

Cp₂TiCl₂-CATALYZED PHOTOREDOX ALLYLATION OF ALDEHYDES WITH VISIBLE LIGHT

Andrea Gualandi, Francesco Calogero, Martino Mazzarini, Simone Guazzi, Andrea Fermi, Giacomo Bergamini, and Pier Giorgio Cozzi

ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.0c00348 • Publication Date (Web): 28 Feb 2020

Downloaded from pubs.acs.org on February 28, 2020

Just Accepted

“Just Accepted” manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides “Just Accepted” as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. “Just Accepted” manuscripts appear in full in PDF format accompanied by an HTML abstract. “Just Accepted” manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). “Just Accepted” is an optional service offered to authors. Therefore, the “Just Accepted” Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these “Just Accepted” manuscripts.

1
2
3
4
5
6
7 **Cp₂TiCl₂-CATALYZED PHOTOREDOX**
8
9
10
11 **ALLYLATION OF ALDEHYDES WITH VISIBLE**
12
13
14
15 **LIGHT**
16
17
18
19

20 *Andrea Gualandi,* Francesco Calogero, Martino Mazzarini, Simone Guazzi, Andrea Fermi,*
21
22 *Giacomo Bergamini,* and Pier Giorgio Cozzi**
23
24
25

26 Dipartimento di Chimica “Giacomo Ciamician”, Alma Mater Studiorum – Università di
27
28 Bologna, Via Selmi 2, 40126, Bologna, Italy
29
30

31 E-mail: andrea.gualandi10@unibo.it; giacomo.bergamini@unibo.it; piergiorgio.cozzi@unibo.it
32
33

34 **KEYWORDS** Titanium • allylation • photoredox catalysis • aldehydes • Hantzsch Ester
35
36
37
38
39
40

41 **ABSTRACT** A Barbier-type Cp₂TiCl₂-mediated (10 mol%) photoredox allylation of aldehydes
42
43 under irradiation with visible light (blue LEDs, 450 nm) and in the presence of an organic dye
44
45 (3DPAFIPN, 5 mol%) with allylbromides is described.
46
47
48
49
50
51

52 Allylation of carbonyls is a key strategy for the preparation of functionalized building blocks
53
54 in the total synthesis of natural products.¹ In particular, allylation reaction realized under Barbier
55
56
57
58
59
60

1
2
3 conditions can give access to transient organometallic reactive allylating species.² Normally,
4 over-stoichiometric amount of sacrificial reductant such as metallic manganese or zinc, in the
5 presence of an active redox metal complex is necessary. In Barbier type allylation performed
6 with catalytic amount of titanium³ or chromium⁴ (Nozaki-Hiyama-Kishi reaction),⁵ the use of a
7 scavenger able to liberate the active metal from the organic product is mandatory for sustaining
8 the catalytic cycle. Pioneering studies reported by Fürstner⁶ and Gansäuer⁷ have introduced the
9 practice of catalytic redox cycle in Organic Synthesis, further developed into interesting
10 stereoselective variants.⁸

11
12
13
14
15
16
17
18
19
20
21
22
23 Photoredox catalysis, by the use of metal complexes, dyes, or semiconductors, can give
24 interesting approaches to radical species by electron transfer (ET) or energy transfer.⁹ The
25 combination of photoredox catalytic cycle with other catalytic cycles, working cooperatively,
26 opens the way to new reaction pathways.¹⁰ Metallaphotoredox catalysis, i.e. metal catalysis
27 merged with photoredox catalysis, is a new and rapidly growing research area.¹¹ Now,
28 photoredox catalysis is starting to explore the possibility to use a clean and rapid access to
29 radicals for generating nucleophilic reagents.¹² This concept, that combines radical and polar
30 chemistry, in a so-called reductive radical-polar crossover (RRPC) was recently reviewed.¹³ In
31 this approach, a suitable alkyl radical is converted into a nucleophile by reduction or by capture
32 with a suitable transition metal complex. These so formed nucleophilic species can then react
33 with electrophiles such as carbonyls or imines.

34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49 Glorius and Kanai have recently reported RRPC photoredox allylation methodologies based on
50 chromium (Figure 1).¹⁴ In these radical reactions, photogenerated allyl radicals are converted
51 into a traditional nucleophilic Cr(III)allyl reagents by means of a single electron reduction
52 carried out by the Cr(II) present in the reaction mixture. The Cr(II) used in catalytic amount was
53
54
55
56
57
58
59
60

re-generated by the photocatalytic cycle. Importantly, these new transformations are still in their infancy, although high enantiomeric excesses can be obtained.^{14b,c}

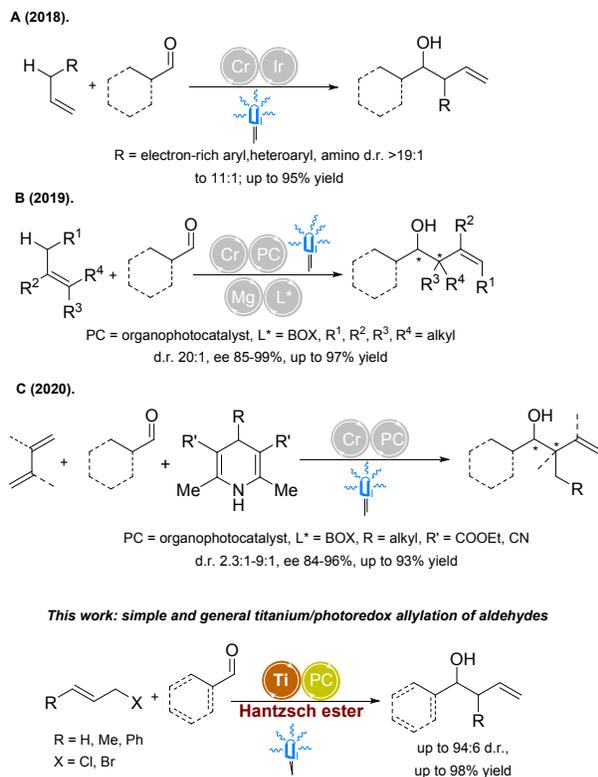
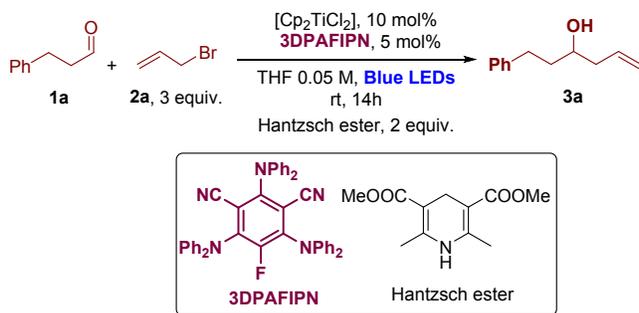


Figure 1. Photoredox synergistic allylations of aldehydes; A, see ref. 14a; B, see ref. 14b; C, see ref. 14c.

In this paper, we report a practical and straightforward radical-polar crossover photoredox allylation of aldehydes mediated by titanium complexes, that give access to a wide range of homoallylic alcohols in high yields. Moreover, the reaction uses 1,3-dicyano-5-fluoro-2,4,6-tris(diphenylamino)-benzene (3DPAFIPN) as the photocatalyst,¹⁵ a cheap and easily prepared organic dye, in the presence of the readily available Hantzsch's ester as sacrificial reductant and scavenger for the titanium complexes.

1
2
3 Recently, we have reported a nickel based dual photoredox approach in the allylation of
4 aldehydes, with a broad scope and functional groups compatibility, by the use of commercially
5 available or easily prepared allylacetates.¹⁶ However, we want to explore the use of affordable
6 green metals and mild reaction conditions. In particular, the use of Cp₂Ti(III)Cl, the Nugent-
7 Rajanbabu reagent,¹⁸ in Barbier-type allylation reactions,¹⁸ is particularly attractive, as titanium
8 is considered non-toxic, environmentally friendly, and abundant.¹⁹
9
10
11
12
13
14
15
16
17

18 Methodologies based on the employment of Cp₂(III)TiCl in catalytic conditions, in the
19 presence of stoichiometric amounts of active metals (Mn) and in combination with 2,4,6-
20 collidine and Me₃SiCl added more interest in this chemistry, leading to the discover of new
21 transformations.²⁰ In addition, recently Gansäuer reported an interesting study on the photoredox
22 titanium mediated reactions of epoxides, combining Cp₂Ti(III)Cl catalysis with photoredox
23 catalysis bypassing the requirement of metallic reductants and stoichiometric acidic additives.²¹
24 Shi and co-workers have recently reported another synergistic utilization of
25 titanocene/photoredox dual catalysis in the radical opening/spirocyclization of epoxyalkynes in
26 the presence of 2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile (4CzIPN) as a photocatalyst and
27 Hantzsch's ester.²² Based on our, Gansäuer and Shi studies, we have settled a new photoredox
28 allylation of aldehydes mediated by catalytic amount of titanium complex, and in Table 1 some
29 key observations about the reaction conditions are reported.
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1. Allylation reaction and variation of some reaction parameters.

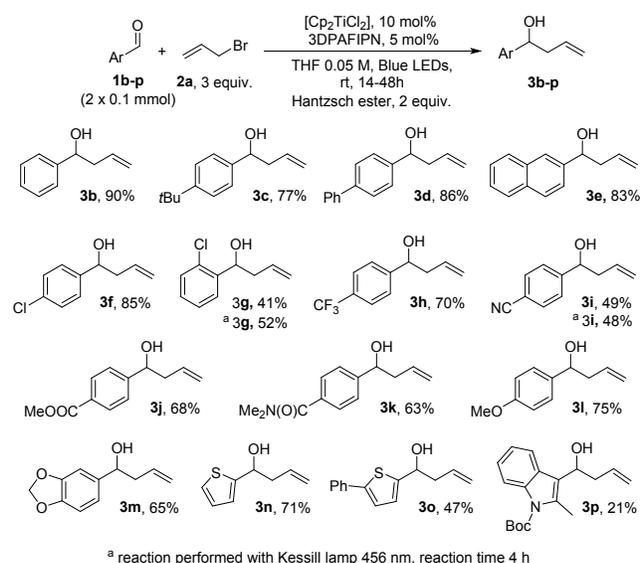
Entry ^a	Deviations from standard conditions	Yield (%) ^b
1	none	>99 (98) ^c
2	40W Kessil [®] lamp 456 nm, 6 h	>99 (98) ^c
3	40W Kessil [®] lamp 456 nm, 14 h, 0.7 mmol scale	>99 (97) ^c
4 ^d	40W Kessil [®] lamp 456 nm, 48 h, 5 mmol scale	>99 (96) ^c
5	4CzIPN instead then 3DPAFIPN	45
6 ^e	{Ir[dF(CF ₃)ppy] ₂ (dtbbpy)}(PF ₆) instead of 3DPAFIPN	96
7 ^e	[Ru(bpy) ₃]Cl ₂ instead of 3DPAFIPN	0
8	No Hantzsch ester	0
9	Allylchloride instead of allylbromide	92
10	No [Cp ₂ TiCl ₂]	0
11	No light	0
12	No degassed solvent	0
13	No photocatalyst, with irradiation at 380 nm	0
14	Toluene instead of THF	60

^a Reactions performed on 0.1 mmol scale. ^b Determined by ¹H-NMR analysis. ^c Isolated yield after chromatographic purification. ^d The reaction was performed using 8 mol% of Cp₂TiCl₂ and 3 mol % of 3DPAFIPN. ^e 1% of the photocatalyst was used.

Hydrocinnamic aldehyde (**1a**) was used in the model reaction, and in general it was found that the reaction was promoted by various photocatalysts (entries 5-6 Table 1, and Table S7), LED sources (entries 1-2, Table 1), with the organic dyes 3DPAFIPN¹⁵ affording good conversions and extremely clean reactions. Other organic dyes were found to be less efficient in promoting the transformation. Different titanium complexes and salts were employed (see Table S3), demonstrating their inferior ability to promote the reaction compared to the cheap and available Cp₂TiCl₂. Reaction conditions were carefully optimized bringing out that THF with a substrate concentration of 0.05 M was crucial. It is also important the role played by the Hantzsch's ester since a series of different sacrificial reductants were found not suitable for the reaction (see Table S5). In this regard, we firstly checked the stability of Cp₂TiCl₂ in the presence of different amines (See Figure S15). The addition of 1,3-dimethyl-2-phenyl-2,3-dihydro-1H-benzo[d]imidazole (BIH), quinuclidine and other aliphatic amines to a mM solution of Cp₂TiCl₂ causes changes in the absorption spectrum attributable to ligand exchange. The bulky triphenylamine (TPA) did not interact with the titanium complex in the ground state, but absorption changes have been observed under visible light irradiation. However, addition of amines was found deleterious, giving practically no conversion (see Table S6). From a practical point of view, the reaction was quite sensitive to traces of oxygen and water. 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. By the use of a Kessil® LED lamp at 456 nm (40 W, for 6 hours, Table 1 entry 2), it was possible to considerably reduce the reaction time and to scale the reaction up to 5 mmol without observing lower conversion and yield (Table 1 entries 3 and 4).

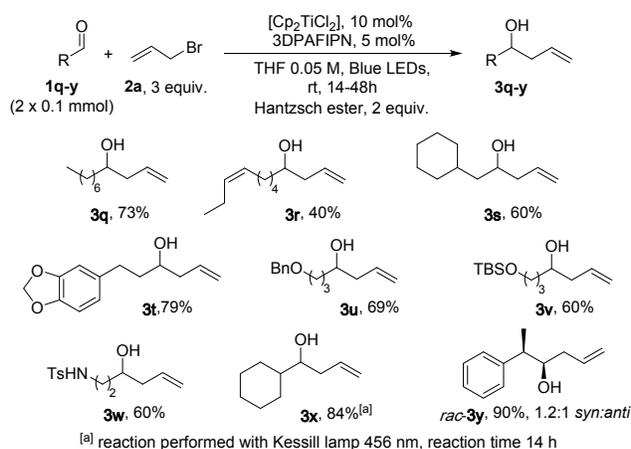
The wide applicability of our initial finding was confirmed with a variety of aromatic and aliphatic aldehydes, and Schemes 1 and 2 illustrate the salient results obtained. As evident by the data reported in Scheme 1, aromatic, and heteroaromatic aldehydes are suitable substrates for the reaction. Yields are good to moderate as a function of the presence of electron-withdrawing groups, that have an impact on the isolated yields. As the Hantzsch ester is oxidized under the reaction conditions to the corresponding protonated pyridinium salt, with concomitant formation of H⁺, acid sensitive substrates such as pyrrole or indole gave lower yields due to decomposition promoted by the presence of Brønsted acids.

Scheme 1. Synergistic allylation reaction of aromatic aldehydes.



Hindered aromatic substrates were found less reactive. In comparison to the published titanium mediated allylation reaction, a minor percentage of titanium (10 vs 20 mol%) it is necessary. No further scavengers or bases are necessary for the titanium as the proton derived from the oxidation of the Hantzsch's ester is able to restore the catalytic cycle acting as a scavenger. Differently substituted linear aliphatic aldehydes are quite suitable substrates as illustrated in Scheme 2 (see Scheme S2 for further substrates studied).

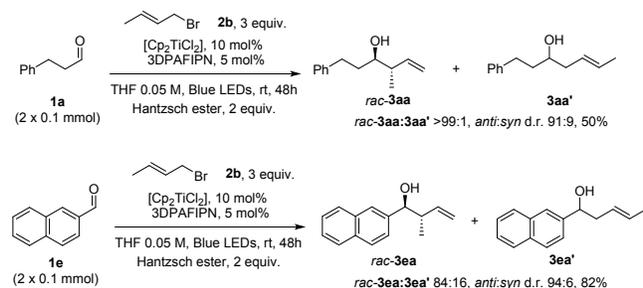
Scheme 2. Synergistic allylation reaction of aliphatic aldehydes.



Hindered aromatic substrates were found less reactive. In comparison to the published titanium irradiation with powerful Kessil[®] lamp is necessary for hindered cyclohexane carboxaldehyde. In the case of pyvalic aldehyde, the reaction gave only low yields (see Scheme S2). Reaction with chiral aldehydes **1y** gave quite moderate diastereoisomeric ratio, in favor of a Felkin-controlled allylation product. The reaction is quite tolerant to functional groups including halides, CF_3 , esters, nitriles, ethers. Interestingly, acidic NH groups were also tolerated although aliphatic or aromatic amines cannot be used.

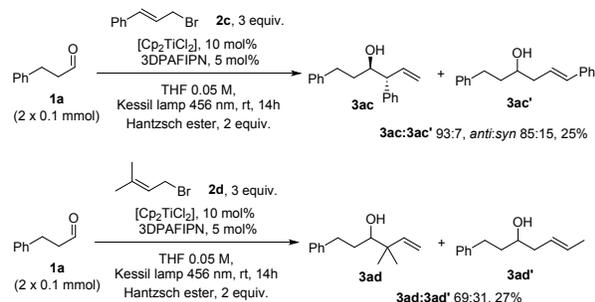
Allyl bromide bearing substituents in three position can be employed with good regioselectivity in favor of the branched products and with moderate to good yields (Scheme 3).

Scheme 3. Synergistic allylation reaction with crotyl bromoderivative.



Allyl substituted reagents are in general less reactive to respect allylbromide under our photoredox condition, as indicated by the preliminary results obtained (Scheme 4) with cinnamyl bromide (**2c**) and in the presence of prenyl bromide (**2d**).

Scheme 4. Synergistic allylation reaction with substituted allyl bromoderivatives.



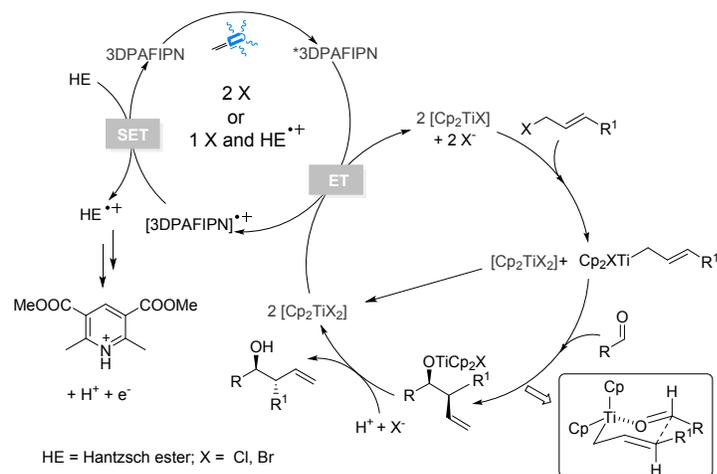
Ketones showed a quite reduced reactivity in this reaction compared to aldehydes, and the corresponding products were isolated in low yields, even using Kessil® lamp (see Scheme S2).

In order to evaluate the photoinduced mechanism of the reaction we investigated the quenching of the photocatalyst's luminescence by each of the components of the reaction (see SI). As observed for similar substituted isophthalonitriles,^{15,23} 3DPAFIPN is particularly suitable in photocatalysis because possesses a very long emission lifetime in degassed solutions at room temperature (0.130 ms in THF at λ_{em} 520 nm, see SI for details). Interestingly, no change in the

1
2
3 intensity and decay of the 3DPAFIPN emission was observed upon addition of the allyl bromide
4 and hydrocinnamic aldehyde (at the same concentrations used to perform the reaction). On the
5
6 other hand, the addition of Hantzsch's ester and Cp_2TiCl_2 induces strong changes in the emission
7
8 intensity of the photocatalyst. In particular, the quenching constants, determined from Stern-
9
10 Volmer experiments, are $1.5 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ for the Hantzsch's ester and $5.2 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ for the Ti
11
12 complex in degassed solutions (as in the employed photoreaction conditions described above). It
13
14 is worth noting that the two Stern-Volmer plots have been obtained using the ratio of the lifetime
15
16 (τ_0/τ) for the quenching relative to Ti, because it re-absorbs the light emitted by 3DPAFIPN, and
17
18 the ratio of the emission intensity (I_0/I) in the case of Hantzsch's ester because of the
19
20 superposition of its emission with pulsed laser source at 405 nm (see SI). To evaluate a possible
21
22 role of the pyridine, produced by the oxidation of the Hantzsch's ester, in the photoinduced
23
24 processes,²⁴ we also test the quenching of 3DPAFIPN emission by this compound. No quenching
25
26 of the excited state of 3DPAFIPN was measured at any concentration of pyridine added (Figure
27
28 S20). The optimized reaction conditions are in line with the photophysical observation, because
29
30 the amount of 3DPAFIPN should be enough to absorb significant blue photons to promote the
31
32 photo induced electron transfer. However, the cost, availability and sustainability of these two
33
34 players, make the present approach extremely competitive for large scale application. The
35
36 determination of the quantum yield carried out gave a value of 1.3 % (see SI for full details).
37
38 Based on the results of the photophysical investigation, and although we cannot exclude short
39
40 radical chains, the tentative catalytic cycle is depicted in Figure 2. The oxidative quenching of
41
42 3DPAFIPN induces the formation of $\text{Cp}_2\text{Ti(III)Cl}$. The 3DPAFIPN $^{\bullet+}$ is a strong oxidant
43
44 ($E_{3\text{DPAFIPN}^{\bullet+}/3\text{DPAFIPN}} = + 1.30 \text{ vs SCE}$)¹⁵ and is reduced by the Hantzsch's ester ($E_{\text{HE}^{\bullet+}/\text{HE}} = +1.0$
45
46 vs SCE).²⁵ The reaction is producing $\text{HE}^{\bullet+}$ that can participate in further electron transfer
47
48
49
50
51
52
53
54
55
56
57
58
59
60

events²⁵ and is a strong reductant. As suggested by Cuerva and Ultra,³ two molecules of $\text{Cp}_2\text{Ti(III)Cl}$ are necessary for the formation of the allyl titanium specie. Two possible scenarios could be envisioned. The two molecules of $\text{Cp}_2\text{Ti(III)Cl}$ are generated by two oxidative quenching of two molecules of *3DPAFIPN. In the other hand, one molecule of Cp_2TiCl_2 is reduced by the *3DPAFIPN and another by the formed $\text{HE}^{\bullet+}$. In experiments carried out with crotyl, cinnamyl, and prenyl reagents (Schemes 3 and 4) we have observed a prevalent γ -regioselectivity. It is well-known that both crotyl-Ti(IV) and prenyl-Ti(IV) reagents react with carbonyl favoring the γ -position.²⁶ As is illustrated in Figure 2, the reaction is probably proceeding through the radical coupling between allyl radicals and $\text{Cp}_2\text{Ti(III)Cl}$, that forms the allylating Ti(IV) reagents. The protonated re-aromatized Hantzsch ester possesses a low pKa (see Scheme S3 for reactions induced by this Brønsted acid), compared to other reagents used as scavengers in the catalytic redox reaction promoted by titanium chemistry (such as collidine and Me_3SiCl), and it is efficient in restoring the catalytic cycle by protonation of the titanium-alkoxy bond.

Figure 2. Proposed mechanism for the reaction.



1
2
3 In summary, we have reported a novel allylation photoredox methodology based on the use of
4 Cp_2TiCl_2 complex. From the point of view of a green chemistry perspective, the abundance and
5 low toxicity of titanium make the procedure attractive for organic synthesis.^{20,27} Careful
6 mechanistic studies has shed light of the application on 3DPAFIPN or parent organic dyes in
7 accessing $\text{Cp}_2\text{Ti(III)Cl}$ reagent, avoiding the use of stoichiometric metal, such as Mn or Zn. The
8 Hantzsch's ester used as stoichiometric reductant is unique for the titanium(III) chemistry, and
9 its oxidized and protonated form is beneficial for the turn-over of the titanium catalyst. Further
10 studies to expand these radical-polar crossover reaction²⁸ and to use other redox reactive metals
11 are in progress and will be reported in due time.
12
13
14
15
16
17
18
19
20
21
22
23

24 AUTHOR INFORMATION

25 26 27 **Corresponding Author**

28 * Prof. P. G. Cozzi Alma Mater Studiorum – Università di Bologna, Via Selmi 2, 40126,
29
30 piergiorgio.cozzi@unibo.it
31
32
33
34

35 36 **Author Contributions**

37
38 A.G., G. B. and P. G. C. conceived the study. Photoredox reactions were carried out by A. G., F.
39 C, and M. M.. S. G and A. F. carried out the photophysical investigations, supervised by G. B..
40
41
42

43 The manuscript was written through contributions of all authors. All authors have given approval
44 to the final version of the manuscript.
45
46
47
48

49 **Funding Sources**

50
51 National project (PRIN 2017 ID: 20174SYJAF) SURSUMCAT "Raising up Catalysis for
52 Innovative Developments" is acknowledged for financial support of this research.
53
54
55
56
57
58
59
60

1
2
3 **Supporting Information.** The following files are available free of charge.

4
5 Reaction optimization studies. Synthetic procedures for allylation reaction and preparation of
6
7 substrates and photocatalysts. Spectroscopic data for new compounds, and copies of NMR
8
9 spectra. Photophysical studies for the model reaction and Stern-Volmer plot.
10
11

12 13 **ACKNOWLEDGMENT**

14
15 Prof. P. Ceroni and Dr. M. Marchini are acknowledged for helpful discussions.
16
17

18 19 **REFERENCES**

20
21 (1) For selected reviews, see:(a) Yus, M.; Gonzalez-Gomez, J. C.; Foubelo, F.
22
23 Diastereoselective Allylation of Carbonyl Compounds and Imines: Application to the Synthesis
24
25 of Natural Products. *Chem. Rev.* **2013**, *111*, 5595-5698; (b) Wang, P.-S.; Shen, M.-L.; Gong, L.-
26
27 Z. Transition-Metal-Catalyzed Asymmetric Allylation of Carbonyl Compounds with Unsaturated
28
29 Hydrocarbons. *Synthesis* **2018**, *50*, 956-967; (c) Spielmann, K.; Niel, G.; de Figueiredo, R. M.;
30
31 Campagne, J.-M. Catalytic Nucleophilic 'Umpoled' π -Allyl Reagents. *Chem. Soc. Rev.* **2018**, *47*,
32
33 1159-1173. (d) Huo, H.-X.; Duvall, J. R.; Huang, M.-Y.; Hong, R. Catalytic Asymmetric
34
35 Allylation of Carbonyl Compounds and Imines with Allylic Boronates. *Org. Chem. Front.* **2014**,
36
37 *1*, 303-320.
38
39
40
41

42
43
44 (2) Enantioselective Chemical Synthesis, E. J. Corey, L. Kürti, 2010, Elsevier, p 79.
45
46

47
48 (3) For the reduction of bis-cyclopentadienyl metal complexes, see: (a) Birmingham, J. M.;
49
50 Fischer, A. K.; Wilkinson, G. The reduction of bis-cyclopentadienyl compounds.
51
52 *Naturwissenschaften* 1955, *42*, 96-96. (b) Estévez, R.E.; Justicia, J.; Bazdi, B.; Fuentes, N.;
53
54 Paradas, M.; Choquesillo-Lazarte, D.; García-Ruiz, J. M.; Robles, R.; Gansäuer, A.; Cuerva, J.
55
56
57
58
59
60

1
2
3 M.; Oltra, J. E. Ti-Catalyzed Barbier-Type Allylations and Related Reactions. *Chem. Eur. J.*
4 **2009**, *15*, 2774-2791; (c) Sancho-Sanz, I.; Miguel, D.; Millán, A.; Estévez, R. E.; Oller-López,
5
6 J. L.; Álvarez-Manzana, E.; Robles, R.; Cuerva, J. M.; Justicia, J. Titanocene(III)-Promoted
7
8 Barbier-type Crotylation of Carbonyl Compounds. *J. Org. Chem.* **2011**, *76*, 732-735.
9

10
11
12
13 (4) Fürstner, A.; Shi, N. Nozaki–Hiyama–Kishi Reactions Catalytic in Chromium. *J. Am.*
14
15 *Chem. Soc.* **1996**, *118*, 12349-12357.
16

17
18
19 (5) Gil, A.; Albericio, F.; Alvarez, M. Role of the Nozaki–Hiyama–Takai–Kishi Reaction in
20
21 the Synthesis of Natural Products. *Chem. Rev.* **2017**, *117*, 8420-8446; and ref. therein. For the
22
23 first catalytic stereoselective variant, see: Bandini, M.; Cozzi, P. G.; Melchioore, P.; Umani-
24
25 Ronchi, A. The First Catalytic Enantioselective Nozaki-Hiyama Reaction. *Angew. Chem. Int. Ed.*
26
27 **1999**, *38*, 3357-3359.
28
29

30
31 (6) Fürstner, A.; Hupperts, A. Carbonyl Coupling Reactions Catalytic in Titanium and the
32
33 Use of Commercial Titanium Powder for Organic Synthesis. *J. Am. Chem. Soc.* **1995**, *117*, 4468-
34
35 4475.
36
37

38
39 (7) Gansäuer, A. Pinacol Coupling of Aromatic Aldehydes Catalysed by a Titanocene
40
41 Complex: a Transition Metal Catalysed Radical Reaction. *Chem. Commun.* **1997**, 457-458.
42
43

44
45 (8) Chromium (Nozaki-Hiyama-Kishi reaction): Hargaden, G. C.; Guiry, P. J. The
46
47 Development of the Asymmetric Nozaki–Hiyama–Kishi Reaction. *Adv. Synth. Catal.* **2007**, *349*,
48
49 2407-2424; Titanium: Gansäuer, A.; Bluhm, H. Reagent-Controlled Transition-Metal-Catalyzed
50
51 Radical Reactions. *Chem. Rev.* **2000**, *100*, 2771-2788.
52
53
54
55
56
57
58
59
60

1
2
3 (9) For a key contribution: Nicewicz, D.; MacMillan, D. W. C. Science Merging Photoredox
4 Catalysis with Organocatalysis: The Direct Asymmetric Alkylation of Aldehydes. *Science* **2008**,
5 322, 77-80. For selected reviews on photoredox catalysis, see: (a) Yoon, T. P.; Ischay, M. A.;
6 Du, J. Visible Light Photocatalysis as a Greener Approach to Photochemical Synthesis. *Nat.*
7 *Chem.* **2010**, 2, 527-532; (b) Narayanam, J. M. R.; Stephenson, C. R. J. Visible Light Photoredox
8 Catalysis: Applications in Organic Synthesis. *Chem. Soc. Rev.* **2011**, 40, 102-113; (c) Xuan, J.;
9 Xiao, W.-J. Visible-Light Photoredox Catalysis. *Angew. Chem. Int. Ed.* **2012**, 51, 6828-6838; (d)
10 Skubi, K. L.; Blum, T. R.; Yoon, T. P. Dual Catalysis Strategies in Photochemical Synthesis.
11 *Chem. Rev.* **2016**, 116, 10035-10074; (e) Lang, X.; Zhao, J.; Chen, X. Cooperative Photoredox
12 Catalysis. *Chem. Soc. Rev.* **2016**, 45, 3026-3038; (f) Pitre, S. P.; McTiernan, C. D.; Scaiano, J. C.
13 Understanding the Kinetics and Spectroscopy Of Photoredox Catalysis And Transition-Metal-
14 Free Alternatives. *Acc. Chem. Res.* **2016**, 49, 1320-1330; (g) N. A. Romero, D. A. Nicewicz,
15 Organic Photoredox Catalysis. *Chem. Rev.* **2016**, 116, 10075-10166; (h) Shaw, M. H.; Twilton,
16 J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, 81,
17 6898-6926. (i) Parasram, M.; Gevorgyan, V. Visible Light-Induced Transition Metal-Catalyzed
18 Transformations: Beyond Conventional Photosensitizers *Chem. Soc. Rev.* **2017**, 46, 6227-6240;
19 (l) Lee, K. N.; Ngai, M.-Y. Recent Developments in Transition-Metal Photoredox-Catalysed
20 Reactions Of Carbonyl Derivatives. *Chem. Commun.* **2017**, 53, 13093-13112; (m) Zou, Y. – Q.;
21 Hoermann, F. M. ; Bach, T.; Iminium and Enamine Catalysis in Enantioselective Photochemical
22 Reactions. *Chem. Soc. Rev.* **2018**, 47, 278-290; (n) Larsen, C. B.; Wenger, O. S. Photoredox
23 Catalysis with Metal Complexes Made from Earth-Abundant Elements. *Chem. Eur. J.* **2018**, 24,
24 2039-2058.
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 (10) Allen, A. E.; MacMillan, D. W. C. Synergistic Catalysis: A Powerful Synthetic Strategy
4 for new Reaction Development. *Chem. Sci.* **2012**, *3*, 633-658.
5
6

7
8 (11) Twilton, J.; Lee, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. The
9 Merger of Transition Metal and Photocatalysis. *Nature Reviews Chemistry* **2017**, *1*, 0052.
10
11

12
13 (12) (a) Pitzer, L.; Sandfort, F.; Strieth-Kalthoff, F.; Glorius, F. Intermolecular Radical
14 Addition To Carbonyls Enabled By Visible Light Photoredox Initiated Hole Catalysis. *J. Am.*
15 *Chem. Soc.* **2017**, *139*, 13652–13655; (b) Pitzer, L.; Sandfort, F.; Strieth-Kalthoff, F.; Glorius, F.
16 Carbonyl-Olefin Cross-Metathesis Through a Visible-Light-Induced 1,3-Diol Formation and
17 Fragmentation Sequence. *Angew. Chem. Int. Ed.* **2018**, *57*, 16219–16223.
18
19
20
21
22
23
24

25
26 (13) Pitzer, L.; Schwarz, J. L.; Glorius, F. Reductive Radical-Polar Crossover: Traditional
27 Electrophiles in Modern Radical Reactions. *Chem. Sci.* **2019**, *10*, 8285-8291.
28
29
30

31
32 (14) (a) Schwarz, J. L.; Schäfers, F.; Tlahuext-Aca, A.; Lückemeier, L.; Glorius, F.
33 Diastereoselective Allylation of Aldehydes by Dual Photoredox and Chromium Catalysis. *J. Am.*
34 *Chem. Soc.* **2018**, *140*, 12705-12709; (b) Mitsunuma, H.; Tanabe, S.; Fuse, H.; Ohkubo, K.;
35 Kanai, M. Catalytic Asymmetric Allylation of Aldehydes with Alkenes Through Allylic C(Sp³)-
36 H Functionalization Mediated by Organophotoredox and Chiral Chromium Hybrid Catalysis.
37 *Chem. Sci.* **2019**, *10*, 3459-3465; (c) Schwarz, J. L.; Huang, H.-M.; Paulisch, T. O.; Glorius, F.
38 Dialkylation of 1,3-Dienes by Dual Photoredox and Chromium Catalysis. *ACS Catal.* **2020**, *10*,
39 1621-1627; (d) Yahata, K.; Sakurai, S.; Yoshioka, S.; Kaneko, Y.; Hasegawa, K.; Akai, S.
40 Coupling Reaction between Aldehydes and Non-Activated Hydrocarbons via the Reductive
41 Radical-Polar Crossover Pathway. *Org. Lett.* **2020**, *22*, 1199-1203; (e) Schwarz, L. J.;
42 Kleinmans, R.; Paulisch, T. O.; Glorius, F. 1,2-Amino Alcohols via Cr/Photoredox Dual-
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 Catalyzed Addition of α -Amino Carbanion Equivalent to Carbonyls. *J. Am. Chem. Soc.* **2020**,
4 142, 2168-2174. For a Photoredox Barbier allylation performed in absence of metals, but limited
5
6 to aromatic aldehydes see: Berger, A. L.; Donabauer, K.; König, B. Photocatalytic Barbier
7
8 Reaction – Visible-Light Induced Allylation And Benzylolation Of Aldehydes and Ketones. *Chem.*
9
10 *Sci.* **2018**, *9*, 7230-7235.
11
12
13
14

15
16 (15) Speckmeier, E.; Fischer, T. G.; Zeitler, K. A Toolbox Approach to Construct Broadly
17
18 Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox
19
20 Potentials and Importance of Halogens in Donor–Acceptor Cyanoarenes. *J. Am. Chem. Soc.*
21
22 **2018**, *140*, 15353-15356.
23
24
25

26 (16) (a) Gualandi, A.; Rodeghiero, G.; Faraone, A.; Patuzzo, F.; Marchini, M.; Calogero, F.;
27
28 Perciaccante, R.; Jansen, T. P.; Ceroni, P.; Cozzi, P. G. Allylation Of Aldehydes By Dual
29
30 Photoredox And Nickel Catalysis. *Chem. Commun.* **2019**, *55*, 6838-6841. For a photoredox
31
32 nickel mediated crotylation of of aldehydes, see: (b) Li, Y.-L.; Li, W.-D.; Gu, Z.-Y.; Chen, J.;
33
34 Xia J.-B. Photoredox Ni-Catalyzed Branch-Selective Reductive Coupling of Aldehydes with 1,3-
35
36 Dienes. *ACS Catal.* **2020**, *10*, 1528-1534.
37
38
39

40
41 (17) (a) Nugent, W. A.; RajanBabu, T. V. Transition-Metal-Centered Radicals in Organic
42
43 Synthesis. Titanium(III)-Induced Cyclization of Epoxy Olefins. *J. Am. Chem. Soc.* **1988**, *110*,
44
45 8561–8562; (b) RajanBabu, T. V.; Nugent, W. A. Selective Generation of Free Radicals from
46
47 Epoxides Using a Transition-Metal Radical. A Powerful New Tool for Organic Synthesis. *J. Am.*
48
49 *Chem. Soc.* **1994**, *116*, 986–997. For a review: c) Rosales, A.; Rodríguez-García I.; Muñoz-
50
51 Bascón, J.; Roldan-Molina, E.; Padial, N. M.; Morales, L. P.; GarcíaOcaña, M.; Oltra, J. E. The
52
53
54
55
56
57
58
59
60

1
2
3 Nugent Reagent: A Formidable Tool in Contemporary Radical and Organometallic Chemistry.
4
5 *Eur. J. Org. Chem.* **2015**, 4567-4591.
6
7

8
9 (18) See reference (3). For a review, see: Rossi, B.; Prosperini, S.; Pastori, N.; Clerici, A.;
10 Punta, C. New Advances in Titanium-Mediated Free Radical Reactions . *Molecules* **2012**, *17*,
11 14700-14732.
12
13

14
15
16 (19) Rodríguez, M. C.; Rodríguez-García, I.; Rodríguez-Maecker, R. N.; Pozo-Morales, L.;
17 Oltra, J. E.; Rosales-Martínez, A. Cp₂TiCl: An Ideal Reagent for Green Chemistry? *Org.*
18 *Process Res. Dev.* **2017**, *21*, 911-923.
19
20
21

22
23
24 (20) Selected references: a) Justicia, J.; Oller-López, J. L.; Campaña, A. G.; Oltra, J. E.;
25 Cuerva, J. M.; Buñuel, E.; Cárdenas, D. J. 7-endo Radical Cyclizations Catalyzed by
26 Titanocene(III). Straightforward Synthesis of Terpenoids with Seven-Membered Carbocycles. *J.*
27 *Am. Chem. Soc.* **2005**, *127*, 14911–14921; (b) Friedrich, J.; Dolg, M.; Gansäuer, A.; Geich-
28 Gimbel, D.; Lauterbach, T. A Combined Theoretical and Experimental Study of Efficient and
29 Fast Titanocene-Catalyzed 3-exo Cyclizations. *J. Am. Chem. Soc.* **2005**, *127*, 7071-7077; c)
30 Friedrich, J.; Walczak, K.; Dolg, M.; Piestert, F.; Lauterbach, T.; Worgull, D.; Gansäuer, A.
31 Titanocene Catalyzed 4-exo Cyclizations: Mechanism, Experiment, Catalyst Design. *J. Am.*
32 *Chem. Soc.* **2008**, *130*, 1788-1796; (d) Gansäuer, A.; Kube, C.; Daasbjerg, K.; Sure, R.;
33 Grimme, S.; Fianu, G. D.; Sadasivam, D. V.; Flowers, R. A. Substituent Effects and
34 Supramolecular Interactions of Titanocene(III) Chloride: Implications for Catalysis in Single
35 Electron Steps. *J. Am. Chem. Soc.* **2014**, *136*, 1663-1671; (e) Funken, N.; Mühlhaus, F.;
36 Gansäuer, A. General, Highly Selective Synthesis of 1,3- and 1,4-Difunctionalized Building
37 Blocks by Regiodivergent Epoxide Opening. *Angew. Chem. Int. Ed.* **2016**, *55*, 12030-12034; (f)
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Mühlhaus, F.; Weißbarth, H.; Dahmen, T.; Schnakenburg, G.; Gansäuer, A. Merging Regiodivergent Catalysis with Atom-Economical Radical Arylation. *Angew. Chem. Int. Ed.* **2019**, *58*, 14208-14212.

(21) Zhang, Z.; Richrath, R. B.; Gansäuer, A. Merging Catalysis in Single Electron Steps with Photoredox Catalysis—Efficient and Sustainable Radical Chemistry. *ACS Catal.* **2019**, *9*, 3208-3212.

(22) Lin, S.; Chen, Y.; Li, F.; Shi, C.; Shi, L. Visible-Light-Driven Spirocyclization of Epoxides via Dual Titanocene and Photoredox Catalysis. *Chem. Sci.* **2020**, *11*, 839-844.

(23) (a) Wex, B.; Kaafarani, B. R. Perspective on Carbazole-Based Organic Compounds As Emitters And Hosts In TADF Applications. *J. Mater. Chem. C*, **2017**, *5*, 8622-8653; (b) Berger, A. L.; Donabauer, K.; König, B. Photocatalytic Carbanion Generation From C–H Bonds – Reductant Free Barbier/Grignard-Type Reactions. *Chem. Sci.* **2019**, *10*, 10991-10996; (c) Meng, Q.-Y.; Schirmer, T. E.; Berger, A. L.; Donabauer, K.; König, B. Photocarboxylation of Benzylic C–H Bonds. *J. Am. Chem. Soc.* **2019**, *141*, 11393-11397.

(24) Bieszczad, B.; Perego, L. A.; Melchiorre, P. Photochemical C-H Hydroxyalkylation of Quinolines and Isoquinolines. *Angew. Chem. Int. Ed.* **2019**, *58*, 16878-16883.

(25) Wang, P. Z.; Chen, J.-R.; Xiao, W.-J. Hantzsch Esters: An Emerging Versatile Class of Reagents In Photoredox Catalyzed Organic Synthesis. *Org. Biomol. Chem.* **2019**, *17*, 6936-6951.

(26) (a) Reetz, M. T.; Sauerwald, M. Reversal of Diastereoselectivity in the BF₃-Promoted Addition of Halobis(Cyclopentadienyl)Crotyltitanium Compounds to Aldehydes. *J. Org. Chem.* **1984**, *49*, 2292 –2295; (b) Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. New, Efficient

1
2
3 Method for the Synthesis of Allyltitanium Compounds from Allyl Halides or Allyl Alcohol
4 Derivatives via Oxidative Addition. A Highly Efficient and Practical Synthesis of Homoallyl
5 Alcohols. *J. Am. Chem. Soc.* **1995**, *117*, 3881-3882.
6
7
8
9

10
11 (27) McCallum, T.; Wu, X.; Lin, S. Recent Advances in Titanium Radical Redox Catalysis. *J.*
12 *Org. Chem.* **2019**, *84*, 14369-14380.
13
14

15
16
17 (28) Propargylic and benzylic bromides are compelling substrates for this chemistry.
18
19
20
21
22
23
24
25
26
27
28
29

