ARTICLE

Visible light-driven conjunctive olefination

Dario Filippini† & Mattia Silvi†*

† – School of Chemistry, University of Nottingham, GlaxoSmithKline Carbon Neutral Laboratories for Sustainable Chemistry, 6 Triumph Road, Nottingham, NG7 2GA, UK.
*email: mattia.silvi@nottingham.ac.uk

Carboxylic acids and aldehydes are ubiquitous in chemistry and are native functionalities in many bioactive molecules and natural products. As such, a general cross-coupling process involving these partners would open new avenues to achieve molecular diversity. Herein, we report a visible light-mediated and metal-free conjunctive olefination which uses an alkene "linchpin" with defined geometry to cross-couple complex molecular scaffolds containing carboxylic acids and aldehydes. The chemistry merges two cornerstones of organic synthesis – namely the Wittig reaction and photoredox catalysis – in a catalytic cycle which couples a radical addition process with the redox generation of a phosphonium ylide. The methodology allows rapid structural diversification of bioactive molecules and natural products in a native form, with remarkable chemoselectivity and high functional group tolerance, while forging a new alkene functional group with programmable *E* - *Z* stereochemistry.

Designing molecular diversity is a core challenge in relevant fields of science and technology,[1] and is often achieved by assembling chemical building blocks through the construction of carbon-carbon bonds. In most cases, metal-catalysed cross-coupling reactions[2] are a fundamental part of these synthetic endeavours, although the corresponding coupling partners are not always easily accessible, as they carry functional groups that are not native in natural molecules, e.g. (pseudo)halides and organometals. Thus, scientists investigated novel strategies to use native functional groups and, in this regard, alkyl carboxylic acids received significant attention.[3] Remarkable examples of metal-catalysed decarboxylative couplings with organometallic reagents[4,5,6] and organohalides[7,8,9] have been recently reported (Figure 1a), significantly expanding the scope of traditional cross-coupling reactions. A number of these strategies involves the use of visible light photoredox catalysis,[10] which is a versatile manifold to perform radical reactions under mild conditions[11,12] with established potential in synthesis.[13,14] Despite these breakthroughs, one of the coupling partners involved in the decarboxylative cross-coupling reactions mentioned above carries a non-native handle, such as an organohalide or organozinc, not always accessible when complex fragments are involved. Thus, new strategies to assemble complex structures involving only native functionalities would complement current cross-coupling methodologies.

Inspired by recent elegant works describing metal-catalysed multicomponent conjunctive cross-couplings[15,16] (Figure 1b), we envisioned a strategy that allows to assemble coupling partners, both carrying functionalities available in nature, through a readily available linking reagent **2** (Figure 1c). We speculated that, if sufficiently robust and chemoselective, such a methodology would allow the cross-coupling of complex natural products and bioactive molecules in a native form, without exogeneous functional groups and no (or very limited) use of protecting groups. Furthermore, if the geometry of adducts **4** could be defined by the user, an additional structural control would be available, important to define chemical properties.

Herein, we describe the realisation of the process described above, through the development of a transition metal-free conjunctive olefination. The process allows to cross-couple complex molecular scaffolds carrying carboxylic acids and aldehydes, native handles in natural products and bioactive molecules,[17] or easily accessible from redox reactivity of other common native functionalities. The chemistry links the complex coupling partners by introducing a synthetically versatile alkenyl linchpin with user-defined *Z* or *E* configuration.

Results and discussion

Design plan. In our process design – depicted in Figure 1c – we envisioned to integrate the ionic reactivity of the Wittig reaction[18,19,20] into a photoredox radical manifold.[11,12] The merger of these two fundamental processes is based upon our hypothesis that commercially available vinyl phosphonium salt **2**,[21] originally reported by Schweizer in tandem nucleophile addition/olefination reactions,[22,23,24] would resemble the photoredox reactivity of simple acrylates[25] due the inductive electron-withdrawing effect of the cationic phosphorus atom.[26] Therefore, nucleophilic radicals **6**[27] - generated from carboxylic acids **1**[10] – would react with **2**,[28,29] to afford radical cation **7**. We then reasoned that by a careful choice of the redox properties of the photoredox catalyst, the radical addition step mentioned above could be coupled with a single electron transfer (SET) event to reduce radical cation **7**, generating reactive ylide **8** *in-situ*. This sequence, featuring an ylide generation through SET, opens a route for the conjunctive olefination of building blocks **1**, **2** and **3** to afford adduct *Z*-**4** through a radical-polar crossover[30,31] process. While a photoredox phosphorus-mediated olefination has been recently reported,[32] the process above, merging photoredox catalysis with the Wittig reaction for a conjunctive process, is unprecedented.

Finally, a user-triggered *in-situ* visible light-induced photoisomerisation was developed to provide access to *E*-**4**, enhancing the potential of the conjunctive process described above by allowing access to both the two isomers of the products from identical reaction precursors (Figure 1c – bottom right).

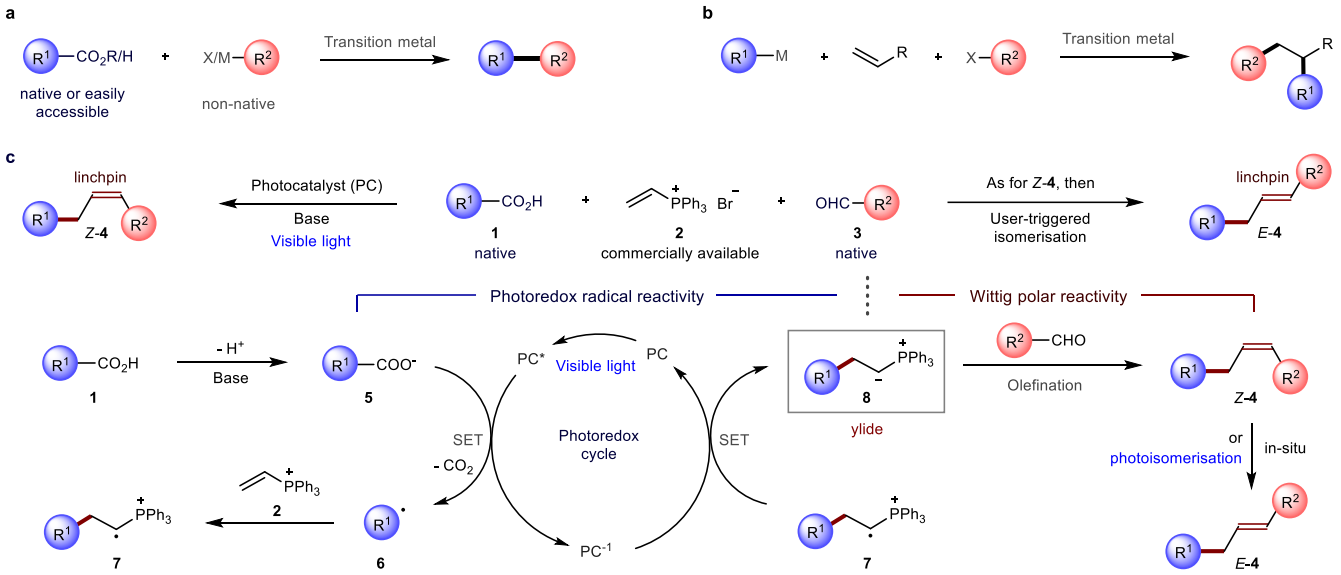


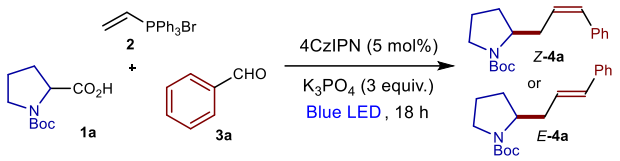
Figure 1 | Conceptual design of the process. a, Reaction scheme of a general decarboxylative cross-coupling. Functional groups not occurring in naturally recurring molecules are generally involved. M: metal X: halogen. **b**, Reaction scheme of a general multicomponent conjunctive cross-coupling: an unsaturated reagent is used to conjoin two partners. **c**, This work: design plan for a conjunctive olefination coupling between aldehydes and carboxylic acids through the merger of photoredox catalysis with the Wittig reaction. The process allows the assembly of complex molecules and selective access to both the *E*/*Z* alkene stereoisomers.

Method optimization. Optimisation studies were carried out by exploring the reaction between *N-tert*-butoxycarbonyl (Boc) proline **1a**, commercially available vinyl triphenyl phosphonium bromide **2** and benzaldehyde **3a**, using 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN)[33] as organic photoredox catalyst and potassium phosphate as base (Table 1). By exposing a dimethylformamide (DMF) mixture of the components to visible light irradiation at 20 °C, only traces of the desired product **4a** were detected (entry 1). However, irradiation of the same mixture for 2 hours at 20 °C, followed by heating at 60°C for 16 hours, led to **4a** in promising 68% yield and 5:1 *Z*/*E* (entry 2), thus suggesting that the olefination process requires mild heating to occur. Results were improved by irradiating the mixture in a minimum amount of DMF for 2 hours, followed by addition of tetrahydrofuran (THF) to reach a composition THF/DMF 9:1 and heating up to 60°C (entry 3). A standard chromatographic purification allowed the isolation of *Z*-**4a** in *Z*/*E* >20:1, with minimum loss in total yield (entry 3, in parenthesis).

We next looked at finding suitable reaction conditions to *in-situ* isomerise the product *Z*-**4a** to its opposite *E* stereoisomer *E*-**4a**. While examples of photocatalytic visible light mediated $E \rightarrow Z$ isomerisations have been recently reported[34,35] and employed in synthesis,[36] the application of analogous strategies for $Z \rightarrow E$ isomerisations has not been previously described. It is well-known that UV irradiation of olefins in the presence of diphenyl disulfide (Ph_2S_2) leads to alkene isomerisation to form the most thermodynamically favoured *E*-isomer.[37,38] The process is mediated by the generation of thiyl radicals by S-S bond photolysis, followed by addition-elimination to the alkene.[39] As common photoredox catalysts have been recently observed to sensitise disulfide bond cleavage,[40] we reasoned that the catalyst already present in the mixture could promote the desired isomerisation process under visible light irradiation. Indeed, by simply adding 1 equivalent of Ph_2S_2 to the reaction mixture and irradiating with blue light for 1 hour, *E*-**4a** was exclusively detected and isolated in 71% yield (entry 4), comparable to its *Z* isomer.

According to the radical and photochemical nature of the process, performing the conjunctive olefination in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxyl free radical (TEMPO), or in the absence of irradiation leads to complete inhibition of the reactivity (entries 5 and 6).

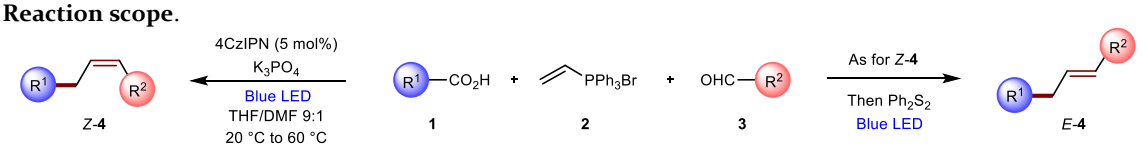
Table 1 | Optimisation studies.



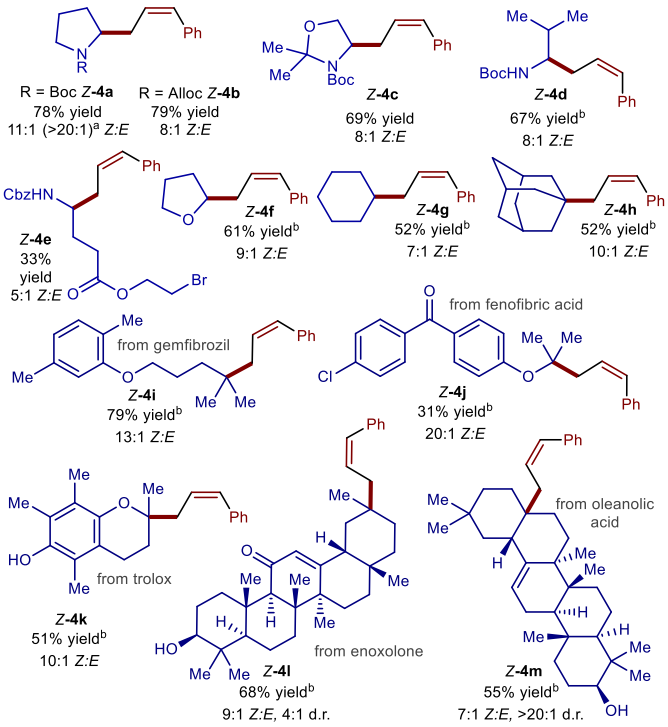
Entry[a]	Solvent	T (°C)	yield (%), *Z*/*E*[b]
1	DMF	20	traces
2[c]	DMF	20 to 60	68, 5:1
3[c,d]	THF/DMF 9:1	20 to 60	91, 11:1 (78, >20:1)
4[c,d,e]	THF/DMF 9:1	20 to 60	78, <1:20 (71, <1:20)
5[c,d,f]	THF/DMF 9:1	20 to 60	traces
6[g]	THF/DMF 9:1	20 to 60	traces

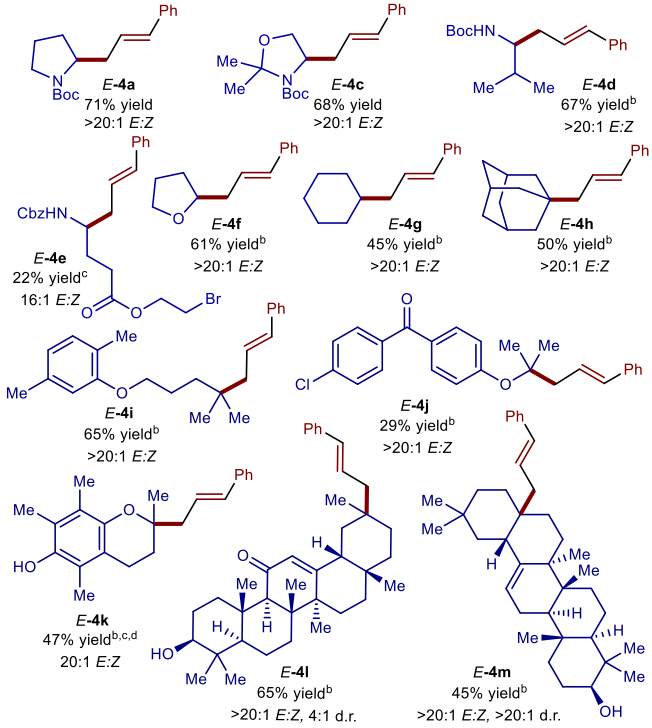
[a] All reactions carried out in a 0.2 mmol scale, using **1** (1 equiv.), **2** (1.2 equiv.) and **3** (3 equiv.), under a 40 W Blue LED light irradiation. When mixture of solvents is used, the composition is intended as after THF addition to the initial DMF mixture. [b] Yield and *Z*/*E* ratio obtained by NMR analysis using CH_2Br_2 as internal standard, in parenthesis yields and *Z*/*E* ratios of isolated material. [c] Irradiation carried out for 2 h at 20°C, followed by heating at 60°C for 16 h. [d] Irradiation carried out in sole DMF, with THF added to the vessel prior to heating. [e] After heating, Ph_2S_2 (1 equiv.) was added to the vessel and the mixture was irradiated with blue light for 1 h at 20 °C. [f] Reaction carried out in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxyl free radical (TEMPO), 1 equiv. [g] No irradiation.

Table 2 | Reaction scope.

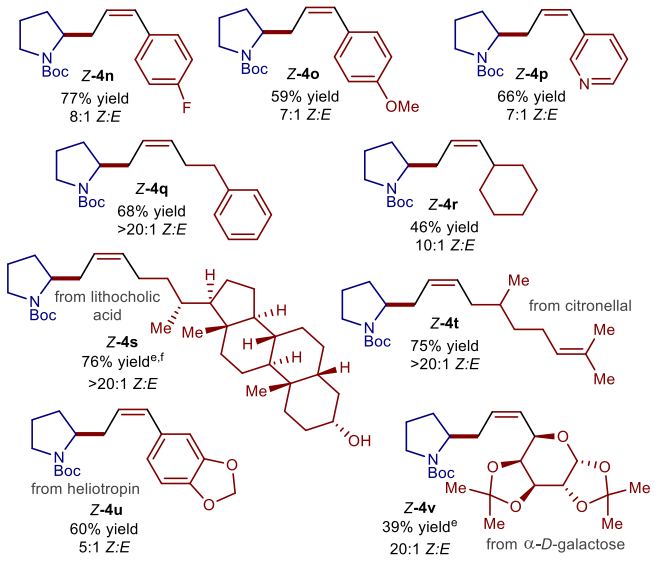


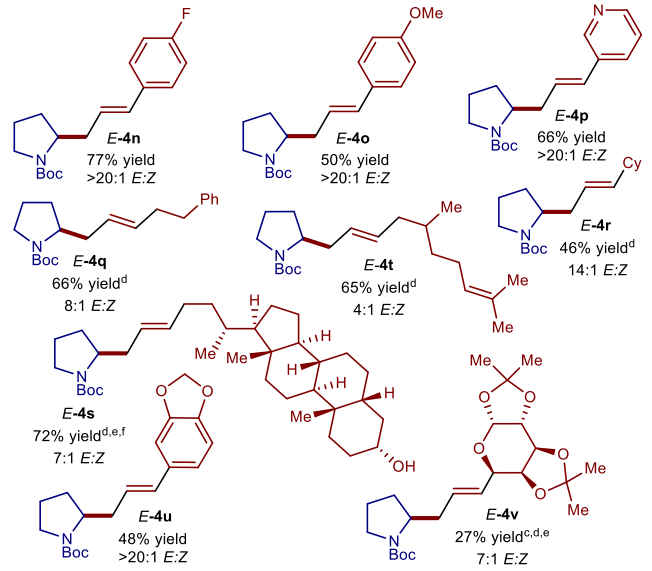
Scope of carboxylic acids:





Scope of aldehydes:





Reactions carried out in a 0.2 mmol scale, yields refer to isolated material, *Z*/*E* and d.r. values measured in crude mixtures by NMR or GC analysis, solvent composition reported as after THF addition to the initial DMF mixture. See section 3 of the Supplementary Information for full experimental details. Products **4s,t,v** are equimolar mixture of epimers on the pyrrolidine chiral centre. [a] *Z*/*E* ratio after a 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] 2 equiv. of Ph_2S_2 used. [e] Aldehyde **3** was used as limiting reagent. [f] 0.1 mmol scale. Boc: *N*-*tert*-butoxycarbonyl; Alloc: *N*-allyloxycarbonyl; Cbz: *N*-benzyloxycarbonyl; Cy: cyclohexyl

Scope of the method. We next investigated the scope of our transformation (Table 2). A number of model carboxylic acids reacts smoothly under our reaction conditions to afford products **4** in moderate to good yields and selectivities (*Z*-**4a** – *Z*-**4h**). Notably, both cyclic and linear *N*-protected amino acids are suitable reactants (*Z*-**4a** – *Z*-**4e**), showing that a carbamate NH bond does not hamper the reactivity. The process is tolerant to the presence of a synthetically versatile pendant bromide, challenging functionality in other traditional Wittig reactions or transition metal alkyl cross-coupling methodologies, and compound *Z*-**4e** could be obtained in moderate yield. Simple alkyl carboxylic acids, generally more difficult to oxidise than the substrates presented above, are suitable reactants (*Z*-**4f** - *Z*-**4h** and *vide infra*), although with such reagents addition of aldehyde **3** after the irradiation and *in-situ* solvent exchange to sole THF was found to significantly improve the results (see sections 3.3 and 3.4 of the Supplementary Information for details). As a limitation of this process, the use of primary carboxylic acids leads to only trace amounts of the desired products. We then tested our methodology in the derivatisation of bioactive compounds and complex natural products containing the carboxylic acid functional group. Functionalisation of gemfibrozil, a medication used to treat abnormal blood lipid levels,[41] leads to derivative *Z*-**4i** in high yield and *Z*-selectivity. Our protocol is suitable even on complex substrates carrying reactive ketone functionalities which may interfere with the desired Wittig olefination, so derivatisation of fenofibric acid led to *Z*-**4j** in excellent *Z*-selectivity and moderate yield, with the remaining mass balance accounting to an undesired proto-dechlorination process. Noteworthy, hydroxyl functionalities are compatible with the reaction, and bioactive molecules trolox, enoxolone and oleanolic acid smoothly undergo the desired process, without the need of cumbersome functional group protection/deprotection sequences (*Z*-**4k** – *Z*-**4m**). The high yield obtained in *Z*-**4l** from unmodified enoxolone - a natural product carrying multiple functionalities, including an alcohol and a carbonyl compound - corroborates the significant functional group compatibility of the process. By following our *in-situ* isomerisation protocol, *E*-**4a** – *E*-**4m** can be accessed with excellent *E*-stereoselectivity, regardless the complexity of the starting materials, and the products were isolated in yields that are comparable to the corresponding *Z*-products. Compounds *E*-**4e** and *E*-**4k** were found to isomerise incompletely under standard conditions but were obtained with excellent *E*-stereoselectivity by using a 370 nm LED (see results presented in section 3.6 of the Supplementary Information for more details).

We then tested our methodology on a number of model aldehydes. Aromatic aldehydes carrying electron-withdrawing, electron-donating groups and Lewis basic heteroaromatics were found to react smoothly, with *Z*-selectivities ranging between 7:1 and 11:1 (*Z*-**4a**; *Z*-**4n** – *Z*-**4p**). Less reactive aliphatic aldehydes are also suitable substrates, generally leading to high to excellent *Z*-selectivity (*Z*-**4q** – *Z*-**4r** and *vide infra*). We then focussed on testing our methodology on aldehydes derived from natural products and complex biomolecules. When valuable, aldehydes can be successfully employed as limiting reagent. Litocholic acid-derived aldehyde (easily accessible from litocholic acid, see section 2.3 of the Supplementary Information) is promptly converted to *Z*-**4s** in high yield and full *Z*-selectivity. Remarkably, even in this case, the presence of a free hydroxyl group in the complex aldehydic scaffold does not hamper our desired reactivity. The terpenoid citronellal, carrying an alkene functionality that may perturb radical reactivity, smoothly undergo our process leading to product *Z*-**4t** in good yield and full *Z*-selectivity. Galactose derivative *Z*-**4v** was obtained in moderate yield and excellent *Z*-selectivity, showing that carbohydrate scaffolds successfully undergo our process. Natural fragrance heliotropin is also a suitable substrate, leading to derivative *Z*-**4u** in good yield and moderate stereoselectivity. By applying our *E*-selective protocol, the products obtained from all aromatic aldehydes (*E*-**4n** – *E*-**4p**) – including heliotropin-derived product *E*-**4u** – were obtained with full *E*-selectivity and comparable yields to the corresponding *Z*-products. *E*-isomers of products obtained from aliphatic aldehydes (i.e., *E*-**4q** - *E*-**4t**; *E*-**4v**), including complex molecules carrying multiple alkenes or free hydroxyl groups, could also be obtained through our *E*-selective protocol, albeit in reduced 4:1 to 14:1 *E*-*Z* ratio and requiring 2 equiv. of Ph_2S_2 and increased irradiation time (see results presented in section 3.6 of the Supplementary Information for more details).

The scalability of the process was tested by performing the reaction in multigram scale (Figure 2), without detrimental effects on the observed efficiency or selectivity (see section 3.7 of the Supplementary Information).

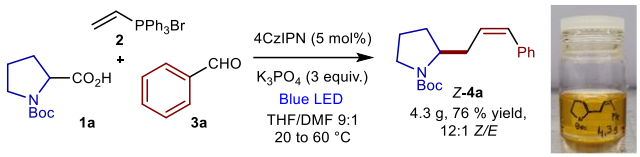


Figure 2 | Scale up studies. Reaction performed in batch in 20 mmol scale, no detrimental effect on the yield was observed by hundredfold scale increase.

Mechanistic investigations. The remarkable functional group tolerance of this reaction, including to alcohol functionalities that may quench semi- and non-stabilised phosphonium ylides by proton transfer, prompted us to investigate the mechanism of this process. To this end, ^{31}P-NMR analysis of the reaction mixture immediately after irradiation at 20°C revealed one major peak corresponding to phosphonium salt **9** (Figure 3a and Supplementary Figure S_3). Subjection of isolated **9** to our reaction conditions at 60 °C in the presence of benzaldehyde **3a** leads to *Z*-**4a** in 80% yield and 10:1 *Z*:*E* selectivity (Figure 3b), comparable to the results depicted in Table 2, *Z*-**4a**.

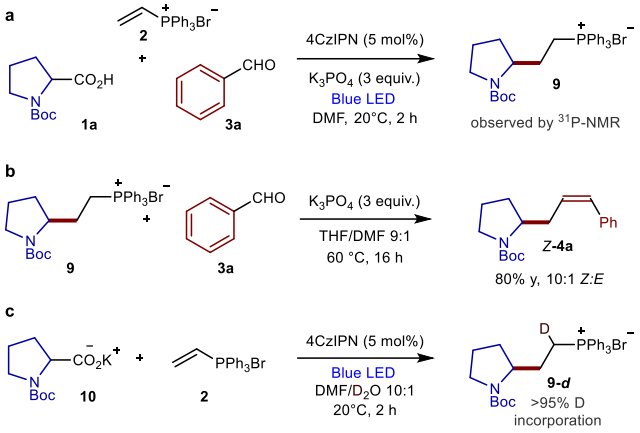


Figure 3 | Experiments for mechanistic insights. a, ^{31}P-NMR analysis of the photochemical reaction carried out at ambient temperature, phosphonium **9** was observed. **b**, Subjection of phosphonium **9** to the reaction conditions at 60 °C, *Z*-**4a** was observed. Experiments **a** and **b** suggest **9** as intermediate of the conjunctive olefination. **c**, Deuterium trapping experiment. Full deuteration was observed, confirming the occurrence of a SET process on an intermediate phosphonium radical cation (see also Figure 1).

The outcome of these experiments suggests that under our reaction conditions the newly generated ylide is involved in an acid-base equilibrium (with the conjugate acid of the phosphate base used) which is shifted towards the corresponding phosphonium salt. Upon moderate heating, the ylide in solution dynamically reacts with aldehydes **3** to afford products **4** in high yield. Finally, in accordance with the SET reduction of phosphonium radical cation **7** depicted in Figure 1c, irradiation of a base-free solution of **10**, vinyl phosphonium **2** and photocatalyst 4CzIPN in the presence of D_2O led to **9-*d*** with full deuterium incorporation (Figure 3c and see Supplementary Figure S4).

Conclusions. In conclusion, we developed a conjunctive olefination reaction based upon a radical-polar crossover process elicited by the merger of photoredox catalysis with the Wittig reaction. The chemistry offers rapid and practical access to complex olefin fragments with programmable *E* - *Z* stereochemistry and remarkable chemoselectivity. We anticipate that the ylide radical-polar reactivity, introduced by this report, will open new opportunities in synthesis.

References

1. Schreiber, S. L. Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery. *Science* **287**, 1964–1969 (2000).
2. de Meijere, A. & Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions, 2nd Edition* (Wiley-VCH, Weinheim, 2004).
3. Schwarz, J. & König, B. Decarboxylative reactions with and without light – a comparison. *Green Chem.* **20**, 323–361 (2018).
4. Qin, T. *et al.* A general alkyl-alkyl cross-coupling enabled by redox-active esters and alkylzinc reagents. *Science* **352**, 801–805 (2016).
5. Edwards, J. T. *et al.* Decarboxylative alkenylation. *Nature* **545**, 213–218 (2017).
6. Cornella, J. *et al.* Practical Ni-Catalyzed Aryl–Alkyl Cross-Coupling of Secondary Redox-Active Esters. *J. Am. Chem. Soc.* **138**, 2174–2177 (2016).
7. Zuo, Z. *et al.* Merging photoredox with nickel catalysis: Coupling of α-carboxyl sp^3-carbons with aryl halides. *Science* **345**, 437–440 (2014).
8. Noble, A., McCarver, S. J. & MacMillan, D. W. C. Merging Photoredox and Nickel Catalysis: Decarboxylative Cross-Coupling of Carboxylic Acids with Vinyl Halides. *J. Am. Chem. Soc.* **137**, 624–627 (2015).
9. Johnston, C. P., Smith, R. T., Allmendinger, S. & MacMillan, D. W. C. Metallaphotoredox-catalysed sp3–sp3 cross-coupling of carboxylic acids with alkyl halides. *Nature* **536**, 322-325 (2016).
10. Jin, Y. & Fu, H. Visible-Light Photoredox Decarboxylative Couplings. *Asian J. Org. Chem.* **6**, 368–385 (2017).
11. Prier, C. K., Rankic, D. A. & MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **113**, 5322–5363 (2013).
12. Shaw, M. H., Twilton, J. & MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **81**, 6898–6926 (2016).
13. Pitre, S. P., Weires, N. A. & Overman, L. E. Forging C(sp3)–C(sp3) Bonds with Carbon-Centered Radicals in the Synthesis of Complex Molecules. *J. Am. Chem. Soc.* **141**, 2800–2813 (2019).
14. Nicholls, T. P., Leonori, D. & Bissember, A. C. Applications of visible light photoredox catalysis to the synthesis of natural products and related compounds. *Nat. Prod. Rep.* **33**, 1248–1254 (2016).
15. Zhang, L. *et al.* Catalytic conjunctive cross-coupling enabled by metal-induced metallate rearrangement. *Science* **351**, 70–74 (2016).
16. Derosa, J., Apolinar, O., Kang, T., Tran, V. T. & Engle, K. M. Recent developments in nickel-catalyzed intermolecular dicarbofunctionalization of alkenes. *Chem. Sci.* **11**, 4287–4296 (2020).
17. Ertl, P., Altmann, E. & McKenna, J. M. The Most Common Functional Groups in Bioactive Molecules and How Their Popularity Has Evolved over Time. *J. Med. Chem.* **63**, 8408–8418 (2020).
18. Wittig, G. Nobel lecture: From Diyls to my idyll https://www.nobelprize.org/uploads/2018/06/wittig-lecture.pdf (1979).
19. Maryanoff, B. E. & Reitz, A. B. The Wittig olefination reaction and modifications involving phosphoryl-stabilized carbanions. Stereochemistry, mechanism, and selected synthetic aspects. *Chem. Rev.* **89**, 863–927 (1989).
20. Nicolaou, K. C., Härter, M. W., Gunzner, J. L. & Nadin, A. The Wittig and Related Reactions in Natural Product Synthesis. *Liebigs Ann.* **1997**, 1283–1301 (1997).
21. Kuźnik, A., Mazurkiewicz, R. & Fryczkowska, B. Vinylphosphonium and 2-aminovinylphosphonium salts – preparation and applications in organic synthesis. *Beilstein J. Org. Chem.* **13**, 2710–2738 (2017).
22. Schweizer, E. E. & Bach, R. D. Phosphonium Salts. II. 2-Bromophenetole and Triphenylphosphorus as Novel Phosphonioethylation Precursors. *J. Org. Chem.* **29**, 1746–1751 (1964).
23. Scheweizer, E. E. Reactions of Phosphorus Compounds. III. A New General Ring Synthesis from Vinyltriphenylphosphonium Bromide. *J. Am. Chem. Soc.* **86**, 2744 (1964).
24. Schweizer, E. E. & O'Neill, G. J. Reactions of Phosphorus Compounds. VI. A General Synthesis of Cycloalkenes. *J. Org. Chem.* **30**, 2082–2083 (1965).
25. Chu, L., Ohta, C., Zuo, Z. & MacMillan, D. W. C. Carboxylic Acids as A Traceless Activation Group for Conjugate Additions: A Three-Step Synthesis of (±)-Pregabalin. *J. Am. Chem. Soc.* **136**, 10886–10889 (2014).
26. Hansch, C., Leo, A. & Taft, R. W. A survey of Hammett substituent constants and resonance and field parameters. *Chem. Rev.* **91**, 165–195 (1991).
27. Giese, B. Formation of CC Bonds by Addition of Free Radicals to Alkenes. *Angew. Chem. Int. Ed. Engl.* **22**, 753–764 (1983).
28. Barton, D. H. R., Togo, H. & Zard, S. Z. Radical addition to vinyl sulphones and vinyl phosphonium salts. *Tetrahedron Lett.* **26**, 6349–6352 (1985).
29. Barton, D. H. R. *et al.* Decarboxylative radical addition to vinylsulphones and vinylphosphonium bromide: Some further novel transformations of geminal (pyridine-2-thiyl) phenylsulphones. *Tetrahedron* **47**, 7091–7108 (1991).
30. Wiles, R. J. & Molander, G. A. Photoredox-Mediated Net-Neutral Radical/Polar Crossover Reactions. *Isr. J. Chem.* **60**, 281–293 (2020).

31. Pitzer, L., Schwarz, J. L. & Glorius, F. Reductive radical-polar crossover: traditional electrophiles in modern radical reactions. *Chem. Sci.* **10**, 8285–8291 (2019).
32. Jiang, M., Yang, H., Lefebvre, Q., Su, J. & Fu, H. Olefination of Alkyl Halides with Aldehydes by Merging Visible-Light Photoredox Catalysis and Organophosphorus Chemistry. *iScience* **6**, 102–113 (2018).
33. Shang, T.-Y., Lu, L.-H., Cao, Z., Liu, Y., He, W.-M. & Yu, B. Recent advances of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) in photocatalytic transformations. *Chem. Commun.* **55**, 5408–5419 (2019).
34. Singh, K., Staig, S. J. & Weaver, J. D. Facile Synthesis of Z-Alkenes via Uphill Catalysis. *J. Am. Chem. Soc.* **136**, 5275–5278 (2014).
35. Metternich, J. B. & Gilmour, R. A Bio-Inspired, Catalytic E → Z Isomerization of Activated Olefins. *J. Am. Chem. Soc.* **137**, 11254–11257 (2015).
36. Molloy, J. J., Schäfer, M., Wienhold, M., Morack, T., Daniliuc, C. G. & Gilmour, R. Boron-enabled geometric isomerization of alkenes via selective energy-transfer catalysis. *Science* **369**, 302–306 (2020).
37. Golub, M. A. The Radiation Induced cis-trans Isomerization of Polybutadiene. II *J. Am. Chem. Soc.* **81**, 54–58 (1959).
38. Moussebois, C. & Dale, J. A method of cis,trans-isomerisation of non-conjugated olefins without double-bond migration. *J. Chem. Soc. C* 260–264 (1966).
39. Seely, G. R. Kinetics of the Photoisomerization of Polybutadiene. *J. Am. Chem. Soc.* **84**, 4404–4407 (1962).
40. Teders, M., Henkel, C., Anhäuser, L., Strieth-Kalthoff, F., Gómez-Suárez, A., Kleinmans, R., Kahnt, A., Rentmeister, A., Guldi, D. & Glorius, F. The energy-transfer-enabled biocompatible disulfide–ene reaction. *Nat. Chem.* **10**, 981–988 (2018).
41. Roy, A. & Pahan, K. Gemfibrozil, stretching arms beyond lipid lowering. *Immunopharmacol. Immunotoxicol.* **31**, 339–351 (2009).

Acknowledgements

M.S. thanks the University of Nottingham and the Green Chemicals Beacon of Excellence for a Nottingham Research Fellowship. D.F. thanks the School of Chemistry, University of Nottingham for a doctoral fellowship. We thank Prof. Ross Denton and Prof. Paolo Melchiorre for stimulating discussions and Dr. Martina Piccinno for proofreading this manuscript.

Author contributions

M.S. conceived and discovered the reactivity, led the project and prepared the manuscript with contributions from the other author. D.F. carried out most of the experimental work within the optimisation studies and the exploration of the reaction scope.

Competing interests

The authors declare no competing interests.

Figure Captions/Tables Legends

Figure 1 | Conceptual design of the process. a, Reaction scheme of a general decarboxylative cross-coupling. Functional groups not occurring in naturally recurring molecules are generally involved. M: metal X: halogen. **b**, Reaction scheme of a general multicomponent conjunctive cross-coupling: an unsaturated reagent is used to conjoin two partners. **c**, This work: design plan for a conjunctive olefination coupling between aldehydes and carboxylic acids through the merger of photoredox catalysis with the Wittig reaction. The process allows the assembly of complex molecules and selective access to both the *E*/*Z* alkene stereoisomers.

Table 1 | Optimisation studies.

[a] All reactions carried out in a 0.2 mmol scale, using **1** (1 equiv.), **2** (1.2 equiv.) and **3** (3 equiv.), under a 40 W Blue LED light irradiation. When mixture of solvents is used, the composition is intended as after THF addition to the initial DMF mixture. [b] Yield and *Z*/*E* ratio obtained by NMR analysis using CH_2Br_2 as internal standard, in parenthesis yields and *Z*/*E* ratios of isolated material. [c] Irradiation carried out for 2 h at 20°C, followed by heating at 60°C for 16 h. [d] Irradiation carried out in sole DMF, with THF added to the vessel prior to heating. [e] After heating, Ph_2S_2 (1 equiv.) was added to the vessel and the mixture was irradiated with blue light for 1 h at 20 °C. [f] Reaction carried out in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxyl free radical (TEMPO), 1 equiv. [g] No irradiation.

Table 2 | Reaction scope.

Reactions carried out in a 0.2 mmol scale, yields refer to isolated material, *Z*/*E* and d.r. values measured in crude mixtures by NMR or GC analysis, solvent composition reported as after THF addition to the initial DMF mixture. See section 3 of the Supplementary Information for full experimental details. Products **4s,t,v** are equimolar mixture of epimers on the pyrrolidine chiral centre. [a] *Z*/*E* ratio after a 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] 2 equiv. of Ph_2S_2 used. [e] Aldehyde **3** was used as limiting reagent. [f] 0.1 mmol scale. Boc: *N*-*tert*-butoxycarbonyl; Alloc: *N*-allyloxycarbonyl; Cbz: *N*-benzyloxycarbonyl; Cy: cyclohexyl

Figure 2 | Scale up studies. Reaction performed in batch in 20 mmol scale, no detrimental effect on the yield was observed by hundredfold scale increase.

Figure 3 | Experiments for mechanistic insights. a, ^{31}P-NMR analysis of the photochemical reaction carried out at ambient temperature, phosphonium **9** was observed. **b**, Subjection of phosphonium **9** to the reaction conditions at 60 °C, *Z*-**4a** was observed. Experiments **a** and **b** suggest **9** as intermediate of the conjunctive olefination. **c**, Deuterium trapping experiment. Full deuteration was observed, confirming the occurrence of a SET process on an intermediate phosphonium radical cation (see also Figure 1).

Methods

All reactions were carried out in oven-dried glassware under argon atmosphere using standard Schlenk manifold technique and dry solvents. Solvents were degassed by argon sparging when needed. Liquid aldehydes were distilled prior to use, other reagents were purchased at the highest commercial quality and were used without further purification, unless otherwise stated. Yields refer to isolated pure materials after chromatographic purification.

General procedure for the conjunctive olefination. 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 in a Schlenk tube. The atmosphere was exchanged to argon, and degassed dry DMF (200 µL) and aldehyde **3** (3 equiv.; 0.6 mmol) were introduced *via* syringe. The vessel was sealed and irradiated with a 40 W blue LED at 20 °C for 2 hours under moderate stirring. Dry THF (1.8 mL) was then introduced through a syringe. The vessel was sealed again and heated at 60°C for 16 h under vigorous stirring without irradiation. The mixture was then filtered through a thin layer of celite/silica, eluting 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**.

For selective access to the opposite isomer *E*-**4**, the procedure was followed as above, except that after heating at 60°C, diphenyl disulfide (1 equiv.; 0.2 mmol; 43.7 mg) was added to the reaction vessel and the reaction mixture was irradiated with a 40 W blue LED at 20 °C for 1 hour under vigorous stirring. The compound was then isolated following the procedure described above.

For full experimental details, including procedures for all reactions, variations from the general procedure above and

characterization of all new compounds, see section 3 of the Supplementary Information.

Data Availability

The data supporting the findings of this study are available within the paper and its Supplementary Information.