



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

ARCHIVIO ISTITUZIONALE
DELLA RICERCA

Alma Mater Studiorum Università di Bologna Archivio istituzionale della ricerca

Photoredox Allylation Reactions Mediated by Bismuth in Aqueous Conditions

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:

Photoredox Allylation Reactions Mediated by Bismuth in Aqueous Conditions / Potenti S.; Gualandi A.; Puggioli A.; Fermi A.; Bergamini G.; Cozzi P.G.. - In: EUROPEAN JOURNAL OF ORGANIC CHEMISTRY. - ISSN 1434-193X. - ELETTRONICO. - 2021:11(2021), pp. 1624-1627. [10.1002/ejoc.202001640]

Availability:

This version is available at: <https://hdl.handle.net/11585/818859> since: 2023-04-11

Published:

DOI: <http://doi.org/10.1002/ejoc.202001640>

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).
When citing, please refer to the published version.

(Article begins on next page)

This is the final peer-reviewed accepted manuscript of:

Photoredox Allylation Reactions Mediated by Bismuth in Aqueous Conditions.

Simone Potenti, Andrea Gualandi, Alessio Puggioli, Andrea Fermi, Giacomo Bergamini, and Pier Giorgio Cozzi

***Eur. J. Org. Chem.* DOI: 10.1002/ejoc.202001640**

The final published version is available online at:

<https://chemistry-europe.onlinelibrary.wiley.com/doi/full/10.1002/ejoc.202001640?af=R>

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

Photoredox Allylation Reactions Mediated by Bismuth in Aqueous Conditions.

Simone Potenti,^[a,b] Andrea Gualandi,^{*[a]} Alessio Puggioli,^[a] Andrea Fermi,^[a] Giacomo Bergamini,^[a] and Pier Giorgio Cozzi^{*[a]}

This paper is dedicated to Prof. Franco Cozzi on occasion of his 70th birthday

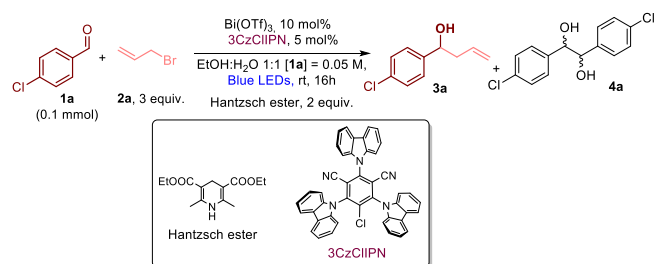
- [a] Mr. S. Potenti, Dr A. Gualandi, Mr. A. Puggioli, Dr. A. Fermi, Prof. G. Bergamini, Prof. P. G. Cozzi
Dipartimento di Chimica "G. Ciamician"
ALMA MATER STUDIORUM, Università di Bologna
Via Selmi 2, 40126, Bologna, Italy
E-mail: andreagualandi10@unibo.it; piorgiorgio.cozzi@unibo.it; <https://site.unibo.it/stereoselective-metal-photoredox-catalysis-lab>
- [b] Mr. S. Potenti
Laboratorio SMART, Scuola Normale Superiore, Piazza dei Cavalieri 7, 56126, Pisa, Italy

Abstract: Organometallic allylic reagents are widely used in the construction of C-C bond by Barbier-type reactions. In this communication, we have described a photoredox Barbier allylation of aldehydes mediated by bismuth, in absence of other metals as co-reductants. Mild reaction conditions, tolerance of oxygen, and use of aqueous solvent make this photoredox methodology attractive for green and sustainable synthesis of homoallylic alcohols.

In recent years, photoredox catalysis has been developed towards effective and practical new synthetic methodologies for C-C and C-X (X = O, N, S, P) bond forming reactions.^[1] Metalla photoredox catalysis, developed from seminal work of Sanford,^[2] Molander,^[3] and MacMillan-Doyle^[4] has considerably expanded the repertoire of reactivity and scope, allowing the development of new, mild, and interesting transformations.^[5] From the application of metalla photoredox catalysis in the context of cross coupling reactions^[6] the methodology has evolved to consider radical to polar cross over mechanism,^[7] in which carbanion^[8] or carbenium ion^[9] are formed by reaction of a metal with a radical generated under photoredox conditions. Recently, allylation reactions were described in Barbier conditions, with the involvement of nickel,^[10] chromium,^[11] titanium,^[12] and cobalt.^[13] Stereoselective allylation reactions with chromium^[14] and nickel^[15] were also developed, showing the possibilities offered by the use of photoredox conditions, in the presence of metals, for asymmetric reactions. Essentially, photoredox Barbier conditions avoid the need of a metal co-reductant (often Mn or Zn). In the examples reported with chromium, the photoredox cycle does not need a sacrificial reducing agent such as organic molecules, e.g. an amine (DIPEA or TEA) or Hantzsch's ester. In the case of nickel, cobalt, and titanium, the catalytic cycle is feasible with the use of an organic reducing agent. In both cases, the allylation reaction is performed in the presence of a photocatalyst (iridium complex or an organic dye), although recently Gansäuer pointed out^[16] that titanium complexes themselves can act as photocatalysts under precise conditions (green light irradiation). The described methodologies are certainly innovative and can be further expanded towards other C-C bond forming transformations. Barbier reactions with certain type of metals (zinc, indium, bismuth, gallium) were developed in aqueous solvents.^[17] To expand further the advantage of photoredox allylation reactions, and explore the use of green and sustainable conditions, we wondered if the mentioned metals could be employed in photoredox allylation reactions under aqueous Barbier conditions, and herein we report the successful endeavor of our investigations.

Bismuth is an inexpensive, safe and environmentally-benign metal, being commonly used in cosmetics, and as a component of oral gastrointestinal drugs.^[18] Bismuth has been used in allylation reactions under various conditions,^[19] and in the presence of stoichiometric metals as reductant, such as Al, Mg, Fe and Zn.^[20] Interestingly, also sodium borohydride was a suitable reductant for Barbier mediated allylation reaction with bismuth.^[21] Based on these reports, we selected bismuth salts as metal catalyst for catalytic photoredox allylation of aldehydes. Starting by employing 4-chlorobenzaldehyde as the model substrate, we have optimized the allylation reaction using allyl bromides and Bi(OTf)₃ (Table 1). We have avoided the employment of metal photocatalysts based on iridium and ruthenium, focusing our investigation on the class of thermally activated delayed fluorescence (TADF) organic dyes based on carbazoyl and diphenylamine substituted dicyanoarenes.^[22] Among all the TADF dyes, 3CzCIIPN^[23] was the dye of choice. We also varied – in the model reaction – the solvent, finding that a 1:1 mixture of EtOH/H₂O was convenient to satisfyingly perform the reaction (Table 1, entry 6). Furthermore, the reaction does not require strictly de-oxygenated solvents, and can be conveniently settled without a freezing-pump thaw procedure to eliminate traces of oxygen (Table 1, entry 7). The reaction is not sensitive to the presence of radical scavenger like (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, Table 1, entry 8). Different bismuth salts were also tested in the model reactions (see Table S3) and we found that BiBr₃ was also a compelling catalyst for the reaction (Table 1 entry 14). Due to the difficult to manage this deliquescent salt, we decide to use Bi(OTf)₃, for the further studies. Interestingly, in absence of the Bi(OTf)₃, but in the presence of 3CzCIIPN the pinacol coupling of the aldehyde is favored (Table 1, entry 9).^[24] If the reaction is carried out without 3CzCIIPN, under irradiation with blue LED (Table 1, entry 10), we have observed a clean allylation reaction, although in quite minor conversion. This was probably due to the ability of bismuth to form a reactive allylating agent with the mediation of Hantzsch's ester under light irradiation. In fact, when bismuth is not introduced in the reaction mixture, and the photocatalyst 3CzCIIPN is absent (Table 1 entry 11), the photoredox properties of the Hantzsch's ester are favoring the pinacol coupling.^[25] The scale up of the reaction it is possible, and in 1 mmol. scale we have reduced to 8% the percentage of bismuth catalyst (entry 15).

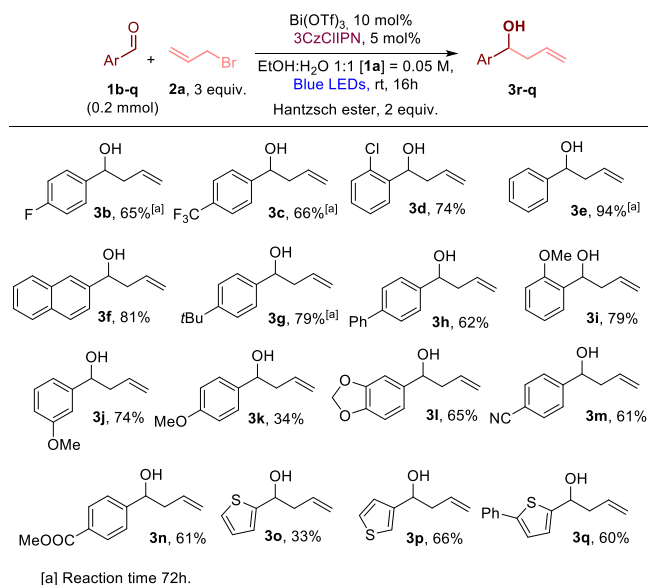
Table 1. Screening of reaction conditions for bismuth mediate catalytic photoredox allylation of aldehydes.



Entry ^[a]	Deviation from standard conditions	Conv. (%) ^[b]	3a (%) ^[c]	3a:4a (%) ^[c]
1	Solvent THF:H ₂ O (1:1)	97	51	52:48
2	Solvent DMF:H ₂ O (1:1)	53	48	85:15
3	Solvent MeCN:H ₂ O (1:1)	81	45	56:44
4	Solvent MeOH:H ₂ O (1:1)	>99	79	79:21
5	Solvent DMSO:H ₂ O (1:1)	98	66	68:32
6	-	>99	83(74)	83:17
7	In air	90	70	79:21
8	In the presence of TEMPO (20 mol%)	>99	95	95:5
9	No $\text{Bi}(\text{OTf})_3$	>99	16	16:84
10	No 3CzCIIPN	59	59	>99:1
11	No $\text{Bi}(\text{OTf})_3$; No 3CzCIIPN	6	0	>1/99
12	No light	0	-	-
13	Allylchloride instead allylbromide	15	7	48:52
14	BiBr_3 instead $\text{Bi}(\text{OTf})_3$	>99	87	87:13
15 ^[e]	1 mmol scale	89	85(77)	95:5

[a] All the reactions were carried out under irradiation with Kessil® 40W blue LED. [b] Conversions were measured by ¹H-NMR. Isolated yields after chromatographic purification are reported in parenthesis. [c] Yield% of the allylated product (**3a**) determined by ¹H-NMR. [d] Ratio% of allylated product (**3a**) and pinacol coupling (**4a**). The d.r. for (**4a**) is ca 1:1 for all the reactions. [e] The reaction was performed with 8 mol% of $\text{Bi}(\text{OTf})_3$ and 3 mol% of 3CzCIIPN.

The optimal reaction conditions were explored with a large variety of aromatic and aliphatic aldehydes, and the salient results are reported in Schemes 1 and 2. In general, with aromatic aldehydes the isolated yields were from moderate to good, with a variety of different functional group compatible with the reactions conditions. Both electron-rich and -poor aromatic aldehydes are reactive and, in some cases, yields could be improved by increase of the reaction time to 72 h. Sterical hindrance in *ortho* position does not hamper the reaction. Heteroaromatic aldehydes can be also employed, with some limitations. We found that electron rich aldehydes bearing pyrrole or indole are unstable during chromatographic purifications due to their attitude to form elimination products. Thiophene is a compatible group, but 2-thiophene carboxaldehyde **1o** was found poorly reactive, probably due to chelation of sulfur to the bismuth reagent. The reactivity is restored when 3-thiophene carboxaldehyde **1p** is employed. When long reaction time (72 h) were applied to the reactions of the aldehydes **1k**, **1o** and **1q**, byproducts were observed. We have detected and isolated (only for **1k**) the corresponding ethyl ether of the homoallylic alcohols (**3k,o,q**) formed by their reaction with ethanol (see Table S4). Although $\text{Bi}(\text{OTf})_3$ is described as catalyst for $\text{S}_{\text{N}}1$ -type reaction of alcohols^[26] the formation of ethers was determined by the Brønsted acidity of the oxidized Hantzsch's ester. This behavior was confirmed by dissolving the alcohol **3k** in EtOH in the presence of the pyridinium salt derived from the oxidation of Hantzsch's ester (see Table S5). The formation of these ether byproducts was observed only for alcohols bearing electron rich aromatic ring.

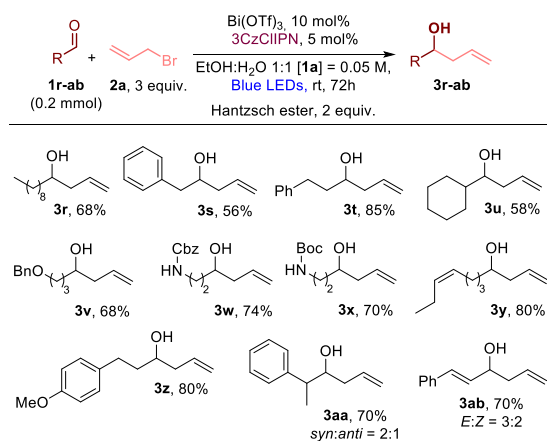


Scheme 1. Photoredox allylation of aromatic aldehydes mediated by bismuth.

On the other hand, the reaction is useful with aliphatic aldehydes **1r-ab**. Several functional groups are tolerated in the reported conditions and the reaction is applicable to linear and branched aldehydes with reaction time of 72h. Interestingly, cinnamaldehyde (**1ab**) gave a mixture of *E* and *Z* isomer of the corresponding allylated product (**3ab**) probably due to photoisomerization of cinnamaldehyde in presence of light and photocatalyst.^[27]

Ketones showed a quite reduced reactivity in this reaction compared to aldehydes, and the corresponding products were isolated only in traces (see Figure S1).

Substituted allyl bromide were tested in the reaction with poor conversions (see Table S6). Whereas the prenyl and crotyl derivatives led to the exclusive formation of branched products, cinnamyl bromide gave a complex mixture of products.



Scheme 2. Photoredox allylation of aliphatic aldehydes mediated by bismuth.

In order to evaluate the mechanism of the reaction we investigated the quenching of the photocatalyst's luminescence by each of the components of the reaction (see SI for details). As reported in our investigation on titanium photoredox allylation,^[12] isophthalonitrile derivatives represent a class of remarkable visible emitters, which can show long emission lifetimes in specific experimental conditions because of their TADF behaviour. Interestingly, 3CzClIPN displays a double deactivation kinetics at $\lambda_{em} = 550 \text{ nm}$ even in air-equilibrated ethanol at r.t. most likely due to a TADF-active regime, featuring a delayed component with lifetime around 150 ns (see SI for full details).

In the presence of increasing amounts of Bi(OTf)_3 or allyl bromide no appreciable decrease in the emission intensities of 3CzClIPN was detected (see figure S3 and S4), thus showing that these two reactants are not involved in quenching mechanisms even at high concentrations. On the other hand, the addition of 4-chlorobenzaldehyde barely decreases the emission intensity of 3CzClIPN ($k_q =$

$6.2 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, see figure S5), explaining the observed pinacol coupling in absence of $\text{Bi}(\text{OTf})_3$. A similar behavior is observed when the Hantzsch's ester is introduced in solutions of 3CzCIIPN, displaying that a significantly more efficient quenching of the emission of the latter is occurring ($k_q = 3.8 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$, see figure S6).

Based on the results of the photophysical investigation and from studies reported in literature,^[20c] we can tentatively suggest that the reductive quenching of 3CzCIIPN by HE induces the formation of $\text{HE}^{*\bullet}$ (Figure 1). The thermodynamic feasibility of the photoinduced electron transfer (PET) process relies on the reduction potential of the excited state of 3CzCIIPN ($E^{1/2}_{3\text{CzCIIPN}^*/3\text{CzCIIPN}^-} = 1.56 \text{ V vs SCE}$)^[23] and on the oxidation potential of the Hantzsch's ester ($E_{\text{HE}^{*\bullet}/\text{HE}} = +1.0 \text{ vs SCE}$).^[27] The reaction is thus producing $\text{HE}^{*\bullet}$ that can participate in further electron transfer events^[27] and is a strong reductant. Furthermore, the reducing 3CzCIIPN⁻ ($E^{1/2}_{3\text{CzCIIPN}/3\text{CzCIIPN}^-} = -1.16 \text{ V vs SCE}$) species is formed. The high tolerance to oxygen and TEMPO is ruling out a radical mechanism and formation of allylic radicals. We have no direct evidence of the actual reduced bismuth species but, as suggested by the literature, the formation of $\text{Bi}(0)$ could be considered. Multiple single electron transfer (SET) events could be responsible of the formation of Bi in low oxidations state from $\text{Bi}(\text{III})$ salt. Insertion of active bismuth to C–Br bond could form allylbismuth(III), diallylbismuth(III), and triallylbismuth(III) as the organometallic intermediates, that react with aldehydes to give the corresponding homoallylic alkoxides. The protonated re-aromatized Hantzsch ester possesses a low pK_a and aqueous conditions are allowing a facile protonation of the intermediate bismuth alkoxide allowing the recycle of bismuth salts. We have demonstrated in previous studies that the pyridine, produced by the oxidation of the Hantzsch's ester, is not participating in quenching processes.

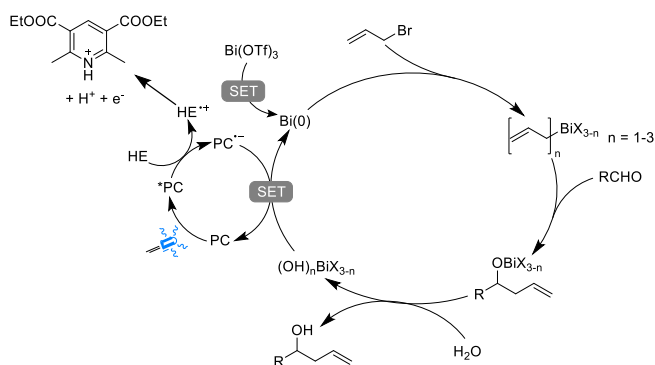


Figure 1. Proposed catalytic cycle for photoredox allylation of aldehydes mediated by bismuth.

To conclude, we have reported a photoredox Barbier allylation reaction that uses green solvents and conditions and employs a not toxic metal such as bismuth. The use of expensive transition metal based photoredox catalysts and stoichiometric metals (e.g. Mn or Zn) is avoided. However, further mechanistic studies are needed to understand the reaction mechanism with the possibility to expand this chemistry to the use of other electrophiles.

Acknowledgements

National PRIN 2017 project (ID: 20174SYJAF, SURSUMCAT) are acknowledged for financial support of this research.

Keywords: photoredox • allylation • aldehydes • Barbier • Organic dye

- [1] a) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363; for a recent review, see: R. C. McAtee, E. J. McClellan, C. R. J. Stephenson, *Trends in Chem.* **2019**, *1*, 111–125.
- [2] D. Kalyani, K. B. McMurtrey, S. R. Neufeldt, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18566–18569.
- [3] J. C. Tellis, D. N. Primer, G. A. Molander, *Science* **2014**, *345*, 433–436.
- [4] Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **2014**, *345*, 437–440.
- [5] J. Twilton, C. Lee, P. Zhang, M. H. Shaw, R. W. Evans, D. W. C. MacMillan, *Nature Rev. Chem.* **2017**, *1*, 0052.
- [6] J. A. Milligan, J. P. Phelan, S. O. Badir, G. A. Molander, *Angew. Chem.* **2019**, *131*, 6212–6224; *Angew. Chem. Int. Ed.* **2019**, *58*, 6152–6163.
- [7] L. Pitzer, J. L. Schwarz, F. Glorius, *Chem. Sci.* **2019**, *10*, 8285–8291.
- [8] K. Donabauer, M. Maity, A. L. Berger, G. S. Huff, S. Crespi, B. König, *Chem. Sci.*, **2019**, *10*, 5162–5166.
- [9] E. W. Webb, J. B. Park, E. L. Cole, D. J. Donnelly, S. J. Bonacorsi, W. R. Ewing, A. G. Doyle, *J. Am. Chem. Soc.* **2020**, *142*, 9493–9500.
- [10] a) A. Gualandi, G. Rodeghiero, A. Faraone, F. Patuzzo, M. Marchini, F. Calogero, R. Perciaccante, T. P. Jansen, P. Ceroni, P. G. Cozzi, *Chem. Commun.* **2019**, *55*, 6838–6841. For a photoredox nickel mediated crotylation of aldehydes, see: b) Y.-L., Li, W.-D. Li, Z.-Y. Gu, J. Chen, J.-B. Xia *ACS Catal.* **2020**, *10*, 1528–1534.
- [11] a) J. L. Schwarz, F. Schäfers, A. Tlahuext-Aca, L. Lückemeier, F. Glorius, *J. Am. Chem. Soc.* **2018**, *140*, 12705–12709; b) H. Mitsunuma, S. Tanabe, H. Fuse, K. Ohkubo, M. Kanai, *Chem. Sci.* **2019**, *10*, 3459–3465; c) L. J.; Schwarz, H.-M. Huang, T. O. Paulisch, F. Glorius, *ACS Catal.* **2020**, *10*, 1621–1627.
- [12] a) A. Gualandi, F. Calogero, M. Mazzarini, S. Guazzi, A. Fermi, G. Bergamini, P. G. Cozzi, *ACS Catal.* **2020**, *10*, 3857–3863; b) A. Fermi, A. Gualandi, G. Bergamini, P. G. Cozzi, *Eur. J. Org. Chem.* **2020**, 6955–6965.

- [13] A. Gualandi, G. Rodeghiero, R. Perciaccante, T. P. Jansen, C. Moreno-Cabrerizo, C. Foucher, M. Marchini, P. Ceroni, P. G. Cozzi; *Adv. Synth. Cat.* **2021**, DOI: 10.1002/adsc.202001250.
- [14] a) J. L. Schwarz, H.-M. Huang, Tiffany O. Paulisch, F. Glorius, *ACS Catal.* **2020**, *10*, 1621–1627; b) S. Tanabe, H. Mitsunuma, M. Kanai, *J. Am. Chem. Soc.* **2020**, *142*, 12374–12381.
- [15] A. Gualandi, F. Calogero, S. Potenti, E. Bassan, P. Ceroni, P. G. Cozzi, manuscript in preparation.
- [16] Z. Zhang, T. Hilche, D. Slak, N. Rietdijk, U. N. Oloyede, R. A. Flowers II; A. Gansäuer, *Angew. Chem.* **2020**, *132*, 9441–9445; *Angew. Chem. Int. Ed.* **2020**, *59*, 9355–9359.
- [17] C. C. K. Keh, C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 4062–4063; and ref. therein.
- [18] P. J. Sadler, H. Li, H. Sun, *Coord. Chem. Rev.* **1999**, *185*, 689–709.
- [19] a) M. Wada, K. Akiba K., *Tetrahedron Lett.* **1985**, *26* 4211–4214; b) M. Wada, H. Ohki, K. Akiba, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1738–1747; c) N. Miyoshi, M. Nishio, S. Murakami, T. Fukuma, M. Wada *Bull. Chem. Soc. Jpn.* **2000**, *73*, 689–692; d) P. C. Andrews, A. C. Peatt, C. L. Raston, *Green Chem.* **2001**, *3*, 313–315; e) D. Miyamoto, N. Daikawa, K. Tanaka, *Tetrahedron Lett.* **2003**, *44*, 6963–6964; f) K. Smith, S. Lock, G. A. El-Hiti, M. Wada, N. Miyoshi, *Org. Biomol. Chem.* **2004**, *2*, 935–938; g) J. H. Dam, P. Fristrup, R. Madsen, *J. Org. Chem.* **2008**, *73*, 3228–3235.
- [20] a) M. Wada, H. Ohki, K.-J. Akiba, *J. Chem. Soc., Chem. Commun.* **1987**, *10*, 708–709; b) M. Wada, T. Fukuma, M. Morioka, T. Takahashi, N. Miyoshi, *Tetrahedron Lett.* **1997**, *38* 8045–8048; c) B. D. Jadhav, S. K. Pardeshi, *Tetrahedron Lett.* **2014**, *55*, 4948–4952; d) M. Minato, J. Tsuji, *Chem. Lett.* **1988**, *17*, 2049–2052.
- [21] R. Ping-Da, P. Shi-Feng, D. Ting-Wei, W. Shi-Hui, *Chin. J. Chem.* **1996**, *14*, 462–465.
- [22] P. Data, Y. Takeda, *Chem. Asian. J.* **2019**, *14*, 1613–1636.
- [23] E. Speckmeier, T. G. Fischer, K. Zeitler, *J. Am. Chem. Soc.* **2018**, *140*, 15353–15365.
- [24] For other pinacol coupling promoted by organic dyes, see: a) A. Gualandi, G. Rodeghiero, E. Della Rocca, F. Bertoni, M. Marchini, R. Perciaccante, T. P. Jansen, P. Ceroni, P. G. Cozzi, *Chem. Commun.*, **2018**, *54*, 10044–10047; b) A. Gualandi, A. Nenov, M. Marchini, G. Rodeghiero, I. Conti, E. Paltanin, M. Balletti, P. Ceroni, M. Garavelli, P. G. Cozzi, *ChemCatChem* **2020**, <https://doi.org/10.1002/cctc.202001690>, and ref. therein.
- [25] P. Z. Wang, J.-R. Chen, W.-J. Xiao, *Org. Biomol. Chem.* **2019**, *17*, 6936–6951.
- [26] M. Rueping, B.J Nachtsheim, *Top. Curr. Chem.* **2012**, *311*, 115–141.
- [27] a) J. B. Metternich, R. Gilmour, *J. Am. Chem. Soc.* **2015**, *137*, 11254–11257; b) W. Cai, H. Fan, D. Ding, Y. Zhang, W. Wang, *Chem. Commun.* **2017**, *53*, 12918–12921; c) N. F. Nikitas, I. Triandafillidi, C. G. Kokotos, *Green Chem.* **2019**, *21*, 669–674.