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# Metal-Free Decarboxylative Allylation of Oxime Esters under Light Irradiation

Lilian Geniller,<sup>[a]</sup> Hiba Ben Kraim,<sup>[a]</sup> Eric Clot,<sup>[a]</sup> Marc Taillefer,<sup>[a]</sup> Florian Jaroschik,<sup>[a]</sup> and Alexis Prieto\*<sup>[a]</sup>

Alllylation reactions, often used as a key step for constructing complex molecules and drug candidates, typically rely on transition-metal (TM) catalysts. Even though TM-free radical allylations have been developed using allyl-stannanes, -sulfides, -silanes or -sulfones, much less procedures have been reported using simple and commercially available allyl halides, that are

used for the preparation of the before-mentioned allyl derivatives. Here, we present a straightforward photocatalytic protocol for the decarboxylative allylation of oxime esters using allyl bromide derivatives under metal-free and mild conditions. This methodology yields a diverse variety of functionalized molecules including several pharmaceutically relevant molecules.

## Introduction

Since the pioneering works developed by Tsuji and Trost, allylation reactions have been spread within synthetic organic chemistry to the extent that they are now among the most productive C–C bond forming processes (Figure 1a).<sup>[1]</sup> As allylations can be performed in regio- and enantioselective manners with a good tolerance towards nucleophiles and electrophiles, they are commonly used for the elaboration of complex molecules and drug candidates.<sup>[2]</sup> Moreover, the allyl unit provides multiple opportunities for further transformations, including the straightforward conversion to functional groups of great importance, such as aldehydes, epoxides or functionalized alkenes.<sup>[3]</sup> The deep understanding of such metal-catalyzed allylations involving an ionic mechanism has subsequently fostered further developments in which radical species might be involved. For instance, in recent years, many reports have demonstrated that carbon-based radical precursors might effectively behave as nucleophile surrogates under light exposure (Figure 1b).<sup>[4]</sup> However, these protocols typically require the use of transition-metal catalysts for the *in-situ* formation of the key  $\pi$ -allyl complex (Figure 1a and b). On the other hand, radical allylation reactions that leverage  $\beta$ -fragmentation of radical leaving groups do not require the use of transition-metal catalysts (Figure 1c). However, such transformations have long been restricted to the use of allylstannane derivatives, in which tin radicals were essential to sustain the

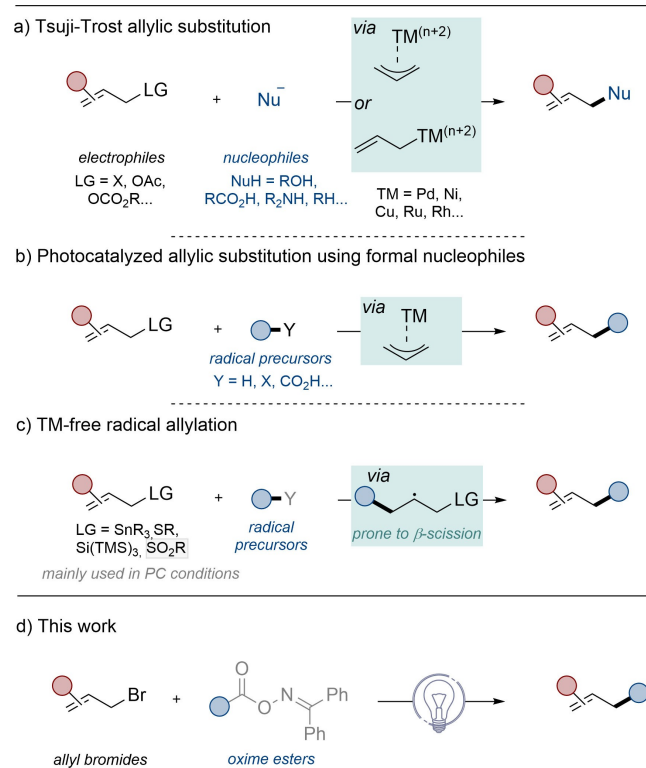


Figure 1. Brief overview of allylation reactions.

radical chain propagation.<sup>[5]</sup> Further developments allowed the employment of less toxic allylic derivatives such as allyl-sulfides,<sup>[6]</sup> -silanes<sup>[7]</sup> and -sulfones.<sup>[8]</sup> Despite extensive studies, radical allylations using photocatalytic conditions are scarce and often limited to the use of allyl sulfones bearing electron withdrawing groups.<sup>[9]</sup> In contrast, allyl halides that are used to prepare the above-mentioned allyl derivatives have been used to a lesser extent for carrying out allylation reactions,<sup>[9a,10]</sup> hence this still constitutes an interesting challenge. Our ongoing research program, focusing on the development of transformations involving radical  $\beta$ -bromo fragmentations,<sup>[11]</sup> in-

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spired us for tackling this demanding task. Indeed, recently, we could demonstrate that oxime esters can be readily employed for the preparation of *gem*-difluoroalkenes in which a  $\beta$ -bromoscion is likely to be involved.<sup>[11a]</sup> Based on this prior work, we considered to use oxime esters as carbon radical source<sup>[12]</sup> for developing a straightforward radical allylation. Herein, we describe a general and effective strategy allowing the photocatalytic decarboxylative allylation of oxime esters using neutral, electron-poor or -rich allyl bromides, yielding a diverse array of functionalized high-value added alkenes.

## Results and Discussion

To outset our investigation, diphenylmethanone *O*-(3-phenylpropanoyl) oxime **1a** and allyl bromide **2a** were selected as model substrates. After several attempts, the best reaction conditions were identified when the reaction was carried out using 3 equivalents of oxime **1a**, 1 equivalent of **2a**, and 10 mol% of thioxanthone (TX) as photocatalyst (PC)<sup>[13]</sup> in AcOEt under 390 nm irradiation, affording the expected product **3a** in an isolated yield of 66% (Table 1, entry 1). It is noteworthy that the brominated by-product **4a** was also formed during the reaction, even under the optimal reaction conditions. The use of other polar solvents had a limited impact on the reaction outcome, delivering **3a** in similar yields, whereas non-polar solvents were deleterious for the reaction yield (Table 1, entries 2–3 & SI). Performing the transformation at a higher temperature was not beneficial to the reaction outcome (Table 1, entry 4). The decrease of either the catalytic loading of TX or

the quantity of oxime **1a** was associated with a lower yield of **3a** (Table 1, entries 5–6). When allyl chloride was used instead of allyl bromide the product **3a** was obtained in a poor yield (Table 1, entry 7). The use of metal-based photocatalysts did not lead to any improvement (Table 1, entry 8 & SI). Reactions performed without TX or in the dark highlight the crucial role of both the photocatalyst and the light for the reaction efficiency (Table 1, entries 9–10).

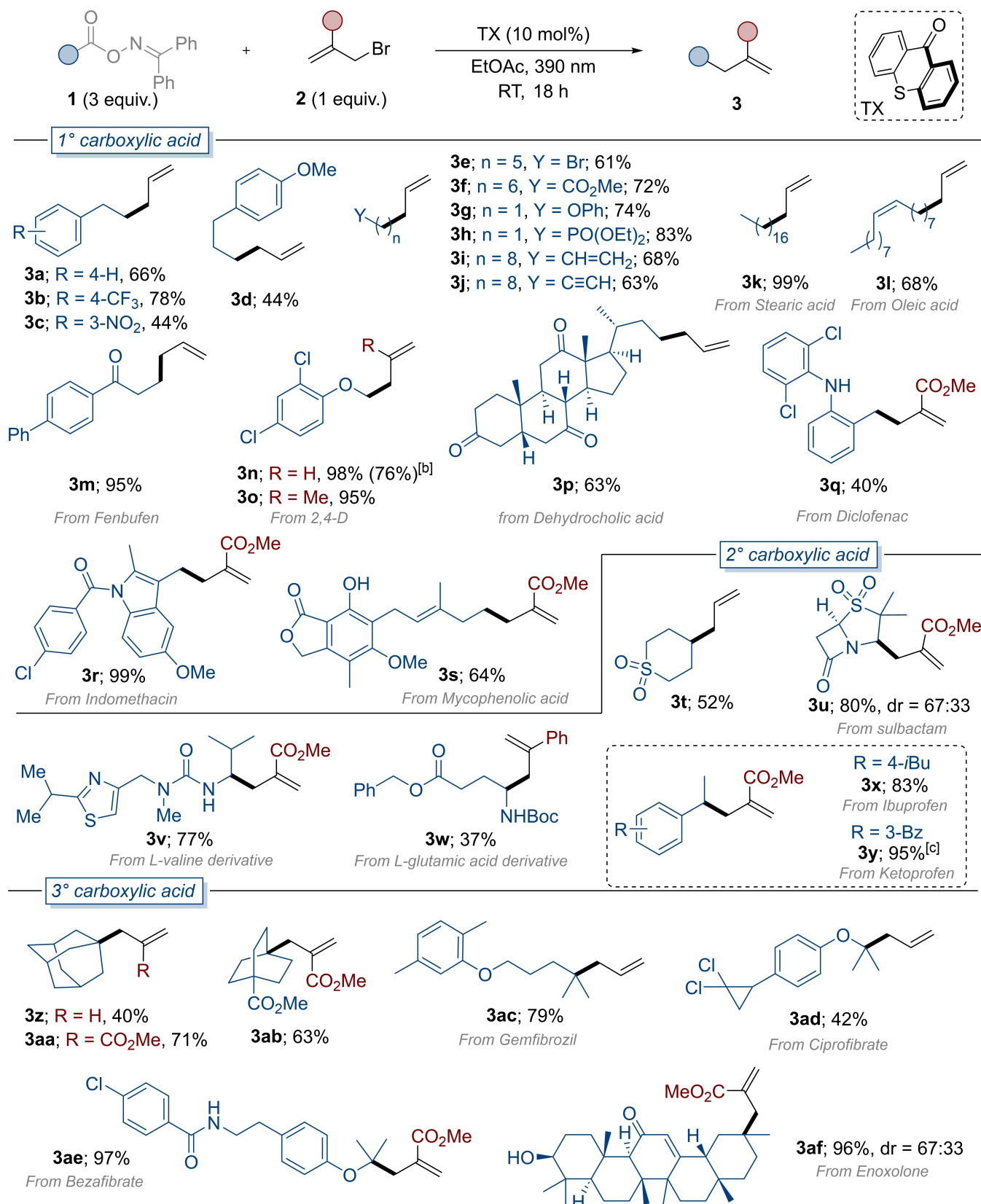
With the optimized reaction conditions in hand, we then started to investigate the scope of the reaction using various allyl bromides and oxime esters (Scheme 1). First, the reaction was explored employing oxime esters derived from primary carboxylic acids. Initial evaluation performed using the allyl bromide **2a** as partner revealed that a large number of simple but functionalized oximes (**1a-1j**) could be engaged, delivering the desired products in moderate to high yields. The allylation transformation was further applied to the modification of other scaffolds derived from compounds of interest (**1k-1s**) using various allyl bromide derivatives. Pleasingly, the reaction was found to be successful using compounds derived from stearic acid, oleic acid, fenbufen, 2,4-D, diclofenac and indomethacin. This part of the scope showcased the ability of the reaction to tolerate nitro groups, phosphonates, alkenes, alkynes, halides, esters, ketones, *NH*-anilines and indoles (Scheme 1). With secondary oxime esters (**1t-1y**), the reaction also proceeded efficiently across a wide range of substrates, including amino acid and sulbactam derivatives, yielding the corresponding compounds **3t-3w** in moderate to good yields. Similar results were obtained using oxime esters derived from ibuprofen and ketoprofen, providing **3x** and **3y**, respectively, in very high yields. These results indicated the compatibility of functional groups such as sulfone, thiazole, urea, carbamate and lactam. Finally, we explored the scope of the reaction using tertiary oxime esters (**1z-1af**), which were effective substrates in the current transformation. A broad scope of oximes derived from simple or from pharmaceutically relevant carboxylic acids could be used in the reaction, such as gemfibrozil, ciprofibrate, benzafibrate and enoxolone derivatives, affording access to the corresponding allylic molecules (**3z-3af**) in moderate to excellent yields. Overall, the reaction is highly tolerant to a wide panel of functional groups. Additionally, as shown in the numerous examples of Scheme 1, several types of allyl bromides might be employed regardless the electronic nature of the substituents. In fact, the reaction was productive with electron neutral (=H, Ar), electron-poor (=CO<sub>2</sub>Me) and electron-rich (=Me) allyl derivatives (Scheme 1). However, it is worthwhile to mention that this approach could not be extended to the use of substituted or sterically hindered allyl bromides such as the 3-bromocyclohexene or 1-bromo-3-methylbut-2-ene. Finally, to demonstrate the interest of this methodology, the reaction was performed on a larger laboratory scale. On a 15 mmol scale, 30-times larger than the initial scale, the reaction was still powerful providing 2.5 g of the product **3n** (76% isolated yield) (Scheme 1).

To obtain insights into the reaction mechanism, we carried out a series of mechanistic experiments.

**Table 1.** Optimization of the reaction.<sup>[a]</sup>

Entry	Deviation from standard conditions	Yields (%) <sup>[b]</sup>	
		<b>3a</b>	<b>4a</b>
1	None	70 (66) <sup>[c]</sup>	40
2	DCM	56	55
3	Acetone	51	53
4	50 °C	67	40
5	TX (5 mol%)	52	35
6	<b>1a</b> (2 equiv.)	45	30
7	Allyl chloride instead of <b>2a</b>	7	50 <sup>[d]</sup>
8	(Ir[dF(CF <sub>3</sub> )ppy] <sub>2</sub> (dtbpy))PF <sub>6</sub> (1 mol%) <sup>[e]</sup>	45	33
9	w/o TX	6	0
10	In the dark	N.R.	

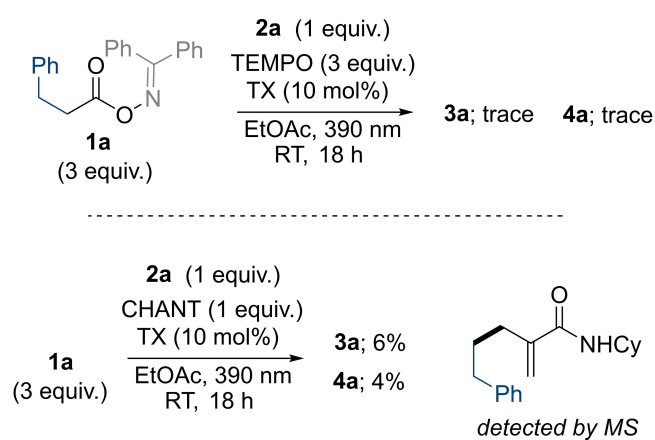
[a] Reaction conditions: **2** (0.3 mmol), **1a** (0.9 mmol) in AcOEt (1 mL).  
 [b] Yields were determined by <sup>1</sup>H NMR using trichloroethylene as an internal standard.  
 [c] Isolated yield.  
 [d] Yield refers to chlorinated compound.  
 [e] Under 450 nm irradiation. TX = Thioxanthone. N.R. = No reaction.



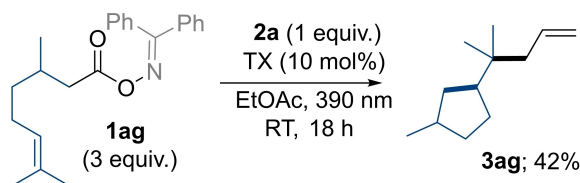
**Scheme 1.** Scope of the allylation reaction.<sup>[a]</sup> [a] Reaction conditions: 2 (0.5 mmol), 1 (1.5 mmol) in AcOEt (1.7 mL). Isolated yields are given. [b] Reaction performed on a 15 mmol scale. [c] NMR yield is given.

First, we decided to conduct the reaction in the presence of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 3 equiv.) (Scheme 2A). In those conditions, only traces of the compounds **3a** and **4a** could be observed by NMR analyses. However, we could not detect any TEMPO-adducts by MS analysis. The reaction was therefore also investigated in the presence of 1 equivalent of the *N*-cyclohexyl-2-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)acrylamide (CHANT), a trapping agent for short-lived radical species.<sup>[14]</sup> In these conditions, the reaction provided only 6% of **3a** and 4% of **4a**. In addition, a by-product stemming from the addition of the PhCH<sub>2</sub>CH<sub>2</sub><sup>•</sup> radical was detected by MS analysis. Then citronelic acid derived oxime **1ag** was employed in the reaction, giving access to the ring-closing product **3ag** in a moderate yield of

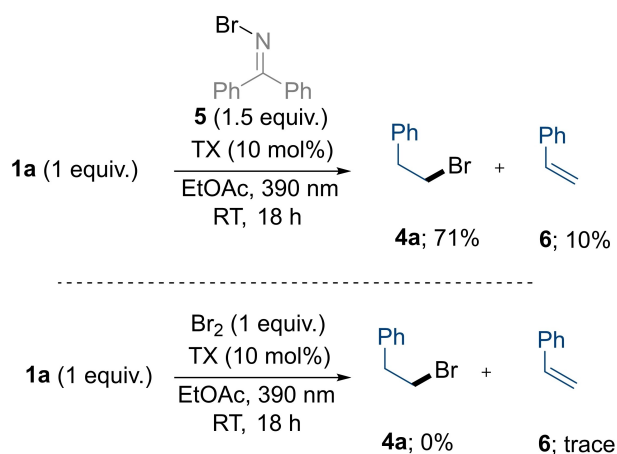
## A/ Radical trapping experiment



## B/ Radical clock experiment



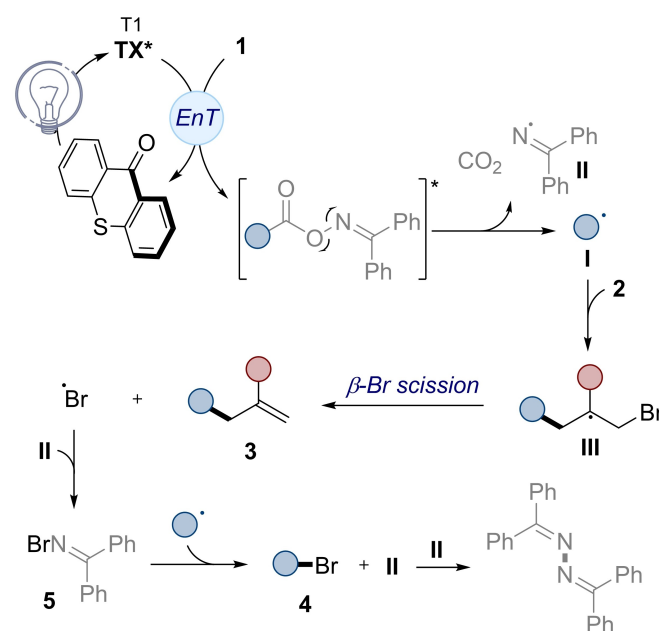
## C/ Bromination reactions



Scheme 2. Mechanistic experiments.

42% (Scheme 2B). These experiments support the proposition that carbon radicals are generated under the described reaction conditions. We then tried to understand and explain the formation of the brominated by-products **4**. Therefore, we undertook to carry out bromination reactions using two putative bromine sources, which might be formed during the reaction process (Scheme 2C). Indeed, we assumed that the by-product **4** would likely result from a reaction with either the *in-situ* generated *N*-bromoimine **5** or bromine.<sup>[11a]</sup> Under our photocatalytic conditions, while the compound **4a** was formed in the reaction using the imine **5**, the formation of the latter was not observed in presence of bromine. These results suggest that the *N*-bromoimine **5** is likely formed during the reaction, thereafter behaving as a bromine source.

In view of the control experiments, bromination reactions and literature precedents,<sup>[12]</sup> the reaction is believed to proceed following the mechanistic route depicted in Scheme 3. First, upon light irradiation the thioxanthone (TX) would reach a singlet excited state that would evolve to a triplet excited state through intersystem crossing (ISC). The triplet energy transfer (EnT) between the excited TX and the oxime ester **1** would trigger the N–O bond cleavage of the oxime,<sup>[15]</sup> resulting in the concomitant formation of the carbon radical **I** and the imine radical **II**. The intermediate **I** would react thereafter with the allyl bromide **2**, providing the radical intermediate **III**. Then, the latter would undergo radical β-bromo fragmentation affording the allylic compounds **3** along with bromine radical. The subsequent scavenging of the bromine radical by imine **II** would lead to the *N*-bromoimine **5** that might further react with carbon radical **I** yielding the formation of the brominated by-product **4**. Finally, the reaction would be ended by the dimerization of the radical **II**.<sup>[16]</sup>



Scheme 3. Mechanistic proposal.

## Conclusions

In conclusion, we have established a photocatalytic TM-free radical allylation reaction using readily-available carboxylic acid derived oxime esters and long-neglected allyl bromides. These transformations provide access to a diverse variety of functionalized allylic molecules, including various pharmaceutically relevant molecules. The reaction is believed to proceed through a radical  $\beta$ -bromo fragmentation, which is favored by the trapping of the bromine radical by the *in-situ* formed imine radical. The mild radical allylation reaction conditions open up many synthetic opportunities which are currently explored in our group.

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

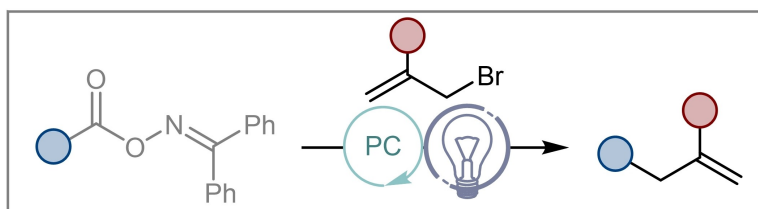
The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** Allylation · Photocatalysis · Radicals · Energy transfer · Oxime esters

- [1] a) O. Pàmies, J. Margalef, S. Cañellas, J. James, E. Judge, P. J. Guiry, C. Moberg, J.-E. Bäckvall, A. Pfaltz, M. A. Pericàs, M. Diéguez, *Chem. Rev.* **2021**, *121*, 4373–4505; b) S. Dutta, T. Bhattacharya, D. B. Werz, D. Maiti, *Chem* **2021**, *7*, 555–605; c) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422; d) B. M. Trost, H.-C. Tsui, F. D. Toste, *J. Am. Chem. Soc.* **2000**, *122*, 3534–3535; e) W. K. Walker, D. L. Anderson, R. W. Stokes, S. J. Smith, D. J. Michaelis, *Org. Lett.* **2015**, *17*, 752–755.
- [2] a) A. Y. Hong, B. M. Stoltz, *Eur. J. Org. Chem.* **2013**, *2013*, 2745–2759; b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2944.
- [3] a) P. A. Byrne, D. G. Gilheany, *Chem. Soc. Rev.* **2013**, *42*, 6670; b) O. M. Ogba, N. C. Warner, D. J. O'Leary, R. H. Grubbs, *Chem. Soc. Rev.* **2018**, *47*, 4510–4544.
- [4] a) H.-M. Huang, P. Bellotti, F. Glorius, *Chem. Soc. Rev.* **2020**, *49*, 6186–6197; b) K. Liu, Z. Wang, A. N. Künzel, M. Layh, A. Studer, *Angew. Chem.*

- Int. Ed. Engl.* **2023**, *62*, e202303473; *Angew. Chem.* **2023**, *135*, e202303473; c) P. Martínez-Balart, B. L. Tóth, Á. Velasco-Rubio, M. Fañanás-Mastral, *Org. Lett.* **2022**, *24*, 6874–6879; d) K. C. Cartwright, J. A. Tunge, *Chem. Sci.* **2020**, *11*, 8167–8175; e) K. Takizawa, T. Sekino, S. Sato, T. Yoshino, M. Kojima, S. Matsunaga, *Angew. Chem. Int. Ed. Engl.* **2019**, *58*, 9199–9203; f) H. Chen, X. Jia, Y. Yu, Q. Qian, H. Gong, *Angew. Chem. Int. Ed. Engl.* **2017**, *56*, 13103–13106; g) Z.-J. Wang, S. Zheng, E. Romero, J. K. Matsui, G. A. Molander, *Org. Lett.* **2019**, *21*, 6543–6547.
- [5] I. J. Rosenstein, *Org. React.* **2022**, *110*, 1–654.
- [6] F. Bertrand, B. Quiclet-Sire, S. Z. Zard, *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 1943–1946.
- [7] a) M. Knorn, T. Rawner, R. Czerwieniec, O. Reiser, *ACS Catal.* **2015**, *5*, 5186–5193; b) S. Mizuta, K. M. Engle, S. Verhoog, O. Galicia-López, M. O'Duill, M. Médebielle, K. Wheelhouse, G. Rassias, A. L. Thompson, V. Gouverneur, *Org. Lett.* **2013**, *15*, 1250–1253; c) J. J. Devery III, J. C. Conrad, D. W. C. MacMillan, R. A. Flowers II, *Angew. Chem. Int. Ed. Engl.* **2010**, *49*, 6106–6110.
- [8] a) P. Wang, P. Du, Q. Sun, J. Zhang, H. Deng, H. Jiang, *Org. Biomol. Chem.* **2021**, *19*, 2023–2029; b) B. Quiclet-Sire, S. Z. Zard, *J. Am. Chem. Soc.* **1996**, *118*, 1209–1210.
- [9] a) P. Hünemörder, E. Mejía, *Catal. Sci. Technol.* **2020**, *10*, 6754–6768; b) F.-L. Haut, R. S. Mega, J. V. Estornell, R. Martin, *Angew. Chem. Int. Ed. Engl.* **2023**, *62*, e202304084; c) Y.-L. Shih, S.-H. Huang, Y.-K. Wu, I. Ryu, *Bull. Chem. Soc. Jpn.* **2022**, *95*, 1501–1505; d) J.-B. Han, A. Guo, X.-Y. Tang, *Chem. Eur. J.* **2019**, *25*, 2989–2994; e) M.-M. Zhang, F. Liu, *Org. Chem. Front.* **2018**, *5*, 3443–3446; f) S. Paul, J. Guin, *Green Chem.* **2017**, *19*, 2530–2534; g) S. Kamijo, K. Kamijo, K. Maruoka, T. Murafuji, *Org. Lett.* **2016**, *18*, 6516–6519; h) D. R. Heitz, K. Rizwan, G. A. Molander, *J. Org. Chem.* **2016**, *81*, 7308–7313; i) A. Baralle, L. Fensterbank, J.-P. Goddard, C. Ollivier, *Chem. Eur. J.* **2013**, *19*, 10809–10813.
- [10] a) S. Ye, X. Li, W. Xie, J. Wu, *Asian J. Org. Chem.* **2019**, *8*, 893–898; b) A. L. Berger, K. Donabauer, B. König, *Chem. Sci.* **2018**, *9*, 7230–7235; c) G. Pratsch, G. L. Lackner, L. E. Overman, *J. Org. Chem.* **2015**, *80*, 6025–6036; d) G. L. Lackner, K. W. Quasdorf, G. Pratsch, L. E. Overman, *J. Org. Chem.* **2015**, *80*, 6012–6024; e) S. Paria, V. Kais, O. Reiser, *Adv. Synth. Catal.* **2014**, *356*, 2853–2858; f) J. A. Struss, M. Sadeghipour, J. M. Tanko, *Tetrahedron Lett.* **2009**, *50*, 2119–2120; g) F. Ek, O. Axelsson, L.-G. Wistrand, T. Frejd, *J. Org. Chem.* **2002**, *67*, 6376–6381.
- [11] a) L. Geniller, M. Taillefer, E. Clot, F. Jaroschik, A. Prieto, *Adv. Synth. Catal.* **2024**. DOI: 10.1002/adsc.202400174; b) L. Geniller, M. Taillefer, F. Jaroschik, A. Prieto, *Chem. Eur. J.* **2022**, *28*, e202201495.
- [12] a) D. S. Lee, V. K. Soni, E. J. Cho, *Acc. Chem. Res.* **2022**, *55*, 2526–2541; b) L. Geniller, M. Taillefer, F. Jaroschik, A. Prieto, *J. Org. Chem.* **2024**, *89*, 656–664; c) X.-L. Luo, S.-S. Li, Y.-S. Jiang, F. Liu, S.-H. Li, P.-J. Xia, *Org. Lett.* **2023**, *25*, 1742–1747; d) J. Kang, H. S. Hwang, V. K. Soni, E. J. Cho, *Org. Lett.* **2020**, *22*, 6112–6116; e) V. K. Soni, S. Lee, J. Kang, Y. K. Moon, H. S. Hwang, Y. You, E. J. Cho, *ACS Catal.* **2019**, *9*, 10454–10463.
- [13] N. F. Nikitas, P. L. Gkizis, C. G. Kokotos, *Org. Biomol. Chem.* **2021**, *19*, 5237–5253.
- [14] P. J. H. Williams, G. A. Boustead, D. E. Heard, P. W. Seakins, A. R. Rickard, V. Chechik, *J. Am. Chem. Soc.* **2022**, *144*, 15969–15976.
- [15] The triplet energy transfer between the PC and oxime 1 is supported by Stern-Volmer experiment, see SI. Additionally, no fluorescence quenching of the PC was observed using the allyl bromide.
- [16] We have previously discussed the essential role of imine radical in this reaction including via DFT calculations (see [11a]). We have now attempted to gain further theoretical insights, by comparing the  $\beta$ -bromo elimination involved in III (derived from allylbromide 2) and the same intermediate derived from BDFP (see SI). Even though the elimination is less favored in the current case of III, a definitive conclusion about the role of the iminyl radical as XAT reagent or radical scavenger could not be drawn.

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An effective and general photocatalyzed allylation reaction has been established. This transformation that uses simple allyl bromides and oxime esters derived from commercially

available and pharmaceutically relevant carboxylic acids, gives access to a wide array of allylic compounds that can be further employed in organic synthesis.

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**Metal-Free Decarboxylative Allylation of Oxime Esters under Light Irradiation**

