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Novel cationic radical acceptors for visible light-mediated reactions

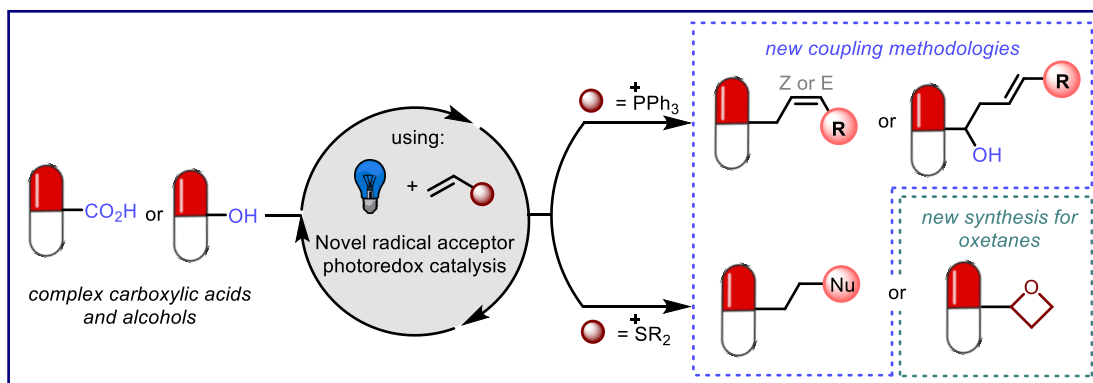
Thesis submitted to the University of Nottingham
For the degree of Doctor of Philosophy

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General Abstract

The addition of carbon-centered radicals to alkenes is a cornerstone process in organic chemistry, which has triggered significant advances in various areas of synthesis. Despite its value, the chemistry often requires specific substitution in either the radical trap or the carbon-centred radical to ensure controllable and efficient reactivity, overall limiting the scope of application of the chemistry.

The aim of the research presented in the following thesis dissertation is to challenge these limitations, exploring the use of vinyl phosphonium and sulfonium ions as radical acceptors in photoredox catalysis. The use of such reagents allowed us to significantly extend the scope of application of classic radical addition to alkenes, opening new avenues in radical chemistry. In Chapter 2 and 3, the radical reactivity of vinyl phosphonium ions is exploited to develop a novel C-C coupling technology to functionalise carboxylic acid and alcohol substrates. The chemistry hinges on merging radical chemistry with the Wittig reaction and was demonstrated to be suitable for the late-stage functionalisation of complex substrates. In Chapter 4 and 5, vinyl sulfonium ions are shown to undergo radical conjugate addition under photoredox conditions. The chemistry was exploited to develop a formal polarity mismatched radical addition upon coupling with nucleophiles and allowed to develop a novel methodology to access oxetanes from aliphatic alcohols.



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Thanks to Simeon, for being my lighthouse, for his constant presence and his continuous support. Thanks for making every place feel like home.

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List of publications

Some projects presented in this thesis have been published:

1. Oxetane Synthesis *via* Alcohol C-H Functionalization
Subhasis Paul,[†] Dario Filippini,[†] Filippo Ficarra,[†] Heorhii Melnychenko,
Christopher Janot and Mattia Silvi
J. Am. Chem. Soc., **2023**, *145*, 15688-15694 DOI: 10.1021/jacs.3c04891
<https://pubs.acs.org/doi/10.1021/jacs.3c04891>
[†] These authors contributed equally to this work
2. Polarity Transduction Enables the Formal Electronically Mismatched Radical
Addition to Alkenes
Subhasis Paul,[†] Dario Filippini,[†] Mattia Silvi
J. Am. Chem. Soc., **2023**, *145*, 2773-2778 DOI: 10.1021/jacs.2c12699
<https://pubs.acs.org/doi/10.1021/jacs.2c12699>
[†] These authors contributed equally to this work
3. The Conceptual Development of a Conjunctive Olefination
Dario Filippini and Mattia Silvi
Synlett, **2022**, *33*, 1011-1016 DOI: 10.1055/a-1787-1159 (Synpacts invited
contribution)
<https://www.thieme-connect.com/products/ejournals/abstract/10.1055/a-1787-1159>
4. Visible Light-Driven Conjunctive Olefination
Dario Filippini and Mattia Silvi
Nat. Chem., **2022**, *14*, 66-70 DOI: 10.1038/s41557-021-00807-x
<https://www.nature.com/articles/s41557-021-00807-x>

List of abbreviations

BDE	Bond Dissociation energy
DCM	Dichloromethane
DMA	Dimethylacetamide
DMF	Dimethylformamide
DMPU	N,N'-Dimethylpropyleneurea
DMSO	Dimethylsulfoxide
EDA	Electron Donor-Acceptor
EDG	Electron Donating Group
EnT	Energy Transfer
EWG	Electron Withdrawing Group
FMO	Frontier Molecular Orbital
HAT	Hydrogen Atom Transfer
HMPA	Hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
LSF	Late Stage Functionalisation
LUMO	Lowest Unoccupied Molecular Orbital
PC	Photocatalyst
SCE	Saturated Calomel Electrode
SET	Single Electron Transfer
SOMO	Single Occupied Molecular Orbital
TBADT	Tetrabutylammonium Decatustate
THF	Tetrahydrofuran
UV	Ultraviolet Light

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Chapter 1. Radical chemistry and photoredox catalysis

1.1. Radicals in organic synthesis

Over the last century, the field of organic synthesis has witnessed impressive conceptual advances, which have largely revolutionised the way organic molecules are designed and constructed e.g., the advent of cross-coupling chemistry and asymmetric catalysis. Most of these synthetic advances were based on polar reactivity, where couples of electrons are involved in the formation of new bonds in chemical reactions, while only limited studies focused on the complementary radical-based reactivity, where only single electrons are involved in the transformations. The reason for such delayed development of the field is ascribable to a generally accepted notion that radicals are “messy, unpredictable, unpromising, and essentially mysterious”,¹ therefore this reactivity has not been explored as much as traditional polar chemistry. However, in the past two decades, new advancements allowed taming the radical reactivity which is now widely used in organic synthesis,² drug discovery³ and polymer chemistry.⁴

Due to their transient nature, radicals require *in-situ* generation, which is classically addressed *via* two main strategies: the homolytic cleavage of a covalent bond (Scheme 1.1, a) and redox chemistry, typically based on single electron transfer (SET) events (Scheme 1.1, b). Homolysis is classically promoted through the use of stoichiometric radical initiators (In-In), generally diazocompounds or peroxides. While the use of such compounds represents a reliable strategy to generate radicals in solution, they are typically toxic, require harsh conditions (high temperatures or UV irradiation) and are potentially explosive (Scheme 1.1, a).⁵

In contrast, redox strategies are based on the ability of substrates to donate or accept single electrons, generating respectively radical anions or radical cations. Such highly reactive charged intermediates undergo rapid fragmentation (mesolysis⁶) to provide neutral radicals (Scheme 1.1, b).⁷ Classically, stoichiometric redox-active species such

¹ Chatgililoglu, C. *Acc. Chem. Res.* **1992**, 25, 188–194.

² Renaud P.; Sibi M. P. *Radicals in Organic Synthesis, Volume 1: Basic Principles*. Wiley-VCH, **2001**.

³ Guillemard, L.; Kaplaneris, N.; Ackermann, L.; Johansson, M. J. *Nat. Rev. Chem.* **2021**, 5, 522–545.; Smith, J. M.; Dixon, J. A.; deGruyter, J. N.; Baran, P. S. *J. Med. Chem.* **2019**, 62, 2256–2264.

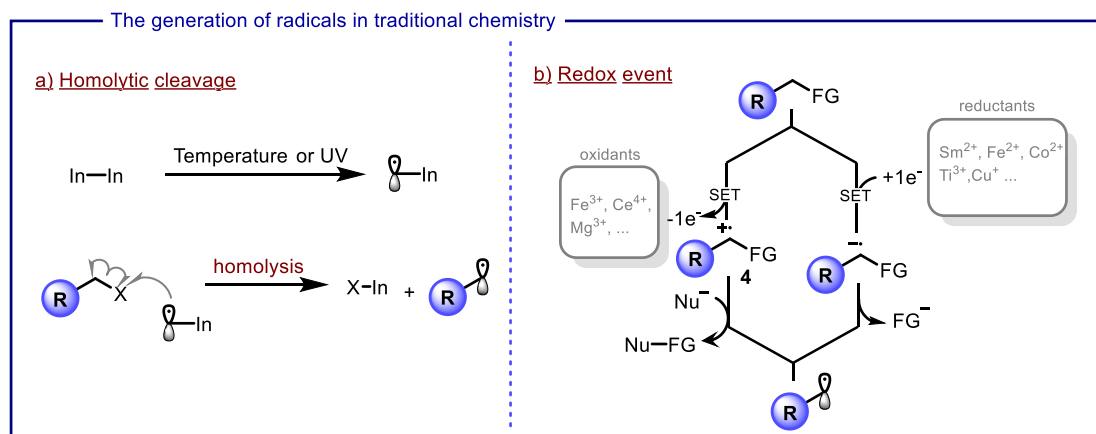
⁴ Matyjaszewski, K.; Spanswick, J. *Mater. Today* **2005**, 8, 26–33.; Parkatidis, K.; Wang, H. S.; Truong, N. P.; Anastasaki, A. *Chem* **2020**, 6, 1575–1588.; Chen, M.; Zhong, M.; Johnson, J. A. *Chem. Rev.* **2016**, 116, 10167–10211.

⁵ Lalevée J.; Fouassier J.P. Overview of Radical Initiation. In *Encyclopedia of Radical in Chemistry, Biology and Materials*. Studer A.; Chatgililoglu C. (Eds.), Wiley: New York, NY, USA, **2012**, Volume 1, Chapter 2.

⁶ IUPAC. *Compendium of Chemical Terminology, 2nd ed. (the "Gold Book")* McNaught, A. D.; Wilkinson, A. *Blackwell Scientific Publications, Oxford* (**1997**).

⁷ Cormier J.-P.; M. G. *Free Radicals: Fundamentals and Applications in Organic Synthesis 2*. Georg Thieme Verlag KG: Stuttgart **2021**.

as transition metal complexes (e.g., copper,⁸ iron,⁹ manganese,¹⁰ cerium,¹¹ titanium¹²), or samarium diiodide¹³ have found wide application in SET chemistry, while recent advances in electrochemistry¹⁴ and photochemistry have promoted the advent of milder catalytic strategies.¹⁵ The science described in this manuscript will largely leverage these novel strategies to develop novel synthetic methodologies.



Scheme 1.1: Different ways to generate a radical: a) with the use of radical initiators; b) with single electron transfer process. In: initiator.

1.2. Visible light photoredox catalysis

1.2.1. Introduction: new lights on organic synthesis

The use of visible light to drive chemical reactions is at the basis of one of the most important chemical processes: photosynthesis. It represents the first example of photocatalysed chemistry, which allowed cells to become autotrophic, providing themselves with the required energy for life.

Despite its importance in chemical biology, radiative solar energy has been exploited in organic chemistry only after the 20th century. The first chemist to systematically study the ability of light to promote organic reactions was Giacomo Ciamician. The Italian chemist was the first to perceive the advantages of photochemistry and its ecological benefit, predicting that chemists would utilize it as a discipline to achieve challenging reactions, utilizing the free energy delivered by the Sun.

“On the arid lands, there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over the plains and glass

⁸ Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464–3484.

⁹ Gualandi, A.; Mengozzi, L.; Cozzi, P. G. *Asian J. Org. Chem.* **2017**, *6*, 1160–1179.

¹⁰ Mondal, M.; Bora, U. *RSC Adv.* **2013**, *3*, 18716–18754.

¹¹ Nair, V.; Deepthi, A. *Chem. Rev.* **2007**, *107*, 1862–1891.

¹² Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859.

¹³ Szostak, M.; Spain, M.; Procter, D. J. *Chem. Soc. Rev.* **2013**, *42*, 9155–9183.

¹⁴ Chicas-Baños, D. F.; Frontana-Urbe, B. A. *Chem. Rec.* **2021**, *21*, 2538–2573.

¹⁵ Crespi, S.; Fagnoni, M. *Chem. Rev.* **2020**, *120*, 9790–9833.

*buildings will rise everywhere; inside of these will take place the photochemical processes [...]*¹⁶

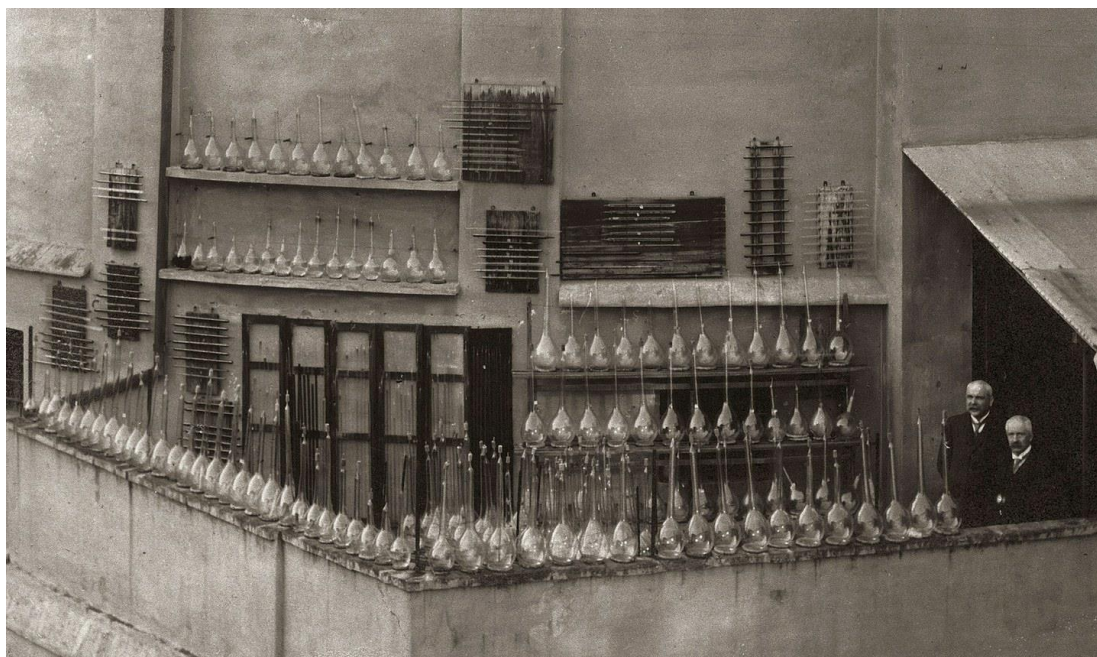


Figure 1.1: Giacomo Ciamician and Paolo Silber on a rooftop carrying out photochemical reactions with sunlight. Bologna, Italy 1915-1920.¹⁷

When a molecule absorbs light, it harvests light energy, storing it in its electronic structure through the promotion of electrons to excited states. As energy-rich species, excited states are expected to be more reactive than the corresponding ground state. This excess of energy is most often associated with an electronic structure significantly different from that of the ground state. Since the electronic structure defines the molecule's reactivity, an excited state must not be considered as a “hot” ground-state molecule, but as essentially a new chemical species, that could potentially allow the discovery of exciting new reactivity.¹⁸

Classic photochemistry mainly relies on the use of high-energy UV light, due to the inability of organic molecules to absorb visible light. However, the use of UV light is disadvantageous in many aspects, and no longer compatible with the modern requirements of organic synthesis. Firstly, UV light can represent a threat to biological systems: although it is useful to synthesize vitamin D¹⁹ and for the growth of skin and bone cells,²⁰ it is also the major responsible for skin cancer²¹ and eye damage.²² Hence, the use of UV light in chemistry requires protective equipment and expensive reactor designs. Secondly, UV light is poorly selective, as more functional groups can be excited, opening more reaction pathways. To address the issues above, the use of milder,

¹⁶ Ciamician, G. *Science*, **1912**, 36, 385-394.

¹⁷ <https://chimica.unibo.it/it/dipartimento/presentazione/storia-del-dipartimento>. Accessed 08/10/23

¹⁸ Balzani, V.; Ceroni, P.; Juris, A. *Photochemistry and Photophysics: Concepts, Research, Applications*, Wiley-WCH, **2014**.

¹⁹ Bikle, D. D. *Chem. Biol.*, **2014**, 21, 319-329.

²⁰ Carlberg, C. *Nutrients*, **2019**, 11, 676-691.

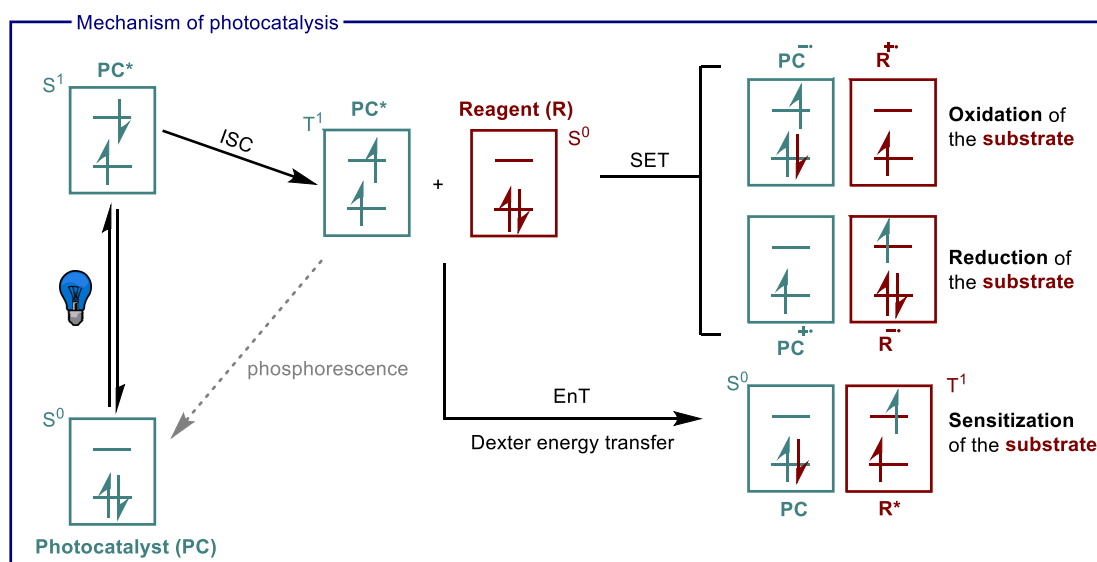
²¹ Narayanan, D. L.; Saladi, R. N.; Fox, J. L. *Int. J. Dermatol.*, **2010**, 49, 978-986.

²² Taylor, R.; Taylor, H. R. *Photochem. Photobiol.*, **1989**, 50, 489-492.

more selective and safer visible light has been the object of research in the last few decades.

1.2.2. Photoredox catalysis

As typical organic molecules are not able to absorb visible light, a common strategy is the use of a reaction component – i.e., a photocatalyst (PC) – that would act as a “light-harvesting antenna”. A photocatalyst is a transition metal complex²³ or an organic dye²⁴ that can absorb visible light energy and transform it into chemical energy which can be transferred to substrates.²⁵ The common operative principle is a charge transfer that occurs between the catalyst centre (which can be a metal centre or an organic core) and its side groups. Light absorption triggers the promotion of an electron from the HOMO (Highest Occupied Molecular Orbital) to the LUMO (Lowest Unoccupied Molecular Orbital) orbital of the PC (Scheme 1.2, left side). This process occurs without any electron spin changes, creating two electrons with opposite spins in two different orbitals. This state is called singlet excited state S^1 . Then, *intersystem crossing* (ISC) occurs to reveal a triplet excited state T^1 with a longer lifetime.²⁶ The latter is usually the active species, promoting most photochemical processes through two main mechanisms: SET giving rise to the area of photoredox catalysis (Scheme 1.2, top right), or Energy Transfer (EnT), the area of triplet sensitization (Scheme 1.2, bottom right).



Scheme 1.2: Mechanism of photocatalysis

²³ a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322–5363. b) Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath, C. P.; MacMillan, D. W. C. *Chem. Rev.* **2022**, *122*, 1485–1542.

²⁴ Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075–10166.

²⁵ Stephenson, C. R. J.; Yoon, T. P.; MacMillan, D. W. C. *Visible light photocatalysis in organic chemistry*, Wiley-WCH, **2018**.

²⁶ Turro, N.J.; Ramamurthy, V.; Scaiano, J.C. *Principles of Molecular Photochemistry: An Introduction*, University of Science Book, **2009**.

As T^1 species, the excited PC bears both an unpaired electron in a high-energy orbital and a vacancy in a lower orbital (previously HOMO). Therefore, it can act as an excellent oxidant or reductant in SET processes,²⁷ leading to redox processes that create radical species in solution.

In triplet sensitization, the PC^* donates to a substrate a high-energy electron and accepts another electron into its vacancy simultaneously. This creates a T^1 state in the substrate without any redox reactivity but as a result of a formal radiative energy transfer.²⁸ This mechanism is called Dexter energy transfer,²⁹ and it will be further discussed in this thesis.

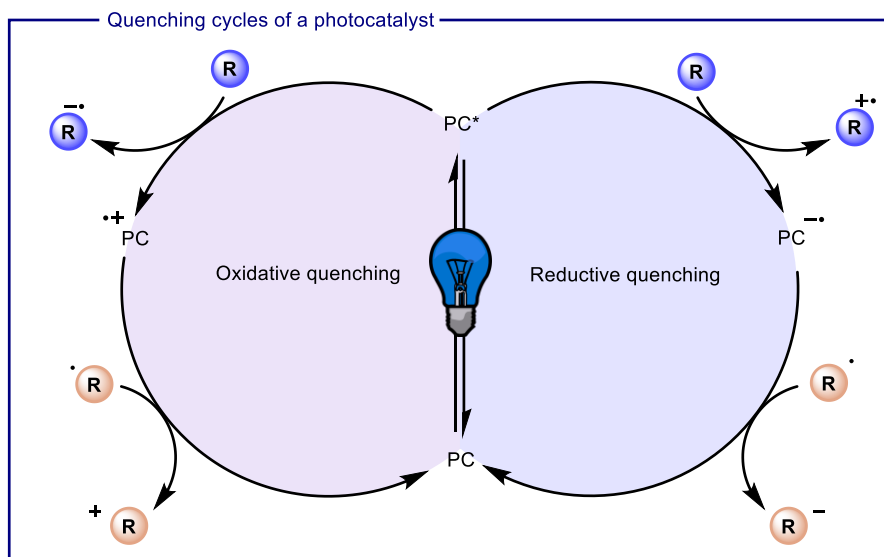
Photoredox catalytic cycles

The ability of the photocatalyst to be both an oxidant and a reductant makes it a versatile redox processes promoter. The same photocatalytic cycle can, indeed, catalyse both oxidative and reductive processes. The excited catalyst PC^* can behave as a reductant, donating an electron to a substrate and becoming a radical cation ($PC^{+\bullet}$). This species can then accept an electron from another substrate (or intermediate) and come back to its ground state (PC). This process is called oxidative quenching (Scheme 1.3, left). Conversely, the PC^* can also behave as an oxidant, accepting an electron into its low-energy vacancy. The catalyst becomes a radical anion ($PC^{\bullet-}$) which then donates an electron regenerating its ground state (PC). This process is called reductive quenching (Scheme 1.3, right). Both oxidative and reductive quenching mechanisms are used in photoredox reactions, depending on the synthetic application. The versatility of the redox features of the reactive states involved allows wide application in redox organic processes.

²⁷ Capaldo, L.; Ravelli, D. *Eur. J. Org. Chem.* **2020**, 2020, 2783–2806.

²⁸ Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. *Chem. Soc. Rev.* **2018**, 47, 7190–7202.

²⁹ Dexter, D. L. *J. Chem. Phys.* **1953**, 21, 836–850.



Scheme 1.3: Different quenching cycles of a photocatalyst. On the left, the oxidative quenching, where the PC* is quenched by reducing a substrate. On the right, the reductive quenching, where the PC* is quenched by oxidation of a substrate.

Tunability of the redox potential

Another important property that makes photocatalysis particularly useful in organic synthesis is the tunability of the photocatalyst redox properties. The structure of the photocatalyst can be varied to impact its ability to accept or donate electrons – i.e., changing the oxidation state of the core or the functionalities present on the ligands – thereby accessing a variety of redox potentials (Figure 1.2). With a library of different catalysts, it is possible to select the appropriate redox match between the photocatalyst and the desired substrate – achieving high selectivity and increasing the reaction tolerance to other sensitive functionalities.

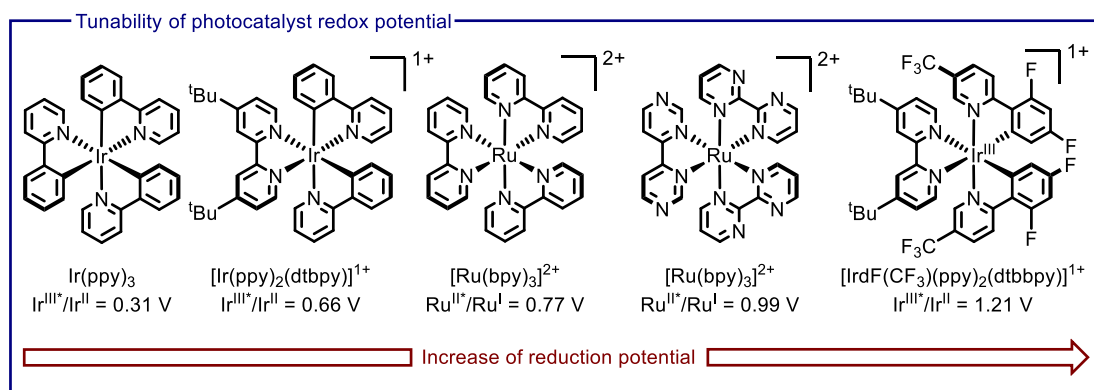


Figure 1.2: Redox potential of different metal-based photocatalysts.³⁰ Potentials are intended vs SCE.

Overall, photocatalysis flourished in the last ten years because it fulfils a variety of needs of modern organic synthesis. It is mild and selective, it unlocks new reactivity – undisclosed in traditional polar chemistry – and it presents clear benefits for sustainability. Photochemistry has found wide application in various areas of synthetic

³⁰ <https://macmillan.princeton.edu/wp-content/uploads/Merck-Photocatalysis-Chart.pdf>. Accessed 08/10/23

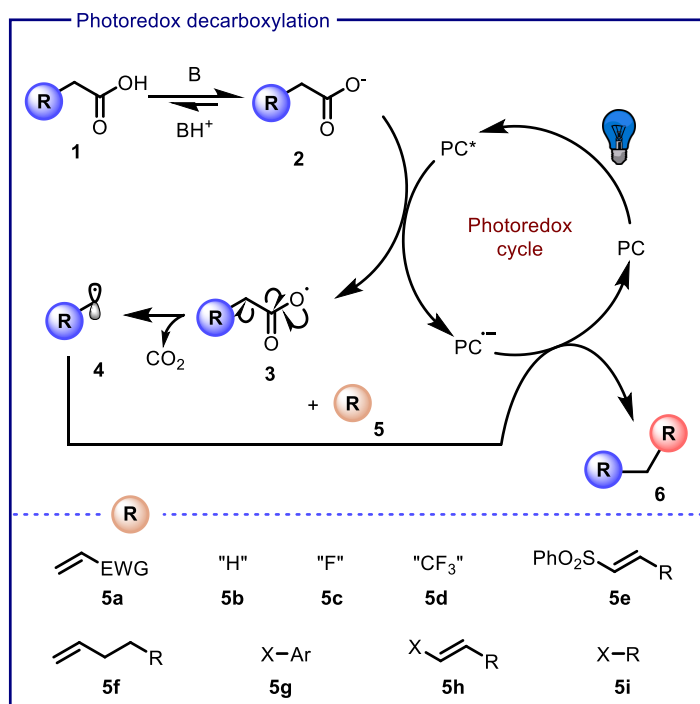
chemistry such as total synthesis,³¹ late-stage functionalisation,³² drug discovery³³ and process chemistry.³⁴

1.2.3. Uses of radicals in modern synthesis

Within the immense pool of photocatalysed reactions, two particular processes must be highlighted as relevant to the research presented in this manuscript: photoredox decarboxylation and hydrogen atom transfer (HAT). The key aspect of these two processes is the use of largely available functionalities – carboxylic acids and the ubiquitous C-H bonds – to generate reactive radicals, selectively and in remarkably mild conditions.

Photoredox decarboxylation

Carboxylic acids are readily available, inexpensive, stable and relatively non-toxic compounds. They can be easily extracted from natural sources, a fact that assures a broad structural diversity. Because of their wide abundance, carboxylic acids have been extensively investigated as radical precursors in photoredox decarboxylative processes.



Scheme 1.4: Scheme of a general photoredox decarboxylation process. X: halide.

³¹ a) Pitre, S. P.; Overman, L. E. *Chem. Rev.* **2022**, 122, 1717–1751. b) Galliher, M. S.; Roldan, B. J.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2021**, 50, 10044–10057.

³² a) Bellotti, P.; Huang, H.-M.; Faber, T.; Glorius, F. *Chem. Rev.* **2023**, 123, 4237–4352. b) Cannalire, R.; Pelliccia, S.; Sancineto, L.; Novellino, E.; Tron, G. C.; Giustiniano, M. *Chem. Soc. Rev.* **2021**, 50, 766–897. c) Capaldo, L.; Quadri, L. L.; Ravelli, D. *Green Chem.* **2020**, 22, 3376–3396.

³³ a) Li, P.; Terrett, J. A.; Zbieg, J. R. *ACS Med. Chem. Lett.* **2020**, 11, 2120–2130. b) McMurray Thomas M.; Howells, Rachel L.; L. M. *Synthesis* **2020**, 52, 1719–1737. c) Li, P.; Terrett, J. A.; Zbieg, J. R. *ACS Med. Chem. Lett.* **2020**, 11, 2120–2130.

³⁴ a) Sambianio, C.; Noël, T. *Trends Chem.* **2020**, 2, 92–106. b) Buglioni, L.; Raymenants, F.; Slattery, A.; Zondag, S. D. A.; Noël, T. *Chem. Rev.* **2022**, 122, 2752–2906.

In a general reaction mechanism (Scheme 1.4), the deprotonation of carboxylic acid **1** forms a carboxylate anion **2**. This anion presents a drastically reduced redox potential, making it easily oxidable (phenylacetic acid $E_{1/2}^{\text{red}} = +2.51 \text{ V vs SCE}$ against phenyl acetate $E_{1/2}^{\text{red}} = +1.27 \text{ V vs SCE}$).³⁵ Simultaneously, a suitable photocatalyst PC is excited by light irradiation to generate its excited state PC*, which can act as a strong oxidant. A SET process then occurs forming the reduced state of the photocatalyst and a carboxylate radical **3**, which rapidly undergoes decarboxylation to give a carbon-centred radical **4** with extrusion of CO₂. Radicals **4** are reactive species which can react with a variety of substrates **5** e.g., electron-poor double bonds **5a**³⁶ or donors of hydrogen **5b**,³⁷ fluorine **5c**,³⁸ and trifluoromethyl group **5d**,³⁹ as well as vinyl sulfones **5e**,⁴⁰ allyl derivatives **5f**⁴¹ or add to a metal in cross-coupling catalytic processes **5g-5i**.⁴² Overall, photoredox decarboxylative processes allow the use of carboxylic acids as convenient alkylating agents in valuable synthetic processes.

Photocatalysed Hydrogen Atom Transfer (HAT)

HAT represents one of the most fundamental strategies to generate radicals, involved in processes as diverse as hydrocarbon combustion, small molecule activation and atmospheric chemistry. In biology, the process is responsible for the radical-trapping antioxidants of several enzymatic reactions and is in charge of preventing premature ageing.⁴³

The use of HAT in radical generation presents several advantages. First, the direct C-H to C-R conversion occurs with the substitution of an H-bond – an ideal scenario in terms of atom economy.⁴⁴ Second, the reactivity is a versatile tool in late-stage functionalisation.⁴⁵ Third, generating a reactive radical from a C-H bond instead of a directing functional group (i.e., the carboxylic acid just discussed above), does not require the loss of a sacrificial functional group, which may be crucial for the activity of a molecule. Moreover, the recent developments in visible light catalysis allow generating the active hydrogen abstractor species under mild conditions and without using toxic and reactive radical generators.⁴⁶

Photocatalysed HAT is divided into three different categories.⁴⁷

³⁵ Capaldo, L.; Buzzetti, L.; Merli, D.; Fagnoni, M.; Ravelli, D. *J. Org. Chem.* **2016**, *81*, 7102–7109.

³⁶ Kitcatt, D. M.; Nicolle, S.; Lee, A.L. *Chem. Soc. Rev.* **2022**, *51*, 1415–1453.

³⁷ Griffin, J. D.; Zeller, M. A.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2015**, *137*, 11340–11348.

³⁸ Ventre, S.; Petronijevic, F. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 5654–5657.

³⁹ Kautzky, J. A.; Wang, T.; Evans, R. W.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2018**, *140*, 6522–6526.

⁴⁰ Noble, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 11602–11605.

⁴¹ Lang, S. B.; O'Nele, K. M.; Douglas, J. T.; Tunge, J. A. *Chem. Eur. J.* **2015**, *21*, 18589–18593.

⁴² a) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437–440. b) Noble, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 11602–11605. c) Johnston, C. P.; Smith, R. T.; Allmendinger, S.; MacMillan, D. W. C. *Nature* **2016**, *536*, 322–325.

⁴³ Costas, M.; Biotti, M. *Acc. Chem. Res.* **2018**, *51*, 2601–2602.

⁴⁴ Moores A. *Atom Economy – Principles and Some Examples, Part 1. Homogeneous Catalysis*, Handbook of Green Chemistry: Online, **2010**.

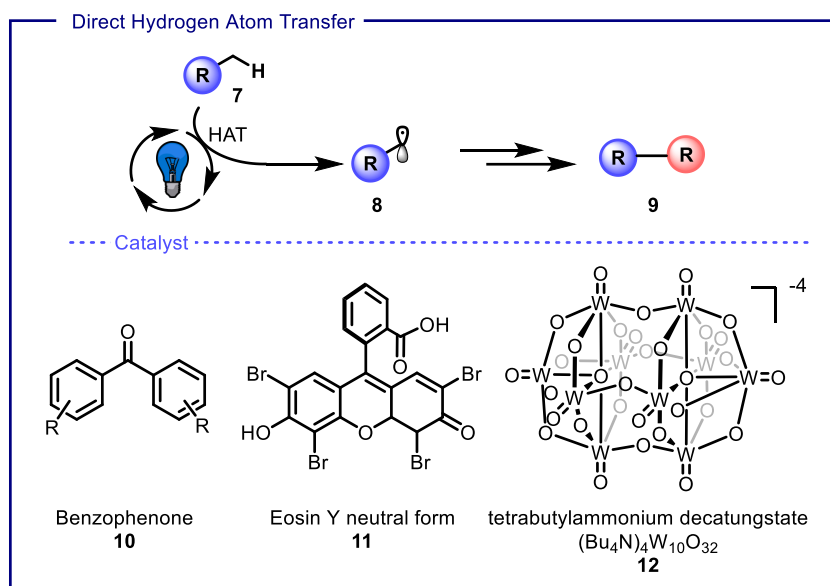
⁴⁵ Ritter, T. *Börgel, J. Chem.* **2020**, *63*, 1877 – 1887.

⁴⁶ Cao, H.; Tang, X.; Tang, H.; Yuan, Y.; Wu, J. *Chem Catal.* **2021**, *1*, 523–598.

⁴⁷ Capaldo, L.; Ravelli, D. *Eur. J. Org. Chem.* **2017**, *2017*, 2056–2071.

Direct HAT

In direct HAT (Scheme 1.5), the photocatalyst itself acts as a HAT agent. Usually, the photocatalyst excited state is a di-radical species able to abstract a hydrogen atom from a substrate. This is a widely diffused strategy, although it requires a PC both able to absorb light and act as a hydrogen abstractor. Only a handful of catalysts are capable to mediate this process. Some of them are reported in the bottom part of Scheme 1.5: benzophenone and its derivatives **10**,⁴⁸ Eosin Y **11** in its neutral form⁴⁹ and tetrabutylammonium decatungstate **12**.⁵⁰



Scheme 1.5: General scheme of the direct Hydrogen Atom Transfer. At the bottom, benzophenone **10**, Eosin Y **11** and TBADT **12**, which are among the most common direct photocatalyst for HAT processes.

Indirect and intramolecular HAT

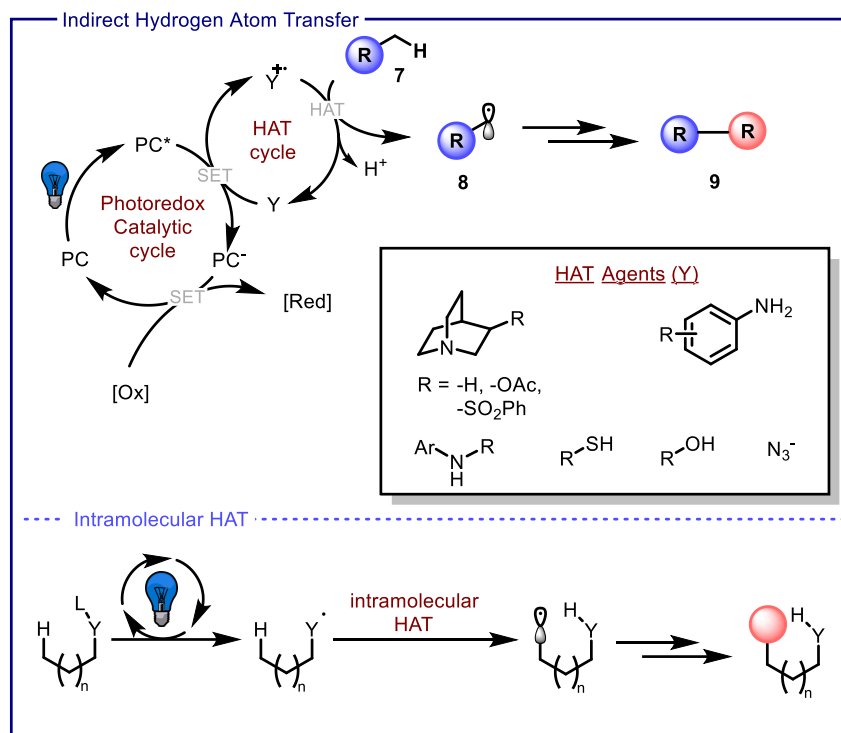
In indirect HAT (Scheme 1.6), the photocatalyst and the HAT agent (Y) are two different chemical entities. The (PC*) undergoes in SET with a HAT agent Y to afford a radical species (i.e., cation Y^+), which undergoes HAT with an organic compound **7** to produce the radical **8**. This radical species can then undergo various reactivity. The advantages of this process are several. First: theoretically, any common photoredox catalyst can be used. Secondly, the use of a second HAT agent allows a better tuning of the system in the way that a suitable catalytic system can be found for a given system. The process can also be intramolecular (Scheme 1.6, bottom)⁵¹ if the hydrogen is abstracted by another region of the same substrate.

⁴⁸ Abadie, B.; Jardel, D.; Pozzi, G.; Toullec, P.; Vincent, J. M. *Chem. Eur. J.* **2019**, 25, 16120–16127.

⁴⁹ Fan, X. Z.; Rong, J. W.; Wu, H. L.; Zhou, Q.; Deng, H. P.; Da Tan, J.; Xue, C. W.; Wu, L. Z.; Tao, H. R.; Wu, J. *Angew. Chem. Int. Ed.* **2018**, 57, 8514–8518.

⁵⁰ Ravelli, D.; Fagnoni, M.; Fukuyama, T.; Nishikawa, T.; Ryu, I. *ACS Catal.* **2018**, 8, 701–713.

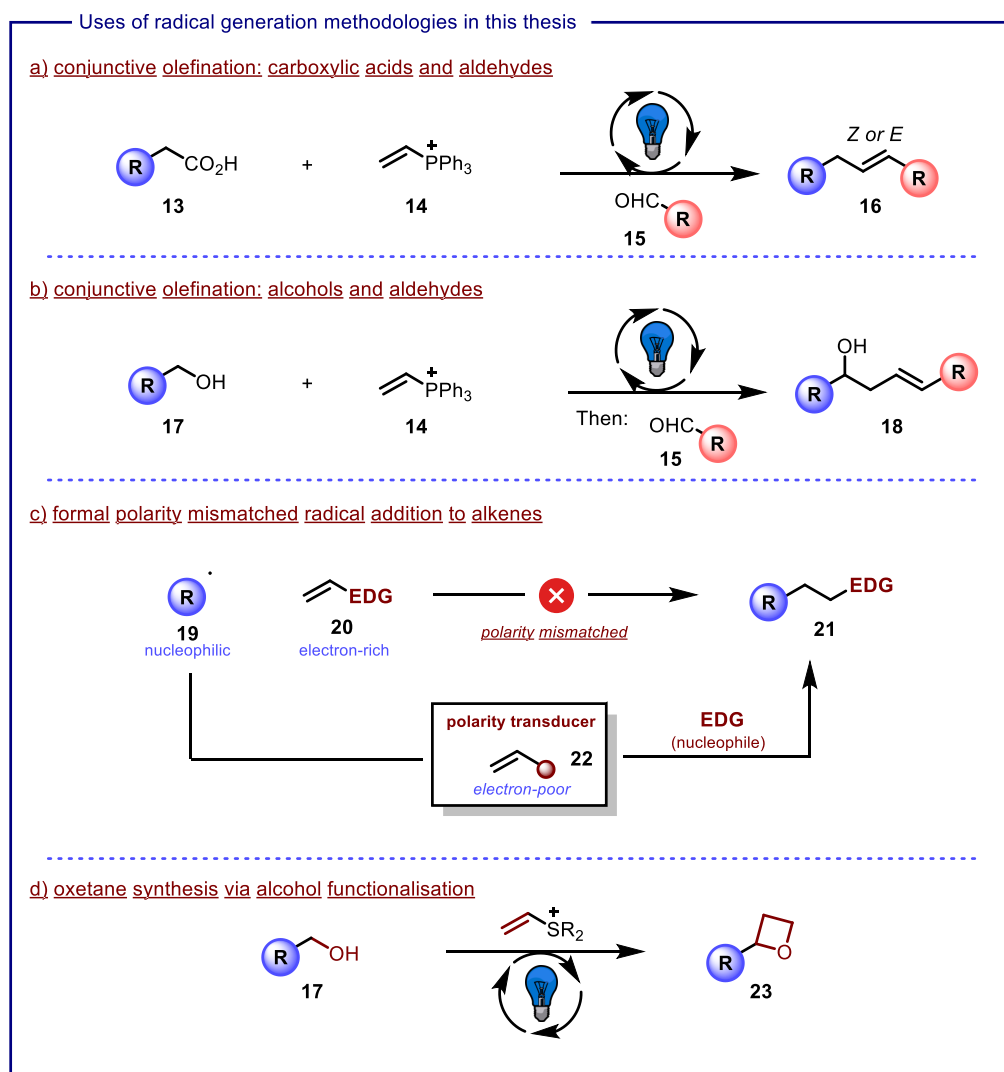
⁵¹ Chen, H.; Yu, S. *Org. Biomol. Chem.* **2020**, 18, 4519–4532.



Scheme 1.6: Top: General scheme of an indirect Hydrogen Atom Transfer. Bottom: General scheme of an intramolecular indirect HAT process

1.3. Methodologies developed in this thesis work

The concepts and the methodologies presented in this introductory chapter will constitute the conceptual base of the work described in this thesis, which focuses on the development of novel strategic methodologies through the introduction of novel radical acceptors. In Chapter 2 and 3 the use of vinyl phosphonium **14** allowed: 1) the development of a multicomponent conjunctive olefination between carboxylic acid **13** and aldehydes **15** (Scheme 1.7, a) and 2) the development of a multicomponent conjunctive olefination between alcohols **17** and aldehydes **15** (Scheme 1.7, b). In Chapter 4 and 5 we introduce the use of a novel vinyl sulfonium **22** in radical chemistry. This allowed: 1) extend the scope of Giese reactions *via* the development of a formal polarity mismatched radical addition to electron-rich olefins (Scheme 1.7, c). 2) A methodology to convert alcohol **17** into oxetanes **23** under remarkably mild conditions (Scheme 1.7, d).

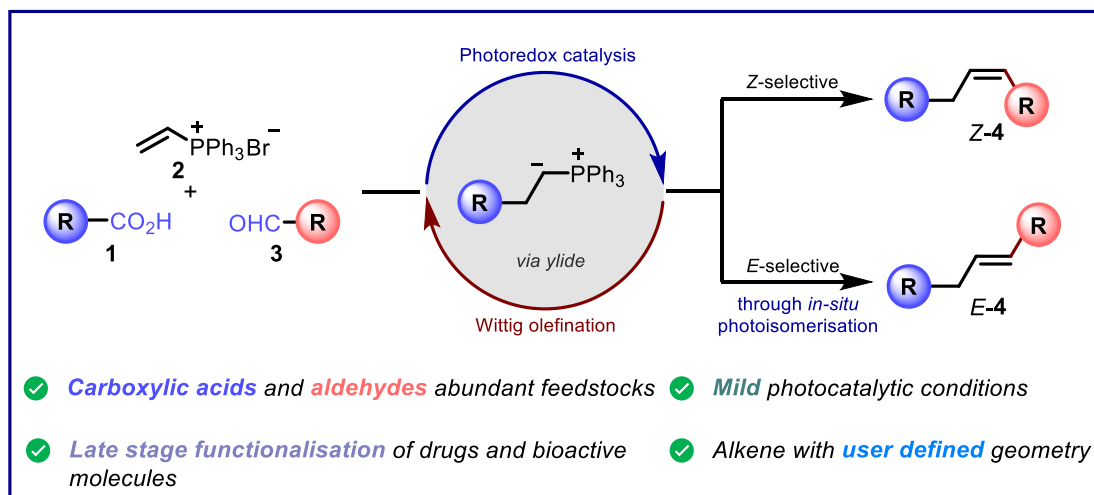


Scheme 1.7: Summary of the methodologies developed in the work of this thesis

All of the methodologies presented above were demonstrated to have wide scope and be applicable in late-stage functionalisation.

Chapter 2. Visible light-driven conjunctive olefination

Carboxylic acids and aldehydes are native functionalities widely present in natural and bioactive compounds. Therefore, the development of a procedure that would connect partners involving these functionalities would open new avenues to achieve molecular diversity. Herein, we present a versatile, novel methodology that uses an alkene “linchpin” to attach complex molecular scaffolds bearing carboxylic acids and aldehydes through $C(sp^3) - C(sp^3)$ bond formation. The chemistry uses two cornerstones of the organic synthesis – photoredox catalysis and the Wittig reaction – in a process that merges radical decarboxylation with the redox generation of a phosphonium ylide, through the synthesis of alkene connectors with a programmable *Z-E* stereochemistry.



The project described below was published, see Filippini, D.; Silvi, M. *Nat. Chem.* **2022**, *14*, 66–70. My contribution was to perform optimisation studies and explore the scope of this process in collaboration with Dr Mattia Silvi. The project is also discussed in our invited synpacts perspective article, see Filippini D., Silvi M. *Synlett* **2022**, *33*, 1011–1016.

2.1. Introduction

Carboxylic acids are among the most abundant and renewable feedstocks. They are inexpensive, stable and generally non-toxic compounds. They can be easily extracted from natural sources and they are frequently present in drugs and natural bioactive compounds (Table 2.1).

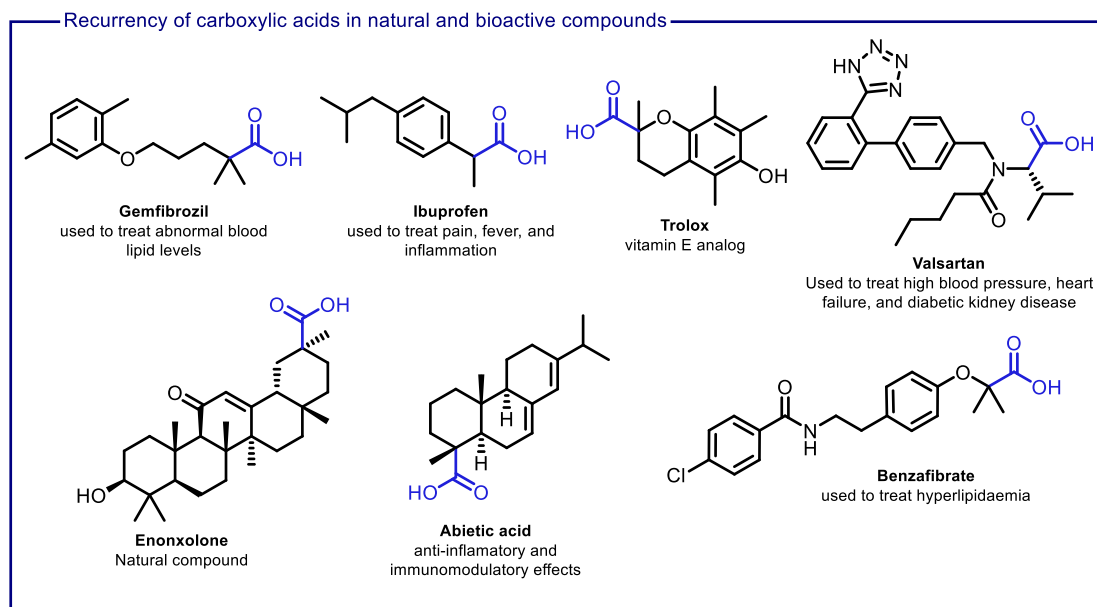


Table 2.1: Examples of natural and bioactive compounds containing the carboxylic acid functionality.

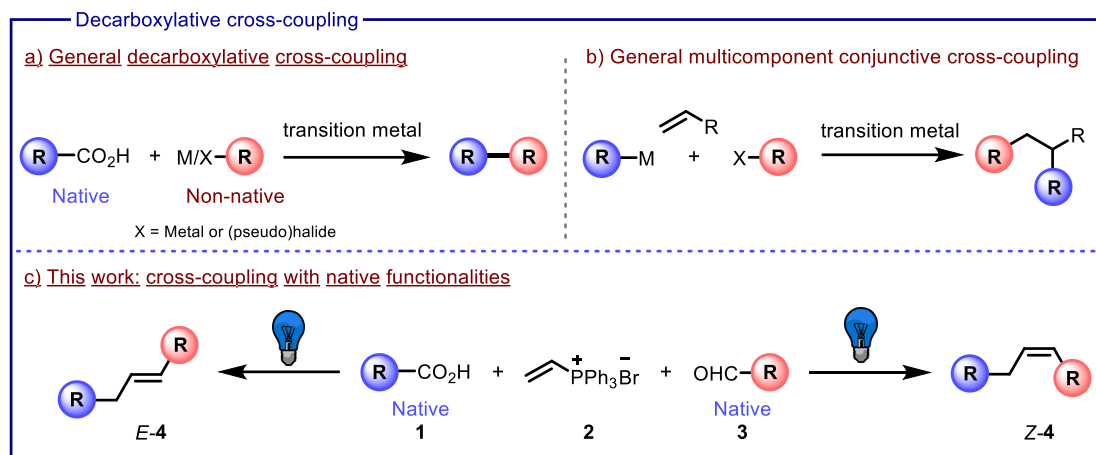
Given their wide availability, the use of alkyl carboxylic acids as alkylating agents in chemical reactions received particular attention in the last decades. Remarkable examples of decarboxylative cross-coupling processes have been recently developed (Scheme 2.1, a).¹ However, although these methodologies had expanded the scope of cross-coupling procedures, one of the coupling partners involved still carries non-native handles (e.g., organohalides or organozinc), which is not always accessible when complex scaffolds are involved.

Therefore, new strategies that assemble complex molecules using only native functionalities would expand the current scope of cross-coupling methodologies. Inspired by a recent work² describing a metal-catalysed multicomponent conjunctive cross-coupling, (Scheme 2.1, c), we designed a novel methodology to connect carboxylic acids **1** and aldehydes **3**, with the aim of providing chemists with a versatile strategy for LSF (Scheme 2.1, c).

¹ a) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science*. **2014**, 345, 437–440. b) Noble, A. McCarver, S. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, 137, 624–627. c) Johnston, C. P.; Smith, R. T.; Allmendinger, S.; MacMillan, D. W. C. *Nature* **2016**, 536, 322–325.

² a) Zhang, L.; Lovinger, G. J.; Edelstein, E. K.; Szymaniak, A. A.; Chierchia, M. P.; Morken, J. P. *Science*. **2016**, 351, 70–74. b) Derosa, J.; Apolinar, O.; Kang, T.; Tran, V. T.; Engle, K. M. *Chem. Sci.* **2020**, 11, 4287–4296.

As this methodology leverages both decarboxylative photoredox chemistry and the reactivity of vinyl phosphonium salts, the next section will briefly describe the state of the arts in both these two areas.



Scheme 2.1: Conceptual design of the process. a) Reaction scheme of a general decarboxylative cross-coupling. Functional groups that do not occur in natural compounds are usually involved. M, metal; X, (pseudo)halide. b) Scheme of a general multi-component conjunctive cross-coupling. In this example, an olefine is used as a linker between the two partners. c) This work: design plan for a conjunctive olefination coupling between carboxylic acid 1 and aldehyde 3. The process depicted enables the assembly of complex fragments bearing only native functionalities.

2.2. State of the Art: Photoredox decarboxylative Giese reaction

2.2.1. Photoredox decarboxylation

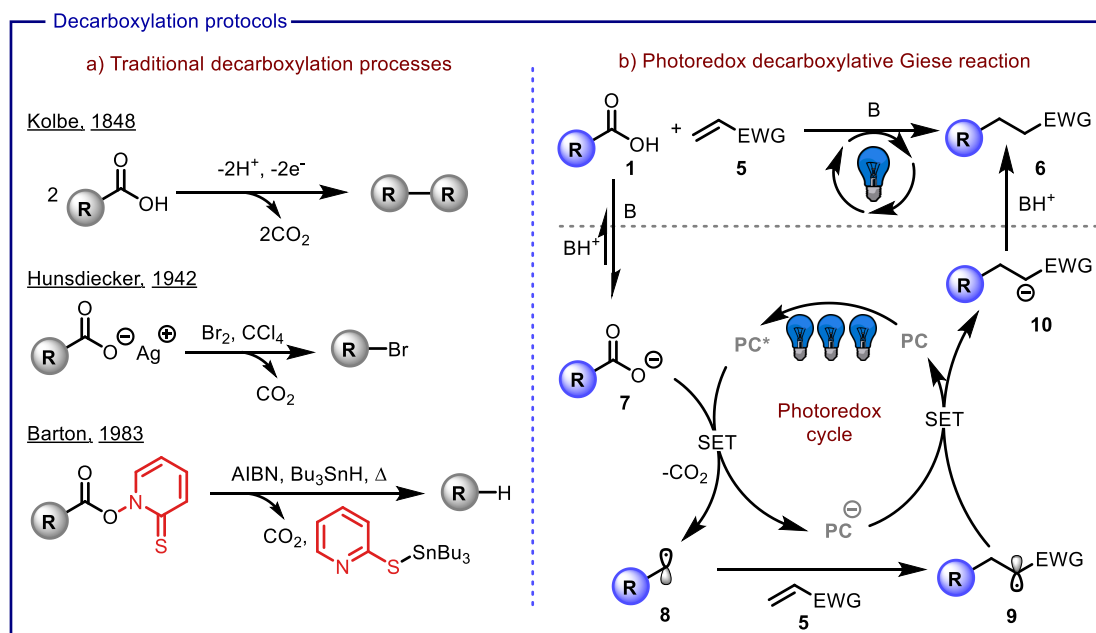
Decarboxylative processes have been known since 1848 from seminal electrochemical studies from Kolbe.³ It took over 100 years to develop other synthetically useful decarboxylative processes e.g., the Hunsdiecker reaction (1942)⁴ and the Barton decarboxylation (1983)⁵ (Scheme 2.2, a). Although these processes represent a breakthrough in radical chemistry, they possess several drawbacks. Indeed, these processes generally require toxic and reactive compounds e.g., toxic solvents, stoichiometric stannanes and potentially explosive initiators. Furthermore, they generally display limited scope, restricting the chemical diversity accessible by these methodologies. The introduction of photoredox methods has provided new versatile strategies for the decarboxylative generation of radicals. A general reaction scheme for a photoredox decarboxylation, coupled with the radical addition to an alkene – Giese reaction⁶ – is presented below (Scheme 2.2, b).

³ Kolbe, H. *Liebigs Ann. Chem.* **1848**, 64, 339–341.

⁴ Hunsdiecker, H.; Hunsdiecker, C. *Berichte der Dtsch. Chem. Gesellschaft A B Ser.* **1942**, 75, 291–297.

⁵ Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc. Chem. Commun.* **1983**, 17, 939–941.

⁶ Giese, B. *Angew. Chem. Int. Ed.* **1983**, 22, 753–764.



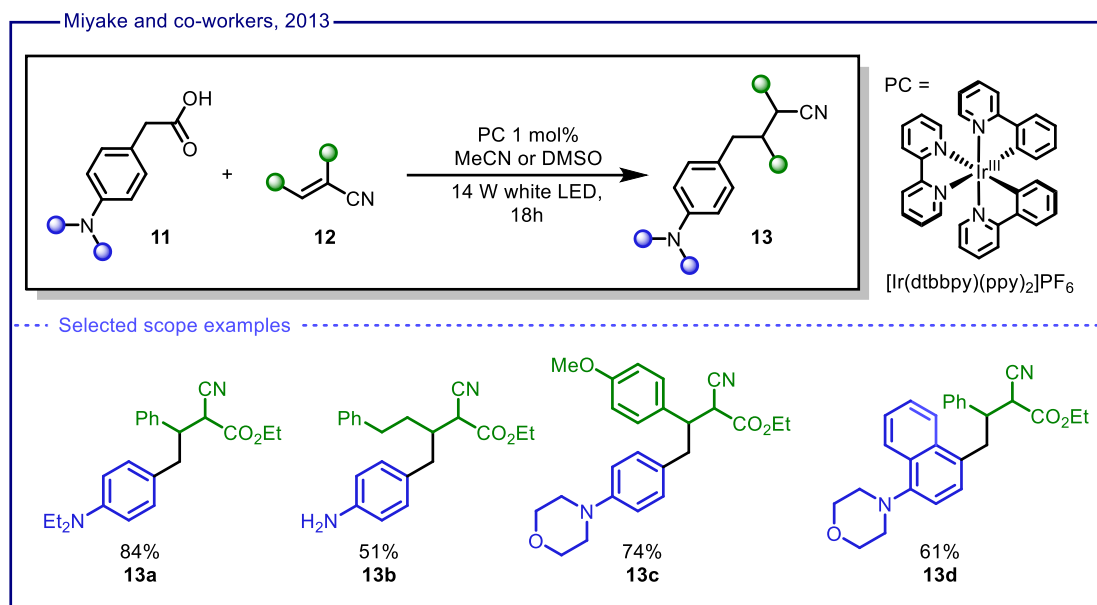
Scheme 2.2: Decarboxylative protocols. a) Traditional methods to achieve decarboxylation. b) General scheme of a photocatalysed decarboxylative Giese reaction.

Under irradiation, the excited catalyst PC^* undergoes reductive quenching, as a result of SET from carboxylate **7**. The resulting radical rapidly extrudes CO_2 , leading to nucleophilic radical **8**. The addition of **8** to an electron-poor double bond **5** leads to adduct **9**, which quickly undergoes SET with the reductive state of the photocatalyst PC^- generating carbanion **10**. Finally, the protonation of **10** affords the final compound **6**.

Application of Photoredox decarboxylative Giese reaction in organic synthesis

The first process regarding a photocatalysed decarboxylative Giese reaction was reported in 2013 by Miyake and co-workers (Scheme 2.3).⁷ In this report, aryl acetic acids **11**, bearing amino groups in the *para*-position, were coupled with cyanoacrylates **12** – used as radical acceptors. Interestingly, no radical homocoupling was observed – a typical side product of older procedures – indicating the advantages of using photoredox catalysis for these transformations. A variety of benzylated adducts **13a–13d** were obtained, containing primary, secondary and tertiary amino groups on the aromatic rings, with yield ranging between 16% to 98%. However, the protocol is limited to *para*-substituted anilines.

⁷ Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun.* **2013**, 49, 7854–7856.

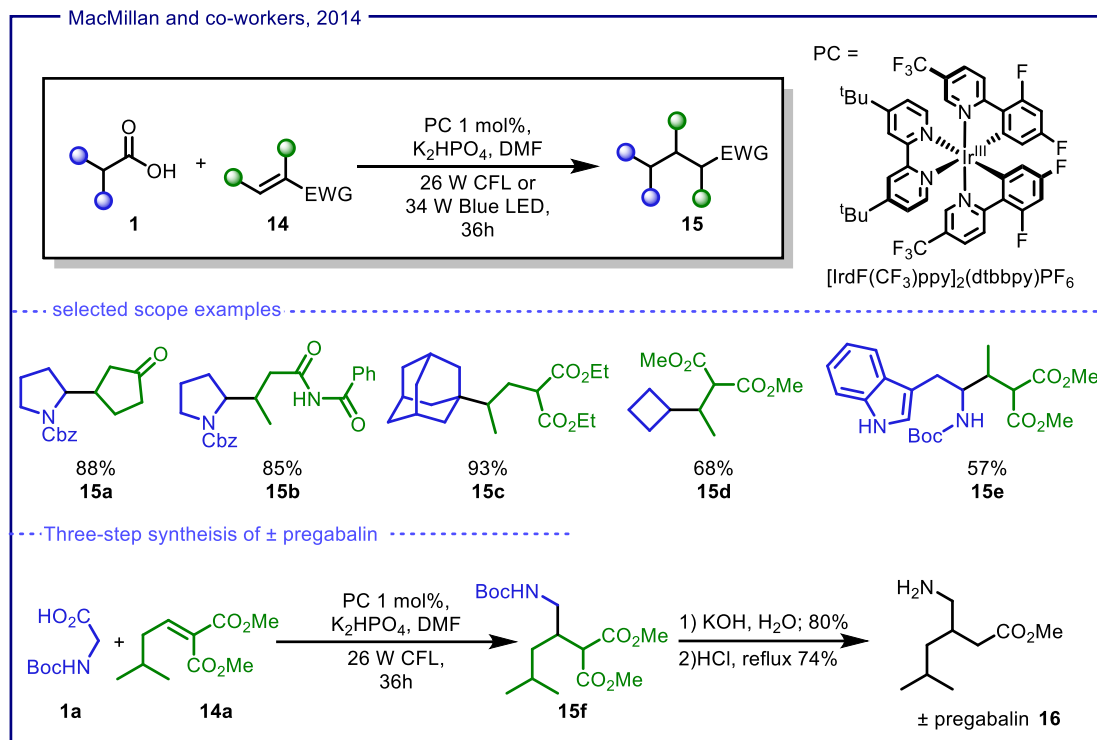


Scheme 2.3: Miyake and co-workers. First report of the use of photoredox decarboxylation combined with a Giese reaction.⁷

Just a year later, in 2014, a much broader protocol was presented by MacMillan and co-workers (Scheme 2.4, top).⁸ A wide variety of carboxylic acids was shown to efficiently undergo Giese addition, thus validating a practical protocol, in which abundant starting material could be used in place of cuprates, boronic acids, halides and Grignard reagents. In the paper, the authors show an extensive scope study. Several functional groups are well tolerated and the protocol is mild, allowing the functionalisation of relatively complex systems. To further demonstrate the potential and the simplicity of the methodology, the authors used this procedure to propose a simpler racemic protocol for the synthesis of pregabalin **16**, an anticonvulsant drug (Scheme 2.4, bottom). Previously, the reaction required seven steps and the use of KCN.⁹ With this procedure, only three steps are required and only mild and non-toxic reagents were handled.

⁸ Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 10886–10889.

⁹ Martinez, C. A.; Hu, S.; Dumond, Y.; Tao, J.; Kelleher, P.; Tully, L. *Org. Process Res. Dev.* **2008**, *12*, 392–398.

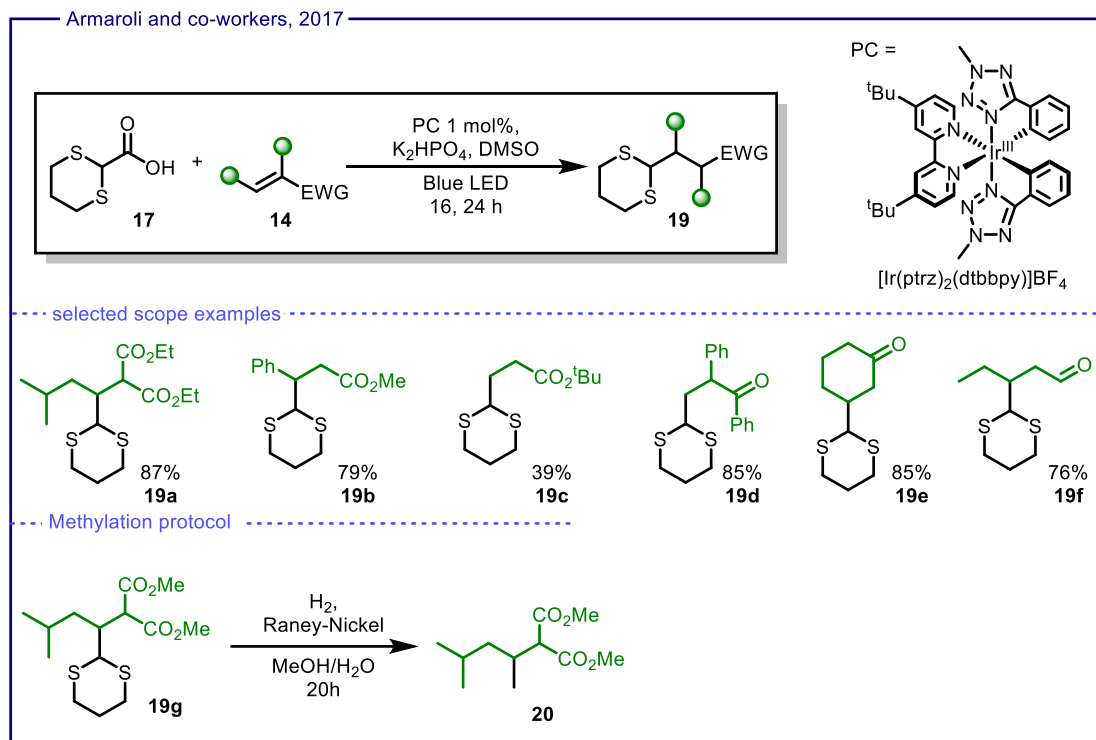


Scheme 2.4: MacMillan and co-workers. Another example of decarboxylative Giese reaction and its application on the synthesis of $\pm$ Pregabalin.⁸

In 2017, Armaroli and co-workers¹⁰ applied the photocatalysed decarboxylative Giese reaction using 1,3-dithiane-2-carboxylic acid **17** (Scheme 2.5). Interestingly, the presence of two sulfur atoms β to the carboxylic acid **17**, strongly contributes to the nucleophilic properties of the radical, enhancing the reactivity toward electron-poor double bonds **14**.¹¹ The procedure has been tested on a variety of radical acceptors e.g. aldehydes, ketones, esters, sulfones and unprotected amides with yields ranging between 39% and 93%. As dithianes **19** are known to be promptly cleaved – upon treatment with RANEY-nickel – to reveal the corresponding alkane backbone, the authors showed the application of this strategy in a formal methylation protocol, see bottom part of Scheme 2.5. This procedure opened a new area of Giese addition. With the use of functional groups that possess a rich radical and polar chemistry, more reactions can be achieved, opening new protocols that are not just limited to the radical addition to double bonds.

¹⁰ Gualandi, A.; Matteucci, E.; Monti, F.; Baschieri, A.; Armaroli, N.; Sambri, L.; Cozzi, P. G. *Chem. Sci.* **2017**, *8*, 1613–1620.

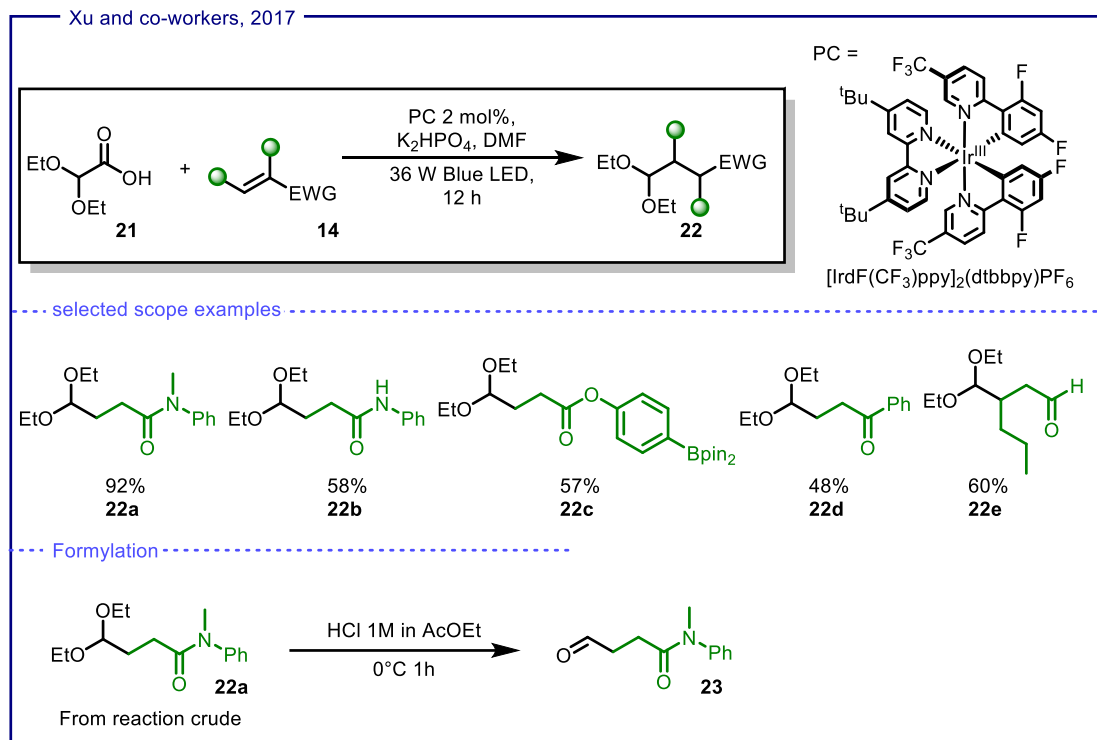
¹¹ Fleming I. *Molecular Orbital and Organic Chemical Reaction: Student Edition*, Wiley & Sons Ltd, **2009**, Chapter 7.



Scheme 2.5: Armaroli and co-workers. Decarboxylative Giese reaction protocol and its application for methylation.¹⁰

Similarly, this concept has been also used by Xu and co-workers.¹² In analogy with the dithiane addition, a decarboxylative Giese reaction that takes advantage of the properties of glyoxylic acid acetals **21** was proposed (Scheme 2.6). A variety of Giese acceptors **14**, including esters, aldehydes, ketones and nitriles, and different functionalities were tested. Remarkably, the glyoxylic adduct **22** can be treated with acids to reveal aldehyde **23**, making the strategy useful for the formal addition of a formyl group – a challenging process in traditional polar chemistry.

¹² Zhang, S.; Tan, Z.; Zhang, H.; Liu, J.; Xu, W.; Xu, K. *Chem. Commun.* **2017**, 53, 11642–11645.



Scheme 2.6: Xu and co-workers. Decarboxylative Giese reaction protocol was applied for formylation.¹²

The procedures mentioned above demonstrate the synthetic usefulness of photoredox-based decarboxylative Giese reactions, and how this versatile chemistry can open access to useful chemistry e.g., methylation and formylation protocols.

In this chapter, we will use decarboxylative photoredox chemistry with an unconventional radical acceptor i.e., vinyl phosphonium bromide, to open new chemistry. To better introduce the reader to the synthetic strategy disclosed, the classic chemistry of vinyl phosphonium bromide is briefly discussed in the next sub-chapter.

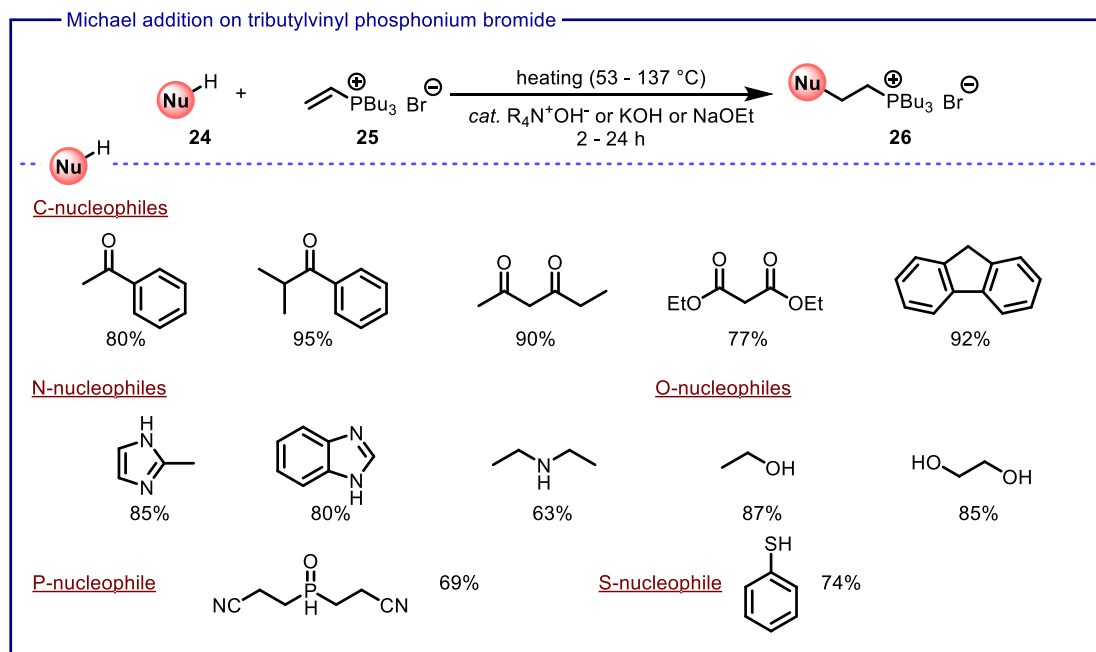
2.2.2. Vinyl triphenylphosphonium bromide

Vinyl phosphonium as a Michael acceptor

Vinylphosphonium salts were first reported by Hofmann in 1861.¹³ However, its chemistry has not been explored for more than 100 years until Keough and Grayson in 1963¹⁴ realised that tributyl vinyl phosphonium bromide **25** can be effectively used as a Michael acceptor. A variety of compounds like carbanion and heteroatom-based nucleophiles undergo addition, leading to phosphonium adducts **26** (Scheme 2.7).

¹³ Hofmann, A. W. *Ann. Suppl.*, **1861**, 1, 275.

¹⁴ Keough, P. T.; Grayson, M.; *J. Org. Chem.*, **1964**, 29, 631–635.


 Scheme 2.7: Uses of vinyl phosphonium **25** as Michael acceptor.¹⁴

In this first report, however, the vinyl phosphonium backbone was not used at its full potential. Ten years later, in 1973, Schweizer¹⁵ demonstrated that Michael addition on vinyl phosphoniums **25** could be used in tandem with Wittig olefination¹⁶ allowing the development of multicomponent reactions (Scheme 2.8). This chemistry was leveraged for the synthesis of a variety of heterocycles **34**. Schweizer used hydroxy ketones¹⁵ or 3-oxobutyl malonate¹⁷ to synthesize respectively dihydrofuran **34a-34b** or cyclopentene rings **34e**. McIntosh¹⁸ used α -mercapto ketones to synthesise dihydrothiophenes **34d-34e** and Hewson used acetamido ketones¹⁹ for the synthesis of pyrrolines **34f**.

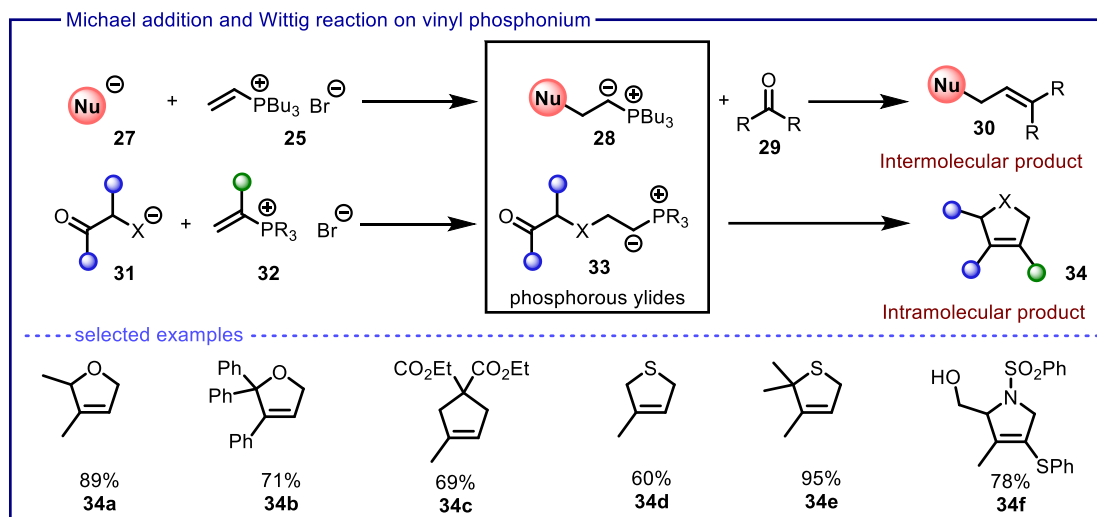
¹⁵ a) Schweizer, E. E. *J. Am. Chem. Soc.*, **1964**, 86, 2744. b) Schweizer, E. E.; Wehman, A. T.; Nycz, D. M. *J. Org. Chem.* **1973**, 38, 1583–1588.

¹⁶ Wittig, G. Nobel Lecture: from Diyls to My Idyll <https://www.nobelprize.org/uploads/2018/06/wittig-lecture.pdf> (1979).

¹⁷ Schweizer, E. E.; O'Neill, G. J. *J. Org. Chem.* **1965**, 30, 2082–2083.

¹⁸ McIntosh, J. M.; Goodbrand, H. B.; Masselc, G. M.; *J. Org. Chem.*, **1974**, 39, 202–206.

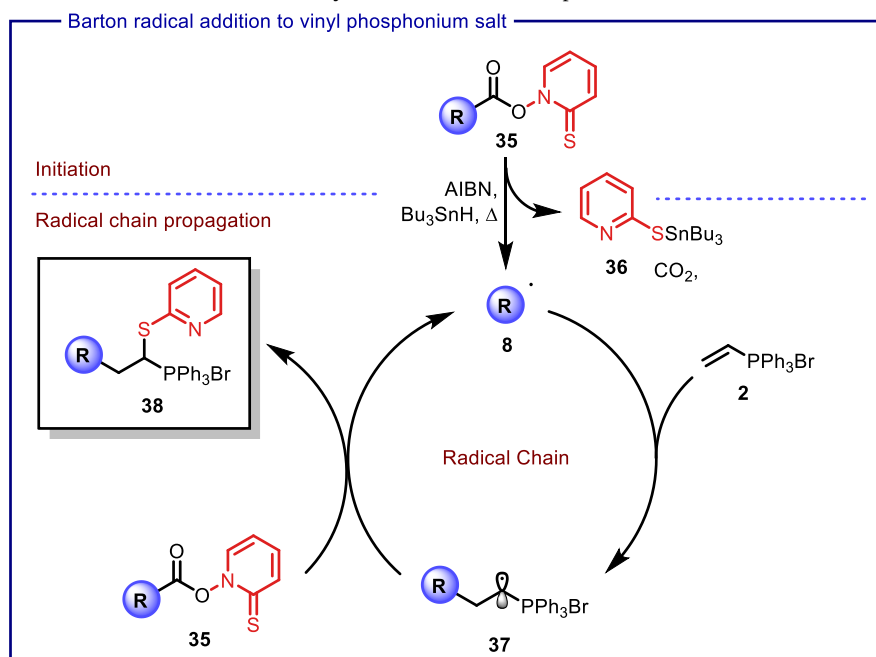
¹⁹ Burley, I.; Hewson, A. T. *Tetrahedron Lett.* **1994**, 35, 7099–7102.



Scheme 2.8: Uses of vinyl phosphonium as Michael acceptor and tandem Wittig olefination.¹⁵

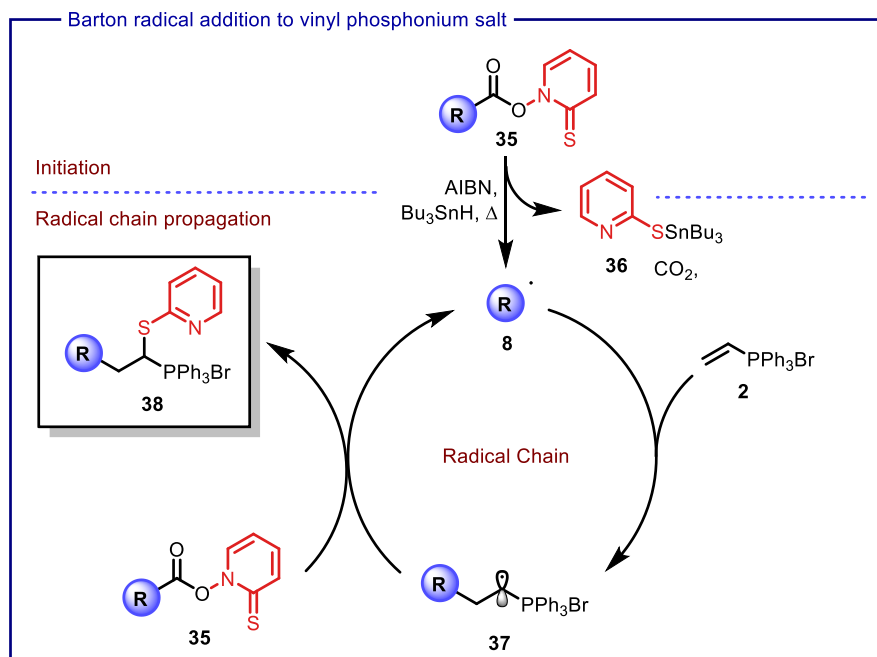
Vinyl phosphoniums as radical acceptors

Inspired by the ability of vinyl phosphonium bromides to participate in Michael addition with nucleophiles, Barton demonstrated, in 1985,²⁰ that they can be also used as Giese acceptors and used in radical decarboxylative chemistry. In the mechanism, depicted in



Scheme 2.9, Barton's redox active ester **35** undergoes decarboxylation in the presence of AIBN and Bu_3SnH , generating carbon-centred radical **8**. The open-shell species **8** then adds to vinyl phosphonium **2**, to generate radical **37**. Group transfer leads to product **38** and the generation of a new carbon-centred radical **8**, which feeds a radical chain propagation.

²⁰ Barton, D. H. R.; Togo, H.; Zard, S. Z. *Tetrahedron Lett.* **1985**, 26, 6349–6352.



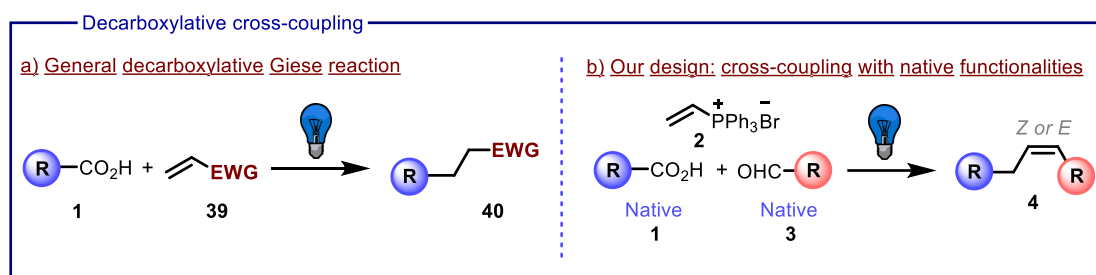
Scheme 2.9: Barton decarboxylation mechanism.²⁰

While effectively describing a novel radical acceptor, the group transfer radical nature of this protocol did not involve the generation of ylides in the mechanistic manifold, thereby not allowing the possibility to access tandem Wittig chemistry. This limited the application of this protocol to a simple “chemical curiosity”.

In the following sections, we demonstrate how exploiting the potential of photoredox catalysis allowed us to successfully combine the radical reactivity of vinyl phosphonium bromide with the Wittig reaction. This strategy introduced a novel methodology that can be leveraged to expand the chemical diversity achievable through standard Giese radical chemistry.

2.3. Aim of the project

As presented in the introduction section of this chapter, decarboxylative Giese additions have found wide application in synthesis, allowing to take advantage of the chemical diversity of carboxylic acids to develop new methodologies. However, the application of this chemistry is limited as it allows only simple modification of the substrate structures through the introduction of an electron-withdrawing group (EWG) connected through methylene units (Scheme 2.10, a). In the following section, we introduce the use of vinyl phosphonium bromide **2** as a novel radical acceptor in photoredox chemistry, which could significantly enhance the synthetic application of decarboxylative Giese-type additions. This methodology allowed to develop of a novel strategy to cross-couple complex molecular fragments bearing native and highly recurrent functionalities i.e. carboxylic acids **1** and aldehydes **3** (Scheme 2.10, b).

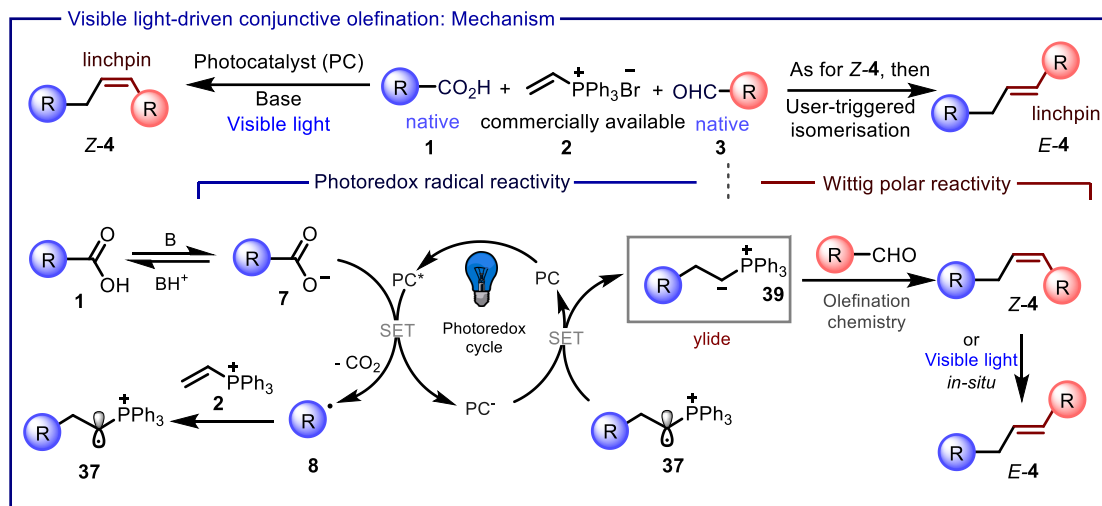


Scheme 2.10: Decarboxylative cross-coupling reactions. a) General decarboxylative Giese reaction. b) This work: conjunctive cross-coupling with native functionalities.

Design of the process

We envision to integrate the ionic reactivity of the Wittig reaction with photoredox decarboxylative radical addition chemistry. The connection of these two fundamental processes is based upon our hypothesis that the phosphorous cation present on the vinyl phosphonium **2** would be an efficient electron-withdrawing group promoting the addition of nucleophilic radicals **8**. At the same time, it would be a useful synthetic handle to achieve subsequent Wittig polar reactivity.

In our plan, presented in Scheme 2.11, nucleophilic radicals **8**, generated from photocatalyst-induced oxidation of carboxylate anion **7**, would add to vinyl phosphonium **2**, to afford radical cation **37**. This electron-deficient radical would then undergo SET with the PC⁻ affording ylide **39** and closing the photocatalytic cycle. In the presence of aldehyde **3**, the ylide **39** would undergo Wittig olefination to afford compound Z-**4**. This sequence opens a route for the conjunctive olefination of building blocks **1**, **2** and **3** to afford adduct **4**.



Scheme 2.11: Reaction design.

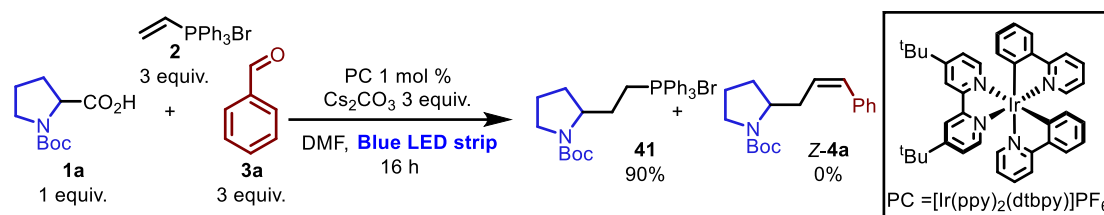
We further envisioned that allowing the users to select the stereochemistry of the generated alkene would significantly extend the synthetic utility of the proposed methodology. As Wittig olefinations are known to be *Z*-selective if non-stabilized ylides are involved, alkenes produced are expected to be *Z*-configured. We speculated that an *in-situ* isomerisation of the products would allow the development of a stereo-divergent process, thereby providing a user-defined isomer of the alkene linchpin.

2.4. Results and Discussion

2.4.1. Optimisation studies

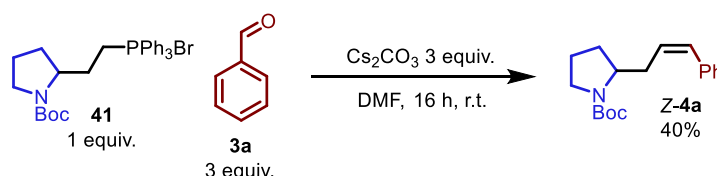
A body of previous optimisation studies, performed by Dr Mattia Silvi led to the conclusions summarised below.

The optimisation began with the irradiation of a mixture of Boc-proline **1a**, phosphonium **2** and benzaldehyde **3a** in DMF (Scheme 2.12). After $^1\text{H-NMR}$ and HRMS analysis, we concluded that the expected product **Z-4a** was not formed. However, the intermediate phosphonium **41** was observed in the solution.



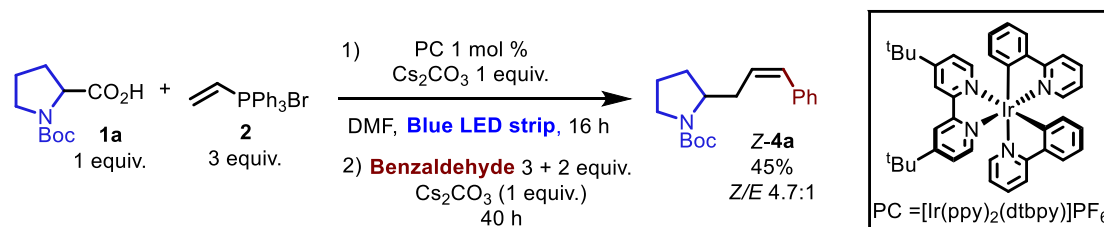
Scheme 2.12: Reaction discovery.

Isolation of the intermediate **41** and its subsequent Wittig olefination, in the presence of benzaldehyde **3a** and cesium carbonate (Scheme 2.13), showed the formation of the expected product **Z-4a** in 40% yield.



Scheme 2.13: Feasibility of Wittig reaction on intermediate **41**.

Interestingly, although the use of a mild base is unusual for Wittig reactions, it was previously observed that inorganic bases effectively promote the Wittig reaction.²¹ Once the feasibility of both steps was confirmed, the full reaction was carried out as depicted in Scheme 2.14, obtaining convincing preliminary results.



Scheme 2.14: Reaction discovery, addition of benzaldehyde **3a** after irradiation.

Since this reaction is a combination of two particularly different processes – the photocatalysed radical addition and the polar Wittig olefination – we decided to perform the optimisation by studying the two processes independently, with the idea of merging

²¹ Le Bigot, Y.; Elgharbi, R.; Delmas, M.; Gaset, A. *Tetrahedron* **1986**, 42, 3813–3823.

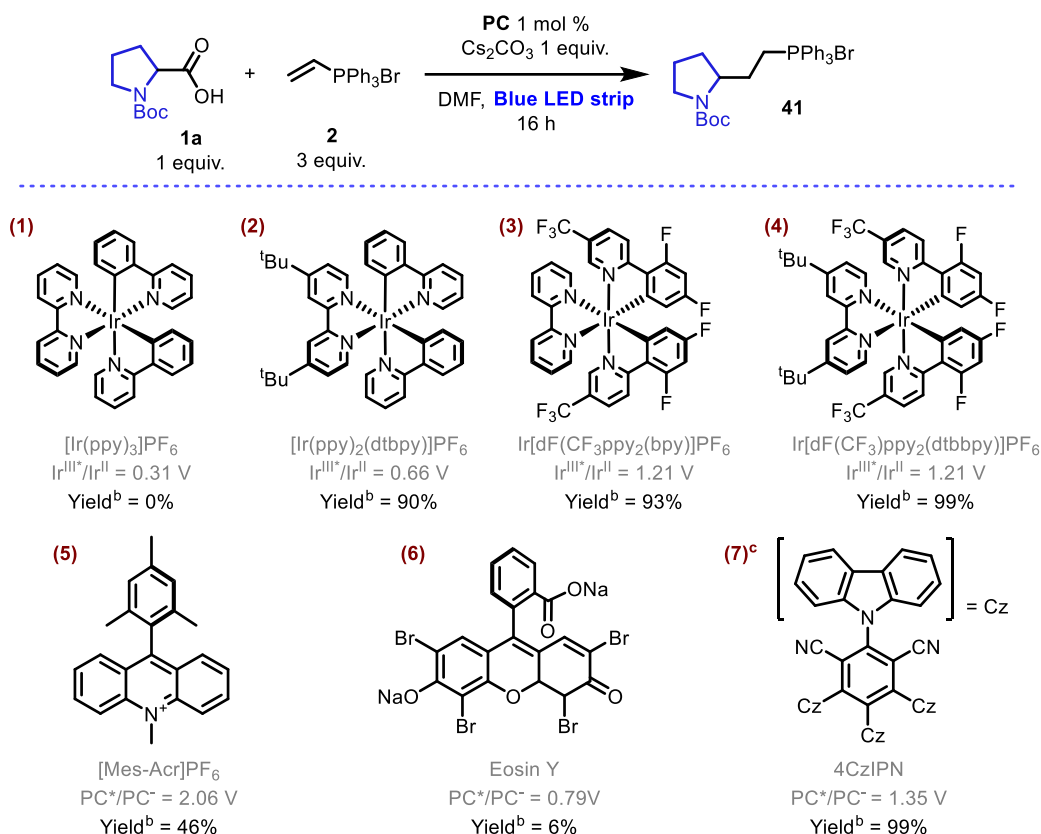
the chemistry in an *in-situ* process. All the following optimisation studies were performed by myself.

Investigation of the radical reactivity

Photocatalyst screening

We submitted a mixture of Boc-proline **1a** and phosphonium **2** in DMF to a variety of photocatalysts. The results are reported below in Table 2.2.

Table 2.2: Photocatalyst screening.



^a Reaction performed in [1a]₀ = 0.05 mmol scale. ^b ³¹P-NMR yield using ethyl triphenylphosphonium bromide as internal standard. ^c Catalyst loading 5 mol%.

We started the study by testing some Ir-based photocatalysts. In accordance with its low oxidative power, Ir(ppy)₃ (entry 1), was not effective in promoting this transformation. Other Ir-based catalysts with higher redox potential led to the desired intermediate **41** in excellent yields (entries 2, 3 and 4). (Ir[dF(CF₃)ppy]₂(dtbbpy))PF₆ (entry 4), was the most effective, presumably due to increased stability thanks to the encumbered ligand *tert*-butyl groups. The employment of organic photocatalysts was then investigated. Neither 9-mesityl-10-methylacridinium (entry 5) nor eosin Y (entry 6) led to improved results. Respectively, total decomposition or full recovery of the starting material was observed. Delightfully, using 5 mol% of the affordable 4CzIPN,²² led to the desired

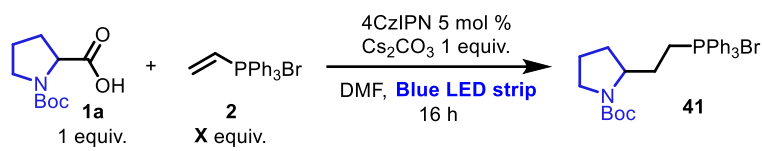
²² Shang, T.-Y.; Lu, L.-H.; Cao, Z.; Liu, Y.; He, W.-M.; Yu, B. *Chem. Commun.* **2019**, 55, 5408–5419.

product **41** in quantitative yield and was chosen as the optimal catalyst for further studies.

Loading of vinyl phosphonium **2**

We then focused on the identification of the best loading of vinyl phosphonium **2** (Table 2.3).

Table 2.3: Vinyl phosphonium **2** loading.



Entry ^a	2 loading (equiv.)	Yield 41 (%) ^b
1	3.00	99
2	2.00	99
3	1.50	94
4	1.20	90
5	1.05	71

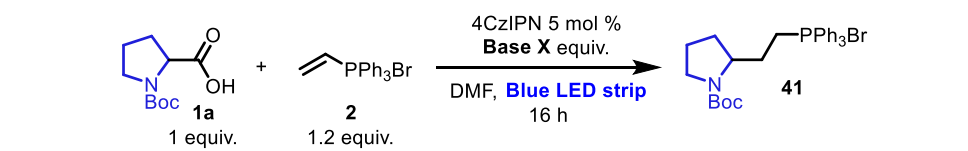
^a Reactions performed in 0.05 mmol scale, [**1a**]₀ = 0.1M. ^b ³¹P-NMR yield using ethyl triphenylphosphonium bromide as internal standard.

Decreasing the excess of phosphonium **2** to 1.05 equivalents, caused a slight reduction in the yield (from 99 % in entry 1 to 71% in entry 5). The use of 1.2 equivalents (entry 4), was chosen as the ideal compromise between atom economy and yield of the process.

Base screening

Different bases were then tested (Table 2.4).

Table 2.4: Base screening.



Entry ^a	Base	Base loading (equiv.)	Yield 41 (%) ^b
1	Cs ₂ CO ₃	1	90
2	K ₃ PO ₄	1	91
3	K ₃ PO ₄	4	82
4	K ₃ PO ₄	5	62

^a Reactions performed in 0.05 mmol scale, [**1a**]₀ = 0.1M. ^b ³¹P-NMR yield using ethyl triphenylphosphonium bromide as internal standard.

The cheaper potassium phosphate (entry 2) gave comparable results to cesium carbonate, so it was chosen as the optimal base. Increasing the base loading to 4 or 5 equivalents (entries 3 and 4) did not improve the results.

Solvent screening

Next, the effect of the reaction media was investigated in the process (Table 2.5).

Table 2.5: Solvent screening.



Entry ^a	Solvent	Yield 41 (%) ^b
1	DMF	90
2	THF	39
3	1,4-dioxane	22
4	ethyl acetate	13
5	toluene	9

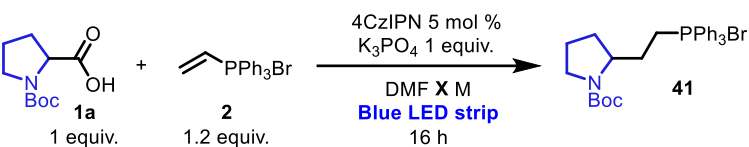
^a Reactions performed in 0.05 mmol scale, $[1\mathbf{a}]_0 = 0.1\text{M}$. ^b ³¹P-NMR yield using ethyl triphenylphosphonium bromide as internal standard.

Among the solvents tested, DMF was the most effective, giving compound **41** in 90% yield (entry 1). Other, less polar solvents – e.g., THF (entry 2), dioxane (entry 3), ethyl acetate (entry 4) and toluene (entry 5) – gave poor to moderate yields, presumably due to poor solubility of both the compound and the catalyst.

Concentration screening

Finally, the effect of concentration was investigated. The results are reported below in Table 2.6.

Table 2.6: Concentration screening.



Entry ^a	$[1\mathbf{a}]_0$ (M)	Yield 41 (%) ^b
1	0.1	90
2	0.5	95
3	1.0	91

^a Reactions performed in 0.05 mmol scale, $[1\mathbf{a}]_0 = 0.1\text{M}$. ^b ³¹P-NMR yield using ethyl triphenylphosphonium bromide as internal standard.

As presented above, the yield of the radical process was found to be relatively insensible to the variation of concentration of the reaction media.

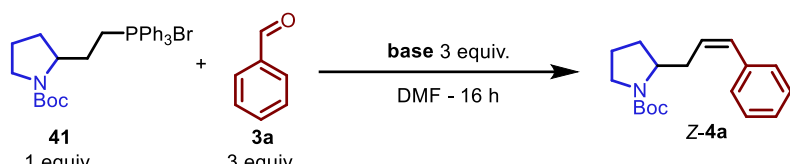
Influence of reaction parameters in the Wittig olefination

Next, to give insight into the Wittig olefination process, intermediate **41** was isolated and used as a model substrate to investigate the reaction conditions.

Base screening

We submitted a mixture of intermediate **41** and benzaldehyde **3a** to a variety of organic and inorganic bases. The results are reported Table 2.7 below.

Table 2.7: Base screening for the Wittig step.



Entry ^a	Base	Base loading (equiv.)	Z/E ^b	Yield Z-4a (%) ^b
1	Cs ₂ CO ₃	3.0	4.8	48
2	K ₂ CO ₃	3.0	6.6	23
3	Na ₃ (PO ₄) ₂	3.0	5.0	6
4	K ₃ PO ₄	3.0	5.2	68
5	K ₃ PO ₄	1.5	7.2	41
6	K ₃ PO ₄	6.0	6.2	72

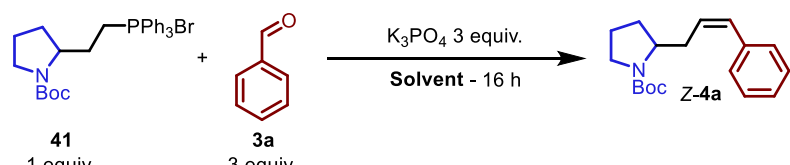
^a Reaction performed in 0.05 mmol scale, [41]₀ = 0.1M. ^b ¹H-NMR yield and ratio using CH₂Br₂ as internal standard.

Cesium carbonate, in entry 1, gave only a moderate yield. Other inorganic bases e.g., potassium carbonate (entry 2) and sodium phosphate (entry 3) gave product Z-4a only in poor yield, probably due to poor solubility in DMF. Potassium phosphate (entry 4), was found to provide optimal results, leading to compound Z-4a in 68% yield. A screening of base loading (entries 4, 5 and 6) revealed that 3 equivalents led to the best results.

Solvent screening

The effect of the reaction media on the reactivity and selectivity of the Wittig olefination was then investigated (Table 2.8).

Table 2.8: Solvent screening for the Wittig step.



Entry ^a	Solvent	Z/E ^b	Yield Z-4a (%) ^b
1	DMF	5.2	68
2	DMSO	4.0	70
3	DMA	6.8	53
4	DCM	2.2	45
5	THF	15	78

^a Unless otherwise stated, reactions performed in 0.05 mmol scale, [41]₀ = 0.1M. ^b ¹H-NMR yield and ratio using CH₂Br₂ as internal standard.

Generally, organic polar aprotic solvent (entries 1 to 3) gave good yields ranging from 53% to 70%. However, the Z/E observed selectivity was poor in all cases. DCM (entries 4) gave poor yield and very little control in the stereoselectivity. Interestingly, THF gave excellent yield and stereoselectivity (entry 5).

Development of the full conjunctive process

Merging the two processes

After having investigated the chemical features of the two elemental processes i.e., the radical reactivity of vinyl phosphonium bromide **2** and the following Wittig olefination, we focused on the identification of suitable reaction conditions to combine the two processes *in-situ*. The aim was to both maximise the yield and the selectivity of the full conjunctive reaction. Therefore, we carried out the full process using the condition optimised above (Table 2.9).

Table 2.9: Temperature optimisation for the full step.

Entry ^a	Temp. (°C)	Time second step (h)	Z/E ^b	Yield Z-4a (%) ^b
1 ^c	r.t.	40	4.7	45
2	40	15	6.3	73
3	60	6	7.4	86
4	90	3	4.4	87
5 ^{d,e,f}	60	16	11	78

^a Unless otherwise stated, reactions performed in 0.05 mmol scale, [1a]₀ = 0.1M. ^b ¹H-NMR yield and ratio using CH₂Br₂ as internal standard. ^c Photochemical step performed with 1 equiv. of Cs₂CO₃ and 1 mol% of [Ir(ppy)₂(dtbbpy)]PF₆. Wittig step performed adding 1 equiv. of Cs₂CO₃ and 5 equiv. of benzaldehyde **3a**. ^d Reactions performed in 0.2 mmol scale, [1a]₀ = 1M. ^e Photochemical step was run with **1a** 1 equiv., **2** 1.2 equiv. benzaldehyde **3a** 3 equiv. and K₃PO₄ 3 equiv. To ensure effective irradiation, Tuna blue Kessil lamp was used instead of blue LED strip. ^f Wittig step performed after adding THF (THF/DMF 9:1).

We observed only a moderate yield if the reaction is carried out a room temperature (entry 1). Therefore, we performed a partial re-optimisation of temperature. At 40 °C (entry 2) the yield raised from 68% to 73%. At 60 °C, the reaction took only 6 h to produce 86% yield. At 90 °C (entry 4) the reaction was completed after only 3h producing compound **Z-4a** in similar 87% yield, but with a poorer stereoselectivity. Therefore, we chose 60 °C as the optimal condition. Finally, to increase the practicality of the reaction and enhance the stereoselectivity observed, the photochemical step was run with all the components together (entry 5) in a minimal amount of DMF (1M). Then, THF was added (THF/DMF 9:1), and the reaction was heated at 60°C, leading to compound **Z-4a** in 78% isolated yield and a Z/E of 11:1.

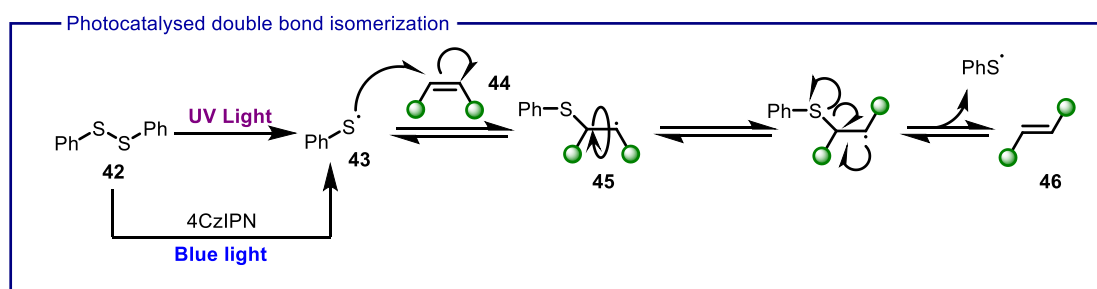
The development of a stereo-divergent process

We then focus on expanding our methodology to access both isomers of the olefin product. To this aim, we envisioned performing our reaction to generate product **Z-4a**, followed by a user-triggered *in-situ* isomerisation to the corresponding *E* isomer.

Generally, double-bond isomerisations are well-studied processes in chemistry. Isomerisation can occur chemically or can be driven by light. Photochemical

isomerisations are relevant in chemical biology i.e., the photoisomerisation of retinal (rhodopsin) is responsible for vision.²³ Although the majority of thermal chemical processes convert the *Z* isomer to the *E* following the thermodynamic equilibria, the light-driven process can act in both directions²⁴ depending on the nature of the irradiated molecules.

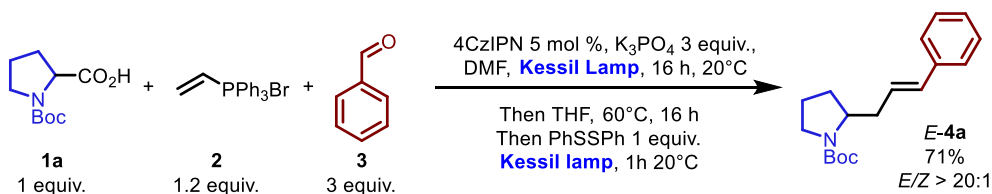
Z to *E* isomerisation procedures have been reported, and involve the use of UV light and diphenyl disulfide **42** (Scheme 2.15).^{25, 26} In this procedure, photolysis of the weak S-S bond in compound **42**, leads to the sulfur-centred radical **43**. This species reversibly attacks the double bond **44**, producing radical intermediate **45** that can freely rotate. Finally, homolytic elimination occurs, extruding S[•] radical **43**, and revealing the most stable, *E* isomer, of the double bond **46**.



Scheme 2.15: Mechanisms of the photocatalysed double bond isomerisation with PhSSPh **42**.

We envisioned that the photocatalyst, already present in the reaction mixture, could promote this process using milder visible light irradiation. In this hypothesis, the addition of PhSSPh and irradiation with blue light, the PC* would promote the disulfide cleavage upon Dexter energy transfer (see Section 1.2). While examples are reported about visible light-mediated *E* → *Z* isomerisation,^{27, 28} the application of analogous strategies for the *Z* → *E* has never been reported before.

As depicted in Scheme 2.16 below, after performing our usual methodology, one equivalent of PhSSPh **42** was added to the reaction vessel. Irradiation under visible light, produced compound *E*-**4a** in excellent stereoselectivity (*E/Z* >20:1) and comparable yield (71%) of the corresponding *Z* isomer.



Scheme 2.16: Isomerisation procedure for our methodology.

²³ Luo, T.; Sakai, Y.; Wagner, E.; Dräger, U. C. *J. Neurobiol.*, **2006**, 66, 677–686.

²⁴ Zhan, K.; Li, Y. *Catalysts*, **2017**, 7, 337–345.

²⁵ Schulte-Elte, K. H.; Ohloff, G. *Helv. Chim. Acta*, **1968**, 51, 548–553.

²⁶ Thalmann, A.; Oertle, K.; Gerlach, H. *Org. Synth.* **1985**, 63, 192.

²⁷ Singh, K.; Staig, S. J.; Weaver, J. D. *J. Am. Chem. Soc.* **2014**, 136, 5275–5278.

²⁸ Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2015**, 137, 11254–11257.

2.4.2. Scope studies

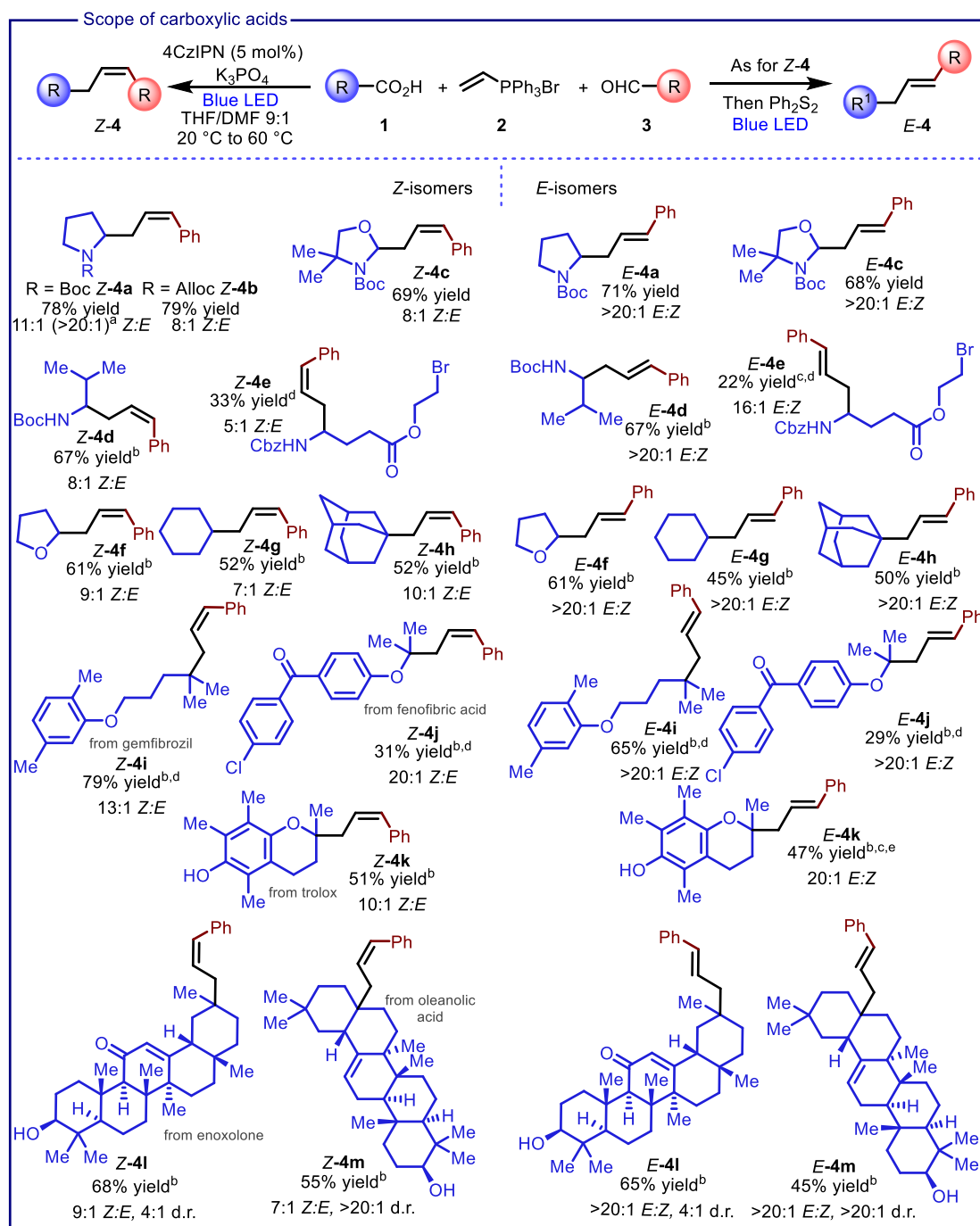
With these results in our hands, we investigated the scope of the process. A variety of carboxylic acids and aldehydes were submitted to our optimised conditions, synthesising both *Z* and *E* isomers.

Study of model carboxylic acids

We started the scope studies by using benzaldehyde **3a** and varying the nature of the carboxylic acids used (Table 2.10).

Several model carboxylic acids (**Z-4a** to **Z-4h**) reacted smoothly under our reaction conditions affording products **Z-4** in moderate to good yield and selectivity. A variety of cyclic and linear *N*-protected amino acids (**Z-4a** to **Z-4e**) easily underwent the expected reactivity, showing that the NH bond does not interfere with the reaction. The process tolerated terminal double bonds **Z-4b**, showing similar yields and only a slight drop in stereoselectivity, presumably due to a smaller steric profile of the carboxylic acid starting material. A pendant bromide – a challenging functionality in other traditional Wittig reactions – underwent the desired reactivity giving compound **Z-4e** in moderate yield and stereoselectivity. Simple alkyl carboxylic acids – generally more challenging substrates due to higher oxidation potential – required modification of our standard procedure to ensure high yields. The irradiation was performed in DMF 0.1M, followed by *in-situ* solvent switch to 0.1M THF, followed by the addition of benzaldehyde **3a** and heating to 60°C for 16h. For details see the General Experimental section. With these conditions, a variety of alkyl carboxylic acids (**Z-4f** to **Z-4h**) underwent the expected reactivity showing good yields and stereoselectivity. Applying our *E*-selective protocol, the corresponding *E* isomers were achieved with excellent *E* selectivity and yields comparable with those of the corresponding *Z* products (**E-4a** to **E-4h**). Compound **E-4e** was found to isomerise incompletely under standard reaction conditions but was obtained in excellent *E*-stereoselectivity by irradiation at 370 nm. Unfortunately, primary carboxylic acids proved to be not suitable for this methodology. This is probably due to their lower oxidability which renders radical generation less effective.

Table 2.10: Carboxylic acids scope.



Scope of model and complex carboxylic acids. Reactions were carried out in a 0.2 mmol scale, yields refer to isolated material, Z:E and d.r. values were measured in crude mixtures by NMR or gas chromatography analysis. Solvent composition is reported as after the THF addition to the initial DMF mixture. See general experimental section for full experimental details. Products **4s**, **4t** and **4v** are an equimolar mixture of epimers on the pyrrolidine chiral centre. ^a Z:E ratio after single-column chromatography purification. ^b Aldehyde addition and *in-situ* solvent exchange to sole THF prior to heating. ^c Isomerisation carried out on the purified material under 370 nm LED irradiation. ^d Compound synthesised by Dr Matti Silvi ^ePh₂S₂ (2 equiv.) was used.

Application in late-stage functionalisation of complex carboxylic acid

A variety of natural and bioactive carboxylic acids – carrying several unprotected and sensitive functionalities – were successfully functionalised through this methodology (Z-4i to Z-4m). To ensure high yield and stereoselectivity, all these entries were

performed using the modified procedure previously described for alkyl carboxylic acids (for details see General Experimental). Gemfibrozil, a medication used to treat abnormal blood lipid levels,²⁹ was effectively functionalised to derivative **Z-4i** in high yield and *Z*-selectivity. Fenofibric acid promptly underwent the desired reactivity, demonstrating the compatibility of our protocol with substrates carrying reactive ketones functionality that may potentially interfere with Wittig olefination chemistry. Its functionalisation led to product **Z-4j** with moderate yield and excellent *Z* stereoselectivity. For this substrate, photo-dechlorination was observed, accounting for the low mass balance observed. Noteworthy, aromatic and aliphatic hydroxyl functionalities were demonstrated to be compatible with our reaction condition. Different bioactive molecules e.g., trolox, enoxolone and oleanoic acid, smoothly underwent our functionalisation process without the need of protecting groups (**Z-4k** to **Z-4m**). In particular, the high yield obtained from the unmodified enoxolone (entry **Z-4l**) bearing a free hydroxyl group and an unsaturated ketone, further confirmed the remarkable functional group tolerability of this methodology. By following our *in-situ* isomerisation protocol, we accessed all the *E* isomers with excellent stereoselectivity, regardless of the complexity of the compounds, without any significant loss of yield compared to the *Z*-selective procedure (**E-4i** to **E-4m**). Trolox derivative **Z-4k** was found to isomerise incompletely under standard conditions. Isolation and irradiation at 370 nm of the *Z* isomer **Z-4k** in the presence of diphenyl disulfide led to compound **E-4k** in good yield and excellent *E*-selectivity. See general experimental section for details.

Study of model aldehydes

We then investigated the scope of our methodology with a variety of aldehydes (Table 2.11). Diverse aromatic aldehydes carrying electron-withdrawing or electron-donating groups and Lewis basic heteroaromatics reacted smoothly, producing respective compounds **Z-4n**, **Z-4o** and **Z-4p** in good yields and stereoselectivity ranging from 7:1 to 8:1. Aliphatic aldehydes, although less reactive, are also suitable substrates leading to compounds **Z-4q** and **Z-4r** good yield and excellent stereoselectivity. By applying our *E*-selective procedure, we obtained similar yields and excellent stereoselectivity for all the model aldehydes (**E-4n** to **E-4r**). Aliphatic aldehydes lead to a reduced *E/Z* ratio ranging from 8:1 to 14:1 (**E-4q** and **Z-4r**), presumably due to the formation of less stabilised unconjugated radicals during the isomerisation procedure (Table 2.11).

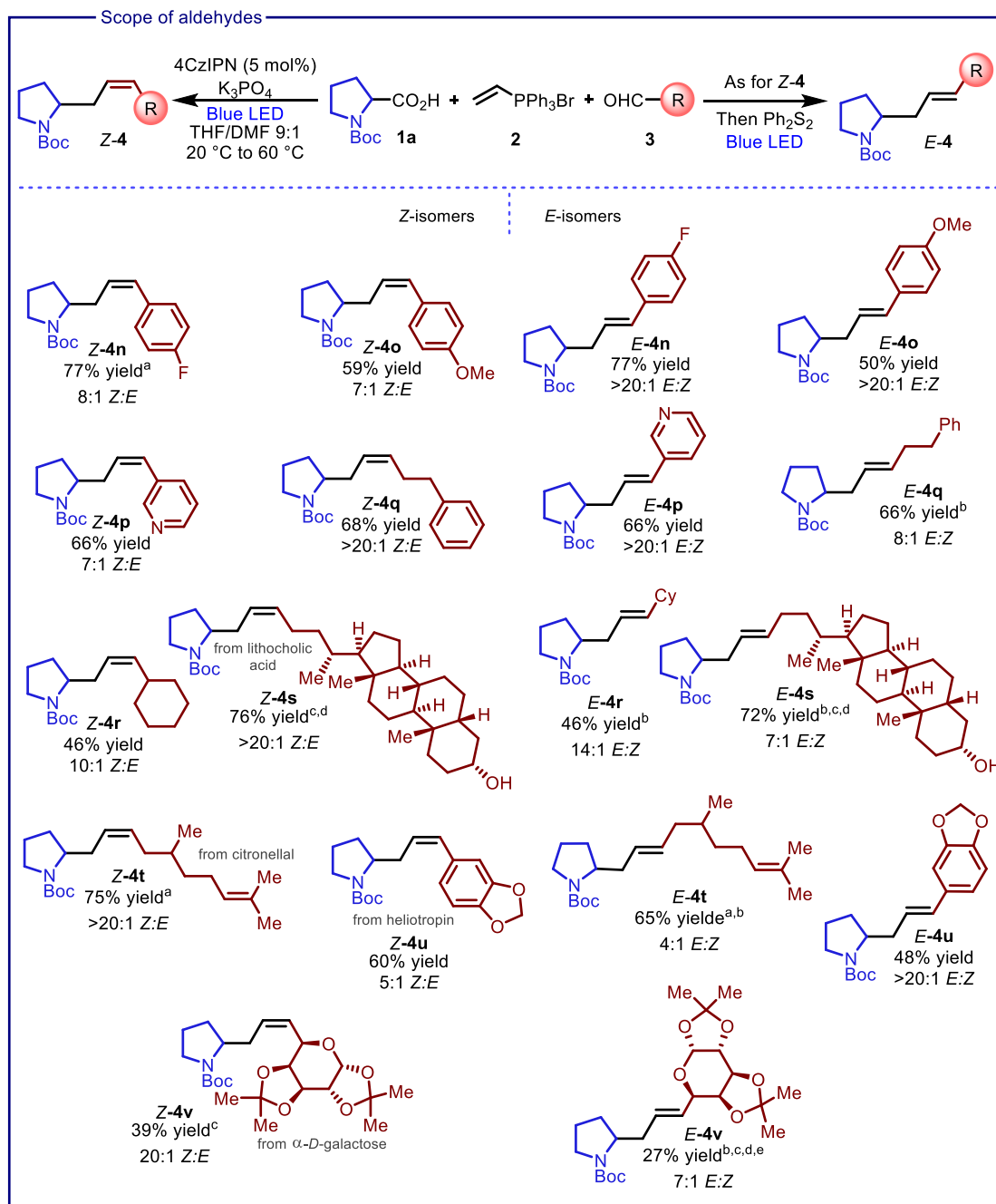
Application in late-stage functionalisation of complex aldehydes

We then applied the methodology in the chemical modification of aldehydes derived from natural products and complex biomolecules (**Z-4s** to **Z-4v**). When needed, the stoichiometry of the reaction was modified to use the valuable aldehydes as limiting reagent. Lithocholic acid-derived aldehyde was successfully converted to compound **Z-**

²⁹ Roy, A.; Pahan, K., *Immunopharmacol. Immunotoxicol.*, **2009**, 31, 339-351.

4s in high yield and full *Z*-selectivity. Remarkably, the presence of a free hydroxyl group in the complex aldehydic scaffold did not hamper our desired reactivity. Citronellal, a monoterpene aldehyde responsible for the lemon scent, underwent our reaction giving the expected product **Z-4t** in good yield and full *Z*-selectivity, despite containing an alkene moiety which may interfere with the radical reactivity.

Table 2.11: Aldehydes reaction scope.



Model and complex aldehydes scope. Reactions were carried out in a 0.2 mmol scale, yields refer to isolated material, *Z*:*E* and d.r. values were measured in crude mixtures by NMR or gas chromatography analysis, solvent composition is reported as after the THF addition to the initial DMF mixture. See general experimental section for full experimental details. Products **4s**, **4t** and **4v** are equimolar mixture of epimers on the pyrrolidinechiral centre. ^a Compound synthesised by Dr Mattia Silvi ^b Ph_2S_2 (2 equiv.) was used. ^c Aldehyde **3** was used as the limiting reagent. ^d 0.1 mmol scale. ^e Isomerisation carried out on the purified material under 370 nm LED irradiation. Boc, *N*-tert-butoxycarbonyl; Alloc, *N*-allyloxycarbonyl; Cbz, *N*-benzyloxycarbonyl; Cy, cyclohexyl.

Piperonal, a natural fragrance containing an aromatic aldehyde, was effectively used in our procedure giving compound **Z-4u** in good yield and moderate stereoselectivity (5:1 *Z:E*). Finally, compound **Z-4v** was obtained in good yield and excellent selectivity from the corresponding aldehyde, demonstrating that carbohydrate scaffolds are competent substrates in our process.

Our *E*-selective procedure allowed access to the corresponding *E*-isomers with excellent stereoselectivity, regardless of the complexity of the compounds, without any significant loss of yield compared to the *Z*-selective procedure (**E-4s** to **E-4v**). The application of our *E*-selective methodology to complex compounds obtained from aliphatic aldehydes – which contain multiple alkenes or free hydroxyl groups – proved to be challenging, resulting in stereoselectivity ranging from 4:1 to 14:1 *E/Z*. In some cases i.e., **E-4s**, **E-4t**, and **E-4v**, 2 equivalents of PhSSPh and longer reaction times were required to promote complete *Z-E* isomerisation (see general experimental section for details).

2.4.3. Multi-gram scale reaction

We then investigated the scalability of the process. To this aim, the model conjunctive olefination of Boc-proline **1a** with benzaldehyde **3a** was performed at different reaction scales, monitoring the impact on the yields obtained.

It is known that photochemistry considerably suffers from scale-up.³⁰ According to the Beer-Lambert law, light transmittance decreases with the second power of the distance from the light source. As a result of the light absorption of the reaction media, the distribution of the light is not homogeneous. In practice, this means that molecules at the centre of the vessel do not receive the same photon flux as the molecules closer to the glass surface. In a small reaction scale, like the one commonly used in research laboratories, the problem is easily overcome with vigorous stirring. Although the irradiation will still be uneven, the stirring ensures the homogeneity of irradiation. In a multi-gram scale process, this is much more difficult. Due to the high reaction volume, the stirring is not sufficient to ensure an even distribution of light, resulting in a sluggish reaction. Furthermore, a reaction performed on a big scale requires a comparatively higher photon flux to ensure full conversion of the starting materials, when compared to a small-scale reaction. A possible solution is to use flow chemistry, a technique where irradiation is carried out in small transparent tubes containing the reaction media.³¹ Although this usually ensures scalability, the technique requires significant modification of the reaction parameters, compared to a standard batch reaction. This is especially true when insoluble inorganic compounds are suspended in the reaction media – i.e., inorganic bases. For this reason, we initially attempted a simple batch

³⁰ Kayahan, E.; Jacobs, M.; Braeken, L.; Thomassen, L. C. J.; Kuhn, S.; Van Gerven, T.; Leblebici, M. E. *Beilstein J. Org. Chem.* **2020**, *16*, 2484–2504.

³¹ Sambiagio, C.; Noël, T. *Trends Chem.* **2020**, *2*, 92–106.

scale-up (Figure 2.1). To ensure full conversion, the irradiation time was increased to 8 hours. The results are reported below in Table 2.12.

Table 2.12: Scale-up of the standard reaction conditions.

Entry ^a	scale 1a (mmol)	Z/E ^b	Yield Z-4a (%) ^b
1	1	9/1	82
2	5	9/1	81
3	20	9/1 (12/1) ^c	79 (76) ^c

^a Reaction performed respectively in 10 mL, 50 mL and 200 mL Schlenk. $[1a]_0 = 0.1M$. ^b Yield and stereoselectivity calculated on an NMR crude sample with CH_2Br_2 as the internal standard.

^c The result in parenthesis are after single chromatography purification.

To our delight the reaction can be run in 1, 5 and 20 mmol scale without any dramatic decrease of the yield, demonstrating excellent scalability of the process even in batch conditions.

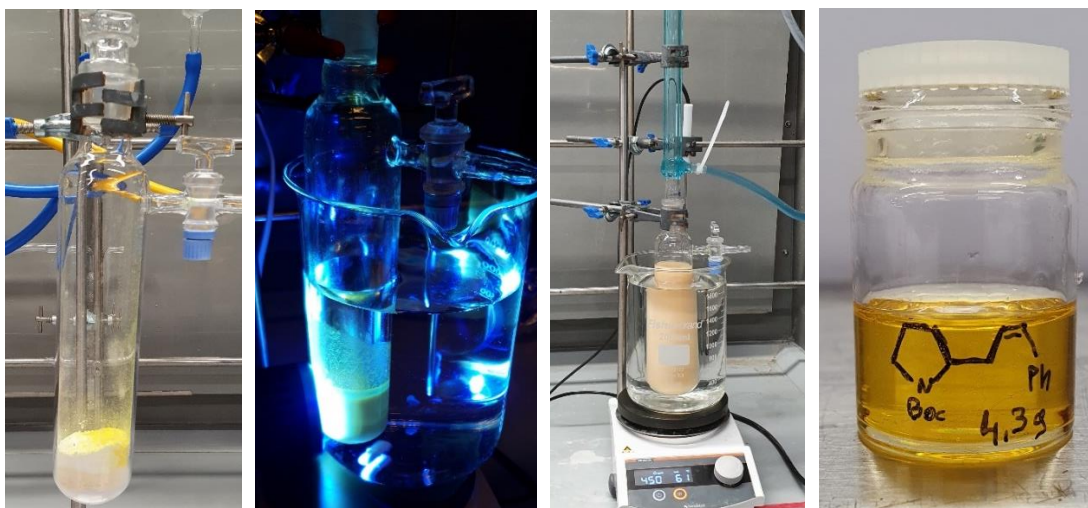


Figure 2.1: From left to right: Preparation of the reaction, weighing all the solids; reaction irradiation with the same Kessil lamps used for the scope studies; Wittig olefination step, heating the THF/DMF mixture at 60°C; final compound after isolation.

2.5. Conclusions

In conclusion, we have developed a conjunctive olefination reaction by successfully merging photoredox catalysis with the Wittig reaction. The chemistry offers rapid and practical access to complex olefin fragments, linking together two reaction partners of various molecular complexity through the constructions of new C-C bonds, and using only native functionalities. The programmable *E* – *Z* stereochemistry ensures the highest possible degree of molecular geometry control, crucial to define the chemical and physical properties of products. Both *Z*- and *E*-selective procedures showed tolerability to several sensitive functionalities such as terminal double bonds, pendant bromides, activated ketones, aliphatic and aromatic alcohols and heteroaromatics. Within this process, the requirement of functional group protection and/or deprotection sequences is to a minimum, making it a suitable choice for late-stage functionalisation chemistry.

This novel reactivity is expected to play an important role in the invention of novel structures applicable in pharmaceuticals, agrochemicals, or the invention of novel materials.

2.6. General experimental

2.6.1. Solvents, reagents, and starting materials

All air and water-sensitive reactions were carried out in oven-dried glassware under an argon atmosphere using standard Schlenk manifold technique. The solvents were degassed when required by bubbling argon through the solvent for five minutes. Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. All solvents were commercially supplied or provided by the communal stills of the School of Chemistry, University of Nottingham. Commercially available compounds were purchased from Sigma Aldrich, Alfa Aesar, Acros, Fluorochem, TCI chemicals or STREM chemicals and used as received. Vinyl phosphonium was purchased from Sigma Aldrich (Product code 150193-25g; batch number: 0000072767) and used without further purification, all liquid aldehydes were distilled prior to use. As not relevant for the process, the absolute stereochemistry of the amino acids, when used as starting materials, is omitted in the schemes for the sake of simplicity: the natural L-stereoisomers have been used in all cases. Dried solvents were purchased from Acros Organic, Extra Dry over molecular sieves, AcroSeal®.

2.6.2. Chromatography and instrumental analysis

Flash column chromatography (FCC) was carried out using Sigma-Aldrich silica gel LC60A-40 (63 μm). All reactions were followed by thin-layer chromatography (TLC) when practical, using Merck Kieselgel 60 F₂₅₄ fluorescent treated silica which was visualised under UV light or by staining with aqueous basic potassium permanganate.

GC-MS analyses were carried out using Thermo Scientific Trace 1300 Gas Chromatography with column Thermo Scientific TG-17MS 30m x 0.25mm x 0.25 μm coupled with a Thermo Fisher ISQ LT Single Quadrupole Mass Spectrometer. Chromatogram were analysed through Chromeleon 7.2 software. Method A: initial T 40 °C (hold 3 min); ramp target T 180 °C (rate 20 °C min⁻¹); ramp target T 280 °C (rate 20 °C min⁻¹, hold time 10 min). Method B: 40 °C (hold 3 min); ramp target T 200 °C (rate 20 °C min⁻¹); ramp target T 250 °C (rate 1 °C min⁻¹, hold time 5 min).

¹H-NMR, ¹³C-NMR and ³¹P-NMR spectra were recorded using Bruker broadband prodigy cryoprobe AV(III)500HD 500 MHz and Bruker AV(III)400HD 400 MHz spectrometers. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz). The ¹H-NMR spectra are reported as follows: ppm (multiplicity, coupling constants, number of protons). High-resolution mass spectra (HRMS) were recorded on a Bruker MicrOTOF II by Electrospray Ionisation (ESI). IR spectra were recorded on a Bruker Vertex 70 FT-IR ATR as a thin film. Only selected absorption maxima (ν_{max}) are reported in wavenumbers (cm⁻¹). **Melting points** were

recorded in degrees Celsius (°C), using a Stuart melting point SMP 20 microscope apparatus and are reported uncorrected.

2.6.3. Naming of compounds

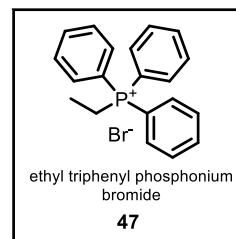
Compound names are those generated by ChemDraw 19.0 software (PerkinElmer), following the IUPAC nomenclature.

2.6.4. LEDs

Kessil lamp A160WE Tuna Blue Saltwater LED Light 40W was used for irradiation of the conjunctive olefination reactions (including the isomerisation step). A Kessil lamp PR160L-370 was used for the *Z* → *E* isomerisation process in the specific cases of *E*-4e, *E*-4k and *E*-4v.

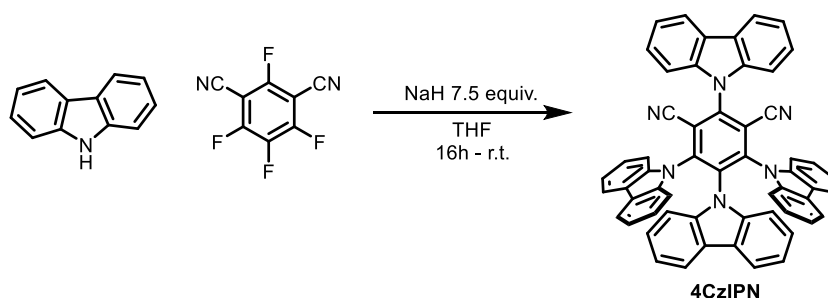
2.6.5. ³¹P-NMR analysis method used in the optimisation studies

All the yields reported in the optimisation studies of the photochemical process were obtained instrumentally through ³¹P analysis. Since the relaxation time T¹ of phosphorous is strongly dependent on its chemical surroundings and oxidation state, ethyl triphenyl phosphonium bromide **47** was used as an internal standard. Given the structural similarities with the intermediate **41**, the two compounds were assumed to have analogous relaxation delay, leading to comparable signal intensity. Data from isolated yields confirmed this assumption.



2.6.6. Synthesis of the photocatalyst and novel starting materials

Synthesis of 4CzIPN



4CzIPN was synthesised through a modification of a known procedure.³²

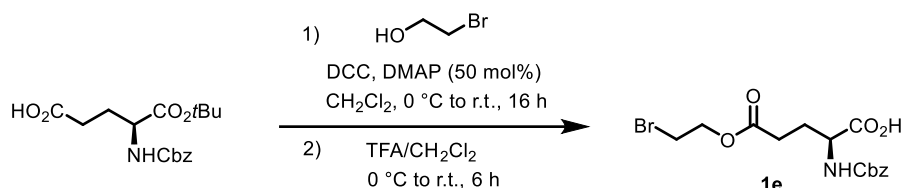
NaH (60% in oil; 15.0 mmol; 600 mg) was added slowly to a stirred solution of 9-carbazole (10.0 mmol; 1.67 g) in dry THF (40 mL) under an argon atmosphere at room

³² Huang, H.; Yu, C.; Zhang, Y.; Zhang, Y.; Mariano, P. S.; Wang, W. *J. Am. Chem. Soc.*, **2017**, *139*, 9799–9802.

temperature. After 30 min, tetrafluoroisophthalonitrile (2.00 mmol; 400 mg) was added. After stirring at room temperature for 12 h, 200 μ L of distilled water were added to the mixture to quench the excess NaH. Then the solvent was evaporated under reduced pressure. The yellow powder was solubilized in DCM and celite was added. The solvent was removed again under reduced pressure and the resulting powder was dry-loaded and purified through column chromatography (SiO₂; gradient 75:25 to 1:1 hexane:DCM) to afford 4CzIPN (1.2 g; 76%) as a bright yellow fine powder. **R_f** (1:1 hexane:DCM) 0.6; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 8.23 (d, J = 7.7 Hz, 2H), 7.81 – 7.62 (m, 8H), 7.49 (ddd, J = 8.0, 6.8, 1.5 Hz, 2H), 7.33 (d, J = 7.7 Hz, 2H), 7.23 (dd, J = 6.8, 2.1 Hz, 4H), 7.12 – 7.05 (m, 8H), 6.89 – 6.78 (m, 4H), 6.64 (t, J = 7.8 Hz, 2H); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 145.4, 144.8, 140.1, 138.3, 137.1, 134.9, 127.1, 125.9, 125.1, 124.9, 124.7, 124.0, 122.6, 122.1, 121.6, 121.1, 120.6, 119.8, 116.5, 111.8, 110.1, 109.6, 109.6.

The spectra match the ones reported.³³

Synthesis of (S)-2-(((benzyloxy)carbonyl)amino)-5-(2-bromoethoxy)-5-oxopentanoic acid (**1e**)

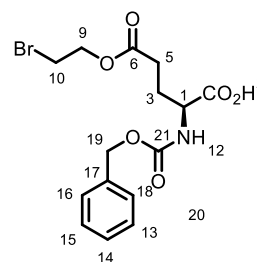


To a stirred solution of Z-L-Glu-OtBu (1.2 equiv; 2.4 mmol; 810 mg) in dry CH₂Cl₂ (7 mL) at 0 °C was added DCC (1.2 equiv.; 2.4 mmol; 465 mg) and DMAP (0.5 equiv.; 1 mmol; 211 mg), followed by 2-bromoethanol (1.0 equiv.; 2.0 mmol; 142 μ L). The reaction was stirred for 5 minutes at 0 °C, followed by 16 h at r.t. The resulting reaction mixture was filtered over a thin layer of celite and silica to remove the precipitated urea by-product, eluting with EtOAc. Volatiles were removed under vacuum and the residue was purified by silica gel chromatography (gradient hexane:EtOAc 85:15 – 80:20) to afford the protected tert-butyl ester intermediate as an oil, which was subjected to deprotection as follows without further characterisation.

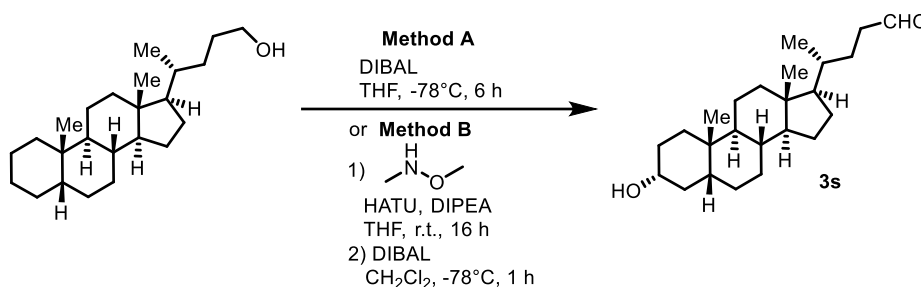
The oil was dissolved in CH₂Cl₂ (1.4 mL) and cooled down to 0 °C. To this solution, TFA (1.4 mL) was added dropwise. The reaction was stirred at r.t. until full consumption of starting material was observed by TLC analysis (6 h). To remove traces of TFA, the residue was dissolved in toluene (10 mL) and evaporated using a rotary evaporator (the process was repeated twice to ensure full removal of the acid). The product **1e** was obtained as a white solid (740 mg; 95%). **M.P.** 91–92 °C; **R_f** (70:30 hexane:EtOAc) 0.1; **IR** (film) ν_{max} /cm⁻¹: 3289, 3035, 1720, 1527, 1454, 1393, 1215, 1058, 777, 741, 699, 574; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 8.79 (br. s, 1H, **2**), 7.41 – 7.30 (m, 5H, **13** -

³³ Garreau, M.; Le Vaillant, F.; Waser, J. *Angew. Chem. Int. Ed.*, **2019**, *58*, 8182–8186.

18), 5.53 (d, $J = 8.2$ Hz, 1H, **12**), 5.20 – 5.07 (m, 2H, **19**), 4.52 – 4.29 (m, 3H, **1** + **9**), 3.52 – 3.43 (m, 2H, **10**), 2.60 – 2.45 (m, 2H, **5**), 2.35 – 2.21 (m, 1H, **3**), 2.06 (dtd, $J = 14.4, 7.9, 6.4$ Hz, 1H, **3'**); $^{13}\text{C-NMR}$ (CDCl_3 , 126 MHz) δ (ppm): 175.9 (**2**), 172.5 (**6**), 156.3 (**21**), 136.1 (**17**), 128.7 (**14**), 128.5 (**18**), 128.3 (**13**), 67.5 (**9**), 64.2 (**19**), 53.3 (**1**), 30.2 (**5**), 28.7 (**10**), 27.4 (**3**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{15}\text{H}_{18}\text{BrNNaO}_6^+$) expected m/z 410.0210; found m/z 410.0211.



Synthesis of 3 α -hydroxy-5 β -cholanal (**3s**)



Method A: Following a previously reported procedure,³⁴ DIBAL (3 equiv.; 12 mmol; 10 mL 1.2 M in toluene) was added dropwise to a solution of lithocholic acid (1 equiv.; 4 mmol; 1.5 g) in THF (40 mL) at -78°C under Ar. The mixture was stirred at the same temperature for 6 h, after which it was removed from the cold bath and quenched by instantaneous addition of 100 mL of saturated Rochelle salts solution. The mixture was stirred until full phase separation was obtained. The aqueous solution was extracted five times with EtOAc (50 mL). The organic phases were collected, washed with brine (50 mL) and dried over magnesium sulfate. The organic phase was evaporated to obtain a residue, which was purified by SiO_2 column chromatography (celite dry loading is recommended) using hexane-AcOEt (3/1) as the eluent to afford pure compound **3s** (173 mg; 12%). Yields can be improved by following method B, below.

Method B: Compound **3s** was synthesised through a modification of a known procedure.^{35, 36}

To a solution of lithocholic acid (1 equiv.; 3 mmol; 1.13g) in dry THF (12 mL) at room temperature, HATU (1.2 equiv.; 3.6 mmol; 1.37g) and DIPEA (3.5 equiv.; 10.5 mmol; 1.8 mL) were added. The mixture was stirred for 1 h at r.t. and N,O -Dimethylhydroxylamine hydrochloride (2 equiv.; 6 mmol; 0.59g) was added and the reaction was left stirring at room temperature for 16 h. The crude was diluted in 100 mL of water and extracted three times with EtOAc (50 mL). Then the organic phases were washed with brine (25 mL) and dried over MgSO_4 . The solvent was removed under reduced pressure and the resulting white powder was purified through flash

³⁴ Fujioka, H.; Okitsu, T.; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Am. Chem. Soc.*, **2006**, 128, 5930–5938.

³⁵ Upasani, R. B.; Harrison, B. L.; Askew, B. C. Jr.; Dodart, J.; Salituro, F. G.; Robichaud, A. J. *Neuroactive Steroids, Compositions, and Uses Thereof*, WO2013/36835 A1, **2013**, Par. 00398, 67.

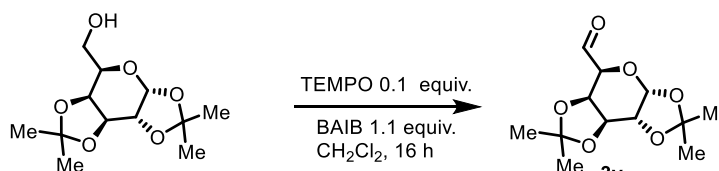
³⁶ Tomkinson, N. C. O.; Willson, T. M.; Russel, J. S.; Spencer, T. A. *J. Org. Chem.* **1998**, 63, 9919–9923.

column chromatography (celite dry loading is recommended; SiO₂; gradient 60:40 to 35:75 hexane:EtOAc) to afford the intermediate (1.25g; 99%) which was subjected to the following step without any further characterisation.

To a stirred solution of the intermediate (1 equiv.; 0.88 mmol; 369 mg) in dry CH₂Cl₂ (18 mL) cooled at -78°C was added dropwise a solution of DIBAL (2 equiv.; 1.8 mmol; 1.5 mL 1.2 M in toluene) over 10 minutes. The reaction was left stirring at -78°C for 1 h. Then, 20 mL of a solution of Rochelle Salt (12 g of sodium tartarate in 40 mL of water) was quickly added under vigorous stirring while the temperature was rapidly risen through an ice bath. The mixture was left at room temperature under vigorous stirring for 3h until the organic phase became transparent. The solution was extracted three times with DCM (20 mL), and the combined organic phases were washed with brine (20 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. The resulting white powder was purified through flash column chromatography (SiO₂; gradient 9:1 to 7:3 hexane:DCM) to afford compound **3s** (242 mg; 67%) as a white powder. ¹H-NMR (CDCl₃, 400 MHz) δ (ppm): 9.76 (t, *J* = 1.8 Hz, 1H), 3.69 – 3.50 (m, 1H), 2.52 – 2.29 (m, 2H), 1.95 (d, *J* = 12.3 Hz, 1H), 1.86 – 1.74 (m, 5H), 1.68 – 1.63 (m, 1H), 1.58 – 1.48 (m, 2H), 1.42 – 1.36 (m, 6H), 1.31 – 1.21 (m, 6H), 1.14 – 1.03 (m, 5H), 0.93 – 0.89 (m, 6H), 0.64 (s, 3H); ¹³C-NMR (CDCl₃, 101 MHz) δ (ppm): 203.4, 72.0, 56.6, 56.1, 42.9, 42.2, 41.1, 40.6, 40.3 (2C), 36.6, 36.0, 35.5, 34.7, 30.7, 28.4, 28.1, 27.3, 26.6, 24.4, 23.5, 21.0, 18.5, 12.2.

The spectra match the ones reported.³⁷

Synthesis of (3a*R*,5*S*,5a*R*,8a*S*,8b*R*)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran-5-carbaldehyde (**3v**)



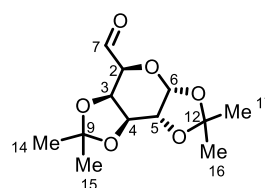
Compound **3v** was synthesised through a reported procedure.³⁸

To a stirred solution of 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (1 equiv.; 4 mmol; 1.04 g) and TEMPO (0.1 equiv.; 0.4 mmol; 62.5 mg) in dry DCM (4 mL), diacetoxyiodobenzene (BAIB) (1.1 equiv.; 4.4 mmol; 1.4g) was added. The reaction was left stirring for 16 h at room temperature. The mixture was diluted in DCM (50 mL) and washed with a saturated aqueous solution of Na₂S₂O₃ (25 mL). The aqueous phases were extracted three times with DCM (50 mL). The combined organic phase were washed with NaHCO₃ 1M (20 mL) followed by brine (20 mL), dried with MgSO₄ and evaporated under reduced pressure. The resulting pale yellow oil was purified by flash column chromatography (SiO₂; gradient 80:20 to 60:40 hexane:EtOAc) to afford

³⁷ Iosub, A. V.; Moravčík, Š.; Wallentin, C. J.; Bergman, J. *Org. Lett.* **2019**, *21*, 7804–7808.

³⁸ Lazzara, N. C.; Rosano, R. J.; Vagadia, P. P.; Giovine, M. T.; Bezpalko, M. W.; Piro, N. A.; Kassel, W. S.; Boyko, W. J.; Zubris, D. L.; Schrader, K. K.; Wedge, D. E.; Duke, S. O.; Giuliano, R. M. *J. Org. Chem.* **2019**, *84*, 666–678.

compound **3v** (650 mg, 63%) as a pale yellow sticky oil. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm): 9.61 (s, 1H, **7**), 5.66 (d, $J = 4.9$ Hz, 1H, **6**), 4.67 – 4.56 (m, 2H, **4 + 5**), 4.38 (dd, $J = 4.9, 2.5$ Hz, 1H, **3**), 4.18 (d, $J = 2.2$ Hz, 1H, **2**), 1.50 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H).; $^{13}\text{C-NMR}$ (CDCl_3 , 101 MHz) δ (ppm): 200.4 (**7**), 110.2 (**6**), 109.2, 96.4, 73.4, 71.9, 70.6, 70.5, 26.2, 25.9, 25.0, 24.4.



The spectra match the ones reported.³⁹

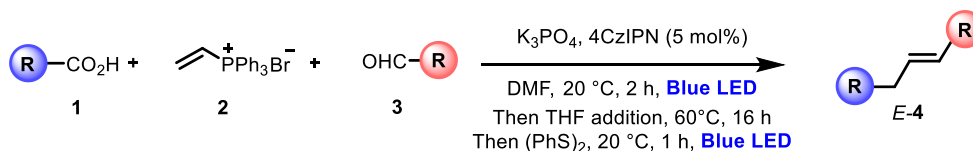
2.6.7. General procedures

General procedure A



Carboxylic acid **1** (1 equiv.; 0.2 mmol), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg) and potassium phosphate (3 equiv.; 0.6 mmol; 127.4 mg) were introduced into a Schlenk tube. The atmosphere was exchanged to argon, and degassed dry DMF (200 μL , previously degassed through 5 min argon sparging) and aldehyde **3** were introduced through a syringe. The vessel was sealed and placed in a glass-wall water bath with temperature controlled at 20 $^{\circ}\text{C}$ (using a standard laboratory crystallising basin). The reaction was irradiated through the glass wall with blue light (Kessil lamp A160WE Tuna Blue Saltwater LED Light 40W) for 2 h under moderate stirring (500 rpm). See Figure 2.2 for visual details. The vessel was then removed from the water bath and dry THF (1.8 mL) was introduced through a syringe. The mixture was heated to 60 $^{\circ}\text{C}$ for 16 h under vigorous stirring (1100 rpm) without irradiation, after which it was filtered through a thin layer of celite/silica and eluted with Et_2O . Volatiles were evaporated under reduced pressure, and the residue was subjected to chromatography purification on silica gel to afford final compounds **Z-4**.

General procedure B



The reaction was carried out following the steps described in General Procedure A, with the following modification: before the workup, diphenyl disulphide (1 equiv.; 0.2 mmol; 43.7 mg) was added to the reaction vessel and the reaction mixture was irradiated with blue light using the irradiation set-up described in General Procedure A for further

³⁹ Brünjes, M.; Sourkouni-Argirusi, G.; Kirschning, A. *Adv. Synth. Catal.*, **2003**, 345, 635–642.

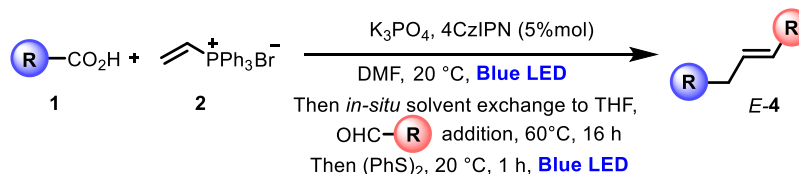
1 h under vigorous stirring (1100 rpm). Follows the workup procedure described in General Procedure A.

General procedure C



Carboxylic acid **1** (1 equiv.; 0.2 mmol), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg) and potassium phosphate (3 equiv.; 0.6 mmol; 127.4 mg) were introduced into a Schlenk tube. The atmosphere was exchanged to argon, after which degassed dry DMF (2 mL, previously degassed through 5 min argon sparging) was introduced through a syringe. The vessel was sealed and placed in a glass-wall water bath with temperature controlled at 20 °C (using a standard laboratory crystallising basin). The reaction was irradiated through the glass wall with blue light (Kessil lamp A160WE Tuna Blue Saltwater LED Light 40W) for 16 h under moderate stirring (500 rpm). See Figure 2.2 for visual details. The solvent was evaporated *in-situ* using a standard Schlenk manifold and exchanged to dry THF (2 mL).⁴⁰ The aldehyde (3 equiv.; 0.6 mmol) was added *via* syringe and the mixture was heated to 60 °C for 16 h under vigorous stirring (1100 rpm) without irradiation. The mixture was then filtered through a thin layer of celite/silica and eluted with Et₂O. Volatiles were evaporated under reduced pressure and the residue was subjected to chromatography purification on silica gel to afford final compounds Z-4.

General procedure D



The reaction was carried out following the steps described in General Procedure C, with the following modification: before the workup, diphenyl disulphide (1 equiv.; 0.2 mmol; 43.7 mg) was added and the reaction mixture was irradiated with blue light using the irradiation set-up described in General Procedure C for further 1 h under vigorous stirring (1100 rpm). Follows the workup procedure described in General Procedure C.

⁴⁰ To facilitate evaporation, the vessel was heated to 60 °C under vacuum (0.1 mBar), total removal of the solvent occurs within 3 minutes. To completely remove traces of solvent, dry THF (500 µL) was added to the residue, sonicated to triturate the solids, evaporated and left to 60 °C for 5 minutes and the cycle was repeated twice. We recommend the use a cold trap (-90 °C) between the vessel and the Schlenk manifold to collect the volatiles. After last addition of dry THF solvent, sonication was performed if adhesion of the solids to the vessel wall was observed.

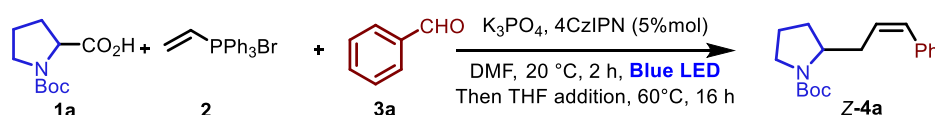
2.6.8. Reaction set-up for irradiation of mixtures with blue LEDs



Figure 2.2: Visual details of the photochemical reaction set-up: top, lateral, and front view.

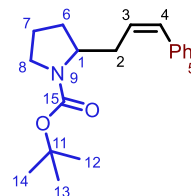
2.6.9. Reaction products and characterisation

tert-butyl (Z)-2-(3-phenylallyl)pyrrolidine-1-carboxylate (Z-4a)



Prepared following general procedure A, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 97:3 to 94:6 hexane:THF) to afford compound **Z-4a** (45 mg; 78%; Z/E

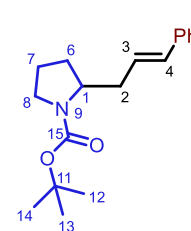
> 20:1) as a yellow oil. **R_f** (97:3 hexane:THF) 0.4; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3007, 2972, 2876, 1693, 1449, 1392, 1365, 1171, 1120, 1100, 771, 700; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.38 – 7.15 (m, 5H, **5**), 6.51 (d, J = 11.7 Hz, 1H, **4**), 5.62 (dt, J = 11.7, 7.8 Hz, 1H, **3**), 3.95 – 3.80 (m, 1H, **1**), 3.42 – 3.23 (m, 2H, **8**), 2.81 – 2.67 (m, 1H, **2**), 2.51 – 2.38 (m, 1H, **2**), 1.96 – 1.83 (m, 1H, **6**), 1.80 – 1.71 (m, 2H, **7**), 1.69 – 1.62 (m, 1H, **6**), 1.42 (s, 9H, **12** - **14**); **¹³C-NMR** (CDCl₃, 126 MHz) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis () δ (ppm): 154.7 (**15**), 137.7 (**5**), (132.3), 130.7 (**4**), 129.0 (**5**), 128.9 (**3**), (128.6), 128.3 (**5**), 126.8 (**5**), (126.2), 79.2 (**11**), 57.3 (**1**), 46.7 (**8**), 33.3 (**2**), 30.5 (**6**), (30.3), 28.6 (**12** - **14**), 23.4 (**7**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₈H₂₅NO₂Na⁺) expected m/z 310.1783; found m/z 310.1776.



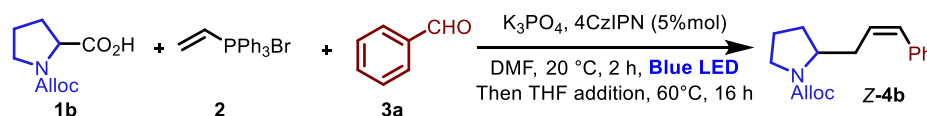
tert-butyl (E)-2-(3-phenylallyl)pyrrolidine-1-carboxylate (**E-4a**)



Prepared following general procedure B, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). Then PhSSPh (1 equiv.; 0.2 mmol; 43.7 mg) was added and the solution irradiated as described in general procedure B. The crude residue was purified by flash column chromatography (SiO₂; static 95:5 hexane:EtOAc) to afford the compound **E-4a** (41 mg; 71%; E/Z > 20:1) as a colourless oil. **R_f** (95:5 hexane:EtOAc) 0.3; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3025, 2972, 2876, 1691, 1451, 1393, 1365, 1171, 1122, 1104, 772, 794; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.35 – 7.27 (m, 4H, **5**), 7.21 (tt, J = 7.2, 1.5 Hz, 1H, **5**), 6.41 (d, J = 15.8 Hz, 1H, **4**), 6.15 (dt, J = 15.8, 7.4 Hz, 1H, **3**), 3.96 – 3.83 (m, 1H, **1**), 3.42 – 3.28 (m, 2H, **8**), 2.68 – 2.56 (m, 1H, **2**), 2.30 (dt, J = 13.6, 8.3 Hz, 1H, **2**), 1.96 – 1.76 (m, 4H, **6** - **7**), 1.47 (s, 9H). **¹³C-NMR** (CDCl₃, 101 MHz) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis () δ (ppm): 154.7 (**15**), 137.7 (**5**), 132.3 (**4**), 128.6 (**5**), (128.3), 127.2 (**3**), 127.1 (**5**), 126.1 (**5**), 79.2 (**11**), 57.2 (**1**), 46.7 (**8**), 38.0 (**2**), (31.6), 30.0 (**6**), 28.7 (**12** - **14**), 23.5 (**7**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₈H₂₅NO₂Na⁺) expected m/z 310.1783, found m/z 310.1775.

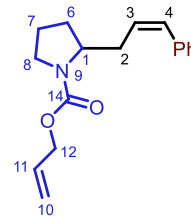


allyl (Z)-2-(3-phenylallyl)pyrrolidine-1-carboxylate (**Z-4b**)

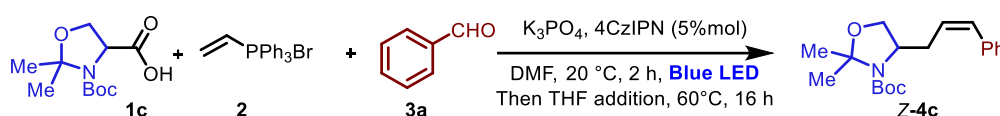


Prepared following general procedure A, using **1b** (1 equiv.; 0.2 mmol; 39.8 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography

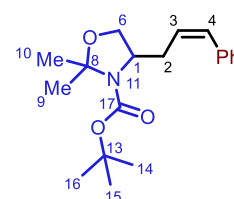
(SiO₂; gradient 9:1 to 7:3 hexane:EtOAc) to afford compound **Z-4b** (43 mg; 79%; Z/E = 8:1) as a pale yellow oil. **R_f** (8:2 hexane:EtOAc) 0.3; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2969, 2877, 1691, 1648, 1494, 1401, 1354, 1330, 1289, 1187, 1097, 983, 918, 769, 699, 520; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.36 – 7.26 (m, 4H, **5**), 7.25 – 7.20 (m, 1H, **5**), 6.52 (d, J = 11.8 Hz, 1H, **4**), 6.03 – 5.71 (m, 1H, **11**), 5.67 – 5.56 (m, 1H, **3**), 5.37 – 5.12 (m, 2H, **10**), 4.59 (d, J = 5.4 Hz, 2H, **12**), 4.04 – 3.89 (m, 1H, **1**), 3.51 – 3.32 (m, 2H, **8**), 2.90 – 2.69 (m, 1H, **2**), 2.52 – 2.29 (m, 1H, **2**), 1.99 – 1.61 (m, 4H, **6** - **7**); **¹³C-NMR** (CDCl₃, 126 MHz) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis () δ (ppm): 154.9 (**14**), 137.6 (**5**), (137.5), 133.5 (**11**), (133.4), 132.5 (**4**), (131.2), 130.9 (**5**), 128.9 (**5**), (128.8), 128.3 (**3**), (126.8), 126.8 (**5**), (117.3), 117.2 (**10**), (65.8), 65.6 (**12**), 57.9 (**1**), (57.3), 47.0 (**8**), (46.6), (33.3), 32.7 (**2**), (30.5), 29.7 (**6**), 23.8 (**7**), (23.0); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₇H₂₁NO₂Na⁺) expected m/z 294.1470; found m/z 294.1464.



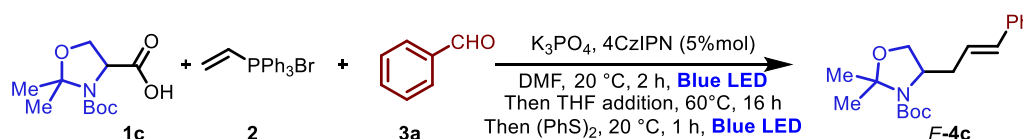
tert-butyl (Z)-2,2-dimethyl-4-(3-phenylallyl)oxazolidine-3-carboxylate (**Z-4c**)



Prepared following general procedure A, using **1c** (1 equiv.; 0.2 mmol; 49 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 9:1 to 1:1 hexane:DCM) to afford compound **Z-4c** (44 mg; 69%; Z/E = 8:1) as a colourless oil. **R_f** (1:1 hexane:DCM) 0.15; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2979, 2935, 2874, 1695, 1454, 1388, 1365, 1257, 1174, 1083, 1068, 1025, 858, 770, 700; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 7.49 – 7.06 (m, 5H, **5**), 6.55 (d, J = 10.2 Hz, 1H, **4**), 5.68 – 5.54 (m, 1H, **3**), 4.14 – 3.63 (m, 3H, **1** - **6**), 2.82 – 2.55 (m, 2H, **2**), 1.70 – 1.26 (m, 15H, **9** - **10** - **14** - **15** - **16**); **¹³C-NMR** (CDCl₃, 101 MHz) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis () δ (ppm): (152.4), 151.9 (**17**), 137.3 (**5**), (133.0), 131.5 (**4**), 128.9 (**5**), (128.7), 128.3 (**3**), 127.9 (**5**), 126.9 (**5**), (126.2), 94.1 (**8**), (93.6), (80.2), 79.7 (**11**), 66.9 (**6**), (66.6), (57.5), 57.3 (**1**), 32.5 (**2**), (31.9), 28.5 (**14** - **15** - **16**), (27.6), 26.8, (24.7), 23.4; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₉H₂₇NO₃Na⁺) expected m/z 340.1889, found m/z 310.1883.

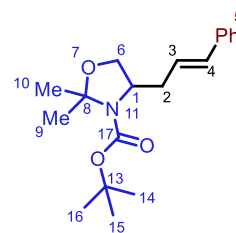


tert-butyl (E)-2,2-dimethyl-4-(3-phenylallyl)oxazolidine-3-carboxylate (**E-4c**)

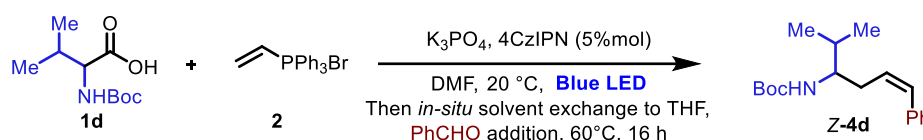


Prepared following general procedure B, using **1c** (1 equiv.; 0.2 mmol; 49 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). Then PhSSPh (1 equiv.; 0.2 mmol; 43.7 mg) was added and the

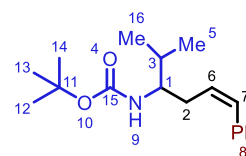
solution irradiated as described in general procedure B. The crude residue was purified by flash column chromatography (SiO₂; gradient 9:1 to 1:1 hexane:DCM) to afford compound *E*-**4c** (43 mg; 68%; E/Z > 20:1) as a colourless oil. **R_f** (1:1 hexane:DCM) 0.15; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2978, 2935, 2874, 1692, 1453, 1387, 1365, 1257, 1174, 1088, 1071, 1025, 851, 767, 693; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 7.43 – 7.01 (m, 5H, **5**), 6.46 (d, J = 15.8 Hz, 1H, **4**), 6.25 – 6.08 (m, 1H, **3**), 4.14 – 3.68 (m, 3H, **1** - **6**), 2.81 – 2.57 (m, 1H, **2**), 2.52 - 2.40 (m, 1H, **2**), 1.73 – 1.37 (m, 15H, **9** - **10** - **14** - **15** - **16**); **¹³C-NMR** (CDCl₃, 101 MHz) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis () δ (ppm): 152.3 (**17**), (151.9), (137.6), 137.4 (**5**), 133.0 (**4**), 128.7 (**3**), (127.4), 127.3 (**5**), 126.4 (**5**), (126.2), (94.1), 93.6 (**8**), 80.2 (**11**), (79.7), (66.7), 66.4 (**6**), 57.4 (**1**), (57.3), (37.4), 36.5 (**2**), 28.7, 28.6 (**14** - **15** - **16**), 27.6, (26.9), 24.7, (23.4); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₉H₂₇NO₃Na⁺) expected m/z 340.1889, found m/z 340.1881.



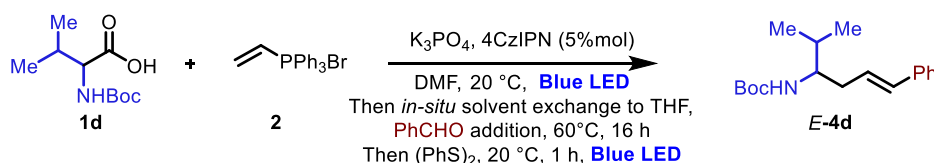
tert-butyl (Z)-(2-methyl-6-phenylhex-5-en-3-yl)carbamate (**Z-4d**)



Prepared following general procedure C, using **1d** (1 equiv.; 0.2 mmol; 43.5 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 1:3 to 1:1 DCM:hexane, then 9:1 hexane:EtOAc) to afford compound **Z-4d** (39 mg; 67%; Z/E = 8:1) as a colourless oil; **R_f** (9:1 hexane:EtOAc) 0.2; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3342, 3012, 2965, 2932, 1699, 1498, 1366, 1309, 1247, 1172, 771, 699; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.37 – 7.17 (m, 5H, **8**), 6.52 (t, J = 11.7 Hz, 1H, **7**), 5.69 (dt, J = 11.7, 7.0 Hz, 1H, **6**), 4.44 – 4.03 (m, 1H, **9**), 3.64 – 3.36 (m, 1H, **1**), 2.61 – 2.45 (m, 1H, **2**), 2.40 – 2.25 (m, 1H, **2**), 1.78 – 1.69 (m, 1H, **3**), 1.44 (s, 9H, **12** - **14**), 0.89 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H); **¹³C-NMR** (CDCl₃, 101 MHz) δ (ppm): 156.1 (**15**), 137.6 (**8**), 130.9 (**7**), 128.9 (**6**), 128.3 (**8**), 126.8 (**8**), 126.2 (**8**), 79.1 (**11**), 56.1 (**1**), 31.9 (**2**), 31.7 (**3**), 28.6 (**12** - **14**), 19.4, 17.8; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₈H₂₇NO₂Na⁺) expected m/z 312.1939, found m/z 312.1933.

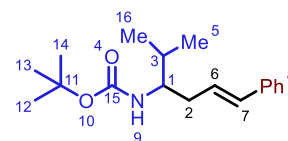


tert-butyl (*E*)-(2-methyl-6-phenylhex-5-en-3-yl)carbamate (**E-4d**)



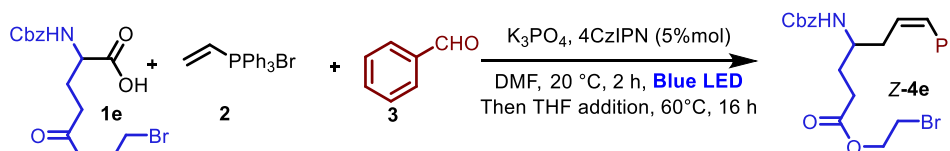
Prepared following general procedure D, using **1d** (1 equiv.; 0.2 mmol; 43.5 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.;

0.6 mmol; 61 μ L). Then PhSSPh (1 equiv.; 0.2 mmol; 43.7 mg) was added and the solution irradiated as described in general procedure D. The crude residue was purified by flash column chromatography (SiO₂; gradient 70:30 to 1:1 DCM:hexane, then 95:5 to 93:7 hexane:EtOAc) to afford compound *E*-**4d** (39 mg; 67%; *E/Z* > 20:1) as a white solid. **MP** = 73 – 75 °C; **R_f** (hexane:EtOAc) 0.2; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3344, 3026, 2964, 2932, 1699, 1498, 1366, 1310, 1246, 1171, 779, 693; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 7.39 – 7.06 (m, 5H, **8**), 6.42 (d, *J* = 15.8 Hz, 1H, **7**), 6.17 (dt, *J* = 15.8, 7.2 Hz, 1H, **6**), 4.48 – 4.17 (m, 1H, **9**), 3.69 – 3.35 (m, 1H, **1**), 2.48 – 2.20 (m, 2H, **2**), 1.86 – 1.68 (m, 1H, **3**), 1.40 (s, 9H, **12** - **14**), 0.96 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); **¹³C-NMR** (CDCl₃, 101 MHz) δ (ppm): 156.0 (**15**), 137.6 (**8**), 132.4 (**7**), 128.6 (**8**), 127.2 (**6**), 127.0 (**8**), 126.2 (**8**), 79.1 (**11**), 55.5 (**1**), 36.4 (**2**), 31.6 (**3**), 28.5 (**12** - **14**), 19.5, 17.9. **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₈H₂₇NO₂Na⁺) expected *m/z* 312.1939, found *m/z* 312.1929.

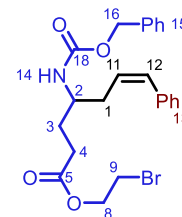


2-bromoethyl (Z)-4-(((benzyloxy)carbonyl)amino)-7-phenylhept-6-enoate (Z-4e)

Compound synthesised by Dr. Mattia Silvi.

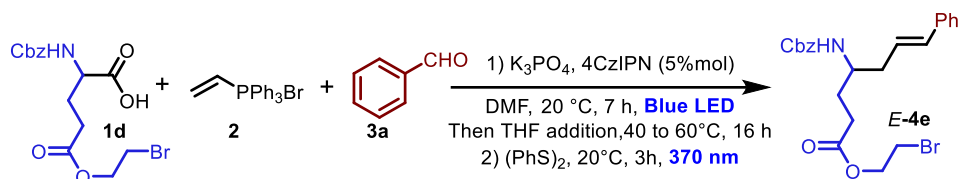


Prepared following general procedure A, with the following modifications: the irradiation was carried out for 7 h, and the heating was carried out at 40 °C for 14 h, followed by 2.5 h at 60 °C. **1e** (1 equiv.; 0.2 mmol; 77.4 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L) were used. The crude residue was purified by flash column chromatography (SiO₂; gradient 85:15 to 80:20 hexane:EtOAc) to afford two fractions of compound *Z*-**4e** (10 mg, *Z/E* > 20:1 and 20 mg, *Z/E* = 3:1, 33% overall yield) as a yellow oil. **R_f** (70:30 hexane:EtOAc) 0.4; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3333, 3028, 2956, 1718, 1530, 1450, 1248, 1158, 1055, 1028, 773, 750, 699; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.43 – 7.19 (m, 10H, **13** - **15**), 6.57 (d, *J* = 11.6 Hz, 1H, **12**), 5.67 (dt, *J* = 11.6, 7.2 Hz, 1H, **11**), 5.09 (s, 2H, **16**), 4.59 (d, *J* = 9.3 Hz, 1H, **14**), 4.42 – 4.30 (m, 2H, **8**), 3.87 – 3.76 (m, 1H, **2**), 3.52 – 3.42 (m, 2H, **9**), 2.64 – 2.45 (m, 2H, **1**), 2.41 (t, *J* = 7.4 Hz, 2H, **4**), 1.93 (dtd, *J* = 14.7, 7.4, 4.2 Hz, 1H, **3**), 1.70 (ddt, *J* = 14.7, 9.5, 7.4 Hz, 1H, **3**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 173.0 (**5**), 156.2 (**18**), 137.2, 136.6, 131.9 (**12**), 128.8, 128.7, 128.4, 128.3, 128.2 (**11**), 127.6, 127.0, 66.8 (**16**), 64.0 (**8**), 51.4 (**2**), 34.5 (**1**), 31.0 (**4**), 30.0 (**3**), 28.8 (**9**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₃H₂₆BrNO₄Na⁺) expected *m/z* 482.0943, found *m/z* 482.0938.

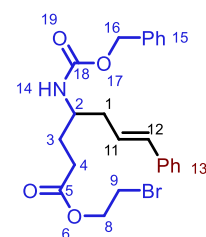


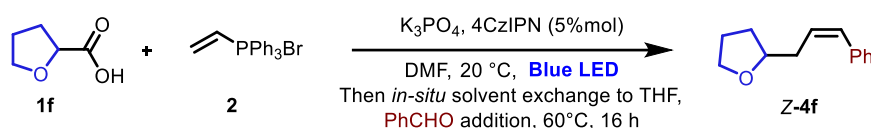
2-bromoethyl (E)-4-(((benzyloxy)carbonyl)amino)-7-phenylhept-6-enoate (E-4e)

Compound synthesised by Dr. Mattia Silvi.

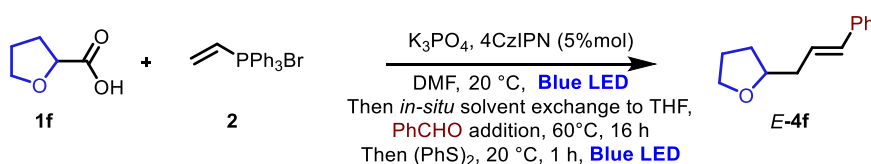


Prepared following general procedure A, with the following modifications: the irradiation was carried out for 7 h, and the heating was carried out at 40 °C for 14 h, followed by 2.5 h at 60 °C. **1e** (1 equiv.; 0.2 mmol; 77.4 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L) were used. The crude residue was purified by flash column chromatography (SiO₂; gradient 85:15 to 80:20 hexane:EtOAc) to afford the compound **Z-4e** (26 mg; 0.056 mmol) as a yellow oil. The compound was dissolved in benzene (560 μ L) and PhSSPh (0.1 equiv.; 0.0056 mmol; 1.2 mg) was added. The solution was degassed through freeze-pump-thaw cycles (x5). The atmosphere was switched to argon and the vessel was placed approximately 3 cm away from a 370 nm LED light, moderately stirred (500 rpm) and irradiated for 1 h. A fan was used to keep the temperature below 40 °C. To get higher ratio between the two stereoisomers, the isomerisation was repeated as follow: PhSSPh was added two more times (0.4 equiv.; 0.022 mmol; 4.9 mg) and (0.5; 0.028 mmol; 6.1 mg) under a strong argon flow. The reaction was irradiated in the same way for 1 h after each addition. Overall, 1 equivalent of PhSSPh was added and irradiated for 3 h. The crude residue was purified by flash column chromatography (SiO₂; gradient 85:15 to 80:20 hexane:EtOAc) to afford compound **E-4e** (20 mg; 22%; E/Z = 16:1) as a pale yellow oil. **R_f** (70:30 hexane:EtOAc) 0.4; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3332, 3028, 2954, 1718, 1531, 1450, 1248, 1155, 1055, 1028, 773, 750, 701; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.37 – 7.20 (m, 10H, **13** - **15**), 6.43 (d, J = 15.7 Hz, 1H, **12**), 6.16 (dt, J = 15.7, 7.3 Hz, 1H, **11**), 5.11 – 5.06 (m, 2H, **16**), 4.68 (d, J = 9.2 Hz, 1H, **14**), 4.40 – 4.30 (m, 2H, **8**), 3.88 – 3.78 (m, 1H, **2**), 3.48 (t, J = 6.1 Hz, 2H, **9**), 2.50 – 2.38 (m, 4H, **1** - **4**), 2.01 – 1.91 (m, 1H, **3**), 1.80 – 1.70 (m, 1H, **3**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 173.0 (**5**), 156.2 (**18**), 137.2, 136.6, 133.5 (**12**), 128.7, 128.7, 128.2, 128.2, 127.5, 126.3, 125.3 (**11**), 66.8 (**16**), 64.0 (**8**), 51.0 (**2**), 39.2 (**1**), 31.1 (**4**), 29.8 (**3**), 28.9 (**9**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₃H₂₆BrNO₄Na⁺) expected m/z 482.0943, found m/z 482.0931.

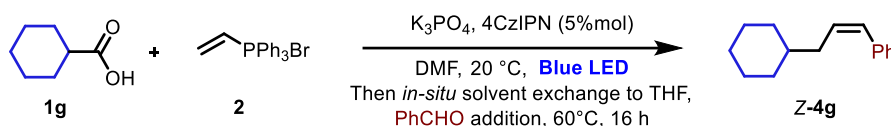


(Z)-2-(3-phenylallyl)tetrahydrofuran (Z-4f)

Prepared following general procedure C, using **1f** (1 equiv.; 0.2 mmol; 19 μ L), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 4:1 to 1:1 hexane:DCM) to afford compound **Z-4f** (23 mg; 61%; Z/E = 9:1) as a colourless oil. **R_f** (1:1 hexane:DCM) 0.25; **IR** (film) $\nu_{\max}/\text{cm}^{-1}$: 3023, 2970, 2867, 1494, 1447, 1067, 917, 770, 700; **¹H-NMR** (CDCl₃, 400 MHz,) δ (ppm): 7.45 – 7.08 (m, 5H, **5**), 6.53 (d, J = 11.7 Hz, 1H, **4**), 5.74 (dt, J = 11.7, 7.2 Hz, 1H, **3**), 4.03 – 3.82 (m, 2H, **1 - 8**), 3.82 – 3.69 (m, 1H, **8**), 2.71 – 2.48 (m, 2H, **2**), 2.10 – 1.78 (m, 3H, **6 - 7**), 1.57 – 1.45 (m, 1H, **6**); **¹³C-NMR** (CDCl₃, 101 MHz) δ (ppm): 137.6 (**5**), 130.7 (**4**), 128.9 (**5**), 128.7 (**3**), 128.3 (**5**), 126.8 (**5**), 79.1 (**1**), 68.1 (**8**), 34.8 (**2**), 31.1 (**6**), 25.9 (**7**); **HRMS** (ESI-TOF) mass calculated for $[M+Na]^+$ (C₁₃H₁₆ONa⁺) expected m/z 211.1099, found m/z 211.1092.

(E)-2-(3-phenylallyl)tetrahydrofuran (E-4f)

Prepared following general procedure D, using **1f** (1 equiv.; 0.2 mmol; 19 μ L mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). Then PhSSPh (1 equiv.; 0.2 mmol; 43.7 mg) was added and the solution irradiated as described in general procedure D. The crude residue was purified by flash column chromatography (SiO₂; gradient 4:1 to 2:3 hexane:DCM) to afford compound **E-4f** (23 mg; 61%; E/Z > 20:1) as a colourless oil. **R_f** (1:1 hexane:DCM) 0.2; **IR** (film) $\nu_{\max}/\text{cm}^{-1}$: 3026, 2970, 2866, 1496, 1449, 1066, 920, 744, 693; **¹H-NMR** (CDCl₃, 400 MHz,) δ (ppm): 7.36 (d, J = 7.6 Hz, 2H, **5**), 7.28 (t, J = 7.6 Hz, 2H, **5**), 7.20 (t, J = 7.6 Hz, 1H, **5**), 6.46 (d, J = 15.7 Hz, 1H, **4**), 6.24 (dt, J = 15.7, 7.1 Hz, 1H, **3**), 4.07 – 3.84 (m, 2H, **1 - 8**), 3.80 – 3.70 (m, 1H, **8**), 2.59 – 2.31 (m, 2H, **2**), 2.06 – 1.83 (m, 3H, **6 - 7**), 1.64 – 1.51 (m, 1H, **6**); **¹³C-NMR** (CDCl₃, 101 MHz,) δ (ppm): 137.7 (**5**), 132.1 (**4**), 128.6 (**5**), 127.2 (**5**), 126.9 (**3**), 126.2 (**5**), 78.9 (**1**), 68.1 (**8**), 39.4 (**2**), 31.0 (**6**), 25.9 (**7**); **HRMS** (ESI-TOF) mass calculated for $[M+Na]^+$ (C₁₃H₁₆ONa⁺) expected m/z 211.1099, found m/z 211.1090.

(Z)-(3-cyclohexylprop-1-en-1-yl)benzene (Z-4g)

Prepared following general procedure C, using **1g** (1 equiv.; 0.2 mmol; 25 μL), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μL). The crude residue was purified by flash column chromatography (SiO_2 ; hexane) to afford compound **Z-4g** (21 mg; 52%; Z/E = 7:1) as a colourless oil. **R_f** (hexane) 0.7; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3010, 2921, 2851, 1447, 964, 767, 698; **¹H-NMR** (CDCl_3 , 400 MHz) δ (ppm): 7.37 – 7.26 (m, 4H, **5**), 7.21 (t, J = 7.1 Hz, 1H, **5**), 6.44 (d, J = 11.8 Hz, 1H, **4**), 5.70 (dt, J = 11.8, 7.3 Hz, 1H, **3**), 2.22 (td, J = 7.3, 1.9 Hz, 2H, **2**), 1.83 – 1.57 (m, 5H), 1.45 – 1.31 (m, 1H, **1**), 1.31 – 1.03 (m, 3H), 1.02 – 0.81 (m, 2H); **¹³C-NMR** (CDCl_3 , 101 MHz) δ (ppm): 138.1 (**5**), 132.1 (**3**), 129.4 (**5**), 129.0 (**4**), 128.2 (**5**), 126.5 (**5**), 38.9 (**1**), 36.4, 33.4 (**2**), 26.7, 26.5.

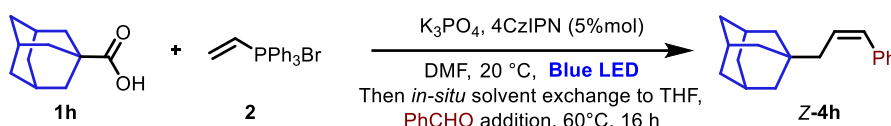
The spectra matched the reported.⁴¹

(E)-(3-cyclohexylprop-1-en-1-yl)benzene (E-4g)

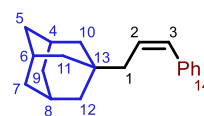
Prepared following general procedure D, using **1g** (1 equiv.; 0.2 mmol; 25 μL), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μL). Then PhSSPh (1 equiv.; 0.2 mmol; 43.7 mg) was added and the solution irradiated as described in general procedure D. The crude residue was purified by flash column chromatography (SiO_2 ; hexane) to afford compound **E-4g** (18 mg; 45%; E/Z > 20:1) as a colourless oil. **R_f** (hexane) 0.7; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3025, 2920, 2850, 1448, 964, 740, 691; **¹H-NMR** (CDCl_3 , 400 MHz) δ (ppm): 7.35 (d, J = 7.7 Hz, 2H, **5**), 7.29 (t, J = 7.7 Hz, 2H, **5**), 7.19 (t, J = 7.3 Hz, 1H, **5**), 6.36 (d, J = 15.8 Hz, 1H, **4**), 6.23 (dt, J = 15.8, 7.2 Hz, 1H, **3**), 2.11 (t, J = 7.2 Hz, 2H, **2**), 1.82 – 1.60 (m, 5H), 1.48 – 1.34 (m, 1H, **1**), 1.32 – 1.08 (m, 3H), 1.06 – 0.87 (m, 2H); **¹³C-NMR** (CDCl_3 , 126 MHz) δ (ppm): 138.1 (**5**), 130.8 (**4**), 129.9 (**3**), 128.6 (**5**), 126.9 (**5**), 126.1 (**5**), 41.2, 38.4 (**1**), 33.4 (**2**), 26.7, 26.5.

The spectra matched the reported.⁴¹

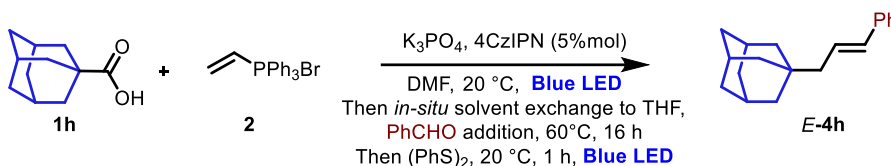
⁴¹ Wang, Z. J.; Zheng, S.; Romero, E.; Matsui, J. K.; Molander, G. A. *Org. Lett.*, **2019**, *21*, 6543–6547.

(3*r*,5*r*,7*r*)-1-((*Z*)-3-phenylallyl)adamantane (**Z-4h**)

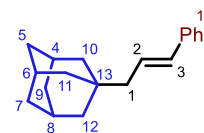
Prepared following general procedure C, using **1h** (1 equiv.; 0.2 mmol; 36.0 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; hexane) to afford compound **Z-4h** (25 mg; 52%; Z/E = 10:1) as a colourless oil. **R_f** (hexane) 0.7; **IR** (film) $\nu_{\max}/\text{cm}^{-1}$: 2901, 2846, 1448, 769, 698; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 7.38 – 7.26 (m, 4H, **14**), 7.21 (t, J = 7.0 Hz, 1H, **14**), 6.50 (d, J = 11.8, 1H, **3**), 5.79 (dt, J = 11.8, 7.5 Hz, 1H, **2**), 2.11 (dd, J = 7.5, 2.1 Hz, 2H, **1**), 1.97 – 1.91 (m, 3H, **4 - 6 - 8**), 1.74 – 1.57 (m, 6H), 1.55 – 1.48 (m, 6H); **¹³C-NMR** (CDCl₃, 101 MHz) δ (ppm): 138.1 (**14**), 130.2 (**3**), 129.0 (**2**), 128.8 (**14**), 128.2 (**14**), 126.4 (**14**), 42.7 (**1**), 42.5, 37.3, 33.3, 28.9 (**4 - 6 - 8**).



The spectra matched the reported.⁴²

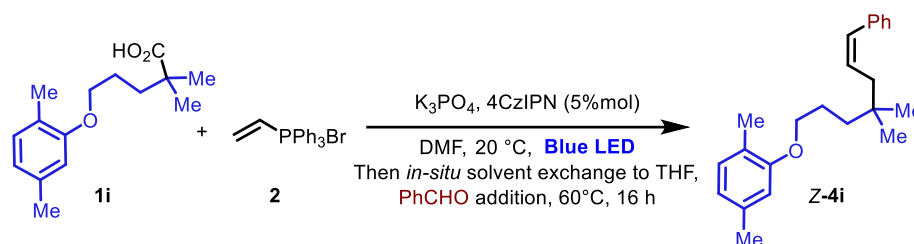
(3*r*,5*r*,7*r*)-1-((*E*)-3-phenylallyl)adamantane (**E-4h**)

Prepared following general procedure D, using **1h** (1 equiv.; 0.2 mmol; 36.0 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). Then PhSSPh (1 equiv.; 0.2 mmol; 43.7 mg) was added and the solution irradiated as described in general procedure D. The crude residue was purified by flash column chromatography (SiO₂; hexane) to afford compound **E-4h** (25 mg; 50%; E/Z > 20:1) as a colourless oil. **R_f** (hexane) 0.7; **IR** (film) $\nu_{\max}/\text{cm}^{-1}$: 2900, 2846, 1449, 746, 691; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 7.37 (d, J = 7.1 Hz, 2H, **14**), 7.31 (t, J = 7.8 Hz, 2H, **14**), 7.20 (t, J = 7.1 Hz, 1H, **14**), 6.45 – 6.17 (m, 2H, **2 - 3**), 2.04 – 1.90 (m, 5H, **1 - 4 - 6 - 8**), 1.82 – 1.59 (m, 6H), 1.55 (s, 6H); **¹³C-NMR** (CDCl₃, 101 MHz) δ (ppm): 138.1 (**14**), 132.0 (**3**), 128.6 (**14**), 127.2 (**2**), 126.9 (**14**), 126.1 (**14**), 48.2 (**1**), 42.7, 37.3, 33.6, 28.9 (**4 - 6 - 8**).



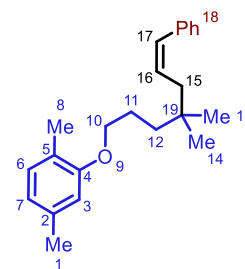
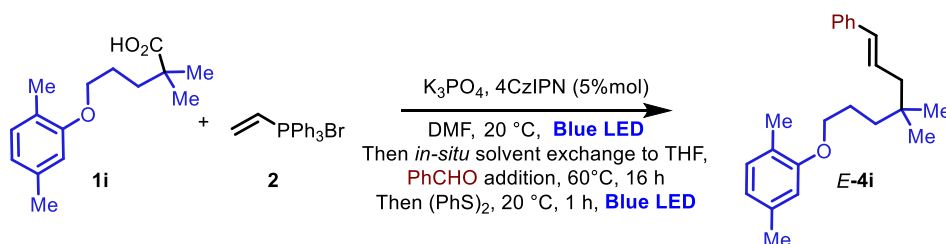
The spectra matched the reported.⁴²

⁴² Savel'eva, S. A.; Leonova, M. V.; Baimuratov, M. R.; Klimochkin, Y. N. *Russ. J. Org. Chem.*, **2018**, 54, 996–1002.

(Z)-2-((4,4-dimethyl-7-phenylhept-6-en-1-yl)oxy)-1,4-dimethylbenzene (Z-4i)

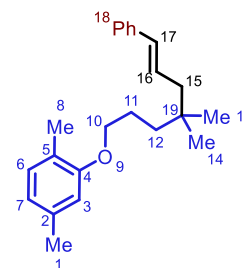
Compound synthesised by Dr. Mattia Silvi.

Prepared following general procedure C, using **1i** (1 equiv.; 0.2 mmol; 50.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 97.5:2.5 to 9:1 hexane:DCM) to afford compound **Z-4i** (51 mg; 79%; Z/E = 13:1) as a colourless oil. **R_f** (9:1 hexane:DCM) 0.3; **IR** (film) $\nu_{\max}/\text{cm}^{-1}$: 3022, 2954, 2869, 1589, 1509, 1470, 1365, 1158, 1130, 843, 771, 699, 587, 504, 448; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 7.37 – 7.21 (m, 5H, **18**), 7.03 (d, J = 7.6 Hz, 1H, **6**), 6.68 (d, J = 7.6 Hz, 1H, **7**), 6.63 (s, 1H, **3**), 6.53 (d, J = 11.8 Hz, 1H, **17**), 5.79 (dt, J = 11.8, 7.3 Hz, 1H, **16**), 3.90 (t, J = 6.5 Hz, 2H, **10**), 2.38 – 2.27 (m, 5H, **1** - **15**), 2.17 (m, 3H, **8**), 1.88 – 1.64 (m, 2H, **11**), 1.47 – 1.37 (m, 2H, **12**), 0.96 (s, 6H, **13** - **14**). **¹³C-NMR** (CDCl₃, 101 MHz) δ (ppm): 157.2 (**4**), 138.0, 136.6, 134.0 (**18**), 133.8 (**18**), 130.4 (**5**), 129.5 (**17**), 129.0 (**16**), 128.2, 126.5, 120.7 (**7**), 112.1 (**3**), 68.7 (**10**), 40.0 (**15**), 38.1 (**12**), 33.5 (**19**), 27.2 (**13** - **14**), 24.4 (**11**), 21.6 (**1**), 15.9 (**8**). **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₃H₃₀ONa⁺) expected m/z 345.2194, found m/z 345.2187.

(E)-2-((4,4-dimethyl-7-phenylhept-6-en-1-yl)oxy)-1,4-dimethylbenzene (E-4i)

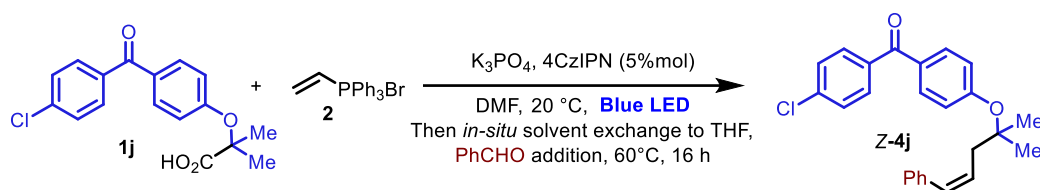
Compound synthesised by Dr. Mattia Silvi.

Prepared following general procedure D, using **1i** (1 equiv.; 0.2 mmol; 50.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). Then PhSSPh (1 equiv.; 0.2 mmol; 43.7 mg) was added and the solution irradiated as described in general procedure D. The crude residue was purified by flash column chromatography (SiO₂; gradient 97.5:2.5 to 9:1 hexane:DCM) to afford compound **E-4i** (42 mg; 65%; E/Z > 20:1) as a colourless oil. **R_f** (9:1 hexane:EtOAc) 0.2; **IR** (film) $\nu_{\max}/\text{cm}^{-1}$: 3026, 2954, 2868, 1585, 1509, 1470, 1365, 1158, 1130, 843, 752, 692, 587, 498, 448; **¹H-**



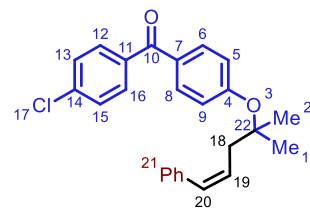
NMR (CDCl₃, 400 MHz) δ (ppm): 7.38 (d, J = 7.5 Hz, 2H, **18**), 7.32 (t, J = 7.5 Hz, 2H, **18**), 7.21 (t, J = 7.2 Hz, 1H, **18**), 7.02 (d, J = 7.4 Hz, 1H, **6**), 6.67 (d, J = 7.5 Hz, 1H, **7**), 6.64 (s, 1H, **3**), 6.41 (d, J = 15.7 Hz, 1H, **17**), 6.28 (dt, J = 15.7, 7.4 Hz, 1H, **16**), 3.94 (t, J = 6.5 Hz, 2H, **10**), 2.33 (s, 3H, **1**), 2.23 – 2.12 (m, 5H, **8** - **15**), 1.88 – 1.75 (m, 2H, **11**), 1.49 – 1.37 (m, 2H, **12**), 0.98 (s, 6H, **13** - **14**). **¹³C-NMR** (CDCl₃, 101 MHz) δ (ppm): 157.2 (**4**), 138.0, 136.6, 132.2 (**17**), 130.4 (**6**), 128.6 (**18**), 127.8 (**16**), 127.0 (**18**), 126.2 (**18**), 123.7, 120.7 (**7**), 112.1 (**3**), 68.7 (**10**), 45.7 (**15**), 38.3 (**12**), 33.8 (**19**), 27.3 (**13** - **14**), 24.5 (**11**), 21.6 (**1**), 15.9 (**8**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₃H₃₀ONa⁺) expected m/z 345.2194, found m/z 345.2182.

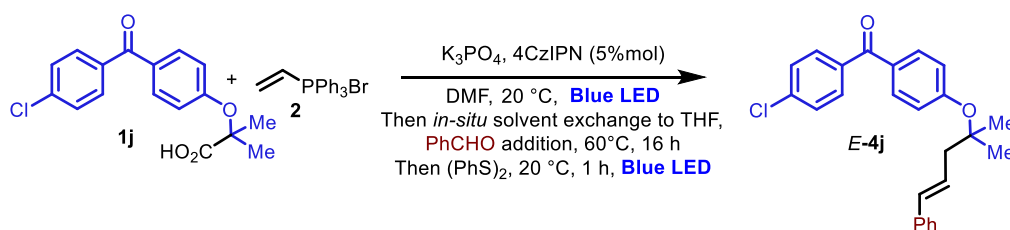
(Z)-(4-chlorophenyl)(4-((2-methyl-5-phenylpent-4-en-2-yl)oxy)phenyl)methanone (Z-4j)



Compound synthesised by Dr. Mattia Silvi.

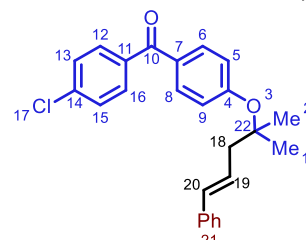
Prepared following general procedure C, using **1j** (1 equiv.; 0.2 mmol; 63.8 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; hexane:DCM 6:4 then gradient 95:5 to 90:10 hexane:EtOAc). The compound was purified a second time by flash column chromatography (SiO₂; 98:2 hexane:tetrahydrofuran) to afford compound **Z-4j** (24 mg; 31%; Z/E = 20:1) as a colourless oil. **R_f** (95:5 hexane:tetrahydrofuran) 0.5; **IR** (film) ν_{max} /cm⁻¹: 2972, 2854, 1656, 1597, 1307, 1274, 1249, 1124, 1090, 928, 764, 700; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.74 – 7.69 (m, 4H, **5** - **6** - **8** - **9**), 7.48 – 7.43 (m, 2H, **12** - **16**), 7.37 – 7.32 (m, 2H, **21**), 7.30 – 7.22 (m, 3H, **21**), 7.07 – 6.99 (m, 2H, **13** - **15**), 6.63 (dt, J = 11.8, 2.0 Hz, 1H, **20**), 5.94 (dt, J = 11.8, 7.0 Hz, 1H, **19**), 2.76 (dd, J = 7.0, 2.0 Hz, 2H, **18**), 1.40 (s, 6H, **1** - **6**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 194.6 (**10**), 160.1 (**7**), 138.6 (**11**), 137.6 (**4**), 136.5 (**14**), 131.8, 131.5 (**20**), 131.4, 128.9, 128.7, 128.4, 127.4 (**19**), 126.9, 122.4, 115.2, 81.6 (**22**), 40.7 (**18**), 26.9 (**1** - **2**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₅H₂₃ClO₂Na⁺) expected m/z 413.1284, found m/z 413.1272.



(E)-(4-chlorophenyl)(4-((2-methyl-5-phenylpent-4-en-2-yl)oxy)phenyl)methanone (E-4j)

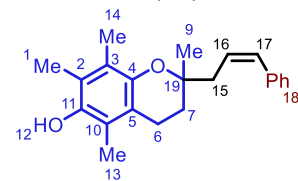
Compound synthesised by Dr. Mattia Silvi.

Prepared following general procedure D, using **1j** (1 equiv.; 0.2 mmol; 63.8 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). Then PhSSPh (1 equiv.; 0.2 mmol; 43.7 mg) was added and the solution irradiated as described in general procedure D. The crude residue was purified by flash column chromatography (SiO₂; 6:4 hexane:DCM then gradient 95:5 to 9:1 hexane:EtOAc). The compound was purified a second time by flash column chromatography (SiO₂; gradient 90:10 to 100:0 toluene) to afford compound **E-4j** (23 mg; 29%; E/Z > 20:1) as a colourless oil. **R_f** (toluene) 0.2; **IR** (film) ν_{max}/cm^{-1} : 2977, 2935, 1655, 1597, 1305, 1274, 1249, 1126, 1090, 928, 764, 693; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.82 – 7.62 (m, 4H, **5 - 6 - 7 - 8**), 7.48 – 7.44 (m, 2H, **12 - 16**), 7.39 – 7.36 (m, 2H, **21**), 7.31 (t, $J = 7.6$ Hz, 2H, **21**), 7.23 (tt, $J = 7.4, 1.3$ Hz, 1H, **21**), 7.12 – 7.06 (m, 2H, **13 - 15**), 6.47 (d, $J = 15.8$ Hz, 1H, **20**), 6.34 (dt, $J = 15.8, 7.3$ Hz, 1H, **19**), 2.64 (d, $J = 7.3$ Hz, 2H, **18**), 1.43 (s, 6H, **1 - 2**). **¹³C-NMR** (126 MHz, CDCl₃) δ (ppm): 194.7 (**10**), 160.2 (**7**), 138.6 (**11**), 137.6 (**4**), 136.5 (**14**), 133.5, 132.7, 131.8, 131.4 (**20**), 128.7, 127.4 (**19**), 126.3, 125.6, 122.5, 115.2, 81.9 (**22**), 46.0 (**18**), 26.8 (**1 - 2**). **HRMS** (ESI-TOF) mass calculated for $[M+Na]^+$ (C₂₅H₂₃ClO₂Na⁺) expected m/z 413.1284, found m/z 413.1277.

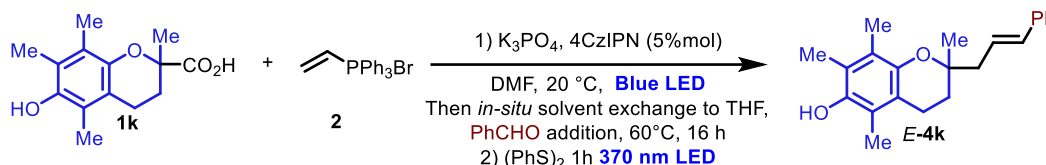
(Z)-2,5,7,8-tetramethyl-2-(3-phenylallyl)chroman-6-ol (Z-4k)

Prepared following general procedure C, using **1k** (1 equiv.; 0.2 mmol; 50.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 95:5 to 9:1 hexane:EtOAc) to afford compound **Z-4k** (33 mg; 51%; Z/E = 10:1) as a white solid. **M.P.** = 67 – 68 °C; **R_f** (9:1 hexane:EtOAc) 0.2; **IR** (film) ν_{max}/cm^{-1} : 3467, 3021, 2973, 2928, 1448, 1420, 1377, 1340, 1256, 1213, 1086, 852, 774, 770; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.43 – 7.17 (m, 5H, **18**), 6.61 (d, $J = 11.7$ Hz, 1H, **17**), 5.91 (dt, $J = 11.7, 7.4$ Hz, 1H, **16**), 2.70 – 2.56 (m, 4H, **6 - 15**), 2.22 – 2.07 (m, 9H, **1 - 13 - 14**), 1.92 – 1.83 (m, 1H, **7**), 1.82 – 1.74 (m, 1H, **15**), 1.26 (s, 3H,

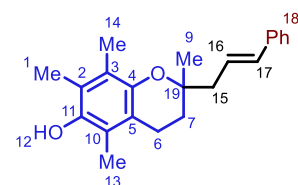
9); $^{13}\text{C-NMR}$ (CDCl_3 , 126 MHz) δ (ppm): 145.4, 144.9, 137.8, 131.0 (**17**), 128.9, 128.3, 127.8 (**16**), 126.7, 122.8, 121.3, 118.7, 117.4, 74.6, 38.3 (**15**), 31.6 (**7**), 24.0 (**9**), 20.8 (**6**), 12.4, 12.0, 11.4; **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{22}\text{H}_{26}\text{O}_2\text{Na}^+$) expected m/z 345.1830, found m/z 345.1821.



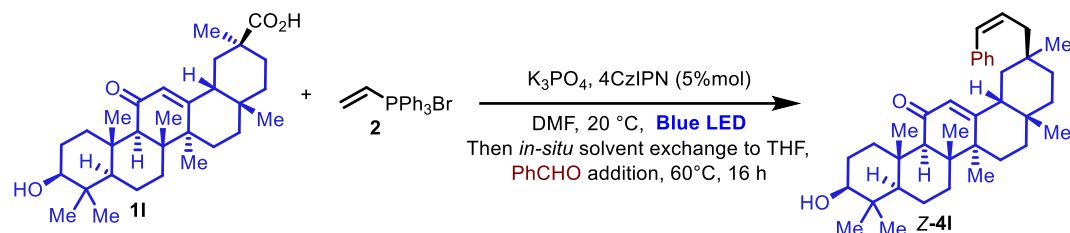
(E)-2,5,7,8-tetramethyl-2-(3-phenylallyl)chroman-6-ol (**E-4k**)



Prepared following general procedure C, using **1k** (1 equiv.; 0.2 mmol; 50.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μL). The crude residue was purified by flash column chromatography (SiO_2 ; gradient 95:5 to 9:1 hexane:EtOAc) to afford compound **Z-4k** (33 mg; 0.11 mmol) as a white solid. The compound was dissolved in cyclohexane (730 μL) and PhSSPh (2 equiv.; 0.22 mmol; 48 mg) was added. The solution was then degassed through freeze-pump-thaw cycles (x5). The atmosphere was switched to argon and the vessel was placed approximately 3 cm away from a 370 nm LED light, moderately stirred (500 rpm) and irradiated for 1 h. A fan was used to keep the temperature below 40°C. The crude residue was purified by flash column chromatography (SiO_2 ; gradient 1:1 to 0:100 hexane:toluene) to afford compound **E-4k** (30 mg; 47%; $Z/E = 20:1$) as a white solid. **R_f** (toluene) 0.15; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3464, 3026, 2973, 2926, 1449, 1419, 1377, 1339, 1251, 1213, 1085, 856, 757, 739, 693; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 7.36 (d, $J = 7.2$, 2H, **18**), 7.31 (t, $J = 7.4$ Hz, 2H, **18**), 7.21 (tt, $J = 7.2$, 1.3 Hz, 1H, **18**), 6.42 (d, $J = 15.8$ Hz, 1H, **17**), 6.31 (dt, $J = 15.8$, 7.8 Hz, 1H, **16**), 4.20 (s, 1H, **12**), 2.68 – 2.62 (m, 2H, **6**), 2.54 (ddd, $J = 13.8$, 6.9, 1.3 Hz, 1H, **15**), 2.45 (ddd, $J = 13.8$, 7.8, 1.1 Hz, 1H, **15**), 2.18 (s, 3H), 2.15 (s, 3H), 2.13 (s, 3H), 1.88 (dt, $J = 13.7$, 6.9 Hz, 1H, **7**), 1.81 (dt, $J = 13.7$, 6.9 Hz, 1H, **7**), 1.29 (s, 3H, **9**); $^{13}\text{C-NMR}$ (CDCl_3 , 126 MHz) δ (ppm): 145.5, 144.9, 137.8, 133.0 (**17**), 128.7, 127.2, 126.2, 126.0 (**16**), 122.8, 121.3, 118.7, 117.4, 74.8, 43.1 (**15**), 31.5 (**7**), 24.4 (**9**), 20.9 (**6**), 12.4, 12.0, 11.4; **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{22}\text{H}_{26}\text{O}_2\text{Na}^+$) expected m/z 345.1830, found m/z 345.1816.

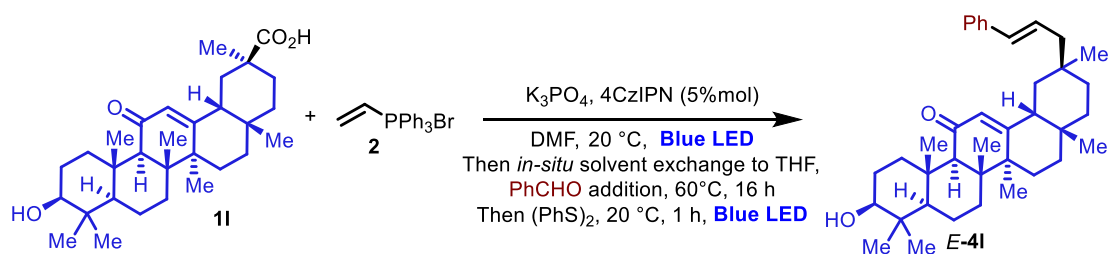


(4aR,6aS,6bR,8aR,10S,12aS,12bR,14bR)-10-hydroxy-2,4a,6a,6b,9,9,12a-heptamethyl-2-((Z)-3-phenylallyl)-1,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,14b-octadecahydropicen-13(2H)-one (Z-4I)



Prepared following general procedure C, using **11** (1 equiv.; 0.2 mmol; 94.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 9:1 to 7:3 pentane:tetrahydrofuran) to afford compound **Z-4I** (74 mg; 68%; Z/E = 9:1, d.r = 4:1 stereochemistry not defined) as a white solid. **M.P.** 90 – 91 °C; **R_f** (4:1 pentane:tetrahydrofuran) 0.25; [α]_D²⁰ +64 (c = 1.00, CHCl₃); **IR** (film) ν_{max} /cm⁻¹: 3427, 2926, 2866, 1652, 1457, 1386, 1360, 1330, 1209, 1039, 994, 919, 879, 754, 700, 667; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.38 – 7.18 (m, 5H), 6.52 (d, *J* = 11.9 Hz, 1H), 5.74 (dt, *J* = 11.9, 7.3 Hz, 1H), 5.58 (s, 1H), 3.26 – 3.19 (m, 1H), 2.79 (dt, *J* = 13.4, 3.6 Hz, 1H), 2.35 – 3.50 (m, 1H), 2.29 – 2.17 (m, 2H), 2.13 (dd, *J* = 13.5, 4.1 Hz, 1H), 2.01 (td, *J* = 13.7, 4.7 Hz, 1H), 1.80 (td, *J* = 13.7, 4.7 Hz, 1H), 1.70 – 1.57 (m, 5H), 1.51 – 1.34 (m, 6H), 1.34 – 1.27 (m, 4H), 1.25 – 1.20 (m, 1H), 1.14 – 1.10 (m, 7H), 1.00 (s, 3H), 0.98 – 0.93 (m, 2H), 0.91 (s, 2H), 0.85 (s, 3H), 0.80 (s, 3H), 0.68 (s, 1H); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 200.4, 170.5, 137.9, 130.7, 129.0, 128.5, 128.4, 128.2, 126.6, 78.9, 61.9, 55.1, 47.3, 47.0, 45.6, 43.9, 43.5, 43.2, 39.3, 37.2, 36.2, 34.6, 34.4, 32.9, 32.7, 32.7, 28.8, 28.2, 27.5, 26.5, 23.6, 21.3, 18.9, 17.6, 16.5, 15.7; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₃₈H₅₄O₂Na⁺) expected *m/z* 565.4022, found *m/z* 565.4008.

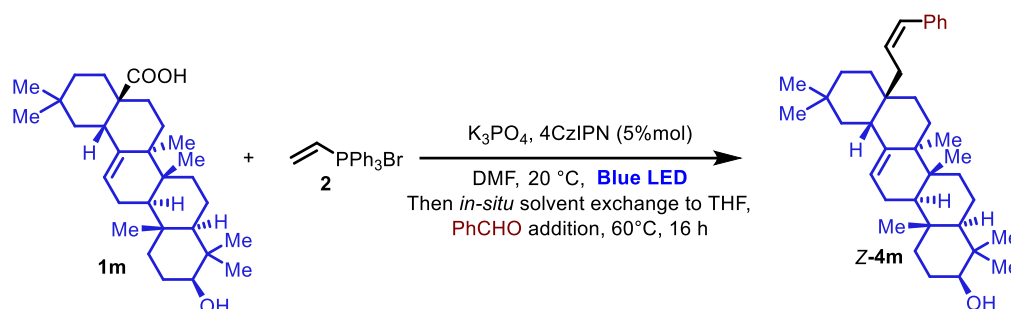
(4aR,6aS,6bR,8aR,10S,12aS,12bR,14bR)-10-hydroxy-2,4a,6a,6b,9,9,12a-heptamethyl-2-((E)-3-phenylallyl)-1,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,14b-octadecahydropicen-13(2H)-one (E-4I)



Prepared following general procedure D, using **11** (1 equiv.; 0.2 mmol; 94.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). Then PhSSPh (1 equiv.; 0.2 mmol; 43.7 mg) was added and the solution irradiated as described in general procedure D. The crude residue was purified by flash column chromatography (SiO₂; gradient 95:5 to 7:3 pentane:tetrahydrofuran) to afford compound **E-4I** (71 mg; 65%; E/Z > 20:1; d.r. = 4:1 stereochemistry not

defined) as a white solid. **M.P.** 90 – 91°C; **R_f** (85:15 pentane:tetrahydrofuran) 0.2; **[α]_D²⁰** +52 (c = 1.00, CHCl₃); **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3438, 2926, 2867, 1655, 1456, 1387, 1360, 1329, 1209, 1040, 994, 920, 879, 754, 674; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.34 (d, *J* = 7.1 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.20 (td, *J* = 7.1, 1.5 Hz, 1H), 6.36 (d, *J* = 15.8 Hz, 1H), 6.21 (dt, *J* = 15.8, 7.6 Hz, 1H), 5.59 (s, 1H), 3.22 (dd, *J* = 11.0, 5.2 Hz, 1H), 2.79 (dt, *J* = 13.5, 3.5 Hz, 1H), 2.34 (s, 1H), 2.19 – 2.13 (m, 1H), 2.11 – 2.03 (m, 3H), 1.86 – 1.78 (m, 1H), 1.78 – 1.71 (t, *J* = 13.8 Hz, 1H), 1.68 – 1.57 (m, 4H), 1.52 – 1.39 (m, 5H), 1.36 (s, 3H), 1.34 – 1.32 (m, 1H), 1.31 – 1.29 (m, 1H), 1.26 – 1.23 (m, 1H), 1.14 (m, 7H), 1.00 (s, 3H), 0.99 – 0.96 (m, 1H), 0.94 (s, 3H), 0.91 (d, *J* = 6.0 Hz, 1H), 0.87 (s, 2H), 0.81 (s, 3H), 0.69 (d, *J* = 11.8 Hz, 1H); **¹³C-NMR** (126 MHz, CDCl₃) δ (ppm): 200.4, 170.5, 137.9, 132.7, 128.6, 128.4, 127.1, 126.8, 126.1, 78.9, 61.9, 55.1, 49.4, 47.4, 47.2, 45.6, 43.5, 39.3, 37.2, 36.2, 34.9, 32.9, 32.8, 32.6, 31.8, 29.8, 28.9, 28.3, 27.5, 26.6, 23.6, 21.6, 18.9, 17.6, 16.5, 15.7; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₃₈H₅₄O₂Na⁺) expected *m/z* 565.4022, found *m/z* 565.4014.

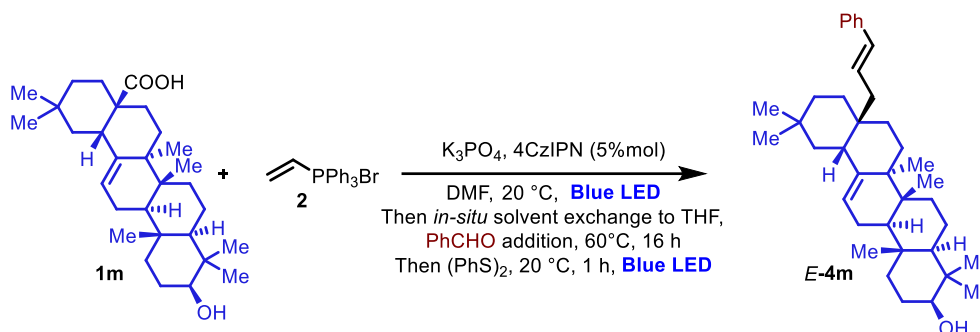
(3*S*,4*aR*,6*aR*,6*bS*,12*aR*,14*aR*,14*bR*)-4,4,6*a*,6*b*,11,11,14*b*-heptamethyl-8*a*-(*Z*-3-phenylallyl)-1,2,3,4,4*a*,5,6,6*a*,6*b*,7,8,8*a*,9,10,11,12,12*a*,14,14*a*,14*b*-icosahydricipicen-3-ol (**Z-4m**)



Prepared following general procedure C, using **1m** (1 equiv.; 0.2 mmol; 91.3 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 9:1 to 85:15 hexane:EtOAc). The compound was purified a second time by flash column chromatography (SiO₂; gradient (95:5 to 85:5 hexane:tetrahydrofuran) to afford compound **Z-4m** as a white solid (59 mg; 55%; *Z/E* = 7:1, d.r. > 20:1 stereochemistry not defined) as white solid. **M.P.** = 97 – 98 °C; **R_f** (85:15 hexane:EtOAc) 0.25; **[α]_D²⁰** +40 (c = 1.00, CHCl₃); **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3392, 2947, 2926, 2866, 1464, 1386, 1363, 1029, 996, 756, 669, 656; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): δ 7.37 – 7.15 (m, 5H), 6.49 (d, *J* = 11.8 Hz, 1H), 5.73 (dt, *J* = 11.8, 7.0 Hz, 1H), 5.17 (t, *J* = 3.7 Hz, 1H), 3.26 – 3.16 (m, 1H), 2.51 (ddd, *J* = 15.7, 7.7, 1.9 Hz, 1H), 2.06 – 1.98 (m, 2H), 1.92 (dd, *J* = 13.9, 4.3 Hz, 1H), 1.87 – 1.80 (m, 2H), 1.71 (t, *J* = 13.5 Hz, 1H), 1.64 – 1.47 (m, 8H), 1.4 – 1.39 (m, 2H), 1.37 – 1.31 (m, 2H), 1.31 – 1.28 (m, 1H), 1.28 – 1.25 (m, 1H), 1.21 – 1.17 (m, 1H), 1.12 (s, 3H), 1.06 – 1.00 (m, 3H), 0.98 (s, 3H), 0.95 – 0.91 (m, 1H), 0.88 – 0.87 (m, 5H), 0.86 (s, 3H), 0.81 – 0.76 (m, 3H), 0.69 (dd, *J* = 11.8, 1.9 Hz, 1H), 0.59 (s, 2H); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 144.7, 138.1, 130.4, 129.0, 129.0, 128.2, 126.5, 122.5, 79.2, 55.3, 47.7, 46.9,

46.6, 41.8, 39.7, 38.9, 38.7, 38.0, 37.0, 35.8, 34.6, 33.4, 33.1, 32.6, 31.1, 28.2, 27.4, 26.2, 25.7, 23.9, 23.8, 23.7, 18.5, 16.5, 15.7, 15.6; **HRMS** (ESI-TOF) mass calculated for $[M+Na]^+$ ($C_{38}H_{56}ONa^+$) expected m/z 551.4229, found m/z 551.4219.

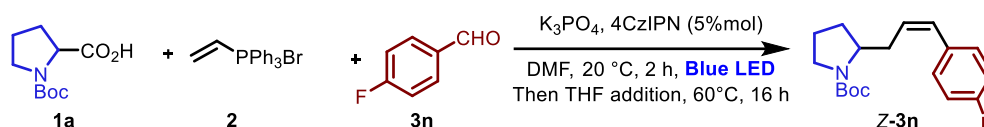
(3*S*,4*aR*,6*aR*,6*bS*,12*aR*,14*aR*,14*bR*)-4,4,6*a*,6*b*,11,11,14*b*-heptamethyl-8*a*-((*E*)-3-phenylallyl)-1,2,3,4,4*a*,5,6,6*a*,6*b*,7,8,8*a*,9,10,11,12,12*a*,14,14*a*,14*b*-icosahydricen-3-ol (*E*-4*m*)



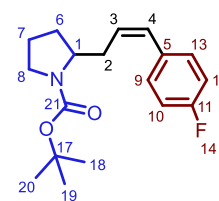
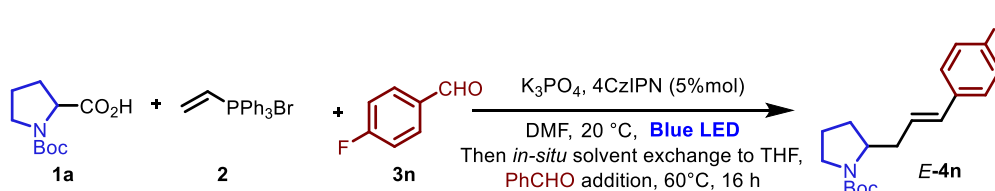
Prepared following general procedure D, using **1m** (1 equiv.; 0.2 mmol; 91.3 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). Then PhSSPh (1 equiv.; 0.2 mmol; 43.7 mg) was added and the solution irradiated as described in general procedure D. The crude residue was purified by flash column chromatography (SiO₂; gradient 9:1 to 85:15 hexane:tetrahydrofuran) to afford compound *E*-**4m** (47 mg; 45%; *E/Z* > 20:1, d.r. > 20:1 stereochemistry not defined) as a white solid. **M.P.** 94 – 95°C; **R_f** (85:15 hexane:tetrahydrofuran) 0.3; $[\alpha]_D^{20} +40$ ($c = 1.00$, CHCl₃); **IR** (film) $\nu_{\max}/\text{cm}^{-1}$: 3401; 2947, 2926, 2861, 1464, 1385, 1363, 1028, 995, 755, 692, 660; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.35 (d, $J = 7.4$ Hz, 2H), 7.29 (t, $J = 7.4$ Hz, 2H), 7.19 (d, $J = 7.3$ Hz, 1H), 6.36 (d, $J = 15.7$ Hz, 1H), 6.23 (dt, $J = 15.7, 7.5$ Hz, 1H), 5.23 (t, $J = 3.6$ Hz, 1H), 3.23 (dd, $J = 11.0, 4.8$ Hz, 1H), 2.41 (dd, $J = 14.0, 7.8$ Hz, 1H), 2.04 (d, $J = 4.1$ Hz, 1H), 1.95 – 1.92 (m, 1H), 1.92 – 1.88 (m, 2H), 1.87 – 1.83 (m, 1H), 1.79 (dd, $J = 13.8, 4.2$ Hz, 1H), 1.74 (t, $J = 13.6$ Hz, 1H), 1.67 – 1.50 (m, 8H), 1.45 – 1.25 (m, 6H), 1.21 – 1.10 (m, 5H), 1.04 (s, 3H), 1.01 (s, 3H), 0.96 (s, 3H), 0.89 – 0.86 (m, 6H), 0.80 (s, 3H), 0.76 (dd, $J = 11.8, 1.8$ Hz, 1H); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 144.8, 138.1, 132.0, 128.6, 127.5, 126.9, 126.1, 122.4, 79.2, 55.3, 47.8, 46.8, 46.7, 43.3, 41.7, 40.1, 38.9, 38.8, 37.1, 36.1, 34.6, 33.6, 33.4, 32.8, 31.1, 28.2, 27.4, 26.3, 25.8, 24.1, 23.8, 23.8, 18.5, 17.2, 15.7, 15.7; **HRMS** (ESI-TOF) mass calculated for $[M+Na]^+$ ($C_{38}H_{56}ONa^+$) expected m/z 551.4229, found m/z 551.4197.

tert-butyl (Z)-2-(3-(4-fluorophenyl)allyl)pyrrolidine-1-carboxylate (Z-3n)

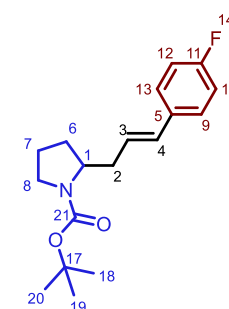
Compound synthesised by Dr. Mattia Silvi.



Prepared following general procedure A, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3n** (3 equiv.; 0.6 mmol; 64 μ L). The crude residue was purified by flash column chromatography (SiO₂; hexane:EtOAc 95:5 – 93:7) to afford compound **Z-4n** (47 mg; 77%; Z/E = 12:1) as a colourless oil. **R_f** (85:15 hexane:EtOAc) 0.5; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2974, 2876, 1692, 1509, 1393, 1365, 1224, 1171, 1120, 1101, 851, 773; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 7.37 – 7.17 (m, 2H, **10** - **12**), 7.00 (t, J = 8.7 Hz, 2H, **9** - **13**), 6.48 (d, J = 11.7 Hz, 1H, **4**), 5.62 (dt, J = 11.7, 7.3 Hz, 1H, **3**), 3.92 – 3.78 (m, 1H, **1**), 3.42 – 3.24 (m, 2H, **8**), 2.88 – 2.53 (m, 1H, **2**), 2.53 – 2.19 (m, 1H, **2**), 1.97 – 1.84 (m, 1H, **6**), 1.79 – 1.70 (m, 2H, **7**), 1.67 – 1.59 (m, 1H, **6**), 1.45 (s, 9H, **18** - **19** - **20**); **¹³C-NMR** (CDCl₃, 101 MHz) δ (ppm): 161.7 (d, J = 245.7 Hz, **11**), 154.7 (**21**), 133.6 (d, J = 3.4 Hz, **5**), 130.4 (d, J = 7.9 Hz, **9** - **13**), 129.6 (**4**), 128.9 (**3**), 115.1 (d, J = 21.3 Hz, **10** - **12**), 79.3 (**17**), 57.2 (**1**), 46.7 (**8**), 33.2 (**2**), 30.2 (**6**), 28.6 (**18** - **19** - **20**), 23.4 (**7**); **¹⁹F-NMR** (CDCl₃, 376 MHz) δ (ppm): -115.6 (s, 1F, **14**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₈H₂₄FN₂O₂Na⁺) expected m/z 328.1689, found m/z 328.1684.

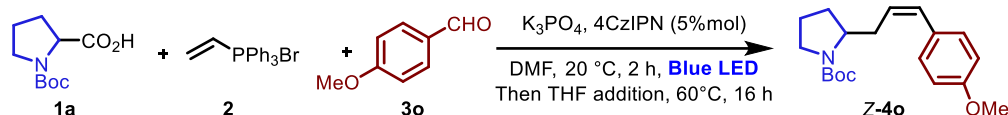
tert-butyl (E)-2-(3-(4-fluorophenyl)allyl)pyrrolidine-1-carboxylate (E-4n)

Prepared following general procedure B, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3n** (3 equiv.; 0.6 mmol; 64 μ L). Then PhSSPh (1 equiv.; 0.2 mmol; 43.7 mg) was added and the solution irradiated as described in general procedure B. The crude residue was purified by flash column chromatography (SiO₂; hexane:EtOAc 95:5 – 93:7) to afford compound **E-4n** (47 mg; 77%; E/Z > 20:1) as a colourless oil. **R_f** (85:15 hexane:EtOAc) 0.45; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2973, 2877, 1689, 1509, 1393, 1365, 1228, 1170, 1105, 853, 770; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 7.32 – 7.25 (m, 2H, **10** - **12**), 6.98 (t, J = 8.7 Hz, 2H, **9** - **13**), 6.37 (d, J = 15.7 Hz, 1H, **4**), 6.06 (dt, J = 15.7, 7.4 Hz, 1H, **3**), 3.93 – 3.83 (m, 1H, **1**), 3.47 – 3.24 (m, 2H, **8**), 2.66 – 2.51 (m, 1H, **2**), 2.35 – 2.20 (m, 1H, **2**), 1.99 – 1.70 (m, 4H, **6** - **7**), 1.47 (s, 9H, **18** - **19** - **20**); **¹³C-NMR** (CDCl₃, 101 MHz) δ (ppm): 162.0 (d, J = 245.5 Hz, **11**), 154.7 (**21**), 133.9 (d, J = 3.3 Hz, **5**), 131.1 (**4**), 127.6 (d, J = 7.8 Hz, **9** - **13**), 126.9 (d, J =

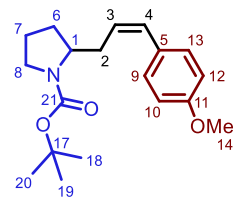


2.2 Hz, **3**), 115.5 (d, $J = 21.6$ Hz, **10 - 12**), 79.2 (**17**), 57.2 (**1**), 46.7 (**8**), 38.0 (**2**), 30.0 (**6**), 28.7 (**18 - 19 - 20**), 23.5 (**7**); ^{19}F -NMR (CDCl_3 , 376 MHz) δ (ppm): -115.4 (s, 1F, **14**); HRMS (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{18}\text{H}_{24}\text{FNO}_2\text{Na}^+$) expected m/z 328.1689, found m/z 328.1690.

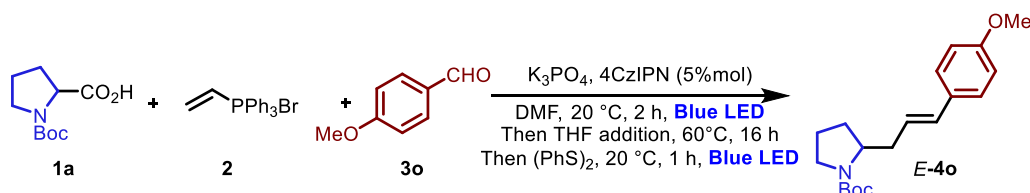
tert-butyl (Z)-2-(3-(4-methoxyphenyl)allyl)pyrrolidine-1-carboxylate (Z-4o)



Prepared following general procedure A, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3o** (3 equiv.; 0.6 mmol; 73 μL). The crude residue was purified by flash column chromatography (SiO_2 ; gradient 3:1 to 100:0 DCM:hexane, then 98:2 DCM:methanol) to afford compound **Z-4o** (37 mg; 59%; Z/E = 7:1) as a colourless oil. **R_f** (DCM) 0.2; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2971, 2831, 1687, 1510, 1391, 1248, 1172, 1118, 1099, 841, 772, 534; ^1H -NMR (CDCl_3 , 400 MHz) δ (ppm): 7.22 (d, $J = 8.6$ Hz, 2H, **9 - 13**), 6.86 (d, $J = 8.6$ Hz, 2H, **10 - 12**), 6.44 (d, $J = 11.7$ Hz, 1H, **4**), 5.51 (dt, $J = 11.7, 7.1$ Hz, 1H, **3**), 3.93 – 3.75 (m, 4H, **1 - 14**), 3.47 – 3.19 (m, 2H, **8**), 2.81 – 2.67 (m, 1H, **2**), 2.44 (dt, $J = 15.6, 8.4$ Hz, 1H, **2**), 1.96 – 1.84 (m, 1H, **6**), 1.82 – 1.71 (m, 2H, **7**), 1.70 – 1.62 (m, 1H, **6**), 1.43 (s, 9H, **18 - 19 - 20**); ^{13}C -NMR (CDCl_3 , 101 MHz) δ (ppm): 158.4 (**21**), 154.7 (**11**), 130.1 (**9 - 13**), 127.4 (**4**), 127.3 (**3**), 114.1 (**5**), 113.7 (**10 - 12**), 79.2 (**17**), 57.4 (**1**), 55.4 (**14**), 46.7 (**8**), 33.3 (**2**), 30.2 (**6**), 28.7 (**18 - 19 - 20**), 23.4 (**7**); HRMS (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{19}\text{H}_{27}\text{NO}_3\text{Na}^+$) expected m/z 340.1889, found m/z 340.1880.

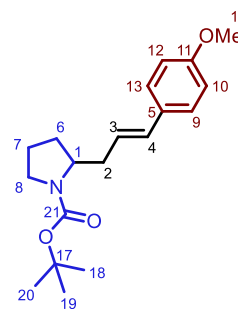


tert-butyl (E)-2-(3-(4-methoxyphenyl)allyl)pyrrolidine-1-carboxylate (E-4o)

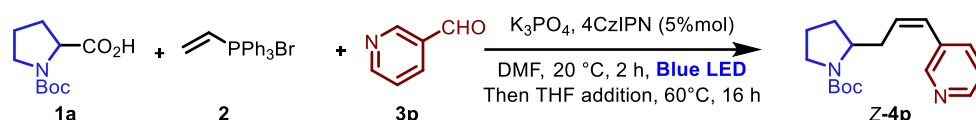


Prepared following general procedure B, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3o** (3 equiv.; 0.6 mmol; 73 μL). Then PhSSPh (1 equiv.; 0.2 mmol; 43.7 mg) was added and the solution irradiated as described in general procedure B. The crude residue was purified by flash column chromatography (SiO_2 ; gradient 3:1 to 100:0 DCM:hexane, then 98:2 DCM:methanol) to afford compound **E-4o** (33 mg; 50%; E/Z > 20:1) as a colourless oil. **R_f** (DCM) 0.2; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2971, 2832, 1688, 1510, 1392, 1247, 1172, 1109, 1035, 830, 772, 527; ^1H -NMR (CDCl_3 , 400 MHz) δ (ppm): 7.26 (d, $J = 8.6$ Hz, 2H, **9 - 13**), 6.84 (d, $J = 8.6$ Hz, 2H, **10 - 12**), 6.35 (d, $J = 15.8$ Hz, 1H, **4**), 6.08 – 5.88

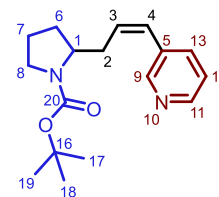
(m, 1H, **3**), 3.91 – 3.71 (m, 4H, **1** - **14**), 3.42 – 3.26 (m, 2H, **8**), 2.71 – 2.46 (m, 1H, **2**), 2.27 (dt, $J = 13.6, 8.4$ Hz, 1H, **2**), 1.96 – 1.62 (m, 4H, **6** - **7**), 1.47 (s, 9H, **18** - **19** - **20**); ^{13}C -NMR (CDCl_3 , 101 MHz) δ (ppm): 158.9 (**21**), 154.7 (**11**), 131.7 (**9** - **13**), 130.5 (**4**), 127.2 (**3**), 124.8 (**10** - **12**), 114.0 (**5**), 79.2 (**17**), 57.3 (**1**), 55.4 (**14**), 46.5 (**8**), 38.3 (**2**), 30.4 (**6**), 28.7 (**18** - **19** - **20**), 23.1 (**7**); HRMS (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{19}\text{H}_{27}\text{NO}_3\text{Na}^+$) expected m/z 340.1889, found m/z 340.1882.

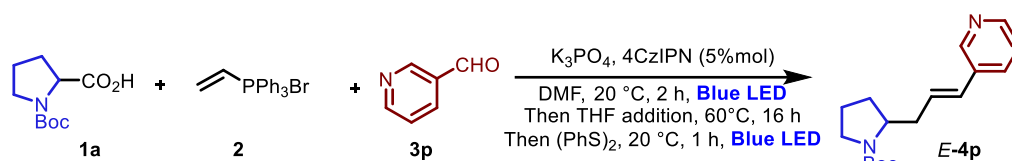


tert-butyl (Z)-2-(3-(pyridin-3-yl)allyl)pyrrolidine-1-carboxylate (**Z-4p**)

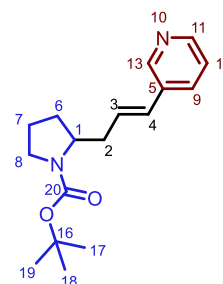
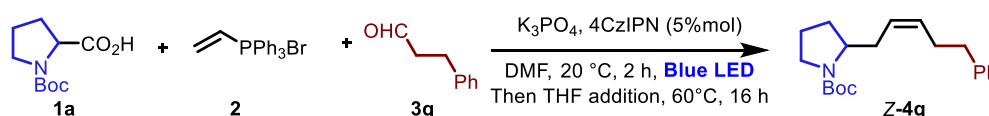


Prepared following general procedure A, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3p** (3 equiv.; 0.6 mmol; 56 μL). The crude residue was purified by flash column chromatography (SiO_2 ; gradient 80:20 to 1:1 DCM:EtOAc). Then the compound was dissolved in hexane and filtered to remove triphenylphosphine oxide. The supernatant was then loaded into a silica plug and eluted with 80:20 hexane:ethyl to afford the compound **Z-4p** (38 mg; 66%; $Z/E = 7:1$) as a colourless oil. **R_f** (1:1 hexane:EtOAc) 0.2; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2972, 2877, 1699, 1393, 1170, 1119, 1099, 1024, 789, 774, 712; ^1H -NMR (CDCl_3 , 400 MHz) δ (ppm): 8.62 – 8.40 (m, 2H), 7.73 – 7.51 (m, 1H), 7.31 – 7.20 (m, 1H), 6.46 (d, $J = 11.7$ Hz, 1H, **4**), 5.85 – 5.71 (m, 1H, **3**), 4.05 – 3.75 (m, 1H, **1**), 3.42 – 3.23 (m, 2H, **8**), 2.84 – 2.56 (m, 1H, **2**), 2.42 (dt, $J = 14.7, 8.4$ Hz, 1H, **2**), 1.96 – 1.83 (m, 1H, **6**), 1.80 – 1.71 (m, 2H, **7**), 1.69 – 1.62 (m, 1H, **6**), 1.42 (s, 9H, **17** - **18** - **19**); ^{13}C -NMR (CDCl_3 , 101 MHz) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis () δ (ppm): 154.7 (**20**), 149.8, 147.8, (147.4), (136.2), 135.9, 133.2, 131.8 (**3**), (131.4), 127.1 (**4**), (126.9), (123.6), 123.3, 79.3 (**16**), 57.1 (**1**), (46.8), 46.5 (**8**), (33.5), 33.1 (**2**), (30.7), 29.8 (**6**), (28.7), 28.6 (**17** - **18** - **19**), (23.7), 23.1 (**7**); HRMS (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2\text{Na}^+$) expected m/z 311.1735; found m/z 311.1729.

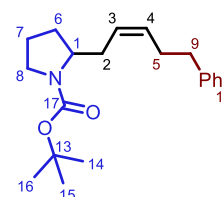


tert-butyl (E)-2-(3-(pyridin-3-yl)allyl)pyrrolidine-1-carboxylate (E-4p)

Prepared following general procedure B, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3p** (3 equiv.; 0.6 mmol; 56 μ L). Then PhSSPh (1 equiv.; 0.2 mmol; 43.7 mg) was added and the solution irradiated as described in general procedure B. The crude residue was purified by flash column chromatography (SiO₂; gradient 80:20 to 70:30 DCM:EtOAc the 1:1 hexane EtOAc). Then the compound was dissolved in hexane and filtered to remove triphenylphosphine oxide. The supernatant was then loaded into a silica plug and eluted with 80:20 hexane:EtOAc to afford the compound **E-4p** (38 mg; 66%; Z/E > 20:1) as a colourless oil. **R_f** (97:3 hexane:THF) 0.4; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3007, 2972, 2876, 1693, 1449, 1392, 1365, 1171, 1120, 1100, 771, 700; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 8.53 (s, 1H, **9**), 8.41 (s, 1H), 7.63 (d, J = 6.4 Hz, 1H), 7.23 – 7.16 (m, 1H), 6.37 (d, J = 15.8 Hz, 1H, **4**), 5.28 – 5.15 (m, 1H, **3**), 4.00 – 3.76 (m, 1H, **1**), 3.48 – 3.23 (m, 2H, **8**), 2.71 – 2.49 (m, 1H, **2**), 2.32 (dt, J = 13.6 Hz, 1H, **2**), 2.06 – 1.66 (m, 4H, **6** - **7**), 1.42 (s, 9H, **17** - **18** - **19**); **¹³C-NMR** (CDCl₃, 101 MHz) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis () δ (ppm): 154.7 (**16**), 148.3 (**9**), 148.2, 133.1, 132.6, (129.8), 129.6 (**3**), 128.7 (**4**), (128.5), 123.5, 79.3 (**16**), 57.0 (**1**), (46.8), 46.5 (**8**), (38.6), 37.8 (**2**), (30.5), 29.7 (**6**), 28.7 (**17** - **18** - **19**), (23.8), 23.1 (**7**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₇H₂₄N₂O₂Na⁺) expected m/z 311.1735; found m/z 311.1727.

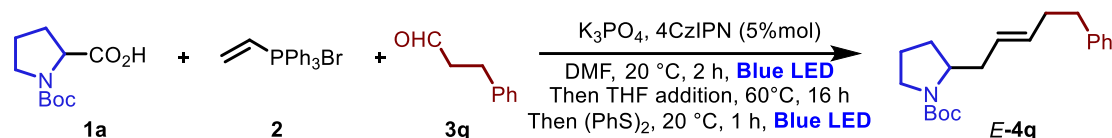
tert-butyl (Z)-2-(5-phenylpent-2-en-1-yl)pyrrolidine-1-carboxylate (Z-4q)

Prepared following general procedure A, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3q** (3 equiv.; 0.6 mmol; 79 μ L). The crude residue was purified by flash column chromatography (SiO₂; 1:1 hexane:dichloromethane) to afford compound **Z-4q** (43 mg; 68% Z/E > 20:1 **GC method B**, retention time (min): **Z** = 26.6; **E** = 26.9) as a colourless oil. **R_f** (1:1 DCM:hexane) 0.2; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2972, 2930, 2874, 1689, 1391, 1365, 1169, 1102, 771, 749, 669; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): δ 7.29 – 7.25 (m, 2H, **10**), 7.18 (d, J = 7.3 Hz, 3H, **10**), 5.55 – 5.46 (m, 1H, **3** - **4**), 5.39 – 5.31 (m, 1H, **3** - **4**), 3.80 – 3.69 (m, 1H, **1**), 3.40 – 3.25 (m, 2H, **8**), 2.70 – 2.63 (m, 2H, **9**), 2.44 – 2.34 (m, 3H, **2** - **5**), 2.14 – 2.03 (m, 1H, **2**), 1.86 – 1.70 (m, 3H, **6** - **7**), 1.58 – 1.53 (m, 1H, **6**), 1.45 (s, 9H, **14** - **15** - **16**); **¹³C-NMR** (CDCl₃, 126 MHz,) δ (ppm): 154.7 (**17**), 142.1 (**10**), 131.1 (**3**

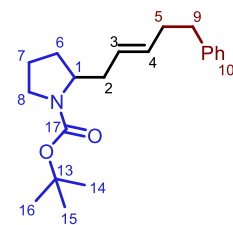


or **4**), 128.6 (**10**), 128.4 (**10**), 126.7 (**3** or **4**), 125.9 (**10**), 79.1 (**13**), 57.2 (**1**), 46.6 (**8**), 36.1 (**9**), 31.9 (**2**), 29.9 (**5**), 29.5 (**6**), 28.7 (**14** - **15** - **16**), 23.4 (**7**); **HRMS** (ESI-TOF) mass calculated for $[M+Na]^+$ ($C_{20}H_{29}NO_2Na^+$) expected m/z 338.2096, found m/z 338.2087.

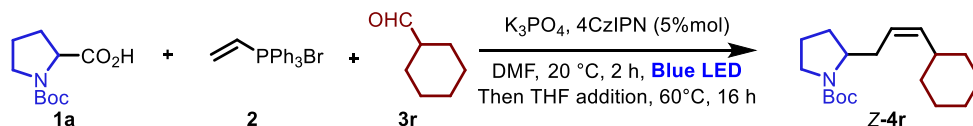
tert-butyl (E)-2-(5-phenylpent-2-en-1-yl)pyrrolidine-1-carboxylate (**E-4q**)



Prepared according to general procedure B, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3q** (3 equiv.; 0.6 mmol; 79 μ L). Then PhSSPh (2 equiv.; 0.4 mmol; 87.3 mg) was added and the solution irradiated as described in general procedure B for 16h. The crude was purified by flash column chromatography (SiO₂; gradient 100:0 to 96:4 toluene:diethyl ether) to afford compound **E-4q** (44 mg; 66%; E/Z = 8:1 **GC method B**, retention time (min): Z = 26.6; E = 26.9) as a colourless oil. **R_f** (toluene) 0.15; **IR** (film) ν_{max}/cm^{-1} : 2972, 2930, 2875, 1692, 1393, 1365, 1170, 1104, 772, 747, 669; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 7.31 – 7.24 (m, 2H, **10**), 7.21 – 7.14 (m, 3H, **10**), 5.55 – 5.43 (m, 1H, **3** - **4**), 5.41 – 5.30 (m, 1H, **3** - **4**), 3.85 – 3.63 (m, 1H, **1**), 3.44 – 3.20 (m, 2H, **8**), 2.67 (t, J = 7.7 Hz, 2H, **9**), 2.50 – 2.27 (m, 3H, **2** - **5**), 2.05 (dt, J = 13.6, 8.2 Hz, 1H, **2**), 1.85 – 1.71 (m, 3H, **6** - **7**), 1.68 – 1.60 (m, 1H, **6**), 1.46 (s, 9H, **14** - **15** - **16**); **¹³C-NMR** (CDCl₃, 101 MHz) δ (ppm): 154.7 (**17**), 142.1 (**10**), 132.2 (**3** or **4**), 128.6 (**10**), 128.4 (**10**), 127.3 (**3** or **4**), 125.9 (**10**), 79.1 (**13**), 57.2 (**1**), 46.5 (**8**), 37.8 (**9**), 36.1 (**2**), 34.6 (**5**), 30.1 (**6**), 28.7 (**14** - **15** - **16**), 23.1 (**7**); **HRMS** (ESI-TOF) mass calculated for $[M+Na]^+$ ($C_{20}H_{29}NO_2Na^+$) expected m/z 338.2096, found m/z 338.2093.

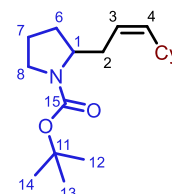


tert-butyl (Z)-2-(3-cyclohexylallyl)pyrrolidine-1-carboxylate (**Z-4r**)

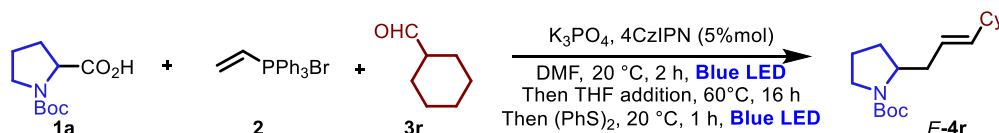


Prepared following general procedure A, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3r** (3 equiv.; 0.6 mmol; 73 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 95:5 to 9:1 hexane:EtOAc) to afford compound **Z-4r** (27 mg; 46% Z/E = 10:1 **GC method A**, retention time (min): Z = 17.7; E = 18.2) as a colourless oil. **R_f** (9:1 hexane:EtOAc) 0.3; **IR** (film) ν_{max}/cm^{-1} : 2972, 2925, 2851, 1696, 1392, 1365, 1172, 1116, 890, 772; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 5.34 – 5.14 (m, 2H, **3** - **4**), 3.93 – 3.63 (m, 1H, **1**), 3.48 – 3.25 (m, 2H, **8**), 2.51 – 2.40 (m, 1H, **2**), 2.29 – 2.18 (m, 1H, **2**), 2.19 – 1.98 (m, 1H, **6**), 1.91 – 1.75 (m, 3H, **6** - **7**), 1.73 – 1.64 (m, 4H, **5**), 1.62

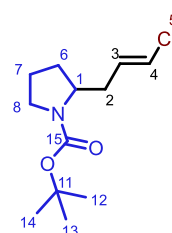
– 1.55 (m, 2H, **5**), 1.47 (s, 9H, **12** - **13** - **14**), 1.28 – 1.01 (m, 5H, **5**); ^{13}C -NMR (CDCl_3 , 101 MHz) δ (ppm): 154.7 (**15**), 138.3 (**3** or **4**), 123.8 (**3** or **4**), 79.1 (**11**), 57.3 (**1**), 46.5 (**8**), 40.9 (**2**), 36.6, 33.5, 33.4, 28.8 (**12** - **13** - **14**), 26.2, 26.0, 23.1 (**7**); HRMS (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{18}\text{H}_{31}\text{NO}_2\text{Na}^+$) expected m/z 316.2252, found m/z 316.2241.



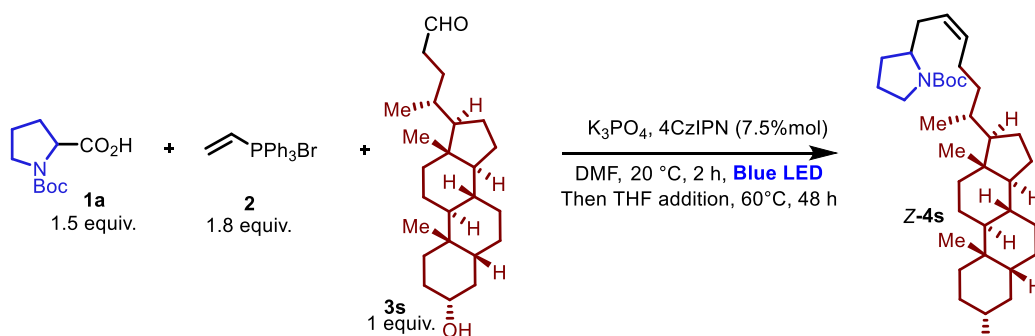
tert-butyl (E)-2-(3-cyclohexylallyl)pyrrolidine-1-carboxylate (**E-4r**)



Prepared according to general procedure B, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3r** (3 equiv.; 0.6 mmol; 73 μL). Then PhSSPh (2 equiv.; 0.4 mmol; 87.3 mg) was added and the solution irradiated as described in general procedure B for 16h. The crude was purified by flash column chromatography (SiO_2 ; gradient 95:5 to 9:1 hexane:EtOAc). The compound was purified by a second column chromatography (SiO_2 ; gradient toluene to 98:2 toluene:EtOAc) to afford compound **E-4r** (27 mg; 46% E/Z = 14:1 **GC method A**, retention time (min): *Z* = 17.7; *E* = 18.2) as a colourless oil. **Rr** (toluene) 0.2; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2971, 2925, 2852, 1696, 1393, 1365, 1172, 1116, 971, 772; ^1H -NMR (CDCl_3 , 400 MHz) δ (ppm) 5.47 – 5.16 (m, 2H, **3** - **4**), 3.81 – 3.69 (m, 1H, **1**), 3.41 – 3.23 (m, 2H, **8**), 2.42 – 2.31 (m, 1H, **2**), 2.04 (dt, J = 13.3, 8.1 Hz, 1H, **2**), 1.97 – 1.58 (m, 10H), 1.46 (s, 9H, **12** - **13** - **14**), 1.35 – 0.91 (m, 5H); ^{13}C -NMR (CDCl_3 , 101 MHz) δ (ppm): 154.7 (**15**), 139.5, 123.8, 79.0 (**11**), 57.3 (**1**), 46.7 (**8**), 40.9 (**2**), 37.4, 33.3, 29.7, 28.7 (**12** - **13** - **14**), 26.4, 26.2, 23.4 (**7**); HRMS (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{18}\text{H}_{31}\text{NO}_2\text{Na}^+$) expected m/z 316.2252, found m/z 316.2238.



tert-butyl-2-((*R,Z*)-6-((3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-hydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)hept-2-en-1-yl)pyrrolidine-1-carboxylate (**Z-4s**)



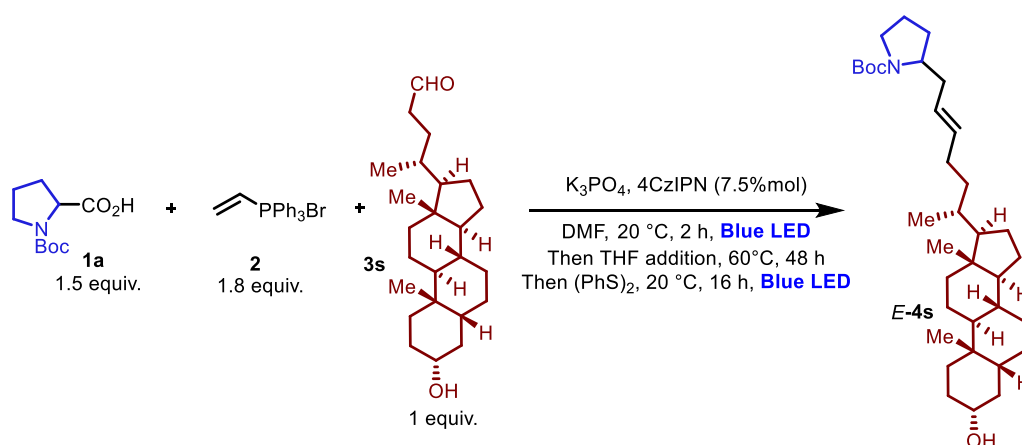
Prepared according to general procedure A, using **1a** (1.5 equiv.; 0.15 mmol; 32.3 mg), vinyl phosphonium bromide **2** (1.8 equiv.; 0.18 mmol; 66.4 mg) and aldehyde **3s** (1 equiv.; 0.1 mmol; 36.1 mg). After the photochemical step, dry THF (900 μL) was added

and the reaction was left 48 h under vigorously stirring (1100 rpm) under argon. Then procedure A was followed for the workup. The crude residue was purified by flash column chromatography (SiO₂; gradient 92.5:2.5 to 80:20 DCM:EtOAc) to afford the **Z-4s** (42 mg; 76%; *Z/E* > 20:1) as a white solid. The product is intended as equimolar mixture of epimers on the pyrrolidine chiral centre. **M.P.** = 53 – 54°C; **R_f** (85:15 DCM:EtOAc) 0.3; [α]_D²⁵ +24 (*c* = 1.00, CHCl₃); **IR** (film) ν_{max} /cm⁻¹: 3394, 2929, 2864, 1677, 1449, 1393, 1365, 1168, 1112, 1069, 1039, 908, 739, 646; **¹H-NMR** (CDCl₃, 500 MHz,) δ (ppm): 5.42 (q, *J* = 7.7 Hz, 1H), 5.34 – 5.24 (q, *J* = 7.7 Hz, 1H), 3.84 – 3.71 (m, 1H), 3.66 – 3.56 (m, 1H), 3.40 – 3.27 (m, 2H), 2.50 – 2.37 (m, 1H), 2.18 – 2.01 (m, 2H), 2.00 – 1.90 (m, 2H), 1.89 – 1.78 (m, 5H), 1.7 (s, 1H), 1.73 (d, *J* = 12.3 Hz, 1H), 1.70 – 1.59 (m, 3H), 1.57 – 1.45 (m, 11H), 1.43 – 1.31 (m, 8H), 1.26 – 1.19 (m, 3H), 1.14 – 0.99 (m, 6H), 0.93 – 0.89 (m, 6H), 0.63 (s, 3H); **¹³C-NMR** (CDCl₃, 126 MHz) rotameric and mixture, resonances are enclosed in parenthesis () δ : 157.7, 132.6, 125.6, (125.6), 79.1, 72.0, (57.3), 57.3, 56.7, 56.4, 46.6, 42.9, 42.2, 40.6, 40.3, 36.6, 36.0, 36.0, (35.7), 35.6, 35.5, 34.7, 31.9, 30.7, 29.3, 28.7, 28.5, 27.3, 26.6, 24.4, (24.3), 24.3, 23.5, 23.4, 21.0, 18.7, (18.7), 12.2; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₃₅H₅₉NO₃Na⁺) expected *m/z* 564.4393, found *m/z* 564.4367.

The *Z/E* has been measured through a 80°C-NMR experiment which allowed us to resolve the *Z* and *E* allylic signals.

¹H-NMR (DMSO-*d*₆; 400 MHz; 80°C) δ (ppm): 5.48 – 5.38 (m, 1H), 5.36 – 5.25 (m, 1H), 3.80 – 3.50 (m, 2H), 3.46 – 3.35 (m, 1H), 3.32 – 3.25 (m, 1H), 3.24 – 3.15 (m, 1H), 2.45 – 2.34 (m, 1H), 2.16 – 2.03 (m, 2H), 2.01 – 1.92 (m, 2H), 1.91 – 1.75 (m, 5H), 1.74 – 1.72 (m, 1H), 1.71 – 1.68 (m, 1H), 1.68 – 1.60 (m, 2H), 1.58 – 1.50 (m, 2H), 1.45 – 1.35 (m, 17H), 1.27 – 1.15 (m, 6H), 1.11 – 1.01 (m, 4H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 3H), 0.64 (s, 3H).

tert-butyl-2-((*R,E*)-6-((3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-hydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)hept-2-en-1-yl)pyrrolidine-1-carboxylate (**E-4s**)



Prepared according to general procedure B, using **1a** (1.5 equiv.; 0.15 mmol; 32.3 mg), vinyl phosphonium bromide **2** (1.8 equiv.; 0.18 mmol; 66.4 mg) and aldehyde **3s** (1

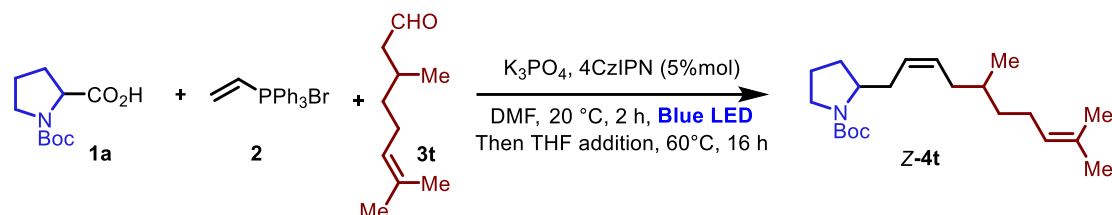
equiv.; 0.1 mmol; 36.1 mg). After the photochemical step, dry THF (900 μ L) was added and the reaction was left 48 h under vigorously stirring (1100 rpm) under argon. PhSSPh (2 equiv.; 0.4 mmol; 87.3 mg) was added and the solution irradiated as described in general procedure B for 16h. Then procedure B was followed for the workup. The crude residue was purified by flash column chromatography (SiO₂; gradient 92.5:2.5 to 80:20 DCM:EtOAc) to afford the compound *E*-**4s** (40 mg; 72%; *E/Z* = 7:1) as a colourless oil. The product is intended as equimolar mixture of epimers on the pyrrolidine chiral centre. **R_f** (85:15 DCM:EtOAc) 0.3; [α]_D²⁵ +20 (*c* = 1.00, CHCl₃); **IR** (film) ν_{max} /cm⁻¹: 3414, 2928, 2864, 1677, 1449, 1395, 1365, 1168, 1113, 1069, 1040, 909, 731, 646; **¹H-NMR** (CDCl₃, 500 MHz,) δ (ppm): 5.42 (dt, *J* = 15.5, 6.7 Hz, 1H), 5.30 (dt, *J* = 15.5, 7.0 Hz, 1H), 3.82 – 3.69 (m, 1H), 3.65 – 3.55 (m, 1H), 3.41 – 3.24 (m, 2H), 2.48 – 2.32 (m, 1H), 2.18 – 2.01 (m, 2H), 1.96 (d, *J* = 12.2 Hz, 1H), 1.91 – 1.74 (m, 8H), 1.72 – 1.62 (m, 2H), 1.61 – 1.51 (m, 3H), 1.50 – 1.44 (m, 10H), 1.42 – 1.33 (m, 7H), 1.27 – 1.20 (m, 3H), 1.15 – 1.00 (m, 6H), 0.93 – 0.87 (m, 6H), 0.63 (s, 3H); **¹³C-NMR** (CDCl₃, 101 MHz) rotameric and diastereomeric mixture, resonances for minor rotamer () and diastereoisomer [] are enclosed in parenthesis δ : 154.7, (133.9), 133.8, [132.6], (126.2), 126.2, [125.6], [79.1], 79.0, 72.0, (57.3), 57.3, [57.3], 56.7, 56.4, [56.4], 46.6, 42.9, 42.3, 40.6, 40.4, 37.5, 36.6, [36.0], 35.9, (35.9), 35.7, [35.7], 35.5, [35.5], 34.7, 31.9, 30.7, 29.8, (29.6), 29.6, [28.7], 28.7, 28.5, 27.4, 26.6, 24.4, [24.3], 23.5, 23.4, 21.0, [18.7], 18.6, (18.6), 12.2; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₃₅H₅₉NO₃Na⁺) expected *m/z* 564.4393, found *m/z* 564.4373.

The *Z/E* has been measured through a 80 °C ¹H-NMR experiment which allowed us to resolve the *Z* and *E* allylic signals.

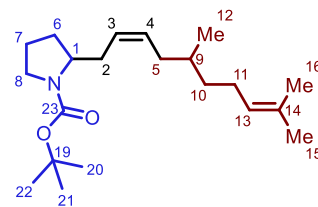
¹H-NMR (DMSO-*d*₆; 400 MHz; 80°C) δ (ppm): 5.49 – 5.27 (m, 2H), 3.88 (bs, 1H), 3.76 – 3.66 (m, 1H), 3.46 – 3.37 (m, 1H), 3.32 – 3.25 (m, 1H), 3.24 – 3.15 (m, 1H), 2.36 – 2.24 (m, 1H), 2.14 – 2.02 (m, 2H), 1.97 – 1.89 (m, 2H), 1.88 – 1.61 (m, 9H), 1.58 – 1.51 (m, 2H), 1.44 – 1.35 (m, 17H), 1.25 – 1.16 (m, 5H), 1.11 – 1.02 (m, 4H), 0.94 – 0.88 (m, 7H), 0.65 (s, 3H).

tert-butyl (Z)-2-(5,9-dimethyldeca-2,8-dien-1-yl)pyrrolidine-1-carboxylate (Z-4t)

Compound synthesised by Dr. Mattia Silvi.

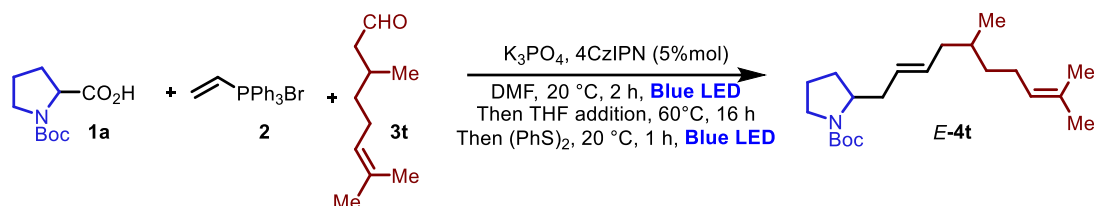


Prepared following general procedure A, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3t** (3 equiv.; 0.6 mmol; 108 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 80:20 to 60:40 hexane:DCM then hexane:EtOAc 100:0 to 94:6). The compound was purified a second time by flash column chromatography (SiO₂; gradient 100:0 to 97.5:2.5 toluene:ethyl ether) to afford the compound **Z-4t** (50 mg; 75%; Z/E > 20:1) as a colourless oil. The product is intended as equimolar mixture of epimers on the pyrrolidine chiral centre. **R_f** (85:15 hexane:EtOAc) 0.5; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2967, 2927, 1697, 1392, 1254, 1172, 1110, 772; **¹H-NMR** (CDCl₃, 400 MHz,) δ (ppm): 5.54 – 5.40 (m, 1H, **3 - 4**), 5.40 – 5.26 (m, 1H, **3 - 4**), 5.08 (t, J = 7.0 Hz, 1H, **13**), 3.91 – 3.76 (m, 1H, **1**), 3.47 – 3.22 (m, 2H, **8**), 2.49 – 2.38 (m, 1H, **2**), 2.22 – 1.73 (m, 8H), 1.67 (s, 4H), 1.59 (s, 3H), 1.52 (s, 10H), 1.40 – 1.28 (m, 1H, **6**), 1.20 – 1.06 (m, 1H, **6**), 0.87 (d, J = 6.7 Hz, 3H, **12**); **¹³C-NMR** (CDCl₃, 101 MHz) rotameric and mixture, resonances are enclosed in parenthesis () δ : 154.7 (**23**), 131.3, 130.8 (**3** or **4**), 126.6 (**3** or **4**), 125.0 (**13**), 79.1 (**19**), 57.3 (**1**), 46.5 (**8**), 36.9 (**6**), (36.9), 34.8 (**2**), 33.2, 32.2, 30.3, 28.7 (**20 - 21 - 22**), 25.9, (25.8), 23.1, 19.6, 19.6, 17.8; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₁H₃₇NO₂Na⁺) expected m/z 358.2722, found m/z 358.2711.

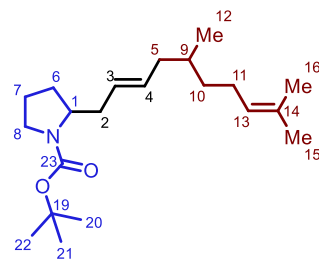
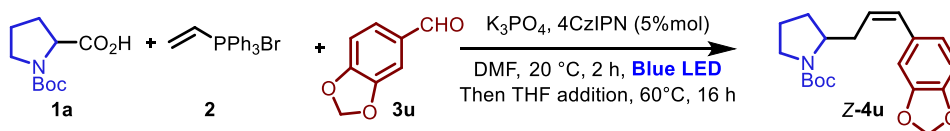


tert-butyl (E)-2-(5,9-dimethyldeca-2,8-dien-1-yl)pyrrolidine-1-carboxylate (E-4t)

Compound synthesised by Dr. Mattia Silvi.

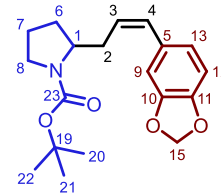


Prepared according to general procedure B, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3t** (3 equiv.; 0.6 mmol; 108 μ L). Then PhSSPh (2 equiv.; 0.4 mmol; 87.3 mg) was added and the solution irradiated as described in general procedure B for 16h. The crude residue was purified by flash column chromatography (SiO₂; gradient 95:5 to 9:1 hexane:ethyl ether). The compound was purified a second time by flash column chromatography (SiO₂; gradient 100:0 to 97.5:2.5 toluene:ethyl ether) to afford the compound **E-4t** (43 mg; 65%; E/Z = 4:1) as a colourless oil. The product is intended as equimolar mixture of epimers on the pyrrolidine chiral centre. **R_f** (97.5:2.5 toluene:ethyl ether) 0.2; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2967, 2927, 1697, 1393, 1254, 1172, 1109, 772; **¹H-NMR** (CDCl₃, 400 MHz), δ (ppm): 5.47 – 5.37 (m, 1H, **3** or **4**), 5.36 – 5.27 (m, 1H, **3** or **4**), 5.08 (t, J = 7.0 Hz, 1H, **13**), 3.86 – 3.66 (m, 1H, **1**), 3.45 – 3.16 (m, 2H, **8**), 2.50 – 2.35 (m, 1H, **2**), 2.11 – 1.90 (m, 4H), 1.90 – 1.70 (m, 5H), 1.68 (s, 3H), 1.59 (s, 3H), 1.46 (s, 10H), 1.39 – 1.21 (m, 1H, **6**), 1.21 – 1.07 (m, 1H, **6**), 0.86 (d, J = 6.7 Hz, 3H, **12**); **¹³C-NMR** (CDCl₃, 101 MHz) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis () δ (ppm): 154.7 (**23**), (131.8), 131.8, (131.3), 131.2, 127.8, 125.0, (125.0), 79.0 (**19**), (57.3), 57.3 (**1**), 46.6 (**8**), (40.2), 40.2, (36.8), 36.7 (**5**), 34.8 (**2**), 33.2, 32.9, (32.9), 29.8, 28.7 (**20 - 21 - 22**), 25.9, (25.7), 23.4, 19.5, (19.5), 17.8; **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ (C₂₁H₃₇NO₂Na⁺) expected m/z 358.2722, found m/z 358.2709.

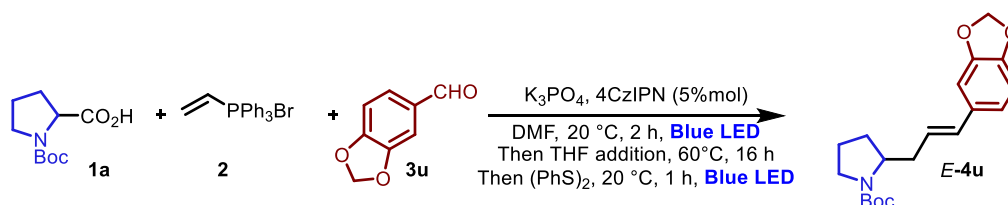
tert-butyl (Z)-2-(3-(benzo[d][1,3]dioxol-5-yl)allyl)pyrrolidine-1-carboxylate (Z-4u)

Prepared following general procedure A, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3u** (3 equiv.; 0.6 mmol; 90.1 mg). The crude residue was purified by flash column chromatography (SiO₂ deactivated flushing 0.5% Et₃N in DCM; DCM, then gradient 9:1 to 8:2 pentane:EtOAc) to afford the compound **Z-4u** (40 mg; 60%; Z/E = 5:1) as a colourless oil. **R_f** (9:1 pentane:EtOAc) 0.3; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2972, 2878, 1687, 1504, 1443, 1390, 1365, 1237, 1169, 1118, 1101, 1039, 938, 864, 816, 772; **¹H-NMR** (CDCl₃, 500

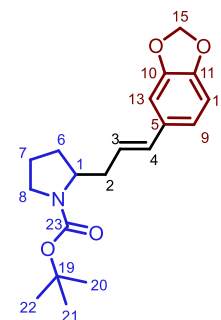
MHz) δ (ppm): 6.81 – 6.70 (m, 3H, **9** - **12** - **13**), 6.39 (d, J = 11.7 Hz, 1H, **4**), 6.00 – 5.90 (m, 2H, **15**), 5.51 (dt, J = 11.7, 7.1 Hz, 1H, **3**), 3.93 – 3.78 (m, 1H, **1**), 3.50 – 3.25 (m, 2H, **8**), 2.78 – 2.67 (m, 1H, **2**), 2.42 (dt, J = 14.7 Hz, 7.5 Hz, 1H, **2**), 1.95 – 1.83 (m, 1H, **6**), 1.82 – 1.72 (m, 2H, **7**), 1.69 – 1.60 (m, 1H, **6**), 1.43 (s, 9H, **20** - **21** - **22**); $^{13}\text{C-NMR}$ (CDCl_3 , 126 MHz) diastereomeric peaks of minor isomer are enclosed in parenthesis [] δ (ppm): 154.7 (**23**), [148.1], 147.5, [146.9], 146.3, [132.3], [131.8], 131.8, 130.2 (**4**), 127.9 (**3**), [125.3], 122.6, [120.5], 109.1, [108.4], 108.2, [105.6], [101.1], 101.1 (**15**), 79.2 (**19**), 57.4 (**1**), [57.2], 46.7 (**8**), 33.3 (**2**), 30.2 (**6**), [28.7], 28.6 (**20** - **21** - **22**), 23.4 (**7**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{19}\text{H}_{25}\text{NO}_4\text{Na}^+$) expected 354.1681 m/z , found 354.1676 m/z .

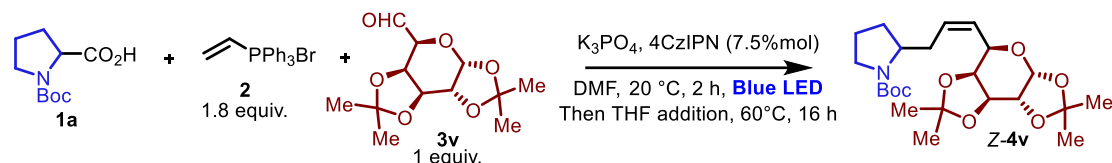


tert-butyl (*E*)-2-(3-(benzo[*d*][1,3]dioxol-5-yl)allyl)pyrrolidine-1-carboxylate (*E*-**4u**)

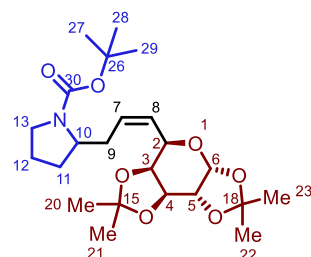


Prepared following general procedure B, using **1a** (1 equiv.; 0.2 mmol; 43.1 mg), vinyl phosphonium bromide **2** (1.2 equiv.; 0.24 mmol; 88.6 mg) and aldehyde **3u** (3 equiv.; 0.6 mmol; 90.1 mg). Then PhSSPh (1 equiv.; 0.2 mmol; 43.7 mg) was added and the solution irradiated as described in general procedure B. The crude residue was purified by flash column chromatography (SiO_2 ; DCM, then gradient 9:1 to 8:2 pentane:EtOAc) to afford the compound *E*-**4u** (32 mg; 48%; *E/Z* > 20:1) as a colourless oil. **R_f** (9:1 pentane:EtOAc) 0.3; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2973, 2880, 1690, 1504, 1446, 1395, 1365, 1250, 1171, 1105, 1039, 939, 864, 815, 772; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 6.88 (d, J = 1.5 Hz, 1H, **9**), 6.79 – 6.70 (m, 2H, **12** - **13**), 6.31 (d, J = 15.7 Hz, 1H, **4**), 6.01 – 5.88 (m, 3H, **3** - **15**), 3.96 – 3.78 (m, 1H, **1**), 3.45 – 3.27 (m, 2H, **8**), 2.70 – 2.45 (m, 1H, **2**), 2.26 (td, J = 13.5, 8.2 Hz, 1H, **2**), 1.93 – 1.72 (m, 4H, **6** - **7**), 1.47 (s, 9H, **20** - **21** - **22**); $^{13}\text{C-NMR}$ (CDCl_3 , 126 MHz) δ (ppm): 154.7 (**23**), 148.1, 146.9, 132.3, 131.8 (**4**), 125.3 (**3**), 120.5 (**13**), 108.4 (**12**), 105.6 (**9**), 101.1 (**15**), 79.2 (**19**), 57.2 (**1**), 46.7 (**8**), 38.2 (**2**), 30.2 (**6**), 28.7 (**20** - **21** - **22**), 23.4 (**7**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{19}\text{H}_{25}\text{NO}_4\text{Na}^+$) expected 354.1681 m/z , found 354.1674 m/z .

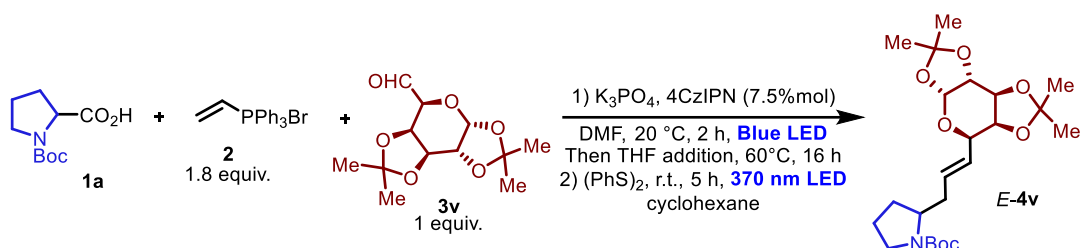


tert-butyl-2-((*Z*)-3-((3*aR*,5*aR*,5*aS*,8*aS*,8*bR*)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d'*]pyran-5-yl)allyl)pyrrolidine-1-carboxylate (**Z-4v**)

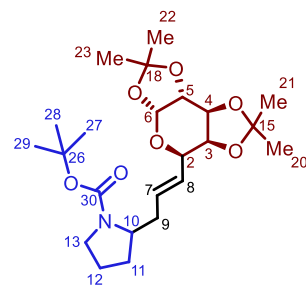
Prepared according to general procedure A, using **1a** (1.5 equiv.; 0.3 mmol; 64.5 mg), vinyl phosphonium bromide **2** (1.8 equiv.; 0.36 mmol; 132.8 mg) and aldehyde **3v** (1 equiv.; 0.2 mmol; 51.6 mg). After the photochemical step, dry THF (1.7 mL) was added and the reaction was left 16h under vigorously stirring (1100 rpm) under argon. Then procedure A was followed for the workup. The crude residue was purified by flash column chromatography (SiO₂; gradient 9:1 to 4:1 hexane:EtOAc) to afford the compound **Z-4v** (34 mg; 39%; *Z/E* = 20:1) as a colourless oil. The product is intended as equimolar mixture of epimers on the pyrrolidine chiral centre. **R_f** (8:2 hexane:EtOAc) 0.2; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2978, 2935, 1693, 1393, 1368, 1256, 1211, 1169, 1104, 1069, 995; **¹H-NMR** (CDCl₃, 400 MHz,) δ (ppm): 5.75 – 5.65 (m, 1H, **8**), 5.65 – 5.57 (m, 1H, **7**), 5.55 (d, *J* = 5.1 Hz, 1H, **6**), 4.64 – 4.48 (m, 2H, **2** - **4**), 4.30 (dd, *J* = 5.2, 2.4 Hz, 1H, **5**), 4.14 (t, *J* = 8.0 Hz, 1H, **3**), 3.94 – 3.72 (m, 1H, **10**), 3.45 – 3.20 (m, 2H, **13**), 2.65 – 2.10 (m, 2H, **9**), 1.92 – 1.65 (m, 4H, **11** - **12**), 1.56 (s, 3H), 1.47 (s, 12H), 1.34 (s, 6H); **¹³C-NMR** (CDCl₃, 101 MHz) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis () δ (ppm): 154.6 (**30**), 131.0 (**7**), (130.4), (127.3), 127.0 (**8**), 109.3 (**15** or **18**), (109.3), (108.5), 108.4 (**15** or **18**), 96.7 (**2**), (96.7), 79.3 (**26**), 73.5 (**5**), (71.0), 71.0 (**4**), 70.4 (**8**), (64.1), 63.9 (**3**), 57.0 (**10**), (56.6), (46.9), 46.5 (**13**), 33.3 (**9**), 31.8, 29.8 (**6**), 28.7 (**27** - **28** - **29**), (26.4), 26.1, (25.0), 25.0, 24.4, 23.4; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₃H₃₇NO₇Na⁺) expected *m/z* 462.2468, found *m/z* 462.2459.



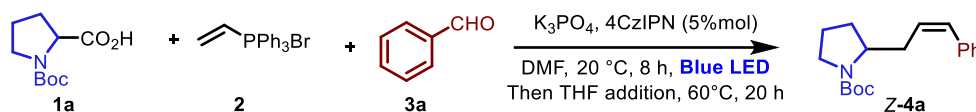
tert-butyl-2-((E)-3-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)allyl)pyrrolidine-1-carboxylate (E-4v)



Prepared according to general procedure A, using **1a** (1.5 equiv.; 0.3 mmol; 64.5 mg), vinyl phosphonium bromide **2** (1.8 equiv.; 0.36 mmol; 132.8 mg) and aldehyde **3v** (1 equiv.; 0.2 mmol; 51.6 mg). After the photochemical step, dry THF (1.7 mL) was added and the mixture was heated to 60°C for 16 h under vigorously stirring (1100 rpm) under argon. Then, general procedure A was followed. The crude residue was purified by flash column chromatography (SiO₂; gradient 9:1 to 4:1 hexane:EtOAc) to afford the compound **Z-4v** (34 mg; 0.08mmol). The compound was dissolved in cyclohexane (800 μ L) and PhSSPh (2 equiv.; 0.16 mmol; 35 mg) was added. The solution was degassed through freeze-pump-thaw cycles (x5). The atmosphere was switched to argon and the vessel was placed approximately 3 cm away from a 370 nm LED light, moderately stirred (500 rpm) and irradiated for 5 h. A fan was used to keep the temperature below 40°C. The crude residue was purified by flash column chromatography (SiO₂; DCM, then gradient 9:1 to 8:2 hexane:EtOAc) to afford compound **E-4v** (24 mg; 27%; E/Z = 7:1) as a colourless oil. The product is intended as equimolar mixture of epimers on the pyrrolidine chiral centre. **R_f** (8:2 hexane:EtOAc) 0.2; ; **IR** (film) ν_{max} /cm⁻¹: 2977, 2935, 1689, 1391, 1367, 1254, 1210, 1165, 1099, 1065, 994; **¹H-NMR** (CDCl₃, 500 MHz,) δ (ppm): 5.78 – 5.58 (m, 2H, **7 - 8**), 5.54 (d, J = 5.1 Hz, 1H, **6**), 4.58 (d, J = 7.8, 1H, **4**), 4.33 – 4.26 (m, 1H, **5**), 4.22 (d, J = 6.4 Hz, 1H, **2**), 4.15 (d, J = 7.8, 1H, **3**), 3.94 – 3.70 (m, 1H, **10**), 3.46 – 3.21 (m, 2H, **13**), 2.60 – 2.39 (m, 1H, **9**), 2.23 – 2.05 (m, 1H, **9'**), 1.89 – 1.68 (m, 4H, **11 - 12**), 1.53 (s, 3H), 1.47 (s, 12H), 1.33 (s, 6H); **¹³C-NMR** (CDCl₃, 126 MHz) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis () δ (ppm): 154.7 (**30**), 131.1 (**8**), 128.3 (**7**), 109.3 (**15** or **18**), 108.5 (**15** or **18**), 96.6 (**6**), 79.2 (**26**), 73.7 (**5**), (73.7), 71.0 (**4**), 70.5 (**2**), (70.5) 69.0 (**19**), (64.1), 63.9 (**3**), 56.9 (**10**), (56.8), 46.6 (**13**), 37.7 (**9**), 28.7 (**27 - 28 - 29**), 26.3, 26.1, 25.1, (25.1), 24.5, (24.4), 23.1; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₃H₃₇NO₇Na⁺) expected m/z 462.2468, found m/z 462.2452.



2.6.10. Multi-gram scale reaction

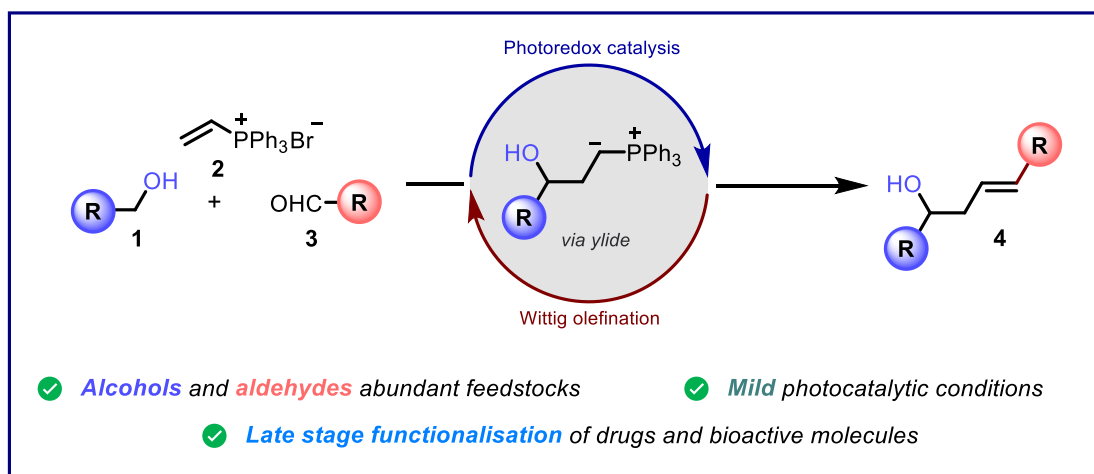


Carboxylic acid **1a** (1 equiv.; 20 mmol; 4.31 g), vinyl phosphonium bromide **2** (1.2 equiv.; 24 mmol; 8.86 g), potassium phosphate (3 equiv.; 60 mmol; 12.74 g) and 4CzIPN (0.05 equiv.; 1 mmol; 789 mg) were introduced into a 250 mL Schlenk tube. The atmosphere was exchanged to argon, after which degassed dry DMF (20 mL, previously degassed through 15 min argon sparging) and aldehyde **3a** (3 equiv.; 60 mmol; 6.11 mL) were introduced through a syringe. The vessel was sealed and placed in a glass-wall water bath with temperature controlled at 20 °C (using 2L Becker). The reaction was irradiated through the glass wall with blue light (Kessil lamp A160WE Tuna Blue Saltwater LED Light 40W) for 8 h under stirring (800 rpm, a large magnetic stirrer is recommended). Careful: the production of CO_2 byproduct will generate some pressure in the vessel. The Schlenk was then removed from the water bath and dry THF (180 mL) was introduced through a cannula. A refrigerant was put in place and the mixture was heated to 60 °C for 20 h under stirring (450 rpm). See Fig.S2 for visual details. The reaction was cooled down to room temperature and was diluted with 200 mL of Et_2O and filtered through a thin layer of celite/silica and eluted with Et_2O . Volatiles were evaporated under reduced pressure and the residue was subjected to chromatography purification on silica gel (SiO_2 ; gradient 98:2 to 94:6 hexane: $EtOAc$) to afford compound **Z-4a** (4.3 g; 76%; $Z/E = 12:1$) as a yellow oil.

Chapter 3. C-H functionalisation of alcohols *via* conjunctive olefination.

In this chapter, we describe a methodology that extends the applicability of the process presented in Chapter 2 to C-H functionalisation chemistry. Attracted by the abundance of the alcohol functionality in organic molecules, we exploit our conjunctive olefination process in the context of selective α -functionalisation of sp^3 alcohols **1**. Substrates are conveniently coupled to aldehydes **3** leading to unsaturated product **4**. The protocol could be used for the functionalisation of complex fragments for late-stage functionalisation purposes.

The work described in this chapter has been performed in collaboration with Joseph Wallen, a 4th-year project student who carried out part of the work within the scope exploration of the reaction under my laboratory supervision. See the experimental section for a detailed outline of the work performed.



3.1. Introduction

The methodology disclosed in Chapter 2 allowed us to achieve a versatile cross-coupling methodology for the modification of complex molecular fragments exploiting functionalities widely present in natural and bioactive compounds. The key aspect of the process includes the use of complex substrates in their native form – without the necessity of exogenous activating or protecting groups. Having this procedure in our hands, we envisioned to further expanding the methodology towards even more abundant and convenient coupling partners. In this regard, we identified aliphatic alcohols as ideal coupling partners, given their recurrence in natural and bioactive compounds (Table 3.1). In contrast to our previous decarboxylative strategy – in which the key carboxylic group is lost in the process – the strategy described in the following sections permits retaining the directing OH group, allowing direct access to novel alcohol derivatives.

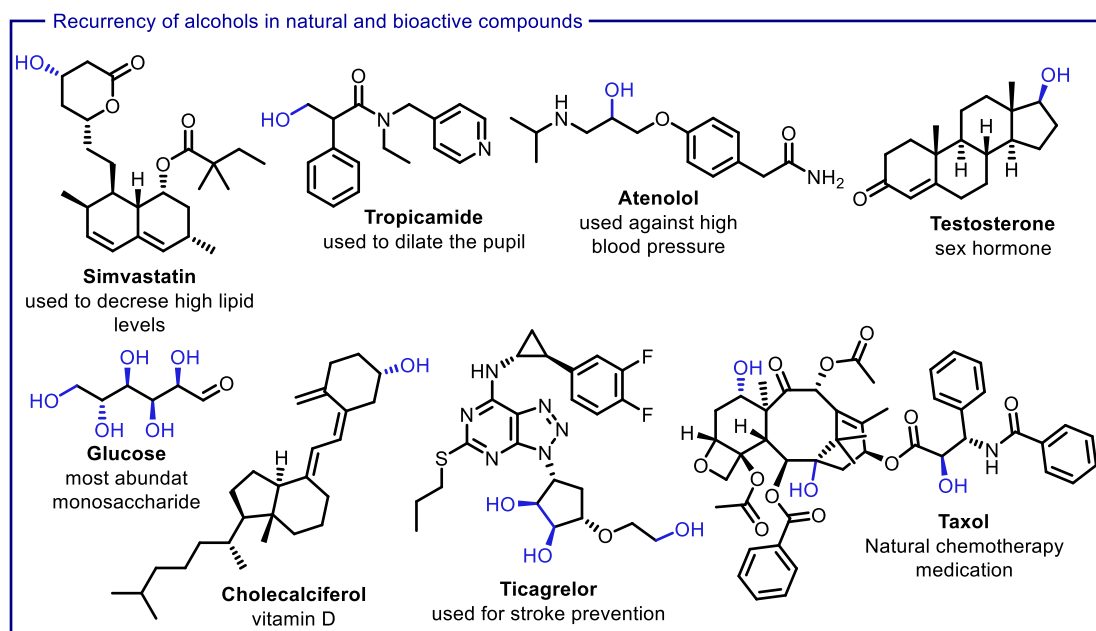


Table 3.1: Examples of natural and bioactive compounds containing a hydroxyl functionality.

3.2. State of the Art: Alcohols in radical chemistry

The hydroxyl group is the most recurrent functionality present in natural products,¹ largely defining chemical, physical and biological properties.² However, while being widely diffused in bioactive natural products, this functionality is comparatively less

¹ Ertl, P.; Schuhmann, T. *J. Nat. Prod.* **2019**, *82*, 1258–1263.

² Bissantz, C.; Kuhn, B.; Stahl, M. *J. Med. Chem.* **2010**, *53*, 5061–5084.

present in the structure of synthetic drugs (Figure 3.1³).⁴ Therefore, several groups have been developing strategies to perform late-stage functionalisation of complex alcohols, with the aim of accessing novel structures with potential applications in medicinal chemistry. In the paragraphs below, selected relevant strategies for the structural modification of alcohol substrates are briefly discussed.

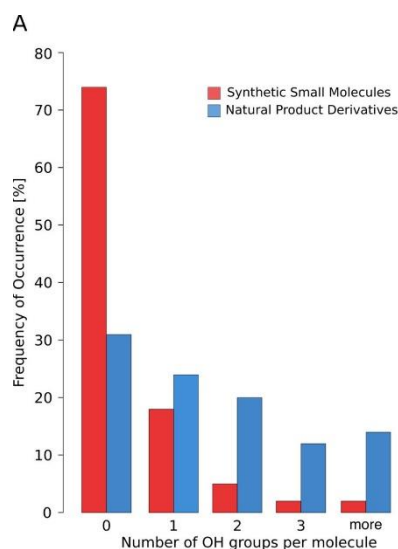


Figure 3.1:³ Frequency of occurrence of the hydroxyl group in small bioactive molecules (red) and natural product derivatives (light blue).

3.2.1. Selective Hydrogen Atom Transfer

Hydrogen Atom Transfer is a highly useful process in LSF as 1) a C-H bond is directly converted into a C-R, with the highest degree of atom economy; 2) any directing functionalities – which control the selectivity of the process – are preserved throughout the reaction, keeping intact groups that may be essential to preserve relevant chemical and physical properties of the initial scaffold. However, as the abstraction occurs on hydrogens – ubiquitous atom in organic compounds – controlling the selectivity of the process is challenging. To address this issue, several selective HAT protocols have been developed.

α C-H of alcohols usually possess a higher BDE compared to other typical functionalities present in organic molecules (Figure 3.2).⁵ However, several research

³ Reprinted (adapted) with permission from {Cramer, J.; Sager, C. P.; Ernst, B. *J. Med. Chem.* **2019**, 62, 8915–8930}. Copyright {2019} American Chemical Society.

⁴ a) Stratton, C. F.; Newman, D. J.; Tan, D. S. *Bioorg. Med. Chem. Lett.* **2015**, 25, 4802–4807 b) Brown, D. G.; Wobst, H. J. *J. Med. Chem.* **2021**, 64, 2312–2338. c) Bhutani, P.; Joshi, G.; Raja, N.; Bachhav, N.; Rajanna, P. K.; Bhutani, H.; Paul, A. T.; Kumar, R. *J. Med. Chem.* **2021**, 64, 2339–2381.

⁵ a) Bordwell, F. G.; Harrelson Jr, J. A. *Can. J. Chem.* **1990**, 68, 1714–1718. b) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, 36, 255–263. c) Laarhoven, L. J. J.; Mulder, P.; Wayner, D. D. M. *Acc. Chem. Res.* **1999**, 32, 342–349 d) Wayner, D. D. M.; Clark, K. B.; Rauk, A.; Yu, D.; Armstrong, D. A. *J. Am. Chem. Soc.* **1997**, 119, 8925–8932.

groups have exploited the oxo-anionic effect⁶ to use alcohol functionalities as directing groups in HAT processes.

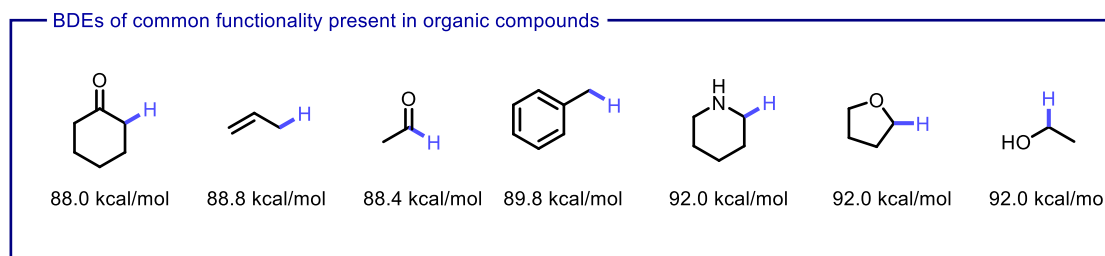


Figure 3.2: BDEs of common functionality present in organic compounds.⁵

This take advantage on the connection between the BDE of α C-H of alcohol and the electron density around the oxygen atom of the hydroxyl functionality. Higher electronic population destabilises the oxygen lone pairs which, therefore, tends to delocalize back to the α -carbon, leading to a weak three-electron bond which consequently reduces the BDE of the α C-Hs. Enhancing the electron density on the oxygen atom can be achieved in different ways – e.g., hydrogen bond formation or Lewis acid-assisted deprotonation to form a metal alkoxide. As the metal usually possesses a lower electronegativity than the hydrogen, the oxygen experiences an increased electron density. Computational calculations estimated that the oxo-anionic effect can decrease the BDE of C-H in α -position to hydroxyl groups by up to 18 kcal/mol.

3.2.2. The oxo-anionic effect in photoredox C-H functionalisation of alcohols

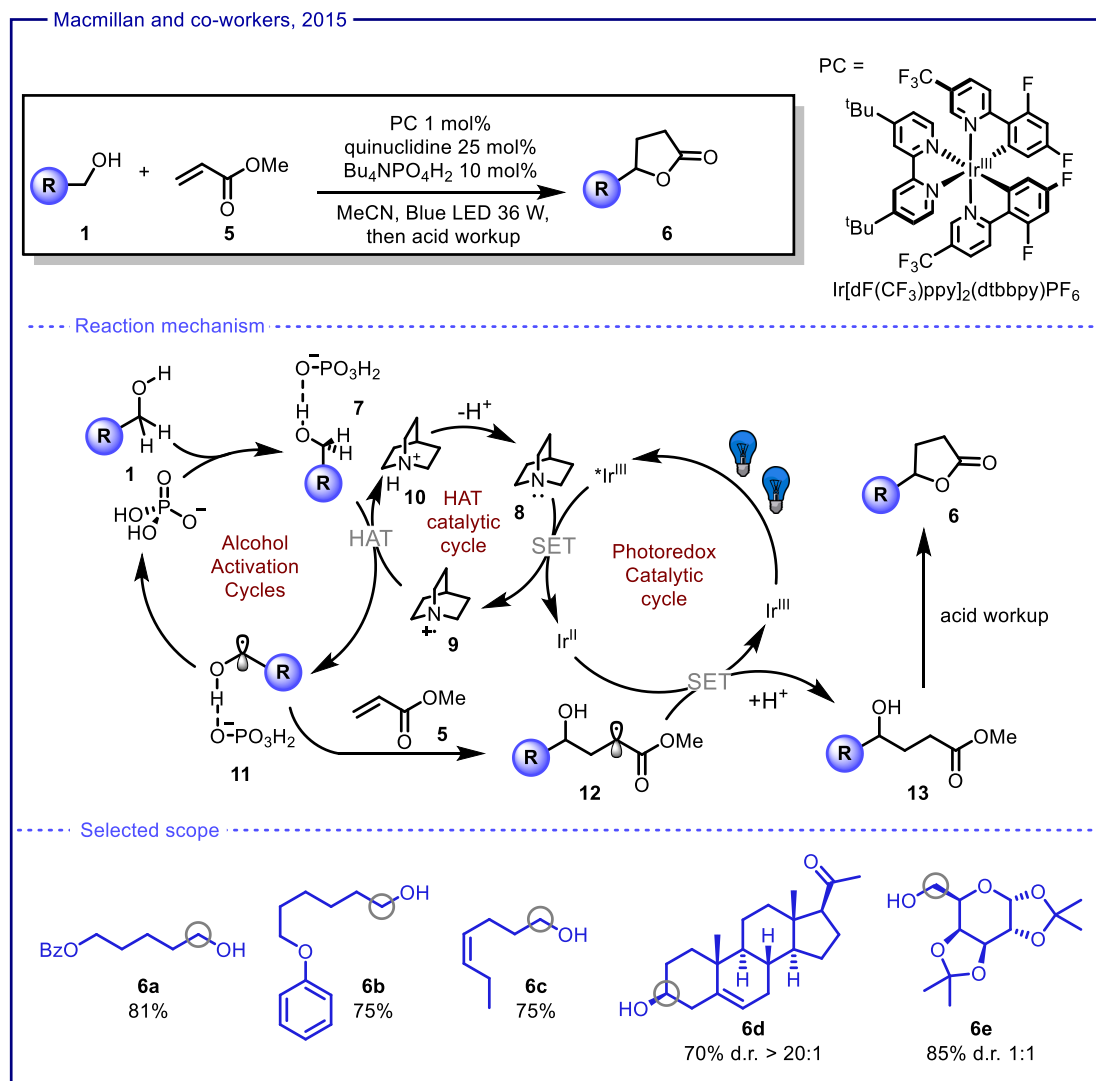
H-bonding directed C-H functionalisation of alcohols

In 2015, the group of MacMillan *et al.*⁷ demonstrated that radicals can be selectively generated in α -position to alcohols **1** via H-bonding directed HAT. The corresponding radicals undergo Giese-type addition to acrylates **5** to give lactones **6** (Scheme 3.1). Catalytic $\text{Bu}_4\text{NPO}_4\text{H}_2$ was used to direct the selectivity of the process by establishing an H-bond with the alcohol substrate **1**. The proposed mechanism involves photoexcitation of an iridium-based photocatalyst (Ir^{III}) to generate $^*\text{Ir}^{\text{III}}$. This highly oxidative electronically excited species undergoes SET with the quinuclidine **8**, to generate quinuclidinium radical cation **9**. The latter is prone to abstract the weakened α C-H to alcohol in complex **7**. As a result, both radicals **11** and quinuclidinium **10** are generated. Deprotonation of **10** reform quinuclidine HAT catalyst **8**, while the nucleophilic radical **11** undergoes Giese addition to the electron-poor acrylate **5** to give **12**. The latter is finally reduced by the reduced photocatalyst Ir^{II} and protonated to give adduct **13** which undergoes *in-situ* lactonization to yield compound **6**.

⁶ Steigerwald, M. L.; Goddard, W. A. I. I.; Evans, D. A. *J. Am. Chem. Soc.* **1979**, *101*, 1994–1997.

⁷ Jeffrey, J. L.; Terrett, J. A.; MacMillan, D. W. C. *Science*. **2015**, *349*, 1532–1536.

The protocol enables the selective HAT of alcohols in the presence of a variety of other functionalities bearing weak C-H bonds. Ether-containing substrates **6a** and **6b** can be functionalised with high regioselectivity leading to the corresponding lactone products in respectively 81% and 75% yield. Similarly, alcohol **6c**, bearing particularly weak allylic hydrogens, is selectively functionalised in the desired alcohol α -position. Remarkably, the authors demonstrated the protocol application in the functionalisation of complex molecules i.e., pregnenolone **6d** and protected sugar **6e**, decorated with a variety of acetal functional groups.



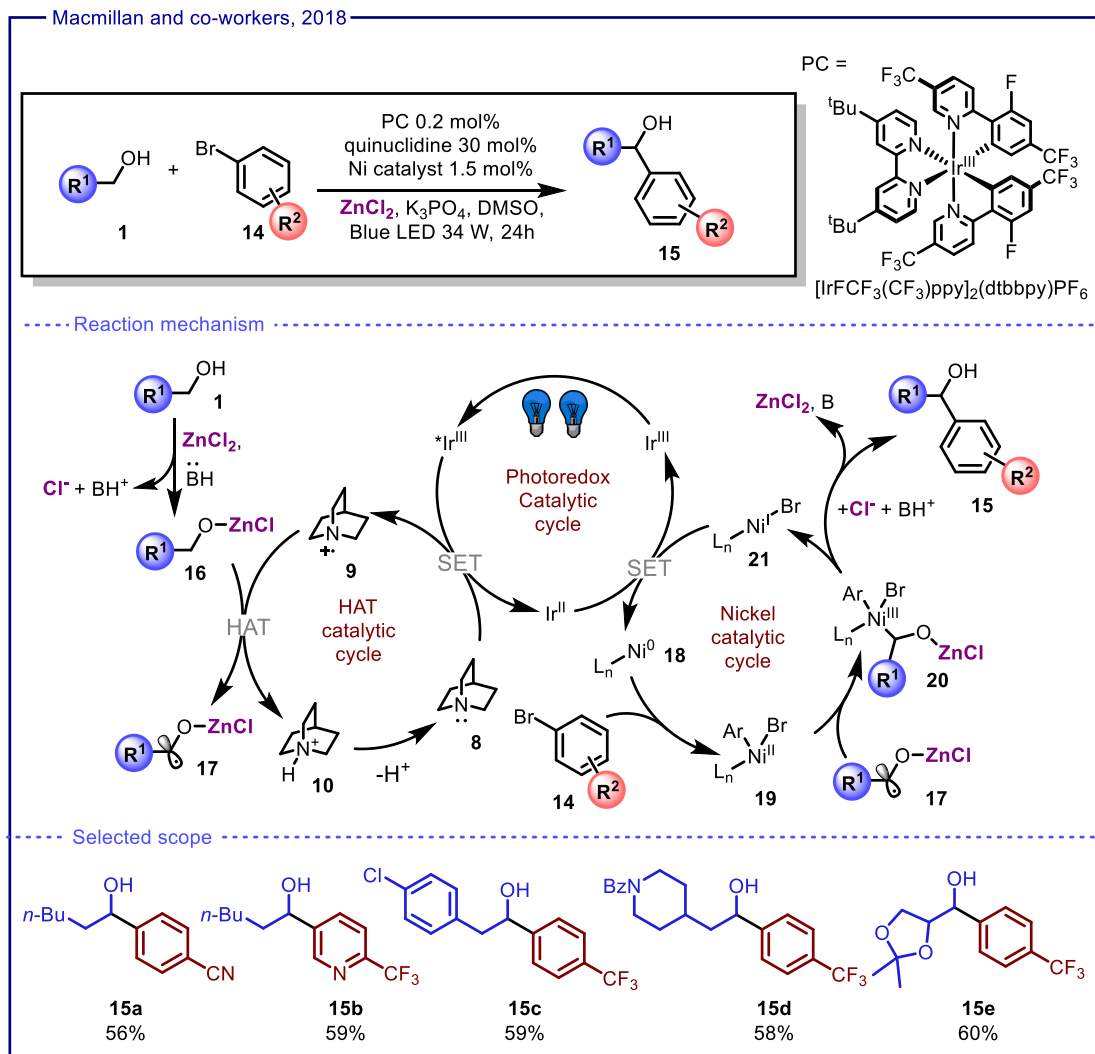
Scheme 3.1: MacMillan, 2015. The methodology allows the selective HAT on α -CH of alcohols.⁷

Metal alkoxide-directed C-H functionalisation of alcohols

A few years later, the same group expanded the synthetic application of the selective radical C-H functionalisation of alcohols in the context of nickel-catalysed cross-coupling chemistry.⁸ In this report, the Lewis acid-assisted deprotonation to form a metal alkoxide was used in place of the formation of a hydrogen bond. The transient

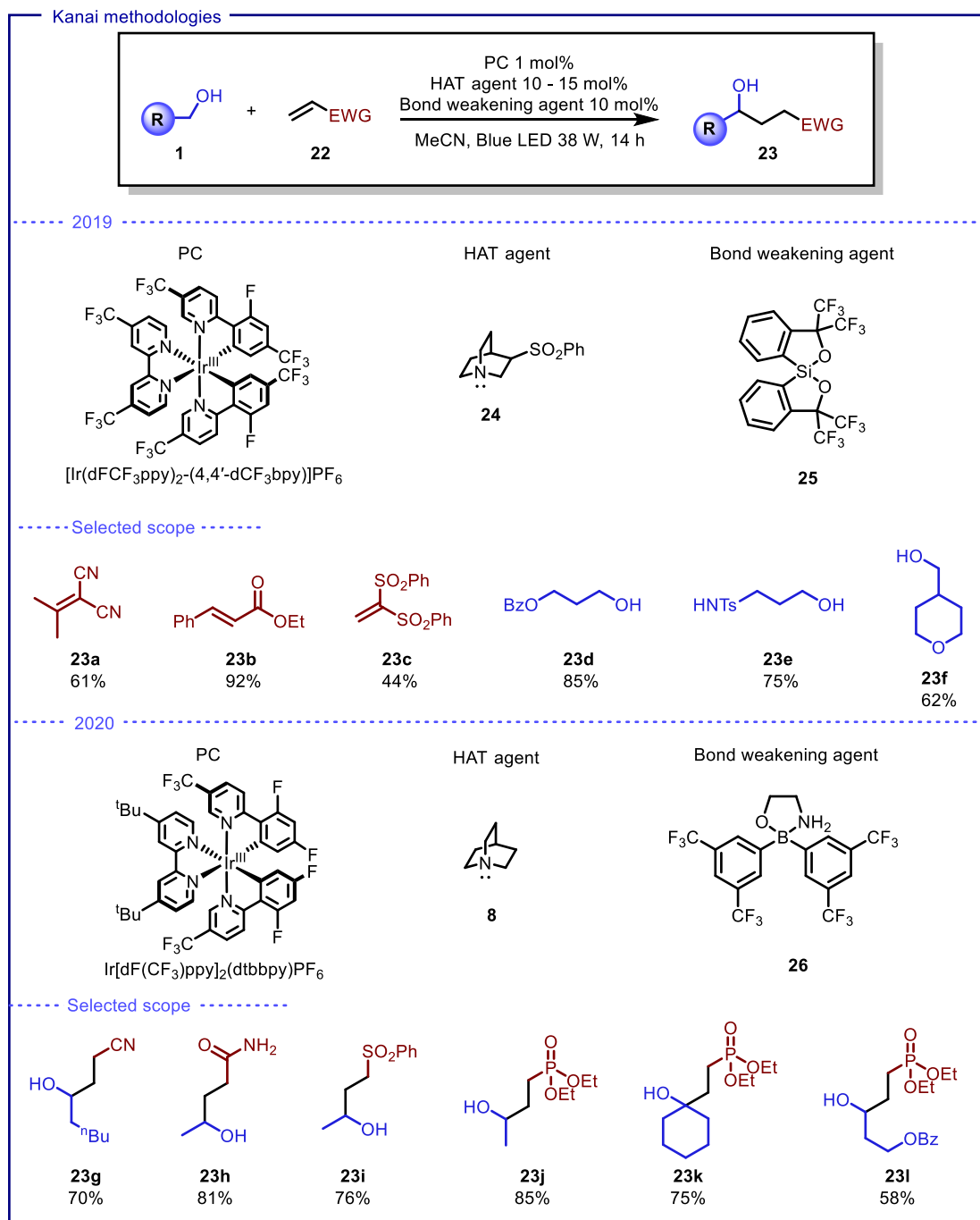
⁸ Twilton, J.; Christensen, M.; DiRocco, D. A.; Ruck, R. T.; Davies, I. W.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2018**, 57, 5369–5373.

metal alkoxide **16** possesses a lowered BDE of the α -C-H to the oxygen, a key step to achieve selective HAT in α -position to the alcohol group.



Scheme 3.2: Application of the selective HAT on α CH of alcohol on a Ni cross-coupling procedure.⁸

The mechanistic manifold, analogous to the one shown in Scheme 3.1 before, is presented in Scheme 3.2. Zinc chloride promotes deprotonation of alcohol **1** leading to intermediate **16**. The corresponding metal alkoxide undergoes selective HAT with the quinuclidinium radical **9**, to afford radical **17**. At the same time, Ni^0 complex **18** undergoes oxidative addition to the bromide **14** leading to nickel (II) complex **19**, which promptly intercepts radical **17** affording the highly oxidised Ni^{III} species **20**. Reductive elimination affords the final compound **15** and Ni^{I} complex **21**, which undergo SET with the reduced photocatalyst (Ir^{II}) to close the metal-based catalytic cycles. A variety of alcohols underwent the expected reactivity with high selectivity in the presence of other functionalities such as protected amines **15d** or acetals **15e**. However, the application of the methodology was not demonstrated on complex substrates, suggesting possible scope limitations.

Scheme 3.3: Kanai methodologies for selective HAT on αCH of alcohols.^{9,10}

Other bond-weakening agents for HAT on $\alpha\text{C-H}$ to alcohols

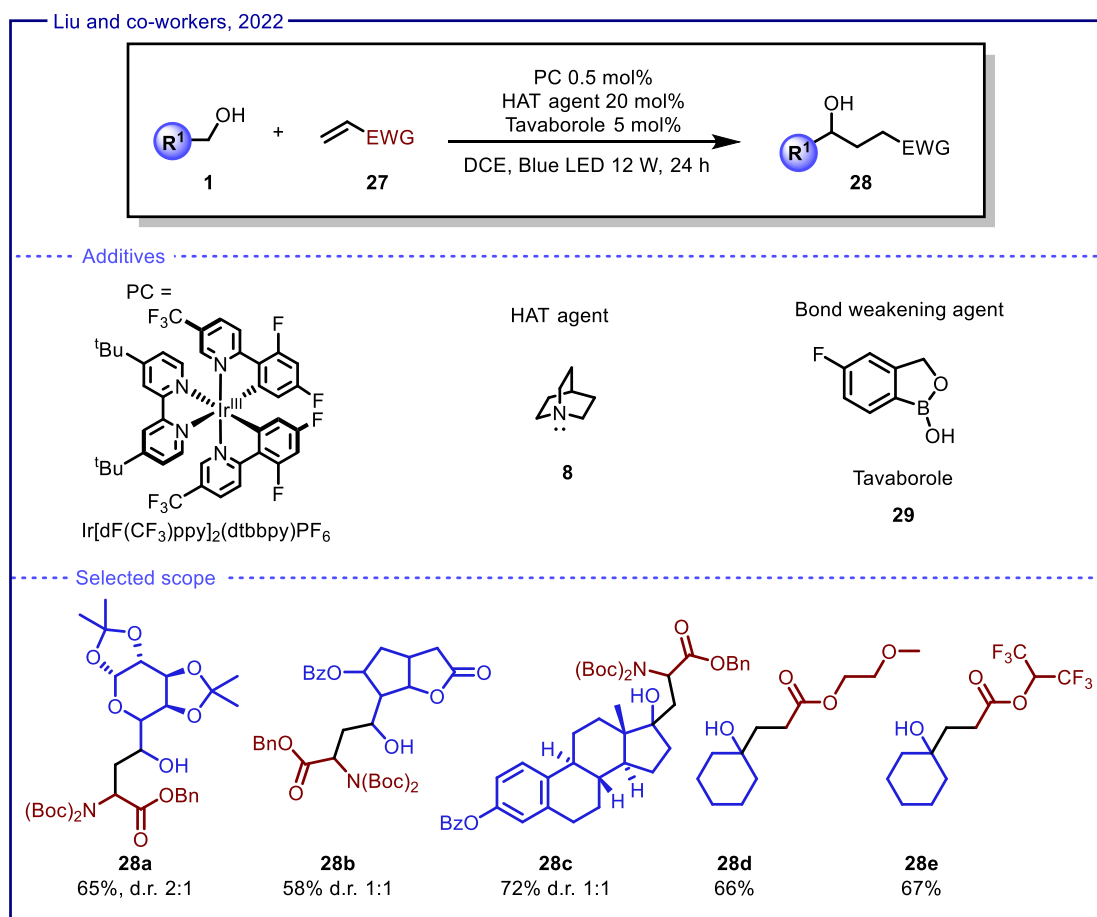
Several other groups followed the lead of MacMillan in this area, proposing many other bond-weakening agents to access selectively the $\alpha\text{C-H}$ to alcohols. The Kanai group in 2019⁹ proposed to use the strong oxophilic property of silanes **25** to form a pentavalent silicate species with the hydroxyl functionality of substrate **1** (Scheme 3.3, top). Thanks to the oxoanionic effect described before, this species presents reduced BDE on the $\alpha\text{C-H}$ to alcohol (calculated by DFT to be about 2 to 3 kcal/mol). This revised catalytic system, compared to

⁹ Sakai, K.; Oisaki, K.; Kanai, M. *Adv. Synth. Catal.* **2020**, 362, 337–343.

the original MacMillan procedure,⁷ allowed an extended scope. Highly activated Giese acceptors e.g., dicyanoethylene **23a**, acrylates **23b** and bis(phenylsulfone)ethylene **23c** readily participate in the reactivity. One year later, the same research group reported a second-generation bond-weakening boron-based reagent **26** (Scheme 3.3, bottom),¹⁰ which allowed enhanced reduction of the BDE of the α C-H to oxygen (4 to 5 kcal/mol).

Notwithstanding the precedent breakthroughs, significant challenges still remain. Precedent procedures mainly focus on the activation of primary alcohols, and display little applicability in structurally complex substrates.

A broader applicability of the oxo-anionic activation for the functionalisation of complex molecules was demonstrated by the group of Liu in 2022.¹¹ In this report, tavorole **29** was used as a bond-weakening reagent. This revised catalytic system allowed more extended applicability of the alcohol activation and enabled LSF examples of carbohydrate derivatives **28a** and **28b** steroids **28c**.



Scheme 3.4: Liu methodology for selective HAT on α CH of alcohols.¹¹

¹⁰ Sakai K.; Oisaki, K.; Kanai, M. *Synth.* **2020**, 52, 2171–2189.

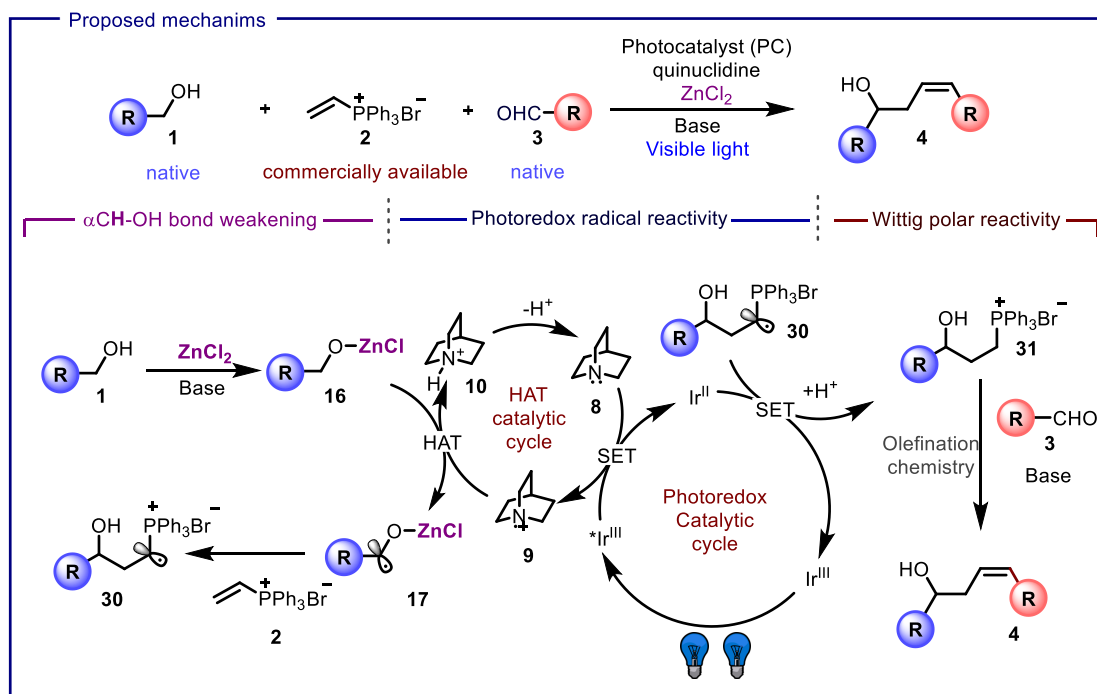
¹¹ Sun, T.; Jin, R.; Yang, Y.; Jia, Y.; Hu, S.; Jin, Y.; Wang, Q.; Li, Z.; Zhang, Y.; Wu, J.; Jiang, Y.; Lv, X.; Liu, S. *Org. Lett.* **2022**, 24, 7637–7642.

3.3. Aim of the project

Delighted by the generality of the conjunctive olefination described in Chapter 2, we envisioned to extend the applicability of this chemistry towards the selective α C-H functionalisation of alcohol substrates. Inspired by the catalytic manifolds discussed in the introductory section, we envisaged a conjunctive olefination coupling between alcohols **1** and aldehydes **3**. Such a versatile process is expected to significantly extend the organic chemist toolbox to perform the late-stage functionalisation of native complex molecules.

Design of the process

Inspired by the oxo-anionic activation originally described by MacMillan *et al.*,⁸ we designed the catalytic manifold depicted in Scheme 3.5.



Scheme 3.5: Reaction design.

Upon visible light irradiation, $^*\text{Ir}^{\text{III}}$ is generated in solution. This oxidative species undergoes SET with quinuclidine **8**, generating quinuclidinium radical cation **9**. This species is prone to abstract the weakened α C-H of alcohol substrate in complex **16** to give radical **17**. The latter promptly adds to the pendant alkene within vinyl phosphonium bromide **2**, giving radical cation **30**. Reduction of this species by the Ir^{II} , and subsequent protonation, leads to the formation of phosphonium **31** which, in the presence of aldehyde **3** and an inorganic base, rapidly undergoes Wittig olefination chemistry, to give alkene **4**.

3.4. Result and Discussion

3.4.1. Optimisation studies

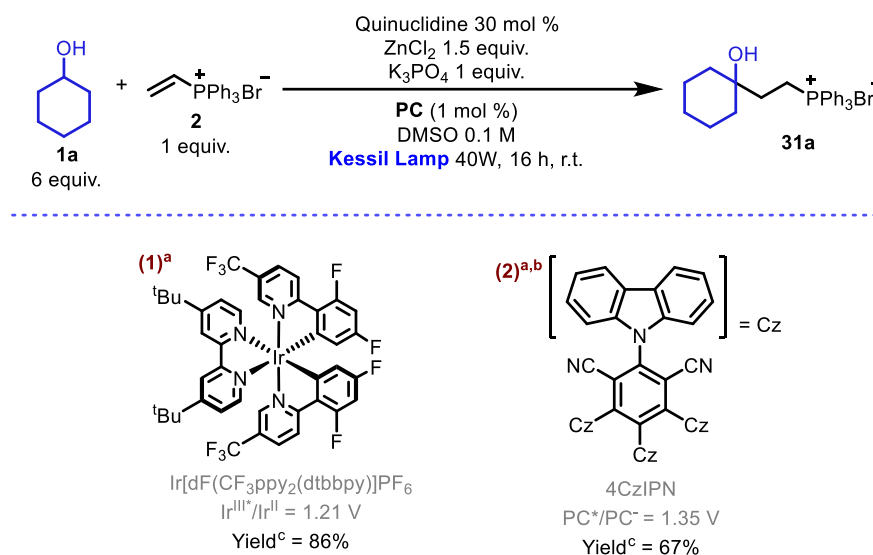
In accordance with the process design depicted above, as a result of the radical reactivity, the generation of phosphonium salt **31** was expected, followed by a Wittig olefination. Thus, in analogy with the studies presented in Chapter 2, the following optimisation studies were performed by investigating the two individual substeps (photoredox radical reactivity and Wittig reactivity), which were finally used to extrapolate final conditions for a telescoped process.

Investigation of the radical reactivity

Photocatalyst screening

The optimisation commenced by performing the reaction in Table 3.2, investigating the effect of different photocatalyst structures on the efficiency of the process.

Table 3.2: Photocatalyst screening.



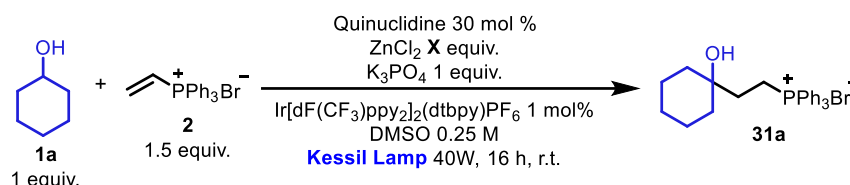
^a Reactions performed in 0.05 mmol scale, $[\mathbf{1a}]_0 = 0.1 \text{ M}$. ^b Photocatalyst loading 5 mol%. ^c ³¹P-NMR yield using ethyl triphenylphosphonium bromide as internal standard.

Although organic photocatalysts could also be used (entry 2), optimal yields were observed using the iridium complex depicted in entry 1. Further studies were not conducted, due to the high yields obtained and the information available in the literature for analogous processes.

ZnCl₂ loading

In related photocatalysed HAT reactions, a typical drawback is the use of large excesses of alcohol substrates.^{8–11} In view of applying our methodology for late-stage functionalisation, we focused on identifying reaction conditions allowing to use alcohol

1a as the limiting reagent. In this regard, the stoichiometry was reversed to 1 equivalent, investigating various ZnCl_2 loadings to maximise the yield of the process (Table 3.3).

Table 3.3: Loading of ZnCl_2 

Entry ^a	ZnCl_2 loading (equiv.)	Yield 31a (%) ^b
1	0.75	40
2	1.5	78
3	2.25	91

^a Reactions performed in 0.05 mmol scale, $[\mathbf{1a}]_0 = 0.1\text{M}$. ^b ^{31}P -NMR yield using ethyl triphenylphosphonium bromide as internal standard.

A clear correlation between ZnCl_2 loading and reaction yield was observed, with 2.25 equivalents providing optimal results (entry 3). Further fine optimisation studies (not presented for brevity), allowed us to identify 0.5 M as the ideal concentration for the photochemical step.

Investigation of the polar reactivity

In order to investigate the impact of standard parameters on the Wittig reactivity, a model phosphonium **31b** was synthesised (see general experimental for details). The optimisation below was conducted predicting analogous chemical behaviour of model system **31b** compared to intermediate **31** presented in the reaction design depicted in section 3.3.

Temperature optimisation

We commenced our studies by investigating the effect of the reaction temperature on the yield of the process (Table 3.4).

Table 3.4: Temperature screening.

Entry ^a	Temperature (°C)	Z/E	Yield 4b (%) ^b
1	r.t.	1:1	8
2	60	1.5:1	30
3	90	2.6:1	44

^a Reactions performed in 0.05 mmol scale, $[\mathbf{31a}]_0 = 0.1$. ^b ^1H -NMR yield using CH_2Br_2 as internal standard.

Running the reaction at room temperature (entry 1), compound **4b** was obtained in poor yield. Increasing the temperature to 60°C (entry 2) or 90°C (entry 3), a general improvement of the reaction yield was observed (entries 2 and 3).

To give some insights into the effect of the temperature on the yields observed, a ^{31}P -NMR study of the crude reaction mixture was conducted (Figure 1.1). At room temperature (bottom), four distinct species were identified: starting material **31b** (25.3 ppm); phosphinoyl **32** ($\delta=34.26$ ppm, resulting from undesired hydrolysis of **31b**, (resulted from carrying these experiments in non-anhydrous condition) triphenylphosphine oxide **33** ($\delta=29.06$ ppm), and oxophospholane ring **34** ($\delta= -53.67$ ppm).

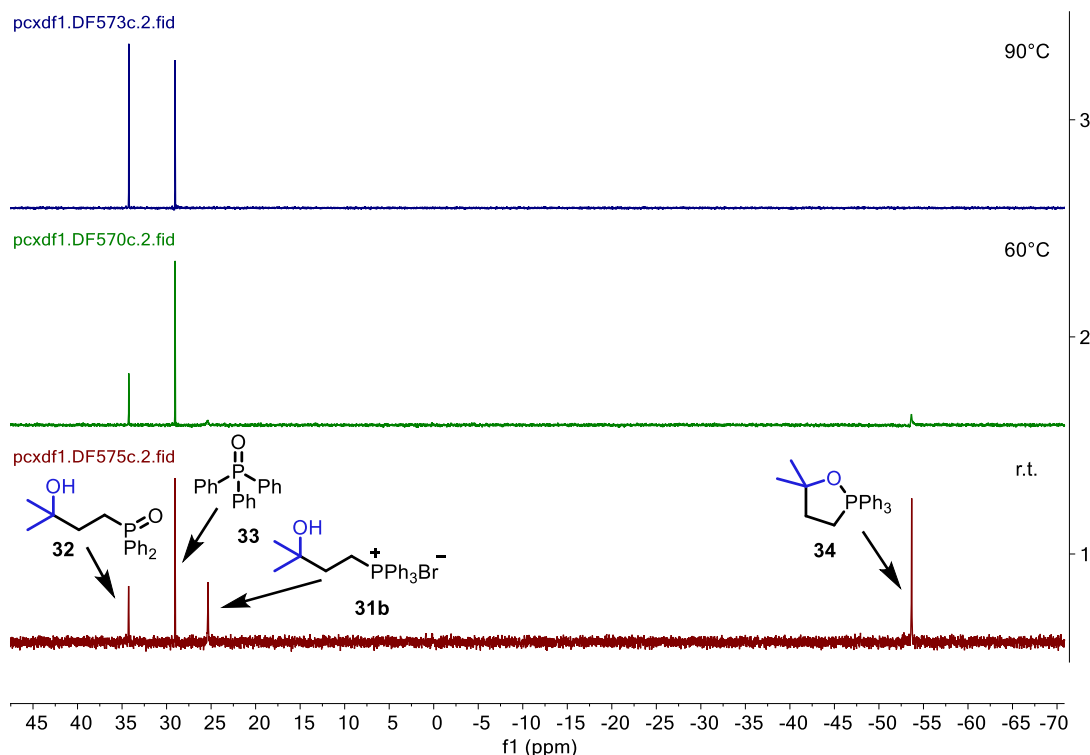
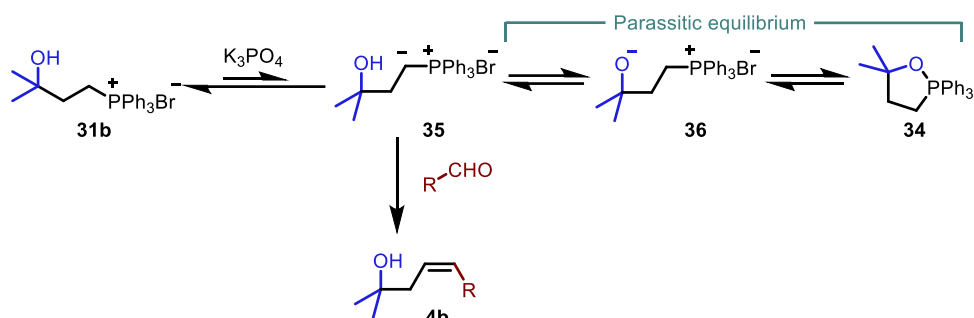


Figure 3.3: ^{31}P -NMRs of the crude reaction mixture. The structure of **32** was confirmed by chromatography purification. The identity of **34** was confirmed by comparison with the known ^{31}P -NMR chemical shift.¹²

The presence of oxophospholane **34** in the experiments at room temperature and at 60°C was rationalised to be the result of a parasitic equilibrium resulting from alkoxide cyclisation on the phosphorus atom to form a relatively unreactive hexavalent P-species (Scheme 3.6).¹³ However, its absence in the reaction performed at 90 °C, together with the improved yield observed (Table 3.4, entry 3), suggests that the conversion of parasitic species **34** to the desired ylide **35** can be promoted by increasing the reaction temperature.

¹² Bestmann H. J.; Riemer C.; Dötzer R.; *Chem. Ber.*, **1992**, 125, 225–229.

¹³ Würtenberger, I.; Angermaier, B.; Kircher, B.; Gust, R. *J. Med. Chem.* **2013**, 56, 7951–7964.



Scheme 3.6: Rationalisation of the slow kinetic observed. The presence of the parasitic equilibrium which forms the oxaphospholane **34** reduces the availability of ylide **35** to participate in the Wittig olefination.

Solvent and base screening

In order to maximise the yield and the stereoselectivity of the reaction, a screening of solvents and bases was performed (Table 3.5).

Table 3.5: Solvent and base screening.

Entry ^a	Solvent	Base	Z:E ^b	Yield 4b (%) ^b
1	DMF	K ₃ PO ₄	1:1	88
2	DCM	K ₃ PO ₄	1:2.5	74
3	THF	K₃PO₄	2.7:1	44
4	THF	K₂CO₃	2.1:1	71
5	ⁱ PrOH	K ₂ CO ₃	1:13	93
6	^t BuOH	K ₂ CO ₃	1:6.7	91
7	EtOH	K ₂ CO ₃	1:13	73

^a Reactions performed in 0.05 mmol scale, [**31b**]₀ = 0.1M. ^b ¹H-NMR yield using CH₂Br₂ as internal standard. The rest of the mass balance has to be accounted for either starting material **31b** left or the hydrolysis product

32. ^c Entries performed using 3 equivalents of K₃PO₄.

The effect of different reaction media was investigated using K₃PO₄ as a base. DMF in entry 1 gave excellent yield but poor *E/Z* selectivity. The use of dichloromethane or tetrahydrofuran did not significantly improve the selectivity of the process, and product **4b** was obtained in reduced yields (entries 2 and 3). We observed that the yield of the process could be improved by using K₂CO₃ in place of K₃PO₄ (entry 4). Remarkably, using alcohols as solvents gave an unexpected selectivity for the *E* isomer (entries 5, 6, and 7). In particular, the use of isopropanol (entry 5) led to optimal results, giving both excellent yield and *E/Z* selectivity.

Rationalisation of the anomalous selectivity of the Wittig reaction in alcohol solvents

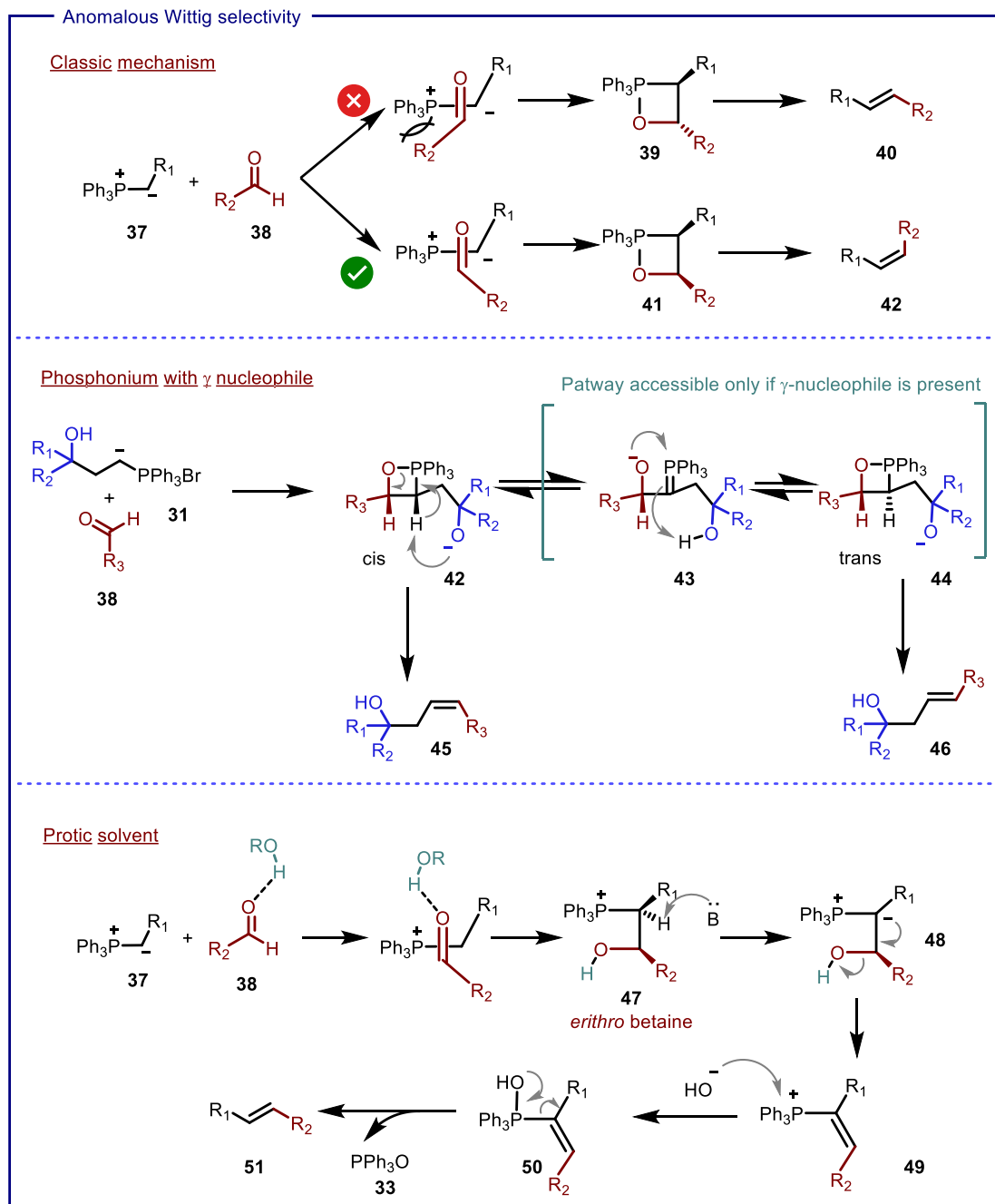
Two main factors were observed to influence the stereoselectivity of the Wittig olefination reaction studied: the presence of a γ O-nucleophile within the structure of phosphonium **31** and the use of polar protic solvents. In the section below, both effects are briefly discussed, to rationalise the stereochemical outcome of the reaction.

Rationalisation of the poor selectivity obtained under standard solvent systems

It is known that γ -alkoxide ylides tend to give anomalous stereoselectivity.¹⁴ In previous literature, ³¹P-NMR studies of oxaphosphetane intermediates formed from the reaction of γ -alkoxy ylides and aldehydes at -55°C were described. These studies showed the initial formation of an unselective mixture of *cis* and *trans* oxaphosphetanes which slowly converge to a common *trans* oxaphosphetane species after only 30 min. The undesired equilibration leads to reduced *E/Z* selectivity of the overall olefination process, as oxetane decomposition is known to be stereospecific. The rationale behind the oxetane equilibration is presented below.

In a classic Wittig reaction, when ylide **37** approaches the aldehyde **38**, the carbonyl and the P-CH⁻ bonds are at about 90° to each other (Scheme 3.7, top). To reduce the repulsion between the R₂ group of aldehyde **38** and the bulky phenyl groups, the ylide **37** prefers to attack the aldehyde from the side where the phenyl and R₂ groups point in different directions leading, irreversibly, to the *cis* oxaphosphetane **41** that consequentially leads irreversibly to the alkene **42** with *Z* configuration. However, with γ -alkoxy ylides **31**, the nucleophile centre can deprotonate the acidic proton in α -position to the phosphorous atom of oxaphosphetane **42** – through a 5-membered-ring transition state – opening the oxetane ring to form ylide **43**. Since this process is reversible, back proton transfer can occur giving *trans* oxetane **44**. Thus, in contrast to standard Wittig reactivity – typically under exclusive kinetic control – a partial thermodynamic equilibration of the oxaphosphetane intermediates is possible, affecting the observed stereoselectivity of the process (Scheme 3.7, middle).

¹⁴ a) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 790–792. b) Kozikowski, A. P.; Ishida, H.; Chen, Y.Y. *J. Org. Chem.* **1980**, *45*, 3350–3352. c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.



Scheme 3.7: Rationalisation of the anomalous stereoselectivity observed in the Wittig step. Top: Mechanism of the classic Wittig olefination. Middle: Wittig olefination in the presence of a γ -nucleophile on the phosphonium ylide **31**. Intramolecular nucleophiles can open oxaphosphetane **42**, which can reversibly close to form oxaphosphetane **44** that led to *trans* olefine **46**. Bottom: Wittig mechanism in the presence of a protic solvent. In this condition, the oxygen of the aldehyde **38** is not available to form oxaphosphetane but to form betaine **47** which, after a series of steps, gives *E* alkene **51**.

Rationalisation of the *E* selectivity obtained using protic polar media

When an alcohol solvent is used, the mechanism of the Wittig reaction is also affected (Scheme 3.7, bottom). Due to hydrogen bonding between the alcohol and the carbonyl group of the aldehyde **38**,¹⁵ the oxygen of the aldehyde is not available to form the oxaphosphetane ring and instead forms an acyclic *erithro* betaine **47**. This is then

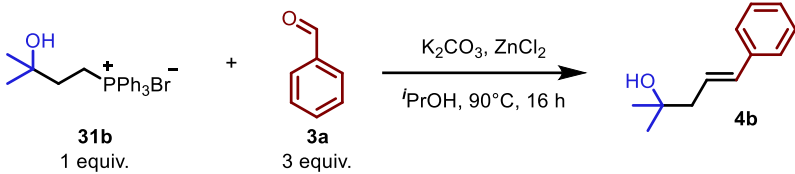
¹⁵ Aksnes, G.; Berg, T. J.; Gramstad, T. *Phosphorus. Sulfur. Silicon Relat. Elem.* **1995**, 106, 79–84.

deprotonated forming ylide **48**, where the configuration of the carbon attached to the group R_1 is lost. E1cB elimination of the HO^- group leads to the thermodynamic alkene *E*-**49**. Finally, the hydroxyl group attacks the phosphorous centre which rapidly leads to the elimination of triphenylphosphine oxide revealing the alkene **51** with *E* configuration.¹⁶

Development of the full conjunctive process

With the optimised conditions in our hands, we focused on combining the two sub-steps studies to develop a unique, telescoped, conjunctive process. Unfortunately, initial attempts to perform the two steps *in-situ* led to the final compound **4b** in poor yield. The poor reactivity observed was rationalised with an incompatibility of the Wittig olefination process with the presence of $ZnCl_2$ salt, required for the radical step. This was confirmed by performing control experiments (Table 3.6), which unambiguously showed inhibition of the Wittig reactivity in the presence of zinc chloride.

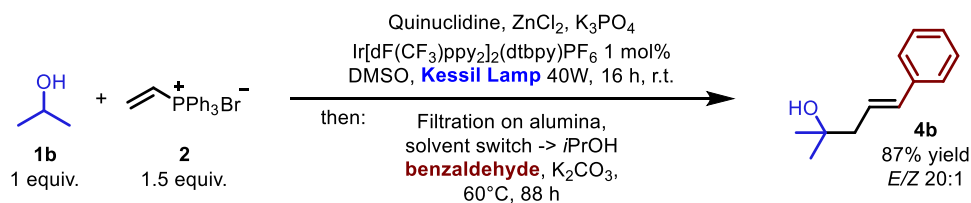
Table 3.6: Poisoning test of the Wittig step with $ZnCl_2$



Entry ^a	$ZnCl_2$ (equiv.)	Recovery 31b ^b	Yield 4b (%) ^c
1	0	0	93
2	1.5	71	20

^a Reactions performed in 0.05 mmol scale, $[31b]_0 = 0.1M$. ^b ^{31}P -NMR yield using ethyl triphenylphosphonium bromide as internal standard. ^c ^1H -NMR yield using CH_2Br_2 as internal standard.

To address this issue, after irradiation, the reaction mixture was simply passed through a plug of basic alumina (see general experimental section for details) to eliminate the zinc chloride from the reaction mixture,¹⁷ the solvent was then exchanged to isopropanol and the reaction was stirred for 88 h at 60°C leading to product **4b** in 87% yield and 19:1 *E/Z* (Scheme 3.8).



Scheme 3.8: Final reaction conditions.

With the optimal conditions in hands, we investigated the scope of the conjunctive process above.

¹⁶ Le Bigot, Y.; Elgharbi, R.; Delmas, M.; Gaset, A. *Tetrahedron* **1986**, 42, 3813–3823.

¹⁷ Cervera, L. M.; Arnal, C. M.; de la Guardia, M. *Anal. Bioanal. Chem.* **2003**, 375, 820–825.

3.4.2. Scope studies

With these results in our hands, we investigated the scope of the process. A variety of alcohols and aldehydes were submitted to our optimized conditions.

Study of model and complex alcohols

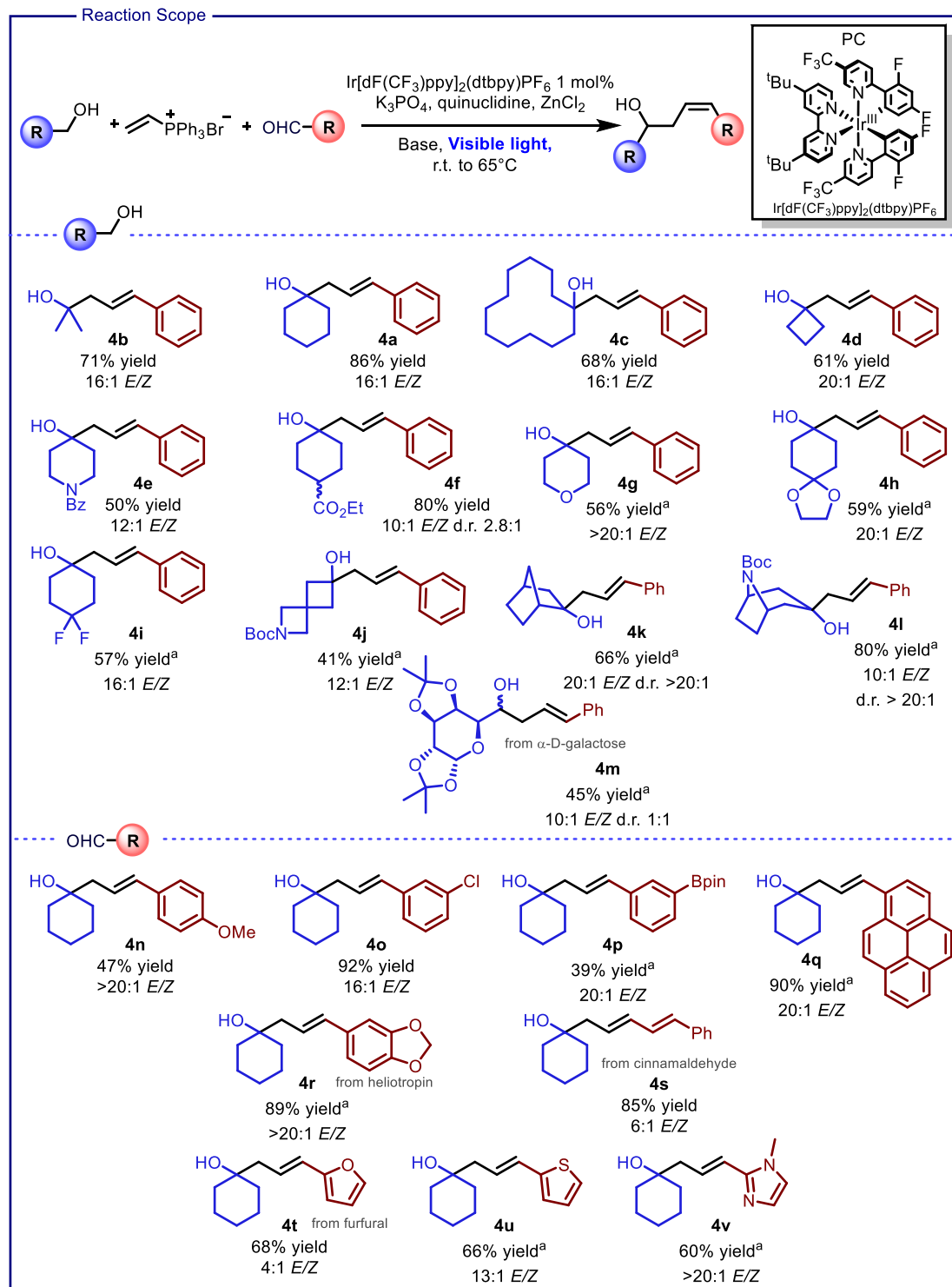
We started the scope studies by using benzaldehyde **3a** and varying the nature of the carboxylic acids used (Table 3.7).

Isopropanol, gave compound **4b** in 71% yield and excellent stereoselectivity. Medium and large cyclic carbinols underwent the desired reactivity giving respectively compounds **4a** and **4c** good yield and selectivity. Strained 4-membered ring alcohol smoothly reacted giving compound **4d** in good yield and excellent stereoselectivity. Alcohols bearing several functionalities which may present HAT selectivity issues i.e., protected amines, esters, ethers and acetals underwent the desired reactivity with good yield and excellent selectivity (**4e** to **4h**). In particular, alcohol bearing other Lewis basic functionalities (**4e** and **4f**) i.e., benzoyl protecting group and ester group, underwent smoothly in the reaction condition proving the tolerability of this chemistry to the presence of other Lewis basic functionality. Fluorinated alcohols reacted smoothly under the reaction conditions affording compound **4i** in 57% and very good stereoselectivity.

A highly strained spirocycle containing 2 four-membered rings and a Boc-protected amine showed good reactivity giving compound **4j** in 41% and good stereoselectivity. Different bicyclic alcohols were successfully submitted to our reaction conditions affording compounds **4k** and **4l** respectively in 66% and 80% yield and full diastereoselectivity. Finally, a galactose derivative was subjected to our reaction condition, leading to derivative **4m** in 45% and good stereoselectivity.

C-H functionalisation of alcohols via conjunctive olefination.

Table 3.7: Reaction Scope.



Scope of alcohols and aldehydes. Reactions were carried out in a 0.2 mmol scale, yields refer to isolated material, Z:E and d.r. values were measured in crude mixtures by NMR. See general experimental section for full experimental details.^a Compound synthesised by Joseph Wallen. Boc, *N*-tert-butoxycarbonyl; Bz, benzoyl

Study of model aldehydes

We then investigated the scope of aldehyde substrates. Both electron-rich and electron-poor aromatic aldehydes successfully underwent the desired process with moderate to good yield and excellent stereoselectivity (**4n** and **4o**). Aromatic aldehyde bearing a

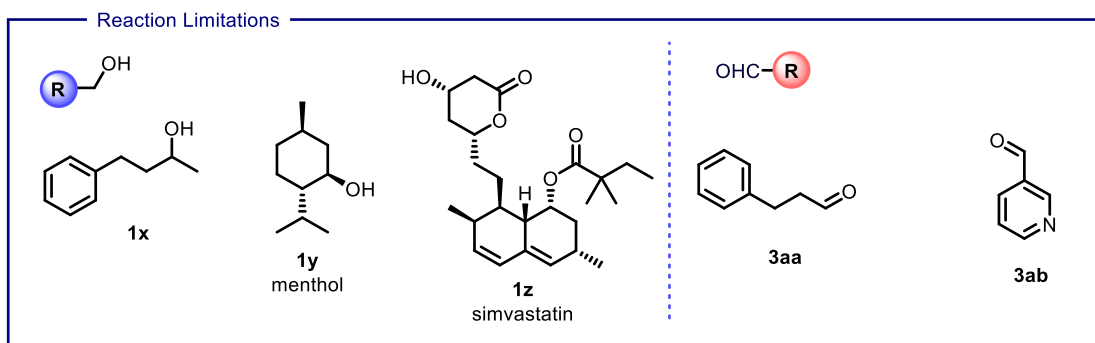
useful boronic ester handle were successfully submitted to our process giving compound **4p** in 39% yield and excellent stereoselectivity. A pyrene aromatic ring, a useful fluorophore with various practical applications, efficiently underwent in our chemistry, producing compound **4q** in excellent 90% yield and stereoselectivity. Heliotropin, a natural compound commonly found in various natural fragrances, underwent the desired reactivity giving compound **4r** in 89% yield and high stereoselectivity. Cinnamaldehyde was a competent substrate for this reaction, leading to compound **4s** in excellent 85% yield and good stereoselectivity. Finally, heteroaromatic aldehydes furfural and thiophene carboxaldehyde underwent the expected reactivity leading to compounds **4t** and **4u** in 68% and 66% yield and good to excellent stereoselectivity. Also, a methylated imidazole bearing an aldehyde group smoothly underwent our reaction, affording compound **4v** in 60% yield and excellent stereoselectivity.

3.4.3. Reaction limitations

Some classes of compounds are not competent substrates for this methodology (Table 3.8). Alcohols bearing unsubstituted benzylic positions – i.e., compound **1x** – do not lead to the desired product. This was rationalised by the presence of weak benzylic hydrogens, which may undergo undesired HAT, disrupting the catalytic cycle. Bulky terpenoids, like menthol **1y**, did not show any reactivity at all, with full recovery of the alcohols at the end of the irradiation. Likely, the demanding bulkiness of the substrate prevents the quinuclidine from abstracting the hydrogen α to the alcohol group. Complex conjugated systems, like simvastatin **1z**, were not suitable in the studied reaction, leading to full decomposition of the starting material.

Aliphatic aldehydes, like hydrocinnamaldehyde **3aa**, are not suitable reagents in this reaction. In this case, aldehyde decomposition was observed during the Wittig process, due to incompatibility with the solvent system. Other solvents were tested e.g., dioxane or *tert*-butanol but poor stereoselectivity (*E/Z* 4:1) was observed. Electron-poor heteroaromatic aldehydes like nicotinaldehyde **3ab** led to a complex mixture of products.

Table 3.8: Reaction limitations



3.5. Conclusion

In conclusion, we have developed a conjunctive olefination protocol that successfully couples together aldehydes with alcohols, through the forge of an alkene linchpin with high *E* selectivity. Alcohols and aldehydes are widely diffused in natural and bioactive compounds, hence the methodology will provide chemists with a novel mild approach for the late-functionalisation of complex molecules. Future studies will focus on the application of the reaction presented in this chapter on a wider variety of complex fragments to show the applicability of the reactivity to LSF purposes.

3.6. General experimental

3.6.1. Solvents, reagents, and starting materials

All air and water-sensitive reactions were carried out in oven-dried glassware under argon atmosphere using standard Schlenk manifold technique. The solvents were degassed when required by bubbling argon through the solvent for five minutes. Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. All solvents were commercially supplied or provided by the communal stills of the School of Chemistry, University of Nottingham. Commercially available compounds were purchased from Sigma Aldrich, Alfa Aesar, Acros, Fluorochem, TCI chemicals or STREM chemicals and used as received. Vinyl phosphonium was purchased from Sigma Aldrich (Product code 150193-25g; batch number: 0000072767) and used after single-column chromatography purification. All liquid aldehydes were distilled prior to use. Dried solvents were purchased from Acros Organic, Extra Dry over molecular sieves, AcroSeal®.

The model compound **31b**^{18, 19} and Bz-pyperidine-4-ol **1e**²⁰ were synthesised following reported procedures.

3.6.2. Chromatography and instrumental analysis

Flash column chromatography (FCC) was carried out using Sigma-Aldrich silica gel LC60A-40 (63 μm). All reactions were followed by thin-layer chromatography (TLC) when practical, using Merck Kieselgel 60 F₂₅₄ fluorescent treated silica which was visualised under UV light or by staining with aqueous basic potassium permanganate.

¹H-NMR, ¹³C-NMR and ³¹P-NMR spectra were recorded using Bruker broadband prodigy cryoprobe AV(III)500HD 500 MHz and Bruker AV(III)400HD 400 MHz spectrometers. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz). The ¹H-NMR spectra are reported as follows: ppm (multiplicity, coupling constants, number of protons). High-resolution mass spectra (HRMS) were recorded on a Bruker MicrOTOF II by Electrospray Ionisation (ESI). IR spectra were recorded on a Bruker Vertex 70 FT-IR ATR as a thin film. Only selected absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Melting points were recorded in degrees Celsius ($^{\circ}\text{C}$), using a Stuart melting point SMP 20 microscope apparatus and are reported uncorrected.

¹⁸ Schwink, L.; Stengelin, S.; Gossel, M.; Böhme, T.; Hessler, G.; Stahl, P.; Dirk Gretzke, D. *Substituted n-arylheterocycles, method for production and use thereof as medicaments*. WO2004072025A2, **2004**.

¹⁹ Fall, Y.; Vitale, C.; Mouriño, A. *Tetrahedron Lett.* **2000**, *41*, 7337–7340.

²⁰ Soullard, V.; Villa, G.; Vollmar, D. P.; Renaud, P. *J. Am. Chem. Soc.*, **2018**, *140*, 155–158.

3.6.3. Naming of compounds

Compound names are those generated by ChemDraw 19.0 software (PerkinElmer), following the IUPAC nomenclature.

3.6.4. LEDs

Kessil lamp A160WE Tuna Blue Saltwater LED Light 40W was used for irradiation of the conjunctive olefination reactions.

3.6.5. General procedures



Alcohol **1** (1.0 equiv.; 0.2 mmol), vinyl triphenyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 105 mg), Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (0.01 equiv.; 0.002 mmol; 2.2 mg), quinuclidine (0.3 equiv.; 0.06 mmol; 6.7 mg), potassium phosphate (1.5 equiv.; 0.3 mmol; 63.7 mg) and ZnCl₂ (2.25 equiv.; 61.2 mg; 0.45 mmol), were introduced into a Schlenk tube. Then 1 mL of dry DMSO (previously degassed through argon sparging for 10 min) was introduced through a syringe into the Schlenk tube. The vessel was sealed and placed in a glass-wall water bath where a fan was blowing air to keep the water temperature between 20 – 25 °C. See Figure 3.4 for visual details of the reaction setup. The reaction was irradiated through the glass wall with blue light (Kessil lamp A160WE Tuna Blue Saltwater LED Light 40W) for 24 h under moderate stirring (500 rpm). To remove the ZnCl₂, a filtration step with alumina is described as follows. See Figure 3.5 for details. The vessel was removed from the water bath (Figure 3.5A Figure 3.5B) and basic alumina powder (3.5 g, Figure 3.5C) was added to the vessel (Figure 3.5D) followed by DCM (10 mL, Figure 3.5E). The suspension was stirred for 1 minute (Figure 3.5F), then using a 5 mL syringe filled with cotton (Figure 3.5G), the aluminium oxide powder was filtered (Figure 3.5H and Figure 3.5I). The syringe with alumina and the Schlenk walls were washed (Figure 3.5J and Figure 3.5K) with a 9:1 DCM:MeOH (8 mL). The filtrate was collected and the volatiles were removed (Figure 3.5L and Figure 3.5M). The residue was then transferred quantitatively into a Schlenk tube (Figure 3.5N) using 2 mL of DCM. The Schlenk was placed into a water bath (70 °C) and nitrogen was blown to remove DCM (Figure 3.5O). The remaining DMSO (Figure 3.5P) was removed by placing the tube under high vacuum (5·10⁻² mbar) at 70 °C (Figure 3.5Q). When the distillation was complete the tube was left under high vacuum at 70 °C for 5 min (Figure 3.5R). The atmosphere was exchanged to Argon (Figure 3.5S) and the crude was submitted to the next step. Potassium carbonate (3 equiv.; 0.6 mmol, 82.92 mg) and aldehyde **3** were introduced to the Schlenk tube with 2 mL of dry

ⁱPrOH. The vessel was sealed and placed in an oil bath at 60 °C for 72 – 88 h under moderating stirring (500 rpm). The reaction mixture was filtered through a thin layer of celite and eluted with DCM. Volatiles were evaporated under reduced pressure, and the residue was subjected to chromatography purification on silica gel to afford final compounds **4**.

3.6.6. Reaction set-up and procedures

This set-up is a modified version of the water-cooled set-up originally reported by MacMillan *et al.*¹¹ Throughout the irradiation, the temperature of the water was monitored with a thermometer to ensure temperature control.

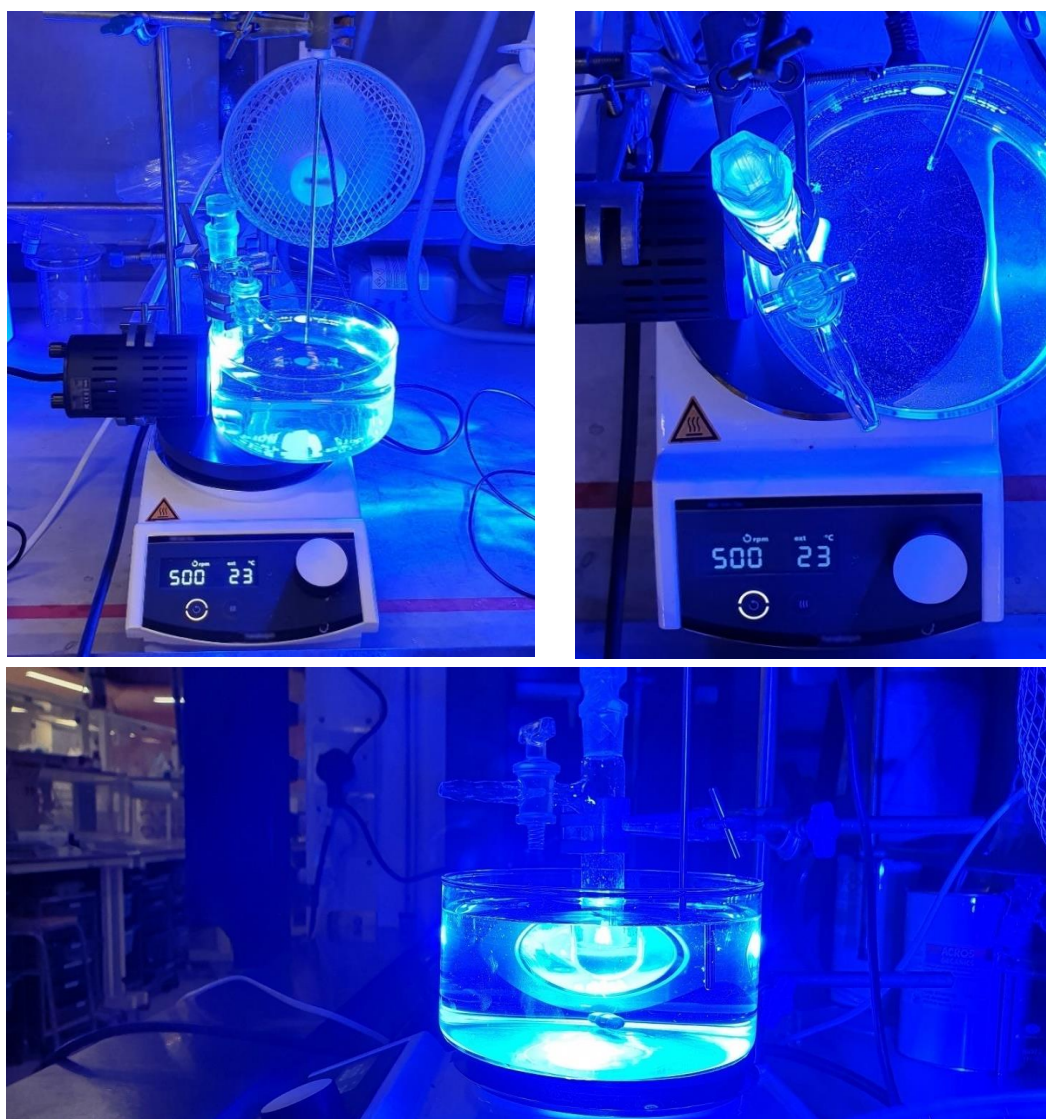
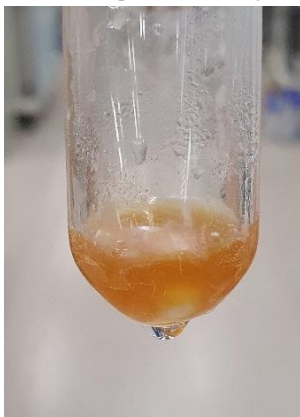


Figure 3.4: Visual details of the photochemical reaction set-up: front, top, and lateral views.

C-H functionalisation of alcohols via conjunctive olefination.

A: after photochemistry



B: preparation of a funnel



C: weighting 3.5 g of alumina



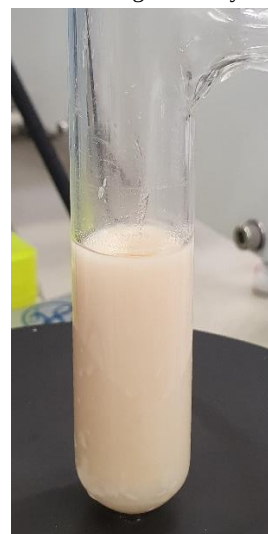
D: addition of alumina



E: addition of 10 mL DCM



F: mixing the slurry



G: preparation of the filter



H: filtering of alumina



I: completing the filtration



C-H functionalisation of alcohols via conjunctive olefination.

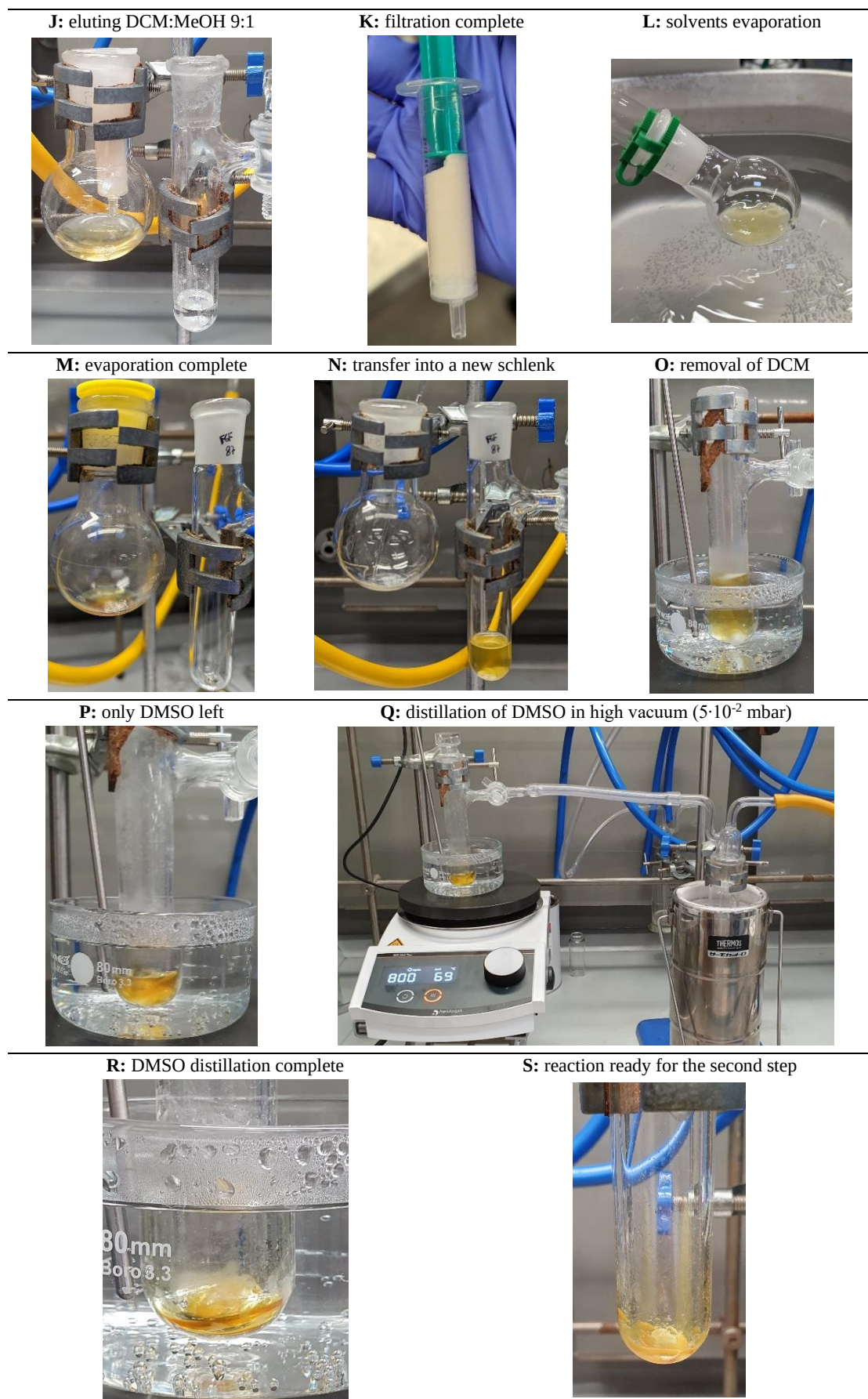
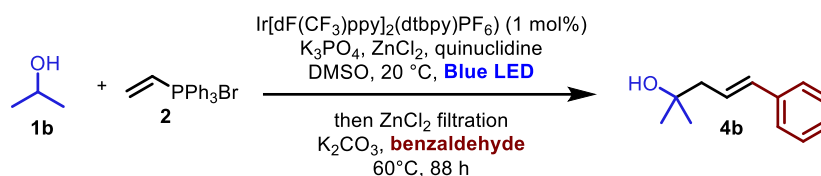


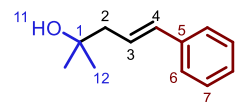
Figure 3.5: Visual details for the ZnCl_2 removal procedure.

3.6.7. Reaction products and characterisation

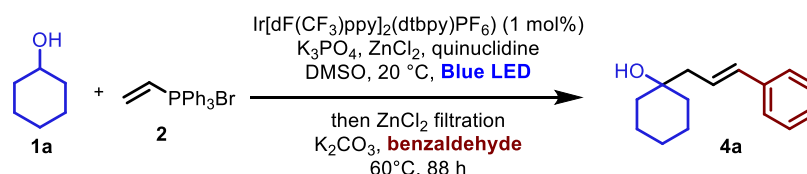
(*E*)-2-methyl-5-phenylpent-4-en-2-ol (**4b**)



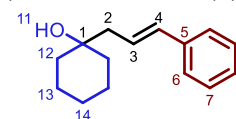
Prepared following general procedure, using **1b** (1 equiv.; 0.2 mmol; 15 μ L), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.7 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 9:1 to 8:2 hexane:ethyl acetate) to afford compound **4b** (25 mg; 71%; *E/Z* = 16:1) as a yellow oil. **R_f** (8:2 hexane:ethyl acetate) 0.2; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3396, 3029, 2970, 2928, 2109, 1988, 1599, 1494, 1456, 1374, 1140, 1070, 967, 906, 761, 734, 693, 597, 533, 476; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.41 (d, *J* = 8.2 Hz, 2H), 7.34 (dd, *J* = 8.2 Hz, 2H), 7.25 (t, *J* = 6.8 Hz, 1H, **8**), 6.49 (d, *J* = 15.8 Hz, 1H, **4**), 6.32 (dt, *J* = 15.8, 7.6 Hz, 1H, **3**), 2.42 (dd, *J* = 7.6, 1.3 Hz, 2H, **2**), 1.30 (s, 6H, **12**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 137.5, 133.8 (**4**), 128.7, 127.4 (**8**), 126.3, 125.9 (**3**), 71.0 (**1**), 47.5 (**2**), 29.4 (**12**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₂H₁₆ONa⁺) expected *m/z* 199.1099; found *m/z* 199.1090.

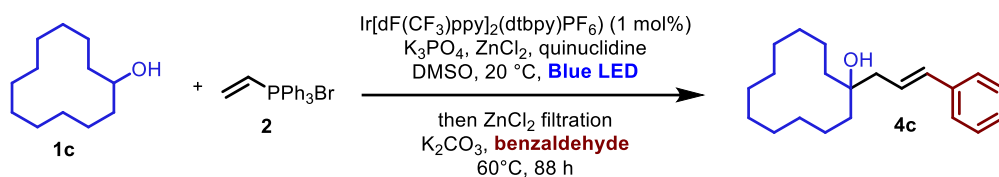


(*E*)-1-(3-phenylallyl)cyclohexan-1-ol (**4a**)

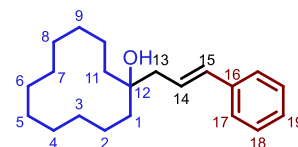
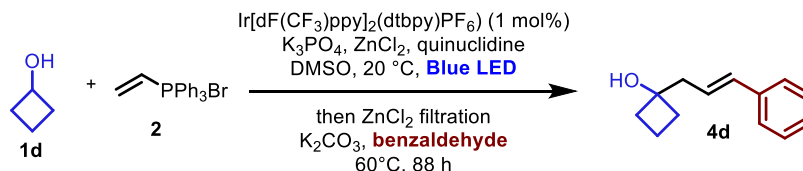


Prepared following the general procedure, using **1a** (1 equiv.; 0.2 mmol; 21 μ L), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.7 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 97:3 to 8:2 hexane:ethyl acetate) to afford compound **4a** (37 mg; 86%; *E/Z* = 16:1) as a yellow oil. **R_f** (97:3 hexane:THF) 0.4; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3410, 3025, 2930, 2856, 1598, 1495, 1262, 1149, 968, 751, 721, 692; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): δ 7.41 – 7.35 (m, 2H), 7.30 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.24 – 7.18 (m, 1H, **14**), 6.46 (d, *J* = 15.9 Hz, 1H, **4**), 6.31 (dt, *J* = 15.9, 7.5 Hz, 1H, **3**), 2.37 (dd, *J* = 7.5, 1.3 Hz, 2H, **2**), 1.66 – 1.46 (m, 10H); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 137.5, 133.8 (**4**), 128.7, 127.3 (**8**), 126.3, 125.5 (**3**), 71.7 (**1**), 46.1 (**2**), 37.7, 25.9, 22.3.; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₅H₂₀Na⁺) expected *m/z* 239.1412; found *m/z* 239.1405.

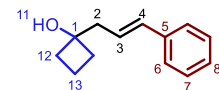


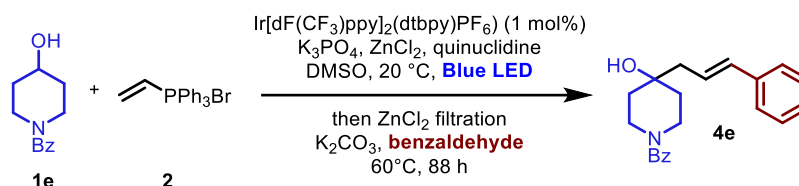
(E)-1-(3-phenylallyl)cyclododecan-1-ol (4c)

Prepared following general procedure, using **1c** (1 equiv.; 0.2 mmol; 37 mg), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.7 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 95:5 to 9:1 hexane:ethyl acetate) to afford compound **4c** (41 mg; 68%; *E/Z* = 16:1) as a white solid. **M.P.**: 63–64°C. **R_f** (9:1 hexane:ethyl acetate) 0.2; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3437, 3026, 2936, 2861, 1598, 1470, 1008, 739, 620; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.38 (d, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H, **19**), 6.47 (d, *J* = 15.9 Hz, 1H, **15**), 6.34 (dt, *J* = 15.9, 7.4 Hz, 1H, **14**), 2.33 (dd, *J* = 7.4, 1.2 Hz, 2H, **13**), 1.62 – 1.54 (m, 2H), 1.46 (dd, *J* = 11.8, 3.7 Hz, 4H), 1.40 – 1.33 (m, 14H); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 137.6, 133.7 (**15**), 128.7, 127.3 (**19**), 126.3, 125.7 (**14**), 75.4 (**12**), 44.6 (**13**), 34.7, 26.6, 26.2, 22.7, 22.2, 19.7; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₁H₃₂ONa⁺) expected *m/z* 323.2351; found *m/z* 323.2346.

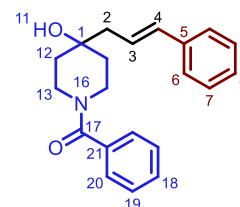
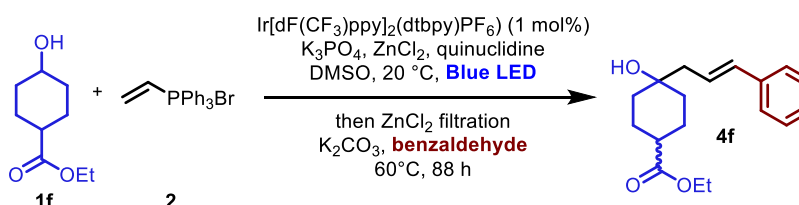
(E)-1-(3-phenylallyl)cyclobutan-1-ol (4d)

Prepared following general procedure, using **1d** (1 equiv.; 0.2 mmol; 16 μ L), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.7 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 9:1 to 8:2 hexane:ethyl acetate) to afford compound **4d** (23 mg; 61%; *E/Z* = 20:1) as a transparent oil. **R_f** (8:2 hexane:ethyl acetate) 0.3; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3365, 3026, 2981, 2931, 1598, 1494, 1448, 1263, 1156, 1122, 1041, 966, 916, 750, 692; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.38 (d, *J* = 8.2 Hz, 2H, **6** - **10**), 7.31 (t, *J* = 7.5 Hz, 2H, **7** - **9**), 7.22 (t, *J* = 7.5 Hz, 1H, **8**), 6.53 (d, *J* = 15.9 Hz, 1H, **4**), 6.29 (dt, *J* = 15.9, 7.4 Hz, 1H, **3**), 2.54 (d, *J* = 7.4 Hz, 2H, **2**), 2.17 – 2.04 (m, 4H, **12**), 1.92 – 1.85 (m, 1H, **11**), 1.82 – 1.73 (m, 1H, **13**), 1.64 – 1.53 (m, 1H, **13**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 137.3 (**5**), 134.1 (**4**), 128.7 (**7** - **9**), 127.5 (**8**), 126.3 (**6**), 125.2 (**3**), 74.6 (**1**), 43.3 (**2**), 35.7 (**12**), 12.1 (**13**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₃H₁₆ONa⁺) expected *m/z* 211.1099; found *m/z* 211.1091.

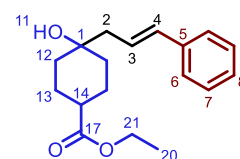


(E)-4-hydroxy-4-(3-phenylallyl)piperidin-1-yl(phenyl)methanone (4e)

Prepared following general procedure, using **1e** (1 equiv.; 0.2 mmol; 41 mg), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.7 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μL). The crude residue was purified by flash column chromatography (SiO_2 ; gradient 1:1 to 3:7 hexane:ethyl acetate) to afford compound **4e** (32 mg; 50%; $E/Z = 12:1$) as a transparent oil. **R_f** (8:2 hexane:ethyl acetate) 0.3; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3385, 2026, 2920, 1600, 1575, 1495, 1436, 1371, 1280, 1176, 1118, 1042, 966, 908, 786, 727, 708, 696, 645, 487, 461; **¹H-NMR** (CDCl_3 , 500 MHz) δ (ppm): 7.40 (s, 5H), 7.37 – 7.34 (m, 2H), 7.31 (t, $J = 7.4$ Hz, 2H), 7.23 (t, $J = 7.4$ Hz, 1H), 6.49 (d, $J = 15.8$ Hz, 1H, **4**), 6.26 (dt, $J = 15.8$, 7.6 Hz, 1H, **3**), 4.47 (bs, 1H, **13**), 3.69 – 3.08 (m, 3H, **13**), 2.41 (d, $J = 7.6$ Hz, 2H, **2**), 1.73 (s, 4H, **12**); **¹³C-NMR** (CDCl_3 , 126 MHz) δ (ppm): 170.5 (**17**), 137.0, 136.3, 135.1 (**4**), 129.7, 128.8, 128.6, 127.7, 127.0, 126.3, 123.7 (**3**), 69.9 (**1**), 46.7 (**2**), 44.0 (**14**), 38.4 (**12**) 37.7; **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{21}\text{H}_{23}\text{NO}_2\text{Na}^+$) expected m/z 344.1626; found m/z 344.1623.

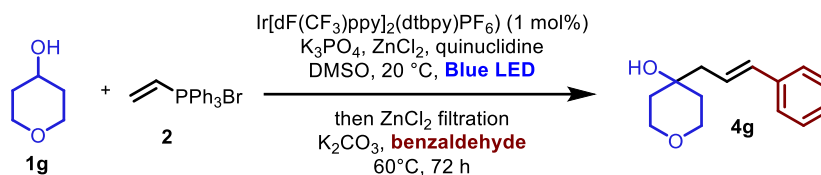
ethyl (E)-4-hydroxy-4-(3-phenylallyl)cyclohexane-1-carboxylate (4f)

Prepared following general procedure, using **1f** (1 equiv.; 0.2 mmol; 32 μL), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.7 mg) and aldehyde **3a** (3 equiv.; 0.6 mmol; 61 μL). The crude residue was purified by flash column chromatography (SiO_2 ; gradient 8:2 to 7:3 hexane:ethyl acetate) to afford compound **4f** (43 mg; 80%; $E/Z = 10:1$; d.r. = 2.8:1) as a transparent oil. **R_f** (7:3 hexane:ethyl acetate) 0.3; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3437, 2936, 1725, 1598, 1495, 1448, 1376, 1185, 1137, 1107, 1069, 1043, 1025, 968, 863, 752, 721, 693, 496; **¹H-NMR** (CDCl_3 , 500 MHz) δ (ppm): 7.39 – 7.34 (m, 2H), 7.32 – 7.29 (m, 2H), 7.24 – 7.20 (m, 1H, **8**), 6.48 (d, $J = 15.9$ Hz, 1H, **4**), 6.29 (dt, $J = 15.9$, 7.6 Hz, 1H, **3**), 4.14 (q, $J = 8.6$ Hz, 2H, **21**), 2.44 (dd, $J = 7.5$, 1.3 Hz, 2H), 1.95 – 1.89 (m, 1H, **14**), 1.85 – 1.68 (m, 5H), 1.53 – 1.36 (m, 3H), 1.26 (t, $J = 8.6$ Hz, 3H, **20**); **¹³C-NMR** (CDCl_3 , 126 MHz) δ (ppm): 175.6 (**17**), 137.3, 134.3 (**4**), 128.7, 127.5 (**8**), 126.3, 124.8 (**3**), 71.5 (**1**), 60.4 (**21**), 47.4, 41.3 (**2**), 36.1, 25.0 (**14**), 14.4 (**20**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{18}\text{H}_{24}\text{O}_3\text{Na}^+$) expected m/z 311.1618; found m/z 311.1616.

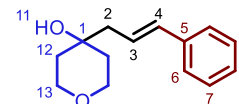


(E)-4-(3-phenylallyl)tetrahydro-2H-pyran-4-ol (4g)

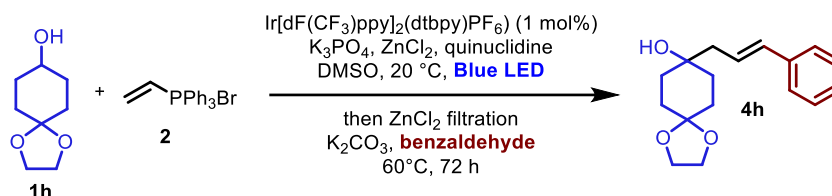
Compound synthesised and characterised by Joseph Wallen.



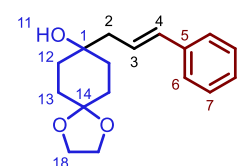
Prepared following general procedure A, using **1g** (1 equiv.; 0.2 mmol; 20.4 μ L), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.6 mg) and benzaldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 7:3 to 5:5 hexane:ethyl acetate) to afford compound **4g** (24.7 mg; 56%; *E/Z* > 20:1) as a yellow oil. **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3424, 3026, 2946, 2885, 2240, 2183, 2163, 2070, 2040, 2005, 1598, 1495 1468, 1449, 1386, 1359, 1302, 1236, 1159, 1129, 1098, 1017, 983, 970, 841, 754, 727, 694, 617, 551, 491, 467, 418; **¹H-NMR** (400 MHz, CDCl₃) 7.40 – 7.20 (m, 5H, **6 – 7 – 8**), 6.50 (d, *J* = 15.6 Hz, 1H, **4**), 6.28 (dt, *J* = 15.6, 7.6 Hz, 1H, **3**), 3.86 – 3.64 (m, 4H, **13**), 2.40 (d, *J* = 7.6, 2H, **2**), 1.77 (m, 2H, **12**), 1.55 – 1.50 (m, 2H, **12**); **¹³C-NMR** (101 MHz, CDCl₃) 137.0, 134.7 (**4**), 128.6, 127.5, 126.2, 123.9 (**3**), 68.9 (**1**), 63.8 (**13**), 46.7 (**2**), 37.7 (**12**); **HRMS** (ESI-TOF) mass calculated for [M+ Na]⁺ (C₁₄H₁₈O₂Na⁺) expected *m/z* 241.1204, found *m/z* 241.1199.

(E)-8-(3-phenylallyl)-1,4-dioxaspiro[4.5]decan-8-ol (4h)

Compound synthesised and characterised by Joseph Wallen.

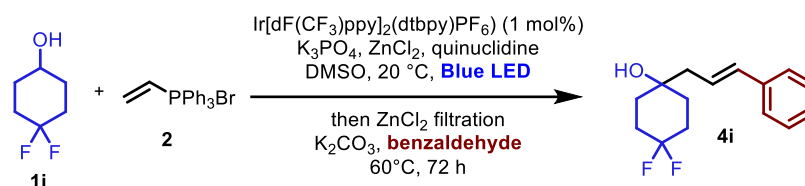


Prepared following general procedure A, using **1h** (1 equiv.; 0.2 mmol; 26.9 μ L), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.6 mg) and benzaldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 7:3 to 5:5 hexane:ethyl acetate) to afford compound **4h** (32.2 mg; 59%; *E/Z* 20:1) as a yellow oil. **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3461, 3026, 2930, 2884, 1704, 1598, 1495, 1447, 1370, 1337, 1260, 1158, 1100, 1035, 985, 967, 933, 900, 753, 724, 694, 668, 489, 449; **¹H-NMR** (400 MHz, CDCl₃) δ (ppm): 8.19 – 6.93 (m, 5H, **6 – 7 – 8**), 6.47 (d, *J* = 15.7 Hz, 1H, **4**), 6.29 (dt, *J* = 15.7, 7.6 Hz, 1H, **3**), 4.20 – 3.74 (m, 4H, **18**), 2.39 (dd, *J* = 7.6, 1.2 Hz, 2H, **2**), 1.92 (td, *J* = 11.9, 5.6 Hz, 2H, **12**), 1.83 – 1.66 (m, 4H, **13**), 1.65 – 1.56 (m, 2H, **12**); **¹³C-NMR** (101 MHz, CDCl₃) δ (ppm): 137.3, 134.2 (**4**), 128.7, 127.5, 126.3, 125.0 (**3**), 108.9 (**14**), 70.7 (**1**), 64.4 (**18**), 46.2 (**2**), 35.0 (**13**), 30.7 (**12**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₇H₂₂O₃Na⁺) expected *m/z* 297.1461, found *m/z* 297.1463.

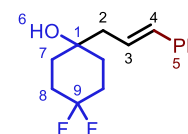


(E)-4,4-difluoro-1-(3-phenylallyl)cyclohexan-1-ol (4i)

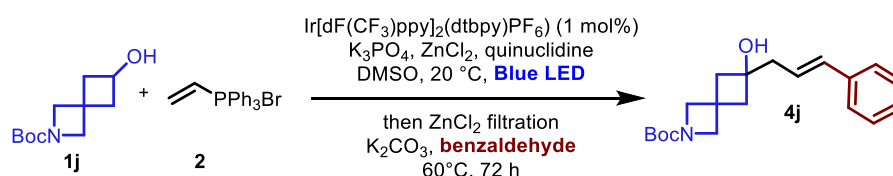
Compound synthesised and characterised by Joseph Wallen.



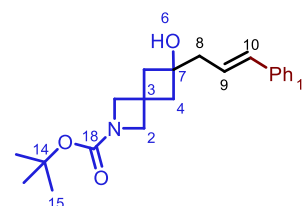
Prepared following general procedure A, using **1i** (1 equiv.; 0.2 mmol; 27.2 mg), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.6 mg) and benzaldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 8:2 to 6:4 hexane:Et₂O) to afford compound **4i** (28.6 mg; 57%; *E/Z* 16:1) as a clear oil. **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3427, 3028, 2943, 1598, 1495, 1442, 1373, 1267, 1155, 1111, 1022, 984, 967, 922, 748, 694, 491, 457; **¹H-NMR** (400 MHz, CDCl₃) δ (ppm): 7.41 – 7.24 (m, 5H, **5**), 6.50 (d, *J* = 15.7 Hz, 1H, **4**), 6.26 (dt, *J* = 15.7, 7.7 Hz, 1H, **3**), 2.40 (dd, *J* = 7.9, 1.3 Hz, 2H, **2**), 2.25 – 2.02 (m, 2H, **8**), 1.95 (m, 2H, **8**), 1.79 – 1.64 (m, 4H, **7**), 1.39 (s, 1H, **6**); **¹³C-NMR** (101 MHz, CDCl₃) δ (ppm): 137.0, 135.0 (**4**), 128.8, 127.8 (d, *J* = 131.1 Hz, **9**), 127.7, 126.3, 124.1 (**3**), 70.05 (d, *J* = 1.6 Hz, **1**), 46.18 (d, *J* = 2.5 Hz, **2**), 33.85 (d, *J* = 9.2 Hz, **8**), 29.73 (d, *J* = 1.5 Hz, **7**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₅H₁₈F₂ONa⁺) expected *m/z* 275.1218, found *m/z* 275.1115.

tert-butyl (E)-6-hydroxy-6-(3-phenylallyl)-2-azaspiro[3.3]heptane-2-carboxylate (4j)

Compound synthesised and characterised by Joseph Wallen.



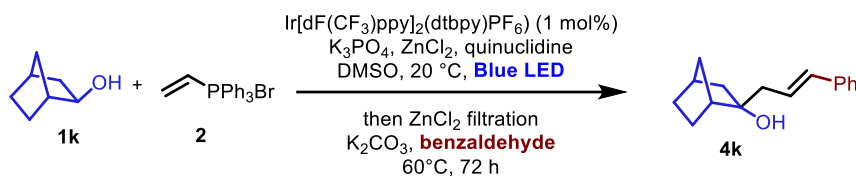
Prepared following general procedure A, using **1j** (1 equiv.; 0.2 mmol; 42.63 mg), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.6 mg) and benzaldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 8:2 to 6:4 toluene:ethyl acetate) to afford compound **4j** (26.8 mg; 41%; *E/Z* 12:1) as a pale yellow solid. **MP** = 179–183 °C; **IR**(film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3416, 2971, 2928, 2871, 1723, 1700, 1419, 1316, 1257, 1166, 969, 773, 752, 700, 595; **¹H-NMR** (400 MHz, CDCl₃) δ (ppm): 7.40 – 7.13 (m, 5H, **11**), 6.50 (d, *J* = 16.0 Hz, 1H, **10**), 6.21 (dt, *J* = 16.0, 7.3 Hz, 1H, **9**), 3.92 (s, 4H, **2**), 2.41 (d, *J* = 7.5 Hz, 2H, **8**), 2.39 – 2.20 (m, 4H, **4**), 1.43 (s, 9H, **15**). **¹³C-NMR** (101 MHz, CDCl₃) δ (ppm): 156.1, 136.9, 134.6 (**10**), 128.6, 127.6, 126.2, 124.0 (**9**), 79.4 (**7**), 70.3 (**14**), 62.7 (**2**), 46.4 (**4**), 44.3 (**8**), 29.2 (**3**), 28.4 (**15**);



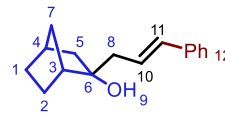
HRMS (ESI-TOF) mass calculated for $[M+Na]^+$ ($C_{20}H_{27}NO_3Na^+$) expected m/z 352.1883, found m/z 352.1885.

(1*R*,2*R*,4*S*)-2-((*E*)-3-phenylallyl)bicyclo[2.2.1]heptan-2-ol (4k)

Compound synthesised and characterised by Joseph Wallen.

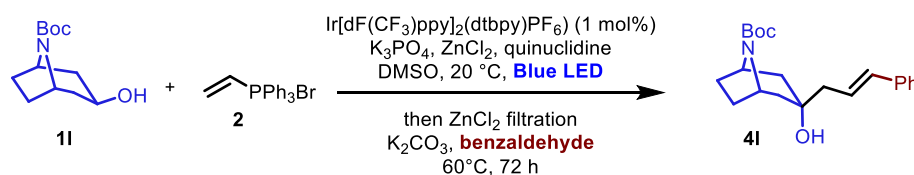


Prepared following general procedure A, using **1k** (1 equiv.; 0.2 mmol; 22.4 mg), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.6 mg) and benzaldehyde **3a** (3 equiv.; 0.6 mmol; 61 L). The crude residue was purified by flash column chromatography (SiO_2 ; gradient 9:1 to 7:3 hexane:Et₂O) to afford compound **4k** (30.3 mg; 66%; $E/Z > 20:1$; d.r. $> 20:1$) as a clear oil. **IR** (film) ν_{max}/cm^{-1} : 3428, 3025, 2949, 2869, 1598, 1495, 1449, 1309, 1232, 1160, 1095, 1037, 1011, 968, 912, 807, 746, 695, 490; **¹H-NMR** (400 MHz, CDCl₃) δ (ppm): 7.40 – 7.35 (m, 2H, **12**), 7.33 – 7.29 (m, 2H, **12**), 7.25 – 7.20 (tt, $J = 7.4, 1.3$ Hz, 2H, **12**), 6.50 (d, $J = 15.9$ Hz, 1H, **11**), 6.32 (dt, $J = 15.9, 7.3$ Hz, 1H, **10**), 2.50 – 2.39 (m, 2H, **8**), 2.26 – 2.20 (m, 1H, **4**), 2.17 – 2.15 (m, 1H, **3**), 2.04 – 1.94 (m, 1H, **2**), 1.70 (ddd, $J = 12.9, 4.6, 2.9$ Hz, 1H, **5**), 1.64 – 1.54 (m, 3H, **1 – 7**), 1.40 – 1.30 (m, 3H, **1 – 2 – 7**), 1.16 (dd, $J = 12.9, 3.3$ Hz, 1H, **5**); **¹³C-NMR** (126 MHz, CDCl₃) δ (ppm): 137.4, 134.2 (**11**), 128.7, 127.4, 126.3, 125.7 (**10**), 79.1 (**6**), 46.5 (**3**), 46.0 (**8**), 45.8 (**5**), 38.8 (**7**), 37.4 (**4**), 28.7 (**1**), 22.3 (**2**); **HRMS** (ESI-TOF) mass calculated for $[M+Na]^+$ ($C_{16}H_{20}ONa^+$) expected m/z 251.1406, found m/z 251.1401.



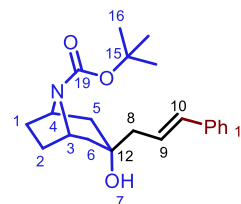
tert-butyl (1*R*,3*r*,5*S*)-3-hydroxy-3-((*E*)-3-phenylallyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (4l)

Compound synthesised and characterised by Joseph Wallen.



Prepared following general procedure A, **1l** (1 equiv.; 0.2 mmol; 45.5 mg), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.6 mg) and benzaldehyde **3a** (3 equiv.; 0.6 mmol; 61 μ L). The crude residue was purified by flash column chromatography (SiO_2 ; gradient 9:1 to 8:2 pentane:ethyl acetate) to afford compound **4l** (54.6 mg; 80%; E/Z 10:1; d.r. $> 20:1$) as a clear oil. **IR** (film) ν_{max}/cm^{-1} : 3439, 2975, 1665, 1477, 1405, 1365, 1334, 1241, 1167, 1100, 1038, 968, 871, 750, 693, 548, 493; **¹H-NMR** (500 MHz, CDCl₃) δ (ppm): 7.36 – 7.19 (m, 5H, **11**), 6.45 (d, $J = 15.9$ Hz, 1H, **10**), 6.20 (dt, $J = 15.6, 7.6$ Hz, 1H, **9**), 4.20 (br. s, 2H, **3 – 4**), 2.24 (dd, $J = 7.6, 1.3$

Hz, 2H, **8**), 2.18 – 2.08 (m, 2H), 2.03 – 1.94 (m, 2H), 1.91 – 1.86 (m, 2H), 1.66 – 1.60 (m, 2H), 1.44 (s, 9H, **16**); ¹³C-NMR (126 MHz, CDCl₃) δ (ppm): 153.6, 137.1, 135.0 (**10**), 128.7, 127.6, 126.3, 124.2 (**9**), 79.2 (**15**), 71.2 (**12**), 53.0, 50.2, 45.0, 42.5, 42.3, 36.5, 28.6 (**16**), 27.9 (**15**); HRMS (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₁H₂₉NO₃Na⁺) expected *m/z* 366.2040, found *m/z* 366.2042.

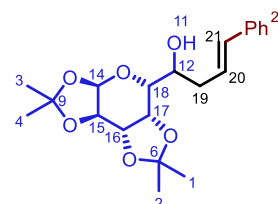


(E)-4-phenyl-1-((3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran-5-yl)but-3-en-1-ol (**4m**)

Compound synthesised and characterised by Joseph Wallen.



Prepared following general procedure A, using **1m** (1 equiv.; 0.2 mmol; 52.5 mg), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.6 mg) and benzaldehyde **3a** (3 equiv.; 0.6 mmol; 61 μL). The crude residue was purified by flash column chromatography (SiO₂; gradient 8:2 to 6:4 hexane:ethyl acetate) to afford compound **4m** (33.9 mg; 45%; *E/Z* 10:1; d.r. 1:1) as a clear oil. α²⁰_D = -57° (c = 1.00, CHCl₃); IR (film): ν_{max}/cm⁻¹: 3504, 2987, 2934, 1382, 1256, 1212, 1168, 1060, 1000, 899, 775, 748, 695, 514; ¹H-NMR (400 MHz, CDCl₃) δ (ppm): 7.40 – 7.11 (m, 5H, **22**), 6.57 – 6.46 (m, 1H, **21**), 6.37 – 6.25 (m, 1H, **20**), 5.60 (dd, *J* = 24.8, 5.1 Hz, 1H, **14**), 4.66 – 4.58 (m, 1H, **16**), 4.54 – 4.43 (m, 1H, **17**), 4.35 – 4.30 (m, 1H, **15**), 4.08 – 3.91 (m, 1H, **12**), 3.68 – 3.62 (m, 1H, **18**), 2.76 – 2.63 (m, 1H, **19**), 2.47 (ddt, *J* = 22.0, 14.7, 7.3 Hz, 1H, **19**), 1.56 – 1.24 (m, 12H, **1** – **2** – **3** – **4**); ¹³C-NMR (101 MHz, CDCl₃) δ (ppm) mixture of diastereoisomers. Minor peaks reported in parenthesis (): (137.5), 133.6 (**21**), 132.8, 128.6, 128.6, (127.3), 127.2, (126.3), 126.3 (**20**), (126.2), (125.8), (109.7), 109.5, 108.8, (108.7), (96.7), 96.7 (**14**), 72.8 (**15**), (71.2), (71.1), 71.1 (**17**), (70.9), (70.7), (70.6), 69.9 (**16**), 69.3 (**12**), (68.6), 37.5 (**19**), (36.2), (26.1), 26.1, (26.0), 25.1, (25.1), 24.6, (24.3); HRMS (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₁H₂₈O₆Na⁺) expected *m/z* 399.1778, found *m/z* 399.1776.

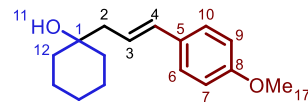


(E)-1-(3-(4-methoxyphenyl)allyl)cyclohexan-1-ol (**4n**)



Prepared following general procedure, using **1a** (1 equiv.; 0.2 mmol; 21 μL), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.7 mg) and aldehyde **3n** (3 equiv.; 0.6 mmol; 74 μL). The crude residue was purified by flash column chromatography

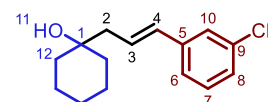
(SiO₂; gradient 95:5 to 9:1 toluene:ethyl ether) to afford compound **4n** (23 mg; 47%; *E/Z* > 20:1) as a transparent oil. **R_f** (9:1 toluene:ethyl ether) 0.25; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3438, 2929, 2856, 1607, 1510, 1443, 1297, 1246, 1174, 1150, 1111, 1035, 969, 835, 524; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.33 – 7.28 (m, 2H, **7 - 9**), 6.87 – 6.81 (m, 2H, **6 - 10**), 6.39 (d, *J* = 15.6 Hz, 1H, **4**), 6.15 (d, *J* = 15.6, 7.6 Hz, 1H, **3**), 3.80 (s, 3H, **17**), 2.34 (dd, *J* = 7.6, 1.3 Hz, 2H, **2**), 1.64 – 1.45 (m, 10H); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 159.1, 133.2 (**4**), 130.4, 127.4 (**7 - 9**), 123.1 (**3**), 114.1 (**6 - 10**), 71.7 (**1**), 55.4 (**17**), 46.0 (**2**), 37.7, 25.9, 22.4; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₆H₂₂O₂Na⁺) expected *m/z* 269.1517; found *m/z* 269.1509.



(E)-1-(3-(3-chlorophenyl)allyl)cyclohexan-1-ol (**4o**)



Prepared following general procedure, using **1a** (1 equiv.; 0.2 mmol; 21 μ L), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.7 mg) and aldehyde **3o** (3 equiv.; 0.6 mmol; 68 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 9:1 to 85:15 hexane:ethyl acetate) to afford compound **4o** (46 mg; 92%; *E/Z* = 16:1) as a yellow oil. **R_f** (9:1 hexane:ethyl acetate) 0.1; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3376, 2928, 2856, 1593, 1565, 1474, 1447, 1425, 1262, 1206, 1149, 1078, 1039, 997, 967, 882, 777, 727, 683, 438; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.3- 7.37 (m, 1H), 7.27 – 7.23 (m, 2H), 7.22 – 7.18 (m, 1H), 6.41 (d, *J* = 15.9 Hz, 1H, **4**), 6.35 (dt, *J* = 15.9, 6.9 Hz, 1H, **3**), 2.39 (d, *J* = 6.9 Hz, 2H, **2**), 1.65 – 1.45 (m, 10H); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 39.4, 134.6, 132.3 (**4**), 129.9, 127.4 (**3**), 127.2, 126.1, 124.5, 71.8 (**1**), 46.0 (**2**), 37.7, 25.8, 22.3; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₅H₁₉OCINa⁺) expected *m/z* 273.1022; found *m/z* 273.1018.



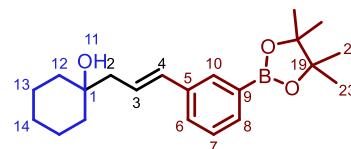
(E)-1-(3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)allyl)cyclohexan-1-ol (**4p**)

Compound synthesised and characterised by Joseph Wallen.



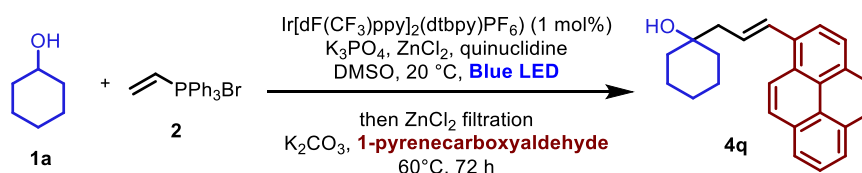
Prepared following general procedure A, using **1a** (1 equiv.; 0.2 mmol; 20.8 μ L), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.6 mg) and aldehyde **3p** (3 equiv.; 0.6 mmol; 139 mg). The crude residue was purified by flash column chromatography (SiO₂; gradient 8:2 to 6:4 hexane:Et₂O). The resulting residue was dissolved in methanol, washed with saturated NaHSO₃ (2 x 5 mL) and extracted with 9:1

hexane:ethyl acetate to remove residual **3p**, affording compound **4p** (26.8 mg; 39%; *E/Z* 20:1) as a clear oil. **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3416, 2978, 2929, 2857, 1601, 1424, 1359, 1312, 1270, 1210, 1143, 1077, 965, 854, 796, 755, 704, 675; **¹H-NMR** (400 MHz, CDCl₃) δ (ppm): 7.82 (s, 1H, **10**), 7.66 (d, *J* = 7.2, 1H, **8**), 7.46 (d, *J* = 7.7, 1H, **6**), 7.31 (t, *J* = 7.5 Hz, 1H, **7**), 6.46 (d, *J* = 15.9 Hz, 1H, **4**), 6.34 (dt, *J* = 15.9, 7.4 Hz, 1H, **3**), 2.36 (d, *J* = 7.4 Hz, 2H, **2**), 1.69 – 1.43 (m, 10H), 1.35 (s, 12H, **23** – **24**); **¹³C-NMR** (101 MHz, CDCl₃) δ (ppm): 136.8 (**9**), 133.7 (**8**), 133.7 (**4**), 132.5 (**10**), 129.2 (**6**), 128.1, (**7**), 127.3 (**5**), 125.6 (**7**), 84.0 (**19**), 71.7 (**1**), 46.1 (**2**), 37.7, 25.9, 25.0, 22.4; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₁H₃₁BO₃Na⁺) expected *m/z* 365.2258, found *m/z* 365.2264.

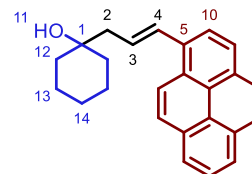


(*E*)-1-(3-(pyren-1-yl)allyl)cyclohexan-1-ol (**4q**)

Compound synthesised and characterised by Joseph Wallen.

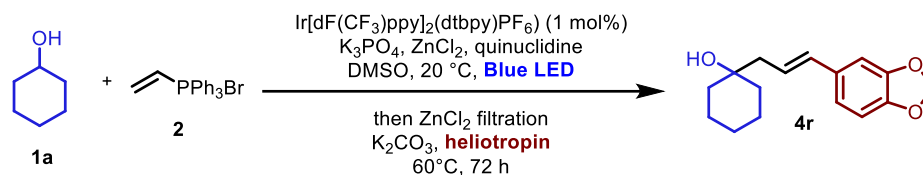


Prepared following general procedure A, using **1a** (1 equiv.; 0.2 mmol; 20.8 μ L), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.6 mg) and aldehyde **3q** (3 equiv.; 0.6 mmol; 138 mg). The crude residue was purified by flash column chromatography (SiO₂; gradient 7:3 to 5:5 hexane:Et₂O) to afford compound **4q** (61.6 mg; 90%; *E/Z* 20:1) as an orange oil. **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3409, 3041, 2929, 2855, 2365, 2184, 2170, 2073, 2013, 1977, 1601, 1447, 1149, 967, 843, 758, 711, 641, 553, 529, 512, 489, 474, 460, 431, 419; **¹H-NMR** (400 MHz, CDCl₃) δ (ppm): 8.37 (d, *J* = 9.3 Hz, 1H), 8.19 – 8.13 (m, 3H), 8.12 – 8.06 (m, 2H), 8.00 (d, *J* = 13.3 Hz, 3H), 7.50 (d, *J* = 15.6 Hz, 1H, **4**), 6.53 (dt, *J* = 15.6, 7.6 Hz, 1H, **3**), 2.58 (d, *J* = 7.6, 2H, **2**), 1.73 – 1.51 (m, 10H); **¹³C-NMR** (101 MHz, CDCl₃) δ (ppm): 132.2, 131.6, 131.0, 130.9, 130.6 (**4**), 129.2 (**3**), 127.8, 127.5, 127.5, 127.1, 126.0, 125.2, 125.1, 125.0, 124.9, 124.8, 124.0, 123.2, 71.8 (**1**), 46.7 (**2**), 37.7, 25.9, 22.3; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₅H₂₄ONa⁺) expected *m/z* 363.1719, found *m/z* 363.1715.

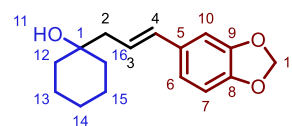
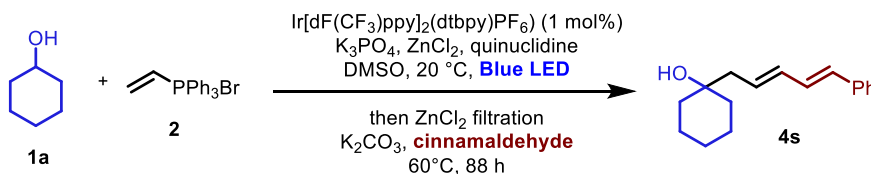


(E)-1-(3-(benzo[d][1,3]dioxol-5-yl)allyl)cyclohexan-1-ol (4r)

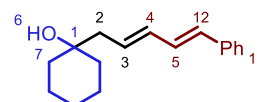
Compound synthesised and characterised by Joseph Wallen.

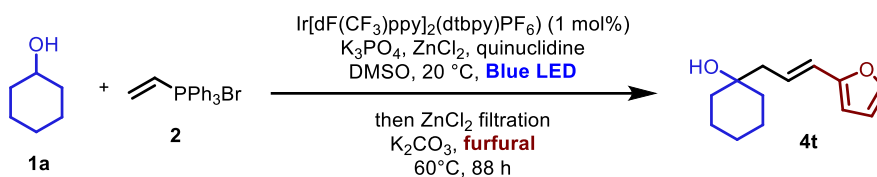


Prepared following general procedure A, using **1a** (1 equiv.; 0.2 mmol; 20.8 μ L), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.6 mg) and aldehyde **3r** (3 equiv.; 0.6 mmol; 90.1 mg). The crude residue was purified by flash column chromatography (SiO₂; gradient 98:2 to 90:1 toluene: Et₂O) to afford compound **4r** (46.7 mg; 89%; *E/Z* > 20:1) as a yellow oil. **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3417, 2927, 2857, 1606, 1503, 1488, 1444, 1357, 1246, 1191, 1149, 1099, 1038, 967, 929, 861, 799; **¹H-NMR** (400 MHz, CDCl₃) δ (ppm): 6.92 (d, *J* = 1.7 Hz, 1H, **10**), 6.83 – 6.59 (m, 2H, **6** – **7**), 6.36 (d, *J* = 15.6 Hz, 1H, **4**), 6.12 (dt, *J* = 15.6, 7.6 Hz, 1H, **3**), 5.93 (s, 2H, **18**), 2.33 (d, *J* = 7.6 Hz, 2H, **2**), 1.65 – 1.41 (m, 9H, **12** to **16**) 1.33 – 1.22 (m, 1H, **12** to **16**); **¹³C-NMR** (101 MHz, CDCl₃) δ (ppm): 148.1, 147.0, 133.2 (**4**), 132.0, 123.6 (**3**), 120.7, 108.3, 105.6 (**10**), 101.1 (**18**), 71.6 (**1**), 45.9 (**2**), 37.6, 25.9, 22.3; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₆H₂₀O₃Na⁺) expected *m/z* 283.1310, found *m/z* 283.1303.

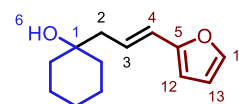
1-((2E,4E)-5-phenylpenta-2,4-dien-1-yl)cyclohexan-1-ol (4s)

Prepared following general procedure, using **1a** (1 equiv.; 0.2 mmol; 21 μ L), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.7 mg) and aldehyde **3s** (3 equiv.; 0.6 mmol; 76 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 97.5:2.5 to 95:5 toluene:ethyl ether) to afford compound **4s** (41 mg; 85%; *E/Z* = 6:1) as a transparent oil. **R_f** (9:1 toluene:ethyl ether) 0.3; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3420, 3023, 2938, 2856, 1595, 1495, 1263, 1151, 1036, 989, 748, 691; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.38 (d, *J* = 7.7 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.78 (dd, *J* = 15.7, 10.4 Hz, 1H, **5**), 6.49 (d, *J* = 15.7 Hz, 1H, **12**), 6.28 (dd, *J* = 15.1, 10.4 Hz, 1H, **4**), 5.89 (dt, *J* = 15.7, 7.8 Hz, 1H, **3**), 2.31 (dd, *J* = 7.8, 1.2 Hz, 2H, **2**), 1.68 – 1.40 (m, 10H); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 137.6, 134.4 (**4**), 131.2 (**12**), 130.1 (**3**), 129.1 (**5**), 128.7, 127.4, 126.4, 71.8 (**1**), 46.0 (**2**), 37.6, 25.9, 22.3; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₇H₂₂O₂Na⁺) expected *m/z* 265.1568; found *m/z* 265.1553.

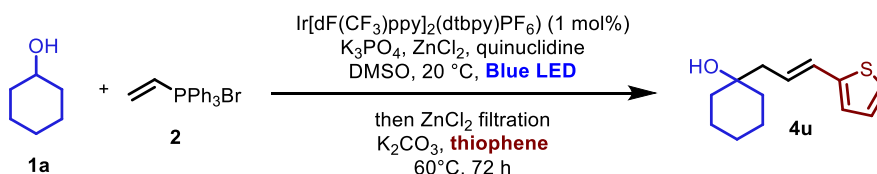


(E)-1-(3-(furan-2-yl)allyl)cyclohexan-1-ol (4t)

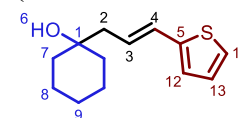
Prepared following general procedure, using **1a** (1 equiv.; 0.2 mmol; 21 μ L), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.7 mg) and aldehyde **3t** (3 equiv.; 0.6 mmol; 50 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 95:5 to 9:1 toluene:ethyl ether) to afford compound **4t** (28 mg; 68%; *E/Z* = 4:1) as a transparent oil. **R_f** (9:1 toluene:ethyl ether) 0.3; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3429, 2930, 2858, 1491, 1448, 1254, 1150, 1012, 965, 926, 884, 793, 731, 594; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.33 – 7.30 (m, 1H), 6.36 – 6.33 (m, 1H, **4**), 6.26 (s, 1H), 6.22 (dt, *J* = 15.8, 7.1 Hz, 1H, **3**), 6.17 (d, *J* = 3.3 Hz, 1H), 2.33 (d, *J* = 7.0 Hz, 2H, **2**), 1.65 – 1.46 (m, 10H); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 153.0 (**5**), 141.6, 124.5 (**3**), 122.2, 111.3 (**3**), 106.9, 71.7 (**1**), 46.0 (**2**), 37.6, 25.9, 22.3; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₃H₁₈O₂Na⁺) expected *m/z* 229.1204; found *m/z* 229.1193.

(E)-1-(3-(1-methyl-1*H*-imidazol-2-yl)allyl)cyclohexan-1-ol (4u)

Compound synthesised and characterised by Joseph Wallen.



Prepared following general procedure A, using **1a** (1 equiv.; 0.2 mmol; 20.8 μ L), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.6 mg) and aldehyde **3u** (3 equiv.; 0.6 mmol; 56 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 99:1 to 95:5 toluene:Et₂O), affording compound **4u** (29.4 mg; 66 %; *E/Z* 13:1) as a clear oil. **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3401, 2930, 2856, 1447, 1261, 1149, 1040, 959, 852, 693, 516; **¹H-NMR** (400 MHz, CDCl₃) δ (ppm): 7.11 (d, *J* = 5.0 Hz, 1H, **14**), 6.98 – 6.86 (m, 2H, **12** – **13**), 6.58 (d, *J* = 15.6 Hz, 1H, **4**), 6.13 (dt, *J* = 15.6, 7.7 Hz, 1H, **3**), 2.33 (dd, *J* = 7.7, 1.3 Hz, 2H, **2**), 1.69 – 1.41 (m, 9H), 1.29 (dtd, *J* = 15.6, 7.7, 4.9 Hz, 1H); **¹³C-NMR** (101 MHz, CDCl₃) δ (ppm): 142.7, 127.4, 126.8 (**4**), 125.4, 124.9 (**3**), 123.7 (**14**), 71.7 (**1**) 46.0 (**2**), 37.6, 25.9, 22.3; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₃H₁₈SONa⁺) expected *m/z* 245.0971, found *m/z* 245.0973.

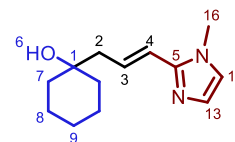


(E)-1-(3-(1-methyl-1*H*-imidazol-2-yl)allyl)cyclohexan-1-ol (**4v**)

Compound synthesised and characterised by Joseph Wallen.



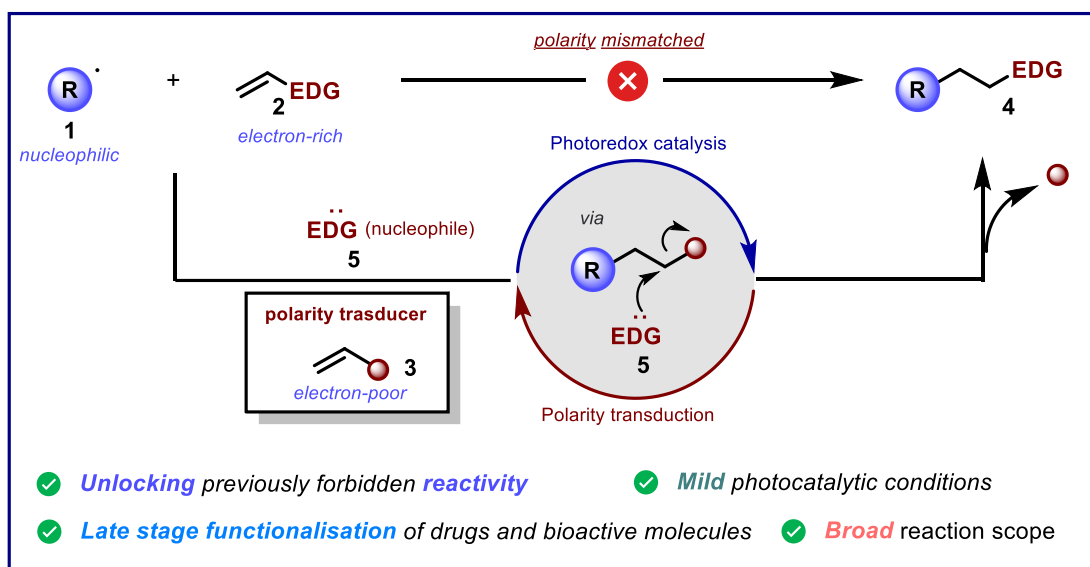
Prepared following general procedure A, using **1a** (1 equiv.; 0.2 mmol; 20.8 μ L), vinyl phosphonium bromide **2** (1.5 equiv.; 0.3 mmol; 110.6 mg) and aldehyde **3v** (3 equiv.; 0.6 mmol; 66 mg). The crude residue was purified by flash column chromatography (SiO₂; gradient 99:1 to 95:5 DCM:MeOH), affording compound **4v** (26.6 mg; 60 %; *E/Z* > 20:1) as a pale yellow solid. **MP** = 177–180 °C; **IR** (film) ν_{max} /cm⁻¹: 3250, 2929, 2854, 1656, 1520, 1485, 1446, 1413, 1285, 1157, 1037, 971, 841, 772, 728, 449, 427, 413; **¹H-NMR** (400 MHz, CDCl₃) δ (ppm): 7.00 (s, 1H, **13 or 14**), 6.84 – 6.73 (m, 2H, **13 or 14 - 3**), 6.32 (dd, *J* = 15.5, 1.4 Hz, 1H, **4**), 3.64 (s, 3H, **16**), 2.40 (dd, *J* = 7.8, 1.4 Hz, 3H, **16**), 1.69 – 1.43 (m, 9H), 1.33 – 1.21 (m, 1H); **¹³C-NMR** (101 MHz, CDCl₃) δ (ppm): 145.5, 131.7 (**3**) 127.9 (**13 or 14**), 121.1 (**13 or 14**), 118.9 (**4**), 71.6 (**1**), 46.3 (**2**), 37.6, 32.9, 25.8, 22.3; **HRMS** (ESI-TOF) mass calculated for [M+H⁺] (C₁₃H₂₁N₂O⁺) expected *m/z* 221.1648, found *m/z* 221.1652.



Chapter 4. Polarity Transduction Enables the Formal Electronically Mismatched Radical Addition to Alkenes

The Giese reaction is a cornerstone of organic chemistry and plays a central role in organic synthesis, allowing to selectively forge carbon-carbon bonds under mild conditions. Despite its wide applicability, the scope of this process is strictly limited by polarity-matching effects. Typically, nucleophilic carbon-centred radicals **1** add to electron-poor alkenes but are unreactive towards electron-rich olefins **2**. This significantly limits the scope of a process that could otherwise be more universally applied. In this chapter, we describe the development of a *polarity transduction* strategy that formally overcomes this electronic limitation.

The project described below was published, see Paul, S.; Filippini, D.; Silvi, M. *J. Am. Chem. Soc.* **2023**, *145*, 2773–2778. The project was carried out equally by me and Dr Subhasis Paul. See the experimental section for a detailed outline of the work.



4.1. Introduction

Radical addition to alkenes¹ is a versatile process which has found widespread application in organic synthesis for the construction of new carbon-carbon bonds.² In the last decades, extensive research has refined this valuable chemical reaction, significantly expanding its applicability in synthesis e.g., in the development of novel stereoselective reactions with wide applicability in total synthesis (Table 4.1).

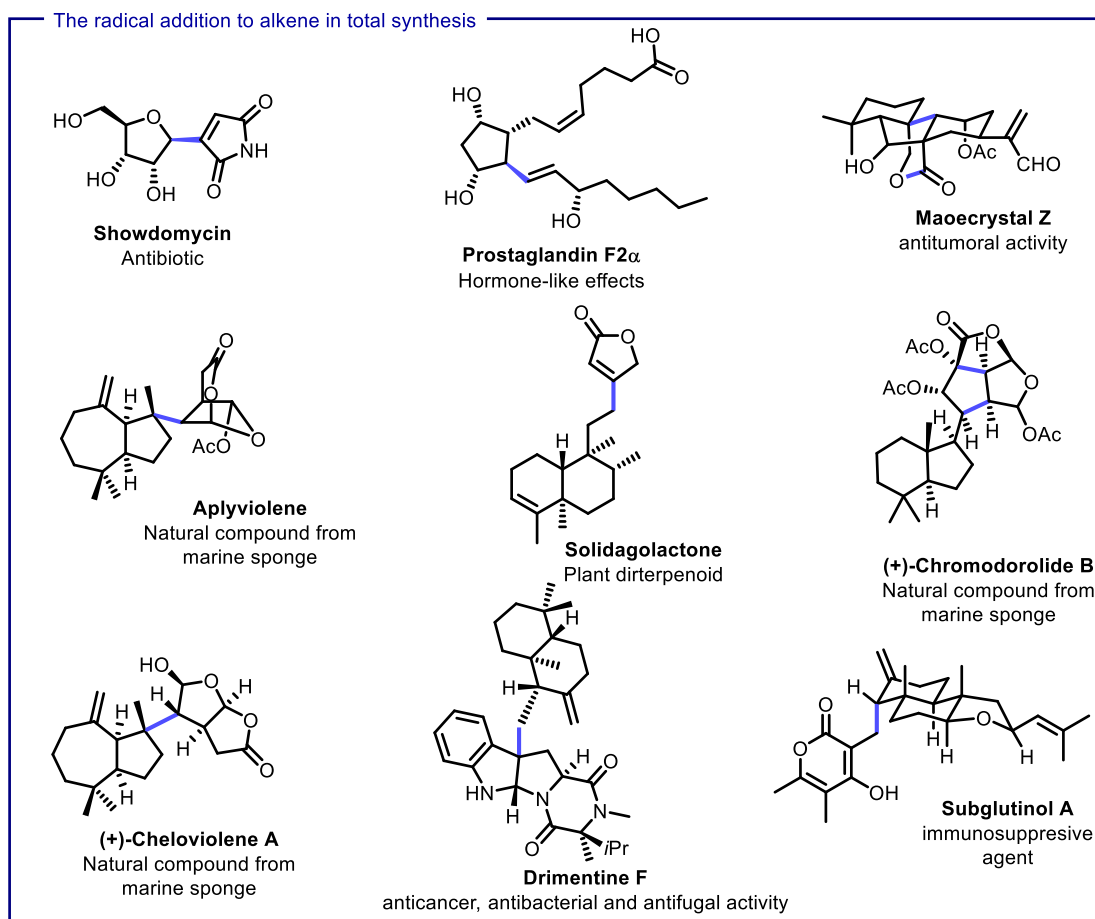


Table 4.1: Examples of uses of the radical addition to alkene reaction for the total synthesis of natural and bioactive compounds.

Notwithstanding the synthetic value of the chemistry, the strict polarity matching requirements (between radicals and alkenes), significantly limit its scope of application. In this project, we envisioned to expand the applicability of the Giese reaction by introducing a strategy that we defined *polarity transduction*, better defined in the following sections of this chapter.

To better understand the value of radical addition to alkene, in the following section, examples of applications and limitations of classic Giese synthesis are presented.

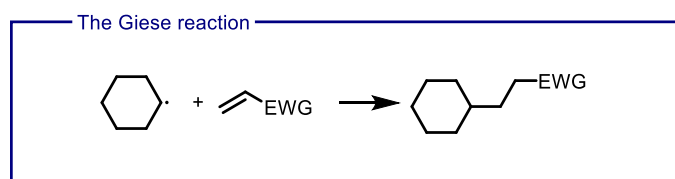
¹ Giese, B. *Angew. Chem. Int. Ed.* **1983**, 22, 753–764.

² a) *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Studer, A.; Chatgililoglu, C.; Eds.; Wiley, **2012**; Subramanian, H. b) Landais, Y.; Sibi, M. P. Radical Addition Reactions. In *Comprehensive Organic Synthesis*, 2nd ed.; Elsevier, **2014**; pp 699–741. c) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, 61, 10377–10441. d) Streuff, J.; Gansäuer, A. *Angew. Chem. Int. Ed.* **2015**, 54, 14232–14242.

4.2. State of the Art: Synthetic uses of the radical addition to alkenes

4.2.1. The Giese reaction

The radical hydroalkylation of the alkene, it is often referred to as the Giese reaction, named after the chemist Bernd Giese who performed pioneering studies in the kinetic of the process (Scheme 4.1).¹



Scheme 4.1: The Giese reaction.

The high potential behind the Giese reaction lies in its ability to forge novel carbon-carbon bonds under mild reaction conditions. This characteristic allowed synthetic chemists to exploit the reaction for several different applications in organic synthesis. In the section below, Some examples of the use of this reaction in modern synthetic strategies (e.g., photoredox catalysis) are presented.

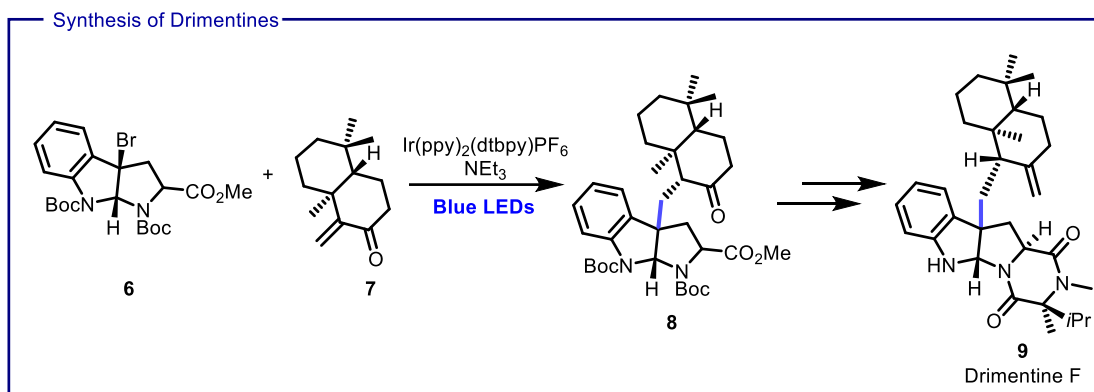
4.2.2. Application of the Giese reaction in organic synthesis

The Giese reaction in total synthesis

Radical addition to alkene has been widely applied in total synthesis³ for its ability in forging novel C-C bonds – allowing practical connection between complex fragments. One of the first methodologies that see Giese radical addition applied in total synthesis was reported by Li *at al.* in 2013.⁴ In their process, the authors proposed a total synthesis of different drimentines **9** starting from a common intermediate **8** – generated by the coupling of a bromide **6** with an electron-poor olefine **7** *via* visible light photoredox catalysis (Scheme 4.2). Upon shining visible light, a SET between the PC* and the bromide **6** cause the mesolysis of the C-Br bond and the formation of a nucleophilic radical which promptly attacks the double bond in fragment **7**. A second reduction from the PC* yields the intermediated **8**. After further elaboration, intermediate **8** is converted to different natural compounds e.g., drimentines A, F and G and indotertine A.

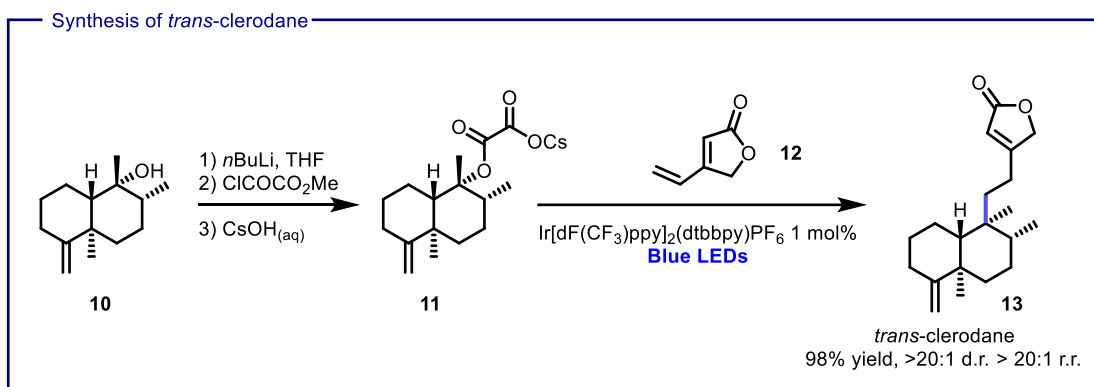
³ Pitre, S. P.; Weires, N. A.; Overman, L. E. *J. Am. Chem. Soc.* **2019**, *141*, 2800–2813.

⁴ Sun, Y.; Li, R.; Zhang, W.; Li, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 9201–9204.



Scheme 4.2: Total synthesis of Dimendrines.⁴

Another remarkable example that leverages the use of the Giese reaction for the connection of complex fragments is the total synthesis of *trans*-clerodane **13**, a terpenoid synthesised by several hundreds of plant species with interesting biological activities (Scheme 4.3).⁵ The synthesis was reported by the MacMillan and the Overman group in 2015.⁶ The procedure consists of the functionalisation of alcohol **10** (obtained from a 4-step procedure) to the corresponding oxalate **11**. The submission of the latter to photochemical conditions in the presence of commercially available 4-vinylfuran-2-one **12** revealed compound **13** with perfect diastero- and regio-selectivity.



Scheme 4.3: Total synthesis of *trans*-clerodane.⁶

The Giese reaction in a bioconjugation procedure

One of the most remarkable examples of the modern uses of the Giese reaction in organic synthesis was proposed by MacMillan *et. al.* in 2018, where they showed the application of the reaction in a selective methodology for the bioconjugation of native peptides.⁷ Traditionally, the modification of native proteins leverages the use of only 2 of the 20 available canonical amino acids: lysine and cysteine – as the only ones that incorporate a nucleophilic heteroatom.⁸ However, single-site functionalisation proved to be challenging as these residues are highly abundant on the protein surface.⁹ In this

⁵ Li, R.; Morris-Natschke, S. L.; Lee, K.H. *Nat. Prod. Rep.* **2016**, *33*, 1166–1226.

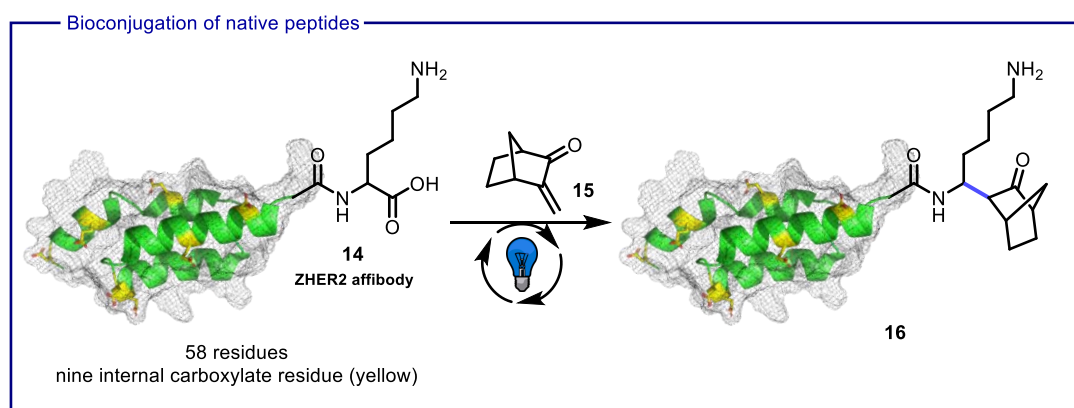
⁶ Nawrat, C. C.; Jamison, C. R.; Slutsky, Y.; MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 11270–11273.

⁷ Bloom, S.; Liu, C.; Kölmel, D. K.; Qiao, J. X.; Zhang, Y.; Poss, M. A.; Ewing, W. R.; Macmillan, D. W. C. *Nat. Chem.*, **2018**, *10*, 205–211.

⁸ Baslé, E.; Joubert, N.; Pucheault, M. *Chem. Biol.* **2010**, *17*, 213–227.

⁹ Miller, S.; Janin, J.; Lesk, A. M.; Chothia, C. *J. Mol. Biol.* **1987**, *196*, 641–656.

work, the authors leveraged the photoredox decarboxylation to produce a nucleophilic, carbon-centred radical, which would easily undergo Giese-type radical addition on electron-poor double bond **15**. Although carboxylic acid groups are naturally abundant in peptides – in the C-terminal position as well as on the aspartate and glutamate residues – the only one engaged in the redox process was the C-terminal α -amino carboxylate as the one possessing the lowest oxidation potential. The reaction scope demonstrated the potential of the process, functionalising regiospecifically different peptides – e.g., Bivalirudin, a thrombin inhibitor, ZHER2 **14** (Scheme 4.4): a single chain peptide containing 58 residues, and even human insulin: constituted by two peptide chains connected by two disulfide bridges.



Scheme 4.4: Photoredox decarboxylative process used for bioconjugation of complex peptides. In the picture, the functionalisation of a 58 residues peptide. Although there are several carboxylic acid groups due to the side chains of aspartic and glutamic acids, the authors were able to selectively functionalise only the one present in the C-terminal position.⁷

The Giese Reaction in asymmetric catalysis

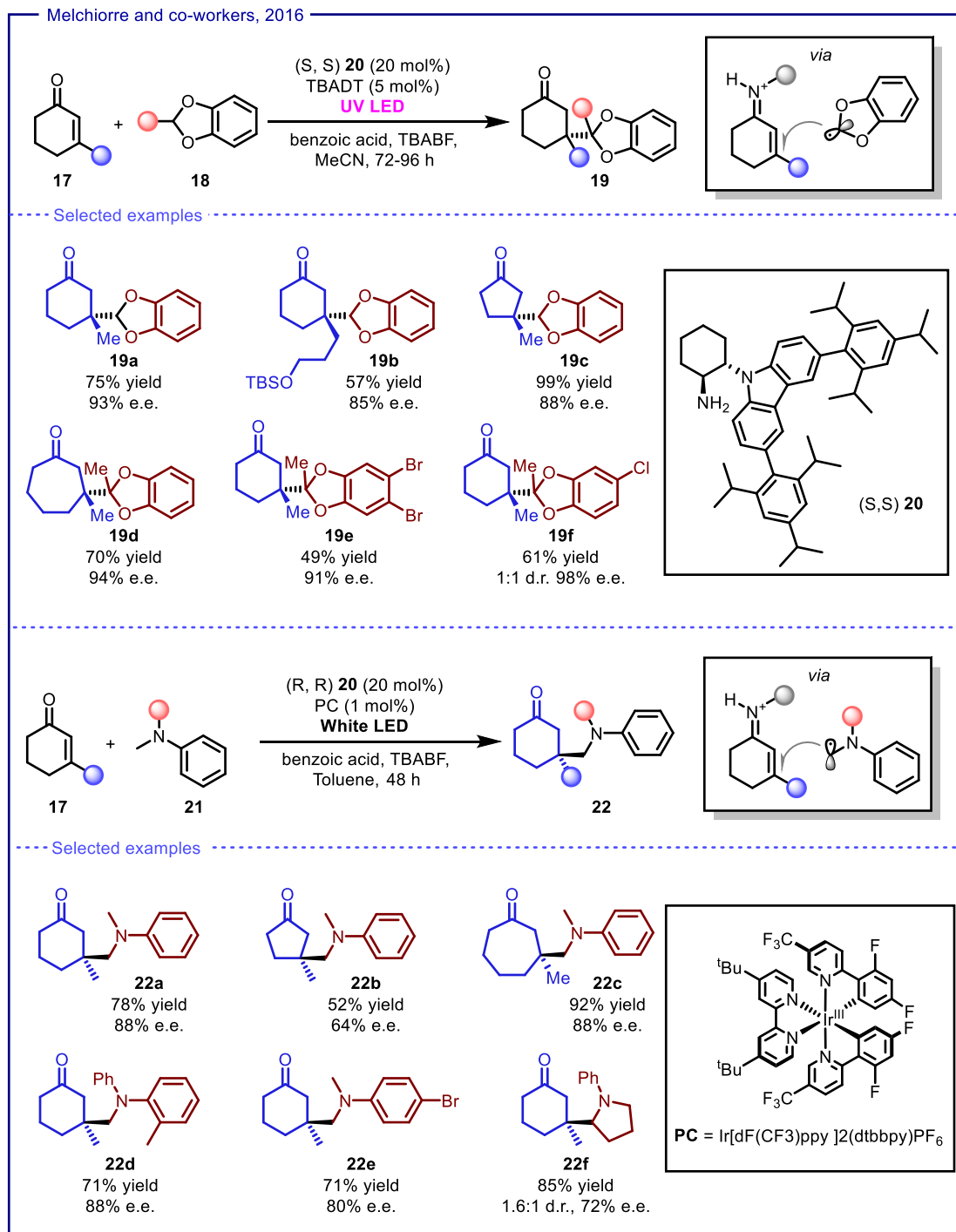
One of the most important aims of organic chemistry is the development of innovative catalytic strategies which allows the production of novel chiral building blocks forging carbon-carbon bonds.¹⁰ Although considerable advancements have been made in the area of polar chemistry, radical transformations have been far less successful. However, in contrast with polar chemistry, radical addition to electron-poor olefine is rather insensitive to steric hindrance,¹¹ making the reaction particularly suitable for the connection of structurally complex centres while forging chiral quaternary centres. In 2016, the Melchiorre group¹⁰ took advantage of this characteristic to propose an iminium ion-mediated procedure to forge novel chiral centres, exploiting the Giese reaction (Scheme 4.5). The group proposed two different procedures which allow the 1,4 functionalisation of unsaturated ketone **17** with different structures. On one side, the authors use benxodioxole scaffolds **18** (Scheme 4.5, top) mediated by TBADT and UV light. On the other side, they used phenyl amines **21** (Scheme 4.5, bottom) mediated by an Ir photocatalyst and white light. Both methods rely on the formation of the iminium ion between the ketone **17** and the bulky amine **20**. Interestingly, in the two reactions, the

¹⁰ Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, 532, 218–222.

¹¹ Fischer, H.; Radom, L. *Angew. Chem. Int. Ed.* **2001**, 40, 1340–1371.

Polarity Transduction Enables the Formal Electronically Mismatched Radical Addition to Alkenes

authors used the two different enantiomers of the amine catalyst **20**, achieving different geometrical configurations of the C4 on the ketone scaffold. The reaction scope presented shows the functionalisation of different unsaturated ketones, containing a synthetically useful protected alcohol **19b**, or different ring sizes (**19a**, **19c**, **19d**, **22a**, **22b** and **22c**). Different benzodioxoles e.g., containing sp^2 halides useful for further manipulation have been successfully applied in this chemistry producing compounds **19e** and **19f**.



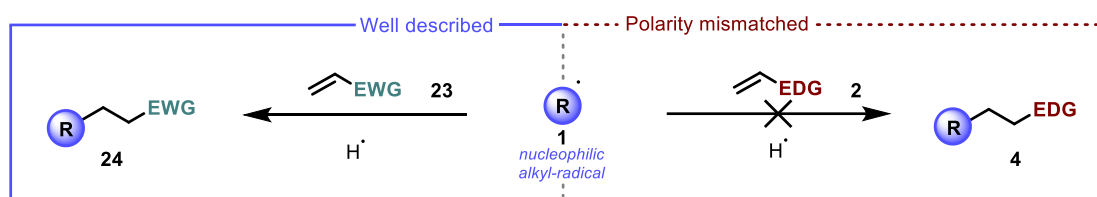
Scheme 4.5: Melchiorre 2016: The use of the Giese reaction for the synthesis of different chiral building blocks.¹⁰

For the visible light-driven section, the author presented several different phenyl amines. In particular, an amine bearing a synthetically useful aromatic bromide was

submitted to this chemistry, producing compound **22e**. Similarly, a tertiary cyclic amine was used to produce adduct **22f**.

4.2.3. Limitations of the Giese reaction

Although the addition of carbon-centred radicals to alkenes represents one of the most important and versatile processes in radical chemistry, the scope of this chemistry is limited by the strict polarity matching required between the radical and the unsaturated partner. As presented in Scheme 4.6, alkyl radical **1** (typical electron-rich) smoothly reacts with electron-poor double bonds **23**, while the addition of the same radical **1** to electron-rich olefin **2** is kinetically unfavoured and does not practically occur.



Scheme 4.6: The addition of electron-rich radical **1** to electron-poor alkene **23** is well described (left). The addition of the same open-shell species **1** to an electron-rich alkene **2** is kinetically unfavored and practically does not occur (right).

The reason for such reactivity can be rationalised in terms of FMO interaction.

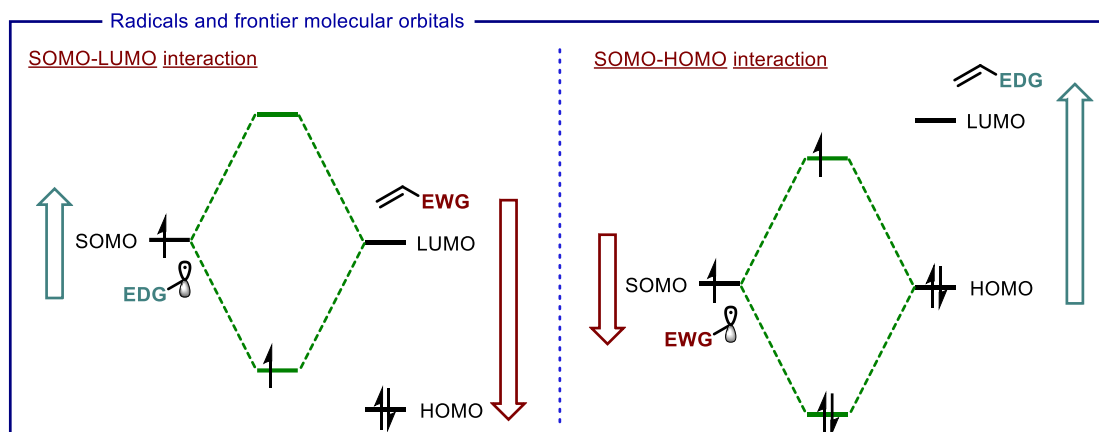
FMO theory behind radical selectivity

The absence of a charge in radicals switches off all the Coulombic interactions that drive and guide the standard polar chemistry. Therefore, the behaviour of radical reactivity can be erratic in organic synthesis if treated with the principles of standard, polar chemistry.¹² Radical reactions are instead driven and guided by frontier molecular orbital (FMO) interactions.¹³ The approaching frontier orbital on the side of the radical is called SOMO (Single Occupied Molecular Orbital). It can react with two of the alkene orbitals: the HOMO or the LUMO. To match the energy of the two orbitals, and so ensure the best interaction, electron-withdrawing and electron-donating groups are required (Scheme 4.7) as they, respectively, decrease or increase the orbital energies. When an electron-rich radical (Scheme 4.7, left) – which has a high energy SOMO – approaches a double bond, the interaction will be favourable if the double bond has an EWG that reduces the energy of the LUMO making the two orbitals similar in terms of energy. On the other hand, when an electron-poor radical (Scheme 4.7, right) – which has a low-energy SOMO – approaches a double bond, the interaction will be favourable if the double bond possesses an EDG which increases the energy of the HOMO.

¹² Walling, C. *Tetrahedron*, **1985**, 41, 3887-3900.

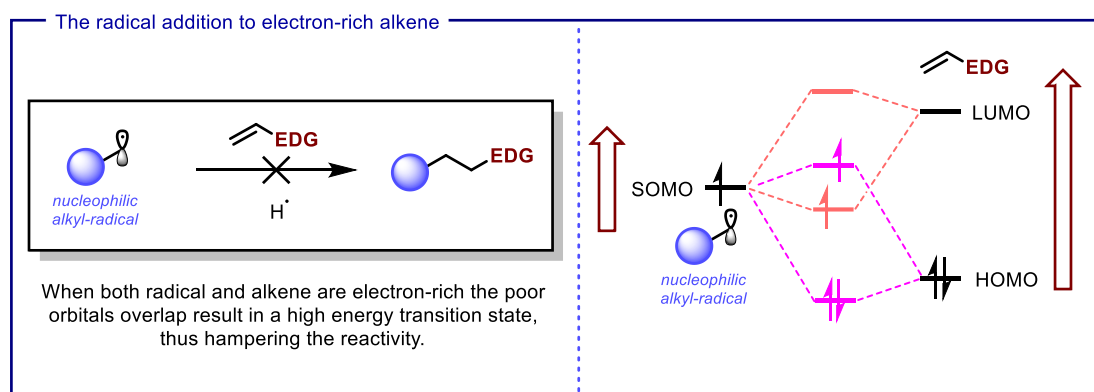
¹³ Fleming I., *Molecular Orbital and Organic Chemical Reaction: Student Edition*. Wiley & Sons Ltd, **2009**, Chapter 7.

Polarity Transduction Enables the Formal Electronically Mismatched Radical Addition to Alkenes



Scheme 4.7: FMOs overlap produces a more stabilised orbital (green) when the overlapping orbitals are similar in energy. EWG or EDG groups change the FMO energy and therefore favour or disfavour a reaction pathway. A radical bearing an EDG group (left) will efficiently overlap with the LUMO of an alkene equipped with an EWG group while a radical bearing an EWG group (right) will more favourably react with an alkene equipped with an EDG group.

Therefore, the addition of a nucleophilic alkyl radical, nucleophilic, radical to an electron-rich unsaturated system is kinetically unfavoured (Scheme 4.8). This leads to a less stabilised transition state, sluggish reaction and other reactivity (e.g., H-atom abstraction from solvent, dimerisation, disproportionation or undesired redox processes).

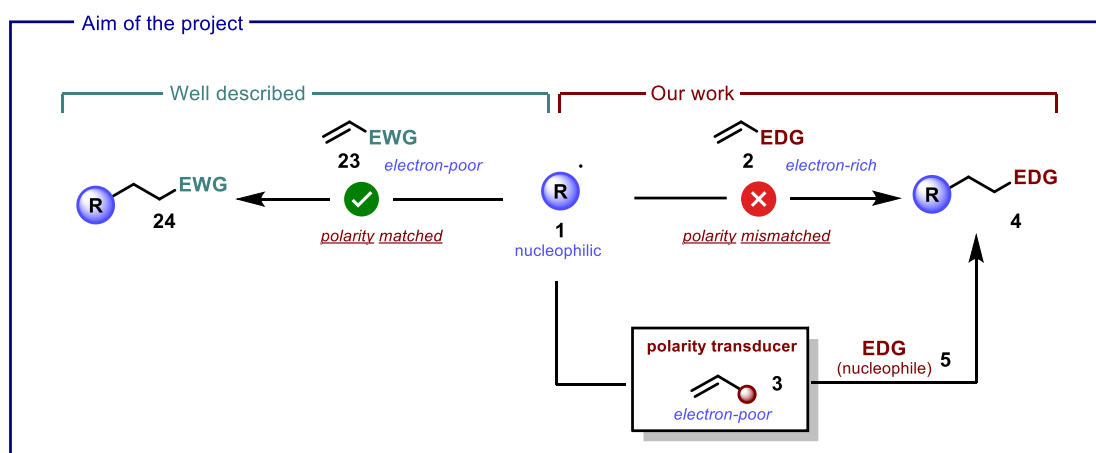


Scheme 4.8: Mismatched orbital overlap between the FMO of an electron-rich radical and the FMO of an electron-rich olefine.

Hence, in the following section, we described a procedure developed during the work of my PhD that formally overcome this important limitation, allowing to significantly extend the scope of classic Giese reactivity

4.3. Aim of the project

In this Chapter we describe the development of a novel strategy which circumvents the polarity-matching limitations of traditional radical addition to alkene (described in the previous section). To this aim, we design a novel strategy in organic synthesis that we defined *polarity transduction*, based on the use of an alkene carrying a functional group able to direct the electronics of the radical process, and can then be displaced by a nucleophile to lead to forbidden products **4**, formally reversing the polarity of the unsaturated system.



Scheme 4.9: Aim of the project: with the development of a *polarity transducer* **3**, the kinetically unfavoured product **4**, formally obtained from the addition of the radical **1** to olefine **2**, can now be efficiently made.

Designing of the process

Designing of the *polarity transducer*

To design our *polarity transducer*, we took into consideration three major factors (Scheme 4.10). First, it should be electron-deficient in nature, removing electron density from the neighbouring π -system, thus lowering the energy of the alkene **2** LUMO and promoting the radical addition. Second, it should be a good leaving group, allowing an easy nucleophilic displacement to access product **4** from Giese adduct **25**. Third, it needs to be stable under radical conditions; its electronic features should inhibit radical polymerisation, a process typically occurring in vinyl halides.¹⁴

¹⁴ Blauer, G.; Shenblat, M.; Katchalsky, A. *J. Polym. Sci.* **1959**, *38*, 189–204.

Visible light irradiation would generate the highly oxidative photoexcited PC*. SET between this species and the carboxylate anion **27**, followed by rapid decarboxylation, would reveal carbon-centred radical **1**, nucleophilic in nature. Subsequent polarity-matched Giese addition to the β position of the electron-poor vinyl sulfonium **2** would lead to radical **28**. Facile SET with the reduced photocatalyst (PC⁻), would lead to sulfonium ylide which would undergo immediate protonation to afford intermediate **25**. Finally, in the presence of nucleophile **5**, intermediate **25** would undergo nucleophilic displacement to provide final compound **4**: the formal product of the forbidden radical addition to an electron-rich double bond.

4.4. Result and Discussion

4.4.1. Optimisation studies

Preliminary studies focused to evaluate the feasibility of the individual radical addition process, the yield of the intermediate **25** (prior to S_N2) was then evaluated by ¹H-NMR analysis of the crude reaction mixture using an internal standard.

Design of the polarity transducer structure

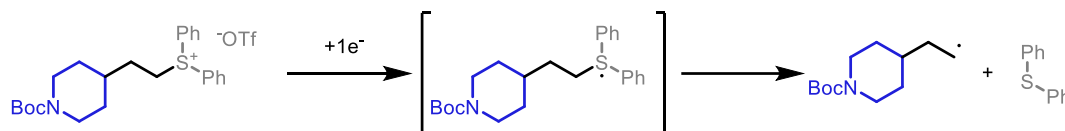
We commenced our investigation by irradiating a mixture of N-Boc-isonicopetic acid **26a**, vinyl systems **2**, potassium phosphate and photocatalyst 4CzIPN (Table 4.2).

Table 4.2: Test results of different polarity transducers.

Entry ^a	X	PC	Yield 25 (%) ^b
1	Br	4CzIPN	0
2	⁺ S(Ph) ₂ [OTf] ⁻	4CzIPN	42
3	⁺ S(Ph) ₂ [OTf] ⁻	3CzClIPN	59

^a Reactions performed in 0.05 mmol scale, using **26a** (1.0 equiv.), **9** (1.5 equiv.), [**26a**]₀ = 0.15M. ^b ¹H-NMR yield using CH₂Br₂ as internal standard.

We first focused our attention on vinyl bromide **2a**, as it is the simplest alkene that could be applied for this methodology. However, polymerisation was observed with no formation of product **25** (entry 1). Interestingly, when known diphenyl sulfonium triflate **2b** (entry 2) was used, the formation of product **25** was observed, albeit in poor yield. In this reaction, ¹H-NMR analysis showed a complex mixture and poor mass balance due to the tendency of di-aryl sulfonium system to undergo undesired reductive cleavage pathways¹⁷ (Scheme 4.12).



Scheme 4.12: Possible decomposition mechanism of sulfonium intermediate **25**.

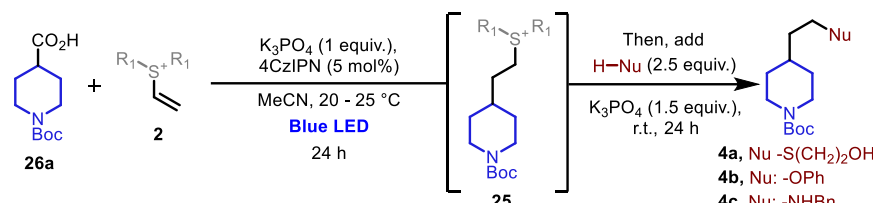
In consonance with this hypothesis, upon changing photocatalyst to the less reductive 3CzClIPN ($E_{1/2}$ (PC/PC⁻) 4CzIPN -1.24 V vs SCE while 3CzClIPN -1.16 V vs SCE)¹⁸ in entry 3; the yield slightly increased from 42% to 59%. While this was an interesting improvement, the yield could not be significantly improved from this value.

¹⁷ a) Péter, Á.; Perry, G. J. P.; Procter, D. J. *Adv. Synth. Catal.* **2020**, 362, 2135–2142. b) Dewanji, A.; van Dalsen, L.; Rossi-Ashton, J. A.; Gasson, E.; Crisenza, G. E. M.; Procter, D. J. *Nat. Chem.* **2023**, 15, 43–52.

¹⁸ Speckmeier, E.; Fischer, T. G.; Zeitler, K. *J. Am. Chem. Soc.* **2018**, 140, 15353–15365.

We envisioned that the functionalisation of the sulfonium structure with more bulky alkyl later chains would improve its stability, thus enhancing the efficiency of the process (Table 4.3).

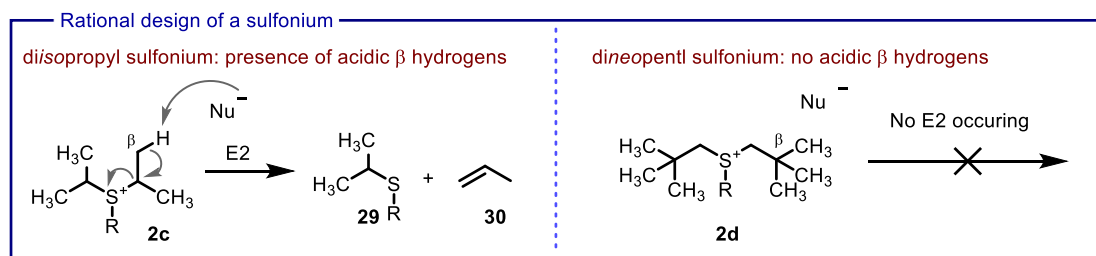
Table 4.3: Test of other structures of the polarity transductor.



Entry ^a	R ₁	Yield 25 (%) ^b	Yield 4a (%) ^b	Yield 4b (%) ^b	Yield 4c (%) ^b
1	Ph	42	35	-	-
2	<i>i</i> Pr	92	90	Traces	Traces
3 ^c	CH ₂ ^t Bu	86	77	64	70 ^d

^a Reactions performed in 0.05 mmol scale, using **26a** (1.0 equiv.), **2** (1.5 equiv.), [**26a**]₀ = 0.15M. Nucleophile addition was performed following the general procedures A, B and C as reported in the general experimental. ^b Unless otherwise stated, ¹H-NMR yield using CH₂Br₂ as internal standard. ^c Reaction scale 0.2 mmol. ^d Second step was performed at 80 °C

Therefore, a vinyl sulfonium ion, bearing two bulky isopropyl groups, was tested. Remarkably, using this alkene **2c**, the formation of intermediate **25** was observed in excellent yield (entry 2). By sequentially adding 2-mercaptoethanol **5a** to the crude reaction mixture (entry 2), the desired product **4a** was obtained in 90% yield. However, only traces of desired products **4b-4c** were detected when N- or O-nucleophiles were used (entry 2). In such cases, the nucleophile acting as a base promote E2 elimination, leading to the formation of sulfide **29** and propene gas **30** (Scheme 4.13, left).¹⁹ To circumvent the issue, a novel sulfonium **2d** fitted with bulky neopentyl groups lacking hydrogens in β position was designed (Scheme 4.13, right). Subjecting this sulfonium to our reaction conditions, intermediate **25** was formed in 86% yield. The intermediate was observed to undergo nucleophilic substitution with high generality, efficiently reacting with sulfur **5a**, oxygen **5b** and nitrogen **5c** nucleophiles.



Scheme 4.13: Rational design of alkyl groups of the sulfonium **2**.

¹⁹ Wang, Y.; Zhang, W.; Colandrea, V. J.; Jimenez, L. S. *Tetrahedron* **1999**, 55, 10659–10672.

Investigation of the standard reaction parameters

Photocatalyst screening

With the aim of maximising the yield of the process, a number of photocatalyst structures were tested, monitoring the yield of the process *via* $^1\text{H-NMR}$ analysis of the reaction mixture.

Table 4.4: Photocatalyst screening.

Entry ^a	PC	Yield 4a (%) ^b
1 ^c	4CzIPN ^d	77
2	Ru(bpy) ₃ (PF ₆) ₂	0
3	[Ir(dtbbpy)(ppy) ₂](PF ₆) ₃	3
4	(Ir[dF(CF ₃)ppy] ₂ (dtbbpy))(PF ₆) ₃	19

^a Reactions performed in 0.05 mmol scale, using **26a** (1.0 equiv.), **2d** (1.5 equiv.) and K₃PO₄ (1 equiv.), [**26a**]₀ = 0.15M. Then 2-mercaptoethanol (2.5 equiv.) and K₃PO₄ (1.5 equiv.) were added. ^b $^1\text{H-NMR}$ yield using CH₂Br₂ as internal standard. ^c Reaction scale 0.2 mmol. ^d photocatalyst loading: 5 mol%.

As presented in Table 4.4, the use of Ru- or Ir-based catalysts did not improve the results. Instead, when such catalysts were used, compound **4a** was obtained in poor yields.

Solvent screening

The effect of the reaction medium was then investigated (Table 4.5).

Table 4.5: Solvent screening.

Entry ^a	Solvent	Yield 4a (%) ^b
1 ^c	MeCN	77
2	DMF	59
3	DMSO	63
4	THF	49

^a Reactions performed in 0.05 mmol scale, using **26a** (1.0 equiv.), **2d** (1.5 equiv.) and K₃PO₄ (1 equiv.), [**26a**]₀ = 0.15M. then 2-mercaptoethanol **5a** (2.5 equiv.) and K₃PO₄ (1.5 equiv.) were added. ^b $^1\text{H-NMR}$ yield using CH₂Br₂ as internal standard. ^c Reaction scale 0.2 mmol.

Both the use of polar (i.e., DMF, DMSO) as well as relatively apolar aprotic solvents (i.e., THF) did not lead to significant improvements (entries 2, 3, and 4), leading to increased decomposition of sulfonium **2d**. Therefore, acetonitrile was selected as the optimal reaction medium.

Extended optimisation studies were performed to identify the best reaction conditions for each nucleophile. Selected studies are presented in the general experimental section for brevity.

4.4.2. Scope studies

With the optimised conditions in hand, we investigated the scope of the process by submitting a variety of sulfur, nitrogen and oxygen nucleophiles to the reaction conditions, using **26a** as model carboxylic acid.

Nucleophile scope

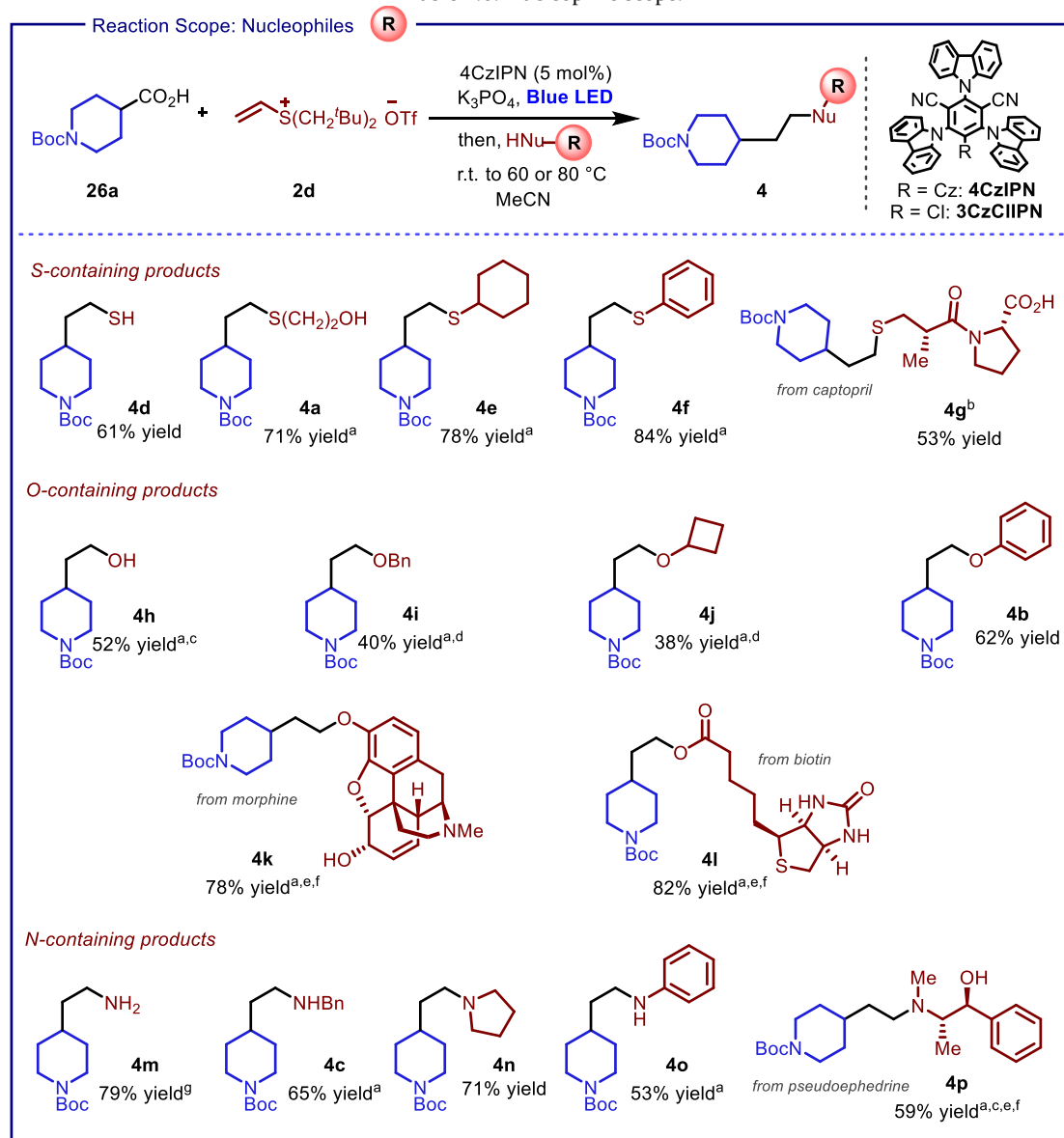
We started our investigation by performing our photochemical process followed by adding a variety of S-nucleophiles to the reaction vessel. Thiol **4d** was conveniently generated in 61% yield using commercial sodium hydrosulfide (see experimental section for optimisation details). Sulfides **4a**, **4e** and **4f** were practically obtained adding from the corresponding thiols. Using the hypertension medicament captopril as a nucleophilic stoichiometric limiting reagent, derivative **4g** was obtained in 53% yield. To avoid undesired alkylation of the carboxylic acid functionality, the reaction was performed by generating the captopril dianion with 2 equivalents of NaH in a separated vessel, followed by addition to the sulfonium mixture in DMF (see experimental section for details).

We then submitted a variety of oxygen nucleophiles to our reaction conditions. Alcohol **4h** was synthesised using a solution of H₂O/HMPA and potassium bicarbonate to promote the solvolysis of the corresponding sulfonium intermediate (experimental section for optimisation details). Primary, secondary and aromatic alcohols were observed to be competent nucleophiles, leading to compounds **4i**, **4j** and **4b** respectively in 40%, 38% and 62% yield. When aliphatic alcohols were used as nucleophiles (**4i** and **4j**), vinyl diphenyl sulfonium triflate **2b** was used in combination with the less reducing catalyst 3CzClIPN (see experimental section for optimisation details) and the second step was performed using potassium *tert*-butoxide as a base. The use of morphine as a nucleophile led to compound **4k** in 78% yield, without detectable side reactivity arising from the nucleophilic allylic alcohol or the tertiary amine present in the complex scaffold. Subjecting unmodified D-biotin as the nucleophilic partner to the reaction mixture produced compound **4l** in 82% yield, opening this chemistry to possible applications in biotinylation strategies.

We then investigated the use of nitrogen nucleophiles. Using a solution of ammonia in methanol as the source of nitrogen, primary amine **4m** was produced in 79% yield. Primary, secondary, and aromatic amines successfully underwent the desired reactivity leading respectively to compounds **4c**, **4n** and **4o** in 65%, 71% and 53% yield. Pseudoephedrine, a decongestant bearing an amine and a neighbour alcohol

functionality, underwent selective N-functionalisation to provide compound **4p** in 59% yield.

Table 4.6: Nucleophile scope.



Reactions were performed in a 0.2 mmol scale, using **26** (1 equiv), **2d** (1.5 equiv), 4CzIPN (5 mol %), and nucleophile (typically 2.5 equiv), in MeCN unless otherwise stated; see general experimental for full experimental details. ^a Compound synthesised by Dr Subhasis Paul. ^b Preformed captopril dianion was used as limiting reagent (see General experimental for full details). ^c After nucleophile addition, the reaction was sealed and heated to 120 °C. ^d Diphenyl vinyl sulfonium triflate **2a**, ^tBuOK, catalytic 3CzClIPN were used and irradiation was performed at 0 °C. ^e Reaction stoichiometry: **26a** (2.0 equiv), **2d** (2.2 equiv), 4CzIPN (10 mol %), and nucleophile (1.0 equiv). ^f 0.1 mmol scale. ^g After nucleophile addition, the reaction was sealed and heated to 100 °C. Cz: carbazoly; Boc, *N*-*tert*-butoxycarbonyl; Bn, benzyl.

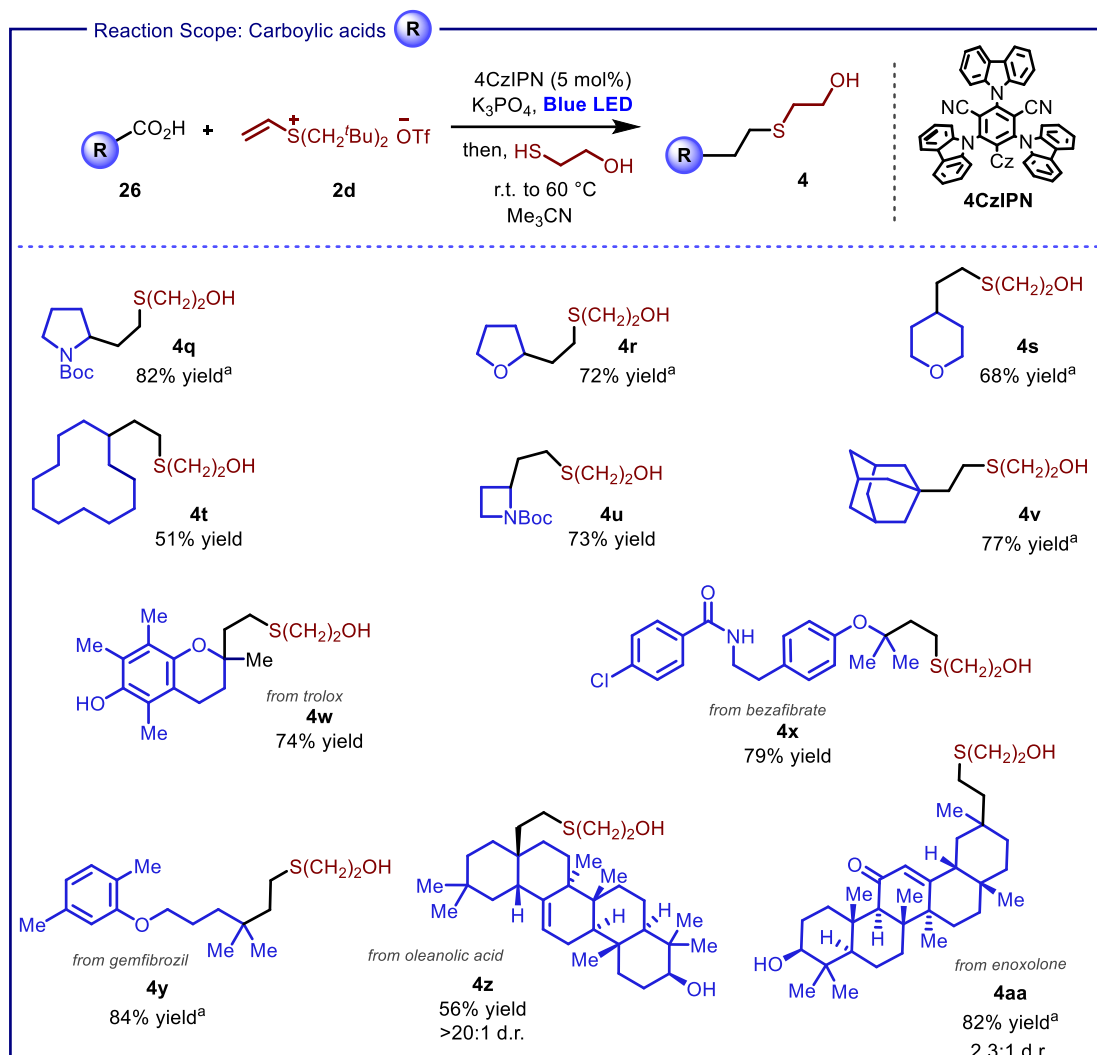
Carboxylic acid scope

We then investigated the generality of our strategy submitting a variety of model and complex carboxylic acids to our reaction conditions. Different N- or O- heterocyclic carboxylic acids promptly underwent the desired reactivity leading to compounds **4q**, **4r** and **4s** in good to excellent yields. Cyclic carboxylic acids with different ring sizes i.e., macrocycle **4t** and strained 4-membered ring **4u**, were obtained respectively in 51%

Polarity Transduction Enables the Formal Electronically Mismatched Radical Addition to Alkenes

and 73% yield. Finally, compound **4v** was obtained in 77% yield from bulky adamantane carboxylic acid.

Table 4.7: Carboxylic acids scope.

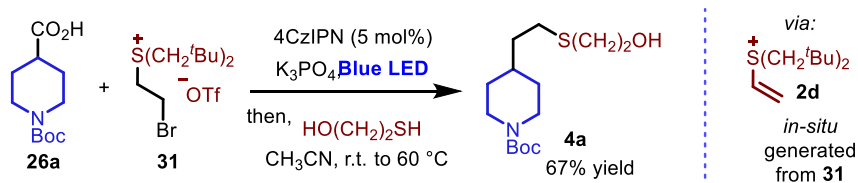


Reactions were performed in a 0.2 mmol scale, using **26** (1 equiv), **2d** (1.5 equiv), 4CzIPN (5 mol %), and nucleophile (typically 2.5 equiv), in MeCN unless otherwise stated; see general experimental for full experimental details.
^aCompound synthesised by Dr Subhasis Paul. Cz: carbazoyl; Boc, *N*-tert-butoxycarbonyl.

We then focused on the application of our chemistry in the LSF of complex and bioactive carboxylic acids. Trolox, a vitamin E analogue, was effectively converted into compound **4w** in 74% yield, with no observable side reactivity arising from the phenolic OH group. Bezafibrate and gemfibrozil, drugs which have found extensive application in the treatment of hyperlipidaemia, successfully underwent the desired reactivity producing respectively compounds **4x** and **4y** in 79% and 84% yield. Finally, complex steroid structures – bearing a variety of functionalities e.g., free alcohols, carbonyl and electron-poor and non-activated alkenes – were successfully converted into desired products **4z** and **4aa** respectively in 56% and 82% yield.

Reaction with the *in-situ* generation of vinyl sulfonium **2d**

To further enhance the synthetic utility of the chemistry, we envisioned to generate *in-situ* the key vinyl sulfonium **2d** from bromo-sulfonium **31**, a synthetic intermediate *in-route* to vinyl sulfonium **2d** (Scheme 4.14).



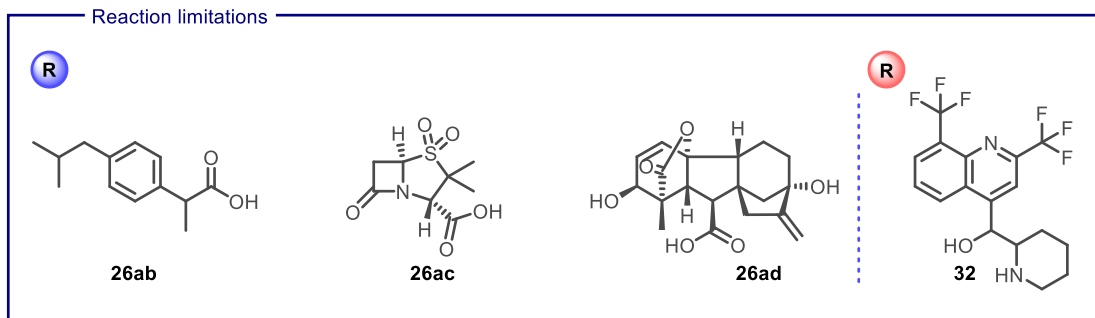
Scheme 4.14: *In-situ* generation of sulfonium **2d**.

Remarkably, by submitting bromo-sulfonium **31** to the reaction conditions led to the desired product **4a** in 67% yield, comparable with the yield obtained using the corresponding vinyl sulfonium salt **2d**.

4.4.3. Reaction limitations

A few substrates did not undergo the expected reactivity (structures reported in Table 4.8). Ibuprofen **26ab** – presumably providing a less reactive benzylic radical – did not undergo the desired reactivity, leading to full recovery of the acid. Sulbactam **26ac**, an inhibitor of β -lactamase, showed complete decomposition with no formation of desired product. Gibberellic acid **26ad**, showed completed and fast decomposition, likely due to unselective intramolecular radical processes occurring on the complex unsaturated substrate scaffold. Finally, mefloquine **32** – an antimalarial medicine – did not show any reactivity, with full recovery of the nucleophile.

Table 4.8: Reaction limitations.



4.5. Conclusion

In this chapter, a novel synthetic strategy which formally circumvents the polarity matching limitations of the intermolecular addition of carbon-centred radicals to alkenes is introduced. By allowing practical access to products that would be the result of the forbidden addition of nucleophilic radical to an electron-rich olefin, the methodology redefines the scope of the classical addition of alkyl radicals to double bonds. Since the Giese reaction is already widely used in different areas of organic chemistry – e.g., total synthesis and late-stage functionalisation – we envision that this methodology will stimulate considerable advances in various areas of synthesis, redefining the scope of the classic addition of carbon-centred radicals to double bonds.

4.6. General experimental

4.6.1. Solvents, reagents, and starting materials

All air and water-sensitive reactions were carried out in oven-dried glassware under argon atmosphere using standard Schlenk manifold technique. The solvents were degassed when required by bubbling argon through the solvent for ten minutes. Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. All solvents were commercially supplied or provided by the communal stills of the School of Chemistry, University of Nottingham. Commercially available compounds were purchased from Sigma Aldrich, Alfa Aesar, Acros, Fluorochem, TCI chemicals and used as received. Dry solvents were purchased from Acros Organic, Extra Dry over molecular sieves, AcroSeal®.

Compounds **26a**,²⁰ **26f**,²¹ diisopropyl(vinyl)sulfonium triflate **2c**,¹⁹ diphenyl(vinyl)sulfonium triflate **2b**²² and 4CzIPN²³ were synthesised following reported procedures.

4.6.2. Chromatography and instrumental analysis

Flash column chromatography (FCC) was carried out using Sigma-Aldrich silica gel LC60A-40 (63 µm). All reactions were followed by thin-layer chromatography (TLC) when practical, using Merck Kieselgel 60 F₂₅₄ fluorescent treated silica which was visualised under UV light, by staining with aqueous basic potassium permanganate, phosphomolybdic acid or with ninhydrin solutions.

¹H-NMR, ¹³C-NMR and ¹⁹F-NMR spectra were recorded using Bruker broadband prodigy cryoprobe AV(III)500HD 500 MHz and Bruker AV(III)400HD 400 MHz spectrometers. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) are given in hertz (Hz). The ¹H-NMR spectra are reported as follows: ppm (multiplicity, coupling constants, number of protons). High resolution mass spectra (HRMS) were recorded on a Bruker MicrOTOF II by Electrospray Ionization (ESI). IR spectra were recorded on a Bruker Vertex 70 FT-IR ATR as a thin film. Only selected absorption maxima (ν_{max}) are reported in wavenumbers (cm⁻¹). Melting points were recorded in degrees Celsius (°C), using a Stuart melting point SMP 20 microscope apparatus and are reported uncorrected. Optical rotation ([α]_D²⁵) was recorded on an Anton Paar MCP 100 at 25 °C, in chloroform, with a concentration of 1g/100mL.

²⁰ Fuentes, J. A.; Carpenter, I.; Kann, N.; Clarke, M. L. *Chem. Commun.* **2013**, 49, 10245–10247.

²¹ Chu, W.; Zhang, J.; Zeng, C.; Rothfuss, J.; Tu, Z.; Chu, Y.; Reichert, D. E.; Welch, M. J.; Mach, R. H. *J. Med. Chem.* **2005**, 48, 7637–7647.

²² Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2008**, 20, 3784–3786.

²³ Huang, H.; Yu, C.; Zhang, Y.; Zhang, Y.; Mariano, P. S.; Wang, W. *J. Am. Chem. Soc.* **2017**, 139, 9799–9802.

4.6.3. Naming of compounds

Compound names are generated by ChemDraw 20.0 software (PerkinElmer), following the IUPAC nomenclature.

4.6.4. LEDs

Irradiation of reaction mixtures was performed using Kessil lamp A160WE Tuna Blue Saltwater LED Light 40W set to blue at maximum intensity. Lamp emission is observed to decay over long usage due to LED chip deterioration. To ensure reproducibility of the results, we recommend using new lamps. If needed, full conversion of the photochemical reactions detailed in section 4.6.8 can be ensured *via* ¹H-NMR analysis of a minimal reaction aliquot after irradiation, monitoring disappearance of the characteristic reagent vinyl signals at 6.38 – 6.32 ppm.

4.6.5. Optimisation studies

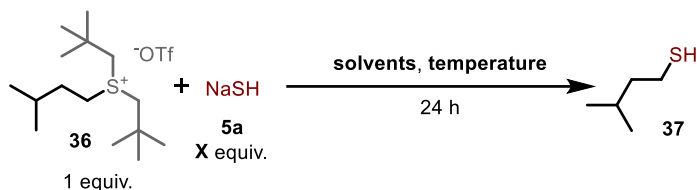
Optimisation studies of the nucleophilic displacement

As we found that different nucleophiles undergo S_N2 reactivity with the intermediate sulfoniums under different conditions, optimisation studies of the standard reaction parameters were performed. For practicality, the optimisations were performed using sulfonium **35**, a model system for intermediate **25**. When possible, the same solvent system and base used in the photochemical step were maintained, to allow to perform the full process by simply adding reagents to the mixture without any manipulation.

Hydrosulfide

The optimisation studies of the reaction condition using an inorganic source of sulfur as nucleophile are presented in Table 4.9 below.

Table 4.9: Hydrosulfide optimisation studies.



Entry ^a	Solvent	NaSH equiv.	Temp. (°C)	Yield (%) ^b	Recover 36 (%) ^c
1	MeOH	1.25	60	49	0
2	MeOH	2.50	60	53	0
3 ^d	MeCN	2.50	r.t.	66	0

^a Reactions performed in 0.05 mmol scale in a 2 mL vial, [**36**]₀ = 0.15M. ^b ¹H-NMR yield using CH₂Br₂ as internal standard. The yields presented in this table may also include variable amounts of symmetric disulfide, difficult to estimate by NMR due to signal overlap. Disulfide formation can be completely suppressed using degassed solvents under Ar (see section 4.6.8 for details). ^c Starting material recovery of the model sulfonium **36** established by ¹H-NMR analysis using CH₂Br₂ as internal standard. ^d 30 mol % of tetrabutyl ammonium bromide was added to increase the solubility of the nucleophile.

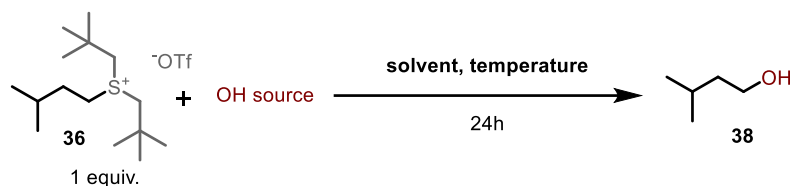
We started this optimisation mixing model sulfonium **36** with 1.25 equivalents of sodium hydrosulfide at 60°C (entry 1). Pleasingly, we observed 49% yield of the expected product **37**. To further increase the yield, a higher loading of NaSH was used in entry 2, however, only a slight increase in yield was observed. A different solvent system was then tested in entry 3. The methanol was changed to MeCN and 30% of tetrabutyl ammonium bromide was used to improve the solubility of the nucleophile. Remarkably, 66% yield was detected already at room temperature.

Water

These studies were performed by Dr. Subhasis Paul.

The optimisation studies of the reaction condition using water as nucleophile are presented in Table 4.10 below.

Table 4.10: Water optimisation studies.



Entry ^a	OH source	Solvent	Temp. (°C)	Yield (%) ^b	Recovery 36 (%) ^c
1	Bu ₄ N ⁺ OH ^d	DCM (0.15M)	60	10	0
2	H ₂ O ^e	DMPU (0.25M)	100	0	88
3	H ₂ O ^e	HMPA (0.25M)	100	50	20
4	H ₂ O ^e	HMPA (0.25M)	120	74	0
5 ^f	H ₂ O ^e	HMPA (0.25M)	120	87	0

^a Reaction performed in a 0.05 mmol scale in a 2 mL Young tube. ^b ¹H-NMR yield using CH₂Br₂ as internal standard. ^c starting material recovery of the model sulfonium **36** established by ¹H-NMR analysis using CH₂Br₂ as internal standard. ^d Bu₄N⁺OH⁻ · 30H₂O. ^e 45 equiv. ^f 1.3 equiv. of KHCO₃ was added.

We started this investigation using tetrabutylammonium hydroxide in DCM as a source of HO⁻ (entry 1). Unfortunately, only 10% yield was detected. Inspiring ourselves on a

similar process performed on alkyl halides,²⁴ we used a mixture of water/HMPA to promote the solvolysis of model compound **36**. Given the toxicity of HMPA, we first tested DMPU, a less toxic solvent but similar in structure to HMPA. However, no product was detected and high recovery of starting material **36** was observed (entry 2). We tested the water/HMPA mixture at 100°C and we were pleased to observe 50% yield of the expected product (entry 3). However, given that there was still 20% of starting material **36** recovery, we tested if we can speed up the reaction by raising the temperature to 120°C (entry 4). Pleasingly we observed that the yield increased to 74%. Finally, we question if a mild base like K₃PO₄ would further improve the reactivity (entry 5). As expected, 87% yield was detected. This can be rationalised by the development of triflic acid as a side product of the reaction which might decompose the model sulfonium **36** before the completion of the reaction.

Ammonia

The optimisation studies of the reaction condition using an ammonia solution as nucleophile are presented in Table 4.11 below.

Table 4.11: Ammonia optimisation studies.

Entry ^a	NH ₃ solution	Temp. (°C)	Yield 39 (%) ^b
1	NH ₄ OH _(aq.) (35%)	100	33
2	NH ₄ OH _(aq.) (35%)	130	55
3	NH ₃ in MeOH (7M)	100	94
4	NH ₃ in MeOH (7M)	80	83

^a Reactions performed in 0.05 mmol scale in a 2 mL microwave vial. ^b ¹H-NMR yield using CH₂Br₂ as internal standard.

In entry 1 we solubilize our model sulfonium in ammonia in water (35%) and we performed the reaction in a sealed tube at 100°C. However, a poor 33% yield was detected. Increasing the temperature to 130°C (entry 2) slightly improved the yield to 55%. Changing to ammonia in methanol (7M) gave excellent result (entry 3). Finally, we tested if we could reduce the temperature to 80°C (entry 4) however, a slightly detrimental effect was observed.

Aliphatic alcohols

These studies were performed by Dr. Subhasis Paul.

The optimisation studies of the reaction condition using aliphatic alcohol as nucleophile are presented in Table 4.12 below. As with this specific class of nucleophiles the results obtained with the model system **36** were found to significantly differ from the full

²⁴ Sambol, M.; Benčić, P.; Erben, A.; Matković, M.; Mihaljević, B.; Piantanida, I.; Kralj, M.; Basarić, N. *Mol.* **2021**, *26*, 3355–3381.

photochemical process, the optimisation study was performed carrying out the full photochemical reaction, as presented below.

Table 4.12: Aliphatic alcohols optimisation studies.

Entry ^a	R ₁	Temp. (°C)	Solvent	Base	Yield 4i (%) ^b
1	CH ₂ ^t Bu	60	MeCN	K ₃ PO ₄ ^c	0
2	CH ₂ ^t Bu	r.t.	MeCN	^t BuOK ^c	10
3	CH ₂ ^t Bu	60	MeCN	^t BuOK	0
4	Ph ^{d,e}	0 to r.t.	MeCN	^t BuOK	31
5	Ph ^{d,e}	0 to r.t.	DMF ^f	^t BuOK	13
6	Ph ^{d,e}	0 to r.t.	DCM ^f	^t BuOK	47

^a Reactions performed in 0.05 mmol scale using **26a** (1.0 equiv.), **2** (1.5 equiv.) and K₃PO₄ (1 equiv.), [**26a**]₀ = 0.15M. ^b ¹H-NMR yield using CH₂Br₂ as internal standard. ^c 2.5 equiv. of base was used. ^d 3CzCIIPN (5 mol%) was used. ^e Photochemical step was performed at 0 °C. ^f *In-situ* solvent exchange using a standard Schlenk vacuum line.

Few parameters were screened in this process: the base used, the solvent, the temperature of the second step and also the nature of the substituent of the sulfonium **2**. With the standard conditions (reported in entry 1) no product **4i** was detected. This was rationalised by the fact that aliphatic alcohols are much less acidic than aromatic ones, and so potassium phosphate is not strong enough to effectively deprotonate them. Therefore, we tested potassium *tert*-butoxide (entry 2), a stronger base, at room temperature, which gave 10% yield. We questioned if raising the temperature would help the process (entry 3), however, product **4i** was not detected and a complete decomposition of intermediate **25** was observed. We then tested this process using diphenyl sulfonium **2b** in entry 4 and remarkably, we observed 31% yield. With a quick solvent screening (entries 4 to 6) we identify DCM as the best solvent, giving compound **4i** in 47% yield. Therefore the final conditions are the ones reported in entry 6.

Aromatic alcohol

The optimisation studies of the reaction condition using aromatic alcohol as nucleophile are presented in Table 4.13 below.

Table 4.13: Aromatic alcohols optimisation studies.

Entry ^a	[36] ₀ (M)	Yield (%) ^b	SMR (%) ^c
1	0.15	69	5
2	0.5	82	0
3	1.0	80	0

^a Reactions performed in 0.05 mmol scale in a 2 mL vial. ^b ¹H-NMR yield using CH₂Br₂ as internal standard. ^c Starting material recovery of the model sulfonium **36** established by ¹H-NMR analysis using CH₂Br₂ as internal standard.

We screened the concentration of the second step, testing 0.15, 0.5 and 1.0 M (respectively entry 1, 2 and 3). In entry 1, we observed traces of the starting material **36** left and we questioned if we could push the reaction further by increasing the concentration. We observed that at 0.5 M the yield improved, passing from 69% to 82%. When the concentration was increased even more (entry 3) however, no positive effect was observed.

Amines

The optimisation studies of the reaction condition using amine as nucleophile are presented in Table 4.14 below.

Table 4.14: Amine optimisation studies.

Entry ^a	Temp. (°C)	[S2] ₀ (M)	Yield (%) ^b	SMR (%) ^c
1	60	0.15	18	77
2	60	0.50	56	44
3	80	0.50	84	0

^a Reactions performed in 0.05 mmol scale in a 2 mL vial. ^b ¹H-NMR yield using CH₂Br₂ as internal standard. ^c starting material recovery of the model sulfonium **36** established by ¹H-NMR analysis using CH₂Br₂ as internal standard.

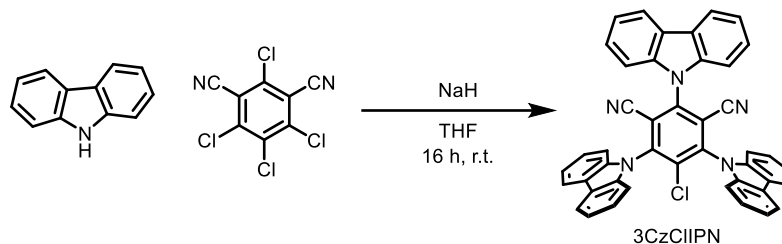
In this optimisation, we screened temperature and concentration. Raising the concentration from 0.15 M (entry 1) to 0.5 M (entry 2), the yield improved, passing from 18% to 56%. However, 44% of starting material **36** was recovered and we questioned if increasing the temperature would help the reaction. Indeed, when we

tested the reaction at 0.5 M at 80°C (entry 3) we were pleased to observe 84% yield of the expected product.

With this condition in our hands, we next looked at studying the generality of our strategy.

4.6.6. Synthesis of the photocatalysts and novel starting materials

Synthesis of 3CzCIIPN



3CzCIIPN was synthesised through a modification of a known procedure.²⁵

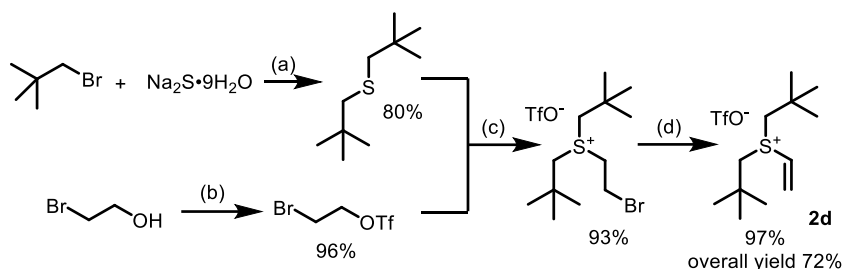
NaH (60% in oil; 4.3 mmol; 103 mg) was slowly added to a stirred solution of 9-carbazole (2.9 mmol; 477 mg) in dry THF (15 mL) under argon atmosphere at room temperature. After 30 min, tetrachloroisophthalonitrile (0.8 mmol; 202 mg) was added. After stirring at room temperature for 16 h, 80 μ L of distilled water were added to the mixture to quench the excess NaH. Then the solvent was evaporated under reduced pressure. The yellow powder was solubilized in DCM and celite was added. The solvent was removed again under reduced pressure and the resulting powder was dry-loaded and purified through column chromatography (SiO₂; gradient 6:4 to 4:6 hexane:DCM) to afford 3CzCIIPN (314 mg; 63%) as a bright yellow fine powder. ¹H-NMR (CDCl₃, 500 MHz) δ (ppm): 8.18 (d, J = 7.7 Hz, 6H), 7.64 – 7.53 (m, 6H), 7.50 – 7.35 (m, 8H), 7.28 (d, J = 8.2 Hz, 4H); ¹³C-NMR (CDCl₃, 126 MHz) δ (ppm): 145.2, 144.4, 139.9, 139.4, 137.2, 127.1, 127.0, 124.9, 124.7, 122.6, 122.3, 121.5, 121.4, 117.7, 110.8, 109.6, 109.4.

The spectra match the ones reported.²⁵

²⁵ Speckmeier, E.; Fischer, T. G.; Zeitler, K. *J. Am. Chem. Soc.* **2018**, *45*, 15353–15365.

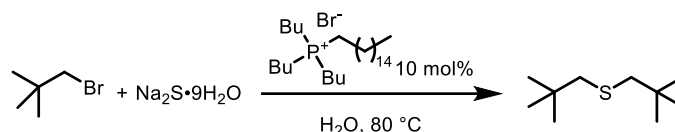
Synthesis of dineopentyl(vinyl)sulfonium triflate (2d)

Dineopentyl(vinyl)sulfonium triflate (**2d**) was synthesised as reported in Scheme 4.15.



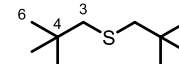
Scheme 4.15: Synthetic route for dineopentyl(vinyl)sulfonium triflate (a) tributylhexadecylphosphonium bromide (10 mol%), H₂O, 80 °C. (b) Tf₂O, Py, DCM, -20 °C to r.t. (c) DCM, r.t. (d) KHCO₃, THF:H₂O (2:1), r.t.

Synthesis of dineopentyl sulfide



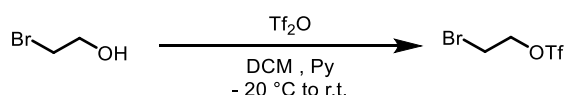
Dineopentyl sulfide was synthesised through a modification of a known procedure.²⁶

Na₂S·9H₂O (0.7 equiv.; 70 mmol; 16.8 g) and tributylhexadecylphosphonium bromide (0.1 equiv.; 10 mmol; 5.1 g) were loaded in a 100 mL round bottom flask equipped with a reflux condenser and dissolved in 30 mL of degassed water (degassed by argon sparging for 20 min). Neopentyl bromide (1.0 equiv.; 100 mmol; 12.6 mL) was added and the mixture was heated up to 80 °C for 24 h under vigorous stirring. The mixture was cooled down to room temperature and the organic layer was separated and vacuum distilled (108 °C at 50 mbar). To further remove traces of water, after the distillation the compound was passed through a Pasteur filled with anhydrous MgSO₄ to obtain the product (7.0 g; 80%) as a transparent oil. ¹H-NMR (CDCl₃, 500 MHz) δ (ppm): 2.45 (s, 4H, **3**), 0.98 (s, 18H, **6**); ¹³C-NMR (CDCl₃, 126 MHz) δ (ppm): 50.1 (**3**), 32.8 (**4**), 29.1 (**6**).



The spectra match the ones reported.²⁷

Synthesis of 2-bromoethyl trifluoromethanesulfonate



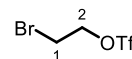
2-bromoethyl trifluoromethanesulfonate was synthesised following a known literature procedure.²²

Trifluoromethanesulfonic anhydride (1.04 equiv.; 83 mmol; 14 mL) was dropwise added to a stirred solution of pyridine (1.08 equiv.; 86 mmol; 7.0 mL) in dry DCM (76 mL) at -20 °C under argon atmosphere and the stirring was continued for 10 minutes. Then 2-bromoethanol (1.00 equiv.; 80 mmol; 5.7 mL) was slowly added to this cold

²⁶ Landini, D.; Rolla, F. *Synth.* **1974**, *8*, 565–566.

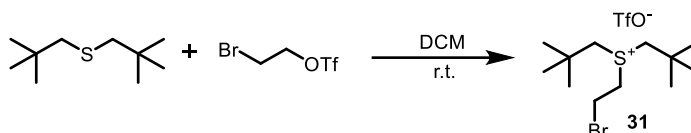
²⁷ Freeman, F.; Angeletakis, C. N.; Maricich, T. J. *Org. Mag. Reson.* **1981**, *17*, 53–58.

reaction mixture. The cooling bath was removed, and the mixture was left warming up to room temperature while stirring for 10 minutes (strictly following this time was found to be important). The resulting suspension was filtered, concentrated (using a rotary evaporator, maintaining the water bath below 20 °C) and petroleum ether (50 mL) was added. The mixture was again filtered and concentrated under reduced pressure and finally dried under high vacuum to give the product (19.7 g; 96%) as a light brown oil which was used for the next step without further purification. **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): δ 4.74 (t, J = 6.4 Hz, 2H, **2**), 3.61 (t, J = 6.4 Hz, 2H, **1**); **¹⁹F-NMR** (CDCl₃, 376 MHz) δ (ppm): -74.5 (s, 3F); **¹³C-NMR** (CDCl₃, 101 MHz) δ (ppm): 74.4 (**2**), 26.3 (**1**).

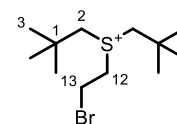


The spectra match the ones reported.²²

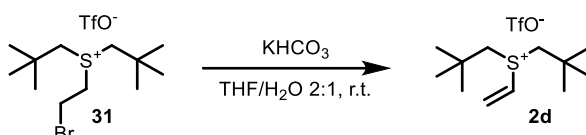
Synthesis of (2-bromoethyl)dineopentylsulfonium triflate (**31**)



Dineopentyl sulfide (1.0 equiv.; 40 mmol; 6.97 g) was dissolved in dry DCM (40 mL). 2-bromoethyl trifluoromethanesulfonate (1.1 equiv.; 42 mmol; 10.8 g) was added and the reaction was left stirring for 4 days at room temperature monitoring the conversion *via* ¹H-NMR analysis of a minimal reaction aliquot. The solvent was removed by rotary evaporation and the white solid was washed three times with 10 mL of hexane to give product **31** (16.1 g; 93%) as a white solid, which was used for the next step without further purifications. **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2965, 2876, 1476, 1400, 1372, 1255, 1157, 1030, 907, 755, 705, 637, 572, 518; **M.P.** = 97 °C; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): δ 4.24 – 4.16 (m, 2H), 3.80 – 3.73 (m, 2H), 3.68 (d, J = 14.4 Hz, 2H), 3.47 (d, J = 14.4 Hz, 2H), 1.19 (s, 18H); **¹⁹F-NMR** (CDCl₃, 376 MHz) δ (ppm): -78.4 (s, 3F); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 58.1, 49.0, 32.9, 29.0, 24.9. **HRMS** (ESI-TOF) mass calculated for [M]⁺ (C₁₂H₂₆BrS⁺) expected m/z 281.0933; found m/z 281.0929.



Synthesis of dineopentyl(vinyl)sulfonium triflate (**2d**)



(2-bromoethyl)dineopentylsulfonium triflate **31** (1.0 equiv.; 37 mmol; 16.1 g) was dissolved in 75 mL of a 2:1 mixture of THF and water. K_2CO_3 (1.5 equiv.; 55 mmol; 5.54 g) was added and the reaction was left stirring for 48 h at room temperature monitoring the conversion *via* ^1H -NMR analysis of a minimal reaction aliquot. THF was removed under reduced pressure and the reaction mixture was extracted in DCM (100 mL $\times$ 3), the organic phases collected, dried over anhydrous MgSO_4 and the solvent was removed through rotary evaporation to give compound **2d** (12.6 g; 97%) as a white solid (see Figure 4.1), which does not require further purifications. **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3046, 2966, 2876, 1602, 1482, 1373, 1255, 1224, 1154, 1033, 639; **M.P.** = 139 $^{\circ}\text{C}$; ^1H -NMR (CDCl_3 , 500 MHz) δ (ppm): δ 7.44 – 7.35 (m, 1H, **11**), 6.41 – 6.31 (m, 2H, **12**), 3.87 (d, J = 14.0 Hz, 2H, **3**), 3.43 (d, J = 14.0 Hz, 2H, **3**), 1.16 (s, 18H, **6 – 7 – 8**); ^1H -NMR ($\text{DMSO}-d_6$, 500 MHz) δ (ppm): 7.01 (dd, J = 16.3, 8.8 Hz, 1H, **11**), 6.81 (dd, J = 16.3, 1.8 Hz, 1H, **12**), 6.54 (dd, J = 8.8, 1.8 Hz, 1H, **12**), 3.65 (d, J = 13.3 Hz, 2H, **3**), 3.47 (d, J = 13.3 Hz, 2H, **3**), 1.08 (s, 18H, **6 – 7 – 8**); ^{19}F -NMR (CDCl_3 , 376 MHz) δ (ppm): -78.4 (s, 3F); ^{13}C -NMR (CDCl_3 , 126 MHz) δ (ppm): 135.5 (**11**), 128.0 (**12**), 60.5 (**3**), 33.1 (**4**), 29.0 (**6 – 7 – 8**). **HRMS** (ESI-TOF) mass calculated for $[\text{M}]^+$ ($\text{C}_{12}\text{H}_{25}\text{S}^+$) expected m/z 201.1672; found m/z 201.1670.

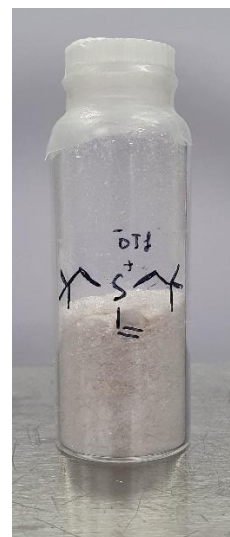
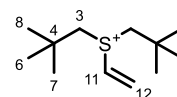
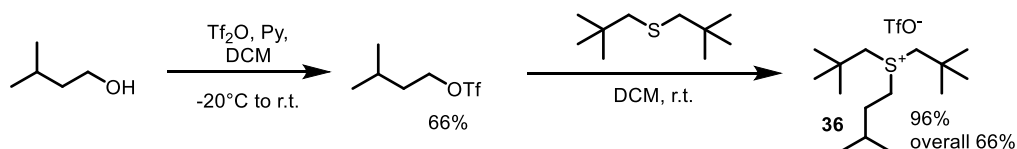


Figure 4.1: compound **2d**.

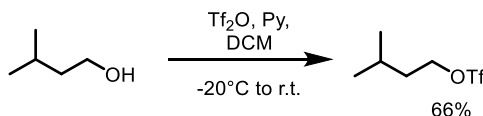


Synthesis of the model isopentyldineopentylsulfonium triflate

The model compound **36** was synthesised through a two-step procedure reported in below in Scheme 4.16.

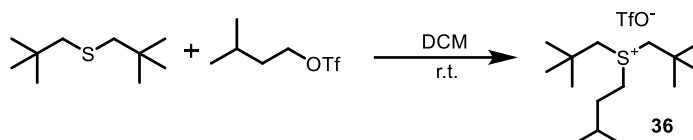


Scheme 4.16: Synthetic route for model compound **36**.

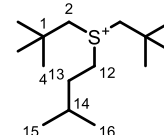


Trifluoromethanesulfonic anhydride (1.04 equiv.; 12.1 mmol; 2 mL) was dropwise added to a stirred solution of pyridine (1.08 equiv.; 11.6 mmol; 0.9 mL) in dry DCM (10 mL) at -20 $^{\circ}\text{C}$ under argon atmosphere and the stirring was continued for 10

minutes. Then isoamyl alcohol (1.00 equiv.; 11.2 mmol; 1.2 mL) was slowly added to this cold reaction mixture. The cooling bath was removed, and the mixture was left warming up to room temperature while stirring for 30 minutes (strictly following this time was found to be important). The resulting suspension was filtered, concentrated (using a rotary evaporator, maintaining the water bath below 20 °C) and petroleum ether (10 mL) was added. The mixture was again filtered and concentrated under reduced pressure and finally dried under high vacuum to give a light brown oil which was used for the next step without further purification.

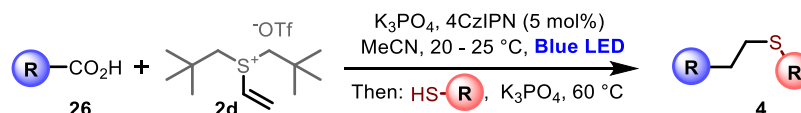


Dineopentyl sulfide (1.0 equiv.; 7.3 mmol; 1.27 g) was dissolved in dry DCM (7.3 mL). Isopentyl trifluoromethanesulfonate (1.01 equiv.; 7.4 mmol; 1.62 g) was added and the reaction was left stirring for 24 h at room temperature monitoring the conversion *via* $^1\text{H-NMR}$ analysis of a minimal reaction aliquot. The solvent was removed by rotary evaporation and the white solid was washed three times with 5 mL of hexane to give the product **36** (2.76 g; 96%) as a white solid, which was used without further purifications. **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2960, 2827, 1470, 1370, 1270, 1251, 1247, 1223, 1154, 1027, 636, 573, 516; **M.P.** = 83 °C; **$^1\text{H-NMR}$** (CDCl_3 , 500 MHz) δ (ppm): δ 3.60 – 3.52 (m, 4H, **2**), 3.48 (d, J = 14.4 Hz, 2H, **12**), 1.77 (hept, J = 6.7 Hz, 1H, **14**), 1.68 – 1.61 (m, 2H, **13**), 1.16 (s, 18H, **4**), 1.00 (d, J = 6.7 Hz, 6H, **15** – **16**); **$^{19}\text{F-NMR}$** (CDCl_3 , 376 MHz) δ (ppm): -78.4 (s, 3F); **$^{13}\text{C-NMR}$** (CDCl_3 , 126 MHz) δ (ppm): 58.0, 43.4, 34.0, 32.6, 29.0, 27.5, 22.1; **HRMS** (ESI-TOF) mass calculated for $[\text{M}]^+$ ($\text{C}_{15}\text{H}_{33}\text{S}^+$) expected m/z 245.2297; found m/z 245.2303.



4.6.7. General procedures

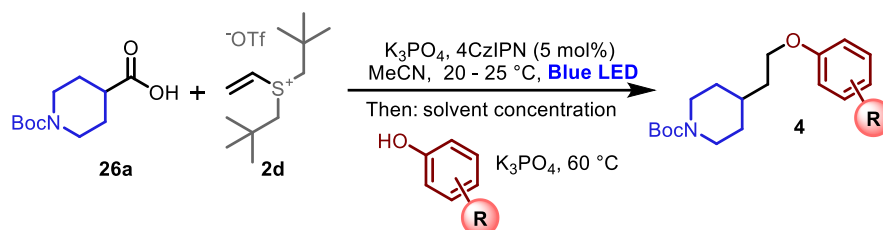
General procedure A



Carboxylic acid **26** (1.0 equiv.; 0.2 mmol), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg) and potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) were introduced into a Schlenk tube. The atmosphere was exchanged to argon, and degassed dry MeCN (1.3 mL, 0.15 M, previously degassed through 10 min argon sparging) was introduced through a syringe. The vessel was sealed and placed in a glass-wall water bath with temperature controlled between 20 - 25 °C. The reaction was irradiated through the glass wall with blue light (Kessil lamp A160WE Tuna Blue Saltwater LED Light 40W) for 24 to 48 h under moderate stirring (500 rpm). See Figure 4.2 for visual details. The vessel was then

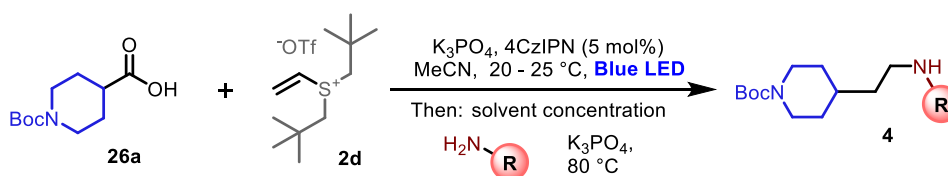
removed from the water bath and the corresponding thiol (2.5 equiv.; 0.5 mmol) and further potassium phosphate (1.5 equiv.; 0.3 mmol; 63.6 mg) were introduced into the vessel. The mixture was heated to 60 °C without irradiation for 24 h under vigorous stirring (700 rpm). The crude was filtered through celite and eluted with DCM. Volatiles were evaporated under reduced pressure, and the residue was subjected to chromatography purification on silica gel to afford final compounds.

General procedure B



1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg) and potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) were introduced into a Schlenk tube. The atmosphere was exchanged to argon, and degassed dry MeCN (1.3 mL, 0.15 M, previously degassed through 10 min argon sparging) was introduced through a syringe. The vessel was sealed and placed in a glass-wall water bath with temperature controlled between 20 - 25 °C. The reaction was irradiated through the glass wall with blue light (Kessil lamp A160WE Tuna Blue Saltwater LED Light 40W) for 24 h under moderate stirring (500 rpm). See Figure 4.2 for visual details. The vessel was then removed from the water bath and the reaction mixture transferred in a 5 mL Young tube (washing the original vessel with DCM to ensure quantitative transfer). The solvent was removed blowing nitrogen. The corresponding aromatic alcohol (2.5 equiv.; 0.5 mmol), potassium phosphate (1.5 equiv.; 0.3 mmol; 63.6 mg) and dry acetonitrile (400 μ L; 0.5 M) were added. The mixture was heated to 60 °C without irradiation for 24 h under vigorous stirring (700 rpm), after which it was filtered through celite and eluted with DCM. Volatiles were evaporated under reduced pressure, and the residue was subjected to chromatography purification on silica gel to afford final compounds.

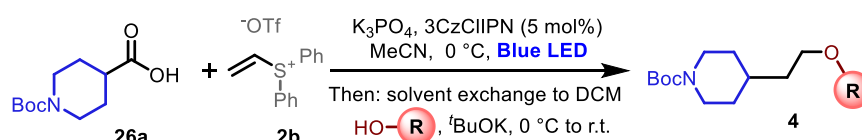
General procedure C



1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg) and potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4

mg) were introduced into a Schlenk tube. The atmosphere was exchanged to argon and degassed dry MeCN (1.3 mL, 0.15 M, previously degassed through 10 min argon sparging) was introduced through a syringe. The vessel was sealed and placed in a glass-wall water bath with temperature controlled between 20 - 25 °C. The reaction was irradiated through the glass wall with blue light (Kessil lamp A160WE Tuna Blue Saltwater LED Light 40W) for 24 h under moderate stirring (500 rpm). See Figure 4.2 for visual details. The vessel was removed from the water bath and the reaction mixture transferred into a 5 mL Young tube or a vial with Teflon-coated cap (washing the original vessel with DCM to ensure quantitative transfer). The solvent was removed blowing nitrogen. The corresponding amine (2.5 equiv.; 0.5 mmol), potassium phosphate (1.5 equiv.; 0.3 mmol; 63.6 mg) and dry acetonitrile (400 μ L; 0.5 M) were added. The mixture was heated to 80 °C without irradiation for 24 h under vigorous stirring (700 rpm), after which it was filtered through celite and eluted with DCM. Volatiles were evaporated under reduced pressure and the residue was subjected to chromatography purification on silica gel to afford final compounds.

General procedure D



Diphenyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 109 mg) was introduced into a Schlenk tube and the atmosphere was exchanged to argon. Then, degassed dry MeCN (1.3 mL, 0.15 M, previously degassed through 10 min argon sparging) was added through a syringe and the resultant solution was cooled down to 0 °C. 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), 3CzClIPN (0.05 equiv.; 0.01 mmol; 6.6 mg) and potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) were added to the solution at 0 °C. The vessel was sealed and placed in a glass-wall 0 °C bath. The reaction was irradiated through the glass wall with blue light (Kessil lamp A160WE Tuna Blue Saltwater LED Light 40W) for 8 h under moderate stirring (500 rpm). To avoid moisture condensation in the glass wall, which may impact the quality of irradiation, a generous flux of dry nitrogen was directed towards the cold glass wall, exactly where the light source points (see Figure 4.3, the transparent plastic tube supplies dry nitrogen). The vessel was then taken out from the low temperature bath and the solvent was removed under vacuum using a standard Schlenk manifold. Dry DCM (1.3 mL, 0.15 M) was introduced into the vessel and cooled down to 0 °C. Aliphatic alcohol (2.5 equiv.; 0.5 mmol) and potassium *tert*-butoxide (1.1 equiv.; 0.22 mmol; 24.7 mg) were added to the reaction mixture at 0 °C. The mixture was slowly warmed up to room temperature, leaving the cold bath melting, and left stirring (700 ppm) at room temperature until complete consumption of sulfonium intermediate monitored by analysing a small aliquot via ^1H -NMR (*disappearance of signal at 4.30 ppm*). The mixture was filtered through a thin layer of

celite and eluted with DCM. Volatiles were evaporated under reduced pressure and the residue was subjected to chromatography purification on silica gel to afford final compounds.

Reaction set-up for irradiation of mixtures with blue LEDs

This set up is a modified version of the water-cooled set up originally reported by MacMillan *et al.*²⁸ Throughout the irradiation, the temperature of the water was monitored with a thermometer to ensure temperature control.

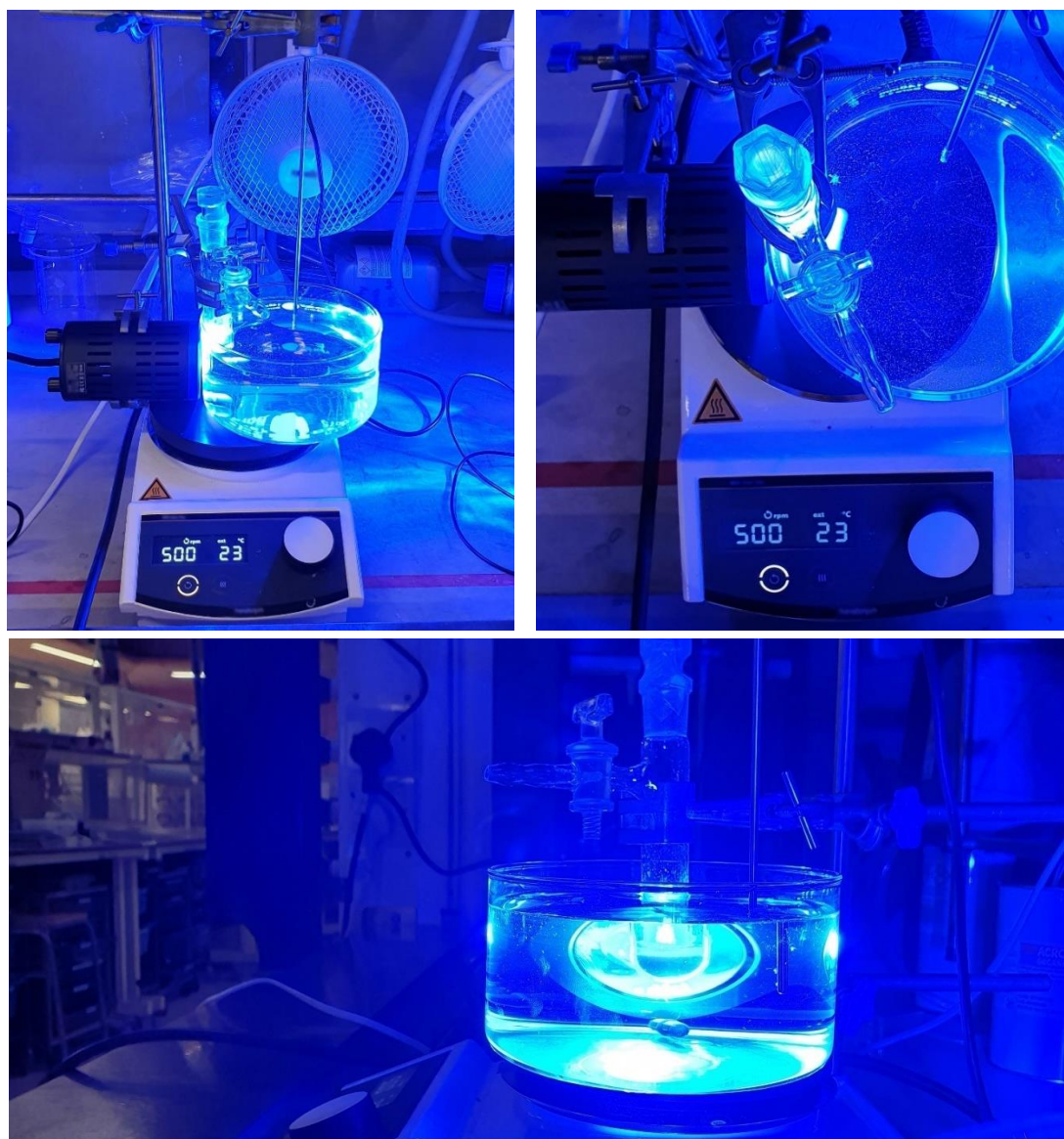


Figure 4.2: Visual details of the photochemical reaction set-up: front, top, and lateral views.

²⁸ Perry, I. B.; Brewer, T.; Sarver, P.J.; Schultz, D. M.; DiRocco, D.A.; MacMillan, D.W.C. *Nature* **2018**, 560, 70–75.

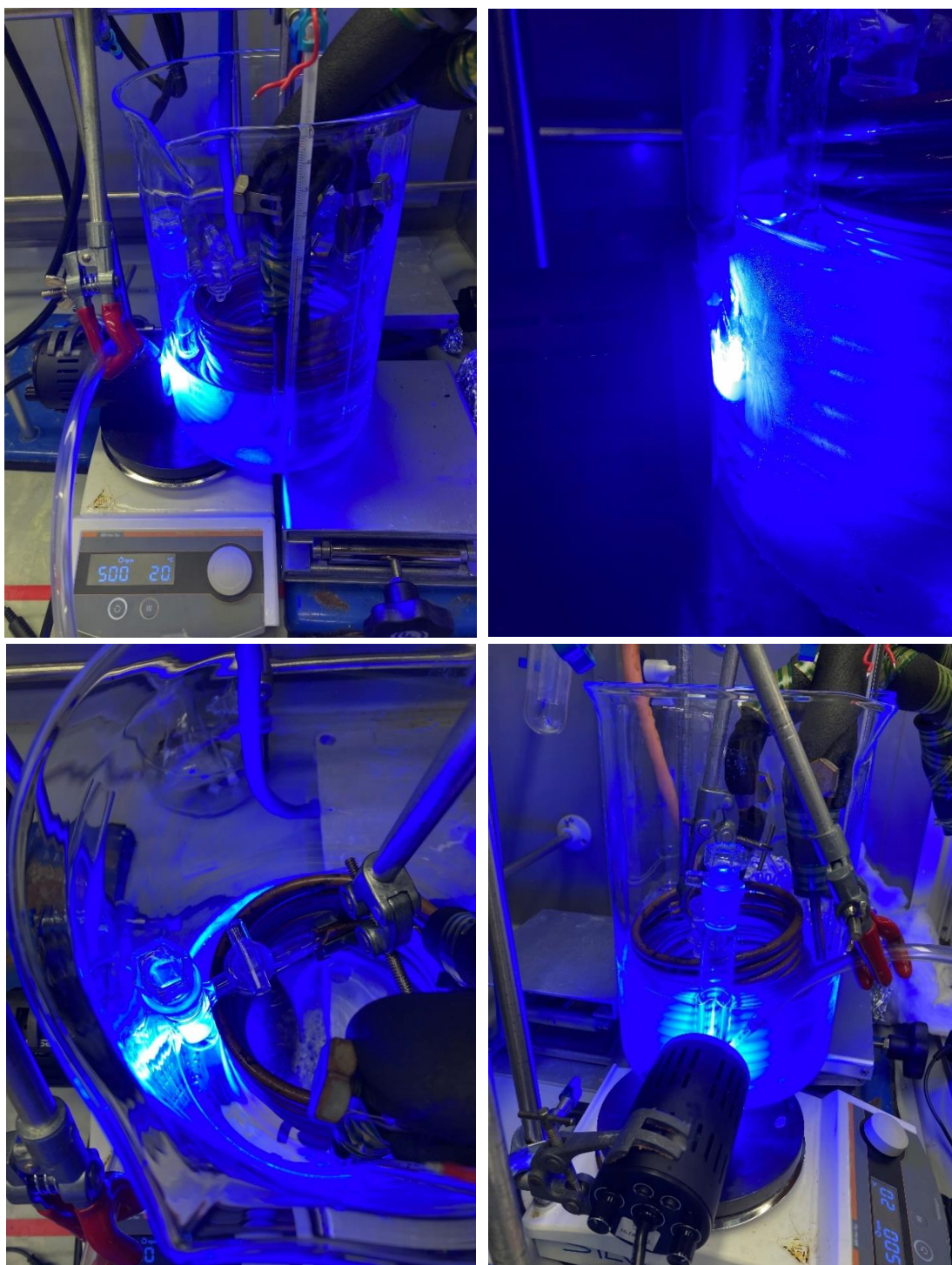
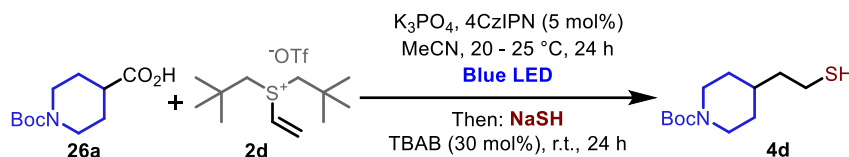


Figure 4.3: Visual details of the photochemical reaction set-up at 0 °C: front, top, and lateral views.

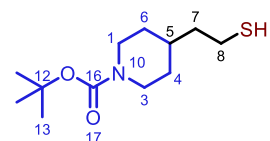
4.6.8. Reaction products and characterisation

In this section only the compound synthesised purified and characterised by me are reported.

tert-butyl 4-(2-mercaptoethyl)piperidine-1-carboxylate (**4d**)

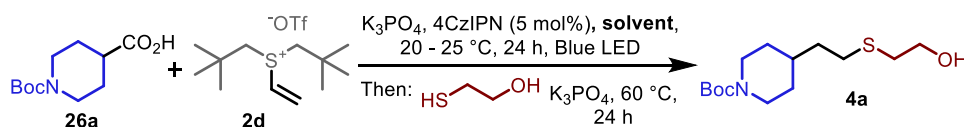


Prepared with a modification of general procedure A, using **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg). The vessel was then removed from the water bath, NaSH·xH₂O (118 mg) and catalytic tetrabutylammonium bromide (0.3 equiv.; 0.06 mmol; 19.3 mg) were added and the reaction was left stirring for 24 h at room temperature. After that, 4 mL of a degassed saturated solution of NH₄Cl were added and the reaction left stirring for 10 min under argon. The mixture was then transferred to a separatory funnel and extracted with DCM (10 mL × 3). The organic phases were collected and dried over anhydrous MgSO₄, filtered and the solvent removed under reduced pressure. The crude residue was purified by flash column chromatography (SiO₂; *to prevent the dimerization of the product, all the solvents were degassed with the sonicator, left bubbling with argon for 10 min and finally the column was run under argon*; gradient 95:5 to 85:15 hexane:ethyl acetate) to afford compound **4d** (30 mg; 61%) as a yellow oil. **R_f** (90:10 hexane:ethyl acetate) 0.2; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2972, 2925, 2555, 1689, 1420, 1366, 127, 1243, 1162, 1121, 1083, 1004, 933, 865, 768; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 4.07 (d, *J* = 13.2 Hz, 2H, **1 - 3**), 2.67 (td, *J* = 13.2, 2.6 Hz, 2H, **1 - 3**), 2.55 (q, *J* = 7.3 Hz, 2H, **8**), 1.67 – 1.60 (m, 2H, **4 - 6**), 1.59 – 1.52 (m, 3H, **4 - 5 - 6**), 1.44 (s, 9H, **13**), 1.32 (t, *J* = 7.6 Hz, 1H, **9**), 1.15 – 1.01 (m, 2H, **7**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 155.0 (**16**), 79.4 (**12**), 44.0 (**1 - 3**), 40.8 (**7**), 34.8 (**5**), 31.8 (**4 - 6**), 28.6 (**13**), 22.0 (**8**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₂H₂₃NO₂SN⁺) expected *m/z* 268.1342; found *m/z* 268.1341.



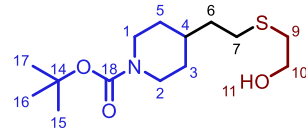
tert-butyl 4-(2-((2-hydroxyethyl)thio)ethyl)piperidine-1-carboxylate (**4a**)

Compound synthesised and characterised by Dr. Subhasis Paul.



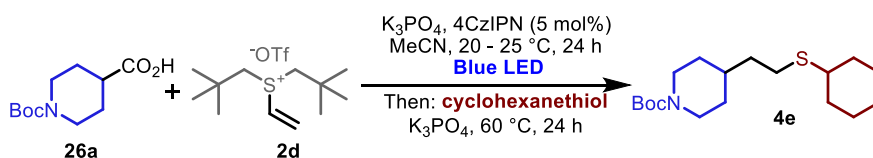
Prepared following general procedure A, using **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) +

(1.5 equiv.; 0.3 mmol; 63.6 mg) and 2-mercaptoethanol (2.5 equiv.; 0.5 mmol; 35.1 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 9:1 to 6:4 DCM:ethyl acetate) to afford compound **4a** (41.2 mg; 71%) as a pale yellow oil. **R_f** (7:3 DCM:ethyl acetate) 0.4; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3416, 2923, 1690, 1425, 1366, 1245, 1150; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 4.07 (br s, 2H, **1 - 2**), 3.75 – 3.68 (m, 2H, **10**), 2.77 – 2.61 (m, 4H, **1 - 2 - 9**), 2.59 – 2.51 (m, 2H, **7**), 2.19 (br s, 1H, **11**), 1.65 (d, $J = 12.7$ Hz, 2H, **3 - 5**), 1.59 – 1.49 (m, 3H, **4 - 6**), 1.44 (s, 9H, **15 - 16 - 17**), 1.16 – 1.02 (m, 2H, **3 - 5**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 155.0 (**18**), 79.4 (**14**), 60.4 (**10**), 44.0 (**1 - 2**), 36.4 (**6**), 35.4 (**9**), 35.2 (**4**), 32.0 (**3 - 5**), 29.0 (**7**), 28.6 (**15 - 16 - 17**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₄H₂₇NO₃SNa⁺) expected m/z 312.1604; found m/z 312.1603.

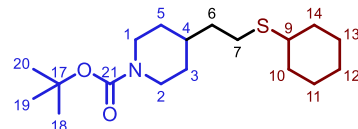


tert-butyl 4-(2-(cyclohexylthio)ethyl)piperidine-1-carboxylate (**4e**)

Compound synthesised and characterised by Dr. Subhasis Paul.



Prepared following general procedure A, using **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) + (1.5 equiv.; 0.3 mmol; 63.6 mg) and cyclohexanethiol (2.5 equiv.; 0.5 mmol; 61.2 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 99.5:0.5 to 95:5 DCM:ethyl acetate) to afford compound **4e** (51.3 mg; 78%) as a transparent oil. **R_f** (199:1 DCM:ethyl acetate) 0.25; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2926, 2851, 1692, 1421, 1365, 1242, 1158, 768; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 4.06 (d, $J = 13.1$ Hz, 2H, **1 - 2**), 2.71 – 2.57 (m, 3H, **1 - 2 - 9**), 2.54 (t, $J = 7.0$ Hz, 2H, **7**), 1.98 – 1.89 (m, 2H), 1.79 – 1.71 (m, 2H), 1.68 – 1.58 (m, 3H, **3 - 4 - 5**), 1.54 – 1.47 (m, 3H), 1.43 (s, 9H, **18 - 19 - 20**), 1.35 – 1.20 (m, 5H), 1.13 – 1.02 (m, 2H, **3 - 5**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 155.0 (**21**), 79.3 (**17**), 44.0 (**9**), 43.7 (**1 - 2**), 36.7, 35.3, 33.8 (**4**), 32.0 (**3 - 5**), 28.6 (**18 - 19 - 20**), 27.4 (**7**), 26.3, 26.0; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₈H₃₃NO₂SNa⁺) expected m/z 350.2124; found m/z 350.2118.

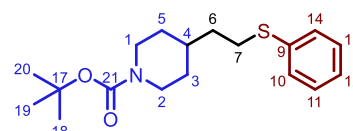


tert-butyl 4-(2-(phenylthio)ethyl)piperidine-1-carboxylate (4f)

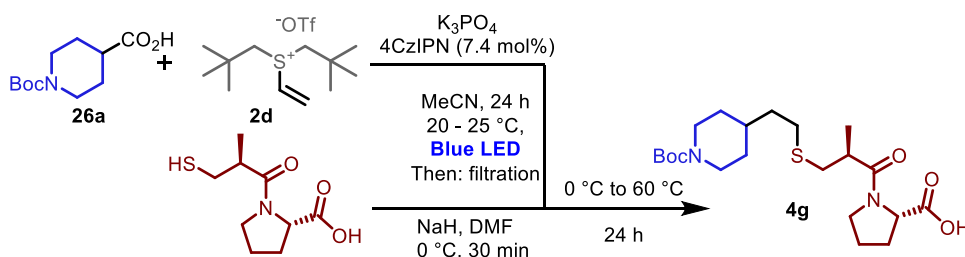
Compound synthesised and characterised by Dr. Subhasis Paul.



Prepared following general procedure A, using **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) + (1.5 equiv.; 0.3 mmol; 63.6 mg) and thiophenol (2.5 equiv.; 0.5 mmol; 51.3 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 95:5 to 9:1 hexane:ethyl acetate) to afford compound **4f** (53.9 mg; 84%) as a pale yellow solid. **R_f** (9:1 hexane:ethyl acetate) 0.4; **M.P.** = 50 – 51 °C; **IR** (film) ν_{max} /cm⁻¹: 2927, 2852, 1691, 1479, 1422, 1243, 1159, 738; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.34 – 7.25 (m, 4H, **10** – **11** – **13** – **14**), 7.19 – 7.14 (m, 1H, **12**), 4.07 (br s, 2H, **1** – **2**), 2.94 (t, *J* = 7.5 Hz, 2H, **7**), 2.75 – 2.58 (m, 2H, **1** – **2**), 1.66 (d, *J* = 13.0 Hz, 2H), 1.63 – 1.52 (m, 3H, **3** – **4** – **5**), 1.45 (s, 9H, **18** – **19** – **20**), 1.17 – 1.02 (m, 2H, **3** – **5**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 154.9 (**21**), 136.7 (**9**), 129.1, 129.0, 126.0 (**12**), 79.4 (**17**), 44.0 (**1** – **2**), 35.8 (**6**), 35.2 (**4**), 31.9 (**3** – **5**), 31.0 (**7**), 28.6 (**18** – **19** – **20**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₈H₂₇NO₂SN⁺) expected *m/z* 344.1654; found *m/z* 344.1653.

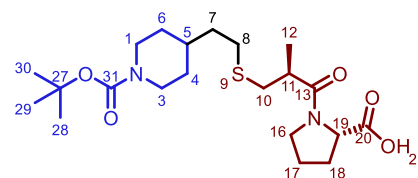


((S)-3-((2-(1-(tert-butoxycarbonyl)piperidin-4-yl)ethyl)thio)-2-methylpropanoyl)-L-proline (4g)



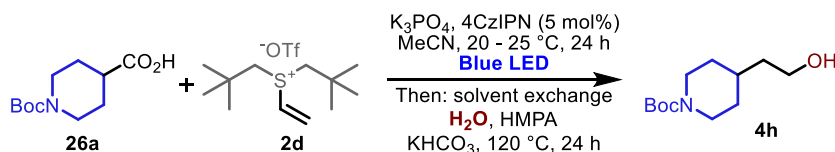
Prepared with a modification of general procedure A, using **26a** (1.4 equiv.; 0.28 mmol; 64.2 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.54 equiv.; 0.31 mmol; 108 mg), 4CzIPN (0.074 equiv.; 0.015 mmol; 11.7 mg) and potassium phosphate (1.4 equiv.; 0.28 mmol; 59.4 mg). After 24 h under irradiation, the mixture was filtered through celite and eluted with DCM. The solution was transferred into another Schlenk tube and the solvent removed by blowing nitrogen. Dry DMF (250 μ L) was added, and the mixture cooled down to 0 °C (Solution A). Captopril (1.0 equiv.; 0.2 mmol; 43.4 mg) and dry DMF (500 μ L) were added in a separate vessel and cooled down to 0 °C. NaH (60% in oil; 2.0 equiv.; 0.4 mmol; 16 mg) was then slowly added and the reaction left stirring at 0 °C for 30 min (Solution B). Solution B was transferred to solution A at 0 °C washing the vessel using other 550 μ L of DMF. The reaction was left for 24 h at 60 °C under

moderate stirring (700 rpm). Saturated NH_4Cl solution (10 mL) was added to the reaction mixture and extracted with DCM (25 mL $\times$ 3). The organic phases were collected and washed once with brine (20 mL) and dried over anhydrous MgSO_4 . The solvent was then removed by rotary evaporation. The crude residue was purified by flash column chromatography (SiO_2 ; gradient 99:1 to 96:4 DCM:methanol + 0.2% AcOH) to afford compound **4g** (45.8 mg; 53%) as a yellow oil. **R_f** (9:1 DCM:methanol + 0.2% AcOH) 0.4; **[α]_D²⁵** = -88 (c = 1.00 CHCl_3); **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2974, 2926, 2845, 1741, 1687, 1644, 1424, 1366, 1318, 1275, 1243, 1157, 1117, 1090, 964, 918, 864, 769, 732; **¹H-NMR** (CDCl_3 , 500 MHz) δ (ppm): 4.64 (dd, J = 8.1, 2.5 Hz, 1H, **19**), 4.07 (br s, 2H, **1 - 3**), 3.67 – 3.54 (m, 2H, **16**), 2.91 – 2.78 (m, 2H, **10, 11**), 2.75 – 2.62 (m, 2H, **10, 11**), 2.61 – 2.46 (m, 4H, **10, 17**), 2.13 – 1.94 (m, 3H, **17, 18**), 1.64 (d, J = 13.1 Hz, 2H, **10, 11**), 1.55 – 1.47 (m, 3H, **5**), 1.45 (s, 9H, **28 - 29 - 30**), 1.24 (d, J = 6.5 Hz, 3H, **12**), 1.14 – 1.02 (m, 2H, **7**); **¹³C-NMR** (CDCl_3 , 126 MHz) δ (ppm): 177.7 (**13**), 171.9 (**20**), 155.0 (**31**), 79.5 (**27**), 60.2 (**19**), 48.1 (**16**), 44.1, 39.3 (**11**), 36.4 (**10**), 35.8 (**5**), 35.2, 32.0 (**7**), 30.6, 28.6, 27.3, 25.0 (**17 - 18**), 17.8 (**12**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}-\text{H}]^-$ ($\text{C}_{21}\text{H}_{35}\text{N}_2\text{O}_5\text{S}^-$) expected m/z 427.2272; found m/z 427.2272.



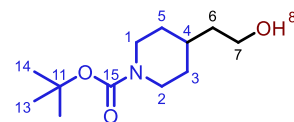
tert-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (**4h**)

Compound synthesised and characterised by Dr. Subhasis Paul.



Irradiated following a modification of general procedure A, using **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg). After photochemical step, the crude was filtered through celite pad and eluted with DCM, concentrated under reduced pressure and transferred in a 5 mL Young tube. Solvent was removed by blowing nitrogen and H_2O (45 equiv.; 9.0 mmol; 162 μL), potassium bicarbonate (1.3 equiv.; 0.26 mmol; 100 mg) and HMPA (800 μL ; 0.25 M) were added. The reaction was heated to 120 $^\circ\text{C}$ for 24 h. After completion, the mixture was cooled down to room temperature, diluted with water (6 mL), added 5% LiCl solution (4 mL), extracted with ethyl acetate (6 mL $\times$ 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous MgSO_4 and the solvent was removed by rotary evaporation. The crude residue was purified by flash column chromatography (SiO_2 ; gradient 6:4 to 3:7 DCM:ethyl acetate) to afford compound **4h** (24.1 mg; 52%) as a pale yellow oil. **R_f** (6:4 DCM:ethyl acetate) 0.3; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3429, 2926, 2857, 1691, 1426, 1367, 1247, 1168, 768; **¹H-NMR** (CDCl_3 , 500 MHz) δ (ppm): 4.06 (br s, 2H, **1 - 2**), 3.70 (t, J = 6.6 Hz, 2H, **7**), 2.76 – 2.60 (m, 2H, **1 - 2**), 1.71 – 1.64 (m, 2H, **3 - 5**), 1.62 – 1.55 (m, 1H, **4**), 1.53 – 1.49 (m, 2H, **6**), 1.44 (s, 9H,

12 – 13 – 14), 1.17 – 1.07 (m, 2H, **3 – 5**); ¹³C-NMR (CDCl₃, 126 MHz) δ (ppm): 155.0 (**15**), 79.4 (**11**), 60.4 (**7**), 44.3 (**1 – 2**), 39.4 (**6**), 32.7 (**4**), 32.3 (**3 – 5**), 28.6 (**12 – 13 – 14**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₂H₂₃NO₃Na⁺) expected *m/z* 252.1570; found *m/z* 252.1571.

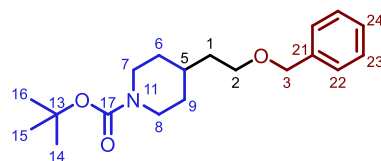


tert-butyl 4-(2-(benzyloxy)ethyl)piperidine-1-carboxylate (**4i**)

Compound synthesised and characterised by Dr. Subhasis Paul.

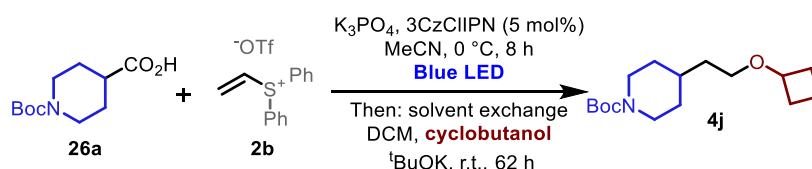


Prepared following general procedure D, using **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), diphenyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 108.7 mg), 3CzClIPN (0.05 equiv.; 0.01 mmol; 6.6 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg). Then, benzyl alcohol (2.5 equiv.; 0.5 mmol; 51.7 μL) and potassium *tert*-butoxide (1.1 equiv.; 0.22 mmol; 24.7 mg) were used. Reaction was continued at r.t. for 39 h. The crude residue was purified by flash column chromatography (SiO₂; gradient 9:1 to 85:15 toluene:Et₂O). The compound was purified a second time by flash column chromatography (SiO₂; gradient 9:1 to 85:15 hexane: ethyl acetate) to afford compound **4i** (25.6 mg; 40%) as a colourless oil. **R_f** (9:1 toluene:Et₂O) 0.35; **IR** (film) ν_{max} /cm⁻¹: 2974, 2925, 2854, 1692, 1421, 1365, 1277, 1171, 736; ¹H-NMR (CDCl₃, 500 MHz) δ (ppm): 7.37 – 7.30 (m, 4H, **22 – 23**), 7.30 – 7.26 (m, 1H, **24**), 4.50 (s, 2H, **3**), 4.06 (br s, 2H, **7 – 8**), 3.51 (t, *J* = 6.3 Hz, 2H, **2**), 2.75 – 2.60 (m, 2H, **7 – 8**), 1.68 – 1.58 (m, 3H, **5 – 6 – 9**), 1.58 – 1.53 (m, 2H, **1**), 1.45 (s, 9H, **14 – 15 – 16**), 1.15 – 1.03 (m, 2H, **6 – 9**); ¹³C-NMR (CDCl₃, 126 MHz) δ (ppm): 155.0 (**17**), 138.6 (**21**), 128.5, 127.8, 127.7 (**24**), 79.3 (**13**), 73.1 (**3**), 67.8 (**2**), 44.1 (**7 – 8**), 36.4 (**1**), 33.1 (**5**), 32.3 (**6 – 9**), 28.6 (**14 – 15 – 16**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₉H₂₉NO₃Na⁺) expected *m/z* 342.2040; found *m/z* 342.2021.



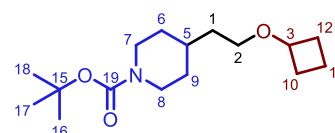
tert-butyl 4-(2-(cyclobutoxy)ethyl)piperidine-1-carboxylate (**4j**)

Compound synthesised and characterised by Dr. Subhasis Paul.

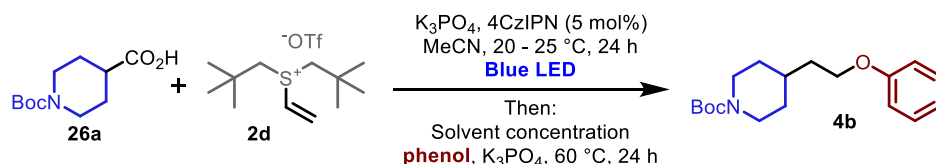


Prepared following general procedure D, using **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), diphenyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 108.7 mg), 3CzClIPN (0.05 equiv.; 0.01 mmol; 6.6 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg). Then, cyclobutanol (2.5 equiv.; 0.5 mmol; 39.2 μL) and potassium *tert*-butoxide (1.1

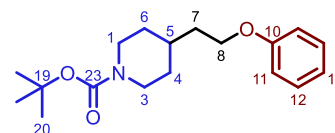
equiv.; 0.22 mmol; 24.7 mg) were used. Reaction was continued at r.t. for 62 h. The crude residue was purified by flash column chromatography (SiO₂; gradient 95:5 to 8:2 toluene:Et₂O) to afford compound **4j** (21.3 mg; 38%) as a colourless oil. **R_f** (95:5 toluene:Et₂O) 0.25; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2974, 2929, 2857, 1695, 1421, 1365, 1243, 1149, 1117, 769; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 4.11 – 4.01 (m, 2H, **7 – 8**), 3.93 – 3.84 (m, 1H, **3**), 3.35 (t, $J = 6.5$ Hz, 2H, **2**), 2.68 (td, $J = 13.1, 2.7$ Hz, 2H, **7 – 8**), 2.25 – 2.13 (m, 2H, **10 – 12**), 1.95 – 1.83 (m, 2H, **10 – 12**), 1.71 – 1.61 (m, 3H, **6 – 9 – 11**), 1.59 – 1.53 (m, 1H, **5**), 1.53 – 1.46 (m, 3H, **1 – 11**), 1.45 (s, 9H, **16 – 17 – 18**), 1.16 – 1.03 (m, 2H, **6 – 9**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 155.0 (**19**), 79.3 (**15**), 73.3 (**3**), 65.0 (**2**), 44.3 (**7 – 8**), 36.5 (**1**), 33.0 (**5**), 32.3 (**6 – 9**), 30.6 (**10 – 12**), 28.6 (**16 – 17 – 18**), 12.7 (**11**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₆H₂₉NO₃Na⁺) expected m/z 306.2040; found m/z 306.2043.



tert-butyl 4-(2-phenoxymethyl)piperidine-1-carboxylate (**4b**)

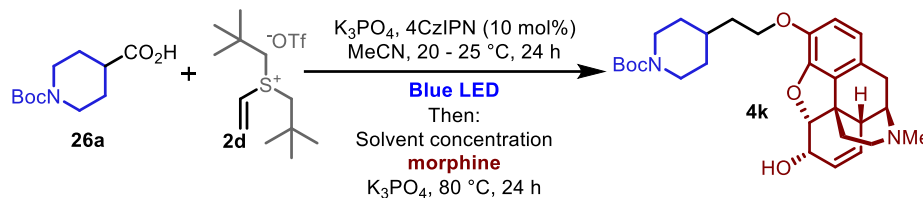


Prepared following general procedure B, using **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg). After the photochemical step the mixture was transferred in a 5 mL Young tube with phenol (2.5 equiv.; 0.5 mmol; 47.1 mg) and potassium phosphate (1.5 equiv.; 0.3 mmol; 63.6 mg). The crude residue was purified by flash column chromatography (SiO₂; gradient 95:5 to 85:15 hexane:ethyl acetate) to afford compound **4b** (38 mg; 62%) as a white solid. **R_f** (8:2 hexane:ethyl acetate) 0.5; **M.P.** = 68 – 69 °C; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2974, 2928, 2864, 1691, 1599, 1587, 1497, 1473, 1447, 1422, 1392, 1365, 1277, 1244, 1171, 1142, 1079, 1032, 979, 866, 754, 692; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.31 – 7.27 (m, 2H), 6.94 (t, $J = 7.4$ Hz, 1H), 6.89 (d, $J = 8.4$ Hz, 2H), 4.09 (br s, 2H, **1 – 3**), 4.01 (t, $J = 6.0$ Hz, 2H, **8**), 2.68 – 2.60 (m, 2H, **1 – 3**), 1.78 – 1.65 (m, 5H, **4 – 5 – 6 – 7**), 1.46 (s, 9H, **20**), 1.24 – 1.10 (m, 2H, **4 – 6 – 7**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 159.1 (**10**), 155.0 (**23**), 129.6 (**12**), 120.8 (**13**), 114.6 (**11**), 79.4 (**19**), 65.3 (**8**), 44.0 (**1 – 3**), 35.9, 33.1 (**5**), 32.2, 28.6 (**20**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₈H₂₇NO₃Na⁺) expected m/z 328.1883; found m/z 328.1876.

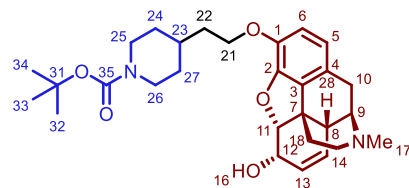


tert-butyl 4-(2-(((4*R*,4*aR*,7*S*,7*aR*,12*bS*)-7-hydroxy-3-methyl-2,3,4,4*a*,7,7*a*-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-9-yl)oxy)ethyl)piperidine-1-carboxylate (**4k**)

Compound synthesised and characterised by Dr. Subhasis Paul.

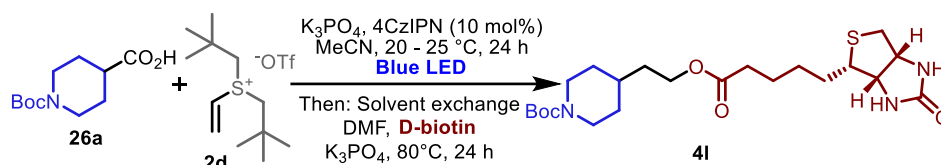


Prepared following a modification of general procedure B, using **26a** (2.0 equiv.; 0.2 mmol; 45.9 mg), dineopentyl(vinyl)sulfonium triflate **2d** (2.2 equiv.; 0.22 mmol; 77.1 mg), 4CzIPN (0.10 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (2.0 equiv.; 0.2 mmol; 42.4 mg). After photochemical step, the crude was transferred in a 5 mL Young tube and solvent was removed by blowing nitrogen and under high vacuum using a standard Schlenk manifold. Then morphine (1.0 equiv.; 0.1 mmol; 28.5 mg), potassium phosphate (1.0 equiv.; 0.1 mmol; 21.2 mg) and dry acetonitrile (660 μ L; 0.15 M) were added. The reaction was heated to 80 $^{\circ}$ C for 24 h. Then the mixture was cooled down to room temperature and saturated NaHCO_3 solution was added (5 mL) and the mixture extracted with DCM (5 mL $\times$ 4). The organic layers were collected and washed with brine (5 mL), dried over anhydrous MgSO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2 ; gradient 95:5 to 94:6 CHCl_3 :MeOH + 2% ammonia in water (35%)). The compound was purified a second time by flash column chromatography (SiO_2 ; gradient 95:5 to 93:7 DCM:MeOH + 1% ammonia in water (35%)) to afford compound **4k** (38.8 mg; 78%) as white solid. **R_f** (95:5 CHCl_3 :MeOH + 2% ammonia in water (35%)) 0.3; **[α]_D²⁵** = -52 (c = 1.00 CHCl_3); **M.P.** = 62 – 63 $^{\circ}$ C; **IR** (film) ν_{max} / cm^{-1} : 3412, 2926, 2856, 1690, 1603, 1499, 1446, 1367, 1277, 1248, 1170, 759; **¹H-NMR** (CDCl_3 , 500 MHz) δ (ppm): 6.64 (d, J = 8.1 Hz, 1H, **6**), 6.54 (d, J = 8.1 Hz, 1H, **5**), 5.73 – 5.66 (m, 1H, **13**), 5.32 – 5.26 (m, 1H, **14**), 4.88 (dd, J = 6.6, 1.2 Hz, 1H, **12**), 4.21 – 4.15 (m, 1H, **11**), 4.14 – 3.98 (m, 4H, **21** – **25** – **26**), 3.34 (dd, J = 6.2, 3.3 Hz, 1H), 3.03 (d, J = 18.6 Hz, 1H), 2.88 (br s, 1H), 2.75 – 2.64 (m, 3H), 2.59 (dd, J = 12.2, 4.5 Hz, 1H), 2.44 (s, 3H, **17**), 2.43 – 2.36 (m, 1H), 2.29 (dd, J = 18.6, 6.3 Hz, 1H), 2.06 (td, J = 12.5, 5.1 Hz, 1H), 1.90 – 1.84 (m, 1H), 1.76 – 1.63 (m, 5H, **22** – **24** – **27**), 1.45 (s, 9H, **32** – **33** – **34**), 1.20 – 1.09 (m, 2H, **24** – **27**); **¹³C-NMR** (CDCl_3 , 126 MHz) δ (ppm): 155.0 (**35**), 146.7, 141.6, 133.5 (**13**), 131.3, 128.4 (**14**), 127.5, 119.8 (**5**), 114.9 (**6**), 91.3 (**12**), 79.4 (**31**), 67.2 (**21**), 66.4 (**11**), 59.0, 46.6, 43.8 (**24** – **27**), 43.2, 43.0 (**17**), 40.9, 36.1 (**24** – **27**), 35.9, 32.9, 32.2 (**37** – **34**), 28.6 (**32** – **33** – **34**), 20.6; **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{29}\text{H}_{41}\text{N}_2\text{O}_5^+$) expected m/z 497.3010; found m/z 497.2997.

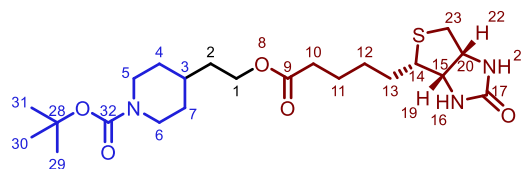


tert-butyl 4-(2-((5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoyl)oxy)ethyl)piperidine-1-carboxylate (**4l**)

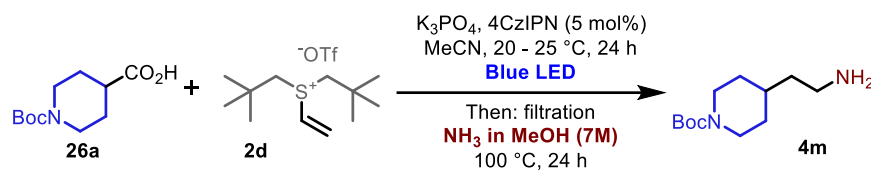
Compound synthesised and characterised by Dr. Subhasis Paul.



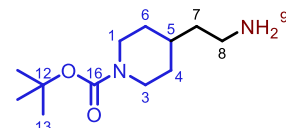
Prepared following a modification of general procedure A, using **26a** (2.0 equiv.; 0.2 mmol; 45.9 mg), dineopentyl(vinyl)sulfonium triflate **2d** (2.2 equiv.; 0.22 mmol; 77.1 mg), 4CzIPN (0.10 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (2.0 equiv.; 0.2 mmol; 42.4 mg). After photochemical step, the solvent was exchanged with DMF (0.66 mL; 0.15M) and D-biotin (1.0 equiv.; 0.1 mmol; 24.4 mg) and potassium phosphate (1.0 equiv.; 0.1 mmol; 21.2 mg) were added. The reaction was heated to 80 °C for 24 h. The crude residue was diluted in EtOAc (50 mL) and extracted with water (40 mL × 5) and brine (30 mL × 1). The solvent was evaporated under reduced pressure and the crude purified by flash column chromatography (SiO₂; gradient 99:3 to 95:5 DCM:MeOH) to afford compound **4l** (37.5 mg; 82%) as a white sticky solid. **R_f** (95:5 DCM:MeOH) 0.35; [α]_D²⁵ = +28 (c = 1.00 CHCl₃); **M.P.** = 75 – 76 °C; **IR** (film) ν_{max} /cm⁻¹: 3211, 2925, 2854, 1732, 1692, 1469, 1422, 1365, 1277, 1246, 1169, 1144, 1080, 1014, 971, 866, 761, 665, 604; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 5.46 (br s, 1H, **16 or 21**), 5.10 (br s, 1H, **16 or 21z**), 4.52 (dd, J = 7.7, 5.0, 1H, **22**), 4.32 (dd, J = 7.8, 4.6 Hz, 1H, **19**), 4.14 – 4.01 (m, 4H, **1 – 5 – 6**), 3.19 – 3.13 (m, 1H, **14**), 2.92 (dd, J = 12.9, 5.0 Hz, 1H, **23**), 2.74 (dd, J = 12.8, 1.1 Hz, 1H, **23**), 2.68 (t, J = 12.7 Hz, 2H, **5 – 6**), 2.33 (t, J = 7.4 Hz, 2H, **10**), 1.77 – 1.62 (m, 6H, **4 – 7 – 11 – 12 – 13**), 1.60 – 1.55 (m, 2H, **2**), 1.55 – 1.50 (m, 1H, **3**), 1.50 – 1.38 (m, 11H, **11 – 12 – 29 – 30 – 31**), 1.12 (qd, J = 12.4, 4.3 Hz, 2H, **4 – 7**); **¹H-NMR** (DMSO-*d*₆, 500 MHz) δ (ppm): 6.42 (s, 1H), 6.35 (s, 1H), 4.30 (dd, J = 7.7, 5.0 Hz, 1H), 4.15 – 4.10 (m, 1H), 4.05 (t, J = 6.2 Hz, 2H), 3.90 (d, J = 13.0 Hz, 2H), 3.12 – 3.06 (m, 1H), 2.82 (dd, J = 12.4, 5.1 Hz, 1H), 2.67 (br s, 2H), 2.58 (d, J = 12.4 Hz, 1H), 2.29 (t, J = 7.4 Hz, 2H), 1.66 – 1.58 (m, 3H), 1.58 – 1.42 (m, 6H), 1.38 (s, 9H), 1.37 – 1.27 (m, 2H), 1.04 – 0.94 (m, 2H); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 173.8 (**9**), 163.4 (**17**), 155.0 (**32**), 79.4 (**28**), 62.3 (**19**), 62.1 (**1**), 60.3 (**22**), 55.5 (**14**), 44.1 (**5 – 6**), 40.7 (**23**), 35.3 (**2**), 34.0 (**10**), 33.1 (**3**), 32.1 (**4 – 7**), 28.6 (**29 – 30 – 31**), 28.5, 28.4, 24.9; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₂H₃₇N₃O₅SSNa⁺) expected m/z 478.2346; found m/z 478.2338.



tert-butyl 4-(2-aminoethyl)piperidine-1-carboxylate (**4m**)

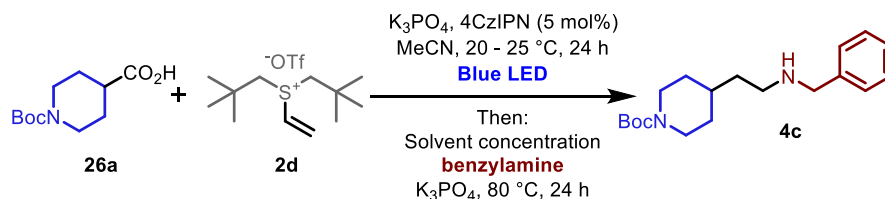


Prepared following a modification of general procedure C, using **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg). After the photochemical step, the crude was filtered through celite, collected in a microwave vial and the solvent removed blowing nitrogen. Ammonia (7M in methanol; 6 mL; 0.03M) was added and the reaction was heated to 100 °C for 24 h covered by a blast shield. A solution of NaOH (2 M; 5 mL) was added and the mixture extracted three times with DCM (20 mL $\times$ 3). The organic phases were collected and dried with anhydrous MgSO₄ and the solvent removed by rotary evaporator. The crude residue was purified by flash column chromatography (SiO₂; gradient 9:1 to 7:3 DCM:MeOH + 0.5% ammonia in water (35%)) to afford compound **4m** (36 mg; 79%) as a yellow oil. **R_f** (8:2 DCM:MeOH + 0.5% ammonia in water (35%)) 0.1; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3369, 2973, 2924, 2855, 1688, 1473, 1423, 1366, 1338, 1277, 1241, 1159, 1099, 1004, 970, 924, 864, 815, 767, 533; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 5.53 (br s, 2H, **9**), 4.07 (br s, 2H, **1 - 3**), 2.92 (t, J = 7.5 Hz, 2H, **8**), 2.75 – 2.61 (m, 2H, **1 - 3**), 1.70 – 1.48 (m, 5H, **4 - 5 - 6 - 7**), 1.44 (s, 9H, **13**), 1.19 – 1.05 (m, 2H, **4 - 6 - 7**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 155.0 (**16**), 79.5 (**12**), 44.0 (**1 - 3**), 38.5, 37.0, 33.6 (**5**), 32.0, 28.6 (**13**); **HRMS** (ESI-TOF) mass calculated for [M+H]⁺ (C₁₂H₂₅N₂O₂)⁺ expected m/z 229.1911; found m/z 229.1911.



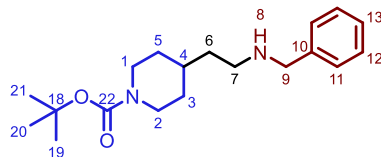
tert-butyl 4-(2-(benzylamino)ethyl)piperidine-1-carboxylate (**4c**)

Compound synthesised and characterised by Dr. Subhasis Paul.

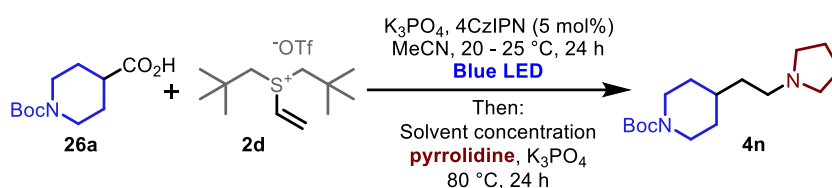


Prepared following general procedure C, using **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg). After photochemical step, the crude was transferred in a 2 mL teflon-coated screw cap vial with benzylamine (2.5 equiv.; 0.5 mmol; 54.6 μ L) and potassium phosphate (1.5 equiv.; 0.3 mmol; 63.6 mg). The crude residue was purified by flash column chromatography (SiO₂; gradient 3:7 to 2:8 DCM:ethyl acetate + 0.5% ammonia in water (35%)) followed by 98:2 to 95:5 DCM:MeOH + 0.5% ammonia in water (35%)) to afford compound **4c** (41.1 mg; 65%) as a yellow oil. **R_f** (98:2 DCM:MeOH + 0.5% ammonia

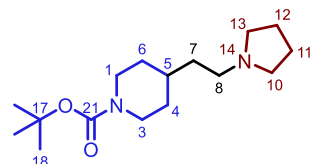
in water (35%)) 0.2; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3316, 2972, 2923, 2851, 1690, 1422, 1365, 1244, 1169, 737; **¹H-NMR** (CDCl_3 , 500 MHz) δ (ppm): 7.34 – 7.29 (m, 4H, **11** – **12**), 7.27 – 7.22 (m, 1H, **13**), 4.05 (br s, 2H, **7**), 3.79 (s, 2H, **9**), 2.72 – 2.59 (m, 4H, **1** – **2**), 1.84 (br s, 1H, **8**), 1.62 (d, $J = 13.1$ Hz, 2H, **3** – **5**), 1.49 – 1.45 (m, 3H, **6** – **4**), 1.44 (s, 9H), 1.15 – 1.03 (m, 2H, **3** – **5**); **¹³C-NMR** (CDCl_3 , 126 MHz) δ (ppm): 155.0 (**22**), 140.2 (**10**), 128.6, 128.3, 127.2 (**13**), 79.3 (**18**), 54.1 (**9**), 46.7 (**1** – **2**), 43.8 (**7**), 36.8 (**6**), 34.1 (**4**), 32.3 (**3** – **5**), 28.6 (**19** – **20** – **21**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{19}\text{H}_{31}\text{N}_2\text{O}_2^+$) expected m/z 319.2380; found m/z 319.2382.



tert-butyl 4-(2-(pyrrolidin-1-yl)ethyl)piperidine-1-carboxylate (4n)

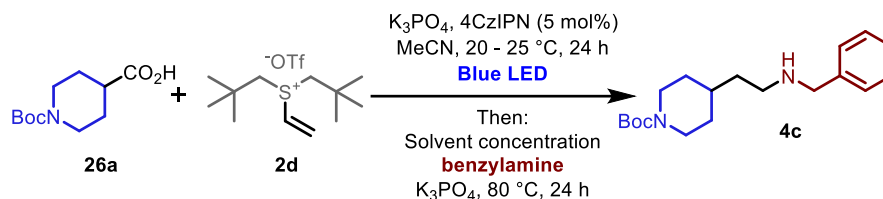


Prepared following general procedure C, using **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg). After photochemical step, the crude was transferred in a 5 mL Young tube with pyrrolidine (2.5 equiv.; 0.5 mmol; 42.3 μL) and potassium phosphate (1.5 equiv.; 0.3 mmol; 63.6 mg). The crude residue was purified by flash column chromatography (SiO_2 ; previously deactivated with 0.5% ammonia in water (35%) in DCM; gradient 95:5 to 9:1 DCM:methanol + 0.5% ammonia in water (35%)) to afford compound **4n** (40 mg; 71%) as a yellow solid. **R_f** (9:1 DCM:methanol + 0.5% ammonia in water (35%)) 0.4; **M.P.** = 158 – 160 °C; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2969, 2928, 2856, 1689, 1423, 1366, 1277, 1245, 1169, 768; **¹H-NMR** (CDCl_3 , 500 MHz) δ (ppm): 4.06 (br s, 2H, **1** – **3**), 2.85 (br s, 4H, **10** – **14**), 2.75 – 2.56 (m, 4H, **1** – **3** – **8**), 1.98 – 1.88 (m, 4H, **11** – **12**), 1.72 – 1.57 (m, 4H, **4** – **6**), 1.53 – 1.46 (m, 1H, **5**), 1.44 (s, 9H, **18**), 1.18 – 1.06 (m, 2H, **4** – **6**); **¹³C-NMR** (CDCl_3 , 126 MHz) δ (ppm): 154.9 (**21**), 79.5 (**17**), 54.1 (**10** – **13**), 53.8 (**1** – **3**), 43.8 (**8**), 34.4 (**5**), 34.1, 32.1, 28.6 (**18**), 23.5 (**11** – **12**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{16}\text{H}_{31}\text{N}_2\text{O}_2^+$) expected m/z 283.2380; found m/z 283.2386.

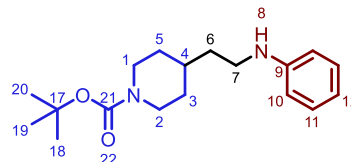


tert-butyl 4-(2-(phenylamino)ethyl)piperidine-1-carboxylate (**4o**)

Compound synthesised and characterised by Dr. Subhasis Paul.

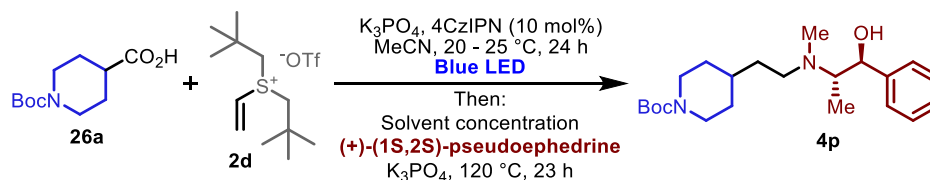


Prepared following a modification of general procedure C, using **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg). After photochemical step, the crude was transferred in a 5 mL Young tube with aniline (2.5 equiv.; 0.5 mmol; 45.6 μ L) and potassium phosphate (1.5 equiv.; 0.3 mmol; 63.6 mg). The reaction was heated to 120 °C for 24 h. The crude residue was purified by flash column chromatography (SiO₂; gradient 97:3 to 95:5 DCM:ethyl acetate) to afford compound **4o** (32.3 mg; 53%) as a yellow solid. **M.P.** = 96 – 97 °C; **R_f** (97:3 DCM:ethyl acetate) 0.3; **IR** (film) ν_{max} /cm⁻¹: 3375, 2974, 2927, 2852, 1680, 1603, 1508, 1425, 1365, 1246, 1170, 748, 693; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.21 – 7.14 (m, 2H, **11**), 6.71 (tt, J = 7.2, 1.1 Hz, 1H, **12**), 6.64 – 6.59 (m, 2H, **10**), 4.09 (br s, 2H, **1** – **2**), 3.19 – 3.11 (m, 2H, **7**), 2.76 – 2.61 (m, 2H, **1** – **2**), 1.69 (d, J = 13.1 Hz, 2H, **6**), 1.61 – 1.53 (m, 3H, **3** – **4** – **5**), 1.46 (s, 9H, **18** – **19** – **20**), 1.21 – 1.10 (m, 2H, **3** – **5**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 155.0 (**21**), 148.4 (**9**), 129.4 (**11**), 117.5 (**12**), 112.9 (**10**), 79.4 (**17**), 44.1 (**1** – **2**), 41.5 (**7**), 36.4 (**6**), 34.0 (**4**), 32.3 (**3** – **5**), 28.6 (**18** – **19** – **20**); **HRMS** (ESI-TOF) mass calculated for [M+H]⁺ (C₁₈H₂₉N₂O₂⁺) expected m/z 305.2224; found m/z 305.2223.



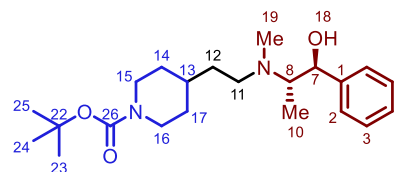
tert-butyl 4-(2-(((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)(methyl)amino)ethyl)piperidine-1-carboxylate (**4p**)

Compound synthesised and characterised by Dr. Subhasis Paul.



Prepared following a modification of general procedure C, using **26a** (2.0 equiv.; 0.2 mmol; 45.9 mg), dineopentyl(vinyl)sulfonium triflate **2d** (2.2 equiv.; 0.22 mmol; 77.1 mg), 4CzIPN (0.10 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (2.0 equiv.; 0.2 mmol; 42.4 mg). After photochemical step, the crude was transferred in a 5 mL Young tube with (+)-(1S,2S)-pseudoephedrine (1.0 equiv.; 0.1 mmol; 16.5 mg) and potassium phosphate (1.0 equiv.; 0.1 mmol; 21.2 mg). The reaction was heated to 120 °C for 23 h. The crude residue was purified by flash column chromatography (SiO₂; gradient 99:1

to 95:5 DCM:MeOH + 1% ammonia in water (35%)) to afford compound **4p** (22.3 mg; 59%) as a yellow oil. **R_f** (97:3 DCM:MeOH + 1% ammonia in water (35%)) 0.25; [α]_D²⁵ = +48 (c = 1.00 CHCl₃); **IR** (film) ν_{max} /cm⁻¹: 3366, 2926, 2855, 1692, 1422, 1367, 1244, 1169, 764, 702; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.38 – 7.31 (m, 4H, **2** – **3**), 7.30 – 7.26 (m, 1H, **4**), 4.22 (d, J = 9.7 Hz, 1H, **7**), 4.09 (br s, 2H, **15** – **16**), 2.78 – 2.53 (m, 4H, **8** – **11** – **15** – **16**), 2.48 – 2.38 (m, 1H, **8** – **11**), 2.28 (s, 3H, **19**), 1.73 – 1.63 (m, 2H, **14** – **17**), 1.56 – 1.48 (m, 3H, **12** – **13**), 1.46 (s, 9H, **23** – **24** – **25**), 1.20 – 1.08 (m, 2H, **14** – **17**), 0.75 (d, J = 6.6 Hz, 3H, **10**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 155.0 (**26**), 142.1 (**1**), 128.4, 127.9, 127.5 (**4**), 79.4 (**22**), 74.8 (**7**), 65.8 (**8**), 51.0 (**11**), 44.3 (**15** – **16**), 36.1 (**19**), 34.8 (**12**), 34.1 (**13**), 32.5 (**14** – **17**), 32.3, 28.6 (**23** – **24** – **25**), 7.5 (**10**); **HRMS** (ESI-TOF) mass calculated for [M+H]⁺ (C₂₂H₃₇N₂O₃⁺) expected m/z 377.282799; found m/z 377.2802.

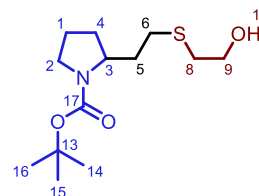


tert-butyl 2-(2-((2-hydroxyethyl)thio)ethyl)pyrrolidine-1-carboxylate (**4q**)

Compound synthesised and characterised by Dr. Subhasis Paul.



Prepared following general procedure A, using **26b** (1.0 equiv.; 0.2 mmol; 43.0 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) + (1.5 equiv.; 0.3 mmol; 63.6 mg) and 2-mercaptoethanol (2.5 equiv.; 0.5 mmol; 35.1 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 6:4 to 1:1 hexane:ethyl acetate) to afford compound **4q** (45.1 mg; 82%) as a pale yellow oil. **R_f** (6:4 hexane:ethyl acetate) 0.25; **IR** (film) ν_{max} /cm⁻¹: 3440, 2966, 2927, 1688, 1399, 1169, 1118, 774; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 3.93 – 3.84 (m, 1H, **3**), 3.72 (t, J = 5.8 Hz, 2H, **9**), 3.41 – 3.33 (m, 1H, **2**), 3.33 – 3.26 (m, 1H, **2**), 2.80 – 2.68 (m, 2H, **8**), 2.59 – 2.46 (m, 2H, **6**), 2.26 – 2.18 (m, 1H), 2.03 – 1.90 (m, 2H, **4** – **5**), 1.89 – 1.77 (m, 2H, **1**), 1.66 – 1.56 (m, 2H, **4** – **5**), 1.45 (s, 9H, **14** – **15** – **16**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 154.9 (**17**), 79.4 (**13**), 60.4 (**9**), 56.5 (**3**), 46.4 (**2**), 35.6 (**8**), 34.8 (**4** or **5**), 30.6 (**4** or **5**), 28.7 (**14** – **15** – **16**), 28.6 (**6**), 23.6 (**1**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₃H₂₅NO₃SN⁺) expected m/z 298.1447; found m/z 298.1444.

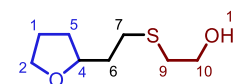


2-((2-(tetrahydrofuran-2-yl)ethyl)thio)ethan-1-ol (**4r**)

Compound synthesised and characterised by Dr. Subhasis Paul.



Prepared following general procedure A, using **26c** (1.0 equiv.; 0.2 mmol; 19.2 μ L), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (0.25 equiv.; 0.05 mmol; 10.6 mg) + (2.25 equiv.; 0.45 mmol; 95.4 mg) and 2-mercaptoethanol (2.5 equiv.; 0.5 mmol; 35.1 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 7:3 to 1:1 DCM:ethyl acetate) to afford compound **4r** (25.3 mg; 72%) as a transparent oil. **R_f** (1:1 DCM:ethyl acetate) 0.4; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3398, 2925, 2867, 1284, 1050, 1014; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 3.95 – 3.88 (m, 1H, **4**), 3.87 – 3.81 (m, 1H, **2**), 3.75 – 3.68 (m, 3H, **2** – **10**), 2.73 (t, J = 5.9 Hz, 2H, **9**), 2.70 – 2.63 (m, 1H, **7**), 2.63 – 2.56 (m, 1H, **7**), 2.38 – 2.31 (m, 1H, **11**), 2.04 – 1.96 (m, 1H, **5**), 1.93 – 1.84 (m, 2H, **1**), 1.84 – 1.72 (m, 2H, **6**), 1.51 – 1.42 (m, 1H, **5**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 77.9 (**4**), 67.9 (**2**), 60.5 (**10**), 35.9 (**6**), 35.6 (**9**), 31.5 (**5**), 28.6 (**7**), 25.8 (**1**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₈H₁₆O₂SN⁺) expected m/z 199.0763; found m/z 199.0762.

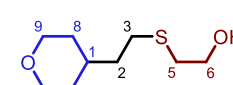


2-((2-(tetrahydro-2H-pyran-4-yl)ethyl)thio)ethan-1-ol (**4s**)

Compound synthesised and characterised by Dr. Subhasis Paul.



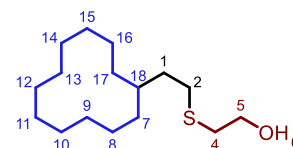
Prepared following general procedure A, using **26d** (1.0 equiv.; 0.2 mmol; 26.0 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) + (1.5 equiv.; 0.3 mmol; 63.6 mg) and 2-mercaptoethanol (2.5 equiv.; 0.5 mmol; 35.1 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 6:4 to 1:1 hexane:ethyl acetate) to afford compound **4s** (26 mg; 68%) as a transparent oil. **R_f** (3:2 hexane:ethyl acetate) 0.3; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3416, 2921, 2847, 1444, 1294, 1089, 857; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 3.97 – 3.92 (m, 2H, **9**), 3.76 – 3.68 (m, 2H, **6**), 3.37 (td, J = 11.8, 2.0 Hz, 2H, **9**), 2.73 (t, J = 6.0 Hz, 2H, **5**), 2.59 – 2.52 (m, 2H, **3**), 2.18 (br s, 1H, **7**), 1.69 – 1.51 (m, 5H, **1** – **2** – **8**), 1.34 – 1.22 (m, 2H, **8**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 68.1 (**9**), 60.4 (**6**), 36.8 (**2**), 35.5 (**5**), 34.2 (**1**), 32.9 (**8**), 28.8 (**3**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₉H₁₈O₂SN⁺) expected m/z 213.0920; found m/z 213.0914.



2-((2-cyclododecylethyl)thio)ethan-1-ol (**4t**)



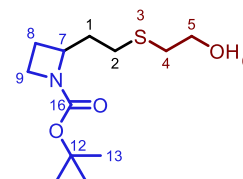
Prepared following general procedure A, irradiated for 48 h, using **26e** (1.0 equiv.; 0.2 mmol; 42.5 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) + (1.5 equiv.; 0.3 mmol; 63.6 mg) and 2-mercaptoethanol (2.5 equiv.; 0.5 mmol; 35.1 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 99:1 to 98:2 DCM:ethyl acetate) to afford compound **4t** (28 mg; 51%) as a transparent oil. **R_f** (97:3 hexane:ethyl acetate) 0.3; **IR** (film) ν_{max} /cm⁻¹: 3366, 2928, 2860, 1470, 1445, 1046, 1012, 719; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 3.72 (q, J = 6.0 Hz, 2H, **5**), 2.73 (t, J = 6.0 Hz, 2H, **4**), 2.57 – 2.48 (m, 2H, **2**), 2.18 (td, J = 6.2, 2.1 Hz, 1H, **6**), 1.55 – 1.45 (m, 3H, **1** – **18**), 1.39 – 1.19 (m, 22H); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 60.2 (**5**), 35.5 (**4**), 35.1, 33.6 (**18**), 29.8 (**2**), 29.0, 24.9, 24.3, 23.5, 23.4, 21.8; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₆H₃₂SONa⁺) expected m/z 295.2066; found m/z 295.2062.



tert-butyl 2-((2-(2-hydroxyethyl)thio)ethyl)azetidine-1-carboxylate (**4u**)



Prepared following general procedure A, using **26f** (1.0 equiv.; 0.2 mmol; 42.5 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) + (1.5 equiv.; 0.3 mmol; 63.6 mg) and 2-mercaptoethanol (2.5 equiv.; 0.5 mmol; 35.1 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 85:15 to 7:3 DCM:ethyl acetate) to afford compound **4u** (38 mg; 73%) as a transparent oil. **R_f** (7:3 DCM:ethyl acetate) 0.2; **IR** (film) ν_{max} /cm⁻¹: 3436, 2972, 2928, 2892, 1697, 1676, 1393, 1366, 1290, 1141, 1047, 863, 775; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 4.34 – 4.26 (m, 1H, **7**), 3.87 – 3.75 (m, 2H, **9**), 3.73 (t, J = 5.9 Hz, 2H, **5**), 2.73 (t, J = 6.0 Hz, 2H, **4**), 2.59 (t, J = 7.6 Hz, 2H, **2**), 2.34 – 2.25 (m, 1H, **6**), 2.20 – 2.09 (m, 2H), 1.93 – 1.79 (m, 2H), 1.43 (s, 9H, **13**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 156.9 (**16**), 79.6 (**12**), 61.1 (**7**), 60.4 (**5**), 46.7 (**9**), 36.0 (**4**), 35.4, 28.6 (**13**), 27.3 (**2**), 22.0; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₂H₂₃NO₃SNa⁺) expected m/z 284.1291; found m/z 284.1296.

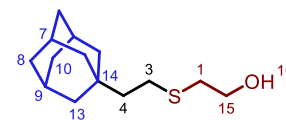


2-((2-((1s,3s)-adamantan-1-yl)ethyl)thio)ethan-1-ol (**4v**)

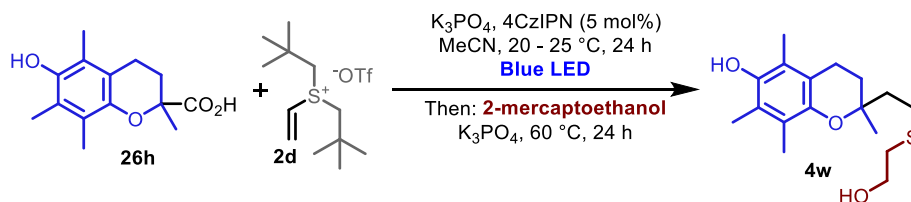
Compound synthesised and characterised by Dr. Subhasis Paul.



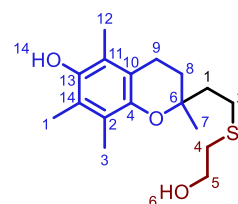
Prepared following general procedure A, using **26g** (1.0 equiv.; 0.2 mmol; 36.0 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) + (1.5 equiv.; 0.3 mmol; 63.6 mg) and 2-mercaptoethanol (2.5 equiv.; 0.5 mmol; 35.1 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 9:1 to 8:2 hexane:ethyl acetate). The compound was purified a second time by flash column chromatography (SiO₂; gradient 95:5 to 9:1 toluene:Et₂O) to afford compound **4v** (37.3 mg; 77%) as a transparent oil. **R_f** (8:2 hexane:ethyl acetate) 0.35; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3386, 2901, 2845, 1448, 1221, 1048, 772; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 3.71 (q, J = 6.0 Hz, 2H, **15**), 2.73 (t, J = 5.9 Hz, 2H, **1**), 2.51 – 2.44 (m, 2H, **3**), 2.21 – 2.15 (m, 1H, **16**), 1.98 – 1.92 (m, 3H), 1.74 – 1.67 (m, 3H), 1.65 – 1.59 (m, 3H), 1.48 (d, J = 2.8 Hz, 6H), 1.39 – 1.33 (m, 2H); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 60.2 (**15**), 44.6, 42.3, 37.2, 35.5, 32.9, 28.7, 25.7; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₄H₂₄OSNa⁺) expected m/z 263.1440; found m/z 263.1447.



2-(2-((2-hydroxyethyl)thio)ethyl)-2,5,7,8-tetramethylchroman-6-ol (**4w**)

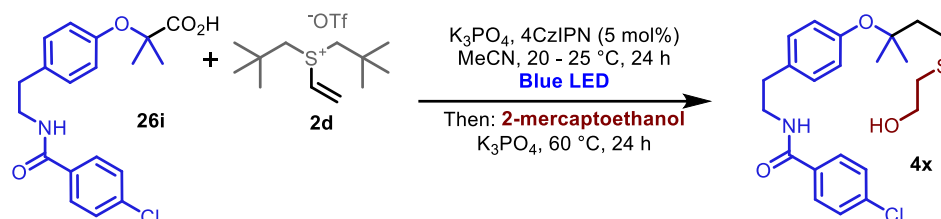


Prepared following general procedure A, using **26h** (1.0 equiv.; 0.2 mmol; 50.0 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) + (1.5 equiv.; 0.3 mmol; 63.6 mg) and 2-mercaptoethanol (2.5 equiv.; 0.5 mmol; 35.1 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 8:2 to 7:3 hexane:acetone) to afford compound **4w** (46 mg; 74%) as a yellow solid. **R_f** (7:3 hexane:acetone) 0.2; **M.P.** = 32 – 33 °C; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3380, 2926, 2868, 1454, 1422, 1379, 1343, 1297, 1166, 1086, 1058, 1008, 925, 856, 608, 575, 549, 519, 477, 447; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 4.28 – 4.22 (m, 1H, **14**), 3.70 (q, J = 5.9 Hz, 2H, **5**), 2.73 – 2.59 (m, 6H, **2** – **4** – **9**), 2.16 (s, 3H, **12**), 2.18 – 2.08 (m, 6H, **0** – **3**), 1.98 – 1.90 (m, 1H, **1** – **8**), 1.86 – 1.74 (m, 3H, **1** – **8**), 1.24 (s, 3H, **15**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 145.2, 145.0, 122.7, 121.3, 118.7, 117.2, 74.0 (**5**), 60.2 (**6**), 40.1 (**1** – **8**), 35.5, 31.8 (**1** – **8**), 25.9, 23.7, 20.7, 12.4 (**12**), 12.0, 11.4;

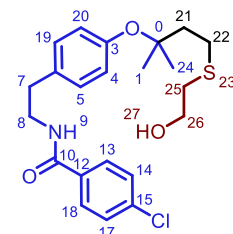


HRMS (ESI-TOF) mass calculated for $[M+Na]^+$ ($C_{17}H_{26}O_3SNa^+$) expected m/z 333.1495; found m/z 333.1489.

4-chloro-N-(4-((4-((2-hydroxyethyl)thio)-2-methylbutan-2-yl)oxy)phenethyl)benzamide (**4x**)

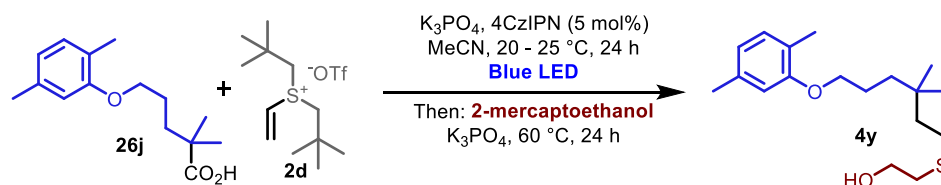


Prepared following general procedure A, using **26i** (1.0 equiv.; 0.2 mmol; 50 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) + (1.5 equiv.; 0.3 mmol; 63.6 mg) and 2-mercaptoethanol (2.5 equiv.; 0.5 mmol; 35.1 μ L). The crude residue was purified by flash column chromatography (SiO_2 ; gradient 1:1 to 4:6 hexane:ethyl acetate) to afford compound **4x** (67 mg; 79%) as a yellow solid. **R_f** (4:6 hexane:ethyl acetate) 0.2; **M.P.** = 37 – 38 °C; **IR** (film) ν_{max}/cm^{-1} : 3317, 3086, 2973, 2930, 2872, 1638, 1597, 1544, 1506, 1487, 1439, 1384, 1367, 1316, 1233, 1193, 1162, 1108, 1094, 1046, 1015, 895, 847, 758, 525; **¹H-NMR** ($CDCl_3$, 500 MHz) δ (ppm): 7.66 – 7.57 (m, 2H, **13** - **18**), 7.44 – 7.34 (m, 2H, **4** - **20**), 7.16 – 7.08 (m, 2H, **14** - **17**), 6.97 – 6.87 (m, 2H, **5** - **19**), 6.15 – 6.04 (m, 1H, **9**), 3.76 – 3.61 (m, 4H, **8** - **26**), 2.88 (t, J = 6.9 Hz, 2H, **25**), 2.79 – 2.67 (m, 4H, **7** - **21**), 2.18 (t, J = 6.4 Hz, 1H, **27**), 1.98 – 1.88 (m, 2H, **22**), 1.29 (s, 6H, **1** - **24**); **¹³C-NMR** ($CDCl_3$, 126 MHz) δ (ppm): 166.5 (**12**), 153.9 (**10**), 137.8 (**3**), 133.8 (**15**), 133.1, 129.5 (**13** - **18**), 129.0 (**4** - **20**), 128.4 (**14** - **17**), 124.1 (**5** - **19**), 79.8 (**0**), 60.4 (**8**), 42.4 (**23**), 41.4, 35.5 (**25**), 35.0, 26.8 (**2** - **22**), 26.4; **HRMS** (ESI-TOF) mass calculated for $[M+Na]^+$ ($C_{22}H_{28}NO_3SClNa^+$) expected m/z 444.1371; found m/z 444.1369.



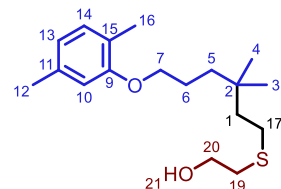
2-((6-(2,5-dimethylphenoxy)-3,3-dimethylhexyl)thio)ethan-1-ol (**4y**)

Compound synthesised and characterised by Dr. Subhasis Paul.

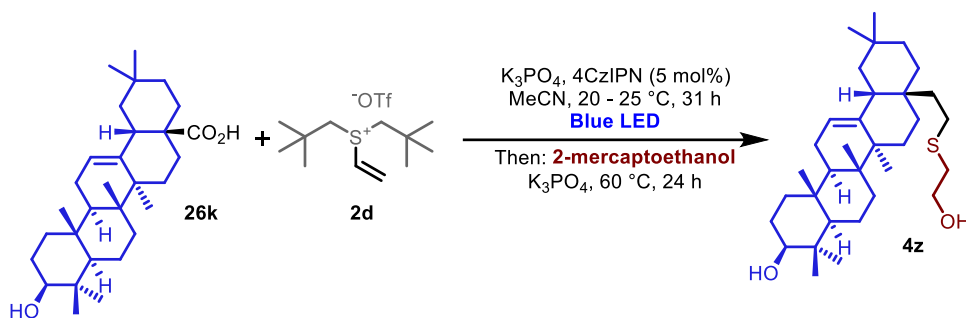


Prepared following general procedure A, using **26j** (1.0 equiv.; 0.2 mmol; 50.1 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) + (1.5 equiv.; 0.3 mmol; 63.6 mg) and 2-mercaptoethanol (2.5 equiv.; 0.5 mmol; 35.1 μ L). The crude residue was purified by flash column chromatography (SiO_2 ; gradient 9:1 to 85:15 hexane:ethyl acetate) to afford compound **4y** (47.4 mg; 84%) as a transparent oil.

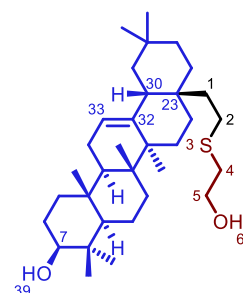
R_f (8:2 hexane:ethyl acetate) 0.35; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3402, 2953, 2867, 1615, 1585, 1509, 1470, 1265, 1157, 1130, 1049, 804; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.01 (d, J = 7.5 Hz, 1H, **13** or **14**), 6.66 (d, J = 7.5 Hz, 1H, **13** or **14**), 6.62 (s, 1H, **10**), 3.92 (t, J = 6.3 Hz, 2H, **7**), 3.72 (t, J = 5.9 Hz, 2H, **20**), 2.74 (t, J = 5.9 Hz, 2H, **19**), 2.53 – 2.46 (m, 2H, **17**), 2.31 (s, 3H, **12** or **16**), 2.18 (s, 3H, **12** or **16**), 1.78 – 1.70 (m, 2H, **6**), 1.57 – 1.51 (m, 2H, **1**), 1.42 – 1.35 (m, 2H, **5**), 0.92 (s, 6H, **3** – **4**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 157.1 (**9**), 136.6, 130.4, 123.7, 120.8, 112.1 (**10**), 68.5 (**7**), 60.3 (**20**), 42.1 (**1**), 38.0 (**5**), 35.5 (**19**), 33.1 (**2**), 27.1 (**3** – **4**), 26.8 (**17**), 24.4 (**6**), 21.5, 15.9; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₈H₃₀O₂SN⁺) expected m/z 333.1859; found m/z 333.1862.



(3*S*,4*aR*,6*aR*,6*bS*,8*aR*,12*aR*,14*aR*,14*bR*)-8*a*-(2-((2-hydroxyethyl)thio)ethyl)-4,4,6*a*,6*b*,11,11,14*b*-heptamethyl-1,2,3,4,4*a*,5,6,6*a*,6*b*,7,8,8*a*,9,10,11,12,12*a*,14,14*a*,14*b*-icosahydricen-3-ol (**4z**)



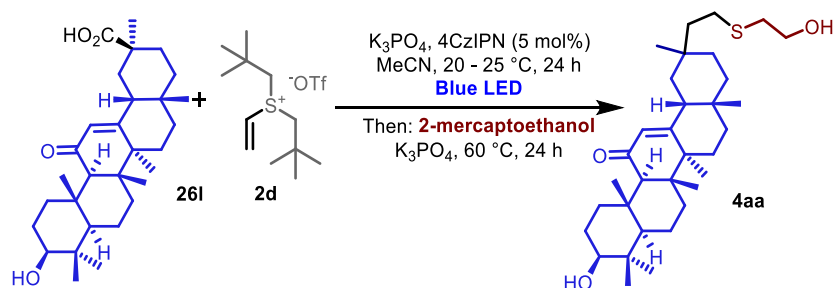
Prepared following general procedure A, irradiating for 31 h, using **26k** (1.0 equiv.; 0.2 mmol; 91.3 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) + (1.5 equiv.; 0.3 mmol; 63.6 mg) and 2-mercaptoethanol (2.5 equiv.; 0.5 mmol; 35.1 μ L). The crude residue was purified by flash column chromatography (SiO₂; gradient 95:5 to 8:2 DCM:ethyl acetate) to afford compound **4z** (57.9 mg; 56%; d.r. >20:1) as a white solid. The stereochemistry is assigned by assuming analogous mechanistic pathway to a Giese reaction reported for the same substrate.²⁹ **R_f** (9:1 DCM:ethyl acetate) 0.2; [α]_D²⁵ = +40 (c = 1.00 CHCl₃); **M.P.** = 121 – 122 °C; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3373, 2923, 2867, 1462, 1383, 1284, 1218, 1137, 1036, 998, 820, 755, 662, 600; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 5.20 (t, J = 3.7 Hz, 1H, **33**), 3.70 (t, J = 5.9 Hz, 2H, **5**), 3.26 – 3.13 (m, 1H, **7**), 2.72 (t, J = 5.9 Hz, 2H, **4**), 2.50 – 2.33 (m, 2H, **2**), 1.98 – 1.90 (m, 2H), 1.89 – 1.80 (m, 3H), 1.78 – 1.67 (m, 3H), 1.65 – 1.59 (m, 3H), 1.58 – 1.51 (m, 3H), 1.52 – 1.48 (m, 1H), 1.41 – 1.37 (m, 1H), 1.36 – 1.33 (m, 1H), 1.32 – 1.28 (m, 2H), 1.28 – 1.22 (m, 1H), 1.22 – 1.17 (m, 1H), 1.16 – 1.10 (m, 4H), 1.06 – 1.02 (m, 1H), 1.01 – 0.91 (m, 12H), 0.87 (s, 3H), 0.86



²⁹ Qin, T.; Malins, L. R.; Edwards, J. T.; Merchant, R. R.; Novak, A. J. E.; Zhong, J. Z.; Mills, R. B.; Yan, M.; Yuan, C.; Eastgate, M. D.; Baran, P. S. *Angew. Chem. Int. Ed.* **2017**, *56*, 260–265.

(s, 3H), 0.79 (s, 3H), 0.75 – 0.71 (m, 1H); ^{13}C -NMR (CDCl_3 , 126 MHz) δ (ppm): 144.4 (32), 122.7 (33), 79.1 (7), 60.1 (5), 55.3, 47.7, 47.1, 46.7, 41.8, 40.3, 40.0, 38.9, 38.7, 37.1, 35.4 (4), 35.3, 34.5, 33.4, 33.2, 32.7, 31.1, 28.2, 27.4, 26.2, 25.9, 25.5 (2), 23.7, 23.7, 23.3, 18.5, 17.0, 15.7, 15.7; HRMS (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{33}\text{H}_{56}\text{O}_2\text{SNa}^+$) expected m/z 539.3893; found m/z 539.3893.

(4aR,6aS,6bR,8aR,10S,12aS,12bR,14bR)-10-hydroxy-2-((2-hydroxyethyl)thio)ethyl)-2,4a,6a,6b,9,9,12a-heptamethyl-1,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,14b-octadecahydricen-13(2H)-one (4aa)



Prepared following general procedure A, using **26l** (1.0 equiv.; 0.2 mmol; 94.2 mg), dineopentyl(vinyl)sulfonium triflate **2d** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (1.0 equiv.; 0.2 mmol; 42.4 mg) + (1.5 equiv.; 0.3 mmol; 63.6 mg) and 2-mercaptoethanol (2.5 equiv.; 0.5 mmol; 35.1 μL). The crude residue was purified by flash column chromatography (SiO_2 ; gradient 97.5:2.5 to 92.5:7.5 DCM:methanol). The compound was purified a second time by flash column chromatography (SiO_2 ; gradient 75:25 to 1:1 DCM:ethyl acetate) to afford compound **4aa** (87.0 mg; 82%; d.r. 2.3:1) as a white solid. R_f (1:1 DCM:ethyl acetate) 0.4; $\text{M.P.} = 113 - 115\text{ }^\circ\text{C}$; $[\alpha]_D^{25} = +72$ ($c = 1.00\text{ CHCl}_3$); IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3394, 2925, 2865, 1652, 1460, 1386, 1208, 1043, 994, 755; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 5.57 (s, 1H), 3.76 – 3.68 (m, 2H), 3.25 – 3.18 (m, 1H), 2.81 – 2.69 (m, 3H), 2.53 – 2.38 (m, 2H), 2.32 (s, 1H), 2.15 – 2.06 (m, 1H), 2.06 – 1.98 (m, 1H), 1.85 – 1.77 (m, 3H), 1.74 – 1.52 (m, 6H), 1.49 – 1.39 (m, 4H), 1.36 – 1.28 (m, 5H), 1.23 – 1.07 (m, 9H), 1.01 – 0.93 (m, 5H), 0.89 (s, 2H), 0.87 – 0.83 (m, 4H), 0.80 (s, 3H), 0.72 – 0.66 (m, 1H); ^{13}C NMR (CDCl_3 , 126 MHz) diastereomeric mixture δ (ppm) : 200.4, 170.2, 128.4, 78.9, 61.9, 60.6, 60.3, 55.1, 47.2, 47.1, 46.1, 45.6, 45.5, 43.5, 43.5, 43.4, 43.2, 39.3, 37.2, 36.0, 35.6, 35.5, 35.4, 34.2, 33.9, 33.0, 32.9, 32.8, 32.6, 32.4, 29.3, 28.8, 28.2, 27.4, 26.8, 26.6, 26.5, 26.2, 23.6, 23.5, 20.8, 18.9, 17.6, 16.5, 15.7; HRMS (ESI-TOF) mass calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{33}\text{H}_{55}\text{O}_3\text{S}^+$) expected m/z 531.3866; found m/z 531.3840.

4.6.9. Reaction with *in-situ* generation of the vinyl sulfonium

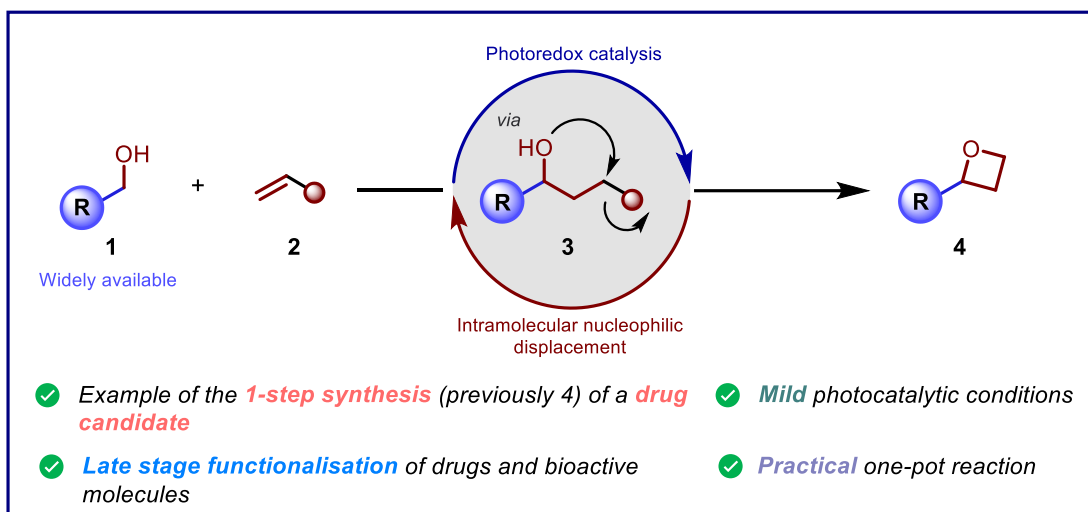


Prepared following general procedure A, using **26a** (1.0 equiv.; 0.2 mmol; 45.9 mg), (2-bromoethyl)dineopentylsulfonium triflate **31** (1.5 equiv.; 0.3 mmol; 129 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), potassium phosphate (2.5 equiv.; 0.5 mmol; 106 mg) + (1.5 equiv.; 0.3 mmol; 63.6 mg) and 2-mercaptoethanol (2.5 equiv.; 0.5 mmol; 35.1 μ L). The crude residue was purified by flash column chromatography (SiO_2 ; gradient 9:1 to 6:4 DCM:ethyl acetate) to afford compound **4a** (38.8 mg; 67%) as a pale yellow oil. See compound **4a** for full characterisation.

Chapter 5. Oxetane Synthesis via Alcohol C-H Functionalisation

Oxetanes are four-membered strained heterocycles which possess unique properties. This class of compounds finds important applications in medicinal chemistry, thanks to their unique physicochemical and biochemical properties e.g., lipophilicity, aqueous solubility and metabolic stability. Despite their remarkable features, the use of oxetanes in organic synthesis remains limited due to the challenges associated to their preparation. In this chapter, we present a methodology which allows the construction of oxetane rings **4** from simple alcohol starting materials **1**. The generality of this approach is demonstrated by the application of this methodology in late-stage functionalisation and in the streamlined synthesis of a known estrogen inhibitor.

The project described below was published, see Paul, S.; Filippini, D.; Ficarra, F.; Melnychenko, H.; Janot, C.; Silvi, M. *J. Am. Chem. Soc.*, **2023**, *145*, 15688-15694. S.P., D.F. and F.F. contributed equally to this work.



5.1. Introduction: The importance of oxetanes

Oxetanes are four-membered heterocycles containing an oxygen atom.¹ They are highly strained ($106 \text{ kJ}\cdot\text{mol}^{-1}$)² and adopt a particular planar structure with a puckering angle of only 8.7° ,³ (in comparison, cyclobutane is 30°).⁴ This strained and flat geometry causes the oxygen lone pairs to be particularly exposed, greatly increasing the oxygen ability to accept hydrogen bonds, making oxetanes equal to other oxygen functionalities present in natural compounds e.g., aliphatic ketones, aldehydes and esters (Figure 5.1).⁵

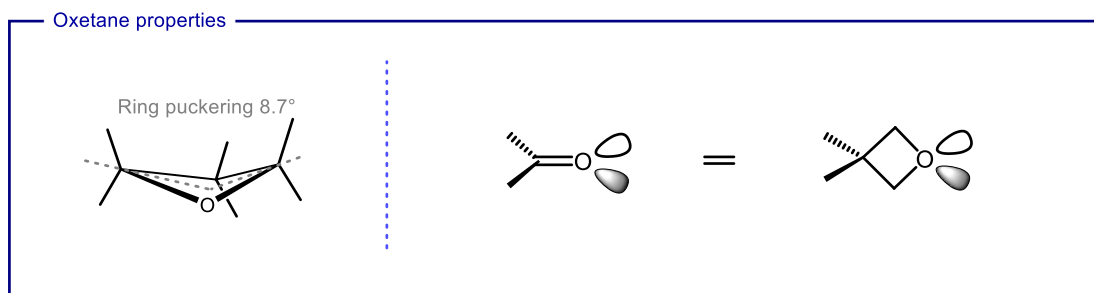


Figure 5.1: Geometric structure of oxetanes

This feature trigger significant uses in medicinal chemistry, as they can act as carbonyl bioisostere, ensuring increased metabolic stability of the active compound.⁶

Over the last few decades, the number of bioactive oxetane-containing compounds has been increasing (Table 5.1). The most well-known example is Taxol, which is a significantly relevant compound possessing anticancer activity. Various other oxetane-containing bioactive molecules have been isolated from natural sources. Oxetanocin A, for example, first isolated from a bacterium, shows *in-vivo* inhibition of the replication of HIV.⁷ Oxetin shows antibacterial and herbicidal effects.⁸ Thromboxane A₂, found in suspensions of human platelets, possesses prothrombotic properties.⁹ Despite the privileged role of the oxetane ring in medicinal chemistry, the development of novel pharmaceuticals bearing this functionality is hampered by their synthesis which, so far, poses significant challenges. Below, a brief review of the current oxetane synthesis is presented.

¹ For selected reviews: a) Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 9052–9067. b) Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F. *Chem. Rev.* **2016**, *116*, 12150–12233. c) Carreira, E. M.; Fessard, T. C. *Chem. Rev.* **2014**, *114*, 8257–8322. d) Rogers-Evans, M.; Knust, H.; Plancher, J.-M.; Carreira, E. M.; Wuitschik, G.; Burkhard, J.; Li, D. B.; Guérot, C. *Chimia* **2014**, *68*, 492.

² Pell, A. S.; Pilcher, G. *Trans. Faraday Soc.* **1965**, *61*, 71–77.

³ Chan, S. I.; Zinn, J.; Gwinn, W. D. *J. Chem. Phys.* **2004**, *34*, 1319–1329.

⁴ Gwinn, W. D. *Discuss. Faraday Soc.* **1955**, *19*, 43–51.

⁵ Besseau, F.; Luçon, M.; Laurence, C.; Berthelot, M. *J. Chem. Soc. Perkin Trans. 2* **1998**, *1*, 101–108.

⁶ Stepan, A. F.; Karki, K.; McDonald, W. S.; Dorff, P. H.; Dutra, J. K.; DiRico, K. J.; Won, A.; Subramanyam, C.; Efremov, I. V.; O'Donnell, C. J.; Nolan, C. E.; Becker, S. L.; Pustilnik, L. R.; Sneed, B.; Sun, H.; Lu, Y.; Robshaw, A. E.; Riddell, D.; O'Sullivan, T. J.; Sibley, E.; Capetta, S.; Atchison, K.; Hallgren, A. J.; Miller, E.; Wood, A.; Obach, R. S. *J. Med. Chem.* **2011**, *54*, 7772–7783.

⁷ Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, A.; Takita, T. *J. Antibiot.* **1986**, *39*, 1623–1625.

⁸ Omura, S.; Murata, M.; Imamura, N.; Iwai, Y.; Tanaka, H.; Furusaki, A.; Matsumoto, H. *J. Antibiot.* **1984**, *37*, 1324–1332.

⁹ Hamberg, M.; Svensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. U. S. A.* **1975**, *72*, 2994–2998.

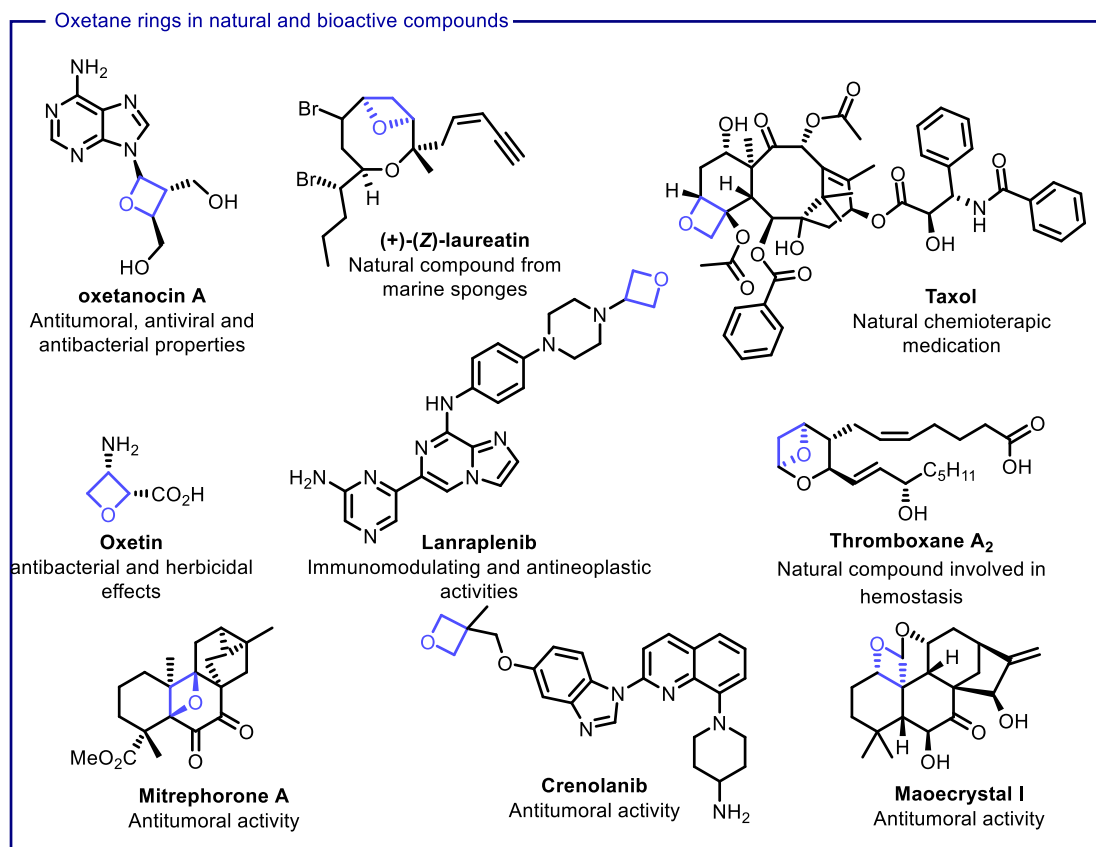


Table 5.1: Recurrency of oxetane rings in natural and bioactive compounds

5.2. State of the Art: Synthesis of oxetanes

Current synthetic methodologies for oxetane rings¹⁰ generally rely on [2+2] cycloadditions or intermolecular Williamson cyclisation, details are presented in the sections below.

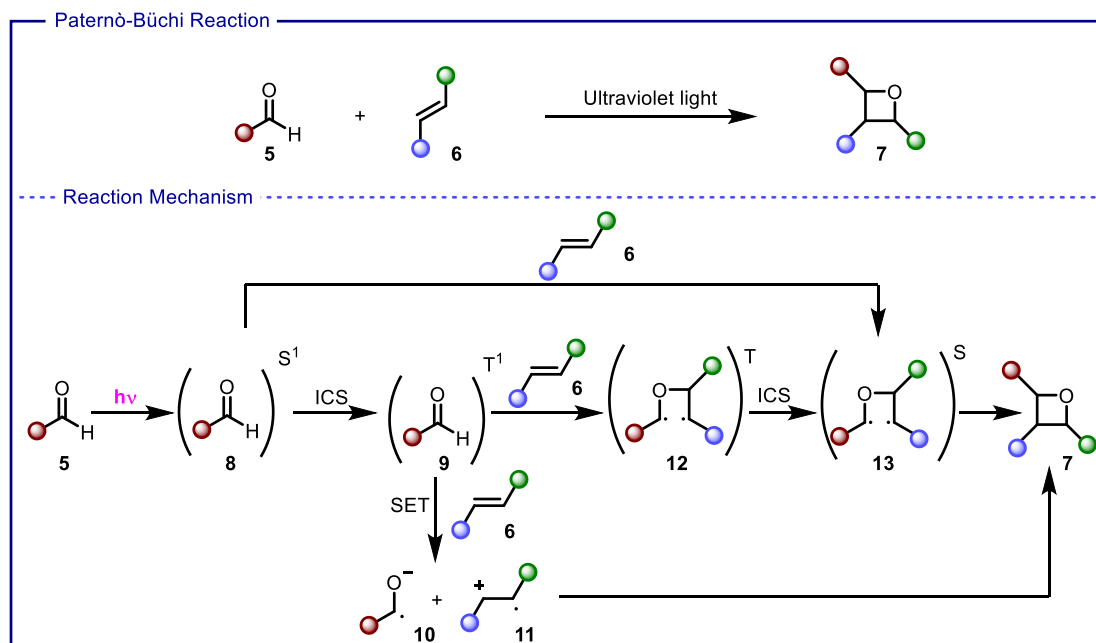
5.2.1. Paternò- Büchi reaction

The Paternò-Büchi reaction is a traditional photochemical process, which was first introduced by Paternò in 1909.¹¹ Initial studies were focused on the analysis of the photochemical reaction between benzaldehyde and amylene. However, only in 1954¹² Büchi elucidated the regioselectivity of the process, so the reaction was historically named after both scientists.

¹⁰ For selected reviews : a) Bach, T. *Synth.* **1998**, 1998, 683–703. b) D'Auria, M.; Racioppi, R. *Mol.* **2013**, 18, 11384–11428. c) Oelgemöller, M.; Hoffmann, N. *Org. Biomol. Chem.* **2016**, 14, 7392–7442. d) D'Auria, M. *Photochem. Photobiol. Sci.* **2019**, 18, 2297–2362.

¹¹ Paternò, E.; Chieffi, G. *Gazz. Chim. Ital.* **1909**, 39, 341–361.

¹² Büchi, G.; Inman, C. G.; Lipinsky, E. S. *J. Am. Chem. Soc.* **1954**, 76, 4327–4331.



Scheme 5.1: Reaction scheme and different reaction mechanisms for the Paternò-Büchi reaction.¹⁰

As presented in Scheme 5.1,^{10c,13} upon absorption of ultraviolet light, aldehyde **5** is excited to its singlet state **8**. The singlet excited state can react with the alkene **6**, revealing the diradical singlet species **13** which rapidly undergoes radical recombination leading to oxetane product **7**.¹⁴ However, singlet excited state **8** can also undergo inter-system crossing (ISC) to generate triplet excited state **9**, which then reacts with alkene **6** to form triplet diradical **12**. Following a further ISC, singlet diradical **13** is generated, which then rapidly cyclises to form oxetane **7**.¹⁴ A third SET pathway is also possible. In this mechanistic manifold, after excitation, aldehyde **9** can accept an electron from the alkene within **6** forming radical anion **10** and radical cation **11**. Rapid coupling between the two reactive species leads to oxetane **7**.

Regioselectivity

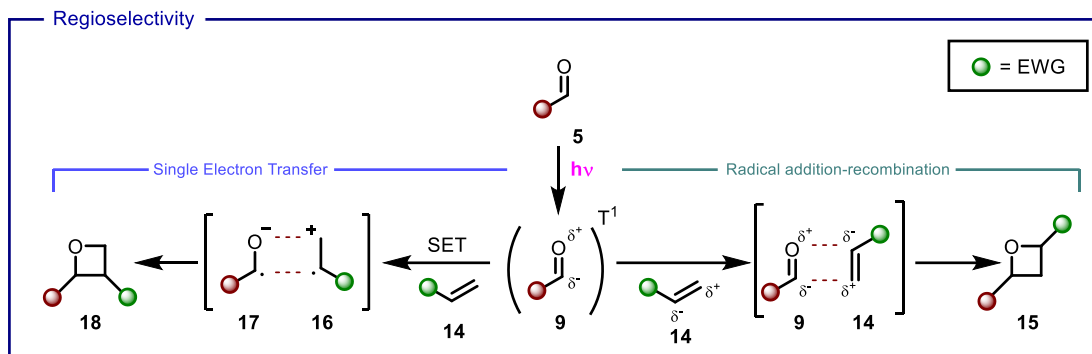
The regioselectivity of the Paternò-Büchi reaction is challenging to predict and is highly substrate dependent, as it largely depends upon the different reaction pathways available (Scheme 5.2).¹⁵ In the excited state, the carbonyl compound **9** presents reversed polarity compared to its ground state **5**, as the oxygen is electrophilic, and the carbon centre is nucleophilic. This dictates the regioselectivity of the reaction, with the oxygen centre attacking the more electron-rich side of the double bond **14**, followed by the carbon attacking the most electron-poor (Scheme 5.2, right) which reveals oxetane **15**. However, if a SET event occurs, the carbonyl radical anion **17** preserves the natural polarity of the original carbonyl,¹⁶ therefore yielding the opposite regioisomer **18** compared to the previous mechanism (Scheme 5.2, left).

¹³ Abe, M.; in *Handbook of Synthetic Photochemistry*, ed. Albini, A.; and Fagnoni, M. Wiley-VCH, Weinheim, **2010**, pp. 217–239; Arnold, D.R. *Adv. Photochem.*, **1968**, 6, 301–423.

¹⁴ Palmer, I. J.; Ragazos, I. N.; Bernardi, F.; Olivucci, M.; Robb, M. A. *J. Am. Chem. Soc.* **1994**, 116, 2121–2132.

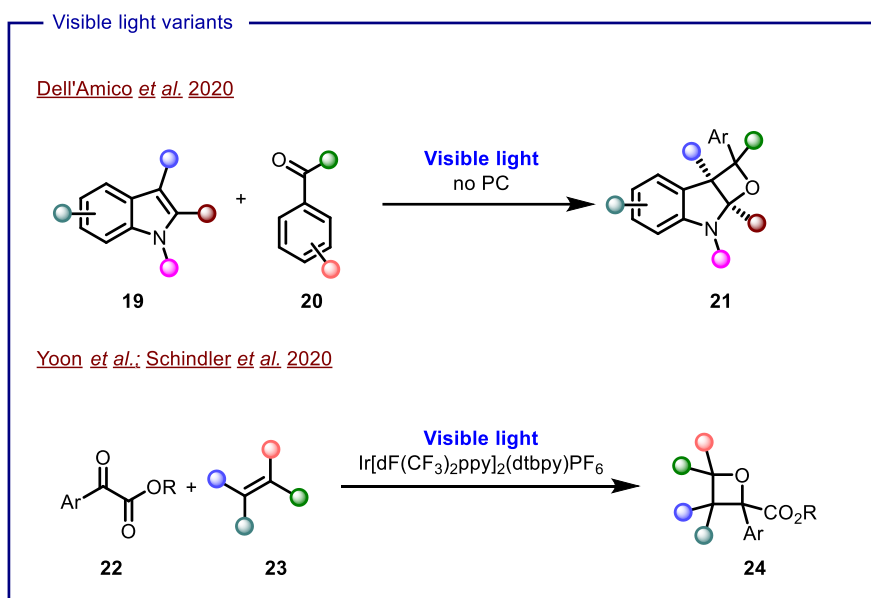
¹⁵ Abe, M.; Shirodai, Y.; Nojima, M. *J. Chem. Soc. Perkin Trans. 1* **1998**, 19, 3253–3260.

¹⁶ Gersdorf, J.; Mattay, J.; Goerner, H. *J. Am. Chem. Soc.* **1987**, 109, 1203–1209.

Scheme 5.2: Regioselectivity of the Paternò-Büchi reaction.¹⁰

Visible-light driven Paternò-Büchi reactions

In recent years, the increased demand in photochemistry to substitute UV light approaches with milder visible light irradiation triggered the development of few Paternò-Büchi reactions based on photoredox catalysis or EDA complex chemistry.

Scheme 5.3: Examples of Paternò-Büchi reactions driven by visible light.^{17,18}

The group of Dell'Amico in 2020¹⁷ proposed a photocatalyst-free methodology that allows the rapid synthesis of oxetanes on indole scaffold **19** (Scheme 5.3, top). The reaction is driven by the visible light absorption of the highly conjugated ketone **20**, which possesses a tail in its absorption spectrum up to 400 nm. In other approaches, different research groups¹⁸ reported the synthesis of highly substituted oxetanes starting from aromatic α -keto esters **22** and using Ir-based photocatalyst following a Dexter energy transfer approach (Scheme 5.3, bottom).

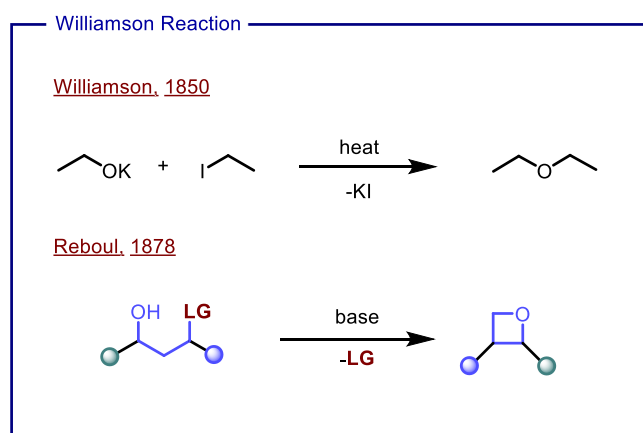
¹⁷ Mateos, J.; Vega-Peñaloza, A.; Franceschi, P.; Rigodanza, F.; Andreetta, P.; Companyó, X.; Pelosi, G.; Bonchio, M.; Dell'Amico, L. *Chem. Sci.* **2020**, *11*, 6532–6538.

¹⁸ a) Zheng, J.; Dong, X.; Yoon, T. P. *Org. Lett.* **2020**, *22*, 6520–6525. b) Rykaczewski, K. A.; Schindler, C. S. *Org. Lett.* **2020**, *22*, 6516–6519.

While these reports introduce the use of visible light irradiation in Paternò-Büchi reactions, they are highly substrate-dependent and allow access only to specific target oxetane structures.

5.2.2. Williamson Reaction

Because of the scope limitations and the difficulties in controlling the selectivity of Paternò-Büchi reactions, the most common methodology to construct oxetanes is the intramolecular Williamson synthesis. The Williamson reaction was discovered in 1850,¹⁹ and explored in its intramolecular version for oxetane synthesis in 1878 by Reboul (Scheme 5.4).²⁰ In the process, an intramolecular nucleophilic substitution between an alcohol and a leaving group in a 1,3-relationship occurs.



Scheme 5.4: Williamson reaction.¹⁹

Due to the elevated product ring strain, the kinetic of the cyclization of four-membered rings is significantly slower than three-, five- and six-membered analogous.²¹ Hence, a good leaving group and a strong base are required to achieve decent yields and, also in the best conditions, they can be modest due to the rise of undesired side reactions e.g., the Grob fragmentation²² into aldehyde and alkene or E2 elimination.²³ Consequently, the reaction is highly substrate-dependent.

Applications in organic synthesis

Despite the above-mentioned limitations, the Williamson synthesis of oxetanes found several applications in total synthesis and in the preparation of bioactive compounds e.g., oxetin **28**, oxetanocin **31** and taxol **33** (Scheme 5.5).^{1b}

In 1985, Omura *et al.*,²⁴ proposed an asymmetric procedure for the synthesis of oxetin **28**, the first antibiotic containing an oxetane ring. In their methodology, the authors

¹⁹ Williamson, A. *London, Edinburgh, Dublin Philos. Mag. J. Sci.* **1850**, 37, 350–356.

²⁰ Reboul, M. *Ann. Chim. (Paris)* **1878**, 14, 495–497.

²¹ Di Martino, A.; Galli, C.; Gargano, P.; Mandolini, L. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1345–1349.

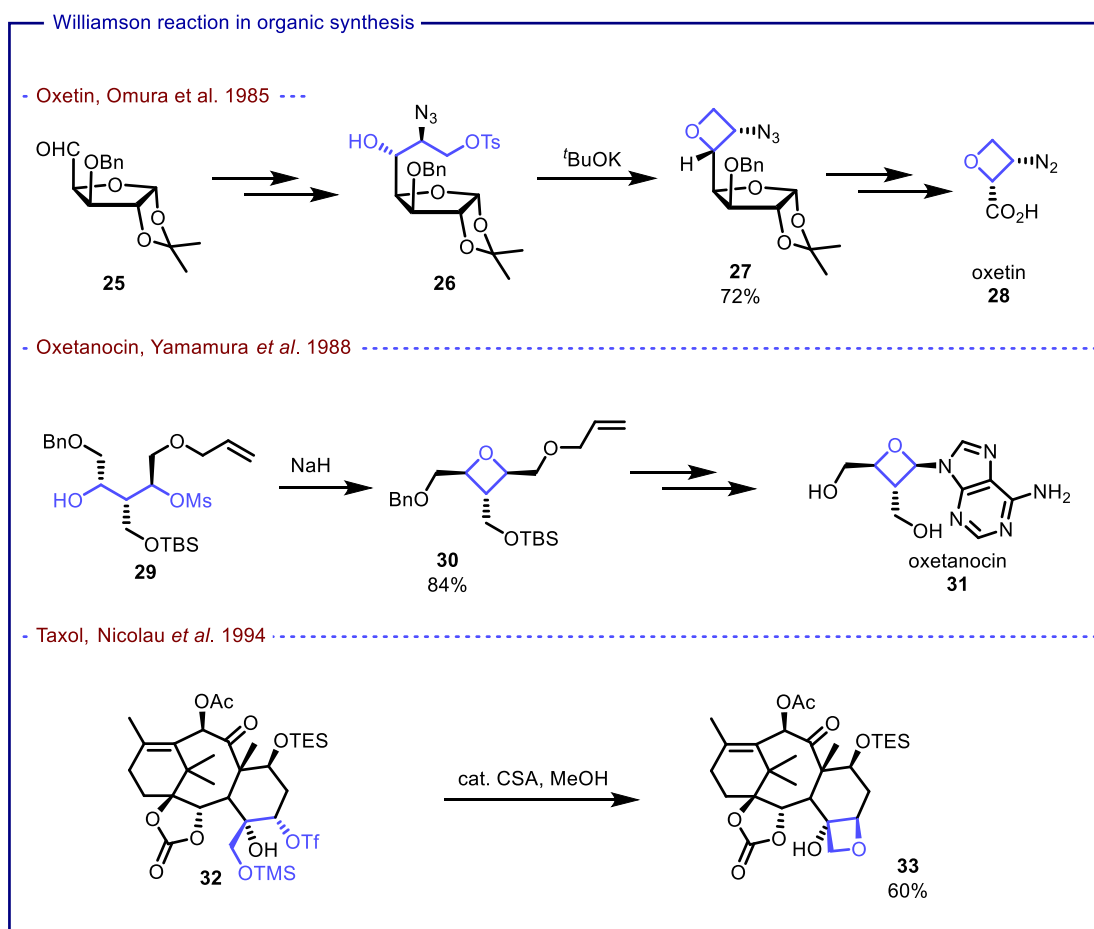
²² Grob, C. A.; Schiess, P. W. *Angew. Chem. Int. Ed.* **1967**, 6, 1–15.

²³ a) Searles, S.; Nickerson, R. G.; Witsiepe, W. K. *J. Org. Chem.* **1959**, 24, 1839–1844. b) Searles, S.; Gortatowski, M. J. *J. Am. Chem. Soc.* **1953**, 75, 3030–3031.

²⁴ Kawahata, Y.; Takatsuto, S.; Ikekawa, N.; Murata, M.; Omura, S. *Chem. Pharm. Bull. (Tokyo)* **1986**, 34, 3102–3110.

performed the asymmetric synthesis of the chiral oxetane ring, using a carbohydrate scaffold **25** as a chiral auxiliary (Scheme 5.5, top). In their synthesis, the authors installed a tosylate group in a 1,3-relationship with a hydroxyl group (compound **26**). Upon treatment with $t\text{BuOK}$, oxetane **27** was obtained in 72% yield, which could be converted into oxetin **28** after further steps.

In 1988, the Yamamura group²⁵ reported the synthesis of oxetanocin **31** – a potent antitumoral, antiviral and antibacterial compound – starting from protected polyol **29**, which bears a free secondary alcohol and a mesityl group. Upon treatment with sodium hydride, rapid Williamson etherification occurs, leading to oxetane **30** in 84% yield. Further steps from this material led to oxetanocin **31** (Scheme 5.5, middle).



Scheme 5.5: Application of the Williamson reaction for the synthesis of bioactive compounds.^{24,25,27}

Finally, one of the most remarkable examples of the synthetic application of the Williamson reaction is in the total synthesis of Taxol, a powerful natural antitumoral compound. Several different groups²⁶ have been using a similar strategy to forge the

²⁵ Nishiyama, S.; Yamamura, S.; Kato, K.; Takita, T. *Tetrahedron Lett.* **1988**, 29, 4743–4746.

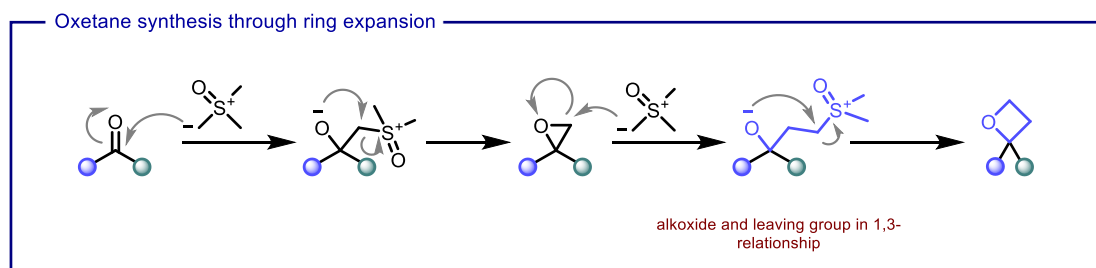
²⁶ For selected examples: a) Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S. *J. Am. Chem. Soc.* **1994**, 116, 1597–1598. b) Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S. *J. Am. Chem. Soc.* **1994**, 116, 1599–1600. c) Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, 122, 3811–3820. d) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1997**, 119, 2757–2758.

oxetane ring in taxol. In particular, the Nicolau group in 1994²⁷ used a triflate leaving group and a protected primary alcohol nucleophile. The treatment of precursor **32** with the chiral camphorsulfonic acid (CSA), revealed the oxetane **33** just after 10 minutes at 25°C in 60% yield (Scheme 5.5, bottom).

Notwithstanding the important position of the Williamson reaction in the oxetane synthesis panorama, the preparation of the starting materials bearing an alcohol and a leaving group in 1,3-position is often challenging and requires cumbersome multi-step synthetic sequences, considerably limiting the landscape of oxetane products accessible.

Synthesis of oxetanes from epoxide ring expansion

The requirements of synthesising the alcohol and the leaving group in 1,3-relationship can be eased by the *in-situ* generation of this reactive species starting from an epoxide upon treatment with methyl sulfoxonium ylide (Scheme 5.6). A ketone could be used to generate the corresponding epoxide in a sequential Corey-Chaykovsky²⁸ approach, although with limited scope.²⁹



Scheme 5.6: Synthesis of oxetanes through a ring expansion methodology.²⁸

While the methodologies above have allowed access to a number of oxetane structures, they all show various limitations. In addition, the synthesis of the target oxetanes using the strategies described above requires tedious multistep procedures or harsh conditions, making them incompatible with LSF purposes. In the following sections of this chapter, we will introduce a novel methodology to access oxetanes from readily available alcohol functionalities.

²⁷ Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, 367, 630–634.

²⁸ Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, 87, 1353–1364.

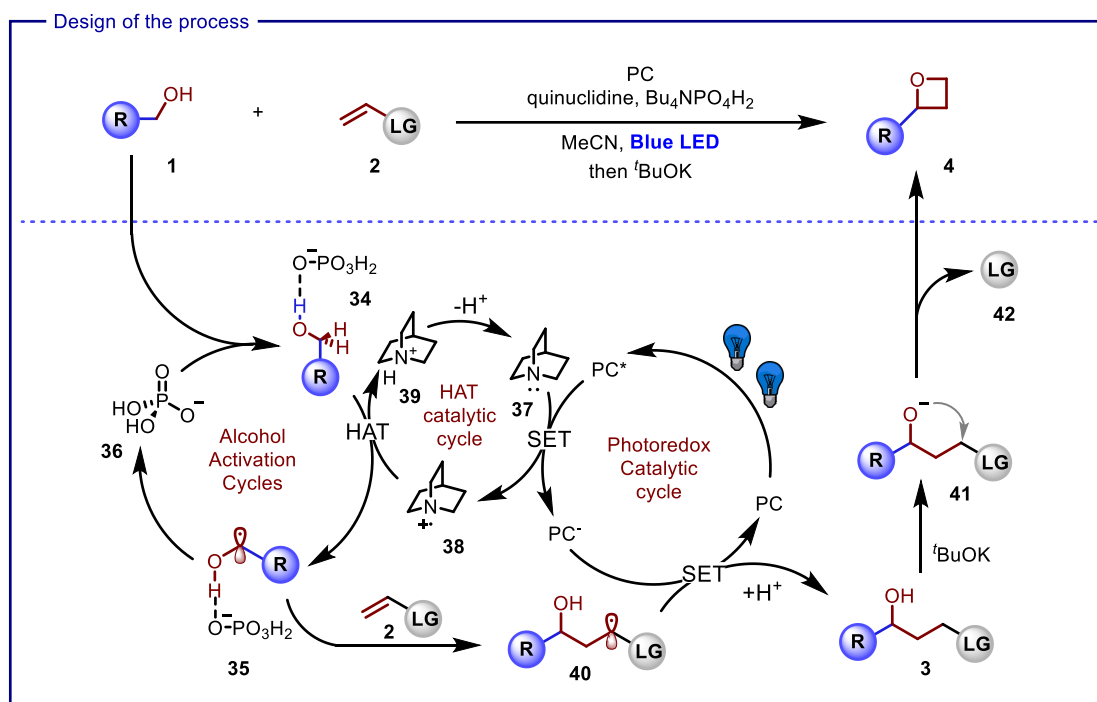
²⁹ a) Welch, S. C.; Rao, A. S. C. P. *J. Am. Chem. Soc.* **1979**, 101, 6135–6136. b) Welch, S. C.; Rao, A. S. C. P.; Lyon, J. T.; Assercq, J. M. *J. Am. Chem. Soc.* **1983**, 105, 252–257. c) Okuma, K.; Tanaka, Y.; Kaji, S.; Ohta, H. *J. Org. Chem.* **1983**, 48, 5133–5134. d) Fitton, J.; Jane, D. E.; Millar, R. *Synth.* **1987**, 1987, 1140–1142.

5.3. Aim of the project

In the following sections, we describe the development of a practical and effective process that introduces a novel synthetic disconnection to convert unmodified alcohol substrates into oxetanes *via* selective C-H functionalisation (Scheme 5.7).

Design of the process

As presented in Scheme 5.7, we envisioned generating a radical in α -position to the oxygen of an alcohol substrate **1** *via* hydrogen atom transfer (see Chapter 3 for introductory discussion about selective HAT in alcohols). The addition of this nucleophilic radical **35** to the electron-poor double bond within **2** would give radical cation **40**. Reduction of this radical by the highly reductive PC^- and its subsequent protonation affords alcohol **3**. The addition of a suitable base would promote *in-situ* cyclization to furnish oxetane **4** (Scheme 5.7).



Scheme 5.7: Reaction design of the synthesis of oxetanes *via* alcohol functionalisation.

In such a strategy, the group LG would play the dual role of controlling the electronics of the alkene moiety within **2** to ensure polarity-matching in the radical addition, while being an excellent leaving group to promote a challenging 4-*exo*-tet S_N2 cyclization. As presented in Chapter 4, vinyl sulfonium ions readily participate in radical additions followed by nucleophilic displacement reactions.³⁰ Therefore, we envisioned that the use of a vinyl sulfonium ion **2** would be an ideal candidate for the realisation of the reaction plan described above.

³⁰ Paul, S.; Filippini, D.; Silvi, M. *J. Am. Chem. Soc.* **2023**, 145, 2773–2778.

5.4. Result and Discussion

5.4.1. Optimisation studies

Vinyl sulfonium screening

We commenced our investigation by testing different sulfonium structures. As presented in Table 5.2, a mixture of cyclohexanol **1a**, sulfonium triflate **2**, catalytic $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbpy})\text{PF}_6$, $n\text{Bu}_4\text{NPO}_4\text{H}_2$ and quinuclidine were irradiated. After 24 h, $t\text{BuOK}$ was added to the vessel and the reaction was stirred at 60°C for 24 h.

Table 5.2: Screening of the vinyl sulfoniums.

Entry ^a	R	Yield 4a (%) ^b
1	-Ph (2a)	Traces
2	-CH ₂ ^t Bu (2b)	97

^a Reactions performed in 0.05 mmol scale, $[\mathbf{1a}]_0 = 0.5\text{M}$. ^b ¹H-NMR yield using CH_2Br_2 as internal standard.

When vinyl sulfonium **2a** was used, traces of the expected product **4a** were detected in the reaction mixture. Low mass balance was observed as a result of various decomposition pathways. Delightfully, when bulkier vinyl dineopentyl sulfonium structure **2b** was tested, instead, compound **4a** was obtained in excellent 97% yield (entry 2). We then focused our attention on screening the base required for the cyclization process, to identify the most convenient reaction condition of the catalytic system.

Screening of the standard reaction parameter

Base screening

Table 5.3: Base screening for the cyclisation step.

Entry ^a	Base	Temp. ($^\circ\text{C}$)	Yield 4a (%) ^b
1	$t\text{BuOK}$	60	97
2 ^c	K_3PO_4	80	72

^a Reactions performed in 0.05 mmol scale, using **1a** (1.0 equiv.), **2a** (1.5 equiv.), $[\mathbf{1a}]_0 = 0.5\text{M}$.; ^b ¹H-NMR yield using CH_2Br_2 as internal standard. ^c The reaction was performed at 80°C for 72h.

As presented in Table 5.3, the desired compound **4a** could be obtained even using the milder base potassium phosphate (entry 2). However, higher temperature (80°C) and longer reaction time were required, and product **4a** was obtained in reduced 72% yield. Therefore, potassium *tert*-butoxide was selected as the optimal base.

Loading of the radical precursor

To allow the convenient use of this process in late-stage functionalisation settings, we envisioned adjusting the reaction stoichiometry to use the valuable alcohols **1** as the limiting reagent. Therefore, the use of alcohol **1a** as the limiting reagent was tested, using only a slight excess (1.5 equivalents) of vinyl sulfonium **2b** (Table 5.4).

Table 5.4: Study of the alcohol loading.

Entry ^a	1a loading (equiv.)	2b loading (equiv.)	Yield 4a (%) ^b
1	2	1	97
2	1	1.5	99

^a Reactions performed in 0.05 mmol scale, [**1a**]₀ = 0.5M. ^b ¹H-NMR yield using CH₂Br₂ as internal standard.

The results in entry 2 showed the feasibility of this approach, therefore these optimal conditions were selected for the following investigations.

Photocatalyst screening

Finally, the use of the more affordable and sustainable organic catalyst 4CzIPN was attempted (Table 5.5).

Table 5.5: Screening of the photocatalyst.

Entry ^a	PC	PC loading (mol%)	4a (%) ^b
1	Ir[dF(CF ₃)ppy] ₂ (dtbbpy)PF ₆	1	99
2	4CzIPN	5	99

^a Reactions performed in 0.05 mmol scale, using **1a** (1.0 equiv.), **2b** (1.5 equiv.), [**1a**]₀ = 0.5M. ^b ¹H-NMR yield using CH₂Br₂ as internal standard.

To our delight, the use of 4CzIPN, although in a higher 5% catalytic loading, had no impact on the efficiency of the protocol, affording spiro-oxetane **4a** in quantitative yield. Therefore, these conditions were selected as the ideal to begin the scope studies.

5.4.2. Scope studies

With the optimized conditions in our hands, we investigated the scope of this methodology (Table 5.6).

We began our studies by submitting different six-membered ring heterocycles containing a variety of ether and acetal functionalities. Remarkably, despite possessing hydridic C-H bonds which could potentially pose selectivity issues, spiro-oxetanes **4b** and **4c** were accessed in good to excellent yields. A sulfone functionality was tolerated, and compound **4d** was obtained in 30% yield, with significant amounts of alcohol starting material recovered. To improve conversion, a ZnCl₂-based catalytic system (analogous to the one presented in Chapter 3) was adapted to the reaction (see general experimental section for details). Using these revised conditions, compound **4d** was obtained in improved 59% yield. Piperidine-derived oxetane **4e** was also obtained in high yields under these conditions. In this case, the Bz protecting group was used over the more classic Boc to ensure high regioselectivity. This is in accordance with similar observations by MacMillan and co-workers in the selectivity of radical cross-coupling reactions.³¹ Spiro-oxetane **4f**, bearing an ester functionality, was obtained starting from the corresponding 1,4 substituted cyclohexanol in moderate yield and stereoselectivity. In this case, the use of potassium phosphate was preferred over ^tBuOK to minimise undesired ester hydrolysis. Cyclic alcohols with different ring sizes underwent the desired reactivity, and both macrocycle **4g** as well as strained spirocycle **4h** were obtained in high yields. Attracted by the known synthetic value of polyspirocyclic oxetane structures,¹ the suitability of this system was investigated to access structures **4i** to **4k**, which were successfully obtained in high yields. Triggered by the interest in medicinal chemistry for bridged structures,³² we efficiently synthesised polycyclic structures **4l**, **4m** and **4n** in high yields. Remarkably, oxetanes **4l** and **4n** were obtained with full diastereoselectivity. Then, a variety of linear secondary alcohols were subjected to the reaction conditions, affording compounds **4o** to **4r** in moderate to good yields. Benzylic systems, ethers, as well as nitrile functionalities, were tolerated. Primary alcohols were also demonstrated to be competent substrates affording corresponding oxetanes **4s** – **4v**. For these substrates, lower yields (ranging between 42% and 56%) were obtained when compared to the corresponding secondary alcohol substrates. These observations are sided by the rise of a competitive E2 elimination pathway occurring from the corresponding sulfonium intermediates. These observations suggest a slower 4-*exo-tet* cyclization due to the less prominent Thorpe-Ingold effect, rather than a lower efficiency of the radical reactivity.³³ Finally, we

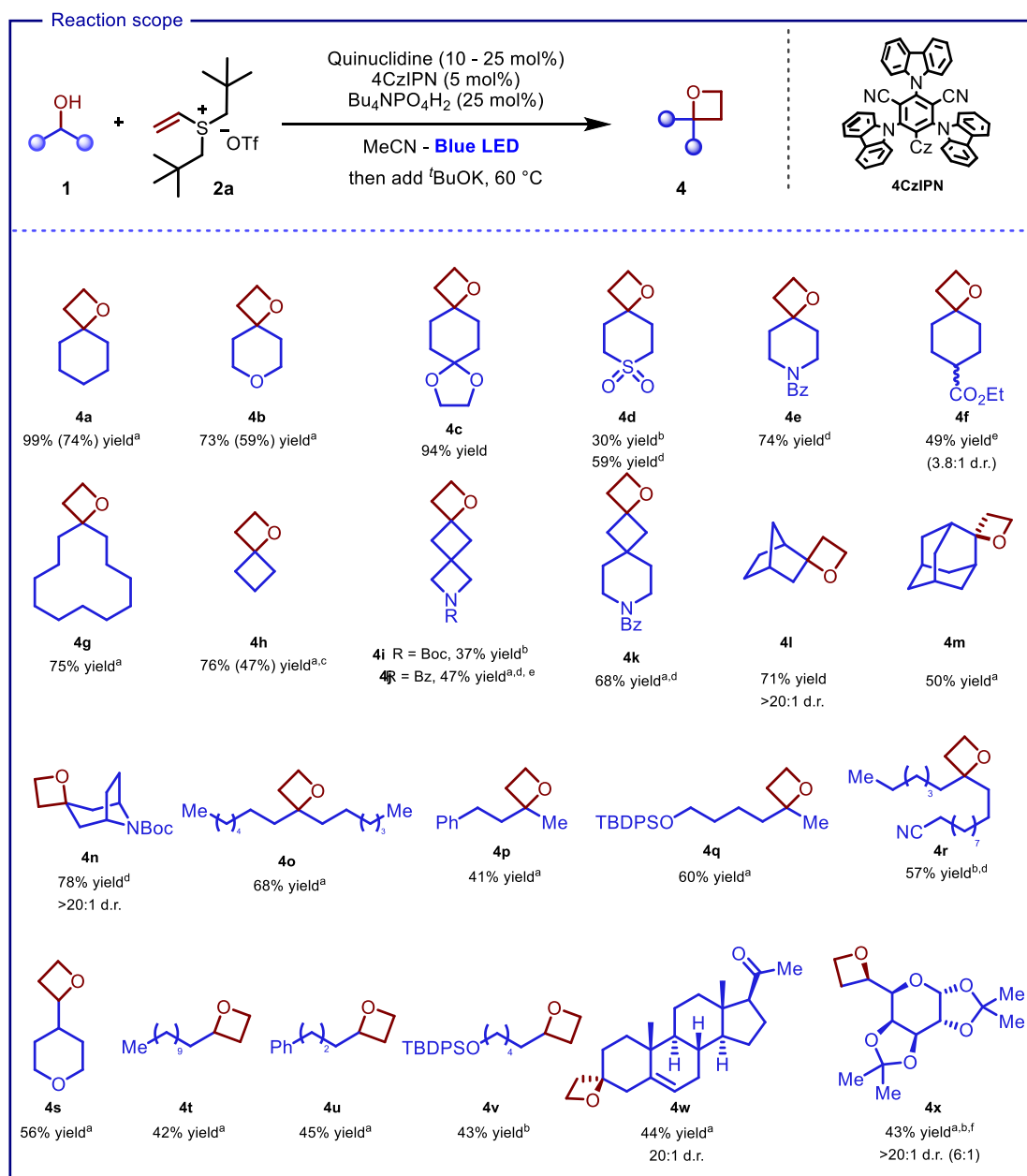
³¹ Twilton, J.; Christensen, M.; DiRocco, D. A.; Ruck, R. T.; Davies, I. W.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2018**, *57*, 5369–5373.

³² a) Oliver, D. W.; Malan, S. F. *Med. Chem. Res.* **2008**, *17*, 137–151. b) Moreno-Vargas, A. J.; Schütz, C.; Scopelliti, R.; Vogel, P. J. *Org. Chem.* **2003**, *68*, 5632–5640. c) Hutchinson, S. A.; Baker, S. P.; Scammells, P. J. *Bioorg. Med. Chem.* **2002**, *10*, 1115–1122. d) Buchbauer, G.; Pauzenberger, I. *Pharmazie* **1999**, *54*, 5–18. Kirby, A. J. *Advances in Physical Organic Chemistry Vol. 17*; Academic Press, London, **1980**, pp. 305–329

³³ a) Ingold, C. K. *J. Chem. Soc. Trans.* **1921**, *119*, 305–329. b) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc. Trans.* **1915**, *107*, 1080–1106.

focused on demonstrating the applicability of the methodology in late-stage functionalisation. Pregnenolone, a steroid bearing a sensitive alkene and ketone functionality, underwent the desired reactivity giving oxetane **4w** in 44% yield and high diastereoselectivity. Galactose-derived oxetane **4x** was also obtained in moderate yield and diastereoselectivity (d.r. 6:1) starting from the corresponding sugar. Remarkably, single-column chromatography allowed the separation of the product **4x** as a single diastereoisomer

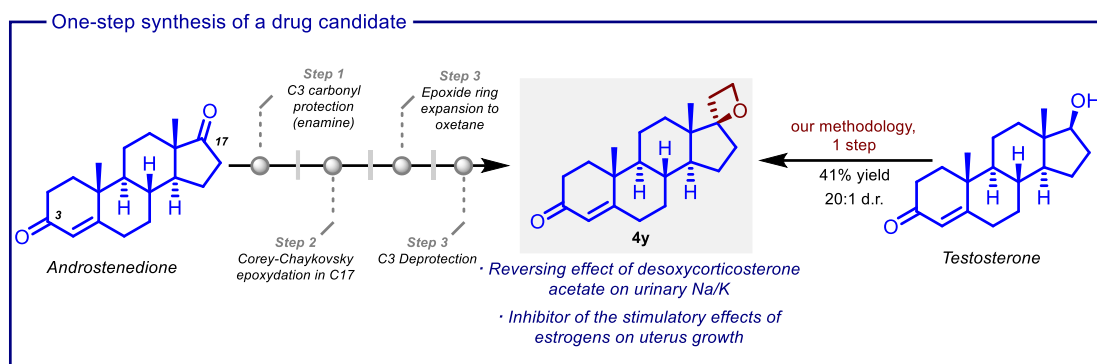
Table 5.6: Scope Studies



Scope of the photochemical conversion of alcohols into oxetanes. Unless otherwise noted, reactions were carried out on 0.2 mmol scale. Yields refer to isolated material after chromatographic purification, see details in the general experimental section. ^a Compound synthesised by Dr Subhasis Paul ^b Compound synthesised by Filippo Ficarra ^c Volatile material, value reported as NMR yield against CH₂Br₂ as internal standard, in parentheses yield of the isolated product after chromatographic purification. ^d Reaction carried out using 2.2 equiv. of ZnCl₂, 1.5 equiv. K₃PO₄, [Ir{dF(CF₃)ppy}₂(dtbpy)]PF₆ 1 mol%. ^e Reaction carried out in 0.1 mmol scale. ^f dr value refers to isolated product after chromatographic purification; the dr observed in the reaction crude mixture is in parentheses. Cz, carbazolyl.

Application of the methodology in streamlining the synthesis of a bioactive molecule

The steroid scaffold containing an oxetane ring **4y** is known to possess interesting biological properties. It is known for its ability in reversing the effects of desoxycorticosterone acetate on urinary sodium and potassium and inhibiting of the stimulatory effects of estrogens on the growth of the uterus.³⁴ However, the study and application of this compound, as well as other steroids bearing an oxetane ring, is limited by their difficult synthesis. As a matter of fact, the most recent route for the synthesis of compound **4y** requires a cumbersome multistep procedure of 4 steps, requiring the use of highly basic reagents and protecting groups.³⁴



Scheme 5.8: Example of one-step synthesis of a drug candidate.

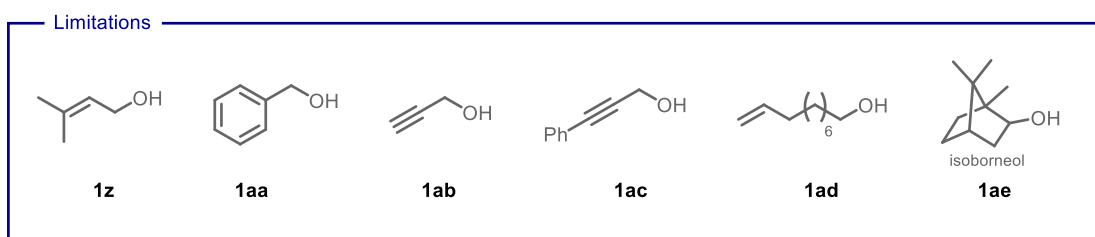
As presented in Scheme 5.8, the synthesis of **4y** requires: 1) the protection of the carbonyl group in C3 with an enamine (more common protecting groups were unsuccessful). 2) A Corey-Chaykovsky epoxidation²⁸ on carbonyl in C17, mediated by a sulfonium ylide. 3) Ring expansion procedure²⁹ to transform the epoxide in oxetane. 4) Finally, the deprotection of the C3 reveals oxetane **4y**.

Delightfully, compound **4y** was obtained in a single-step process - in moderate yield and excellent diastereoselectivity - by subjecting native testosterone to our reaction conditions. This demonstrates the potential of this synthetic approach in medicinal chemistry applications.

³⁴ a) Gella, I. M.; Bryzgalova, G. A.; Sergienko, L. Y. *Pharm. Chem. J.* **1994**, 28, 650–653. b) E. A. Brown, E.A. *Spiro(estrene/androstene-17,2'-oxetane)-3-one and intermediates*, US3422096A, **1969**.

5.4.3. Reaction limitations

During the study of the reaction scope, a few limitations were identified (Scheme 5.9). Activated alcohols (allyl **1z**, benzyl **1aa**, and propargylic **1ab-1ac** alcohols) and alcohols bearing terminal olefine i.e., **1ad**, did not undergo the desired reactivity, showing extensive recovery of the alcohol starting material. Steric hindrance also pose a limitation in this reaction as demonstrated by the isoborneol substrate **1ae** which showed extensive recovery of the starting material. In contrast, the less hindered norborneol led to good result (entry **4l**).



Scheme 5.9: Reaction limitations.

5.5. Conclusion

In this chapter, we introduced a new synthetic disconnection to access oxetanes from simple alcohols. The chemistry is general, occurs under mild conditions and is applicable for late-stage functionalisation purposes. The methodology described in this chapter is expected to find various applications in total synthesis and medicinal chemistry.

5.6. General experimental

5.6.1. Solvents, reagents, and starting materials

All air and water-sensitive reactions were carried out in oven-dried glassware under argon atmosphere using standard Schlenk manifold technique. The solvents were degassed when required by bubbling argon through the solvent for ten minutes. Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. All solvents were commercially supplied or provided by the communal stills of the School of Chemistry, University of Nottingham. Commercially available compounds were purchased from Sigma Aldrich, Alfa Aesar, Acros, Fluorochem, TCI chemicals and used as received. Dried solvents were purchased from Acros Organic, Extra Dry over molecular sieves, AcroSeal®.

Compounds 11-bromoundecanal³⁵, **1e**³⁶, **1v**³⁷, 4CzIPN,³⁸ and dineopentyl(vinyl)sulfonium triflate **2b**³⁰ were synthesised following reported procedures.

5.6.2. Chromatography and instrumental analysis

Flash column chromatography (FCC) was carried out using Sigma-Aldrich silica gel LC60A-40 (63 μm). THF and Et₂O were distilled prior to use. All reactions were followed by thin-layer chromatography (TLC) when practical, using Merck Kieselgel 60 F₂₅₄ fluorescent treated silica which was visualised under UV light, by staining with aqueous basic potassium permanganate, phosphomolybdic acid or with ninhydrin solution.

¹H-NMR, ¹³C-NMR and ¹⁹F-NMR spectra were recorded using Bruker broadband prodigy cryoprobe AV(III)500HD 500 MHz and Bruker AV(III)400HD 400 MHz spectrometers. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in hertz (Hz). The ¹H-NMR spectra are reported as follows: ppm (multiplicity, coupling constants, number of protons). High resolution mass spectra (HRMS) were recorded on a Bruker MicrOTOF II by Electrospray Ionisation (ESI). IR spectra were recorded on a Bruker Vertex 70 FT-IR ATR as a thin film. Only selected absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Melting points were recorded in degrees Celsius ($^{\circ}\text{C}$), using a Stuart melting point SMP 20 microscope apparatus and are reported uncorrected. Optical rotation ($[\alpha]_{\text{D}}^{25}$) was recorded on an Anton Paar MCP 100 at 25 $^{\circ}\text{C}$, in chloroform, with a concentration of 1g/100mL.

³⁵ Huang, H.-M.; Bellotti, P.; Pflüger, P. M.; Schwarz, J. L.; Heidrich, B.; Glorius, F. *J. Am. Chem. Soc.* **2020**, *142*, 10173–10183.

³⁶ Soulard, V.; Villa, G.; Vollmar, D. P.; Renaud, P. *J. Am. Chem. Soc.* **2018**, *140*, 155–158.

³⁷ Paraja, M.; Matile, S. *Angew. Chem. Int. Ed.*, **2020**, *59*, 6273–6277.

³⁸ Huang, H.; Yu, C.; Zhang, Y.; Zhang, Y.; Mariano, P. S.; Wang, W. *J. Am. Chem. Soc.* **2017**, *139*, 9799–9802.

5.6.3. Naming of compounds

Compound names are generated by ChemDraw 20.0 software (PerkinElmer), following the IUPAC nomenclature.

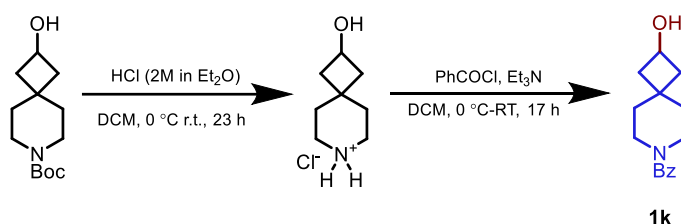
5.6.4. LEDs

Irradiation of reaction mixtures was performed using Kessil lamp A160WE Tuna Blue Saltwater LED Light 40W set to blue at maximum intensity. Lamp emission is observed to decay over long usage due to LED chip deterioration. To ensure good reproducibility of the results, we recommend using new lamps.

5.6.5. Synthesis of novel starting materials

Synthesis of (2-hydroxy-7-azaspiro[3.5]nonan-7-yl)(phenyl)methanone (**1k**)

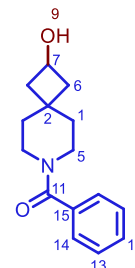
Compound synthesised and characterised by Dr Subhais Paul.



tert-butyl 2-hydroxy-7-azaspiro[3.5]nonane-7-carboxylate (1.0 equiv.; 2.0 mmol; 500.0 mg) was dissolved in dry DCM (0.5 M, 4.1 mL) and cooled down at 0 °C. A solution of HCl (2M in Et₂O) (24.0 equiv.; 49.7 mmol; 24.9 mL) was slowly added to the mixture at 0 °C. The reaction mixture was slowly allowed to warm up at room temperature and stirred for 23 h. The solution was then concentrated under reduced pressure. To this mixture, Et₂O (50 mL) was added and the solid filtered out. The solid was washed thoroughly with Et₂O (3 × 20 mL) and dried under vacuum to obtain the chloride salt (338.5 mg; 92%) as a white solid. **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3181, 2959, 2924, 2808, 2714, 2478, 1590, 1436, 1336, 1234, 1181, 1158, 1080, 973, 947, 899, 676, 546, 477; **¹H-NMR** (CD₃OD, 500 MHz) δ (ppm): 4.26 (p, J = 7.2 Hz, 1H), 3.15 – 3.04 (m, 4H), 2.36 – 2.28 (m, 2H), 1.85 – 1.72 (m, 6H); **¹³C-NMR** (CD₃OD, 126 MHz) δ (ppm): 62.9, 42.8, 42.7, 42.5, 36.9, 34.1, 29.9; **HRMS** (ESI-TOF) mass calculated for [M]⁺ (C₈H₁₆NO⁺) expected m/z 142.1226; found m/z 142.1218.

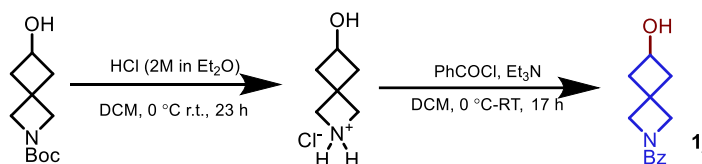
2-Hydroxy-7-azaspiro[3.5]nonan-7-ium chloride (1.0 equiv.; 0.5 mmol; 89.0 mg) was dissolved in DCM (0.5 M, 1.0 mL) and cooled down at 0 °C. Then Et₃N (2.5 equiv.; 1.25 mmol; 174.2 μ L) was added to the mixture followed by dropwise addition of benzoyl chloride (1.1 equiv.; 0.55 mmol; 64.0 μ L) at 0 °C. The reaction mixture was allowed to slowly warm up at room temperature and stirred for 17 h. The reaction was quenched by water (15 mL) and extracted with DCM (3 × 20 mL). Combined organic

layers were washed with 2M HCl solution (2 × 10 mL) followed by saturated NaHCO₃ solution (2 × 10 mL), water (15 mL) and brine (15 mL), dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO₂; gradient 20:80 to 1:99 hexane:EtOAc) to afford compound **1k** (90.6 mg; 74%) as a white solid. **M. P.** = 122-123 °C; **R_f** (20:80 hexane:EtOAc) 0.2; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3390, 2921, 2849, 1613, 1576, 1445, 1372, 1275, 1055, 603, 568; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 7.38 (br. s, 5H, 12 – 13 – 14), 4.34 (br. s, 1H, 7), 3.83 – 3.10 (m, 4H, **5**), 2.42 – 2.21 (m, 2H, **6**), 1.89 – 1.65 (m, 4H, **1** – **6**), 1.61 – 1.45 (m, 2H, **1**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 170.5 (**11**), 136.4, 129.6, 128.6, 127.0, 63.3 (**7**), 45.2, 42.7, 39.5, 36.5, 30.7; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₅H₁₉NO₂Na⁺) expected m/z 268.1308; found m/z 268.1307.

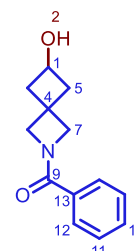


Synthesis of 6-hydroxy-2-azaspiro[3.3]heptan-2-yl(phenyl)methanone (**1j**)

Compound synthesised and characterised by Filippo Ficarra.



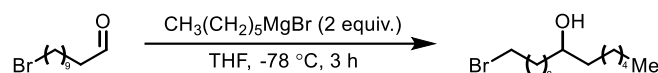
tert-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate (1.0 equiv.; 0.5 mmol; 107 mg) was dissolved in dry DCM (0.5 M, 4.1 mL) and cooled down at 0 °C. A solution of HCl (2M in Et₂O) (24.0 equiv.; 49.7 mmol; 24.9 mL) was slowly added to the mixture at 0 °C. The reaction mixture was slowly allowed to warm up at room temperature and stirred for 23 h. The solution was then concentrated under reduced pressure. To this mixture, Et₂O (50 mL) was added and the solid filtered out. The solid was washed thoroughly with Et₂O (3 × 20 mL) and dried under vacuum to obtain the hydrochloride salt which was used directly in the next step without further purification. The hydrochloride salt was dissolved in DCM (0.5 M, 1.0 mL) and cooled down at 0 °C. Then Et₃N (2.5 equiv.; 1.25 mmol; 174.2 μ L) was added to the mixture followed by dropwise addition of benzoyl chloride (1.1 equiv.; 0.55 mmol; 64.0 μ L) at 0 °C. The reaction mixture was allowed to slowly warm up at room temperature and stirred for 24 h. The reaction was quenched by water (15 mL) and extracted with DCM (3 × 20 mL). Combined organic layers were washed with 2M HCl solution (2 × 10 mL) followed by saturated NaHCO₃ solution (2 × 10 mL), water (15 mL) and brine (15 mL), dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO₂; gradient 30:70 to 0:100 hexane:EtOAc) to afford compound **1j** as a white solid (23.7 mg, 22%). **R_f** (EtOAc) 0.2; **M.P.** = 97 – 100 °C; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3391, 2928, 2869, 1728, 1615, 1572, 1452, 1432, 1053, 791, 711; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.61 – 7.58 (m, 2H, **12**), 7.46 – 7.43 (m, 1H, **10**), 7.40 – 7.37 (m, 2H, **11**), 4.24 – 4.14 (m, 5H, **1** – **7**), 2.61



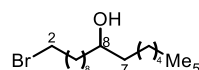
– 2.53 (m, 2H, **5**), 2.17 – 2.07 (m, 2H, **5**); $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis () $\delta(\text{ppm})$: 170.3 (**9**), 133.3 (**13**), 131.1 (**10**), 128.5 (**11**), 128.0 (**12**), (65.9), 64.6 (**7**), 62.2 (**1**), 61.2 (**7**), (59.9), (44.1), 43.9 (**5**), 30.4 (**4**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{13}\text{H}_{15}\text{NO}_2\text{Na}^+$) expected m/z 240.09951; found m/z 240.0994.

Synthesis of 17-bromoheptadecan-7-ol

Compound synthesised and characterised by Filippo Ficarra.

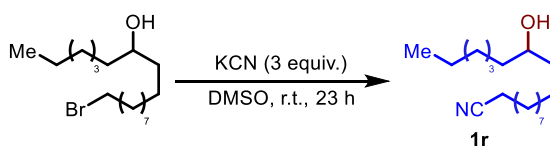


11-bromoundecanal (1 equiv., 13.8 mmol, 3.45 g) was dissolved in dry THF (20 mL) and cooled down to $-78\text{ }^\circ\text{C}$. A solution of hexylmagnesium bromide (0.8 M in THF, 27.6 mmol, 34.5 mL) was added dropwise at $-78\text{ }^\circ\text{C}$. The reaction mixture was then stirred at $-78\text{ }^\circ\text{C}$ for 3 h. The mixture was quenched at $-78\text{ }^\circ\text{C}$, by addition of a saturated NH_4Cl solution (25 mL), and extracted with EtOAc (3 x 25 mL). The organic layers were combined and dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 ; 95:5 to 90:10 hexane:EtOAc) to afford the compound (1.08 g, 24%) as a white solid. **R_f** (90:10 hexane:EtOAc) 0.5; **M.P.** = $48 - 52\text{ }^\circ\text{C}$; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3355, 2922, 2851, 1694, 1466, 1052, 884, 859, 723; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 3.61 – 3.55 (m, 1H, **8**), 3.41 (t, $J = 7.0\text{ Hz}$, 2H, **2**), 1.88 – 1.82 (m, 2H), 1.47 – 1.38 (m, 8H), 1.34 – 1.25 (m, 18 H), 0.88 (t, $J = 7.1\text{ Hz}$, 3H, **5**); $^{13}\text{C-NMR}$ (CDCl_3 , 101 MHz) δ (ppm): 72.2 (**8**), 37.7, 37.6, 34.2 (**2**), 33.0, 32.0, 29.8, 29.7, 29.6, 29.6, 29.5, 28.9, 28.3, 25.8, 25.8, 22.8, 14.2 (**5**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{17}\text{H}_{35}\text{BrONa}^+$) expected m/z 357.1763; found m/z 357.1764.

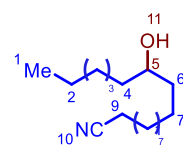


Synthesis of 12-hydroxyoctadecanenitrile (**1r**)

Compound synthesised and characterised by Filippo Ficarra.



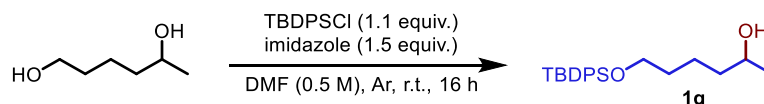
KCN (3 equiv., 3 mmol, 195 mg) was added to a solution of 17-bromoheptadecan-7-ol (1 equiv., 1 mmol, 335 mg) in dry DMSO (10 mL) at room temperature. The mixture was stirred at room temperature for 23 h. Et₂O (15 mL) was then added to the mixture and the organic layers were washed with water (3 x 10 mL) and once with brine (10 mL). The organic solvent was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2 ; 90:10 to 90:20 hexane:EtOAc) to afford compound **1r** (253 mg, 90%) as a white solid. **R_f** (90:10 hexane:EtOAc) 0.2; **M.P.**: $56 - 60\text{ }^\circ\text{C}$; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3324, 2917, 2849, 2244,



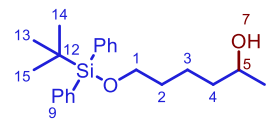
1466, 1421, 1132, 1076, 1032, 997, 916, 862, 723; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 3.61 – 3.56 (m, 1H, **5**), 2.33 (t, J = 7.2 Hz, 2H, **9**), 1.65 (quint, J = 7.2 Hz, 2H), 1.47 – 1.38 (m, 8H), 1.34 – 1.25 (m, 18 H), 0.89 (t, J = 7.1 Hz, 3H, **1**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 120.0 (**10**), 72.2 (**5**), 37.7, 37.6, 32.0, 29.8, 29.7, 29.6, 29.5, 29.4, 28.9, 28.8, 25.8, 25.5, 22.8, 17.3 (**9**), 14.2 (**1**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₈H₃₅NONa⁺) expected m/z 304.2611; found m/z 304.2610.

Synthesis of 6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-ol (**1q**)

Compound synthesised and characterised by Dr Subhais Paul.

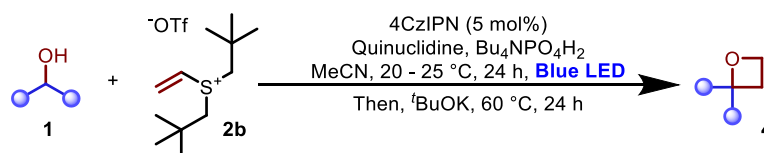


Hexane-1,5-diol (1.0 equiv.; 1.0 mmol; 120 μ L) was dissolved in dry DMF (0.5 M, 2.0 mL). Imidazole (1.5 equiv.; 1.5 mmol; 102.4 mg) was added at room temperature, followed by a slow addition of *tert*-butyldimethylsilyl chloride (1.1 equiv.; 1.1 mmol; 286 μ L). The reaction mixture was stirred at room temperature for 16 h. Then reaction mixture was diluted with 30 mL ethyl acetate. The organic phase was washed with water (4 $\times$ 30 mL) and brine (20 mL), dried over of anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO₂; gradient 80:20 to 75:25 hexane:EtOAc) to afford compound **1q** (342.6 mg; 96%) as a transparent oil. **R_f** (80:20 hexane:EtOAc) 0.3; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3351, 3071, 2930, 2857, 1472, 1428, 1109, 1007, 823, 739, 701, 613, 505; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 7.71 – 7.63 (m, 4H, **9**), 7.46 – 7.34 (m, 6H, **9**), 3.82 – 3.72 (m, 1H, **5**), 3.68 (t, J = 6.4 Hz, 2H, **1**), 1.63 – 1.53 (m, 2H, **2**), 1.47 – 1.35 (m, 5H), 1.18 (d, J = 6.2 Hz, 3H, **6**), 1.05 (s, 9H, **13 – 14 – 15**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 135.7, 134.2, 129.7, 127.7, 68.2 (**5**), 63.9 (**1**), 39.1, 32.6 (**2**), 27.0 (**13 – 14 – 15**), 23.6 (**6**), 22.1, 19.4; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₂H₃₂O₂SiNa⁺) expected m/z 379.2064; found m/z 379.2063.



5.6.6. General procedures

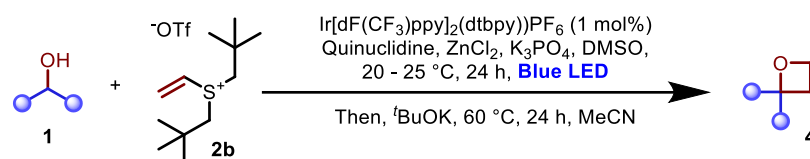
General procedure A



Alcohol **1** (1.0 equiv.; 0.2 mmol), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg), and tetra-*n*-butylammonium phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg) were introduced into a Schlenk tube. The atmosphere was exchanged to argon and degassed dry MeCN (0.4 mL, 0.5 M, previously degassed through 10 min

argon sparging) was introduced through a syringe. The vessel was sealed and placed in a glass-wall water bath where a fan was blowing air to keep the water temperature between 20 - 25 °C. See Fig. S2 for visual details of the reaction setup. The reaction was irradiated through the glass wall with blue light (Kessil lamp A160WE Tuna Blue Saltwater LED Light 40 W) for 24 h under moderate stirring (500 rpm). The vessel was then removed from the water bath and ^tBuOK (2.0 equiv.; 0.4 mmol; 44.9 mg) was introduced into the vessel. The mixture was heated to 60 °C without irradiation for 24 h under vigorous stirring (700 rpm). The crude was subjected to chromatographic purification on silica gel to afford final compounds.

General Procedure B



Alcohol **1** (1.0 equiv.; 0.2 mmol), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), Ir[dF(CF₃)ppy]₂(dtbbpy))PF₆ (0.01 equiv.; 0.002 mmol; 2.2 mg), quinuclidine (0.3 equiv.; 0.06 mmol; 6.7 mg) and potassium phosphate (1.5 equiv.; 0.3 mmol; 63.7 mg), were introduced into a Schlenk tube. In an oven-dried vial, ZnCl₂ (2.7 mmol; 367.2 mg) was added to 6 mL of dry DMSO. The solution was degassed through 10 min argon sparging and sonicated until complete solubilization of ZnCl₂. Then, 1 mL of this solution (containing 2.25 equiv.; 61.2 mg; 0.45 mmol of ZnCl₂) was introduced through a syringe into the Schlenk tube. The vessel was sealed and placed in a glass-wall water bath where a fan was blowing air to keep the water temperature between 20 - 25 °C. See Figure 5.2 for visual details of the reaction setup. The reaction was irradiated through the glass wall with blue light (Kessil lamp A160WE Tuna Blue Saltwater LED Light 40W) for 24 h under moderate stirring (500 rpm). To remove the ZnCl₂, a filtration step with alumina is described as follows.

The vessel was removed from the water bath and basic alumina powder (3.5 g) was added, followed by DCM (10 mL). The suspension was stirred for 1 minute then, using a 5 mL syringe filled with cotton, the aluminium oxide powder was filtered. The syringe with alumina and the Schlenk walls were washed with a 9:1 DCM:MeOH solution (8 mL). The filtrate was collected and the volatiles were removed. The residue was then transferred quantitatively into a Schlenk tube using 2 mL of DCM. The Schenk was placed into a water bath (70°C) and nitrogen was blown to remove DCM. The remaining DMSO was removed by placing the tube under high vacuum (5·10⁻² mbar) at 70 °C. When the distillation was complete, the tube was left under high vacuum at 70 °C for 5 min to ensure complete distillation of DMSO. Finally, the atmosphere in the tube was exchanged to argon and the crude was submitted to the next step. See general experimental section of Chapter 3 for visual details.

Dry MeCN (1 mL) was introduced through a syringe. ^tBuOK (2 equiv.; 0.4 mmol; 44.9 mg) was added and the mixture was heated to 60 °C for 24 h under vigorous stirring. Volatiles were evaporated under reduced pressure, and the residue was subjected to chromatographic purification on silica gel to afford final compounds.

5.6.7. Reaction set-up for irradiation of mixtures with blue LEDs

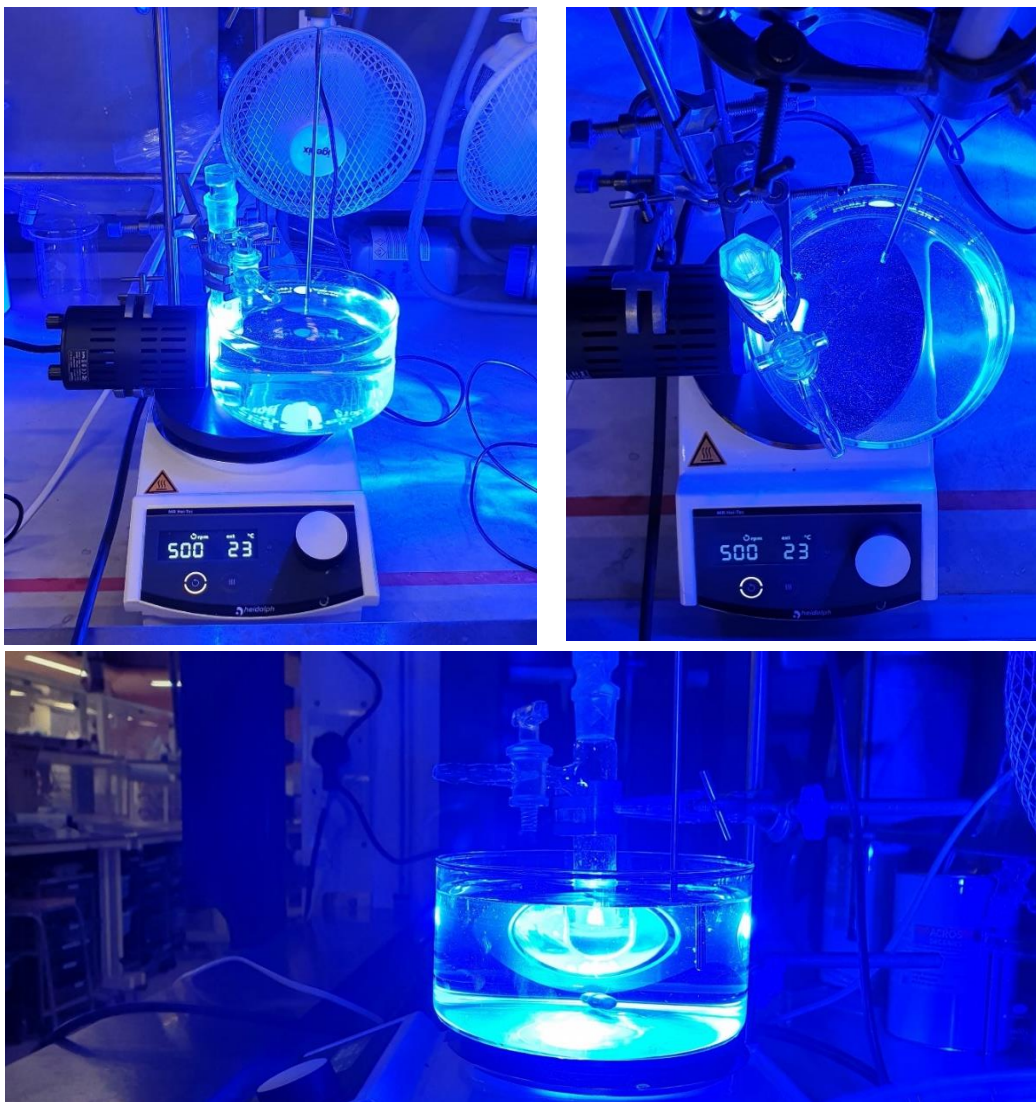
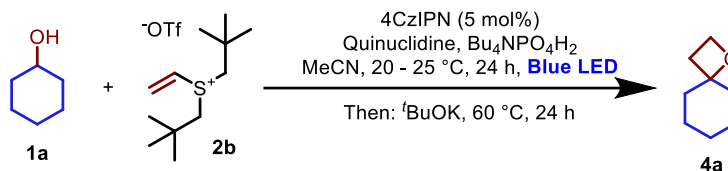


Figure 5.2: Visual details of the photochemical reaction set-up: front, top, and lateral views.

5.6.8. Reaction products and characterisation

1-oxaspiro[3.5]nonane (**4a**)

Compound synthesised and characterised by Dr Subhais Paul.

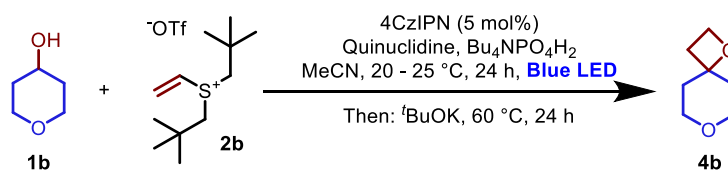


Prepared following general procedure A, using cyclohexanol **1a** (1.0 equiv.; 0.2 mmol; 21.1 μ L), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.10 equiv.; 0.02 mmol; 2.2 mg) and *t*BuOK (2.0 equiv.; 0.4 mmol; 44.9 mg). Due to high volatility of compound **4a**, the NMR yield was measured (99%) using CH₂Br₂ as internal standard. The crude residue was purified by flash column chromatography (SiO₂; gradient 99:1 to 97:3 pentane:THF; eluent removed using a rotary evaporator, maintaining the water bath below 25 °C and vacuum pressure 450 – 80 mbar) to afford compound **4a** (18.7 mg; 74%) as a transparent oil. **R_f** (97:3 pentane:THF) 0.4; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2939, 2876, 2855, 1446, 1370, 1337, 1282, 1246, 1222, 1143, 1058, 993, 962, 919, 890, 846, 656, 476, 447, 415; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 4.49 (t, *J* = 7.8 Hz, 2H, **8**), 2.31 (t, *J* = 7.8 Hz, 2H, **9**), 1.88 – 1.76 (m, 2H), 1.74 – 1.58 (m, 4H), 1.42 – 1.24 (m, 4H); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 86.7 (**6**), 64.9 (**8**), 38.8, 32.5 (**9**), 25.2, 22.6; **HRMS** (ESI-TOF) mass calculated for [2M+Na]⁺ (C₁₆H₂₈O₂Na⁺) expected *m/z* 275.1982; found *m/z* 275.1989.



1,7-dioxaspiro[3.5]nonane (**4b**)

Compound synthesised and characterised by Dr Subhais Paul

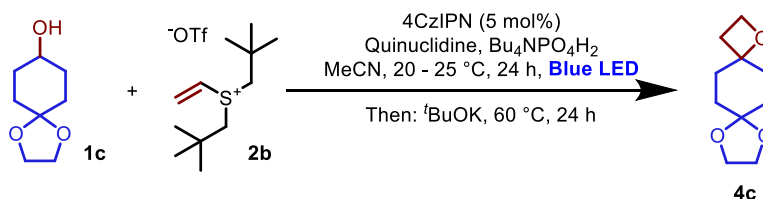


Prepared following General Procedure A, using 4-hydroxytetrahydropyran **1b** (1.0 equiv.; 0.2 mmol; 19.1 μ L), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and *t*BuOK (2.0 equiv.; 0.4 mmol; 44.9 mg). Due to high volatility of compound **4b**, the NMR yield was measured (73%) using CH₂Br₂ as internal standard. The crude residue was purified by flash column chromatography (SiO₂; 100% DCM to gradient 60:40 to 40:60 pentane:Et₂O; eluent removed using a rotary evaporator, maintaining the water bath below 25 °C and vacuum pressure 450 – 80 mbar) to afford compound **4b** (15.1 mg; 59%) as a pale yellow oil. **R_f** (60:40

pentane:Et₂O) 0.25; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2955, 2924, 2858, 1454, 1389, 1363, 1335, 1313, 1260, 1220, 1155, 1121, 1101, 1028, 994, 970, 949, 843, 749, 619; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 4.54 (t, J = 7.8 Hz, 2H, **8**), 3.77 (ddd, J = 11.4, 7.5, 3.8 Hz, 2H, **2**), 3.56 (ddd, J = 11.2, 6.6, 3.9 Hz, 2H, **2**), 2.41 (t, J = 7.8 Hz, 2H, **9**), 1.96 – 1.83 (m, 4H, **1**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 83.3 (**6**), 65.0 (**8**), 64.2 (**2**), 39.0 (**1**), 32.6 (**9**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₇H₁₂O₂Na⁺) expected m/z 151.0730; found m/z 151.0735.



1,8,11-trioxadispiro[3.2.4⁷.2⁴]tridecane (**4c**)

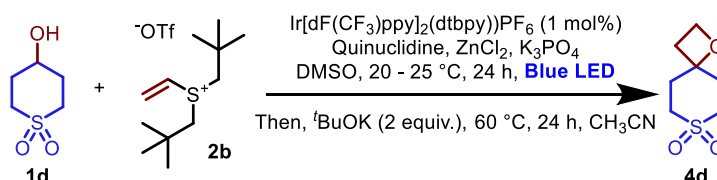


Prepared following general procedure A, using ethyl 1,4-dioxaspiro[4.5]decane-8-ol **1c** (1.0 equiv.; 0.2 mmol; 31.6 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and ^tBuOK (2.0 equiv.; 0.4 mmol; 44.9 mg) at 60 °C for 24 h. The crude residue was purified by flash column chromatography (SiO₂; gradient 60:40 to 50:50 pentane:Et₂O; eluent removed using a rotary evaporator, maintaining the water bath below 25 °C and vacuum pressure 450 – 80 mbar) to afford compound **4c** (34.6 mg; 94%) transparent oil. **R_f** (1:1 pentane:Et₂O) 0.5; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2935, 2877, 1442, 1375, 1329, 1249, 1153, 1092, 1034, 1000, 954, 921, 865, 770, 667, 540, 475, 432; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 4.49 (t, J = 7.8 Hz, 2H, **8**), 3.98 – 3.87 (m, J = 3.5 Hz, 4H, **11**), 2.37 (t, J = 7.8 Hz, 2H, **9**), 2.06 – 1.97 (m, 2H), 1.90 – 1.82 (m, 2H), 1.81 – 1.73 (m, 2H), 1.61 – 1.53 (m, 2H); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 108.1, (**3**), 85.1 (**6**), 64.9 (**6**), 64.4 (**8**), 64.4 (**11**), 35.6, 31.9 (**6**), 30.6; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₀H₁₆O₃Na⁺) expected m/z 207.0992; found m/z 207.0989.



1-oxa-7-thiaspiro[3.5]nonane 7,7-dioxide (**4d**)

Compound synthesised and characterised by Filippo Ficarra.

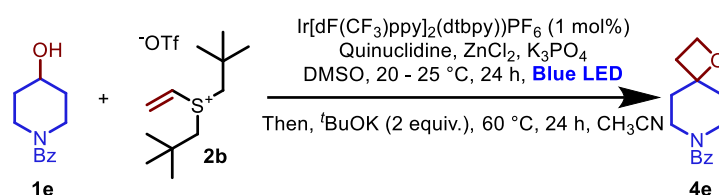


Prepared following general procedure B, using tetrahydro-2H-thiopyran-4-ol 1,1-dioxide **1d** (1.0 equiv.; 0.2 mmol; 31.6 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), Ir[dF(CF₃)ppy]₂(dtbbpy))PF₆ (0.01 equiv.; 0.002 mmol; 2.2 mg), quinuclidine (0.3 equiv.; 0.06 mmol; 6.7 mg), potassium phosphate (1.5 equiv.; 0.3 mmol; 63.7 mg) and zinc chloride (2.25 equiv.; 0.45 mmol; 61.3 mg). After 24 h,

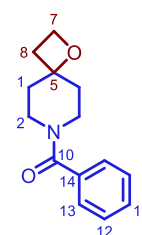
^tBuOK (2.0 equiv.; 0.4 mmol; 44.9 mg) was added and the mixture heated at 60 °C for 24 h. The crude residue was purified by flash column chromatography (SiO₂; 90:10 to 80:20 DCM:EtOAc) to afford compound **4d** (20.9 mg; 59%) as a yellow solid. **R_f** (80:20 DCM:EtOAc) 0.3; **M.P.** = 99 – 100 °C; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2924, 1425, 1313, 1286, 1228, 1187, 1130, 1090, 1059, 980, 952, 880, 943, 703; **¹H-NMR** (500 MHz, CDCl₃) δ (ppm): 4.56 (t, *J* = 7.8 Hz, 2H, **8**), 3.31 – 3.25 (m, 2H, **2**), 2.91 – 2.86 (m, 2H, **2**), 2.54 – 2.45 (m, 4H, **1** – **9**), 2.34 – 2.28 (m, 2H, **1**); **¹³C-NMR** (126 MHz, CDCl₃) δ (ppm): 81.3 (**6**), 65.1 (**8**), 46.8 (**2**), 35.7 (**1**), 31.8 (**9**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₇H₁₂SO₃Na⁺) expected *m/z* 199.0399; found *m/z* 199.0398.

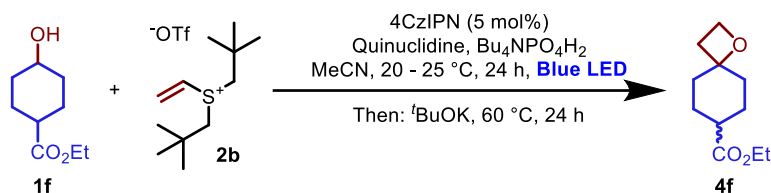


phenyl(1-oxa-7-azaspiro[3.5]nonan-7-yl)methanone (**4e**)

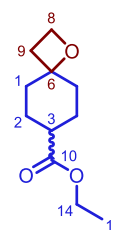


Prepared following general procedure B, using (4-hydroxypiperidin-1-yl)(phenyl)methanone **1e** (1.0 equiv.; 0.2 mmol; 41.0 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), Ir[dF(CF₃)ppy]₂(dtbbpy))PF₆ (0.01 equiv.; 0.002 mmol; 2.2 mg), quinuclidine (0.3 equiv.; 0.06 mmol; 6.7 mg), potassium phosphate (1.5 equiv.; 0.3 mmol; 63.7 mg) and zinc chloride (2.25 equiv.; 0.45 mmol; 61.3 mg). After 24 h, ^tBuOK (2.0 equiv.; 0.4 mmol; 44.9 mg) was added and the mixture heated at 60 °C for 24 h. The crude residue was purified by flash column chromatography (SiO₂; 80:20 to 30:70 DCM:Et₂O) to afford compound **4e** (34.4 mg; 74%) transparent oil. **R_f** (1:1 pentane:Et₂O) 0.6; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3436, 2961, 2926, 2852, 1703, 1682, 1455, 1394, 1367, 1455, 1394, 1367, 1256, 1174, 1047, 988, 922, 862, 775; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.42 – 7.36 (m, 5H, **11** – **13**), 4.59 – 4.50 (m, 2H, **7**), 3.95 (bs, 1H, **2**), 3.63 – 3.28 (m, 3H, **2**), 2.50 – 2.32 (m, 2H, **8**), 2.15 – 1.62 (m, 4H, **1**); **¹³C-NMR** (CDCl₃, 126 MHz) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis () δ (ppm): 170.5 (**10**), 136.2, 129.7, 128.6, 126.9, 83.8 (**5**), 65.0 (**7**), 43.8, 38.4, (37.5), 32.1 (**8**); **HRMS** (ESI-TOF) mass calculated for [M+H]⁺ (C₁₄H₁₈NO₂⁺) expected *m/z* 232.1332; found *m/z* 232.1327.

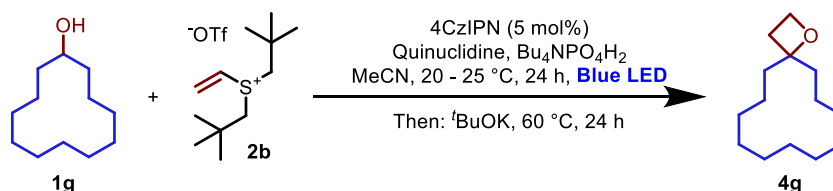


ethyl 1-oxaspiro[3.5]nonane-7-carboxylate (**4f**)

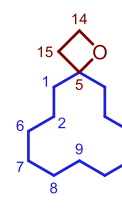
Prepared following general procedure A, using ethyl 4-hydroxycyclohexane-1-carboxylate **1f** (1.0 equiv.; 0.2 mmol; 34.4 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.1 equiv.; 0.05 mmol; 2.2 mg). Then K₃PO₄ (2.0 equiv.; 0.4 mmol; 84.8 mg) was added and the reaction left under stirring at 80 °C for 72 h. The crude residue was purified by flash column chromatography (SiO₂; 97.5:2.5 DCM:Et₂O then gradient 6:4 to 1:1 pentane:Et₂O) to afford compound **4f** (19.5 mg; 49%; d.r. = 3.8:1) as yellow oil. **R_f** (1:1 pentane:Et₂O) 0.6; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2935, 2877, 1720, 1445, 1377, 1350, 1306, 1185, 1136, 1069, 1040, 992, 971, 919, 861, 656, 520; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 4.49 (t, J = 7.8 Hz, 2H, **8**), 4.11 (qd, J = 7.1, 1.7 Hz, 2H, **14**), 2.36 (t, J = 7.8 Hz, 2H, **9**), 2.28 – 2.20 (m, 1H, **3**), 2.16 – 2.08 (m, 2H), 2.00 – 1.91 (m, 2H), 1.60 – 1.44 (m, 4H), 1.24 (t, J = 7.3 Hz, 3H, **13**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 175.5 (**10**), 86.0 (**6**), 65.0 (**8**), 60.4 (**14**), 41.6 (**3**), 37.3, 31.9 (**9**), 25.3, 14.4 (**13**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₁H₁₈O₃Na⁺) expected m/z 221.1148; found m/z 221.1153.

1-oxaspiro[3.11]pentadecane (**4g**)

Compound synthesised and characterised by Dr Subhasis Paul.



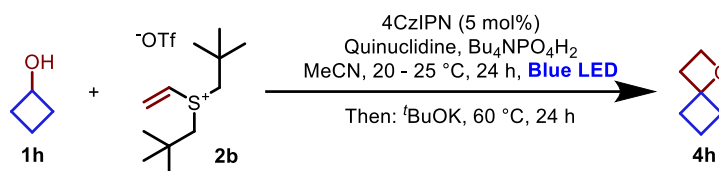
Prepared following general procedure A, using cyclododecanol **1g** (1.0 equiv.; 0.2 mmol; 36.9 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and *t*BuOK (2.0 equiv.; 0.4 mmol; 44.9 mg). The crude residue was purified by flash column chromatography (SiO₂; gradient 95:5 to 90:10 pentane:Et₂O) to afford compound **4g** (31.7 mg; 75%) as a white solid. **R_f** (95:5 pentane:Et₂O) 0.25; **M. P.** = 35–36 °C; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2936, 2865, 2850, 1470, 1445, 1347, 1285, 1244, 1055, 981, 960, 863, 724, 474; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 4.49 (t, J = 7.8 Hz, 2H, **14**), 2.31 (t, J = 7.8 Hz, 2H, **15**), 1.94 – 1.82 (m, 2H, **1**), 1.79 – 1.66 (m, 2H, **1**), 1.44 – 1.22 (m, 18H); **¹³C-NMR** (CDCl₃, 101 MHz) δ (ppm): 89.4 (**5**), 65.0 (**15**), 34.9 (**1**), 32.6, 26.4, 26.0, 22.7, 22.4,



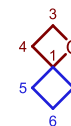
18.8; **HRMS** (ESI-TOF) mass calculated for $[M+H]^+$ ($C_{14}H_{27}O^+$) expected m/z 211.2056; found m/z 211.2056.

1-oxaspiro[3.3]heptane (4h)

Compound synthesised and characterised by Dr Subhasis Paul.

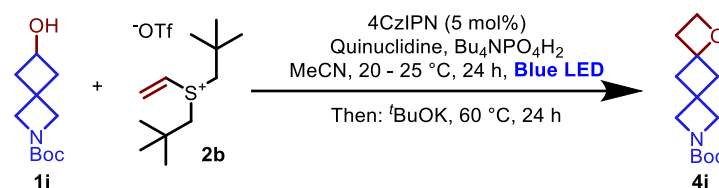


Prepared following general procedure A, using cyclobutanol **1h** (1.0 equiv.; 0.2 mmol; 15.7 μ L), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and *t*BuOK (2.0 equiv.; 0.4 mmol; 44.9 mg). Due to high volatility of compound **4h**, the NMR yield was measured (76%) using CH_2Br_2 as internal standard. The crude residue was purified by flash column chromatography (SiO_2 ; gradient 95:5 to 90:10 pentane:Et₂O; eluent removed using a rotary evaporator, maintaining the water bath below 25 °C and vacuum pressure 450 – 80 mbar) to afford compound **4h** (9.2 mg; 47%) as a transparent oil. **R_f** (95:5 pentane:Et₂O) 0.3; **IR** (film) ν_{max}/cm^{-1} : 2926, 2854, 1451, 1327, 1119, 748, 725; **¹H-NMR** ($CDCl_3$, 500 MHz) δ (ppm): 4.49 (t, J = 7.5 Hz, 2H, **3**), 2.68 (t, J = 7.5 Hz, 2H, **4**), 2.28 – 2.19 (m, 4H, **5**), 1.68 – 1.59 (m, 1H, **6**), 1.49 – 1.39 (m, 1H, **6**); **¹³C-NMR** ($CDCl_3$, 126 MHz) δ (ppm): 87.8 (**1**), 65.6 (**3**), 38.4 (**5**), 34.3 (**4**), 11.0 (**6**); **HRMS** (ESI-TOF) mass calculated for $[2M+Na]^+$ ($C_{12}H_{20}O_2Na^+$) expected m/z 219.1356; found m/z 219.1358.

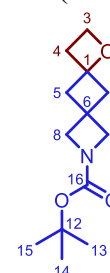


tert-butyl 1-oxa-8-azadispiro[3.1.36.14]decane-8-carboxylate (4i)

Compound synthesised and characterised by Filippo Ficarra



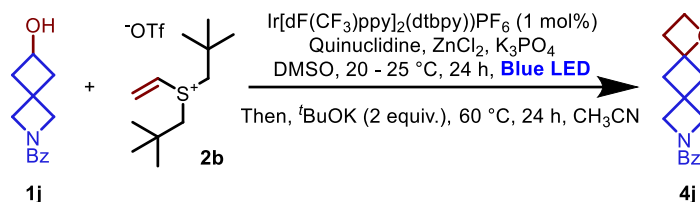
Prepared following general procedure A, using tert-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate **1i** (1.0 equiv.; 0.2 mmol), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and *t*BuOK (2.0 equiv.; 0.4 mmol; 44.9 mg). The crude residue was purified by flash column chromatography (SiO_2 ; gradient 85:15 to 70:30 DCM:EtOAc) to afford compound **4i** (17.3 mg, 37%) as a yellow oil. **R_f** (70:30 DCM:EtOAc) 0.4; **IR** (film) ν_{max}/cm^{-1} : 3415, 2962, 2925, 2854, 1703, 1455, 1394, 1367, 1256, 1171, 1047, 988, 922, 861; **¹H-NMR** ($CDCl_3$, 500



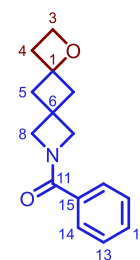
MHz) δ (ppm): 4.50 (t, J = 7.5 Hz, 2H, **3**), 3.86 (d, J = 4.3 Hz, 4H, **8**), 2.64 (t, J = 7.5 Hz, 2H, **4**), 2.50 – 2.46 (m, 2H, **5**), 2.44 – 2.40 (m, 2H, **5**), 1.42 (s, 9H, **13** – **14** – **15**); $^{13}\text{C-NMR}$ (CDCl_3 , 126 MHz) δ (ppm): 156.3 (**16**), 83.5 (**1**), 79.5 (**6**), 65.9 (**3**), 59.9 (**8**), 48.7 (**5**), 33.9 (**4**), 28.9 (**12**), 28.5 (**13** – **14** – **15**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{13}\text{H}_{21}\text{NO}_3\text{Na}^+$) expected m/z 262.1414; found m/z 262.1414.

(1-oxa-8-azadispiro[3.1.36.14]decan-8-yl)(phenyl)methanone (**4j**)

Compound synthesised and characterised by Dr Subhasis Paul.

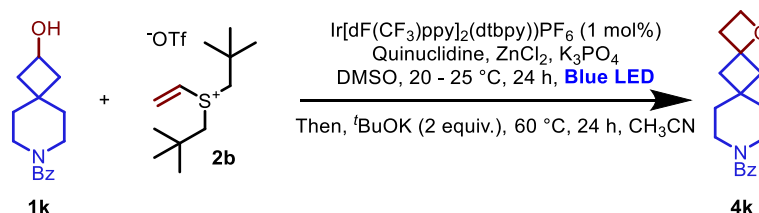


Prepared following general procedure B, using (6-hydroxy-2-azaspiro[3.3]heptan-2-yl)(phenyl)methanone **1j** (1.0 equiv.; 0.1 mmol; 21.7 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.15 mmol; 52.6 mg), Ir[dF(CF₃)ppy]₂(dtbpy)PF₆ (0.01 equiv.; 0.001 mmol; 1.1 mg), quinuclidine (0.3 equiv.; 0.03 mmol; 3.3 mg), potassium phosphate (1.5 equiv.; 0.15 mmol; 31.8 mg) and zinc chloride (2.25 equiv.; 0.23 mmol; 30.6 mg) and *t*BuOK (2.0 equiv.; 0.2 mmol; 22.4 mg). The crude residue was purified by flash column chromatography (SiO₂; gradient 50:50 to 0:100 DCM:EtOAc) to afford compound **4j** (11.4 mg; 47%) as a pale yellow oil. **R_f** (EtOAc) 0.25; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3472, 2924, 2873, 1630, 1575, 1450, 1416, 1314, 1287, 979, 952, 795, 713; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 7.61 – 7.59 (m, 2H, **14**), 7.46 – 7.43 (m, 1H, **12**), 7.40 – 7.37 (m, 2H, **13**), 4.52 – 4.48 (m, 2H, **3**), 4.23 (d, J = 11.8 Hz, 2H, **8**) 4.17 – 4.13 (m, 2H, **8**), 2.69 (t, J = 7.6 Hz, 1H, **4**) 2.61 (t, J = 6.8 Hz, 1H, **4**), 2.58 – 2.42 (m, 4H, **5**); $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis () δ (ppm): 170.3 (**11**), (133.4) 133.3 (**15**), 128.5 (**12**), 128.0 (**13**), 124.96 (**14**), 83.5 (**1**), (83.2), 66.1 (**3**), (65.9), (65.7) 64.4 (**8**), 60.9 (**8**), (59.7), (48.9), 48.8 (**5**), (33.8), 33.7 (**4**), 29.7 (**6**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{12}\text{H}_{17}\text{NO}_2\text{Na}^+$) expected m/z 266.1151; found m/z 266.1152.



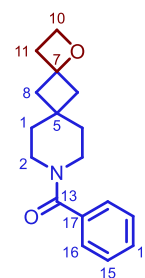
(1-oxa-9-azadispiro[3.1.5⁶.1⁴]dodecan-9-yl)(phenyl)methanone (**4k**)

Compound synthesised and characterised by Dr Subhasis Paul.

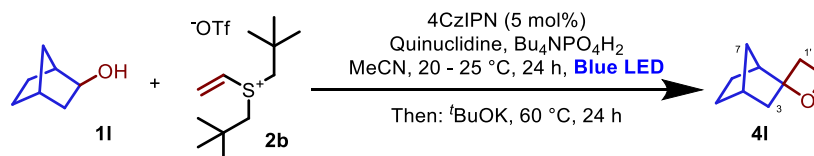


Prepared following general procedure B, using (2-hydroxy-7-azaspiro[3.5]nonan-2-yl)(phenyl)methanone **1k** (1.0 equiv.; 0.2 mmol; 49.0 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.15 mmol; 52.6 mg), Ir[dF(CF₃)ppy]₂(dtbpy)PF₆ (1 mol%), Quinuclidine, ZnCl₂, K₃PO₄ in DMSO, 20 – 25 °C, 24 h, Blue LED, Then, *t*BuOK (2 equiv.), 60 °C, 24 h, CH₃CN.

sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), Ir[dF(CF₃)ppy]₂(dtbpy))PF₆ (0.01 equiv.; 0.002 mmol; 2.2 mg), quinuclidine (0.3 equiv.; 0.06 mmol; 6.7 mg), potassium phosphate (1.5 equiv.; 0.3 mmol; 63.7 mg) and zinc chloride (2.25 equiv.; 0.45 mmol; 61.3 mg) and ^tBuOK (2.0 equiv.; 0.4 mmol; 44.9 mg). The crude residue was purified by flash column chromatography (SiO₂; gradient 50:50 to 30:70 hexane:EtOAc) to afford compound **4k** (36.8 mg; 68%) as a pale yellow oil. **R_f** (50:50 hexane:EtOAc) 0.25; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2914, 1600, 1433, 1275, 1248, 1061, 981, 952, 788, 709; **¹H-NMR** (CDCl₃, 400 MHz) δ (ppm): 7.41 – 7.32 (m, 5H, **14** – **15** – **16**), 4.52 (t, J = 7.5 Hz, 2H, **10**), 3.65 (br. s, 2H, **2**), 3.27 (br. s, 2H, **2**), 2.67 (m, 2H, **11**), 2.34 – 2.04 (m, 4H, **8**), 1.70 – 1.34 (m, 4H, **1**); **¹³C-NMR** (CDCl₃, 126 MHz) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis () δ (ppm): 170.5 (**13**), 136.4 (**17**), 129.6 (**14**), 128.6 (**15**), 126.9 (**16**), 84.8 (**7**), 66.2 (**10**), 47.9 (**8**), 45.2 (**2**), 39.7 (**2**), 39.2 (**1**), (38.2), (37.4), 36.5 (**1**), 35.8 (**11**), 30.1 (**5**); **¹H-NMR** (DMSO-*d*₆, 400 MHz, 80 °C) δ (ppm): 7.46 – 7.38 (m, 3H), 7.38 – 7.30 (m, 2H), 4.38 (t, J = 7.5 Hz, 2H), 3.47 – 3.24 (m, 4H), 2.63 (t, J = 7.5 Hz, 2H), 2.28 – 2.19 (m, 2H), 2.06 – 1.97 (m, 2H), 1.53 – 1.40 (m, 4H); **¹³C-NMR** (DMSO-*d*₆, 101 MHz, 80 °C) δ (ppm): 168.6, 136.2, 128.7, 127.8, 126.1, 83.7, 64.5, 46.9, 37.8, 35.9, 34.6, 29.4; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₇H₂₁NO₂Na⁺) expected m/z 294.1465; found m/z 294.1468.

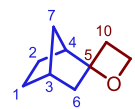


spiro[bicyclo[2.2.1]heptane-2,2'-oxetane] (**4l**)



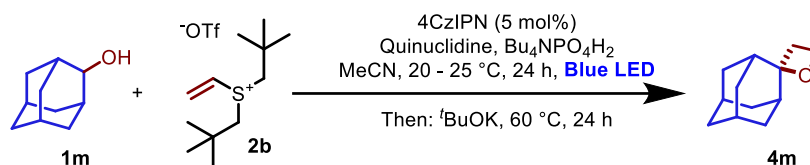
Prepared following general procedure A, using *exo*-Norborneol **1l** (1.0 equiv.; 0.2 mmol; 22.4 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and ^tBuOK (2.0 equiv.; 0.4 mmol; 44.9 mg). Due to high volatility of compound **4l**, the NMR yield was measured (92%) using CH₂Br₂ as internal standard. The crude residue was purified by flash column chromatography (SiO₂; 97.5:2.5 to 9:1 pentane:Et₂O; eluent removed using a rotary evaporator, maintaining the water bath below 25 °C and vacuum pressure 450 – 80 mbar) to afford compound **4l** (19.7 mg; 71%; >20:1 d.r.) transparent oil. The stereochemistry of the final compound was unambiguously inferred by NOESY analysis by detecting strong NOE interaction between H_{1'} and both H₇ and H_{3(equat.)}. **R_f** (1:1 pentane:Et₂O) 0.6; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2949, 2872, 1704, 1449, 1333, 1311, 1236, 1180, 1135, 1100, 1061, 986, 970, 917, 883, 447; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 4.42 – 4.36 (m, 2H, **9**), 2.56 – 2.42 (m, 2H, **10**), 2.41 (d, J = 4.4 Hz, 1H, **4**), 2.19 – 2.13 (m, 1H, **3**), 1.84 – 1.71 (m, 2H, **2** – **6**), 1.52 – 1.43 (m 2H, **1** – **6**), 1.36 (tt, J = 12.4, 4.1 Hz, 1H, **2**), 1.29 – 1.14 (m, 3H, **1** – **7**); **¹³C**

NMR (CDCl₃, 126 MHz) δ (ppm): 92.6 (**5**), 64.4 (**9**), 47.6 (**4**), 46.9 (**6**), 37.1 (**10**), 37.0 (**3**), 36.0 (**7**), 28.9 (**1**), 20.0 (**2**); **HRMS** (ESI-TOF) mass calculated for [M+H]⁺ (C₉H₁₅O⁺) expected m/z 139.1117; found m/z 139.1113.

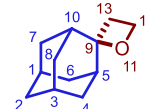


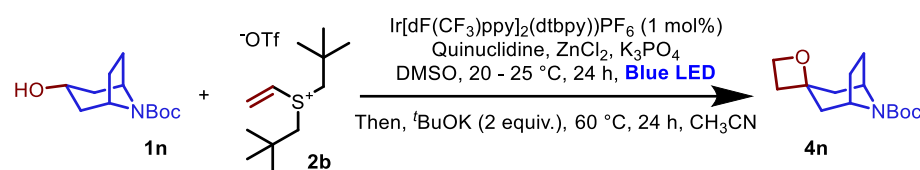
spiro[adamantane-2,2'-oxetane] (**4m**)

Compound synthesised and characterised by Dr Subhasis Paul.

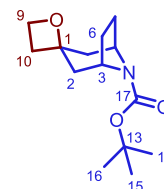


Prepared following general procedure A, using 2-adamantanol **4m** (1.0 equiv.; 0.2 mmol; 30.4 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and *t*BuOK (2.0 equiv.; 0.4 mmol; 44.9 mg). After the heating step, a minor amount of an unknown olefin was formed. To effectively removed it, the crude mixture was filtered through celite, eluted with DCM, and concentrated under reduced pressure. The mixture was dissolved in dry DCM (0.1 M, 2.0 mL), cooled down at 0 °C and *m*CPBA (70%) (4.0 equiv.; 0.8 mmol; 197 mg) was slowly added. The reaction mixture was then warmed up to room temperature – allowing the ice bath to melt – and left stirring (700 ppm) at room temperature until complete consumption of olefin monitored via ¹H-NMR analysis of a small reaction aliquot (*disappearance of multiplet at 5.70 – 5.61 ppm*). Then, the mixture was diluted with DCM (20 mL), washed with saturated NaHCO₃ solution (10 mL), followed by water (15 mL) and brine (15 mL), dried over anhydrous MgSO₄. Finally, the solution was filtered and the solvent removed under reduced pressure. The crude residue was purified by flash column chromatography (SiO₂; gradient 95:5 to 85:15 pentane:Et₂O) to afford compound **4m** (17.7 mg; 50%) as a white solid. **R_f** (90:10 pentane:Et₂O) 0.3; **M. P.** = 61-62 °C; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2902, 2852, 1467, 1449, 1351, 1230, 1134, 1102, 1083, 1003, 981, 919, 825, 662, 488; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 4.43 (t, J = 7.8 Hz, 2H, **12**), 2.37 (t, J = 7.8 Hz, 2H, **13**), 2.19 – 2.13 (m, 2H, **5 – 10**), 2.03 – 1.95 (m, 2H, **1 – 3**), 1.78 – 1.61 (m, 8H), 1.57 – 1.52 (m, 2H, **2**); **¹³C-NMR** (CDCl₃, 101 MHz) δ (ppm): 90.5 (**9**), 64.1(**12**), 38.7 (**5 – 10**), 36.9, 33.6, 32.6 (**13**), 31.9, 26.8, 26.7; **HRMS** (ESI-TOF) mass calculated for [M+NH₄]⁺ (C₁₂H₂₂NO⁺) expected m/z 196.1696; found m/z 196.1688.

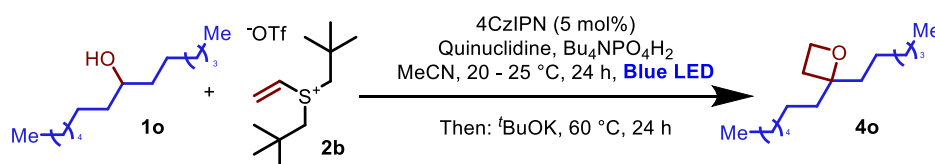


tert-butyl (1*R*,3*S*,5*S*)-8-azaspiro[bicyclo[3.2.1]octane-3,2'-oxetane]-8-carboxylate (**4n**)

Prepared following general procedure B, using *tert*-butyl 3-endo-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate 1,1-dioxide **1n** (1.0 equiv.; 0.2 mmol; 45.5 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (0.01 equiv.; 0.002 mmol; 2.2 mg), quinuclidine (0.3 equiv.; 0.06 mmol; 6.7 mg), potassium phosphate (1.5 equiv.; 0.3 mmol; 63.7 mg) zinc chloride (2.25 equiv.; 0.45 mmol; 61.3 mg) and ^tBuOK (2.0 equiv.; 0.4 mmol; 44.9 mg). The crude residue was purified by flash column chromatography (SiO₂; 95:5 to 75:25 hexane:THF) to afford compound **4n** (39.6 mg; 78%; >20:1 d.r.) as a yellow oil. The stereochemistry of the final compound was elucidated by NOESY analysis at 80°C by total absence of NOE interaction between H₁ and H₅. **R_f** (80:20 hexane:THF) 0.4; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2975, 2877, 1689, 1477, 1390, 1364, 1329, 1307, 1256, 1228, 1170, 1119, 1097, 1081, 1011, 986, 960, 879, 838, 796, 770, 572, 541, 497; **¹H-NMR** (500 MHz, CDCl₃) δ (ppm): 4.45 (t, *J* = 7.4 Hz, 2H, **9**), 4.28 – 4.05 (m, 2H, **3**), 2.35 – 2.25 (m, 4H, **2 – 10**), 2.07 – 2.00 (m, 2H, **6**), 1.94 – 1.75 (m, 4H, **2 – 6**), 1.45 (s, 9H, **14 – 15 – 16**); **¹³C-NMR** (126 MHz, CDCl₃) rotameric mixture, resonances for minor rotamer are enclosed in parenthesis () δ (ppm): 153.5 (**17**), 85.3 (**1**), 79.3 (**13**), 65.1 (**9**), 53.5 (**3**), (52.7), 44.0 (**2**), (43.2), 34.6 (**10**), 28.6 (**14 – 15 – 16**), 27.7 (**6**), (27.1); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₄H₂₃NO₃Na⁺) expected *m/z* 276.1570; found *m/z* 276.1568; **¹H-NMR** (400 MHz, DMSO-*d*₆, 80°C) δ (ppm): 4.36 (t, *J* = 7.8 Hz, 2H), 4.11 – 4.01 (m, 2H), 2.29 (t, *J* = 7.8 Hz, 2H), 2.26 – 2.18 (m, 2H), 2.02 – 1.94 (m, 2H), 1.81 – 1.71 (m, 4H), 1.40 (s, 9H); **¹³C-NMR** (101 MHz, DMSO-*d*₆, 80°C) δ (ppm): 152.2, 83.7, 77.9, 63.7, 52.3, 42.5, 33.5, 27.8, 26.5.

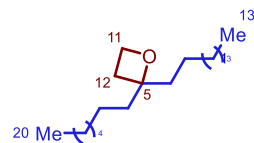
2-heptyl-2-hexyloxetane (**4o**)

Compound synthesised and characterised by Dr Subhasis Paul.



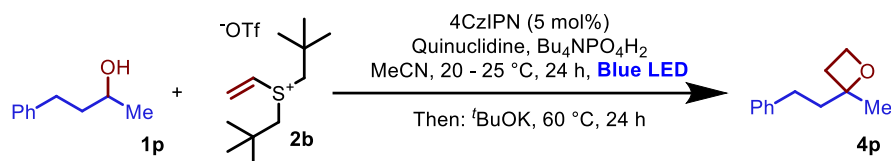
Prepared following general procedure A, using 7-tetradecanol **1o** (1.0 equiv.; 0.2 mmol; 42.9 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and ^tBuOK (2.0 equiv.; 0.4 mmol; 44.9 mg). The crude residue was purified by flash column chromatography (SiO₂; gradient 96:4 to 95:5 pentane:Et₂O) to afford compound **4o** (32.8 mg; 68%) as a transparent oil. **R_f** (95:5 pentane:Et₂O) 0.3; **IR** (film)

$\nu_{\max}/\text{cm}^{-1}$: 2955, 2926, 2872, 2856, 1465, 1378, 1229, 1139, 964, 843, 725; **$^1\text{H-NMR}$** (CDCl_3 , 500 MHz) δ (ppm): 4.43 (t, $J = 7.9$ Hz, 2H, **11**), 2.33 (t, $J = 7.9$ Hz, 2H, **12**), 1.72 – 1.56 (m, 4H), 1.37 – 1.23 (m, 18H), 0.93 – 0.84 (m, 6H, **13** – **20**); **$^{13}\text{C-NMR}$** (CDCl_3 , 126 MHz) δ (ppm): 89.0 (**5**), 64.8 (**11**), 39.9, 32.1, 32.0, 30.7, 30.2 (**5**), 29.9, 29.5, 23.3, 23.2, 22.8, 22.8, 14.2; **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{H}]^+$ ($\text{C}_{16}\text{H}_{33}\text{O}^+$) expected m/z 241.2531; found m/z 241.2529.



2-methyl-2-phenethyloxetane (**4o**)

Compound synthesised and characterised by Dr Subhasis Paul.

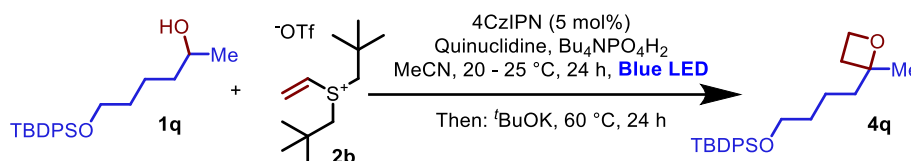


Prepared following general procedure A, using 4-phenyl-2-butanol **1o** (1.0 equiv.; 0.2 mmol; 31.0 μL), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and $t\text{BuOK}$ (2.0 equiv.; 0.4 mmol; 44.9 mg). The crude residue was purified by flash column chromatography (SiO_2 ; gradient 50:50 pentane:DCM to 95:5-85:15 pentane: Et_2O) to afford compound **4p** (14.6 mg; 41%) as a transparent oil. **R_f** (95:5 pentane: Et_2O) 0.35; **IR** (film) $\nu_{\max}/\text{cm}^{-1}$: 3026, 2964, 2927, 1603, 1497, 1453, 1373, 1258, 1140, 1097, 1031, 962, 857, 750, 699, 568, 509; **$^1\text{H-NMR}$** (CDCl_3 , 500 MHz) δ (ppm): 7.32 – 7.27 (m, 2H, **1**), 7.25 – 7.17 (m, 3H, **1**), 4.57 – 4.50 (m, 1H, **7**), 4.50 – 4.44 (m, 1H, **7**), 2.77 – 2.67 (m, 2H, **2**), 2.50 (ddd, $J = 10.9, 9.0, 6.8$ Hz, 1H, **8**), 2.37 (ddd, $J = 10.9, 8.8, 6.6$ Hz, 1H, **8**), 2.03 – 1.95 (m, 2H, **3**), 1.48 (s, 3H, **5**); **$^{13}\text{C-NMR}$** (CDCl_3 , 126 MHz) δ (ppm): 142.4, 128.6, 128.5, 125.9, 86.5 (**4**), 64.4 (**7**), 44.1 (**3**), 32.5 (**8**), 30.1 (**2**), 27.5 (**5**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{12}\text{H}_{16}\text{ONa}^+$) expected m/z 199.1099; found m/z 199.1095.

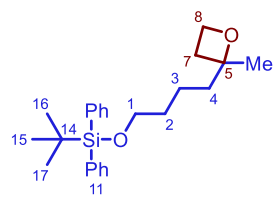


tert-butyl(4-(2-methyloxetan-2-yl)butoxy)diphenylsilane (4q)

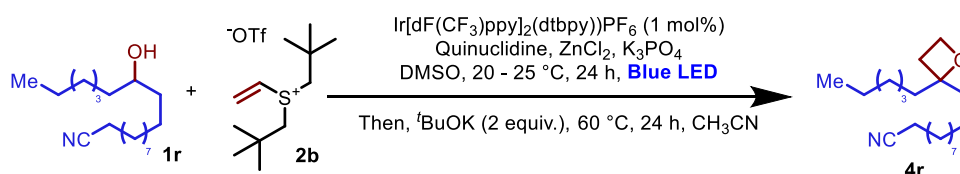
Compound synthesised and characterised by Dr Subhasis Paul.



Prepared following general procedure A, using 6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-ol **1q** (1.0 equiv.; 0.2 mmol; 71.3 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and ^tBuOK (2.0 equiv.; 0.4 mmol; 44.9 mg). The crude residue was purified by flash column chromatography (SiO₂; gradient 95:5 to 85:15 pentane:Et₂O) to afford compound **4q** (45.6 mg; 60%) as a transparent oil. **R_f** (90:10 pentane:Et₂O) 0.3; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3071, 3049, 2931, 2858, 1589, 1472, 1428, 1389, 1373, 1257, 1188, 1110, 994, 964, 823, 740, 702, 614, 505; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.70 – 7.65 (m, 4H, **11**), 7.45 – 7.35 (m, 6H, **11**), 4.49 (dt, J = 8.9, 6.4 Hz, 1H, **8**), 4.41 (dt, J = 8.9, 6.4 Hz, 1H, **8**), 3.69 (t, J = 6.4 Hz, 2H, **1**), 2.47 – 2.39 (m, 1H, **7**), 2.34 – 2.26 (m, 1H, **7**), 1.68 – 1.58 (m, 4H), 1.48 – 1.41 (m, 2H), 1.39 (s, 3H, **6**), 1.06 (s, 9H, **15** – **16** – **17**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 135.7, 134.2, 129.7, 127.7, 86.8 (**5**), 64.3 (**8**), 63.9 (**1**), 42.0, 33.0, 32.4 (**7**), 27.3, 27.0 (**15** – **16** – **17**), 20.1 (**6**), 19.4; **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₄H₃₄O₂SiNa⁺) expected m/z 405.2220; found m/z 405.2216.

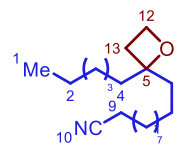
11-(2-hexyloxetan-2-yl)undecanenitrile (4r)

Compound synthesised and characterised by Filippo Ficarra.



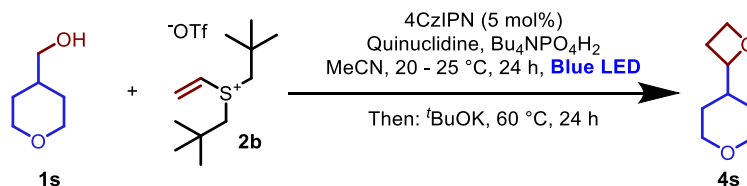
Prepared following general procedure B, using 12-hydroxyundecanenitrile **1r** (1.0 equiv.; 0.2 mmol; 56.3 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (0.01 equiv.; 0.002 mmol; 2.2 mg), quinuclidine (0.3 equiv.; 0.06 mmol; 6.7 mg), potassium phosphate (1.5 equiv.; 0.3 mmol; 63.7 mg), zinc chloride (2.25 equiv.; 0.45 mmol; 61.3 mg) and ^tBuOK (2.0 equiv.; 0.4 mmol; 44.9 mg). The crude residue was purified by flash column chromatography (SiO₂; gradient 95:5 to 90:10 hexane:THF) to afford compound **4r** (35.0 mg; 57%) as a pale yellow oil. **R_f** (90:10 hexane:THF) 0.4; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2926, 2855, 2247, 1693, 1459, 1430, 1403, 1379, 1333, 1257, 1180, 1051, 962, 909, 882, 848, 723, 684; **¹H-NMR** (500 MHz, CDCl₃) δ (ppm): 4.43 (t, J = 7.8 Hz, 2H, **12**),

2.35 – 2.32 (m, 4H, **9** – **13**), 1.70 – 1.61 (m, 6H), 1.47 – 1.41 (m, 2H), 1.36 – 1.26 (m, 20H), 0.89 (t, $J = 7.0$ Hz, 3H, **1**); $^{13}\text{C-NMR}$ (CDCl_3 , 126 MHz) δ (ppm): δ 120.0 (**10**), 89.0 (**2**), 64.8 (**12**), 39.9, 39.8, 32.0, 30.7 (**13**), 30.2, 29.9, 29.7, 29.6, 29.4, 28.9, 28.8, 25.5, 23.3, 22.8, 17.3, 14.2 (**1**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{20}\text{H}_{37}\text{NONa}^+$) expected m/z 330.2767 found m/z 330.2768.

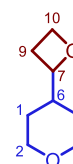


4-(oxetan-2-yl)tetrahydro-2H-pyran (**4s**)

Compound synthesised and characterised by Dr Subhasis Paul.

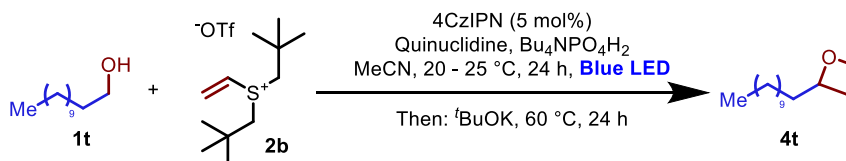


Prepared following general procedure A, using tetrahydropyran-4-methanol **1s** (1.0 equiv.; 0.2 mmol; 23.0 μL), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and $t\text{BuOK}$ (2.0 equiv.; 0.4 mmol; 44.9 mg). Due to high volatility of compound **4s**, the NMR yield was measured (68%) using CH_2Br_2 as internal standard. The crude residue was purified by flash column chromatography (SiO_2 ; gradient 60:40 to 40:60 pentane: Et_2O ; eluent removed using a rotary evaporator, maintaining the water bath below 25°C and vacuum pressure 450 – 80 mbar) to afford compound **4s** (16.0 mg; 56%) as a pale yellow oil. **R_f** (50:50 pentane: Et_2O) 0.35; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2934, 2845, 1446, 1387, 1235, 1132, 1080, 1017, 979, 751; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 4.72 – 4.64 (m, 1H, **10**), 4.54 (q, $J = 7.4$ Hz, 1H, **7**), 4.47 (dt, $J = 9.2, 5.8$ Hz, 1H, **10**), 4.04 – 3.97 (m, 2H, **2**), 3.44 – 3.33 (m, 2H, **2**), 2.64 – 2.55 (m, 1H, **9**), 2.44 – 2.35 (m, 1H, **9**), 1.95 – 1.85 (m, 1H, **6**), 1.77 – 1.70 (m, 1H, **1**), 1.54 – 1.47 (m, 1H, **1**), 1.34 – 1.21 (m, 2H, **1**); $^{13}\text{C-NMR}$ (CDCl_3 , 126 MHz) δ (ppm): 85.8 (**7**), 68.5 (**10**), 67.7 (**2**), 67.6 (**2**), 41.9 (**6**), 27.7 (**1**), 26.2 (**1**), 25.3 (**9**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_8\text{H}_{14}\text{O}_2\text{Na}^+$) expected m/z 165.0886; found m/z 165.0880.



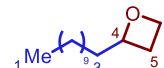
2-undecyloxetane (**4t**)

Compound synthesised and characterised by Dr Subhasis Paul.



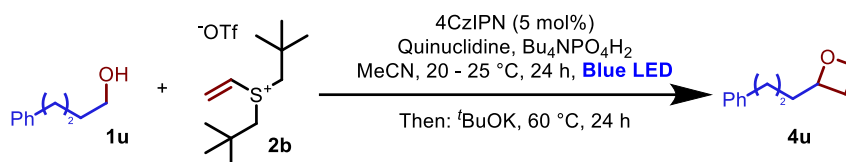
Prepared following general procedure A, using 1-dodecanol **1t** (1.0 equiv.; 0.2 mmol; 44.7 μL), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen

phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and ^tBuOK (2.0 equiv.; 0.4 mmol; 44.9 mg). The crude residue was purified by flash column chromatography (SiO₂; gradient 97:3 to 95:5 pentane:Et₂O) to afford compound **4t** (17.9 mg; 42%) as a pale yellow oil. **R_f** (95:5 pentane:Et₂O) 0.4; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2922, 2874, 2853, 1465, 1376, 1225, 981, 722; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 4.81 (p, *J* = 6.9 Hz, 1H, **4**), 4.65 (td, *J* = 8.0, 5.9 Hz, 1H, **6**), 4.49 (dt, *J* = 9.1, 5.8 Hz, 1H, **6**), 2.68 – 2.59 (m, 1H, **5**), 2.36 – 2.27 (m, 1H, **5**), 1.84 – 1.75 (m, 1H, **3**), 1.69 – 1.61 (m, 1H, **3**), 1.33 – 1.21 (m, 18H), 0.88 (t, *J* = 6.9 Hz, 3H, **1**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 83.0 (**4**), 68.2 (**6**), 38.2 (**3**), 32.1, 29.8, 29.8, 29.7, 29.6, 29.5, 27.9 (**5**), 24.2, 22.8, 14.3 (**1**); **HRMS** (ESI-TOF) mass calculated for [M+NH₄]⁺ (C₁₄H₃₂NO⁺) expected *m/z* 230.2484; found *m/z* 230.2477.

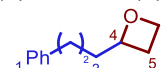


2-(3-phenylpropyl)oxetane (**4u**)

Compound synthesised and characterised by Dr Subhasis Paul.

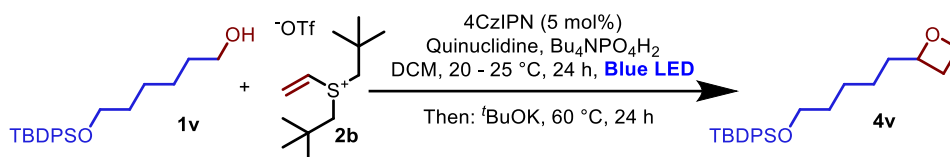


Prepared following general procedure A, using 4-phenyl-1-butanol **1u** (1.0 equiv.; 0.2 mmol; 30.5 μL), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and ^tBuOK (2.0 equiv.; 0.4 mmol; 44.9 mg). The crude residue was purified by flash column chromatography (SiO₂; gradient 100% DCM to 85:15-80:20 pentane:Et₂O) to afford compound **4u** (15.9 mg; 45%) as a transparent oil. **R_f** (85:15 pentane:Et₂O) 0.4; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3061, 3026, 2932, 2877, 1603, 1496, 1463, 1379, 1225, 1079, 1030, 976, 919, 773, 748, 699; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 7.30 – 7.26 (m, 2H, **7**), 7.21 – 7.16 (m, 3H, **7**), 4.87 – 4.80 (m, 1H, **4**), 4.66 (td, *J* = 8.0, 5.9 Hz, 1H, **6**), 4.49 (dt, *J* = 9.1, 5.8 Hz, 1H, **6**), 2.70 – 2.60 (m, 3H **1** – **5**), 2.36 – 2.28 (m, 1H, **5**), 1.89 – 1.80 (m, 1H, **3**), 1.74 – 1.66 (m, 2H, **2** – **3**), 1.66 – 1.59 (m, 1H, **2**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 142.4 (**7**), 128.6 (**7**), 128.4 (**7**), 125.9 (**7**), 82.7 (**4**), 68.2 (**6**), 37.7 (**3**), 35.8 (**1**), 27.7 (**5**), 26.0 (**2**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₁₂H₁₆ONa⁺) expected *m/z* 199.1093; found *m/z* 199.1095.

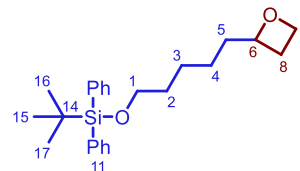


tert-butyl((5-(oxetan-2-yl)pentyl)oxy)diphenylsilane (**4v**)

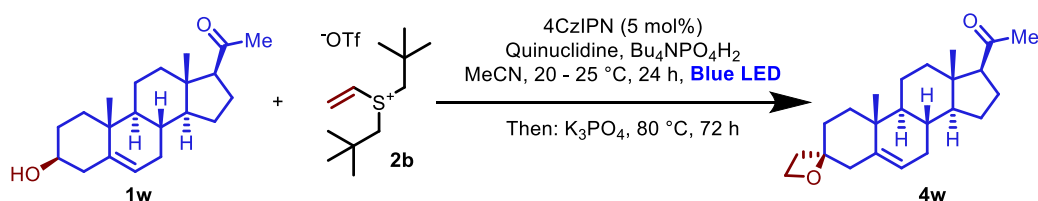
Compound synthesised and characterised by Filippo Ficarra.



Prepared following general procedure A, using 6-((*tert*-butyldiphenylsilyl)oxy)hexan-1-ol **1v** (1.0 equiv.; 0.2 mmol;), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) After 24 h, DCM was removed by blowing with nitrogen, and the solvent was switched to anhydrous MeCN (0.4 mL), then *t*BuOK (2.0 equiv.; 0.4 mmol; 44.9 mg) was added and the mixture heated at 60 °C for 24 h. The crude residue was purified by flash column chromatography (SiO₂; gradient 95:5-90:10 pentane:Et₂O) to afford compound **4v** (32.3 mg, 43%) as a yellow oil. **R_f** (90:10 pentane:Et₂O) 0.3; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 3071, 2931, 2858, 1472, 1428, 1389, 1111, 980, 823, 740, 720, 614, 504, 490, 435; **¹H-NMR** (500 MHz, CDCl₃) δ (ppm): 7.68 – 7.66 (m, 4H, **11**), 7.43 – 7.36 (m, 6H, **11**), 4.82 – 4.77 (m, 1H, **6**), 4.67 – 4.63 (m, 1H, **9**), 4.53 – 4.49 (dt, *J* = 9.2 Hz, 5.7 Hz, 1H, **9**), 3.66 (t, *J* = 6.5 Hz, 2H, **1**), 2.67 – 2.60 (m, 1H, **8**), 2.34 – 2.37 (m, 1H, **8**), 1.82 – 1.75 (m, 1H, **5**), 1.67 – 1.62 (m, 1H, **5**), 1.60 – 1.54 (m, 2H, **2**), 1.41 – 1.35 (m, 2H, **3**), 1.34 – 1.23 (m, 2H, **4**), 1.05 (s, 9H, **15** – **16** – **17**); **¹³C-NMR** (126 MHz, CDCl₃) δ (ppm): 135.7 (**11**), 134.2 (**11**), 129.6 (**11**), 127.7 (**11**), 82.9 (**6**), 68.2 (**9**), 64.0 (**1**), 38.1 (**5**), 32.7 (**2**), 27.8 (**8**), 27.0 (**15** – **16** – **17**), 25.8 (**3**), 24.0 (**4**), 19.4 (**14**); **HRMS** (ESI-TOF) mass calculated for [M+Na]⁺ (C₂₄H₃₄O₂SiNa⁺) expected *m/z* 405.2220; found *m/z* 405.2226.

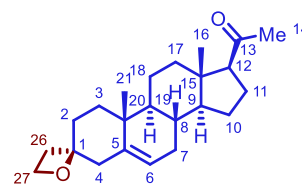
1-((3*S*,8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-10,13-dimethyl-1,2,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydrospiro[cyclopenta[*a*]phenanthrene-3,2'-oxetan]-17-yl)ethan-1-one (**4w**)

Compound synthesised and characterised by Dr Subhasis Paul.



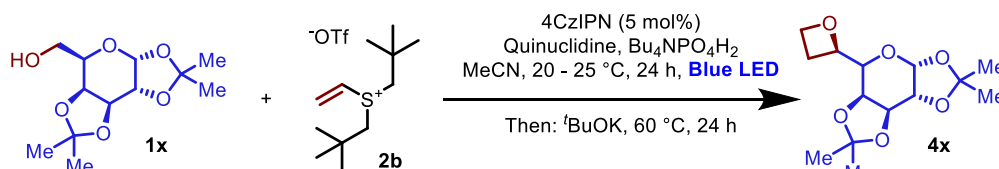
Prepared following general procedure A, using pregnenolone **1w** (1.0 equiv.; 0.2 mmol; 63.3 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and DCM (0.4 mL, 0.5 M). After photochemical step, the crude was transferred in a 5 mL Young tube. K₃PO₄ (2.0 equiv.; 0.4 mmol; 84.8 mg) was added and the

mixture heated at 80 °C for 72 h. The crude residue was purified by flash column chromatography (SiO₂; gradient 90:10 to 80:20 hexane:EtOAc) to afford compound **4w** (30.6 mg; 44%; >20:1 d.r.) as a white solid. The stereochemistry of the final compound was elucidated by NOESY analysis by detecting strong NOE interaction between H_{1'} and H_{4(equat.)} and the absence of NOE interaction between H_{1'} and H_{4(axial.)}. **R_f** (80:20 hexane:EtOAc) 0.4; [α]_D²⁵ = +23 (c = 1.00 CHCl₃); **M. P.** = 174-175 °C; **IR** (film) ν_{max} /cm⁻¹: 2935, 2878, 2845, 1698, 1437, 1384, 1355, 1225, 1136, 1064, 975, 958, 758, 593; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 5.41 – 5.36 (m, 1H, **6**), 4.53 – 4.44 (m, 2H, **27**), 2.52 (t, *J* = 9.0 Hz, 1H, **12**), 2.50 – 2.41 (m, 2H, **4**), 2.31 – 2.21 (m, 2H, **26**), 2.20 – 2.14 (m, 1H), 2.12 (s, 3H, **14**), 2.08 – 1.96 (m, 3H, **2**), 1.83 – 1.75 (m, 1H), 1.75 – 1.59 (m, 4H, **2**), 1.57 – 1.53 (m, 1H, **3**), 1.53 – 1.39 (m, 3H), 1.28 – 1.19 (m, 1H), 1.17 – 1.10 (m, 1H), 1.06 – 1.00 (m, 1H), 0.99 (s, 3H, **21**), 0.98 – 0.91 (m, 1H), 0.63 (s, 3H, **16**); **¹³C-NMR** (CDCl₃, 126 MHz) δ (ppm): 209.7 (**13**), 139.8 (**5**), 122.4 (**6**), 87.5 (**1**), 64.9 (**27**), 63.9 (**12**), 57.1, 50.1, 45.8 (**4**), 44.1, 39.0 (**2**), 36.7, 35.5, 34.9, 32.0 (**26**), 31.9 (**14**), 31.7 (**3**), 31.3, 24.6, 23.0, 21.3, 19.1 (**21**), 13.4 (**16**); **HRMS** (ESI-TOF) mass calculated for [M+H]⁺ (C₂₃H₃₅O₂) expected *m/z* 343.2637; found *m/z* 343.2630.



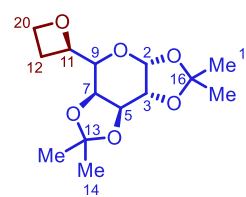
(3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-tetramethyl-5-((*R*)-oxetan-2-yl)tetrahydro-5*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran (**4x**)

Compound synthesised Dr Subhasis Paul and characterised by Dr Subhasis Paul and Filippo Ficarra.



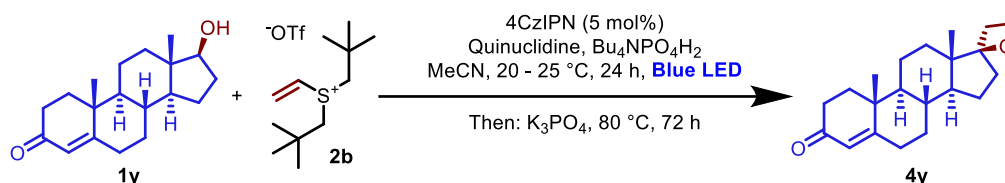
Prepared following general procedure A, using 1,2:3,4-Di-*O*-isopropylidene- α -D-galactopyranose **4x** (1.0 equiv.; 0.2 mmol; 52.1 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetra-*n*-butylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and *t*BuOK (2.0 equiv.; 0.4 mmol; 44.9 mg). The crude residue was purified by flash column chromatography (SiO₂; gradient 80:20 to 70:30 hexane:EtOAc) allowing separation of the minor diastereoisomer to afford compound **4x** (24.9 mg; 43%; >20:1 d.r.) as a pale yellow oil. The d.r. detected by ¹H-NMR in the crude reaction mixture was 6:1. **R_f** (80:20 hexane:EtOAc) 0.3; [α]_D²⁵ = –38 (c = 1.00 CHCl₃); **IR** (film) ν_{max} /cm⁻¹: 2987, 2936, 1456, 1382, 1255, 1212, 1169, 1067, 1000, 916, 896, 773, 510; **¹H-NMR** (CDCl₃, 500 MHz) δ (ppm): 5.59 (d, *J* = 5.0 Hz, 1H, **2**), 4.95 (q, *J* = 6.9 Hz, 1H, **11**), 4.68 (td, *J* = 8.0, 5.8 Hz, 1H, **20**), 4.64 – 4.57 (m, 2H, **5** – **20**), δ 4.33 (dd, *J* = 5.0, 2.4 Hz, 1H, **3**), 4.31 (dd, *J* = 8.0, 1.9 Hz, 1H, **7**), 3.96 (dd, *J* = 6.2, 1.9 Hz, 1H, **9**), 2.74 – 2.64 (m, 2H, **12**), 1.58 (s, 3H, **17**), 1.43 (s, 3H,

14), 1.35 (s, 3H, **17**), 1.32 (s, 3H, **14**); $^{13}\text{C-NMR}$ (CDCl_3 , 126 MHz) δ (ppm): 109.4 (**13**), 108.8 (**16**), 96.5 (**2**), 80.2 (**11**), 70.8 (**5**), 70.7 (**3**), 70.3 (**9**), 70.2 (**7**), 70.1 (**20**), 26.3 (**17**), 26.0 (**14**), 25.1 (**17**), 24.9 (**12**), 24.4 (**14**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{14}\text{H}_{22}\text{O}_6\text{Na}^+$) expected m/z 309.1309; found m/z 309.1310.



(8R,9S,10R,13S,14S,17R)-10,13-dimethyl-1,6,7,8,9,10,11,12,13,14,15,16-dodecahydrospiro[cyclopenta[a]phenanthrene-17,2'-oxetan]-3(2H)-one (**4y**)

Compound synthesised and characterised by Dr Subhasis Paul.



Prepared following general procedure A, using testosterone **4y** (1.0 equiv.; 0.2 mmol; 57.7 mg), dineopentyl(vinyl)sulfonium triflate **2b** (1.5 equiv.; 0.3 mmol; 105 mg), 4CzIPN (0.05 equiv.; 0.01 mmol; 7.9 mg), tetrabutylammonium dihydrogen phosphate (0.25 equiv.; 0.05 mmol; 17.0 mg), quinuclidine (0.25 equiv.; 0.05 mmol; 5.6 mg) and DCM (0.4 mL, 0.5 M). After photochemical step, the crude was transferred in a 5 mL Young tube. Then K_3PO_4 (2.0 equiv.; 0.4 mmol; 84.8 mg) was added and heated at 80 °C for 72 h. The crude residue was purified by flash column chromatography (SiO_2 ; gradient 75:25 to 60:40 hexane:EtOAc) to afford compound **4y** (25.9 mg; 41%; >20:1 d.r.) as a white solid. The stereoselectivity was determined by performing a full NMR characterisation of the product **4y**. The stereochemistry of the final compound was elucidated by NOESY analysis by detecting total absence of NOE interaction between $\text{H}_{21'}$ and H_{18} . **R_f** (70:30 hexane:EtOAc) 0.3; $[\alpha]_{\text{D}}^{25} = +69$ ($c = 1.00$ CHCl_3); **M. P.** = 170-171 °C; **IR** (film) $\nu_{\text{max}}/\text{cm}^{-1}$: 2944, 2875, 1674, 1616, 1451, 1270, 1229, 1185, 1066, 1044, 978, 868; $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 5.72 (s, 1H, **5**), 4.46 – 4.40 (m, 1H, **25**), 4.34 – 4.27 (m, 1H, **25**), 2.76 (ddd, $J = 11.0, 8.5, 6.2$ Hz, 1H, **26**), 2.45 – 2.31 (m, 3H), 2.31 – 2.23 (m, 2H, **26**), 2.10 – 2.01 (m, 3H, **12**), 1.90 – 1.80 (m, 2H, **15**), 1.76 – 1.69 (m, 1H, **12**), 1.66 – 1.57 (m, 2H), 1.57 – 1.45 (m, 3H), 1.34 – 1.22 (m, 1H), 1.20 (s, 3H, **19**), 1.03 – 0.96 (m, 1H), 0.96 – 0.85 (m, 2H), 0.81 (s, 3H, **14**); $^{13}\text{C-NMR}$ (CDCl_3 , 126 MHz) δ (ppm): 199.7 (**1**), 171.3 (**6**), 124.0 (**5**), 96.4 (**23**), 65.0 (**25**), 53.8, 48.0, 44.6, 38.8, 37.8, 36.3, 35.9, 34.1, 32.9, 32.1, 31.6, 31.0 (**26**), 23.2, 20.8, 17.6 (**19**), 12.0 (**14**); **HRMS** (ESI-TOF) mass calculated for $[\text{M}+\text{Na}]^+$ ($\text{C}_{21}\text{H}_{30}\text{O}_2\text{Na}^+$) expected m/z 337.2138; found m/z 337.2127.

