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Access to high value sp^3-rich frameworks using photocatalyzed [2 + 2]-cycloadditions of γ-alkylidene–γ-lactams†‡

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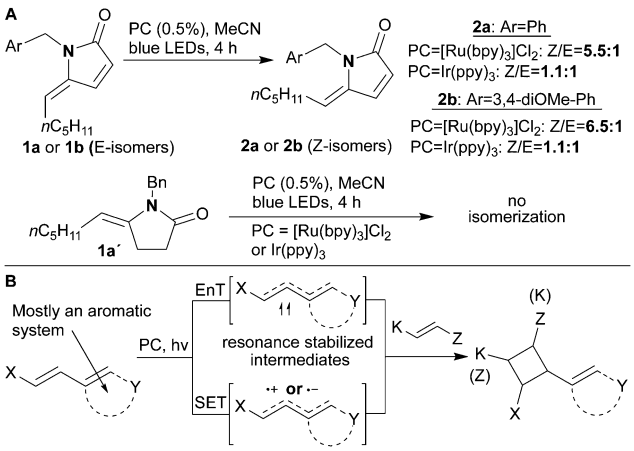
By harnessing an energy transfer process, new photocatalyzed [2 + 2]-cycloadditions occurring between γ-alkylidene–γ-lactams and unsaturated substrates have been developed. The reaction mode is particularly powerful because it leads to the formation of different high value sp^3-rich frameworks and further diversity can be introduced through cascade sequences wherein strain releasing opening of the cyclobutane intermediates gives access to complex polycyclic alkaloid frameworks.

Achieving greater structural novelty[1] and a higher sp^3 carbon count[2] have been identified as key ways to improve both the quality of pharmaceutical hits and the frequency with which they can be found. Thus, these two features have become essential prerequisites when developing new screening sets. As a result, three-dimensionally rich spirocyclic compounds[3] have attracted particular attention. Interest that has been bolstered by the fact that the rigidity of these highly saturated frameworks endows the compounds with further benefits; such as, the lowering of the entropy penalty incurred when docking at a receptor site[3a] and the potential to reduce receptor promiscuity.[1,2b]

During our work on functionalizing γ-lactams,[4] we noticed that lactams of type **1** (**1a** or **1b**, Scheme 1A) had an inclination to isomerize substantially (from *E* to *Z*) when irradiated with blue light in the presence of $[Ru(bpy)_3]Cl_2$ (**1a**/**b** → **2a**/**b**). This behavior was also seen with $Ir(ppy)_3$, albeit with lower final *Z*/*E* ratios; whereas, the direct irradiation of **1** without a catalyst led to only 8.5% isomerization. Lactam **1a′** proved to be inert to the isomerization conditions. Interestingly, this observation is in keeping with the known isomerization of the structurally similar heam-metabolite, bilirubine, which forms the basis of light therapy for neonatal jaundice.[5] Thus, we began to develop a strategy predicated on the hypothesis that this isomerization involved an energy transfer reaction which might be harnessed to give a series of novel photocatalytic [2 + 2]-cycloadditions.

The initial target groups would be architecturally complex sp^3-rich cyclobutanes formed by intra- or intermolecular reactions. Cyclobutanes not only feature in many biologically active compounds,[6] but are also useful intermediates due to their potential to undergo ring strain releasing reactions.[7] There are other methods to make cyclobutanes,[8] but these are mostly eclipsed by the widespread use of [2 + 2]-photocycloadditions.[9] Within this class the historic variant involves the olefin absorbing UV light directly.[9] Milder and newer methods using visible light and a photocatalyst operate either *via* an energy transfer (EnT)[10] or single electron transfer (SET) mechanisms.[11] The photocatalytic variants require some form of extended conjugation because it affords the substrates with lower triplet state energies and lower redox potentials to facilitate the generation of stabilized open shell intermediates (resonance stabilization, Scheme 1B). This feature



Scheme 1 (A) Observed *E*–*Z* isomerization of unsaturated lactams of type **1**. (B) Photocatalytic [2 + 2]-cycloaddition reaction modes.

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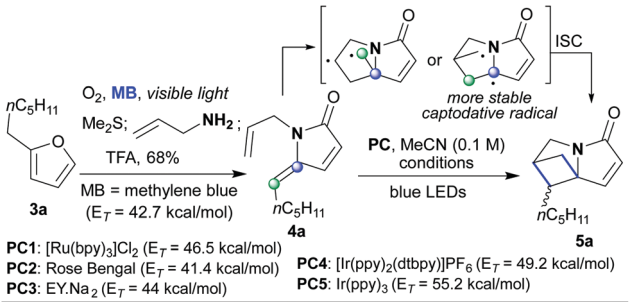
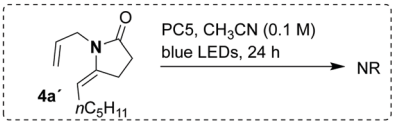
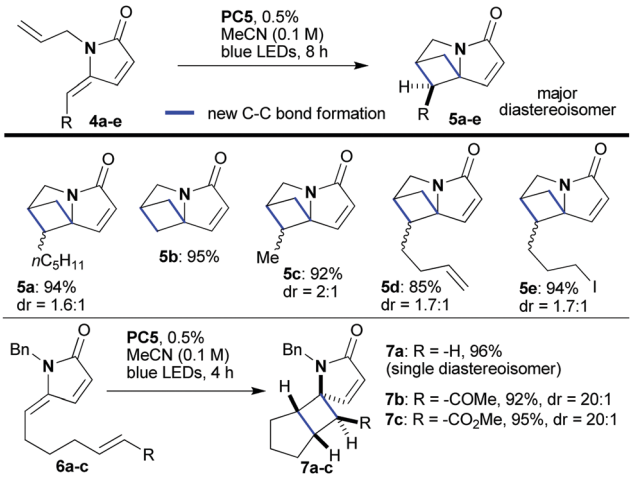


Entry	PC (mol %)	time (h)	conv (%)[a]	yield of **5a** (%)[b]
1	PC1 (0.5%)	24	42	–
2	PC1 (2.5%)	24	65	–
3	PC2 (5%, white LEDs)	24	<5	–
4	MB (5%, white LEDs)	24	NR	–
5	PC3 (5%, white LEDs)	24	<5	–
6	**PC4 (0.5%)**	**8**	**100**	**92 (dr = 1.6:1)**
7	**PC5 (0.5%)**	**8**	**100**	**94 (dr = 1.6:1)**
8	–	24	NR[c]	–
9	PC5 (0.5%), no light	24	NR	–
10				

Scheme 2 Optimization of the intramolecular [2 + 2]-cycloaddition of **4a**. [a]Determined by ^{1}H-NMR of the crude reaction mixture. [b]Isolated yield. [c]*E*/*Z* isomerization was observed (*E*/*Z* = 2.4 : 1).

has, therefore, often limited reaction scope to substrates bearing aromatic substituents. Photocatalyzed isomerization of conjugated alkenes from E to Z is also an energy transfer process sometimes used to access *cis* alkenes from their more readily synthesized *trans* analogs.[12] It was for this reason that we believed the previously observed isomerization might indicate that γ-alkylidene–γ-lactams could be uniquely suitable non-aromatic substrates for photocatalyzed [2 + 2]-cycloadditions to form new cyclobutanes *via* an energy transfer mechanism. Notably, a number of the N-substituted cyclobutane products would share key structural features with natural alkaloids and pharmaceuticals.[3a,13]

We began our investigation with the facile synthesis of the γ-alkylidene–γ-lactam **4a** from furan **3a** and allylamine using our previously developed photocatalytic protocol (Scheme 2).[4f] Substrate **4a** has a double bond on the amide side chain that could partner with the exocyclic double bond in a cross [2 + 2]-cyclization to yield the tightly packed sp^3-rich polycycle **5a**. Indeed, when **4a** was treated with PC1 in CH_3CN (0.1 M) and irradiated with blue LEDs, the desired reaction occurred; however, the reactions did not reach completion even after 24 h (entries 1 and 2). In surveying photocatalysts, it was found that organic dyes PC2, PC3 and methylene blue (MB), all of which have only moderate triplet energies,[14] were not competent catalysts for the reaction (entries 3–5). In contrast, PCs 4 and 5, which have high triplet energies,[14] proved to be highly efficient converting **4a** into **5a** within 8 h in high yield (92 and 94% yield, respectively). The reaction did not proceed in the absence of the photocatalyst or light; although with the former, a small degree of double bond isomerisation did take place (*E*:*Z*, 2.4 : 1, entry 8). Extended conjugation in the substrates is a requirement as shown by the inert nature of **4a′** to the reaction conditions (entry 10).



Scheme 3 Photocatalytic intramolecular [2 + 2]-cycloaddition reactions of unsaturated lactams of type **4** and **6**.

We expanded the set of substrates **4** and showed that they all reacted efficiently (85–95% yield, 1.6 : 1–2 : 1 dr, Scheme 3). Substrates that include groups sometimes sensitive to radicals and/or other photocatalyzed reactions they also successfully provided the desired products (**5d** and **5e**). Interestingly, framework **5** contains the skeleton of the natural amino acid 2,4-methanoproline,[15] which, along with its analogs, has been shown to exhibit a range of biological activities.[16] It was also possible to relocate the partner double bond in these intramolecular [2 + 2]-photocycloadditions; for example, substrates of type **6** afforded polycyclic products **7** with excellent diastereoselectivity (**7a–7c**, 92–96% yield, Scheme 3).

Next, we sought to move on to the more challenging intermolecular variant of the reaction in which the γ-alkylidene–γ-lactam would react with a second molecule containing an electron deficient double bond. The reaction would give us access to relatively rare 5,4-spirocycles of type **9** (Scheme 4). A variety of combinations were tested in which lactams **8** were combined with an excess (10 equiv.) of the unsaturated carbonyl compound under the previously optimized conditions (0.5% of PC5 in CH_3CN). All the reactions worked well, affording the products **9** in good to high yield (**9a–9g**, 60–82%) and with excellent regioselectivity. Despite the fact that every reaction furnished a mixture of diastereomers (1.6 : 1, by ^{1}H NMR), the products with a keto or aldehyde group were epimerized to a single stereoisomer upon chromatographic purification (**9a–9c**, **9e–9g**). Only in the case of **9d** (bearing an ester group less able to drive epimerization) did the reaction afford a 1 : 1 ratio of diastereomers which remained unchanged during purification. The intermolecular [2 + 2]-cycloaddition with the more electron-rich alkene styrene also works, but it is quite messy.

An interesting result emerged when product **9g** was treated with formic acid. The acidic conditions catalyzed a retro-Mannich reaction, presumably, driven by opening of the strained cyclobutane ring, which was followed by nucleophilic attack of the aromatic group on the resulting *N*-acyliminium cation, to furnish lactam **10a** as a sole product (92% yield). Such N-containing aromatic polycycles of type **10** constitute the basic

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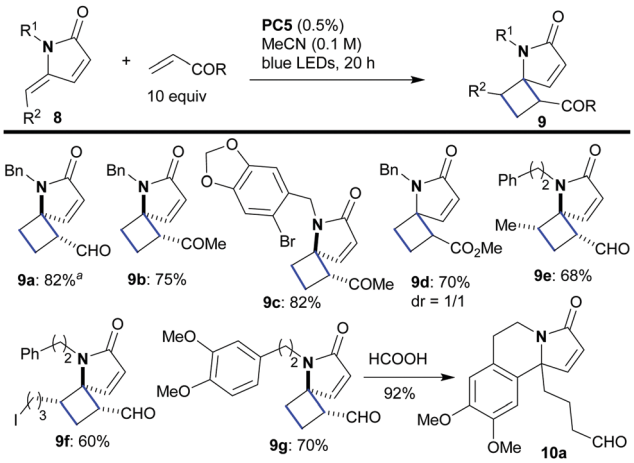
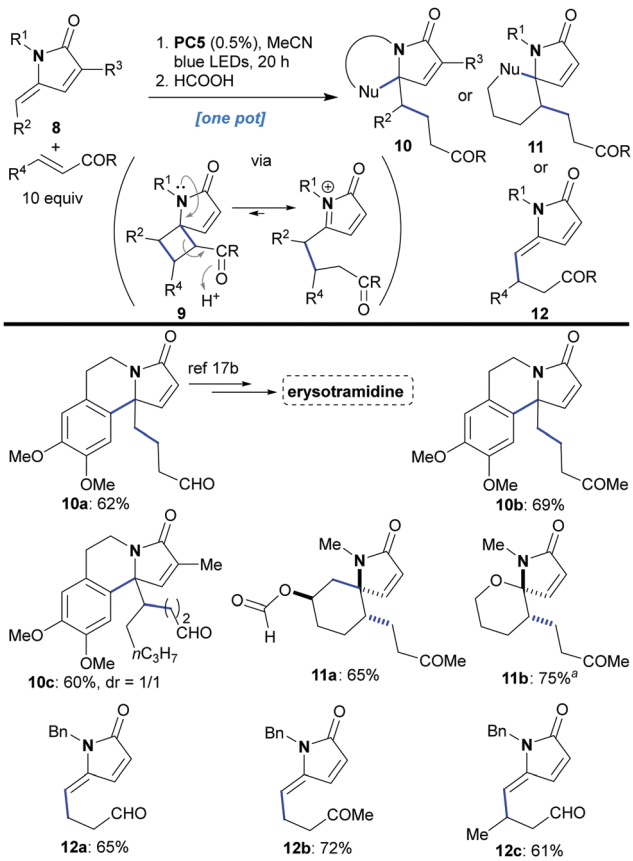


Scheme 4 Photocatalytic synthesis of spirocyclic compounds of type **9** *via* intermolecular [2 + 2]-cycloaddition. [a]The reaction occurred similarly using 0.5% of PC4.

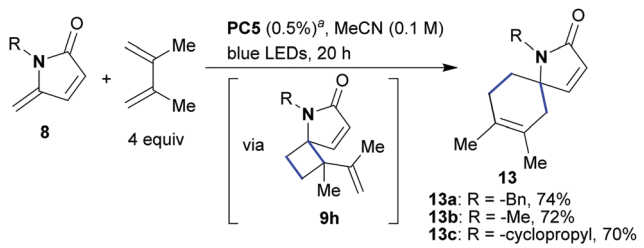
skeleton of many natural alkaloids (**10a** has been used as a precursor for the synthesis of erysotramidine, Scheme 5).[17a,b] The retro-Mannich ring opening of **9g**[7] was intriguing because it opened up the possibility for developing cascade sequences that could diversify the type of products accessible to us through this methodology (**8** → **10–12**, Scheme 5). In practice, lactams **8**, with internal nucleophilic groups at either R^1 or R^2, first underwent the [2 + 2]-photocycloaddition using an excess (10 equiv.) of acrolein or methyl vinyl ketone. The intermediates of type **9** were not isolated, but, instead, acid was added to attain a range of alternative products. More specifically, when R^1 bore an electron rich aromatic group, treatment with formic acid catalyzed further transformation into products of type **10** (overall **8** → **10a–10c** in one pot with yields ranging from 60 to 69%). Similarly, when an appropriate nucleophile was appended to R^2, various products could be attained depending on the nature of that nucleophile. For example, spirocycles **11a** and **11b** were formed diastereoselectively in good yields in a single operation starting from lactam **8** (for **11a** formic acid was used while for **11b** PTSA was employed, Scheme 5). These compounds constitute the skeleton of marine Clavelina[17c] and marineosins[17d] alkaloids. Furthermore, chain homologation (a form of C–H activation) could be achieved for substrates with no internal nucleophile through a similar acid catalyzed cyclobutane ring opening reaction sequence. Thus, lactams of type **12** could be synthesized in one pot (**8** → **12a–12c**, yields 61–72%, Scheme 5). The retro-Mannich ring opening does not work with ester **9d**, because the ester group is less electron withdrawing compared to aldehydes and ketones.



Scheme 5 Functionalization of γ-alkylidene–γ-lactams based on photocatalytic [2 + 2]-cyclization followed by cyclobutane ring opening. [a]The second step was performed using PTSA·H_2O (2 equiv.) in CH_2Cl_2.

Finally, we wanted to investigate the reaction of γ-alkylidene–γ-lactams with 2,3-dimethylbuta-1,3-diene. 1,3-Dienes have previously been utilized in photocycloadditions, producing either vinylcyclobutans or cyclohexenes depending on which mechanism is in operation (EnT or ET).[18] When the optimized conditions were applied to conjugated lactams of type **8** in the presence of 2,3-dimethylbuta-1,3-diene (4 equiv., Scheme 6), spirocyclic compounds of type **13** were formed as the sole products (**13a–13c**, 70–74% yield, Scheme 6). Monitoring the reaction by ^{1}H NMR, we observed the formation of the vinylcyclobutane **9h** (Scheme 6) during the early stages of the process. This intermediate subsequently disappeared and spirocyclic product **13** was formed. This observation implies two sequential steps; an initial [2 + 2]-cycloaddition yielding **9h** with subsequent rearrangement to **13** to give overall a [4 + 2]-transformation.

Stern–Volmer quenching and voltammetry studies were undertaken (see, ESI‡) and the results were consistent with an energy transfer from the excited state of the photocatalyst to the γ-alkylidene–γ-lactam being the mechanistic mode operating in



Scheme 6 Photocatalytic cyclization of unsaturated γ-alkylidene–γ-lactams with 2,3-dimethylbuta-1,3-diene. [a]The reactions occurred similarly using 0.5% of PC4.

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these [2 + 2] cycloadditions. More precisely, compound **8a** quenches the excited state of PC5 at a significantly higher rate than methylvinyl ketone or 2,3-dimethylbuta-1,3-diene and the redox potentials of PC4 and PC5 are not appropriate for initiation of an electron transfer pathway with **4a** (see ESI‡).

Overall, a series of mild and highly efficient methodologies to access a diverse range of unusual rigid sp^3-rich spirocycles, complex alkaloid frameworks or chain homologated products have been developed. Synthesis of the latter two groups was achieved by incorporating ring strain relieving cyclobutane opening into highly effective one pot cascade reaction sequences. The methodologies all rely initially on a novel photocatalyzed (visible light + PC) [2 + 2]-cycloaddition between γ-alkylidene–γ-lactams and an unsaturated partner which occurs *via* an energy transfer mechanism.

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Conflicts of interest

There are no conflicts to declare.

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