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## Three-Component Olefin Dicarbofunctionalization Enabled by Nickel/Photoredox Dual Catalysis

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### Abstract

An intermolecular, photocatalytic dicarbofunctionalization (DCF) of olefins enabled by the merger of Giese-type addition with Ni/photoredox dual catalysis has been realized. Capitalizing on the rapid addition of 3° radicals to alkenes and their reluctance toward single electron metalation to Ni complexes, regioselective alkylation and arylation of olefins is possible. This dual catalytic method not only permits elaborate species to be assembled from commodity materials, but also allows quaternary and tertiary centers to be installed in a singular, chemoselective olefin difunctionalization. This multi-component process occurs under exceptionally mild conditions, compatible with a diverse range of functional groups and synthetic handles such as pinacolboronate esters. This technology was directly applied to the synthesis of an intermediate to a preclinical candidate (TK-666) and its derivatives.

### Graphical Abstract

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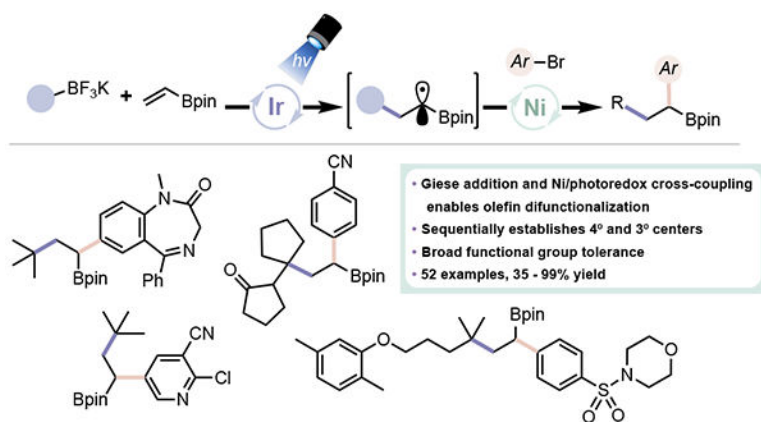
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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and spectral data (PDF)

The authors declare no competing financial interest.



## Introduction

Alkenes are versatile commodity feedstocks that can be rapidly converted into functional group-rich species via classical methods (Figure 1).<sup>1</sup> They can be readily diversified using an array of vicinal difunctionalization reactions to establish 1,2-substituted alkanes (in some cases with excellent stereochemical fidelity). An attractive subset of vicinal functionalization processes that is of increasing focus are vicinal alkene dicarbofunctionalization (DCF) reactions. DCF allows olefins to be appended to two different carbon fragments, thus enabling a dramatic increase in molecular complexity. Classically, DCF has been accomplished with organometallic nucleophiles and electrophilic olefins or via cycloaddition onto activated alkenes (e.g., Diels-Alder reactions).<sup>2</sup> Recently, methods for olefin diarylation or arylation/alkylation via palladium- or nickel catalysis have been developed.<sup>3</sup> Although milestones in DCF, these protocols typically rely on stoichiometric reductants to sustain catalytic cycles and, as such, are less than ideal. Further, many still rely on organometallics that display sensitivities to a variety of functional groups. In addition, Csp<sup>3</sup>-hybridized nucleophiles are rare in transition metal-mediated DCF because of their tendency to undergo facile  $\beta$ -hydride elimination, protonation, and/or dimerization after metalation.<sup>4</sup> Additionally, recent advances in radical chemistry have facilitated other DCF approaches (Figure 1).<sup>5</sup>

Alkyl radicals can be viewed as surrogates of Csp<sup>3</sup>-hybridized nucleophiles that avoid off-target polar reactivity while retaining the ability to form C–C bonds with olefins.<sup>6</sup> Further, alkyl radicals can be engaged by Ni in place of more traditional Pd catalysts for DCF, mitigating the propensity of  $\beta$ -hydride elimination.<sup>7</sup> With these aspects in mind and the reliability of generating alkyl radicals using visible light-activated catalysts,<sup>8</sup> the merger of Ni/photoredox dual catalysis<sup>9</sup> and Giese-type addition for DCF was considered.<sup>10</sup>

The crux of this approach is a series of well-orchestrated, radical-mediated bond-forming processes. Specifically, the following series of events (Figure 2) was envisioned: (1) visible light-mediated photoexcitation of the appropriate photocatalyst **I** to its excited state **II**; (2) reductive quenching via SET oxidation of radical precursor **IV**, (3) homolytic fragmentation of **IV** followed by Giese-type addition<sup>11</sup> of the resulting radical **V** onto an olefin **VI** to generate **VII**; (4) Single-electron metalation of **VII** onto Ni<sup>0</sup> species **VIII** to generate

alkylnickel(I) adduct **IX**;<sup>12</sup> (5) Oxidative addition of aryl halides **X** onto **IX** to give Ni<sup>III</sup> complex **XI**; (6) Reductive elimination to give DCF product **XII** and Ni<sup>I</sup> species **XIII**, the latter of which undergoes SET reduction by **III** to regenerate **VIII**. Importantly, the process is contingent on radical **V** adding selectively to the olefin rather than engaging in direct cross-coupling via single electron metalation to Ni<sup>0</sup> species **VIII**. Speculatively, ligation of the olefin **VI** to Ni<sup>0</sup> could enable radical capture and metalation without formally proceeding through **VII**, thus permitting greater diversity of radical structure.

## Results and Discussion

Initial exploration into the proposed DCF process focused on using **3** as the olefin of choice and a class of radical precursors that would furnish 3° radicals. The former was selected because it is among a privileged class of olefins that are competent radical acceptors<sup>13,14</sup> and retain a synthetic handle capable of incredibly diverse downstream functionalization.<sup>15</sup> Indeed, because the boronate can be used in myriad carbon-carbon bond-forming reactions or post-transformational functionalizations, this olefin can serve as a masked enol, vinyl fluoride, enamine, etc., thus complementing previous approaches outlined in Figure 1 and demonstrating the valuable modular nature of this protocol.<sup>15c</sup> Tertiary radicals were used initially because of their reluctance toward single electron metalation onto Ni, which would alleviate the aforementioned challenges concerning competitive (interrupted) cross coupling. Alkyltrifluoroborates<sup>16</sup> emerged as the most effective class of radical precursors for such transformations. If not commercial, these boronate species can be accessed from a number of different feedstocks.

These include carboxylic acids, alkenes, alkyl halides, and even activated C-H bonds.<sup>15a-b,16</sup> The reactions to convert these feedstocks to organotrifluoroborates can be carried out in high yield under simple reaction conditions.<sup>16b</sup> Given the diverse set of materials from which these precursors can be generated (especially for accessing tertiary radicals), we elected to use them to evaluate the proposed DCF process. Model studies utilizing trifluoroborate **2** (+1.26 V vs SCE)<sup>17</sup> in tandem with boronate **3** and aryl bromide **1** revealed that Ni/photoredox DCF was viable (Table 1). Examination of solvent and photocatalyst identified THF and [Ir(dFCF3ppy)<sub>2</sub>bpy] PF<sub>6</sub> (E<sup>1/2</sup> M<sup>\*/</sup>M<sup>-</sup> = +1.32 V)<sup>18</sup> as a suitable pairing for effecting DCF (see Supporting Information). More rigorous refinement of conditions focused on assessing an array of Ni/ligand combinations, base identity, and stoichiometry (see Supporting Information). The results of these studies led to the conditions provided in Table 1. Interestingly, more intense irradiation (30 W Kessil lamp vs 4 W LED strips, entry 5) resulted in the formation of multiple side products and erosion of product yield. A “zero-precautions” experiment (non-rigorously dried solvent, reaction performed under an air atmosphere) showed a rather significant decrease in yield compared to standard conditions (compare entries 1 and 9), thus emphasizing the need for conducting the reaction free of moisture and air. Control studies confirmed that this DCF process was indeed dual catalytic in nature (Table 1, entries 10–12) and that all the components of the reaction were necessary to ensure successful olefin difunctionalization.

With suitable conditions established, the scope of the DCF process was evaluated. The initial focus was on examining aryl halide diversity (Table 2). A wide array of aryl bromides were

competent in the DCF process. Sensitive functional groups, including acidic (**13**, **15**), electrophilic (**18**, **26**) and homolytically labile C-H bonds (**17**, **27**), were all tolerated in the Ni/photoredox DCF process. In general, aryl bromides substituted with electron-withdrawing groups fared best, although electron-neutral and electron-donating groups also gave moderate to good yields. The efficacy of the reaction was not significantly impacted by sterically demanding *ortho*-substituted aryl bromides (**21**, **22**), albeit these did require extended reaction times. Pharmaceutically relevant moieties with functional group-rich architectures or isosteric moieties could be engaged (**25**, **30**, **31**). Hetero-cyclic bromides were also compatible with the DCF process. Some of these substrates yielded a product without the boronate functional group (**33**, **34**), exposing one potential limitation of the method. Reaction monitoring revealed that protodeborylation occurred under the reaction conditions, likely because of the presence of a Lewis basic nitrogen in these systems combined with the electron-withdrawing nature of a-pyridyl groups.<sup>19</sup> Finally, a series of bifunctional reagents could be prepared (**36–39**, and **4**), providing linchpins for rapid assembly of complex structures. Compound **39** is of particular interest as it arises from selective mono-functionalization of a diiodide.

Next, the amenability toward other olefins and radicals was assessed (Table 3). Owing to recently developed protocols, accessing tertiary boronate esters is straightforward, and numerous feedstocks exist for their construction.<sup>20</sup> Initial efforts focused on organotrifluoroborates derived from  $\beta$ -borylated carbonyls.<sup>20</sup> These radical precursors provided good to moderate yield of the desired products and are especially valuable given that they retain a carbonyl functional handle. Other tertiary alkyltrifluoroborates, prepared via a radical decarboxylation/borylation sequence,<sup>21</sup> were competent in the DCF process. Excellent yields were obtained when using polycyclic BF<sub>3</sub>Ks (**43** and **44**). Such moieties are of high value given their potential to function as bioisosteres and because of their unique architecture and “freedom to operate” from patent infringement.<sup>22</sup>

In addition, a derivative of gemfibrozil, **49**, was prepared. Although structurally distinct from the marketed API, this example demonstrates the potential of this reaction to prepare a target core and rapidly elaborate it, which could be of use in a medicinal chemistry setting.

In addition to **3**, other electronically deficient alkenes were also successfully incorporated into this reaction protocol. Olefins bearing ester and nitrile functional groups gave high yields similar to that when using **3**. The range of functional groups that were successfully incorporated into the olefin acceptor demonstrates the potential applicability of this method to the synthesis of complex molecular architectures.

Despite their known propensity toward Ni/photoredox cross-coupling,<sup>23</sup> attempts to utilize 2° alkyltrifluoroborates were made. After a slight modification of the original conditions, these radicals were found to be quite competent in the DCF process (Table 3). A variety of 2° radicals gave the DCF products in synthetically useful yields (**55–60**), with the major competing pathway being direct cross-coupling to afford materials analogous to that of **4'** (Figure 3).

In addition to improving the scope of the described process, the competency of these 2° radicals indicates that Giese-type addition is competitive with metalation to Ni *or* pre-complexation by the olefin with Ni<sup>0</sup>, thus affording selective sequential olefin difunctionalization.<sup>24</sup> A competition experiment between secondary (cyclohexyl) and tertiary (*tert*-butyl) radicals revealed that DCF is 16 times faster than traditional Ni/photoredox cross-coupling for 3° radicals and 2.5 times faster for secondary radicals, emphasizing the particular efficacy of 3° radicals in Ni/photoredox DCF processes (Figure 3). Attempts to leverage other more stabilized radicals (e.g., benzyl,  $\alpha$ -oxy,  $\alpha$ -amino, etc.) were met with either a lack of reactivity or exclusive C $sp^2$ -C $sp^3$  cross-coupling, indicating poor reactivity in the Giese addition step.<sup>24b,c</sup>

Attempts to utilize the alkyltrifluoroborate derived from verbenone led to an unexpected radical cascade, giving bis-borylated product **61** (Figure 4). Although radical fragmentations of this type are known,<sup>25</sup> this is to the best of our knowledge, the first time that this has been used in a DCF process. The formation of this product provides insight into the relative rate of radical additions to olefins in comparison to nickel single electron metalation. The rate of Giese radical addition to **3** must fall below the rate of radical ring opening in this system ( $1.1 \times 10^7 \text{ s}^{-1}$ ).<sup>26</sup> Further, the fact that no direct cross-coupling products were observed is suggestive that the rate of 3° radical single electron metalation to the catalytic nickel complex is quite slow compared to both reaction with **3** and to the cyclization of the borylated 2° alkyl radical intermediate formed as well.

Although already possessing a broad scope in terms of radical source, aryl halide structure, and olefin type, we sought to gauge the limitations of this method. An HPLC-based robustness assay<sup>27</sup> confirmed that Ni/photoredox DCF can be carried out in the presence of a variety of functional groups not explicitly examined in the scope, including protic groups (alcohols and phenols), alkyl halides, aldehydes, and certain Lewis basic heterocycles (see the Supporting Information). Some displayed excellent tolerance, whereas others still allowed DCF with diminished yield. Though robustness assays do have limitations, these experiments provide a general guide for possible applications of the process developed.

To gain a better understanding of the DCF process, additional experiments were conducted (Figure 5). A Ni-mediated Heck reaction<sup>28</sup> of the vinyl boronate and aryl bromide followed by radical addition was considered. As anticipated, under similar reaction conditions, no detectable amount of **3** reacted with **1** (see the Supporting Information). Next, an alkyltrifluoroborate bearing a pendent alkene was subjected to Ni/photoredox DCF. After Giese addition, 5-*exo-trig* cyclization (rate =  $2 \times 10^5 \text{ s}^{-1}$ )<sup>29</sup> of the intermediate radical resulted in formation of **62**. Although not definitive, this suggests that the olefin is not bound to Ni during Giese addition and supports the initial mechanistic proposal. This also suggests that the rate of single electron metalation of the resulting  $\alpha$ -boryl radical is somewhat slow or reversible. Further experiments are underway to understand the sequence of events in this novel DCF process.

With a better understanding of the limits of this reaction in the context of scope and reaction rate, selective olefin functionalization was attempted. An allylic aryl bromide readily underwent selective DCF, giving **63**. This is notable for two reasons: 1) No reaction of the

electron-rich olefin was observed, despite their propensity toward oxidation<sup>30</sup> 2) No H-atom abstraction of the benzyl-stabilized allylic methylene was observed.<sup>9f</sup> Using a functionalized acrylate containing a pendent alkene, selective 1,2 difunctionalization of the electron-deficient olefin was observed, yielding **64** (Figure 6). This example demonstrates remarkable selectivity given the lack of steric bias in this system, and relies exclusively on the innate polarity-matching of oddelectron species. In addition, selective functionalization was possible in several other poly-olefin systems (**65-68**). Those derived from steroids or containing strained olefins readily underwent selective DCF. More complex terpenebased species were similarly tolerated and did not display any off-target Giese products, although the yields were somewhat diminished because of incomplete conversion in the standard reaction time.

Finally, to demonstrate the inherent synthetic value of the developed DCF process and, more specifically, the boronate functional group installed in DCF products, several derivatization experiments were undertaken (Figure 7), using **4** as a model substrate. Oxidation with perborate yielded the benzylic alcohol **4b** in excellent yield. Using a recently developed procedure by Aggarwal,<sup>31</sup> a new C-C bond was forged via Matteson-type lithiation/migration sequence to give **4a**, whereas traditional Pd-mediated cross coupling gave **4c** in excellent yield.<sup>32</sup>

The success of the model perborate oxidation of **4** led us to pursue the preparation of a key intermediate (**69**) in the synthesis of a gram-positive bacterial thymidylate kinase inhibitor (TK-666).<sup>33</sup> This particular TMK inhibitor shows picomolar activity against antibiotic resistant *S. pneumoniae*, *S. aureus*, and *Enterococcus*. Incorporation of DCF in the early steps of this synthesis provided a dramatic increase in the yield of an analogous benzylic alcohol intermediate. Further, alteration of the alkyl group installed has been shown to have a dramatic effect on potency. As such, the modular nature DCF process described here is highly suitable for rapid exploration of the arene and alkyl group chemical space because of their commercial availability and/or ease of synthetic preparation. To demonstrate this, we utilized an advanced aryl bromide in DCF with various alkyltrifluoroborates to prepare novel TK-666 derivative analogues (**70-72**). Further oxidation of **70** gave the corresponding benzylic alcohol (**70a**) that would serve as an intermediate toward a chloroarene variant of TK-666. In addition to the oxidation protocol described here, these DCF-derived alkylboronates open up exploration into the role of the benzylic functional group (given the vast array of functional group transformations available from the boronate ester) in the context of medicinal chemistry.

## Conclusion

In summary, a dicarbofunctionalization of olefins enabled by Ni/photoredox dual catalysis has been realized. The DCF process accommodates a broad palette of aryl halides, olefins, and radical architectures. This three-component process enables two C-C bonds to be formed in a single step (Csp<sup>3</sup>-Csp<sup>3</sup> and Csp<sup>3</sup>-Csp<sup>2</sup>), sets both quaternary *and* tertiary centers, all while retaining the mild, functional group tolerant nature characteristic of Ni/photoredox dual catalysis. The inherent mechanistic underpinnings enable selective olefin functionalization in polyolefinic systems based on olefin electronics. In addition, the

amenability of vinyl boronates is particularly attractive from the standpoint of late-stage functionalization and enabled the preparation of an intermediate to a preclinical antibiotic. Overall, the developed DCF process allows a rapid buildup of molecular complexity from simple building blocks. The implications of the developed process have sparked additional mechanistic investigations whose findings will be reported in due course.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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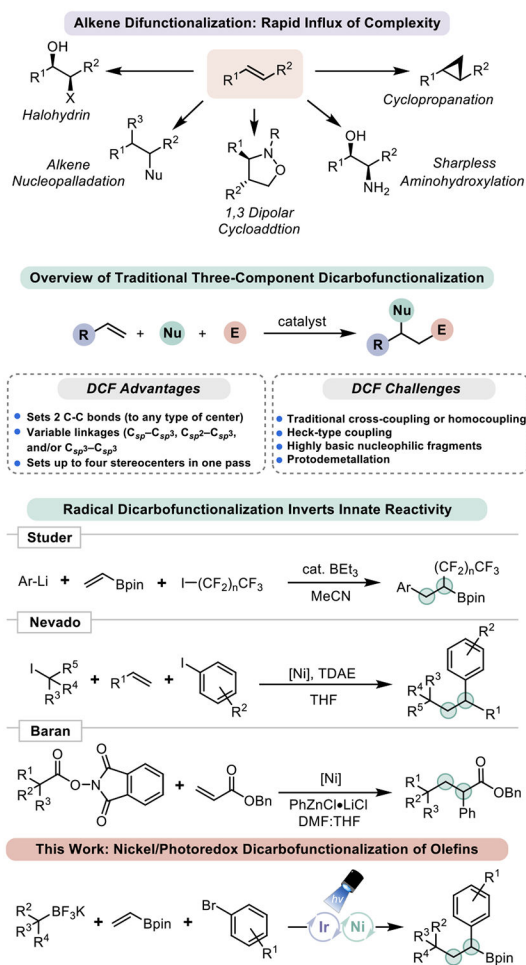
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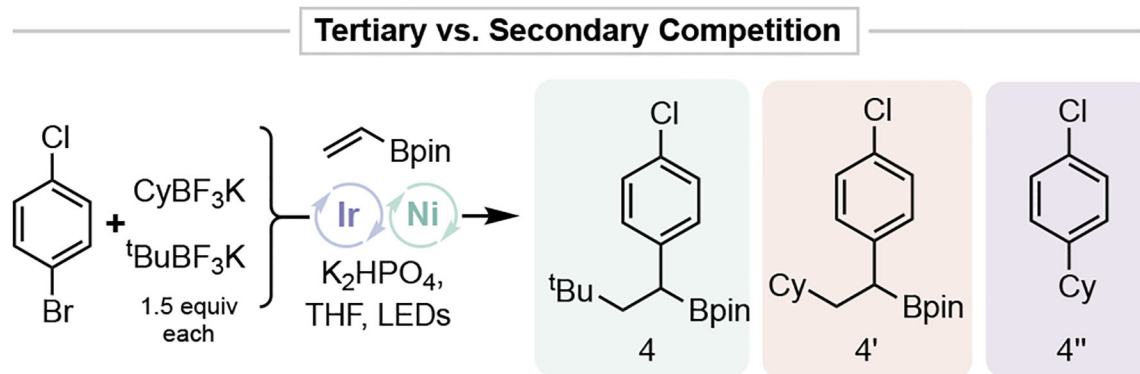
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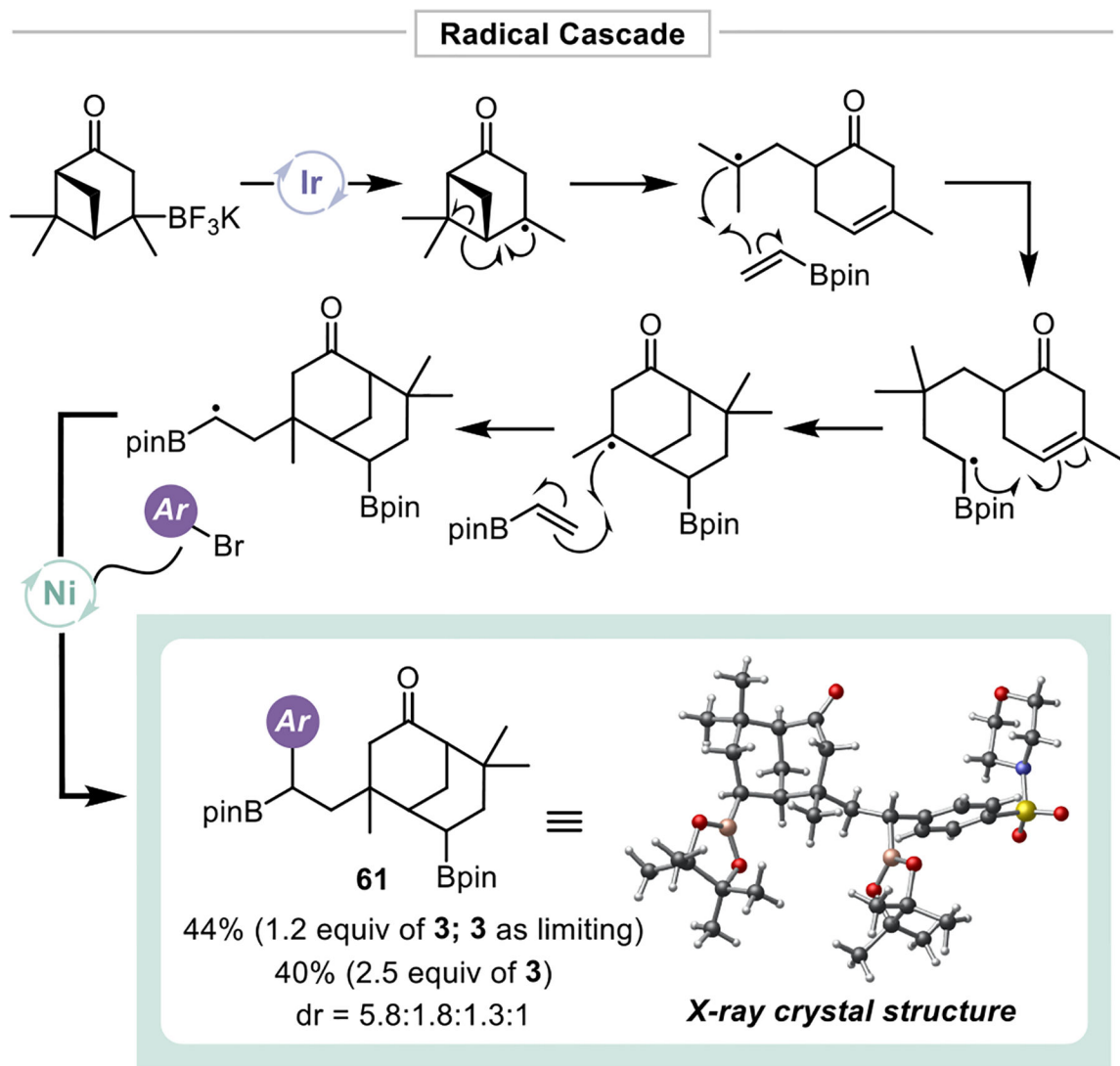


**Figure 1.** Utility of olefin difunctionalization reactions and comparison of the prior art to Ni/photoredox DCF.

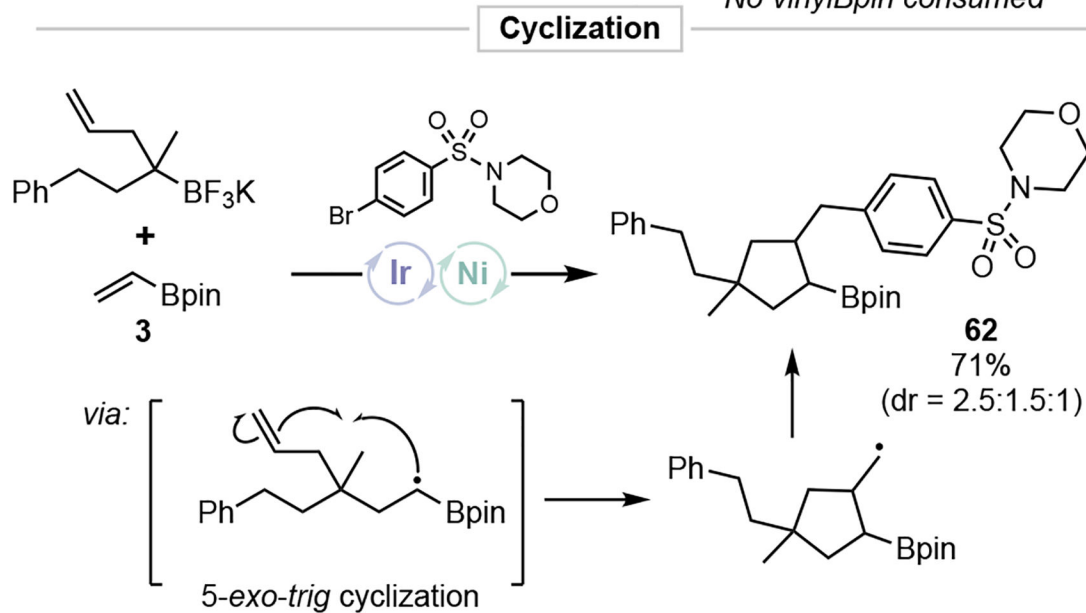
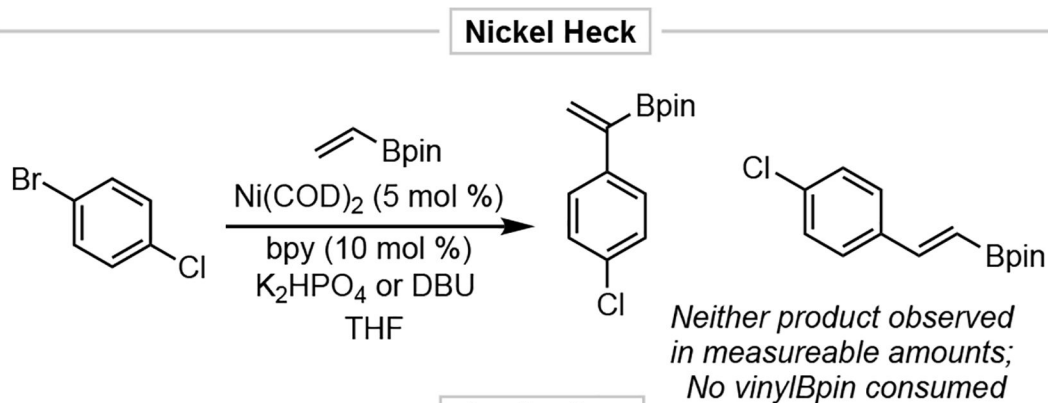




**Figure 3.**  
Secondary versus tertiary radical competition.



**Figure 4.**  
Radical ring opening leads to bis-borylated DCF product.



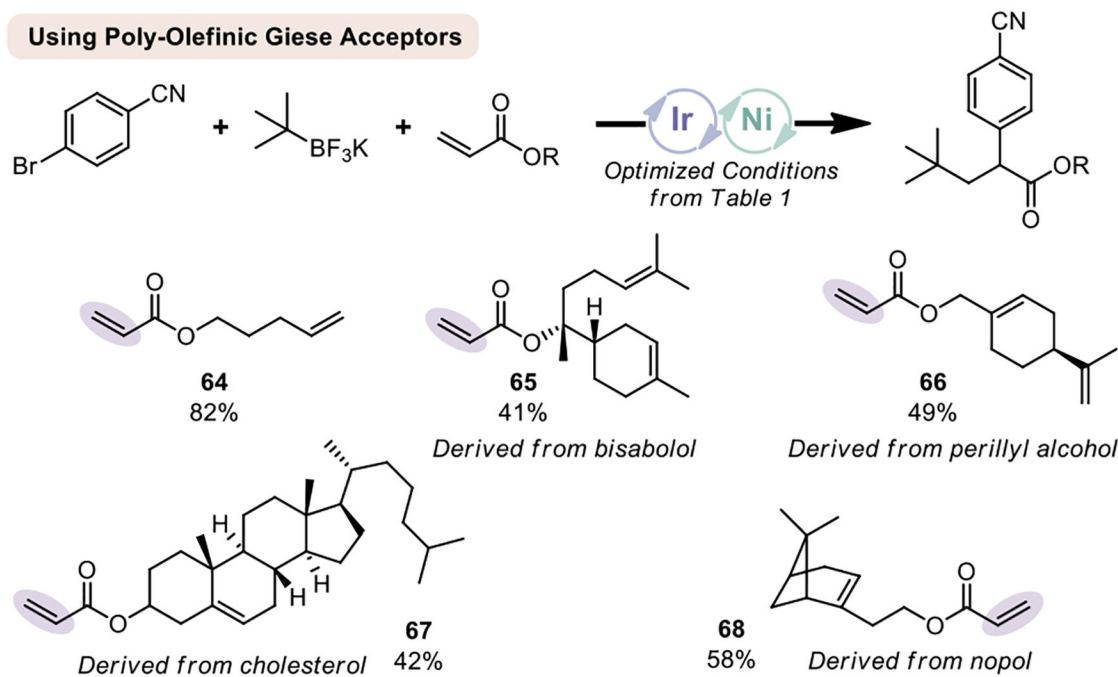
**Figure 5.**  
Mechanistic studies.

### Selective Dicarbofunctionalization

#### Using an Olefinic Aryl Bromide

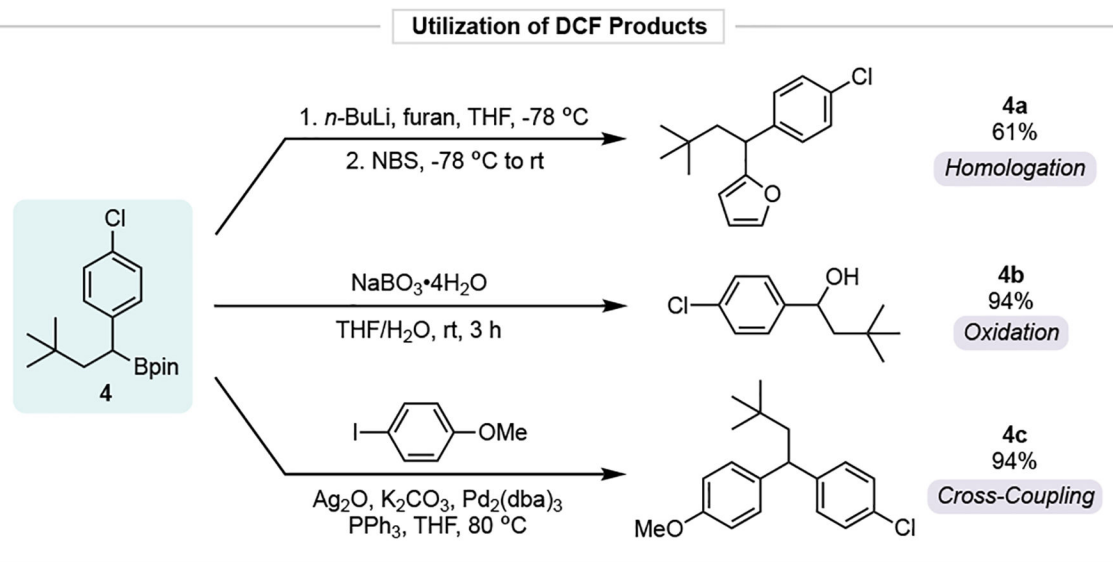


#### Using Poly-Olefinic Giese Acceptors

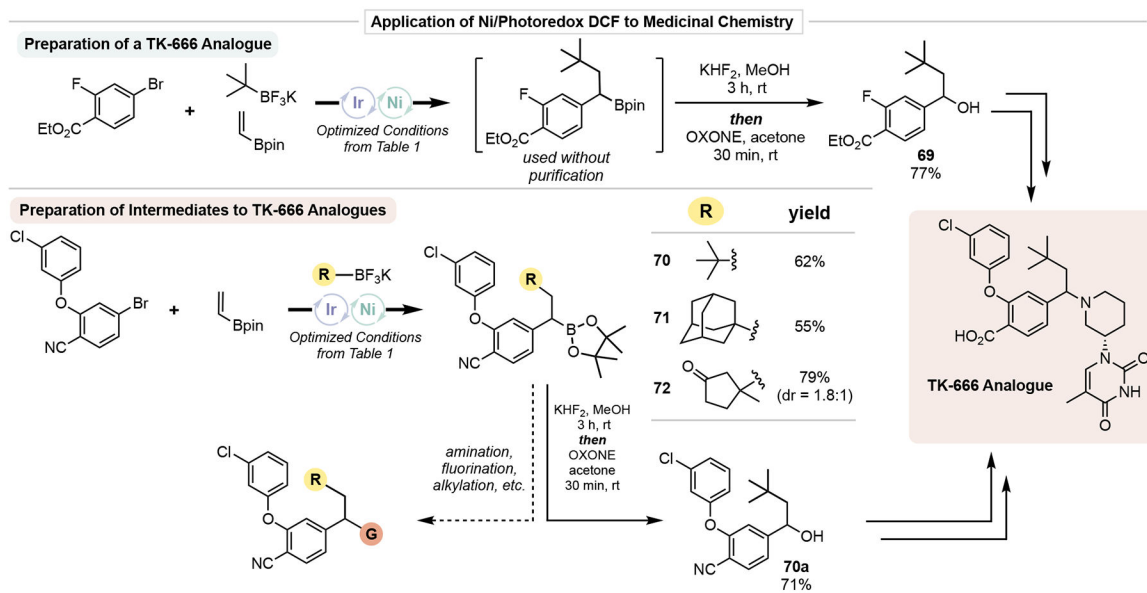


**Figure 6.**  
Selective dicarbofunctionalization of olefins using Ni/photoredox dual catalysis



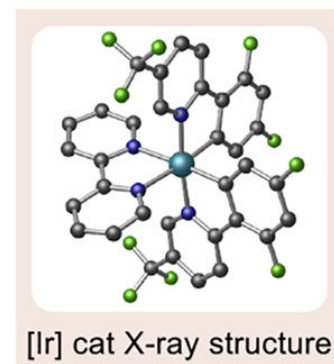
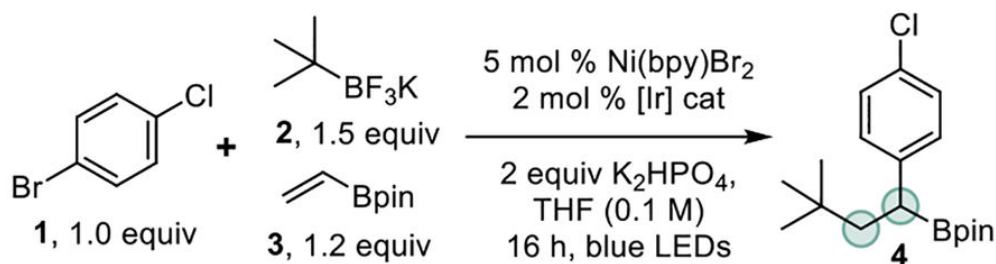


**Figure 7.** Utilization of DCF products to enhance molecular complexity and application to the synthesis of a preclinical candidate.



**Figure 8.** Utilization of Ni/photoredox DCF to prepare medicinally-relevant molecular architectures.

Table 1.

Selected Optimization for Ni/Photoredox DCF<sup>a</sup>

entry	deviation from standard conditions	NMR yield of <b>4</b>
1	none	70% (69%) <sup>c</sup>
2	no base	55%
3	0.05 M concentration	67%
4	0.25 M concentration	39%
5	Kessil lamp in place of blue LEDs	60%
6	5 mol % [Ir] cat, 3 mol % [Ni]	59%
7	5 mol % [Ir] cat, 10 mol % [Ni]	66%
8	Cl-4CzIPN in place of [Ir]	(40%) <sup>c</sup>
9	“zero precautions”	44% <sup>d</sup>
10	No [Ni] catalyst	0%
11	No [Ir] photocatalyst	0%
12	No light	0%

<sup>a</sup>Optimization performed using 4-chloro-1-bromobenzene (0.1 mmol) for 16 h at 27 °C; [Ir] = [Ir{dF(CF<sub>3</sub>)<sub>2</sub>ppy}<sub>2</sub>(bpy)]PF<sub>6</sub>.

<sup>b</sup>Yields in parentheses are isolated yield of **4** after purification.

<sup>c</sup>Reaction performed using 2,4,5,6-tetrakis(3,6-dichloro-9H-carbazol-9-yl)isophthalonitrile (Cl-4CzIPN) as the photocatalyst.

<sup>d</sup>Reaction performed under air with non-rigorously dried solvent.

Table 2.

Aryl Halide Scope of Ni/Photoredox DCF<sup>a,b</sup>

Reaction Scheme		Aryne Scope		yield
		R	yield	
	4: Cl		69%	
	5: H		62%	
	6: Me		66%	
	7: CN		86% <sup>c</sup>	
	8: CO <sub>2</sub> Me		66%	
	9: CF <sub>3</sub>		81% <sup>d</sup>	
	10: OMe		53% <sup>e</sup>	
	11: Ph		91%	
	12: SO <sub>2</sub> Me		80%	
	13: CH <sub>2</sub> OH		58%	

Aryne Scope		Pharmacophores		Scale Up		Bifunctional Reagents	
14: 98%	15: 86%	16: 70%	17: 59%	18: 81%	19: 74%	20: 85% (98% <sup>f</sup> )	21: 63%
22: 43% <sup>c</sup>	23: 55% <sup>c</sup>	24: 81%	25: 46%	26: 76%	27: 59%	28: 52%	29: 86%, 1.86 grams <sup>b</sup>
30: 76%	31: 88%	32: 73%	33: 42%	34: 79%	35: 61%	36: 90%	37: 70%
38: 64%	39: 64%						

**Pharmacophores:** Phenazapam<sup>™</sup> (benzodiazepine) psychiatric therapeutic; Romazicon<sup>™</sup> (flumazenil) derivative GABA receptor antagonist.

**Bifunctional Reagents:** polynucleophilic (SiMe<sub>3</sub>), nucleophile/electrophile hybrids (OTT).

**Heterocycles:** protodeborylated (CO<sub>2</sub>Me, CN).

<sup>a</sup> Values indicate yield of the isolated product. pin = 2,3-dimethylbutane-2,3-diol.<sup>b</sup> Conditions unless otherwise noted: aryl halide (1 equiv, 0.5 mmol), **3** (1.2 equiv, 0.6 mmol), [Ir(dFCF<sub>3</sub>ppy)<sub>2</sub>bpy]<sub>2</sub>PF<sub>6</sub> (2 mol %, 0.010 mmol), Ni(bpy)Br<sub>2</sub> (5 mol %, 0.025 mmol), K<sub>2</sub>HPO<sub>4</sub> (2 equiv, 1.0 mmol), THF (0.1 M), 16 h, irradiating with blue LEDs (6 W).

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<sup>c</sup> Reaction time extended to 48 h.

<sup>d</sup> Ni(dtbbpy)Br<sub>2</sub> used as the Ni catalyst.

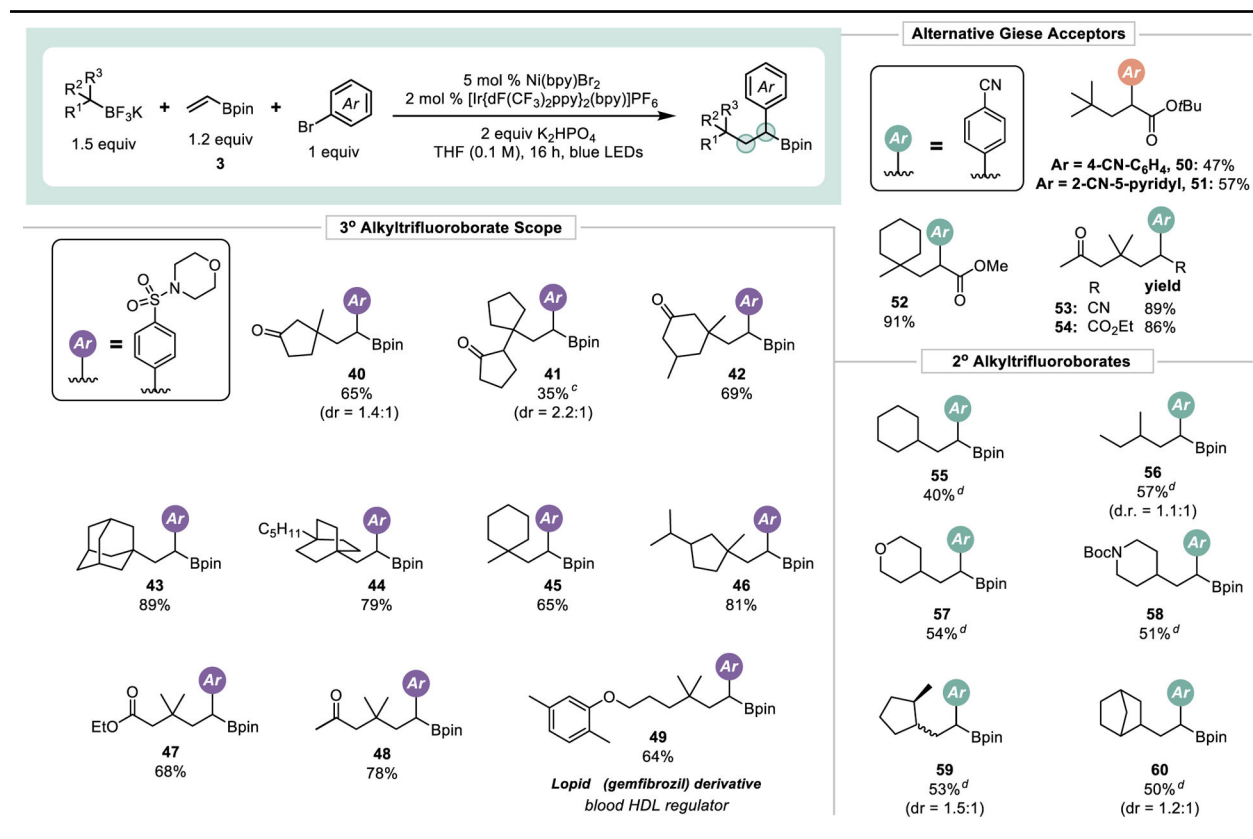
<sup>e</sup> Ni(phen)Br<sub>2</sub> used as the Ni catalyst.

<sup>f</sup> Isolated yield as BF<sub>3</sub>K salt.

<sup>g</sup> <sup>1</sup>H NMR yield of boronate ester

<sup>h</sup> Reaction performed on 5 mmol scale of aryl halide.

Table 3.

Alkyltrifluoroborate and Giese Acceptor Scope of Ni/Photoredox DCF<sup>a,b</sup><sup>a</sup>Values indicate the yield of the isolated product. pin = 2,3-dimethylbutane-2,3-diol.<sup>b</sup>Conditions unless otherwise noted: aryl halide (1 equiv, 0.5 mmol), potassium alkyltrifluoroborate (1.5 equiv, 0.75 mmol), Giese acceptor (1.2 equiv, 0.60 mmol), [Ir(dFCF<sub>3</sub>ppy)<sub>2</sub>(bpy)]PF<sub>6</sub> (2 mol %, 0.010 mmol), Ni(bpy)Br<sub>2</sub> (5 mol %, 0.025 mmol), K<sub>2</sub>HPO<sub>4</sub> (2 equiv, 1.0 mmol), THF (0.1 M), 16 h, irradiating with blue LEDs (6 W).<sup>c</sup>Reaction time extended to 48 h. <sup>d</sup>Ni(phen)Br<sub>2</sub> (5 mol %, 0.025 mmol) and **3** (3.0 equiv, 1.5 mmol) were used.