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## Friedel–Crafts arylation of aldehydes with indoles utilizing arylazo sulfones as the photoacid generator†

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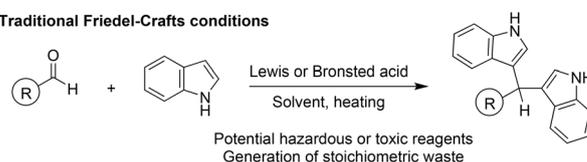
A versatile, inexpensive and sustainable protocol for the preparation of valuable bis-indolyl methanes *via* visible light-mediated, metal-free Friedel–Crafts arylation has been developed. The procedure, that exploits the peculiar behavior of arylazo sulfones as non-ionic photoacid generators (PAGs), was applied to the conversion of a variety of aliphatic and aromatic aldehydes into diarylmethanes in good to highly satisfactory yields, employing a low-catalyst loading (0.5 mol%) and irradiation at 456 nm.

### Introduction

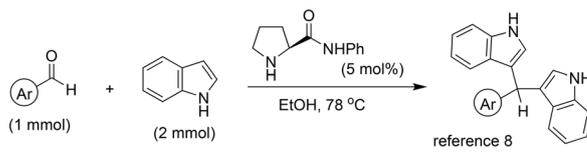
Friedel–Crafts processes, introduced in 1877 by Friedel and Crafts,<sup>1</sup> are the most known and applied strategies to functionalize an aromatic ring *via* an Ar–H bond activation, and nowadays constitutes a textbook reaction for undergraduate studies.<sup>2</sup> Among the several targets that can be achieved *via* Friedel–Crafts alkylation, the synthesis of bis-indolyl methanes (BIMs) and their analogues is considered a significant goal, in view of the biological and pharmacological properties of these compounds, including anti-cancer, anti-oxidant, anti-bacterial, anti-inflammatory, and anti-proliferative activity.<sup>3</sup> Furthermore, an indole-3-carbinol metabolite, the dimer 3,3'-bis-indolyl-methane, plays a key-role in the prevention of breast cancer.<sup>4</sup> The interest for BIMs is evidenced by the impressive variety of synthetic routes proposed for their preparation, being the Friedel–Crafts-type coupling between aldehydes and indoles the most common one (Scheme 1). In such traditional approach, an acid, either Lewis or Brønsted, is usually required and the use of high temperature or toxic reagents (Scheme 1a) represents the main limitation.<sup>5</sup> To improve the sustainability of the synthesis of BIMs, neat reaction conditions, infrared<sup>6a</sup> sonochemistry or microwave irradiations,<sup>6</sup> as well as the use of solid-supported acid cata-

#### Previous Methods

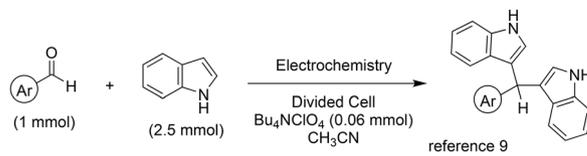
##### a) Traditional Friedel–Crafts conditions



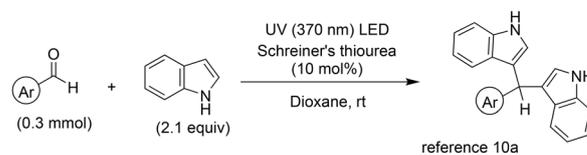
##### b)



##### c)



##### d)



#### This work



■ mild conditions    ■ cheap photochemical setup    ■ wide substrate scope  
 ■ low catalyst loading

**Scheme 1** (a–d) Common synthetic pathways for the Friedel–Crafts-type reaction between indoles and aldehydes; (e) our work.

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lysts<sup>7</sup> have been proposed. More recently, different approaches have been applied with success to this target, including, among others, organocatalysis (Scheme 1b),<sup>8</sup> electrochemistry (Scheme 1c)<sup>9</sup> and even photochemistry,<sup>10a</sup> the potential of which in terms of sustainability has been pointed out in the last decades.<sup>11–13</sup> In this context, the peculiar behavior of Schreiner's thiourea was exploited to promote a photoacidic process under blue light irradiation (Scheme 1d).<sup>10a</sup>

Since 2014, the group of Kokotos is actively involved in the design of innovative organic photocatalysts and photoinitiators and their use in sustainable photocatalyzed processes.<sup>14</sup> Furthermore, in the last decade the research group of Fagnoni and Protti has investigated in detail the photoreactivity of arylazo sulfones.<sup>15</sup> Such bench stable compounds contained a photolabile dyedauxiliary substituent (CH<sub>3</sub>SO<sub>2</sub>N<sub>2</sub>) that, upon visible light irradiation, undergoes N–S bond homolysis and releases an aryl/methanesulfonyl radical pair.<sup>15a</sup> Among the different applications of arylazo sulfones in synthesis<sup>15</sup> and in chemistry of materials,<sup>16</sup> their use as non-ionic photoacid generators (PAGs) able to generate methanesulfonic acid in oxygen-saturated or air equilibrated solution has been recently investigated.<sup>17</sup> We thus decided to merge the experience of our groups to propose a fast, versatile and efficient procedure for the visible-light driven synthesis of diarylmethanes *via* Friedel–Crafts type synthesis of coupling of aldehydes and (hetero)arenes (Scheme 1e).

## Results and discussion

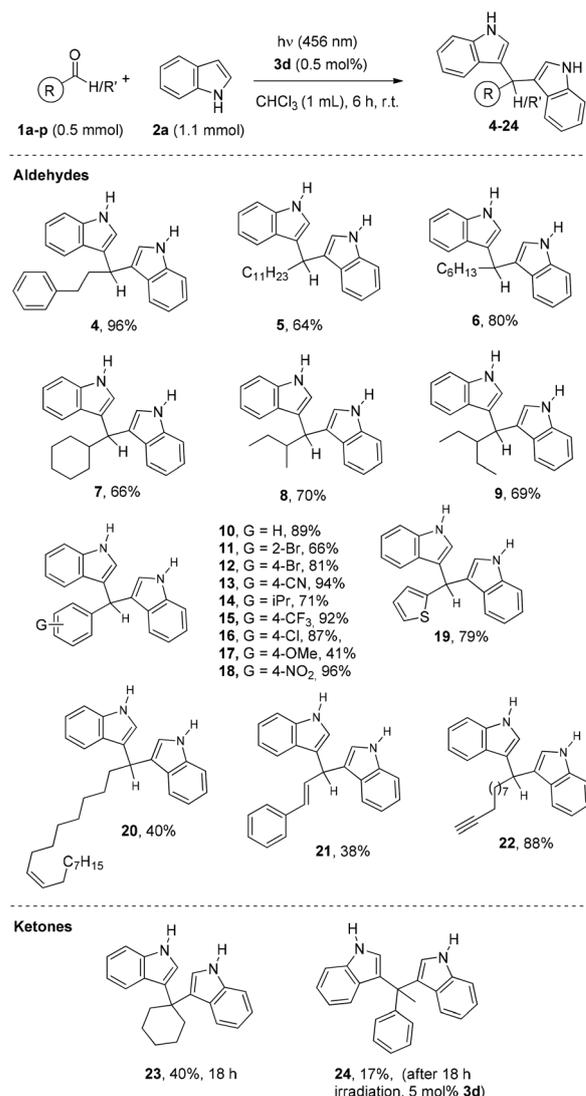
We began our investigations by studying the reaction between 3-phenyl propanal (**1a**) and 1*H*-indole (**2a**) to form 3,3'-(3-phenylpropane-1,1-diyl)bis(1*H*-indole) (**4**). A detailed optimization of the synthetic procedure considering the irradiation time and wavelengths, catalyst loading, substrates concentration (see Tables S1–5 in the ESI†) has been pursued.<sup>18</sup> In particular, we screened a number of common organic solvents (Table S2†), but despite the different green media tested, chloroform proved to be the best (Table S2,† entry 3). We then tested differently substituted arylazo sulfones (**3a–h**) as PAGs with *p*-*tert*-butylphenylazo sulfone (**3d**) affording the most satisfactory yield (96%) with a very low catalyst loading (0.5 mol%, Table 1).<sup>18</sup> Finally, control experiments pointed out that the simultaneous presence of light and the arylazo sulfone is mandatory for the positive outcome of the reaction (Table S8†).<sup>18</sup> We thus optimized the reaction conditions as follows: aldehyde **1** (0.5 mmol, 0.5 M), indole **2** (1.1 mmol) and arylazo sulfone **3d** (0.5 mol%) in chloroform (1 mL), irradiated at room temperature for 6 h at 456 nm (40 W Kessil lamp).

Having in hand the optimized-reaction conditions, we turned our attention in exploring the substrate scope (Schemes 2 and 3). Initially, we employed indole (**2a**) as representative heteroaromatic and a variety of aliphatic aldehydes were tested (Scheme 2). We began our investigation with aliphatic derivatives, since in literature, to the best of our knowledge, there is a single example concerning the photochemical conversion of

**Table 1** Arylazo sulfones as catalysts for the Friedel–Crafts-type reaction between indole (**2a**) and 3-phenyl propanal (**1a**)

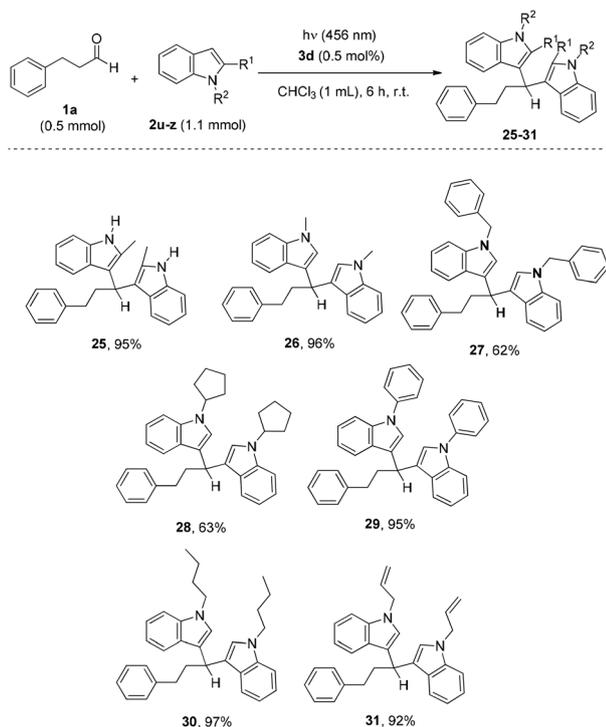
Arylazo sulfone (0.5 mol%)	Yield of <b>4</b> <sup>a</sup> (%)
<b>3a</b> , G = 4-CH <sub>3</sub> CO	63
<b>3b</b> , G = 4-CH <sub>3</sub>	86
<b>3c</b> , G = 4-Cl	76
<b>3d</b> , G = 4- <i>t</i> Bu	96
<b>3e</b> , G = 3-CH <sub>3</sub> CO	89
<b>3f</b> , G = 3-CN	90
<b>3g</b> , G = 3-Br	90
<b>3h</b> , G = 2-Br	92

<sup>a</sup> Yield after isolation by column chromatography.



**Scheme 2** Substrate scope: substituted carbonyls.





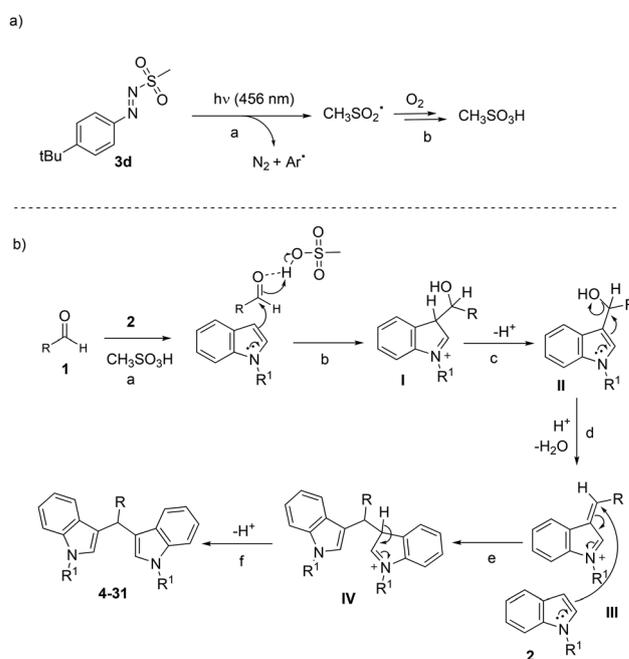
**Scheme 3** Substrate scope: substituted indoles.

an aliphatic aldehyde (**1a**), that led to **4** in 61% yield.<sup>10a</sup> Moving to linear substrates, bis-indoles **5** and **6** were isolated in good to high yields. Also, we explored three different cases in the class of  $\alpha,\alpha$ -disubstituted aldehydes, and in all cases, the desired products **7-9** were obtained in good yields (66–70%, Scheme 2). We then explored the scope of the aromatic aldehydes. Benzaldehyde provided the double addition product **10** in a good yield. Bromine incorporation either in the *para*-position or the *ortho*-position of the aromatic ring was well tolerated, leading to products **11** or **12** in good to excellent yields. Both electron-withdrawing and electron-donating groups were well tolerated, and derivatives **12-18** were isolated in good to excellent yields, with the only exception being that of 4-methoxy derivative **17** (41%). Finally, heteroaromatic thiophene-2-carboxaldehyde (**1q**) afforded diarylmethane **19** in 79% yield. To further extend the scope of this synthetic proposal, we also envisaged the use of aliphatic aldehydes having double and triple bonds, as well as ketones. Oleyl aldehyde **1q** was employed successfully, leading to **20** in 40% yield. Another naturally occurring compound, cinnamaldehyde, led to **21** only in discrete yield, whereas aldehyde **1s** that contains a triple bond was also efficiently converted to the corresponding arylated compound **22**. In the cases where low yields were obtained, the starting aldehyde (or its corresponding acid *via* photooxidation) were identified in the NMR of the crude reaction mixture. Unfortunately, ketones did not prove as good substrates. Cyclohexanone required prolonged reaction time (18 h), affording **23** in 40% yield, while acetophenone only gave 17% yield of the isolated product **24** even after 18 h of reaction and an increase of the catalyst loading up to 5 mol%.

The latter result comes as no surprise, since when we attempted the same reaction (acetophenone with indole in  $\text{CHCl}_3$ ) for 18 h under dark in the presence of 5 mol%  $\text{MeSO}_3\text{H}$ , an extremely low yield of 6% of **24** was obtained.

Once the substrate scope of the carbonyl counterpart was investigated, we moved in testing the scope of indoles in photochemical reaction (Scheme 3). A variety of *N*-substituted indoles were functionalized making use of 3-phenylpropanal (**1a**) as the reaction partner. Sterically hindered 2-methyl indole was proved to act as a competent nucleophile, providing access to **25** in 95% yield. Then, the substitution pattern on the nitrogen of the indole was probed. Simple *N*-alkyl substituents, like methyl, butyl or benzyl, secondary alkyl substituents, like cyclopentyl, aryl substituents, like phenyl or allyl substituent were well tolerated, leading to the desired products **26-31** in good to excellent yields.

The photochemical behavior of the arylazo sulfones as visible light PAGs has already been studied in literature<sup>17</sup> and a proposed mechanism is described in Scheme 4. Visible-light excitation of **3d** results in the homolytic cleavage of the N-S bond to release nitrogen and an aryl ( $\text{Ar}^\bullet$ )/methane sulfonyl ( $\text{CH}_3\text{SO}_2^\bullet$ ) radical pair (Scheme 4a, path a).<sup>15</sup> The  $\text{CH}_3\text{SO}_2^\bullet$  is then trapped by oxygen (path b) and generates methanesulfonic acid  $\text{CH}_3\text{SO}_3\text{H}$ . Protonation enhances the electrophilic character of the carbonyl moiety, making it susceptible to nucleophilic attack from the indole (Scheme 4b, paths a and b), leading to intermediate **I**. Aromatization to **II** (path c) and protonation thus leads to iminium derivative **III** (path d), which after indole's nucleophilic addition (path e) and aromatization of the so obtained cation **IV** (path f) affords the



**Scheme 4** Proposed reaction mechanism for (a) methanesulfonic acid generation and (b) synthesis of BIMs.



desired product **4–31**. In order to verify the reaction mechanism, aldehyde **1a** reacted with indole (**2a**) in the presence of 0.5 mol% of MeSO<sub>3</sub>H under dark and a lower 63% yield of isolated **4** was obtained after 6 h.

## Conclusions

In conclusion, a simple, cheap and efficient photochemical protocol was developed for the activation of aldehydes in their reaction with indoles, leading to triarylmethanes. This method relies on a small organic molecule, an arylazo sulfone, belonging to an intriguing class of shelf-stable and colored compounds for the visible-light photochemical catalytic release of acid under blue LED lamp irradiation. This slow-released acid activates efficiently both aliphatic and aromatic aldehydes to react, leading to diarylmethanes in good to high yields by adopting only a very low catalyst loading (0.5 mol%). We believe this activation mode will find more applications in the near future.

## Experimental

### General procedure for the photochemical reaction between indoles and aldehydes

In a glass vial, catalyst **3d** (0.9 mg, 0.0025 mmol 0.5 mol%) in CHCl<sub>3</sub> (1 mL), aldehyde **1** (0.50 mmol, 0.5 M) and indole **2** (1.10 mmol) were added consecutively. The vial was left stirring under blue LED bulb irradiation (456 nm) for 6 h (except where otherwise noticed, see ESI† for further details). The desired product was isolated after purification by column chromatography.

## Author contributions

Conceptualization: C. G. K. and S. P.; reaction optimization, substrate scope and compound characterization: E. G.; synthesis of catalysts: L. T. and S. P.; writing original draft: E. G. and C. G. K.; writing, reviewing and editing: S. P., M. F. and C. G. K.; supervision and project administration: C. G. K.; funding acquisition: E. G. and C. G. K.

## Conflicts of interest

There are no conflicts to declare.

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## References

- (a) C. Friedel and J. M. Crafts, *Compt. Rend.*, 1877, **84**, 1392–1395; (b) C. Friedel and J. M. Crafts, *Compt. Rend.*, 1877, **84**, 1450–1454.
- For selected and recent reviews on Friedel–Crafts reactions, see: (a) M. Rueping and B. J. Nachtsheim, *Beilstein J. Org. Chem.*, 2010, **6**(6), DOI: [10.3762/bjoc.6.6](https://doi.org/10.3762/bjoc.6.6); (b) R. Sunke, S. B. Nallapati, J. S. Kumar, K. S. Kumar and M. Pal, *Org. Biomol. Chem.*, 2017, **15**, 4042–4057.
- (a) M. Kobayashi, S. Aoki, K. Gato, K. Matsunami, M. Kurosu and I. Kitagawa, *Chem. Pharm. Bull.*, 1994, **42**, 2449–2451; (b) G. Sivaprasad, P. T. Perumal, V. R. Prabavathy and N. Mathivanan, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 6302–6305; (c) M. Damodiran, D. Muralidharan and P. T. Perumal, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3611–3614; (d) A. Kamal, M. N. A. Khan, K. S. Reddy, Y. V. V. Srikanth, S. K. Ahmed, K. P. Kumar and U. S. N. Murthy, *J. Enzyme Inhib. Med. Chem.*, 2009, **24**, 559–565; (e) K. Abdelbaqi, N. Lack, E. T. Guns, L. Kotha, S. Safe and T. Sanderson, *Prostate*, 2011, **71**, 1401–1412; (f) K. Yoon, S. Lee, S. Cho, K. Kim, S. Khan and S. Safe, *Carcinogenesis*, 2011, **32**, 836–842; (g) G. S. S. Kumar, S. Kumaresan, A. A. M. Prabhu, N. Bhuvanesh and P. G. Seethalakshmi, *Spectrochim. Acta, Part A*, 2013, **101**, 255–263.
- (a) Y. S. Kim and J. A. Milner, *J. Nutr. Biochem.*, 2005, **16**, 65–73; (b) E. G. Rogan, *In Vivo*, 2006, **20**, 221–228.
- For a review, see: (a) M. Shiri, M. A. Zolfigol, H. G. Kruger and Z. Tanbakouchian, *Chem. Rev.*, 2010, **110**, 2250–2293. For selected examples, see: (b) J. S. Yadav, B. V. S. Reddy, C. V. S. R. Murthy, G. M. Kumar and C. Madan, *Synthesis*, 2001, 783–787; (c) R. Nagarajan and P. T. Perumal, *Tetrahedron*, 2002, **58**, 1229–1232; (d) G. Gupta, G. Chaudhari, P. Tomar, Y. Gaikwad, R. Azad, G. Pandya, G. Waghulde and K. Patil, *Eur. J. Chem.*, 2012, **3**, 475–479; (e) J. Beltrá, M. C. Gimeno and R. P. Herrera, *Beilstein J. Org. Chem.*, 2014, **10**, 2206–2214; (f) H. Veisi, B. Maleki, F. H. Eshbala, H. Veisi, R. Masti, S. S. Ashrafi and M. Baghayeri, *RSC Adv.*, 2014, **4**, 30683–30688.
- For selected examples, see: (a) G. Penieres-Carrillo, J. G. García-Estrada, J. L. Gutiérrez-Ramírez and C. Alvarez-Toledano, *Green Chem.*, 2003, **5**, 337–339; (b) J. Li, H. Dai, W. Xu and T. Li, *Ultrason. Sonochem.*, 2006, **13**, 24–27; (c) N. Azizi, L. Torkian and M. R. Saidi, *J. Mol. Catal. A: Chem.*, 2007, **275**, 109–112; (d) M. Zahran, Y. Abdin and H. Salama, *ARKIVOC*, 2008, 256–265; (e) A. K. Chakraborti, S. R. Roy, D. Kumar and P. Chopra, *Green Chem.*, 2008, **10**, 1111–1118; (f) J. Li, M. Sun, G. He and X. Xu, *Ultrason. Sonochem.*, 2011, **18**, 412–414; (g) S. Handy and N. M. Westbrook, *Tetrahedron Lett.*, 2014, **55**, 4969–4971; (h) U. N. Yadav and G. S. Shankarling, *J. Mol. Liq.*, 2014, **191**, 137–141.
- S. B. Kamble, R. K. Swami, S. S. Sakate and C. V. Rode, *ChemPlusChem*, 2013, **78**, 1393–1399.
- G. Basumatary, R. Mohanta, S. D. Baruah, R. C. Deka and G. Bez, *Catal. Lett.*, 2020, **150**, 106–111.



- 9 C. Liu, Z. Xiao, S. Wu, Y. Shen, K. Yuan and Y. Ding, *ChemSusChem*, 2020, **13**, 1997–2001.
- 10 (a) Z. M. Salem, J. Saway and J. J. Badillo, *Org. Lett.*, 2019, **21**, 8528–8532 For a similar use of Schreiner's thiourea for the acetalization of aldehydes, see: (b) N. Spiliopoulou, N. F. Nikitas and C. G. Kokotos, *Green Chem.*, 2020, **22**, 3539–3545.
- 11 For selected reviews, see: (a) K. L. Skubi, T. R. Blum and T. P. Yoon, *Chem. Rev.*, 2016, **116**, 10035–10074; (b) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel and T. Noël, *Chem. Rev.*, 2016, **116**, 10276–10341; (c) M. N. Hopkinson, A. Tlahuext-Aca and F. Glorius, *Acc. Chem. Res.*, 2016, **49**, 2261–2272; (d) J. Twilton, C. Le, P. Zhang, M. H. Shaw, R. W. Evans and D. W. C. MacMillan, *Nat. Rev. Chem.*, 2017, **1**, 0052; (e) *Visible Light Photocatalysis in Organic Chemistry*, ed. C. R. J. Stephenson, T. P. Yoon and D. W. C. MacMillan, Wiley, Weinheim, 2018; (f) J. Schwarz and B. König, *Green Chem.*, 2018, **20**, 323–361; (g) M. Silvi and P. Melchiorre, *Nature*, 2018, **554**, 41–49; (h) S. Reischauer and B. Pieber, *iScience*, 2021, **24**, 102209.
- 12 For selected examples, see: (a) D. A. Nicewicz and D. W. C. MacMillan, *Science*, 2008, **322**, 77–80; (b) T. P. Yoon, M. A. Ischay and J. Du, *Nature*, 2010, **2**, 527–532; (c) R. Brimiouille and T. Bach, *Science*, 2013, **342**, 840–843; (d) Y. Y. Loh, K. Nagao, A. J. Hoover, D. Hesk, N. R. Rivera, S. L. Colletti, I. W. Davies and D. W. C. MacMillan, *Science*, 2017, **358**, 1182–1187; (e) A. Fawcett, J. Pradeilles, Y. Wang, T. Mutsuga, E. L. Myers and V. K. Aggarwal, *Science*, 2017, **357**, 283–286; (f) A. Trowbridge, D. Reich and M. J. Gaunt, *Nature*, 2018, **561**, 522–527; (g) E. Speckmeier, T. Fische and K. Zeitler, *J. Am. Chem. Soc.*, 2018, **140**, 15353–15365; (h) S. P. Morcillo, E. D. Dauncey, J. H. Kim, J. J. Douglas, N. S. Sheikh and D. Leonori, *Angew. Chem., Int. Ed.*, 2018, **57**, 12945–12949; (i) J. Wu, P. S. Grant, X. Li, A. Noble and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2019, **58**, 5697–5701; (j) T. Patra, S. Mukherjee, J. Ma, F. Strieth-Kalthoff and F. Glorius, *Angew. Chem., Int. Ed.*, 2019, **58**, 10514–10520; (k) A. Ruffoni, F. Julia, T. D. Svejstrup, A. McMillan, J. J. Douglas and D. Leonori, *Nat. Chem.*, 2019, **11**, 426–433.
- 13 For selected reviews, see: (a) M. Fagnoni, D. Dondi, D. Ravelli and A. Albini, *Chem. Rev.*, 2007, **107**, 2725–2756; (b) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075–10166; (c) D. Ravelli, S. Protti and M. Fagnoni, *Chem. Rev.*, 2016, **116**, 9850–9913; (d) C. Raviola, S. Protti, D. Ravelli and M. Fagnoni, *Chem. Soc. Rev.*, 2016, **45**, 4364–4390; (e) S. Garbarino, D. Ravelli, S. Protti and A. Basso, *Angew. Chem., Int. Ed.*, 2016, **55**, 15476–15484; (f) S. Protti, A. Albini, R. Viswanathan and A. Greer, *Photochem. Photobiol.*, 2017, **93**, 1139–1153; (g) M. Silvi and P. Melchiorre, *Nature*, 2018, **554**, 41–49; (h) I. K. Sideri, E. Voutyritsa and C. G. Kokotos, *Org. Biomol. Chem.*, 2018, **16**, 4596–4614; (i) C. Raviola, S. Protti, D. Ravelli and M. Fagnoni, *Green Chem.*, 2019, **21**, 748–764; (j) M. A. Theodoropoulou, N. F. Nikitas and C. G. Kokotos, *Beilstein J. Org. Chem.*, 2020, **16**, 833–857; (k) C. Raviola and S. Protti, *Eur. J. Org. Chem.*, 2020, 5292–5304; (l) N. F. Nikitas, P. L. Gkizis and C. G. Kokotos, *Org. Biomol. Chem.*, 2021, **19**, 5237–5253; (m) S. Protti, D. Ravelli and M. Fagnoni, *Trends Chem.*, 2022, **4**, 305–317.
- 14 For contributions employing metal complexes in photo-redox reactions, see: (a) I. Triandafillidi, M. G. Kokotou and C. G. Kokotos, *Org. Lett.*, 2018, **20**, 36–39 For contributions employing organic molecules in photochemical reactions, see: (b) G. N. Papadopoulos, D. Limnios and C. G. Kokotos, *Chem. – Eur. J.*, 2014, **20**, 13811–13814; (c) N. Kaplaneris, A. Bisticha, G. N. Papadopoulos, D. Limnios and C. G. Kokotos, *Green Chem.*, 2017, **19**, 4451–4456; (d) E. Voutyritsa and C. G. Kokotos, *Angew. Chem., Int. Ed.*, 2020, **59**, 1735–1741; (e) G. N. Papadopoulos, M. G. Kokotou, N. Spiliopoulou, N. F. Nikitas, E. Voutyritsa, D. I. Tzaras, N. Kaplaneris and C. G. Kokotos, *ChemSusChem*, 2020, **13**, 5934–5944; (f) E. Voutyritsa, M. Garreau, M. G. Kokotou, I. Triandafillidi, J. Waser and C. G. Kokotos, *Chem. – Eur. J.*, 2020, **26**, 14453–14460; (g) N. Spiliopoulou and C. G. Kokotos, *Green Chem.*, 2021, **23**, 546–551; (h) C. S. Batsika, C. Mantzourani, D. Gkikas, M. G. Kokotou, O. G. Mountanea, C. G. Kokotos, P. K. Politis and G. Kokotos, *J. Med. Chem.*, 2021, **64**, 5654–5666; (i) C. S. Batsika, C. Koutsilieris, G. S. Koutoulogenis, M. G. Kokotou, C. G. Kokotos and G. Kokotos, *Green Chem.*, 2022, **24**, 6224–6231.
- 15 (a) S. Crespi, S. Protti and M. Fagnoni, *J. Org. Chem.*, 2016, **81**, 9612–9619; (b) M. Malacarne, S. Protti and M. Fagnoni, *Adv. Synth. Catal.*, 2017, **359**, 3826–3830; (c) L. Onuigbo, C. Raviola, A. D. Fonzo, S. Protti and M. Fagnoni, *Eur. J. Org. Chem.*, 2018, 5297–5303; (d) H. O. Abdulla, A. A. Amin, C. Raviola, T. Opatz, S. Protti and M. Fagnoni, *Eur. J. Org. Chem.*, 2020, 1448–1452; (e) D. Qui, C. Lion, J. Mao, Y. Ding, Z. Liu, L. Wei, M. Fagnoni and S. Protti, *Adv. Synth. Catal.*, 2019, **361**, 5239–5244; (f) C. Lian, G. Yue, J. Mao, D. Liu, Y. Ding, Z. Liu, D. Qiu, X. Zhao, K. Lu, M. Fagnoni and S. Protti, *Org. Lett.*, 2019, **21**, 5187–5191; (g) L. Di Terlizzi, S. Scaringi, C. Raviola, R. Pedrazzani, M. Bandini, M. Fagnoni and S. Protti, *J. Org. Chem.*, 2022, **87**, 4863–4872; (h) D. Qiu, C. Lian, J. Mao, M. Fagnoni and S. Protti, *J. Org. Chem.*, 2020, **85**, 12813–12822; (i) L. Blank, M. Fagnoni, S. Protti and M. Rueping, *Synthesis*, 2019, **51**, 1243–1252; (j) A. Li, Y. Li, J. Liu, J. Chen, K. Lu, D. Qiu, M. Fagnoni, S. Protti and X. Zhao, *J. Org. Chem.*, 2021, **86**, 1292–1299.
- 16 (a) J. Médard, P. Decorse, C. Mangeney, J. Pinson, M. Fagnoni and S. Protti, *Langmuir*, 2020, **36**, 2786–2793; (b) L. Lombardi, A. Kovtun, S. Mantovani, G. Bertuzzi, L. Favaretto, C. Bettini, V. Palermo, M. Melucci and M. Bandini, *Chem. – Eur. J.*, 2022, **28**, e202200333.
- 17 L. D. Terlizzi, A. Martinelli, D. Merli, S. Protti and M. Fagnoni, *J. Org. Chem.*, 2022, DOI: [10.1021/acs.joc.2c01248](https://doi.org/10.1021/acs.joc.2c01248).
- 18 For detailed experimental procedures, optimization studies and mechanistic experiments, see ESI.†

