Potent Reductants via Electron-Primed Photoredox Catalysis: Unlocking Aryl Chlorides for Radical Coupling

Nicholas G. W. Cowper[†],
University of Wisconsin-Madison, Madison, Wisconsin

Colleen P. Chernowsky[†],
University of Wisconsin-Madison, Madison, Wisconsin

Oliver P. Williams,
University of Wisconsin-Madison, Madison, Wisconsin

Zachary K. Wickens
University of Wisconsin-Madison, Madison, Wisconsin

Abstract

We describe a new catalytic strategy to transcend the energetic limitations of visible light by electrochemically priming a photocatalyst prior to excitation. This new catalytic system is able to productively engage aryl chlorides with reduction potentials hundreds of millivolts beyond the potential of Na^0 in productive radical coupling reactions. The aryl radicals produced via this strategy can be leveraged for both carbon–carbon and carbon–heteroatom bond-forming reactions. Through direct comparison, we illustrate the reactivity and selectivity advantages of this approach relative to electrolysis and photoredox catalysis.

Activation of organic molecules through single electron transfer (SET) is a pillar of preparative chemistry. New strategies to induce redox events have the potential to significantly impact organic synthesis.[1] In the past decade, visible-light photoredox catalysis has enabled a tremendous array of carbon–carbon and carbon–heteroatom bond-forming reactions.[2,3] Unfortunately, blue light (440 nm) possesses sufficient energy for a maximum driving force of only 2.8 eV, and the available energy is further diminished by nonradiative pathways and intersystem crossing.[4] Thus, despite catalyst design improvements,[5,6] many desirable substrates remain inert to visible-light photoredox catalysis.[7] As a result of this limitation, dissolving metal conditions,[8] which employ reactive alkali metals in condensed ammonia, remain uniquely potent reductants in the synthetic arsenal[9] and are still commonly used despite significant hazards and poor chemoselectivity.[10,11] Aiming to provide safer and

more scalable conditions for challenging reductions, recent efforts have exploited overcharge protection to unlock deeply reducing cathodic potentials for electroorganic synthesis.[12] However, the requisite electrode overpotentials intrinsically limit the functional group tolerance. Furthermore, radical intermediates generated at a cathode are prone to reduction to anions.[13] Overall, a new catalytic paradigm to access extremely reducing potentials under mild conditions and without reduction of radical intermediates would address a long-standing challenge in organic synthesis (Figure 1).

To overcome the energetic limitations of blue photons, König and co-workers recently introduced an appealing approach designed to drive challenging SET events using the energy of two photons rather than one.[14,15] This strategy relies on the light-mediated generation and subsequent photochemical excitation of catalytic radical anion intermediates. Although these systems push the limits of photoredox catalysis, they remain many orders of magnitude less reducing than alkali metals. Inspired by photophysical studies suggesting that other organic radical ions can serve as potent photoreductants,[16,17] we questioned whether an alternative means of priming a photoredox catalyst with an electron prior to excitation could provide a general catalyst design platform to transcend the energetic limitations of visible light.

We hypothesized that electrochemistry[18,19] could offer a more flexible approach than photoreduction to generate electron-primed photoredox catalysts. In addition to providing access to new catalysts, this approach eliminates the complications[20] that can arise from the terminal reductants commonly used in photoredox catalysis, such as Et_3N. This strategy builds on both long-standing[21] and recent[22] pioneering efforts combining electrochemistry with photochemistry.[23] The majority of these examples take advantage of the desirable features of electrochemistry to generate known photochemically active intermediates or catalysts. However, electrochemical generation of new families of photocatalysts for organic synthesis remains largely unexplored. Recently, Lambert and co-workers reported a new and highly oxidizing photocatalyst (with a calculated potential of +3.3 V vs SCE) that is electrochemically accessible under a mildly oxidizing potential.[22d] Concurrently, we were exploring the use of electrochemistry to access new, electronically destabilized photocatalysts for challenging reductions.[24] Herein we demonstrate that electrochemistry is a viable strategy to generate highly reducing electron-primed photoredox catalysts. We exploit this approach to identify an aryl imide photocatalyst capable of engaging substrates with reduction potentials on par with alkali metals in SET-initiated radical coupling reactions under otherwise mild conditions.

To explore this idea, we targeted the reductive generation of aryl radicals from unactivated precursors. These reactive intermediates are known to participate in a range of synthetically useful carbon–carbon and carbon–heteroatom bond-forming reactions; however, they are typically generated from diazonium salts or aryl iodides using modern photoredox catalysts.[25] With the most reducing visible-light photoredox catalysts, aryl bromides are suitable radical precursors.[26,27] Unfortunately, aryl chlorides comprise over half of the commercially available aryl halides[28] yet are inert under conventional visible-light photoredox catalysis unless they bear electron-withdrawing groups.[29–31] This limitation is a result of the combination of thermodynamically challenging SET and the low fragmentation rate due to the relatively strong $C(sp^2)$–Cl bond.[32]

To assess the viability of the proposed electrophotocatalytic approach, we investigated the dehalogenation of 4-bromobiphenyl (**1**) because of its reduction potential beyond the standard range of photoredox catalysts (−2.4 V vs SCE) and rapid fragmentation after reduction, as this provides a highfidelity readout for successful SET.[32] Using this model reaction, we assessed a series of aryl imides for activity under visible-light irradiation and an appropriate electrochemical potential to reductively activate the imide (Table 1). The radical anion derived from perylene diimide (**PDI**) can act as an electron-primed photoredox catalyst under two-photon conditions[14a] and is also well-behaved electrochemically.[33] Unfortunately, **PDI** proved ineffective in the dehalogenation of **1** under these conditions. Photophysical studies have indicated that naphthlene-based analogues (**NpDI** and **NpMI**) are more potent photoreductants after they are primed with an electron,[17c] but they have yet to be leveraged in synthesis. Excitingly, under electrophotocatalytic conditions both **NpDI** and **NpMI** promoted the dehalogenation of **1**, despite significant electrochemical underpotentials in each case (1.6 and 1.1 V vs SCE respectively). While both **NpMI** and **NpDI** are sufficiently potent photoreductants to reduce **1**, **NpMI** promoted dehalogenation significantly more efficiently. However, further stripping down the aromatic core to a phthalimide derivative, **PhMI**, resulted in a less effective photocatalyst than **NpMI**. On the basis of these data, we selected **NpMI** for further study after verifying that no significant conversion was observed in the absence of an applied voltage, light, or the catalyst.

Having identified a promising electrochemically accessible photocatalyst, we explored whether this system could engage abundant but much more challenging aryl chlorides in radical coupling reactions. We first probed the viability of a photo-Arbuzov process,[34] a classic carbon–heteroatom bond-forming reaction that proceeds through an aryl radical intermediate (Table 2). For these studies, we employed more convenient constant-current conditions.[35] We found that under simultaneous electrolysis and irradiation, **NpMI** induced the high-yielding coupling of aryl chlorides with reduction potentials at and beyond the limits of conventional visible-light photoredox catalysis (**2**–**3**). To identify the limits of this catalytic system, we next evaluated increasingly electron-rich aryl chloride substrates. Excitingly, aryl chloride substrates bearing electron-donating groups still underwent efficient SET-induced phosphorylation (**4**–**7**) even though they possess reduction potentials comparable to that of Na^0 (−2.9 V vs SCE). Notably, an exceptionally electron-rich aryl chloride (−3.4 V vs SCE)[36] was successfully reduced to produce **7**. This result indicates that these conditions provide potency comparable to that of Li^0 (−3.3 V vs SCE). To our delight, despite the presence of such a potent reductant, aryl chloride substrates bearing potentially sensitive functional groups[7,37] such as esters (**8**), nitriles (**9**), carbamates (**10**), organoboron reagents (**11**), and heterocycles (**12** and **13**) all underwent productive SET-induced radical phosphorylation, and the corresponding products were isolated in good to excellent yields.

Having established the viability of carbon–heteroatom bond-forming reactions from diverse aryl chlorides, we next aimed to intercept the aryl radical intermediate with a heterocycle to form a new carbon–carbon bond (Table 3). We found that the aryl radical intermediates generated under these conditions from neutral to electron-rich aryl chlorides (**14**–**18**) could be effectively coupled to *N*-methylpyrrole, a classic radical trap.[38] Again, reductively

sensitive functional groups were well-tolerated despite the potency of the photoreductant employed (**19**–**21**).

With a new catalytic strategy in hand, we next compared its efficacy to those of traditional photochemical and electrochemical approaches for the reductive activation of aryl chlorides (Figure 2). To this end, we investigated the relative yields of *N*-methylpyrrole coupling and dehalogenation within a subset of aryl chloride substrates ranging from electron-deficient to electron-rich. When the electron-primed photoredox system was used, each substrate delivered the desired product with excellent selectivity for radical coupling over dehalogenation. In contrast, 10-phenylphenothiazine (PTH), an exceptionally reducing photoredox catalyst (−2.1 V vs SCE),[26a] could only induce the coupling of the electron-deficient aryl chloride. The neutral and electron-rich substrates were unconverted by PTH, consistent with the energetic limitations of visible-light photoredox Direct electrolysis, on the other hand, provided significantly diminished selectivity for coupling of the electron-deficient substrate (2:1) and the other two substrates yielded in exclusively dehalogenation. These results are consistent with over-reduction at the electrode surface that precludes radical coupling reactions at the requisite potentials for aryl chloride reduction.

We next subjected radical clock **22** to both electron-primed photoredox and direct electrolysis conditions to probe the presence of an aryl radical intermediate and benchmark the rate of its over-reduction (Scheme 1). The aryl radical derived from **22** undergoes radical cyclization with a rate of 8×10^9 s^{-1}.[39] As anticipated, **NpMI** under blue-light irradiation and constant-current electrolysis delivered selective cyclization (54% yield,   20:1 selectivity for cyclization over dehalogenation and aryl anion-derived[40] isomerization products). This result is fully consistent with the proposed intermediacy of an aryl radical intermediate and high selectivity for radical chemistry instead of over-reduction. Direct electrolysis, however, provided no observable cyclization and generated only dehalogenation and isomerization products consistent with anionic intermediates. This indicates that under the direct electrolysis conditions investigated, any radical reactions with rate constants lower than 10^9 s^{-1} will not be viable because of competitive electrochemical reduction of the radical. This is consistent with the facile reduction of aryl radical intermediates at electrode surfaces (phenyl radical E_{red} = +0.05 V vs SCE).[41]

Finally, we aimed to gain preliminary insight into the promising chemoselectivity observed with this potent catalytic reductant. Notably, classic photoredox approaches are sensitive to not only the reduction potential of the substrate but also the fragmentation rate of the radical anion formed via SET.[25a] This is likely due to competition between back electron transfer and the productive fragmentation and coupling. Although back electron transfer can be a hindrance,[42] we suspect that this feature also contributes to the excellent chemoselectivity profiles observed in photoredox catalysis. Thus, we wanted to ascertain whether the exceptionally potent photoreductant explored herein exhibited analogous reactivity or whether SET was irreversible.

To this end, we conducted a series of one-pot intermolecular competition experiments between bromo- and chlorobiphenyl (Figure 3). These halogen congeners possess the same reduction potential (−2.4 V vs SCE), but their radical anions exhibit significantly different

fragmentation rates.[32,43] We subjected a 1:1 mixture of the two aryl halides to **NpMI** under simultaneous irradiation and a working potential of −1.3 V vs SCE. We found that the initial rate of $C(sp^2)$–Br cleavage was significantly higher than that of $C(sp^2)$–Cl cleavage ($k_{rel} = 8$) despite the fact the two aryl halides possess identical reduction potentials. This observation excludes that conversion is based exclusively on the reduction potential. In stark contrast, the two substrates are converted at similar rates under direct electrolysis conditions ($k_{rel} = 2$).[44] Consistent with prior work in photoredox catalysis, PTH promoted the dehalogenation of bromobiphenyl more rapidly than that of the chloride ($k_{rel} = 15$). Taken together, these data indicate that productive conversion is not governed exclusively by the reduction potential under either electron-primed or conventional photoredox catalysis. This observation provides a plausible rationale for the promising chemoselectivity observed under the conditions reported herein relative to deeply reducing direct electrolysis, which predominantly commits to product formation on the basis of the substrate reduction potential.

Overall, we have demonstrated that electrochemical stimulation is a viable strategy to generate catalytic photoreductants capable of transcending the limits of modern photoredox catalysis. We report effective radical couplings of substrates hundreds of millivolts more challenging to reduce than previous photoredox strategies, including substrates with reduction potentials well beyond that of Na^0 and more negative than that of Li^0. Crucially, despite accessing such negative potentials, the reactions possess functional group tolerance profiles more consistent with traditional photoredox catalysis than direct electrolysis and result in high selectivity for radical coupling over dehalogenation. Beyond unlocking electronically diverse aryl chlorides as aryl radical precursors, these data lay the foundation for a new catalyst design paradigm. We anticipate that electrochemically priming photocatalysts prior to excitation will allow much more challenging reductions than are feasible with blue light alone and will result in a myriad of transformations inspired by what is feasible under dissolving metal conditions and beyond.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

REFERENCES

(1) (a). Ashby EC Single-Electron Transfer, a Major Reaction Pathway in Organic Chemistry. An Answer to Recent Criticisms. Acc. Chem. Res 1988, 21, 414–421.(b)Zhang N; Samanta SR; Rosen BM; Percec V Single Electron Transfer in Radical Ion and Radical-Mediated Organic,

Materials and Polymer Synthesis. Chem. Rev 2014, 114, 5848–5958. [PubMed: 24750169] (c)Broggi J; Terme T; Vanelle P Organic Electron Donors as Powerful Single-Electron Reducing Agents in Organic Synthesis. Angew. Chem., Int. Ed 2014, 53, 384–413.(d)Girard P; Namy JL; Kagan HB Divalent Lanthanide Derivatives in Organic Synthesis. 1. Mild Preparation of Samarium Iodide and Ytterbium Iodide and Their Use as Reducing or Coupling Agents. J. Am. Chem. Soc 1980, 102, 2693–2698.(e)Eberson L Electron-Transfer Reactions in Organic Chemistry. Adv. Phys. Org. Chem 1982, 18, 79–185.

(2). (a)For selected reviews of visible-light photoredox catalysis, see: Prier CK; Rankic DA; MacMillan DWC Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. Chem. Rev 2013, 113, 5322–5363. [PubMed: 23509883] (b)Shaw MH; Twilton J; MacMillan DWC Photoredox Catalysis in Organic Chemistry. J. Org. Chem 2016, 81, 6898–6926. [PubMed: 27477076] (c)Romero NA; Nicewicz DA Organic Photoredox Catalysis. Chem. Rev 2016, 116, 10075–10166. [PubMed: 27285582] (d)Skubi KL; Blum TR; Yoon TP Dual Catalysis Strategies in Photochemical Synthesis. Chem. Rev 2016, 116, 10035–10074. [PubMed: 27109441] (e)DiRocco DA; Dykstra K; Krska S; Vachal P; Conway DV; Tudge M Late-Stage Functionalization of Biologically Active Heterocycles Through Photoredox Catalysis. Angew. Chem., Int. Ed 2014, 53, 4802–4806.(f)Narayanam JMR; Stephenson CRJ Visible Light Photoredox Catalysis: Applications in Organic Synthesis. Chem. Soc. Rev 2011, 40, 102–113. [PubMed: 20532341]

(3). For a special issue on photoredox catalysis in organic chemistry, see: Accounts of Chemical Research 2016, Vol. 49, Issue 10.

(4). Arias-Rotondo DM; McCusker JK The Photophysics of Photoredox Catalysis: A Roadmap for Catalyst Design. Chem. Soc. Rev 2016, 45, 5803–5820. [PubMed: 27711624]

(5). (a)For selected examples of design improvements of organic photoredox catalysts, see: Theriot JC; Lim C-H; Yang H; Ryan MD; Musgrave CB; Miyake GM Organocatalyzed Atom Transfer Radical Polymerization Driven by Visible Light. Science 2016, 352, 1082–1086. [PubMed: 27033549] (b)Speckmeier E; Fischer TG; Zeitler K A Toolbox Approach To Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor-Acceptor Cyanoarenes. J. Am. Chem. Soc 2018, 140, 15353–15365. [PubMed: 30277767] (c)Joshi-Pangu A; Lévesque F; Roth HG; Oliver SF; Campeau L-C; Nicewicz D; DiRocco DA Acridinium-Based Photocatalysts: A Sustainable Option in Photoredox Catalysis. J. Org. Chem 2016, 81, 7244–7249. [PubMed: 27454776]

(6). (a)For selected progress toward the design of earth-abundant photoredox catalysts, see: Hockin BM; Li C; Robertson N; Zysman-Colman E Photoredox Catalysts Based on Earth-Abundant Metal Complexes. Catal. Sci. Technol 2019, 9, 889–915.(b)Larsen CB; Wenger OS Photoredox Catalysis with Metal Complexes Made from Earth-Abundant Elements. Chem. - Eur. J 2018, 24, 2039–2058. [PubMed: 28892199] (c)Herr P; Glaser F; Büldt LA; Larsen CB; Wenger OS Long-Lived, Strongly Emissive, and Highly Reducing Excited States in Mo(0) Complexes with Chelating Isocyanides. J. Am. Chem. Soc 2019, 141, 14394–14402. [PubMed: 31464429] (d)Stevenson SM; Shores MP; Ferreira EM Photooxidizing Chromium Catalysts for Promoting Radical Cation Cycloadditions. Angew. Chem., Int. Ed 2015, 54 (22), 6506–6510.(e)Ahn JM; Peters JC; Fu GC Design of a Photoredox Catalyst That Enables the Direct Synthesis of Carbamate-Protected Primary Amines via Photoinduced, Copper-Catalyzed N-Alkylation Reactions of Unactivated Secondary Halides. J. Am. Chem. Soc 2017, 139, 18101–18106. [PubMed: 29200268]

(7). Roth HG; Romero NA; Nicewicz DA Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single-Electron Redox Chemistry. Synlett 2016, 27, 714–723.

(8) (a). Bouveault L; Blanc G Preparation des Alcools Primaires aú Moyen des Acides Correspondants. C. R. Acad. Sci 1903, 136, 1676–1678.(b)Birch AJ 117 Reduction by Dissolving Metals. Part I. J. Chem. Soc 1944, 430–436.

(9). (a)Although not as reducing as dissolving metal conditions, SmI2/HMPA can promote challenging reductions and has been broadly employed in synthesis. For reviews, see: Edmonds DJ; Johnston D; Procter DJ Samarium(II)-Iodide-Mediated Cyclizations in Natural Product Synthesis. Chem. Rev 2004, 104, 3371–3404. [PubMed: 15250745] (b)Nicolaou KC; Ellery SP; Chen JS

Samarium Diiodide Mediated Reactions in Total Synthesis. Angew. Chem., Int. Ed 2009, 48, 7140–7165.

(10). (a)For recent examples where dissolving metal conditions were crucial to a successful synthesis, see: Chuang KV; Xu C; Reisman SE A 15-Step Synthesis of (+)-Ryanodol. Science 2016, 353, 912–915. [PubMed: 27563092] (b)Liu Y-T; Li L-P; Xie J-H; Zhou Q-L Divergent Asymmetric Total Synthesis of Mulinane Diterpenoids. Angew. Chem., Int. Ed 2017, 56, 12708–12711.(c)He C; Stratton TP; Baran PS Concise Total Synthesis of Herqulines B and C. J. Am. Chem. Soc 2019, 141, 29–32. [PubMed: 30575396]

(11). For an example of large-scale use of dissolving metal conditions and an illustration of the necessary engineering controls, see: Joshi DK; Sutton JW; Carver S; Blanchard JP Experiences with Commercial Production Scale Operation of Dissolving Metal Reduction Using Lithium Metal and Liquid Ammonia. Org. Process Res. Dev 2005, 9, 997–1002.

(12). Peters BK; Rodriguez KX; Reisberg SH; Beil SB; Hickey DP; Kawamata Y; Collins M; Starr J; Chen L; Udyavara S; Klunder K; Gorey TJ; Anderson SL; Neurock M; Minteer SD; Baran PS Scalable and Safe Synthetic Organic Electroreduction Inspired by Li-Ion Battery Chemistry. Science 2019, 363, 838–845. [PubMed: 30792297]

(13) (a). Nelleborg P; Lund H; Eriksen J Photochemical vs. Electrochemical Electron-Transfer Reactions. One-Electron Reduction of Aryl Halides by Photoexcited Anion Radicals. Tetrahedron Lett 1985, 26, 1773–1776.(b)Costentin C; Robert M; Savéant J-M Fragmentation of Aryl Halide π Anion Radicals. Bending of the Cleaving Bond and Activation vs Driving Force Relationships. J. Am. Chem. Soc 2004, 126, 16051–16057. [PubMed: 15584739]

(14) (a). Ghosh I; Ghosh T; Bardagi JI; König B Reduction of Aryl Halides by Consecutive Visible Light-Induced Electron Transfer Processes. Science 2014, 346 (6210), 725–728. [PubMed: 25378618] (b)Ghosh I; König B Chromoselective Photocatalysis: Controlled Bond Activation through Light-Color Regulation of Redox Potentials. Angew. Chem., Int. Ed 2016, 55 (27), 7676–7679.(c)Neumeier M; Sampedro D; Májek M; de la Peña O'Shea VA; Jacobi von Wangelin A; Pérez-Ruiz R Dichromatic Photocatalytic Substitutions of Aryl Halides with a Small Organic Dye. Chem. - Eur. J 2018, 24, 105–108. [PubMed: 29131437]

(15). For a recent example of high-power laser irradiation allowing excitation of the excited state of a photoredox catalyst to produce solvated electrons, see: Kerzig C; Guo X; Wenger OS Unexpected Hydrated Electron Source for Preparative Visible-Light Driven Photoredox Catalysis. J. Am. Chem. Soc 2019, 141, 2122–2127. [PubMed: 30672694]

(16). (a)For reviews covering photochemically active radical anions, see: La Porte NT; Martinez JF; Chaudhuri S; Hedström S; Batista VS; Wasielewski MR Photoexcited Radical Anion Super-Reductants for Solar Fuels Catalysis. Coord. Chem. Rev 2018, 361, 98–119.(b)Fox MA The Photoexcited States of Organic Anions. Chem. Rev 1979, 79, 253–273.

(17). (a)For relevant examples of photophysical studies of radical anions, see: Fukuzumi S; Ohkubo K; Chen Y; Pandey RK; Zhan R; Shao J; Kadish KM Photophysical and Electrochemical Properties of New Bacteriochlorins and Characterization of Radical Cation and Radical Anion Species. J. Phys. Chem. A 2002, 106, 5105–5113.(b)Fujitsuka M; Kim SS; Lu C; Tojo S; Majima T Intermolecular and Intramolecular Electron Transfer Processes from Excited Naphthalene Diimide Radical Anions. J. Phys. Chem. B 2015, 119, 7275–7282. [PubMed: 25397719] (c)Gosztola D; Niemczyk MP; Svec W; Lukas AS; Wasielewski MR Excited Doublet States of Electrochemically Generated Aromatic Imide and Diimide Radical Anions. J. Phys. Chem. A 2000, 104, 6545–6551.

(18). (a)For general reviews of electroorganic synthesis, see: Yan M; Kawamata Y; Baran PS Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. Chem. Rev 2017, 117, 13230–13319. [PubMed: 28991454] (b)Yoshida J; Kataoka K; Horcajada R; Nagaki A Modern Strategies in Electroorganic Synthesis. Chem. Rev 2008, 108, 2265–2299. [PubMed: 18564879] (c)Wiebe A; Gieshoff T; Möhle S; Rodrigo E; Zirbes M; Waldvogel SR Electrifying Organic Synthesis. Angew. Chem., Int. Ed 2018, 57, 5594–5619.(d)Moeller KD Using Physical Organic Chemistry To Shape the Course of Electrochemical Reactions. Chem. Rev 2018, 118, 4817–4833. [PubMed: 29498518]

(19). (a)For reviews specifically focused on electrocatalysis, see: Francke R; Little RD Redox Catalysis in Organic Electrosynthesis: Basic Principles and Recent Developments. Chem. Soc. Rev 2014, 43, 2492–2521. [PubMed: 24500279] (b)Meyer TH; Finger LH; Gandeepan P;

Ackermann L Resource Economy by Metallaelectrocatalysis: Merging Electrochemistry and C-H Activation. Trends Chem 2019, 1, 63–76.

(20). Et$_3$N can promote premature radical quenching through hydrogen atom transfer and back electron transfer to Et$_3$N$^{\bullet+}$. For details, see ref 2c.

(21) (a). Lund H; Simonet J Anion Radicals and Dianions as Electron Transfer Reagents. J. Electroanal. Chem 1975, 65, 205–218.(b)Shukla SS; Rusling JF Photoelectrocatalytic Reduction of 4-Chlorobiphenyl Using Anion Radicals and Visible Light. J. Phys. Chem 1985, 89, 3353–3358.(c)Lund H; Carlsson HS; Nishida T; Enzell CR; Matsuno T Photochemistry of Radical Ions. Acta Chem. Scand 1978, 32b, 505–509.(d)Eriksen J; Lund H; Nyvad AI; Yamato T; Mitchell RH; Dingle TW; Williams RV; Mahedevan R Electron-Transfer Fluorescence Quenching of Radical Ions. Acta Chem. Scand 1983, 37b, 459–466.(e)Scheffold R; Orlinski R Synthesis and Reactions of Porphine-Type Metal Complexes. 15. Carbon-Carbon Bond Formation by Light Assisted B12-Catalysis. Nucleophilic Acylation of Michael Olefins. J. Am. Chem. Soc 1983, 105, 7200–7202.

(22) (a). Li T; Kasahara T; He J; Dettelbach KE; Sammis GM; Berlinguette CP Photoelectrochemical Oxidation of Organic Substrates in Organic Media. Nat. Commun 2017, 8, 390. [PubMed: 28855502] (b)Yan H; Hou Z-W; Xu H-C Photoelectrochemical C-H Alkylation of Heteroarenes with Organotrifluoroborates. Angew. Chem., Int. Ed 2019, 58, 4592–4595.(c)Wang F; Stahl SS Merging Photochemistry with Electrochemistry: Functional-Group Tolerant Electrochemical Amination of C(Sp^3)-H Bonds. Angew. Chem., Int. Ed 2019, 58, 6385–6390.(d)Huang H; Strater ZM; Rauch M; Shee J; Sisto TJ; Nuckolls C; Lambert TH Electrophotocatalysis with a Trisaminocyclopropenium Radical Dication. Angew. Chem., Int. Ed 2019, 58, 13318–13322.

(23). For a highlight of recent efforts combining electrochemical and photochemical stimulation for organic synthesis, see: Capaldo L; Quadri LL; Ravelli D Merging Photocatalysis with Electrochemistry: The Dawn of a New Alliance in Organic Synthesis. Angew. Chem., Int. Ed 2019, 58, 17508–17510.

(24). As we were preparing this Communication, Lin, Lambert and co-workers uploaded to ChemRxiv a manuscript disclosing a similar concept. See: Kim H; Kim H; Lambert T; Lin S Reductive Electrophotocatalysis: Merging Electricity and Light to Achieve Extreme Reduction Potentials. ChemRxiv, 10 8, 2019, ver. 2. DOI: 10.26434/chemrxiv.9936623.v2.

(25) (a). Ghosh I; Marzo L; Das A; Shaikh R; König B Visible Light Mediated Photoredox Catalytic Arylation Reactions. Acc. Chem. Res 2016, 49, 1566–1577. [PubMed: 27482835] (b)Wang C-S; Dixneuf PH; Soulé JF Photoredox Catalysis for Building C-C Bonds from C(Sp2)-H Bonds. Chem. Rev 2018, 118, 7532–7585. [PubMed: 30011194]

(26) (a). Discekici EH; Treat NJ; Poelma SO; Mattson KM; Hudson ZM; Luo Y; Hawker CJ; Read de Alaniz J A Highly Reducing Metal-Free Photoredox Catalyst: Design and Application in Radical Dehalogenations. Chem. Commun 2015, 51, 11705–11708.(b)Devery JJ; Nguyen JD; Dai C; Stephenson CR J. Light-Mediated Reductive Debromination of Unactivated Alkyl and Aryl Bromides. ACS Catal 2016, 6, 5962–5967.(c)Boyington AJ; Riu M-LY; Jui NT Anti-Markovnikov Hydroarylation of Unactivated Olefins via Pyridyl Radical Intermediates. J. Am. Chem. Soc 2017, 139, 6582–6585. [PubMed: 28472584]

(27). (a)tert-BuOK in combination with a nitrogen base can reductively generate aryl radical intermediates. See: Cheng Y; Gu X; Li P Visible-Light Photoredox in Homolytic Aromatic Substitution: Direct Arylation of Arenes with Aryl Halides. Org. Lett 2013, 15, 2664–2667. [PubMed: 23688041] (b)Cheng Y; Gu X; Li P Visible-Light Photoredox in Homolytic Aromatic Substitution: Direct Arylation of Arenes with Aryl Halides. Org. Lett 2013, 15, 2664–2667. [PubMed: 23688041]

(28). Weix and co-workers recently conducted an analysis concluding that there are more commercially available ArCl than ArI, ArBr, and ArOH combined. See: Huang L; Ackerman LKG; Kang K; Parsons AM; Weix DJ LiCl-Accelerated Multimetallic Cross-Coupling of Aryl Chlorides with Aryl Triflates. J. Am. Chem. Soc 2019, 141, 10978–10983. [PubMed: 31257881]

(29). For examples of photoredox catalysts reductively activating aryl chlorides bearing electron-withdrawing groups, see ref 14a, ref 25a, and the following reference: Ghosh I; Shaikh RS; König B Sensitization-Initiated Electron Transfer for Photoredox Catalysis. Angew. Chem., Int. Ed 2017, 56, 8544–8549.

(30). For an example of a cocatalytic system composed of highly reducing DyI2 and an organic dye photochemically reducing aryl chlorides, see: Meyer AU; Slanina T; Heckel A; König B Lanthanide Ions Coupled with Photoinduced Electron Transfer Generate Strong Reduction Potentials from Visible Light. Chem. - Eur. J 2017, 23, 7900–7904. [PubMed: 28429580]

(31). (a)For examples of UV-light-promoted dichlorination of aryl chlorides, see: Yin H; Jin Y; Hertzog JE; Mullane KC; Carroll PJ; Manor BC; Anna JM; Schelter EJ The Hexachlorocerate(III) Anion: A Potent, Benchtop Stable, and Readily Available Ultraviolet A Photosensitizer for Aryl Chlorides. J. Am. Chem. Soc 2016, 138, 16266–16273. [PubMed: 27936638] (b)Matsubara R; Yabuta T; Md Idros U; Hayashi M; Ema F; Kobori Y; Sakata K UVA- and Visible-Light-Mediated Generation of Carbon Radicals from Organochlorides Using Nonmetal Photocatalyst. J. Org. Chem 2018, 83, 9381–9390. [PubMed: 30005575]

(32). Costentin C; Robert M; Saveant J-M. Fragmentation of Aryl Halide π Anion Radicals. Bending of the Cleaving Bond and Activation vs Driving Force Relationships. J. Am. Chem. Soc 2004, 126, 16051–16057. [PubMed: 15584739]

(33). Sun G; Ren S; Zhu X; Huang M; Wan Y Direct Arylation of Pyrroles via Indirect Electroreductive C-H Functionalization Using Perylene Bisimide as an Electron-Transfer Mediator. Org. Lett 2016, 18, 544–547. [PubMed: 26800089]

(34). Plumb JB; Obrycki R; Griffin CE Phosphonic Acids and Esters. XVI. Formation of Dialkyl Phenylphosphonates by the Photoinitiated Phenylation of Trialkyl Phosphites1,2. J. Org. Chem 1966, 31 (8), 2455–2458.

(35). Both constant current and constant cell potential conditions allow the working electrode potential to vary over the reaction. We found that the working potential dropped over the course of a standard reaction. Control experiments verified that in each stage of the reaction both light and electrolysis were necessary. See the SI for details.

(36). The reduction wave for LiClO$_4$ in DMSO begins before reduction of the aryl chloride leading to 7. Differential pulse voltammetry deconvoluted these features and provided an E_{red} of −3.4 V vs SCE. See the SI for details.

(37). Each of these functional groups possess an E_{red} less negative than the substrates productively engaged in radical coupling.

(38). Beveridge S; Huppatz JL The Pschorr Cyclization. A Novel Pschorr Reaction with a Pyrrole Derivative: Synthesis of a Pyrrolo[1,2-*c*]Quinazoline and a New Route to Arylpyrroles. Aust. J. Chem 1970, 23, 781–789.

(39). Newcomb M Radical Kinetics and Clocks In Encyclopedia of Radicals in Chemistry, Biology and Materials; Wiley, 2012.

(40). Kimura M; Miyahara H; Moritani N; Sawaki Y Electroreductive Dehalogenation of Chlorinated Aromatic Ethers. Unexpected Electrogenerated Base-Catalyzed Reactions. J. Org. Chem 1990, 55 (12), 3897–3902.

(41). Andrieux CP; Pinson J The Standard Redox Potential of the Phenyl Radical/Anion Couple. J. Am. Chem. Soc 2003, 125, 14801–14806. [PubMed: 14640655]

(42). Ruccolo S; Qin Y; Schnedermann C; Nocera DG General Strategy for Improving the Quantum Efficiency of Photoredox Hydroamidation Catalysis. J. Am. Chem. Soc 2018, 140, 14926–14937. [PubMed: 30372046]

(43). Takeda N; Poliakov PV; Cook AR; Miller JR Faster Dissociation: Measured Rates and Computed Effects on Barriers in Aryl Halide Radical Anions. J. Am. Chem. Soc 2004, 126, 4301–4309. [PubMed: 15053620]

(44). Ke J; Wang H; Zhou L; Mou C; Zhang J; Pan L; Chi YR Hydrodehalogenation of Aryl Halides through Direct Electrolysis. Chem. - Eur. J 2019, 25, 6911–6914. [PubMed: 30950097]
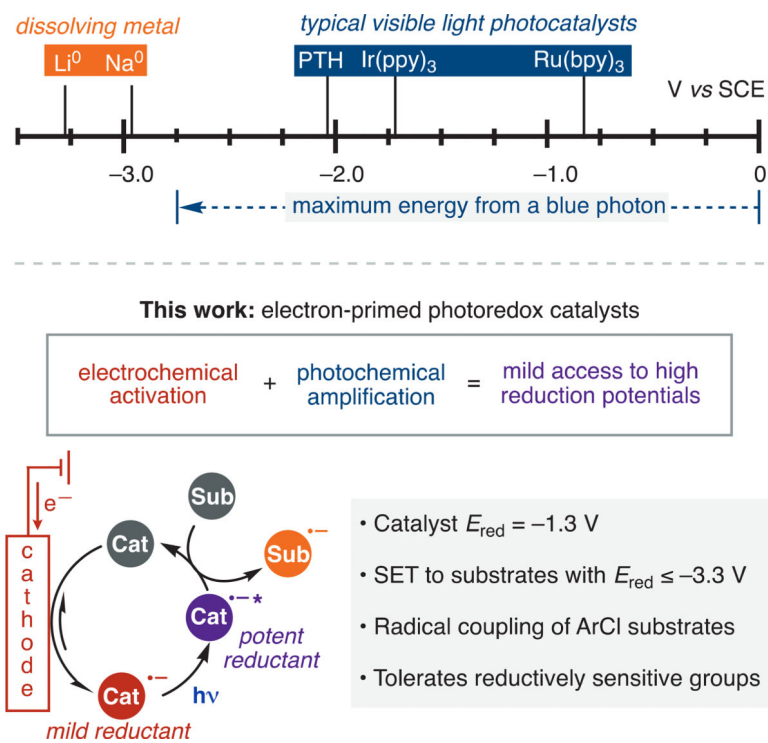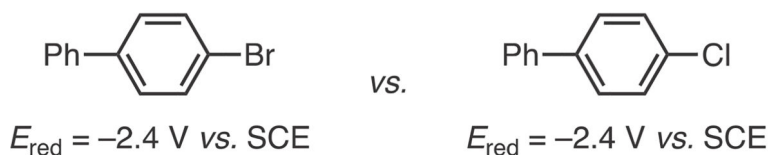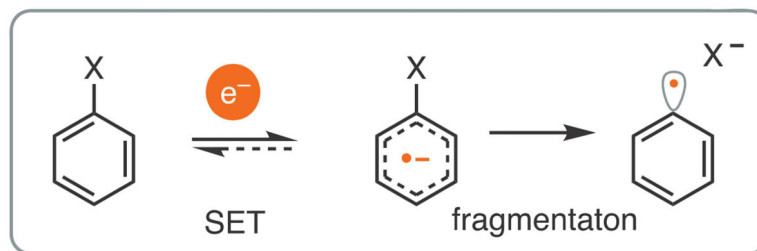
Figure 1.
Strategies to induce SET reduction. All potentials shown are relative to SCE. PTH = 10-phenylphenothiazine.
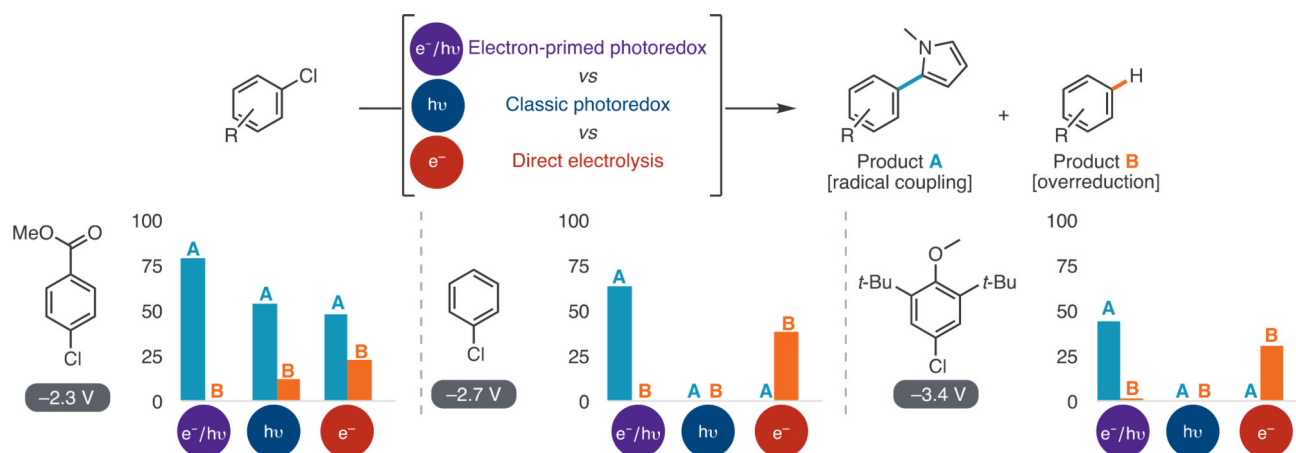
Figure 2.
Comparison of reactivities and selectivities observed with various methods of generating aryl radical intermediates using *N*-methylpyrrole as a radical trap. Yields of coupling and dehalogenation were measured relative to an internal standard. The electron-primed photoredox conditions were the same as in Table 3. The photoredox conditions followed pyrrole coupling procedures from the literature employing PTH as a photocatalyst. Several direct electrolysis conditions were attempted. The reported conditions provided the highest yield of A and were standard reaction conditions from Table 3 without catalyst. For further details, see the SI.

two step aryl radical generation

$E_{red} = -2.4$ V *vs.* SCE   *vs.* $E_{red} = -2.4$ V *vs.* SCE

SET strategy	Intermolecular k_{rel}
Electron-primed photoredox	8
Direct electrolysis	2
Photoredox	15

Figure 3.
Comparison of one-pot competition experiments. k_{rel} is given as k_{Br}/k_{Cl} and was measured by gas chromatography based on reactions run to low conversion (<20%). The electron-primed photoredox conditions followed from Table 1. The direct electrolysis conditions were those reported in ref 44. Previously reported photoredox conditions were employed 26a. See the SI for details.
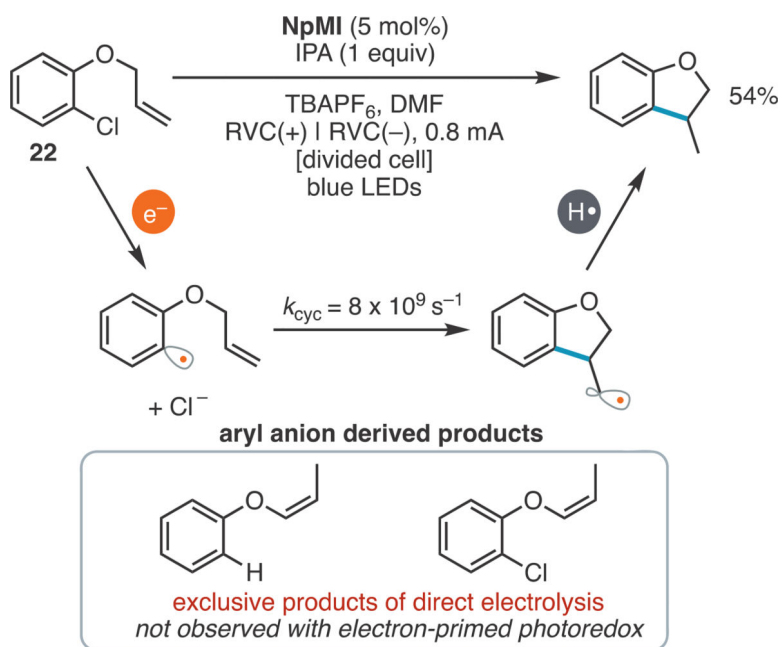
Scheme 1.

Comparison of Radical Clock Outcomes[a]

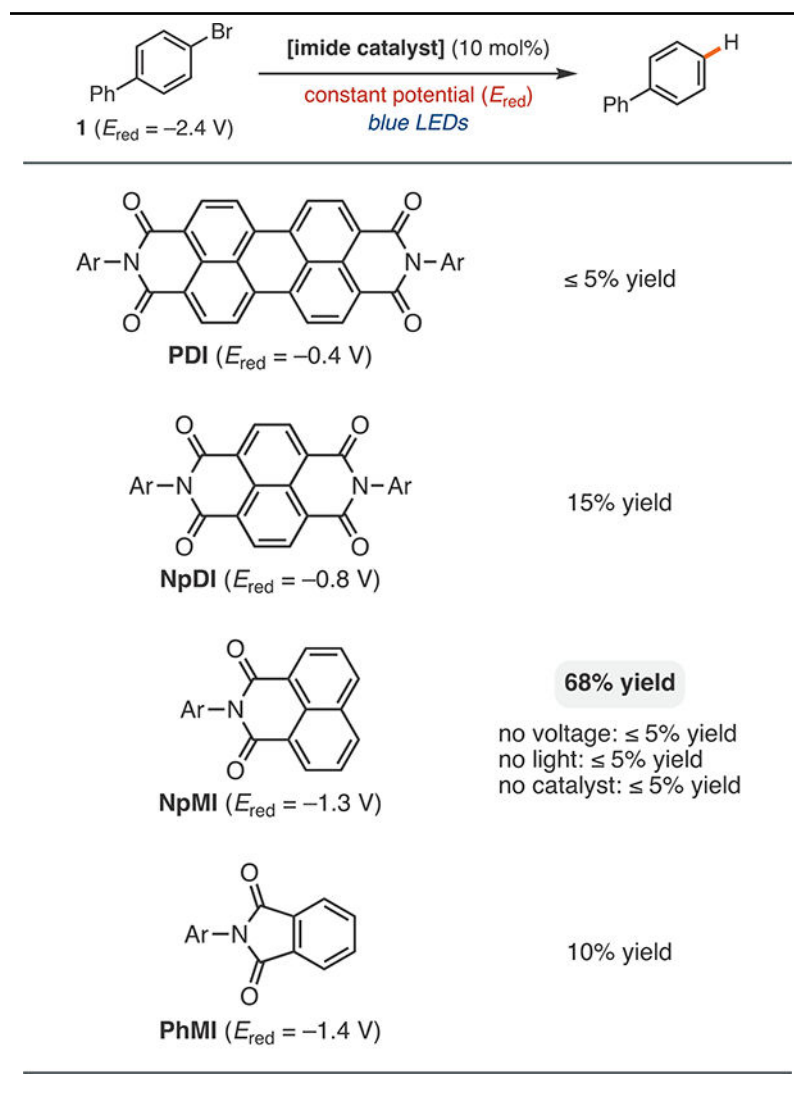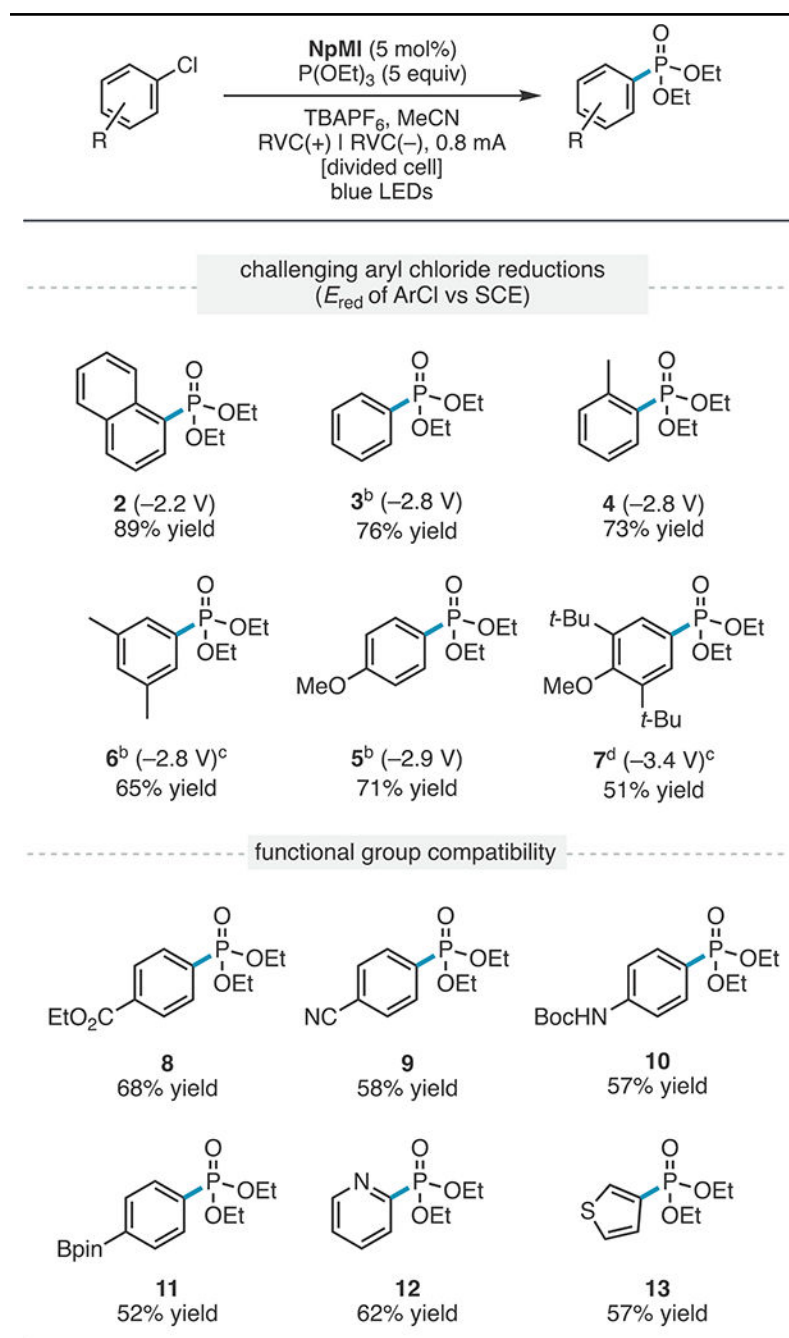[a]The reaction was conducted on a 0.4 mmol scale for 20 h.´

Table 1.

Electrochemical Access to Electron-Primed Photocatalysts[a,b,c]

Table 2.

Scope of Aryl Chloride Phosphorylation[a]

Reaction scheme: ArCl with NpMI (5 mol%), P(OEt)$_3$ (5 equiv), TBAPF$_6$, MeCN, RVC(+) | RVC(−), 0.8 mA, [divided cell], blue LEDs.

challenging aryl chloride reductions
(E_{red} of ArCl vs SCE)

2 (−2.2 V)
89% yield

3[b] (−2.8 V)
76% yield

4 (−2.8 V)
73% yield

6[b] (−2.8 V)[c]
65% yield

5[b] (−2.9 V)
71% yield

7[d] (−3.4 V)[c]
51% yield

functional group compatibility

8
68% yield

9
58% yield

10
57% yield

11
52% yield

12
62% yield

13
57% yield

[a]Reactions were conducted on a 0.4 mmol scale and run for 8 h. Et$_3$N (2 equiv) was employed in the anode as the counter reaction. See the SI for further experimental details.

[b]The reaction was run for 14 h.

$^c E_{\mathrm{red}}$ was determined by differential pulse voltammetry
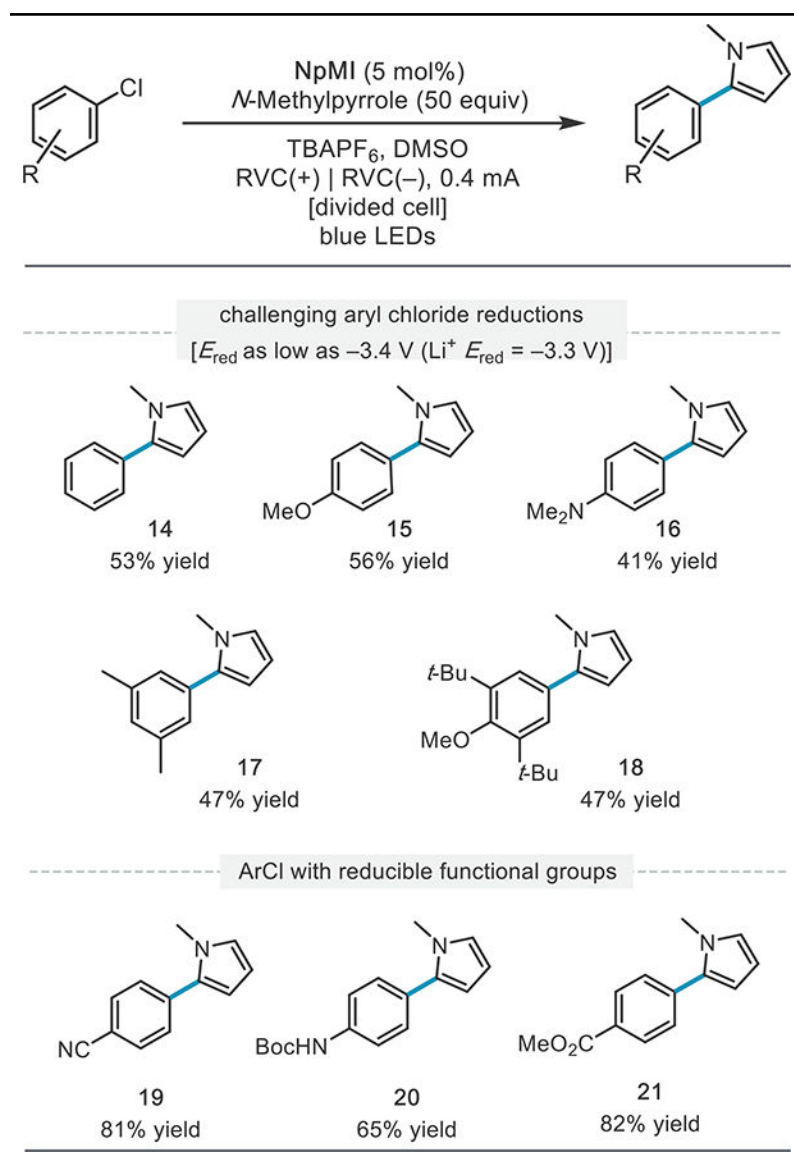
^{d}0.4 mA current.

Table 3.

Scope of Aryl Chloride (Hetero)arylation[a]