



Scheme 2 Optimization of the intramolecular [2 + 2]-cycloaddition of **4a**. ^aDetermined by ¹H-NMR of the crude reaction mixture. ^bIsolated 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 sp³-rich polycycle **5a**. Indeed, when **4a** was treated with PC1 in CH₃CN (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 CH₃CN). 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 ¹H 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





Scheme 4 Photocatalytic synthesis of spirocyclic compounds of type **9** via intermolecular [2 + 2]-cycloaddition. ^aThe 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



Scheme 5 Functionalization of γ -alkylidene- γ -lactams based on photocatalytic [2 + 2]-cyclization followed by cyclobutane ring opening. ^aThe second step was performed using PTSA-H₂O (2 equiv.) in CH₂Cl₂.

through this methodology (**8** \rightarrow **10–12**, Scheme 5). In practice, lactams **8**, with internal nucleophilic groups at either R¹ or R², 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 R¹ bore an electron rich aromatic group, treatment with formic acid catalyzed further transformation into products of type **10** (overall **8** \rightarrow **10a–10c** in one pot with yields ranging from 60 to 69%). Similarly, when an appropriate nucleophile was appended to R², 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** \rightarrow **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.

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 ¹H 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. ^aThe reactions occurred similarly using 0.5% of PC4.



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 sp³-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.

Notes and references

- J.-L. Reymond, *Acc. Chem. Res.*, 2015, **48**, 722.
- (a) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752; (b) P. A. Clemons, N. E. Bodycombe, H. A. Carrinski, J. A. Wilson, A. F. Shamji, B. K. Wagner, A. N. Koehler and S. L. Schreiber, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 18787.
- (a) E. M. Carreira and T. C. Fessard, *Chem. Rev.*, 2014, **114**, 8257; (b) Y. Zheng, C. M. Tice and S. B. Singh, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3673; (c) K. Hiesinger, D. Dar'in, E. Proschak and M. Krasavin, *J. Med. Chem.*, 2021, **64**, 150.
- (a) D. Kalaitzakis, A. Bosveli, K. Sfakianaki, T. Montagnon and G. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2021, **60**, 4335; (b) S. Hoxha, D. Kalaitzakis, A. Bosveli, T. Montagnon and G. Vassilikogiannakis, *Org. Lett.*, 2021, **23**, 5354; (c) T. Montagnon, D. Kalaitzakis, M. Sofiadis and G. Vassilikogiannakis, *Org. Biomol. Chem.*, 2020, **18**, 180; (d) G. I. Ioannou, T. Montagnon, D. Kalaitzakis, S. A. Pergantis and G. Vassilikogiannakis, *ChemPhotoChem*, 2018, **2**, 860; (e) D. Kalaitzakis, M. Triantafyllakis, G. I. Ioannou and G. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2017, **56**, 4020; (f) D. Kalaitzakis, A. Kouridaki, D. Noutsias, T. Montagnon and G. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2015, **54**, 6283.
- (a) R. Bonnett, J. E. Davies and M. B. Hursthouse, *Nature*, 1976, **262**, 327; (b) K. Mreihil, A. F. McDonagh, B. Nakstad and T. W. R. Hansen, *Pediatr. Res.*, 2010, **67**, 656.
- (a) J. Li, K. Gao, M. Bian and H. Ding, *Org. Chem. Front.*, 2020, **7**, 136; (b) M. Wang and P. Lu, *Org. Chem. Front.*, 2018, **5**, 254.
- J. D. Winkler, C. M. Bowen and F. Liotta, *Chem. Rev.*, 1995, **95**, 2003.
- (a) M. R. Fructos and A. Prieto, *Tetrahedron*, 2016, **72**, 355; (b) Y. Xu, M. L. Conner and M. K. Brown, *Angew. Chem., Int. Ed.*, 2015, **54**, 11918.
- (a) N. Hoffmann, *Chem. Rev.*, 2008, **108**, 1052; (b) M. D. Kärkäs, J. A. Porco and C. R. J. Stephenson, *Chem. Rev.*, 2016, **116**, 9683; (c) S. Poplata, A. Tröster, Y.-Q. Zou and T. Bach, *Chem. Rev.*, 2016, **116**, 9748; (d) B. Cox, K. I. Booker-Milburn, L. D. Elliott, M. Robertson-Ralph and V. Zdorichenko, *ACS Med. Chem. Lett.*, 2019, **10**, 1512.
- For selected reviews see: (a) F. Strieth-Kalthoff, M. J. James, M. Teders, L. Pitzer and F. Glorius, *Chem. Soc. Rev.*, 2018, **47**, 7190; (b) Q.-Q. Zhou, Y.-Q. Zou, L.-Q. Lu and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2019, **58**, 1586; For selected non-enantioselective examples see: (c) Z. Lu and T. P. Yoon, *Angew. Chem., Int. Ed.*, 2012, **51**, 10329; (d) Y.-Q. Zou, S.-W. Duan, X.-G. Meng, X.-Q. Hua, S. Gao, J.-R. Chen and W.-J. Xiao, *Tetrahedron*, 2012, **68**, 6914; (e) A. E. Hurlley, Z. Lu and T. P. Yoon, *Angew. Chem., Int. Ed.*, 2014, **53**, 8991; (f) V. Mojz, E. Svobodová, K. Straková, T. Neveselý, J. Chudoba, H. Dvořáková and R. Cibulka, *Chem. Commun.*, 2015, **51**, 12036; (g) J. Zhao, J. L. Brosmer, Q. Tang, Z. Yang, K. N. Houk, P. L. Diaconescu and O. Kwon, *J. Am. Chem. Soc.*, 2017, **139**, 9807; (h) M. J. James, J. L. Schwarz, F. Strieth-Kalthoff, B. Wibbeling and F. Glorius, *J. Am. Chem. Soc.*, 2018, **140**, 8624; (i) R. F. Higgins, S. M. Fatur, N. H. Damrauer, E. M. Ferreira, A. K. Rappé and M. P. Shores, *ACS Catal.*, 2018, **8**, 9216; (j) F. M. Hörmann, T. S. Chung, E. Rodriguez, M. Jakob and T. Bach, *Angew. Chem., Int. Ed.*, 2018, **57**, 827; (k) T. Neveselý, C. G. Daniliuc and R. Gilmour, *Org. Lett.*, 2019, **21**, 9724; (l) L. D. Elliott, S. Kayal, M. W. George and K. Booker-Milburn, *J. Am. Chem. Soc.*, 2020, **142**, 14947.
- For selected examples see: (a) N. L. Bauld, *Tetrahedron*, 1989, **45**, 5307; (b) M. A. Miranda and H. García, *Chem. Rev.*, 1994, **94**, 1063; (c) T. P. Yoon, *ACS Catal.*, 2013, **3**, 895; (d) M. Riene and D. A. Nicewicz, *Chem. Sci.*, 2013, **4**, 2625.
- For relative reviews see: (a) Y. Yokoyama, *Chem. Rev.*, 2000, **100**, 1717; (b) J. B. Metternich and R. Gilmour, *Synlett*, 2016, 2541; (c) J. J. Molloy, T. Morack and R. Gilmour, *Angew. Chem., Int. Ed.*, 2019, **58**, 13654.
- (a) V. M. Dembitsky, *J. Nat. Med.*, 2008, **62**, 1; (b) V. M. Dembitsky, *Phytomedicine*, 2014, **21**, 1559; (c) A. Sergeiko, V. V. Poroikov, L. O. Hanuš and V. M. Dembitsky, *Open J. Med. Chem.*, 2008, **2**, 26.
- For the triplet energy of the current applied photosensitizers see: (a) For PC1: D. P. Rillema, G. Allen, T. J. Meyer and D. Conrad, *Inorg. Chem.*, 1983, **22**, 1617; (b) For PC2, PC3 and MB: T. Shen, Z.-G. Zhao, Q. Yu and H.-J. Xu, *J. Photochem. Photobiol., A*, 1989, **47**, 203; (c) For PC4: J. D. Slinker, A. A. Gorodetsky, M. S. Lowry, J. Wang, S. Parker, R. Rohl, S. Bernhard and G. G. Malliaras, *J. Am. Chem. Soc.*, 2004, **126**, 2763; (d) For PC5: A. Singh, K. Teegardin, M. Kelly, K. S. Prasad, S. Krishnan and J. D. Weaver, *J. Organomet. Chem.*, 2015, **776**, 51.
- (a) E. A. Bell, M. Y. Qureshi, R. J. Pryce, D. H. Janzen, P. Lemke and J. Clardy, *J. Am. Chem. Soc.*, 1980, **102**, 1409; (b) C. V. Stevens, G. Smagghe, T. Rammeloo and N. De Kimpe, *J. Agric. Food Chem.*, 2005, **53**, 1945.
- B. Cox, J. Duffy, V. Zhdorichenko, C. Bellanger, J. Hurcum, B. Laleu, K. I. Booker-Milburn, L. D. Elliot, M. Robertson-Ralph, C. J. Swain, S. J. Bishop, I. Hallyburton and M. Anderson, *ACS Med. Chem. Lett.*, 2020, **11**, 2497.
- (a) M. E. Amer, M. Shamma and A. J. Freyer, *J. Nat. Prod.*, 1991, **54**, 329; (b) A. J. Blake, C. Gill, D. A. Greenhalgh, N. S. Simpkins and F. Zhang, *Synthesis*, 2005, 3287; (c) S. M. Weinreb, *Chem. Rev.*, 2006, **106**, 2531; (d) C. Boonlarppradab, C. A. Kauffman, P. R. Jensen and W. Fenical, *Org. Lett.*, 2008, **10**, 5505.
- Energy transfer based cyclizations with 1,3-dienes afford vinylcyclobutanes. For examples see: (a) Ref. 10c, *e*, *j*; (b) F. Tang, L. Tang, Z. Guan and Y.-H. He, *Tetrahedron*, 2018, **74**, 6694; (c) T. R. Blum, Z. D. Miller, D. M. Bates, I. A. Guzei and T. P. Yoon, *Science*, 2016, **354**, 1391; (d) Recently (ref. 10i), using isoprene as the 1,3-diene an overall-[4 + 2] reaction was observed.

