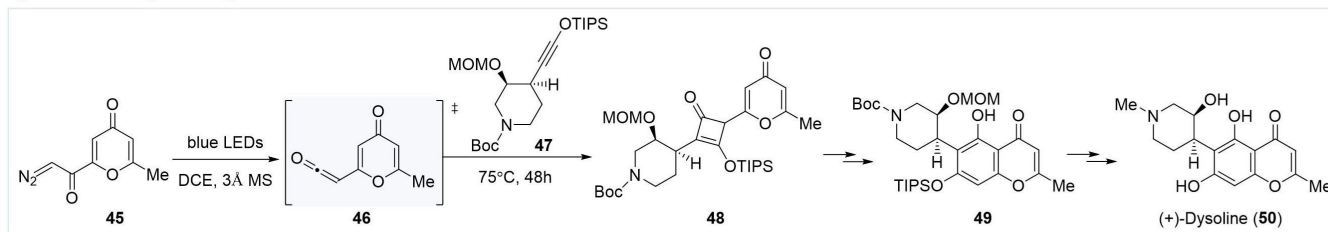
Ready and colleagues used this benzannulation strategy employing photogenerated ketenes to achieve the enantioselective synthesis of the chromone alkaloid (+)-Dysoline (**50**), a natural product containing polysubstituted benzenes (Scheme 19b).<sup>59</sup> Irradiation of the unsaturated diazo ketone **45** with blue LED generated the ketene intermediate **46**, which underwent selective [2 + 2] cycloaddition with the alkynyl ether **47** to produce the important cyclobutenone intermediate **48**. The key benzannulation product **49** was obtained after ring cleavage, electrocyclic closure, and aromatisation. Ultimately, the enantioselective synthesis of alkaloid **50**, which is selectively



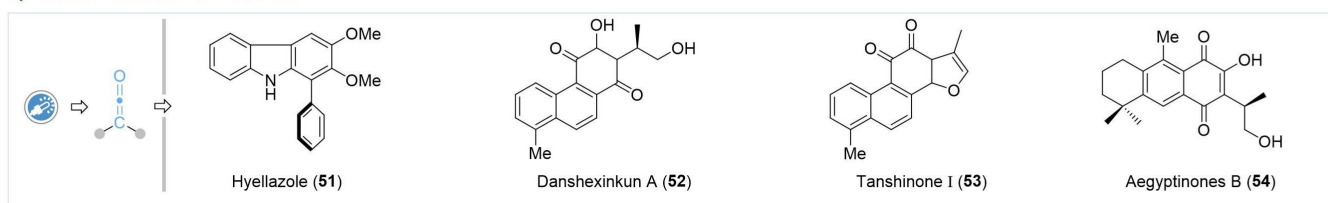
## a) The Danheiser Group



## b) The Ready Group



## c) Other Research Cases



Scheme 19. a) General process of Danheiser benzannulation involving photogenerated ketenes. b) Selective synthesis of (+)-Dysoline using a Danheiser benzannulation with photogenerated ketenes. c) Several natural products are synthesized utilizing Danheiser benzannulation involving photogenerated ketenes.

cytotoxic to HT1080 fibrosarcoma cells ( $IC_{50}$  of 0.21  $\mu$ M), was completed after subsequent transformations.

Moreover, this innovative benzannulation strategy has been successfully applied to the synthesis of various complex natural products containing polysubstituted benzenes such as Hyellazole (**51**), Danshexinkun A (**52**), Tanshinone I (**53**), and Aegyptinones B (**54**), demonstrating its utility in constructing highly functionalized complex molecules (Scheme 19c).<sup>58, 60, 61</sup>

Overall, this photochemical methodology offers remarkable advantages over traditional  $\alpha$ -diazo ketone-to-ketene conversion for the synthesis of natural products. By adopting milder and more environmentally friendly conditions, it differentiates itself from classical cyclization methods, avoiding harsh conditions such as high temperature. Additionally, this state-of-the-art approach enables the synthesis of complex polycyclic aromatic hydrocarbons and heteroaromatic systems frequently found in complex bioactive molecules, which are unattainable using the original version of this annulation strategy. Importantly, the photochemical method provides access to a broad spectrum of substituted ketenes, originating from a wide variety of carbonyl precursors, thereby expanding the possibilities for functionalizing products and advancing their potential applications in the pharmaceutical industry.

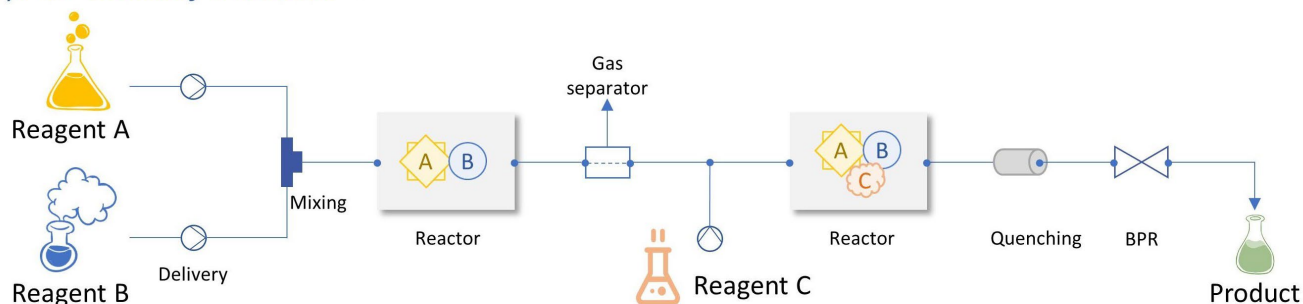
## 5. Expanding Applications of Photogenerated Ketenes in Flow Chemistry

The utilization of light as a green and traceless energy source is a captivating aspect of photochemistry. Over the past decade,

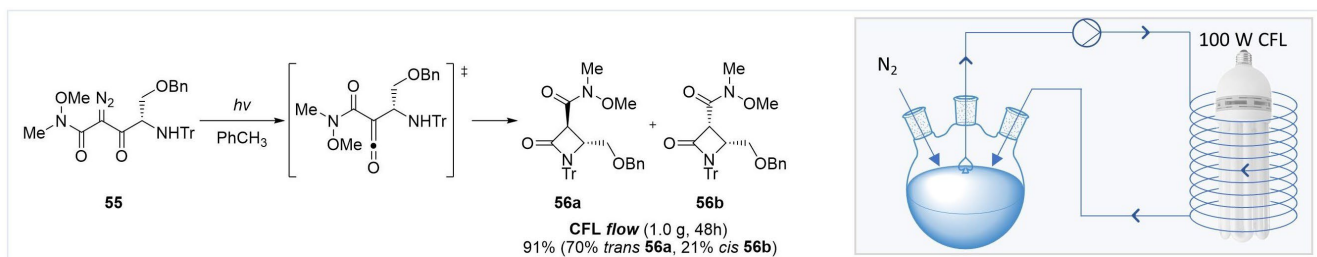
the development of light as a sustainable chemical tool has been rapid due to the mild photoreaction conditions. Visible-light-dependent photochemical reactions require adequate exposure to ensure comprehensive reaction progression. However, the attenuation effect of photon transport (Bouguer–Lambert–Beer law) considerably hinders the implementation of these strategies on large scales.<sup>62</sup> Specifically, incomplete reactions, unexpected by-products, and complex purification processes can arise due to insufficient or excessive irradiation. Thus, new technologies or strategies are urgently required to overcome these issues.

Flow chemistry, acclaimed as one of the top ten emerging technologies in chemistry by the International Union of Pure and Applied Chemistry (IUPAC), has gained substantial recognition within the pharmaceutical industry (Scheme 20a).<sup>63–66</sup> The narrow inner diameter and the higher surface-to-volume ratio of the microreactor in flow chemistry provide photochemical reagents with a more uniform and sufficient opportunity for irradiation, resulting in shorter reaction times, fewer by-products, and higher yields. Moreover, scale-up reaction can be smoothly achieved by merely accelerating the flow rate and extending reaction time. The narrow reaction space of the microreactor prevents the accumulation of hazardous substances, addressing the safety issues in large-scale reaction processes. Incorporating microfluidics, lab-on-a-chip devices, real-time online detection, and other cutting-edge tools promotes the development of miniaturized and intelligent flow chemistry systems, which marks a new era for continuous reaction production processes in the pharmaceutical industry. Therefore, the integration of photochemistry and flow

## a) Flow chemistry illustration

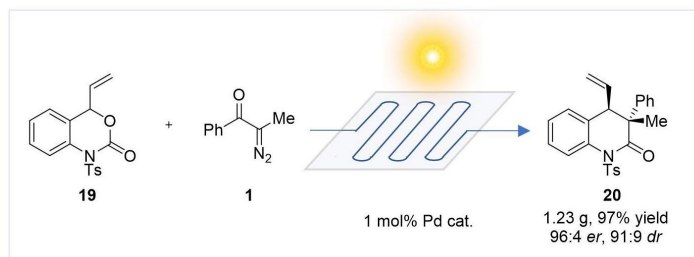
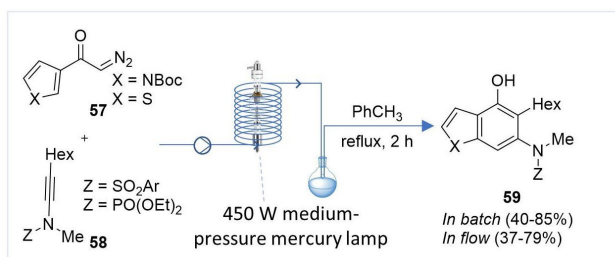


## b) The Konopelski Group



## c) The Danheiser Group

## d) The Xiao Group



Scheme 20. a) General processes of flow chemistry. b) Preparation of valuable  $\beta$ -Lactams from continuous flow photolysis using CFL. c) Synthesis of polycyclic and heterocyclic aromatic hydrocarbons by reaction of Ynamides and photogenerated ketenes in a flow chemistry system. d) Sunlight-driven gram-scale preparation of products in flow chemistry systems. BPR, Back Pressure Regulators; CFL, Compact Fluorescent Light.

chemistry has emerged as a burgeoning trend, and recent cases, including the successful synthesis of ibuprofen, have validated the feasibility of photochemical pharmaceuticals in flow chemistry.<sup>62, 67-69</sup>

As known, photogenerated ketenes originating from  $\alpha$ -diazo ketones have demonstrated compatibility with flow chemical systems. Basso et al. have demonstrated that the productivity of photogenerated ketene-based reaction has been significantly improved under continuous flow conditions compared to batch processes.<sup>70</sup> Additionally, the explosive nature of diazo compounds makes it challenging to use them on a large scale in conventional batch reactions. Factors such as sufficient light radiation and safety must be taken into account. From this perspective, flow chemistry is undoubtedly one of the most suitable options. Significantly, the continuous release of the precursor  $\alpha$ -diazo ketone to the ketenes under photochemical conditions maintains a low concentration of the ketene intermediates, thus avoiding their dimerization. Several pioneer works have been reported that demonstrate the potential of photogenerated ketenes in this field.

As early as in 2010, Konopelski and colleagues reported a ground-breaking achievement using photogenerated ketenes in

a continuous flow system (Scheme 20b).<sup>71</sup> The team successfully prepared  $\beta$ -lactams **56**, a promising class of medicinal compounds, through the Wolff rearrangement and intramolecular ring closure of  $\alpha$ -diazo- $\beta$ -ketoamides **55**. The narrow inner diameter of the flow tube and the efficient light transmission properties played a crucial role in ensuring the smooth and efficient progression of the reaction. The 100 W compact fluorescent light offers a safe and environmentally friendly photochemical solution and does not require additional cooling. This improved protocol significantly reduces the reaction time, with the reaction completed in 48 hours on a 1 g scale (compared to 0.1 g, 18 hours for the batch process). This breakthrough represents a significant step forward in applying photogenerated ketenes in flow chemistry and demonstrates their potential for industrialization.

Later, Rick L. Danheiser's group documented the cyclization of the precursor of photogenerated ketenes,  $\alpha$ -diazo ketones **57**, with various reaction partners **58**, including N-phosphonoalkynylamine and N-sulfoalkynylamine, in flow photochemistry (Scheme 20c).<sup>72</sup> This process generated a range of heterocyclic structures **59**, such as polysubstituted indoles and benzothiophenes. Although the yield in the continuous-

flow FEP coiled reactor was not significantly improved, the greatly reduced reaction time (from 50 hours to 33 minutes) ensured that the reaction proceeded efficiently and protected the functional groups from photolysis, thus making direct scale-up possible. Following this work, the Xiao group conducted a comprehensive investigation of the combined utility of an asymmetric [2 + 4] cycloaddition reaction involving  $\alpha$ -diazo ketones **1** and vinyl benzoxazinones **19**, attaining promising results (Scheme 20d).<sup>39</sup> This approach enabled gram-scale preparation under flow chemistry conditions, utilizing sunlight directly as the light source and yielding chiral quinolinones **20** with significantly reduced catalyst loading (down to 1 mol%) on par with laboratory outcomes.

Undoubtedly, these findings underscore the potential of photoreactions for industrial applications and suggest that photogenerated ketenes derived from  $\alpha$ -diazo ketones serve as valuable reaction precursors for pharmaceutical applications in flow chemistry under photochemical conditions.

## 6. Conclusions

Light has emerged as a promising, clean, and efficient energy source for modern chemistry in recent years. One of the most exciting developments in this field is the emergence of photogenerated ketenes, a novel class of organic compounds that offer a solution to the limitations associated with classic ketene preparation and preservation, with reduced preparative costs and simplified processes. Photogenerated ketenes have simplified the construction of diverse heterocyclic architectures through [2 + n] cyclization reactions.

Nevertheless, several challenges persist in the field of photogenerated ketenes. For instance, the conversion of photogenerated ketenes to unconventional cycles, particularly more challenging macrocyclic conformations, remains infrequent due to entropic factors and transannular interactions. Therefore, it is essential to identify suitable substrates capable of achieving these transformations to construct targeted complex molecules accurately and effectively. Inducing chiral environments for photogenerated ketenes via asymmetric synthetic strategies is particularly challenging, likely due to their short lifetime, necessitating additional solutions. Although co-catalytic models have enabled chiral control and the production of optically pure products, establishing chiral environments for photogenerated ketenes beyond chiral isothiouras or carbenes has not been extensively studied. Further mechanistic studies are necessary to enhance our understanding of ketene properties, such as the observation that ketene intermediates selectively participate in [2 + 3] cyclization reactions via C=O and C=C bonds, a phenomenon not observed in other reaction types.

Despite these challenges, photogenerated ketenes have demonstrated remarkable potential in both laboratory and industrial settings, enabling the updating and broadening of classic ketene reactions to expand their applicability. This has been impressively reflected in the total synthesis of complex natural products through Danheiser benzannulation and the

potential for flow chemistry to benefit the pharmaceutical industry. Notably, recent reports of versatile electrophilic reagents containing ketenes as molecular probes suggest their potential in the biotherapeutic field as photoaffinity probes.<sup>73-77</sup>

In conclusion, pursuing more efficient and sustainable synthetic routes utilizing photogenerated ketenes has the potential to revolutionize the construction of diverse cyclic architectures. By addressing the challenges and limitations through interdisciplinary efforts of researchers worldwide focused on investigating the mechanisms underlying photogenerated ketenes' behaviour, breakthrough discoveries can be made, driving the field forward. We believe that the horizons of photogenerated ketenes can be expanded into new areas and provide further benefits to green and sustainable chemistry in the foreseeable future.

## Author Contributions

Bo Han: conceptualization, writing – review & editing, supervision, funding acquisition. Xiang Li: conceptualization; investigation; writing – review & editing; funding acquisition. Wei Li: writing – review & editing, investigation. Wei-Fang Zuo: conceptualization, writing – original draft, investigation. Qian Liu: conceptualization, writing – review & editing. Xin Xie: writing – review & editing, investigation. Qiwen Pang: writing – review & editing. All authors read and approved the submitted version.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (No. 82073998, 82104376), the Sichuan Science and Technology Program (No. 2023NSFSC1108, 2022NSFSC0626), and the Innovation Team and Talents Cultivation Program of National Administration of Traditional Chinese Medicine (No: ZYXCXTD-D-202209), the Postdoctoral Research Project of Sichuan Province, and the Xinglin Scholar Research Promotion Project of Chengdu University of TCM.

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