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Allylic Compounds

Photocatalytic Generation of π-Allyltitanium Complexes via Radical Intermediates

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Abstract: *The addition of π-allylmetal complexes to carbonyls is the most important route to homoallylic alcohols. This study reports the first photocatalytic generation of π-allyltitanium complexes by a radical strategy. This novel strategy enables the three-component allylation of carbonyls with 1,3-butadiene, providing rapid access to valuable homoallylic alcohols (over 60 examples). The exceptional regio- and diastereoselectivity provided by dual photoredox/Ti catalysis is comparable to that of the Cr-catalyzed Nozaki–Hiyama–Kishi allylation reaction.*

The development of more sustainable and efficient synthetic strategies is at the core of organic chemistry. Homoallylic alcohols and their derivatives are important building blocks for the synthesis of various pharmaceuticals and biologically active natural products. The addition of various π-allylmetal complexes to carbonyls is one of the most powerful methods that has been developed to access homoallylic alcohols and has contributed to the fast growth of synthetic and medicinal chemistry in the past decades.[1,2] However the tedious and uneconomical preparation of sensitive π-allylmetal complexes that relies on pre-activated allylic halides and stoichiometric metallic reductants has restricted their widespread application.[3]

Among the various transition metals, titanium is one of the cheapest and in general nontoxic and environmentally friendly.[4] These features and its rich redox properties make it especially attractive for organic transformations.[5,6] Usually, π-allyltitanium complexes **1** are prepared by the reaction of Cp_2TiCl_2 with allylmagnesium bromide or oxidative addition of allyl halides to Cp_2TiCl_2 in the presence of stoichiometric metallic reductants (Figure 1a).[7,8] Given that $Cp_2Ti^{III}Cl$ is a powerful and mild single-electron reductant,[9–11] we wondered whether π-allyltitanium^{IV} complexes **1** can be produced via single-electron reduction of the allylic radicals with $Cp_2Ti^{III}Cl$ (Figure 1b). Recently, Glorius et al. reported the generation of π-allylpalladium complexes by the addition of a hybrid alkyl Pd^{I} radical to butadiene.[12] Another example for the generation of π-allylchromium complexes from butadiene was reported by Takai et al. and recently further developed by the groups of Zhang and Glorius.[13]

Metallaphotoredox catalysis has become a powerful tool in organic synthesis.[14–19] In this respect, we envisioned that under photoreductive conditions the Ti^{III}, as well as the alkyl radical would be generated via the photoinduced SET process (Figure 1c).[20,21] The highly reactive allyl radical **2**, resulting from the addition of an alkyl radical to a butadiene, is anticipated to be captured by the mild reducing agent Ti^{III}, thus producing the nucleophilic π-allyltitanium complexes **1** that could be successively coupled with carbonyls.[22,23] There are several challenges to complete this process: (i) alkyl radical should be added to butadiene quickly, or else it will be over-reduced to alkane; (ii) Ti^{III} should selectively capture the allyl radical **2** and not react with alkyl radical, as the resulting alkyl-Ti species can be hydrolyzed quickly under acidic conditions; (iii) aromatic aldehydes and ketones are known to be reduced by photocatalysis in the presence of Hantzsch ester (HE).[24]

With the aforementioned challenges in mind, we started our study by examining butadiene, phenylpropionaldehyde **5a**, and ethyl bromodifluoroacetate **4** as radical precursors. After a systematic variation of different reaction parameters, we successfully identified the optimal reaction conditions in which a mixture of Cp_2TiCl_2 (5.0 mol%), [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (**Ir-2**, 1.0 mol%, $E_{1/2}^{IV/III*} = -0.96$ V vs. SCE in acetonitrile), HE (2.0 equiv) and **5a** (1.0 equiv) in tetrahy-

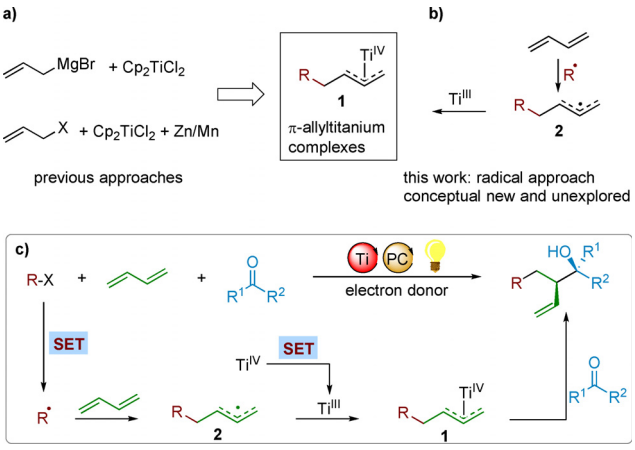

Figure 1. a) Previous ionic approaches. b) Conceptual new radical approach (unexplored). c) Three-component allylation of carbonyls with 1,3-butadiene and alkyl halides.

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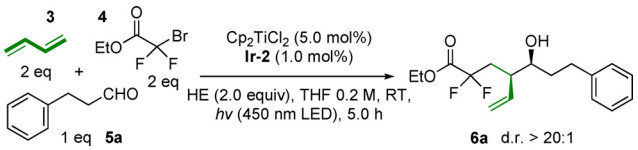
drofuran (THF) at room temperature under irradiation with a 450 nm light emitting diode (LED) lamp for only 5 hours afforded the desired product **6a** with an excellent yield of 89% (d.r. > 20:1, Table 1, entry 1). Further screening of other photosensitizers revealed that the low-cost and readily available organic dye 4CzIPN ($E_{1/2}^{P/P-} = -1.21$ V vs. SCE in acetonitrile) is a suitable alternative, which led to full conversion with an 85% yield (entry 3). Slightly decreasing the reaction concentration to 0.1 M led to an increase in the yield to the highest level of 92% (entry 5). Various solvents, including dichloroethane, acetonitrile, and toluene, were evaluated, and they all resulted in less yields but did not affect the diastereoselectivity (entries 6–8). The use of other organic electron donors, such as N,N-diisopropylethylamine (DIPEA) instead of HE, resulted in no product (entry 9). Irradiation with a white LED instead of a 450-nm LED for 20 hours produced **6a** with 73% yield (entry 10). Use of various transition metals did not give any product **6a** (entry 11). Notably, the reaction did not proceed in the absence of HE, the photocatalyst, or visible light. Condition-based sensitivity screening[25] revealed that the reaction is sensitive toward H_2O and high oxygen concentration (see Section 5 in the Supporting Information).

Next we undertook to optimize the allylation reaction for more challenging ketones. To the best of our knowledge, three-component allylation of ketones with butadiene has not been reported.[13,22] Under optimal conditions for aldehydes, the yield of the product was only 28% (Table 2, entry 1). This is probably due to the rapid consumption of **4**. With this in mind, we found that tuning the light source to a low energy white LED slowed down the generation of allyl radical **2** and increased the yield to 59% (entry 2). Further optimization of the conditions revealed that increasing the Cp_2TiCl_2 loading increased the yield up to 78% after 40 hours (entries 3 and 4).

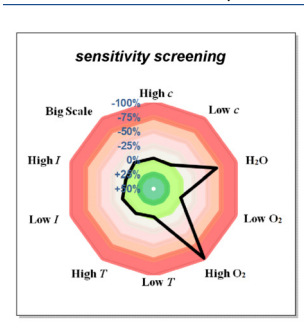
After establishing the optimal conditions, we then investigated the scope of the allylation reactions. Notably, the reaction worked well with various aliphatic/aromatic aldehydes as well as aliphatic/aromatic ketones and afforded the homoallylic alcohols in generally good to excellent yield with surprisingly high diastereoselectivity (Table 3). It was found that the aromatic ring substituent effect can affect the regioselectivity of the product. The electron-rich group **5m** or neutral group **5k** only produced γ-adducts **6m** and **6k**. Carbonyls with electron withdrawing groups, such as fluorine (**5s** and **7l**), led to α-adducts. However, this α-addition pathway can be significantly suppressed by adding LiCl (for detailed discussion, please see the mechanism section). Unsymmetrical dialkyl ketones are extremely challenging substrates for allylation due to the minimal steric differentiation between the two different alkyl groups attached to the carbonyl. Excitingly, our system displayed outstanding regio- and diastereoselectivity for this type of substrate, including **7i** and **7j**. Additionally, the highly active conjugated aldehyde **5h**, and the steric hindered aldehydes **5l** and **5j** were successfully allylated. Ring strain molecules, such as cyclobutanone **7a** and 3-oxetanone **7b** were used and produced alcohols **8a** and **8b** in good yield. Heteroatoms, such as oxygen **7b**, sulfur **7h** and protected amine **5e**, did not interfere with the catalytic cycle. Furthermore, various heteroarenes, the most widely used core structures in pharmaceutical synthesis, were also compatible with this dual catalysis system, including furan **5w**, thiophene **5y**, benzothiophene **7r** and benzofuran **7s**. Photocatalytic conditions provided broad compatibility with numerous synthetically important and sensitive functional groups due to the extremely mild conditions. These included free phenols **5n**, ether **5m**, alkene **5i**, and iodobenzene **7o**. In further substrate scope studies, screening of alkyl halides and nonfluoro α-

Table 1: Reaction optimization for aldehydes.[a,b,c]



Entry	Variation from standard conditions	Yield [%]
1	none	89
2	$Ir(ppy)_2(dtbbpy)PF_6$ **Ir-1** instead of **Ir-2**	86
3	4CzIPN instead of **Ir-2**	85
4	$Ru(bpy)_3(PF_6)_2$ **Ru-1** instead of **Ir-2**	0
5	0.1 M instead of 0.2 M	92
6	dichloroethane instead of THF	77
7	acetonitrile instead of THF	68
8	toluene instead of THF	82
9	DIPEA instead of HE	0
10	white LED instead 450 nm LED, 20 h	73
11	$CoCl_2$,$NiCl_2$,$ZnCl_2$,$FeCl_3$,$TiCl_4$ instead of Cp_2TiCl_2	0

[a] Reaction conditions: **5a** (1.0 mmol scale). [b] Yields were determined by ^{1}H NMR spectroscopy versus an internal standard. [c] Diastereomeric ratios were determined by ^{1}H NMR spectroscopy.



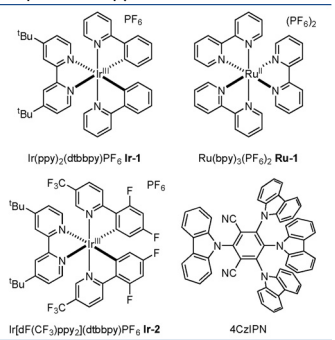
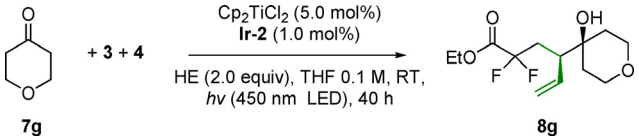


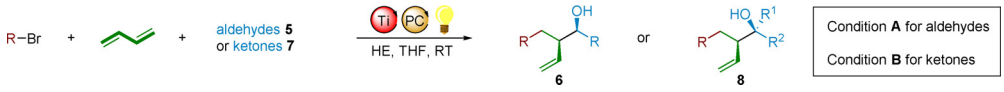
Table 2: Reaction optimization for ketones.[a,b,c]

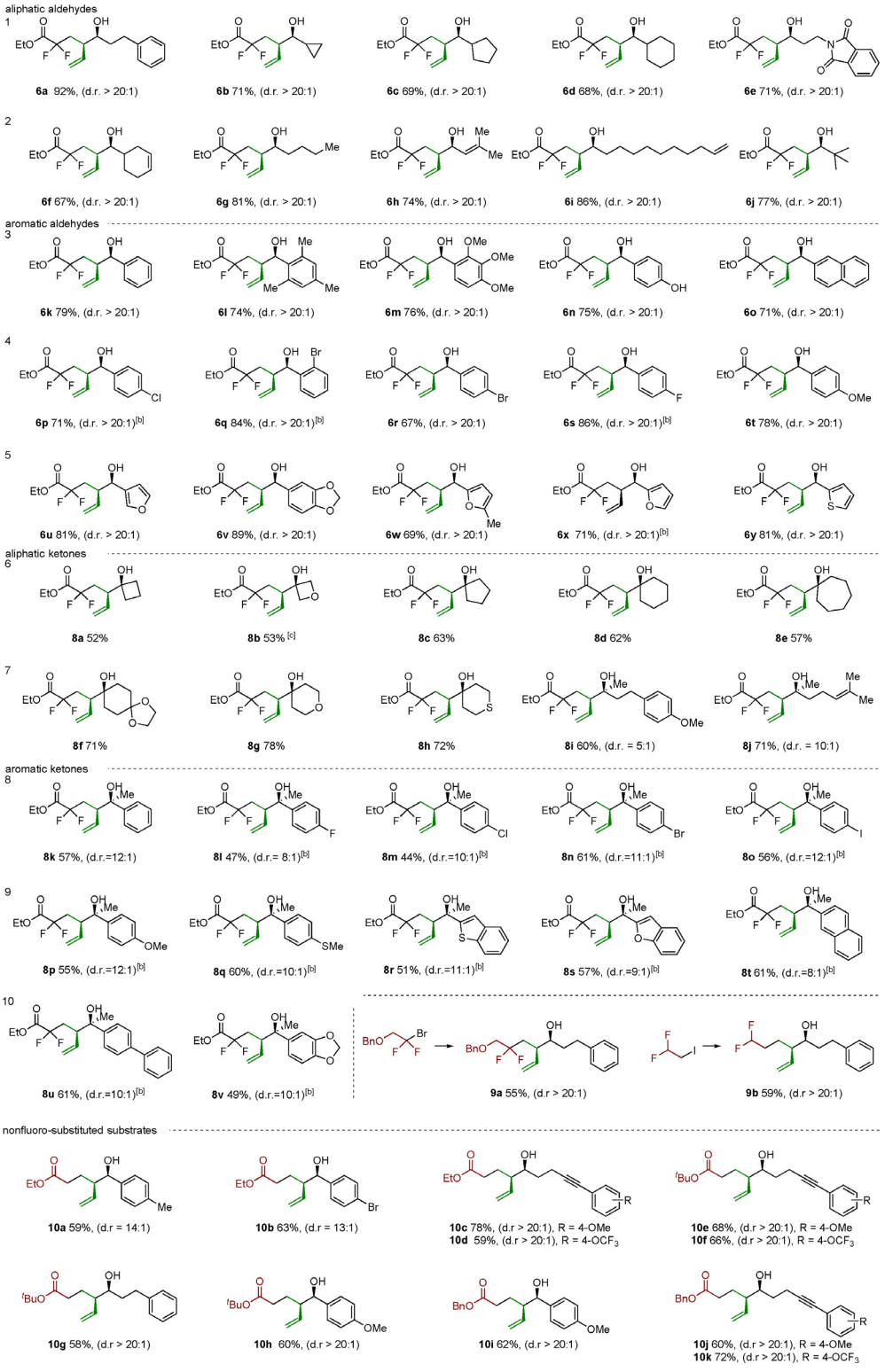


Entry	Variation from standard conditions	Yield [%]
1	none	28
2	white LED instead 450 nm LED	59
3	white LED instead 450 nm LED, 10 mol% Cp_2TiCl_2	71
4	white LED instead 450 nm LED, 20 mol% Cp_2TiCl_2	78

[a] Reaction conditions: **7g** (1.0 mmol scale). [b] Yields were determined by ^{1}H NMR spectroscopy versus an internal standard. [c] Diastereomeric ratios were determined by ^{1}H NMR spectroscopy.

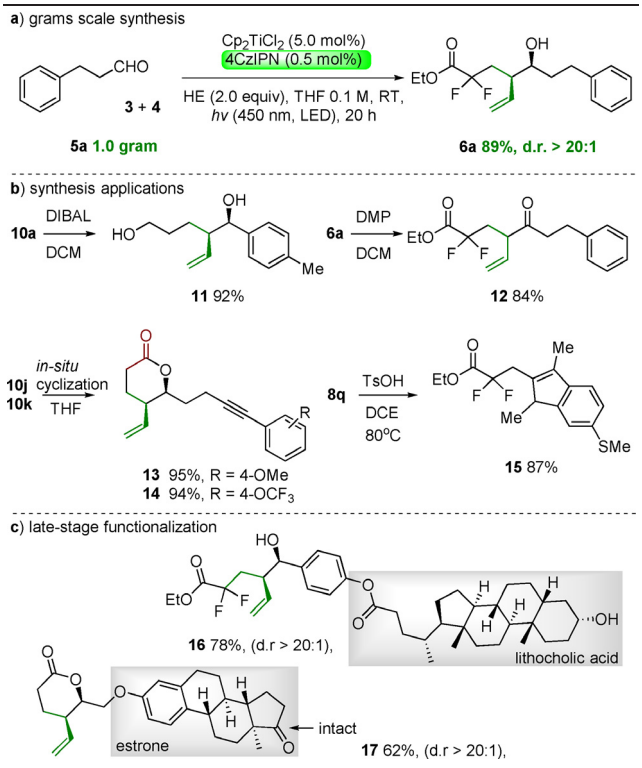
Table 3: Scope of allylation with butadiene.[a]





[a] Reactions were performed on a 1.0-mmol scale of **5** or **7** (THF 0.1 M); Condition **A**: Cp_2TiCl_2 (5.0 mol%), **Ir-2** (1.0 mol%), HE (2 equiv), butadiene (2.0 equiv), 450 nm LED, **2** (2 equiv), **5** (1 equiv), 10 hours; condition **B**: Cp_2TiCl_2 (20.0 mol%), **Ir-2** (1.0 mol%), HE (2 equiv), butadiene (2.0 equiv), **2** (2 equiv), **7** (1 equiv), white LED, 40 hours (for details please see Section 7 in the Supporting Information). [b] 2.0 equiv of LiCl was added. [c] **8b** is unstable and gives product **8b′** (see Section 8 in the Supporting Information).

Table 4: synthetic applications.[a]



[a] DIBAL-H = diisobutyl aluminium hydride, DMP = Dess–Martin periodinane, TsOH = 4-methylbenzenesulfonic acid.

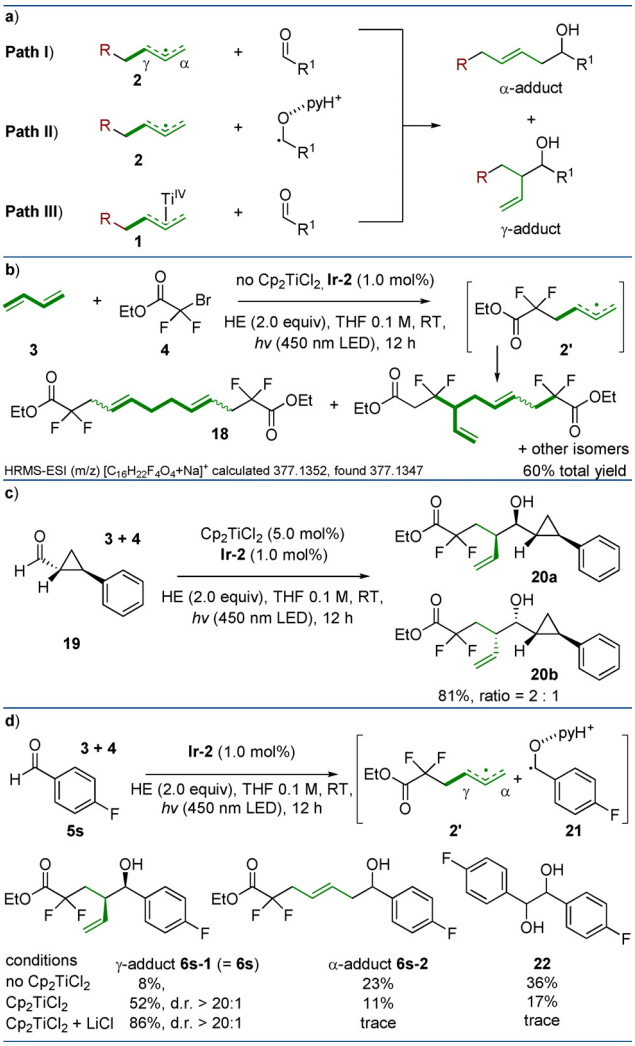


Figure 2. a) Possible reaction pathways. b) The presence of an allyl radical **2′** and its dimerization. c) Radical clock experiments. d) Radical–radical coupling of **2′** and ketyl radical **21**, stereochemistry of γ-adduct **6s-1** is identical to **6s** based on NMR spectroscopy analysis.

bromo carboxylates showed them to be good substrates as well. Moreover, good yields and excellent d.r. values of **9(a-b)** and **10(a-k)** were obtained.

A gram-scale synthesis of **6a** was performed using 4CzIPN with a photocatalyst loading of just 0.5 mol% (Table 4). Satisfyingly, an 89% yield of **6a** was obtained, showing the scalability of the reaction. Homoallylic alcohols are valuable intermediates in organic synthesis and can participate in a wide range of transformations. To explore the utility of the allylation products, product **10a** was subjected to DIBAL-H reduction resulting in the formation of diol **11**. Oxidation of **6a** by DMP produced ketone **12**. Interestingly, alcohol **10j** and **10k** could be transformed in situ to δ-lactones **13** and **14** smoothly. Notably, treatment of **8q** gave indene **15** with 87% yield. Both δ-lactones and indenes are prevalent moieties in natural products or biologically active pharmaceutical agents. To show the potential applicability of our strategy in late-stage functionalization, lithocholic acid and estrone derivatives were used and the desired product **16** and **17** were obtained in good yield without addition to ketone.

There are three possible pathways for the reaction (Figure 2a), including the addition of allyl radical **2** to carbonyls (path **I**), radical coupling of **2** and ketyl radical (path **II**), and the addition of **1** (path **III**) to carbonyls. First, the reactions were performed in the absence of Ti and carbonyls. In this case the allyl radical dimerization product **18**, together with its isomeric products, were isolated in 60% yield (Figure 2b). Thus, the allyl radical **2′** is indeed generated under the photocatalytic conditions independent of Ti and can be added to butadiene before further reduction. Second, the successful allylation of 2-phenyl-cyclopropane-1-carboxaldehyde **19** suggested that the ketyl radical intermediates are not likely involved in the reaction (Figure 2c). For the same reaction, but without Ti, aldehyde **19** was recovered and only dimer **18** was obtained. Therefore, path **I** can be excluded. Additionally, electron-deficient substrates, such as *p*-fluorobenzaldehyde **5s** was used for the allylation in the absence of Ti (Figure 2d). In this case pinacol **22** was obtained via dimerazation of ketyl radical **21**. The α-adduct **6s-2** and γ-adduct **6s-1** (identical to **6s**) were also obtained by the radical–radical coupling of **2′** and ketyl radical **21**. In contrast, the same reaction in the presence of Ti gave **6s-1** as a major product together with **6s-2**. These results clearly indicated that both path **II** and **III** were operative. However, path **III** was the main pathway when Ti participated in catalytic cycle and transformed allyl radical **2′** to a nucleophilic π-allyltitanium complex **1** that led to **6s-1** as major product. The yield of **6s-1** can be further improved to 86% by adding LiCl.

Although its exact role is not clear at this stage, it seems that LiCl can suppress the formation of ketyl radical **21** under the current conditions.

To further understand the nature of the photocatalytic process, several photochemical experiments were performed. First, Stern–Volmer luminescence quenching studies revealed that HE, Cp_2TiCl_2, and **4** can quench the excited state of the photocatalyst, thus both reductive and oxidative quenching can occur (see Section 2 in the Supporting Information). Second, the reaction is light-dependent as indicated by the on-off-light experiment. Furthermore, the quantum yield of the reaction was calculated to be 0.08 (see Section 4 in the Supporting Information).

Based on these results, we tentatively propose the following catalytic cycle (Figure 3). First, alkyl halides are reduced by the $\mathbf{Ir^{III}}$ complex to produce the alkyl radical, which can be rapidly added to butadiene to form the allyl radical **2**. Concurrently, Ti^{IV} is reduced by another $\mathbf{Ir^{III}}$ to Ti^{III}. The strong oxidant $\mathbf{Ir^{IV}}$ species is then reduced by HE to $\mathbf{Ir^{III}}$ and produce $HE^{\bullet+}$, which can further participate in electron transfer events and eventually produce $\mathbf{pyH^+}$. Ti^{III} can trap allyl radicals **2** to form nucleophilic **1** that subsequently coupled with carbonyls. After hydrolysis by $\mathbf{pyH^+}$, the homoallylic alcohols would be obtained and free Ti^{IV} is released. Ultimately, the catalytic cycle would be closed by SET between $\mathbf{Ir^{III}}$ and Ti^{IV}. The *anti*-selectivity of homoallylic alcohols can be explained by Zimmerman–Traxler transition state (see Section 6 in the Supporting Information).

In summary, we have developed a novel photocatalytic approach for the production of π-allyltitanium complexes by a radical strategy. The synthetic application was demonstrated through the three-component allylation of carbonyls with feedstock butadiene. This environmentally benign and operationally simple method provides access to a broad range of novel and valuable homoallylic alcohols with exceptional regio- and diastereoselectivities.

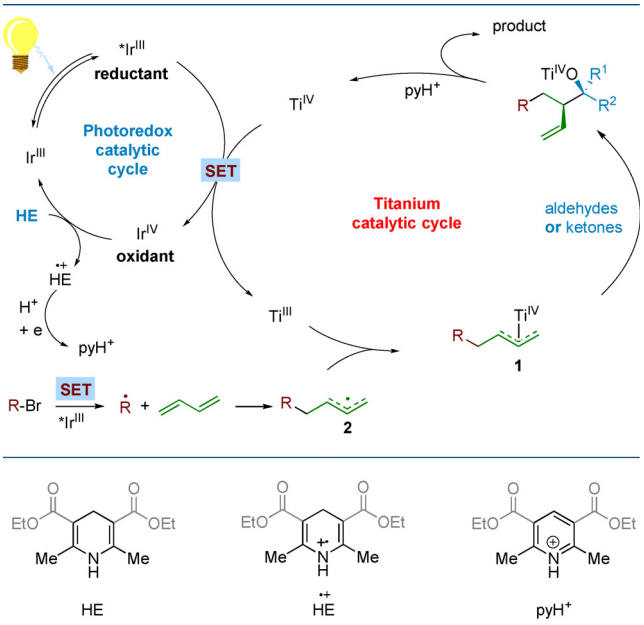


Figure 3. Proposed catalytic mechanism.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: allylic compounds · dienes · photocatalysis · radicals · titanium

[1] S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763.
[2] M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.* **2013**, *113*, 5595.
[3] P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302; *Angew. Chem.* **2003**, *115*, 4438.
[4] D. Montvydien, D. Mar Iulionien, *Environ. Toxicol.* **2004**, *19*, 351.
[5] A. Rosales, I. Rodríguez-García, J. Muñoz-Bascón, E. Roldan-Molina, N. M. Padial, L. P. Morales, M. García-Ocaña, J. E. Oltra, *Eur. J. Org. Chem.* **2015**, 4567.
[6] T. McCallum, X. Wu, S. Lin, *J. Org. Chem.* **2019**, *84*, 14369.
[7] F. Sato, K. Iida, S. Iijima, H. Moriya, M. Sato, *J. Chem. Soc. Chem. Commun.* **1981**, 1140.
[8] A. Kasatkin, T. Nakagawa, S. Okamoto, F. Sato, *J. Am. Chem. Soc.* **1995**, *117*, 3881.
[9] W. A. Nugent, T. V. RajanBabu, *J. Am. Chem. Soc.* **1988**, *110*, 8561.
[10] A. Gansäuer, H. Bluhm, M. Pierobon, *J. Am. Chem. Soc.* **1998**, *120*, 12849.
[11] M. P. Plesniak, H. Huang, D. J. Procter, *Nat. Rev. Chem.* **2017**, *1*, 77.
[12] a) H. Huang, M. Koy, E. Serrano, P. M. Pflüger, J. L. Schwarz, F. Glorius, *Nat. Catal.* **2020**, *3*, 393; b) H. Huang, P. Bellotti, P. M. Pflüger, J. L. Schwarz, B. Heidrich, F. Glorius, *J. Am. Chem. Soc.* **2020**, *142*, 10173.
[13] a) K. Takai, N. Matsukawa, A. Takahashi, T. Fujii, *Angew. Chem. Int. Ed.* **1998**, *37*, 152; *Angew. Chem.* **1998**, *110*, 160; b) Y. Xiong, G. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 2735; c) J. L. Schwarz, H. Huang, T. O. Paulisch, F. Glorius, *ACS Catal.* **2020**, *10*, 1621.
[14] J. Twilton, C. C. Le, P. Zhang, M. H. Shaw, R. W. Evans, D. W. C. MacMillan, *Nat. Rev. Chem.* **2017**, *1*, 52.
[15] J. C. Tellis, C. B. Kelly, D. N. Primer, M. Jouffroy, N. R. Patel, G. A. Molander, *Acc. Chem. Res.* **2016**, *49*, 1429.
[16] K. L. Skubi, T. R. Blum, T. P. Yoon, *Chem. Rev.* **2016**, *116*, 10035.
[17] D. Staveness, I. Bosque, C. R. J. Stephenson, *Acc. Chem. Res.* **2016**, *49*, 2295.
[18] I. Ghosh, L. Marzo, A. Das, R. Shaikh, B. König, *Acc. Chem. Res.* **2016**, *49*, 1566.
[19] Y. Chen, S. Lin, F. Li, X. Zhang, L. Lin, L. Shi, *ChemPhotoChem* **2020**, *4*, 659.
[20] a) S. Lin, Y. Chen, F. Li, C. Shi, L. Shi, *Chem. Sci.* **2020**, *11*, 839; b) F. Li, Y. Chen, S. Lin, C. Shi, X. Li, Y. Sun, Z. Guo, L. Shi, *Org. Chem. Front.* **2020**, *7*, 3434.
[21] a) Z. Zhang, R. B. Richrath, A. Gansäuer, *ACS Catal.* **2019**, *9*, 3208; b) M. Parasram, B. J. Shields, O. Ahmad, T. Knauber, A. G. Doyle, *ACS Catal.* **2020**, *10*, 5821; c) Z. Zhang, T. Hilche,

D. Slak, N. R. Rietdijk, U. N. Oloyede, R. A. Flowers II, A. Gansäuer, *Angew. Chem. Int. Ed.* **2020**, *59*, 9355; *Angew. Chem.* **2020**, *132*, 9441; d) A. Gualandi, F. Calogero, M. Mazzarini, S. Guazzi, A. Fermi, G. Bergamini, P. G. Cozzi, *ACS Catal.* **2020**, *10*, 3857.

[22] Recent progress of butadiene in catalytic allylation process. a) J. A. Boerth, S. Maity, S. K. Williams, B. Q. Mercado, J. A. Ellman, *Nat. Catal.* **2018**, *1*, 673; b) C. Li, R. Y. Liu, L. T. Jesikiewicz, Y. Yang, P. Liu, S. L. Buchwald, *J. Am. Chem. Soc.* **2019**, *141*, 5062; c) J. R. Zbieg, E. Yamaguchi, E. L. McInturff, M. J. Krische, *Science* **2012**, *336*, 324.

[23] R. E. Estévez, J. Justicia, B. Bazdi, N. Fuentes, M. Paradas, D. Choquesillo-Lazarte, J. M. García-Ruiz, R. Robles, A. Gansäuer, J. M. Cuerva, J. E. Oltra, *Chem. Eur. J.* **2009**, *15*, 2774.

[24] L. Qi, Y. Chen, *Angew. Chem. Int. Ed.* **2016**, *55*, 13312; *Angew. Chem.* **2016**, *128*, 13506.

[25] L. Pitzer, F. Schäfers, F. Glorius, *Angew. Chem. Int. Ed.* **2019**, *58*, 8572; *Angew. Chem.* **2019**, *131*, 8660.

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