Decarboxylative Cross-Coupling: A Radical Tool In Medicinal Chemistry

Gabriele Laudadio,¹[‡] Maximilian D. Palkowitz,¹[‡] Tamara El-Hayek Ewing,¹ Phil S. Baran¹*

¹ Department of Chemistry, Scripps Research, 10550 North Torrey Pines Road, La Jolla, CA 92037, United

KEYWORDS: Decarboxylative Cross-Coupling, Medicinal Chemistry, Radical Retrosynthesis, Electrochemistry

ABSTRACT: Carboxylic acids, the most versatile and ubiquitous diversity input used in medicinal chemistry for canonical polar bond constructions such as amide synthesis, can now be employed in a fundamentally different category of reaction to make C–C bonds by harnessing the power of radicals. This outlook serves as a user guide to aid practitioners in both the design of syntheses that leverage the simplifying power of this disconnection and the precise tactics that can be employed to enable them. Taken together this emerging area holds the potential to rapidly accelerate access to chemical space of value to modern medicinal chemistry.

The development of transition metal-catalyzed crosscoupling reactions ushered in a new era of retrosynthetic disconnections that subsequently changed the way medicinal chemists design and synthesize molecules.¹ At first, enabling $C(sp^2)-C(sp^2)$ and $C(sp^2)-C(sp)$ bond formation in a robust and reliable way set the stage for modern diversification strategies and led to a rapid expansion of the medicinal chemistry toolkit.² The development of this versatile platform witnessed an exponential growth after the 1990s both in terms of publications and patents, until it reached its peak after 2010. Nowadays, the construction of C-C bonds via Suzuki,3 Negishi,4 Kumada,5 Stille,⁶ Sonogashira,⁷ and Heck⁸ couplings is considered intuitive and logical. As a result, the problem of crafting $C(sp^2)$ - $C(sp^2)$ and $C(sp^2)$ -C(sp) linkages is perceived as largely solved (Figure 1A). On the other hand, the logical extension of this concept to C(sp²)-C(sp³) bond formation has remained underdeveloped. The use of alkyl organometallic reagents in the context of Pd-catalyzed cross-couplings is not as general as their aryl/alkenyl counterparts, as many concerns arise on the stability of the requisite alkyl organometallic reagents, chemoselectivity issues, and the challenge of β-hydride elimination that can affect the outcome of such catalytic transformations.⁹ This limitation represents a striking opportunity for innovation within the landscape of molecular design, due to ubiquitous presence of aryl/alkyl or alkenyl/alkyl bonds in Nature as well as pharmaceutical or agrochemical compounds.¹⁰

Decades of research on canonical polar approaches for $C(sp^2)$ - $C(sp^3)$ cross-coupling have iterated on the lessons learned in classic Suzuki, Kumada, and Negishi couplings.⁹ Despite extensive modifications of conditions and ligands to effect such transformations, a robust strategy to enable a level

of diversification akin to the (sp²)-C(sp²) and C(sp²)-C(sp) ones remains elusive. From first principles, even a fully optimized variant of such chemistry would require the synthesis of bespoke alkyl-M fragments which is not ideal for a medicinal chemistry campaign (Figure 1A). Over the last decade the community has begun to embrace a different retrosynthetic logic that departs from polar-bond analysis and instead makes polarity-agnostic convergent disconnections resulting in radical synthons. Radical retrosynthesis relies on the use of convenient precursors (often ubiquitous) to expand the selection of coupling partners. The pioneering work of Kochi, and Morrell,¹¹ also provided the basis for using transition metals other than palladium thereby mitigating the problem of β hydride elimination.¹² Among the wide array of radical-based, transition metal-catalyzed cross-coupling reactions, the decarboxylative cross-coupling (DCC) approach is perhaps most appealing, as carboxylic acids are widely commercially available (more so than any other functional group), benchtop stable and amenable to multiple modes of functionalization.¹³ Not surprisingly, numerous publications have been released on this topic in the last decade, with a similar scenario emerging to canonical cross-coupling during the 90s (Figure 1A).

The use of carboxylic acids as convenient and easily accessible cross-coupling handles can be grouped into two categories: those that leverage the free carboxylic acid and those that use a redox-active ester (RAE)¹⁴ capable of SET derived from the corresponding carboxylic acid.¹⁵ Amongst these two sets of starting materials, there are three distinct catalytic cycles that are operative depending on one's choice of starting material and means of activation. These include (i) cross-coupling of RAEs with nucleophiles, (ii) cross-coupling of free acids (Figure

1B).¹⁶ Aside from approaches that involve transition metal catalyzed process (programmed coupling)¹⁷, tactics that rely on the innate reactivity of an unfunctionalized heterocycle to radical addition have been well explored in the context of the Minisci reaction. While such reports employ carboxylic acid starting materials, they are outside the scope of this perspective and have been reviewed elsewhere.^{18, 19}

Within the first category, it has been shown that NHPI and TCNHPI RAEs can engage in cross-coupling with a variety of C(sp²) aryl organozinc coupling partners under Ni-catalysis.¹⁴ Since then, the scope of this transformation has been expanded to a broad range of aryl,²⁰ alkenyl²¹ and alkynyl²² organometallic reagents including organoboron species²³ as well as Grignard reagents under Fe-catalysis.²⁴ Mechanistically, these couplings are hypothesized to proceed by initial transmetallation of the $C(sp^2)$ nucleophile equivalent to a Ni(I) species. The corresponding Ni(I) complex then donates an electron to the RAE generated a cationic Ni(II) intermediate. Upon reduction by the Ni(I), the RAE fragments to liberate CO₂ and phthalimide to generate a carbon-centered radical. This radical then rapidly recombines with the Ni(II) to afford a Ni(III) intermediate that upon reductive elimination generates the cross coupled product and a Ni(I) species that can re-enter the catalytic cycle.¹⁴ Operationally these reactions are akin to amide-bond formation wherein the RAE can be prepared in situ and used directly upon exposure to the organometallic nucleophile and catalyst.

While the above approach tolerates a wide range of coupling partners and functionality, it is not without its limitations. Namely, there are a limited number of commercial organometallic reagents compared to that of the carboxylic acid. This often requires the practitioner to synthesize bespoke organometallic reagents for more structurally complex crosscoupling partners, which undoubtedly adds additional concession steps to any synthesis. To this end, several reports have emerged that leverage an exogenous reductant (Zn,²⁵⁻²⁷ Hantzsch ester under photochemical activation,^{28, 29}, dual photoredox/Ni-catalysis³⁰ or electrochemical reduction³¹⁻³³) and C(sp²)-electrophile equivalents to mimic the overall transformations achieved in the organometallic approach but under milder reaction conditions. Further, this approach leverages more commercially available and benchtop stable C(sp²)-halides and pseudohalides. Such modifications fall under the second category of reductive activation for decarboxylative cross-coupling.16

While the mechanism for such reductive cross electrophile couplings is still under investigation, it is generally hypothesized that they adhere to the following catalytic cycle. First, the Ni(II) precursor is reduced by the exogenous reductant to afford a low valent Ni(I) species. This reduced species undergoes oxidative addition to the C(sp²)-halide to generate at Ni(III) complex which undergoes comproportionation to generate a Ni(II) intermediate. This intermediate captures a radical generated from decarboxylation of the RAE to give a Ni(III) species. This species undergoes reductive elimination to give the desired coupled product and a Ni(I) species which can trigger decarboxylation of the RAE through SET and re-enter the catalytic cycle as Ni(II).³² As previously mentioned, the mechanism for these reductive radical cross-couplings is still under heavy investigation. Additional mechanisms proceeding through Ni(0/II/III/I) cycles have also been proposed.^{34, 35} Additionally, efforts are further complicated by the mechanistic fluidity of such systems as a function of the starting materials enlisted (ex: alkyl halide vs. alkyl RAEs).³⁶

On the other side of the reactivity paradigm lies methods that leverage oxidative activation of a free carboxylic acid typically under photoinduced electron transfer (PET) conditions using an excited state iridium(III)-based photocatalyst and C(sp²) electrophiles.^{37, 38} Upon excitation, the iridium(III) catalyst enters an excited triplet state after intersystem crossing. This excited species can act as a strong oxidant which oxidizes the carboxylic acid to generate a carbon-centered radical with loss of CO2. The reduced photocatalyst then facilitates the generation of Ni(0) and regenerates the Ir(III) photocatalyst. Ni(0) undergoes oxidative addition with the electrophile to generate a Ni(II) complex which captures a carbon centered radical affording a transient Ni(III) intermediate. This intermediate undergoes reductive elimination to afford the desired cross coupled product and a Ni(I) intermediate that can re-enter the catalytic cycle upon reduction by the reduced Ir(II) photocatalyst.39-41

The three possible ways to control and promote the decarboxylative $C(sp^3)$ - $C(sp^2)$ cross-coupling offer unique advantages and disadvantages in terms of functional group tolerance and robustness (Figure 1C).¹⁶ The nucleophilic crosscoupling approach is limited by the organometallic species, which may compromise the chemoselectivity of the reaction. The electrophilic cross-coupling is generally the most versatile and robust, due to the mild reaction conditions. Recent works from our group showed that the use of silver-nanoparticle functionalized electrodes can expand the scope of the reductive coupling to challenging vinyl iodides and aryl halides, delivering molecules that were otherwise difficult to access (vide infra).³² However, reactions that involve the use of redox active esters are limited by the presence of unprotected primary and secondary amines, which can react with the activated esters. Finally, the oxidative cross-coupling approach provides an orthogonal process to forge $C(sp^3)$ - $C(sp^2)$ in a decarboxylative fashion. Moreover, the use of carboxylic acid can be advantageous in avoiding the intermediacy of RAEs.⁴² One limiting factor of the oxidative strategy is that redox labile functional groups can competitively quench the photocatalyst, affecting the outcome of the reaction. The complementary nature of these different categories is graphically outlined in a "user-guide" format in Figure 1C with references to assist medicinal chemists in need of the best conditions for a particular use-case.

The undeniable value of this transformation can be contextualized in the case studies outlined in Figure 2. These examples are organized by contrasting well-trodden multi-step polar-bond approaches to the simplified routes enabled by radical retrosynthesis (DCC).⁴³ For example, a popular synthesis of unnatural amino acids originates from glutamic acid via Negishi coupling. This polar tactic for the construction of these molecules relies on the synthesis of the $C(sp^3)$ organometallic reagents via multiple FG manipulations.44 In contrast, the same product can be obtained with a reductive decarboxylative cross-coupling starting from the RAE of the native amino acid and the desired arvl halide partner. In this case, the use of Ag-Ni electrocatalysis is singularly successful amongst all methods evaluated (when free phenols and heterocycles are employed).³¹ Thus, the DCC approach is attractive in terms of ideality, scalability, and rapid access to diversity.

Another emblematic approach to such molecules utilizes reliable $C(sp^2)$ - $C(sp^2)$ Suzuki-Miyaura couplings followed by hydrogenation. This conventional strategy, often applied to secondary carbons, leverages the formation of a vinyl halide starting from the corresponding ketone, followed by Miyaura borylation and the cross-coupling step, after which the hydrogenation of the undesired alkene is required. ⁴⁵ This sequence usually requires protecting groups and chemoselectivity issues can arise when other reducible or basesensitive functionality are present. On the other hand, radical cross-coupling of the carboxylic acid overcomes the necessity of the aforementioned FG interconversions and concession steps to address chemoselectivity issues.³¹ Whereas traditional approaches often require three separate uses of Pd-catalysts, the DCC-approach employs a single Ni-catalyst to forge the key carbon-carbon linkage with the correct oxidation state.

Polar strategies are drastically limited when the construction of quaternary centers is desired through cross-coupling.⁴⁶ As a workaround for this challenge, practitioners have enlisted electron deficient olefins as gateways for the formation of quaternary centers owing to the copious literature precedent for conjugate addition.⁴⁷ For example, the antimicrobial compound **1** was synthesized via this approach using a Rh-catalyzed conjugate addition with an aryl boronic acid. Although the target is accessed, the efficiency of the route is undermined by a reliance on a vinyl sulfone which is not expressed in the final product thus necessitating its reductive removal.⁴⁸ A radical approach facilitates a more intuitive and convergent disconnection, wherein the key C(sp²)-C(sp³) linkage can be made directly from oxetane acid **2** and aryl zinc reagent **3** under modified DCC conditions.⁴⁶

Unlike substituted heteroaromatic systems, access to substituted saturated heterocyclic systems often necessitates ring synthesis logic. As such, polar bond analysis dictates the use of nucleophilic additions and displacements as central tactics, requiring bespoke multistep routes. The typical synthesis of C-3 arylated N-boc morpholine derivatives such as 4 are a good example of this scenario. The stepwise construction of 4 requires eight steps wherein the key diversity input (the arene) is introduced at the outset. This multistep approach forges one bond at a time and uses thionyl chloride, TMSdiazomethane, and hydrobromic acid along the wav.49 Alternatively, the acid-bearing saturated heterocycle 5 can be purchased and directly coupled with an arene of interest through DCC in a single, diversity incorporating step.³¹ Another compelling example of the simplifying effect that decarboxylative approaches can have on synthetic planning can be found in its application to the antipsychotic drug Asenapine (Saphris) 6. This substituted chiral pyrrolidine bears two contiguous stereocenters that only differ by the placement of a chlorine atom on the aryl ring substituents. Polar approaches require multistep sequences to access this substituted pyrrolidine wherein diversity elements are incorporated in the early stages making rapid analog generation time-consuming. One approach leverages a Claisen rearrangement to set the stereocenters en route to the saturated heterocycle. This 12-step route requires the use of strong base, diazomethane, and osmium which limit its overall practicality.⁵⁰ Alternatively, combining the power of pericyclic cycloaddition chemistry to rapidly build the core followed by two consecutive DCC reactions results in a simpler approach more amenable to library synthesis. Thus, meso-7, derived from a dipolar cycloaddition reaction, can be desymmetrized to afford an enantioenriched intermediate bearing a free acid for cross-coupling and a protected methyl ester for a subsequent coupling upon hydrolysis. Iterative cross-couplings established the desired stereochemical configurations at the $C(sp^2)$ - $C(sp^3)$ linkages. Importantly the desired trans stereochemistry leveraged the unique ability for radicals to undergo inversion of configuration to avoid steric clashes in the cross coupled products. Finally, intramolecular aryl etherification led to **6** in 8 total steps.⁵¹

So far, we have outlined how the use of radical DCC for the construction of C(sp²)-C(sp³) can tangibly simplify the way one can access useful targets. It is not unreasonable to predict that the use of radical cross-coupling will extend far beyond C(sp²)-C(sp³) linkages to forge other strategically important bonds. To this end, several emerging horizons are beginning to surface that can capitalize on these versatile starting materials. For example, an electrochemically driven reductive double DCC for the synthesis of a multitude of structures via a convergent C(sp³)-C(sp³) coupling (Figure 3).^{52, 53} The ramifications for such a method to simplify retrosynthetic logic are enormous as practically any carbon-carbon bond can be cleaved with this transform. As an example, unnatural amino acid 8 was previously prepared in an eight-step sequence involving a pyridine hydrogenation-based strategy where no C-C bonds were forged.⁵⁴ In contrast, commercially available acids 10 and 11 were directly coupled to access methyl ester analogue 9 in a single step. Extending beyond carbon-carbon bonds, alkyl carboxylic acids serve as precursors to electrochemically generated cations via two sequential one-electron transfers. These reactive intermediates can then react with Lewis-basic heteroatoms as nucleophiles to forge valuable compounds such as hindered ethers and alkylated heterocycles (Figure 3).55, 56 For instance, hindered dialkyl ether 12 was previously synthesized in a six-step sequence starting from the corresponding tertiary alcohol involving a borylation, oxidation, Wittig then reduction sequence.⁵⁷ Alternatively, alcohol 13 and tertiary carboxylic acid 14 were coupled to afford the 12 in a single step. N-alkyl pyrazole 15, which was employed in the synthesis of a Cereblon binder, was previously made through a pyrazole ring synthesis strategy in six steps.⁵⁸ Instead, commercially available pyrazole 17 and carboxylic acid 16 could be simply combined in a single step. In both instances the decreased step counts and increased convenience in accessing medicinally relevant structures relative to classic polar approaches is compelling.

In writing this perspective, we do not mean to imply that radical retrosynthetic approaches will solve all problems encountered in medicinal chemistry. To be sure, canonical polar approaches will likely always remain as powerful means to construct key carbon-carbon linkages in compounds of interest. That is partly because they have benefitted from nearly a century of refinement. Indeed, in recent surveys of reaction types most used in pharmaceutical chemistry, radical reactions are nowhere to be found. This may be due to the long-held notion that radical chemistry is difficult to tame and best employed in intramolecular settings or for simple deoxygenations.^{59, 60} However, as complexity demands in modern medicinal chemistry increase, combined with shrinking timelines needed to go from hit to lead, there is a real need for methods that depart from convention and classic dogma.⁶¹ Radical cross-coupling represents such an approach and is still in its infancy. Its use often overcomes the need for monotonous functional group manipulations and allows the direct coupling of easily accessible starting materials. The convergency,

modularity, and rapid build-up of complexity they facilitate can therefore have a tangible impact on the medicinal chemist's ability to not only accelerate but even enable access to high value scaffolds.^{17, 43, 61} In reflecting on the cutting-edge nature of amide-bond formation in the 1950's and its status today as perhaps the most used reaction of our time, one wonders if radical cross-coupling methods in 2050 will be viewed as commonplace and, perhaps, even boring.⁶²

AUTHOR INFORMATION

Corresponding Author

* pbaran@scripps.edu

Author Contributions

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

Funding Sources

Financial support for this work was provided by the NIH (MIRA GM-118176), NSF Center for Synthetic Organic Electrochemistry (CHE-2002158). M.D.P. thanks Richard and Nicola Lerner for the Endowed Fellowship and BMS for the Graduate Research Fellowship. G.L. Thanks the George E. Hewitt Foundation for the postdoctoral fellowship.

ACKNOWLEDGMENT

G.L. thanks the George E. Hewitt Foundation for the postdoctoral fellowship. M.D.P. thanks Richard and Nicola Lerner for the Endowed Fellowship and BMS for the Graduate Research Fellowship. B. Smith and A. Pollatos for helpful discussions.

ABBREVIATIONS

DCC,	Decarboxylative	Cross-Coupling;	NHPI,	N-
Hydroxyphthalimide;		TCNHPI,		N-
Hydroxy	tetrachlorophthalimi	de.		

REFERENCES

1. Negishi, E.-i., *Handbook of Organopalladium Chemistry for Organic Synthesis*. John Wiley & Sons, Inc.: 2002.

2. Buskes, M. J.; Blanco, M.-J., Impact of Cross-Coupling Reactions in Drug Discovery and Development. *Molecules* **2020**, *25* (15), 3493.

3. Miyaura, N.; Suzuki, A., Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95* (7), 2457-2483.

4. Haas, D.; Hammann, J. M.; Greiner, R.; Knochel, P., Recent Developments in Negishi Cross-Coupling Reactions. *ACS Catal.* **2016**, *6* (3), 1540-1552.

5. Heravi, M. M.; Zadsirjan, V.; Hajiabbasi, P.; Hamidi, H., Advances in Kumada–Tamao–Corriu cross-coupling reaction: an update. *Monatsh. Chem.* **2019**, *150* (4), 535-591.

6. Farina, V.; Krishnamurthy, V.; Scott, W. J., The Stille Reaction. In *Organic Reactions*, John Wiley and Sons, I., Ed. 2004.

7. Chinchilla, R.; Nájera, C., The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry. *Chem. Rev.* **2007**, *107* (3), 874-922.

8. Beletskaya, I. P.; Cheprakov, A. V., The Heck Reaction as a Sharpening Stone of Palladium Catalysis. *Chem. Rev.* **2000**, *100* (8), 3009-3066.

9. Jana, R.; Pathak, T. P.; Sigman, M. S., Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. *Chem. Rev.* **2011**, *111* (3), 1417-1492.

10. 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.

11. Morrell, D. G.; Kochi, J. K., Mechanistic studies of nickel catalysis in the cross coupling of aryl halides with alkylmetals. Role of arylalkylnickel(II) species as intermediates. *J. Am. Chem. Soc.* **1975**, *97* (25), 7262-7270.

12. Tsou, T. T.; Kochi, J. K., Mechanism of oxidative addition. Reaction of nickel(0) complexes with aromatic halides. *J. Am. Chem. Soc.* **1979**, *101* (21), 6319-6332.

13. Rodríguez, N.; Goossen, L. J., Decarboxylative coupling reactions: a modern strategy for C–C-bond formation. *Chem. Soc. Rev.* **2011**, *40* (10), 5030-5048.

14. 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.

15. Murarka, S., N-(Acyloxy)phthalimides as Redox-Active Esters in Cross-Coupling Reactions. *Adv. Synth. Catal.* **2018**, *360* (9), 1735-1753.

16. 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.

17. Yan, M.; Lo, J. C.; Edwards, J. T.; Baran, P. S., Radicals: Reactive Intermediates with Translational Potential. *J. Am. Chem. Soc.* **2016**, *138* (39), 12692-12714.

18. Proctor, R. S. J.; Phipps, R. J., Recent Advances in Minisci-Type Reactions. *Angew. Chem. Int. Ed.* **2019**, *58* (39), 13666-13699.

19. Duncton, M. A. J., Minisci reactions: Versatile CHfunctionalizations for medicinal chemists. *MedChemComm* **2011**, 2 (12), 1135-1161.

20. Sandfort, F.; O'Neill, M. J.; Cornella, J.; Wimmer, L.; Baran, P. S., Alkyl–(Hetero)Aryl Bond Formation via Decarboxylative Cross-Coupling: A Systematic Analysis. *Angew. Chem. Int. Ed.* **2017**, *56* (12), 3319-3323.

21. Edwards, J. T.; Merchant, R. R.; McClymont, K. S.; Knouse, K. W.; Qin, T.; Malins, L. R.; Vokits, B.; Shaw, S. A.; Bao, D.-H.; Wei, F.-L.; Zhou, T.; Eastgate, M. D.; Baran, P. S., Decarboxylative alkenylation. *Nature* **2017**, *545* (7653), 213-218.

22. Smith, J. M.; Qin, T.; Merchant, R. R.; Edwards, J. T.; Malins, L. R.; Liu, Z.; Che, G.; Shen, Z.; Shaw, S. A.; Eastgate, M. D.; Baran, P. S., Decarboxylative Alkynylation. *Angew. Chem. Int. Ed.* **2017**, *56* (39), 11906-11910.

23. Wang, J.; Qin, T.; Chen, T.-G.; Wimmer, L.; Edwards, J. T.; Cornella, J.; Vokits, B.; Shaw, S. A.; Baran, P. S., Nickel-Catalyzed Cross-Coupling of Redox-Active Esters with Boronic Acids. *Angew. Chem. Int. Ed.* **2016**, *55* (33), 9676-9679.

24. Toriyama, F.; Cornella, J.; Wimmer, L.; Chen, T.-G.; Dixon, D. D.; Creech, G.; Baran, P. S., Redox-Active Esters in Fe-Catalyzed C–C Coupling. *J. Am. Chem. Soc.* **2016**, *138* (35), 11132-11135.

25. Salguiero, D. C.; Chi, B. K.; Garcia-Reynaga, P.; Weix, D. J., Arylation of Pharmaceutically Relevant Strained Rings Using Electronically Tuned Redox-Active Esters. *ChemRxiv* **2022**, 10.26434/chemrxiv-2022-7914g.

26. Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; DiBenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J., Decarboxylative Cross-Electrophile Coupling of N-Hydroxyphthalimide Esters with Aryl Iodides. *J. Am. Chem. Soc.* **2016**, *138* (15), 5016-5019.

27. Huang, L.; Olivares, A. M.; Weix, D. J., Reductive Decarboxylative Alkynylation of N-Hydroxyphthalimide Esters with Bromoalkynes. *Angew. Chem. Int. Ed.* **2017**, *56* (39), 11901-11905.

28. 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.

29. 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.

30. Behnke, N. E.; Sales, Z. S.; Li, M.; Herrmann, A. T., Dual Photoredox/Nickel-Promoted Alkylation of Heteroaryl Halides with Redox-Active Esters. *J. Org. Chem.* **2021**, *86* (18), 12945-12955.

31. Palkowitz, M. D.; Laudadio, G.; Kolb, S.; Choi, J.; Oderinde, M. S.; El-Hayek Ewing, T.; Bolduc, P.; Chen, T.; Zhanh, H.; Cheng, P. T. W.; Zhang, B.; Mandler, M.; Richter, J. M.; Collins, M. R.; Schioldager, R. L.; Dhar, M.; Vokits, B.; Echeverria, P.-G.; Poss, M. A.; Shaw, S. A.; Clementson, S.; Nasser Petersen, N.; Mykhailiuk, P.; Baran, P. S., Overcoming Limitations in Decarboxylative Arylation via Ag-Ni Electrocatalysis. *ChemRxiv* **2022**, 10.26434/chemrxiv-2022rpnp8.

32. 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.

33. 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.

34. Weix, D. J., Methods and Mechanisms for Cross-Electrophile Coupling of Csp2 Halides with Alkyl Electrophiles. *Acc. Chem. Res.* **2015**, *48* (6), 1767-1775.

35. Diccianni, J. B.; Diao, T., Mechanisms of Nickel-Catalyzed Cross-Coupling Reactions. *Trends in Chemistry* **2019**, *1* (9), 830-844.

36. 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.

37. Bell, J. D.; Murphy, J. A., Recent advances in visible light-activated radical coupling reactions triggered by (i) ruthenium, (ii) iridium and (iii) organic photoredox agents. *Chem. Soc. Rev.* **2021**, *50* (17), 9540-9685.

38. 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.

39. 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.

40. Noble, A.; McCarver, S. J.; MacMillan, D. W. C., Merging Photoredox and Nickel Catalysis: Decarboxylative Cross-Coupling of Carboxylic Acids with Vinyl Halides. *J. Am. Chem. Soc.* **2015**, *137* (2), 624-627.

41. Mao, Y.; Zhao, W.; Lu, S.; Yu, L.; Wang, Y.; Liang, Y.; Ni, S.; Pan, Y., Copper-catalysed photoinduced decarboxylative alkynylation: a combined experimental and computational study. *Chem. Sci.* **2020**, *11* (19), 4939-4947.

42. 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.

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

44. Usuki, T.; Yanuma, H.; Hayashi, T.; Yamada, H.; Suzuki, N.; Masuyama, Y., Improved Negishi Cross-Coupling Reactions of an Organozinc Reagent Derived from 1-Aspartic Acid with Monohalopyridines. *J. Heterocycl. Chem.* **2014**, *51* (1), 269-273.

45. Burch, J. D.; Lau, K.; Barker, J. J.; Brookfield, F.; Chen, Y.; Chen, Y.; Eigenbrot, C.; Ellebrandt, C.; Ismaili, M. H. A.; Johnson, A.; Kordt, D.; MacKinnon, C. H.; McEwan, P. A.; Ortwine, D. F.; Stein, D. B.; Wang, X.; Winkler, D.; Yuen, P.-W.; Zhang, Y.; Zarrin, A. A.; Pei, Z., Property- and Structure-Guided Discovery of a Tetrahydroindazole Series of Interleukin-2 Inducible T-Cell Kinase Inhibitors. *J. Med. Chem.* **2014**, *57* (13), 5714-5727.

46. Chen, T.-G.; Zhang, H.; Mykhailiuk, P. K.; Merchant, R. R.; Smith, C. A.; Qin, T.; Baran, P. S., Quaternary Centers by Nickel-Catalyzed Cross-Coupling of Tertiary Carboxylic Acids and (Hetero)Aryl Zinc Reagents. *Angew. Chem. Int. Ed.* **2019**, *58* (8), 2454-2458.

47. Zheng, K.; Liu, X.; Feng, X., Recent Advances in Metal-Catalyzed Asymmetric 1,4-Conjugate Addition (ACA) of Nonorganometallic Nucleophiles. *Chem. Rev.* **2018**, *118* (16), 7586-7656.

48. Marson, C. M., New and unusual scaffolds in medicinal chemistry. *Chem. Soc. Rev.* **2011**, *40* (11), 5514-5533.

49. Galley, G.; Pflieger, P.; Norcross, R.; Cecere, G.; Shen, H.; Hu, Y. Preparation of morpholinylpyridine derivatives for use as TAAR modulators. WO2015165835, 2015.

50. Anugu, R. R.; Mainkar, P. S.; Sridhar, B.; Chandrasekhar, S., The Ireland–Claisen rearrangement strategy towards the synthesis of the schizophrenia drug, (+)-asenapine. *Org. Biomol. Chem.* **2016**, *14* (4), 1332-1337.

51. Chen, T. G.; Barton, L. M.; Lin, Y.; Tsien, J.; Kossler, D.; Bastida, I.; Asai, S.; Bi, C.; Chen, J. S.; Shan, M.; Fang, H.; Fang, F. G.; Choi, H.-w.; Hawkins, L.; Qin, T.; Baran, P. S., Building C(sp3)-rich complexity by combining cycloaddition and C–C cross-coupling reactions. *Nature* **2018**, *560* (7718), 350-354.

52. 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.

53. Kang, K.; Weix, D. J., Nickel-Catalyzed C(sp3)–C(sp3) Cross-Electrophile Coupling of In Situ Generated NHP Esters with Unactivated Alkyl Bromides. *Org. Lett.* **2022**, *24* (15), 2853-2857.

54. Adang, A. E. P.; Peters, C. A. M.; Gerritsma, S.; de Zwart, E.; Veeneman, G., Solution-phase and solid-phase synthesis of novel transition state inhibitors of coagulation enzymes incorporating a piperidinyl moiety. *Bioorg. Med. Chem. Lett.* **1999**, *9* (9), 1227-1232.

55. 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.

56. 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.

57. Altmann, E.; Hommel, U.; Lorthios, E. L. J.; Maibaum, J. K.; Ostermann, N.; Quancard, J.; Randl, S. A.; Rogel, O.; Simic, O.; Vulpetti, A.; Stark-Rogel, V. Complement pathway modulators and uses thereof. US20120295884A1.2012.

58. Veits, G. K.; He, M.; Henderson, J. A.; Nasveschuk, C. G.; Phillips, A. J.; Good, A. C. Cereblon binders for the degradation of ikaros. WO2019191112A1. 2019.

59. Ingold, K. U., Kinetic and mechanistic studies of free radical reactions in the 21st century. *Pure Appl. Chem.* **1997**, 69 (2), 241-244.

60. Walling, C., Some properties of radical reactions important in synthesis. *Tetrahedron* **1985**, *41* (19), 3887-3900.

61. Eastgate, M. D.; Schmidt, M. A.; Fandrick, K. R., On the design of complex drug candidate syntheses in the pharmaceutical industry. *Nat. Rev. Chem.* **2017**, *1* (2), 0016.

62. Brown, D. G.; Boström, J., Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016**, *59* (10), 4443-4458.







Figure 1. (A) The role of decarboxylative cross-coupling within the medicinal chemistry toolkit. (B) Reaction mechanism of the three crosscoupling strategies. (C) Functional group compatibility user-guide of the different decarboxylative cross-coupling strategies.



Figure 2. Strategic applications of the decarboxylative cross-coupling strategy compared with the literature polar syntheses.



Figure 3. Emerging horizons for decarboxylative cross-coupling.