A Paradigm Shift in Catalysis: Electro- and Photomediated Nickel-Catalyzed Cross-Coupling Reactions

Maximilian D. Palkowitz,[a] Megan A. Emmanuel,[b] Martins S. Oderinde*[c].

[a]Small Molecule Drug Discovery, Bristol Myers Squibb, 250 Water Street, Cambridge, MA, 02141, USA.

[b]Chemical Process Development, Bristol Myers Squibb, 1 Squibb Drive, New Brunswick, New Jersey, 08901, USA.

[c]Small Molecule Discovery Chemistry, Bristol Myers Squibb Research & Early Development, Route 206 & Province Line Road, Princeton, New Jersey, 08543, USA.

Electrocatalysis, Photocatalysis, Metallaphotoredox, Radical Cross-Coupling.

Conspectus: Transition-metal catalyzed cross-coupling reactions are fundamental reactions in organic chemistry, facilitating strategic bond formations for accessing natural products, organic materials, agrochemicals, and pharmaceuticals. Redox chemistry enables access to elusive cross-coupling mechanisms through single-electron processes as an alternative to classical two-electron strategies, which are predominated by palladium catalysis. The hallmark of this redox platform is the

systematic modulation of transition-metal oxidation states by a photoredox catalyst or at a heterogeneous electrode surface. Electrocatalysis and photocatalysis enhance transition metal catalysis' capacity for bond formation through electron- or energy-transfer processes. Cross-coupling conditions promoted by electrocatalysis and photocatalysis are mild and bond formation proceeds with exceptionally high chemoselectivity and wide functional group tolerance. The interfacing of abundant first-row transition-metal catalysis with electrocatalysis and photocatalysis has brought about a paradigm shift in cross-coupling technology. In particular, the merger of Ni catalysis with electro- and photochemistry ushered in a new era for carbon-carbon and carbon-heteroatom cross-couplings. We have developed enabling photo- and electrochemical methods throughout our research experience in industry (BMS, AstraZeneca), academia (Professor Baran, Scripps Research), and cross-disciplinary collaborative environments. In this Account, we will outline recent progress from our past and present labs in photo- and electrochemically mediated Ni-catalyzed cross-couplings. By highlighting these cross-coupling methodologies, we will also compare mechanistic features of both electro– and photochemical strategies for forging $C(sp^2)$–$C(sp^3)$, $C(sp^3)$–$C(sp^3)$, C–O, C–N, and C–S bonds. In each case study where we did not specifically develop both approaches, we will highlight related work from others for education. Through these side-by-side comparisons, we hope to demystify the subtle differences between the two complementary tools to enact redox control over transition metal catalysis. Finally, building off the collective experience of ourselves and the rest of the community, we propose a user guide to photo- and electrochemically-driven cross-coupling reactions to aid the practitioner in rapidly applying such tools in their synthetic designs.
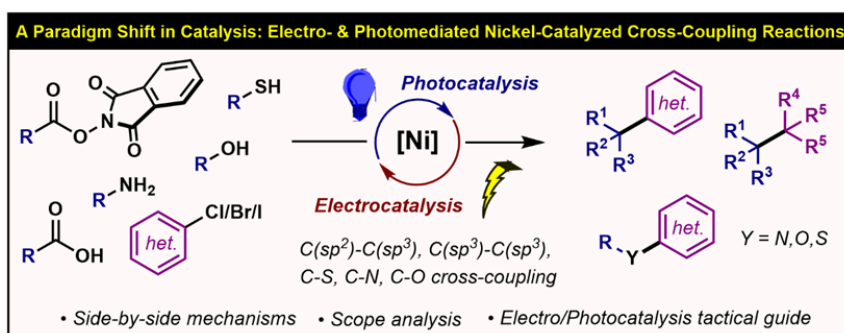
KEY REFERENCES:

- Oderinde, M. S.; Frenette, M.; Robbins, D. W.; Aquila, B.; Johannes, J. W., Photoredox Mediated Nickel Catalyzed Cross-Coupling of Thiols with Aryl and Heteroaryl Iodides via Thiyl Radicals. *J. Am. Chem. Soc.* **2016,** *138* (6), 1760-1763
- Pitchai, M.; Ramirez, A.; Mayder, D. M.; Ulaganathan, S.; Kumar, H.; Aulakh, D.; Gupta, A.; Mathur, A.; Kempson, J.; Meanwell, N.; Hudson, Z. M.; Oderinde, M. S., Metallaphotoredox Decarboxylative Arylation of Natural Amino Acids via an Elusive Mechanistic Pathway. ACS Catal. 2023, 13 (1), 647-658
- Palkowitz, M. D.; Laudadio, G.; Kolb, S.; Choi, J.; Oderinde, M. S.; Ewing, T. E.-H.; Bolduc, P. N.; Chen, T.; Zhang, H.; Cheng, P. T. W.; Zhang, B.; Mandler, M. D.; Blasczak, V. D.; Richter, J. M.; Collins, M. R.; Schioldager, R. L.; Bravo, M.; Dhar, T. G. M.; Vokits, B.;

Zhu, Y.; Echeverria, P.-G.; Poss, M. A.; Shaw, S. A.; Clementson, S.; Petersen, N. N.; Mykhailiuk, P. K.; Baran, P. S., Overcoming Limitations in Decarboxylative Arylation via Ag–Ni Electrocatalysis. *J. Am. Chem. Soc.* **2022**, *144* (38), 17709-17720

- Zhang, H.-J.; Chen, L.; Oderinde, M. S.; Edwards, J. T.; Kawamata, Y.; Baran, P. S., Chemoselective, Scalable Nickel-Electrocatalytic O-Arylation of Alcohols. *Angew. Chem. Int. Ed.* **2021**, *60* (38), 20700-20705

INTRODUCTION

The tremendous advancements in organic chemistry and the success of the chemical science industries in the past century can be credited to catalysts based on transition metals such as palladium, platinum, cobalt, rhodium, gold, ruthenium, and rare earth metals. However, the past decade has also witnessed a renaissance in using cheap and abundant first-row transition metals such as Ni, Cu, and Fe as catalysts in organic synthesis. Numerous academic and industrial processes now involve 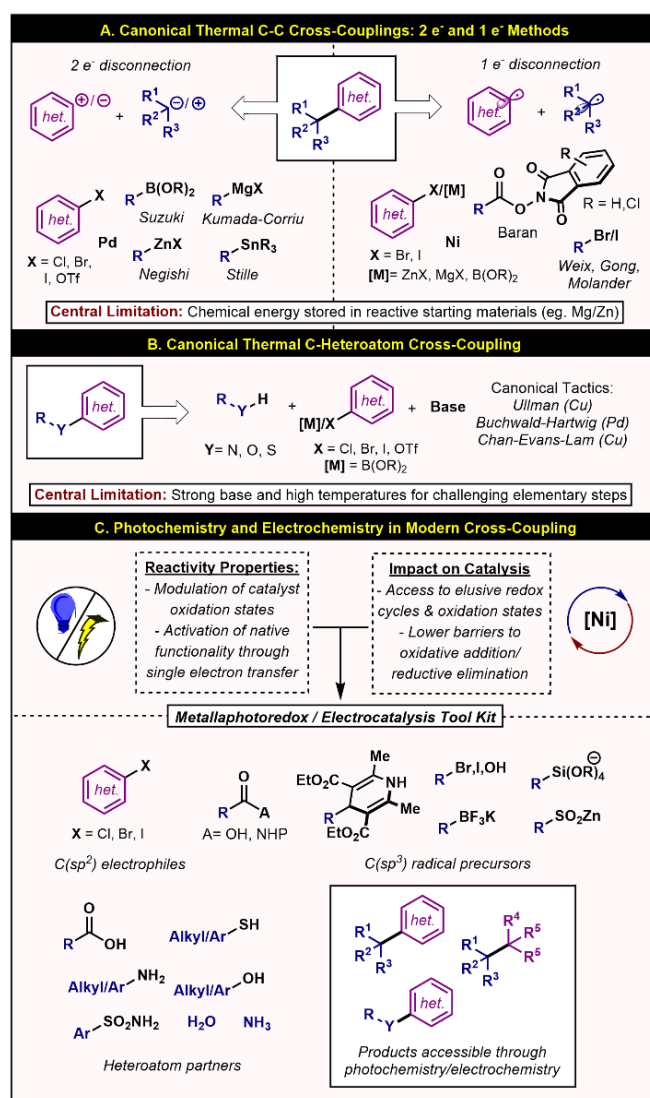first-row transition metals catalysts supported with cheap ligand frameworks.[1] The seminal reports of Baran,[2-3] MacMillan,[4] Doyle,[5] Molander,[6] Weix,[7-9] Lin,[10-11] Fu,[12] Reisman,[13] Diao,[14-15] and others[16-17] in merging redox perturbation (photochemical, electrochemical, and purely chemical) with catalysis are pivotal to the resurgence and mechanistic understanding of first-row transition metal-based catalysis.

Owing to the wide range of oxidation states in which first-row metals can exist, their reactivity towards radical intermediates allows them to forge bonds from easy-to-access radical precursors. For the sake of illustration, consider a general $C(sp^2)$–$C(sp^3)$ linkage. Following conventional retrosynthetic analysis along the lines of polar bond disconnections would lead to powerful cross-coupling tactics such as Suzuki, Kumada-Corriu, Negishi, and Stille most often mediated by a palladium catalyst (Figure 1A).[18-20] In such cases, the nucleophilic component is either introduced as a $C(sp^2)$ anion equivalent (organomagnesium, organozinc, organoboron, etc.) which can impact chemoselectivity and functional group compatibility. Alternatively, a $C(sp^2)$ electrophile in the presence of an exogenous can be used in a cross-electrophile coupling.[21] In contrast, following a radical disconnection leads the practitioner to building blocks such as carboxylic acids and alkyl esters pioneered by Baran and MacMillan as well as alkyl halides popularized by Weix, Gong, and Molander.[18-20] While the emergence of radical-based cross couplings has expanded the range of chemical space accessible in the synthesis of fine chemicals, there yet lie limitations. Whether following a polar or radical disconnection, the use of thermally driven crosscouplings relies on the energy needed for the reaction being a core component of the starting materials. However, the high reactivity of starting materials can be detrimental to the overall functional group compatibility of the process and strongly influence synthetic design necessitating unattractive protecting group strategies.[22-23]

A similar limitation can be found in widely employed C-heteroatom cross-coupling reactions (Figure 1B). Ullman, Buchwald-Hartwig, and Chan-Evans-Lam remain powerful synthetic tools, yet the harsh conditions needed for challenging elementary steps compromise overall functional group compatibility in the pursuit of densely functionalized architectures.[24-25] The merger of transition metal catalysis with photochemical and electrochemical modulation has become a popular strategy to overcome such limitations (Figure 1C).[26-29] By either oxidizing or reducing a metal catalyst, a photo- or electrocatalyst can coax reactivity towards otherwise reluctant functionality with tight control of chemoselectivity. In addition, the redox perturbation of a metal catalyst's oxidation state can permit entry to elusive catalytic cycles and lower the energy barriers to challenging elementary steps. Combining the reactivity properties of redox control with broad access to radical intermediates has expanded the toolkit of the modern chemist to access valuable chemical space from simple, safe, and often readily available starting materials. Specifically, photochemistry and electrochemistry both have had profound impacts on $C(sp^2)$–$C(sp^3)$, $C(sp^3)$–$C(sp^3)$, and C–Heteroatom cross-coupling. In addition to these tactics, the use of metallic reductants such as Zn and Mn to drive reductive crosscoupling has emerged as an alternative answer to such challenges.[30] While such reactions have similar mechanistic features and practical advantages, they are outside the scope of our labs' work and will not be discussed.

Figure 1. A) Conventional cross-coupling approaches using two-electron and single-electron disconnections. B) Conventional C-Heteroatom cross-coupling approaches. C) Impact of photochemistry and electrochemistry on modern catalysis and products accessible through such tactics

Getting Involved in Photoredox Catalysis

The perturbation of chemical and transition metal reactivity with light has long been appreciated by the commu-

nity.[31-33] Seminal work by Marcus,[34] Okada,[35-36] Barton,[37] Fagnoni,[38-39] Mattay,[40] Tanaka,[41] Fukuzumi,[42] Schuster,[43-45] and others[46] served to build the foundation upon which the resurgence of photochemical methodologies of the past decade is built. Inspired by the recent work by MacMillan, Doyle, and Molander, we became interested in the exploration of Ni-catalyzed decarboxylative cross-coupling with aryl halides enabled by visible-light with an eye towards applications in drug discovery.[4, 6] Following those disclosures, we conducted preliminary mechanistic investigations of the dual-catalyzed reactions. Those efforts led to uncovering the unexpected tolerance of the cross-coupling regime to molecular oxygen.[47] We also studied how different solvents and light wavelengths affect coupling efficiency. We then developed other Ni-based metallaphotoredox cross-coupling methodologies for forging C–C, C–S, C–N, and C–O bonds. We have also contributed to the overall mechanistic understanding of metallaphotoredox cross-couplings. Our mechanistic findings highlight (i) that the photoredox catalyst allows access to Ni(I)-species, which promotes certain cross-couplings, (ii) reductive-elimination of a Ni(II) aryl alky complex is the rate-limiting step in C(sp^2)–C(sp^3) cross-coupling, (iii) Ni(0)-species is not always involved in the cross-coupling reactions, (iv) the energy-transfer process plays an essential role in C-heteroatom cross-coupling reactions. With the knowledge that energy transfer processes are involved in metallaphotoredox C–heteroatom cross-coupling reactions, we collaborated with Professor Zachary Hudson and designed organic materials for energy transfer photocatalysis. Although it is outside the scope of this account, we have also developed energy transfer-mediated, inter-, and intramolecular, dearomatizing, and non-dearomatizing [2+2] cycloaddition reactions.[48-51]

Getting Involved in Electrochemistry

Electrocatalysis has only recently become a practical tool for organic synthesis through a vibrant renaissance building off the pioneering work of Perichon,[52-53] Shono,[54] Little,[55] Yoshida,[56] Moeller,[57-58] and others.[59-60] Electrochemical oxidation or reduction allows precise tuning of reaction conditions to match substrate needs and limit side reactions from classical reagents that operate in fixed potential windows. The electrocatalytic strategy represents an eco-friendly and economically sustainable method because it provides a more selective source of electron transfer as opposed to chemical reagents, generates less waste, and works under mild conditions. Electrochemistry and electrocatalysis have advanced significantly over the last ten years, with improvements in instrumentation facilitating implementation in both academic and industrial settings. An academic-industrial collaboration between our labs at Bristol Myers Squibb and Baran's lab was established to advance Ni electrocatalysis in the context of drug discovery. The collaboration with Baran's lab quickly led to the identification of general platforms for electrochemical Ni-catalyzed C(sp^2)–C(sp^3), C(sp^3)–C(sp^3), and C–O cross-couplings.

C(sp^2)–C(sp^3) Decarboxylative Arylation

To further advance metallaphotoredox C(sp^2)–C(sp^3) cross-coupling, broaden its industrial applicability, and gain a better understanding of its mechanism, we reinvestigated the decarboxylative cross-coupling reaction of α-amino acids with aryl halides (Figure 2A-C).[61] This reaction is desirable in medicinal chemistry because it uses abundant and cheap α-amino acids feedstock as diverse alkyl inputs. The optimization of the reported metallaphotoredox conditions

resulted in the identification of a new set of conditions comprising of cheap and simple Ni catalyst system (H$_2$O)$_6$Ni(BF$_4$)$_2$ and bipyridine (bpy). Running the reaction in DMA and irradiating with violet-LEDs (λ = 400 nm) gave a higher yield of products compared to the combination of DMF and blue-LEDs (λ = 450 nm) used in the original report.[4] With the use of new conditions, we were able to extend the scope to encompass α-amino acids bearing pharmacophoric elements, which were previously unexplored coupling partners. α-amino acids bearing broad functional groups, including heterocycles, successfully underwent decarboxylative arylation with a diverse set of aryl bromides. Some intriguing observations that triggered new mechanistic investigations were made during the scope studies, namely: (i) proto-debromination and olefin side-products were observed in some reactions, and (ii) electron-rich aryl bromides generally failed. Although beneficial effects have been observed in certain reactions,[62] the inclusion of phthalimide as an additive in the reaction had little influence on the coupling with electron-rich arenes.[63] Those observations prompted other questions about the accepted Ni(0)/Ni(II)/Ni(III)/Ni(I)/Ni(0) catalytic pathway, leading us to suspect that Ni could operate by an alternative pathway in this reaction. Results from experimental control reactions with Ni(II)-complexes, cyclic voltammetry (CV) and computational studies led us to propose an alternative mechanistic pathway for the decarboxylative arylation (Figure 2A). The dual-catalytic process begins with the SET oxidation of the carboxylate by the excited photocatalyst *Ir^{III} ($E_{1/2}^{red}$[*Ir^{III}/Ir^{II}] = +1.21 V vs. SCE (Saturated Calomel Electrode) in CH$_3$CN) to generate an α-amino radical after CO$_2$ extrusion. Concurrent with the photoredox cycle, the oxidative addition of a Ni(0) species into the aryl halide would produce a Ni(II)ArBr intermediate. Distinct from previous proposals, the SET reduction of the Ni(II)ArBr complex ($E_{1/2}^{red}$ –1.25 to (−1.37) V vs. SCE in CH$_3$CN depending on Ar substitution) by Ir^{II} species ($E_{1/2}^{red}$[Ir^{III}/Ir^{II}] = −1.37 V vs. SCE in CH$_3$CN) is thermodynamically feasible, forging a Ni(I)Ar species. The Ni(I)Ar species would rapidly intercept the α-amino radical, forming a Ni(II)Ar(R) adduct, which upon undergoing reductive elimination delivers the cross-coupled product with the concomitant release of Ni(0) species. Comprehensive Density Functional Theory (DFT) studies provide qualitative support for the viability of the Ni(I)Ar intermediate and suggest that the reductive elimination from Ni(II)Ar(R) intermediate is turnover limiting. In addition to undergoing reductive elimination, Ni(II)Ar(R) can also engage in a competitive β-hydride elimination resulting in proto-debromination and olefin side-products. While the previously discussed photochemical methodology and related work by MacMillan, Doyle, and others have proven effective at promoting C(sp^2)–C(sp^3) from readily available carboxylic acids, key limitations hinder its broader utility in diverse drug discovery programs.[4, 60, 61] First, the range of aryl coupling partners that perform well in decarboxylative cross-couplings is limited to electron-deficient arenes and heterocycles with few reports of electron-rich (hetero)arenes. Second, alkyl partners are generally limited to α-heteroatom carboxylic acids that generate stabilized radicals. Recently, MacMillan reported that the addition of phthalimide expands the substrate scope to include unactivated carboxylic acids.[63] Notwithstanding, the intolerance of other functionalities such as electron-rich arenes and oxidizable tertiary amines presents a current substrate limitation of the photochemically driven process.[64]

In contrast, a reductive coupling approach driven by electricity should offer a solution to such challenges. During a

3

terpene total synthesis campaign, Baran and coworkers discovered that the addition of silver nitrate to an electrochemically driven decarboxylative alkenylation reaction allowed for a chemoselective electron transfer to the Ni catalyst in the presence of other reductively labile functional groups.[65] This additive led to expanded functional group tolerance and allowed for a streamlined series of natural product syntheses with minimal protecting groups. They postulated that silver nitrate *in situ* forms a silver nanoparticle (AgNP) layer on the cathode surface which protected against substrate and catalyst cathodic degradation. Taken together, our labs envisioned that such reactivity benefits from electrochemistry in the pursuit of linear terpenes could have a similarly significant impact on pharmaceutical synthesis (Figure 2D-F). Mechanistically, the electrochemically driven arylation with RAEs is distinct from that of photochemical arylation with acids. First, the silver nitrate is reduced to AgNP's that deposit on the cathode surface before the catalytic cycle begins. Then, Ni(II) is reduced to a low valent Ni(I) complex that undergoes oxidative addition to an aryl-halide to afford a Ni(III)-aryl(X)$_2$ intermediate. Next, the Ni(III) species is reduced to a Ni(II)-aryl(X) complex either by disproportionation with Ni(I) or through cathodic reduction. The Ni(II)-aryl(X) then captures an alkyl radical to form a Ni(III)-aryl(alkyl)(X) complex that undergoes reductive elimination to afford the desired aryl-

alkyl product and a Ni(I)X species. The resulting Ni(I)X species can reduce the RAE through a SET to afford an alkyl radical while concomitantly producing a Ni(II) species that re-enters the catalytic cycle.

The result of the collaborative effort led to the development of a simple set of electrolytic conditions to furnish a range of C(sp^2)–C(sp^3) coupled products from readily available RAE and (hetero)aryl halides.[66] The reaction tolerates molecular oxygen (air) and both electron-rich and electron-deficient (hetero)aryl halides as suitable coupling partners, including those that bear sensitive and oxidizable functionalities such as Lewis basic heteroatoms. Despite the perceived challenges of setting up electrochemical reactions,[67] the robust nature of the coupling permitted a simple dump-and-stir procedure. Additionally, relying on electric current to propagate the Ni-cycle allowed the reaction to be complete within 2 hours in contrast to the typical >24-hour reaction times found in most photochemical variants. While mostly efficacious using aryl iodides and bromides, some electron-deficient aryl chlorides were found suitable as well. Furthermore, by leveraging a recirculating flow reactor, some reactions were performed on decagram scale. The process is also amenable to parallel library synthesis using the IKA E-Hive setup, a commercial medium throughput electrochemical reactor. Despite the expanded scope of decarboxylative arylation, limitations
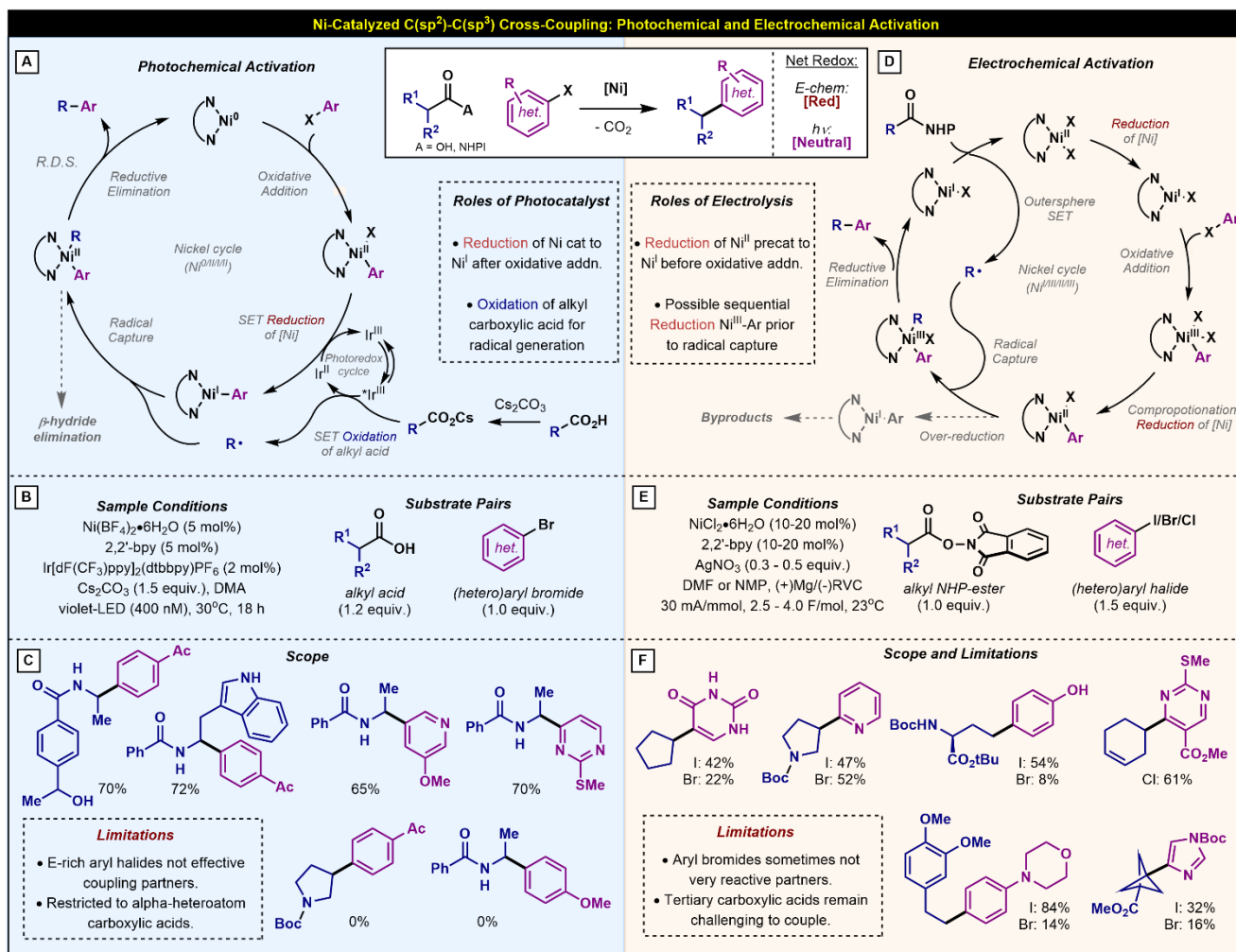
Figure 2. (A-F) Mechanistic and tactical overview of Ni-catalyzed C(sp^2)-C(sp^3) cross-couplings driven by photochemical and electrochemical strategies.

4

include the poor reactivity of electron-rich aryl bromides and RAEs derived from tertiary carboxylic acids.

Tertiary C(sp²)–C(sp³) Decarboxylative Arylation

The construction of fully substituted carbon centers remains a challenge for modern C(sp²)-C(sp³) radical cross-coupling. Often, the answer to this challenge is not a straight-forward application of existing methods that excel at coupling primary and secondary alkyl partners. Inspired by this, we sought to develop a metallaphotoredox method for decarboxylative C(sp²)-C(sp³) cross-coupling of tertiary carboxylic acids with aryl halides (Figure 3A-C).[68] Initial attempts with traditional bipyridyl-based Ni-catalysts led to trace product formation and a significant amount of ester byproduct. By employing high throughput experimentation (HTE), we identified Ni(TMHD)$_2$ as a suitable catalyst that promotes the desired tertiary cross-coupling selectively with complete suppression of the esterification reaction. As depicted in Figure 3A, we proposed that our cross-coupling follows a mechanism similar to what has been described for other related tertiary alkyl systems.[69-70] DFT studies support that an outer sphere reductive elimination process between Ni(TMHD)ArX and the tertiary alkyl radical delivers the cross-coupled product.

A wide range of tertiary radicals could be coupled to various aryl bromides in the preparative reaction (Figure 3B & 3D). While most examples were tertiary α-amino carboxylic acids, some examples of forging all-carbon quaternary centers were demonstrated, albeit in a substrate-dependent manner. This report represents one of the rare cases where tertiary all-carbon carboxylic acids could be productively coupled under photoredox conditions, thus filling a critical gap in the literature.

Several limitations hindered the broader application of our metallaphotoredox system. Heterocyclic aryl bromides were not tolerated, and the use of non-stabilized radicals was highly substrate dependent. Recalling the electrochemical AgNP approach, we wondered if the heightened functional group tolerance of that system could be leveraged to provide a complimentary electrochemical solution to tertiary decarboxylative cross-coupling with the analogous RAEs (Figure 3D-F). In collaboration with the Baran lab, we found that the extension of our previous C(sp²)-C(sp³) methodology (*vide supra*) was a useful starting point to address tertiary couplings.[71] While modest yields of tertiary products were obtained, a significant amount of isomeric branched products were observed, presumably the result of a stepwise β-hydride elimi
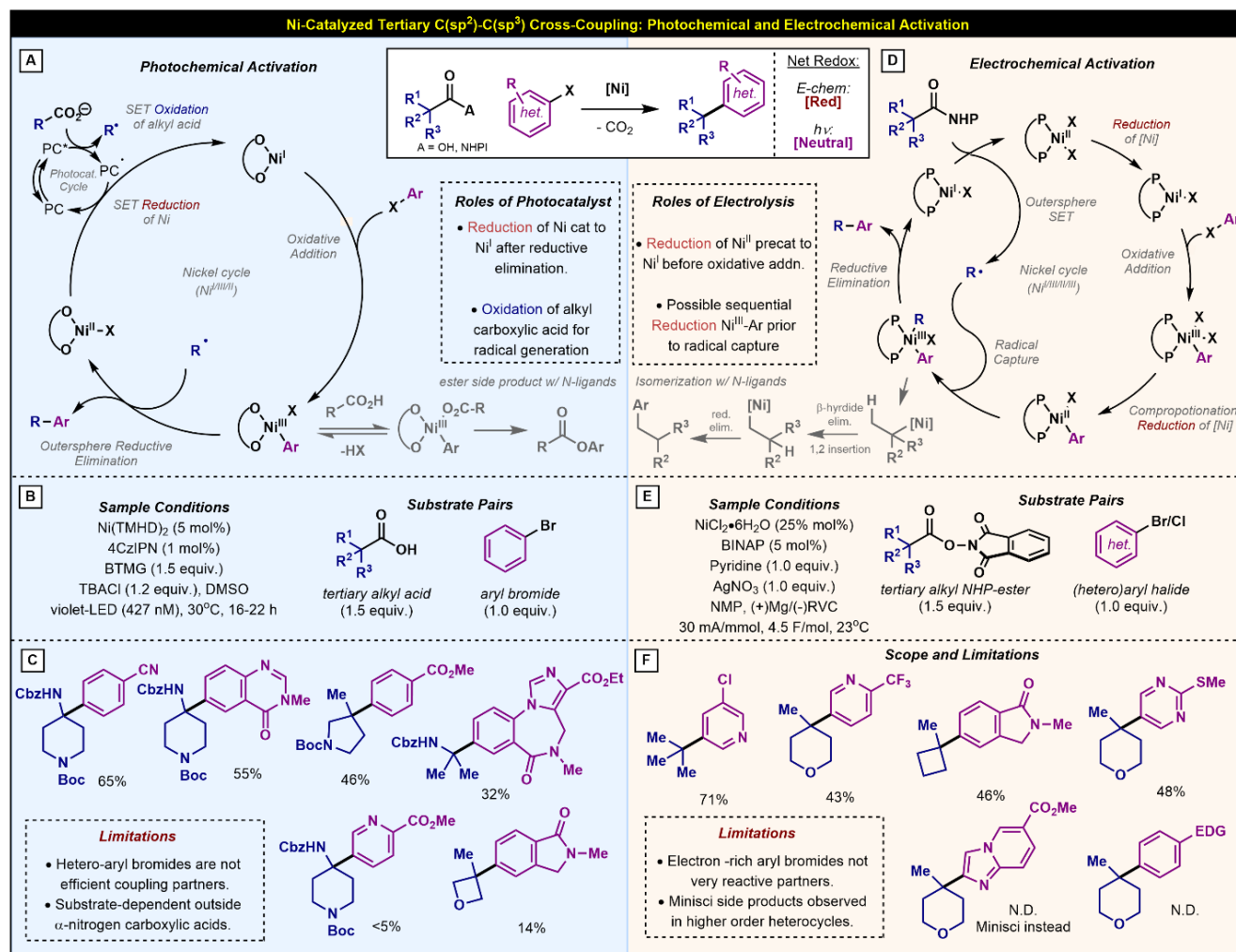
Figure 3. (A-F) Mechanistic and tactical overview of Ni-catalyzed tertiary C(sp²)-C(sp³) cross-couplings driven by photochemical and electrochemical strategies.

5

nation, re-insertion, and reductive elimination. The inclusion of BINAP suppressed this side reaction and boosted the yield. While the mechanism is expected to be homologous to the one outlined in Figure 2, mechanistic experiments are currently underway to explore the role of phosphine. With these altered conditions, RAEs derived from many diverse stabilized and unstabilized radical precursors were efficiently coupled with a range of (hetero)aryl bromides. Notably, the method broadly allows access to all carbon quaternary centers. Comparative studies between this method and the previously discussed photochemical approach reveal a complementary scope. In head-to-head comparisons, the photochemical method gives higher yields with α-amino carboxylic acids and benzenes. However, the electrochemical approach enabled a more diverse heteroarene scope with α-amino carboxylic acids *albeit* in lower yields. Electron-rich benzenes are not competent in the electrochemical approach but are accessible in low yet synthetically tractable yields leveraging photochemistry and the corresponding aryl iodide. Unfortunately, such iodides were not competent in the electrochemical variant. When it comes to unactivated acids, the electrochemical method is more general and higher yielding than the photochemical approach, but these nucleophilic radicals are uniquely susceptible to off-target Minisci reactivity with higher-order heterocycles. While no single method fills the gap in the literature, the two together grant the practitioner access to otherwise elusive chemical space.
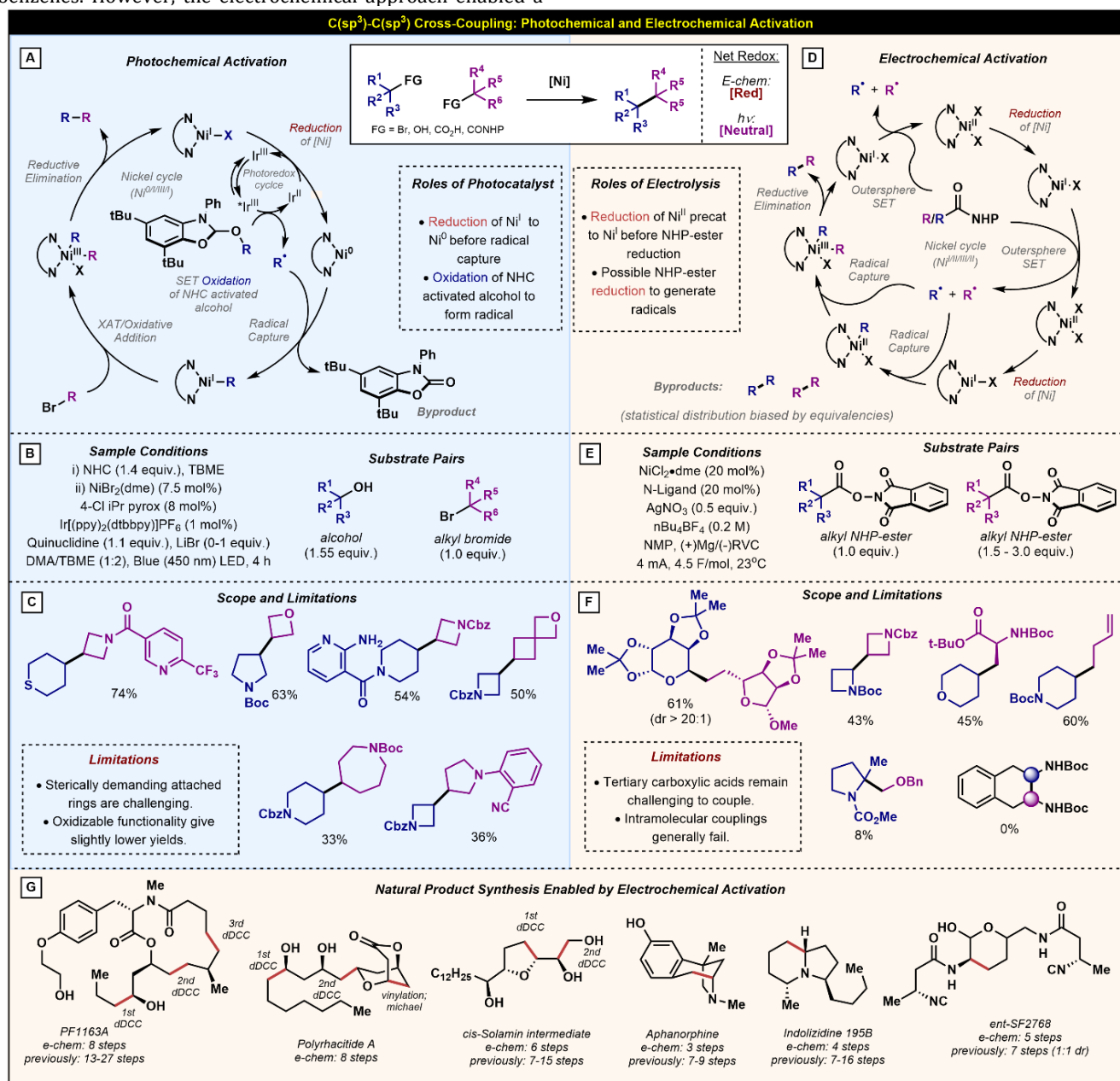
Figure 4. (A-G) Mechanistic and tactical overview of Ni-catalyzed C(sp^3)–C(sp^3) cross-couplings driven by photochemical and electrochemical strategies. G) Selected examples of natural products made by dDCC

6

C(sp³)–C(sp³) Radical Cross-Coupling

The cross-coupling of two alkyl partners to forge a new C(sp³)–C(sp³) bond is a major challenge. Due to the increasing sp³ character in novel therapeutics, methodologies that promote C(sp³)–C(sp³) cross-couplings of native functionalities would have a profound impact on drug discovery.[72-73] To this end, several groups have undertaken the challenge of developing efficient alkyl-alkyl cross-coupling protocols.[74] Recently, MacMillan reported a metallaphotoredox C(sp³)–C(sp³) cross-coupling methodology that provides access to complex, *sp³*-rich, and polycyclic frameworks. With that photo-mediated methodology, they uncovered an elusive C(sp³)–C(sp³) cross-coupling and employed alcohols (NHC-activated) and alkyl halides as the coupling partners (Figure 4A-C).[75] Mechanistically, the coupling begins with the photoexcited *Ir(III) oxidative fragmentation of the NHC-activated alcohol to produce a carbon-centered radical that is rapidly captured by Ni(0) affording Ni(I)-alkyl and Ir(II)-complexes. Subsequently, Ni(I) undergoes halogen-atom-abstraction (XAT)/oxidative addition with an alkyl halide to forge a Ni(III) intermediate, which upon reductive elimination produces the desired C(sp³)–C(sp³) bond with concomitant formation of Ni(I)X species that reenters the catalytic cycle. One advantage of the proposed mechanism is the activation of each alkyl partner by distinct mechanisms, which avoids excessive homocoupling (*vide infra)*. The coupling protocol tolerates a range of functionalities including sulfides, anilines, and nitrogen-rich heterocycles. However, cross-couplings involving sterically demanding, large rings and oxidizable functionality were less efficient but still provided synthetic yields that are useful for medicinal chemistry efforts.

On the other end of the spectrum, electrochemistry has embraced the challenge of C(sp³) radical cross-coupling for decades.[76-77] The Kolbe reaction reported more than 170 years ago, represents one of the first examples of electrochemically driven decarboxylative C(sp³)–C(sp³) cross-couplings.[78] However, this reaction was neglected by the synthetic community owing to the highly oxidizing conditions and poor functional group tolerance.[79] This report served as an inspiration for the Baran group in collaboration with our labs to develop a modern electrochemical solution to the challenge of C(sp³)–C(sp³) cross-coupling.[80] Rather than relying on the harsh oxidation of carboxylic acids, we chose to explore a comparatively easier reduction strategy by engaging the corresponding RAEs as coupling partners (Figure 4D-F).[81-82] Now referred to as doubly decarboxylative cross-coupling (dDCC), the process is initiated by the cathodic reduction of a Ni(II) precatalyst to Ni(I). The generated Ni(I) can then activate the RAE through a reductive fragmentation process to produce an alkyl radical and a Ni(II) species. At this point, the Ni(II) species can either be reduced to provide a Ni(I) that is required to produce more alkyl radicals or accept an alkyl radical to form a Ni(III) species. These species can be further reduced and then trap another alkyl radical to form a Ni(III)R₁R₂(X) intermediate, which upon reductive elimination can forge the desired cross-coupled product and a Ni(I) species. An observable limitation of this coupling design is the lack of kinetic bias in the reduction of two different RAEs leading to a statistical distribution of cross-coupled and homo-coupled products. To overcome this synthetic limitation and minimize the production of the less desirablehomo-coupled products, a larger excess of one of the partners was required (1.5–3.0 equivalents). Another scope limitation in the initial report was the intolerance of α-heteroatom RAEs. When RAE substrates were used,

cathodic reduction of the starting materials was observed with minimal formation of the desired cross-coupled product. As a mitigation strategy, the key silver nitrate additive from our previously developed C(sp²)–C(sp³) decarboxylative arylation (*vide supra*) was leveraged and the *in situ* AgNP layer that forms on the cathode protects the reductively-labile RAE from cathodic reduction.

With this new electrochemical cross-coupling platform, elusive C(sp³)–C(sp³) linkages were accessed with high relevance to pharmaceuticals and natural products.[83] As an example, this method was amenable to forging vicinal amines and alcohols to form 1,2-substituted alkanes with complete diastereoselectivity through ligand choice, a strategically powerful tool in natural product synthesis. Impressively, the alternate retrosynthetic disconnection enabled by this transformation expedited access to several diverse natural products with a dramatic reduction in overall step count (Figure 4G). Despite the breadth of chemical space that is accessible with this doubly decarboxylative protocol, the efficient engagement of RAEs derived from tertiary carboxylic acids, and the achievement of an intramolecular variant of this coupling remain elusive. Overcoming the above challenges represents an attractive horizon being explored in our labs.

C–S Cross-Coupling

In 2016, we reported the first Ni-based metallaphotoredox C–S cross-coupling reaction involving thiyl radicals (Figure 5A-C). Although it was known that thiols can be readily oxidized to thiyl radicals by a suitable photocatalyst, metal-catalyzed cross-coupling of thiyl radicals with aryl halides was elusive.[84-85] We reasoned that engaging thiyl radicals in C–S cross-coupling with aryl halides could solve several problems including catalyst deactivation by thiolate anions, poor functional group tolerance, the need for specialized ligands, and harsh reaction conditions. Therefore, we developed an operationally simple metallaphotoredox C–S methodology.[86] The coupling reaction is air tolerant with a broad scope allowing for the formation of a wide variety of thioethers in high efficiency and remarkable chemoselectivity. This work, uniquely enabled by photoredox catalysis, also represents the first example of heteroatom radicals engaging with a transition metal cross-coupling catalyst. Distinct from previously reported metallaphotoredox cross-couplings, a Ni(0) intermediate is not involved in this C–S cross-coupling, and the reaction is mediated by Ni(I)-species. Since the reaction is reliant on the use of a coordinating pyridine base, we postulated that the base may be stabilizing the coordinatively unsaturated Ni(I)X and/or Ni(I)-sulfide species, especially allowing the former to engage thiyl radicals. We proposed that visible light excitation of the Ir(III) photocatalyst generates a long-lived, and highly oxidizing triplet state *Ir(III) complex ($E_{1/2}$ = +1.21 V vs. SCE). Single-electron oxidation of the thiol ($E_{1/2}$ = +0.83 V vs. SCE for benzyl thiol) by the photoexcited *Ir(III) complex produces a thiol radical cation with the concomitant formation of an Ir(II) complex. In the presence of a weak base, the thiol radical cation generates thiyl radicals that are trapped by Ni(I)X species to generate a Ni(II)SR(X) complex, which can be reduced to a Ni(I)SR complex by the Ir(II) photocatalyst with concomitant regeneration of the Ir(III) photocatalyst. The Ni(I)SR complex can then undergo oxidative addition into an aryl iodide to form a Ni(III)SR(X)Ar complex, which upon reductive elimination delivers the desired thioether product and a Ni(I)X species. This proposed mechanism has since been vali-

7

dated by several groups and invoked in other C–heteroatom cross-coupling reactions.[87-90]

In 2019, Pan disclosed an electrochemical version of the Ni-catalyzed C–S cross-coupling reaction (Figure 5D-F).[91] Using an undivided cell and constant potential conditions, a wide variety of alkyl/aryl thiols were coupled with aryl iodides. Like the photochemical conditions, the electrochemical method requires the use of a coordinating pyridine base. This report shows similar scope to ours owing to the mechanistic similarities between homogenous photocatalysis and paired electrolysis. The mechanism proposed for the electrochemical C–S cross-coupling is depicted in Figure 5D. While these pioneering photochemical and electrochemical C–S cross-coupling methods were limited to aryl iodides, other groups have extended these methodologies to encompass aryl bromides and chlorides.[90, 92]

C–N Cross-Coupling

The past three decades have witnessed major developments in Pd-catalyzed C–N cross-coupling of amines with aryl halides to form anilines, a common structure found in bioactive drug molecules. Many Pd-catalyzed methods rely on the use of sterically bulky ligands and elevated temperatures to facilitate reductive elimination from a destabilized metal center.[24] We envisioned that a general and complementary method for C–N bond formation could be developed through the destabilization of a metal amido complex via either an electron or energy transfer process, thus providing an alternative approach to the use of structurally complex ligand systems and harsh conditions.[93-97]

Building off our previous efforts in C–S cross-coupling, we explored the engagement of aminyl radicals in Ni-catalyzed cross-coupling (Figure 6A-C). Gratifyingly, the arylation of anilines was achieved when pyridine was replaced with triethylamine.[98] We proposed a mechanism that involves a Ni(I/II/III) catalytic pathway whereby a photoexcited *Ir(III) catalyst ($E_{1/2}$ = +1.21 V vs SCE) oxidizes the aniline to form the anilinium radical cation, which upon deprotonation forms anilinium radical. Emission quenching studies show that aniline is a more effective quencher of the photocatalyst excited state than triethylamine. The trapping of the N–centered radical by a Ni(I) halide complex forms a Ni(II)-amido complex. Reduction of the Ni(II) amido complex by Ir(II) gives a Ni(I)-amido complex that can undergo oxidative addition to the aryl halide to form a Ni(III)amido(Ar)(X) complex with the concomitant regeneration of the Ir(III) photocatalyst. Reductive elimination from the Ni(III) complex affords the desired product and Ni(I) complex. Distinct from C–S cross-coupling, Ni(0) catalysts are also competent catalysts in this reaction suggesting that an alternative mechanism such as energy transfer may also be operative (*vide infra*).[17, 99] In the preparative reactions, several electronically diverse anilines and sulfonamides could be chemoselectively cross-
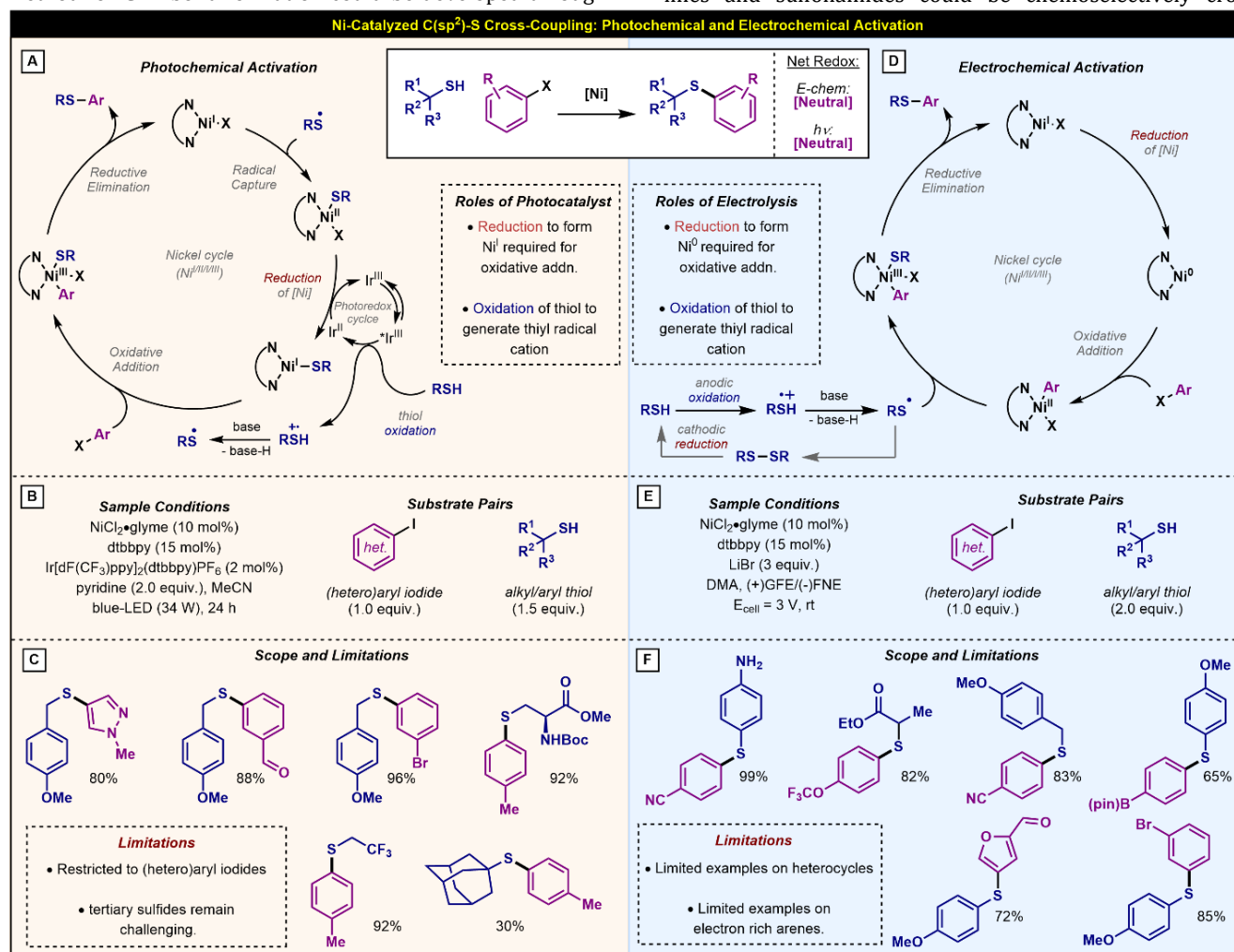
Figure 5. (A-F) Mechanistic and tactical overview of Ni-catalyzed C(sp2)–S cross-couplings driven by photochemical and electrochemical strategies.

8

coupled with a variety of aryl iodides and bromides and the reactions possess high functional group tolerance.[98] Limitations of this photochemical approach are the inferior performance of secondary anilines and alkylamines in the cross-coupling. MacMillan lab in collaboration with Buchwald lab concurrently reported metallaphotoredox arylation of alkylamines.[100]

Contemporaneously with our efforts, the Baran lab developed an electrochemical approach leveraging paired electrolysis outside the scope of our existing collaborative efforts (Figure 6D-F).[101-102] Intriguingly, the mechanistic underpinnings of the electrochemically driven C–N cross-coupling are distinct from the photochemical approach and access an orthogonal set of chemical space. While the photochemical approach previously described excels at coupling anilines and poorly tolerates alkyl amines, the electrochemical approach follows the opposite trend. A careful analysis of the two mechanisms reveals the origin of this observation. Critical to the success of this reaction is the oxidation of Ni(II) to Ni(III) to promote a challenging reductive elimination. Additionally, by relying on a base-mediated nitrogen atom activation over a radical oxidative approach, the reaction covers a range of nucleophilic alkyl amines with otherwise unstable radical species. However, poorly nucleophilic nitrogen coupling partners fail. Concerning the aryl coupling partner, a wide range of (hetero)aryl (pseudo)halides are tolerated. The Baran lab demonstrated several powerful applications of this reaction in preparing N-arylated oligonucleotides, polypeptides, and DNA-encoded libraries,[103] which is a testament to the mild conditions of electrochemical redox control. Additionally, the reaction can be scaled to deliver decagram quantities of a product by employing a recirculating flow setup.

C–O Cross-Coupling

Our previous strategy of forming C-, S-, and N-centered radicals with photoexcited catalysts and engaging them in Ni-catalyzed cross-couplings is not amenable to C–O cross-coupling. Unlike carboxylates, thiols, and anilines, the high oxidation potentials of alcohols preclude them from the oxidation process with available photocatalysts.[104] As detailed by Hillhouse and others, singlet state Ni(II) heteroatomic complexes tend not to undergo reductive elimination.[96, 105] However, SET oxidation of a Ni(II) Ar-heteroatomic complex or an EnT-induced excitation to its triplet state would promote reductive elimination (Figure 7A).[99, 106] Triplet-triplet EnT is a powerful activation pathway in photocatalysis that unlocks new organic transformations and improves the efficiency of metal-catalyzed cross-couplings. Many current reports, however, still rely on precious metal-based complexes as EnT photosensitizers, with associated prohibitive costs and environmental impacts (Figure 7A).[106-107] We recognized that photosensitizers exhibiting thermally activated delayed fluorescence (TADF) could be an attractive fully organic alterna-
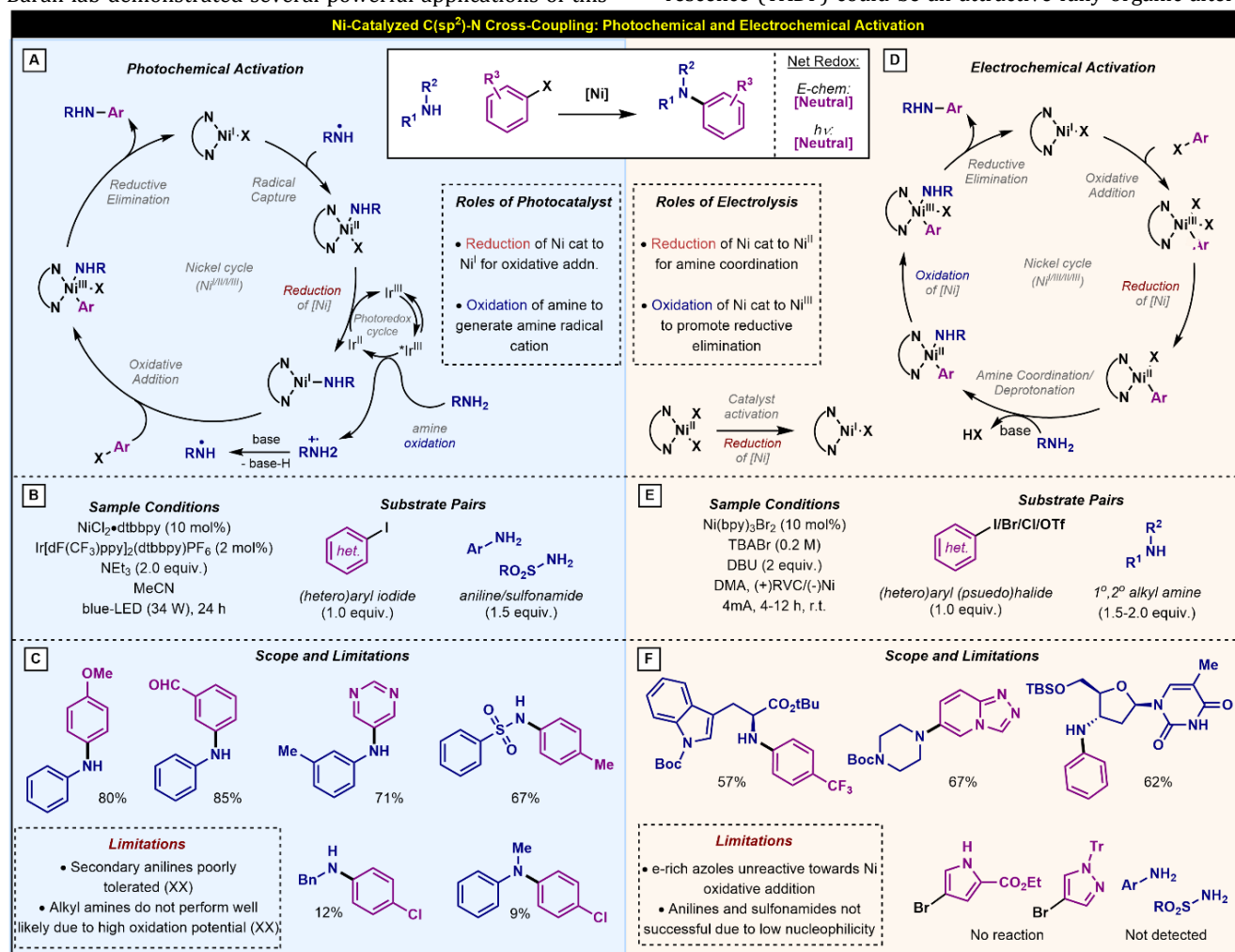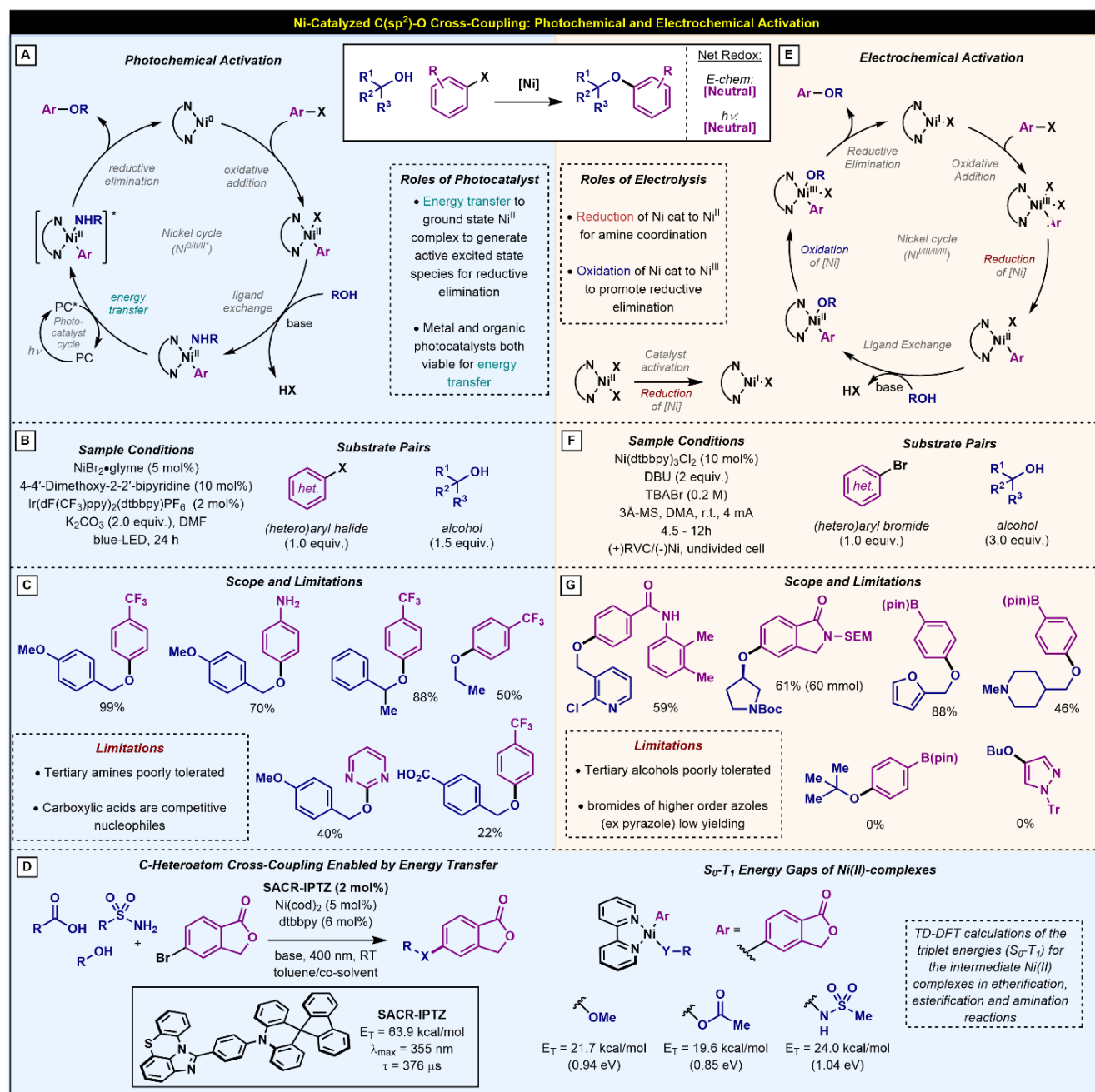

Figure 6. (A-F) Mechanistic and tactical overview of Ni-catalyzed C(sp^2)–N cross-couplings driven by photochemical and electrochemical strategies.

9

tive in EnT photocatalysis and collaborated with Professor Zachary Hudson to explore TADF materials in Ni-catalyzed C–heteroatom cross-couplings. That collaboration led to the design of **SACR-IPTZ**, an imidazophenothiazine (IPTZ)-based, fully organic material, with a high triplet energy and exceptionally long-lived excited triplet state (τ = 367 μs).[108] **SACR-IPTZ** was designed to use structural constraint and the heavy atom effect (sulfur atom) to improve excited-state lifetimes and spin-orbit coupling for utility in EnT photocatalysis. **SACR-IPTZ** efficiently promoted Ni-catalyzed C–O (etherification and esterification), C–N cross-couplings (Figure 7C), and other chemical reactions. DFT calculations indicated that the triplet energies of the Ni(II)-heteroatomic com

plexes involved in the reductive elimination step are much lower (E_T = 19.6 - 24 kcal/mol) than the triplet energy of **SACR-IPTZ** (E_T = 63.9 kcal/mol), which is a requirement for an EnT process (Figure 7C). The dual catalytic cycles are illustrated in Figure 7A.

In addition to our work in photochemically driven C–O cross-coupling, a collaboration with the Baran group yielded a complimentary electrochemical approach (Figure 7E-G).[109] The explicit mechanism of this electrochemical variant is still uncertain but is expected to follow a similar paired electrolysis mechanism as the electrochemical C–N coupling (*vide supra*). Control experiments suggest the need for paired electrolysis to carry out the reaction suggesting both oxidative

Figure 7. (A-G) Mechanistic and tactical overview of Ni-catalyzed C(sp^2)–O cross-couplings driven by photochemical and electrochemical strategies. (D) An imidazophenothiazine-based TADF material, **SACR-IPTZ** with ultra long-lived excited states for energy transfer mediated Ni-catalyzed C(sp^2)–heteroatom cross-couplings.

10

and reductive events are critical to the overall bond-forming process. The preparative electrochemical C–O cross-coupling employs a cheap Ni(II) precatalyst and di-*tert*-butyl bipyridyl (dtbbpy) ligand framework and proceeds in a user-friendly undivided cell setup. The addition of molecular sieves to the reaction significantly improved the performance as trace water was found to be deleterious. The reaction tolerates a wide range of aryl bromide and alcohol coupling partners used in excess. Owing to the mild oxidative environment of the anode, tertiary alkyl amines are tolerated. Such functionality was shown to be a critical hindrance to the performance of photochemically driven couplings in head-to-head comparisons. Additionally, select substrates were scaled to decagram quantities and many applications to pharmaceutically relevant motifs were exemplified. While a powerful electrochemical approach to C–O coupling, limitations include the inability to couple tertiary alcohols and electron-rich azoles. Alternate bond disconnections could afford these challenging chemotypes leveraging electrogenerated cations also developed by the Baran group.[110-111] However, such highly oxidizing methods and the weak nucleophilicity of phenoxides may hamper such efforts.

Tactical Overview of Photochemically and Electrochemically Driven Cross-Couplings

Throughout this account, the unique strengths of photochemical and electrochemical approaches toward modulating Ni-catalysishave been demonstrated. While the literature is replete with several reports of unique transformations leveraging both tactics, it is still unclear how to choose an appropriate mode of activation. This is especially the case in drug discovery as medicinal chemistry is often performed across the entire span of electron-rich benzenes and electron-deficient heterocycles with a wide range of different alkyl and heteroatomic fragments. Over the past decade, several strategies towards C(sp^2)–C(sp^3),[4, 6, 61-63, 66, 68, 70-71, 112-129] C(sp^3)–C(sp^3),[74-75, 80, 83, 130-135] and C-heteroatom[86, 89, 91-92, 98, 100-101, 107, 136-142] cross-couplings have been enabled by photo- and electrochemistry.[4, 63] Throughout our experience in developing Ni-catalyzed photo- and electrochemically-driven C–C and C–heteroatom cross couplings, we, as well as others, have noticed several reactivity trends.[143] To aid the community in discerning the appropriate tactic, we have assembled a user guide to help navigate photo- and electrochemically-driven cross-coupling reactions as well as to highlight useful technologies developed by others in the field (Figure 8).

In consideration that assigning rank can be highly subjective, we have opted for a qualitative approach to categorizing the proposed substrate union's likelihood of success. In green, there is plenty of precedent of that substructure being achievable in good yield (>50% yield) barring the competition of other functional groups. In yellow, there are fewer reports of that substructure present or the general yield in accessing that substructure is moderate (20% to 50% yield). In red, the target substructure is a current limitation or stretch of the method (<20% yield). Finally, grey represents cases where there is no report of such a cross-coupling being achieved either photo- or electrochemically. If anything, the red and grey indications are meant to highlight exciting areas for future research efforts. Notably absent, and outside the scope of these accounts, is the plethora of contemporary methodologies that forge similar bonds using organic or metallic reductants and oxidants. Rather than describe every possible pairing, key observations from this guide and their

implications on the frontiers of first-row transition metal catalysis will be highlighted.

Mechanistically, photochemistry has an advantage over electrochemistry in the oxidative activation of native functionalities to form radicals. The Ni reduction and oxidative activation do not need to overcome significant diffusion to engage in productive photocatalysis. On the other hand, electrochemistry excels at sequential reductive activation processes. The localized cathodic generation of the key low valent Ni species for substrate activation is easy to attain with the physical separation of redox events in electrochemistry. As the couplings become more ambitious, the critical limitations of Ni-catalysis, regardless of activation methods, are unveiled. For instance, Ni struggles with cross-couplings of sterically demanding alkyl radicals independent of the redox strategy. However, the differences between the two modes of activation reveal staggering differences when starting material access and preparation are considered. When considering the available starting materials for a proposed synthetic sequence, electrochemistry with RAEs appears superior in forging (hetero)aryl C(sp^2)-C(sp^3) linkages with Med-Chem relevant electron-rich heteroarenes. The interference of oxidizable heteroatoms and the requirement of stabilized radicals severely limit an oxidative activation approach from the corresponding alkyl carboxylic acid, despite being a slightly more accessible starting material since no pre-functionalization is required compared to RAEs. However, these limitations of photochemistry are ameliorated by switching starting materials. Alkyl halides and alcohols appear to offer expanded scope compared to their acid counterparts at the cost of substrate synthesis/availability. For instance, the scope of the NHC-activated alcohol C(sp^2)-C(sp^3) cross-coupling is comparable to state-of-the-art RAE chemistry despite requiring a boutique activating handle.[121]

Secondary to starting materials accessibility is consideration of the synthetic goal. Within drug discovery, there are two key objectives i) make enough of a substance quickly to interrogate an initial biological hypothesis (mg-scale regime) and, if that compound is exciting, ii) scale up to enable PK across species, PD/efficacy studies, and clinical trials (>decagram needed). Photo- and electrochemistry now offer complementary use cases in modern drug discovery in achieving these key objectives. Photochemistry is easier to scale down to mg-amounts of material. Owing to the latest improvements in instrumentation, photochemical reactions can be run in 24 - 384 microwell HTE plates on nano- to milligram scale for library studies and rapid SAR (Structure Activity Relationship) exploration.[144] On the other hand, scaling down electrochemical reactions is challenging owing to the heterogeneous variables (electrode surface/submersion) that need to be considered. Recently, the emergence of high throughput electrochemical reactors is likely to address this practical gap.[145] On the other end of the scale regime, electrochemistry is more scalable than photochemistry. Many of the largest chemical processes are electrochemically driven due to the fine control of reaction parameters, low cost of energy input, and reproducibility.[146] Photochemistry still suffers from light permeation on a large scale and the prohibitive cost of precious metal-based photocatalysts. That being said, flow technologies for photochemistry along with the discovery of new organic-based photocatalysts have emerged as promising solutions to these challenges.[147]

Considering the various attributes between the two modes of activation, we encourage researchers in the field to place themselves in the position of the end user of their techn

Carbon-Carbon Cross-Coupling: Photochemical and Electrochemical Activation

$C(sp^2)/C(sp^3)$ partner	[1° radical] R^1		[2° radical] R^1R^2		[3° radical] $R^1R^2R^3$		[stabilized 1° radical] R^1-X		[stabilized 2° radical] R^1-X-R^2		[stabilized 3° radical] R^1-X-R^2R^3	
	[photochem]	[e-chem]	[photochem]	[e-chem]	[photochem]	[e-chem]	[photochem]	[e-chem]	[photochem]	[e-chem]	[photochem]	[e-chem]
EDG—X	Refs: 63, 115, 116, 121, 129	Refs: 66, 117, 118, 119, 123	Refs: 63, 115, 116, 121, 122, 124, 129	Refs: 66, 117, 118, 119	Refs: 68, 113	Refs: 71, 119	Refs: 4, 62, 63	Refs: 66, 125	Refs: 4, 61, 62, 63	Ref: 66	Ref: 68	Ref: 71
EWG—X	Refs: 63, 112,115, 116, 121, 122, 128, 129	Refs: 66, 114, 117, 118, 119, 120, 123	Refs: 63, 112, 115, 116, 121, 122, 124, 129	Refs: 66, 114, 117, 118, 119, 120	Refs: 68, 70, 113, 121	Refs: 71, 119	Refs: 4, 62, 63, 112, 127	Refs: 66, 125	Refs: 4, 61, 62, 63, 112	Ref: 66	Ref: 68	Ref: 71
EDG (het.)—X	Refs: 63, 115, 116, 121, 129	Refs: 66, 123	Refs: 63, 115,116, 121, 124, 129	Refs: 66, 123	Refs: 68, 113	Ref: 71	Refs: 62, 63	Ref: 66	Refs: 62, 63	Ref: 66	Ref: 68	Ref: 71
EWG (het.)—X	Refs: 63, 112, 115, 116, 121, 122, 128, 129	Refs: 66, 117, 118, 120, 123	Refs: 63, 112, 115, 116, 121, 122, 124, 129	Refs: 66, 117, 118, 120	Refs: 68, 113, 121	Ref: 71	Refs: 4, 62, 63, 112, 127	Refs: 66, 125	Refs: 4, 61, 62, 63, 112	Ref: 66	Ref: 68	Ref: 71
(A,X,Y,Z = N,O,S)—X	Refs: 63, 115, 116, 121	Ref: 66	Refs: 63, 115, 116, 121	Ref: 66	Ref: 68	Ref: 71	Ref: 63	Ref: 66	Ref: 63	Ref: 66	Ref: 68	Ref: 71
R^1 [1° radical]	Ref: 130, 134 135	Ref: 80, 83	Ref: 130, 131, 134, 135	Ref: 80, 83	Ref: 74, 130, 135	Ref: 80, 83	Ref: 130, 135	Ref: 83, 133	Ref: 132, 135	Ref: 83, 133	Ref: 74	Ref: 83, 133
R^1R^2 [2° radical]			Ref: 75, 134	Ref: 80, 83	Ref: 130	Ref: 83	Ref: 130, 135	Ref: 83	Ref: 132	Ref: 83	Ref: 74	Ref: 83
$R^1R^2R^3$ [3° radical]								Ref: 83				
R^1-X [stabilized 1° radical]								Ref: 83		Ref: 83		Ref: 83

Radical Precursors

Carbon-Heteroatom Cross-Coupling: Photochemical and Electrochemical Activation

$C(sp^2)$ partner	[anilines/heteroaryl amines] R-het.-NH₂		[alkylamines]		[phenols] R-het.-OH		[alcohols]		[(hetero)aryl thiols] R-het.-SH		[thiols]	
	[photochem]	[e-chem]	[photochem]	[e-chem]	[photochem]	[e-chem]	[photochem]	[e-chem]	[photochem]	[e-chem]	[photochem]	[e-chem]
EDG—X	Ref: 98	Ref: 142	Refs: 100, 138	Ref: 101	Refs: 139, 140, 141		Ref: 137	Ref: 136	Refs: 86, 89	Ref: 92	Refs: 86, 89	Ref: 91
EWG—X	Ref: 98	Ref: 142	Refs: 100, 138	Ref: 101	Refs: 139, 140, 141		Ref: 137	Refs: 101, 136	Refs: 86, 89	Ref: 92	Refs: 86, 89	Ref: 91
EDG (het.)—X		Ref: 142	Refs: 100, 138	Ref: 101			Ref: 137	Ref: 136	Refs: 86, 89	Ref: 92	Refs: 86, 89	Ref: 91
EWG (het.)—X	Ref: 98	Ref: 142	Refs: 100, 138	Ref: 101	Refs: 139, 140, 141		Ref: 137	Ref: 136	Refs: 86, 89	Ref: 92	Refs: 86, 89	
(A,X,Y,Z = N,O,S)—X			Refs: 100, 138	Ref: 101				Ref: 136	Refs: 86, 89		Refs: 86, 89	

Figure 8. User guide for tactic choice in photochemically and electrochemically driven cross-coupling reactions.

ologies. If a reaction permits access to unprecedented chemical space yet is limited to 15% yield, then such a reaction is useful in the initial testing of a biological hypothesis (early medicinal chemistry) but punts the problem if that compound does become a drug candidate and reliable multi-kilogram amounts are routinely needed (early process chemistry). Contrarily, if a method is routinely high yielding but limited to a certain substrate class, the explorable chemical space for SAR is limited. While limitations initially exist with new methodologies and technologies, academic-industrial partnerships are critical to addressing them, thereby fostering innovation, and promoting cross-disciplinary research endeavors.

Conclusion and Outlook

The merger of photochemical and electrochemical technologies with transition metal catalysis has led to a watershed of new tools for the synthetic community that would have otherwise been impossible a decade ago. The powerful nature of these redox tools to coax elusive reactivity out of first-row transition metals has been highlighted throughout our efforts in C–C and C-heteroatom cross-couplings. By comparing the mechanistic and substrates scope features of the two strategies, chemical practitioners can form a strong basis upon which mode of activation is best fit for a proposed synthetic target with the assistance of a tactical guide. The practical utility of redox control enacted by photochemistry and electrochemistry is compelling and will certainly grow as a tool for developing more powerful transformations so long as efforts in understanding the mechanistic underpinnings of the current limitations are undertaken. We hope that this account inspires the next generation of researchers to confront fundamental challenges in first-row transition metal catalysis through cross-disciplinary collaborative efforts.

Author Biographies

Maximilian D. Palkowitz received his Ph.D. from Scripps Research in 2022 working in Professor Phil Baran's group where he investigated AgNP-enabled electrochemical cross-coupling methodologies applied to terpene total synthesis and medicinal chemistry settings. He is now a medicinal chemist at Bristol Myers Squibb in Cambridge, MA.

Megan A. Emmanuel received her Ph.D. from Princeton University in 2020. Under the supervision of Professor Todd Hyster, she conducted research on the discovery and development of new-to-nature enzymatic reactions enabled by photochemistry and photoredox catalysis. She is currently a Senior Scientist in the Chemical Process Development group at Bristol Myers Squibb in New Brunswick, New Jersey.

Martins S. Oderinde received an M.Sc. in Organic Chemistry at the University of Alberta, Canada in 2008. He joined Gilead Sciences as a Process Chemist and worked there for less than 2 years before going back to graduate school. He received his Ph.D. at York University, Canada, in 2013 under the supervision of Professor Michael G. Organ, where he carried out research in metal catalysis, and mechanistic studies and developed new radical-based synthetic methodologies. After an academic postdoctoral study with Professor Justin Du Bois at Stanford University, he joined AstraZeneca, MA, for an industrial postdoctoral study, where he studied metallaphotoredox catalysis. He began his industrial career at Pfizer, CT as a senior scientist in the Inflammation & Immunology group. He joined Bristol Myers Squibb, New Jersey in 2018 where he is currently a Senior Principal Scientist in the Department of Discovery Synthesis.

ASSOCIATED CONTENT

This material is available free of charge via the Internet at http://pubs.acs.org." For instructions on what should be included in the Supporting Information as well as how to prepare this material for publication, refer to the journal's Instructions for Authors.

AUTHOR INFORMATION

Corresponding Author

* Martins S. Oderinde *Small Molecule Discovery Chemistry, Bristol Myers Squibb Research & Early Development, Route 206 & Province Line Road, Princeton, New Jersey, 08543, USA.*
Email: martins.oderinde@bms.com

Present Addresses

Maximilian D. Palkowitz *Small Molecule Drug Discovery, Bristol Myers Squibb, 250 Water Street, Cambridge, MA, 02141, USA*

Megan A. Emmanuel *Chemical Process Development, Bristol Myers Squibb, 1 Squibb Drive, New Brunswick, New Jersey, 08901, USA*

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ABBREVIATIONS

AgNP – silver nanoparticle

bpy – 2,2'-bipyridine

DCC – Decarboxylative cross-coupling

dDCC – Doubly decarboxylative cross-coupling

DFT – Density Functional Theory

DMA – N, N'-dimethylacetamide

DMF – N, N'-dimethylformamide

EnT – energy transfer

HTE – high throughput experimentation

NHC – N-heterocyclic carbene

PD – pharmacodynamics

PK – pharmacokinetics

RAE – Redox active ester

SAR – Structure-activity relationship

SCE – Saturated Calomel Electrode

SET – Single electron transfer

TADF – thermally activated delayed fluorescence

TMHD - 2,2,6,6-tetramethyl-3,5-heptanedionate

XAT – Halogen atom transfer.
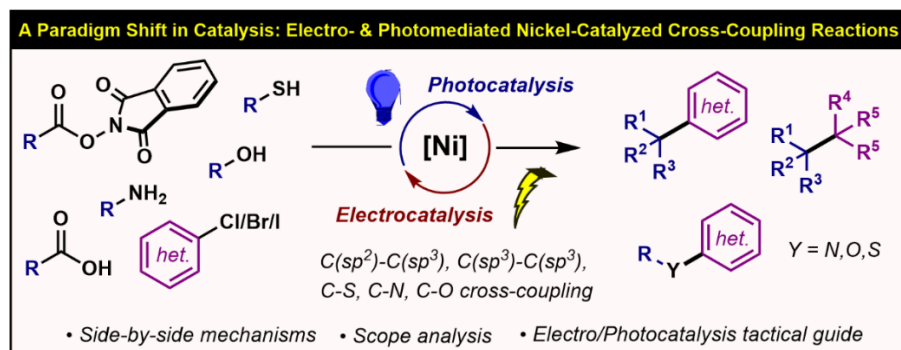
REFERENCES

1.   Cherney, A. H.; Kadunce, N. T.; Reisman, S. E., Enantioselective and Enantiospecific Transition-Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagents To Construct C–C Bonds. *Chem. Rev.* **2015,** *115* (17), 9587-9652.
2.   Cornella, J.; Edwards, J. T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C.-M.; Gianatassio, R.; Schmidt, M.; Eastgate, M. D.; Baran, P. S., Practical Ni-Catalyzed Aryl–Alkyl Cross-Coupling of Secondary Redox-Active Esters. *J. Am. Chem. Soc.* **2016,** *138* (7), 2174-2177.
3.   Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S., A general alkyl-alkyl cross-coupling enabled by redox-active esters and alkylzinc reagents. *Science* **2016,** *352* (6287), 801-805.
4.   Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C., Merging photoredox with nickel catalysis: Coupling of α-carboxyl sp3-carbons with aryl halides. *Science* **2014,** *345* (6195), 437-440.
5.   Shields, B. J.; Doyle, A. G., Direct C(sp3)–H Cross Coupling Enabled by Catalytic Generation of Chlorine Radicals. *J. Am. Chem. Soc.* **2016,** *138* (39), 12719-12722.
6.   Tellis, J. C.; Primer, D. N.; Molander, G. A., Single-electron transmetalation in organoboron cross-coupling by photoredox/nickel dual catalysis. *Science* **2014,** *345* (6195), 433-436.
7.   Everson, D. A.; Shrestha, R.; Weix, D. J., Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2010,** *132* (3), 920-921.
8.   Biswas, S.; Weix, D. J., Mechanism and Selectivity in Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2013,** *135* (43), 16192-16197.
9.   Everson, D. A.; Weix, D. J., Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. *J. Org. Chem.* **2014,** *79* (11), 4793-4798.
10.   Fu, N.; Sauer, G. S.; Saha, A.; Loo, A.; Lin, S., Metal-catalyzed electrochemical diazidation of alkenes. *Science* **2017,** *357* (6351), 575-579.
11.   Sauer, G. S.; Lin, S., An Electrocatalytic Approach to the Radical Difunctionalization of Alkenes. *ACS Catal.* **2018,** *8* (6), 5175-5187.
12.   Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C., Enantioselective Decarboxylative Arylation of α-Amino Acids via the Merger of Photoredox and Nickel Catalysis. *J. Am. Chem. Soc.* **2016,** *138* (6), 1832-1835.
13.   Cherney, A. H.; Kadunce, N. T.; Reisman, S. E., Catalytic Asymmetric Reductive Acyl Cross-Coupling: Synthesis of Enantioenriched Acyclic α,α-Disubstituted Ketones. *J. Am. Chem. Soc.* **2013,** *135* (20), 7442-7445.

14.	Lin, Q.; Diao, T., Mechanism of Ni-Catalyzed Reductive 1,2-Dicarbofunctionalization of Alkenes. *J. Am. Chem. Soc.* **2019,** *141* (44), 17937-17948.

15.	Lin, Q.; Fu, Y.; Liu, P.; Diao, T., Monovalent Nickel-Mediated Radical Formation: A Concerted Halogen-Atom Dissociation Pathway Determined by Electroanalytical Studies. *J. Am. Chem. Soc.* **2021,** *143* (35), 14196-14206.

16.	Walker, B. R.; Sevov, C. S., An Electrochemically Promoted, Nickel-Catalyzed Mizoroki–Heck Reaction. *ACS Catal.* **2019,** *9* (8), 7197-7203.

17.	Sun, R.; Qin, Y.; Nocera, D. G., General Paradigm in Photoredox Nickel-Catalyzed Cross-Coupling Allows for Light-Free Access to Reactivity. *Angew. Chem. Int. Ed.* **2020,** *59* (24), 9527-9533.

18.	Smith, J. M.; Harwood, S. J.; Baran, P. S., Radical Retrosynthesis. *Acc. Chem. Res.* **2018,** *51* (8), 1807-1817.

19.	Laudadio, G.; Palkowitz, M. D.; El-Hayek Ewing, T.; Baran, P. S., Decarboxylative Cross-Coupling: A Radical Tool in Medicinal Chemistry. *ACS. Med. Chem. Lett.* **2022,** *13* (9), 1413-1420.

20.	Fernández, D. F.; González-Esguevillas, M.; Keess, S.; Schäfer, F.; Mohr, J.; Shavnya, A.; Knauber, T.; Blakemore, D. C.; MacMillan, D. W. C., Redefining the Synthetic Logic of Medicinal Chemistry. Photoredox-Catalyzed Reactions as a General Tool for Aliphatic Core Functionalization. *Org. Lett.* **2023**.

21.	Wang, X.; Dai, Y.; Gong, H., Nickel-Catalyzed Reductive Couplings. *Top. Curr. Chem.* **2016,** *374* (4), 43.

22.	Shenvi, R. A.; O'Malley, D. P.; Baran, P. S., Chemoselectivity: The Mother of Invention in Total Synthesis. *Acc. Chem. Res.* **2009,** *42* (4), 530-541.

23.	Peters, D. S.; Pitts, C. R.; McClymont, K. S.; Stratton, T. P.; Bi, C.; Baran, P. S., Ideality in Context: Motivations for Total Synthesis. *Acc. Chem. Res.* **2021,** *54* (3), 605-617.

24.	Dorel, R.; Grugel, C. P.; Haydl, A. M., The Buchwald–Hartwig Amination After 25 Years. *Angew. Chem. Int. Ed.* **2019,** *58* (48), 17118-17129.

25.	West, M. J.; Fyfe, J. W. B.; Vantourout, J. C.; Watson, A. J. B., Mechanistic Development and Recent Applications of the Chan–Lam Amination. *Chem. Rev.* **2019,** *119* (24), 12491-12523.

26.	Malapit, C. A.; Prater, M. B.; Cabrera-Pardo, J. R.; Li, M.; Pham, T. D.; McFadden, T. P.; Blank, S.; Minteer, S. D., Advances on the Merger of Electrochemistry and Transition Metal Catalysis for Organic Synthesis. *Chem. Rev.* **2022,** *122* (3), 3180-3218.

27.	Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath, C. P.; MacMillan, D. W. C., Metallaphotoredox: The Merger of Photoredox and Transition Metal Catalysis. *Chem. Rev.* **2022,** *122* (2), 1485-1542.

28.	Novaes, L. F. T.; Liu, J.; Shen, Y.; Lu, L.; Meinhardt, J. M.; Lin, S., Electrocatalysis as an enabling technology for organic synthesis. *Chem. Soc. Rev.* **2021,** *50* (14), 7941-8002.

29.	Liu, Y.; Li, P.; Wang, Y.; Qiu, Y., Electroreductive Cross-Electrophile Coupling (eXEC) Reactions. *Angew. Chem. Int. Ed.* **2023,** *n/a* (n/a), e202306679.

30.	Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Jacobi von Wangelin, A., Reductive Cross-Coupling Reactions between Two Electrophiles. *Chem. Eur. J.* **2014,** *20* (23), 6828-6842.

31.	Fagnoni, M.; Dondi, D.; Ravelli, D.; Albini, A., Photocatalysis for the Formation of the C−C Bond. *Chem. Rev.* **2007,** *107* (6), 2725-2756.

32.	Mueller, F.; Mattay, J., Photocycloadditions: control by energy and electron transfer. *Chem. Rev.* **1993,** *93* (1), 99-117.

33.	Mattay, J., Charge Transfer and Radical Ions in Photochemistry. *Angew. Chem. Int. Ed.* **1987,** *26* (9), 825-845.

34.	Marcus, R. A., On the Theory of Oxidation-Reduction Reactions Involving Electron Transfer. I. *J. Chem. Phys.* **1956,** *24* (5), 966-978.

35.	Mizuno, K.; Kaji, R.; Okada, H.; Otsuji, Y., Addition of furans to electron-rich olefins through photo-induced electron-transfer in the presence of electron acceptors. *ChemComm* **1978,** (14), 594-595.

36.	Okada, K.; Okamoto, K.; Oda, M., A new and practical method of decarboxylation: photosensitized decarboxylation of N-acyloxyphthalimides via electron-transfer mechanism. *J. Am. Chem. Soc.* **1988,** *110* (26), 8736-8738.

37.	Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M., A NEW PHOTOCHEMICAL REACTION. *J. Am. Chem. Soc.* **1960,** *82* (10), 2640-2641.

38.	Mella, M.; Fagnoni, M.; Albini, A., Radicals through Photoinduced Electron Transfer. Addition to Olefin and Addition to Olefin-Aromatic Substitution Reactions. *J. Org. Chem.* **1994,** *59* (19), 5614-5622.

39.	Fagnoni, M.; Mella, M.; Albini, A., Radical Addition to Alkenes via Electron Transfer Photosensitization. *J. Am. Chem. Soc.* **1995,** *117* (30), 7877-7881.

40.	Heidbreder, A.; Mattay, J., PET-Oxidative Cyclization of Unsaturated Enol Silyl Ethers. *Tetrahedron Lett.* **1992,** *33* (15), 1973-1976.

41.	Hironaka, K.; Fukuzumi, S.; Tanaka, T., Tris(bipyridyl)ruthenium(II)-photosensitized reaction of 1-benzyl-1,4-dihydronicotinamide with benzyl bromide. *J. Chem. Soc., Perkin trans II* **1984,** (10), 1705-1709.

42.	Imahori, H.; Tamaki, K.; Guldi, D. M.; Luo, C.; Fujitsuka, M.; Ito, O.; Sakata, Y.; Fukuzumi, S., Modulating Charge Separation and Charge Recombination Dynamics in Porphyrin−Fullerene Linked Dyads and Triads: Marcus-Normal versus Inverted Region. *J. Am. Chem. Soc.* **2001,** *123* (11), 2607-2617.

43.	Kim, J. I.; Schuster, G. B., Enantioselective catalysis of the triplex Diels-Alder reaction: addition of trans-.beta.-methylstyrene to 1,3-cyclohexadiene photosensitized with (-)-1,1'-bis(2,4-dicyanonaphthalene). *J. Am. Chem. Soc.* **1990,** *112* (26), 9635-9637.

44.	Calhoun, G. C.; Schuster, G. B., Radical cation and triplex Diels-Alder reactions of 1,3-cyclohexadiene. *J. Am. Chem. Soc.* **1984,** *106* (22), 6870-6871.

45.	Akbulut, N.; Hartsough, D.; Kim, J. I.; Schuster, G. B., The triplex Diels-Alder reaction of 1,3-dienes with enol, alkene, and acetylenic dienophiles: scope and utility. *J. Org. Chem.* **1989,** *54* (11), 2549-2556.

46.	Hernández, R.; Rivera, A.; Salazar, J. A.; Suárez, E., Nitroamine radicals as intermediates in the functionalization of non-activated carbon atoms. *ChemComm* **1980,** (20), 958-959.

47.   Oderinde, M. S.; Varela-Alvarez, A.; Aquila, B.; Robbins, D. W.; Johannes, J. W., Effects of Molecular Oxygen, Solvent, and Light on Iridium-Photoredox/Nickel Dual-Catalyzed Cross-Coupling Reactions. *J. Org. Chem.* **2015,** *80* (15), 7642-7651.

48.   Oderinde, M. S.; Jin, S.; Dhar, T. G. M.; Meanwell, N. A.; Mathur, A.; Kempson, J., Advances in the synthesis of three-dimensional molecular architectures by dearomatizing photocycloadditions. *Tetrahedron* **2022,** *103*, 132087.

49.   Sauvé, E. R.; Mayder, D. M.; Kamal, S.; Oderinde, M. S.; Hudson, Z. M., An imidazoacridine-based TADF material as an effective organic photosensitizer for visible-light-promoted [2 + 2] cycloaddition. *Chem. Sci.* **2022,** *13* (8), 2296-2302.

50.   Oderinde, M. S.; Ramirez, A.; Dhar, T. G. M.; Cornelius, L. A. M.; Jorge, C.; Aulakh, D.; Sandhu, B.; Pawluczyk, J.; Sarjeant, A. A.; Meanwell, N. A.; Mathur, A.; Kempson, J., Photocatalytic Dearomative Intermolecular [2 + 2] Cycloaddition of Heterocycles for Building Molecular Complexity. *J. Org. Chem.* **2021,** *86* (2), 1730-1747.

51.   Oderinde, M. S.; Mao, E.; Ramirez, A.; Pawluczyk, J.; Jorge, C.; Cornelius, L. A. M.; Kempson, J.; Vetrichelvan, M.; Pitchai, M.; Gupta, A.; Gupta, A. K.; Meanwell, N. A.; Mathur, A.; Dhar, T. G. M., Synthesis of Cyclobutane-Fused Tetracyclic Scaffolds via Visible-Light Photocatalysis for Building Molecular Complexity. *J. Am. Chem. Soc.* **2020,** *142* (6), 3094-3103.

52.   Rollin, Y.; Troupel, M.; Tuck, D. G.; Perichon, J., The coupling of organic groups by the electrochemical reduction of organic halides: Catalysis by 2,2′-bipyridinenickel complexes. *J. Organomet. Chem.* **1986,** *303* (1), 131-137.

53.   Chaussard, J.; Folest, J.-C.; Nedelec, J.-Y.; Perichon, J.; Sibille, S.; Troupel, M., Use of Sacrificial Anodes in Electrochemical Functionalization of Organic Halides. *Synthesis* **1990,** *1990* (05), 369-381.

54.   Shono, T.; Matsumura, Y.; Tsubata, K., Electroorganic chemistry. 46. A new carbon-carbon bond forming reaction at the .alpha.-position of amines utilizing anodic oxidation as a key step. *J. Am. Chem. Soc.* **1981,** *103* (5), 1172-1176.

55.   Little, R. D.; Fox, D. P.; Van Hijfte, L.; Dannecker, R.; Sowell, G.; Wolin, R. L.; Moens, L.; Baizer, M. M., Electroreductive cyclization. Ketones and aldehydes tethered to .alpha.,.beta.-unsaturated esters (nitriles). Fundamental investigations. *J. Org. Chem.* **1988,** *53* (10), 2287-2294.

56.   Yoshida, J.-i.; Murata, T.; Isoe, S., Electrochemical oxidation of organosilicon compounds I. Oxidative cleavage of carbon-silicon bond in allylsilanes and benzylsilanes. *Tetrahedron Lett.* **1986,** *27* (29), 3373-3376.

57.   Moeller, K. D., Synthetic Applications of Anodic Electrochemistry. *Tetrahedron* **2000,** *56* (49), 9527-9554.

58.   Moeller, K. D., Intramolecular Anodic Olefin Coupling Reactions: Using Radical Cation Intermediates to Trigger New Umpolung Reactions. *Synlett* **2009,** *2009* (08), 1208-1218.

59.   Semmelhack, M. F.; Chou, C. S.; Cortes, D. A., Nitroxyl-mediated electrooxidation of alcohols to aldehydes and ketones. *J. Am. Chem. Soc.* **1983,** *105* (13), 4492-4494.

60.   Steckhan, E., Indirect Electroorganic Syntheses—A Modern Chapter of Organic Electrochemistry [New Synthetic Methods (59)]. *Angew. Chem. Int. Ed.* **1986,** *25* (8), 683-701.

61.   Pitchai, M.; Ramirez, A.; Mayder, D. M.; Ulaganathan, S.; Kumar, H.; Aulakh, D.; Gupta, A.; Mathur, A.; Kempson, J.; Meanwell, N.; Hudson, Z. M.; Oderinde, M. S., Metallaphotoredox Decarboxylative Arylation of Natural Amino Acids via an Elusive Mechanistic Pathway. *ACS Catal.* **2023,** *13* (1), 647-658.

62.   Sloane, J. L.; Santos, A. B.; Simmons, E. M.; Sherwood, T. C., Metallaphotoredox-Mediated Decarboxylative Cross-Coupling of α-Oxy Morpholine Carboxylic Acids and (Hetero)Aryl Halides. *Org. Lett.* **2023,** *25* (23), 4219-4224.

63.   Prieto Kullmer, C. N.; Kautzky, J. A.; Krska, S. W.; Nowak, T.; Dreher, S. D.; MacMillan, D. W. C., Accelerating reaction generality and mechanistic insight through additive mapping. *Science* **2022,** *376* (6592), 532-539.

64.   Dombrowski, A. W.; Gesmundo, N. J.; Aguirre, A. L.; Sarris, K. A.; Young, J. M.; Bogdan, A. R.; Martin, M. C.; Gedeon, S.; Wang, Y., Expanding the Medicinal Chemist Toolbox: Comparing Seven C(sp2)–C(sp3) Cross-Coupling Methods by Library Synthesis. *ACS. Med. Chem. Lett.* **2020,** *11* (4), 597-604.

65.   Harwood, S. J.; Palkowitz, M. D.; Gannett, C. N.; Perez, P.; Yao, Z.; Sun, L.; Abruña, H. D.; Anderson, S. L.; Baran, P. S., Modular terpene synthesis enabled by mild electrochemical couplings. *Science* **2022,** *375* (6582), 745-752.

66.   Palkowitz, M. D.; Laudadio, G.; Kolb, S.; Choi, J.; Oderinde, M. S.; Ewing, T. E.-H.; Bolduc, P. N.; Chen, T.; Zhang, H.; Cheng, P. T. W.; Zhang, B.; Mandler, M. D.; Blaszczak, V. D.; Richter, J. M.; Collins, M. R.; Schioldager, R. L.; Bravo, M.; Dhar, T. G. M.; Vokits, B.; Zhu, Y.; Echeverria, P.-G.; Poss, M. A.; Shaw, S. A.; Clementson, S.; Petersen, N. N.; Mykhailiuk, P. K.; Baran, P. S., Overcoming Limitations in Decarboxylative Arylation via Ag–Ni Electrocatalysis. *J. Am. Chem. Soc.* **2022,** *144* (38), 17709-17720.

67.   Kingston, C.; Palkowitz, M. D.; Takahira, Y.; Vantourout, J. C.; Peters, B. K.; Kawamata, Y.; Baran, P. S., A Survival Guide for the "Electro-curious". *Acc. Chem. Res.* **2020,** *53* (1), 72-83.

68.   Guo, J.; Norris, D.; Ramirez, A.; Sloane, J. L.; Simmons, E. M.; Ganley, J. M.; Oderinde, M. S.; Dhar, T. G. M.; Davies, G. H. M.; Sherwood, T. C., Unlocking Tertiary Acids for Metallaphotoredox C(sp2)-C(sp3) Decarboxylative Cross-Couplings. *ChemRxiv* **2023**, 10.26434/chemrxiv-2023-tbvsv.

69.   Yuan, M.; Song, Z.; Badir, S. O.; Molander, G. A.; Gutierrez, O., On the Nature of C(sp3)–C(sp2) Bond Formation in Nickel-Catalyzed Tertiary Radical Cross-Couplings: A Case Study of Ni/Photoredox Catalytic Cross-Coupling of Alkyl Radicals and Aryl Halides. *J. Am. Chem. Soc.* **2020,** *142* (15), 7225-7234.

70.   Dorsheimer, J. R.; Ashley, M. A.; Rovis, T., Dual Nickel/Photoredox-Catalyzed Deaminative Cross-Coupling of Sterically Hindered Primary Amines. *J. Am. Chem. Soc.* **2021,** *143* (46), 19294-19299.

71.   Laudadio, G.; Philipp, N.; Péter, Á.; Emmanuel, M. A.; Palkowitz, M. D.; Oderinde, M. S.; Sloane, J. L.; Gillman, K. W.; Ridge, D.; Bolduc, P. N.; Nicastri, M.; Zhang, B.; Clementson, S.; Petersen, N. N.; Martín-Gago, P.; Mykhailiuk, P.; Schmidt, M.; Mandler, M. D.; Baran, P. S., Ni-Electrocatalytic Decarboxylative Arylation to Access Quaternary Centers. *ChemRxiv* **2023**.

72.   Kombo, D. C.; Tallapragada, K.; Jain, R.; Chewning, J.; Mazurov, A. A.; Speake, J. D.; Hauser, T. A.; Toler, S., 3D Molecular Descriptors Important for Clinical Success. *J. Chem. Inf. Model.* **2013,** *53* (2), 327-342.

73.   Ishikawa, M.; Hashimoto, Y., Improvement in Aqueous Solubility in Small Molecule Drug Discovery Programs by Disruption of Molecular Planarity and Symmetry. *J. Med. Chem.* **2011,** *54* (6), 1539-1554.

74.   Liu, W.; Lavagnino, M. N.; Gould, C. A.; Alcázar, J.; MacMillan, D. W. C., A biomimetic SH2 cross-coupling mechanism for quaternary sp3-carbon formation. *Science* **2021,** *374* (6572), 1258-1263.

75.   Lyon, W. L.; MacMillan, D. W. C., Expedient Access to Underexplored Chemical Space: Deoxygenative C(sp3)–C(sp3) Cross-Coupling. *J. Am. Chem. Soc.* **2023,** *145* (14), 7736-7742.

76. Leech, M. C.; Lam, K., Electrosynthesis Using Carboxylic Acid Derivatives: New Tricks for Old Reactions. *Acc. Chem. Res.* **2020,** *53* (1), 121-134.
77. Yan, M.; Kawamata, Y.; Baran, P. S., Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017,** *117* (21), 13230-13319.
78. Kolbe, H., Beobachtungen über die oxydirende Wirkung des Sauerstoffs, wenn derselbe mit Hülfe einer elektrischen Säule entwickelt wird. *Journal für Praktische Chemie* **1847,** *41* (1), 137-139.
79. Utley, J., Trends in organic electrosynthesis. *Chem. Soc. Rev.* **1997,** *26* (3), 157-167.
80. Zhang, B.; Gao, Y.; Hioki, Y.; Oderinde, M. S.; Qiao, J. X.; Rodriguez, K. X.; Zhang, H.-J.; Kawamata, Y.; Baran, P. S., Ni-electrocatalytic Csp3–Csp3 doubly decarboxylative coupling. *Nature* **2022,** *606* (7913), 313-318.
81. Parida, S. K.; Mandal, T.; Das, S.; Hota, S. K.; De Sarkar, S.; Murarka, S., Single Electron Transfer-Induced Redox Processes Involving N-(Acyloxy)phthalimides. *ACS Catal.* **2021,** *11* (3), 1640-1683.
82. Murarka, S., N-(Acyloxy)phthalimides as Redox-Active Esters in Cross-Coupling Reactions. *Adv. Synth. Catal.* **2018,** *360* (9), 1735-1753.
83. Zhang, B.; He, J.; Gao, Y.; Levy, L.; Oderinde, M. S.; Palkowitz, M. D.; Dhar, T. G. M.; Mandler, M. D.; Collins, M. R.; Schmitt, D. C.; Bolduc, P. N.; Chen, T.; Clementson, S.; Petersen, N. N.; Laudadio, G.; Kawamata, Y.; Baran, P. S., Radical Simplification of Complex Molecule Retrosynthesis Enabled by Electrocatalytic Cross-Coupling of a-Substituted Carboxylic Acids. *ChemRxiv* **2023**.
84. Dénès, F.; Pichowicz, M.; Povie, G.; Renaud, P., Thiyl Radicals in Organic Synthesis. *Chem. Rev.* **2014,** *114* (5), 2587-2693.
85. Huston, P.; Espenson, J. H.; Bakac, A., Reactions of thiyl radicals with transition-metal complexes. *J. Am. Chem. Soc.* **1992,** *114* (24), 9510-9516.
86. Oderinde, M. S.; Frenette, M.; Robbins, D. W.; Aquila, B.; Johannes, J. W., Photoredox Mediated Nickel Catalyzed Cross-Coupling of Thiols With Aryl and Heteroaryl Iodides via Thiyl Radicals. *J. Am. Chem. Soc.* **2016,** *138* (6), 1760-1763.
87. Ting, S. I.; Williams, W. L.; Doyle, A. G., Oxidative Addition of Aryl Halides to a Ni(I)-Bipyridine Complex. *J. Am. Chem. Soc.* **2022,** *144* (12), 5575-5582.
88. Tang, T.; Hazra, A.; Min, D. S.; Williams, W. L.; Jones, E.; Doyle, A. G.; Sigman, M. S., Interrogating the Mechanistic Features of Ni(I)-Mediated Aryl Iodide Oxidative Addition Using Electroanalytical and Statistical Modeling Techniques. *J. Am. Chem. Soc.* **2023,** *145* (15), 8689-8699.
89. Wang, G.; Gao, L.; Feng, Y.; Lin, L., Visible-Light-Activated Nickel Thiolates for C–S Couplings. *Org. Lett.* **2023,** *25* (23), 4340-4344.
90. Qin, Y.; Sun, R.; Gianoulis, N. P.; Nocera, D. G., Photoredox Nickel-Catalyzed C–S Cross-Coupling: Mechanism, Kinetics, and Generalization. *J. Am. Chem. Soc.* **2021,** *143* (4), 2005-2015.
91. Wang, Y.; Deng, L.; Wang, X.; Wu, Z.; Wang, Y.; Pan, Y., Electrochemically Promoted Nickel-Catalyzed Carbon–Sulfur Bond Formation. *ACS Catal.* **2019,** *9* (3), 1630-1634.
92. Liu, D.; Ma, H.-X.; Fang, P.; Mei, T.-S., Nickel-Catalyzed Thiolation of Aryl Halides and Heteroaryl Halides through Electrochemistry. *Angew. Chem. Int. Ed.* **2019,** *58* (15), 5033-5037.
93. Wolfe, J. P.; Buchwald, S. L., Nickel-Catalyzed Amination of Aryl Chlorides. *J. Am. Chem. Soc.* **1997,** *119* (26), 6054-6058.
94. Chen; Yang, L.-M., Arylation of Diarylamines Catalyzed by Ni(II)−PPh3 System. *Org. Lett.* **2005,** *7* (11), 2209-2211.
95. Desmarets, C.; Schneider, R.; Fort, Y., Nickel(0)/Dihydroimidazol-2-ylidene Complex Catalyzed Coupling of Aryl Chlorides and Amines. *J. Org. Chem.* **2002,** *67* (9), 3029-3036.
96. Koo, K.; Hillhouse, G. L., Carbon-Nitrogen Bond Formation by Reductive Elimination from Nickel(II) Amido Alkyl Complexes. *Organomet.* **1995,** *14* (9), 4421-4423.
97. Lin, B. L.; Clough, C. R.; Hillhouse, G. L., Interactions of Aziridines with Nickel Complexes: Oxidative-Addition and Reductive-Elimination Reactions that Break and Make C−N Bonds. *J. Am. Chem. Soc.* **2002,** *124* (12), 2890-2891.
98. Oderinde, M. S.; Jones, N. H.; Juneau, A.; Frenette, M.; Aquila, B.; Tentarelli, S.; Robbins, D. W.; Johannes, J. W., Highly Chemoselective Iridium Photoredox and Nickel Catalysis for the Cross-Coupling of Primary Aryl Amines with Aryl Halides. *Angew. Chem. Int. Ed.* **2016,** *55* (42), 13219-13223.
99. Escobar, R. A.; Johannes, J. W., A Unified and Practical Method for Carbon–Heteroatom Cross-Coupling using Nickel/Photo Dual Catalysis. *Chem. Eur. J.* **2020,** *26* (23), 5168-5173.
100. Corcoran, E. B.; Pirnot, M. T.; Lin, S.; Dreher, S. D.; DiRocco, D. A.; Davies, I. W.; Buchwald, S. L.; MacMillan, D. W. C., Aryl amination using ligand-free Ni(II) salts and photoredox catalysis. *Science* **2016,** *353* (6296), 279-283.
101. Kawamata, Y.; Vantourout, J. C.; Hickey, D. P.; Bai, P.; Chen, L.; Hou, Q.; Qiao, W.; Barman, K.; Edwards, M. A.; Garrido-Castro, A. F.; deGruyter, J. N.; Nakamura, H.; Knouse, K.; Qin, C.; Clay, K. J.; Bao, D.; Li, C.; Starr, J. T.; Garcia-Irizarry, C.; Sach, N.; White, H. S.; Neurock, M.; Minteer, S. D.; Baran, P. S., Electrochemically Driven, Ni-Catalyzed Aryl Amination: Scope, Mechanism, and Applications. *J. Am. Chem. Soc.* **2019,** *141* (15), 6392-6402.
102. Li, C.; Kawamata, Y.; Nakamura, H.; Vantourout, J. C.; Liu, Z.; Hou, Q.; Bao, D.; Starr, J. T.; Chen, J.; Yan, M.; Baran, P. S., Electrochemically Enabled, Nickel-Catalyzed Amination. *Angew. Chem. Int. Ed.* **2017,** *56* (42), 13088-13093.
103. Flood, D. T.; Asai, S.; Zhang, X.; Wang, J.; Yoon, L.; Adams, Z. C.; Dillingham, B. C.; Sanchez, B. B.; Vantourout, J. C.; Flanagan, M. E.; Piotrowski, D. W.; Richardson, P.; Green, S. A.; Shenvi, R. A.; Chen, J. S.; Baran, P. S.; Dawson, P. E., Expanding Reactivity in DNA-Encoded Library Synthesis via Reversible Binding of DNA to an Inert Quaternary Ammonium Support. *J. Am. Chem. Soc.* **2019,** *141* (25), 9998-10006.
104. Wu, X.; Wang, M.; Huan, L.; Wang, D.; Wang, J.; Zhu, C., Tertiary-Alcohol-Directed Functionalization of Remote C(sp3)−H Bonds by Sequential Hydrogen Atom and Heteroaryl Migrations. *Angew. Chem. Int. Ed.* **2018,** *57* (6), 1640-1644.
105. Ilies, L.; Matsubara, T.; Nakamura, E., Nickel-Catalyzed Synthesis of Diarylamines via Oxidatively Induced C–N Bond Formation at Room Temperature. *Org. Lett.* **2012,** *14* (21), 5570-5573.
106. Welin, E. R.; Le, C.; Arias-Rotondo, D. M.; McCusker, J. K.; MacMillan, D. W. C., Photosensitized, energy transfer-mediated organometallic catalysis through electronically excited nickel(II). *Science* **2017,** *355* (6323), 380-385.
107. Kim, T.; McCarver, S. J.; Lee, C.; MacMillan, D. W. C., Sulfonamidation of Aryl and Heteroaryl Halides through Photosensitized Nickel Catalysis. *Angew. Chem. Int. Ed.* **2018,** *57* (13), 3488-3492.

108. work, P. f. y. t. b. p.
109. Jiang, M.; Li, H.; Yang, H.; Fu, H., Room-Temperature Arylation of Thiols: Breakthrough with Aryl Chlorides. *Angew. Chem. Int. Ed.* **2017,** *56* (3), 874-879.
110. Xiang, J.; Shang, M.; Kawamata, Y.; Lundberg, H.; Reisberg, S. H.; Chen, M.; Mykhailiuk, P.; Beutner, G.; Collins, M. R.; Davies, A.; Del Bel, M.; Gallego, G. M.; Spangler, J. E.; Starr, J.; Yang, S.; Blackmond, D. G.; Baran, P. S., Hindered dialkyl ether synthesis with electrogenerated carbocations. *Nature* **2019,** *573* (7774), 398-402.
111. Sheng, T.; Zhang, H.-J.; Shang, M.; He, C.; Vantourout, J. C.; Baran, P. S., Electrochemical Decarboxylative N-Alkylation of Heterocycles. *Org. Lett.* **2020,** *22* (19), 7594-7598.
112. Kammer, L. M.; Badir, S. O.; Hu, R.-M.; Molander, G. A., Photoactive electron donor–acceptor complex platform for Ni-mediated C(sp3)–C(sp2) bond formation. *Chem. Sci.* **2021,** *12* (15), 5450-5457.
113. Polites, V. C.; Badir, S. O.; Keess, S.; Jolit, A.; Molander, G. A., Nickel-Catalyzed Decarboxylative Cross-Coupling of Bicyclo[1.1.1]pentyl Radicals Enabled by Electron Donor–Acceptor Complex Photoactivation. *Org. Lett.* **2021,** *23* (12), 4828-4833.
114. Koyanagi, T.; Herath, A.; Chong, A.; Ratnikov, M.; Valiere, A.; Chang, J.; Molteni, V.; Loren, J., One-Pot Electrochemical Nickel-Catalyzed Decarboxylative Sp2–Sp3 Cross-Coupling. *Org. Lett.* **2019,** *21* (3), 816-820.
115. Zhang, P.; Le, C. C.; MacMillan, D. W. C., Silyl Radical Activation of Alkyl Halides in Metallaphotoredox Catalysis: A Unique Pathway for Cross-Electrophile Coupling. *J. Am. Chem. Soc.* **2016,** *138* (26), 8084-8087.
116. Sakai, H. A.; Liu, W.; Le, C. C.; MacMillan, D. W. C., Cross-Electrophile Coupling of Unactivated Alkyl Chlorides. *J. Am. Chem. Soc.* **2020,** *142* (27), 11691-11697.
117. Truesdell, B. L.; Hamby, T. B.; Sevov, C. S., General C(sp2)–C(sp3) Cross-Electrophile Coupling Reactions Enabled by Overcharge Protection of Homogeneous Electrocatalysts. *J. Am. Chem. Soc.* **2020,** *142* (12), 5884-5893.
118. Zackasee, J. L. S.; Al Zubaydi, S.; Truesdell, B. L.; Sevov, C. S., Synergistic Catalyst–Mediator Pairings for Electroreductive Cross-Electrophile Coupling Reactions. *ACS Catal.* **2022,** *12* (2), 1161-1166.
119. Hamby, T. B.; LaLama, M. J.; Sevov, C. S., Controlling Ni redox states by dynamic ligand exchange for electroreductive Csp3–Csp2 coupling. *Science* **2022,** *376* (6591), 410-416.
120. Franke, M. C.; Longley, V. R.; Rafiee, M.; Stahl, S. S.; Hansen, E. C.; Weix, D. J., Zinc-free, Scalable Reductive Cross-Electrophile Coupling Driven by Electrochemistry in an Undivided Cell. *ACS Catal.* **2022,** *12* (20), 12617-12626.
121. Dong, Z.; MacMillan, D. W. C., Metallaphotoredox-enabled deoxygenative arylation of alcohols. *Nature* **2021,** *598* (7881), 451-456.
122. Zhang, X.; MacMillan, D. W. C., Alcohols as Latent Coupling Fragments for Metallaphotoredox Catalysis: sp3–sp2 Cross-Coupling of Oxalates with Aryl Halides. *J. Am. Chem. Soc.* **2016,** *138* (42), 13862-13865.
123. Li, Z.; Sun, W.; Wang, X.; Li, L.; Zhang, Y.; Li, C., Electrochemically Enabled, Nickel-Catalyzed Dehydroxylative Cross-Coupling of Alcohols with Aryl Halides. *J. Am. Chem. Soc.* **2021,** *143* (9), 3536-3543.
124. Primer, D. N.; Karakaya, I.; Tellis, J. C.; Molander, G. A., Single-Electron Transmetalation: An Enabling Technology for Secondary Alkylboron Cross-Coupling. *J. Am. Chem. Soc.* **2015,** *137* (6), 2195-2198.
125. Luo, J.; Hu, B.; Wu, W.; Hu, M.; Liu, T. L., Nickel-Catalyzed Electrochemical C(sp3)–C(sp2) Cross-Coupling Reactions of Benzyl Trifluoroborate and Organic Halides**. *Angew. Chem. Int. Ed.* **2021,** *60* (11), 6107-6116.
126. Mo, Y.; Lu, Z.; Rughoobur, G.; Patil, P.; Gershenfeld, N.; Akinwande, A. I.; Buchwald, S. L.; Jensen, K. F., Microfluidic electrochemistry for single-electron transfer redox-neutral reactions. *Science* **2020,** *368* (6497), 1352-1357.
127. Lacker, C. R.; DeLano, T. J.; Chen, E. P.; Kong, J.; Belyk, K. M.; Piou, T.; Reisman, S. E., Enantioselective Synthesis of N-Benzylic Heterocycles by Ni/Photoredox Dual Catalysis. *J. Am. Chem. Soc.* **2022,** *144* (44), 20190-20195.
128. Cauley, A. N.; Sezen-Edmonds, M.; Simmons, E. M.; Cavallaro, C. L., Increasing saturation: development of broadly applicable photocatalytic Csp2–Csp3 cross-couplings of alkyl trifluoroborates and (hetero)aryl bromides for array synthesis. *React. Chem. Eng.* **2021,** *6* (9), 1666-1676.
129. Cauley, A. N.; Ramirez, A.; Barhate, C. L.; Donnell, A. F.; Khandelwal, P.; Sezen-Edmonds, M.; Sherwood, T. C.; Sloane, J. L.; Cavallaro, C. L.; Simmons, E. M., Ni/Photoredox-Catalyzed C(sp2)–C(sp3) Cross-Coupling of Alkyl Pinacolboronates and (Hetero)Aryl Bromides. *Org. Lett.* **2022,** *24* (31), 5663-5668.
130. Tsymbal, A. V.; Bizzini, L. D.; MacMillan, D. W. C., Nickel Catalysis via SH2 Homolytic Substitution: The Double Decarboxylative Cross-Coupling of Aliphatic Acids. *J. Am. Chem. Soc.* **2022,** *144* (46), 21278-21286.
131. Yang, T.; Wei, Y.; Koh, M. J., Photoinduced Nickel-Catalyzed Deaminative Cross-Electrophile Coupling for C(sp2)–C(sp3) and C(sp3)–C(sp3) Bond Formation. *ACS Catal.* **2021,** *11* (11), 6519-6525.
132. Zhang, Z.; Cernak, T., The Formal Cross-Coupling of Amines and Carboxylic Acids to Form sp3–sp3 Carbon–Carbon Bonds. *Angew. Chem. Int. Ed.* **2021,** *60* (52), 27293-27298.
133. Zhang, W.; Lu, L.; Zhang, W.; Wang, Y.; Ware, S. D.; Mondragon, J.; Rein, J.; Strotman, N.; Lehnherr, D.; See, K. A.; Lin, S., Electrochemically driven cross-electrophile coupling of alkyl halides. *Nature* **2022,** *604* (7905), 292-297.
134. Smith, R. T.; Zhang, X.; Rincón, J. A.; Agejas, J.; Mateos, C.; Barberis, M.; García-Cerrada, S.; de Frutos, O.; MacMillan, D. W. C., Metallaphotoredox-Catalyzed Cross-Electrophile Csp3–Csp3 Coupling of Aliphatic Bromides. *J. Am. Chem. Soc.* **2018,** *140* (50), 17433-17438.
135. Sakai, H. A.; MacMillan, D. W. C., Nontraditional Fragment Couplings of Alcohols and Carboxylic Acids: C(sp3)–C(sp3) Cross-Coupling via Radical Sorting. *J. Am. Chem. Soc.* **2022,** *144* (14), 6185-6192.
136. Zhang, H.-J.; Chen, L.; Oderinde, M. S.; Edwards, J. T.; Kawamata, Y.; Baran, P. S., Chemoselective, Scalable Nickel-Electrocatalytic O-Arylation of Alcohols. *Angew. Chem. Int. Ed.* **2021,** *60* (38), 20700-20705.
137. Terrett, J. A.; Cuthbertson, J. D.; Shurtleff, V. W.; MacMillan, D. W. C., Switching on elusive organometallic mechanisms with photoredox catalysis. *Nature* **2015,** *524* (7565), 330-334.
138. Park, B. Y.; Pirnot, M. T.; Buchwald, S. L., Visible Light-Mediated (Hetero)aryl Amination Using Ni(II) Salts and Photoredox Catalysis in Flow: A Synthesis of Tetracaine. *J. Org. Chem.* **2020,** *85* (5), 3234-3244.
139. Zhu, D.-L.; Jiang, S.; Wu, Q.; Wang, H.; Li, H.-Y.; Li, H.-X., Nickel-Catalyzed Etherification of Phenols and Aryl Halides through Visible-Light-Induced Energy Transfer. *Org. Lett.* **2021,** *23* (21), 8327-8332.

140.   Tan, Y.; Muñoz-Molina, J. M.; Fu, G. C.; Peters, J. C., Oxygen nucleophiles as reaction partners in photoinduced, copper-catalyzed cross-couplings: O-arylations of phenols at room temperature. *Chem. Sci.* **2014,** *5* (7), 2831-2835.

141.   Liu, L.; Nevado, C., Diaryl Ether Formation Merging Photoredox and Nickel Catalysis. *Organomet.* **2021,** *40* (14), 2188-2193.

142.   Zhu, C.; Kale, A. P.; Yue, H.; Rueping, M., Redox-Neutral Cross-Coupling Amination with Weak N-Nucleophiles: Arylation of Anilines, Sulfonamides, Sulfoximines, Carbamates, and Imines via Nickelaelectrocatalysis. *JACS Au* **2021,** *1* (7), 1057-1065.

143.   Beutner, G. L.; Simmons, E. M.; Ayers, S.; Bemis, C. Y.; Goldfogel, M. J.; Joe, C. L.; Marshall, J.; Wisniewski, S. R., A Process Chemistry Benchmark for sp2–sp3 Cross Couplings. *J. Org. Chem.* **2021,** *86* (15), 10380-10396.

144.   Sun, A. C.; Steyer, D. J.; Robinson, R. I.; Ginsburg-Moraff, C.; Plummer, S.; Gao, J.; Tucker, J. W.; Alpers, D.; Stephenson, C. R. J.; Kennedy, R. T., High-Throughput Optimization of Photochemical Reactions using Segmented-Flow Nanoelectrospray-Ionization Mass Spectrometry**. *Angew. Chem. Int. Ed.* **2023,** *62* (28), e202301664.

145.   Rein, J.; Annand, J. R.; Wismer, M. K.; Fu, J.; Siu, J. C.; Klapars, A.; Strotman, N. A.; Kalyani, D.; Lehnherr, D.; Lin, S., Unlocking the Potential of High-Throughput Experimentation for Electrochemistry with a Standardized Microscale Reactor. *ACS Cent. Sci.* **2021,** *7* (8), 1347-1355.

146.   Möhle, S.; Zirbes, M.; Rodrigo, E.; Gieshoff, T.; Wiebe, A.; Waldvogel, S. R., Modern Electrochemical Aspects for the Synthesis of Value-Added Organic Products. *Angew. Chem. Int. Ed.* **2018,** *57* (21), 6018-6041.

147.   Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T., Applications of Continuous-Flow Photochemistry in Organic Synthesis, Material Science, and Water Treatment. *Chem. Rev.* **2016,** *116* (17), 10276-10341.