Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Sci.*, 2023, **14**, 12767

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

Received 5th October 2023
Accepted 28th October 2023

DOI: 10.1039/d3sc05263j

rsc.li/chemical-science

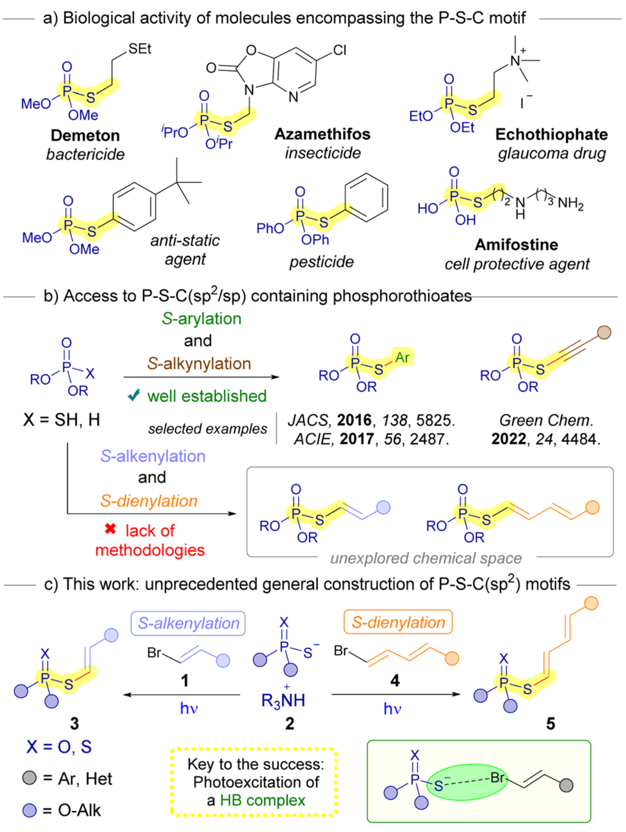
Photochemical halogen-bonding assisted carbothiophosphorylation reactions of alkenyl and 1,3-dienyl bromides†

Helena F. Piedra, Victoria Gebler, Carlos Valdés and Manuel Plaza*

Herein, we present a synthetic procedure for the facile and general preparation of novel *S*-alkenyl and dienyl phosphoro(di)thioates for the first time. Extensive mechanistic investigations support that the reactions rely on a photochemical excitation of a halogen-bonding complex, formed with a phosphorothioate salt and an alkenyl or dienyl bromide, which light-induced fragmentation leads to the formation of the desired products through a radical-based pathway. The substrate scope is broad and exhibits a wide functional group tolerance in the formation of the final compounds, including molecules derived from natural products, all with unknown and potentially interesting biological properties. Eventually, a very efficient continuous flow protocol was developed for the upscale of these reactions.

1 Introduction

The development of novel synthetic methodologies for the construction of C–S bonds is an important undertaking in organic chemistry.[1] In particular, the design of new organic transformations oriented to the formation of sulfur-containing organophosphorous compounds is particularly attractive. This is due to the interesting properties these compounds feature from both a biological and chemical point of view.[2] A prominent class of these organosulfur compounds encompasses phosphorothioate diesters that contain a P–S–C(sp^2) structural motif.[3] These compounds are reported to be useful as pesticides,[4] therapeutic molecules[5] and valuable building blocks in organic synthesis.[6] The significance of these compounds is underscored by the numerous methodologies that have been documented in recent years centered around their synthesis.[7] While both metal-catalyzed[8] and metal-free[9] procedures have been well established for creating *S*-arylated phosphorothioates (Scheme 1b), we could only find one example of a synthetic methodology for the preparation of the analogous *S*-alkenylated compounds.[10] However, this protocol contemplates a very limited scope (6 examples), making use of uncommon iodonium salts. When it comes to the *S*-alkynylation of phosphorothioate diesters, Tang has recently reported an elegant approach through a dual photoredox/copper catalysis under operationally simple conditions.[11] However, to the best of our knowledge there are currently still no procedures reported for the *S*-dienylation of phosphorotioate diesters. Considering the intriguing potential biological attributes inherent in these novel



Scheme 1 State of the art in the synthesis of P–S–C(sp^2/sp) containing molecules.

Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Química Organometálica "Enrique Moles", Centro de Innovación en Química Avanzada (ORFEO-CINQA), Universidad de Oviedo, Julián Clavería 8, 33006 Oviedo, Spain. E-mail: plazamanuel@uniovi.es

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d3sc05263j

organophosphorous compounds, it is highly desirable to develop general, sustainable and simple procedures for their synthesis.

Our research group has recently developed a procedure for the cross-coupling between alkenyl halides and thiolates, enabled by photochemical excitation of halogen-bonding complexes.[12] Notably, this method offers a photocatalyst-free alternative to other contemporary light-driven approaches used for synthesizing similar compounds, such as thiol-yne reactions, which typically involve starting materials like alkynes and thiolates.[13]

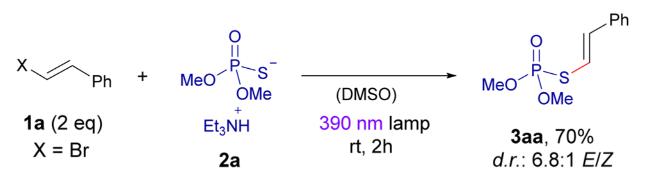
The photochemical activation of halogen-bonding complexes has gained significant attention in recent years for the generation of carbon-centered radicals,[14] facilitating novel organic transformations to occur.[15] The halogen bond is a type of weak interaction that falls under the category of σ-hole interactions.[16] Specifically, it involves a partial $n \rightarrow \sigma^*$ charge-transfer from a non-bonding orbital of a nucleophilic electron donor (HB acceptor) to an antibonding orbital (σ^*) of an electron acceptor, the corresponding organic halide (HB donor).[17] This stabilizing interaction is responsible for the formation of halogen-bonding complexes, which are a specific type of EDA (electron donor–acceptor) complexes.[18] By inducing a photochemical fragmentation of the HB complex through the reduction of the C–halogen bond, two different radical species can be generated from the synthetic precursors. These radicals can then directly recombine to form the desired cross-coupling product. Based on all the above, we saw potential in the photochemical halogen-bonding-assisted reaction between alkenyl halides **1** and phosphorothioate salts **2** for the construction of *S*-alkenylated or dienylated phosphorothioates **3** or **5**, respectively (Scheme 1c). It should be pointed out that.

2 Results and discussion

We initiated our experimental studies employing the dimethyl phosphorothioate **2a** and β-bromostyrene **1a** as the coupling partners in our photochemical reaction. As it will be discussed later in more detail, a preliminary UV-vis analysis of a solution containing both compounds revealed the formation of a charge-transfer (CT) band, which was indicative of the formation of the desired halogen-bonding complex and gave us precious information on which excitation wavelength could potentially be used to promote the coupling reaction (370–400 nm).

A summary of the optimization process is presented in the Table 1. Much to our pleasure, our preliminary reaction conditions employing the 390 nm lamp (2 h of irradiation) and DMSO as the solvent, afforded the formation of the desired compound **3aa** with a 70% isolated yield. Control experiments revealed that the presence of light was necessary to carry out the transformation (entry 1). It was noticed that longer irradiation times led to significant degradation of the final product, which is not photostable over 16 hours of irradiation with violet light (entry 2). The use of light with either lower (366 nm) or higher (427 nm) wavelength failed to improve the reaction yield (entries 3 and 4). The use of other polar solvents like acetonitrile or DMF was compatible with the reaction, albeit providing lower yields in the obtention of **3aa**. A change in the molar ratio of the reaction partners **1a** and **2a** led to a significant drop in the yield of the transformation (entries 7 and 8). Eventually, the employment of alkenyl chlorides or iodides (entries 9 and 10) provided the coupling product with low and very low yield, respectively; a quite expected result considering our previous experience in halogen-bonding assisted alkenylations.[12]

Table 1 Screening of the optimal reaction conditions. Preliminary reaction conditions: alkenyl bromide **1** (0.3 mmol) and phosphorodithioate salt **2** (0.15 mmol) in 3 mL of DMSO, irradiation with a 390 nm lamp (52 W) over 2 hours. Isolated yields after flash chromatography are presented



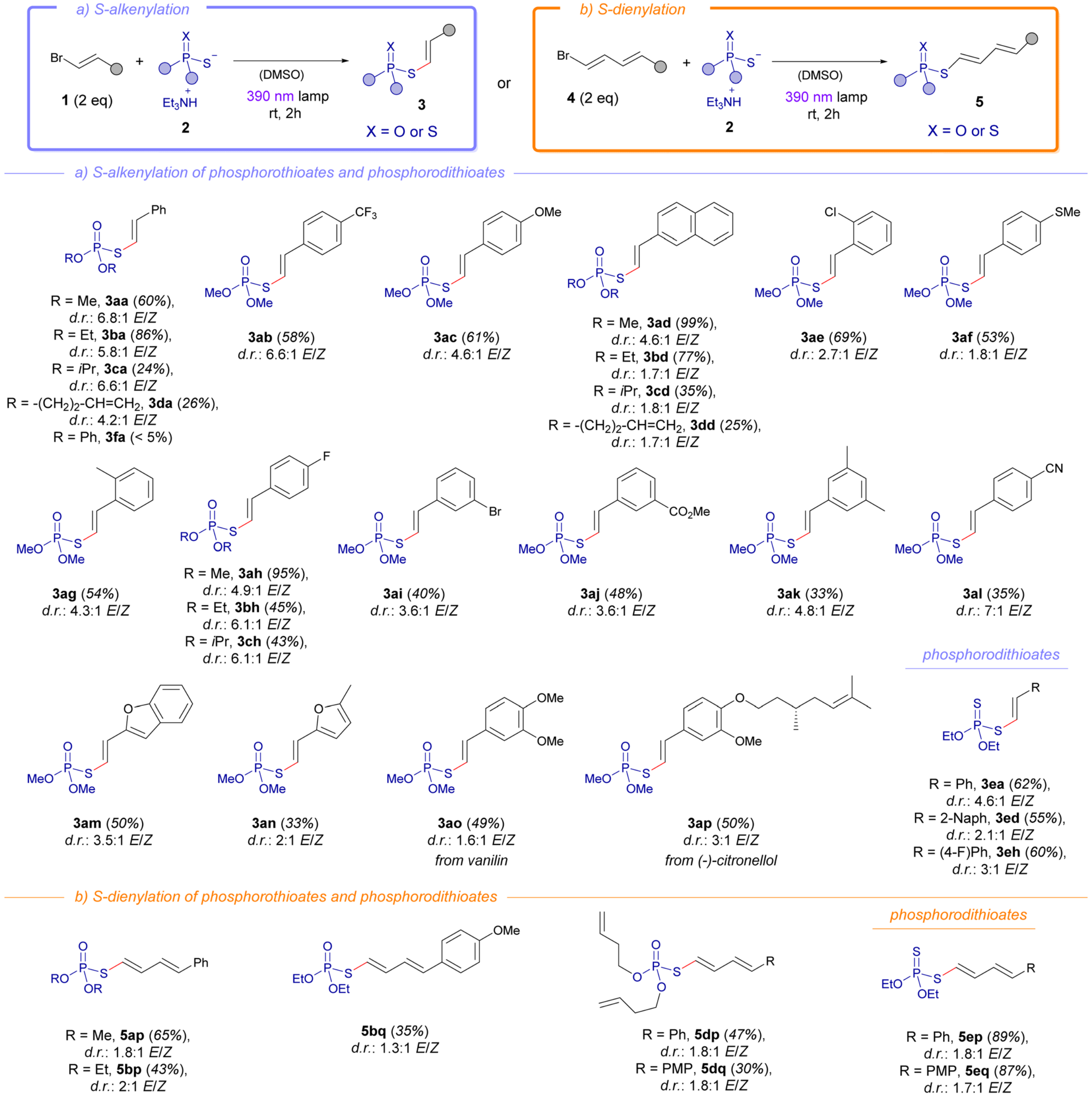
1a (2 eq)
X = Br

2a

3aa, 70%
d.r.: 6.8:1 *E*/*Z*

Entry	Deviation from standard conditions	Yield **3aa**
1	Dark, 24 h	—
2	16 h of irradiation	27%
3	366 nm instead of 390 nm lamp	24%
4	427 nm instead of 390 nm lamp	10%
5	MeCN instead of DMSO	45%
6	DMF instead of DMSO	58%
7	2 : 1 molar ratio **1a**/**2a**	5%
8	1 : 1 molar ratio **1a**/**2a**	23%
9	X = Cl	35%
10	X = I	5%

Having established the optimal conditions for the photochemical alkenylation reaction, we next examined the scope of this novel transformation (Scheme 2a). This methodology demonstrated remarkable versatility by accommodating a diverse array of functional groups on the alkenylated phosphorothioate diesters, validating the robustness of the transformation. For instance, electron-withdrawing moieties could be installed in the final products such as the trifluoromethyl group (**3ab**), halogens (**3ae**, **3ai**, **3ah**), esters (**3aj**) and nitriles (**3al**). Neutral aromatic groups such as the phenyl (**3aa**) or 2-naphtyl (**3ad**) were also compatible with this methodology. Remarkably, the presence of electron-donating groups at the alkenyl fragment, which theoretically could diminish the strength of the halogen-bond, also enabled the formation of the phosphorothioate diesters. These include for example compounds bearing a methoxy (**3ac**) or thiomethoxy (**3af**) functionalities. Importantly, the presence of heterocycles such as benzofuran (**3am**) or furan (**3an**) in the alkenyl fragment was compatible with our methodology. Shifting focus to the examination of the phosphorothioate salts **2**, we observed tolerance for different alkyl groups such as methyl, ethyl, isopropyl, or homoallyl. This protocol could be extended even to fragments resembling natural products, as demonstrated by the synthesis of vanillin-derived (**3ao**) and (−)-citronellol-derived (**3ap**) compounds. However, it should be pointed out that aromatic esters lead to the formation of the *S*-alkenylated

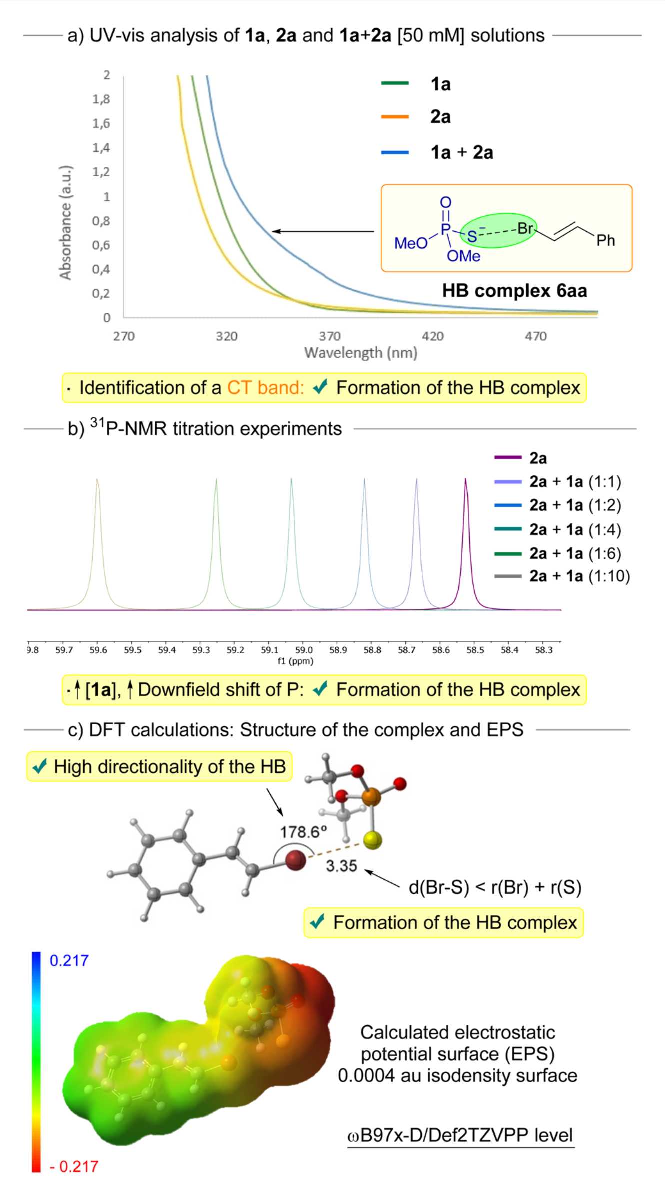


Scheme 2 Scope of the *S*-alkenylation (light purple) and *S*-dienylation (orange) of phosphorothioate and phosphorodithioate diesters. General reaction conditions: alkenyl bromide **1** (0.3 mmol) and phosphorodithioate salt **2** (0.15 mmol) in 3 mL of DMSO, irradiation with a 390 nm lamp (52 W) over 2 hours. Isolated yields after flash chromatography are presented. PMP = 4-methoxyphenyl.

phosphorothioate **3fa** in barely traces. Particularly interesting is the synthesis of the compound **3ai**, which leaves intact the aromatic bromide at **1i**, also prone to form a HB complex with **2a**. This result is in line with previous competition experiments carried out in our group in transformations based on photochemical activation of HB complexes.[12]

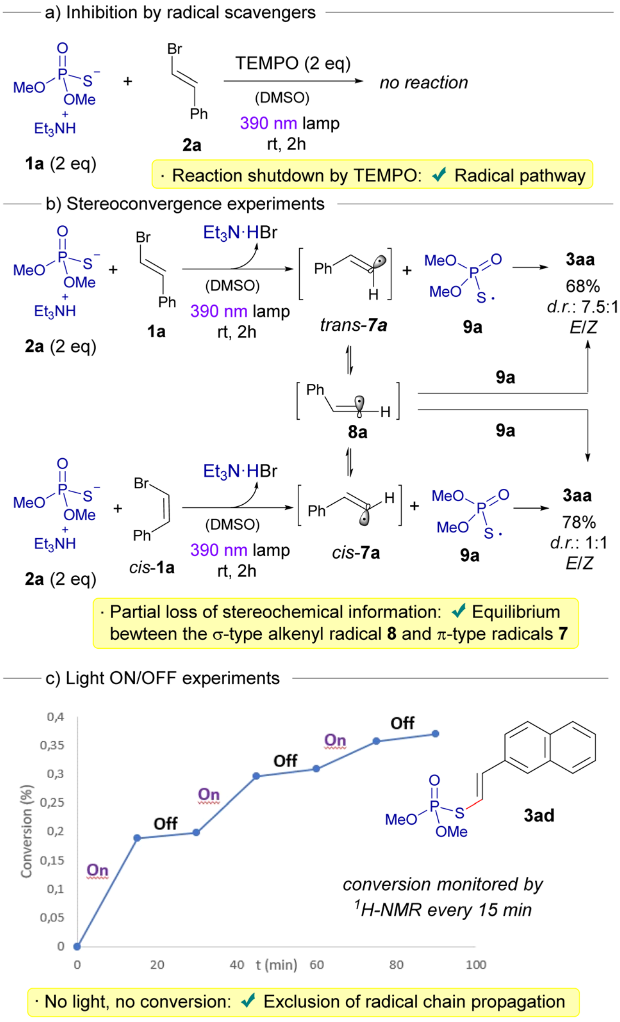
In an extension of our work, we successfully conducted the alkenylation reaction using phosphorodithioate diesters, yielding the target compounds **3ea**, **3ed** and **3eh** with commendable yields. Given the success of the alkenylation reaction, we wondered if the analogous 1,3-dienylation could take place, which would significantly expand the scope of the photochemical halogen-bonding assisted reaction. Indeed, the reaction of the phosphorothioate salts **2** with the 1,3-dienyl bromides **4** granted the formation of the dienylated phosphorothioates **5** under the same reaction conditions as for the alkenylation reaction (Scheme 2b). In this context, different variations at the alkyl fragment of the phosphorothioate salts **2** were compatible in the reaction with the dienyl bromides, validating the synthetic utility of our *S*-dienylation reaction for the preparation of the compounds **5ap** to **5dp** in moderate to good yields. Remarkably, the incorporation of a phosphorodithioate fragment could be accomplished, giving rise to the compounds **5ep** and **5eq** with very good yields.

A set of mechanistic studies was carried out to support the formation of a halogen-bonding complex during the transformation. First, we recorded the UV-vis profiles of solutions of the individual compounds **1a** and **2a**. Importantly, when mixing equimolar amounts of both reaction components in DMSO, a distinctive red-shifted charge transfer (CT) band could be observed, a telltale sign of the formation of the halogen-bonding complex **6aa** (Scheme 3a).[14,19] This observation aligns with our rationale behind selecting the 390 nm lamp, strategically chosen to facilitate the photoexcitation of the HB complex **6aa**. Additional evidence for the existence of the halogen-bonding (HB) complex emerged through the implementation of ^{31}P-NMR titration experiments (Scheme 3b).[14,19,20] Within this context, we meticulously tracked a striking downfield shift, nearing 1 ppm, of the ^{31}P-NMR signal of **2a** as we systematically introduced incremental quantities of **1a** while maintaining a consistent molar amount of **2a** (see ESI† for details). Eventually, we carried out preliminary DFT computational studies (ω-B97x-D3/Def2TZVPP level) to identify the nature of the halogen-bonding complex **6aa** (Scheme 3c). These endeavors led to the identification of a halogen-bonding assembly involving **1a** and **2a**, validated as a local minimum on the potential energy surface. Notably, the halogen bond interaction between the bromine and sulfur atoms demonstrated a strikingly defined directionality, as evidenced by a dihedral angle of 178.6° within the C(sp^2)–Br–S bonds. This linear geometry, characterized by dihedral angles spanning from 160° to 180° within the HB complex, concurs with findings documented in prior investigations.[21] Indeed, in the electrostatic potential surface, it is observed that a positively charged bromine σ–hole zone is located at almost the center of the C–Br axis. Furthermore, the distance between the bromine and sulfur atoms within the halogen-bonding complex **6aa** (3.35 Å) is distinctly shorter than the cumulative van der Waals radii of these atoms (3.65 Å). This observation bolsters the notion of a substantial non-covalent interaction binding these atoms, most likely attributed to the formation of the halogen bond.

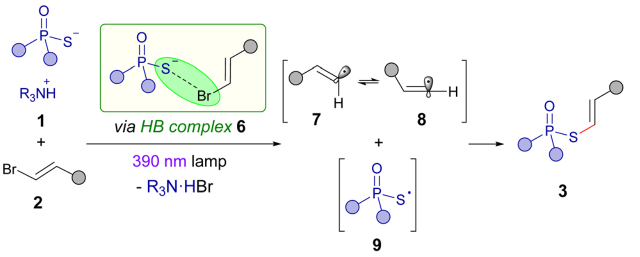


Scheme 3 Set of mechanistic studies run towards the identification of the structure and nature of the halogen-bonding complex **6aa**. EPS = Electrostatic Potential Surface.

Having initially hypothesized the emergence of alkenyl radicals during our transformation, we undertook a distinct series of mechanistic investigations to probe the radical nature of our reaction. Primarily, we noted that the introduction of radical scavengers, such as TEMPO, caused a complete cessation of the transformation, a compelling endorsement of the radical-mediated pathway (Scheme 4a). Next, the nature of the alkenyl radical formed during the transformation was studied. Since two different structures are normally speculated for the photochemical generation of a vinyl radical (a bent σ-type or a linear π-type),[22] we embarked on stereoconvergence experiments to offer deeper insights into the inherent structure of these highly-reactive alkenyl radicals (Scheme 4b).[23] To achieve this, we investigated the stereochemical outcomes in the formation of the compound **3aa** arising from the reaction between either a *cis*-configured alkenyl bromide *cis*-**1a** or **1a** with **2a**, respectively. In each of the reactions, a photochemical fragmentation of the HB complex would initially lead to the formation of the sulfur-centered radical **9a** and, the angular π-type radicals *cis*-**7a** or *trans*-**7a**, respectively. At this point, two distinct processes can unfold: (1) a direct diastereoretentive recombination of the radical **9a** with either *cis*-**7a** or *trans*-**7a**, respectively, to forge **3aa**; or (2) a kinetic- and/or thermodynamically driven geometric isomerization, transitioning from each of the angular π-type **7a** radicals to the linear σ-type radical **8a**, which eventually can recombine with **9a** to create **3aa**, displaying a complete loss of the initial stereogenic information from **1a**. Remarkably, the absence of a fully stereoconvergent process in both reactions generating **3aa** can be attributed to the coexistence of both these aforementioned processes. This fact effectively accounts for the limited extent of stereoconvergence and the unequal loss of stereochemical information observed across both reactions.[22] Interestingly, the group of



Scheme 4 Elucidation of the radical pathway.



Scheme 5 Mechanistic rationale for the photochemical reaction.

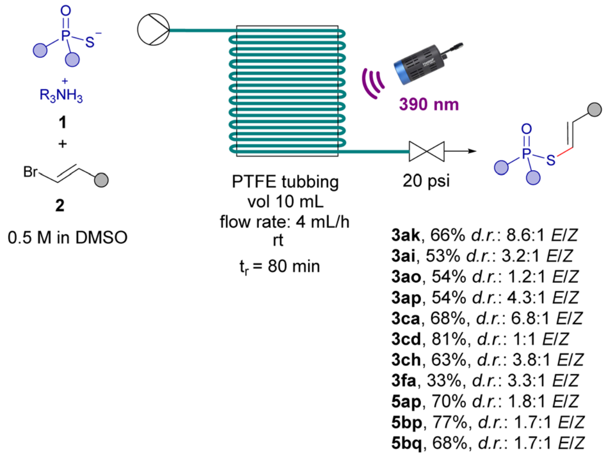
Kanai recently reported that thiyl radicals emerging from BINOL-derived phosphorothioate diesters can be useful as hydrogen atom transfer catalysts in photochemical processes.[24] This is due to the rather long lifetimes these sulfur-centered radicals exhibit (greater than 1000 ns), as demonstrated by transient absorption measurements.

Furthermore, we conducted light on/off experiments, strategically designed to both underscore the indispensability of light and ascertain the presence of radical chain propagation events (Scheme 4c).[15d,25] The latter were conclusively ruled out, given the absence of conversion in the reaction during long intervals when the light source was deactivated, as gauged by monitoring the reaction progression *via* ^{1}H-NMR.

Based on our mechanistic investigations and the precedent set by other photochemical halogen-bonding assisted reactions,[14] the mechanism described in the Scheme 5 is proposed. First, the formation of a halogen-bonding complex **6** between the alkenyl bromide **1** and phosphorothioate salt **2** is proposed to be formed. Photoexcitation and subsequent fragmentation of this aggregate would lead to the creation of the sulfur centered radical **9** and the angular π-type alkenyl radical **7**, which is in equilibrium with the corresponding linear σ-type vinyl radical **8**. A radical recombination of either **7** or **8** with **9** would eventually forge the final products **3**.

The last part of our work was devoted to the development of a continuous flow protocol to enable the scale up of the photochemical transformations. In general, the development of light-driven reactions through continuous flow protocols offers several advantages, which encompass: rapid scalability, enhanced security, better reproducibility and easier control.[26] Therefore, we conducted an initial investigation to assess the feasibility of this potential application using a flow reactor constructed from PTFE tubing (see ESI† for details). Our preliminary protocol involved flowing a solution of both reaction components **1** and **2** in DMSO through the flow reactor while subjecting it to 80 min of illumination from a 390 nm lamp. Significantly, thanks to the enhanced efficiency of our process, we have achieved notable improvements in several key aspects compared to the corresponding batch reactions: (a) a remarkable 20–50% general enhancement in reaction yields accross the scope, exemplified, for instance, by the compounds **3ak**, **3ca**, **5bp**, **5bq** and **3cd**; (b) reduced reaction times (80 min of irradiation *versus* 120 min in batch); (c) higher diastereomeric ratios in favour of the *trans* isomer, due to the less exposure time to irradiation of our reaction products (Scheme 6).

Remarkably, following our flow protocol, the synthesis of the phenyl phosphorothioate **3fa** could be accomplished, which was not possible under batch conditions. All in all, these



Scheme 6 Scale up through a continuous flow protocol.

advancements underscore the value of our flow procedure for facilitating the upscaling and improving reaction efficiencies of the photochemical alkenylations and dienylations.

3 Conclusions

In summary, we have now reported a simple, general and mild procedure for the preparation of novel *S*-alkenyl and *S*-dienyl phosphoro(di)thioate esters. The procedure relies on a photochemical excitation with visible-light of a halogen-bonding complex formed between an alkenyl or dienyl bromide with a phosphoro(di)thioate salt. Importantly, there are no other methodologies available for the synthesis of these compounds in a general and straightforward manner. A very efficient flow protocol was developed to upscale the transformations. Overall, we believe the ongoing advancements in the synthesis of novel organosulfur compounds with alkenyl and dienyl substituents within the P–S–C(sp^2) structural motif could potentially lead to the discovery of new molecules with improved biological properties and important applications in various fields, such as the agrochemical or drug industries.

Data availability

All of the necessary data had been included in the ESI.†

Author contributions

H. F. Piedra and V. Gebler conducted all of the reactions, DFT calculations, experimental mechanistic studies and full characterization of the compounds. C. Valdés contributed to the supervision and direction of the project. M. Plaza conceptualized and directed the project and wrote the manuscript. All the authors contributed to scientific discussions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support of this work by a FICYT (Principality of Asturias) "Margarita Salas Joven" postdoctoral grant to M. P. (AYUD/2021/58397) and Ministerio de Ciencia e Innovación of Spain (Agencia Estatal de Investigación: PID2019-107580GB-I00/AEI/10.13039/501100011033). A "Severo Ochoa" predoctoral fellowship to H. F. P. (BP21/050) by FICYT and an Erasmus+ scholarship to V. G. are also gratefully acknowledged.

Notes and references

1 Selected reviews: (*a*) C.-F. Lee, R. S. Basha and S. S. Badsara, *Top. Curr. Chem.*, 2018, **376**, 25; (*b*) P. Annamalai, K. Liu, S. Singh Badsara and C. Lee, *Chem. Rec.*, 2021, **21**, 3674–3688; (*c*) I. P. Beletskaya and V. P. Ananikov, *Chem. Rev.*, 2022, **122**, 16110–16293; (*d*) Z. Wu and D. A. Pratt, *Nat. Rev. Chem*, 2023, **7**, 573–589; (*e*) J. Feng, Y. Zhang, X. Wang, J. Liu, V. Benazzi, K. Lu, X. Zhao and S. Protti, *Adv. Synth. Catal.*, 2023, **365**, 3413–3431.

2 (*a*) J. Purcell and A. C. Hengge, *J. Org. Chem.*, 2005, **70**, 8437–8442; (*b*) A. B. Lowe, *Polym. Chem.*, 2010, **1**, 17–36; (*c*) E. A. Ilardi, E. Vitaku and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 2832–2842; (*d*) M. Nassir, M. Ociepa, H.-J. Zhang, L. N. Grant, B. J. Simmons, M. S. Oderinde, Y. Kawamata, A. N. Cauley, M. A. Schmidt, M. D. Eastgate and P. S. Baran, *J. Am. Chem. Soc.*, 2023, **145**, 15088–15093.

3 (*a*) L. D. Quin, *A Guide to Organophosphorus Chemistry*, Wiley, New York, 2000; (*b*) P. J. Murphy, *Organophosphorus Reagents: A Practical Approach in Chemistry*, Oxford University Press, New York, 2004.

4 (*a*) L. L. Murdock and T. L. Hopkins, *J. Agric. Food Chem.*, 1968, **16**, 954–958; (*b*) K. D. Wing, A. H. Glickman and J. E. Casida, *Pestic. Biochem. Physiol.*, 1984, **21**, 22–30.

5 (*a*) N.-S. Li, J. K. Frederiksen and J. A. Piccirilli, *Acc. Chem. Res.*, 2011, **44**, 1257–1269; (*b*) J. Duschmalé, H. F. Hansen, M. Duschmalé, E. Koller, N. Albaek, M. R. Møller, K. Jensen, T. Koch, J. Wengel and K. Bleicher, *Nucleic Acids Res.*, 2020, **48**, 63–74; (*c*) H.-J. Zhang, M. Ociepa, M. Nassir, B. Zheng, S. A. Lewicki, V. Salmaso, H. Baburi, J. Nagel, S. Mirza, B. Bueschbell, H. Al-Hroub, O. Perzanowska, Z. Lin, M. A. Schmidt, M. D. Eastgate, K. A. Jacobson, C. E. Müller, J. Kowalska, J. Jemielity and P. S. Baran, *Nat. Chem.*, DOI: **10.1038/s41557-023-01347-2**.

6 Selected examples: (*a*) S. Ohuchi, H. Ayukawa and T. Hata, *Chem. Lett.*, 1992, **21**, 1501–1504; (*b*) Y. Nishiyama, Y. Hazama, S. Yoshida and T. Hosoya, *Org. Lett.*, 2017, **19**, 3899–3902.

7 Recent reviews: (*a*) D. J. Jones, E. M. O'Leary and T. P. O'Sullivan, *Adv. Synth. Catal.*, 2020, **362**, 2801–2846; (*b*) X. Liu, L. Zhou, R. Yang, X.-R. Song and Q. Xiao, *Adv. Synth. Catal.*, 2023, **365**, 2280–2298.

8 Selected examples: (*a*) J. Bai, X. Cui, H. Wang and Y. Wu, *Chem. Commun.*, 2014, **50**, 8860–8863; (*b*) Y. Zhu, T. Chen, S. Li, S. Shimada and L.-B. Han, *J. Am. Chem. Soc.*, 2016, **138**, 5825–5828; (*c*) S. Kovács, B. Bayarmagnai, A. Aillerie and L. J. Gooßen, *Adv. Synth. Catal.*, 2018, **360**, 1913–1918.

9 Selected examples: (*a*) S. Song, Y. Zhang, A. Yeerlan, B. Zhu, J. Liu and N. Jiao, *Angew. Chem., Int. Ed.*, 2017, **56**, 2487–2491; (*b*) J. Shen, Q.-W. Li, X.-Y. Zhang, X. Wang, G.-Z. Li, W.-Z. Li, S.-D. Yang and B. Yang, *Org. Lett.*, 2021, **23**, 1541–1547; (*c*) P. Ghosh and A. Hajra, *Adv. Synth. Catal.*, 2022, **364**, 4157–4165.

10 J. Yan and Z.-C. Chen, *Synth. Commun.*, 1999, **29**, 3605–3612.

11 Z. Zheng, J. He, Q. Ma, Y. Zhang, Y. Liu, G. Tang and Y. Zhao, *Green Chem.*, 2022, **24**, 4484–4489.

12 H. F. Piedra and M. Plaza, *Chem. Sci.*, 2023, **14**, 650–657.

13 Selected examples on recent photochemical thiol-yne reactions: (*a*) S. S. Zalesskiy, N. S. Shlapakov and V. P. Ananikov, *Chem. Sci.*, 2016, **7**, 6740–6745; (*b*) S. Kaur, G. Zhao, E. Busch and T. Wang, *Org. Biomol. Chem.*, 2019, **17**, 1955–1961; (*c*) J. V. Burykina, N. S. Shlapakov, E. G. Gordeev, B. König and V. P. Ananikov, *Chem. Sci.*, 2020, **11**, 10061–10070.

14 For a recent review, see: H. F. Piedra, C. Valdés and M. Plaza, *Chem. Sci.*, 2023, **14**, 5545–5568.

15 Selected recent examples: (*a*) T. Li, K. Liang, J. Tang, Y. Ding, X. Tong and C. Xia, *Chem. Sci.*, 2021, **12**, 15655; (*b*) Y. Shen, N. Lei, C. Lu, D. Xi, X. Geng, P. Tao, Z. Su and K. Zheng, *Chem. Sci.*, 2021, **12**, 15399–15406; (*c*) S. Cuadros, C. Rosso, G. Barison, P. Costa, M. Kurbasic, M. Bonchio, M. Prato, G. Filippini and L. Dell'Amico, *Org. Lett.*, 2022, **24**, 2961; (*d*) N. Kato, T. Nanjo and Y. Takemoto, *ACS Catal.*, 2022, **12**, 7843; (*e*) C. Zhang, H. Zuo, G. Y. Lee, Y. Zou, Q.-D. Dang, K. N. Houk and D. Niu, *Nat. Chem.*, 2022, **14**, 686.

16 Reviews and selected publications on the importance of halogen-bonding interactions: (*a*) T. M. Beale, M. G. Chudzinski, M. G. Sarwar and M. S. Taylor, *Chem. Soc. Rev.*, 2013, **42**, 1667–1680; (*b*) L. C. Gilday, S. W. Robinson, T. A. Barendt, M. J. Langton, B. R. Mullaney and P. D. Beer, *Chem. Rev.*, 2015, **115**, 7118–7195; (*c*) G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati and G. Terraneo, *Chem. Rev.*, 2016, **116**, 2478–2601; (*d*) R. L. Sutar and S. M. Huber, *ACS Catal.*, 2019, **9**, 9622–9639; (*e*) M. Breugst and J. J. Koenig, *Eur. J. Org Chem.*, 2020, **2020**, 5473–5487.

17 A. Karpfen, *J. Phys. Chem. A*, 2000, **104**, 6871–6879.

18 For some recent reviews covering photochemistry of EDA-complexes, see: (*a*) G. E. M. Crisenza, D. Mazzarella and P. Melchiorre, *J. Am. Chem. Soc.*, 2020, **142**, 5461; (*b*) Y. Yuan, S. Majumder, M. Yang and S. Guo, *Tetrahedron Lett.*, 2020, **61**, 151506; (*c*) Y. Sempere, M. Morgenstern, T. Bach and M. Plaza, *Photochem. Photobiol. Sci.*, 2022, **21**, 719.

19 M. Erdélyi, *Chem. Soc. Rev.*, 2012, **41**, 3547.

20 P. Metrangolo, W. Panzeri, F. Recupero and G. Resnati, *J. Fluorine Chem.*, 2002, **114**, 27–33.

21 (*a*) M. G. Sarwar, B. Dragisic, L. J. Salsberg, C. Gouliaras and M. S. Taylor, *J. Am. Chem. Soc.*, 2010, **132**, 1646–1653; (*b*) L. Maugeri, E. M. G. Jamieson, D. B. Cordes, A. M. Z. Slawin and D. Philp, *Chem. Sci.*, 2017, **8**, 938–945.

22 (*a*) *Free Radicals in Organic Chemistry*, ed. J. Fossey, D. Lefort and J. Sorba, Wiley and Masson, 1995; (*b*) T. P. M. Goumans, K. Van Alem and G. Lodder, *Eur. J. Org Chem.*, 2008, **2008**, 435–443.

23 S. K. Pagire, T. Föll and O. Reiser, *Acc. Chem. Res.*, 2020, **53**, 782.

24 H. Fuse, Y. Irie, M. Fuki, Y. Kobori, K. Kato, A. Yamakata, M. Higashi, H. Mitsunuma and M. Kanai, *J. Am. Chem. Soc.*, 2022, **144**, 6566–6574.

25 A. Nandy, I. Kazi, S. Guha and G. Sekar, *J. Org. Chem.*, 2021, **86**, 2570–2581.

26 For some reviews on continuous flow photochemistry: (*a*) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel and T. Noël, *Chem. Rev.*, 2016, **116**, 10276–10341; (*b*) L. Buglioni, F. Raymenants, A. Slattery, S. D. A. Zondag and T. Noël, *Chem. Rev.*, 2022, **122**, 2752–2906.