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Intramolecular photochemical [2 + 1]-cycloadditions of nucleophilic siloxy carbenes†

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Visible light induced singlet nucleophilic carbenes undergo rapid [2 + 1]-cycloaddition with tethered olefins to afford unique bicyclo[3.1.0]hexane and bicyclo[4.1.0]heptane scaffolds. This cyclopropanation process requires only visible light irradiation to proceed, circumventing the use of exogenous (photo)catalysts, sensitisers or additives and showcases a vastly underexplored mode of reactivity for nucleophilic carbenes in chemical synthesis. The discovery of additional transformations including a cyclopropanation/retro-Michael/Michael cascade process to afford chromanones and a photochemical C−H insertion reaction are also described.

Introduction

Cyclopropane derivatives including donor–acceptor cyclopropanes and cyclopropanols are valuable building blocks in chemical synthesis.[1] These three-membered carbocyclic rings are widely prevalent in natural products for example peyssonnoside A (Fig. 1).[2] Cyclopropanes also play a valuable role in medicinal chemistry,[3] as exemplified by the potent indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor recently reported by Hamilton and co-workers who highlighted the significant advantages that conformationally constrained bicyclo[3.1.0]hexane scaffolds offered in terms of improving metabolic stability and limiting off-target effects when used as a cyclohexane isostere (Fig. 1).[4]

Common strategies to construct cyclopropanes include the Johnson–Corey–Chaykovsky or Simmons–Smith reaction.[5] However, the [2 + 1]-cycloaddition of olefins with carbenes generated from diazo derivatives remains the most widely employed cyclopropanation strategy.[6] Such cycloadditions typically involve reaction of alkenes with electrophilic carbene (or carbenoid) intermediates formed from diazoacetates or hydrazones in the presence of catalytic rhodium, iron, copper and cobalt complexes or boron derivatives.[7]

In recent years, more economical and sustainable catalyst-free methods for chemical synthesis have emerged employing visible light irradiation to generate reactive intermediates in the absence of photocatalysts or photosensitisers.[8] Within this context, catalyst-free [2 + 1]-photocycloadditions of olefins with carbenes generated from diazo compounds have been
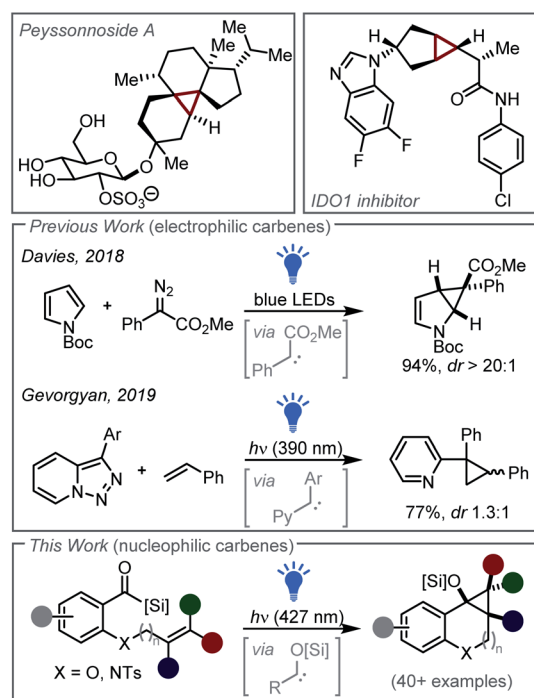

Fig. 1 Cyclopropanes are a valued motif in natural products and medicinal chemistry however relative to electrophilic singlet carbenes, the [2 + 1]-cycloaddition reaction of olefins with nucleophilic carbenes remains vastly underexplored.

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developed.[9] For example, in 2018 Davies first demonstrated that electrophilic carbenes generated photochemically from diazo-acetates underwent [2 + 1]-cycloaddition with unsaturated carbocycles and heterocycles (Fig. 1).[10] Subsequently, the visible-light induced cyclopropanation of indoles using aryl(diazo) acetates was reported by Zhang and co-workers,[11] and the Koenigs group discovered a [2 + 1]-photocycloaddition of olefins using donor–acceptor diazoalkanes or tosyl hydrazone reagents in both batch and continuous flow.[12] Building on these pioneering works, in 2021, Barham and co-workers reported the visible-light included cyclopropanation of heteroarenes in continuous flow using dimethyl carbonate as a more environmentally friendly solvent.[13]
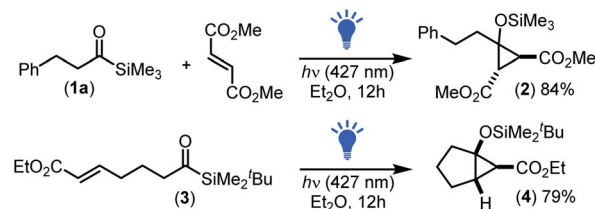
A limitation, however, for both the metal-catalyzed and photochemical [2 + 1]-cycloaddition reactions developed to date is the requirement that carbene intermediates be generated from unstable and toxic diazo reagents that typically require electron-withdrawing groups for stability. To circumvent this requirement, new catalyst- and diazo-free photochemical strategies have been recently discovered involving the cyclopropanation of styrenes *via* the photochemical generation of iodomethyl carbonyl radicals from diiodoacetates,[14] diradicals from iodonium ylides,[15] or pyridyl carbenes from triazoles (Fig. 1).[16]

It is known that nucleophilic siloxy carbene intermediates—generated photochemically from bench-stable acyl silanes *via* visible light irradiation—are valuable intermediates in chemical synthesis, participating in reactions including boron–hydrogen insertion and 1,2-carbonyl addition.[17] We thus questioned whether a new catalyst- and diazo-free cyclopropanation strategy might be accessible *via* the [2 + 1]-cycloaddition reactions of visible light induced siloxy carbenes with olefins. It was envisaged that such a strategy would afford access to unique cyclopropanol derivatives highly amenable to subsequent functionalization.

Whilst the cyclopropenation of alkynes with siloxy carbenes is known (affording strained cyclopropenes that undergo spontaneous ring-opening and silicon transfer to afford vinyl silanes),[17g,h] only two isolated examples of the cyclopropanation of nucleophilic siloxy carbenes exist, both involving [2 + 1]-photocycloaddition with diethyl fumarate as reported by Brook in 1971 and Dalton in 1981.[18] In fact, relative to electrophilic carbenes the cyclopropanation of nucleophilic carbenes is vastly underexplored and has been seldom reported.[18,19] To address this, we herein report that visible light induced nucleophilic carbenes undergo rapid and stereospecific catalyst- and diazo-free [2 + 1]-cycloadditions with olefins including styrene, acrylamide, and vinyl phosphonate derivatives,[20] showcasing a significantly underexplored reaction mode for nucleophilic carbenes.[21]

Results and discussion

To begin, we investigated the intermolecular cyclopropanation of phenethyl acyl silane **1a** with olefins including styrene, ethyl acrylate, beta-nitrostyrene, *N*-benzylmaleimide and dimethyl fumarate using visible light irradiation at 427 nm (a wavelength

Scheme 1 Carbenes generated from alkyl acyl silanes participated in both inter- and intramolecular photochemical [2 + 1]-cycloaddition processes.

commonly used to excite both aryl and alkyl acyl silanes).[17d,j] However, the only olefin sufficiently activated enough to undergo intermolecular cyclopropanation was the fumarate possessing two electron withdrawing groups on the alkene, yielding *trans*-cyclopropane **2** in 84% yield (Scheme 1). This lack of reactivity for many of the alkenes correlates with that observed previously for the intermolecular [2 + 1]-cycloaddition of siloxy carbenes with alkynes,[17g,h] where two electron withdrawing groups were required to sufficiently lower the LUMO$_{alkene}$ energy to enable interaction with the filled carbene sp^2-orbital (HOMO$_{carbene}$).[22]

To further investigate the viability of a [2 + 1]-cycloaddition of siloxy carbenes with olefins other than fumarate, we next explored an intramolecular approach. This involved preparation and subsequent photochemical irradiation of acrylate derivative **3** (427 nm LED, 40 W) which afforded bicyclo[3.1.0] hexane **4** in good yield with exclusive formation of the *exo*-isomer (Scheme 1), demonstrating for the first time that the [2 + 1]-photocycloaddition of nucleophilic carbenes proceeded efficiently for olefins other than fumarates.

Table 1 Optimization of the cyclopropanation reaction conditions[a]

Entry	Solvent	Conversion[b] (%)
1	Et$_2$O	96%
2	CH$_2$Cl$_2$	92%
3	THF[c]	91%
4	CHCl$_3$[c]	87%
5	MeCN[c]	94%
6	Toluene[c]	83%
7	Et$_2$O[c]	99% (89%)[e]
8	Et$_2$O[c,d]	0%
9	CH$_2$Cl$_2$[c]	97%
10	Dimethyl carbonate[c]	97%

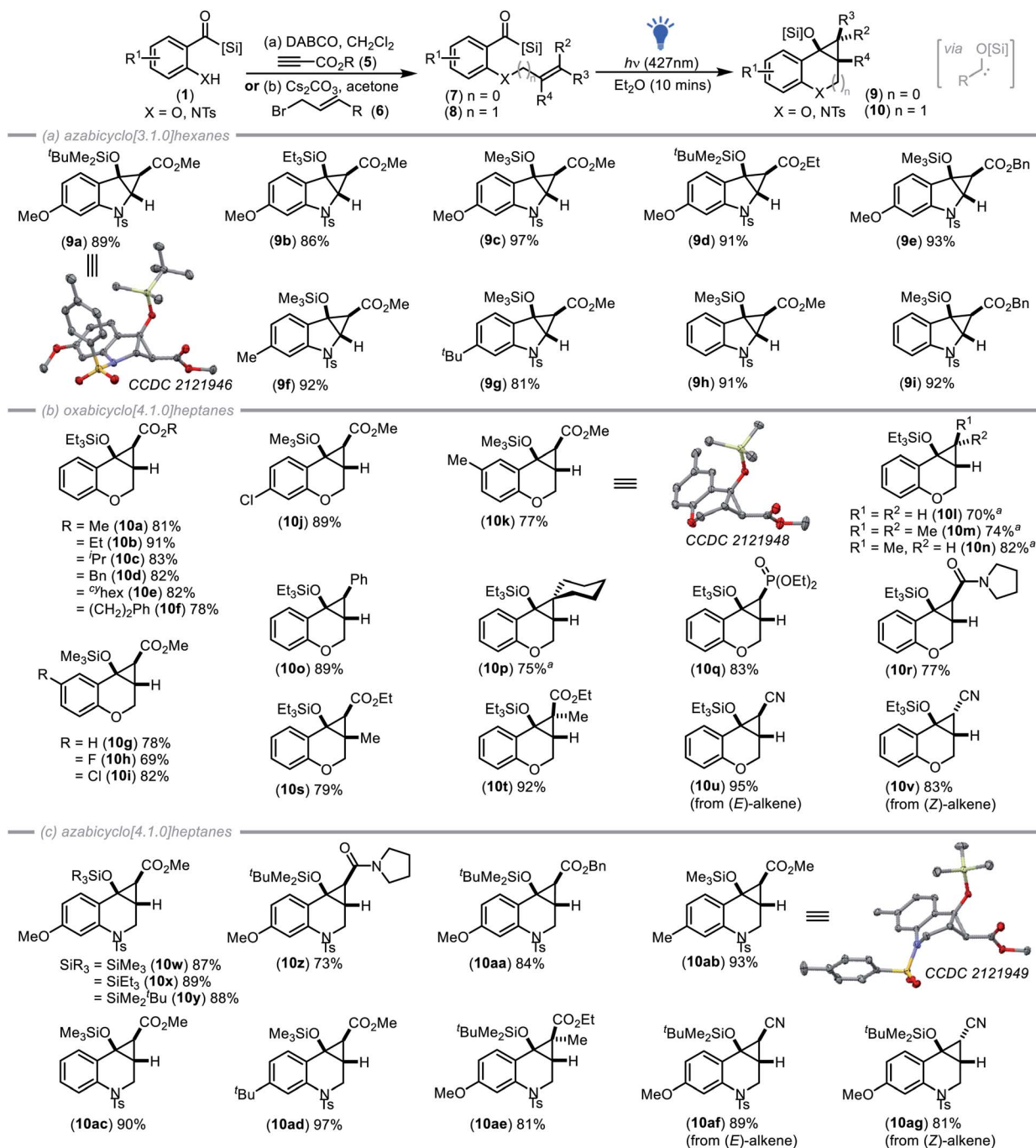[a] Reaction conducted on 0.2 mmol scale in 1 mL of solvent. [b] Conversion of acyl silane to product as assessed by ^{1}H NMR. [c] 4 Å molecular sieves included in reaction vial. [d] Reaction conducted in the dark. [e] Isolated yield.

Building on this outcome, we considered that phenol or aniline derived aroyl silanes would best facilitate an in-depth investigation into this cyclopropanation process enabling rapid variation of the olefin tether using commercially available reagents and a common starting material. We thus prepared a sulfonamide derived benzoyl silane containing an electron-deficient olefin (7a).[23] Exposure of a solution of aroyl silane 7a in diethyl ether to visible light irradiation (427 nm LED, 40 W)

led to a colour change from bright yellow to colourless after only 10 minutes, affording *tert*-butyldimethylsiloxy azabicyclo[3.1.0] hexane (9a), readily identifiable by ^{1}H NMR analysis from the distinctive cyclopropane C–H resonances at $\delta = 4.71$ ppm and $\delta = 0.82$ ppm.

Optimisation of the reaction conditions confirmed that several solvents were suitable including dimethyl carbonate, however diethyl ether remained the preferred choice (Table 1).

Scheme 2 A novel photochemical [2 + 1]-cycloaddition of nucleophilic carbenes was developed to access to a series of cyclopropyl-fused heterocyclic scaffolds including (a) azabicyclo[3.1.0]hexanes (b) oxabicyclo[4.1.0]heptanes and (c) azabicyclo[4.1.0]heptanes. Crystal structures of 9a (CCDC 2121946†), 10k (CCDC 2121948†) and 10ab (CCDC 2121949†) depicted at 50% probability (hydrogen atoms omitted for clarity): carbon (grey), oxygen (red), nitrogen (blue), sulfur (orange) and silicon (yellow). [a]Reaction time of 2 hours required.

X-ray crystallography of **9a** (CCDC 2121946†) confirmed the structure (Scheme 2a), with the *exo*-isomer formed as the sole isomer as indicated by both NMR and X-ray analysis. Subsequently, *ortho*-sulfonamido aroyl silanes were reacted with various propiolates to afford a series of acyl silanes containing olefin tethers (**7**).

Visible light irradiation of these substrates (427 nm LED, 40 W) produced a series of azabicyclo[3.1.0]hexanes (**9a–9i**, Scheme 2a). In each case, the *exo*-diastereoisomer was produced as the sole diastereoisomer, with variations in the silyl, aryl, and ester functional groups well tolerated. Advantageously, this cyclopropanation process is complete in less than 10 minutes and is operationally simple, requiring only visible light irradiation, circumventing the use of exogenous catalysts, or additives including photosensitisers.

To further probe the [2 + 1]-photocycloaddition, we set out to vary the heteroatom and extend the tether length to investigate if bicyclo[4.1.0]heptane frameworks were also accessible. To achieve this, we employed salicylaldehyde derived acyl silanes that were *O*-alkylated *via* reaction with various bromocrotonate derivatives. Subsequent irradiation of the functionalised acyl silanes (**8**) with visible light (427 nm LED, 40 W) afforded oxabicyclo[4.1.0]heptane scaffolds (**10a–10k**, Scheme 2b) with variation in the structure of both the crotonate ester group and benzoyl silane well tolerated. The oxabicyclo[4.1.0]heptane products were readily identified by ^{1}H NMR analysis from the distinctive cyclopropane C–H resonances at $\delta = 2.60$ ppm and $\delta = 2.20$ ppm ($J = 5.8$ Hz). X-ray crystallographic analysis of **10k** (CCDC 212194†) confirmed the structure and *exo*-configuration.

With the reaction performing well for ester derived electron deficient alkenes, we next explored the influence of alternative alkene substituents. Neutral olefins situated within allyl, methyl allyl and dimethyl allyl tethers all underwent photochemical cyclopropanation reaction with visible light induced nucleophilic carbenes, however these less activated alkenes required reaction times of up to 2 hours to achieve complete conversion (Scheme 2b, **10l–10n**, 70–82%). The orbital interaction required to drive [2 + 1]-cycloaddition for less activated alkenes is that between the filled alkene π-orbital ($HOMO_{alkene}$) and the vacant carbene 2p-orbital ($LUMO_{carbene}$). Thus, the fact that these relatively electron-rich olefins undergo cycloaddition with siloxy carbenes at all is impressive, given that the $LUMO_{carbene}$ energy is considerably higher due to interaction of the oxygen atom's non-bonding valence electrons with the unoccupied 2p carbene orbital.[17b]

To further explore reactivity with less activated alkenes, styrene derivative **8r** was prepared *via* alkylation of the acyl silane with cinnamyl bromide and again visible light irradiation (427 nm LED, 40 W) afforded cyclopropanol **10r** in excellent yield (89%) in under 10 minutes. A cyclohexyl derived olefin tether was also installed which underwent cyclopropanation to afford spirocyclic derivative **10p** (75%) generating two new ring systems and contiguous quaternary carbon centres (Scheme 2). Of note, the ability of nucleophilic carbenes to undergo cyclopropanation with relatively electron rich olefins produces highly substituted cyclopropanols that are not accessible using traditional diazo-based cyclopropanation strategies (where electron-

withdrawing groups are typically required to stabilise both the diazo reagent and electrophilic carbene).

Further variation of the alkene substitution pattern revealed that phosphonate (**10q**, 83%) and amide (**10r**, 77%) derived cyclopropane frameworks were readily accessible *via* the photocycloaddition of nucleophilic carbenes and that tri-substituted alkenes could also be employed to yield penta-substituted cyclopropanes **10s** (79%) and **10t** (92%).

The alkylation of phenol derived acyl silanes with a 1 : 1 (*E*)/(*Z*) mixture of 4-bromobut-2-enenitrile enabled us to gain additional insight into the reaction process as the (*E*)- and (*Z*)-alkenyl acyl silanes were readily separable. Irradiation of each of these substrates (427 nm LED, 40 W) resulted in rapid [2 + 1]-cycloaddition with the (*E*)-alkene leading to exclusive formation of the *exo*-isomer **10u** while the (*Z*)-alkene afforded the *endo*-isomer as the major product **10v** (Scheme 2b). This outcome infers that mechanistically, this [2 + 1]-cycloaddition occurs in a concerted and highly stereospecific fashion.

The opportunity to access azabicyclo[4.1.0]heptanes (Scheme 2c) was next explored. To achieve this, *ortho*-sulfonamido acyl silanes were alkylated using bromocrotonate derivatives with subsequent visible light irradiation (427 nm LED, 40 W) producing a series of azabicyclo[4.1.0]heptanes (**10w–10ag**, Scheme 2c). The cyclopropane adducts were identified by ^{1}H NMR analysis from the distinctive cyclopropane C–H resonances at $\delta = 2.60$ ppm and $\delta = 1.30$ ppm ($J = 5.6$ Hz). Variations within the silyl group, aryl ring and alkene substituents were well tolerated to afford tetra- or penta-substituted cyclopropanes using only visible-light irradiation.
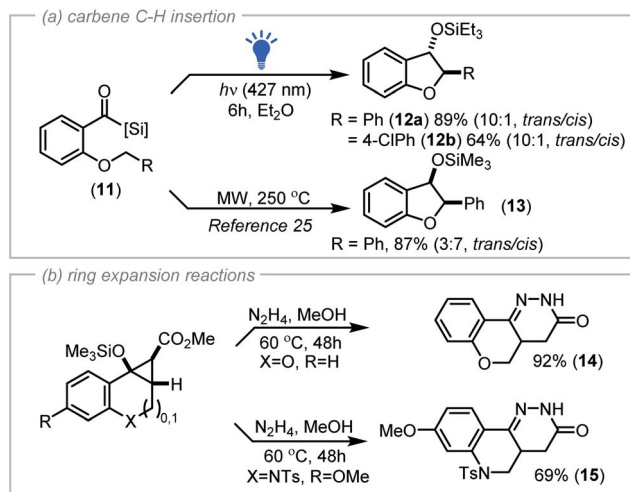
The structure and configuration of azabicyclo[4.1.0]heptane was again confirmed *via* X-ray crystallographic analysis of **10ab** (CCDC 2121949†) and **10w** (CCDC 2121947†).[24] Furthermore, the use of the 1 : 1 (*E*)/(*Z*) mixture of 4-bromobut-2-enenitrile afforded access to both the *endo* and *exo* isomers of the cyano-derived cyclopropane derivatives **10af** and **10ag** (Scheme 2c). Intriguingly, it was observed that in deuterated chloroform the kinetically favoured *endo*-product **10ag** produced from the (*Z*)-cyano-alkene isomerised over time to the thermodynamically favoured *exo*-isomer **10af** (proposedly *via* a ring opening/closing process).[24]

During investigations into the cyclopropanation of less activated alkenes (to produce **10l–10n**), up to 20% conversion of the acyl silane to the dihydrobenzofuran product arising from C–H insertion of the carbene into the allylic CH_2 moiety was observed *via* NMR analysis. A related transformation involving C–H insertion of thermally generated siloxy carbenes (250 °C, microwave irradiation) to afford 2-phenyldihydrobenzofurans **13** was reported by the Dong group in 2009 with the *cis*-diastereoisomer formed as the major product (Scheme 3a).[25]

Supported by computational analysis, the Wang group subsequently proposed that Dong's thermal carbene insertion process proceeded *via* an excited singlet carbene intermediate *via* abstraction of a hydrogen atom from the proximal benzylic position that afforded a diradical that could undergo diradical coupling to afford *cis*-dihydrofuran **13**.[26]

Building on our observation that photochemically generated siloxy carbenes could undergo C–H insertion, we were intrigued
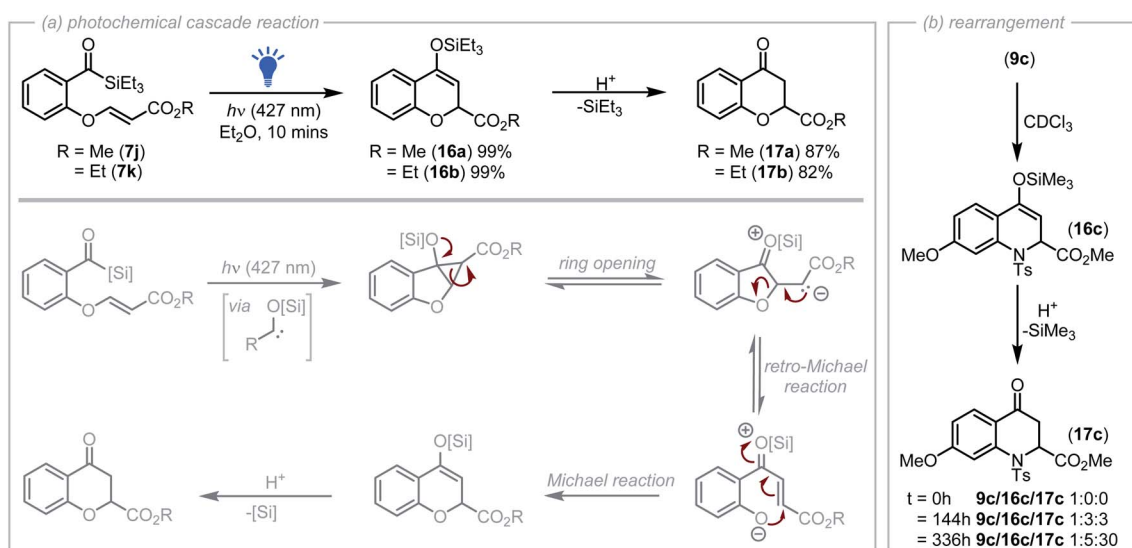
Scheme 3 (a) A highly diastereoselective C–H insertion process of visible-light induced carbenes was also discovered; (b) ring expansion *via* reaction with hydrazine afforded new heterocyclic scaffolds.

by the possibility of replicating the process reported by Dong using visible light irradiation at ambient temperature. To explore this, we prepared benzyloxy aroyl silanes **11a** and **11b** and following irradiation with visible light (427 nm LED, 40 W, 6 h), we successfully isolated the corresponding 2-phenyl-dihydrofurans **12a** (89% yield) and **12b** (64% yield) (Scheme 3a). Intriguingly, the major product formed *via* our photochemical reaction in both cases was the *trans*-diastereomer in a ratio of 10 : 1, inferring that the photochemical process occurs *via* an alternative mechanism to the thermal process reported by Dong, an observation currently under further investigation within our group.

As is the case for donor–acceptor cyclopropanes, ring opening and expansion protocols exploiting the inherent ring strain of bicyclo[3.1.0]hexane and bicyclo[4.1.0]heptane derivatives have been reported.[27] To this end, we also demonstrated that both aza- and oxa-bicyclo[4.1.0]heptanes prepared using the photochemical cyclopropanation process described herein readily underwent ring expansion reaction with hydrazine to afford valuable heterocyclic frameworks (Scheme 3b).[28] Due to the facile and catalyst-free nature of the [2 + 1]-photocycloaddition process, the development of additional telescoping strategies to rapidly generate molecular complexity are currently under investigation.

During initial studies into the cyclopropanation of salicylaldehyde derived acyl silanes, acyl silanes **7j** and **7k** containing an electron deficient olefin were prepared *via* the DABCO catalysed reaction of the phenolic –OH with a propiolate.[23] Visible-light irradiation (427 nm LED, 40 W) of a solution of diethyl ether containing acyl silane **7j** led to a colour change from bright yellow to colourless after only 10 minutes. Analysis of the reaction mixture by NMR spectroscopy indicated that no cyclopropane was present and instead complete conversion of the acyl silane to a new product had occurred.

Further analysis revealed the structure of the new product to be that of the silyl enol ether derived pyran **16a** (Scheme 4a). Formation of this product proposedly occurs *via* a photochemical cascade reaction initiated by rapid cyclopropanation of the carbene with the proximal alkene, followed by ring opening that generates an enolate intermediate that drives a retro-oxa-Michael reaction to afford a phenolate that undergoes Michael addition onto the activated acceptor producing **16a** A related retro-Michael/Michael addition mechanism was previously reported by Tang and co-workers who in 2006 reported the tetrahydrothiophene catalysed synthesis of 2*H*-chromenes from benzyl bromides containing tethered acrylates.[29] Subsequent

Scheme 4 (a) A unique photochemical cascade reaction involving cyclopropanation, ring opening, retro–Michael and Michael addition to afford new heterocyclic derivatives was discovered. (b) In deuterated chloroform, cyclopropane **9c** also gradually underwent a related ring opening, retro-Michael, Michael addition rearrangement process.

hydrolysis of silyl enol ether **16a** during silica-gel chromatography afforded chromanone **17a** (Scheme 4a). Acyl silane **7k** prepared from ethyl propiolate also underwent the photochemical cascade process to afford **16b** and following hydrolysis, **17b**.

For the photochemical cascade reaction outlined in Scheme 4a, it could be considered that the first step of this process is Michael-type addition of the nucleophilic carbene to the alkene rather than cyclopropanation. However, gradual isomerisation of the corresponding tosylamido cyclopropane **9c** to quinoline **16c** in deuterated chloroform and subsequent hydrolysis to afford **17c** was observed by NMR analysis (Scheme 4b).[24] This isomerisation proposedly occurs *via* the analogous ring-opening, retro-aza-Michael/Michael addition process, inferring that the first step of the rapid photochemical cascade reaction that produces **16a** and **16b** is indeed cyclopropanation.

Conclusions

It was discovered that visible light induced nucleophilic carbene intermediates underwent rapid [2 + 1]-cycloaddition with varying olefins generating valuable bicyclo[3.1.0]hexane and bicyclo[4.1.0]heptane scaffolds with simultaneous formation of two new ring systems (and in some cases contiguous quaternary carbon centres). Advantageously, this highly stereospecific reaction requires only visible light irradiation avoiding the requirement for exogenous additives, sensitisers or (photo) catalysts to afford a unique class of silicon-derived donor–acceptor cyclopropanes.

Owing to the inherent nucleophilicity of the siloxy carbene intermediates, the reaction was highly compatible with electron-deficient olefins including acrylates, acrylamides, and vinyl phosphonates, yet also proceeded with less activated olefins including a cyclohexylidene derivative to afford a spirocyclic framework. Investigations into the reactivity of visible light induced nucleophilic carbenes also unveiled a novel photochemical C–H insertion process to afford 2-phenyldihydrofurans with high diastereoselectivity, and a unique photochemical cascade reaction involving sequential cyclopropanation/ring-opening/retro-Michael/Michael addition steps.

Overall, it is anticipated that the discoveries described herein will provide valuable insight into the reactivity of singlet nucleophilic carbenes and pave the way for the development of new synthetic transformations that capitalize on the ability of nucleophilic carbene intermediates to participate in synthetically useful catalyst- and diazo-free [2 + 1]-photocycloaddition processes.

Data availability

All the relevant data is contained within the ESI.†

Author contributions

A. B. and D. L. P. performed the experiments, C. H. conducted the X-ray crystallographic analysis, A. P. and D. L. P. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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21 To note, during the processing of our manuscript, two related reports emerged regarding the cyclopropenation and cyclopropanation of carbene intermediates derived from acyl silanes; see: (a) G. Zhou and X. Shen, *Angew. Chem., Int. Ed.*, 2022, **61**, e202115334, DOI: 10.1002/anie.202115334; (b) S. Sakurai, T. Inagaki, T. Kodama, M. Yamanaka and M. Tobisu, *J. Am. Chem. Soc.*, 2022, **144**, 1099–1105.

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