Chromoselective access to $Z$- or $E$-allylated amines and heterocycles by a photocatalytic allylation reaction

Ana María Martínez-Gualda$^1$, Rafael Cano$^2$, Leyre Marzo$^1$, Raúl Pérez-Ruiz$^3$, Javier Luis-Barrera$^1$, Rubén Mas-Ballesté$^{2,4}$, Alberto Fraile$^1,4$, Víctor A. de la Peña O’Shea$^5$ & José Alemán$^{1,4}$

The most useful strategies for the alkylation of allylic systems are related to the Tsuji-Trost reaction or the use of different Lewis acids. Herein we report a photocatalytic approach for the allylation reaction of a variety of nucleophiles, such as heteroarenes, amines and alcohols. This method is compatible with a large variety of pyrroles and indoles, containing different substituents such as electron-withdrawing and electron-donating groups, unprotected nitrogen atoms and bromo derivatives. Moreover, this methodology enables the chromoselective synthesis of $Z$- or $E$-allylated compounds. While the use of UV-light irradiation has allowed the synthesis of the previously inaccessible $Z$-allylated products, $E$-isomers are prepared simply by changing both the light source to the visible region, and the catalytic system. Based on mechanistic and photochemical proofs, laser flash photolysis studies and DFT calculations, a rational mechanism is presented.
he Preparation of allyl-substituted compounds has attracted a special interest due to their utility as building blocks in organic synthesis. The Tsuji–Trost reaction is one of the most powerful methodologies for the allylation of alkylic systems, which is commonly catalyzed by palladium, and the allylic position is usually activated by a halide, an acetate, or a carbonate (eq. a, Fig. 1) and affords exclusively the E-isomer. The high selectivity and the general scope of this reaction makes it one of the most prominent Csp3–Csp3 bond formation methodologies. Indoles and pyrroles are versatile and useful heterocycles for the synthesis of a large variety of biologically active compounds and natural products. Different authors have reported the allylation of indoles at the C-3 position via the Tsuji–Trost reaction in a racemic manner. However, although this methodology is very important, to the best of our knowledge, no photocatalytic approaches for the allylation of heterocycles have been reported so far.

Over the past decade, photocatalysis has emerged as a powerful tool for the construction of new bonds that are difficult to obtain using other established procedures. A large number of photocatalytic methodologies have been described for the formation of new Csp2–Csp2 bonds. In particular, the arylation of (hetero)-aromatic rings, usually pyrroles, under different photocatalytic systems has been recently reported. However, one of the major problems related to this photocatalytic arylation is the large excess of the heterocycle required in this reaction (24–40 equiv.). Although the photocatalytic heteroatomatic ring arylation has been extensively studied, the photoallylation of heterocycles remains an elusive process.

We hypothesize that the reduction of the allylic derivative by a photocatalyst with the adequate redox potential would result in the appropriate intermediate, which will allow the functionalization of the allylic position. There are two prerequisites to achieve this goal: (i) the development of a photocatalytic system able to activate the C–O bond; (ii) since an unsaturation is present, it is necessary to control the isomerization of the double bond (Z or E).

In this work, we present a chromoselective photocatalytic allylation of heteroaromatic rings, using smooth conditions and short reaction times to access the Z- or E-double bonds, depending on the reaction conditions (eq. b, Fig. 1). In addition, mechanistic and photochemical proofs, DFT calculations, and laser flash photolysis studies enabled us to postulate a plausible mechanistic pathway.

**Results**

**Optimization of the model reaction.** Based on the previous photocatalytic arylation reactions, we started the screening of the reaction using the acetate allylic derivative and pyrrole (18 equiv.) in the presence of different photocatalysts under light irradiation (Table 1). Transition-metal-based photocatalysts failed to promote the formation of the allylated heterocycle (entries 1 and 2). Several photoorganocatalysts with different reductive power failed to give the Z-allylated pyrrole with low conversion under 420-nm LED irradiation (entries 3–6). Encouraged by these results, we used an irradiation source with a wavelength closer to the maximum absorption of PTH (entry 7). Pleasantly, using a 365-nm LED, a 65% conversion was obtained with a similar selectivity for the Z-isomer. In the absence of a photocatalyst, light, and both, the allylation did not proceed, confirming the photocatalytic nature of this transformation. Different solvents were then evaluated, and the best result was obtained using CH3CN (entries 7 and 11–14). To increase the amount of heterocycle, the reaction was carried out using 10 and 2 equivalents of (entries 15 and 16) and (entry 17). A good yield of 58% was obtained in only 3 h, using just five equivalents of the heterocycle. The use of inorganic bases (Na2CO3, LiOAc) afforded the final product, although with moderate yield, due to the lower solubility of such bases in acetonitrile (entries 17 and 18).

**Substrate scope.** Having established the best conditions (Table 1, entry 16), we performed the scale of the reaction (Table 2). With N-methyl pyrrole, the allylic derivative was obtained with a better yield than 4a and with a similar selectivity for the Z-isomer. Other substituents were tolerated at the N-atom of the pyrrole (4c and 4d) with excellent Z/E selectivity (up to 96:4) and with a slight decrease for the phenyl derivative 4c. Indoles without protecting groups at the nitrogen were also employed, keeping the high selectivity for the Z-isomers, and with better yields than with the pyrroles (compare 4e and 4f with 4a and 4b). Electron-donating groups (EDGs) were well tolerated at different positions of the indole ring (4g, 4h, and 4i) as well as electron-withdrawing groups (EWG) at the aromatic ring (4j). A methyl substituent next to the indolinic nitrogen (4k) or the reactive C-3 center (4l)

---

**Fig. 1** The photocatalytic allylation reaction. **a** Precedents in the Tsuji–Trost allylation and **b** this work.
Table 1 Optimization of the photocatalytic allylation reaction

| Entry | 3 (mol%) | Light (nm) | Solvent | Pyrrole (equiv.) | t (h) | 4a:5a<sup>b</sup> |
|-------|----------|------------|---------|-----------------|------|-----------------|
| 1     | 3a (5)   | 420        | MeCN    | 18              | 1    | n.r.            |
| 2     | 3b (5)   | 420        | MeCN    | 18              | 1    | n.r.            |
| 3     | 3c (5)   | 530        | MeCN    | 18              | 1    | n.r.            |
| 4     | 3d (5)   | 420        | MeCN    | 18              | 1    | n.r.            |
| 5     | 3e (5)   | 420        | MeCN    | 18              | 1    | 100:0 (5%)<sup>c</sup> |
| 6     | 3f (10)  | 455        | MeCN    | 18              | 41   | n.r.            |
| 7     | 3e (5)   | 365        | MeCN    | 18              | 1    | 100:0 (65%)<sup>c</sup> |
| 8     | 3e (5)   | –          | MeCN    | 18              | 1    | n.r.            |
| 9     | –        | 365        | MeCN    | 18              | 1    | n.r.            |
| 10    | –        | –          | MeCN    | 18              | 1    | n.r.            |
| 11    | 3e (5)   | 365        | DMSO    | 18              | 1    | 100:0 (61%)<sup>c</sup> |
| 12    | 3e (5)   | 365        | DMF     | 18              | 1    | 100:0 (49%)<sup>c</sup> |
| 13    | 3e (5)   | 365        | Toluene | 18              | 1    | 100:0 (21%)<sup>c</sup> |
| 14    | 3e (5)   | 365        | DCM     | 18              | 1    | 100:0 (10%)<sup>c</sup> |
| 15    | 3e (5)   | 365        | MeCN    | 10              | 3    | 94:6 (86%)<sup>c</sup> |
| 16    | 3e (5)   | 365        | MeCN    | 2               | 3    | 94:6 (91%)<sup>c,d</sup> |
| 17    | 3e (5)   | 365        | MeCN    | 2               | 3    | 80:20 (33%)<sup>c</sup> |
| 18    | 3e (5)   | 365        | MeCN    | 2               | 3    | 78:22 (28%)<sup>c</sup> |

<sup>a</sup>Conditions: 1a (0.1 mmol), 2a (see table), DIPEA (0.5 mmol), and catalyst (mol%) in the solvent indicated (1.0 mL)
<sup>b</sup>Conversion in the crude mixture
<sup>c</sup>Optimized conditions highlighted in bold
<sup>d</sup>Reaction carried out under standard conditions but using Na<sub>2</sub>CO<sub>3</sub> (0.5 mmol) instead of DIPEA
<sup>e</sup>Reaction carried out under standard conditions but using LiOAc (0.5 mmol) instead of DIPEA

Use of the photocatalyst under 365-nm irradiation, we found a mixture of 60/40 E/Z-1a, while in the presence of 3e, this isomerization to Z-1a was complete (Fig. 2). According to theoretical calculations, photosensitization and subsequent isomerization of E-1a by the photocatalyst is feasible, while photosensitization and subsequent isomerization of Z-1a cannot take place (see Supplementary Information Fig. 25). The absorption spectra of E-1a at the reaction conditions revealed a significant absorption at 365 nm (see Supplementary Information Fig. 8), while at 420 nm, it was negligible, suggesting that the reaction must be carried out in the visible-light region to avoid isomerization. Under 420-nm irradiation, only 5% of the E-1a was isomerized to the Z-isomer after 3 h. Therefore, a photocatalyst with high reduction potential (≥2.35 V vs. SCE) and absorption in the visible-light region is required. The phenoxazine 3g, that meets all these criteria, resulted in only a small amount of Z-1a at 420-nm irradiation after 3 h (Fig. 2). Therefore, under these conditions (using photocatalyst 3g and 420-nm irradiation), it should be possible to avoid the isomerization step and selectively form E-allylated products 5.
Table 2 Scope of the allylation reaction for the synthesis of Z-isomers with pyrroles and indoles under catalyst 3e\textsuperscript{a,b}

| Ar           | Ph | Het                  | 2 \((2 \text{ equiv})\) + 3e \((5 \text{ mol\%})\) \text{MeCN, DIPEA 365 nm, rt, 3 h} | Product 4 |
|--------------|----|----------------------|---------------------------------------------|----------|
|              |    |                      | Ar–1a                                      | 4a       |
|              |    |                      | 3e (5 mol%)                                | 4b, 70% Yield, Z:E: 92:8 |
|              |    |                      | 3e (5 mol%) in MeCN (1 mL)                  | 4c, 55% Yield, Z:E: 75:25 |
|              |    |                      | 3e (5 mol%)                                | 4d, 46% Yield, Z:E: 96:4 |
|              |    |                      | 3e (5 mol%)                                | 4e, 66% Yield, Z:E: 91:9 |
|              |    |                      | 3e (5 mol%)                                | 4f, 77% Yield, Z:E: 89:11 |
|              |    |                      | 3e (5 mol%)                                | 4g, 55% Yield, Z:E: 94:6 |
|              |    |                      | 3e (5 mol%) in MeCN (1 mL)                  | 4h, 50% Yield, Z:E: 92:8 |
|              |    |                      | 3e (5 mol%)                                | 4i, 43% Yield, Z:E: 91:9 |
|              |    |                      | 3e (5 mol%)                                | 4j, 66% Yield, Z:E: 94:6 |
|              |    |                      | 3e (5 mol%)                                | 4k, 70% Yield, Z:E: 91:9 |
|              |    |                      | 3e (5 mol%)                                | 4l, 78% Yield, Z:E: 90:10 |
|              |    |                      | 3e (5 mol%) in MeCN (1 mL)                  | 4m, 53% Yield, Z:E: 88:12 |

\textsuperscript{a}Conditions: 1 \((0.1 \text{ mmol})\), 2 \((0.2 \text{ mmol})\), DIPEA \((0.5 \text{ mmol})\), and 3e \((5 \text{ mol\%})\) in MeCN (1.0 mL)

\textsuperscript{b}Isolated yields after flash chromatography

\textsuperscript{c}Combined isolated yield along with the C2-allylated compound

Fig. 2 Isomerization studies. Isomerization proofs of E-1a under different catalysts (3e and 3g) and different irradiation wavelengths

To our delight, when carrying out the reaction between the allylic derivative 1a and pyrrole (2a) in the presence of the photocatalyst 3g under 420-nm irradiation, the allylated product E-5a was obtained with a good yield as the major isomer (Table 3). Other N-substituted pyrroles were also employed and maintained the same selectivity (5b–5c). Only compound 5d was obtained as a complex mixture. The reaction with indoles afforded even better yield and selectivity than pyrroles (5e and 5f). Unprotected indolic nitrogen as well as different substituents were tolerated, from EDGs (5g–I) to EWGs (5j), methyl (5k–I), or bromo derivatives (5m), obtaining in all cases good yields (67–92%) and excellent selectivities (up to > 98:2). The isomerization of the final product 5e under 420-nm irradiation was also studied, obtaining a Z/E mixture 30/70 after 3 h of irradiation, without the photocatalyst, while in the presence of the photocatalyst 3g, a Z/E mixture 20/80 was obtained. The final product is present in the reaction in higher concentrations only after 2 h of reaction. Therefore, the irradiation time is not enough to produce its isomerization, which explains the obtaining of the E-isomer as the major one.

Mechanistic studies. The proposed reaction mechanism is outlined in Fig. 3a. After light absorption by the photocatalyst under LED irradiation \((\lambda = 365 \text{ or } 420 \text{ nm})\), single-electron transfer (SET) takes place from its \(S_1\) excited state \((E_{S_1} = 3.2 \text{ eV})\,\text{see Supplementary Information Figs. 11 and 12}\) to 1a. Steady-state and time-resolved fluorescence quenching studies in the
presence of 1a afforded a quenching rate constant of \( k_q (S_0) = 4.7 \times 10^7 \, \text{M}^{-1} \text{s}^{-1} \) (see Supplementary Information Fig. 9a), indicating that the radical ion pair (PC\(^+\) + 1a\(^−\)) formation occurs at nearly diffusion rate. In addition, SET from the excited singlet state would be an exergonic process, taking into account the free energy change (\( \Delta G_{ET} = -4.0 \, \text{kcal mol}^{-1} \)) associated with the electron transfer (see Supplementary Note 4 for Rehm–Weller equation).

Importantly, photooxidation of DIPEA (\( E_{ox} = 0.94 \, \text{V vs. SCE} \))\(^{12}\), DIPA (\( E_{ox} = 1.17 \, \text{V vs. SCE} \))\(^{13}\), or pyrrole (\( E_{ox} = 1.04 \, \text{V vs. SCE} \))\(^{44}\) by PC \( S_1 \) excited state could not occur, taking into account the oxidation power of 3e and 3g (\( E ( \text{PC}^*/\text{PC}^-) = -0.3 \, \text{V vs. SCE} \) for 3e and 3g, see Supplementary Note 4), and was further confirmed by fluorescent-quenching studies (see Fig. 3b). The fate of such reduced species has been investigated by DFT calculations, considering both Z- and E-isomers (Fig. 3d). Initial single-electron transfer process from the photocatalyst (PC) to 1a generates the radical cation PC\(^+\) and the radical anion 1a\(^−\), that evolves through the C–O bond scission to afford acetate anion and the radical intermediate I (INT I). This step is a very exergonic process (\(-22 \text{ or } -21.3 \, \text{kcal mol}^{-1}\)) and proceeds through a very shallow kinetic barrier (\( E_k = 1.4 \text{ or } 3.2 \, \text{kcal mol}^{-1}\)). Then, the oxidation of INT I by the oxidized photocatalyst (PC\(^+\)), results in the regeneration of the photocatalyst (PC) and formation of a carbocationic intermediate II (INT II) (Fig. 3d). Such electron transfer is calculated as a thermodynamically favorable process (\(-8.7 \text{ or } -11.8 \, \text{kcal mol}^{-1}\)). The calculated energetic barriers for \( E \) to \( Z \) isomerizations for radical or carbocation intermediates I and II rule out this process from such transient species (see Supplementary Information Fig. 28). Formation of this carbocation II was experimentally confirmed, carrying out the reaction in the presence of \( \text{H}_2\text{O}^{18} \) as the nucleophile obtaining the isotopically labeled compound 7 (Fig. 3c). In addition, when two nonsymmetric allylic derivatives bearing different aryl groups were studied, an equimolecular mixture of products was obtained (see Supplementary Fig. 30, compounds 6 and 6\'), indicating that the reaction takes places through a common intermediate. Then, a Friedel–Crafts reaction between the carbocation INT II and pyrrole takes place, generating the protonated intermediate III (INT III). This step is also theoretically found exergonic (\(-14 \text{ or } -26.3 \, \text{kcal mol}^{-1}\)) and kinetically favorable (\( E_k = 3.8 \, \text{kcal mol}^{-1}\)). A final rearomatization by deprotonation of INT III gives the final product (Fig. 3d). For such deprotonation, both DIPEA and the anion acetate (formed during the reaction) would act as a base through very exergonic processes (see entries 16 and 17 from Table 1 for reactions in the presence of \( \text{Na}_2\text{CO}_3 \) and \( \text{LiOAc} \)).

In order to gain a better understanding of the reaction mechanism, laser flash photolysis (LFP) measurements have been carried out. Excitation of 3g at 355 nm results in two peaks at 468 and 530 nm at 40 ns after the laser pulse, which are assigned to the 3g radical cation (3g\(^{+}\)) and the excited triplet state of 3g (3g\(^{3}\)), respectively (Fig. 4a, black line, for further details, see also Supplementary Note 2). This experiment was performed in the presence of 1a to identify the possible transient reaction intermediates (Fig. 4a, red line). Two new absorption bands at 360 and 490 nm are clearly observed, which correspond to intermediates I and II, respectively, based on literature data\(^{45}\). The lifetime of the carbocation INT II also depends on the nucleophilicity of the anionic leaving group (see Supplementary Information Fig. 4). In order to check whether formation of INT II and INT I is instantaneous with the laser pulse, additional LFP experiments of 3g in the presence of increasing amounts of 1a were performed (Fig. 4c and d). Generation of INT II is practically instantaneous even at lower concentration of 1a (Fig. 4d), whereas lifetimes of INT I are not affected by higher amounts of 1a (Fig. 4c). This result suggests that SET from 3g\(^{+}\) to 1a at

Table 3 Scope of the allylation reaction for the synthesis of \( E \)-isomers with pyrroles and indoles under catalyst 3g\(^{+}\)\(^{-}\)

| Entry | Product | Yield | Z:E Ratio |
|-------|---------|-------|------------|
| 5a    | 1a      | 71%   | 5:95       |
| 5b    | 1b      | 40%   | 10:90      |
| 5c    | 1c      | 59%   | 8:92       |
| 5d    | 1d      | complex mixture | |
| 5e    | 1e      | 78%   | 4:96       |
| 5f    | 1f      | 94%   | 7:93       |
| 5g    | 1g      | 73%   | 6:94       |
| 5h    | 1h      | 73%   | 8:94       |
| 5i    | 1i      | 83%   | 6:94       |
| 5j    | 1j      | 67%   | 13:87      |
| 5k    | 1k      | 92%   | 4:96       |
| 5l    | 1l      | 69%   | 2:98       |
| 5m    | 1m      | 76%   | 17:83      |

\( ^a \) Conditions: 1a (0.1 mmol), 2 (0.2 mmol), DIPEA (0.5 mmol), and 3g (5 mmol) in MeCN (1.0 mL)

\( ^b \) Isolated yields after flash chromatography

\( ^c \) Combined isolated yield along with the C2-allylated compound
diffusion control rate (see Supplementary Information Fig. 9) gives rise to the contact radical ion pair at this singlet stage (Fig. 3a). All processes in the contact radical ion pairs undergo in the sub-nanosecond scale 46. Fast acetate release from 1a− led to INT I, which is still in close contact with 3g+. At this point, INT I undergoes an ultrafast back electron transfer with 3g+ restoring 3g and generating INT II, whose amount is slightly dependent on the concentration of 1a in the sample (Fig. 4d). In addition, 3g+ and INT I can split up, forming the corresponding free 3g+ and free INT I, that are detected in the LFP experiments with lifetimes in the microsecond scale (Fig. 4a, red line). Once the detection of both intermediates I and II by LFP has been established, the question arises whether INT I or INT II (radical or carbocation) would react with a trapping agent (Fig. 4e and transient absorption spectrum in Fig. 4b). Addition of pyrrole to a 3g/1a mixture results only in a marked decrease of the INT II lifetime (Fig. 4g), while the band corresponding to INT I (360 nm) is not affected (Fig. 4f). Therefore, this experiment clearly corroborated with the previous data (Fig. 3) that the carbocation INT II is the reactive intermediate in our reaction. A quantum yield of 1.5% was found, suggesting a
Fig. 4 Laser flash photolysis ($\lambda_{\text{exc}} = 355$ nm, MeCN/Ar) experiments. a Transient absorption spectra recorded at 40 ns after the laser pulse of $3g$ (50 mM) without $1a$ (black), with 70 mM of $1a$ (red). b Transient absorption spectra recorded at 40 ns after the laser pulse of $3g$ (50 mM) with 70 mM of $1a$ (black) and with 35 mM of $2a$ (red). c Decay kinetics at 360 nm after 355-nm LFP of $3g$ (50 µM) in the presence of increasing amounts of $1a$. d Decay kinetics at 485 nm after 355-nm LFP of $3g$ (50 µM) in the presence of increasing amounts of $1a$. e Scheme of the formation of intermediate II from intermediate I and their reaction with $2a$. f Lifetime of INT I: decays monitored at 360 nm of $3g$ (50 mM) and $1a$ (70 mM) (black line) and in the presence of $2a$ (37 mM) (red line). g Lifetime of INT II: decays monitored at 490 nm of $3g$ (50 mM) and $1a$ (70 mM) (black line) and in the presence of $2a$ (37 mM) (red line).
photocatalytic process without a significant radical chain propagation\(^7\).  

**Scope with alcohols and amines.** Once that we proved that the reaction takes place through a carbocation intermediate formation, we decided to study other nucleophiles to prove the generality of our protocol. Allylic amines are very useful compounds that can be employed as building blocks for the synthesis of amino acids, alkaloids, and carbohydrate derivatives\(^{48-50}\). Moreover, this structure is present in numerous natural products and drugs with antifungal, antibacterial, and anti-inflammatory action\(^{51-53}\). Different amines were tried under UV irradiation in order to obtain the Z-allylated amines which are not accessible by other methodologies (Table 4). Aniline gave the corresponding Z-allylated amine 9a with high selectivity. Aromatic amines with EDGs were well tolerated (9b–d) with moderate selectivity, whereas anilines with EWGs gave significant better yield (9e) and Z/E ratio. In addition, the presence of Br at the aromatic ring was tolerated without detecting the corresponding reduced product (9f). Aliphatic primary and secondary amines were also suitable for the reaction conditions (9g–h). Cyclic allylated amine 9i was obtained in good selectivity (Z:E = 91:9) and good yield. Moreover, the use of morpholine as a nucleophile can be employed for the synthesis of 9j with excellent selectivity. The preparation of allylic ethers has a great interest, as they are also present in numerous pharmaceuticals and natural products\(^{54-57}\). For this reason, alcohols were employed as nucleophiles, obtaining Z-allylated ethers with good yields and good selectivities (9k–m)\(^{58}\).

Using the visible-light irradiation conditions and photocatalyst 3g with amines and alcohols is possible to obtain the corresponding E-isomers (Table 5). Aromatic amines gave the corresponding allylated compounds with high selectivities and good yields with EDGs (10b–d) and EWGs (10e), or ortho-bromo substituents (10f). Aliphatic primary (10g) and secondary amines (10h–j) were employed, keeping in all the cases high Z/E selectivity. Moreover, allylated ethers can also be obtained under visible-light irradiation with excellent selectivities (10k–m). A similar mechanistic scenario was found for amines and alcohols, using p-toluidine 8b as a nucleophile in the LFP and photochemical mechanistic probes (see Supplementary Fig. 9).

**Discussion**

In summary, a chromoselective photocatalytic approach for the allylation of indoles, pyroles, amines, and alcohols has been developed. This approach represents a photocatalytic allylation reaction for the synthesis of demand of Z- or E-isomers, with only two equivalents of the desired nucleophile. Therefore, under UV-light irradiation Z-allylated products are obtained, while the E-isomer is simply prepared by changing both the light source to the visible region, and the catalytic system. DFT calculations, photochemical proofs, and mechanistic experiments indicate that the most plausible mechanism involves a nucleophilic attack to an allyl-cation intermediate.

**Methods**

**Procedure for the preparation of Z-allylic compounds.** A vial equipped with a magnetic stir bar and fitted with a Teflon screw cap septum was charged with the corresponding allylic compound 1 (0.1 mmol), the corresponding heterocycle, amine, or alcohol (0.2 mmol), N-phenyl phenothiazine (1.4 mg, 5 mol%), DIPEA (86 µL, 0.5 mmol), and acetonitrile (1 mL). The reaction was degassed with three freeze–pump–thaw cycles. The vial was then backfilled with N\(_2\) and stirred under 365-nm LED irradiation (8.2460 W m\(^{-2}\) intensity; approximate distance was 2 cm from the vial) at 20 °C. After 3 h, the vial was opened, the solvent evaporated, and the crude product was purified by column chromatography to give the corresponding products 4 or 9.

---

**Table 4 Scope of the allylation reaction with amines and alcohols for the synthesis of Z-isomers under photocatalyst 3e**

| Compound | Yield (%) | Z:E Ratio |
|----------|-----------|-----------|
| 9a       | 61        | 87:13     |
| 9b       | 48        | 76:24     |
| 9c       | 77        | 36:64     |
| 9d       | 53        | 65:35     |
| 9e       | 76        | 88:12     |
| 9f       | 67        | 84:16     |
| 9g       | 61        | 93:7      |
| 9h       | 77        | 85:15     |
| 9i       | 68        | 91:9      |
| 9j       | 76        | 94:6      |
| 9k       | 76        | 88:12     |
| 9l       | 69        | 86:14     |
| 9m       | 66        | 86:14     |

*Conditions: 1a (0.1 mmol), 2 (0.2 mmol), DIPEA (0.5 mmol), and 3g (5 mol%) in MeCN (1.0 mL) *Isolated yields after flash chromatography.
Procedure for the preparation of E-allylic compounds. A vial equipped with a magnetic stir bar and fitted with a Teflon screw cap septum was charged with the corresponding allylic compound (0.1 mmol), the corresponding heterocycle, amine, or alcohol (0.2 mmol), 3-(4-methoxyphenyl)-10-phenyl-10H-phenoxazine (1.7 mg, 5 mol%), DIPEA (70 µL, 0.5 mmol), only base is needed for reactions with heterocycles as nucleophile), and acetonitrile (1 mL). The reaction was degassed with three freeze−pump−thaw cycles. The vial was then backfilled with N₂ and stirred under 420-nm LED irradiation (18.3396 W m⁻²; approximate distance was 2 cm from the vial) at room temperature. After 3 h, the vial was opened, the solvent evaporated, and the crude product was purified by column chromatography to give the corresponding products 5 or 10.

Data availability
The authors declare that all data supporting the findings of this study are available within the article and Supplementary Information files, and also are available from the corresponding author upon reasonable request.

Received: 30 November 2018 Accepted: 13 May 2019
Published online: 14 June 2019

References
1. Trost, B. M. & Strege, P. E. Asymmetric induction in catalytic allylic alkylation. J. Am. Chem. Soc. 99, 1649−1651 (1977).
2. Trost, B. M. New rules of selectivity: allylic alkylations catalyzed by palladium. Acc. Chem. Res. 13, 385−393 (1980).
3. Tsuji, J., Minami, I. & Shimizu, I. Palladium-catalyzed alkylation of ketones and aldehydes with allylic carbonates via silyl enol ethers under neutral conditions. Chem. Lett. 12, 1325−1326 (1983).
4. Trost, B. M. & Van Vranken, D. L. Asymmetric transition metal-catalyzed allylic alkylation. Chem. Rev. 96, 395−422 (1996).
5. De Meijere, A., Diederich, F. (eds) Metal-Catalyzed Cross-coupling Reactions, 2nd edn (Wiley, Weinheim, 2008).
6. D’Ischia, A., Napolitano, A. & Pezzella, A. Pyroles and their Benzo Derivatives: Application in Comprehensive Heterocyclic Chemistry III (eds Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V. & Taylor, R. J. K.) 353−386 (Elsevier Science, Amsterdam, 2008).
7. Malkov, A. V., Davis, S. L., Bazendale, I. R., Mitchell, W. L. & Kočovský, P. Molybdenum(II)-catalyzed alkylation of electron-rich aromatics and heteroaromatics. J. Org. Chem. 64, 2751−2764 (1999).
8. Bandini, M., Melloni, A. & Umani-Ronchi, A. New versatile Pd-catalyzed alkylation of indoles via nucleophilic allylic substitution: controlling the regioselectivity. Org. Lett. 6, 3199−3202 (2004).
9. Kimura, M., Futamura, M., Mukai, R. & Tamara, Y. Pd-catalyzed C3-selective alkylation of indoles with allyl alcohols promoted by triethylborane. J. Am. Chem. Soc. 127, 4592−4593 (2005).
10. Stanley, L. M. & Hartwig, J. F. Iridium-catalyzed regio- and enantioselective N-alkylation of indoles. Angew. Chem. Int. Ed. 48, 7841−7844 (2009).
11. Xu, K., Gilles, T. & Breit, B. Asymmetric synthesis of N-allylic indoles via regio- and enantioselective alkylation of aryl hydrazines. Nat. Commun. 6, 7616 (2015).
12. Lee, J. Y., Ha, H., Bae, S., Han, I. & Joo, J. M. Catalytic C-2 alkylation of indoles by electronic modulation of the indole ring and its application to the synthesis of functionalized carbazoles. Adv. Synth. Catal. 358, 3458−3470 (2016).
13. Narayanam, J. M. R. & Stephenson, C. R. J. Visible light photoredox catalysis: applications in organic synthesis. Chem. Soc. Rev. 40, 102−113 (2011).
14. 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).
15. Meggers, E. Asymmetric catalysis activated by visible light. Chem. Commun. 51, 3290−3301 (2015).
16. Ravelli, D., Protti, S. & Fagnoni, M. Carbon−carbon bond forming reactions via photogenerated intermediates. Chem. Rev. 116, 9850−9913 (2016).
17. Skubi, K. L., Blum, T. R. & Yoon, T. P. Dual catalysis strategies in photochemical synthesis. Chem. Rev. 116, 10035−10074 (2016).
18. Pitre, S. P., McTierman, C. D. & Scaino, J. C. Understanding the kinetics and spectroscopy of photoredox catalysis and transition-metal-free alternatives. Acc. Chem. Res. 49, 1320−1330 (2016).
19. Tellis, J. C. et al. Single-electron transmetalation via photoredox/nickel dual catalysis: unlocking a new paradigm for sp³-sp² cross-coupling. Acc. Chem. Res. 49, 1429−1439 (2016).
20. Gentry, E. C. & Knowles, R. R. Synthetic applications of proton-coupled electron transfer. Acc. Chem. Res. 49, 1546−1556 (2016).
21. Hernandez-Perez, A. C. & Collins, S. Heteroleptic Cu-based sensitizers in photoredox catalysis. Acc. Chem. Res. 49, 1557−1565 (2016).
22. Goddard, J.-P., Ollivier, C. & Fensterbank, L. Photoredox catalysis for the generation of carbon centered radicals. Acc. Chem. Res. 49, 1924−1936 (2016).
23. Morris, S. A., Wang, J. & Zheng, N. The prowess of photogenerated amine radical cations in cascade reactions: from carbocycles to heterocycles. Acc. Chem. Res. 49, 1957–1968 (2016).

24. Fabry, D. C. & Rueping, M. Merging visible light photoredox catalysis with metal catalyzed C-H activations on the role of oxygen and superoxide ions as oxidants. Acc. Chem. Res. 49, 1969–1979 (2016).

25. Majek, M. & von Wangelin, A. J. Mechanistic perspectives on organic photoredox catalysis for aromatic substitutions. Acc. Chem. Res. 49, 2316–2327 (2016).

26. Shaw, M. H., Twilton, J. & MacMillan, D. W. C. Photocatalysis in organic chemistry. J. Org. Chem. 81, 6898–6926 (2016).

27. Zhou, W.-J., Zhang, Y.-H., Gui, Y.-Y., Sun, L. & Yu, D.-G. Merging transition-metal photocatalysis with aryl diazonium salts: an environmentally friendly strategy for C-H functionalization. Synthesis 50, 3359–3377 (2018).

28. Garrido-Castro, A. F., Carmen Maestro, M. & Alemán, J. Asymmetric induction in photocatalysis — discovering a new side to light-driven chemistry. Tetrahedron Lett. 59, 1286–1294 (2018).

29. Marzo, L., Pagire, S. K., Reiser, O. & König, B. Visible-light photocatalysis: does it make a difference in organic synthesis. Angew. Chem. Int. Ed. 57, 10034–10072 (2018).

30. Wang, C.-S., Dixneuf, P. H. & Soule, J.-F. Photoredox catalysis for building C-C bonds from C(sp²)-H bonds. Chem. Rev. 118, 7532–7585 (2018).

31. Hari, D. P. & König, B. The photocatalyzed Meerwein arylation: classic reaction of aryl diazonium salts in a new light. Angew. Chem. Int. Ed. 52, 4733–4743 (2013).

32. Ghosh, I., Marzo, L., Das, A., Shaikh, R. & König, B. Visible-light mediated photocatalytic arylation reactions. Acc. Chem. Res. 49, 1566–1577 (2016).

33. Hari, D. P., Schroll, P. & König, B. Metal-free, visible-light-mediated direct C-H arylation of heteroarenes with aryl diazonium salts. J. Am. Chem. Soc. 134, 5958–5961 (2012).

34. Ghosh, I., Ghosh, T., Bardagi, J. I. & König, B. Reduction of aryl halides by photocatalysis — a new side to light-driven chemistry. Science 346, 725–728 (2014).

35. Meyer, A. U., Slanina, T., Yao, C.-J. & König, B. Metal-free perfluoroarylation by visible light photocatalysis. ACS Catal. 6, 369–375 (2016).

36. Ghosh, I. & König, B. Chromoexciplex photocatalysis: controlled bond activation through light-color regulation of redox potentials. Angew. Chem. Int. Ed. 55, 7676–7679 (2016).

37. Marzo, L., Ghosh, I., Esteban, F. & König, B. Metal-free photocatalyzed cross coupling of bromoheteroarenes with pyrroles. ACS Catal. 6, 6780–6784 (2016).

38. Kalyani, D., McMurtrey, K. R., Neufeldt, S. R. & Sanford, M. S. Room-temperature C-H arylation: merger of pd-catalyzed C-H functionalization and visible-light photocatalysis. J. Am. Chem. Soc. 133, 18566–18569 (2011).

39. Zoller, J., Fabry, D. C. & Rueping, M. Unexpected dual role of titanium dioxide in the visible light heterogeneous catalysed C-H arylation of heteroarenes. ACS Catal. 5, 3900–3904 (2015).

40. Maiti, P., Kundu, D. & Ranu, B. C. Multigram four-step synthesis of 1,4,7-triazacyclononanes with 2R,2R,N-functionalization pattern by starting from diethylammonium. Eur. J. Org. Chem. 2015, 1727–1734 (2015).

41. McCarthy, B. G. et al. Structure-property relationships for tailoring photoxenonates as reducing photoredox catalysts. J. Am. Chem. Soc. 140, 5088–5110 (2018).

42. Roth, H. G., Romero, N. A. & Nicewicz, D. A. Experimental and calculated electrochemical potentials of common organic molecules for applications to single-electron redox chemistry. Synlett 27, 714–723 (2016).

43. Adenier, A., Chehimi, M. M., Gallardo, I., Pinson, J. & Villa, N. Electrochemical oxidation of aliphatic amines and their attachment to carbon and metal surfaces. Langmuir 20, 8243–8253 (2004).

44. Garrido-Castro, A. F., Choubane, H., Daoua, M., Maestro, M. C. & Alemán, J. Asymmetric radical alklylation of N-sulfon-imines under visible light photocatalytic conditions. Chem. Commun. 53, 7764–7767 (2017).

45. Miranda, M. A., Perez-Prieto, J., Font-Sanchis, E., Kónya, K. & Scaino, J. C. Flash photolysis of 1,3-dichloro-1,3-diphenylpropane in polar solvents: generation of a stabilized v-chloropropyl cation, subsequent formation of a propenyl cation, and nucleophilic trapping of both cations. J. Phys. Chem. A 102, 5724–5727 (1998).

46. Matty, J. & Vondenhoff, A. Contact and solvent-separated radical ion pairs in organic. In Photoinduced electron transfer III. Topics in Current Chemistry (Ed. Mattay, J.) 219–255 (Springer, Heidelberg, 1991).

47. Kuhn, H. J., Bralslavsky, S. E. & Schmidt, R. Chemical actinometry (IUPAC technical report). Pure Appl. Chem. 76, 2105–2146 (2004).

48. Cheikh, R. B., Chaabouni, R., Laurent, A., Mison, P. & Nafti, A. Synthesis of primary allylic amines. Synthesis 685–700 (1983).

49. Johansson, M. & Jörgensen, K. A. Allylic amination. Chem. Rev. 98, 1659–1708 (1998).

50. Trost, B. M. & Crawley, M. L. Asymmetric transition-metal-catalyzed allylic alkylations: applications in total synthesis. Chem. Rev. 103, 2921–2943 (2003).

51. Petranj, B., Györy, N. S. & Stutz, A. Allylamine derivatives: new class of synthetic antifungal agents inhibiting fungal squaleine epoxidase. Science 224, 1239–1241 (1984).

52. Stutz, A. Allylamine derivatives—a new class of active substances in antifungal chemotherapy. Angew. Chem. Int. Ed. 26, 320–328 (1987).

53. Nanavati, S. M. & Silverman, R. B. Mechanisms of inactivation of gamma-aminobutyric acid aminotransferase by the antiepilepsy drug gamma-vinyl GABA (vigabatrin). J. Am. Chem. Soc. 113, 9341–9349 (1991).

54. Mizuguchi, E. & Achiwa, K. Chiral palladium complex-catalyzed synthesis of optically active vinylchroman. Chem. Pharm. Bull. 45, 1269–1271 (1997).

55. Nicolaou, K. C. et al. Natural product-like combinatorial libraries based on privileged structures. 1. General principles and solid-phase synthesis of benzopyrans. J. Am. Chem. Soc. 122, 9939–9953 (2000).

56. Cao, B., Park, H. & Joullé, M. M. Total synthesis of Cistoxin D. J. Am. Chem. Soc. 124, 520–521 (2002).

57. Ishibashi, H., Ishihara, K. & Yamamoto, H. A new artificial cyclase for polypropenones: enantioselective total synthesis of (−)-chromazanol, (−)-8-epi-pupegoldine, and (−)-11′-deoxyxatoediol methyl ether. J. Am. Chem. Soc. 126, 11122–11123 (2004).

58. Pochetti, G. et al. Structural insight into peroxisome proliferator-activated receptor γ binding of two ureido diketiminate enaminites by molecular dynamics, cofactor interaction analysis, and site-directed mutagenesis. J. Med. Chem. 53, 4354–4366 (2010).