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Visible-Light-Induced Cycloaddition of α-Ketoacylsilanes with Imines: Facile Access to β-Lactams

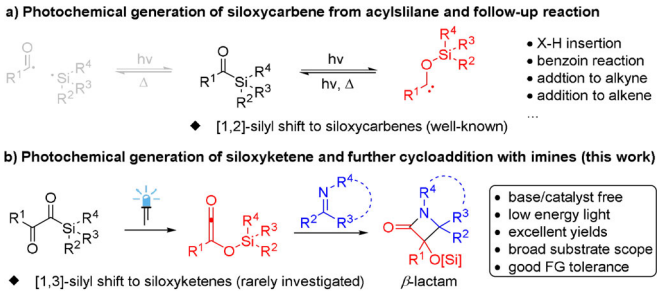
*Jian-Heng Ye, Peter Bellotti, Tiffany O. Paulisch, Constantin G. Daniliuc, and Frank Glorius**

Dedicated to Professor Peter Kündig on the occasion of his 75th birthday

Abstract: *We report the synthesis of β-lactams from α-ketoacylsilanes and imines, which proceeds via a formal [2+2] photochemical cycloaddition with in situ generation of siloxyketene. This mild and operationally simple reaction proceeds in an atom-economic fashion with broad substrate scope, including aldimines, ketimines, hydrazones, and fused nitrogen heterocycles, affording a variety of important β-lactams with satisfactory diastereoselectivities in most cases. This reaction also features good functional-group tolerance, facile scalability and product diversification. Experimental and computational studies suggest that α-ketoacylsilanes can serve as photochemical precursors by engaging in a 1,3 silicon shift to the distal carbonyl group.*

Organosilanes are highly important compounds and widely used in organic synthesis and materials science.[1] In particular, acylsilanes, with the silicon atom directly attached to the carbonyl group, are a fascinating class of compounds which exhibit unique physical and chemical properties. The use of acylsilanes in a variety of synthetic routes and improved methodologies for their preparation have turned acylsilanes into important reagents for organic chemistry.[2] In recent years, much effort has been devoted towards the development of both their preparation and novel transformations.

Interestingly, acylsilanes display unusual spectroscopic properties owing to the inductive release of electrons from the silicon atom to the carbonyl moiety. The relatively low energy of the n-π* electron transition leads to an abnormally long absorption wavelength with a relatively large extinction coefficient. Silyl ketones can therefore undergo interesting photochemical transformations, other than α-cleavage. Pioneered by Brook and co-workers, siloxycarbenes can be generated photochemically via the 1,2-Brook rearrangement of acyl silanes (Scheme 1 a).[3] Generally speaking, the reactivity patterns of siloxycarbenes correspond with nucleophilic carbene chemistry,[3,4] which have been attributed to resonance stabilization of the singlet state by donor substituents. Such intermediates possess the ability to (i) undergo X-H insertion (X = C, N, O, Si, B, etc);[5] (ii) undergo addition to electrophilic compounds, for instance cross-coupling with organoboronic esters,[6] benzoin reaction with aldehydes,[7] addition to alkynes[8] or electron-poor alkenes,[9] and participation in electrocyclization processes.[10] In addition to siloxycarbenes, other reactive intermediates generated from acylsilanes and their applications in organic synthesis remain to be addressed.[11]



Scheme 1. Photochemistry of acylsilanes.

The β-lactam (2-azetidinone) is a unique and important scaffold in terms of its bioactivity and utility as synthetic intermediate, and thus straightforward methods for its formation are highly valued in organic synthesis (Figure 1).[12] The formal [2+2] cycloaddition of ketenes with imines, the so-called Staudinger cycloaddition, undoubtedly offers the most direct access to β-lactams.[12,13] The most common methods for generation of ketenes are: 1) de-(hydro)halogenation of acid chlorides by trialkylamines or zinc; 2) ring opening of cyclobutenones; 3) Wolff rearrangement of α-diazoketones; 4) pyrolysis of anhydrides or esters; 5) cracking of diketenes. Despite the above advancements, the identification of new ketene precursors and their reactivities towards cycloadditions with imines are still of significant importance. With our continuing interest in acyl silane chemistry,[5h] we turned our attention to α-ketoacylsilanes, which are a rarely explored class of compounds.[14] Besides [1,2]-silyl migration of acylsilanes to form siloxycarbenes, we envisaged that α-ketoacylsilanes could theoretically

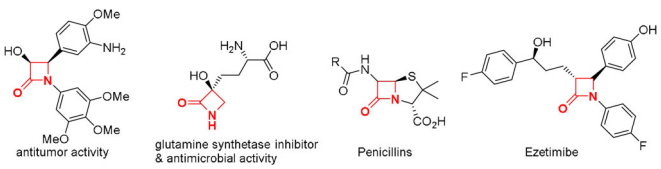


Figure 1. Bioactive β-lactam-containing compounds.

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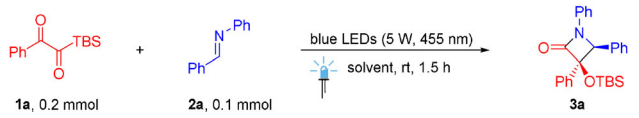
undergo [1,3]-silyl migration to form ketene intermediates. Herein, we report a mild, visible-light-induced method to generate ketenes from α-ketoacylsilanes without additives such as stochiometric base or metal, and their cycloadditions with imines (Scheme 1 b).

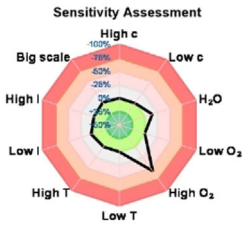
We commenced our investigations by studying the reaction of 1-(*tert*-butyldimethylsilyl)-2-phenylethane-1,2-dione (**1a**) and *N*-benzylideneaniline (**2a**) under light irradiation. After extensive optimization, we were pleased to obtain the desired β-lactam **3a** in 95% yield with excellent diastereoselectivity (>19:1) using acetonitrile as solvent under irradiation with blue LEDs (5 W, 455 nm) (Table 1, entry 1). Other

Table 1: Optimization of the reaction conditions.[a]



1a, 0.2 mmol **2a**, 0.1 mmol **3a**

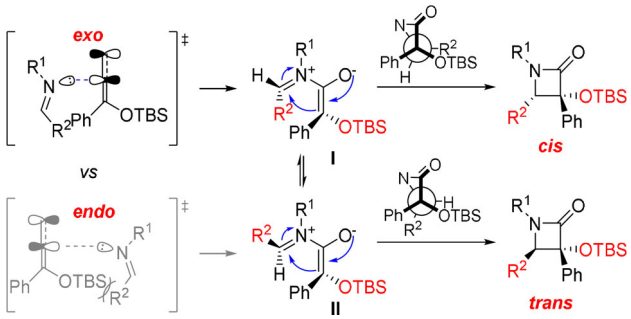
Entry	Solvent	Yield [%][b]
1	CH_3CN	97 (95)[c]
2	THF	70
3	1,4-dioxane	74
4	*n*-Hexane	83
5	CH_2Cl_2	87
6	$PhCF_3$	85
7[d]	CH_3CN	N.D.
8[d,e]	CH_3CN	N.D.
9[f]	CH_3CN	87



[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), solvent (1 mL), 5 W blue LEDs (λ_{max} = 455 nm), rt, 1.5 h. [b] Determined by crude GC-FID with dodecane as internal standard. [c] Isolated yield. The diastereoisomeric ratio of product **3a** is >19:1, determined by ^{1}H-NMR. [d] In the dark. [e] 100 °C. [f] **1a** (0.1 mmol), **2a** (0.2 mmol). N.D. = not detected.

solvents gave suboptimal yields and unsatisfactory diastereoselectivity (entries 2–6). Without irradiation, most of the starting material **1a** was not converted, even upon increasing the temperature to 100 °C (entries 7–8). Interestingly, comparable results could be obtained with **1a** as the limiting reagent. The results of the sensitivity assessment[15] revealed that the most important reaction parameter is oxygen content, while temperature, concentration, water, and light intensity showed little impact on the reaction outcome.

With the optimal reaction conditions (Table 1, entry 1) in hand, we first investigated the reaction scope with respect to the aldimines (Table 2). *N*-phenyl imines derived from aromatic aldehydes were first examined in this reaction. Both excellent yields and diastereoselectivities were obtained using substrates bearing electron-rich or electron-neutral substituents on the aromatic rings (**3b**–**3j**). *ortho*-Substituted aldimine **2o** underwent the reaction to smoothly afford β-lactam **3o** with satisfactory results. Electron withdrawing group substituted imines afforded good to excellent yields, but with decreased diastereoselectivities (**3k**–**3n**). Notably, the electronic influence on diastereoselectivity was also observed when aniline-derived aldimines (**3p**–**3q**) were employed. These findings are in accordance with the mechanistic scenarios proposed by Cossío[16] and Xu[17] (Scheme 2):



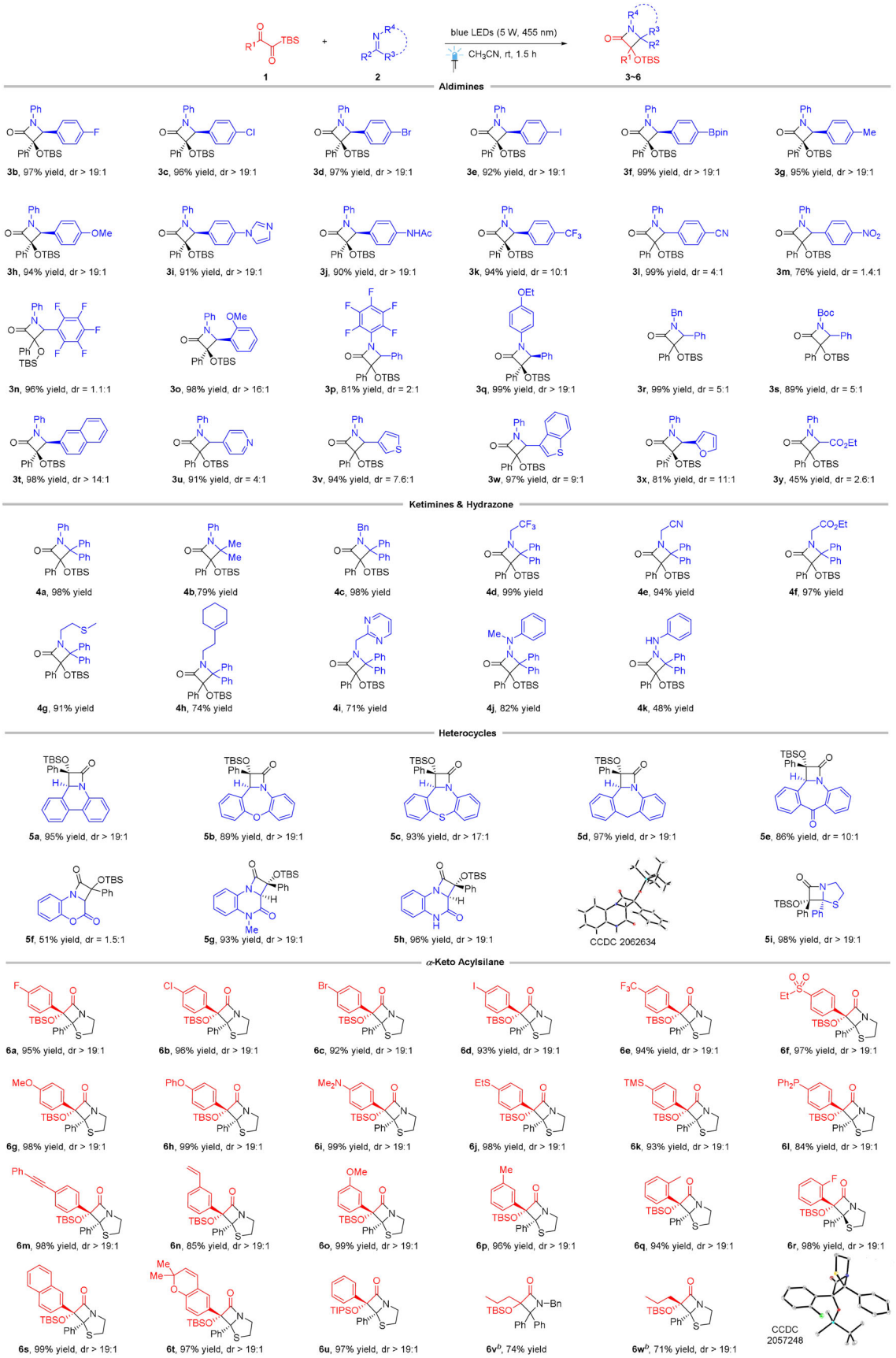
Scheme 2. Mechanistic rationale for the stereochemical outcome of the Staudinger reaction.

initial *exo*-attack from the nitrogen to the more accessible ketene face generates a zwitterionic adduct **I**, which can undergo either conrotatory ring closure (*cis* product) or C=N bond isomerization to **II**, followed by cyclization (*trans* product). In the presence of electron-withdrawing groups, the enhanced rate of isomerization[18] likely causes erosion of the *cis*-diastereoselectivity. In addition to the phenyl group, *N*-substitution can include benzyl (Bn) and *tert*-butylcarbamate (Boc), giving the corresponding β-lactam **3r** and **3s** in excellent yields and moderate dr values. Substrates bearing naphthalene and heteroaromatic rings, such as pyridine, thiophene, benzothiophene, and furan were all suitable, resulting in their corresponding products with high yields and moderate to good diastereoselectivities (**3t**–**3x**). Interestingly, a glyoxylate-derived imine was successfully subjected to the reaction conditions, albeit in moderate yield and low dr value. It is worth noting that reactive functional groups such as halogens (**3b**–**3e**), Bpin (**3f**), amide (**3j**), nitrile (**3l**), nitro (**3m**), Boc (**3s**), and ester (**3y**), were all well tolerated in this reaction, thus allowing for downstream chemistry.

We then investigated different ketimines and hydrazones. *N*-(diphenylmethylene)aniline underwent smooth cycloaddition to give **4a** in 98% yield. An *N*-phenylketimine derived from acetone also gave the product **4b** with good yield. Moreover, *N*-alkyl imines with different functional groups, including trifluoromethyl (**4d**), nitrile (**4e**), ester (**4f**), and thioether (**4g**), all afforded the corresponding β-lactams in excellent yields. A heterocyclic substrate bearing pyrimidine reacted smoothly and gave the product **4i** in 71% yield. Interestingly, an *N*-alkyl imine containing alkene moiety (**4h**) proved to be an amenable substrate, without detection of cyclobutanone, indicating that the [2+2] ketene-imine cycloaddition is favored over the [2+2] ketene-alkene cycloaddition. Besides these, *N*,*N*-disubstituted hydrazone also gave the desired product **4j** in good yield, while *N*-monosubstituted hydrazone only gave the desired product **4k** in moderate yield.

We next turned our attention to heterocycles as imine coupling partners. Phenanthridine displayed remarkable reactivity, giving product **5a** in both excellent yield and diastereoselectivity. Since dibenzazepines constitute an essential component of second generation or atypical antipsychotics, these tricyclic moieties were subjected to the photochemically [2+2] cycloaddition conditions. Dibenzoxazepine, dibenzothiazepine, and 11*H*-dibenzo[*b*,*e*]azepine all under-

Table 2: Scope of visible-light-induced cycloaddition of α-ketoacylsilanes with imines.[a]



[a] The standard reaction condition (Table 1, entry 1), isolated yields. Diastereomeric ratio (dr) was determined by ^{1}H-NMR. The explicit relative stereochemistry for examples with dr < 10:1 was not shown. [b] Modified conditions. See the Supporting Information for full experimental details.

went cycloaddition efficiently, giving access to the products with very high yields and diastereoselectivities (**5b–5d**). As their analogue, dibenzazepin-11-one could give the product **5e** with a comparable yield and good diastereoselectivity. 4-Azacoumarin afforded the product **5f** in synthetically useful yield with separable diastereomers. Both *N*-methyl quinoxalinone and quinoxalinone showed excellent reactivity and selectivity (**5g** and **5h**[19]). To our delight, phenylthiazoline also reacted well, giving the product **5i** containing the penam core structure of penicillins.

With phenylthiazoline as cycloaddition partner, different α-ketoacylsilanes were examined. We were pleased to find that electronic effects did not significantly influence the reactivity and selectivity of the process. α-Ketoacylsilanes with electron-neutral, electron-donating, and electron-withdrawing substituents on the aromatic ring were all well-tolerated. Moreover, the substituents on the phenyl ring could be located at the *para* (**6a–6m**), *meta* (**6n–6p**), and *ortho* (**6q–6r**) position. The obtained crystal structure of compound **6r** confirmed the *anti*-relationship between the two aromatic rings, which is in agreement with the above-mentioned mechanistic rationale.[19] As shown, the manifold provided the desired products in the presence of different halogens (**6a–6d**, **6r**), sulfone (**6f**), ether (**6g–6h**), amine (**6i**), thioether (**6j**), TMS (**6k**), and phosphine (**6l**) decoration on the phenyl moiety. Remarkably, both alkyne (**6m**) and alkene (**6n** and **6t**) were well-accommodated in this reaction. Naphthalene and chromene containing substrates were also tolerated and converted into the desired product **6s** and **6t**. Besides TBS, the translocating silyl group could also be TIPS (**6u**). Finally, alkyl α-ketoacylsilanes also showed good reactivity and excellent diastereoselectivity (**6v** and **6w**).

The scalability of the reaction is demonstrated in Figure 2a, in which product **3a** was prepared in good yield with slightly diminished diastereoselectivity. Moreover, comparable results could be obtained under higher concentration and lower loading of the α-ketoacylsilane, giving product **3f** by simple recrystallization, bypassing the need for chromatographic purification. The products were further derivatized to illustrate potential synthetic applications (Figure 2b): desilylation (**7**), oxidative deborylation (**8**), and Suzuki–Miyaura coupling (**9**) reactions all proceeded in high yields. Importantly, crystal structures of compounds **7** and **8** could be obtained, thus confirming the *anti*-relationship between the two aromatic rings.[19]

To gain more insight into this reaction, mechanistic studies were conducted. Attempts to prove the formation of the ketene intermediate using additional trapping agents (Figure 2c) were fruitful. The ketene intermediate can be trapped by methanol, piperidine, and 4-toluenethiol to give the corresponding carboxylic acid derivatives in high yields. As for the generation of ketenes by photolysis, two possibilities of the photorearrangement were considered. One process involves a single-step [1,3]-silyl shift[20] to the distal carbonyl group. Alternatively, a two-step mechanism, that a [1,2]-shift of silicon to the adjacent carbonyl group with generation of a siloxycarbene, followed by a Wolff rearrangement, could be operative. It is noteworthy that we did not detect the product generated from the hypothetic reaction of the siloxycarbene

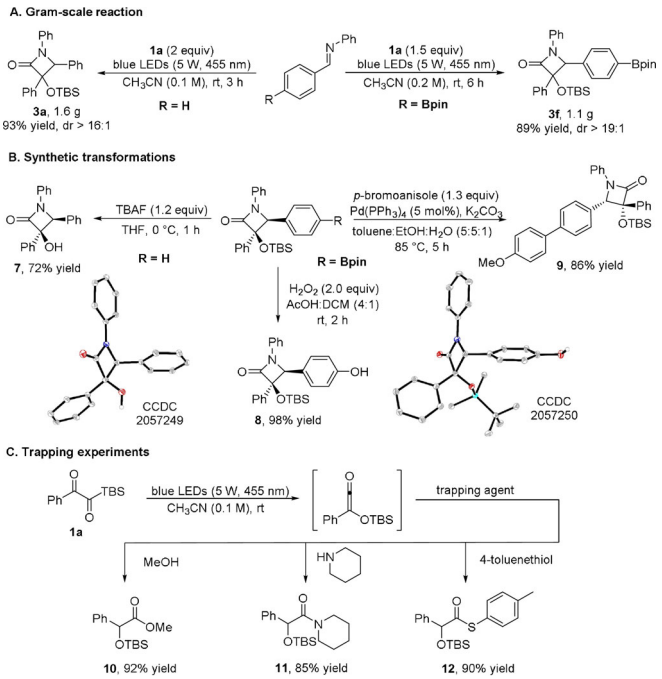


Figure 2. (A) Gram-scale reaction. (B) Synthetic transformations of β-lactam products. (C) Trapping experiments.

with additional trapping agents. These observations indicate that the ketene is likely generated from the single-step [1,3]-silyl shift.

Computational investigations into the reaction mechanism (Figure 3) show that direct excitation of α-ketoacylsilane **1a** in the visible light region is feasible and gives rise to the vertically excited n→π* state ^{1*}**[A]**, which undergoes geometrical relaxation to ^{1*}**A** ($\Delta G_{1*[A]/1*A} = -7.8$ kcal mol^{-1}). The n→π* triplet state ^{3}**A** was shown to be the lowest excited triplet state, whose population from ^{1*}**A** was computed to be thermodynamically favorable ($\Delta G_{1*A/3A} = -9.7$ kcal mol^{-1}). From triplet state ^{3}**A**, two competitive pathways towards ketene intermediate ^{3}**B** could be envisioned, either via direct [1,3]-silyl migration, or via [1,2]-silyl migration and subsequent [1,2]-phenyl shift: The former [1,3]-silyl migration is

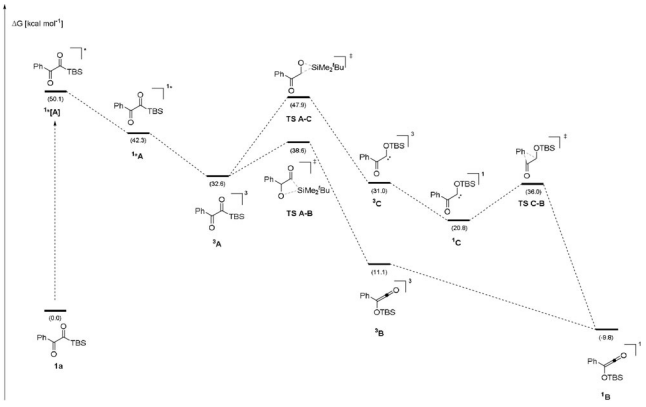


Figure 3. Calculated reaction profiles for the excitation of α-ketoacylsilane **1a**, and two potential pathways for the formation of the siloxyketene (B3LYP/def2-TZVPP).

accompanied by a small activation barrier of 6.0 kcal mol^{-1}, and the generation of ketene intermediate ^{3}**B** is exergonic by $\Delta G_{3A/3B} = -21.5$ kcal mol^{-1}. Subsequent intersystem crossing to singlet ketene ^{1}**B** was computed to be thermodynamically favored ($\Delta G_{3B/1B} = -20.9$ kcal mol^{-1}), rendering the overall reaction pathway both kinetically and thermodynamically feasible. In comparison, a [1,2]-silyl migration of α-ketoacylsilane from its triplet state ^{3}**A** shows a higher kinetic barrier of 15.3 kcal mol^{-1} and only a small thermodynamic driving force ($\Delta G_{3A/3C} = -1.6$ kcal mol^{-1}) to form the triplet siloxycarbene ^{3}**C**. Since the following reaction pathway of ^{3}**C** to form the singlet ketene intermediate ^{1}**B** is significantly higher in energy than the pathway of [1,3]-silyl migration, we propose the latter to be the operative mechanism. (For more details, see the Supporting Information.)

In summary, we have developed a protocol for the visible-light-induced generation of siloxyketenes and their cycloaddition with imines to directly access valuable β-lactams, complementing other well-established methodologies. A variety of imines, including aldimines, ketimines, hydrazones, and different fused nitrogen heterocycles, were found to be compatible. This protocol shows noteworthy functional-group compatibility, satisfactory diastereoselectivity, straightforward scalability, and facile product diversification. Mechanistic studies indicate that the reaction likely proceeds via the formation of a singlet siloxyketene from the T_1 state of the α-ketoacylsilane precursor. Ultimately, we believe that this methodology will greatly influence method development in the area of the photochemistry of acylsilanes.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: acylsilane · cycloaddition · siloxyketene · visible light · β-lactam

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Communications

Photochemistry

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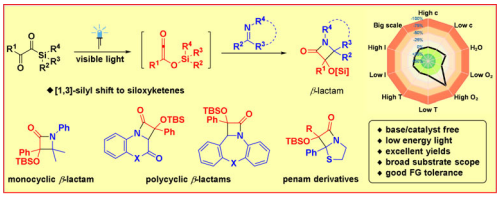
Visible-Light-Induced Cycloaddition of α-Ketoacylsilanes with Imines: Facile Access to β-Lactams



The synthesis of β-lactams from α-ketoacylsilanes and imines is reported, which proceeds via a [2+2] photochemical cycloaddition with in situ generation of siloxyketene. This reaction proceeds in an atom-economic fashion with broad substrate scope, including aldimines, ketimines, hydrazones, and fused nitrogen heterocycles, and good functional-group tolerance, affording a variety of β-lactams with satisfactory diastereoselectivities.