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Organocatalysis | Hot Paper

A General Light-Driven Organocatalytic Platform for the Activation of Inert Substrates

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Abstract: Due to their strong covalent bonds and low reduction potentials, activating inert substrates is challenging. Recent advances in photoredox catalysis offered a number of solutions, each of which useful for activating specific inert bonds. Developing a general catalytic platform that can consistently target a broad range of inert substrates would be synthetically useful. Herein, we report a readily available indole thiolate organocatalyst that, upon excitation with 405 nm light, acquires a strongly reducing power. This excited-state reactivity served to activate, by single-electron reduction, strong C–F, C–Cl, and C–O bonds in both aromatic and aliphatic substrates. This catalytic platform was versatile enough to promote the reduction of generally recalcitrant electron-rich substrates ($E_{red} < -3.0$ V vs SCE), including arenes that afforded 1,4-cyclohexadienes. The protocol was also useful for the borylation and phosphorylation of inert substrates with a high functional group tolerance. Mechanistic studies identified an excited-state thiolate anion as responsible of the highly reducing reactivity.

The activation of inert substrates is a substantial challenge. Fluoro- and chloro-arenes, alkyl chlorides,[1] and unsubstituted arenes[2] typically require strongly reducing alkali metals, transition metal complexes, or electrochemical methods.[3] Recent advances in photoredox catalysis offered effective solutions under mild conditions, but traditional photocatalysts are limited by their relatively low reducing power (> −2.0 V, Figure 1a).[4] Innovative light-driven systems have been developed to overcome this limitation (Figure 1b).[5] The consecutive photoinduced electron transfer (ConPET) manifold,[6] in which a second photon is used to excite a previously photogenerated radical anion, proved effective for the reduction of challenging substrates, including aryl and alkyl chlorides.[7] This reducing system served also for realizing a photochemical Birch reduction of unfunctionalized arenes.[8] Other methods, based on electrochemically mediated photoredox catalysis (e-PRC)[9] or proton-coupled electron transfer (PCET),[10] were suitable to activate aryl chlorides and generate the corresponding radicals amenable to further trasformations.[10a] A versatile approach used anionic organic catalysts[11] that, upon light excitation, could activate challenging substrates via single-electron transfer (SET) reduction,[12] including aryl fluorides.[12d] Anionic catalysts have the distinct advantage of

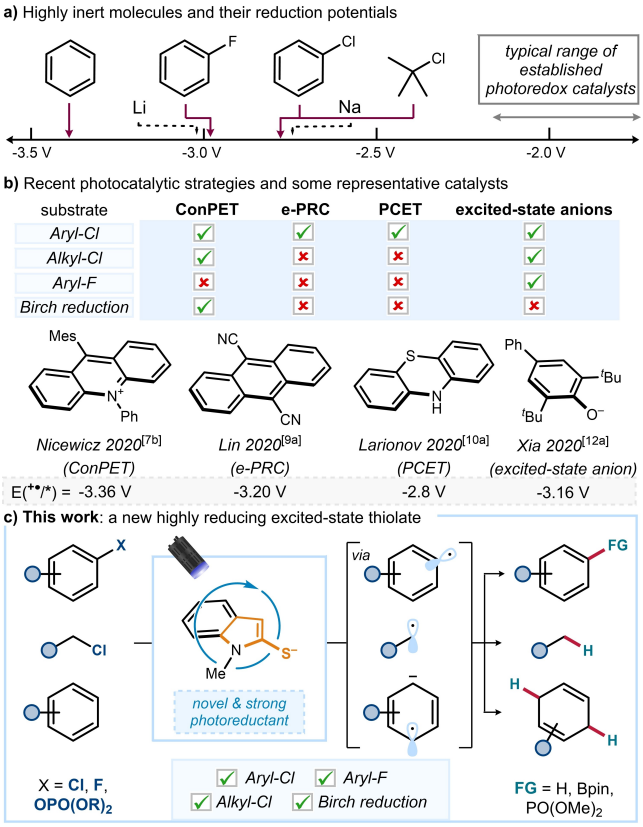

Figure 1. (**a**) Reduction potential of inert substrates. (**b**) Different photocatalytic strategies available for inert-bond activation and representative photocatalysts. (**c**) The new indole-thiolate photocatalyst suitable for the reduction of a wide range of highly inert molecules.

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acquiring a high redox potential in the excited state (< −3 V vs SCE), along with a greater ability to absorb visible light.

While each of these methods permit the reduction of specific functional groups, a general and practical protocol based on a single catalyst capable to activate a large variety of inert substrates is not available. Herein, we report a highly reducing anionic indole thiolate organocatalyst that, upon activation with visible light, can consistently activate an array of strong bonds through SET reduction (Figure 1c).

Our design plan was motivated by recent reports from our laboratory[13] and others[12c–e] demonstrating that sulfur anions, upon excitation, can serve as strong SET reductants to activate substrates and generate radicals (see section B in the Supporting Information for additional details on catalyst design). We surmised that the electron-rich thiolate anion **I**, generated in situ upon deprotonation of the cyclic thioamide catalyst **C1**, would access a highly reducing excited state **I*** under light irradiation (Figure 2a). SET activation of a difficult-to-reduce electron-rich C(sp^2)–X substrate to generate aryl radicals was considered a significant testbed. γ-Terpinene, acting as a hydrogen atom donor, would quench the aryl radical via hydrogen-atom transfer (HAT) affording the reduced product **3**. The resulting cyclohexadienyl radical **III** would then reduce the sulfur-centered radical **II** via an SET, thus turning over the catalyst.[14]

The cyclic thioamides **C1**–**C4** were tested as catalysts in the hydrodechlorination and defluorination of 4-chloroanisole **1a** (E_{red} = −2.9 V *vs.* SCE) and 4-fluoroanisole **2a** (E_{red} = < −3.0 V *vs.* SCE). The reactions were conducted using 5 mol % of the catalyst, Cs_2CO_3 as the base (2 equiv., needed to form the thiolate anion **I** in situ) and γ-terpinene under 405 nm light irradiation (Figure 2b). The reduction of **1a** was performed in DMSO, while *N*-methyl-2-pyrrolidone (NMP) was used with aryl fluoride **2a**. Cyclic 1-methylindoline-2-thione **C1** offered the best results, affording the anisole product **3a** in 80 % yield upon reduction of both the C(sp^2)–Cl and C(sp^2)-F bond. Structurally related thioamides **C2–3** also catalyzed the dechlorination reaction of **1a**, albeit with slightly diminished yield, while the analogous oxygen-containing catalyst **C4** was ineffective. However, catalyst **C1** clearly outperformed other analogues in the activation of 4-fluoroanisole **2a**. Control experiments showed that the presence of catalyst, light and the base were all essential for reactivity (Figure 2b, entry 2). Other inorganic bases, including K_2CO_3 (**3a** formed in 75 % yield), could be used, but the results did not exceed those obtained

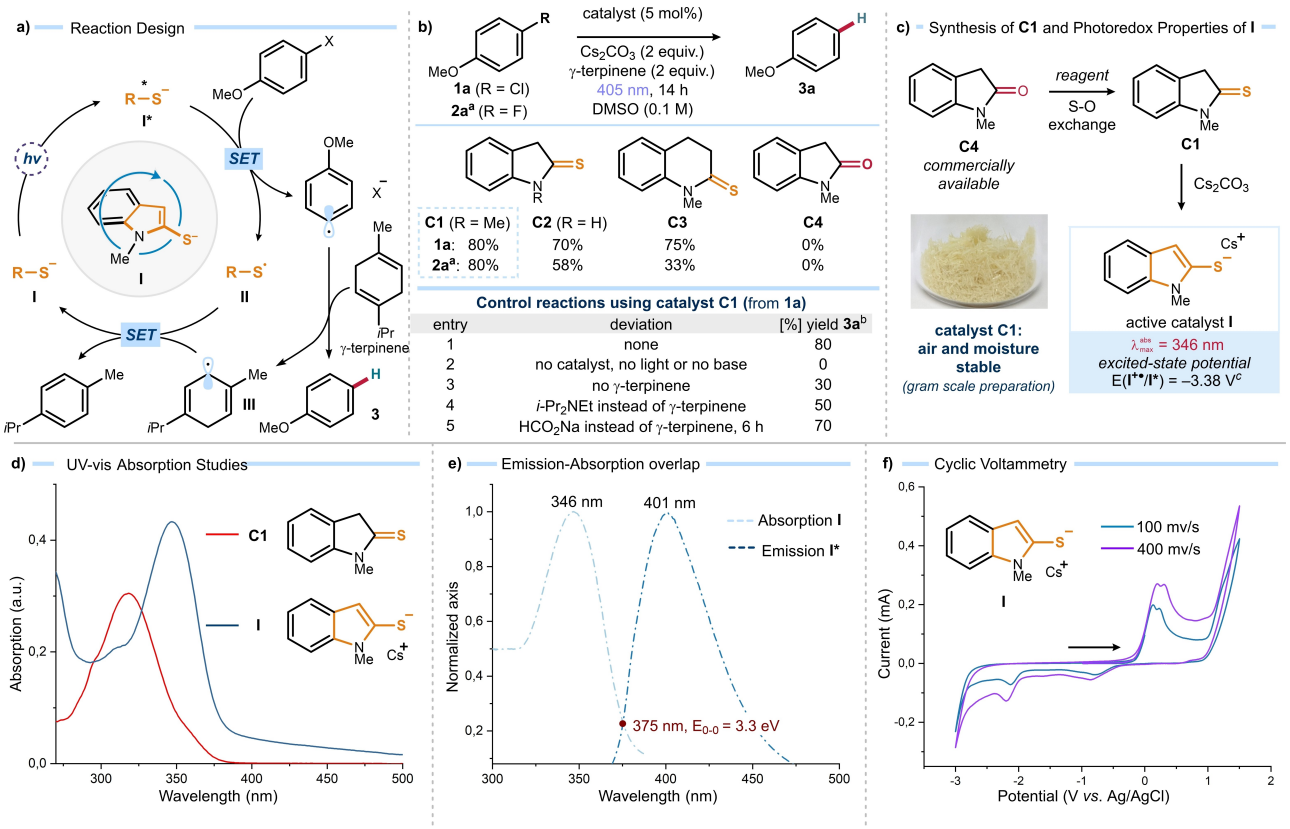

Figure 2. (**a**) Proposed mechanism of the hydrodefunctionalization of inert aryl halides. (**b**) Catalyst screening and control experiments. (**c**) Synthesis of catalyst **C1** and preparation of the thiolate salt **I**. (**d**) UV/Vis absorption spectra of catalyst **C1** and thiolate salt **I** (formed in situ treating **C1** with Cs_2CO_3) measured in DMSO. (**e**) Emission of the excited thiolate salt **I*** in DMSO (formed in situ treating **C1** with Cs_2CO_3) upon irradiation at 350 nm and its intercept with the absorption spectrum at 375 nm, with a 0–0 transition energy ($E_{0,0}$) of 3.3 eV. (**f**) Cyclic voltammetry measurements of the thiolate salt **I** carried out in DMSO *vs* Ag/AgCl at a scan rate of 100 and 400 ms/V. [a]γ-terpinene (1 equiv.), 390 nm irradiation, NMP as solvent. [b]NMR yield using 1,3,5-trimethoxybenzene as internal standard. [c]Estimated redox potential *vs* SCE in acetonitrile; NMP: *N*-methyl-2-pyrrolidone.

with Cs_2CO_3. Decreasing the amount of Cs_2CO_3 to 0.5 or 1 equiv. resulted in a significant decrease in reactivity (detailed optimization studies can be found in Table S1 in the Supporting Information). The reaction proceeded poorly in the absence of γ-terpinene (entry 3), while replacement with *i*-Pr_2NEt gave moderate yield (entry 4). Sodium formate (HCO_2Na) was a suitable H donor, since product **3a** was obtained in 70 % yield (entry 5). The successful use of hydrogen donors other than γ-terpinene, along with the possibility of successfully performing the Birch reduction of unfunctionalized arenes (see the discussion below), is congruent with the proposed SET-based mechanism and rules out a possible halogen transfer mechanism mastered by γ-terpinene.[15] Catalyst **C1** is an air-stable solid that can be prepared on gram-scale through oxygen-sulfur exchange of the commercially available *N*-methyl oxindole **C4** (Figure 2c). Treatment of **C1** with Cs_2CO_3 (2 equiv.) resulted in rapid formation of the thiolate salt **I**, as confirmed by ^1H NMR studies. While catalyst **C2** was also fully deprotonated under these conditions, **C3** and **C4** exhibited a much lower propensity for deprotonation (see section E1 in the Supporting Information).

We then performed investigations to gain mechanistic insights. Absorption spectroscopic investigations established that catalyst **C1** does not absorb visible light, while the addition of Cs_2CO_3, leading to anion **I**, induced a clear bathochromic shift in the visible region (Figure 2d). We also ruled out any ground-state association between catalyst **C1** and substrate **1a**. Upon irradiation at 350 nm of a DMSO solution of catalyst **C1** and Cs_2CO_3 (in situ formation of **I**), we detected emission centered at 401 nm (Figure 2e). This confirmed that the deprotonated catalyst **I** could access an electronically excited state. From the crossing point of the emission and absorption profiles at 375 nm, a 0–0 transition energy ($E_{0,0}$) of 3.3 eV could be inferred.[16] Next, the ground-state redox properties of the deprotonated catalyst **I** were determined by cyclic voltammetry (Figure 2f). A first irreversible oxidation peak was found at +0.01 V *vs* Ag/AgCl in DMSO, which was assigned to the formation of the sulfur-radical **III**.[17] Applying the Rehm–Weller formalism,[18] the redox potential of the excited thiolate [$E(\mathbf{I}^{\bullet}/[\mathbf{I}^{-}]^{*})$] was estimated as −3.38 V *vs* SCE. This confirmed that the anion of catalyst **C1** acquires a strongly reducing power upon excitation.

Using the conditions described in Figure 2b entry 1, we then tested the reducing power of our light-driven organocatalytic platform (Figure 3). We first evaluated the possibility to activate aryl chlorides **1**. A series of difficult-to-reduce electron-rich substrates underwent hydrodechlorination to afford the corresponding arenes in high yields (products **3a**–**d**). Bis-chloroanisole was doubly-dechlorinated (**3e**) while electron neutral and electron deficient aryl chlorides, including the antidepressant drug *moclobemide*, were reduced efficiently (adducts **3f**–**k**). To further test the generality of organocatalyst **C1**, we then targeted aryl phosphates **4**[9c,10a] and alkyl chlorides **5**.[7e,12c,20] These substrates are particularly recalcitrant to SET activation because of their low redox potentials ($E_{red} < -2.8$ V *vs.* SCE). Electron-rich and electron-neutral phosphates were reduced in good yields to afford products **3a**, **3h**, **3l**, and **3m**, while primary, secondary, and tertiary alkyl chlorides **5** all afforded the reduced adducts in high yields (products **7a**–**f**). We then focused on the challenging reductive defunctionalization of aryl fluorides **2**. Their activation is hampered by both the poor leaving group ability of the fluoride and the highly negative reduction potentials ($E_{red} < -3$ V *vs.* SCE). Previous catalytic methods suitable for the activation of electron-rich aryl fluorides[12d] usually required harsh conditions, including UV light irradiation[21a] or a strong base.[21b,c] Our protocol could achieve the activation of neutral or electron-rich substrates under mild conditions, affording the hydrodefluorination products in high yield (adducts **3a**, **3l**, **3o**–**3q**). Interestingly, addition of water allowed us to reduce electron-poor aryl fluorides too, leading to products **3f**, **3i**, **3j** and **3r**.[22] To the best of our knowledge, those substrates were out of reach of previously reported photochemical reducing protocols. Some aryl fluorides proved unreactive under our conditions, and they are listed in Figure S6. Synthetically, it is worth noting the tolerance of this highly reducing protocol towards a variety of functional groups, including unprotected amines (adducts **3o**–**3p**), amides (**3h**, **3k**), a carboxylic acid (**3r**), an ester (**3j**), a nitril (**3i**), and a boron-derivative (**3g**).

We then evaluated the potential of catalyst **C1** to promote the light-driven Birch reduction of inactivated arenes **6**.[8,23] This process is complicated by the absence of leaving groups within the aromatic substrates, which might result in an unproductive back-electron transfer. Our catalytic system, when using a NMP/H_2O solvent mixture, successfully activated naphthalene derivatives and phenanthrene, leading to the desired di-hydro products **8a**–**8f** in good yields. *N*-Me-Indole, anisole, and benzene were also converted to the corresponding dienes (adducts **8g**–**i**). A list of reactive or poorly reactive substrates is provided in Figure S7 of the Supporting Information. Overall, these results proved that catalyst **C1** can activate, via SET reduction, electron-rich arenes with very negative redox potentials ($E_{red} < -3.3$ V *vs* SCE).

We then used the highly reducing power of catalyst **C1** to functionalize aromatic substrates (Figure 4). Phosphorylation of aryl chlorides **1** using trimethyl phosphite $P(OMe)_3$ was successfully achieved under standard conditions and using HCO_2Na instead of γ-terpinene.

Aryl chlorides with electron-rich substituents at the *ortho*, *meta*, and *para* positions all reacted smoothly to afford the corresponding products **9a**–**9i**. Electron-neutral (adducts **9j**–**9m**), electron-poor (**9n**–**9o**), bicyclic, and heterocyclic (**9p**–**9u**) moieties were tolerated well. High functional group tolerance was observed, allowing the use of alkyl alcohols (**9h**), amides (**9l**), esters (**9o**), sulfones (**9n**), and amines (**9i**). The chemoselective activation of the C(sp^2)–Cl over C(sp^2)–F bond was demonstrated with the formation of product **9m**, which was formed in 46 % yield leaving the C–F bond untouched. To probe the synthetic utility of the protocol, the phosphorylation reaction was conducted on a 5 mmol gram scale leading to product **9a** in 63 % yield (680 mg isolated). The organocatalytic platform was also suitable for the borylation of aromatic chlorides

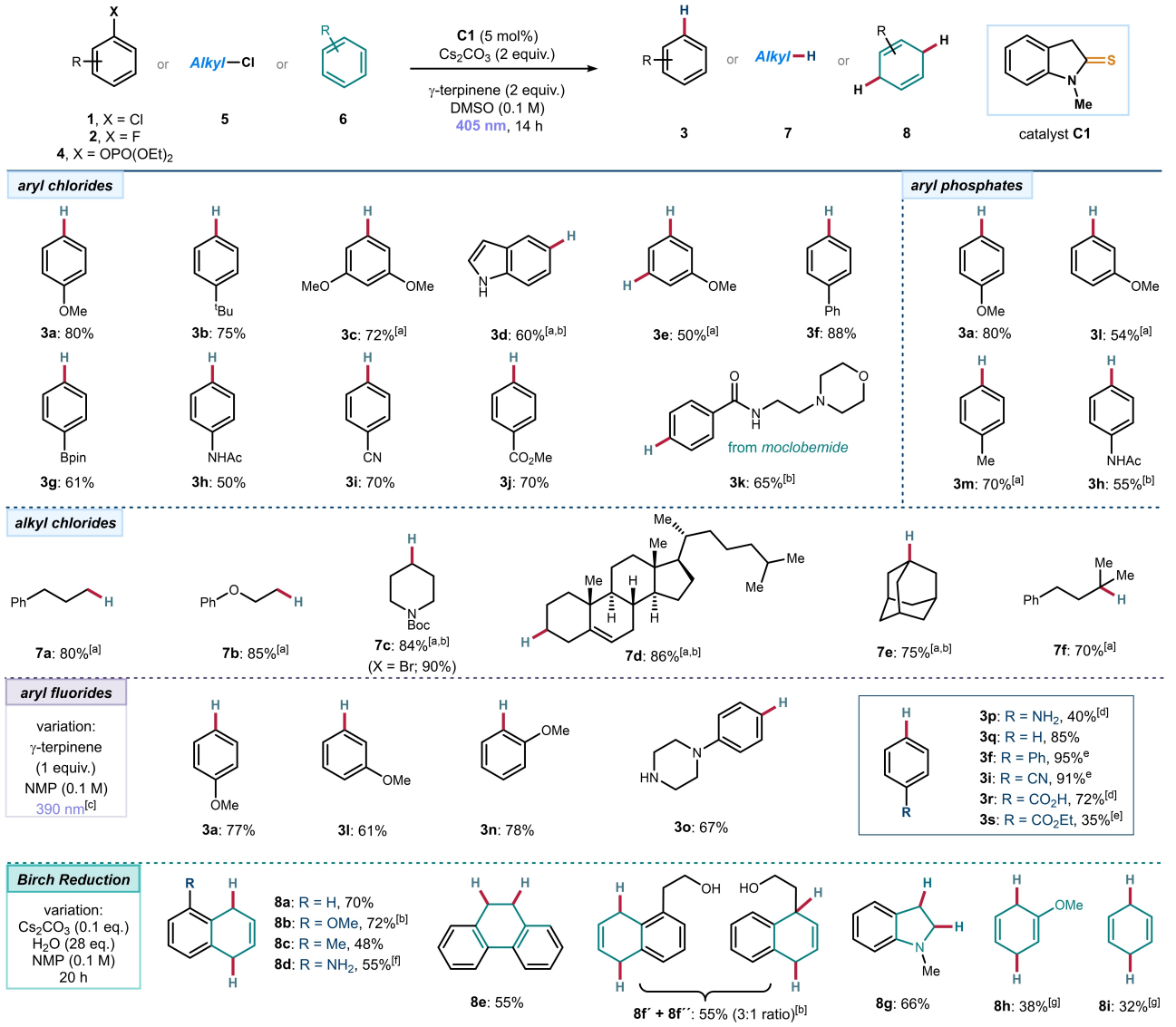

Figure 3. Photocatalytic reduction of inert substrates. Reactions performed on a 0.2 mmol scale at 40 °C. Yields of products 3, 7–8 measured by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. [a]Performed using HCO_2Na instead of γ-terpinene. [b]Yields of isolated products. [c]Reactions with fluorides 2 performed using a 3D printed reactor[19] with 390 nm irradiation. [d]Performed in the presence of H_2O (5 equiv.). [e]40 equiv. of H_2O. [f] Performed in the absence of H_2O. NMP: *N*-methyl-2-pyrrolidone.

using bis(pinacolato)diboron (B_2pin_2), although a higher catalyst loading was needed (10 mol % of **C1**, Figure 4, bottom panel). Here, the use of acetonitrile as solvent minimized the competitive dechlorination reaction. Electron-rich and neutral substrates were effectively converted into the borylated products **10a**–**10f**, while electron-poor aryl chlorides offered only low yields (*p*-CN and *p*-CO_2Me substituents offered less than 20 % yield). The more challenging borylation of aryl fluorides was also possible,[12e] and products **10a** and **10b** were isolated in moderate yield.

Finally, we carried out further mechanistic investigations to confirm that catalyst **C1** could activate the substrates via SET. Stern–Volmer studies revealed that all the model substrates quenched the emission of the excited anionic catalyst **I*** with the following relative rate: 4-chloroanisole **1a** > chloro-*N*-boc-piperidine > naphthalene > 4-fluoroanisole **2a**. Possible mechanisms for the described transformations are detailed in section E8 of the Supporting Information.

In summary, we have identified a simple indole thiolate organocatalyst that becomes a strong reductant upon deprotonation and light excitation. This light–driven catalytic platform demonstrated a wide generality, since it could master the reductive activation of inert C–F, C–Cl and C–O bonds and the Birch-type reduction of unfunctionalized arenes. The mild conditions and the wide applicability suggest that this readily available organocatalyst could find widespread use for the photochemical activation of inert substrates.

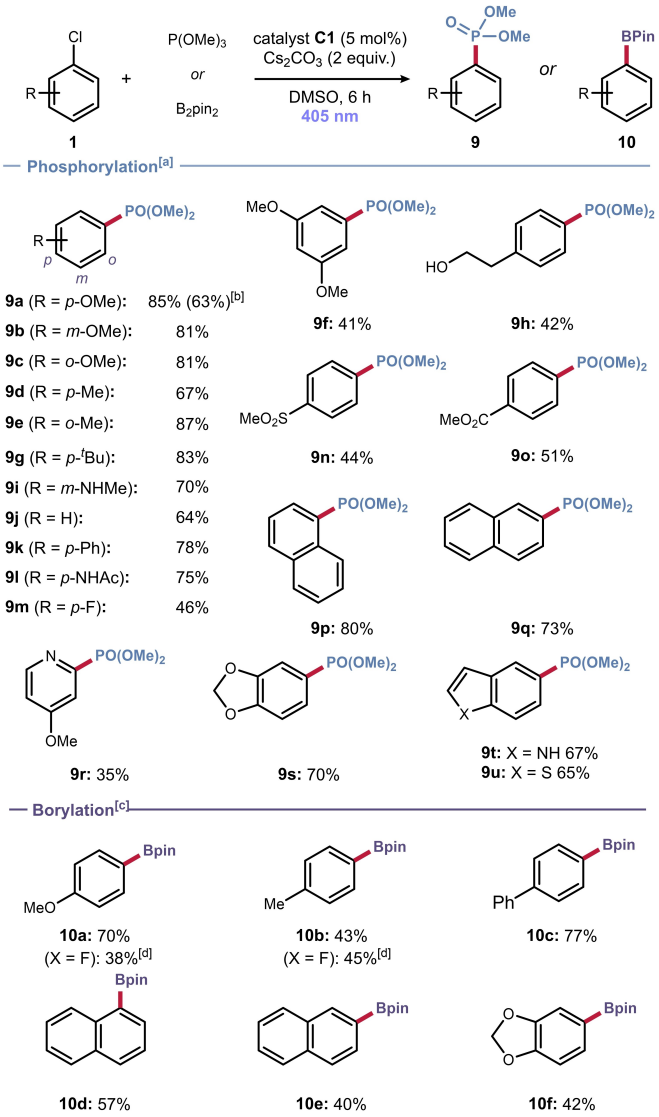

Figure 4. Photocatalytic phosphorylation and borylation of aryl chlorides 1. Reactions performed on a 0.2 mmol scale. Yields refer to isolated product 9 and 10. [a]Performed using $P(OMe)_3$ (5 equiv.), C1 (5 mol%), and HCO_2Na (1 equiv.). [b]5 mmol scale reaction. [c]Performed using B_2pin_2 (3 equiv.), catalyst C1 (10 mol%) in CH_3CN/DMSO (3:1, 0.5 M) as solvent. [d]Using CH_3CN/NMP (3:1, 0.5 M) as solvent; NMP: *N*-methyl-2-pyrrolidone.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Radical Chemistry · Organocatalysis · Photocatalysis · Reaction Mechanisms · Reductions

[1] a) H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *109*, 2119–2183; b) L. J. Cheng, N. P. Mankad, *Chem. Soc. Rev.* **2020**, *49*, 8036–8064.
[2] P. W. Rabideau, Z. Marcinow, *Organic Reactions*, Wiley, Hoboken **1992**, pp. 1–334, https://doi.org/10.1002/0471264180.or042.01.
[3] M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230–13319.
[4] Y. Wu, D. Kim, T. S. Teets, *Synlett* **2022**, *33*, 1154–1179.
[5] L. L. Liao, L. Song, S. S. Yan, J. H. Ye, D. G. Yu, *Trends Chem.* **2022**, *4*, 512–527.
[6] F. Glaser, C. Kerzig, O. S. Wenger, *Angew. Chem. Int. Ed.* **2020**, *59*, 10266–10284.
[7] a) I. Ghosh, T. Ghosh, J. I. Bardagi, B. König, *Science* **2014**, *346*, 725–728; b) I. A. MacKenzie, L. Wang, N. P. R. Onuska, O. F. Williams, K. Begam, A. M. Moran, B. D. Dunietz, D. A. Nicewicz, *Nature* **2020**, *580*, 76–80; c) A. F. Chmiel, O. P. Williams, C. P. Chernowsky, C. S. Yeung, Z. K. Wickens, *J. Am. Chem. Soc.* **2021**, *143*, 10882–10889; d) J. Xu, J. Cao, X. Wu, H. Wang, X. Yang, X. Tang, R. W. Toh, R. Zhou, E. K. L. Yeow, J. Wu, *J. Am. Chem. Soc.* **2021**, *143*, 13266–13273; e) M. Giedyk, R. Narobe, S. Weiß, D. Touraud, W. Kunz, B. König, *Nat. Catal.* **2020**, *3*, 40–47.
[8] J. P. Cole, D. F. Chen, M. Kudisch, R. M. Pearson, C. H. Lim, G. M. Miyake, *J. Am. Chem. Soc.* **2020**, *142*, 13573–13581.
[9] a) H. Kim, H. Kim, T. H. Lambert, S. Lin, *J. Am. Chem. Soc.* **2020**, *142*, 2087–2092; b) N. G. W. Cowper, C. P. Chernowsky, O. P. Williams, Z. K. Wickens, *J. Am. Chem. Soc.* **2020**, *142*, 2093–2099; c) C. P. Chernowsky, A. F. Chmiel, Z. K. Wickens, *Angew. Chem. Int. Ed.* **2021**, *60*, 21418–21425.
[10] a) S. Jin, H. T. Dang, G. C. Haug, R. He, V. D. Nguyen, V. T. Nguyen, H. D. Arman, K. S. Schanze, O. V. Larionov, *J. Am. Chem. Soc.* **2020**, *142*, 1603–1613; b) T. Yabuta, M. Hayashi, R. Matsubara, *J. Org. Chem.* **2021**, *86*, 2545–2555; c) T. Bortolato, G. Simionato, M. Vayer, C. Rosso, L. Paoloni, E. M. Benetti, A. Sartorel, D. Lebœuf, L. Dell'Amico, *J. Am. Chem. Soc.* **2023**, *145*, 1835–1846.
[11] <M. Schmalzbauer, M. Marcon, B. König, *Angew. Chem. Int. Ed.* **2021**, *60*, 6270–6292.
[12] a) K. Liang, Q. Liu, L. Shen, X. Li, D. Wei, L. Zheng, C. Xia, *Chem. Sci.* **2020**, *11*, 6996–7002; b) D. Wei, X. Li, L. Shen, Y. Ding, K. Liang, C. Xia, *Org. Chem. Front.* **2021**, *8*, 6364–6370; c) H. Li, X. Tang, J. H. Pang, X. Wu, E. K. L. Yeow, J. Wu, S. Chiba, *J. Am. Chem. Soc.* **2021**, *143*, 481–487; d) S. Wang, H. Wang, B. König, *Chem* **2021**, *7*, 1653–1665; e) S. Wang, H. Wang, B. König, *J. Am. Chem. Soc.* **2021**, *143*, 15530–15537.
[13] E. Le Saux, E. Georgiou, I. A. Dmitriev, W. C. Hartley, P. Melchiorre, *J. Am. Chem. Soc.* **2023**, *145*, 47–52.
[14] A HAT path from the cyclohexadienyl radical **III** that reduces the sulfur radical **II** to turnover catalyst **C1** cannot be excluded, see: E. De Pedro Beato, D. Mazzarella, M. Balletti, P. Melchiorre, *Chem. Sci.* **2020**, *11*, 6312–6324.
[15] T. Constantin, B. Górski, M. J. Tilby, S. F. Chelli, J. Juliá, K. J. LlaveriaGillen, H. Zipse, S. Lakhdar, D. Leonori, *Science* **2022**, *377*, 1323–1328.
[16] L. Buzzetti, G. E. M. Crisenza, P. Melchiorre, *Angew. Chem. Int. Ed.* **2019**, *58*, 3730–3747.

[17] The non-reversible behaviour of **I** can be rationalised with the fast formation of the S–S dimer once the sulfur radical **II** is formed. We could not isolate the dimer of catalyst **I** but indirect evidence has been collected, see section E2 in the Supporting Information.
[18] S. Farid, Dinnocenzo, J. P. Merkel, P. B. Young, R. H. Shukla, D. Guirado, G. *J. Am. Chem. Soc.* **2011**, *133*, 11580–11587.
[19] F. Schiel, C. Peinsipp, S. Kornigg, D. Böse, *ChemPhotoChem* **2021**, *5*, 431–437.
[20] a) R. Matsubara, T. Yabuta, U. Md Idros, M. Hayashi, F. Ema, Y. Kobori, K. Sakata, *J. Org. Chem.* **2018**, *83*, 9381–9390; b) Y. Li, Z. Ye, Y.-M. Lin, Y. Liu, Y. Zhang, L. Gong, *Nat. Commun.* **2021**, *12*, 2894.
[21] a) N. Toriumi, K. Yamashita, N. Iwasawa, *Chem. Eur. J.* **2021**, *27*, 12635–12641; b) H. Sheng, Q. Liu, B. B. Zhang, Z. X. Wang, X. Y. Chen, *Angew. Chem. Int. Ed.* **2023**, *62*, e202218468; c) J. T. Moore, M. J. Dorantes, Z. Pengmei, T. M. Schwartz, J. Schaffner, S. L. Apps, C. A. Gaggioli, U. Das, L. Gagliardi, D. A. Blank, C. C. Lu, *Angew. Chem. Int. Ed.* **2022**, *61*, e202205575.
[22] Addition of H_2O presumably facilitates C–F bond cleavage by means of a Cs^+–F interaction, see: H. Plenio, *ChemBioChem* **2004**, *5*, 650–655.
[23] a) A. Chatterjee, B. König, *Angew. Chem. Int. Ed.* **2019**, *58*, 14289–14294; b) T. Yuan, L. Sun, Z. Wu, R. Wang, X. Cai, W. Lin, M. Zheng, X. Wang, *Nat. Catal.* **2022**, *5*, 1157–1168.

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