Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2025, **16**, 21475

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 16th August 2025
Accepted 6th October 2025

DOI: 10.1039/d5sc06269a

rsc.li/chemical-science

Visible-light induced click reactions of acylsilanes with pyruvate electrophiles

Rowan L. Pilkington, [a] Rosa Kössler, [b] Jesse Molloy,[a] Stefan Bräse [b] and Daniel L. Priebbenow *[a]

Siloxycarbene intermediates induced *via* the visible light irradiation of acylsilanes undergo highly efficient benzoin-type click reactions with pyruvate derivatives. This process requires no reagents other than visible light, proceeds with high efficiency and is tolerant of a wide range of functional groups. Pyruvate esters, thioesters, amides, nitriles and phosphonates were all identified as suitable electrophiles including those tethered to complex drug or biomolecule scaffolds. The visible-light induced carbon–carbon bond forming process was scalable using both batch and flow methodologies, accompanied by diversification studies on the corresponding addition products. Mechanistic insights into siloxycarbene reactivity were also obtained by DFT analysis.

Introduction

Thiamine diphosphate (ThDP), the biologically active form of vitamin B1, is an enzyme cofactor required for cellular metabolism across all organisms.[1] ThDP dependent enzymes including pyruvate dehydrogenase complex E1-subunit (PDH E1), pyruvate decarboxylase (PDC), and pyruvate oxidase (PO) catalyse a diversity of biochemical reactions including the formation and cleavage of C–C, C–N, C–S and C–O bonds.[1a,c]

ThDP-dependent enzymes typically comprise three key structural domains: the N-terminal aminopyrimidine pocket which binds the pyrimidine ring of ThDP, a central domain containing a thiazolium ring and the C-terminal diphosphate pocket.[1a] An exemplar enzymatic mechanism is outlined in Fig. 1, in which the catalytically active ThDP-carbene (or its ylide resonance form generated *via* deprotonation at C2 of the thiazolium ring) undergoes nucleophilic addition to the α-carbonyl motif of a pyruvic acid derivative.[1a,2] Following nucleophilic addition, a tetrahedral intermediate is formed that upon extrusion of carbon dioxide forms an 'activated aldehyde' or enamine (a Breslow-type intermediate).[2] This enamine can react as a nucleophile with a secondary acceptor molecule, such as an aldehyde, to generate a carboligation product (Fig. 1).[2]

A number of ThDP-dependent enzymes have been successfully employed as biocatalysts in asymmetric synthesis.[1b,2a,3] Furthermore, N-heterocyclic carbene (NHC) catalysts that resemble the thiazolium ylide involved in ThDP enzymatic and related biological processes have become a cornerstone of

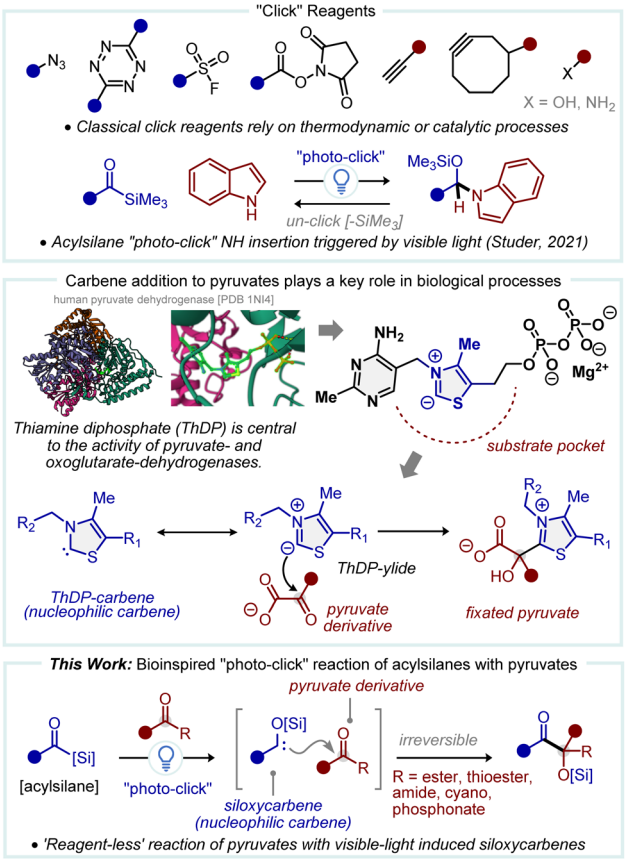


Fig. 1 Thiamine diphosphate is a biologically omnipresent N-heterocyclic carbene that catalyses the fixation of pyruvates in biological systems. In this work, we present a bio-inspired photoinduced approach to pyruvate fixation employing acylsilane derived siloxycarbenes.

[a]*Medicinal Chemistry Theme, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC, 3052, Australia. E-mail: daniel.priebbenow@monash.edu*
[b]*Institute of Biological and Chemical Systems (IBCS-FMS), Karlsruhe Institute of Technology, Kaiserstraße 12, 76131 Karlsruhe, Germany*

(asymmetric) organocatalysis.[4] This class of highly stabilised singlet nucleophilic carbenes catalyse a diversity of synthetic transformations including the benzoin reaction between aldehydes, ketones and α-ketoester (pyruvate) derivatives.[5]

Acylsilanes are of increasing utility in synthesis.[6] Siloxycarbenes—another class of singlet nucleophilic carbene—can be readily generated from acylsilanes *via* a 1,2-Brook rearrangement initiated by direct photochemical irradiation or triplet–triplet energy transfer photocatalysis.[7] Siloxycarbenes are known to react in transformations including [2 + 1]-cycloadditions,[8] 1,4-conjugate addition,[9] and X–H insertion.[7c,10] Siloxycarbenes can also be engaged as nucleophiles in 1,2-carbonyl addition processes (benzoin-type reactions) with carbonyl-derived electrophiles including aldehydes,[7d,11] carbon dioxide,[12] fluorinated ketones,[13] amides,[14] and esters.[15]

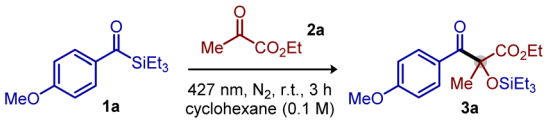
Inspired by the carbene promoted reactivity of ThDP-dependent enzymes with α-keto acids, we hypothesised that α-keto esters (pyruvate derivatives) should be sufficiently electrophilic to react with visible-light induced nucleophilic siloxycarbenes. Given that such carbene intermediates can be readily generated using only visible-light irradiation (negating the requirement for photocatalysts and additives), we strategised the development of a novel bioinspired photoinduced click reaction between acylsilanes and pyruvate derivatives enabling the rapid formation of a new carbon–carbon bond with perfect atom economy. The realisation of this strategy is described herein.

Results and discussion

We first explored the photochemical activation of (4-methoxyphenyl)(triethylsilyl)methanone **1a** using visible light irradiation (427 nm, 40 W) in the presence of 1.5 equivalents of ethyl pyruvate **2a**. This resulted in the formation of α-siloxyketone **3a** *via* 1,2-addition of the intermediary siloxycarbene and subsequent silyl transfer. Screening of the reaction conditions revealed that non-polar solvents such as cyclohexane (99% isolated yield, Table 1, entry 1) or toluene (entry 2) delivered nearly quantitative yields of the expected product (with no by-products formed). When the reaction was performed in other solvents including acetonitrile or ethyl acetate, diminished yields were observed (entries 3–7) concomitant with the preferential formation of *p*-anisaldehyde as by-product following adventitious hydrolysis of the siloxycarbene. The inclusion of molecular sieves, previously demonstrated to improve reactivity in related transformations,[13] did not lead to enhanced results in this process (entry 8) and both an inert atmosphere (entry 9) and light irradiation (entry 10) were deemed necessary to achieve high yields. Conveniently, reaction progress could be readily monitored by disappearance of the yellow colour of the acylsilane as this substrate was consumed over time.

With optimised conditions in hand, we explored the scope of substrates amenable to this reaction. Initially, diversity in the silyl group on the acylsilane was investigated, with the triethylsilyl and trimethylsilyl derivatives affording quantitative yields of the siloxyketones **3a** and **3b** in only 1–2-hour reaction time with ethyl pyruvate. The *tert*-butyldimethylsilyl and dimethylphenylsilyl analogues also performed well to afford **3c** and **3d** however the inclusion of the bulkier triisopropylsilyl and triphenylsilyl groups led to significantly reduced yields of the α-siloxyketone adducts **3e** and **3f**, respectively.

Table 1 Optimisation of reaction conditions[a]



Entry	Deviation from standard conditions	Yield **3a** (%)
1	None	99% (99%)
2	PhMe	96%
3	MTBE	25%
4	EtOAc	15%
5	DCM	63%
6	DCE	73%
7	MeCN	15%
8	4A MS	84%
9	Under air	30%
10	In darkness	0%

[a] Conducted on 0.1 mmol scale using 1.5 equivalents of **2a** Light source is 2 × 40 W 427 nm LEDs. Yields determined by ^{1}H NMR analysis of the reaction mixture relative to an internal standard. Brackets refers to isolated yield.

Benzoylsilanes containing various aryl substitution patterns were next explored, with the reaction highly tolerant of neutral, electron-donating, and electron-withdrawing substituents to afford a series of α-siloxyketone adducts (**3g–v**) containing a range of halide, ether, and ester residues. Notably, functional groups such as alkenes were unreactive towards the singlet siloxycarbene. Heterocyclic siloxyketones **3w** and **3x** were also readily accessible *via* reaction of the corresponding furanoyl and thiophenoyl silanes.

Alkenyl- and alkyl-substituted acylsilanes also reacted cleanly with ethyl pyruvate to afford the α-siloxyketone adducts **3y–3ab**. For the latter examples, the poor absorption profiles of alkyl acylsilanes in the visible light range necessitated the inclusion of 0.5 mol% $Ir(dFCF_3ppy)_2dtbbpy\cdot PF_6$ as a triplet–triplet energy transfer photosensitiser (with 12-hour reaction times) to obtain the insertion products. Notably, the reaction was also amenable to preparative multigram scales (10.0 mmol) in batch, affording 2.77 g of **3g** (94%) with a slightly longer reaction time (3 hours) and without the need for chromatographic purification.

After demonstrating that aryl, alkenyl and alkyl acylsilanes reacted rapidly with ethyl pyruvate, we next explored variation within the pyruvate substrate. Whilst aryl pyruvates failed to react, a range of alkyl pyruvate derivatives bearing alkyl-derived ketones or different ester groups reacted rapidly and cleanly (with reaction times ranging from 5 minutes to 2 hours) to afford a range of α-siloxyketones (Scheme 2). Toluene, or mixtures of cyclohexane and toluene were used as the reaction

solvent in some cases where the pyruvate was sparingly soluble in cyclohexane.

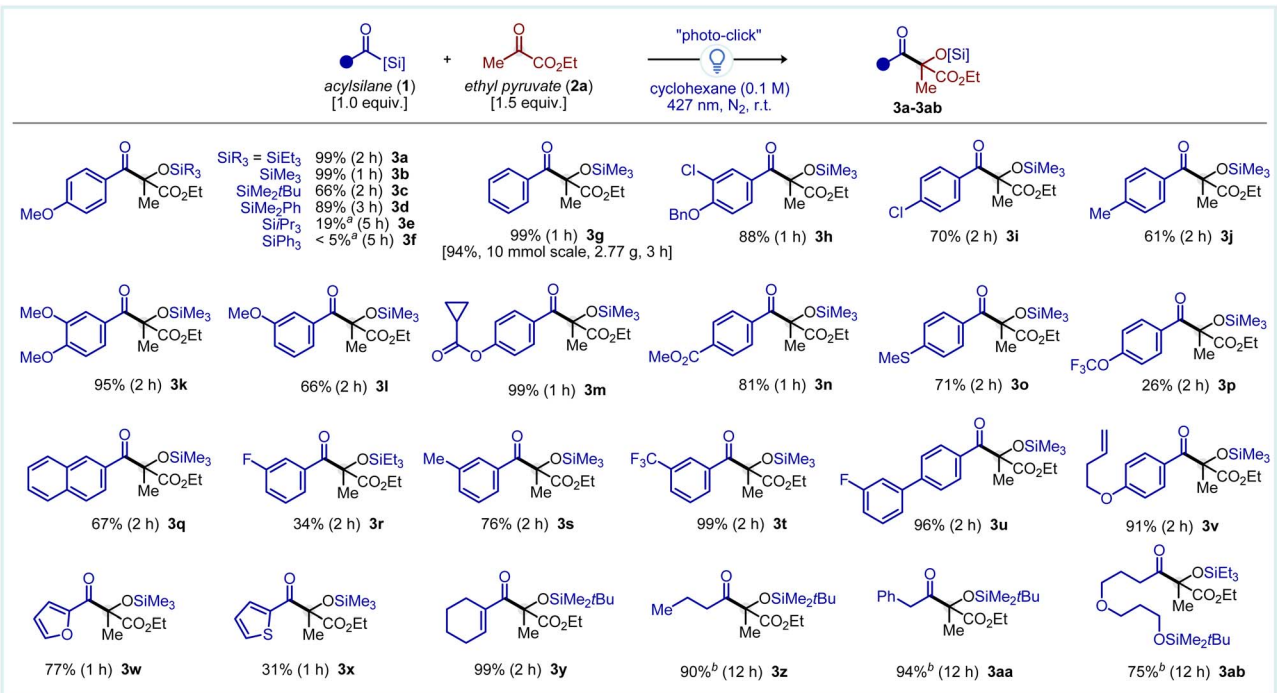
Various alkyl pyruvates with cyclic, linear and branched alkyl chains were well tolerated (**4a–e**), including one example containing an α-bromo ketone (**4d**) which reacted extremely rapidly (5 min). In the case of phenethyl-substituted compound **4e**, desilylation was conducted using 1 M HCl to expedite chromatographic separation from the unreacted pyruvate starting material. A cyclic, sterically hindered α-keto lactone also engaged the siloxycarbene to provide the expected product **4f** in high yield.

Trifluoromethyl pyruvate, an excellent electrophile, reacted very quickly to afford **4g** (99%). Variation of the ester component within the pyruvates also provided a diverse selection of the crossed benzoin-type adducts: *tert*-butyl (**4h**), benzyl (**4i**), allyl (**4j**), propargyl (**4k**), aryl (**4t**) and ethyl(trimethylsilyl) (**4n**) esters typically provided the products in quantitative yields, with the potential for orthogonal deprotection strategies.

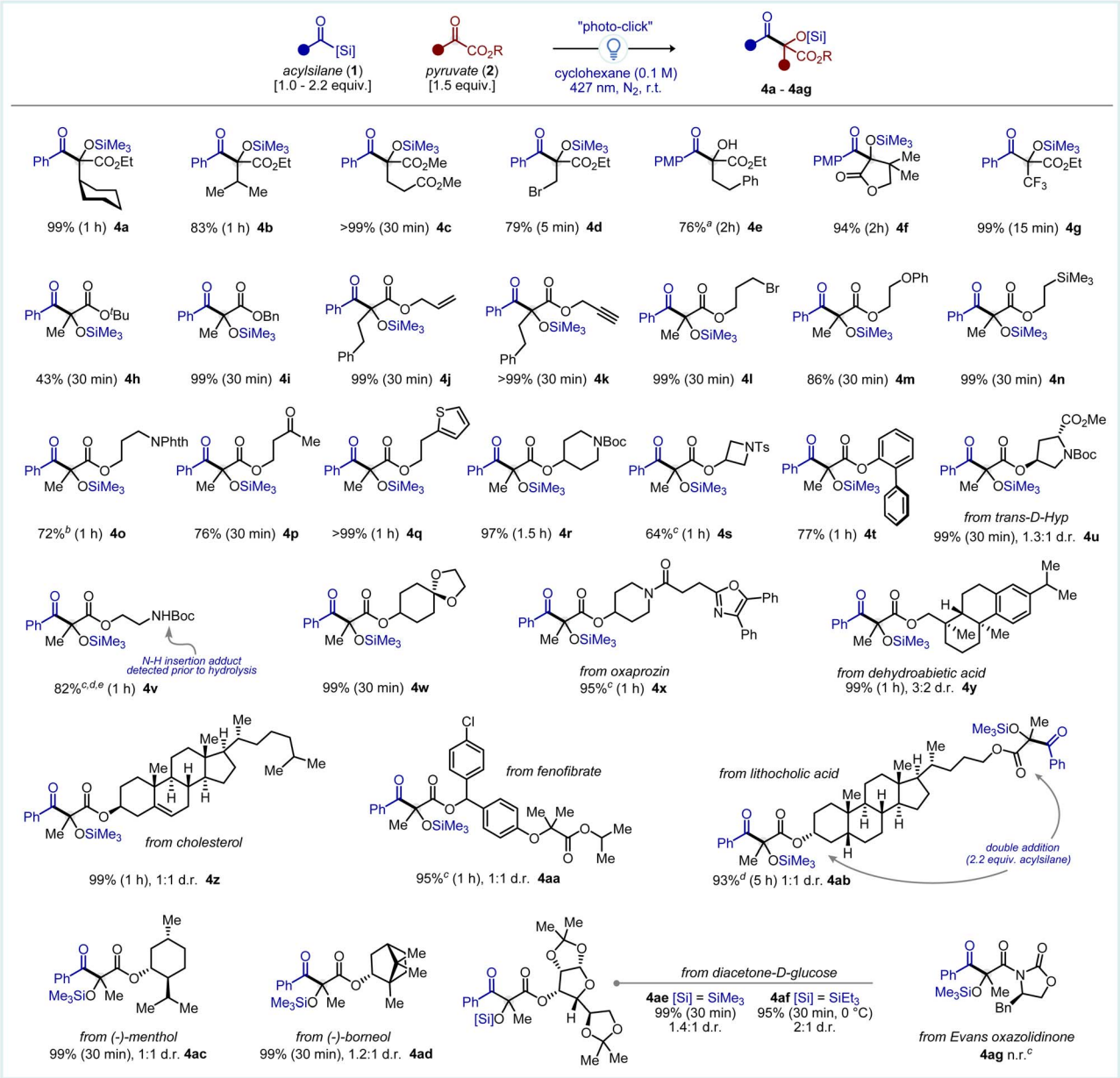
Further substrates containing alkyl bromide (**4l**), *N*-Boc (**4r**), phthalimide (**4o**) and sulfonamide (**4o**), ketones (**4p**), acetal (**4w**), and thiophene (**4q**) functionalities all proved successful. Generally, all were visibly complete with reaction times <1 hour. One exception was the pyruvate substrate bearing a tethered primary carbamate, which upon reaction with excess siloxycarbene afforded the siloxyketone adduct bearing an *N*,*O*-acetal generated *via* N–H insertion of a second siloxycarbene intermediate (detected *via* ^{1}H NMR analysis). Hydrolysis of this unstable *N*,*O*-acetal under mildly acidic aqueous conditions provided a means to ultimately afford the desired mono-addition product **4v**. Pyruvates derived from more synthetically mature frameworks including oxaprozin, dehydroabietic acid, cholesterol and fenofibrate also reacted well to afford siloxyketones **4x–4aa**. Finally, a lithocholic acid derivative bearing two pyruvate functional groups was prepared and irradiated in the presence of 2.2 equivalents of acylsilane which afforded the bis-addition product (**4ab**) in exceptional yield (93%).

Attempts to achieve the diastereoselective 1,2-addition of siloxycarbenes was investigated utilising pyruvate esters derived from chiral alcohols such as hydroxyproline, menthol, and borneol. Although high yields of the desired siloxyketone products were obtained in each case (**4u**, **4ac**, **4ad**), limited diastereoselectivity was achieved. This observation is consistent with a high degree of rotation within the ester group of the chiral pyruvates which obviates chiral influence. Among the adducts, diacetone-D-glucose derived pyruvate provided the greatest diastereomeric ratio (1.4 : 1 d.r., **4ae**) upon photoreaction with benzoyl(trimethyl)silane, which was further improved by employing a bulkier benzoyl(triethyl)silyl analogue and conducting the reaction at 0 °C (95%, 2 : 1 d.r., **4af**). Unfortunately, the Evans' oxazolidinone derived pyruvyl imide failed to react under the standard conditions (**4ag**).

Having established the visible-light induced 1,2-addition of siloxycarbenes with both fluorinated ketones[13] and α-ketoesters (Schemes 1 and 2) proceeds to afford a variety of α-siloxyketone derivatives, we were intrigued to explore if ketones bearing alternative electron-withdrawing groups were competent electrophiles in the photochemical 1,2-carbonyl addition transformation. To this end, the visible-light irradiation of acylsilanes in the presence of α-ketothioesters was conducted,



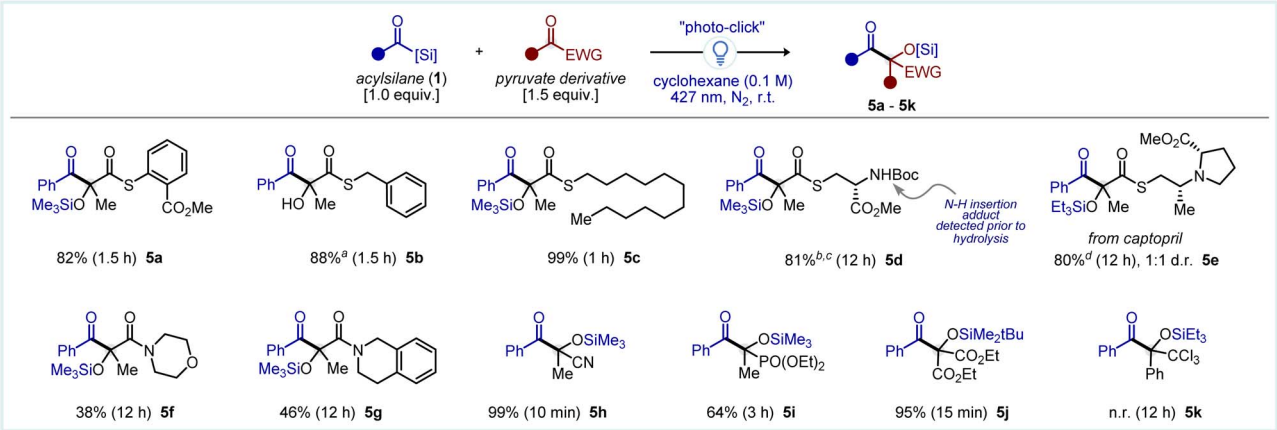
Scheme 1 The reaction of ethyl pyruvate was explored using a variety of acylsilane substrates encompassing aryl, alkenyl and alkyl acylsilanes. Reactions conducted on 0.10–0.40 mmol scales; isolated yields unless otherwise noted. [a]Spectroscopic yield obtained *via* ^{1}H NMR analysis using an internal standard; [b]irradiation conducted in the presence of $Ir(dFCF_3ppy)_2dtbbpy\cdot PF_6$ (0.5 mol%) in PhMe.



Scheme 2 The reaction of acylsilanes was explored using pyruvate substrates encompassing a range of compatible functional groups. 0.1–0.4 mmol scales; isolated yields unless otherwise noted; d.r. values obtained by ^{1}H NMR analysis; n.r. = no reaction. [a]Obtained after hydrolysis of the silyl ether using 1 M HCl (aq.)/THF, r.t.; [b]conducted in 1 : 1 v/v cyclohexane/PhMe as solvent; [c]conducted in PhMe as solvent; [d]2.2 equivalents of acylsilane used; [e]obtained after hydrolysis of the N–H insertion adduct in H_2O/THF.

affording the thioester-containing α-siloxyketones **5a–e** in excellent yields (Scheme 3). In line with that described previously, the α-ketothioester derived from cysteine bearing a carbamate tether reacted with two siloxy carbene intermediates to afford the siloxyketone bearing an *N*,*O*-acetal generated *via* carbene N–H insertion, which under mild acidic conditions was hydrolysed to afford **5d** as the major product. The pyruvyl thioester derived from captopril, an antihypertensive bioactive, also provided the drug-containing conjugate **5e** in good yield. The reaction of α-ketoamides with acylsilanes was also realised (**5f**, **5g**), albeit in reduced yields and requiring longer reaction times due to the reduced electrophilicity of these reactants. Pyruvonitrile and acylphosphonate also reacted cleanly to afford **5h** and **5i**, in 99% and 64% yield respectively. Finally, the tricarbonyl compound diethyl 2-oxomalonate reacted in only 15 min to afford siloxyketone **5j** in an excellent yield of 95%. 2,2,2-Trichloroacetophenone was an unreactive electrophile under the standard conditions and **5k** was not detected. 1,2-Diketones, such as 1,2-diacetyl, afforded a complex mixture of products presumably due to competing photodecomposition of this electrophile.

Photochemical reactions with large volumes suffer from attenuated light penetration through solution according to the Beer–Lambert Law, leading to sluggish conversion rates and



Scheme 3 Pyruvate derivatives containing electron withdrawing groups including thioesters, amides, and phosphonates were also amenable to reaction with acylsilanes. [a]Obtained after hydrolysis of the crude silyl ether using 1 M HCl (aq.)/THF, r.t.; [b]2.2 equivalents of acylsilane used; [c]product obtained after hydrolysis of the N–H insertion adduct in H_2O/THF; [d]cyclohexane/PhMe 1 : 1 v/v was used as solvent. N.r. = no reaction.

altered product profiles. In order to effectively scale photochemical reactions, flow chemical processing is often employed. The miniaturised reactor dimensions in a flow chemical reactor effectively nullify light attenuation allowing for more efficient irradiation of the reaction mixture and enabling consistent scale-up using a scale-out approach.[16] The novel reaction described herein was thus adapted to flow photochemistry conditions (Fig. 2a) by passaging a solution of the reagents through a transparent 1.0 mL glass chip reactor irradiated by a 427 nm (40 W) LED lamp. The reaction was conducted on 3.0 mmol scale, requiring 8 minutes residence time to produce over 800 mg of the product **3g** isolated in excellent yield and purity after concentrating the mixture without chromatographic purification. The space-time-yield (STY) for this process was determined to be 0.10 g min^{-1} mL^{-1}.

With a quantity of α-siloxyketone **3g** in hand, derivatisation was conducted to further demonstrate the synthetic utility of the adducts (Fig. 2b). The ketone group was selectively reduced in the presence of $NaBH_4$ to afford geminal diol **7**, while the use of $LiAlH_4$ afforded triol **8** by global reduction. α-Siloxyketone **3g** was reactive towards methylphosphonium ylide in a Wittig reaction to provide styryl derivative **9** in exceptional yield. These systems proceeded with concomitant hydrolysis of the siloxy substituent, a reaction which can be otherwise achieved using 1 M HCl to generate the α-hydroxyketone (**6**) in nearly quantitative yield. When α-siloxyketone was treated with trimethylsulfonium ylide, the homologated compound **10** was the major product. Attempts to hydrolyse the ethyl ester of **3g** under basic conditions afforded benzoic acid quantitatively, presumably following a retro-benzoin type fragmentation (see SI for details). Finally, condensation with hydrazine or hydroxylamine afforded in high yield heterocycles **11** and **12**, respectively.

The free energy profile of the siloxycarbene insertion was interrogated using Density Functional Theory (DFT) methods (Fig. 2c). The photoinduced formation of siloxycarbenes proposedly proceeds *via* 1,2-Brook rearrangement from the acylsilane triplet excited state, from which the initially formed triplet carbene ($\mathbf{T_0}$) equilibrates *via* inter-system crossing (ISC) to the singlet siloxycarbene ($\mathbf{S_0}$). The carbene stabilisation energy (CSE) for this process, which is exergonic, reflects the predominantly singlet character of siloxycarbenes owing to the stabilising effect of the non-bonding electrons on the adjacent oxygen atom on the vacant 2p orbital at the carbene centre.[17] The singlet siloxycarbene thus is significantly nucleophilic and is predisposed to undergo 1,2-addition to ethyl pyruvate *via* **TS1**, approaching the carbonyl group at the Bürgi–Dunitz angle (107°) to form zwitterionic intermediate **INT1**. This species may traverse a ring-closure, ring-opening mechanism *via* epoxide **INT2**,[18] or otherwise undergo an energetically spontaneous 1,4-silyl transfer (**TS3**) to the oxyanion to ultimately form the final silicon-trapped α-siloxyketone (**PROD**).

It is likely that **INT1** is destabilised in non-polar solvent such as cyclohexane, leading rapidly to barrier-less silicon transfer *via* **TS3**.[19] Overall the process is calculated to be highly exergonic (−72.1 kcal mol^{-1}) from the singlet siloxycarbene which is congruent with the experimentally observed exceptional reaction efficiency and rapid rate of this visible-light induced protocol. 1,2-Dicarbonyl compounds such as ethyl pyruvate are known to possess low lying triplet energies as well as associated photochemistry.[20] Comparison of the calculated triplet energies of the benzoylsilane **1g** and ethyl pyruvate **2a** suggest that relaxation of the triplet excited state acylsilane by energy transfer to ethyl pyruvate, which would hinder reactivity and lead to photodecomposition of the pyruvate, is disallowed due to the higher triplet energy of the pyruvate. Furthermore, as evidenced by UV-Vis analysis in Fig. 2d-i, direct photodecomposition of ethyl pyruvate is avoided due to its limited absorbance in the visible light region. Of the reactants, only benzoylsilane absorbs visible light (427 nm) energy, whilst pyruvate and the insertion product absorb at wavelengths beyond the visible light spectrum (<400 nm). These spectral differences readily enable the reaction to be tracked visually, or by *ex situ* UV-Vis analysis (Fig. 2d-ii), in which the characteristic yellow absorption profile of the benzoylsilane (**1g** $\lambda_{max} \sim 420$

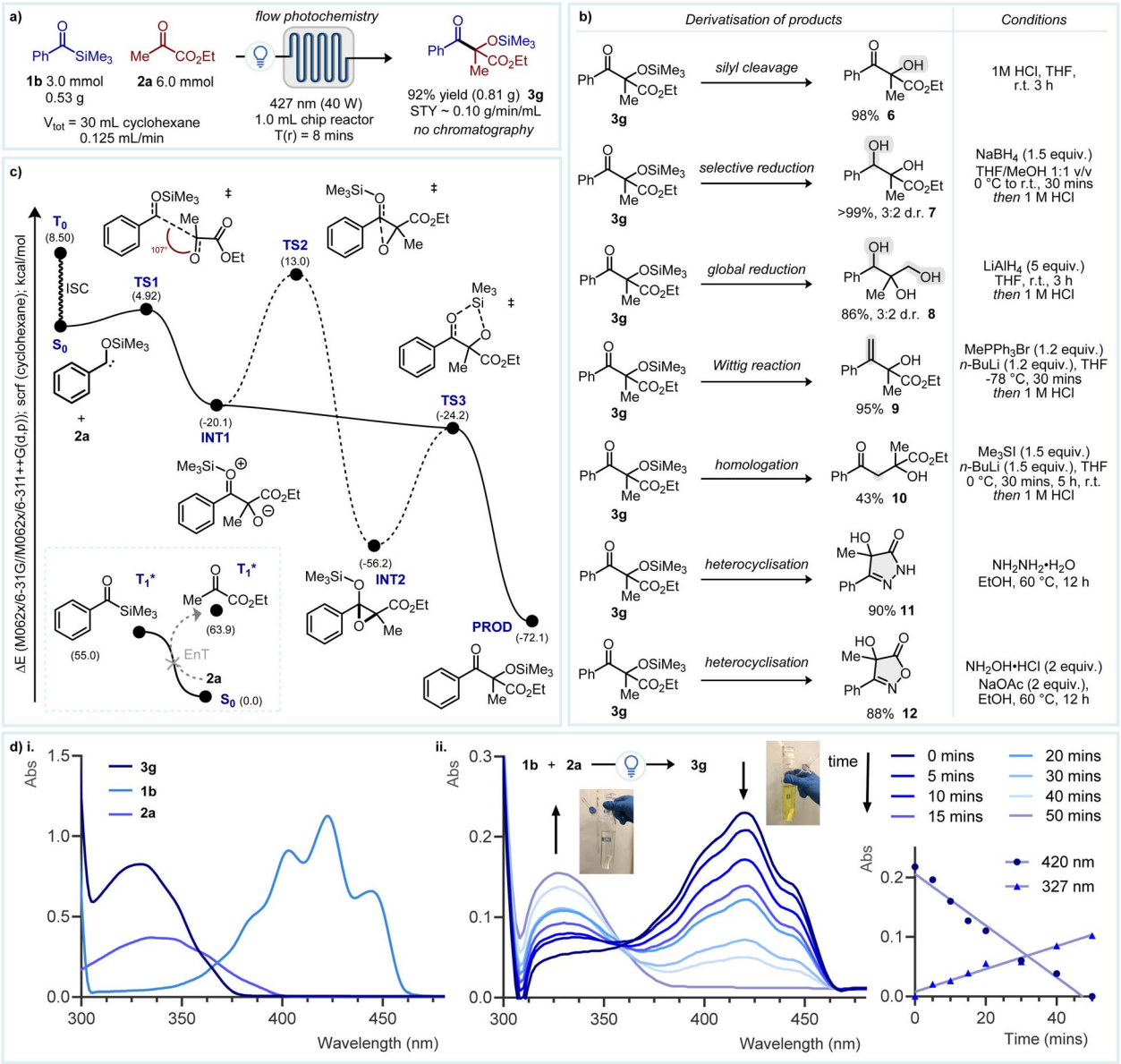


Fig. 2 (a) Flow photochemical preparation of **3g**; (b) product derivatisation reactions and conditions, isolated yields; (c) calculated potential energy profile for pyruvate insertion by singlet siloxycarbene; (d) UV-Vis spectra showing (i) benzoyl(trimethyl)silane **1g**, ethyl pyruvate **2a**, and α-siloxy ketone **3g**; 10 μM in cyclohexane; (ii) *ex situ* reaction profile over time illustrating gradual conversion of benzoyl(trimethyl)silane to a colourless solution of **3g**; reaction conducted under standard conditions; recorded at 2.0 μM in cyclohexane.

nm) is extinguished over time and the absorbance of **3g** develops in the UV-region (**3g** $\lambda_{max} \sim 327$ nm).

In 2001, Sharpless and co-workers introduced click chemistry as a concept for the modular and rapid synthesis of functional molecules.[21] Typically, a set of efficiency criteria must be met for a transformation to be considered a click reaction. For example, the reaction should: (i) be easy to perform and applicable to a diversity of substrates; (ii) be rapid, high yielding, and selective; (iii) generate minimal waste (with any by-products readily removable); and (iv) be carried out under ambient conditions in non-hazardous solvents or neat.[22] Many photochemical reactions readily satisfy these criteria, inspiring the development of visible light induced click chemistry reactions, termed photo-click chemistry.[23] To date, a number of photo-click chemistry strategies have been developed including the visible-light induced azirine–alkene cycloaddition,[24] thiol sulfoxonium ylide reaction,[25] acyl fluoride exchange,[26] Diels–Alder cycloadditions,[27] and the N–H insertion of siloxycarbenes with indole scaffolds.[28]

To this end, the properties of the novel visible light induced reaction described herein align strongly with that required for a (photo)click reaction: operationally simple, rapid, requires visible-light irradiation, proceeds with 100% atom economy (no-byproducts) and is highly modular.[23c] Given this set of desirable properties, the application of this visible light induced process as a photo-click reaction beyond chemical synthesis

(*e.g.* in both bioconjugation and materials science applications) is currently under investigation, with the outcomes to be reported in due course.

Conclusions

The visible light driven reaction of siloxycarbenes (derived from acylsilanes) with pyruvate derivatives has been realised, representing an elusive example of 1,2-addition of siloxycarbenes with ketone functional groups. The process is typically free of toxic and metallic additives, catalysts and reagents beyond innocuous visible light; and allows for rapid, efficient, and selective generation of α-siloxyketone adducts in an operationally simple manner. The reaction shows excellent functional group tolerance with high modularity and was applied to the synthesis of a diverse library of siloxyketones and their subsequent derivatisation. Protocols for preparative multigram scale syntheses were established using both batch and flow methods. Modest diastereoselectivity in the siloxycarbene insertion could be achieved using a pyruvate bearing a chiral auxiliary. Overall, we highlight the synthetic utility of acylsilanes as powerful photo-triggered reagents for chemical synthesis as well as unique compounds of photochemical interest.

Author contributions

D. L. P. and R. L. P. conceived the project. R. L. P., R. K. and J. M. conducted the experiments. R. L. P. conducted the computational analysis. R. L. P., R. K., J. M., S. B. and D. L. P. analysed the data and contributed to writing the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: computational and experimental details including characterisation data and NMR spectra. See DOI: **https://doi.org/10.1039/d5sc06269a**.

Acknowledgements

D. L. P. acknowledges the Australian Research Council (ARC) for their generous funding support (DE200100949; DP240100102). R. L. P. acknowledges the Australian Government RTP for a PhD Scholarship.

References

1 (*a*) F. H. Andrews and M. J. McLeish, *Bioorg. Chem.*, 2012, **43**, 26–36; (*b*) U. Schörken and G. A. Sprenger, *Biochim. Biophys. Acta, Protein Struct. Mol. Enzymol.*, 1998, **1385**, 229–243; (*c*) Y. Kim, S. H. Lee, P. Gade, M. Nattermann, N. Maltseva, M. Endres, J. Chen, P. Wichmann, Y. Hu, D. G. Marchal, Y. Yoshikuni, T. J. Erb, R. Gonzalez, K. Michalska and A. Joachimiak, *Commun. Chem.*, 2024, **7**, 160.

2 (*a*) P. Lehwald, M. Richter, C. Röhr, H.-w. Liu and M. Müller, *Angew. Chem., Int. Ed.*, 2010, **49**, 2389–2392; (*b*) J. Uranga, F. Rabe von Pappenheim, K. Tittmann and R. A. Mata, *J. Phys. Chem. B*, 2023, **127**, 9423–9432.

3 (*a*) M. Pohl, G. A. Sprenger and M. Müller, *Curr. Opin. Biotechnol.*, 2004, **15**, 335–342; (*b*) M. Pohl, B. Lingen and M. Müller, *Chem.–Eur. J.*, 2002, **8**, 5288–5295.

4 Y. Hachisu, J. W. Bode and K. Suzuki, *Adv. Synth. Catal.*, 2004, **346**, 1097–1100.

5 (*a*) D. Enders and A. Henseler, *Adv. Synth. Catal.*, 2009, **351**, 1749–1752; (*b*) D. Enders, O. Niemeier and T. Balensiefer, *Angew. Chem., Int. Ed.*, 2006, **45**, 1463–1467; (*c*) C. G. Goodman and J. S. Johnson, *J. Am. Chem. Soc.*, 2014, **136**, 14698–14701; (*d*) H. Ji, J. Xu and H. Ren, *Synthesis*, 2019, **51**, 2191–2197; (*e*) C. A. Rose, S. Gundala, C.-L. Fagan, J. F. Franz, S. J. Connon and K. Zeitler, *Chem. Sci.*, 2012, **3**, 735–740; (*f*) H. Takikawa, Y. Hachisu, J. W. Bode and K. Suzuki, *Angew. Chem., Int. Ed.*, 2006, **45**, 3492–3494; (*g*) K. Thai, S. M. Langdon, F. Bilodeau and M. Gravel, *Org. Lett.*, 2013, **15**, 2214–2217; (*h*) J. Xu, J. Peng, C. He and H. Ren, *Org. Chem. Front.*, 2019, **6**, 172–176; (*i*) A. Rizzo, R. J. Mayer and D. Trauner, *J. Org. Chem.*, 2019, **84**, 1162–1175.

6 (*a*) L. Atkin and D. L. Priebbenow, *Chem. Commun.*, 2022, **58**, 12604–12607; (*b*) P. Becker, R. Pirwerdjan and C. Bolm, *Angew. Chem., Int. Ed.*, 2015, **54**, 15493–15496; (*c*) B. Huang, M. Wei, E. Vargo, Y. Qian, T. Xu and F. D. Toste, *J. Am. Chem. Soc.*, 2021, **143**, 17920–17925; (*d*) T. Inagaki, S. Sakurai, M. Yamanaka and M. Tobisu, *Angew. Chem., Int. Ed.*, 2022, **61**, e202202387; (*e*) K. Ito, H. Tamashima, N. Iwasawa and H. Kusama, *J. Am. Chem. Soc.*, 2011, **133**, 3716–3719; (*f*) R. Masuda, Y. Anami and H. Kusama, *Org. Lett.*, 2024, **26**, 8011–8016; (*g*) S. S. Patel, S. Gupta and C. B. Tripathi, *Chem.–Asian J.*, 2024, **19**, e202400240; (*h*) S. Sakurai, T. Inagaki, T. Kodama, M. Yamanaka and M. Tobisu, *J. Am. Chem. Soc.*, 2022, **144**, 1099–1105; (*i*) M. Saleem, A. Ratwan, P. Yamini and D. Yadagiri, *Org. Lett.*, 2024, **26**, 2039–2044; (*j*) T. Takeuchi, T. Aoyama, K. Orihara, K. Ishida and H. Kusama, *Org. Lett.*, 2021, **23**, 9490–9494; (*k*) Y. Ueda, Y. Masuda, T. Iwai, K. Imaeda, H. Takeuchi, K. Ueno, M. Gao, J.-y. Hasegawa and M. Sawamura, *J. Am. Chem. Soc.*, 2022, **144**, 2218–2224; (*l*) Z.-Y. Xie, Q.-Q. Li, Y. Liu, B.-G. Cai and J. Xuan, *Org. Lett.*, 2024, **26**, 5827–5832; (*m*) H.-J. Zhang, D. L. Priebbenow and C. Bolm, *Chem. Soc. Rev.*, 2013, **42**, 8540–8571; (*n*) G. Zhou, Z. Guo, S. Liu and X. Shen, *J. Am. Chem. Soc.*, 2024, **146**, 4026–4035; (*o*) Q. Zhao, Q. Geng, Y. Li, J. Li and Z. Liu, *Org. Chem. Front.*, 2023, **10**, 1316–1321; (*p*) R. L. Pilkington and D. L. Priebbenow, *ACS Catal.*, 2025, **15**, 6881–6894; (*q*) X. Shen, *Acc. Chem. Res.*, 2025, **58**, 1519–1533; (*r*) Y. Zhang, G. Zhou, S. Liu and X. Shen, *Chem. Soc. Rev.*, 2025, **54**, 1870–1904; (*s*) V. K. Rawat and M. Tobisu, *ACS Catal.*, 2025, **15**, 8706–8723; (*t*) Y. Guo, G. Zhou and X. Shen, *Chin. J. Chem.*, 2024, **42**, 887–902.

7 (*a*) D. L. Priebbenow, *Adv. Synth. Catal.*, 2020, **362**, 1927–1946; (*b*) G. Zhou, Z. Guo and X. Shen, *Angew. Chem., Int. Ed.*, 2023, **62**, e202217189; (*c*) J.-H. Ye, L. Quach, T. Paulisch and F. Glorius, *J. Am. Chem. Soc.*, 2019, **141**, 16227–16231; (*d*) K. Ishida, H. Yamazaki, C. Hagiwara, M. Abe and H. Kusama, *Chem.–Eur. J.*, 2020, **26**, 1249–1253.

8 (*a*) A. Bunyamin, C. Hua, A. Polyzos and D. L. Priebbenow, *Chem. Sci.*, 2022, **13**, 3273–3280; (*b*) P. Becker, D. L. Priebbenow, H.-J. Zhang, R. Pirwerdjan and C. Bolm, *J. Org. Chem.*, 2014, **79**, 814–817; (*c*) H.-J. Zhang, P. Becker, H. Huang, R. Pirwerdjan, F.-F. Pan and C. Bolm, *Adv. Synth. Catal.*, 2012, **354**, 2157–2161; (*d*) Y. Zhang, G. Zhou, X. Gong, Z. Guo, X. Qi and X. Shen, *Angew. Chem., Int. Ed.*, 2022, **61**, e202202175; (*e*) G. Zhou and X. Shen, *Angew. Chem., Int. Ed.*, 2022, **61**, e202115334; (*f*) G. Zhou, Y. Yao, X. He, W. Zhang, S. Liu and X. Shen, *Chem*, 2025, 102721.

9 (*a*) R. L. Pilkington, H. J. Ross, L. Atkin and D. L. Priebbenow, *Chem. Sci.*, 2024, **15**, 19328–19335; (*b*) Y. Liu, Z. Zhu, Y. Zhang, Y. Zhang, S. Liu and X. Shen, *Org. Lett.*, 2024, **26**, 5911–5916; (*c*) Z. Zhu, W. Zhang, Y. Zhang, S. Liu and X. Shen, *CCS Chem.*, 2023, **5**, 325–333.

10 Z. Li, Z. Zhang, Z. Zhang, G. Zhou, Y. Zhang, S. Liu and X. Shen, *Sci. China Chem.*, 2024, **67**, 3662–3668.

11 (*a*) K. Ishida, F. Tobita and H. Kusama, *Chem.–Eur. J.*, 2018, **24**, 543–546; (*b*) L. Ma, Y. Yu, L. Xin, L. Zhu, J. Xia, P. Ou and X. Huang, *Adv. Synth. Catal.*, 2021, **363**, 2573–2577.

12 Z. Fan, Y. Yi, S. Chen and C. Xi, *Org. Lett.*, 2021, **23**, 2303–2307.

13 D. L. Priebbenow, R. L. Pilkington, K. N. Hearn and A. Polyzos, *Org. Lett.*, 2021, **23**, 2783–2789.

14 R. Vaggu, N. Thadem, M. Rajesh, R. Grée and S. Das, *Org. Lett.*, 2023, **25**, 2594–2599.

15 L. Atkin, H. J. Ross and D. L. Priebbenow, *J. Org. Chem.*, 2023, **88**, 14205–14209.

16 (*a*) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel and T. Noël, *Chem. Rev.*, 2016, **116**, 10276–10341; (*b*) J. P. Knowles, L. D. Elliott and K. I. Booker-Milburn, *Beilstein J. Org. Chem.*, 2012, **8**, 2025–2052; (*c*) C. Sambiagio and T. Noël, *Trends Chem.*, 2020, **2**, 92–106; (*d*) L. Capaldo, Z. Wen and T. Noël, *Chem. Sci.*, 2023, **14**, 4230–4247.

17 D. L. Priebbenow, *J. Org. Chem.*, 2019, **84**, 11813–11822.

18 The diastereomer of **INT2** (**INT2′**) and its corresponding transition state (**TS2′**) were also considered and the lowest energy diastereomer is shown. Details can be found in the SI.

19 **INT1** modelled in cyclohexane (scrf) was destabilised by +4.86 kcal mol^{-1} relative to the structure optimised in DMSO. **TS3** is stabilised in cyclohexane (−2.40 kcal mol^{-1}) relative to DMSO.

20 R. W. Binkley, *Synth. Commun.*, 1976, **6**, 281–284.

21 H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021.

22 (*a*) C. D. Hein, X.-M. Liu and D. Wang, *Pharm. Res.*, 2008, **25**, 2216–2230; (*b*) N. K. Devaraj and M. G. Finn, *Chem. Rev.*, 2021, **121**, 6697–6698.

23 (*a*) M. A. Tasdelen and Y. Yagci, *Angew. Chem., Int. Ed.*, 2013, **52**, 5930–5938; (*b*) G. S. Kumar and Q. Lin, *Chem. Rev.*, 2021, **121**, 6991–7031; (*c*) Y. Fu, N. A. Simeth, W. Szymanski and B. L. Feringa, *Nat. Rev. Chem.*, 2024, **8**, 665–685; (*d*) B. D. Fairbanks, L. J. Macdougall, S. Mavila, J. Sinha, B. E. Kirkpatrick, K. S. Anseth and C. N. Bowman, *Chem. Rev.*, 2021, **121**, 6915–6990.

24 R. K. V. Lim and Q. Lin, *Chem. Commun.*, 2010, **46**, 7993–7995.

25 C. Wan, Z. Hou, D. Yang, Z. Zhou, H. Xu, Y. Wang, C. Dai, M. Liang, J. Meng, J. Chen, F. Yin, R. Wang and Z. Li, *Chem. Sci.*, 2023, **14**, 604–612.

26 L. Deng, C. Zhang, B. Li, J. Fu, Z. Zhang, S. Li, X. Zhao, Z. Su, C. Hu and Z. Yu, *Chem. Sci.*, 2023, **14**, 3630–3641.

27 S. Arumugam and V. V. Popik, *J. Am. Chem. Soc.*, 2011, **133**, 5573–5579.

28 (*a*) C. Stuckhardt, M. Wissing and A. Studer, *Angew. Chem., Int. Ed.*, 2021, **60**, 18605–18611; (*b*) J. Reimler and A. Studer, *Chem.–Eur. J.*, 2021, **27**, 15392–15395.