ACS Medicinal Chemistry Letters

pubs.acs.org/acsmedchemlett Letter

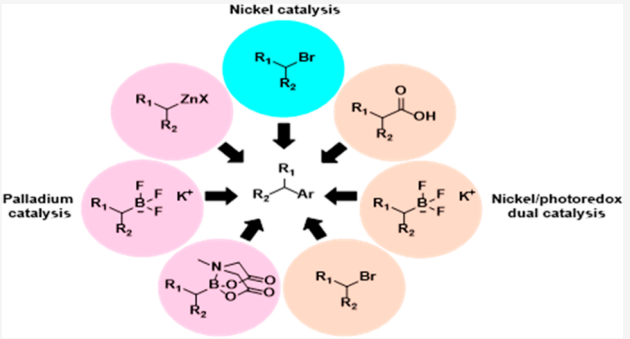
Expanding the Medicinal Chemist Toolbox: Comparing Seven C(sp^2)−C(sp^3) Cross-Coupling Methods by Library Synthesis

Amanda W. Dombrowski,*,‖ Nathan J. Gesmundo,*,‖ Ana L. Aguirre, Katerina A. Sarris, Jonathon M. Young, Andrew R. Bogdan, M. Cynthia Martin, Shasline Gedeon, and Ying Wang

Cite This: ACS Med. Chem. Lett. 2020, 11, 597−604 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Despite recent advances in the field of C(sp^2)−C(sp^3) cross-couplings and the accompanying increase in publications, it can be hard to determine which method is appropriate for a given reaction when using the highly functionalized intermediates prevalent in medicinal chemistry. Thus a study was done comparing the ability of seven methods to directly install a diverse set of alkyl groups on "drug-like" aryl structures via parallel library synthesis. Each method showed substrates that it excelled at coupling compared with the other methods. When analyzing the reactions run across all of the methods, a reaction success rate of 50% was achieved. Whereas this is promising, there are still gaps in the scope of direct C(sp^2)−C(sp^3) coupling methods, like tertiary group installation. The results reported herein should be used to inform future syntheses, assess reaction scope, and encourage medicinal chemists to expand their synthetic toolbox.



KEYWORDS: *C(sp^2)−C(sp^3) cross-coupling, parallel library synthesis, synthetic toolbox, photoredox catalysis, method comparison*

Analyses in recent publications have shown that medicinal chemistry is dominated by a small set of reactions, and many chemists have expressed concerns about the resulting effects on compound diversity.[1−5] New promising methodologies, such as photoredox chemistry, have had a limited impact on drug discovery because of their slow adoption in discovery chemistry. However, those who do adopt new methods can be rewarded with a competitive advantage, possessing an expanded "synthetic toolbox" and techniques to quickly make more structurally diverse compounds.

The degree of saturation of a compound can have profound effects on its physical properties, such as the aqueous solubility and the crystallinity. Studies have shown that increasing the number of sp^3-hydridized carbons, and thus decreasing the planarity, is a way to make a compound more drug-like.[6] Importantly, the degree of saturation was shown to increase from discovery through each stage of development to marketed drugs.[7] Robust synthetic methods, which enable the installation of sp^3 character or alkyl groups onto aryl rings, are critical. This is an active area of academic research, which is highly valuable to medicinal chemists in their pursuit of quality drug candidates. Several recent publications show that interest in direct C(sp^2)−C(sp^3) couplings applied to drug discovery is growing.[8−17]

Traditionally, some medicinal chemists have been reluctant to directly install certain alkyl groups in their molecules due to the heavy time investment and the high risk of failure. Many substrates need tailored methods, and there is an assumption of low success rates when combining modern synthetic methods with the complex, highly functionalized structures in medicinal chemistry. As a result, the installation of some groups, such as simple cyclic alkyl groups, on (hetero)aryl substrates has been achieved using a two-step route composed of a vinyl Suzuki coupling followed by hydrogenation. While reliable, this sequence increases the design−synthesis−test (DST) cycle time, and adapting this route for parallel synthesis is challenging.

Recent advances in the field of C(sp^2)−C(sp^3) couplings (Figure 1) have renewed interest in direct approaches to form aryl−alkyl bonds within discovery chemistry. However, with several methods of this type being published each year, it is not obvious which method should be chosen to install a given alkyl group. This is partially due to literature substrate scopes not reflecting the structural diversity found in medicinal chemistry and the fast-paced nature of early drug discovery, where time for method scouting is limited. Thus a comparative study of seven C(sp^2)−C(sp^3) cross-coupling methods was undertaken,

Received: February 21, 2020
Accepted: March 23, 2020
Published: March 23, 2020

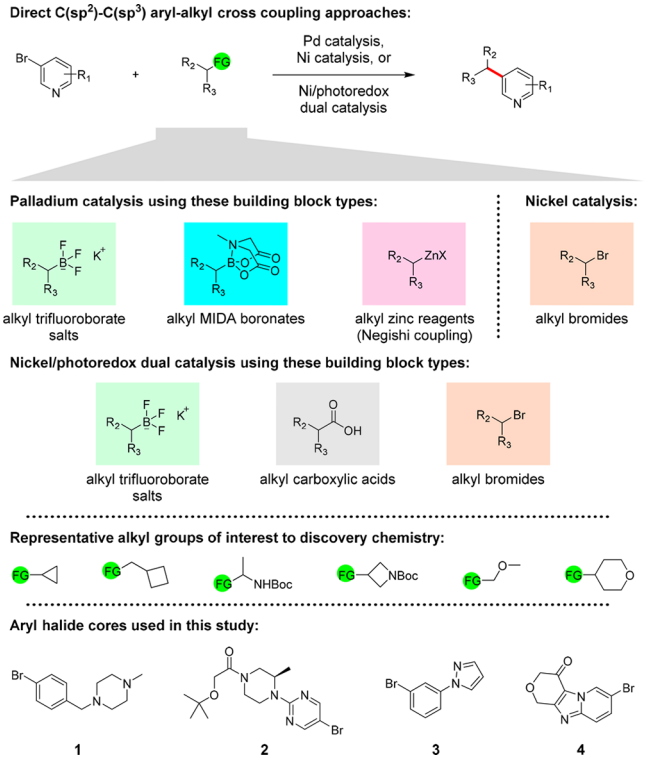


Figure 1. Modern strategies to install alkyl groups on heteroaromatic cores.

focusing on direct aryl−alkyl couplings with which our discovery organization has built up experience or interest to guide future syntheses, to assess method scopes for adoption in parallel library synthesis, and to expand chemists' "synthetic toolbox".

Seven methods were selected based on a combination of factors, such as the commercial availability of building blocks, internal experience, and reaction mechanism diversity. The palladium-catalyzed Suzuki cross-coupling (with alkyl potassium trifluoroborate (BF_3K) salts or alkyl *N*-methyliminodiacetic acid (MIDA) boronates)[18−20] and palladium-catalyzed Negishi coupling were tested.[21−23] A nickel-catalyzed reductive cross-electrophile coupling (CEC) using alkyl bromides was also tested[8,24,25] along with three nickel/photoredox dual-catalysis methods: the alkyl BF_3K coupling,[9,26−30] the decarboxylative coupling,[13,31−33] and CEC.[13,34] From preliminary results, these methods appeared to be reliable, robust enough for library synthesis, and amenable to wide adoption. Additionally, all of the methods use aryl halide coupling handles, which are ubiquitous in medicinal chemistry. To test the generality of the methods, the comparison was done using a standard library synthesis workflow, incorporating parallel synthesis, reverse-phase HPLC purification, and automated liquid handling (see the SI).[35] Parallel library synthesis is critical for structure−activity relationship (SAR) studies; thus, for a method to have maximum impact in medicinal chemistry, it must be amenable to library synthesis. The number of reaction conditions used was minimized (one to two per method) to enable the efficiency of library synthesis, and they were chosen from publications and internal expertise. Isolated yields were not further optimized.

For this study, 29 alkyl building blocks were selected to ensure overlap between methods so clear comparisons could be made. Building blocks, which are desirable to discovery project teams, such as cyclic ethers and bifunctional-protected cyclic amines, were included. When possible, the alkyl groups were selected to maximize electronic and steric diversity. Primary, secondary, tertiary, and benzylic groups were represented, and a variety of ring sizes were included. Heteroatoms at proximal and distal locations were tested when available. In addition, the effects of basicity in amine-containing alkyl groups was also investigated. Critically, several of the alkyl groups shown here were not used as substrates in previous publications but are of high interest to the medicinal chemistry community. Likewise, the aryl bromides used in this study were selected as relevant examples of structural motifs used in medicinal chemistry (Figure 1). Finally, each method tested additional building blocks, which were not available for every other method (total library sizes ranged from 13 to 41 building blocks). The results of this study, from a total of 28 libraries (7 methods × 4 aryl bromides), are reported herein.

Figure 2 focuses on a series of simple alkyl groups and two of the aryl halides, a subset of the overall data set, to compare the previously described coupling methods. Primary, secondary, and tertiary examples were tested, and results using bromides **1** and **2** are shown. For the Negishi coupling, many simple primary and secondary alkyl organozinc reagents are readily available and worked well to install alkyl groups, such as *n*-hexyl, cyclopropyl (**5** and **6**), *iso*-propyl (**7** and **8**), and benzyl (**9** and **10**). The nickel/photoredox BF_3K coupling performed well for secondary alkyl groups, such as *iso*-propyl (**7** and **8**) and cyclopentyl, but not for cyclopropyl or α-methylbenzyl groups. Primary BF_3K salts with remote electron-withdrawing groups were not tolerated (**11** and **12**), but primary benzylic and primary all-carbon BF_3K salts gave some product. Methyl and *tert*-butyl gave no product. Compared with the BF_3K photoredox method, the Suzuki coupling using BF_3K salts worked well across the series of primary alkyl reagents. Methyl and cyclopropyl group installation was successful. However, this method did not perform well for the installation of most secondary groups, demonstrating the complementarity of the two methods. The MIDA boronate coupling gave moderate-to-good yields for a few reactions with bromide **2** to incorporate methyl, *n*-butyl, and cyclopropyl groups, but otherwise, yields were low (<20%). Additionally, alkyl MIDA boronate availability was a significant constraint, the most limited of the methods. Product yields were also low for the nickel/photoredox decarboxylative coupling in this series (all <10%). While discouraging given the abundance of alkyl carboxylic acids utilized in pharmaceutical research, this result was not surprising because this reaction performs best with stabilized α-oxy and α-amino carboxylic acid building blocks.[31,32] Finally, both CEC methods delivered moderate-to-good yields with primary and secondary alkyl bromides. Methylation was possible using this photoredox method, but *tert*-butyl and benzylic groups were unsuccessful in both methods.

Both bromides **1** and **2** worked well in this study and revealed differences in monomer reactivity. Dehalogenation was a byproduct observed in many methods; however, yields for some reactions with **2** were further suppressed through the formation of regioisomeric dehalogenation−Minisci reaction products.[13] This byproduct pathway was only observed in nickel-catalyzed radical methods and represents a potential limitation of these platforms.

The obvious gap is tertiary groups, as seen by the *tert*-butyl column (Figure 2). No method that we evaluated was able to

https://dx.doi.org/10.1021/acsmedchemlett.0c00093
ACS Med. Chem. Lett. 2020, 11, 597−604

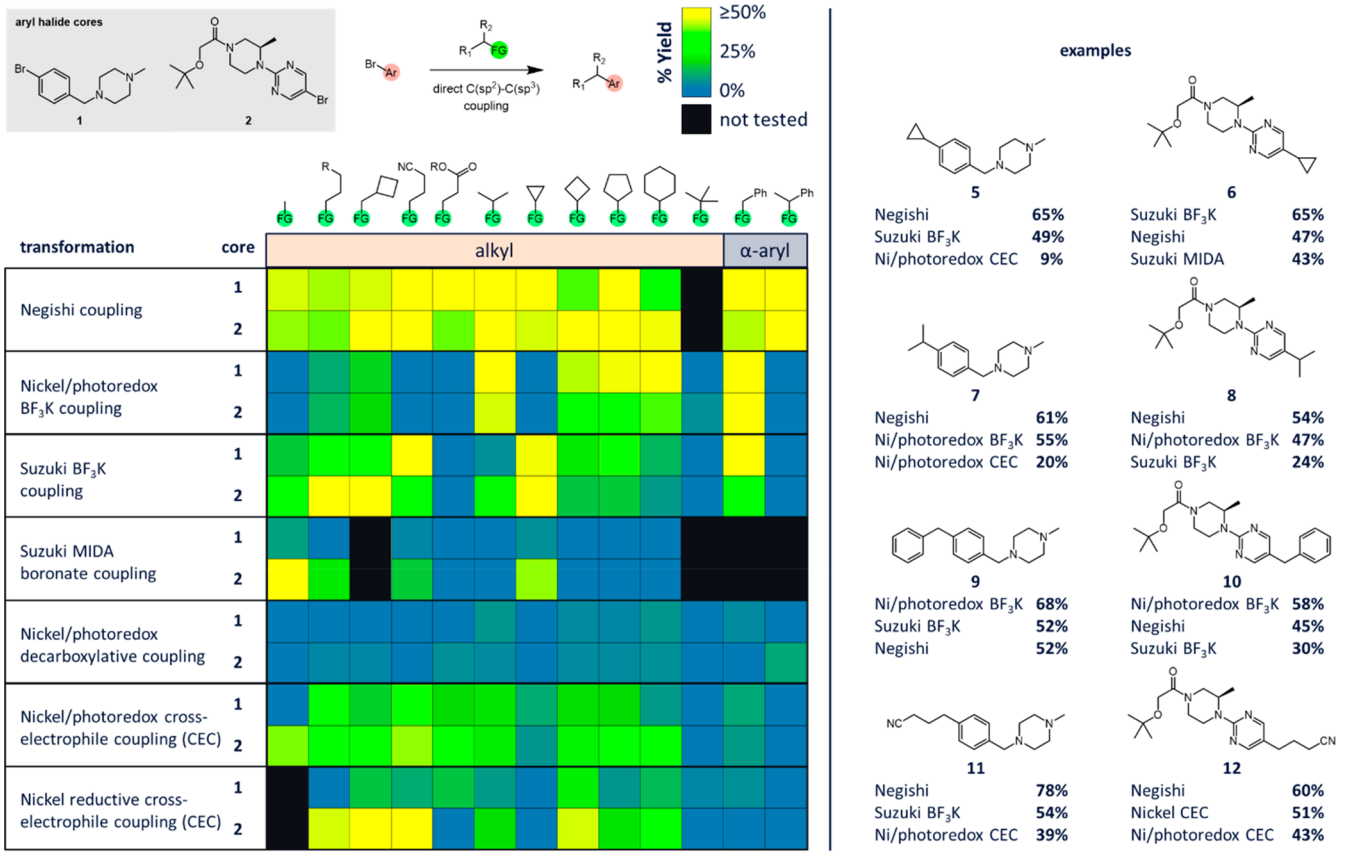


Figure 2. Comparison of methods using simple alkyl groups. For the linear alkyl Negishi coupling (column 2), R = *n*-propyl. For all other methods (column 2), R = methyl. For the pendant-ester Negishi coupling (column 5), R = ethyl. For all other methods (column 5), R = methyl. Negishi coupling: 5% Pd-PEPPSI-IPent^{Cl}, 0.09 M THF. Nickel/photoredox BF_3K coupling: 2% $Ir(dF(CF_3)ppy)_2(bpy)PF_6$, 5% $NiCl_2(dtbbpy)$, 2 equiv of 2,6-lutidine, 0.05 M 4:1 dioxane/DMA, 450 nm LEDs. Nickel/photoredox BF_3K coupling (tertiary examples): 1% $Ir(dF(CF_3)ppy)_2(bpy)PF_6$, 10% $Ni(TMHD)_2$, 10% $ZnBr_2$, 1 equiv of K_2HPO_4, 0.1 M DMA, 450 nm LEDs. Suzuki BF_3K coupling: 5% CataCXium A Pd G3, 3 equiv of Cs_2CO_3 (7 M in H_2O), 0.2 M toluene, 100 °C. Suzuki MIDA coupling: 5% SPhos Pd G3, 7.5 equiv of K_3PO_4 (3 M in H_2O), 0.5 M dioxane, 60 °C. Nickel/photoredox decarboxylative coupling: 2% $Ir(dF(CH_3)ppy)_2(dtbbpy)PF_6$, 5% $NiCl_2(dtbbpy)$, 1.5 equiv of BTMG, 0.1 M DMSO, 450 nm LEDs. Nickel/photoredox decarboxylative coupling (phenylacetic acid derivatives): 2% $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, 5% $NiCl_2(dtbbpy)$, 1.5 equiv of Cs_2CO_3, 0.1 M DMA, 450 nm LEDs. Nickel/photoredox CEC: 1% $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, 0.5% $NiCl_2(dtbbpy)$, 1.2 equiv of $(TMS)_3SiH$, 2 equiv of 2,6-lutidine, 0.13 M DME, 450 nm LEDs. Nickel-catalyzed reductive CEC: 7% $NiCl_2$-glyme, 7% ligand, 25% NaI, 2 equiv of Zn flake, 10% TFA, 0.015 M DMA, 60 °C, ligand = 4,4′-di-*tert*-butyl-2,2′-bipyridine, [2,2′-bipyridine]-6-carboximidamide hydrochloride or (2*Z*,6*Z*)-*N*′2,*N*′6-dicyanopyridine-2,6-bis(carboximidamide).

install a *tert*-butyl group. Additionally, whereas a benzyl group was coupled efficiently by several methods (**9** and **10**), an *α*-methylbenzyl group was challenging for all of the methods except the Negishi coupling. Cyclopropyl installation was also low-yielding for many methods but proceeded smoothly when a Negishi or BF_3K Suzuki coupling was utilized (**5** and **6**). The reactivity for the methyl group and the ester-containing group was very method-dependent. Encouragingly, several of the alkyl groups in this figure worked in most of the methods, including the *n*-butyl, *iso*-propyl, remote nitrile (**11** and **12**), and cycloalkanes (excluding cyclopropyl).

The installation of alkyl groups containing polar functionality, such as ethers or amines, is often pursued to tune the properties of or add functional handles to drug candidates. Thus we analyzed a subset of data focusing on **3** and **4** to compare each method's ability to install a series of primary and secondary alkyl groups incorporating polar functionality proximal or distal to an aryl ring (Figure 3). For the Negishi coupling, the commercial availability and the stability of organozinc reagents were limiting factors. The Negishi coupling worked well for the groups tested with **3** and **4** (reagents that were commercially available or stable upon *in situ* formation).[21−23] This highlights a limitation of this method compared with other coupling methods, such as the BF_3K couplings, decarboxylative coupling, and CEC, where the broader availability of monomers enables the synthesis of a wider array of compounds.

The nickel/photoredox BF_3K salt coupling delivered moderate-to-good yields for most of these alkyl groups. Only the primary examples with distal electron-withdrawing groups and the 3-oxetane reagent failed. 3-Tetrahydrofuran, 4-tetrahydropyran (**13** and **14**), and a series of boc-protected amines (**15** and **16**) were all readily installed. Importantly, *α*-oxy and *α*-amino BF_3K salts were also tolerated under the reaction conditions (**17**−**20**). In contrast, the Suzuki coupling with alkyl BF_3K salts delivered coupling products for primary examples but generally failed with secondary BF_3K salts. This reactivity again highlights the complementarity of the two BF_3K methods.

The decarboxylative coupling worked well with protected *α*-amino acids and **3** (e.g., **19**). Some carboxylic acids, like tetrahydropyran-4-carboxylic acid and *N*-boc-4-piperidinecar-

https://dx.doi.org/10.1021/acsmedchemlett.0c00093
ACS Med. Chem. Lett. 2020, 11, 597−604

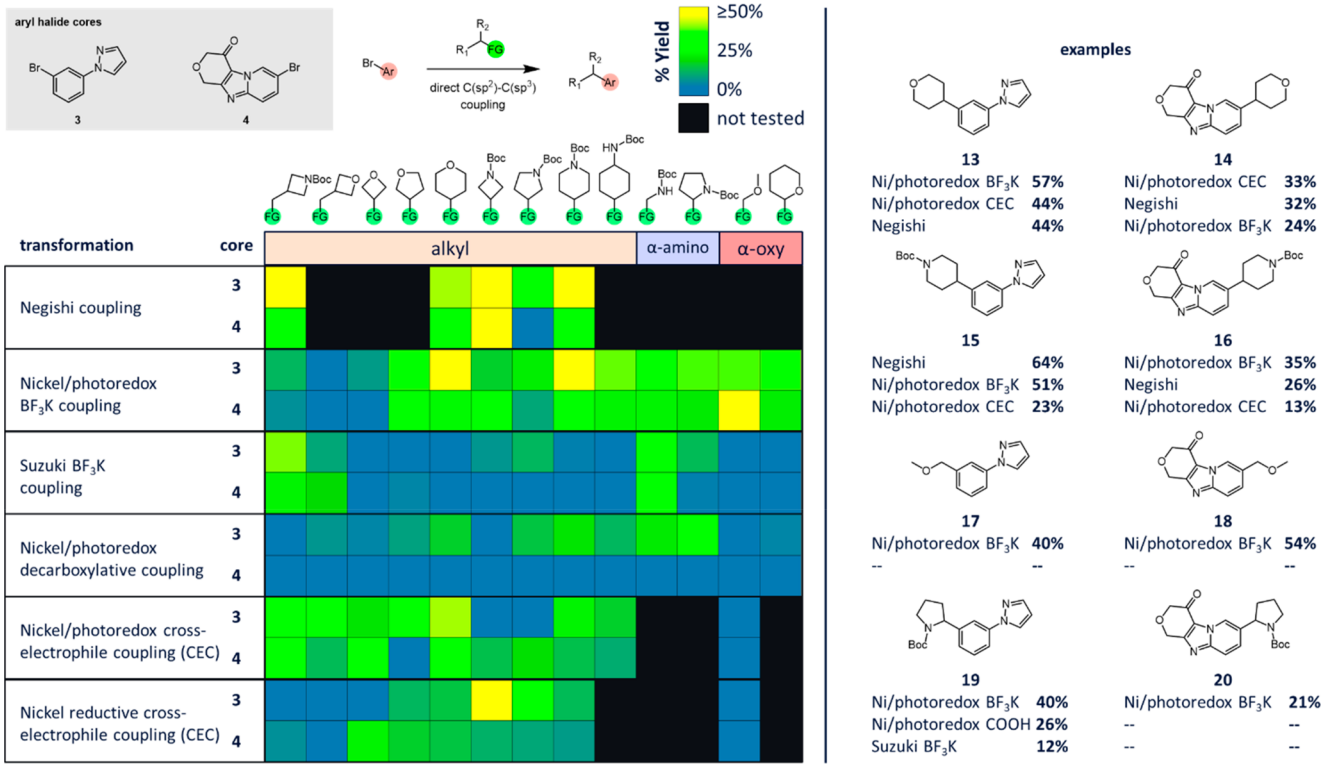


Figure 3. Installing alkyl groups containing polar functionality. Negishi couplings: 5% Pd-PEPPSI-IPent^{Cl}, 0.09 M THF. Negishi couplings (*in situ* prepared organozincs): 5% SPhos Pd G4, 0.09 M DMA. Nickel/photoredox BF_3K couplings: 2% $Ir(dF(CF_3)ppy)_2(bpy)PF_6$, 5% $NiCl_2$(dtbbpy), 2 equiv of 2,6-lutidine, 0.05 M 4:1 dioxane/DMA, 450 nm LEDs. Suzuki BF_3K couplings: 5% CataCXium A Pd G3, 3 equiv of Cs_2CO_3 (7 M in H_2O), 0.2 M toluene, 100 °C. Nickel/photoredox decarboxylative couplings (α-alkyl carboxylic acids): 2% $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, 5% $NiCl_2$(dtbbpy), 1.5 equiv of BTMG, 0.1 M DMSO, 450 nm LEDs. Nickel/photoredox decarboxylative couplings (α-amino and α-oxy carboxylic acids): 2% $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, 5% $NiCl_2$(dtbbpy), 1.5 equiv of Cs_2CO_3, 0.1 M DMA, 450 nm LEDs. Nickel/photoredox CEC: 1% $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, 0.5% $NiCl_2$(dtbbpy), 1.2 equiv of $(TMS)_3SiH$, 2 equiv of 2,6-lutidine, 0.13 M DME, 450 nm LEDs. Nickel-catalyzed reductive CEC: 7% $NiCl_2$-glyme, 7% ligand, 25% NaI, 2 equiv of Zn flake, 10% TFA, 0.015 M DMA, 60 °C, ligand = 4,4′-di-*tert*-butyl-2,2′-bipyridine, [2, 2′-bipyridine]-6-carboximidamide hydrochloride or (2*Z*,6*Z*)-*N*′2,*N*′6-dicyanopyridine-2,6-bis(carboximidamide).

boxylic acid, gave product under modified reaction conditions (**13** and **15**, respectively), but most examples gave low yields.[13,32] Surprisingly, with **4**, the desired decarboxylative cross-couplings failed, and only regioisomeric products were observed. Presumably these products are produced through a dehalogenation−Minisci reaction route, as seen with **2**, representing a liability of this method.[13] The formation of these byproducts under the decarboxylative coupling conditions was surprising because these byproducts were not observed for other methods studied with **4**. (See the SI for details.)

The photoredox CEC gave reasonable yields with most alkyl bromides tested and both aryl bromides. A notable advantage of this reaction is that it does not discriminate between primary and secondary alkyl bromides. The reductive CEC also worked well for secondary alkyl bromides. Notable limitations of both CEC methods are alkyl bromides with α-heteroatoms (due to the availability, stability, and reactivity). Methoxymethyl bromide was tested in both methods and failed to form **17** or **18** (Figure 3).[36] The MIDA boronate Suzuki coupling was left out of Figure 3 because the two alkyl building blocks available failed to give product. This illustrates a challenge when adopting new methodologies; the building blocks are not always readily available.

Key alkyl coupling products, which were formed in good yields using multiple coupling methods, include 4-tetrahydropyran (**13** and **14**, Figure 3) and 4-*N*-boc-piperidine (**15** and **16**). We have observed that these groups are popular targets among medicinal chemists, and they were formed using the Negishi, nickel/photoredox BF_3K, and CEC methods. Whereas there was good method overlap for many couplings, there were also notable differences. In general, primary alkyl coupling partners possessing distal withdrawing groups only worked under the Negishi coupling (when tested), Suzuki coupling, and nickel/photoredox CEC. Oxetane was also a challenging group to install. Palladium-catalyzed methods failed to furnish 3-oxetane coupling products; the CEC methods using 3-bromooxetane worked modestly. Finally, α-oxy alkyl coupling partners were a limitation of most methods when factoring in the commercial availability or the stability of the necessary reagents. Only the nickel/photoredox BF_3K coupling was able to install a methoxymethyl group, as shown in Figure 3 (**17** and **18**). The same conditions also installed the 2-tetrahydropyran moiety on bromides **3** and **4**, which could not be done with other methods.

An advantage of the two CEC methods over most methods studied here is building block availability. Many structurally diverse alkyl bromides are commercially available, which is attractive for SAR studies. Furthermore, the literature conditions appear to be quite general.[8,13,24,34] When directly comparing the two CEC methods, both worked well with a variety of primary and secondary alkyl groups, regardless of functional groups (Figure 4a). As previously discussed, tertiary alkyl halides and benzyl groups were not tolerated (Figure

https://dx.doi.org/10.1021/acsmedchemlett.0c00093
ACS Med. Chem. Lett. 2020, 11, 597−604

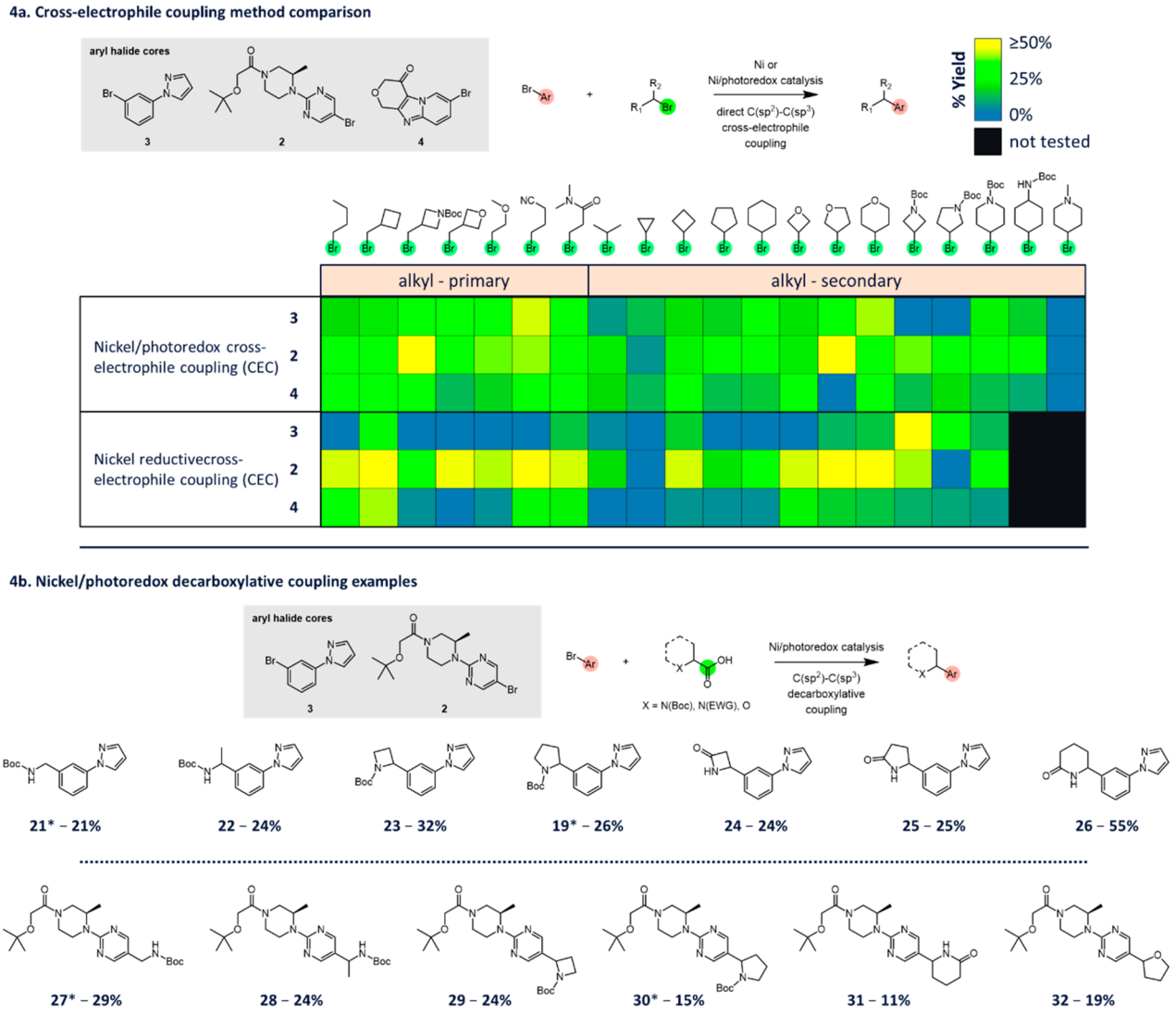


Figure 4. Showcase of methods with high monomer availability. (a) Comparison of two CEC methods and (b) use of unique carboxylic acid building blocks. (4a) Nickel/photoredox CEC: 1% $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, 0.5% $NiCl_2(dtbbpy)$, 1.2 equiv of $(TMS)_3SiH$, 2 equiv of 2,6-lutidine, 0.13 M DME, 450 nm LEDs. Nickel-catalyzed reductive CEC: 7% $NiCl_2$-glyme, 7% ligand, 25% NaI, 2 equiv of Zn flake, 10% TFA, 0.015 M DMA, 60 °C, ligand = 4,4′-di-*tert*-butyl-2,2′-bipyridine, [2,2′-bipyridine]-6-carboximidamide hydrochloride, or (2*Z*,6*Z*)-*N*′2, *N*′6-dicyanopyridine-2,6-bis(carboximidamide). (4b) Asterisks (*) denote alkyl group overlap with another method in this study. Nickel/photoredox decarboxylative coupling: 2% $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$, 5% $NiCl_2(dtbbpy)$, 1.5 equiv of Cs_2CO_3, 0.1 M DMA, 450 nm LEDs.

2).[37] The nickel/photoredox CEC conditions gave some product in most reactions across the 3 (hetero)aryl bromides and 20 alkyl bromides shown here, demonstrating its library-amenable nature. The reductive CEC was more variable; the reactions worked either very well or poorly. As a result, the two methods showed nice complementarity. For example, most reactions with **3** under the reductive CEC conditions failed; however, small nitrogen-containing rings, like protected azetidine and pyrrolidine, worked well. In contrast, those reactions with **3** failed in the photoredox CEC, but most other alkyl bromides coupled successfully. The protected azetidine and pyrrolidine did work with bromides **2** and **4**. Considering the similarities between the methods, these trends would be hard to predict. A limitation of the photoredox CEC method observed during this study is that basic amines were not tolerated, as seen in the example of 4-bromo-*N*-methylpiperidine. Similarly, a limitation of the reductive coupling method observed during this study was cyclopropane installation, which was possible under photoredox conditions, albeit in low yields, <15%.

Like the CEC methods, the nickel/photoredox decarboxylative coupling is privileged by alkyl carboxylic acid building block diversity and availability. Decarboxylative coupling is a low-barrier reaction to install many alkyl groups arising from α-oxy and α-amino carboxylic acid building blocks; some examples are shown in Figure 4b.[13,16,31,32] Amino acids like boc-L-proline and boc-L-alanine could be used to install α-amino alkyl groups, which could be functionalized in downstream steps (**19**, **21**−**23**, **27**−**30**). Carboxylic acids with pendant lactams, building blocks unique to this monomer class, enabled the installation of cyclic amide polar groups (**24**−**26**, **31**). α-Oxy carboxylic acids, such as tetrahydro-2-furoic acid, enabled the synthesis of ether-containing products that are inaccessible by other methods in this study (**32**). For analogue synthesis with the decarboxylative cross coupling, success was mixed. We minimized the number of reaction conditions in this study to realize parallel synthesis efficiencies,

https://dx.doi.org/10.1021/acsmedchemlett.0c00093
ACS Med. Chem. Lett. 2020, 11, 597−604

but reaction optimization can expand the scope for some alkyl carboxylic acids. This has been shown by other groups.[13,16,32,33] The wide range of monomers available and the reactivity trends observed during this study make the decarboxylative coupling a complementary method to many others studied here.

When considering the number of successful reactions (defined as ≥10% yield) versus the total number of reactions, the methods showed a wide range of success rates, from 21 to 86% (Supplementary Table 1). From the data presented herein, it was observed that 332 of the 658 reactions were successful (50%).[38] This success rate is on par with heavily used reactions in medicinal chemistry, such as C−N couplings.[39−41] In aggregate, the trend seems to indicate that the steric environment affects the reactivity, with primary alkyl groups showing >50% success rate, secondary alkyl groups showing just under 50%, and tertiary alkyl groups showing <20%.[41] Notable deviations were the nickel/photoredox BF_3K coupling and the Negishi coupling. Electronic factors seemed to be dominant for the nickel/photoredox BF_3K coupling when comparing alkyl groups that coupled well with those that did not, which is consistent with the primary literature.[26−28] For the Negishi coupling, the secondary alkyl group coupling success rate was higher than the primary alkyl success rate (96% versus 83%).[42]

In summary, a comparison of seven direct $C(sp^2)-C(sp^3)$ coupling methods has been conducted to inform medicinal chemists of the capabilities of these reactions as well as to guide chemists to methods with higher chances of success for future syntheses. The methods included traditional palladium-catalyzed methods, such as the Suzuki and Negishi couplings, as well as emerging methods, such as the nickel-catalyzed reductive CEC and three nickel/photoredox dual-catalysis methods. The MIDA boronate Suzuki coupling performed poorly for all but a few small alkyl groups and has very limited reagent availability. In contrast, the Suzuki coupling using BF_3K salts has broader reagent availability and showed good general reactivity for primary alkyl groups, regardless of functional groups. Demonstrating nice complementarity, secondary alkyl BF_3K salts show consistently good reactivity in the nickel/photoredox coupling. The Negishi coupling worked very well for all of the alkyl groups that were tested; however, a lack of diversity in available reagents limits the generality of the method. The nickel/photoredox decarboxylative coupling benefited from unique substrates that are not available to the other methods but only performed consistently with groups containing α-heteroatoms. Both CEC methods have broad building block availability and general substrate scopes; the presence of basic amines, tertiary groups, and benzyl groups are the only limitations.

General guidelines, on the basis of this study, recommending methods for each alkyl group type, are outlined as follows. The availability of the desired building block(s) should be considered when choosing a method. For a methyl group, the best methods are Negishi, Suzuki BF_3K coupling, Suzuki MIDA coupling, or nickel/photoredox CEC. For primary alkyl groups, Negishi, Suzuki BF_3K coupling, or nickel/photoredox CEC is the most reliable. For secondary alkyl groups, Negishi, nickel/photoredox BF_3K coupling, nickel/photoredox CEC, and nickel reductive CEC give the best results. For benzylic groups, the Negishi, nickel/photoredox BF_3K coupling, or Suzuki BF_3K couplings are best. α-Oxy alkyl groups couple the best with nickel/photoredox BF_3K or nickel/photoredox decarboxylative couplings. For α-amino alkyl groups, nickel/photoredox BF_3K, nickel/photoredox decarboxylative, or Suzuki BF_3K couplings are recommended. Secondary benzylic and *tert*-butyl groups are challenging to couple using these methods.

The analysis of the complete data set shows that with a combined reaction success rate of 50%, $C(sp^3)-C(sp^2)$ coupling has the potential to be as successful as C−N couplings in a medicinal chemistry setting. Thus this comparison provides a guide to enable the installation of a variety of alkyl groups on heteroaromatic rings. Because no alkyl group worked in all methods, the method(s) with the highest chance of success in installing a desired alkyl group should be chosen based on the data presented herein. Additionally, this study highlights a few remaining challenges for the community to focus on, such as the direct installation of a *tert*-butyl group and the limited availability of building blocks for many methods, such as groups containing basic amines. We hope that this work will inspire academic groups to incorporate diverse substrates and medicinal-chemistry-relevant structures in their methodology development. In addition, we hope that this Letter will encourage all medicinal chemists to incorporate newly published methods into their "synthetic toolbox" to enable access to more structural diversity in discovery chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.0c00093.

Full data table used for figure creation (XLSX)

General experimental procedures, specific synthetic details, and characterization of the compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Amanda W. Dombrowski − *AbbVie, Inc., North Chicago, Illinois 60064, United States;* orcid.org/0000-0001-9596-263X; Email: amanda.dombrowski@abbvie.com

Nathan J. Gesmundo − *AbbVie, Inc., North Chicago, Illinois 60064, United States*; Email: nathan.gesmundo@abbvie.com

Authors

Ana L. Aguirre − *AbbVie, Inc., North Chicago, Illinois 60064, United States*

Katerina A. Sarris − *AbbVie, Inc., North Chicago, Illinois 60064, United States*

Jonathon M. Young − *AbbVie, Inc., North Chicago, Illinois 60064, United States*

Andrew R. Bogdan − *AbbVie, Inc., North Chicago, Illinois 60064, United States;* orcid.org/0000-0003-0913-0779

M. Cynthia Martin − *Northwestern University Center for Molecular Innovation and Drug Discovery, Evanston, Illinois 60208, United States*

Shasline Gedeon − *Florida A&M University College of Pharmacy and Pharmaceutical Sciences, Tallahassee, Florida 32307, United States*

Ying Wang − *AbbVie, Inc., North Chicago, Illinois 60064, United States;* orcid.org/0000-0001-9516-3483

Complete contact information is available at: https://pubs.acs.org/10.1021/acsmedchemlett.0c00093

https://dx.doi.org/10.1021/acsmedchemlett.0c00093
ACS Med. Chem. Lett. 2020, 11, 597−604

Author Contributions

[‖]A.W.D. and N.J.G. contributed equally to this work. The manuscript was written by A.W.D. and N.J.G. A.W.D., N.J.G., A.L.A., K.A.S., J.M.Y., A.R.B., M.C.M., and S.G. collected data. Y.W. contributed intellectually to the work. All authors have given approval to the final version of the manuscript.

Funding

S.G. was supported by a Department of Education award, Minority Science and Engineering Improvement Program (MSEIP), Capacity Competitiveness Enhancement Model (CCEM), award no. P120A160115- Florida A&M University.

Notes

The authors declare no competing financial interest.

A.W.D., N.J.G., A.L.A., K.A.S., J.M.Y., A.R.B., and Y.W. are employees of AbbVie. M.C.M. was a postdoctoral researcher, and S.G. was an intern at the time of the study. The design, study conduct, and financial support for this research were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.

■ ACKNOWLEDGMENTS

We thank the following AbbVie scientists for technical support: Ian Marsden, Rick Yarbrough, Leena Bhatt, Anita McGreal, and Frank Wagenaar.

■ ABBREVIATIONS

DST, design−synthesis−test; SAR, structure activity relationship; CEC, cross-electrophile coupling; BF_3K, potassium trifluoroborate salt; MIDA, *N*-methyliminodiacetic acid

■ REFERENCES

(1) Boström, J.; Brown, D. G.; Young, R. J.; Keserü, G. M. Expanding the Medicinal Chemistry Synthetic Toolbox. *Nat. Rev. Drug Discovery* **2018**, *17*, 709−727.

(2) 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*, 4443−4458.

(3) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54*, 3451−3479.

(4) Boström, J.; Brown, D. G. Stuck in a Rut with Old Chemistry. *Drug Discovery Today* **2016**, *21*, 701−703.

(5) Campbell, I. B.; Macdonald, S. J. F.; Procopiou, P. A. Medicinal chemistry in Drug Discovery in Big Pharma: Past. *Drug Discovery Today* **2018**, *23*, 219−234.

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

(7) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752−6756.

(8) Hansen, E. C.; Pedro, D. J.; Wotal, A. C.; Gower, N. J.; Nelson, J. D.; Caron, S.; Weix, D. J. New Ligands for Nickel Catalysis from Diverse Pharmaceutical Heterocycle Libraries. *Nat. Chem.* **2016**, *8*, 1126−1130.

(9) Palaychuk, N.; DeLano, T. J.; Boyd, M. J.; Green, J.; Bandarage, U. K. Synthesis of Cycloalkyl Substituted 7-Azaindoles via Photoredox Nickel Dual Catalytic Cross-Coupling in Batch and Continuous Flow. *Org. Lett.* **2016**, *18*, 6180−6183.

(10) Knauber, T.; Chandrasekaran, R.; Tucker, J. W.; Chen, J. M.; Reese, M.; Rankic, D. A.; Sach, N.; Helal, C. Ru/Ni Dual Catalytic Desulfinative Photoredox C_{sp^2}−C_{sp^3} Cross-Coupling of Alkyl Sulfinate Salts and Aryl Halides. *Org. Lett.* **2017**, *19*, 6566−6569.

(11) Hsieh, H.-W.; Coley, C. W.; Baumgartner, L. M.; Jensen, K. F.; Robinson, R. I. Photoredox Iridium−Nickel Dual-Catalyzed Decarboxylative Arylation Cross-Coupling: From Batch to Continuous Flow via Self-Optimizing Segmented Flow Reactor. *Org. Process Res. Dev.* **2018**, *22*, 542−550.

(12) Raynor, K. D.; May, G. D.; Bandarage, U. K.; Boyd, M. J. Generation of Diversity Sets with High sp^3 Fraction Using the Photoredox Coupling of Organotrifluoroborates and Organosilicates with Heteroaryl/Aryl Bromides in Continuous Flow. *J. Org. Chem.* **2018**, *83*, 1551−1557.

(13) Zhang, R.; Li, G.; Wismer, M.; Vachal, P.; Colletti, S. L.; Shi, Z. Profiling and Application of Photoredox $C(sp^3)$-$C(sp^2)$ Cross-Coupling in Medicinal Chemistry. *ACS Med. Chem. Lett.* **2018**, *9*, 773−777.

(14) Brill, Z. G.; Ritts, C. B.; Mansoor, U. F.; Sciammetta, N. Continuous Flow Enables Metallaphotoredox Catalysis in a Medicinal Chemistry Setting: Accelerated Optimization and Library Execution of a Reductive Coupling between Benzylic Chlorides and Aryl Bromides. *Org. Lett.* **2020**, *22*, 410−416.

(15) Mennie, K. M.; Vara, B. A.; Levi, S. M. Reductive sp^3−sp^2 Coupling Reactions Enable Late-Stage Modification of Pharmaceuticals. *Org. Lett.* **2020**, *22*, 556−559.

(16) Shea, M. D.; Mansoor, U. F.; Hopkins, B. A. A Metallaphotoredox Method for the Expansion of Benzyl SAR on Electron-Deficient Amines. *Org. Lett.* **2020**, *22*, 1052−1055.

(17) VanHeyst, M. D.; Qi, J.; Roecker, A. J.; Hughes, J. M. E.; Cheng, L.; Zhao, Z.; Yin, J. Continuous Flow-Enabled Synthesis of Bench-Stable Bicyclo[1.1.1]pentane Trifluoroborate Salts and Their Utilization in Metallaphotoredox Cross-Couplings. *Org. Lett.* **2020**, *22*, 1648−1654.

(18) Knapp, D. M.; Gillis, E. P.; Burke, M. D. A General Solution for Unstable Boronic Acids: Slow-Release Cross-Coupling from Air-Stable MIDA Boronates. *J. Am. Chem. Soc.* **2009**, *131*, 6961−6963.

(19) Molander, G. A.; Gormisky, P. E. Cross-Coupling of Cyclopropyl- and Cyclobutyltrifluoroborates with Aryl and Heteroaryl Chlorides. *J. Org. Chem.* **2008**, *73*, 7481−7485.

(20) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. Efficient Cross-Coupling of Secondary Alkyltrifluoroborates with Aryl Chlorides−Reaction Discovery Using Parallel Microscale Experimentation. *J. Am. Chem. Soc.* **2008**, *130*, 9257−9259.

(21) Pompeo, M.; Froese, R. D. J.; Hadei, N.; Organ, M. G. Pd-PEPPSI-$IPent^{Cl}$: A Highly Effective Catalyst for the Selective Cross-Coupling of Secondary Organozinc Reagents. *Angew. Chem., Int. Ed.* **2012**, *51*, 11354−11357.

(22) Alonso, N.; Miller, L. Z.; de M. Muñoz, J. M.; Alcázar, J.; McQuade, D. T. Continuous Synthesis of Organozinc Halides Coupled to Negishi Reactions. *Adv. Synth. Catal.* **2014**, *356*, 3737−3741.

(23) Berton, M.; Huck, L.; Alcázar, J. On-demand Synthesis of Organozinc Halides Under Continuous Flow Conditions. *Nat. Protoc.* **2018**, *13*, 324−334.

(24) Weix, D. J. Methods and Mechanisms for Cross-Electrophile Coupling of Csp^2 Halides with Alkyl Electrophiles. *Acc. Chem. Res.* **2015**, *48*, 1767−1775.

(25) Hansen, E. C.; Li, C.; Yang, S.; Pedro, D.; Weix, D. J. Coupling of Challenging Heteroaryl Halides with Alkyl Halides via Nickel-Catalyzed Cross-Electrophile Coupling. *J. Org. Chem.* **2017**, *82*, 7085−7092.

(26) Tellis, J. C.; Primer, D. N.; Molander, G. A. Single-electron transmetalation in organoboron cross-coupling by photoredox/nickel dual catalysis. *Science* **2014**, *345*, 433−436.

(27) 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*, 2195−2198.

(28) Karakaya, I.; Primer, D. N.; Molander, G. A. Photoredox Cross-Coupling: Ir/Ni Dual Catalysis for the Synthesis of Benzylic Ethers. *Org. Lett.* **2015**, *17*, 3294−3297.

https://dx.doi.org/10.1021/acsmedchemlett.0c00093
ACS Med. Chem. Lett. 2020, 11, 597−604

(29) Primer, D. N.; Molander, G. A. Enabling the Cross-Coupling of Tertiary Organoboron Nucleophiles through Radical-Mediated Alkyl Transfer. *J. Am. Chem. Soc.* **2017**, *139*, 9847−9850.
(30) Milligan, J. A.; Phelan, J. P.; Badir, S. O.; Molander, G. A. Alkyl Carbon-Carbon Bond Formation by Nickel/Photoredox Cross-Coupling. *Angew. Chem., Int. Ed.* **2019**, *58*, 6152−6163.
(31) 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 sp^3-Carbons with Aryl Halides. *Science* **2014**, *345*, 437−440.
(32) 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*, 624−627.
(33) Le, C.; Wismer, M. K.; Shi, Z.-C.; Zhang, R.; Conway, D. V.; Li, G.; Vachal, P.; Davies, I. W.; MacMillan, D. W. C. A General Small-Scale Reactor To Enable Standardization and Acceleration of Photocatalytic Reactions. *ACS Cent. Sci.* **2017**, *3*, 647−653.
(34) Zhang, P.; Le, 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*, 8084−8087.
(35) Vasudevan, A.; Bogdan, A. R.; Koolman, H. F.; Wang, Y.; Djuric, S. W. Chapter One- Enabling Chemistry Technologies and Parallel Synthesis—Accelerators of Drug Discovery Programmes. *Prog. Med. Chem.* **2017**, *56*, 1−35.
(36) An example reported in ref 10 suggests that methoxymethyl chloride may be a suitable replacement in the nickel/photoredox CEC.
(37) Examples reported in ref 14 suggest that benzylic chlorides may work in the nickel/photoredox CEC.
(38) See the Supporting Information for the entire 796 reaction dataset. The 658 reaction subset used in this analysis represents the reactions run with the four aryl bromides and the alkyl groups presented in Figures 2−4.
(39) Buitrago Santanilla, A.; Regalado, E. L.; Pereira, T.; Shevlin, M.; Bateman, K.; Campeau, L.-C.; Schneeweis, J.; Berritt, S.; Shi, Z.-C.; Nantermet, P.; Liu, Y.; Helmy, R.; Welch, C. J.; Vachal, P.; Davies, I. W.; Cernak, T.; Dreher, S. D. Nanomole-scale high-throughput chemistry for the synthesis of complex molecules. *Science* **2015**, *347*, 49−53.
(40) Kutchukian, P. S.; Dropinski, J. F.; Dykstra, K. D.; Li, B.; DiRocco, D. A.; Streckfuss, E. C.; Campeau, L.-C.; Cernak, T.; Vachal, P.; Davies, I. W.; Krska, S. W.; Dreher, S. D. Chemistry Informer Libraries: a Chemoinformatics Enabled Approach to Evaluate and Advance Synthetic Methods. *Chem. Sci.* **2016**, *7*, 2604−2613.
(41) AbbVie. North Chicago, IL. Internal unpublished data, 2020.
(42) See the Supporting Information, Supplementary Table 1 for the success rates of coupling methods by building block class.

https://dx.doi.org/10.1021/acsmedchemlett.0c00093
ACS Med. Chem. Lett. 2020, 11, 597−604