Photoredox Propargylation of Aldehydes Catalytic in Titanium

Francesco Calogero, Andrea Gualandi,* Marco Di Matteo, Simone Potenti, Andrea Fermi, Giacomo Bergamini, and Pier Giorgio Cozzi*

ABSTRACT: A practical and effective photoredox propargylation of aldehydes promoted by 10 mol % of [Cp₂TiCl₂] is presented. No stoichiometric metals or scavengers are used for the process. A catalytic amount of the cheap and simply prepared organic dye 3DPAFIPN is used as the reductant for titanium. The reaction displayed a broad scope, and no traces of allenyl isomers were detected for simple propargyl bromide, whereas mixtures of propargyl and allenyl isomers were observed for substituted propargyl bromides.

In just a few years, photoredox catalysis has reached an extraordinary level of advancement, introducing new and exciting methodologies in organic chemistry.1 Besides electron transfer, many interesting reactions can also be promoted by photocatalytic methodologies using energy transfer (EnT) to reach a reactive transition state in molecules or complexes.2 Now, dual photoredox catalysis,3 that is the combination of metal-promoted processes with photoredox cycles, is in continuous development.4 From the application of synergistic dual photoredox catalysis to cross-coupling reactions, metal-catalyzed processes were addressed to radical to polar crossover reactions (RPC),5 with the aim of developing important C–C bond-forming reactions.6 In this context, alkylation methodologies were introduced with chromium,7 nickel,8 and titanium.9 Particularly, the earth-abundant titanium can give important advantages in terms of sustainability and eco-friendliness of the process,10 and its use in combination with photoredox catalysis was first explored by Gansäuer.11 In addition, the interesting photophysical properties of titanium complexes make the further exploration of their chemistry in the excited state even more intriguing.12 We recently have reported the propargylation reaction of aldehydes, employing 10 mol % of the inexpensive [Cp₂TiCl₂], in the presence of an organic dye, 3DPAFIPN, and Hantzsch’s ester as the stoichiometric reductant.9 Preliminarily, we have also mentioned that the propargylation reaction of aldehydes was also accessible by the dual photoredox-mediated catalysis with titanium,9,16 and herein we illustrate the potentiality, cleanliness, and simplicity of the propargylation reaction conducted under photoredox conditions by the use of propargyl bromide.

Starting by employing hydrocinnamic aldehyde 1a, we have optimized the model propargylation reaction using propargyl bromide, and in general, it was found that the reaction was promoted by the organic dyes 3DPAFIPN, affording the product 3a in good yields. 4CzIPN17 and 3CzClIPN18 were also tested in the model reactions and gave inferior results (Table 1, entries 3 and 4, respectively). All reactions were performed with the cheap and commercially available [Cp₂TiCl₂]. As reported in our allylation reaction,9a the use of THF, with a substrate concentration of 0.05 M, was important to allow the desired transformation due to the strong overlap in the absorbance of the photocatalyst and the titanium complex. The optimized conditions are in line with the photophysical observation because the concentration of the red titanium complex ($\varepsilon$₄₅₅nm ≈ 250 M⁻¹ cm⁻¹) allows a significant absorption of the blue photons by 3DPAFIPN ($\varepsilon$₄₅₅nm ≈ 2900 M⁻¹ cm⁻¹) to promote the photoinduced electron transfer. Hantzsch’s ester was found to be the best choice as the stoichiometric reductant since various sacrificial reductants (i.e., different amines) were proved to be not suited for the propargylation reaction. This is in part related to the

Received: March 4, 2021
Published: April 22, 2021
lack of stability of [Cp2TiCl2] in the presence of different amines under irradiation.16 The propargylation reaction was quite sensitive to traces of oxygen and water, and low yields were isolated, performing the reaction in the presence of oxygen (Table 1, entry 8). It is worth noting that the photocatalyst does not decompose during the photoreaction and can be easily recovered at the end of the reaction by flash chromatography.

It was possible to scale the reaction up to 1.0 mmol, increasing the reaction time to 48 h without observing an appreciable decrease of the yield (Table 1, entry 2).

The selected reaction conditions were employed to test the scope of the reaction with aromatic and aliphatic aldehydes. As evident by the data reported in Scheme 1, aromatic and heteroaromatic aldehydes are suitable substrates for the reaction. Yields are, in general, from good to moderate. The presence of electron-withdrawing groups on the aromatic ring reduced the yield of the reaction. Sterical hindrance in the ortho-position does not hamper the reactivity, with either activating or deactivating groups. Although the oxidized product of Hantzsch’s ester (the corresponding protonated pyridinium) is strongly acidic and could favor undesired reaction pathways involving the indole ring, indole substrates are reactive in the propargylation reaction, giving much better yields compared to what was observed for the allylation reaction.9a Various substituted thiophene carboxaldehydes are suitable substrates for the transformation. As already noted in the allylation reaction, no additives or scavengers are required for the release of the desired homopropargylic alcohol with the concomitant restoration of the titanium complex from homopropargylic alkoxide. As a matter of fact, the protonated pyridine derivative obtained by the oxidation of the Hantzsch’s ester behaves as a scavenger for the reaction, enabling the desired turnover of the employed titanium complex. As was observed for the allylation reaction, also in the photoredox propargylation reaction, 10 mol % of the [Cp2TiCl2] complex gave the optimal catalyst concentration. In all reported examples with aromatic aldehydes, no traces of the possible allenic product were detected by 1H NMR analysis of the crude reaction mixture. The reaction is also quite effective with aliphatic aldehydes (3q–v), and excellent results were obtained (Scheme 2). Branched aliphatic aldehydes were found to be reactive substrates, furnishing the respective homopropargylic alcohols in good yields. In addition, aliphatic aldehydes with acidic protons, whose propargylation products can suffer from undesired water elimination pathways, are suitable substrates. No modifications in the conditions were made to perform the reaction with aliphatic aldehydes with respect to aromatic substrates.

In general, the reactions ran smoothly without any significant inconveniences. Also, with aliphatic aldehydes, the reactions favored the propargylic derivatives in all examined cases. We have briefly investigated the outcome of the reaction in the case of different propargyl bromides (Scheme 3).
Interestingly, the presence of aliphatic or aromatic substituents on the propargylic moiety favors the allenyl product, probably due to the major sterical hindrance of the allenyl titanium intermediate, compared to the propargylic. The synthesis and structural characterizations of allenyl titanocene- (IV) and propargyl titanocene(IV) were reported in literature. These compounds are involved in fast metal-totropic allenyl–propargyl equilibria in solution prior to the electrophilic quenching, as confirmed by DFT calculations. Therefore, the reactivity of differently substituted propargyl halides are controlled by the different energy barriers in transition states relative to the reaction of the propargyl and allenyl titanium(IV) precursors with carbonyls via $S_2^2$ mechanism and not by the metal-totropic equilibria.

The reaction with secondary propargyl bromides gave unsatisfactory simple diastereoselection; in this case, the result could be imputable to the absence of control in the formation of the allenyl titanium intermediate. We have conducted the Stern–Volmer analysis of the reaction, similarity to our previous study of allylation, by simply varying the concentration of propargyl bromide added to the 3DPAFIPN. As illustrated in Figure S3B (see Supporting Information), in air-equilibrated solution, the emission intensity of 3DPAFIPN is barely decreasing upon increasing the concentration of propargyl bromide, thus highlighting a slow diffusional quenching ($k_q \approx 1.0 \times 10^8 M^{-1} s^{-1}$).

The same conclusions can be drawn by observing the negligible changes in the emission lifetime in the presence of propargyl bromide at concentrations up to ca. 0.13 M (Figure S3C). In degassed solutions, the long-excited state lifetime of pristine 3DPAFIPN (172 $\mu$s) is decreasing to 41 $\mu$s upon the addition of propargyl bromide at high concentrations (ca. 0.11 M). The estimated quenching constant is 3 orders of magnitude lower than that determined for $[\text{Cp}_2\text{TiCl}_2]$ in the same experimental conditions ($k_q \approx 10^9$ and $5.2 \times 10^8 M^{-1} s^{-1}$, respectively; see Figure S4B), pointing out that a photo-induced electron transfer is more likely to occur to the latter. However, the 3DPAFIPN is responsible for the formation of $[\text{Cp}_2\text{TiCl}]$ and 3DPAFIPN$^*$. The latter is a strong oxidant ($E(\text{PC}^*/\text{PC}) = +1.30$ vs SCE), and the photoredox cycle is closed by the Hantzsch’s ester ($E(\text{HE}^*/\text{HE}) = +1.0$ vs SCE), which reduces the 3DPAFIPN$^*$ back to 3DPAFIPN. The reaction produces the strong reductant HE$^*$ that can participate in further electron transfer events, generating the rearomatized Hantzsch’s ester, in the form of its pyridinium salt. Furthermore, the oxidative quenching of the photocatalyst in its excited state by the titanium complex $[\text{Cp}_2\text{TiCl}_2]$ generates the $[\text{Cp}_2\text{TiCl}]$ species. A radical-mediated addition $^{32}$ of $[\text{Cp}_2\text{TiCl}]$ to the propargyl bromide gave the corresponding allenyl/proaprgyllic titanium reagents. Subsequent reaction of the allenyl species with aldehydes gave the titanium-alkoxy derivatives that are transformed into the corresponding Hantzsch’s ester pyridinium salt. In fact, the latter is an acidic compound, and it features a low $pK_a$ compared to other reagents used as scavengers in the catalytic redox reaction promoted by titanium chemistry (such as collidine-HCl).$^{23}$

In summary, we have described a direct photoredox propargylation reaction mediated by a cheap and not toxic titanium complex that allows the desired homopropargylic alcohols by acidic protons available from the oxidized Hantzsch’s ester pyridinium salt. In fact, the latter is an acidic compound, and it features a low $pK_a$ compared to other reagents used as scavengers in the catalytic redox reaction promoted by titanium chemistry (such as collidine-HCl).$^{23}$

We have already reported$^{9}$ that Hantzsch’s ester and $[\text{Cp}_2\text{TiCl}_2]$ are effective quenchers of the photocatalyst. It is also worth mentioning that we have also established that the pyridine salt formed in the reaction is not a quencher at any concentration. In the case of propargylation, the absence of quenching with propargylic bromide suggests the mechanism illustrated in Figure 1. The oxidative quenching of

![Figure 1. Proposed catalytic cycle.](https://doi.org/10.1021/acs.joc.7b00521)
doublet of doublet of doublet, td = triplet of doublet, m = multiplet), coupling constants (Hz). Chromatographic purifications were performed with 240–400 mesh silica gel. HPLC-MS analyses were performed on an Agilent Technologies HP1100 instrument coupled with an Agilent Technologies MSD1100 single-quadrupole mass spectrometer using a Phenomenex Gemini C18 3 μm (100 mm × 3 mm) column; mass spectrometric detection was performed as follows: in full-scan mode from m/z 50 to 2500, scan time 0.1 s in positive ion mode, ESI spray voltage 4500 V, nitrogen gas 35 psi, drying gas flow rate 11.5 mL min⁻¹, and fragmentor voltage 30 V. HRMS was performed on a Waters Xevo G2-XX QTof, ESI⁺, cone voltage 40 V, Capillary 3KV, with a source temperature of 120 °C. All reactions were set up under an argon atmosphere in oven-dried glassware (borosilicate) using standard Schlenk techniques. The reaction mixture was irradiated with a Kessil PR160L@456 nm. Lamp technical specifications are available on the manufacturer’s web site. The reaction vessel was placed 10 cm approximately from the lamp, and the temperature was maintained at room temperature by cooling with a PR160 ring w/fan kit. 3DPAFIPN, 4CzIPN, 3CzClIPN, and diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Hantzsch’s Ester) were prepared following literature procedures.

Standard Procedure for Photoredox Titanium-Catalyzed Propargylation of Aldehydes. All reactions were performed on a 0.2 mmol scale of aldehyde. A dry 10 mL Schlenk tube, equipped with a Rotaflow stopcock, magnetic stirring bar, and argon supply tube, was first charged under argon with the organic photocatalyst 2,4,6-tris(diphenylamino)-5-fluoroisophthalonitrile 3DPAFIPN (5 mol %, 0.010 mmol, 6.4 mg), [Cp₂TiCl₂] catalyst (10 mol %, 0.02 mmol, 5.0 mg), and diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, i.e., Hantzsch’s ester (2 equiv, 0.04 mmol, 100 mg). Inhibitor-free dry THF (4 mL, in order to obtain a 0.05 M solution of aldehyde) was then added, the reaction mixture was further subjected to a freeze–pump–thaw procedure (three cycles), and the vessel was refilled with argon. Then, propargyl bromide derivative 2a–d (0.6 mmol, 3 equiv) and the substrate 1a–v (0.2 mmol) were added. The reaction was irradiated under vigorous stirring for 14 h. After that, the reaction mixture was quenched with H₂O (approximately 5 mL) and extracted with AcOEt (4 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, and the solvent was removed under reduced pressure. The crude was subject of flash column chromatography (SiO₂) to afford the products 3a–v, 4a–c, and 5a–b in the stated yields.

Procedure for 1 mmol Scale. A dry 50 mL Schlenk tube, equipped with a magnetic stirring bar and argon supply tube, was first charged under argon with the organic photocatalyst 3DPAFIPN, 2,4,6-tris(diphenylamino)-5-fluoroisophthalonitrile 3DPAFIPN (5 mol %, 0.010 mmol, 6.4 mg), [Cp₂TiCl₂] catalyst (10 mol %, 0.02 mmol, 5.0 mg), and diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, i.e., Hantzsch’s ester (2 equiv, 2 mmol, 0.500 g). Inhibitor-free dry THF (20 mL in order to obtain a 0.05 M solution of aldehyde) was then added, the reaction mixture was further subjected to a freeze–pump–thaw procedure (four cycles), and the vessel was refilled with argon. Then, propargyl bromide 2a (0.80 mmol, 3 equiv) and the substrate 1a (1 mmol, 0.134 g, 0.132 mL) were added. The reaction was irradiated under vigorous stirring for 48 h. After that, the solvent was removed under reduced pressure. The crude was subjected to flash column chromatography (SiO₂) to afford the products 3a in 93% yield (0.93 mmol, 0.162 g). 1-Phenylhex-5-yn-3-ol (3a): brown oil, 98% (0.195 mmol, 34 mg). The general procedure was applied using 1a (0.2 mmol, 26 μL) previously distilled and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 μL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.

1-(2-Chlorophenyl)but-3-yn-1-ol (3c): brown oil, 76% (0.15 mmol, 27 mg). The general procedure was applied using 1c (0.2 mmol, 22.4 μL) previously distilled and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 μL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.

1-(4-Fluorophenyl)but-3-yn-1-ol (3d): brown oil, 78% (0.16 mmol, 22.3 mg). The general procedure was applied using 1d (0.2 mmol, 22 μL) previously distilled and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 μL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.

1-(4-Trifluoromethyl)phenyl)but-3-yn-1-ol (3e): brown oil, 40% (0.08 mmol, 18 mg). The general procedure was applied using 1e (0.2 mmol, 28 μL) previously distilled and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 μL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.

1-(Naphthalen-2-yl)but-3-yn-1-ol (3f): brown oil, 71% (0.14 mmol, 28 mg). The general procedure was applied using 1f (0.2 mmol, 32 mg) and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 μL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.

1-Phenylbut-3-yn-1-ol (3g): brown oil, 58% (0.12 mmol, 18 mg). The general procedure was applied using 1g (0.2 mmol, 20.4 μL) previously distilled and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 μL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.

1-(1,1'-Biphenyl)-4-yl)but-3-yn-1-ol (3h): brown oil, 68% (0.14 mmol, 30.2 mg). The general procedure was applied using 1h (0.2 mmol, 36 mg) and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 μL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.

1-(4-(Tert-Butyl)phenyl)but-3-yn-1-ol (3i): brown oil, 50% (0.1 mmol, 20.2 mg). The general procedure was applied using 1i (0.2 mmol, 32 μL) previously distilled and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 μL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.

1-(4-Methoxyphenyl)but-3-yn-1-ol (3j): brown oil, 56% (0.11 mmol, 19 mg). The general procedure was applied using 1j (0.2 mmol, 26 μL) and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 μL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.

1-(3-Methoxyphenyl)but-3-yn-1-ol (3k): brown oil, 71% (0.14 mmol, 25 mg). The general procedure was applied using 1k (0.2 mmol, 26 μL) and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 μL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.

1-(2-Methoxyphenyl)but-3-yn-1-ol (3l): brown oil, 62% (0.12 mmol, 22 mg). The general procedure was applied using 1l (0.2 mmol, 26 μL) and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 μL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.

1-(Benz[d][1,3]dioxol-5-yl)but-3-yn-1-ol (3m): brown oil, 67% (0.13 mmol, 25 mg). The general procedure was applied using 1m (0.2 mmol, 38 mg) and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 μL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.

1-(Thiophen-3-yl)but-3-yn-1-ol (3n): brown oil, 75% (0.15 mmol, 23 mg). The general procedure was applied using 1n (0.2 mmol, 28 mg) and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 μL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.
mmol, 18 µL) and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 µL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.1

1-(Thiophen-2-yl)but-3-yn-1-ol (3o): brown oil, 40% (0.08 mmol, 12 mg). The general procedure was applied using 1e (0.2 mmol, 8 µL) and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 µL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.2

tert-Butyl 3-(1-Hydroxybut-3-yn-1-yl)-2-methyl-1H-indole-1-carboxylate (3p): brown oil, 68% (0.14 mmol, 41 mg). The general procedure was applied using 1p (0.2 mmol, 52 mg) and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 µL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.3

Pentadec-1-yn-4-ol (3r): brown oil, 99% (0.2 mmol, 36 mg). The general procedure was applied using 1r (0.2 mmol, 32 µL) and 2a (solution 80% v/v in toluene, 0.6 mmol, 56 µL, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM).3

1-(4-Chlorophenyl)-2-phenylhepta-1,3-dien-1-ol and 1-(4-Chlorophenyl)penta-2,3-dien-1-ol (4a′−4b′): brown oil, 76% (0.14 mmol, 36 mg) as a mixture of regioisomers 4a′/4a′ (91:9). The general procedure was applied using 1b (0.2 mmol, 28 mg) and 2b (0.6 mmol, 117 mg, 3 equiv). The ratio of regioisomer was calculated considering the 1H NMR spectrum of the reaction crude and comparing the integral of the signal at 5.10 ppm for 4a′ and at 4.91 ppm for 4b′. The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.4

1-(4-Chlorophenyl)-2-methylpent-3-yn-1-ol and 1-(4-Chlorophenyl)-2-phenylbuta-2,3-dien-1-ol (4b′−4c′): brown oil, 46% (0.11 mmol, 18 mg) as a mixture of regioisomers 4b′/4c′ (66:34). The general procedure was applied using 1b (0.2 mmol, 28 mg) and 2c (0.6 mmol, 52 µL, 3 equiv). The regioisomeric ratio was calculated considering the 1H NMR spectrum of the reaction crude and comparing the integral of the signal at 5.01 ppm for 4b′ and at 4.77 ppm for 4c′. The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.5

Methyl-1-phenylethoxa-4,5-dien-3-ol and 1-phenylethyn-5-yn-3-ol (4d−4e): brown oil, 90% (0.18 mmol, 34 mg) as a mixture of regioisomers 4d/4e (71:29). The general procedure was applied using 1v (0.2 mmol, 26 µL) and 2c (0.6 mmol, 52 µL, 3 equiv). The regioisomeric ratio was calculated considering the 1H NMR spectrum of the reaction crude and comparing the integral of the signal at 4.81 ppm related for 4c′ and at 4.72 ppm for 4e′. The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.4

1-(4-Chlorophenyl)-2-methylpent-3-yn-1-ol and 1-(4-Chlorophenyl)penta-2,3-dien-1-ol (5a−5a′): brown oil, 80% (0.16 mmol, 31 mg) as a mixture of regioisomers and diastereoisomers 5a/5a′ of 97:3, 5a/5a′ and 5a/5a′ dr of 1:1. The regioisomeric ratio was calculated considering the 1H NMR spectrum of the reaction crude and comparing the peaks related for 5a′ and at 5.29 ppm for 5a. The diastereomeric ratio was calculated considering the 1H NMR spectrum of the reaction crude and comparing the integral of the signal at 4.71 ppm for 5a′ and at 4.51 ppm for 5a. The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.5

Methyl-1-phenylethoxa-4,5-dien-3-ol and 1-phenylethyn-5-yn-3-ol (4d−4e): brown oil, 90% (0.18 mmol, 34 mg) as a mixture of regioisomers 4d/4e (71:29). The general procedure was applied using 1v (0.2 mmol, 26 µL) and 2c (0.6 mmol, 52 µL, 3 equiv). The regioisomeric ratio was calculated considering the 1H NMR spectrum of the reaction crude and comparing the integral of the signal at 4.81 ppm related for 4c′ and at 4.72 ppm for 4e′. The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.4

1-(4-Chlorophenyl)-2-methylpent-3-yn-1-ol and 1-(4-Chlorophenyl)penta-2,3-dien-1-ol (5a−5a′): brown oil, 80% (0.16 mmol, 31 mg) as a mixture of regioisomers and diastereoisomers 5a/5a′ of 97:3, 5a/5a′ and 5a/5a′ dr of 1:1. The regioisomeric ratio was calculated considering the 1H NMR spectrum of the reaction crude and comparing the peaks related for 5a′ and at 5.29 ppm for 5a. The diastereomeric ratio was calculated considering the 1H NMR spectrum of the reaction crude and comparing the integral of the signal at 4.71 ppm for 5a′ and at 4.51 ppm for 5a. The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.5
spectrum of the reaction crude, comparing the integral of the signal at 3.54 ppm related to the product $S_{\text{b}}$, and the multiplet (1H) at 3.49 ppm related to the product $S_{\text{b,ate}}$. The general procedure was applied using 1a (0.2 mmol, 26 μL) and 2d (0.6 mmol, 79 mg, 3 equiv). The title compound was isolated by flash column chromatography (100% DCM). Spectroscopic data were in agreement with those reported in literature.15

**Photophysical and Mechanistic Studies.** All photophysical analyses were carried out in air-equilibrated tetrahydrofuran at 298 K unless otherwise specified. UV–vis absorption spectra were recorded with a PerkinElmer £40 spectrophotometer using quartz cells with an optical path length of 1.0 cm. Degassed solutions are obtained by means of repeated pump–freeze–thaw cycles (ca. 4 × 10⁻⁶ mbar) in sealed quartz cuvettes. Luminescence spectra were performed with a PerkinElmer LS-50, a Varian Cary Eclipse, or an Edinburgh FLS920 spectrofluorimeter equipped with a Hamamatsu R928 phototube. Lifetimes shorter than 10 μs were measured by the above-mentioned Edinburgh FLS920 spectrofluorimeter equipped with a TCC900 card for data acquisition in time-correlated single-photon counting experiments (0.5 ns time resolution). The estimated experimental errors are 2 nm on the band maximum, 5% on the molar absorption coefficient, and luminescence lifetime.

**ACKNOWLEDGMENTS**

Prof. P. Ceroni and Dr. M. Marchini are acknowledged for helpful discussions. National project (PRIN 2017 ID: 20174SVYAF) SURSUMCAT “Raising up Catalysis for Innovative Developments” is acknowledged for financial support of this research.

**REFERENCES**

1 For a key contribution, see: Nicewicz, D. A.; MacMillan, D. W. C. Merging Photoredox Catalysis with Organocatalysis: The Direct Asymmetric Alkylation of Aldehydes. Science 2008, 322 (5908), 777–80. For selected reviews on photoredox catalysis, see: (a) Yoon, T. P.; Ischay, M. A.; Du, J. Visible Light Photocatalysis as a Greener Approach to Photochemical Synthesis. Nat. Chem. 2010, 2 (7), 527–532. (b) Narayanam, J. M. R.; Stephenson, C. R. J. Visible Light Photoredox Catalysis: Applications in Organic Synthesis. Chem. Soc. Rev. 2011, 40 (1), 102–113. (c) Xuan, J.; Xiao, W. J. Visible-Light Photoredox Catalysis. Angew. Chem., Int. Ed. 2012, 51 (28), 6828–6838. (d) Skubi, K. L.; Blum, T. R.; Yoon, T. P. Dual Catalysis Strategies in Photochemical Synthesis. Chem. Rev. 2016, 116 (17), 10033–10074. (e) Lang, X.; Zhao, J.; Chen, X. Cooperative Photoredox Catalysis. Chem. Soc. Rev. 2016, 45 (11), 3026–3038. (f) Piret, S. P.; McTiernan, C. D.; Sciano, J. C. Understanding the Kinetics and Spectroscopy of Photoredox Catalysis and Transition-Metal-Free Alternatives. Acc. Chem. Res. 2016, 49 (6), 1320–1330. (g) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. Chem. Rev. 2016, 116 (17), 10075–10166. (h) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. J. Org. Chem. 2016, 81 (16), 6898–6926. (i) Pararasa, M.; Georgyvan, V. Visible Light-Induced Transition Metal-Catalyzed Transformations: Beyond Conventional Photonsensitizers. Chem. Soc. Rev. 2017, 46 (29), 6227–6240. (j) Lee, K. N.; Ngai, M. Y. Recent Developments in Transition-Metal Photoredox-Catalysed Reactions of Carbonyl Derivatives. Chem. Commun. 2017, 53 (98), 13093–13112. (m) Zou, Y. Q.; Hörmann, F. M.; Bach, T. Iminium and Enamine Catalysis in Enantioselective Photochemical Reactions. Chem. Soc. Rev. 2018, 47 (2), 278–290. (n) Larsen, C. B.; Wenger, O. S. Photoredox Catalysis with Metal Complexes Made from Earth-Abundant Elements. Chem. - Eur. J. 2018, 24 (9), 2039–2058.

2 (a) Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. Energy transfer catalysis mediated by visible light: principles, applications, directions. Chem. Soc. Rev. 2018, 47, 7190–7202. (b) Zhou, Y.; Cao, Q.; Wu, Y.; Zhou, Y.; Qiao, L.; Qiu, J.; Xiao, W. Visible-Light-Induced Organic Photochemical Reactions through Energy-Transfer Pathways. Angew. Chem., Int. Ed. 2019, 58 (6), 1586–1604.

3 (Twilton, J.; Le, C. C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. The Merger of Transition Metal and Photocatalysis. Nat. Rev. Chem. 2017, 1, 0052.

4 (Zhang, H. H.; Chen, H.; Zhu, C.; Yu, S. A Review of Enantioselective Dual Transition Metal/Photoredox Catalysis. Sci. China: Chem. 2020, 63 (5), 637–647.

5 (Pitzer, L.; Schwarz, J. L.; Glorius, F. Reductive Radical-Polar Crossover: Traditional Electrophiles in Modern Radical Reactions. Chem. Sci. 2019, 10 (36), 8285–8291.

6 (Wiles, R. J.; Molander, G. A. Photoredox-Mediated Net-Neutral Radical/Polar Crossover Reactions. Isr. J. Chem. 2020, 60 (3–4), 281–293.

7 (a) Schwarz, J. L.; Schäfers, F.; Tlahuext-Aca, A.; Lückemeier, L.; Glorius, F. Diastereoselective Allylation of Aldehydes by Dual Photoredox and Chromium Catalysis. J. Am. Chem. Soc. 2018, 140 (40), 12705–12709. (b) Mitsuhashi, H.; Tanabe, S.; Fuse, H.; Ohkubo, K.; Kanai, M. Catalytic Asymmetric Allylation of Aldehydes with Alkenes through Allylic C(sp³)–H Functionalization Mediated by Organophotoredox and Chiral Chromium Hybrid Catalysis. Chem. Sci. 2019, 10 (12), 3459–3465. (c) Schwarz, J. L.; Huang, H. M.; Paulisch, T. O.; Glorius, F. Dialkylation of 1,3-Dienes by Dual Photoredox and Chromium Catalysis. ACS Catal. 2020, 10 (2), 1621–1627. (d) Tanabe, S.; Mitsuhashi, H.; Kanai, M. Catalytic

**ASSOCIATED CONTENT**

1 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00521.

Photos of reaction setup, copies of NMR spectra, and photophysical study results (PDF)

**AUTHOR INFORMATION**

**Corresponding Authors**

Andrea Gualandi — Alma Mater Studiorum, Università di Bologna, Dipartimento di Chimica “G. Ciamician”, 40126 Bologna, Italy; orcid.org/0000-0003-2403-4216; Email: andrea.gualandi10@unibo.it

Pier Giorgio Cozzi — Alma Mater Studiorum, Università di Bologna, Dipartimento di Chimica “G. Ciamician”, 40126 Bologna, Italy; orcid.org/0000-0002-2677-101X; Email: piergiorgio.cozzi@unibo.it

**Authors**

Francesco Calogero — Alma Mater Studiorum, Università di Bologna, Dipartimento di Chimica “G. Ciamician”, 40126 Bologna, Italy

Marco Di Matteo — Alma Mater Studiorum, Università di Bologna, Dipartimento di Chimica “G. Ciamician”, 40126 Bologna, Italy

Simone Potenti — Alma Mater Studiorum, Università di Bologna, Dipartimento di Chimica “G. Ciamician”, 40126 Bologna, Italy; Scuola Normale Superiore, 56126 Pisa, Italy; orcid.org/0000-0002-6300-3124

Andrea Fermi — Alma Mater Studiorum, Università di Bologna, Dipartimento di Chimica “G. Ciamician”, 40126 Bologna, Italy

Giacomo Bergamini — Alma Mater Studiorum, Università di Bologna, Dipartimento di Chimica “G. Ciamician”, 40126 Bologna, Italy; orcid.org/0000-0002-2135-4073

Complete contact information is available at: https://pubs.acs.org/doi/10.1021/acs.joc.1c00521

**Notes**

The authors declare no competing financial interest.
A. Bergamini, G.; Cozzi, P. G. Cp2TiCl2-Catalyzed Photoredox Catalysis. *Chem. - Eur. J.* 2019, 55 (48), 6838–6841. For a photoredox nickel mediated cyclotropy of aldehydes, see: (b) Li, Y.; Li, W. D.; Gu, Z. Y.; Chen, J.; Xiao, J. B. Photoredox Ni-Catalyzed Branch-Selective Reductive Coupling of Aldehydes with 1,3-Dienes. *ACS Catal.* 2020, 10 (2), 1528–1534.

(9) Gualandi, A.; Calogero, F.; Mazzarini, M.; Guazzi, S.; Fermi, A.; Bergamini, G.; Cozzi, P. G. Cp2TiCl2-Catalyzed Photoredox Allylation of Aldehydes with Visible Light. *ACS Catal.* 2020, 10 (6), 3857–3863. (b) Li, F.; Lin, S.; Chen, Y.; Shi, C.; Yan, H.; Li, C.; Wu, C.; Lin, L.; Duan, C.; Shi, L. Photocatalytic Generation of π-Allyltitanium Complexes via Radical Intermediates. *π C.*

Flowers, R. A.; Gansäuer, A. Titanocenes as Photoredox Catalysts and Ketones Catalyzed by Titanocene(III). *Adv. Synth. Catal.* 2017, 11, 2412–2414. Visit https://www.kessil.com/science/PR160Rig.php. See Supporting Information for reaction set-up pictures.

(14) Ding, C. H.; Hou, X. L. Catalytic Asymmetric Propargylation. *Chem. Rev.* 2011, 111 (3), 1914–1937.

(15) Huang, H. M.; Belotti, P.; Danilucci, C. G.; Glorius, F. Radical Carboligation by Dual Catalysis. *Angew. Chem., Int. Ed.* 2021, 60 (5), 2464–2471.

(16) An isolated example of photoredox mediated propargylation of 4-methoxybenzaldehyde with propargyl bromide and chloride was recently reported, see: (a) Gualandi, A.; Calogero, F.; Mazzarini, M.; Guazzi, S.; Fermi, A.; Bergamini, G.; Cozzi, P. G. Cationic and Anionic Photocatalytic Allylation of Aldehydes and Ketones: Via Dual Titanium and Nickel Catalysis. *Eur. J. Org. Chem.* 2016, 2017 (1), 2427–2439. (b) Justicia, J.; Sancho-Sanz, I.; Alvarez-Manzaneda, R.; Jansen, T. P.; Moreno-Cabrerizo, C.; Foucher, C.; Marchini, M.; Ceroni, P.; Cozzi, P. G. Catalytic Photoredox Allylation of Aldehydes Promoted by a Cobalt Complex. *Adv. Synth. Catal.* 2021, 363 (4), 1105–1111. (b) Potenti, S.; Gualandi, A.; Puggioli, A.; Fermi, A.; Bergamini, G.; Cozzi, P. G. Photoredox Allylation Reactions Mediated by Bismuth in Aqueous Conditions. *Eur. J. Org. Chem.* 2021, 2021, 1624–1627.

(25) https://www.kessil.com/science/PR160L.php. See Supporting Information for reaction set-up pictures.

(27) Schneider, L. M.; Schmiedel, V. M.; Pecchioli, T.; Lentz, D.; Merton, C.; Christmann, M. Asymmetric Synthesis of Carbocyclic Propellanes. *Org. Lett.* 2017, 19, 2310–2313.

(28) Liang, T.; Woo, S. K.; Kirsch, M. J. C-Propargylation Overrides O-Propargylation in Reactions of Propargyl Chloride with Primary Alcohols: Rhodium-Catalyzed Transfer Hydrogenation. *Angew. Chem., Int. Ed.* 2016, 55 (32), 9207–9211.

(29) We have recently reported a photoredox allylation mediated by cobalt and bismuth: (a) Gualandi, A.; Calogero, F.; Mazzarini, M.; Guazzi, S.; Fermi, A.; Bergamini, G.; Cozzi, P. G. Cationic Photoredox Allylation of Aldehydes and Ketones Catalyzed by Titanocene(III). *Adv. Synth. Catal.* 2019, 120, 12849–12859. (b) Gansäuer, A.; Bluhm, H.; Pierobon, M. Emergence of a Novel Catalytic Radical Reaction: Titanocene-Catalyzed Reductive Opening of Epoxides. *J. Am. Chem. Soc.* 1998, 120, 12849–12859. (c) We have recently reported a photoredox allylation mediated by cobalt and bismuth: (a) Gualandi, A.; Calogero, F.; Mazzarini, M.; Guazzi, S.; Fermi, A.; Bergamini, G.; Cozzi, P. G. Cationic Photoredox Allylation of Aldehydes and Ketones Catalyzed by Titanocene(III). *Adv. Synth. Catal.* 2019, 55 (48), 6838–6841. For a photoredox nickel mediated cyclotropy of aldehydes, see: (b) Li, Y.; Li, W. D.; Gu, Z. Y.; Chen, J.; Xiao, J. B. Photoredox Ni-Catalyzed Branch-Selective Reductive Coupling of Aldehydes with 1,3-Dienes. *ACS Catal.* 2020, 10 (2), 1528–1534.

(9) Gualandi, A.; Calogero, F.; Mazzarini, M.; Guazzi, S.; Fermi, A.; Bergamini, G.; Cozzi, P. G. Cp2TiCl2-Catalyzed Photoredox Allylation of Aldehydes with Visible Light. *ACS Catal.* 2020, 10 (6), 3857–3863. (b) Li, F.; Lin, S.; Chen, Y.; Shi, C.; Yan, H.; Li, C.; Wu, C.; Lin, L.; Duan, C.; Shi, L. Photocatalytic Generation of π-Allyltitanium Complexes via Radical Intermediates. *π C.*
(42) Li, W.; Lin, Z.; Chen, L.; Tian, X.; Wang, Y.; Huang, S. H.; Hong, R. Highly Stereoselective Kinetic Resolution of α-Allenic Alcohols: An Enzymatic Approach. *Tetrahedron Lett.* 2016, 57 (5), 603–606.

(43) Miao, W.; Chung, L. W.; Wu, Y. D.; Chan, T. H. Experimental and Theoretical Studies of the Propargyl-Allenylindium System. *J. Am. Chem. Soc.* 2004, 126 (41), 13326–13334.

(44) Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. Scope and Stereochemical Course of the Addition of (Trimethylsilyl)Allenes to Ketones and Aldehydes. A Regiocontrolled Synthesis of Homopropargylic Alcohols. *J. Org. Chem.* 1986, 51 (20), 3870–3878.