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Photocatalytic deoxygenative *Z*-selective olefination of aliphatic alcohols

Sai Rohini Narayanan Kolusu [ORCID], Irene Sánchez-Sordo [ORCID], Carla Aira-Rodríguez [ORCID], Emanuele Azzi [ORCID] & Manuel Nappi [ORCID] [✉]

Alcohols are one of the most abundant functional groups in commercially available materials and biologically active compounds. Herein, we report a metal-free photocatalytic method for the deoxygenative *Z*-selective olefination of aliphatic alcohols. Key to this methodology is the radical olefination and isomerization of unstabilized open-shell species generated in situ by a catalytic reductive scission of benzoate esters. These processes are simultaneously orchestrated by a single phenothiazine photocatalyst via singlet and triplet excited states. Our protocol is distinguished by its wide substrate scope and broad applicability, even in the context of pharmaceuticals and saccharides. Given the mild and water-compatible conditions, our chemistry can also be utilized to functionalize DNA headpieces for DELs applications.

Over the past few decades, metal-catalysed cross-coupling reactions have revolutionized the field of synthetic chemistry, enabling the rapid construction of complex molecular architectures from simple organic materials, as well as the late-stage functionalization of bioactive compounds and advanced synthetic intermediates[1–4]. While a wide range of cross-couplings protocols are available for the synthesis of unsaturated compounds from sp²-hybridized coupling partners[5], significant limitations remain with respect to the formation of $C(sp^2)–C(sp^3)$ and $C(sp^3)–C(sp^3)$ bonds[6], with alkyl halides[7] and alkyl-organometallics[8] being the most commonly employed sp³-hybridized starting materials.

The advent of metallaphotoredox catalysis[9–11], cross-electrophile coupling reactions[12] and synthetic organic electrochemistry[13] has enabled the use of carboxylic acids and alcohols as sp³-hybridized coupling partners. Especially attractive are the deoxygenative $C(sp^2)–C(sp^3)$ cross-coupling reactions of alcohols, the latter being the most abundant functional groups in commercially available materials and biologically active compounds[14]. While several outstanding methods have been developed for the coupling of aliphatic alcohols and heteroarenes[15–21], only few examples of deoxygenative olefination have been reported[22–24]. Notably, all the methodologies provide the thermodynamically favoured *E* isomer as the sole product. Given the ubiquity of *Z*-alkenes in synthetic and biologically relevant molecules, and the sporadic examples of *Z*-selective olefinations from native and abundant functional groups[25–27], a cross-coupling reaction that can directly provide *Z*-olefins using aliphatic
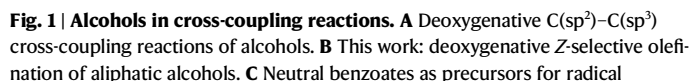
alcohols as sp³-hybridized starting materials is highly desirable yet elusive.

Herein, we present a mild photocatalytic method for the deoxygenative *Z*-selective olefination of benzoate esters derived from aliphatic alcohols (Fig. 1B). Feedstock and complex aliphatic alcohols can be readily converted into value-added olefin products in high yields, even in the case of pharmaceuticals and saccharides. Given the mild reaction conditions and compatibility with dilute aqueous media, our chemistry can also be utilized to functionalize DNA headpieces for applications in DNA-encoded libraries synthesis.

Results

Design plan

At the outset of our investigation, we envisioned a photocatalytic system that would simultaneously orchestrate: i) the activation of aliphatic alcohols to liberate unstabilized radicals, ii) the radical functionalization of alkenyl species and iii) the in-situ *E* to *Z* isomerization of the final olefin product. We recognized that the main challenge in our design plan is the merger of a general catalytic method that allows the generation of unstabilized radicals from aliphatic alcohols and the alkenylation/isomerization processes. We identified the reductive fragmentation of readily accessible benzoates as ideal compatible activation mode (Fig. 1C). Indeed, previous works have established that neutral benzoylated alcohols can undergo $C(sp^3)–O$ bond cleavage upon single electron reduction, releasing

Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Departamento de Química Orgánica, Universidade de Santiago de Compostela, Rúa de Jenaro de la Fuente, s/n, 15705 Santiago de Compostela, A Coruña, Spain. [✉]e-mail: manuel.nappi@usc.es

Fig. 1 | Alcohols in cross-coupling reactions. A Deoxygenative C(sp²)−C(sp³) cross-coupling reactions of alcohols. **B** This work: deoxygenative Z-selective olefination of aliphatic alcohols. **C** Neutral benzoates as precursors for radical functionalization reactions. **D** Design plan for the deoxygenative Z-selective olefination of alcohols. PC photocatalysis, FG functional group, PHT phenothiazine, SET single electron transfer, EnT energy transfer.

unstabilized alkyl radicals[28]. However, stoichiometric reductants[29,30], UV photosensitizers[31], or deeply reducing electrodes[32], in combination with elevated temperatures, were necessary to enable the reductive scission, due to the very low reduction potential of benzoate substrates ($E_{1/2}$(MeOBz/MeOBz•⁻) = −2.2 V vs SCE)[33] and slow mesolytic fragmentation. Recently, a mild procedure for the deoxygenation of benzoates was reported[34]. Nevertheless, the reaction still requires the use of a stoichiometric reductant (CO₂•⁻), which was generated in situ from formate by photoredox catalysis. Moreover, to the best of our knowledge, all reported methods for the reductive activation of neutral benzoates have been used only for the deoxygenation reaction, without further functionalization of the resulting alkyl radicals. Here, we proposed a photocatalytic system (Fig. 1D) where a phenothiazine (**5**) can directly perform the required electron reduction via the singlet excited state (**6**, $E_{1/2}$(PHT•⁺/PHT*) = −2.5 V vs SCE)[35,36]. We reasoned that an alkenyl boron species (**3**) would be the perfect coupling partner for our strategy: not only is it a source of the sp²-hybridized fragment[37–40], but can also form a Lewis acid-base complex (**4**) with the alcohol benzoates, increasing the kinetics of the challenging reductive β-scission (**8**)[34]. Subsequent radical addition (**9**) provides the corresponding benzyl radical (**10**), which is converted to carbocation **11** via a radical-polar crossover process by the oxidized phenothiazine (**7**), concomitantly restoring the ground state of the photocatalyst (**5**). Elimination of B(OR)₃ provides the thermodynamically favoured E-alkene **12**. Given the high triplet state energy of phenothiazine (~62 kcal/mol)[41], we anticipated that the photocatalyst would also promote in situ E to Z isomerization of the product

(E = 60.5 kcal/mol for E-propenylbenzene)[42] via an energy transfer mechanism, providing the desired Z-olefin **13** as a final product[43,44]. It is noteworthy that both the singlet and the triplet excited states of the phenothiazine would be active in our deoxygenative olefination, representing a rare example where a single photocatalyst promotes both SET and energy transfer events through different excited states[45].

Optimization studies

We began our investigation by evaluating the efficiency of alkyl radical formation from alcohol benzoate **14** with an N-phenylphenothiazine photocatalyst **16**, in the presence of γ-terpinene (as a H atom source) and DMSO under 390 nm purple light irradiation (Fig. 2A).

Pleasingly, deoxygenated product **15** was obtained in 25% yield, confirming that phenothiazine **16** is a matched reductant to reduce benzoate **14**. A fast screening of substituted phenothiazine derivatives (**17-20**) identified thioether **19** as the best photocatalyst, providing product **15** in a promising 41% yield, along with 58% of unreacted **14**. As expected, the slow mesolytic fragmentation for the generation of unstabilized radicals hampered the efficient activation of benzoate **14**, confirming the necessity of using a Lewis acid as an additive[34].

Encouraged by these preliminary results, we next evaluated our proposed deoxygenative Z-selective olefination of **14** using various styryl boronic acid derivatives (**22-24**) in the presence of catechol, phenothiazine **19** and DMSO under 390 nm purple light irradiation (Fig. 2B). Surprisingly, no conversion was observed when styryl boronic acid **22** was used (entry 1), while styryl trifluoroborate salt **24**
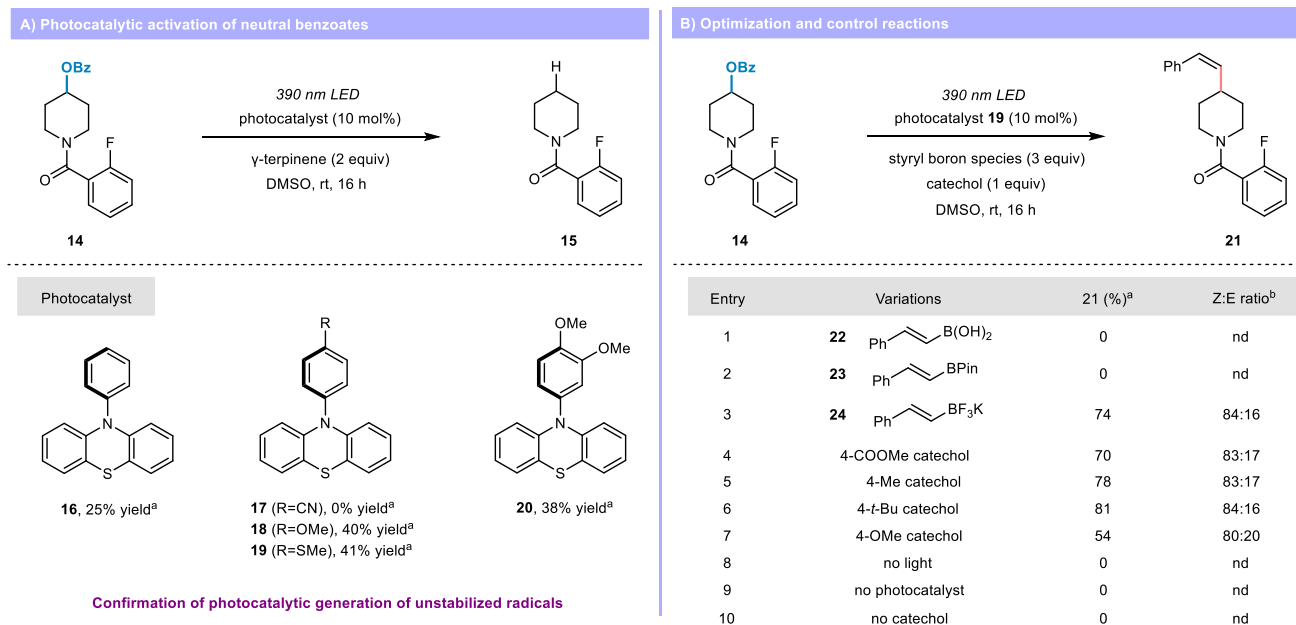
Fig. 2 | Optimization studies. A Screening of phenothiazine derivatives for the photocatalytic activation of neutral benzoates. Reaction conditions: **14** (0.1 mmol), γ-terpinene (0.2 mmol), photocatalyst (10 mol%) in DMSO (0.1 M) at rt for 16 h, 390 nm LED. **B** Optimization and control experiments for the deoxygenative Z-selective olefination of alcohols. Reaction conditions: **14** (0.1 mmol), styryl boron species (0.3 mmol), catechol (0.1 mmol), photocatalyst **19** (10 mol%) in DMSO (0.33 M) at rt for 16 h, 390 nm LED. [a] ^{1}H NMR yields using methyl 3,5-dinitrobenzoate as internal standard. [b] Z:E ratio determined by ^{1}H NMR. DMSO: dimethyl sulfoxide.

provided the desired olefination product **21** in 74% yield with a Z:E ratio of 84:16 (entry 3). Variation of the catechol electronics showed a moderate effect on the outcome of the deoxygenative coupling (entries 4-7). The best result was obtained with *t*-butyl catechol, affording olefin **21** in 81% yield and Z:E ratio = 84:16 (entry 6). The molecular structure of the photocatalyst is strictly correlated with the energy of its triplet state and therefore the photostationary state composition of the E to Z isomerization process. A final screening of phenothiazine derivatives confirmed that thioether **19** is the best choice in terms of yield and Z:E ratio (Table S4). As expected, other types of photocatalysts such as Ru(bpy)$_3$, Ir(ppy)$_3$ and 4-CzIPN failed to activate benzoate **14**. Lastly, additional control reactions demonstrated that purple light, photocatalyst and catechol are fundamental for the observed reactivity (entries 8–10), consistent with the mechanistic blueprint outlined in Fig. 1D.

Scope of the reaction

With optimal conditions in hand (entry 6, Fig. 2B), we next evaluated the alcohol scope for this transformation. As evident from the results compiled in Fig. 3, our photocatalytic deoxygenative Z-selective olefination could be conducted with a wide variety of benzoate esters derived from primary and secondary aliphatic alcohols. Cyclic (**25-42**) and acyclic (**43-53**) secondary alcohols were readily converted to the coupling products in good yields and Z:E ratio. Viable motifs in this transformation include amides (**25, 38**), sulfonamides (**26**), terminal alkynes (**28**), furans (**52**), thiophenes (**55**), indoles (**50**), triazoles (**53**), caffeine (**51**) and N-Boc protected amines (**29, 39, 41** and **42**).

Bicyclic and spirocyclic structures (**40-42**), acetate (**46**), *p*-OMe-benzoate (**48**) and unprotected tertiary alcohol (**49**) were well tolerated, delivering the corresponding Z-olefins in moderate yields to good yields. When a substrate containing both primary and secondary benzoates was exposed to our olefination protocol (**47**), we observed the selective formation of the product derived from the activation of the secondary OBz. Notably, we could apply our methodology for the activation of the simple primary alcohols such as ethanol (**57**) and methanol (**58**); the latter being a rare example of a methylation cross-coupling reaction. While the Z:E ratio of these last examples was not optimal, the product

mixtures were readily converted in situ to the corresponding E-olefins (please see section 4: "Photocatalytic Deoxygenative Z-selective olefination of aliphatic alcohols" in the SI). Remarkably, phenothiazine **19** was recovered in 98% yield from a scale-up experiment (**25**), demonstrating the robustness of our photocatalytic system.

Finally, we were delighted to find that this method is also amenable to a variety of biologically relevant molecules (**59-65**).

Substrates containing pharmaceutical cores such as etodolac (**59**) and oxaprozin (**60**) were converted into the desired Z-olefins with moderate to good yields. Notably, late-stage deoxygenative olefination of atorvastatin (**61**) proceeded smoothly, providing the coupled product in 84% yield. The hemiacetal at the anomeric carbon of commercially available furanose (**63**) could be activated to provide the coupled product with excellent diastereoselectivity. Similarly, a chiral secondary alcohol on the glucose core (**64**) and the primary alcohol on the galactose (**65**) were activated to generate the corresponding Z-olefins.

Pleasingly, our deoxygenative Z-selective olefination was found to be applicable with a wide array of alkenyl trifluoroborate salts (Fig. 4). Electron-rich and electron-poor substituents on the styryl moiety in the *para* (**66-70**) and *meta* (**71-73**) positions posed no problems, including the methyl group in *ortho* position (**74**). Heteroaromatics such as thiophene (**76**) and indole (**77**) were well tolerated, delivering the corresponding coupling products in moderate yields. Finally, a substrate containing the pharmaceutical core of gemfibrozil (**78**) was successfully coupled to obtain the desired Z-olefin.

Preliminary mechanistic studies

To gain mechanistic insight into the proposal detailed in Fig. 1D, we conducted a series of preliminary experiments summarized in Fig. 5. Stern–Volmer quenching studies confirmed the activation of benzoate **14** by phenothiazine photocatalyst **18**, showing a linear correlation between the amount of benzoate and the ratio I_0/I (Fig. 5A). When the standard reaction was conducted in the presence of 1,4-dinitrobenzene (E$_{red}$ = −0.64 V vs. SCE)[46,47], benzoate **14** was completely recovered, suggesting the single electron reduction of the ester in standard conditions. A radical-clock experiment using primary benzoate **79** furnished the coupled product **80**, demonstrating the open-shell nature of the
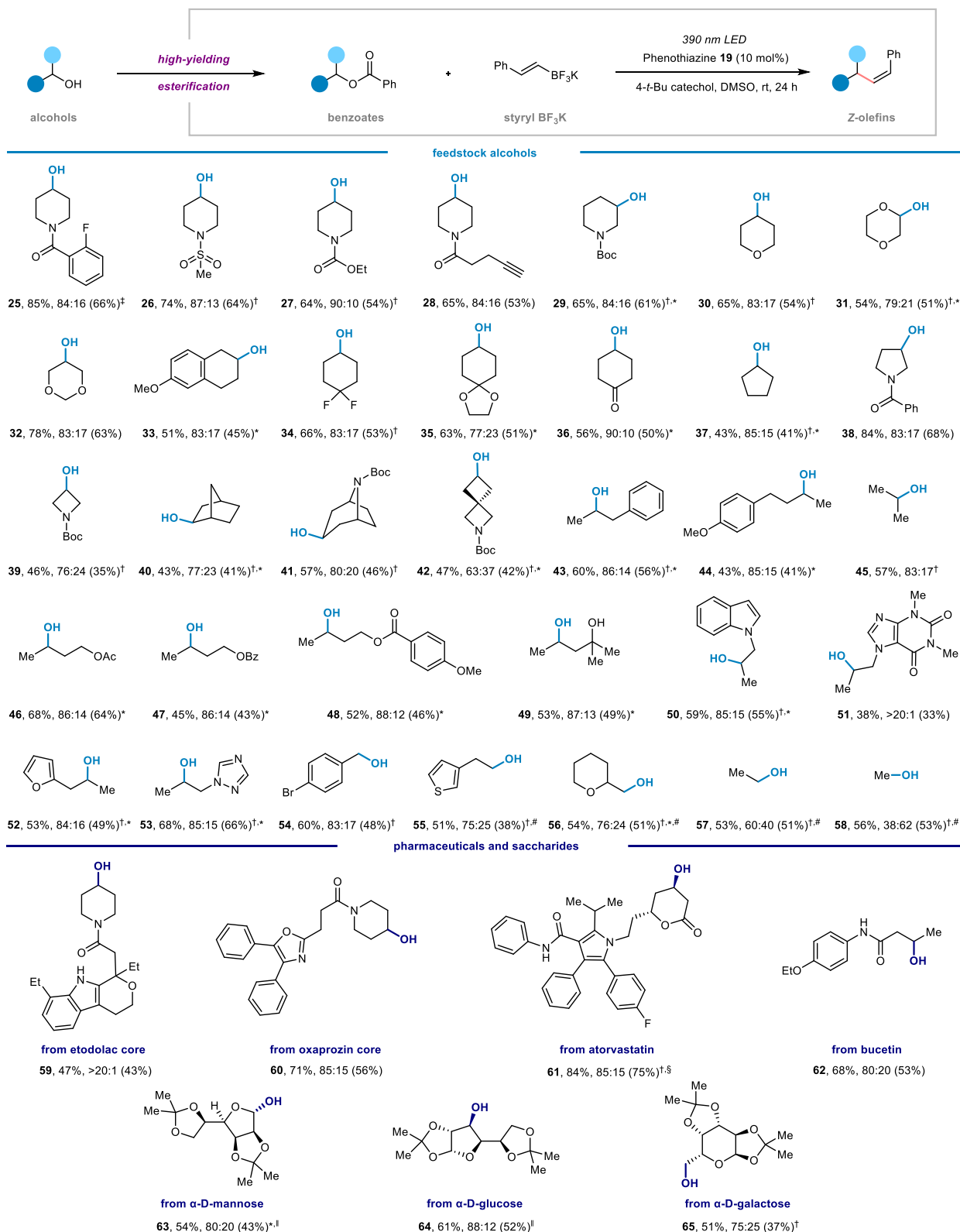
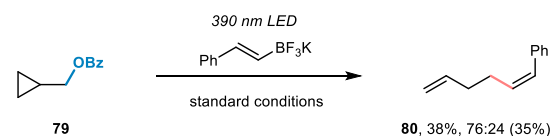**Fig. 3 | Aliphatic alcohols scope of the photocatalytic deoxygenative Z-selective olefination.** Reaction conditions as Fig. 2B (entry 6), 0.2 mmol scale. Yield and Z:E ratio determined by ¹H NMR using methyl 3,5-dinitrobenzoate as internal standard. In brackets isolated yields of Z-olefin, unless otherwise noted. All yields refer to the photocatalytic process only. ‡2 mmol scale. †Catechol is used instead of 4-t-Bu catechol, 16 h. *Isolated as mixture of isomers. #2 lamps. §dr = 1.6:1. ||dr > 20:1. DMSO: dimethyl sulfoxide.

Alkenyl BF₃K scope of the photocatalytic deoxygenative Z-selective olefination
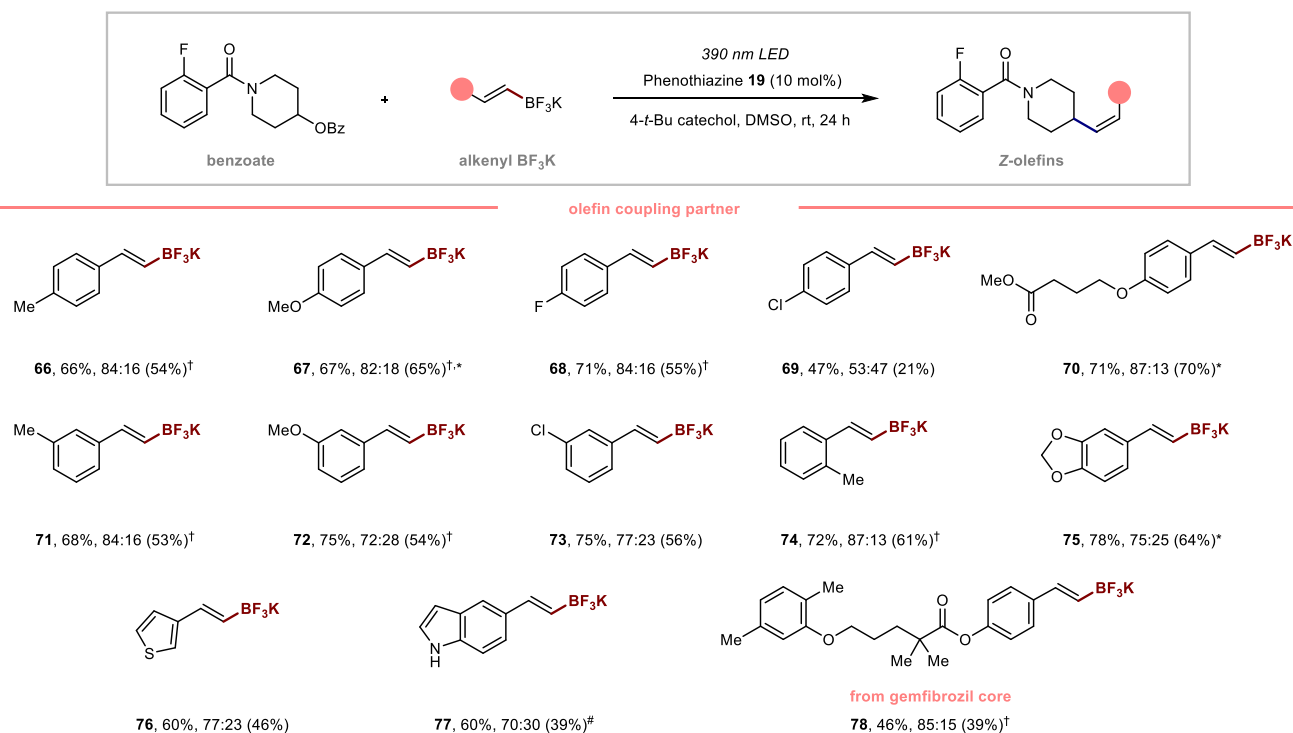
Fig. 4 | Alkenyl BF₃K scope of the photocatalytic deoxygenative Z-selective olefination. Reaction conditions as Fig. 2B (entry 6), 0.2 mmol scale. Yield and Z:E ratio determined by ^{1}H NMR using methyl 3,5-dinitrobenzoate as internal standard. In brackets isolated yields of Z-olefin, unless otherwise noted. All yields refer to the photocatalytic process only. [†]Catechol is used instead of 4-t-Bu catechol, 16 h. *Isolated as mixture of isomers. [#]2 lamps, 6 h. DMSO: dimethyl sulfoxide.
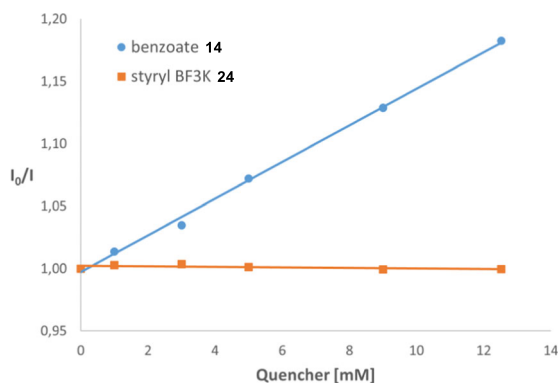
Fig. 5 | Preliminary mechanistic studies and on-DNA reactions for DELs applications. A Stern-Volmer quenching studies. **B** Radical-clock experiment. **C** Photoisomerization of the couped product E isomer. **D** On-DNA reactions for DELs applications. DMSO dimethyl sulfoxide, PHT phenothiazine.

deoxygenated intermediate (Fig. 5B). When *E* isomer **81** was exposed to phenothiazine **19** and purple light, a mixture of isomers with *Z:E* ratio of 70:30 was recovered after 16 hours, confirming the ability of the triplet excited state of phenothiazine **19** to promote in-situ photoisomerization of the coupled product (Fig. 5C). Finally, we sought to better understand the role of catechol in our olefination protocol. Several studies have shown that phenoxides can be used as photocatalysts and photoreductants[48–51]. While we have never observed the formation of catecholates, we performed UV-Vis studies and control experiments to exclude the possible photoactivity of these species (please see section 5: "Preliminary mechanistic studies" in the SI). The results, together with the control experiment without photocatalyst (entry 9, Fig. 2B), strongly suggest that catechol and catecholates are not productive photoactive molecules in our reaction conditions. However, we have found a possible non-covalent interaction between the styryl-BF$_3$K **24** and catechol (please see section 5: "Preliminary mechanistic studies" in the SI), which may be responsible for a unique activation mode of the styryl-BF$_3$K and the overall reactivity observed.

On-DNA reactions for DELs applications

Given the mild reaction conditions, we aimed to investigate the aqueous compatibility of our system for its use in synthesizing DNA-encoded libraries (DELs). DELs are a powerful technology that has gained extensive use in medicinal chemistry as an efficient and cost-effective platform for discovering new pharmaceutical candidates[52–54]. In our previous studies, we reported a straightforward method for the deoxygenative cross-coupling of alcohols and DNA-pyridine conjugates[21]. However, only benzylic alcohols could be activated and incorporated onto DNA headpieces. Given the importance of DELs in medicinal chemistry, and the abundance of alcohols building blocks available, we focused our efforts on expanding the scope towards aliphatic alcohols and saccharides.

Preliminary results are shown in Fig. 5D. We were delighted to find that our deoxygenative olefination could be used to functionalize DNA−styryl trifluoroborate conjugate **82** with mannofuranose **83** in 60% yield. Despite the dilute aqueous conditions, the key coupling process took place in just 20 minutes. Remarkably, the DNA remained intact during the photochemical process and no oxidation was observed by mass spectrometry. Nevertheless, when other aliphatic alcohols were tested, the desired coupling products were obtained in low yields (10-20%, please see section 6: "On-DNA Deoxygenative Z-selective olefination of aliphatic alcohols" in the SI). Further investigations into the reaction mechanism under aqueous conditions and optimization of the on-DNA reaction are currently ongoing in our laboratory.

Discussion

In summary, we have developed a catalytic protocol for the deoxygenative *Z*-selective olefination of aliphatic alcohols. Key to this methodology is the use of a phenothiazine photocatalyst, which concurrently activates the aliphatic alcohols, promotes the cross-coupling of bench-stable alkenyl trifluoroborate salts and enables the isomerization of the final product to deliver *Z*-olefins. This method is distinguished by its wide substrate scope and broad applicability, even in the context of pharmaceuticals and saccharides. Given the mild and water-compatible reaction conditions, our chemistry can also be used to functionalize DNA headpieces for DELs applications. Overall, we believe that the flexibility and simplicity of our deoxygenative *Z*-selective olefination will make this procedure appealing to chemists in both industrial and academic settings, particularly those in medicinal chemistry.

Methods
General procedure for the photocatalytic *Z*-selective olefination of aliphatic alcohols

In a 10 mL microwave vial equipped with stir bar, the appropriate alcohol derivative (0.2 mmol, 1 eq.), (*E*)−2-arylvinyl-BF$_3$K (0.6 mmol, 3.0 eq.), appropriate phenothiazine photocatalyst (0.02 mmol, 0.1 eq.) and 4-*tert*-butyl catechol or catechol (0.2 mmol, 1 eq.) were dissolved in DMSO (0.6 mL) under air. The vial was then flushed under Argon for 15 seconds and capped. The reaction was then degassed via Argon purging for 10 minutes and irradiated with 390 nm light. *Note: The M.W. vial was placed at 5.0 cm distance from the Kessil 390 nm LED lamp and the reaction temperature was kept constant using a fan placed on top of the reaction at 33 cm distance.* After 16 or 24 hours, the vial was decapped and (5 mL) of 1 M NaOH was added and stirred for 5 minutes. The reaction mixture was then transferred using EtOAc (sonication to ensure homogenization) to a separating funnel and the organic phase was extracted. The organic phase was washed once again with (2 mL) of 1 M NaOH and (10 mL) of saturated brine solution, dried over sodium sulfate and concentrated under reduced pressure. The reaction crude was purified by flash column chromatography (silica gel) under the stated conditions to provide the pure *Z*-olefin product.

General procedure for the photocatalytic *Z*-selective olefination of primary alcohols

In a 10 mL microwave vial equipped with stir bar, the appropriate alcohol derivative (0.2 mmol, 1 eq.), (*E*)−2-arylvinyl-BF$_3$K (0.6 mmol, 3.0 eq.), appropriate phenothiazine photocatalyst (0.02 mmol, 0.1 eq.) and 4-*tert*butyl catechol or catechol (0.2 mmol, 1 eq.) were dissolved in DMSO (0.6 mL) under air. The vial was then flushed under Argon for 15 seconds and capped. The reaction was then degassed via Argon purging for 10 minutes and irradiated with 390 nm light. *Note: The M.W. vial was placed between two Kessil 390 nm LED lamps at 3 cm distance from each lamp and the reaction temperature was kept constant using a fan placed on top of the reaction at 33 cm distance.* After 16 or 24 hours, the vial was decapped and (5 mL) of 1 M NaOH was added and stirred for 5 minutes. The reaction mixture was then transferred using EtOAc (sonication to ensure homogenization) to a separating funnel and the organic phase was extracted. The organic phase was washed once again with (2 mL) of 1 M NaOH and (10 mL) of saturated brine solution, dried over sodium sulfate and concentrated under reduced pressure. The reaction crude was purified by flash column chromatography (silica gel) under the stated conditions to provide the pure Z-olefin product.

General procedure for on-DNA *Z*-selective olefination of protected saccharides

A 2 mL microwave vial was charged with the appropriate alcohol derivative (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 eq), catechol (5 μL of 50 mM stock solution in DMSO, 250 nmol, 100 eq), **PHT 84** (5 μL of 20 mM stock solution in DMSO, 100 nmol, 40 eq), DMSO (22.5 μL), H$_2$O (11.5 μL), and DNA derivative **82** (1.0 μL of 1 mM stock solution in H$_2$O, 1.0 nmol, 1 eq). The vial was flushed 15 seconds with Argon and sealed. The reaction was irradiated with 390 nm light for 20 or 30 minutes. *Note: the vial was placed at 8 cm distance from the Kessil LED lamp and the reaction temperature was kept constant using a fan placed on top of the reaction at 33 cm distance.* After irradiation, the reaction was transfer to a 1,5 mL Eppendorf tube and 5 μL of 3.0 M acetate buffer (pH=7) and 1 mL of cold absolute (EtOH) were added. The mixture was vortexed and allowed to stand at −65 °C for 30 min. The resulting suspension was centrifuged at 12446 x g for 5 min. The supernatant was discarded, and the sample was washed with 1 mL of cold absolute ethanol and centrifuged again at 12446 x g for 5 min. After discarding the supernatant, the pellets were dried under a flux of compressed air and redissolved in H$_2$O to provide a stock solution of the desired concentration.

Data availability
The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary Information files.

Should any raw data files be needed in another format they are available from the corresponding author upon request.

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Author contributions

M.N. and S.R.N.K conceived the project. M.N., S.R.N.K., I.S.-S., C.A.-R. and E.A. designed the experiments. S.R.N.K., I.S.-S., C.A.-R. and E.A. performed the experiments. M.N. wrote the manuscript, secured the fundings and supervised the project.

Competing interests

The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to Manuel Nappi.

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